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EDITORIAL

Improving the radiological diagnosis of hepatic artery thrombosis after liver transplantation: Current approaches and future challenges

Cristian Lindner, Raúl Riquelme, Rodrigo San Martín, Frank Quezada, Jorge Valenzuela, Juan P Maureira, Martín Einersen

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Abstract

Hepatic artery thrombosis (HAT) is a devastating vascular complication following liver transplantation, requiring prompt diagnosis and rapid revascularization treatment to prevent graft loss. At present, imaging modalities such as ultrasound, computed tomography, and magnetic resonance play crucial roles in diagnosing HAT. Although imaging techniques have improved sensitivity and specificity for HAT diagnosis, they have limitations that hinder the timely diagnosis of this complication. In this sense, the emergence of artificial intelligence (AI) presents a transformative opportunity to address these diagnostic limitations. The development of machine learning algorithms and deep neural networks has demonstrated the potential to enhance the precision diagnosis of liver transplant complications, enabling quicker and more accurate detection of HAT. This article examines the current landscape of imaging diagnostic techniques for HAT and explores the emerging role of AI in addressing future challenges in the diagnosis of HAT after liver transplant.

Key Words: Liver transplantation; Postoperative complications; Hepatic artery; Thrombosis; Radiology; Artificial intelligence

Core Tip: Hepatic artery thrombosis (HAT) is a severe vascular complication after liver transplant requiring prompt diagnosis and intervention to prevent graft loss and patient death. However, current imaging methods have limitations. Artificial intelligence (AI), especially deep learning, holds promising potential to enhance precise and accurate HAT diagnosis. This article explores current HAT imaging techniques and highlights the potential role of AI-based methods, aiming to improve diagnostic performance and recipient survival.

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INTRODUCTION

Liver transplantation has emerged as the treatment of choice for patients with end-stage liver diseases (ESLD), including advanced stages of both cholestatic and non-cholestatic cirrhosis, as well as the early stages of hepatocellular carcinoma [1-3]. In recent years, there has been a sustained increase in liver transplant cases, resulting in improved survival prognoses and quality of life for ESLD patients[4,5].

Continuous progress in the development of surgical techniques and novel immunosuppressive agents has contributed to enhanced survival rates among recipients[6,7], with a current five-year survival rate of up to 75%[8-10]. However, strict postoperative multidisciplinary surveillance is imperative to identify and address potential complications that may affect both the graft and the recipient[11,12]. Despite ongoing advancements in the field of liver transplantation, postoperative vascular complications, particularly those related to the hepatic artery (HA), remain one of the primary causes of graft failure and recipient mortality[11].

HA thrombosis (HAT) is a severe complication after liver transplantation, associated with biliary complications such as ischemic cholangiopathy, which may occur even after a successful revascularization treatment, resulting in late graft loss and therefore having a critical impact on quality of life[12,13]. Furthermore, HAT is considered as a risk factor for development of biliary stones in liver graft, which is associated with recurring cholangitis, secondary biliary cirrhosis, and graft failure[14,15].

HAT can be classified according to its temporal onset. Thrombotic occlusion of the HA occurring within the first 30 d following liver transplantation is classified as early HAT (eHAT), which is believed to result from technical problems and perioperative risk factors such as artery kinking, donor arterial anatomic variation, different diameters of the arteries in the anastomosis, or low quality of the donor's or recipient's arteries[16,17].

On the other hand, the later development of HAT, known as late HAT, is usually related to ischemic or immunologic risk factors such as cytomegalovirus-positive donors and hepatitis C seropositive recipient[17-19]. A large study including 4234 cases of adult and pediatric liver transplants reported an overall HAT incidence of 5%, which was higher in pediatric liver transplant recipients than in adults (8% *vs* 3.9% respectively)[20]. In addition, a systematic review comprising 21822 cases of orthotopic liver transplantation, reported an overall incidence of eHAT of 4.4% with an overall mortality of 33.3%, which was also significantly higher in children (34.3%) than in adults (25%)[16].

Strikingly, the cause of this difference remains unknown. Nevertheless, the most likely explanation is the small size of the vessels and the associated technical difficulties of anastomosing[16,21,22]. The reported incidence of late HAT is highly variable, ranging widely from 1% to 25%, with mortality rates of 50%[20,23]. In addition, median times reported to diagnosis of eHAT were 6.9 d (range: 1-17.5 d postoperative), while for late HAT, median times were 6 mo, ranging from 1.8 to 79 mo[16].

The clinical presentation of HAT widely varies according to the timing of onset and the development of collateral vessels, which could maintain blood flow to the allograft[17,20]. Clinically, eHAT manifests with fever, abdominal pain, elevated transaminases, and leukocytosis, which can be followed by septic shock[20,24-27]. Late HAT has an insidious course, characterized by progressive abdominal pain, alteration of liver function tests, relapsing fever, recurring cholangitis, and bacteremia[27,28].

Color-doppler ultrasound (CDUS) is the modality of choice for the postoperative surveillance of liver graft vasculature during the postoperative period, which could depict hemodynamic changes that require further assessment with second-line diagnostic tools such as computed tomography angiography (CTA) or conventional hepatic arterial angiography[17,29,30].

Currently, there are three different modalities for HAT treatment: Retransplantation, surgical revascularization, and endovascular revascularization[17,25]. However, the most effective treatment approach remains controversial[24]. Bekker *et al*[16], reported that retransplantation was more frequently performed in pediatric liver transplant recipients (61.9%) than in adults (50%), and was the treatment of choice in the overall cases of eHAT. In another large study, retransplantation was performed in 71% of patients with eHAT and 51% of patients with late HAT[20].

CTA is the second line of choice when a hemodynamic HA abnormality is suspected on doppler ultrasound evaluation [29,31]. The interpretation of CTA still requires a detailed evaluation of all abdominal vascular structures, which is a time- and labor-intensive process that requires high expertise in abdominal imaging. Although several studies have reported

the high sensitivity of CTA for HAT diagnosis, its specificity remains somewhat low (83.5-87.5%)[32,33].

In this sense, considering the invasiveness and risk of diagnostic angiography, which is the current gold standard for HAT confirmation, it is necessary to improve the diagnostic performance of CTA[34]. The emergence of artificial intelligence (AI), particularly deep learning (DL) algorithms, is gaining growing attention for its performance in image-recognition tasks, achieving high performance on CTA analysis[35-37].

Recent studies have developed different DL-based algorithms, which have resulted in shorter time and high diagnostic performance for CTA diagnosis of vessel occlusion at different anatomic sites, thus improving management outcomes of vascular time-dependent pathologies[37-41].

This article explores the current landscape of multimodality imaging for HAT, highlighting the potential of DL-based algorithms as emerging technologies that could improve HAT diagnosis post-liver transplantation.

MULTIMODALITY IMAGING OF HEPATIC ARTERY THROMBOSIS AFTER LIVER TRANSPLANTATION

Ultrasound (US) evaluation is the modality of choice for assessing liver graft vasculature. It offers a rapid, comprehensive, and accurate grayscale and CDUS evaluation of liver parenchyma at the patient's bedside[29,42], which allows precise assessment of the entire graft vasculature, particularly the blood flow in the HA anastomosis[28].

The arterial anastomosis is typically located in the porta hepatis and can be identified by the presence of intense focal color aliasing and elevated velocity on spectral doppler images surrounding the porta hepatis[43]. Normal doppler evaluation of the HA shows a continuous diastolic flow with a rapid systolic upstroke, an acceleration time of less than 80 msec, and a resistive index that ranges between 0.5 and 0.7[44] (Figure 1).

In 1996, Nolten and Sproat[45] described some qualitative hemodynamic changes in the HA that may anticipate its thrombotic occlusion, including the loss of diastolic flow, dampening of the systolic peak, and finally, the complete loss of arterial flow. The detection of low-velocity and high-resistance flow, nonvisualization, or absence of Doppler color flow in the HA and its intrahepatic branches are findings highly suggestive of HAT[24,46], requiring prompt assessment using CTA or conventional hepatic angiography[44,47].

CTA plays a crucial role in the detection of HAT following liver transplantation. Its high-resolution, contrast-enhanced images provide detailed anatomical information, making it a crucial tool for diagnosing HAT, allowing the assessment of vessel patency and identification of thrombus formation, as well as the evaluation of collateral circulation and ischemia-related biliary complications such as biloma and abscess[48,49].

The lack of opacification of HA and its intrahepatic branches strongly suggest eHAT. However, it should be confirmed in specific detail with maximum intensity projection images[25,48] (Figure 2). On the other hand, the development of collaterals, mainly raised from the phrenic arteries, and the temporal onset are crucial signs that suggest the diagnosis of late HAT[11,16].

Magnetic resonance offers detailed images of the graft parenchyma and biliary ducts within the postoperative surveillance period (Figure 3). However, it may be less readily available and time-consuming compared to the US and CTA[50]. In addition, retrospective studies have reported similar diagnostic accuracy to US but with a higher number of false positives and a more demanding examination[51].

As mentioned above, hepatic arterial angiography is considered the gold standard for the diagnosis of HAT, which can involve diagnostic and therapeutic approaches for the endovascular management of this complication[52] (Figure 4).

EMERGING ROLE OF DL IN HEPATIC ARTERY THROMBOSIS DIAGNOSIS

AI has emerged as a revolutionary technology with a critical impact on the field of medicine. By enhancing diagnostic accuracy, improving efficiency, and enabling early detection of diseases, its continued integration into radiology practices holds the promise of further improving patient care and advancing our understanding of complex diseases[53,54].

Recent research showed that AI-based technology can significantly support the field of liver transplantation by optimizing organ allocation, donor-recipient matching, survival prediction analysis, and the diagnosis of postoperative complications in liver graft recipients[55,56].

As mentioned above, AI algorithms have improved the analysis of medical images, detecting subtle abnormalities, quantifying disease progression, and identifying patterns that might be challenging for human radiologists to discern[57].

DL is a subfield of AI based on neural networks inspired by the human brain structure. It focuses on using artificial neural networks with multiple layers, often referred to as deep neural networks, to model and solve complex tasks and approximate very complex nonlinear relationships[57,58].

Convolutional neural networks (CNNs) are a type of DL artificial neural network specifically designed for processing and analyzing visual data, such as images and videos, for tasks involving visual perception. Therefore, the emerging CNN algorithms have had a profound impact on the field of radiology, revolutionizing the way medical images are interpreted, analyzed, and utilized for diagnosis and treatment planning[59].

Currently, the increasing use of CNN algorithms in medical image analysis has demonstrated interesting results in improving rapid frontline CTA detection of life-threatening large vessel occlusion, with promising diagnostic performance[60-64].

Tajbakhsh *et al*[65] investigated the feasibility of a novel CNN algorithm as an emergent mechanism to improve the diagnosis of thromboembolism detection, showing that their DL algorithm outperforms classic machine learning techniques with a sensitivity of 83% for detecting thromboembolism on CTA[65,66]. Additionally, they also developed a

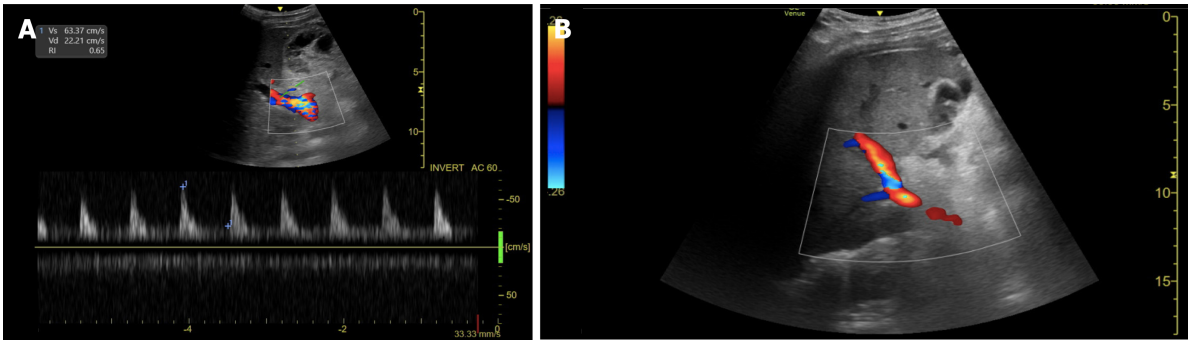

Figure 1 Doppler ultrasound evaluation of the hepatic artery. A: Intercostal color and spectral doppler image of a normal hepatic artery at the porta hepatis in the liver graft of a 51-year-old woman on postoperative day 3 after transplant, depicting a rapid systolic upstroke with continuous low-velocity diastolic flow and a normal resistive index; B: Subcostal color doppler image of the right hepatic lobe in a 46-year-old man on postoperative day 2 demonstrates vascular flow in the portal vein, with no hepatic artery flow detected on color or spectral doppler images at the porta hepatis.

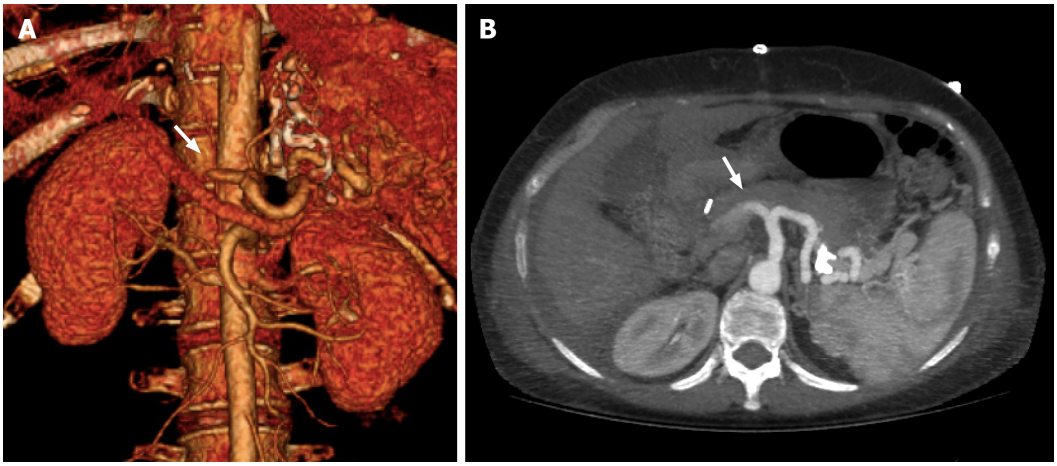

Figure 2 Computed tomography angiography evaluation of hepatic artery thrombosis in liver graft. A 51-year-old woman on postoperative day 7 after a liver transplant. A: Axial abdominal computed tomography angiography (CTA) images at maximum intensity projection (white arrow); B: Coronal 3D volume rendering CTA reconstruction showing absence of vascular opacification of vessels distal to occlusion of the hepatic artery (white arrow).

novel computer-aided embolism diagnosis system, providing radiologists with an effective visualization tool to conveniently examine the vessel lumen from multiple perspectives and confidently report filling defects. Their vessel-oriented image representation offers a multi-view representation of the embolus, summarizing the 3D contextual information around it[67].

Huan *et al*[68] developed the PENet-3D CNN model to detect thromboembolic occlusion using the entire volumetric CTA imaging data, achieving an areas under receiver operating characteristic curve (AUROC) of 0.85. Later, they optimize their model by integrating clinical data from the electronic medical record to achieve 0.87 [95%CI: 0.871-0.875], 0.87 [95%CI: 0.872-0.877], and 0.947 [95%CI: 0.946-0.948] of sensitivity, specificity, and AUROC respectively, for the task of automatically detecting thromboembolism on volumetric CTA image analysis[69].

Ma *et al*[70] proposed a new DL model for embolism detection using the CNN-based network Gradient-weighted Class Activation Mapping (Grad-Cam), a localization technique that provides visual explanations on CTA scans. The algorithm achieved a sensitivity of 0.86 with a specificity of 0.85, which is competitive with radiologists' sensitivities ranging from 0.67 to 0.87 and specificities of 0.89-0.99 for embolism detection on CTA[71].

A recent multicenter study was performed to validate a DL-based application designed with CNN (CINA-PE), to automatically detect embolism on CTA and alert radiologists for urgent interpretation. This algorithm achieved a sensitivity of 91.4% (95%CI: 86.4%-95.0%) and specificity of 91.5% (95%CI: 86.8%-95.0%), leading to an accuracy of 91.5% [72].

Additionally, an automated CNN-based algorithm designed by Fu *et al*[39], that could be trained to complete lumen segmentation automatically reduced the radiologists report writing time of CTA from 28.8 min ± 5.6 to 12.4 min ± 2.0. Therefore, it offers a time-saving and accurate method to analyze CTA to provide optimized clinical workflow.

These experiments further confirm the potential of DL algorithms for medical imaging applications[59]. In particular, the implementation of CNN-based algorithms for image analysis in patients with high clinical suspicion of thrombotic occlusion of HA within the perioperative period could improve the diagnostic performance of the radiologist, optimizing its sensitivity, specificity, and report writing time. Thereby leading to an early and efficient multidisciplinary workflow and therapeutic response, ultimately improving patient prognosis.

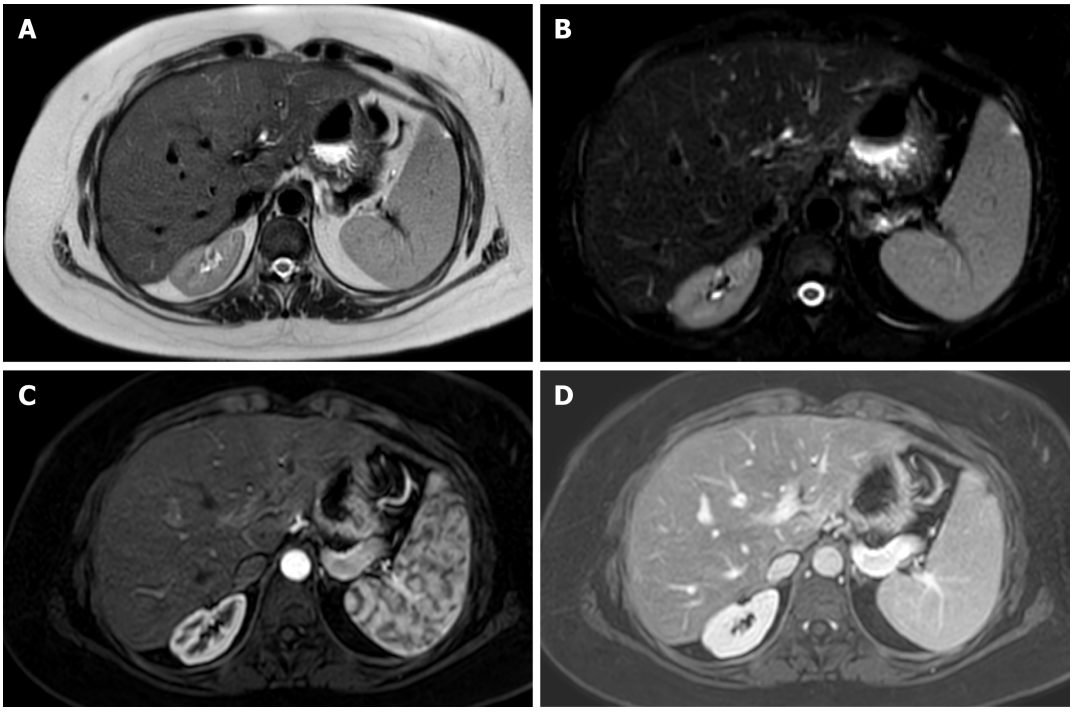

Figure 3 Magnetic resonance imaging of liver graft. Axial T_2-weighted single-shot fast spin-echo image. A: Fat saturation (Fat-sat); B: Contrast enhanced T_1-weighted gradient-echo image in late arterial; C: Portal phase; D: Depicts a homogeneous signal intensity at graft parenchyma, with adequate representation of intrahepatic and extrahepatic arterial branches, venous vessels and biliary ducts, in a 32-year-old man on postoperative surveillance after a liver transplantation.

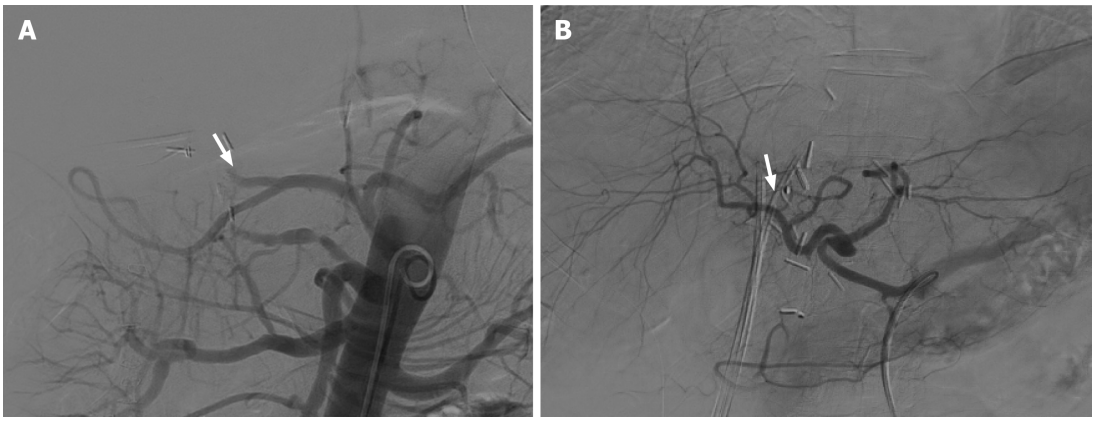

Figure 4 Visceral angiography performed 3 d after orthotopic liver transplant. A: Demonstrated complete occlusion of the hepatic artery (white arrow); B: Recanalization of the hepatic artery after thrombectomy, with improved intrahepatic blood flow (white arrow).

CONCLUSION

Despite the continuous advances in the field of liver transplantation, HAT remains a significant cause of morbidity and mortality in recipient patients. While there are different imaging studies that allow the assessment of the HA, they have limitations that prevent an early diagnosis of this complication.

AI can potentially revolutionize HAT detection by enhancing the interpretation of imaging data and facilitating rapid and precise diagnosis. The integration of AI into existing imaging modalities, such as CTA, holds the potential to streamline clinical workflows, reduce healthcare costs, and ultimately improve patient outcomes.

Future investigations should be focused on improving the diagnostic performance of non-invasive imaging techniques for life-threating diseases. HAT is a severe complication that significantly increases the risk of graft loss and patient mortality. In this regard, emergent DL-based algorithms have demonstrated high diagnostic performance for arterial occlusion at different anatomical sites. Considering these findings, the development of new DL algorithms focused on the CTA analysis of the liver graft vasculature could assist radiologists in improving sensitivity, specificity, and diagnostic reporting time for HAT, thus enhancing early treatment for this time-dependent complication.

FOOTNOTES

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EDITORIAL

Predicting outcomes after kidney transplantation: Can Pareto's rules help us to do so?

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Abstract

Kidney transplantation is the best option for kidney replacement therapy, even considering that most of the times the grafts do not survive as long as their recipients. In the Khalil *et al*'s experience, published in this issue of the Journal, they analyze their second kidney graft survival and describe those significant predictors of early loss. This editorial comments on the results and put in perspective that most of the times, long-term graft survival could be inadvertently jeopardized if the immunosuppressive therapy is reduced or withdrawn for any reason, and that it could happen frequently if the transplant physician intends to innovate with the clinical care without proper evidence-based data.

Key Words: Kidney transplantation; Graft survival; Acute rejection; Interstitial fibrosis and tubular atrophy; Immunosuppression

Core Tip: Most of the times, kidney graft and recipient survivals do not match because of earlier graft failure. Apart from surgical or urological complications, the reason frequently is the appearance of donor-specific antibodies that mediate acute and chronic allograft damage because treating physicians intend to construct a tailor-made immunosuppressive therapy to each of their patients.

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INTRODUCTION

Kidney transplantation is the best option for kidney replacement therapy, even considering that most of the times the grafts do not survive as long as their recipients. In those patients who experience the failure of the transplanted graft, it is still possible to perform a second, or even a third, transplant, because these organs still perform better than dialysis.

From a process management perspective, the best option to prolong the survival of those patients suffering from end-stage renal disease is to optimize dialysis quality while they are waiting for a transplant. Then, efforts should be taken to try to prolong the survival of their first kidney graft. The question is how to accomplish this last issue in the real world.

In 1906, Vilfredo Pareto postulated that 80% of the consequences come from 20% of causes[1] and from this perspective, the main causes of transplant failures should be few. In the Khalil *et al*'s experience[2], published in this issue of the Journal, they state that the first graft failed mainly because of two drivers: Primary non-function, explained by a recipient high body mass index ($P = 0.009$), and first graft loss because of acute rejection ($P = 0.025$). They also found that the survival of the second graft was reduced if the first one presented delayed graft function ($P = 0.008$ and $P < 0.001$, respectively), and also if the first graft underwent an acute rejection in the first year after the first transplant ($P = 0.053$) [2]. It is possible to think that Khalil *et al*[2] describe two main determinants that explain their failures: Rejection due to primary non-function, and immunological and inflammatory progressive damage to the graft. The first determinant may be explained by organ donor maintenance quality before organ harvesting, cold and warm ischemia times lasting too long, and not enough expertise of the implanting surgeons, which are expected to decrease as the procurement and surgical teams get experience, as it is observed in countries with high rates of kidney transplants[3]. Regarding the second determinant, it is more difficult to avoid having acute rejection episodes because there are several graft-recipient pair factors that intervene in their development, such as human leukocyte antigen mismatches, prior sensitization, immunosuppressive schemes, drug quality, and patient compliance.

Putting our focus on rejection, there are several experiences that analyze graft biopsies from failing kidney transplants with an intention to answer why those kidney grafts fail in the medium-to-long term. Most of the time, either graft rejection (9%-64%) or non-specific chronic injury or, in other words, interstitial fibrosis and tubular atrophy (IFTA, 24%-47%), is found[4]. It is also found that the rejection types and IFTA vary in parallel with the recipients' age and time after transplantation. But characteristically, there are more T-cell mediated rejections in the first 5 years after transplantation, and more antibody mediated rejections (ABMR) and IFTA after that period, while other causes of graft failure happen in young recipients[5].

By the way, what is IFTA? Is it synonymous with the term chronic allograft nephropathy (CAN)? At the end of last century, some experts thought that as grafts get older, they accumulate specific and non-specific damage resulting in sclerosis, increase in the interstitium collagen content, and tubular atrophy. This hypothesis was endorsed in a prospective protocol biopsy cohort of both kidney and pancreas transplantation in type 1 diabetics[6]. In fact, in this experience, Nankivell *et al*[6] showed that rejections predominated soon after transplantation, and both chronic damage and arteriolar hyalinosis predominated later on. Regrettably, a secondary hypothesis resulting from this experience was that calcineurin inhibitors (CNI), mostly cyclosporine, could be the culprit, which stimulated the transplant community to take non-evidence-based action to decrease or even withdraw the use of CNI. Some years later, we observed the appearance of donor-specific antibodies (DSA), and subsequently, of ABMR and graft losses as consequences. The histological morphology of these grafts reminded of the old CAN and, at the same time, the newer term IFTA, closing the circle of the main cause of the mismatch of kidney graft and transplanted recipient survivals, which is a chronic allograft rejection due to insufficient immunosuppression.

Nevertheless and sadly, this is not the whole story. Not providing enough immunosuppression could happen also because some doctors aspire to prescribe "patient-tailored therapies" based on their own perceptions/experiences, and believe more on that than on evidence-based medicine. There are several experiences, systematic reviews, and meta-analyses that show us that decreasing, or even worse, withdrawing any of the chronic immunosuppressive agents such as CNI, antiproliferatives, or steroids, is associated with the appearance of DSA, ABMR, and IFTA. These pathogenic mechanisms would be responsible for the decrease in graft survival and early graft loss[7-11].

Another explanatory variable could be frequent mycophenolate dose reduction, to even 50% below the standard and approved dose, occurring soon after transplantation, which is further associated with an increase in IFTA[12,13]. Moreover, this unintended and naïve behavior, which tries to ameliorate drug-related adverse events, could be accompanied with a decrease in CNI dose, resulting in less immunosuppression than prudence suggests[14].

CONCLUSION

From Khalil *et al*'s data[2], it is interesting to learn that for achieving a long kidney transplant survival, it is advisable to be prepared in different frontlines: (1) Having a well-trained team in order to surpass surgical technical difficulties, such as

primary non-function because of recipient's body mass index; and (2) prescribing a well-balanced immunosuppressive therapy to maximize patients' adherence, and minimize the probability of DSA, ABMR, IFTA, and of course, drug-related adverse effects, issues that may threaten the task of prolonging the survival of a first (or second) transplanted allograft, with the objective of matching it with the survival of the recipient blessed by that transplant.

FOOTNOTES

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REVIEW

Pros and cons of live kidney donation in prediabetics: A critical review and way forward

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Abstract

There is shortage of organs, including kidneys, worldwide. Along with deceased kidney transplantation, there is a significant rise in live kidney donation. The prevalence of prediabetes (PD), including impaired fasting glucose and impaired glucose tolerance, is on the rise across the globe. Transplant teams frequently come across prediabetic kidney donors for evaluation. Prediabetics are at risk of diabetes, chronic kidney disease, cardiovascular events, stroke, neuropathy, retinopathy, dementia, depression and nonalcoholic liver disease along with increased risk of all-cause mortality. Unfortunately, most of the studies done in prediabetic kidney donors are retrospective in nature and have a short follow up period. There is lack of prospective long-term studies to know about the real risk of complications after donation. Furthermore, there are variations in recommendations from various guidelines across the globe for donations in prediabetics, leading to more confusion among clinicians. This increases the responsibility of transplant teams to take appropriate decisions in the best interest of both donors and recipients. This review focuses on pathophysiological changes of PD in kidneys, potential complications of PD, other risk factors for development of type 2 diabetes, a review of guidelines for kidney donation, the potential role of diabetes risk score and calculator in kidney donors and the way forward for the evaluation and selection of prediabetic kidney donors.

Key Words: Live kidney donation; Prediabetes; Impaired fasting glucose; Impaired glucose tolerance; Review

Core Tip: An increasing number of prediabetic kidney donors are encountered by transplant physicians. The decision to allow or to not allow these donors is always challenging. Prediabetics are prone to multiple complications in the future, including diabetes mellitus and chronic kidney disease. Variability in recommendations by various organizations and societies about kidney donation in prediabetics leads to even further confusion in decision making. This extensive review focuses on evidence from both the general population and kidney donors regarding kidney donation in prediabetics. This review will help clinicians to take well informed decisions and to identify a direction for further research and the need for a uniform position by international transplant societies like The Transplantation Society or International Society of Nephrology.

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INTRODUCTION

Prediabetes (PD) is described as high blood glucose levels which do not satisfy the criteria for the diagnosis of diabetes mellitus (DM). A fasting plasma glucose level of 126 mg/dL (6.99 mmol/L) or greater, and glycated hemoglobin (HbA1c) level of 6.5% or greater, or a 2-h post prandial level of 200 mg/dL (11.1 mmol/L) or greater are consistent with the diagnosis of type 2 diabetes. On the other side, a fasting plasma glucose level of 100 to 125 mg/dL (5.55-6.94 mmol/L), an HbA1c level of 5.7% to 6.4%, or a 2-h post prandial glucose level of 140 to 199 mg/dL (7.77-11.04 mmol/L) are consistent with PD[1]. The World Health Organization (WHO) and numerous other diabetes organizations define the impaired fasting glucose (IFG) cutoff to be 110 mg/dL (6.1 mmol/L)[1]. The global prevalence of PD reported in literature has been variable due to a variety of reasons. Firstly, the definition of PD by WHO and the American Diabetes Association (ADA) has been different and as a result prevalence has varied among different studies depending on the definition being used. Secondly, studies used different parameters such as fasting glucose, glucose tolerance test or glycosylated hemoglobin to define PD, which could also have led to variable prevalence. Rooney *et al*[2] used the WHO definition of PD and reported the global prevalence of impaired glucose tolerance (IGT) in 2021 as 9.1% (464 million) and projected it to go up by 10% (638 million) in 2045. Similarly, the global prevalence of IFG in 2021 was 5.8% (298 million) and it was projected to increase by 6.5% (414 million) in 2045[2]. Bullard *et al*[3] used the ADA definition and reported the prevalence of PD in adults aged ≥ 18 years as 29.2% in 1999-2002, increasing to 36.2% in 2007-2010 in United States population[3]. A study from China used the ADA 2010 definition and reported prevalence at 50.1%[4]. Around 5%-10% of people with PD develop DM annually[5,6] although the conversion rate varies by population characteristics and the exact criteria used for the definition of PD. IFG is a predictor of cardiovascular mortality and it increases cardiovascular mortality by 20%[7,8].

Kidney transplantation (KT) is the treatment of choice for end stage renal disease (ESRD)[9]. KT improves quality of life and survival rates of patients with ESRD[10,11]. Living kidney donation leaves the kidney donor with a single kidney for the rest of their life, hence increasing their vulnerability to acquire kidney impairment in the future. Recent studies comparing donors to healthy non-donors found that kidney donation is related to a small but statistically significant increased risk of ESRD[12,13]. Prediabetic kidney donors have a seven-fold increased risk of DM (15.6%) compared to donors with normal glucose levels (2.2%)[14]. In view of this significant risk, it is important for KT physicians to carefully assess donors with PD for eligibility of donation.

PATHOLOGICAL EFFECTS OF PREDIABETES ON KIDNEYS AND POTENTIAL IMPLICATIONS FOR KIDNEY DONORS

Abnormal glomerular hemodynamic homeostasis has been proposed as an important factor in the pathogenesis of renal diseases. This is usually manifested as increased hyperfiltration leading to an increase glomerular filtration rate (GFR)[15]. PD has been shown to cause hyperfiltration and increased GFR in both animal and human studies. Experimental glucose infusion in dogs has been shown to cause a reactive increase in GFR[16]. Similarly, in human clinical studies, hyperfiltration was implicated in the development of diabetic nephropathy[17,18]. The association of impaired fasting with hyperfiltration has been shown to be independent of age, sex, body mass index (BMI), blood pressure and insulin status[19]; with subsequent development of microalbuminuria. A Korean study reported an odd ratio (OR) of 2.57 in an individual having both IFG and IGT[20]. Two studies from Italy and Australia showed high prevalence of microalbuminuria in IFG and IGT as compared to a normoglycemic individual. The study from Italy reported the prevalence of microalbuminuria as 6.9%, 5.6%, and 4.3% in IFG, IGT and normoglycemic groups, respectively[21]. The study from Australia reported the prevalence of microalbuminuria as 8.3% in IFG, 9.9% in IGT, and 4.3% in those with normal glucose[22]. Presence of microalbuminuria is of clinical importance because it is an established risk factor for cardi-

ovascular events and chronic kidney disease (CKD)[23]. Furthermore, the presence of microalbuminuria in donors with PD could result in a suboptimal kidney being donated to the recipient. Histological evaluation of PD through kidney biopsy is not done routinely in this group of patients, hence it is often not easy to determine the extent of pre-existing kidney damage. Mac-Moune Lai *et al*[24] were the first to describe the histological manifestation of PD through an analysis of 23 patients who had diffuse thickening of the glomerular basement membrane on electron microscopy. They found that the basement membrane thickness was associated with incidental abnormalities of glucose levels with no correlation with age, smoking, body weight, hyaline arteriosclerosis, and hypertension. The authors followed their cohort for development of glucose metabolism. They found diabetes in 20% of patients at the time of biopsy. On further follow up, 44% developed diabetes at 6 months and another 70% develop diabetes latter at 24 months. Seven patients showed no evidence of diabetes at the follow-up[24]. The authors speculated that isolated diffuse thickening of glomerular capillary basement membrane may be a renal lesion in PD. Thickening of the glomerular basement membrane has also been identified as an early diabetic lesion in young diabetics[25,26]. From a pathophysiological standpoint, it can be deduced that PD induces high GFR with subsequent microalbuminuria and compensatory histological thickening of glomerular basement membrane.

The synergistic deleterious effects of PD and donor nephrectomy in the development of CKD in kidney donors is not well studied. Post-kidney donation often causes mild proteinuria and reduced GFR, with incidence of proteinuria ranging from less than 5% to more than 20%[27]. The proteinuria usually becomes more pronounced over a period of time[27]. Kidney donation is also associated with a 30%-35% dip of GFR in the earlier period[28], but compensatory hyperfiltration in the remaining kidney can lessen the expected GFR reduction.

RISK OF CHRONIC KIDNEY DISEASE

Early CKD in kidney donors is mostly due to glomerulonephritis[13,29-32]. However late CKD in kidney donors is due to Denovo DM[13,29-31] and hypertensive nephrosclerosis[32]. PD has been implicated in hyperfiltration[16-18] and the development of microalbuminuria[21,22] in the general population, which are usually early manifestations of renal injury. Though the risk of conversion from PD to diabetes is higher in kidney donors (15.6%) when compared to healthy control (2.2%)[14], the real risk of CKD reported in few studies is minimal. Chandran *et al*[14] found that prediabetic patients are not at risk of developing CKD in the short term[14]. Similarly, a study from Japan compared donors with PD and diabetes with those having normal glucose and found no difference in surgical complications, mortality or risk of ESRD[33]. Hebert *et al*[34] and his colleagues also did not find increased risk of CKD in donors with PD[34]. The annual incidence rate of development of DM is 6%-11%. Around 70% of individuals with PD will eventually develop DM in their life time[35]. About 40% of diabetics will develop CKD in their life span[36]. Microalbuminuria and hyperfiltration develop 5-10 years after the initial diagnosis of DM (or PD). Macroalbuminuria develops in another 15 years and ESRD will ensue in 19 years from the diagnosis of diabetes[37]. Therefore, to know the real impact of PD we need long term studies of at least greater than 19 years to see the real sequalae of PD. Most of the studies done in prediabetic donors have a short period of follow up ranging from 88 months[33] to 10.4 years[14], which may miss out patients with late onset DM and diabetic kidney disease.

Many studies have been conducted on PD and the risk of CKD in the general population, with mixed findings. In the Framingham Heart Study, odds of developing CKD were 0.98 (95%CI: 0.67-1.45), 1.71 (95%CI: 0.83-3.55), and 1.93 (95%CI: 1.06-3.49) among those with IFG or IGT, newly diagnosed DM, or known DM when compared to those with a normal glucose level. The authors of this study proposed that cardiovascular disease risk factors explained much of the relationship between PD and the development of CKD[38]. With a mean follow-up of 14 years, study participants without baseline diabetes had glycosylated hemoglobin of 5.7%-6.4% and ≥ 6.5%, and < 5.7% were found to have a hazard ratio (HR) of 1.12 (0.94-1.34) and 1.39 (1.04-1.85) for development of CKD. Selvin *et al*[39] in their study with a mean follow-up of 14 years of study participants without baseline diabetes compared glycosylated hemoglobin of 5.7-6.4% and ≥ 6.5%, with < 5.7%, and found a HR of 1.12 (0.94-1.34) and 1.39 (1.04-1.85) for development of CKD. The corresponding HR for ESRD were 1.51 (0.82-2.76) and 1.98 (0.83-4.73), respectively[39]. In a study from Korea[20], the OR for microalbuminuria and CKD in an individual with PD having impaired fasting were 1.54 (95%CI: 1.02-2.33) and 1.58 (1.10-2.25). The OR significantly went up to 2.57 (1.31-5.06) in individuals having both IFG and IGT. The National Health and Nutrition Examination Survey study (1999-2006) showed that 17.7% of participants with PD had CKD as compared to 10.6% with no diabetes[40]. Redon *et al*[41] found that there was a close relationship between abnormal urinary albumin excretion and renal insufficiency in patients with essential hypertension, which was more pronounced in patients with the highest IFG (110-125.9 mg/dL).

However, there are also studies which did not find associations between PD and development of CKD. In a study from Germany, the prevalence of risk for CKD and the incidence of CKD were higher in subjects with PD than in subjects with euglycemia. However, the authors found that the increased risk did not persist after adjusting for established cardiovascular risk factors. After careful adjustments for established cardiovascular risk factors, the relative risk (RR) for IFG was 0.97 (95%CI: 0.75-1.25) and for HbA1c -defined PD was 1.03 (95%CI: 0.86-1.23). This led the authors to conclude that the higher incidence reduced kidney function in subjects with PD is most likely caused by increased cardiovascular risk factors[42]. In secondary analysis of the Systolic Blood Pressure Intervention Trial, where participants were followed for a median of 3.3 years, 41.8% had IFG but IFG was not associated with worsening kidney function or albuminuria[43]. Similarly, a study from Japan found an association of PD with the development of proteinuria but it failed to show any association between PD and CKD[44].

A meta-analysis of 9 cohort studies, the participants of which were mainly Asian and white, found increased risk of CKD in PD. Eight studies used the definition of impaired fasting as 6.1-6.9 mmol/L and after adjustment for established risk factors, the RR of CKD was 1.11 (95%CI: 1.02-1.21). One study in this meta-analysis used definition of IFG as 5.6-6.9 mmol/dL. Combining all studies together, the overall RR of CKD was 1.12 (95%CI: 1.02-1.21; Table 1)[45].

IS CKD THE ONLY CONCERN OF PD?

PD causes various other complications other than CKD. These complications should be kept in mind and should be taken into consideration before allowing a potential donor to donate. PD can cause overt DM, cardiovascular events, stroke, microvascular complications such as neuropathy and retinopathy and has been associated with dementia, depression, cancer and an increase in all-cause mortality[46,47].

Development of diabetes

Risk of progression from PD to diabetes varies widely due to differences in the definition of PD, heterogeneity of PD, and social and physical environment[48]. The lower cut-off point for IFG, which is still used by WHO, is 6.1 mmol/L[49]. In 2003, this cut-off point was lowered to 5.6 mmol/L by the ADA[50]. As a result, there is variability in the prevalence of PD and its subsequent progression to diabetes. Around 10%-50% of individuals will develop diabetes in next 5-10 years [35,51,52]. On the other hand, 30%-60% will revert to normoglycemia within 1-5 years[51].

The risk of progression of PD to diabetes is less well studied in kidney donors. Various studies done in kidney donors reported the incidence of diabetes as 1.5%-7.4%. However, most of these studies were cross sectional in nature, having a sampling bias with a lack of baseline glucose levels before donation[53-62]. The risk of diabetes in kidney donors with PD is 6 times more compared to donor without PD[14]. In a retrospective review with 1826 kidney donors, patients with IFG (100-126) were compared to those with normal blood glucose (< 100 mg/dL) and donors with a fasting glucose ≥ 126 mg/dL[34]. IFG was associated with a higher risk of diabetes and hypertension, but these patients were not found to be at higher risk of proteinuria or ESRD. Only 3.5% of donors from this cohort with normal glucose developed diabetes, at 15.4 ± 10.9 years, compared to 5.5% donors with IFG who developed diabetes 10.6 ± 8.8 years after donation.

Risk of cardiovascular diseases

Post kidney donation living donors are prone to high blood pressure and proteinuria[27,63-65]. Proteinuria, hypertension and reduced GFR are known risk factors for cardiovascular events[66-68]. There are mixed findings regarding the post donation risk of cardiovascular events. A recent long-term follow-up (11.3 years) of kidney donors showed that donors were at an increased risk of ischemic heart disease when compared with healthy controls[69]. Conversely, there are also studies which did not find an increased risk of cardiovascular events[70,71]. PD is a well-known risk for cardiovascular events. Unfortunately, there is paucity of data linking PD to cardiovascular events in kidney donors. However, most of the evidence linking PD to cardiovascular illness has been gathered from the general population. PD has been implicated as a risk factor for cardiovascular diseases in a range of studies[7,72,73]. PD shows a 20% higher risk of developing cardiovascular disease compared to those with normal blood sugar[74]. Insulin resistance, inflammation and endothelial dysfunction in PD are linked to more cardiovascular events[75]. IGT is more often associated with cardiovascular events than IFG[76-78], with an overall similar cardiovascular risk to type 2 DM in many landmark trials such as Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe[76], Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia[79] and Funagata Diabetes study[73]. Similarly, increase in glycosylated hemoglobin even within a normal range has been shown to cause more cardiovascular mortality. In the European Prospective Investigation into Cancer (EPIC) Norfolk study, even a small 1% increase in HbA1c within the normal range caused an increase in 10-year cardiovascular mortality[80]. Since PD causes insulin resistance, inflammation and endothelial dysfunction[75], KT physicians have to be more mindful on potential future cardiovascular risks.

Stroke/cerebrovascular accident

Stroke is one of the macrovascular complications of PD. The prevalence of PD in patient with a recent ischemic stroke or transient ischemic attack (TIA) is around 37%[81]. Two-hour IGT is a stronger predictor of stroke and cardiovascular events compared to IFG[76,82,83]. IGT has also been implicated in recurrent ischemic stroke and TIA and it increases risk of recurrent TIA and minor stroke by 2 folds[82]. A meta-analysis of 15 prospective cohort studies found a positive association between PD and stroke. The authors, after excluding studies with undiagnosed diabetes, found that IGT or the combination of IFG and IGT were independent risk factors for stroke[84]. Unfortunately, the association of PD with stroke in kidney donors is not well studied and there is need to explore this group of individuals for risk of stroke.

Neuropathy

Neuropathy is one of the microvascular complications. Around 35% of newly diagnosed type 2 diabetics have peripheral neuropathy indicating an early subclinical phase before the development of diabetes[85]. PD has been linked to the development of peripheral neuropathy in the general population, though its prevalence is varied in different studies. The 1999-2004 cohort from Katon *et al*[86] reported the RR of peripheral neuropathy of 1.1 in PD and 1.7 in diabetes[86]. A study from Germany reported significant peripheral neuropathy of 24% in individuals who have both IFG and IGT. However, isolated IFG or IGT in this study failed to show significance for development of peripheral neuropathy[87]. The MONICA/KORA study found that neuropathy was more common in patients with IGT when compared to control[88]. Authors of this study used Michigan Neuropathy Screening Instrument and found that neuropathy, predominantly

Table 1 Showing association of prediabetes with chronic kidney disease

Ref.	Journal/Year	Study type	Objective	Findings
Fox *et al*[38]	*Diabetes Care*/2005	Follow up of Framingham Heart Study (1991-1995) after 75-gram oral glucose tolerance test	To study the impact of IFG and IGT on development of CKD	The odd of developing CKD was 0.98 (95%CI: 0.67-1.45), 1.71 (95%CI: 0.83-3.55) and 1.93 (95%CI: 1.06-3.49) among patients with IFG or IGT, newly diagnosed diabetes or known diabetes
Redon *et al*[41]	*J Am Soc Nephrol*/2006	Prospective multicenter, cross-sectional study	To assess the relationship between UAE and glomerular filtration rate in patients with glucose metabolism abnormalities having hypertension	The prevalence of abnormal UAE, > or = 3.4 mg/mmol across the spectrum of glucose abnormalities were 39.7%, 46.2%, 48.6%, and 65.6% for normoglycemic, low-range, and high-range impaired fasting glucose and diabetes. Predictors of low GFR < 60 mL/min were UAE ≥ 3.4 mg/mmol (OR 1.87; 95%CI: 1.61 to 2.17), IFG and diabetes (OR 1.30; 95%CI: 1.05 to 1.62), and BP ≥ 140/90 mmHg, or ≥ 130/80 mmHg if diabetes (OR 1.23; 95%CI: 1.04 to 1.45)
Plantinga *et al*[40]	*Clin J Am Soc Nephrol*/2010	Retrospective analysis of 1999-2006 national health and nutrition examination survey	To measure and compare the prevalence of CKD among people with diagnosed diabetes, undiagnosed diabetes, PD, or no diabetes	39.6% of people with diagnosed and 41.7% with undiagnosed diabetes had CKD; 17.7% with PD and 10.6% without diabetes had CKD. Among those with CKD, 39.1% had undiagnosed or PD
Okamoto *et al*[33]	*Transplantation*/2010	Retrospective study	To assess the indications for live kidney donation in glucose intolerance and to analyze perioperative complications associated with donor nephrectomies and its long-term consequences	Perioperative complications, survival rates and mortality were not significant between glucose intolerance and those with normal glucose tolerance
Selvin *et al*[39]	*Diabetes*/2011	Prospective cohort and cross-sectional analyses of ARIC study	To examine association between 2010 American Diabetes Association diagnostic cut points for glycated hemoglobin and microvascular outcomes (CKD, ESRD and retinopathy)	Risk of CKD, with adjusted HRs of 1.12 (0.94-1.34) and 1.39 (1.04-1.85) was found for glycated hemoglobin 5.7%-6.4% and ≥ 6.5%, respectively, as compared with < 5.7% (P = 0.002). HR for ESRD were 1.51 (0.82-2.76) and 1.98 (0.83-4.73)
Schöttker *et al*[42]	*Prev Med*/2013	Prospective study	(1) To determine the risk for incident reduced kidney function in participants with pre-diabetes; and (2) To determine dose-response relationships of fasting glucose and HbA1c with reduced kidney functions in subjects with manifest diabetes mellitus	Reduced kidney function risk factor prevalences and incidences were higher in participants with pre-diabetes than without PD. Increased risk did not persist after adjusting for established cardiovascular risk factors [RR (IFG): 0.97 (95%CI: 0.75-1.25) and RR (HbA1c-defined pre-diabetes): 1.03 (95%CI: 0.86-1.23)]
Chandran *et al*[14]	*Transplantation*/2014	Retrospective study	To compare development of diabetes, the estimated glomerular filtration rate, and the level of albumin excretion in donors with IFG to matched controls with normal pre-donation fasting glucose	(1) Higher proportion of IFG donors had developed DM (15.56% *vs* 2.2%, P = 0.06); (2) eGFR at 10.4 years was 70.7 ± 16.1 *vs* 67.3 ± 16.6 mL/min/1.73 m^2, P = 0.21) was similar between 2 groups; and (3) Urine albumin/creatinine 9.76 ± 23.6 *vs* 5.91 ± 11 mg/g, P = 0.29) was similar between 2 groups
Echouffo-Tcheugui *et al*[45]	*Diabet Med*/2016	Metanalysis	To assess the effect of PD on the incidence of CKD	Relative risk of CKD after adjustment for established risk factors was 1.11 (95%CI: 1.02-1.21) when IFG was defined as 6.1-6.9 mmol/L
Bigotte Vieira *et al*[43]	*J Clin Endocrinol Metab*/2019	Post hoc analysis of participants of the SPRINT trial	To find association of PD with adverse kidney outcomes	Impaired fasting glucose was not associated with higher rates of the composite outcome (HR: 0.97; 95%CI: 0.8 to 1.16), worsening kidney function (HR: 1.02; 95%CI: 0.75 to 1.37), or albuminuria (HR: 0.98; 95%CI: 0.78 to 1.23)
Furukawa *et al*[44]	*Diabet Med*/2021	Retrospective analysis of health check-up in 2014 in Japan	To investigate the associations of PD with the proteinuria and eGFR decline	PD was independently associated with the proteinuria development (OR 1.233; 95%CI: 1.170-1.301). No association was found with eGFR decline (OR 0.981; 95%CI: 0.947-1.017)
Hebert *et al*[34]	*Transplantation*/2022	Retrospective data analysis of The RELIVE study	To study mortality, proteinuria, and ESKD according to donation FPG: < 100 mg/dL, 100-125 mg/dL, and ≥ 126 mg/dL	IFG was associated with a higher diabetes risk (adjusted HR, 1.65; 95%CI: 1.18-2.30) and hypertension (adjusted HR 1.35; 95%CI: 1.10-1.65; P = 0.003 for both), but not higher risk of proteinuria or ESKD

PD: Prediabetes; CKD: Chronic kidney disease; IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; UAE: Urinary albumin excretion; GFR: Glomerular filtration rate; eGFR: Estimated glomerular filtration rate; HR: Hazard ratios; ESRD: End stage renal disease; ARIC: Atherosclerosis risk in communities; OR: Odds ratio; ESKD: End-stage kidney disease; FPG: Fasting plasma glucose; RELIVE: Renal and lung living donors evaluation; BP: Blood press; HbA1c: Glycated hemoglobin; SPRINT: Systolic blood pressure intervention trial; DM: Diabetes mellitus.

involving small nerve fibers, were present in 13.3% of patients with diabetes, 8.7% of patients with IGT, 4.2% of patients with IFG and 1.2% of patients with normoglycemia[88]. The Prospective Metabolism and Islet Cell Evaluation study followed patients for peripheral neuropathy and at 3 years follow up. Authors found that prevalence was highest among individuals who progressed to diabetes (50%) and followed by those who developed PD (49%), compared to individuals with normoglycemia who have an incidence of 29%[89]. A meta-analysis found that there was a wide range of prevalence estimates from 2%-77%, but most studies included in this analysis reported a prevalence ≥ 10%[90]. Unfortunately, there is lack of data on peripheral neuropathy in prediabetic kidney donors.

Retinopathy

The prevalence of retinopathy has been different in various studies. In an epidemiological study done in Pima Indians, retinopathy was reported in 12% of patients with IGT[91]. Diabetes Prevention Program study who had elevated blood glucose, but no history of diabetes, showed that retinopathy was present in 7.9% in patients with PD[92]. Post hoc analysis of a systematic review[93] showed lower median retinopathy in patients with a normal glucose tolerance of 3.2% (interquartile range 0.3%-7.3%) compared to 6.6% (interquartile range 1.9%-9.8%) in prediabetics. Reduced retinal arteriolar dilatation has been in implicated as manifestation of retinopathy in PD[94]. The Maastricht Study using spectral domain optical coherence tomography found that macular thickness is reduced in PD even before the onset of diabetic retinopathy. Hypertension, abdominal obesity and hyperglycemia were found to be predictors of incident retinopathy across all glucose levels from normoglycemia to PD and diabetes[95]. Though the association of retinopathy in the general population is strong, this is again not thoroughly investigated in kidney donors with PD.

Dementia

Dementia has been a recognized complication of PD. Insulin and insulin-like growth factors have an important role in the vital functions of neurons including survival and neuron growth, gene expression, protein synthesis, myelin production and maintenance in oligodendrocytes, synapse formation and plasticity[96,97]. PD, like diabetes, is a state of hyperinsulinism with insulin resistance which affects the function of brain cells (neurons and glial cells) leading to neurodegeneration and dementia[98-100]. A study from Sweden has shown significant brain volume loss affecting predominantly white matter leading to progressive cognitive impairment over a period of 9 years in both PD and DM [101]. Similarly, another study in elderly women showed risk of the development of cognitive impairment among participants with IFG (OR 1.64) and DM (OR 1.79)[102]. Prediabetics in the Maastricht study participants were found to have more cerebral lacunar infarcts, white matter lesions and loss of brain volume when compared with normoglycemic participants[103]. Hyperglycemia is a continuum from normoglycemia to PD. Diabetes and increasing hyperglycemia across this spectrum in prediabetic and diabetics affected executive functions in the NHANES 2011-2014 cohort[104]. In another population-based study, PD and DM were associated with minor deficits in global cognitive function, processing speed and executive functioning and an inverse correlation between glucose level with cognitive abilities in non-diabetics was found[105].

Depression

PD has been linked to risk of depression in various studies[106,107], likely through insulin resistance. Insulin resistance in the brain induces mitochondrial and dopaminergic dysfunction leading to anxiety and depressive-like behaviors[108]. Two meta-analyses done on the association of PD with depression reported mixed findings; one metanalysis reported that the prevalence of depression is moderately increased in prediabetic and in undiagnosed diabetic patients[109] and the other found that prediabetics are not at a higher risk of depression[110]. Some studies have also shown that the combination of PD with depression increases the risk of progression to the development of diabetes[111-113]. Since anxiety, depression and regret have been reported in some kidney donors[114-116], therefore, it is important to understand the potential future neurological sequelae of PD.

Cancers

PD has been reported to be associated with cancers in several studies[117-119]. A community-based study from China reported that glucose intolerance (PD & DM) was associated with stomach, colorectal, and kidney cancer in individuals aged < 65 year[120]. PD is associated with obesity and overweight, which are the recognized risk factors for cancer[121]. Hyperglycemia has been linked to the increased production of reactive oxygen species, reduced levels of antioxidant capacity, and increased levels of DNA damage which may be a potential mechanism of carcinogenesis in these patients [122]. A meta-analysis of 16 prospective studies found that PD was associated with an increased risk of cancer overall (RR 1.15; 95%CI: 1.06-1.23). The analysis also found that cancer of the stomach/colorectum, liver, pancreas, breast and endometrium were significantly associated with PD ($P < 0.05$). However, no association was found with cancer of the bronchus/Lung, prostate, ovary, kidney or bladder[121].

Kidney donors have a similar incidence of liver cancer, melanoma, breast cancer, and non-Hodgkin lymphoma 7 years post donation as compared to the general population. However, there is an increased incidence of colorectal cancer (adjusted incidence rate ratio 2.07, 95%CI: 154-2.79) and kidney cancer (2.97, 1.58-5.58) in kidney donors[123]. Given the evidence, kidney donors with PD, especially those who are overweight and are actively smoking, may be more prone to develop tumors post donation.

Nonalcoholic fatty liver disease

The prevalence of nonalcoholic fatty liver disease (NAFLD) is 48.25% in patients with PD[124]. In a study from United States, 44%-62% of the adults with PD had NAFLD[125] Prevalence in the general population is 26%, which is much

lower than PD[126]. Obesity associated insulin resistance increases free fatty acid levels which leads to more storage of fat in the liver. This leads to more hepatic insulin resistance and activation of inflammatory pathways and oxidative stress, which promote fibrosis in liver[127]. Subclinical chronic hepatic inflammation and insulin resistance has been shown to cause NAFLD in PD[128]. NAFLD has been linked with reduced GFR[129]. Living kidney donors do not have underlying kidney disease but have reduced GFR as a result of nephrectomy. However, a study reported that reduced kidney function after kidney donation is not associated with increased incidence or progression of NAFLD[130], but that data on prediabetic kidney donors is lacking. Looking at data from the general population, it will be interesting to evaluate the association between NAFLD and PD in kidney donors.

All-cause mortality

PD has been linked to increased all-cause mortality[131]. A study from Japan showed that PD was significantly associated with increased risk of death from all causes and cancer but not cardiovascular diseases[132]. PD along with hypertension not only caused increased all-cause mortality but also increased cardiovascular mortality[8]. Another recent metanalysis of 16 studies found that PD was associated with an increased risk of all-cause mortality[46]. Inactivity and obesity are common among PDs. Physical activity is of utmost important in prediabetics. A recent study showed that conversion of euglycemia along with physically activity was associated with a lower risk of death compared with persistent PD and physical inactivity[133]. Keeping these facts in mind, it is important to fully educate prediabetic kidney donors about physical activity prior to donation. Figure 1 showed potential complications which can happen in a kidney donor.

Other complications

Various other complications such as sleep disturbances[134], snoring[135], obstructive sleep apnea[136], increase fracture risk[137] and high mean platelet volume and platelet distribution width[138] have been reported in PD.

WHAT RISK FACTORS MAKE PD RISKIER?

Various risk factors, when present in prediabetics, make them prone to develop diabetes. KT should be cognizant of these risk factors before allowing a prediabetic kidney donor to donate. These risk factors are as follows:

Age

The elderly have a higher prevalence of diabetes and PD than young and middle-aged people[139,140]. Age is an important risk factor for the development of diabetes because of inflammation, mitochondrial dysfunction and abnormal lipid metabolism[141]. However, there are studies which showed that the majority of the PD either remained stable or reverted to normoglycemia[142,143]. Since PD is a continuous and cumulative risk, most transplant programs may discourage young prediabetics to donate.

Obesity

Obesity is a potentially modifiable risk factor for diabetes[144]. Obesity is characterized by insulin resistance which is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output[145]. Individual adipose cell type composition, adipose mitochondrial gene expression and body fat percentage have been shown to predict insulin resistance in both prediabetics and obese individuals[146]. Excess visceral fat and insulin resistance, rather than general adiposity, were found to be associated with the development of PD and diabetes[147].

Kidney donors with BMI ≥ 25 kg/m^2 at the time of donation are prone to develop significant weight gain over 1-year post-donation[148]. Praga *et al*[148] found that kidney donors with higher BMI had a greater risk for the development of proteinuria and renal dysfunction[149]. Similarly, another study also found a significant relationship between increasing BMI and the rate of kidney insufficiency after kidney donation[150]. Therefore, prediabetics with obesity should be evaluated carefully due to the risks of the development of diabetes, proteinuria and renal dysfunction.

Smoking

Smoking has been shown to decrease insulin action and increased insulin resistance in experimental settings[150]. Coronary artery risk development in young adults (CARDIA-study) studied the effect of active and passive smoking on glucose intolerance. At a 15-year follow-up, glucose intolerance was highest among smokers (21.8%), followed by passive smokers who never smoked (17.2%) and ex-smokers (14.4%), compared to 11.5% in individuals who never smoked[151]. Another study found that 5-10 pack-years of smoking increased odds of PD by 2-fold, which is reversible with smoking cessation[152]. Smokers are 30% to 40% more likely to develop diabetes compared to non-smokers[153]. Various studies have shown strong associations between cigarette smoking and the development of DM[154-157]. Smoking is common in kidney donors, though pre-donation education usually reduces incidence of smoking[158]. Active or passive smoking in kidney donors may lead to higher serum creatinine compared to non-smokers[158,159]. Therefore, prediabetic kidney donors with a history of smoking should be advised to stop and be evaluated thoroughly for future risk of DM.

Ethnicity/race

Certain ethnicities are more prone to developing diabetes and its complications. The United States is populated by multiple ethnic groups. The rate of diagnosis of diabetes is 14.5% in American Indian/Alaskan Natives, 12.1% in non-

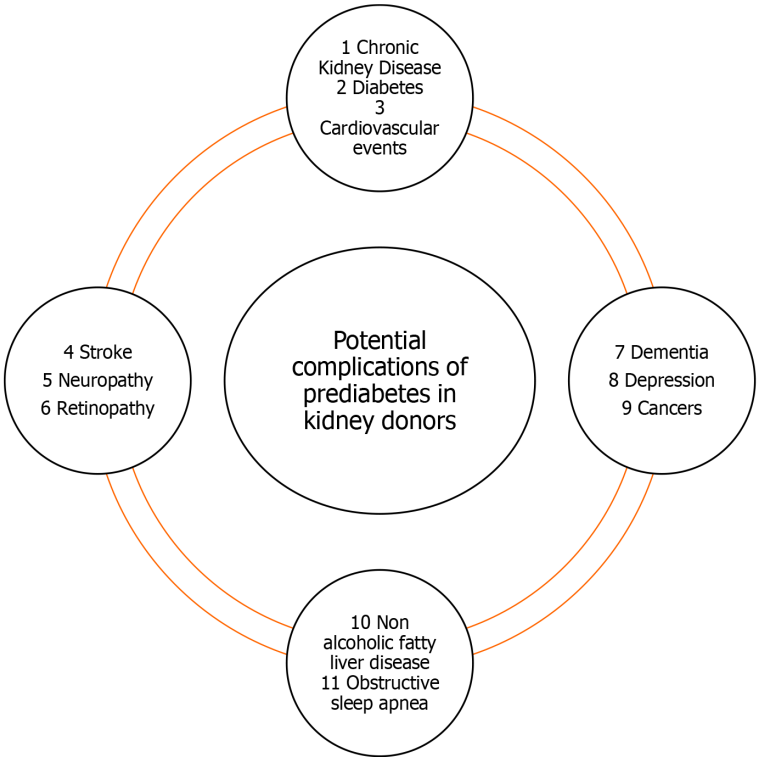

Figure 1 Showing potential complications of prediabetes in kidney donors.

Hispanic blacks, 11.8% in Hispanics, 9.5% in Asian Americans and 7.4% in non-Hispanic whites. Among Asian Americans, 12.6% of Asian Indians have diabetes, followed by Filipinos (10.6%) and Chinese (5.6%). Among Hispanic adults, 14.4% have diabetes followed by 14.4% Puerto Ricans[160]. Similarly, in the United Kingdom, the prevalence of type 2 diabetes is indeed higher among Asian, Black and minority ethnic groups[161]. Health Survey for England found reported prevalence of type 2 diabetes in Black Caribbean (9.5% men, 7.6% women), Indian (9.2% men, 5.9% women), Pakistani (7.3% men, 8.4% women), and Bangladeshi (8.0% men, 4.5% women) people[161]. The percentage of change in the number of people with diabetes between years 2000 to 2030 has been 97% for Sub-Saharan Africa, 67% for Middle East, and 42% for Asia and Islands[162]. The propensity for development of diabetes among various ethnic groups should be kept in mind before allowing a pre-diabetic kidney donor to donate his kidney.

Gestational diabetes

Gestational diabetes has been an important recognized risk factor for future development of diabetes. Insulin resistance along with pancreatic β-cell dysfunction has been proposed as a mechanism for gestational diabetes[163]. The risk of the development of diabetes is 7-10 times higher in women with gestational diabetes[164,165]. After the diagnosis of gestational diabetes, rapid conversion to overt diabetes is seen within 5 years, with a slower progression subsequently [166]. Furthermore, women with gestational diabetes are at higher risk of developing metabolic syndrome[167,168] and are at increased risk of cardiovascular events[167]. It should also be kept in mind that subsequent pregnancy post-donation makes female donors more prone to a higher risk of preeclampsia, gestational hypertension and preterm birth [169]. Therefore, female kidney donors with PD and a history of gestational diabetes should be thoroughly assessed for risk *vs* benefits.

Metabolic syndrome

The combination of glucose intolerance, hypertension, dyslipidemia and obesity is known as metabolic syndrome[170]. In the Beaver Dam study, the OR for the incidence of diabetes was 9.37 if three abnormalities of metabolic syndrome were present. The OR went up to 33.67 if four or more abnormalities were present[171]. In the Framingham Heart Study Offspring Study, the RR for type 2 diabetes increased with the number of metabolic syndrome components[171]. The West of Scotland Coronary Prevention Study used National Cholesterol Education Program definition for metabolic syndrome with or without the inclusion of C-reactive protein. The study found a RR for diabetes at 7.26 with three abnormalities of metabolic syndrome. The RR went up to 24.4 for four more abnormalities of metabolic syndrome[172]. The British Regional Heart study found the RR for diabetes to be at 4.56 for three abnormalities. The RR for the development of diabetes went up to 10.88 for four more abnormalities[173].

IFG is one of the components of metabolic syndrome. Various studies have shown that IFG is one of the strongest predictors of the development of diabetes compared to the other elements of metabolic syndrome. In a study from Finland[174], the HR for the development for IFG was 5.16, which was the highest when compared with obesity (HR 1.75), triglyceride (HR 1.34), High density liptein-cholesterol (HR 1.60) and blood pressure (HR 1.87). The Framingham Offspring Study showed that individuals with metabolic syndrome which included IFG showed a high RR of 11, which

was much higher than the RR of 5 in individuals for whom IFG was excluded in analysis[175].

The development of metabolic syndrome has been studied in kidney donors. An analysis of 2018 Living kidney donors, when matched with control non-donors, found that the living kidney donors showed a lower absolute prevalence for all metabolic risk factors, except for those who were either overweight or obese[176]. However, in another study, more donors developed new onset metabolic syndrome compared to the control group[177]. Martín-Alemañy *et al*[178] reported that living kidney donors had a high frequency of cardiometabolic risk factors and metabolic syndrome at the time of donation, which significantly increased over time[178]. In fact, metabolic syndrome was found to be a major barrier to kidney donation in one of the studies[179]. Therefore, one should carefully evaluate potential donors with PD and metabolic syndrome as they may be at risk of developing DM and cardiovascular complications.

Family history

Family history is one of the recognized risk factors for the development of type 2 diabetes. Familial predisposition is usually due to a combination of environmental and behavioral risk factors with genetic propensity due to various genes [180,181]. The prevalence of diabetes among individuals who have a first-degree relative with diabetes was 14.3% and it was significantly higher than individuals without a family history (3.2%)[180]. The authors classified family history risk categories of diabetes as high (at least two generations have first degree relative with diabetes), moderate (one generation of first-degree relatives with diabetes) and average (no first-degree relatives with diabetes). The prevalence rates of diabetes were 32.7% in a high-risk family, 20.1% in a moderate risk family and 8.4% in an average risk family[182]. Therefore, family history risk categories of diabetes have a significant and graded association with the prevalence of diabetes. In the EPIC-InterAct study, the authors investigated the association between a family history of diabetes among different family members and the incidence of type 2 diabetes and also studied the extent of genetic, anthropometric and lifestyle risk factors in familial predisposition. The study found that lifestyle, anthropometric and genetic risk factors contributed only minimally, with most of the risk being attributed to positive family history[183]. The Health Examinees-Gem study was done in Korea and aimed to find associations between a family history of diabetes with adherence to regular exercise, healthy diet and body composition, and clusters of healthy behaviors. The participants of the study were found to be strictly adherent to exercise and healthy diet but were found to not have a normal body composition[184]. Therefore, prediabetic kidney donors should always be evaluated with respect to their detailed family history of DM or PD. Figure 2 shows potential risk factors of the development of diabetes in a prediabetic kidney donor.

WHAT GUIDELINES RECOMMEND KIDNEY DONATION IN PD?

The Amsterdam Forum on the Care of the Living Kidney Donor (2006)[185] recommends to exclude individuals with a history of diabetes or fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L) on at least two occasions[or 2-h glucose with oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L)], but do not have any recommendations for PD[185].

Caring for Australian and New Zealanders with Kidney Impairment (CARI) guidelines[186] recommend checking fasting blood sugar twice in all kidney donors. Those with sugar ≥ 7 mmol/L on both occasions are considered diabetic and this is considered to be an absolute contraindication. The guidelines used the criteria of IFG as 6.1-6.9 mmol/L. Any donor with at least one occasion of IFG should have a 2 h oral glucose tolerance test. Those with normal fasting sugars were allowed to donate. Patients at high risk for the development of type 2 DM were advised to have an oral glucose tolerance test. The characteristics of high risk for developing type 2 diabetes mentioned in CARI guidelines included family history, age > 45 years, being an Aboriginal or Torres Strait Islander and obesity. If the 2-h glucose of an oral glucose tolerance test result is ≥ 11.1 mmol/L then the patient is considered diabetic and this is an absolute contra-indication to a living kidney donation. Donors with IGT and a blood sugar between 7.8-11.0 mmol/L are considered not fit to donate. Donors with glucose tolerance < 7.8 mmol/L are normal and considered to not be a contraindication to donation. Furthermore, a past history of gestational diabetes was considered as contraindication to donation.

The American Society of Transplantation (AST)[187] states that the risk of DM in donors with PD is higher than that for a healthy donor. PD also increases the future risk of diabetic kidney disease. United Network of Organ Sharing excludes donors with diabetes from donation whilst AST recommend potential donors with PD to do lifestyle modifications. The AST recommends changes in diet, to do more exercise and to lose weight to achieve euglycemia and reduce the risk for future DM[187].

The British Transplantation Society (BTS) and United Kingdom Renal Association published their guidelines in 2018 [188]. All potential living kidney donors must have a fasting plasma glucose done. A fasting plasma glucose concentration between 6.1-6.9 mmol/L is suggestive of IFG and an oral glucose tolerance test should be undertaken in these donors. These guidelines also recommend an oral glucose tolerance test in prospective donors with an increased risk of type 2 diabetes such as a family history of diabetes, history of gestational diabetes, ethnicity or obesity. If an oral glucose tolerance test shows persistent IFG or IGT, then careful assessment should be clinically done using the diabetes risk calculator[189]. Unlike other guidelines, these guidelines do not exclude the diabetic completely. Diabetics can be taken as donors provided there is no target organ damage and cardiovascular risk factors such as obesity, hypertension or hyperlipidemia are optimally managed. Furthermore, thorough assessment should be done to ascertain the lifetime risk of cardiovascular and progressive CKD in the presence of a single kidney.

The Kidney Disease: Improving Global Outcomes (KDIGO) published its guidelines for the care of live kidney donors in 2019. The guidelines suggest to take a history of DM, gestational diabetes, and family history of diabetes. Blood sugar status should be assessed by checking fasting blood glucose and/or HbA1c before donation. The guidelines also recommend doing a two-hour glucose tolerance testing or HbA1c testing for donor candidates with elevated fasting

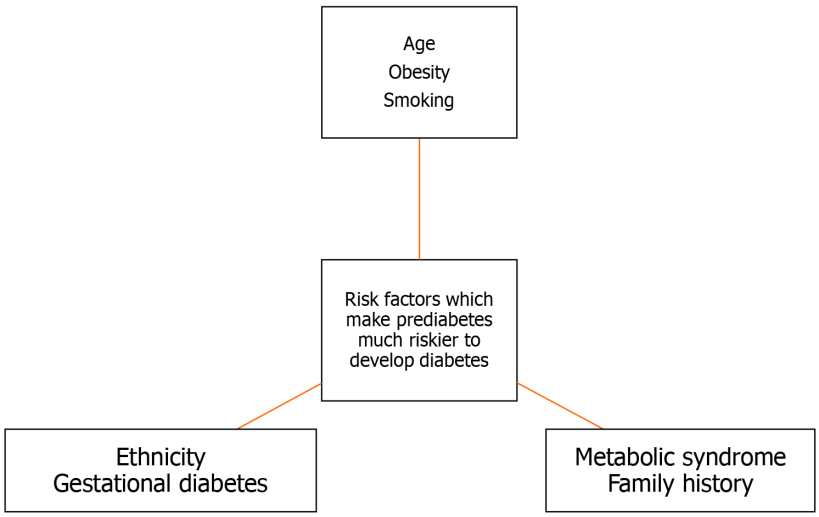

Figure 2 Showing risk factors for development of diabetes.

blood glucose, history of gestational diabetes, or family history of diabetes in a first-degree relative. Decisions regarding donors with PD or DM should be taken on an individual basis, keeping in view their future risk. Furthermore, KDIGO guidelines recommend that donors with PD and DM should be explained that their condition may progress and could result in end organ damage[190].

European Best Practice Guidelines, published in 2015, recommended that DM is a contra-indication to donation, other than in exceptional circumstances (1D), and that IGT is not an absolute contra-indication to donation (2C)[191].

Looking at these guidelines, there is variability in recommendation for donations in prediabetics and there is a need to build a uniform consensus among the transplant community across the globe.

USE OF DIABETES RISK SCORE AND RISK CALCULATORS IN KIDNEY DONORS

Various diabetes risk scores and risk calculators have been reported in the literature. The AST guidelines have mentioned the diabetes risk calculator provides accurate and individualized risk for future development of diabetes[187-192]. The Renal Association and BTS also recommend a diabetic risk calculator[188,189]. The University of Minnesota developed an apparatus that predicted risk of hypertension, type 2 diabetes, and reduced e GFR using data of living kidney donor program from 1963 through 2017 with a median follow up of 22.8 years. It requires donor age, sex, race, smoking status, estimated GFR, serum creatinine, (capillary or serum) glucose, BMI, systolic blood pressure, diastolic blood pressure, family history of hypertension and dyslipidemia. It also took into consideration the relationship to the recipient and whether the recipient has type 1 or type 2 DM. Unfortunately, prediction for hypertension and diabetes may not be valid for non-white donors[193].

There are various risks score models and risk calculators available. Prominent risk assessment tools include the Australian 5-year type 2 Diabetes Risk Assessment (AUSDRISK)[194], the Diabetes United Kingdom 10-year Know your Risk[195], The Finnish Diabetes Risk Score (FINDRISC)[196], and the ADA type 2 Diabetes Risk Test[197]. Age, sex, family history of diabetes, BMI and history of hypertension are included in all the country-specific calculators. The ADA calculator does not include ethnicity but takes gestational diabetes into consideration. The AUSDRISK and United Kingdom calculator, on the other hand, take ethnicity but not gestational diabetes into consideration. The AUSDRISK also includes smoking, fruit and vegetable intake and personal history of elevated glucose level. Waist circumference is included in both the AUSDRISK and United Kingdom calculators. Physical activity is included in the AUSDRISK and ADA calculators. The FINDRISC diabetes calculator includes gender, weight, height, age, waist circumference, and physical activity for more than 30 min, vegetable and fruits intake, use of blood pressure medications, high glucose level in past, and family history of diabetes in two generations. A systematic review done in 2011 identified 43 risk models for the prediction of the risk of DM[198]. This systematic review found poor methods including pre-screening univariate variables, the categorization of continuous risk predictors and the poor handling of missing data which could jeopardize model development. The other problem found was universal validation. Most risk scores show overall good results in predicting DM in populations for whom they were developed. However, the performance of these risk scores is more heterogeneous and generally weaker in external populations[199]. Unfortunately, most of these risk detection models have not been validated in kidney donors. It may be reasonable to use a well validated local risk calculator or risk score for all prediabetic kidney donors in that particular area to provide more accurate and individualized risk for the future development of diabetes.

WHAT SHOULD BE THE WAY FORWARD?

There were about 88751 patients on the waiting list for a kidney until September 2023, as per Organ Procurement & Transplant Network data. Only 20445 of the patients were transplanted until September 2023[200]. About 15824 kidneys were obtained from deceased donors and another 4621 were from living donors. This reflects that approximately only a quarter of the patients on the waiting list could get a kidney. Because of a global organ shortage and unmet needs for kidneys, many centers accept increasingly complex live donors including prediabetics. The lack of evidence for long-term outcomes for pre-diabetic kidney donors for the future risk of development of diabetes, development of CKD and other complications of PD have contributed to the conundrum of using complex donors. As discussed, a couple of studies with short term duration (ranging from 88 months to 10.4 years) in kidney donors having PD did not find an increased risk of CKD[14,33,34]. After progression of PD to DM, approximately another 19 years are needed for progression of microalbuminuria to macroalbuminuria and then to development of ESRD[37]. Keeping these facts in mind, to know the real sequelae of PD in a kidney donor, we need long term studies of at least 19 years to effectively follow up.

Post donation, the prediabetic kidney donors are left with only one kidney. Most of the evidence regarding PD and its complications are derived from studies done in the general population[20,39,41]. Development of diabetes and CKD are not the only worries. Other complications of PD including cardiovascular disease[7,72,73], stroke[76,81-84], neuropathies [85-88,90,122], retinopathy[91-95], dementia[96-101,103-105], depression[106-116], cancers[117-119], non-alcoholic fatty liver disease[124-128] and increased all-cause mortality[46,131,132] are well established in the general population. Therefore, it is the responsibility of the transplant team that there should be no maleficence and every effort should be taken to follow the ethical principle "first do no harm"[201]. Every effort should be made to avoid any subtle form of coercion from the family in case of live related kidney donation. A well-informed consent form showing detailed risk *vs* benefits and alternative options other than a transplant should be available for both the donor and recipient to protect both of them equally. Unfortunately, the guidelines from various societies and organizations are variable, leading to further confusion[185-187,190,191]. We feel that, while evaluating a potential prediabetic kidney donor, one has to look at overall risk of development of diabetes. Donors with IFG should undergo a glucose tolerance test and, if IGT is detected, then great care should be taken to further evaluate these donors. The combination of IFG and IGT poses a great risk of developing renal dysfunction[20] and peripheral neuropathy[88]. Similarly, two hours IGT has been a strong predictor of stroke and cardiovascular events[76,83]. Therefore, prediabetic kidney donors with IFG and IGT should be considered as high risk and may not be suitable candidates. Those with isolated IFG with normal glucose tolerance should be further evaluated. If they have no risk factors (age, ethnicity, smoking, obesity, gestational diabetes and metabolic syndrome) they may represent a low-risk case. IFG along with a single or combination of risk factors such as age, family history, ethnicity, smoking, obesity, gestational diabetes and metabolic syndrome may contribute to the status of a high-risk donor. A well designed and validated local risk score or calculator may be used in these cases. Those with high risk should be excluded and those with low risk may be accepted provided they are willing to undergo long term lifestyle modification and accept the risk.

RECOMMENDATION

We suggest the following recommendations:

There is a need for greater consensus amongst regional societies to call for unified position statements regarding kidney donation in donors with PD, through international transplant societies like The Transplantation Society or International Society of Nephrology.

Kidney donor with PD and abnormal IFG along with IGT are considered high risk even in the absence of other risk factors. If appropriate lifestyle modification fails a reversion to euglycemia, they then should not donate.

Kidney donors with isolated IFG with normal IGT should be evaluated for other risk factors such as age, family history, ethnicity, smoking, obesity, gestational diabetes and metabolic syndrome. The presence of any risk factors in kidney donors, along with IFG, make them high risk. Appropriate lifestyle modifications are recommended to achieve euglycemia and possible donation in the future.

A locally well designed and validated risk score or risk calculator may be helpful in identifying high risk donors and should be used to identify high risk donors.

All kidney donors with PD should be advised about modifiable risk factors such as smoking, weight loss and correction of any component of a metabolic syndrome, if present.

Comprehensive risk explanations should be done. The donor should be aware of possible development of diabetes and various complications of PD, including CKD and cardiovascular events. Both the donors and recipient should know about alternative therapies such as hemodialysis and peritoneal dialysis. Donors with a poor track record or history and who are unable to lose weight or quit smoking should be excluded through collaboration with donor advocacy or social workers.

In case if donation is made, there is a need for an enhanced medical follow up of a kidney donor who has history of PD. They should have greater access to clinics, health club memberships, a dietician and medications. Lifestyle modification should be re-enforced through continuous education.

There is a need for long-term well designed prospective studies in kidney donors with PD to know the long-term risk of diabetes and the various complications associated with PD.

It will be interesting to assess the efficacy of sodium-glucose cotransporter-2, glucagon like peptide 1, mineralocorticoid receptor antagonist and renin angiotensin inhibitors in kidney donors with PD and the effect of this on long term

renal and cardiovascular outcomes.

Most of the knowledge regarding PD and the risk of DM and other complications is derived from studies done in the general population. Unfortunately, there is limited work done in kidney donors with PD. Most of these studies are retrospective in nature, with a small sample size and a shorter follow up. As a result, this is one of the limitations of our review.

CONCLUSION

The global prevalence of PD is high. PD increases the risk of DM, CKD, cardiovascular events, stroke, neuropathy, retinopathy, dementia, depression, cancer, non-alcoholic fatty liver disease and increases all-cause mortality. Increasing age, obesity, smoking, certain ethnicities, gestational diabetes, metabolic syndrome and a family history of diabetes make it riskier for prediabetics to donate. There is limited research on the impact of PD in kidney donors and there is a need for prospective long term follow up studies. The combination of IFG and IGT has greater association with CKD, cardiovascular events, stroke and peripheral neuropathy, and patients with these issues should not make donations. Those with isolated IFG should be evaluated for other risk factors of diabetes with the use of a validated risk calculator. Those with isolated IFG and no other risk factors may donate after appropriate long term lifestyle modifications. There is variability in recommendations among the transplant community regarding kidney donation in prediabetics and there is a need to build up a consensus to ensure uniform practice and better outcomes for both donors and recipients.

FOOTNOTES

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MINIREVIEWS

Autologous hematopoietic stem cell transplantation conditioning regimens and chimeric antigen receptor T cell therapy in various diseases

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Abstract

Conditioning regimens employed in autologous stem cell transplantation have been proven useful in various hematological disorders and underlying malignancies; however, despite being efficacious in various instances, negative consequences have also been recorded. Multiple conditioning regimens were extracted from various literature searches from databases like PubMed, Google scholar, EMBASE, and Cochrane. Conditioning regimens for each disease were compared by using various end points such as overall survival (OS), progression free survival (PFS), and leukemia free survival (LFS). Variables were presented on graphs and analyzed to conclude a more efficacious conditioning regimen. In multiple myeloma, the most effective regimen was high dose melphalan (MEL) given at a dose of 200/mg/m^2. The comparative results of acute myeloid leukemia were presented and the regimens that proved to be at an admirable position were busulfan (BU) + MEL regarding OS and BU + VP16 regarding LFS. In case of acute lymphoblastic leukemia (ALL), BU, fludarabine, and etoposide (BuFluVP) conferred good disease control not only with a paramount improvement in survival rate but also low risk of recurrence. However, for ALL, chimeric antigen receptor (CAR) T cell therapy was preferred in the context of better OS and LFS. With respect to Hodgkin's lymphoma, mitoxantrone (MITO)/MEL overtook carmustine, VP16, cytarabine, and MEL in view of PFS and *vice versa* regarding

OS. Non-Hodgkin's lymphoma patients were administered MITO (60 mg/m^2) and MEL (180 mg/m^2) which showed promising results. Lastly, amyloidosis was considered, and the regimen that proved to be competent was MEL 200 (200 mg/m^2). This review article demonstrates a comparison between various conditioning regimens employed in different diseases.

Key Words: Conditioning regimens; Multiple myeloma; Lymphoma; Hodgkin; Non-Hodgkin; Acute leukemia

Core Tip: This literature review study is based on real-world data collected from various published research introducing multiple conditioning regimens for different disorders. Comparisons between regimens of an individual disorder were made using variables such as overall survival, progression free survival, complete remission, and leukemia free survival to conclude a laudable conditioning regimen having trivial adverse effects. The article is designed to discuss the conditioning regimens employed in autologous stem cell transplantation for various diseases. The primary objective of conducting this review is to highlight the various conditioning regimens, and discuss both the positive and the negative consequences along with proposing a treatment that is both efficacious and harmless.

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INTRODUCTION

Over the years, many treatment regimens have been crafted for multifarious diseases, and consequently, endorsement of hematopoietic stem cell (HSC) transplantation (HSCT) was a strategic approach for hematological disorders or underlying malignancy[1]. HSCs have the potential to develop into all types of blood cells, including white blood cells, red blood cells, and platelets, specifying them as an ideal choice[2]. The rationale behind the HSCT procedure is to replace the recipient's damaged cells with infused healthy stem cells and immune cells after exposure to a short course of chemotherapy or radiotherapy[3].

According to recent research, peripheral blood is 99% of the time used as a donor in autologous stem cell transplants [3]. In contrast, blood cells used in allogeneic stem cell transplantation (Allo-SCT) are taken from potential donors or cord blood units[4]. Today, more than 50000 HSCT procedures are performed annually worldwide. In Europe, are more than one-half of autologous transplants that are performed are autologous[5].

Conditioning regimens are devised in order to eradicate tumor cells and prevent graft rejection. In the 1970s, successful bone marrow transplantation (BMT) using cyclophosphamide (Cy) and total body irradiation (TBI) was reported[6]. Carmustine, etoposide, cytarabine, and melphalan (BEAM) is the most used conditioning regimen for Hodgkin's lymphoma, and it has a lower mortality rate when compared to other regimens[7]. Conditioning regimens with low toxicity are now generally preferred for patients with primary immunodeficiency[8]. To eliminate the damaged cells in the body, HSCT conditioning requires chemotherapy and/or radiation, but this procedure can have life-threatening side effects. Therefore, HSCT is primarily used to treat malignant illnesses where its advantages outweigh its potentially deadly hazards[9]. As an alternative to the traditional conditioning regimen, a reduced-intensity and non-myeloablative conditioning regimen has been presented[10]. According to research from the Fred Hutchinson Cancer Research Center, patients undergoing nonmyeloablative conditioning (grades III–IV acute graft-*vs*-host illness) had a considerably decreased incidence of severe acute graft-*vs*-host disease[11]. According to data from the Centre for International Blood and Bone Marrow Transplant Research, multiple myeloma (MM) and lymphoma are the most prevalent symptoms[3].

This article is designed to discuss the conditioning regimens employed in autologous stem cell transplantation (Auto-SCT) for various diseases. The primary objective of conducting this review is to highlight the various conditioning regimens, and discuss both the positive and the negative consequences along with proposing a treatment that is both efficacious and harmless.

HEMATOPOIESIS FROM HEMATOPOIETIC STEM CELLS

The discovery of induced pluripotent stem cells by the reprogramming of human and mouse fibroblasts in 2006 with traits like embryonic stem cells (ESCs) proved to be a landmark in the field of medicine[12]. This discovery ultimately paved the way for modern and significant contributions to drug discovery, cell therapy, basic research, and the widespread use of autologous cell-based therapy[13]. Since the isolation of human ESCs, valuable approaches have been made generally focused on directed differentiation to generate pluripotent hematopoietic stem and progenitor cells to be

manipulated in cellular therapy and to treat malignancies[14-16].

Since the very beginning, the stem cell concept has been crafted into a hierarchical tree-like model where the stem cells are sitting on the root of a branching family tree and the multipotent stem cells originate in an orderly branching fashion from their ancestral root[17]. To summarize, HSCs are immature ESCs that harbor the potential to differentiate into their lineage of cells including red blood cells, white blood cells, and platelets as shown in Figure 1[18].

HSCT

HSCT is the most widely used cellular immunotherapy, and is an indispensable treatment for many malignant, congenital, and acquired hematological ailments[19]. HSCT is a requisite after chemotherapy or radiotherapy to consolidate a patient's recovery and provide a lasting cure[20].

Auto-SCT

In autologous hematopoietic stem cell transplantation (ASCT), the stem cells are harvested from the recipient's own bone marrow, peripheral blood, or umbilical cord units. This mode of transplantation is effective since it reduces the occurrence of immunocompromise and transplant rejection[4].

Allo-SCT

Allogeneic transplantation uses fresh HSCs, so the collection from the donor as well as the conditioning of the patient occurs at the same time and reduces the risk of cell reduction *via* thawing or freezing[21]. Patients who undergo Allo-SCT require a longer period of immunosuppression in order to avert the likelihood of transplant rejection.

DISEASES TREATED BY AUTO-SCT

Owing to the great advancements in the field of medicine, Auto-SCT has now been regarded as an established therapeutic approach for many haemato-oncological, immunological, and hereditary conditions with the potential of cure. In 2012, the number of Auto-SCTs performed reached over one million[4]. There are following diseases for which the ASCT is being performed more frequently (Figure 2).

AUTO-SCT CONDITIONING REGIMENS IN VARIOUS DISEASES

Autologous HSCT conditioning regimens in MM

MM is an incurable, malignant B-cell neoplasm characterized by uncontrolled, destructive growth of mutated plasma cells along with the dissemination of multiple tumor cells throughout the bone marrow[22]. With the progress in the field of medical oncology, various drugs of paramount significance have been developed for the treatment of MM (*e.g.*, proteasome inhibitors and immunomodulatory drugs)[23].

The process of Auto-SCT is carried out in four basic steps: The mobilization, apheresis of mobilized stem cells, utilization of conditioning regimen and, finally, reinfusion[24]. According to a retrospective study by Brioli *et al*[25] involving 187 patients with MM and a comparison of high dose melphalan (MEL) 200 mg/m^2 (MEL 200) and low dose MEL 140 mg (MEL 140) conditioning regimens, the MEL 200 was used in 112 (60%) and MEL 140 in 75 (40%) of the patients. OS was found higher among patients treated with MEL 200 as compared to those who were given MEL 140 (66% *vs* 51% at 5 years) as mentioned in Figure 3.

A study by Nishihori *et al*[26] reviewing the effectiveness of various treatment modalities in MM also showed promising benefits by utilization of Bortezomib along with high dose MEL.

During the last decade, genetically engineered chimeric antigen receptor (CAR)-T cell therapy has been developed with the identification of several target antigens like CD19, CD38, CD138, and B-cell maturation antigen (BCMA)[27]. However, CAR-T cells targeting CD19 are the most identified CAR-T cells that are being used in hematological malignancies, and BCMA-targeted CAR-T cells are being evaluated to be used against MM. These new treatment strategies have brought a ray of hope to cure MM with reduced mortality rates and improved OS[28].

ASCT conditioning regimens in acute myeloid leukemia

In recent years, the therapeutic and prognostic profile of acute myeloid leukemia (AML) has been improved due to recent advances in chemotherapeutic agents and the rising trend of ASCT to consolidate adult patients with AML[29]. AML is a rare diagnosis. Due to high neoplasm potential, it is associated with a large number of leukemia-associated deaths with a reduced OS rate. The presence of balanced translocation between chromosome 8 and 21 [t(8;21)], inversion of chromosome 16, and translocation between chromosomes 15 and 17 [t(15;17)] has also been implicated in acute promyelocytic leukemia pathogenesis along with some genetic and epigenetic alterations[30]. Although recent advances have been paving an excellent pathway for halting the disease progression and improving OS rate, AML is still posing some serious therapeutic challenges to be overcome.

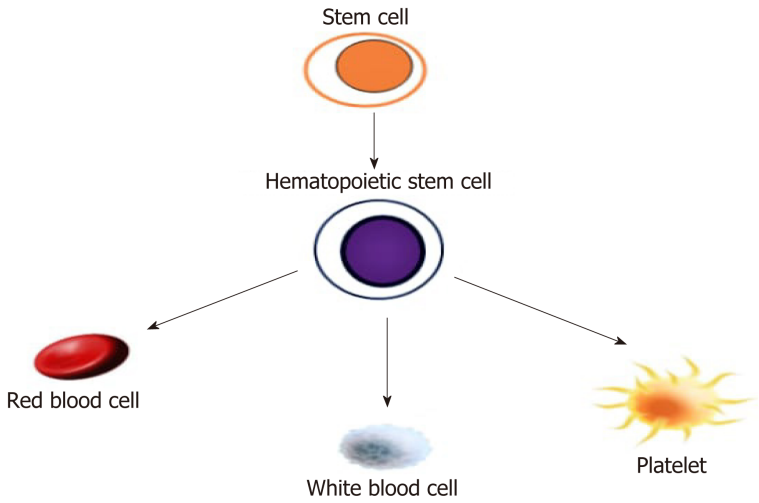

Figure 1 Differentiation of pluripotent embryonic stem cells into hematopoietic stem cells.

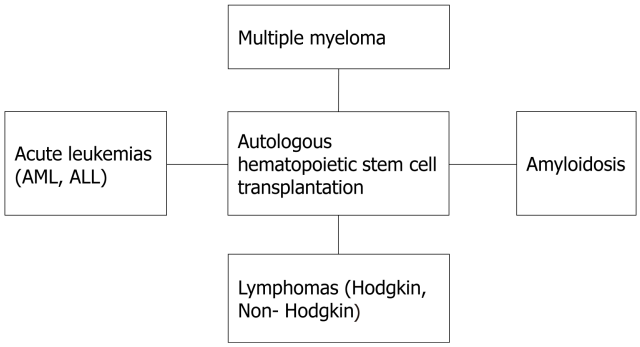

Figure 2 Pattern of various diseases treated by autologous hematopoietic stem cells transplantation. AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia.

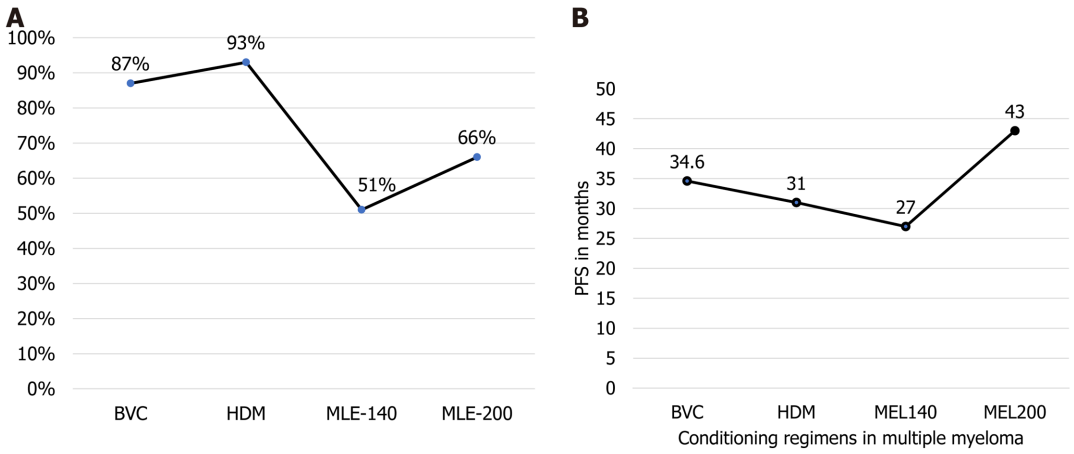

Figure 3 Comparison of various conditioning regimens in multiple myeloma. A: Comparison of overall survival between busulfan 0.8 mg/kg along with etoposide IV 400 mg/m^2 plus cyclophosphamide 50 mg/kg (BVC), melphalan (MEL) given at a dose of 100 mg/m^2/d (HDM), high dose MEL 200 mg/m^2 (MEL 200), and low dose MEL given at a dose of 140 mg (MEL 140); B: Comparison of progression free survival between BVC, HDM, MEL 200, and MEL 140.

According to a retrospective analytical study involving 952 patients with AML by Nagler *et al*[31], the median age of patients was 50.5 years with 56% of the population (n = 531) consisting of the male population. The effectiveness of intravenous (IV) busulfan (BU) in ASCT was ascertained in this study and comparison was made with oral BU utilization in patients undergoing ASCT. IV conditioning regimens based mainly on BU (12.8 mg/kg) combined with Cy (120 mg/kg) were administered in about 517 patients, the combination of IV BU (12.8 mg/kg) and MEL (140 mg/kg) was given to 234 patients, a combination of IV BU and etoposide was tried in 82 patients, and the IV BU and idarubicin were

administered in 46 patients. Outcomes in terms of 2-year OS, leukemia free survival (LFS), and relapsed incidence were assessed. However, the effectiveness of all combinations was surprisingly higher in patients aged less than 50 as compared to older patients; OS was 67% ± 2%, LFS was 53% ± 2%, and relapse incidence (RI) was 40% ± 2%. Out of all the combinations discussed herein, the combination of IV BU (12.8 mg/kg) with MEL (140 mg/kg) was associated with significantly improved OS as compared to other three combinations, validating the effectiveness of IV BU and MEL as a regimen of choice when compared with other regimens used either IV or oral BUT that was actually showing the greater toxicity profile than IV BU administration with a low incidence of veno-occlusive disease[31].

The conditioning regimen is now considered the real estate of Auto-SCT success because it not only creates the space to transplant the HSCs but also eradicates the disease itself. A study conducted by Gorin *et al*[32] using the data from a registry of the European Society for Blood and Marrow Transplantation to compare the effectiveness of two standard conditioning regimens, *i.e.*, BU + MEL and BU + Cy, in Auto-SCT for AML patients. The first regimen consisted of BU (12.8 mg/kg) and MEL (140 mg/kg) combined (BUMEL) and the second consisted of BU (12.8 mg/kg) and Cy (120 mg/kg) (BUCY). This study involved 853 patients with available cytogenetics of AML and BUMEL therapy was used in 30% of the patients (n = 257), while 70% of the patients (n = 596) were administered with BUCY therapy and the outcomes were evaluated in terms of RI, LFS, and finally OS. The findings were truly mandating the utilization of the BUMEL regimen against BUCY due to reduced RI (39.5% *vs* 52.2%; P = 0.003), better LFS (55.4% *vs* 44.6%; P = 0.005), and finally better OS rate (73.8% *vs* 63%; P = 0.0007), validating the higher effectiveness of BUMEL regimen in ASCT[32]. When the OS was compared between other conditioning regimens used *vs* BUMEL in ASCT for patients with AML, the BUMEL regimen was found to be highly effective on all grounds, making it the conditioning regimen of choice with excellent ultimate outcomes as shown in Figure 4.

The construction of a CD-70 CAR-T cell can prove to be a breakthrough in the field of oncology and medicine. CD70 is a type 2 transmembrane glycoprotein and a member of the tumor necrosis factor ligand family that is now increasingly being utilized as a therapeutic target for the treatment of AML; however, there is still very much to discover about this therapeutic approach. The antitumor activity of a CD70-specific monoclonal antibody along with hypomethylating agents for the treatment of patients with AML has been showing promising benefits[33]. Therefore, we can hope that in the future, designing of CAR-T cells will be conducive to the treatment of hematological malignancies with minimal myelotoxicity.

Autologous HSCT conditioning regimens in acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a familiar pediatric carcinoma marked by chromosomal translocations and somatic mutations[34].

Lee *et al*[35] carried out a retrospective study using myeloablative therapy. They inducted 44 patients from March 2009 to January 2014 and the efficacy was assessed by complete remission (CR). These patients underwent HSCT using a once-daily IV conditioning regimen. The regimen included BU (120 mg/m^2 for patients > 1 year of age and 80 mg/m^2 for patients < 1 year of age), fludarabine 40 mg/m^2, and etoposide 20 mg/kg. Results showed that 28 (63.6%), 12 (27.3%), and 1 (2.3%) patients achieved 1st, 2nd, and 3rd CR, respectively, while two (4.5%) patients had no remission at the time of HSCT. The complications reported in this study included elevated AST and/or ALT or total bilirubin[35].

To compare the efficacy of TBI plus etoposide and myeloablative regimen (including fludarabine, thiotepa, and IV BU/treosulfan), Peters *et al*[36] in 2021 conducted a multi-centre and randomized trial in high-risk ALL patients. Efficacy was measured in terms of treatment related mortality (TRM). They inducted 417 patients and randomly assigned them to two cohorts. Cohort 1 was given TBI and IV etoposide (60 mg/kg) while cohort 2 was administered with fludarabine (30 mg/m^2) once daily, thiotepa (5 mg/kg) twice daily, and treosulfan (14 g/m^2)/BU once daily. Following the TBI-based regimen and myeloablative regimen, the 2-year TRM was 0.02 [95% confidence interval (95%CI): 0.01 to 0.05] and 0.09 (95%CI: 0.05 to 0.14), respectively, thus showing that TBI plus etoposide regimen had good disease control.

For hematologic malignancies, CAR-T cell therapy has been unfolded as an efficacious therapeutic option. Its mechanism of action involves the patient's own T-cells that in turn express receptors modified to recognize specific epitopes of tumor-associated antigens on the target cell surface[37]. Numerous trials have been carried out to investigate the efficacy of this therapy. Subklewe *et al*[38] conducted "the pivotal global ELIANA trail" (NCT02435849) using genetically modified CD19-directed T-cell products, "Tisagenlecleucel". In another phase 1 trial (NCT01044069), Davila *et al*[39] pointed out the plausibility of CAR-T cell therapy. In this study, 16 patients were enrolled and given a 19-28z infusion of CAR-T cells after salvage chemotherapy. This blatantly boosted the overall complete response rate to 88%, which is higher than that expected with salvage chemotherapy alone.

To sum up, the introduction of CAR-T cell therapy has provided new directions to the field of oncology and medicine; however, ASCT is widely preferred because of being inexpensive. Moreover, CAR-T cell therapy needs further evolution by health professionals.

Autologous HSCT conditioning regimens in Hodgkin lymphoma

A retrospective, multi-center study by Yeral *et al*[42] involving 142 patients with HL undergoing ASCT showed the comparison of two conditioning regimens with end points represented by OS and progression free survival (PFS). The two conditioning regimens used were BEAM (carmustine 300 mg/m^2 given at day 6, etoposide 200 mg/m^2 and cytarabine 200 mg/m^2 between day 2 to day 5, MEL 140 mg/m^2 at day 1) was administered in 108 patients and 34 patients were administered with mitoxantrone (MITO) 60 mg/m^2 in three divided doses at day 5 along with MEL 180 mg/m^2 in three divided doses at day 2 constituting a group with MITO/MEL.

According to a study by Chen *et al*[43] involving 1012 patients with HL, BEAM and Cy, carmustine, and etoposide (CBV)-low or CBV-high were the most used regimens with a 3-year OS of 79% and PFS of 62% in the BEAM group, OS of 73% and PFS of 60% in the CBV-low, and OS of 68% and PFS of 57% in the CBV-high group. However, the BEAM-based

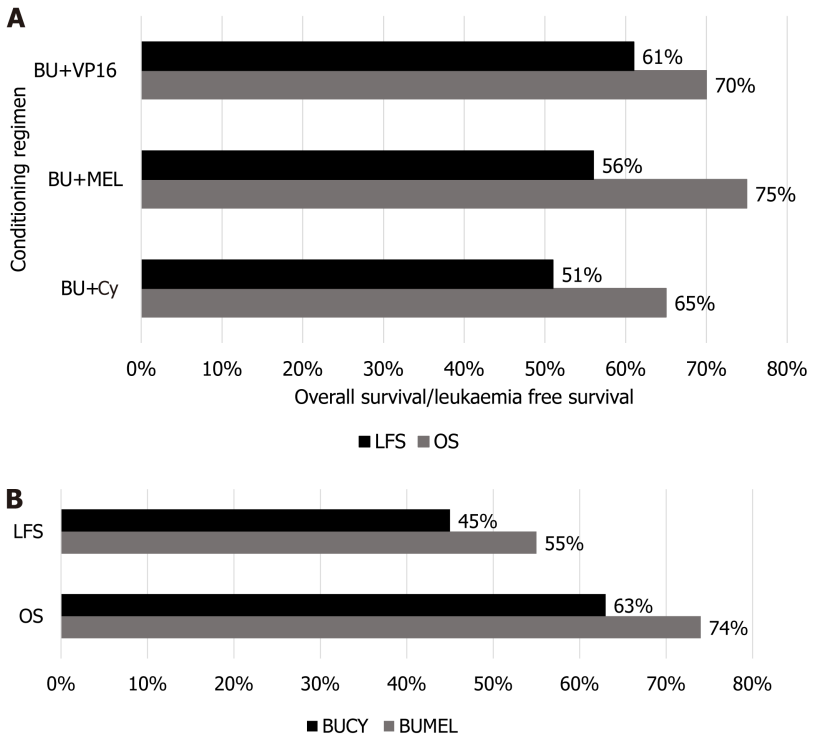

Figure 4 Comparison of various conditioning regimens in acute myeloid leukemia. A: Comparison of leukemia free survival (LFS) and over survival (OS) between intravenous busulfan (12.8 mg/kg) combined with cyclophosphamide (120 mg/kg), melphalan (140 mg/kg), and etoposide; B: Comparison of LFS and OS between busulfan (12.8 mg/kg) plus melphalan (140 mg/kg) and busulfan (12.8 mg/kg) plus cyclophosphamide (120 mg/kg). BU: Busulfan; MEL: Melphalan; Cy: Cyclophosphamide; LFS: Leukemia free survival; OS: Over survival; BUCY: Busulfan and cyclophosphamide; BUMEL: Busulfan and melphalan.

regimen was most effective in HL with better OS and PFS as compared to other regimens as shown in Figure 5.

CAR T-cell therapy of B-cell malignancies has proved to be effective. Ramos *et al*[44] showed how the same approach of CAR-T cells specific for CD30 (CD30.CAR-Ts) can be used to treat HL.

Autologous HSCT conditioning regimens in non-HL

Non-HLs (NHLs) are a diverse collection of lymphoproliferative tumors with a greater propensity to expand to extranodal sites than HLs. Both nodal and extranodal regions are involved in the majority of NHL cases[45]. The mobilization of HSCs is followed by apheresis of the mobilized stem cells, use of a conditioning regimen, and finally reinfusion[46].

Between May 19, 2015 and September 15, 2016, Locke *et al*[47] carried out a single-arm, multicenter phase 1/2 study in which 119 patients were enrolled and 108 were given axicabtagene ciloleucel. Seven patients participated in phase 1, while the remaining 107 were enrolled in phase 2 studies. After receiving IV fludarabine and Cy as conditioning chemotherapy, participants received one dose of axicabtagene ciloleucel. Only pronounced adverse events, such as neurological events, hematological events, infections, autoimmune disorders, and secondary malignancies were documented after 3 mo.

Between February 25, 2011 and April 3, 2014, Okay *et al*[48] selected 1503 previously untreated patients for a randomized, open-label, phase 3 study. The forecasts for OS at 5 years, survival without disease, and survival without events were 81.9%, 46.5%, and 41.4%, respectively. All patients displayed neutropenia and thrombocytopenia. All individuals had nausea, mucositis, and vomiting. Hahn *et al*[49] assessed consecutive lymphoma patients who received BEAM HDCT and BeEAM followed by ASCT between 2015 and 2019. BEAM had a 3-year OS of 78.1% while BeEAM had a 3-year OS of 71.0%. BEAM had a 3-year PFS of 71.3% while BeEAM had a 3-year PFS of 74.1%.

CAR T-cell therapy has emerged as a standard of care for treating a number of disorders in recent years, overcoming any potential drawbacks associated with conventional therapies. Clinical trials of anti-CD19 CAR-T cell therapy for the treatment of refractory or relapsed B-NHL have produced encouraging effective outcomes[50].

Autologous HSCT conditioning regimens in amyloidosis

Amyloidosis (AL) is a clonal plasma cell dyscrasia characterized by the accumulation of misfolded fibrillar proteins in extracellular tissues, leading to organ failure and eventually death. Though associated with high treatment-related mortality, for nearly 20 years Auto-SCT has been used and demonstrated improved survival and a prolonged treatment-free interval[51].

According to a study by Tandon *et al*[52] involving 457 diagnosed cases of light chain AL undergoing AHSCT, two conditioning regimens, one with full dose MEL (200 mg/m^2) and the other with low or reduced intensity MEL (100 mg/kg), were compared. Complete response was observed in high dose Mel group (53% *vs* 37%, $P = 0.003$), and the PFS was also validating the effectiveness of high dose Mel regimen when compared with low dose Mel group (55% *vs* 31%; $P < 0.001$) as shown in Figure 6.

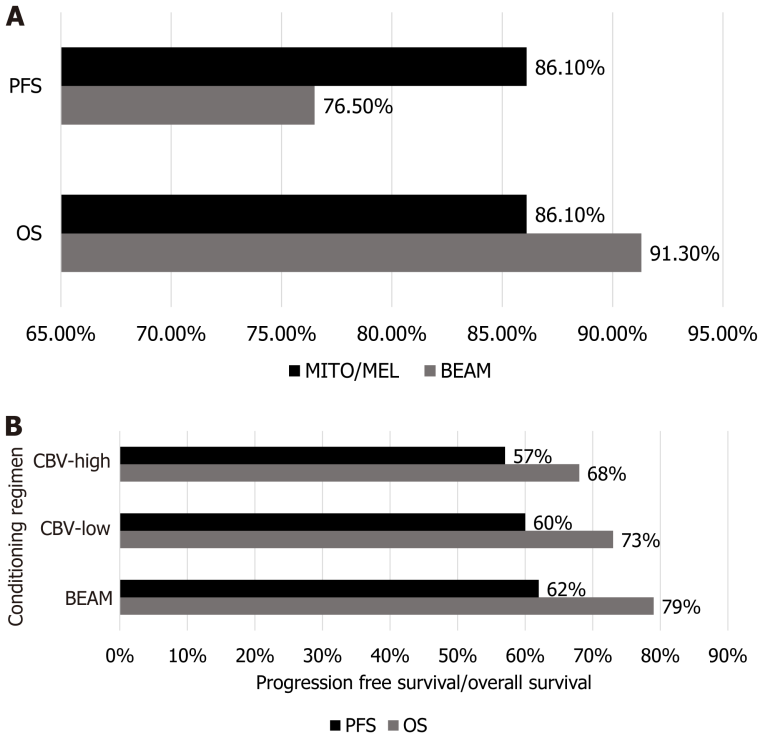

Figure 5 Comparison of various conditioning regimens in Hodgkin lymphoma. A: Comparison of progression free survival (PFS) and overall survival (OS) between carmustine, etoposide, cytarabine, and melphalan (BEAM) [carmustine 300 mg/m^2 given at day 6, etoposide 200 mg/m^2 and cytarabine 200 mg/m^2 between day 2 to day 5, melphalan (MEL) 140 mg/m^2 at day 1] and mitoxantrone (MITO) 60 mg/m^2 in three divided doses at day 5 along with MEL 180 mg/m^2 in three divided doses at day 2 constituting a group with MITO/MEL; B: Comparison of PFS and OS between BEAM (n = 313), CBV-low (cyclophosphamide, carmustine, and etoposide) (n = 279), and CBV-high (cyclophosphamide, carmustine, and etoposide) (n = 219). PFS: Progression free survival; OS: Over survival; BEAM: Carmustine, etoposide, cytarabine, and melphalan; MITO: Mitoxantrone; MEL: Melphalan.

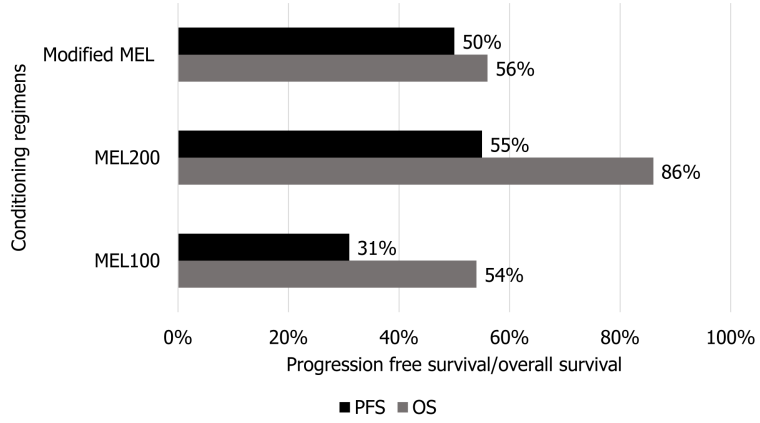

Figure 6 Comparison of progression free survival and overall survival between full dose melphalan (MEL) (200 mg/m^2), low or reduced intensity MEL (100 mg/m^2), and modified MEL (100 mg/m^2). PFS: Progression free survival; OS: Over survival; MEL: Melphalan.

Similarly, a trial labeled SWOG (S0115) conducted by Sanchorawala *et al*[53] involved 93 patients diagnosed with ligh-chain amyloidosis (AL), AL with myeloma (AM), and host-based high-risk myeloma (hM), with 59, 9, and 25 patients in each group. The patients were treated with sequential doses of modified MEL (100 mg/m^2). The estimated 2- and 5-year OS was 69%, 56%, and 80%, and 56%, 42%, and 55% for AL, AM, and hM, respectively. The estimated 5-year PFS was 50%, 30%, and 50% in AL, ALM, and hM, respectively. Skinner *et al*[54] evaluated 701 consecutive patients with AL between July 1994 and June 2002. Fifty-six percent (394) of the patients met the eligibility criteria for high dose MEL treatment. Overall median survival was 4.6 years and 56% of the patients remained alive. The estimated 5-year survival rate was 47%.

Strategies for the treatment of hematologic malignancies have evolved as the use of immunotherapy is an attractive approach. Rosenzweig *et al*[55] provided preclinical data evaluating bone marrow specimens for BCMA and CS1 expression in ten AL patients. All the AL samples expressed high levels of CS1 (76.5% ± 4.7%) but low levels of BCMA (4.9% ± 0.8%). The study reported the unique nature of plasma clonal cells in AL patients because of the scarcity of BCMA

expression.

CONCLUSION

This literature review study is based on real-world data collected from various published research introducing multiple conditioning regimens for different disorders. Comparisons between regimens for an individual disorder were made using variables such as OS, PFS, CR, and LFS to conclude a laudable conditioning regimen having trivial adverse effects. In MM, the most effective regimen was high dose MEL given at a dose of 200 mg/m^2/d. However, for ALL, CAR-T cell therapy was preferred in the context of better OS and LFS. With respect to HL, MITO/MEL overtook BEAM in view of PFS and *vice versa* regarding OS. NHL patients were administered MITO (60 mg/m^2) and MEL (180 mg/m^2) which showed promising results. Lastly, AL is considered, and the regimen that proved to be competent was MEL 200 (200 mg/m^2). This article presents a descriptive picture of diseases and the regimens employed in them along with mentioning the most successful regimen.

FOOTNOTES

Author contributions: Maqbool S, Baloch MF, Khan MAK, and Khalid A contributed significantly and equally to the preparation of the manuscript, including primary and final drafting; Maqbool S, Khalid A, and Naimat K conceived, designed, and performed the study; all authors read and approved the final manuscript.

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MINIREVIEWS

Artificial kidney: Challenges and opportunities

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Abstract

This review aims to present the developments occurring in the field of artificial organs and particularly focuses on the presentation of developments in artificial kidneys. The challenges for biomedical engineering involved in overcoming the potential difficulties are showcased, as well as the importance of interdisciplinary collaboration in this marriage of medicine and technology. In this review, modern artificial kidneys and the research efforts trying to provide and promise artificial kidneys are presented. But what are the problems faced by each technology and to what extent is the effort enough to date?

Key Words: Artificial kidney; Implantable kidney; Hemodialysis; Peritoneal dialysis; End-stage kidney disease

Core Tip: Different technologies of artificial kidneys have been proposed and still there is no one capable of fully replacing the renal function properly. Many problems such as bioavailability, potential contamination and other variables must be controlled to make such a device successful. Herein, the most important efforts for the creation of wearable and implantable kidneys are mentioned and in addition, the principles that these devices should be governed are discussed as well.

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INTRODUCTION

This report aims to present the developments occurring in the field of artificial organs and particularly focuses on the presentation of developments in artificial kidneys. Through the operation of the biological kidneys that takes place within the exhibition, the difficulties and requirements that must be overcome by the biomedical engineering community in order to achieve the creation of fully functional artificial kidneys can be seen. Next, the modern artificial kidneys and the research efforts trying to provide and promise artificial kidneys are presented. But what are the problems faced by each technology and to what extent is the effort enough to date?

To begin with, the function of each organ in the human body is special and many times its function is irreplaceable since each one is charged with at least one distinct function. Nevertheless, there are functions in the organism that may be covered by two or more organs or systems since the control of a parameter may be influenced by more than one factor. An example is the pH balance of the blood which is controlled by the lungs, kidneys and by regulatory means within the tissues and blood. These include the need to control and measure the operation process of the instrument, which is a multifactorial function since each instrument is charged with many functions.

The kidney is the first organ to be replaced *ex vivo*[1] and today its support with artificial kidneys is a widespread rationale. Hemodialysis in general is an expensive procedure with alternatives to other methods of artificial kidneys and solutions, pharmaceutical methods and kidney transplantation. Transplantation is difficult to happen since it is difficult to find a donor but even if found it is very likely that the transplant will not be compatible. For all these reasons and for other shortcomings of conventional treatment, the existence and research of artificial kidneys is essential. But has it reached a satisfactory level so far? As stated in Groth *et al*[2], "By 2030, 14.5 million people will have end- stage kidney disease (ESKD, or CKD stage 5)".

TECHNICAL DIFFICULTIES OF CREATING AN ARTIFICIAL KIDNEY

A purely technical difficulty that needs to be overcome is the biocompatibility of an instrument. Biocompatibility according to IUPAC is "the ability of a material to be in contact with a living system without producing undesirable effects"[3]. Compatibility with blood is also required so that it does not coagulate or create clots and deposits in the devices. An additional technical difficulty is the risk of contamination in each of the existing artificial kidney devices that are being investigated especially in those handled by patients.

Another important factor for the creation of an artificial organ is the understanding of homeostasis, *i.e.* the innate function of the organism to keep its values constant is the main parameter that must be considered for the total replacement of an organ with an artificial one and an adequate device must cover all functions of the instrument. The artificial organ should be able to communicate with the organism's environment and not be a passive device that will include reagents to achieve the final result.

KIDNEYS

In the human body there are two kidneys that work in parallel in the blood flow. Their shape is cuboid and its size is about 11-13 cm long, 6 cm wide and 3 cm thick. They weigh approximately 120-170 g each and in the human body are located within the retroperitoneal space, lateral to the spine at the level of the T12-L3 vertebrae. The function of the kidneys in the human body is multidimensional. Its main function is to filter the blood from harmful and unnecessary substances for the functioning of the body and finally to clean it. It is typical that the kidneys produce about 2 L of excretes per day[4]. Blood pH, the concentration of various ions, blood pressure, blood toxicity and the volume of water excreted by the body are controlled.

In addition to these functions, the kidney is responsible for the secretion of hormones for the functioning of the body's homeostasis. For this reason, it is also called an endocrine organ. More specifically, the kidney can: Regulates blood pressure through renin, prostaglandins and kinins; Regulates red blood cell production with erythropoietin; It contributes to the regulation of vitamin D metabolism; They are a major source of the growth hormone BMP-7.

The kidneys receive 1.2-1.3 L/min of blood, about 25% of the minute blood volume. From this amount of blood the amount that is cleaned or filtered per unit of time from unwanted substances is the known glomerular filtration rate (GFR) and in a healthy kidney it is 50-60 mL/min[5]. 99% of the filtered liquid is reabsorbed. The GFR is a measure of whether a kidney is functioning adequately and whether a transplant or mechanical support is needed. When the two kidneys give a GFR of about 30 mL/min, then the symptoms of kidney failure begin to appear. Hemodialysis treatment is recommended when GFR is around 5-9 mL/min and when there are other indications without GFR being the only criterion[6].

Diseases in which the patient needs mechanical support or transplantation and which artificial kidneys aim to help are acute renal failure and chronic renal failure, but other diseases may also require a patient to use an artificial kidney. So each device should cover the above functions and requirements and if it is implantable it should cover the spatial requirements given by the human structure.

DIALYSIS

Dialysis is an old method that was used and is still used today by patients with kidney failure. Dialysis and specifically hemodialysis devices are the first artificial kidneys, even though they were not implantable in the body.

It is based on the use of diffusion as well as ultrafiltration. In essence, the blood flows on one side of a semi-permeable membrane and on the other side of the membrane there is a solution and due to the difference in concentrations of the substances, waste leaves the body. An obvious shortcoming of the method is that it cannot replace the endocrinological function of the kidney. That is, it does not produce or provide the body with the hormones produced by a kidney.

Dissolution includes two main types by which it is applied: Hemodialysis (HD); Peritoneal dialysis (PD).

The operating principle of hemodialysis is simple blood and a solvent liquid with approximately similar concentrations of substances to human plasma. The two fluids flow countercurrently for greater efficiency separated by a semipermeable membrane where substance exchange takes place and thus unwanted components are removed from the blood. During hemodialysis, however, only the blood is cleaned, not all the substances produced by a normal kidney are produced by the artificial kidney device.

Hemodialysis is performed continuously for patients in hospitals and in hemodialysis care units or clinics, but it is also performed intermittently for 3-5 h each time and 3-4 times per week, constituting a time-consuming process. To avoid this dead time (*i.e.*, 9-20 h per week), which can affect a patient's psychology, the procedure in some countries is done while the patient is sleeping at night. Another negative of hemodialysis is that since the blood is cleaned periodically, there are times when the patient has very high concentrations of harmful and unnecessary substances in the blood, so they may feel discomfort. Although hemodialysis technology has improved considerably, patient mortality and morbidity rates seem to be quite high for decades[7]. It is also worth noting that researchers have shown that better results for the patient exist with continuous hemodialysis or more frequently than is done now[7].

Peritoneal dialysis is a method that does not involve blood. It is done inside the peritoneal cavity and the patient has a tube with which he can put a solvent into the cavity, exchange substances with the vessels in the cavity and the liquid expels it through the tube outside the cavity. Relatively fewer patients choose this route, approximately 11% of the population, than hemodialysis[8]. The method can be applied to the patient with mechanical support, with automated peritoneal dialysis or done manually by the patient with continuous ambulatory peritoneal dialysis (CAPD).

Due to the above, many researchers thought that portable devices should be created that, in the best of cases, could be worn by the patient in a vest or a special case in order to achieve continuity in hemodialysis or peritoneal dialysis and to provide the possibility for the patient to be more autonomous from the hemodialysis clinics.

THE WEARABLE DEVICES

The idea of creating a portable kidney that can be applied on a belt or vest would give benefits from more frequent hemodialysis and the psychological benefit that patients would have from the ability to go wherever they want and not have the routine of hemodialysis in hospital is worth researching such a device. These devices show several advantages over conventional methods.

The first attempts were made by Willem Kolff and coworkers, as stated in a recent paper of Kooman *et al*[9], where they created a wearable artificial kidney device that weighed 3.5 kg a downside to the hypothesis was that it required the device to be periodically connected to 20 L of diluting fluid[9]. A few years later in 1986 a technique using adsorbents and enzymes was developed on which the wearable artificial kidney (WAK) device was based[9]. The device was tested on humans using it as a dialysis device for 4-8 h[9,10]. The device went through many improvements, and it was studied whether the blood and diluent supply should be continuous or pulsatile, where pulsatile flow was found to be better[11]. It is a device that was among the three winning devices in the Food and Drug Administration's (FDA) Innovation Pathway 2.0 competition in April 2012[12]. In general, it is the crown jewel of wearable artificial kidneys and is expected to greatly help patients with kidney failure. In a recent FDA-approved human trial of the wearable artificial kidney the results showed that the treatment with the wearable artificial kidney was well tolerated and in addition the treatment resulted in fluid homeostasis and effective uremic solute clearance and maintenance of electrolyte[13].

Beyond this logic there is also another way to create an artificial kidney capable of being worn using peritoneal dialysis as a starting point. For the creation of such a device it has been proposed under the name Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD)[14]. The device has not yet been tested in clinical trials and does CAPD[14], the device uses minimal solvent fluid which is regenerated using sorbent media. Even with the device, the patient can see the course of his treatment through a control panel or a computer.

The efforts of scientists from California[15,16] are also in the same way, *i.e.* the creation of a peritoneal dialysis device, called AWAK (Automated Wearable Artificial Kidney), that can be worn by the patient. Their device is already manufactured and cannot be bought yet[16].

Additionally, another notable effort is that of Wearable Bioartificial Kidney which uses sorbents to filter the peritoneal fluid and bioartificial renal epithelial cell systems (BRECS), units in which human renal epithelial cells are preserved, technology to give metabolic abilities thanks to the renal epithelial cells[17]. With the use of BRECS, a corresponding portable device could be made where hemodialysis would be performed instead of peritoneal dialysis[17].

Although the above devices solve the problem of the periodicity of blood purification by giving continuous hemodialysis and give patients the possibility to move autonomously, they are not implantable and are visible when the patient wears them.

A recent idea for a miniaturized wearable dialysis device capable for CE marking is the Wearable Artificial Kidney (WEAKID). WEAKID is based on continuous flow peritoneal dialysis using single lumen fluidic access (*i.e.*, abdomen). The peritoneal dialysate is continuously circulated and refreshed by a wearable sorption unit. Thus the device is removing toxins from the dialysate. The technology of the WEAKID has been demonstrated in preclinical research. It is suited both for portable dialysis (8 h/night) and wearable dialysis (16 h/d)[18].

Another device is the Carry Life System that was designed by the Swedish company Triomed AB (Lund, Sweden)[2]. This device uses two single- lumen catheters that provide continuous flow peritoneal dialysis with continuous dialysate recirculation. More on this device can be found on the recent review of Groth *et al*[2].

BIOARTIFICIAL KIDNEY

In this category belong devices that use, in addition to filtering the blood, the technology of biotechnology. These are devices that are connected in series with a membrane or some other material to filter the blood, but also a bioreactor with kidney cells inside to achieve metabolic and endocrinological functions corresponding to those of a natural kidney.

This operating concept was first initiated by Aebischer[7] and his colleagues and thus began the bioartificial kidney (BAK). Since the late 1990s, two main groups have been working on the idea of creating such a device, although there are several other researchers[10]. One team is based in Japan with Akira Saito and his colleagues and the other team is based in the United States with David Humes and his colleagues.

Humes' team created the first BAK device to receive approval for clinical trials from the FDA. The device had a polymeric semipermeable polysulfone or polysulfone membrane. To get there he started using porcine kidney cells or LLC-PK1 getting positive results and later for safety reasons in case toxins were created in the body, human kidney epithelial cells were used and finally human cells were clinically tested in humans. However, the program was terminated for safety reasons[1,10]. More specifically, the device construction and maintenance as well as the problem of cell maintenance and supply were reasons why the program did not proceed to the next phase [1]. It is worth noting that the device that the device worked as an extracorporeal device and needed a pump for blood flow. Saito's group also did many tests with LLC-PK1 and concluded that it would be better to use other cells[7]. In 2013 a group of Oo el al. made a BAK device with better than usual hemocompatibility and better results than other studies, the study was done in large animals[19].

General difficulties in creating BAK are that there is a good filter to filter the blood, that there is safe and sufficient functioning of renal epithelial cells, and that all parts of the system are fully biocompatible and do not react with blood so that the filter does not clog. There was still the difficulty of preserving the cells so that there would be enough of them, which was done with BRECS where they can store epithelial kidney cells from humans and they were able to preserve them through cryopreservation of cells for six months (Buffington *et al*[1], 2014). So, the cell preservation problem seems to have a solution. BRECS have only been tested in preclinical settings.

The principle of operation of Humes' devices was taken as a basis for work by a group of scientists led by Shuvo Roy and William H. Fissell and with several collaborators among them and Humes' idea was to create an implantable BAK device which created the kidney project and in turn the implantable BAK, which was one of the three winning ideas in the Innovation Pathway 2.0 competition[12]. The device contains a series of silicon membranes and will be coated to achieve biocompatibility with blood, which has been tested in short-term trials in pigs and rats[20]. Another innovation of the device is that it does not require a pump for blood flow to the device but only needs the human heart to work[20]. The device has not yet entered human clinical trials and is expected to begin during this decade. Currently the device is on a Phase 2 trial and program leaders aspire that the device will begin manufacturing[21]. In Table 1, there is a summary of the wearable and implantable devices referred in the current article. A great, question to be answered is what will be the fouling in the silicon-based filters and how this could be overcame. In addition, what kind of renal cells will be used and how their perpetual growth will be sure for a prolonged period. What is the cutoff cell mass and total surface area necessary to mimic the working performance of two fully functional kidneys? Finally, will this device be economically viable for a company and the patients.

FUTURISTIC APPROACHES

From a technology that is already almost in use (*i.e.*, wearable kidneys) and a technology that could be used in this or the next decade in patients (*i.e.*, implantable kidney) we are moving to technologies that are quite far from clinical application considering the problems that these technologies must solve for successful clinical application and large-scale production. This technology concerns tissue engineering and regenerative medicine, both are branches of biomedical engineering, as well as the previous devices (*i.e.*, wearable kidneys and implantable kidney) are also included, where from scratch or with the use of a scaffold it is attempted to create a part of the organ or a fully functional organ.

Table 1 A summary of the wearable and implantable devices referred in the current article

Device name	Brief characteristics	Mode of work
WAK	Hemodialysis device	Wearable
ViWAK PD	Not yet tested in clinical trials, peritoneal dialysis device	Wearable
AWAK	Peritoneal dialysis device	Wearable
WEBAK	Peritoneal dialysis device	Wearable
WEAKID	Peritoneal dialysis device	Wearable
CLS	Peritoneal dialysis device	Wearable
iBAK	Contains silicon membranes, not yet tested in clinical trials, does not require external power source	Implantable

WAK: Wearable Artificial Kidney; ViWAK PD: Vicenza Wearable Artificial Kidney for Peritoneal Dialysis; AWAK: Automated Wearable Artificial Kidney; WEBAK: Wearable Bioartificial Kidney; WEAKID: Wearable Artificial Kidney; CLS: Carry Life System; iBAK: Implantable Bioartificial Kidney.

To better understand the achievements of tissue engineering and regenerative medicine, their efforts should be divided into efforts to create a whole kidney and efforts to create a part of the kidney.

The first category includes techniques such as the decellularization and recellularization of a scaffold and 3D printing. The second category includes techniques such as 3D printing as well as the use of microfluidics in order to create glomerulus-on-a-chip and tubule-on-a-chip. It is useful to comment that even if not used in the near future in kidney transplantation, it is possible that these technologies will be used in drug testing and in the study of disease pathophysiology. More on these technologies can be found in two recent reviews of Peired *et al*[22] and Ibi *et al*[23].

CONCLUSION

Comparing all the functions and different technologies of artificial kidneys from the first devices until today it is evident that the researchers wanted to provide the first and main solution to the non-functioning of the kidneys, *i.e.* the purification of the blood from unnecessary substances. The other functions of the kidneys were replaced by medicinal solutions. The problem of non-portability and the inability to move due to the large devices gave efforts to the research of wearable artificial kidneys, this solution looks very promising, but these devices are not implantable. Also, the logic of fully approaching the functions of the kidneys by a device is given by the Renal Assist Device and they are still being studied today and have reached very good and promising results to achieve the final goal of an implantable kidney. The research effort so far has positive results and indications for even better, but even more work and research are needed now that the population of the earth is increasing, and the costs of conventional hemodialysis remain high.

FOOTNOTES

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MINIREVIEWS

Immunology demystified: A guide for transplant hepatologists

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Abstract

Liver transplantation has become standard practice for treating end-stage liver disease. The success of the procedure relies on effective immunosuppressive medications to control the host's immune response. Despite the liver's inherent capacity to foster tolerance, the early post-transplant period is marked by significant immune reactivity. To ensure favorable outcomes, it is imperative to identify and manage various rejection types, encompassing T-cell-mediated, antibody-mediated, and chronic rejection. However, the approach to prescribing immunosuppressants relies heavily on clinical judgment rather than evidence-based criteria. Given that the majority of patients will require lifelong immuno-suppression as the mechanisms underlying operational tolerance are still being

investigated, healthcare providers must possess an understanding of immune responses, rejection mechanisms, and the pathways targeted by immunosuppressive drugs. This knowledge enables customization of treatments and improved patient care, even though a consensus on an optimal immunosuppressive regimen remains elusive.

Key Words: Liver transplantation; Allograft rejection; Operational immune tolerance; Immune reaction; Immunosuppression

Core Tip: Liver transplantation is standard practice for treating end-stage liver disease, requiring effective immunosuppressive medications to regulate the recipient's immune response. In the post-transplant period, vigilance is necessary to recognize and manage various rejection types (T-cell-mediated, antibody-mediated, and chronic rejection). As the majority of patients require lifelong immunosuppression while the mechanisms of operational tolerance are still being explored, healthcare providers must possess a solid understanding of immune responses, rejection mechanisms, and the targets of immunosuppressive drugs. Despite the absence of consensus on an ideal immunosuppressive regimen, customization remain crucial.

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INTRODUCTION

Immunology plays a crucial role in liver transplantation (LT), influencing procedure success and long-term outcomes. The liver's unique immunological traits contribute to its heightened tolerogenic response compared to other solid organs [1,2]. However, despite these advantages, immunologic rejection remains a significant clinical concern[1]. The immune response involves complex interactions among various cell types, including T-lymphocytes, B-lymphocytes, macrophages, hepatocytes, and stromal cells, which produce cytokines and chemokines that govern the immune response and determine the fate of the graft[1]. T-lymphocyte activation and recognition of antigens by the recipient's immune system are critical steps in initiating the immune response against the graft resulting in T-cell mediated rejection[1]. Additionally, the production of donor-specific antibodies (DSA) represents a distinct risk factor for early and late antibody-mediated rejection (AMR) and graft loss[3]. In recent years operational immune tolerance induction in LT has gained interest, aiming to achieve long-term graft acceptance without the need for lifelong immunosuppression[2,4]. This review will further explore the main mechanisms of the immunologic reaction and types of graft rejection alongside the most commonly utilized immunosuppressive protocols.

IMMUNOLOGICAL CONSIDERATIONS IN LIVER TRANSPLANTATION

Several important features make the liver a unique organ in the field of LT. As in the transplantation of other organs, ABO blood group matching between the donor and recipient is strongly recommended, but, in general, there is no need for human leukocyte antigen (HLA) matching. Liver transplant actively participates in tolerance induction toward itself and operational tolerance can be achieved in 20%-40% of recipients[5,6]. Nevertheless, adequate immunosuppressive therapy is a cornerstone in successful graft survival.

ABO compatibility in LT

It is well documented that the transplantation of liver from ABO incompatible donor greatly increases the risk for graft loss due to hyperacute rejection[7,8]. In such scenario, natural antibodies against blood antigens from the plasma of the recipient may bind for blood antigens expressed in transplant, leading to activation of complement, cell destruction and inflammation. As ABO antigens are not expressed exclusively on donor red blood cells, but also on endothelial liver cells and biliary cells severe organ damage may occur[9]. The downside of ABO compatible donor selection is reduction of the pool of appropriate donors. As ABO incapability is not an absolute contraindication for successful transplantation, in urgent cases transplantation from ABO incompatible donors may be considered when no other options are available. Various approaches to remove ABO barrier and thus to broad the pool of available donors have been developed[10,11].

One available approach is therapeutic plasma exchange (TPE, therapeutic plasmapheresis), a form of apheresis in which the fundamental process is extracting a small portion of whole blood from either a donor or a patient and then dividing it into its constituent parts. One of the parts is gathered and preserved, while the remaining components are recombined and then returned to the individual. If performed on a patient to remove specific blood component it is called therapeutic apheresis (TA) and a process of removing different agents (antibodies, antigens, toxins) from plasma is called

plasmapheresis, the most common TA procedure. The removal of anti-A and anti-B isoagglutinins from the bloodstream of the liver recipient can be rapidly achieved, but it doesn't have the capacity to halt the generation of new antibodies by the preexisting plasma cells. Hence, after ABO-incompatible LT, repeated plasmapheresis is frequently required for patients experiencing an increase in isoagglutinin levels until the target titers are achieved[12,13]. There are different regimens and target titers of immunoglobulin M (IgM) and immunoglobulin G (IgG) isoagglutinins, but the typical isogglutinin target ranges from less than 1:64 to less than 1:8[14,15]. When appropriate TPE protocols and immunosuppressive agents are effectively employed, along with the attainment of target levels of isoagglutinins, there is no significant contrast in transplantation outcomes between the groups with initially high and low IgM and IgG isoagglutinin levels[16]. It is noteworthy, though, that the peak titer of pre- and post-LT IgG or IgM isoagglutinin levels exhibits a notable association with intrahepatic biliary complications and graft necrosis[17,18]. Nonetheless, in the context of preoperative rituximab treatment, the significance of preoperative isoagglutinin levels lacks conclusive data, especially as some report on no significant correlation between ABO antibody titer and antibody-mediated liver rejection[13,15,19,20]. Typical complications linked to TPE are connected to factors such as the selection of anticoagulants, replacement fluids, and vascular access. These may encompass citrate-induced hypocalcemia, hemodynamic instability, and transfusion reactions[21].

Application of rituximab, an anti-CD20 specific human-murine chimeric monoclonal antibody often used in treating patients with autoimmune diseases and hematological malignancies, was first reported in context of ABO-incompatible LT 20 years ago[22]. CD20 is a B-cell marker expressed by most B cells starting from late pre-B lymphocytes as well as memory B cells, and its expression is lost in terminally differentiated plasmablasts and plasma cells[23-25]. However, certain stages of plasma cells express CD20, suggesting their potential responsiveness to rituximab treatment[23]. There are different mechanisms od rituximab action in depleting B cells upon binding to CD20 including complement-dependent cytotoxicity, complement-dependent cellular cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and direct apoptosis induction[24]. Following rituximab infusion, B cells are depleted after 24-72 h from the peripheral blood, the full effect occurs by the third month and usually lasts six to nine months. Several studies have documented the administration of rituximab monotherapy at a dosage of 300-375 mg/m^2 two weeks before a living donor LT[26,27]. Notably, these studies demonstrated that this approach effectively eliminated the necessity for TPE and local infusion therapy. Importantly, it was found that this strategy did not have an adverse impact on patients' survival, which holds significance due to the well-documented infection risk associated with rituximab[27].

Local infusion therapy is another option to overcome the ABO-incompatibility barrier. This method involves the insertion of a catheter into the portal vein or hepatic artery, through which a combination of methylprednisolone, prostaglandin E1, and gabexate mesilate is infused. The underlying mechanism centers on inhibiting the disseminated intravascular coagulation induced by autoreactive antibodies. However, this approach sees limited application due to associated complications and is typically reserved for emergency situations where rituximab-mediated B cell depletion is insufficient[13,14]. Intraoperative splenectomy was once considered to deplete the substantial reservoir of large B cells and plasma cells. However, it was ultimately discarded as an option due to complications, concerns about immunocompromising the patient and the observation of comparable survival outcomes in patients who did not undergo splenectomy[13,14]. Post-transplant intravenous immunoglobulins (IVIG) is another approach. IVIGs have Fab – and Fc-mediated immunomodulatory properties, affecting both B cells, T cells, dendritic cells, complement cascade and cytokine levels but the routine incorporation of IVIG into desensitization protocols faces limitations such as limited experience, the lack of long-term outcome data, high treatment expenses, and potential adverse reactions[14,28].

HLA matching in LT

In contrast to ABO compatility, HLA matching in LT is largely considered unnecessary and it is not routinely performed [29]. In kidney transplantation, when the organ lacks HLA-matching, allogenic major histocompatibility complex molecules on the kidney can interact with the recipient's T cells through three distinct mechanisms[30]. One mechanism involves direct recognition occurring in the lymph nodes, where CD4+ and CD8+ T cells of the recipient directly recognize MHC-II and MHC-I molecules, respectively, on donor dendritic cells or other antigen-presenting cells. CD4+ cells and CD8+ cells differentiate into helper and cytotoxic cells, respectively - the former will secrete cytokines and help both B cells to produce antibodies and activate macrophages and the latter will directly target and eliminate graft tissue cells that display the donor's MHC-peptide complex. When alloantigen recognition is indirect, the recipient's antigen-presenting cells will internalize and process donor allogenic MHC molecules. Subsequently, they present these processed peptides by the recipient's MHC molecules to recipient T cells. Finally, in a semidirect pathway, recipient APCs acquire and present intact donor-derived HLA[30]. In liver, however, with adequate immunosuppressive therapy MHC mismatch is well tolerated, although a minor negative effect was detected in few novel studies[29,31,32]. Some studies have even reported a positive effect of HLA class II incompatibility[33]. One of the primary explanations for the limited impact of HLA mismatch is believed to be the low expression of MHC molecules. However, it is likely that several other mechanisms promote tolerance. The presentation of antigens in the liver by dendritic cells, as well as other cell types including hepatocytes, is associated with low expression of costimulatory molecules. This leads to lymphocyte anergy and supression of their response to the presented antigens. Furthermore, hepatocytes are able to secrete immunosuppressive cytokines such as interleukin-10. They can also promote the development of regulatory T-cells (Tregs) and stimulate apoptosis of lymphocytes through FasL and TNFα expression[34,35]. Persistently high plasma concentrations of MHC-I molecules originating from the allograft can potentially induce immune tolerance[36]. Despite these mechanisms of immunotolerance in liver, application of immunosuppressive drugs is necessary to prevent rejection of liver graft.

Humoral immunity in LT

A humoral arm of immune system is also able to react on donor HLA molecules by production of DSA. While this possibility was not considered a major issue in the past, the clinical significance of DSA is being increasingly recognised [37,38]. DSA can be either preformed, existing in the patient's circulation before transplantation, or formed de novo, produced after transplantation. Several factors can contribute to the occurrence of preformed DSA, including previous pregnancies in female patients and frequent blood transfusions. Additionally, viral infections have been identified as a potential risk factor for DSA occurrence due to molecular mimicry. Preformed DSA can lead to acute rejection of the allograft. Detection of preformed DSAs before LT is possible, however, a positive crossmatch test does not preclude transplantation, even in cases of dual organ transplantation. De novo DSAs (dnDSA) are synthesized after LT and may lead to AMR. The presence of dnDSA should be suspected in case of steroid refractory rejection and when analysis of liver biopsy suggests antibody mediated rejection[39]. Younger age of the recipient and lower MELD score are known risk factors associated for dnDSA production[39,40].

OPERATIONAL TOLERANCE

Among individuals who have undergone LT, there is a subgroup referred to as "operationally tolerant." This term is used to describe those who can cease all immunosuppressive medications for a duration of one year or longer while preserving allograft function[41]. This phenomenon is recognized as "spontaneous operational immunotolerance". Furthermore, immunotolerance can be intentionally induced through medical means, which is referred to as "therapeutic operational immunotolerance." There are excellent recent reviews available that delve into the role of liver cells in instigating tolerance, as well as studies on tolerance-related biomarkers[2,34,42,43]. This concise review provides a brief immunological overview tailored for clinicians. The liver's unique role in maintaining immune tolerance is attributed to its exposure to a variety of environmental antigens due to the portal circulation, which supplies 75% of its blood flow. The liver must distinguish between pathological and physiological antigens, and this process includes several key immune cell types including hepatocytes, Kupffer cells, liver sinusoidal endothelial cells (LSEC), liver-specific dendritic cells (DCs), and stellate cells within liver sinusoids enabling close interactions with circulating lymphocytes and maintaining a balance between defensive immune responses and immune tolerance[44]. LSECs, hepatic immune "gatekeepers," serve as unconventional antigen-presenting cells, facilitating the development of Tregs and suppressing strong immune reactions by employing inhibitory mechanisms such as programmed death ligand-1 signaling, in conjunction with stellate cells, and by inducing apoptosis *via* the Fas-FasL pathway to promote immune tolerance[2,34,42,43]. Furthermore, hepatic DCs are in an immature state, displaying reduced immunogenicity with low expression of MHC class II and co-stimulatory molecules (CD80 and CD86), similar to Kupffer cells, as well as minimal IL-12 secretion[2,34,42,43].

In addition, several alternative theories have been posited including the soluble donor MHC class I molecules, the passenger leukocyte theory, and the influence of high antigen loads. Liver allografts release significant amounts of soluble MHC class I molecules into the recipient's circulation, which may contribute to LT tolerance by inducing T cell apoptosis through direct MHC-TCR recognition in the absence of a secondary signal[34]. Additionally, the presence of donor organ-derived leukocytes in the recipient's bloodstream, referred to as microchimerism, has been demonstrated to trigger graft rejection in skin, lung, and kidney transplants, whereas in LT patients, it promotes immune tolerance[2,34,42]. Finally, it was proposed that the liver's size dilutes alloreactive T cells and cytokines, while high-load antigens favor T cell exhaustion, offering another possible explanation for liver tolerance[34].

There are numerous ongoing clinical trials to induce liver tolerance including early, staged withdrawal (up to 2 years) of immunosuppression, donor-derived regulatory dendritic cells (DCreg) infusion, donor alloantigen-reactive Treg (darTreg) therapy, low-dose recombinant IL-2 treatment or autologous Treg-enriched cell product given early post-transplant[45].

CATEGORIES OF LIVER ALLOGRAFT REJECTION AND THEIR CLINICAL SIGNIFICANCE

Liver allograft rejection can be categorized based on various factors, including the timing of onset, histological findings from graft biopsy, impact on graft survival and response to treatment. Current knowledge indicates that approximately up to 35% of transplant recipients will experience some form of acute rejection[46]. Acute rejection can be further subcategorized into acute T cell–mediated rejection (TCMR) and AMR, depending on the dominant underlying immune mechanism. Hyperacute rejection, characterized by severe graft injury moments after reperfusion, is exceedingly rare and primarily observed in ABO incompatible transplantation, resulting from pre-existing high-titer host antibodies against donor liver antigens, leading to immediate graft dysfunction and often fatal consequences. Tables 1 and 2 provide systematic categorizations and respective characteristics of different types of rejection.

Acute T cell-mediated rejection

Acute TCMR stands as the most prevalent form of rejection and is the primary cause of allograft dysfunction. Typically, it occurs within 90 d post-transplantation with a median onset of 8 d[47]. Prolonged cold ischemia time, female-to-male donor-recipient pairing, cytomegalo virus viremia, immune-mediated liver diseases, hepatitis C infection, and the type and level of immunosuppression are established risk factors for acute cellular rejection[48].

Table 1 Types of acute rejection and clinical manifestations

	T cell-mediated rejection	Antibody-mediated rejection
Time of occurrence	Within 90 d after LT with a median onset of 8 d[47]	Within the first few weeks after LT
Incidence	10%–30%[92,93]	0.3%–2%[94]
Clinical manifestations	Elevation of serum aminotransferases, alkaline phosphatase, gamma-glutamyl transpeptidase and/or bilirubin	Elevated aminotransferases; Graft injury with refractory thrombocytopenia, hyperbilirubinemia, low serum complements levels; Rapid allograft failure, hemorrhagic necrosis
Diagnostic criteria (histology needed)	Quantitative scoring - Rejection activity index (RAI): Portal inflammation - mixed (predominantly mononuclear activated lymphocytes, neutrophils, and eosinophils); Bile duct inflammation/damage; Venous endothelial inflammation; Each of these parameters is scored as 1 to 3 and thus a maximum score of 9 is possible; 0–2 is no rejection,3 borderline (consistent with), 4–5 is mild, 6–7 is moderate and 8–9 as severe ACR[49]	Histology: endothelial cell hypertrophy, portal capillary dilatation, microvasculitis with monocytes, eosinophils and neutrophils, and portal/peri-portal edema. Microvascular involvement involving the central veins can distinguish acute AMR from other types of injury early after LT; Elevated DSA; Diffuse C4d deposition of microvasculature in ABO-compatible tissues, or portal stroma in ABO-incompatible tissues; Exclusion of other liver diseases[49]

ACR: Acute cellular rejection; AMR: Antibody-mediated rejection; C4d: Complement component 4d; DSA: Donor-specific antibodies; LT: Liver transplantation; RAI: Rejection activity index.

Table 2 Types of chronic rejection after liver transplantation

	T cell-mediated chronic rejection	Antibody-mediated chronic rejection
Time of occurrence	Months to years after LT[95]	
Incidence	2%-5%[96]	Unknown[65]
Clinical manifestations	Cholestatic-pattern in liver function tests – the most typical presentation; Range from mild alterations in blood tests to liver failure and death[65]	Normal liver tests despite histologic evidence of allograft injury; Abnormal liver tests during immunosuppression weaning; Graft injury and/or advanced fibrosis; Development of portal hypertension after transplantation[97]
Definition (liver histology required)	(1) Presence of bile duct atrophy/pyknosis affecting most bile ducts; OR; (2) Bile duct loss in more than 50% of the portal tracts; OR; and (3) Foam cell obliterative arteriopathy[49]	(1) Histopathological pattern of injury - both required: Otherwise unexplained and at least mild mononuclear portal and/or perivenular inflammation with interface and/or perivenular necro-inflammatory activity; At least moderate portal/periportal, sinusoidal and/or perivenular fibrosis; (2) Positive DSA within 3 months of biopsy; (3) Focal C4d positivity (> 10%) portal tracts; and (4) Exclusion of other liver insults[49]

AMR: Antibody-mediated rejection; C4d: Complement component 4d; DSA: Donor-specific antibodies; LT: Liver transplantation.

Clinical presentations of acute TCMR may range from asymptomatic to abdominal pain, jaundice, fever and anorexia. Clinically and biochemically, it is often indistinguishable from other causes of allograft injury, such as hepatic artery thrombosis, biliary tract stenosis, infection or reactivation of the underlying immune disease. The gold standard for diagnosis and assessment of the severity of cellular rejection remains histological analysis of the graft. Characteristic features include portal inflammation with mixed inflammatory infiltrate, bile duct injuries and vascular endotheliitis[49]. Each of these elements can be assigned a score ranging from 1 to 3, which collectively yields the rejection activity index (RAI), determining the severity of rejection. It is important to note that RAI does not correlate with treatment response or long-term graft survival.

Antibody mediated rejection

Antibody-mediated rejection, known to be more prevalent in other solid organ transplants, occurs when host antibodies target MHC antigens of the allograft, leading to microvascular damage and graft rejection. In LT, this phenomenon is traditionally considered rare and seldom associated with graft injury, though further research is needed to fully understand its incidence and clinical significance[50]. As previously mentioned, it can manifest as hyperacute rejection, but more frequently presents as acute rejection a few weeks post-transplantation. Primary risk factors include immunological mismatch between donor and recipient and the production of DSA. Clinical presentation usually mimics that of TCMR. Elevated DSA levels, thrombocytopenia and reduced complement levels are characteristic of this form of rejection, making DSA titer determination important for diagnosis and prediction.

Diagnosis of AMR is based on four criteria: (1) Histological evidence of endothelial cell hypertrophy, portal capillary hypertrophy, microvasculitis, and periportal/portal edema; (2) elevated DSA levels; (3) diffuse C4d deposition in the microvasculature; and (4) exclusion of other conditions and complications[49]. The impact of AMR on patient and graft survival remains incompletely understood, with conflicting results in previous studies, primarily focusing on DSA titers. While some studies report a higher incidence of advanced fibrosis one year post-transplantation in cases with high DSA titers and AMR, others find no correlation[51,52]. Given the lack of consistent association between high DSA levels and

AMR occurrence, routine DSA level determination as part of pre- and post-transplant management is not currently recommended. However, in cases of treatment-resistant cellular rejection or rejection with an unclear etiology, DSA determination may serve as an indicator of AMR[53].

Most of the approaches in treating AMR have been adopted from the kidney transplantation studies[54]. The first step involves using immunosuppressive drugs (detailed later) to address cell-mediated rejection. Additionally, TPE and immunoadsorption in combination with IVIG is employed to mitigate the adverse impact of the humoral immune response. This approach has proven effective in facilitating successful transplantation for patients with positive crossmatches, and for many, it remains the primary method for desensitization before transplantation[12]. IVIG is combined to not only decrease the occurrence of infection events but also to exert immunomodulatory effects through neutralization of circulating anti-HLA antibodies with anti-idiotypic antibodies, the inhibition of complement activation, and binding to Fc receptors on immune cells[12,55]. Anti-CD20 therapy to reduce DSA remains controversial, as a recent Japanese study reported that two of the three patients with acute AMR died due to graft failure and rituximab treatment showed no therapeutic efficacy[56]. Lee *et al*[55] emphasize that IVIG is preferred over anti-CD20 agents because, although rituximab reduces circulating B cells, it does not significantly alter peripheral IgG levels in contrast to the reduction in DSAs achieved with IVIG. To address the issue of CD20 absence on plasma cells, several studies have explored proteasome inhibitors, but a drawback is their tendency to cause hepatotoxicity[12,55]. More recent efforts in the field of solid organ transplant have focused on targeted depletion of anti-HLA producing plasma cells with specific anti-CD38 antibody highly expressed on plasma cell membranes[57].

Chronic T cell-mediated rejection and chronic antibody-mediated rejection

The nomenclature itself implies an inclination towards manifestation in the later stages post-transplantation; however, chronic rejection may manifest within a few months, culminating in graft failure within a year after transplantation[58]. The risk factors for chronic rejection mirror those associated with acute rejection, further accentuated in patients with a history of late-phase acute cell-mediated rejection. The incidence of chronic rejection ranges from 3%-17%, a rate significantly lower compared to other solid organ transplantations[48]. Notably, the incidence has markedly declined in the tacrolimus-dominant era of immunosuppressive therapy, currently resting at just 3.1% based on recent research[59].

Chronic rejection may assume cell-mediated or antibody-mediated forms, or even a combination thereof, resulting in chronic arterial occlusion and direct immune-mediated bile duct injury[60]. These pathological processes precipitate the loss of bile ducts, cholestasis, fibrosis, and graft insufficiency. Clinical manifestations frequently exhibit an indolent course, with patients often presenting with newly developed cholestatic graft injury. Over time, icterus, pruritus and fatigue may develop. In advanced stages, signs of liver disease decompensation emerge. In cases where chronic rejection is suspected initially, diligent evaluation should exclude hepatic artery thrombosis, biliary tree pathology, and recurrence of the underlying disease (*e.g*., PSC, PBC).

Key histological features of chronic rejection encompass bile duct loss without ductal response, obliterative arteriopathy and inflammation and fibrosis within zone 3 and terminal hepatic venules. These characteristics are defined and categorized according to the latest Banff criteria, as of 2016[49]. Notably, chronic rejection can be reversible, particularly in instances where bile duct loss affects less than 50% of portal spaces or in early cell-mediated chronic rejection. The recent recognition of chronic AMR has started an entirely novel field of research, the full clinical implications and graft impact of which remain areas of ongoing investigation.

Patient care after solid organ transplantation is focused on the prevention of acute rejection, as it is a clinically significant event that jeopardizes the survival of both the graft and the recipient. An exception to that paradigm was LT because the results before 2000 indicated that acute rejection after LT is not associated with graft dysfunction and patient death[48]. However, a study from 2017 involving two large cohorts of LT recipients [adult to adult living donor liver transplantation (A2ALL) and scientific registry of transplant recipients (SRTR) cohorts] found that biopsy-proven acute rejection is a clinically important event even after LT[48]. Precisely, the acute rejection within six months post-transplant in A2ALL and SRTR cohorts was associated with a higher risk of graft failure (HR 1.91, 95%CI: 1.21-3.01; and HR 1.77, 95%CI: 1.63-1.92, respectively) and death (HR 1.86, 95%CI: 1-3.47; and HR 1.66, 95%CI: 1.52-1.83, respectively)[48]. These contrasting findings can be attributed to the differences in the underlying data. The previous data were based on studies involving a small number of patients who underwent protocol biopsies, meaning that patients without apparent clinical or laboratory signs of rejection were treated earlier, resulting in improved outcomes[61,62]. Moreover, patients in both cohorts were older and had more concurrent medical conditions, rendering them more vulnerable to the impact of rejection on graft function and to the increased immunosuppression required to treat rejection[48]. Subsequently, Jadlowiec *et al*[63] noted that only late TCMR (> six weeks after transplant) was associated with increased risk of mortality (HR, 1.89; 95%CI: 1.35-2.65; P = 0.001) and graft loss (HR, 1.71; 95%CI: 1.23-2.37; P = 0.001), whereas early mild TCMR was not associated with adverse outcomes. Furthermore, several studies have indicated that rejection occurring at a later stage, and resistance to steroid treatment are all linked to poorer graft outcomes[48,63,64].

Chronic rejection of liver grafts can result in graft failure, potentially necessitating retransplantation. Nevertheless, there is limited available data regarding both graft and patient survival after chronic rejection in LT recipients. Chronic T cell-mediated rejection precipitates graft loss in 15%-20% of cases, whereas such data remains unknown for chronic AMR [65]. Chronic rejection emerges as an independent predictor of total mortality within the 5-year post-transplantation interval, contributing to approximately 16% of retransplantations[49].

Emerging biomarkers in liver allograft rejection

While liver biopsy currently serves as the gold standard for diagnosing and differentiating various types of allograft rejection, its invasive nature and associate complications limit its routine use[66]. Therefore, ongoing efforts focus on developing less invasive biomarkers to improve monitoring and diagnosis. An ideal biomarker should be highly

sensitive, specific, noninvasive, readily available, reproducible, and cost-effective[66]. Donor-derived cell-free DNA (dd-cfDNA) shows promise as a novel biomarker for identifying graft injury[67]. In one of the initial investigations, it was established that the levels of dd-cfDNA in the plasma could serve as indicators of cell death, originating from necrotic or apoptotic cells within the transplanted organ[68]. Consequently, this biomarker holds potential for predicting rejection before apparent clinical signs such ase elevated liver enzymes. Furthermore, gene expression profiles, as well as serum and plasma proteins like cytokines, metabolites, and antibodies, represent potential biomarkers for identifying signatures of allograft rejection in blood samples; examination of specific T-cell and B-cell immunophenotypes in LT recipients has the potential to offer predictive insights regarding allograft rejection[69].

In conclusion, it is important to recognize both acute and chronic rejection of liver grafts as significant clinical events linked to an increased risk of graft failure and mortality. To prevent rejection after LT, it is necessary to carefully consider optimal donor and recipient selection, appropriate immunosuppression protocol and implementation of immune monitoring strategies.

ADVANCEMENTS AND CHALLENGES IN IMMUNOSUPPRESSIVE THERAPY FOR LIVER TRANSPLANTATION

Since the first human LT in 1963, important progress has been made in the field of immunosuppressive therapy. Initially, azathioprine and corticosteroids were the main immunosuppressive drugs used. In 1982, the introduction of cyclosporin, a calcineurin inhibitor (CNI), greatly improved 1-year patient survival from 26% to 70% solidifying CNI based regimens as the cornerstone of immunosuppression[70]. Subsequent developments have led to the integration of new agents into treatment protocols. Although existing protocols are successful in preventing rejection, there is a demand for novel medications that can minimize the adverse effects of immunosuppression and strengthen the immune system's ability to fight infections and detect tumors.

In LT, immunosuppression comprises of two phases: induction and maintenance. The induction phase, initiated during transplantation, involves the administration of immunosuppressive drugs to prevent early forms of rejection and promote graft acceptance. Subsequently, a gradual reduction of immunosuppressive medication, known as tapering, is employed. The maintenance phase is then designed to sustain long-term allograft acceptance, preventing late-onset forms of rejection. This approach leverages the natural decline of the direct immunologic pathway, characterized by immediate and robust immune responses that associated with acute rejection. In contrast, the indirect pathway involves slower, less intense immune responses, typically associated with chronic rejection, as described in the preceding section.

Immunosuppression in LT targets various immunological pathways to prevent graft rejection and promote graft survival. These pathways include the activation of T-cells through stimulatory and costimulatory pathways, cytokine release, and T-cell differentiation into memory T-cells[1]. Additionally, the inhibition of the mechanistic target of rapamycin (mTOR) pathway has been shown to attenuate intracellular signaling involved in AMR[71]. The emergence of dnDSA is now recognized as a novel risk factor for graft rejection. Immunosuppressive therapy is designed to inhibit dnDSA formation by reducing plasma cells, and consequently, antibody production[3]. Other pathways targeted include B-cell mediated activation of T-cells, and Treg function[72]. The characteristics of the primary immunosuppressive drugs used in LT are presented in Table 3, with the respective mechanisms and site of action shown in Figure 1.

Common immunosuppressive protocols in LT

The most common immunosuppressive protocol, employed in two-thirds of recipients in LT, is a triple-drug regimen, featuring the CNI tacrolimus (TAC), often combined with mycophenolate mofetil or azathioprine, and short-term steroid therapy[73]. CNIs, notably TAC, play a crucial role in preventing acute rejection and improving graft and patient survival, establishing their fundamental position in immunosuppressive protocols. Induction therapy with the administration of monoclonal anti-IL2 receptor antibodies, *e.g.* basiliximab, polyclonal anti-T lymphocyte antibodies, or anti-thymocyte antibodies, is also used in approximately one-third of recipients[74]. Tapering of immunosuppression is a common practice, typically starting with steroids, which are gradually reduced and ideally discontinued to minimize potential side effects associated with prolonged use[73]. The aim in patients with stable long-term graft function is to minimize immunosuppression. Moreover, adopting a monotherapy regimen of extended-release TAC appears to be as effective as standard twice-daily formulations, offering the added benefit of reducing the medication burden for patients with stable graft function[75].

Efficacy and safety of mTOR inhibitors in liver transplants

While standard multidrug immunosuppression regimens are commonly used, they may not significantly reduce clinically relevant episodes of T-cell-mediated rejection and may even have counterproductive effects in low-risk transplant candidates[1,73]. Furthermore, although CNIs effectively prevent rejection episodes, they are linked to various side effects, such as nephrotoxicity, chronic renal dysfunction, increased cardiovascular disease risk, hypertension, diabetes, and malignancies. These side effects contribute to increased morbidity and mortality, making CNI-free or -sparing protocols in LT a topic of interest[76-78].

Despite initial concerns regarding the potential for hepatic artery thrombosis and decreased wound healing due to anti-angiogenic properties, numerous studies have demonstrated the safety and efficacy of mTOR inhibitors when used in conjunction with reduced TAC (rTAC) dosages, even as early as 7 d post-LT[76]. In pivotal trials like H2304 and H2307, introducing everolimus (EVR) approximately 30 ± 5 d post-OLT alongside an rTAC regimen maintained comparable

Table 3 Immunosuppressive therapy in liver transplantation: Drugs used for induction and maintenance

Drug name (Class)	Mechanism of Action	Dosing	Comments
Induction			
Basiliximab (Immunosuppressant Agent, Monoclonal Antibody)	Directed against the IL-2 receptor on activated T lymphocytes; does not cause lymphocyte depletion.	IV: 20 mg on day 0 and 4 post-LT	Induction by IL-2R antibodies is linked to less renal impairment, fewer rejection episodes, and lower post-transplant diabetes rates. Is not potent enough to be used as monotherapy, usually used in CNI sparing regimens- CNIs introduced later or at reduced doses, especially in chronic kidney disease. Used in steroid-free regimes
Methylprednisolone (Systemic Corticos-teroid)	Inhibition of lymphocyte activation and proliferation.	Subject to variations across different centres and disease aethiology. Up to 1000 mg used in induction, IV	Adverse effects are common with high-doses. Delirium is a common early issue. Infections and metabolic problems (*e.g.* hypertension, hyperlipidemia, diabetes, obesity) pose short-term health risks
Maintenance			
Azathioprine (Antimeta-bolite)	Purine synthase antagonist inhibiting lymphocyte prolif-eration	Oral or IV administration. Typically, 1 to 2 mg/kg once daily as part of combination therapy. No established maximum dose; however, experts advise not exceeding 200 mg/d	Off-label use in LT
Mycophenolate (Antimetabolite)	MMF and MNa are prodrugs of MPA, a reversible inhibitor of inosine monophosphate dehidro-genase. MPA blocks the synthesis of guanosine nucleotides utilized by B- ant T-cell lymphocytes for proliferation exerting a significant cytostatic effect	MMF: Oral, IV: 500 mg to 1.5 g twice daily. MNa: Oral: 360 to 1080 mg twice daily	MMF is quickly absorbed in the stomach, while MNa is a delayed-release formulation absorbed in the small intestine. Both formulations have high bioavail-ability, TDM is possible but not recommended due to poor correlation between drug levels and toxicity. Common side effects include bone marrow disorders and GI upset. Both MMF and MNa have teratogenic properties
Cyclosporine (CNI)	Interacts with cyclophilin in T-cells, inhibiting calcineurin, a calcium-dependent phosphatase, which in turn blocks IL-2 transcription and T-cell activation	Oral or IV administration. Oral: Starting 10-15 mg/kg daily divided into 2 doses. IV: Initial dose: 5 to 6 mg/kg/d or one-third of the oral dose as a single dose, infused over 2-6 h	TDM and tapering according to C2 or C0 is advised. Not commonly used as initial choice in modern era. Gingival hypertrophy and hirsutism can occur
Tacrolimus (CNI)	Inhibits calcineurin by binding to FKBP12, in turn blocking IL-2 transcription and T-cell activation. More potent than cyclosporine	Oral or IV administration. Oral: Starting 0.075 mg/kg daily divided into 2 doses, increased to 0.1-0.15 mg/kg daily divided into 2 doses. IV: 0.03-0.05 mg/kg/d as a continuous infusion	Extender release formulations are in use for patients with stable graft function and IS levels, conversion is done used 1:1 ratio (mg:mg) using a previously established total daily dose. Administer once daily
Prednizone, Prednizolone (Systemic Corticosteroids)	Inhibition of lymphocyte activation and proliferation.	Prednison or prednisolon commonly used with starting maintenance dose of 20 mg daily, typically tapered and discontinued within 3-6 months. For moderate to severe rejection, common regimen is intravenous methylprednisolone (500-1000 mg daily, then tapered). In patients transplanted for AIH, low-dose prednisone (5-10 mg/day) reduces recurrence	Numerous side-effects with prolonged use, including hypertension, hyperglycemia, hyperlipidemia, weight gain, sleep disturbances, psychosis
Sirolimus (mTORi)	Inhibits the mTOR pathway which prevents IL-2 signalling to T-cells and stops T-cell prolif-eration	CNI minimization: Oral: 2 mg once daily in combination with CNI, adjust to a trough level of 4-10 ng/mL. CNI avodiance: Oral: 2-4 mg once daily in combination with MPA derivates, with or without corticosteroids, adjust to trough level of 5-10 ng/mL	Despite similar structure to tacrolimus, they do not compete and can be used simultaneously
Everolimus (mTORi)	Inhibits the mTOR pathway which prevents IL-2 signalling to T-cells and stops T-cell prolif-eration	Oral: Initial 1 mg twice daily, adjust to a trough level of 3-8 ng/mL	Half-life is shorter than sirolimus (30 *vs* 60 h) which might facilitate dose adjustment

AIH: Autoimmune hepatitis; CNI: Calcineurin inhibitor; GI: Gastrointestinal; IL-2: Interleukin-2; IV: Intravenous; LT: Liver transplantation; MMF: Mycophelonate mofetil; MNa: Mycophenolate sodium; MPA: Mycophenolate acid; mTORi: Mammalian target of rapamycin inhibitor; TDM: Therapeutic drug monitoring.

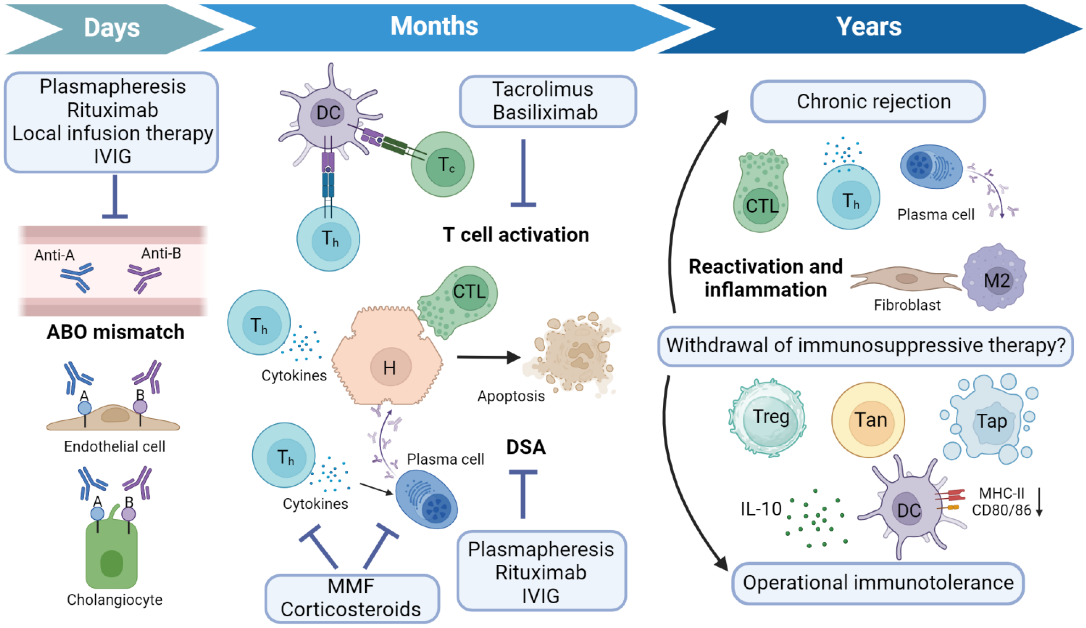

Figure 1 Key immunological events in liver transplantation. A: A antigen; Anti-A: Anti-A isoagglutinin; Anti-B: Anti-B isoagglutinin; B: B antigen; CTL: Effector CD8$^+$ cytotoxic T cell; DC: Dendritic cell; DSA: Donor-specific antibodies; H: Hepatocyte; IL-10: Interleukin 10; IVIG: Intravenous immunoglobulin; M2: M2 macrophage; MHC-II: Major histocompatibility complex molecule class II; MMF: Mycophenolate mofetil; Tan: Anergic T cell; Tap: Apoptotic T cell; Tc: CD8$^+$ cytotoxic T cell; Th: CD4$^+$ helper T cell; Treg: Regulatory T cell. Created with Biorender.com.

efficacy and safety to standard-exposure TAC (sTAC) while preserving renal function over the long term[79]. Recent research, exemplified by the HEPHAISTOS study (NCT01551212, EudraCT 2011-003118-17), has demonstrated that initiating EVR within 7-21 d after transplantation in combination with rTAC results in comparable efficacy, safety, and renal function preservation at month 12 when compared to standard sTAC therapy[80]. The safety and effectiveness of mTOR inhibitor use has been affirmed in a recent systematic review and meta-analysis[81]. Furthermore, use of mTOR inhibitors is a well-established strategy to facilitate the gradual reduction or withdrawal of CNIs ensuring the long-term renal function after transplantation[82].

In addition to their immunosuppressive properties, mTOR inhibitors exhibit antiproliferative effects, possibly reducing the risk of posttransplant recurrence and de novo malignancies[83,84]. Sirolimus seems to offer the most pronounced benefits to low-risk patients during the initial 3-5 years[85]. Furthermore, mTOR inhibitor based immunosuppression not only reduces recurrence rates but also improves overall survival in patients transplanted due to hepatocellular carcinoma [76].

Nonetheless, certain challenges persist in the utilization of mTOR inhibitors, most notably increased infection rates and the development of metabolic syndrome[86]. Additionally, the available data on the combination of mTOR inhibitors with various concomitant therapies and their potential relationship to dnDSA formation and AMR present conflicting findings, underscoring the need for further prospective studies[3,71].

Minimizing risk: Immune monitoring, novel medications and immunomodulatory strategies

The prevention of complications following organ transplantation is a multifaceted challenge that extends beyond managing rejection and its therapies. While transplant rejection remains a central concern, infectious complications can significantly impact post-transplant outcomes. To address this, immune monitoring strategies are gaining recognition for their potential to prevent infectious complications.

Several immune monitoring tests are available following LT, including antigen-specific assays (limiting dilution assays, mixed lymphocyte reactions, ELISPOT), Immune competence scores, Tregs, soluble CD30, and methods for identifying operational tolerant recipients. However, routine use is hindered by factors such as labor-intensiveness, inconsistent results, and the lack of sufficient validation studies, limiting their widespread applicability[87].

IgG serum level monitoring has garnered attention as a marker for identifying patients at an elevated risk of post-transplantation infections. Numerous studies have underscored the relevance of IgG levels in this context. For instance, low IgG levels have been linked to an increased susceptibility to infections in various transplant recipient groups, including heart, lung, and liver transplant recipients[88-90]. Moreover, the immunosuppressive therapies administered post-transplantation can disrupt the immune system, potentially impairing immunoglobulin development and response. Therefore, monitoring IgG levels after transplantation serves not only as a tool to assess infection risk, but also offers valuable insights into the overall immune status of the transplant recipient. Maintaining adequate IgG levels appears crucial not only for preventing infections but also for enhancing overall clinical outcomes in solid organ transplant recipients[91]. In conclusion, the development of a non-invasive and reliable biomarker to personalize immune system control after transplant, and mitigate infection risk, remains a challenge.

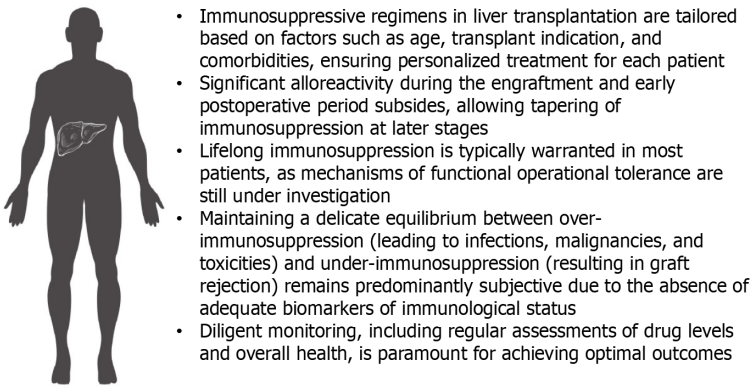

Figure 2 Immunosuppression in liver transplantation: Personalization and monitoring.

Emerging therapies and personalized approaches to rejection management in LT have gained attention in recent years. Studies have explored innovative strategies to promote immunosuppressive drug minimization or withdrawal, such as adoptive transfer of regulatory immune cells to induce operational tolerance[2]. Therapeutic options like combined hematopoietic stem-cell transplantation and solid organ transplant, thymus transplantation and intra-thymic injection of donor alloantigens have shown promise in promoting tolerance[1]. Additionally, the use of proteasome inhibitors to deplete plasma cells and decrease antibody production is being investigated[72]. Personalized approaches aim to identify biomarkers and clinical parameters that can predict rejection and guide individualized immunosuppressive strategies. Nevertheless, challenges persist in determining the outcomes of these emerging therapies, with further research needed to optimize these approaches and improve rejection management in LT.

CONCLUSION

In conclusion, the field of transplant immunology and LT has witnessed remarkable progress since its inception. The induction phase of immunosuppression in LT plays a critical role in preventing acute rejection and promoting graft acceptance by harnessing Tregs and creating an immunosuppressive environment. Meanwhile, maintenance immunosuppression remains essential for sustaining long-term graft survival and preventing chronic rejection, often relying on well-established agents like TAC, cyclosporine, mycophenolate mofetil, and mTOR inhibitors.

The pursuit of the ideal immunosuppressive regime persists, driven by the overarching objective of achieving optimal graft acceptance while mitigating the adverse effects associated with immunosuppression. Ongoing efforts are guided by the ultimate aspiration of attaining operational tolerance, thus eliminating the need for prolonged immunosuppressive therapy. Until the objective of operational tolerance is realized, it remains imperative to prioritize a multifaceted approach in patient care, including the principles of tailoring, tapering, and diligent monitoring of immunosuppressive therapies (Figure 2). These strategies collectively play a crucial role in optimizing transplant outcomes and patient well-being.

FOOTNOTES

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MINIREVIEWS

Management strategies for common viral infections in pediatric renal transplant recipients

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Abstract

Viral infections have been considered as a major cause of morbidity and mortality after kidney transplantation in pediatric cohort. Children are at high risk of acquiring virus-related complications due to immunological immaturity and the enhanced alloreactivity risk that led to maintenance of high immunosuppressive regimes. Hence, prevention, early detection, and prompt treatment of such infections are of paramount importance. Among all viral infections, herpes viruses (herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus), hepatitis B and C viruses, BK polyomavirus, and respiratory viruses (respiratory syncytial virus, parainfluenza virus, influenza virus and adenovirus) are common in kidney transplant recipients. These viruses can cause systemic disease or allograft dysfunction affecting the clinical outcome. Recent advances in technology and antiviral therapy have improved management strategies in screening, monitoring, adoption of prophylactic or preemptive therapy and precise treatment in the immunocompromised host, with significant impact on the outcome. This review discusses the etiology, screening and monitoring, diagnosis, prevention, and treatment of common viral infections in pediatric renal transplant recipients.

Key Words: Viral infections; Post renal transplant; Immunosuppressive regimes; Herpes simplex virus; Varicella zoster virus; Epstein-Barr virus; Cytomegalovirus; Hepatitis B virus; BK polyomavirus; Viral monitoring

Core Tip: Pediatric renal transplant recipients are at high risk of acquiring virus-related complications due to immunological immaturity and the enhanced alloreactivity risk that led to maintenance of high immunosuppressive regimes. Prevention, early detection, and prompt treatment of such infections are important. Recent advances in technology and antiviral therapy have improved management strategies in screening, monitoring, adoption of preemptive therapy and precise treatment in the immunocompromised host, with significant impact on the outcome.

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INTRODUCTION

Renal transplantation is a life-saving yet cost-effective treatment modality for children having end-stage kidney disease[1, 2]. More effective and potent immunosuppressive strategies have resulted in improved graft survival amongst renal transplant recipients receiving histo-incompatible grafts. However, immunosuppression has its own costs which can result in increased risk and severity of specific viral infection itself, infections by opportunistic bacteria and immunomodulating viruses[3]. These infections may result from reactivation of latent viruses due to immunosuppression or transmission from a donor allograft. These viral infections have the potential to cause damage to the allograft and acute rejection adding to increased morbidity and mortality[4] and poor graft and recipient outcomes over long run.

Thus, it is of paramount importance to develop effective strategies to control post-transplant viral infections. This needs considerable effort in establishing a viral monitoring mechanism which should be feasible and cost-effective. Formulating a sensitive, specific and reliable diagnostic assay using quantification of viral load is essential for the clinical utility of viral monitoring. Recent advances in technology and antiviral therapy have improved management strategies in screening, monitoring, adoption of prophylactic or preemptive therapy and precise treatment in the immunocompromised host, with significant impact on the outcome. This review discusses the etiology, screening and monitoring, diagnosis, prevention, and treatment of common viral infections in pediatric renal transplant recipients.

ETIOLOGY

Viral infections are one of the common complications seen amongst children following renal transplantation. A child can acquire viral infections following the renal transplantation through several mechanisms and these infections account for significant mortality and morbidity. Blood products and donor allografts act as potential sources of viral infection whilst the reactivation of viruses present in the recipient can occur due to heavy immunosuppression.

Common viral infections in renal transplant recipients include cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex viruses, varicella-zoster virus (VZV), respiratory viruses (respiratory syncytial virus, parainfluenza virus, influenza virus and adenovirus), hepatitis B and C viruses, and human BK polyomavirus (BKPyV)[5].

Cytomegalovirus

Cytomegalovirus infection is highly prevalent globally and most primary infections occur in early childhood and are generally asymptomatic[6]. Transplant recipient is at a higher and constant risk for severe cytomegalovirus infections following immunosuppression. These infections are caused by several mechanisms including reactivation of a latent infection, superinfection of the donor graft and primary infections. The patients are particularly at a higher risk if they are seronegative for CMV and received a seropositive donor kidney[7] or receive treatment with lymphocyte depleting antibodies (*e.g.* anti-thymocyte globulin)[8]. The symptoms due to CMV are caused by viral replication within the immunocompromised host, cytopathic effect and organ spreading[9]. The severe clinical manifestations range from gastrointestinal manifestations such as colitis, oesophagitis and other organ effects such as myocarditis, hepatitis, retinitis and pneumonitis[10]. Endothelial damage, vasculopathy and immunomodulation caused by CMV leads to secondary opportunistic infections such as severe fungal disease[11] and listeriosis[12].

Epstein-Barr virus

Most children acquire primary EBV infection during early years of life and EBV results in a self-limiting clinical syndrome commonly known as infectious mononucleosis. EBV has the ability to remain within dormant following primary infection and reactivate in the presence of impaired T-cell immunity[13]. The most significant complication that occurs following EBV infection is post-transplant lymphoproliferative disorder that carries a mortality as high as 50%[14].

Polyomavirus BK

Polyomavirus associated nephropathy can lead to graft dysfunction and loss and is one of the serious complications seen in kidney transplant recipients[15]. The virus replicates in renal tubular epithelium and urothelium and higher viral replication rates are a strong risk factor for nephropathy in the grafted kidney[16]. Highest incidence of nephropathy is seen during the first year following transplantation[17].

Herpesvirus 6

Herpesvirus remains latent following the primary infection and reactivation following immunosuppression during the post transplantation period can result in serious complications such as bone marrow suppression, cholestatic hepatitis and interstitial pneumonitis[18].

Respiratory viruses

Respiratory viruses are the most common as a single group seen amongst children who are kidney transplant recipients [19]. Influenza viruses, respiratory syncytial virus, adenoviruses, and parainfluenza viruses are the most common respiratory viruses[20]. Immunosuppression often leads to a prolonged course and are associated with an increased risk of complications following these viral infections.

Varicella zoster virus

Primary infection is rare following immunization, but can lead to severe disease with high morbidity and mortality. Reactivation of primary varicella zoster infection leading to herpes zoster is seen more commonly in transplant recipients. The risk for herpes zoster is increased by use of lymphocyte depleting agents as immunosuppression, lack of anti-CMV prophylaxis and low natural killer cells counts[21,22].

Hepatitis B and C viruses

Children with renal transplant, notably those received hemodialysis, may be at increased risk for Hepatitis B and C. Enhanced viremia following immunosuppression would lead to reduce graft survival and increased liver mortality[23, 24].

SCREENING AND MONITORING

Detection of CMV antigenemia by means of identification of lower matrix phosphoprotein pp65 in CMV-infected leukocytes is widely used for screening and monitoring of cytomegalovirus in transplant recipients[25]. Detection CMV DNA titers is performed by quantitative nucleic acid amplification testing. These methods are used to guide preemptive therapy following renal transplantation. In high-risk recipients (CMV IgG +ve donor (D+)/ CMV IgG –ve recipient (R-), CMV polymerase chain reaction (PCR) should be monitored monthly for 3-6 mo and then, 3 monthly during the first year following transplantation. Subsequent CMV PCR should only be requested in response to clinical need. The CMV IgG negative patients should have annual CMV serology until positive (Table 1).

The main complication seen in patients with EBV infection is post-transplantation lymphoproliferative disorder. Although this complication is seen less frequently compared to most other solid organ transplant recipients, the risk is increased with longer duration of immunosuppression and in those with high-risk (donor EBV seropositive/recipient seronegative) renal transplant recipients. It is recommended that all seronegative patients who undergo kidney transplantation are monitored for EBV DNA titers in their plasma[26]. Kidney disease Improving Global Outcomes clinical practice guideline recommend that monitoring high-risk (donor EBV seropositive/recipient seronegative) renal transplant recipients for EBV PCR: Once in the first week after transplantation; monthly for the first 3–6 mo after transplantation; then 3 monthly during the first year following transplantation. EBV R+ patients do not generally need frequent monitoring to detect EBV DNA in plasma.

Early diagnosis of polyomavirus associated nephropathy is crucial in improving graft outcomes. This necessitates renal biopsy and demonstration of polyomavirus related interstitial nephritis and cytopathic changes[27]. Although polyomavirus viruria precedes viraemia by several weeks due to predominant proliferation of the virus in the urothelium, the correlation with viruria and nephropathy is poor. Therefore, detection of viraemia by quantitative PCR on plasma is considered most predictive for screening for development of polyomavirus associated nephropathy[28]. On the contrary, negative viruria has a higher negative predictive value and viruria may be used as a first line screening test in suspecting early nephropathy[29]. However, given the limited specificity of viruria, it is required to establish the nephropathy before deciding to reduce the immunosuppression. Although the practices can vary across institutions, it is generally recommended to monitor the viral activity monthly for first 3 mo, 3-monthly thereafter during the first year, 6-monthly during the second year and annually thereafter during the first five years following transplantation[15].

Reactivation of hepatitis B virus (HBV) after transplantation is a major concern. Markers to detect hepatitis B infection include positive HBsAg and antibody to hepatitis B core antigen (Table 2). HBV serology testing in donors is important in reducing the risk of post-transplant infections. Screening for Hepatitis C sero-positivity using anti-HCV antibodies should be performed in all transplant candidates.

Table 1 Pre-transplant screening and diagnostic work-up for kidney transplant recipients

CMV	CMV IgG serology in both donors and recipients
EBV	Screening by EBV serology in both donors and recipients
BKPyV	Not done at present
HSV	HSV antibodies in blood
VZV	Pretransplant screening for previous VZV infectio
Hepatitis B & C	HBV
	HBsAg and antibody to hepatitis B core antigen (antiHBc)
	HCV
	HCV antibody test
Respiratory viruses	Nasopharyngeal wash or bronchoalveolar lavage fluid (BAL) specimens (in the case of Adeno virus - stools or plasma), by conventional viral culture, PCR, or direct immunofluorescence

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKPyV: Human BK polyomavirus; HSV: Herpes simplex viruses; VZV: Varicella zoster virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 2 Post-transplant screening and diagnostic work-up for kidney transplant recipients

CMV	Quantitative CMV viral load
	Diagnosis- presence of CMV DNA in whole blood or plasma
	Tissue biopsy
	Diagnosis- presence of CMV inclusion or immunostaining
	CMV serology
	Diagnosis- presence of CMV IgG post kidney transplantation in
	CMV R- patients
EBV	Quantitative EBV viral load
	Tissue biopsy
	EBV serology
BKPyV	Urine cytology
	Quantitative BK viral load in urine
	Quantitative BK viral load in plasma
	Allograft biopsy
HSV	Direct fluorescence antibody for HSV from vesicular lesions or PCR from CSF or visceral tissue samples
VZV	Direct fluorescence antibody for VZV from vesicular lesions or PCR from CSF or visceral tissue samples
Hepatitis B & C	HBV
	HBsAg and antibody to hepatitis B core antigen (antiHBc)
	HCV
	HCV antibody test
Respiratory viruses	Nasopharyngeal wash or bronchoalveolar lavage fluid (BAL) specimens, (in the case of Adeno virus - stools or plasma), by conventional viral culture, PCR, or direct immunofluorescence

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKPyV: Human BK polyomavirus; HSV: Herpes simplex viruses; VZV: Varicella zoster virus; HBV: Hepatitis B virus; PCR: Polymerase chain reaction.

DIAGNOSIS

Cytomegalovirus infections are diagnosed with either detection of CMV antigenaemia or nuclear amplification techniques to determine CMV DNA titers. Immunodiagnostic methods such as determination of CMV specific IgM or IgG antibodies are useful in CMV infections mainly during the first year following transplantation. Resistant CMV infections often need more advanced testing such as genotypic resistance testing to detect resistant strains of CMV.

The diagnosis polyomavirus BK viraemia is made demonstration of viral DNA in plasma. The polyomavirus associated nephropathy is confirmed by renal biopsy to demonstrate cytopathic changes characteristic of the viral proliferation in the presence of positive viral DNA in plasma. Plasma DNA level is used for determining treatment thresholds.

Due to high prevalence of Herpesvirus 6 in otherwise healthy children, detection of active replication distinctly from existing primary infection can be challenging. Quantitative PCR assays and biopsy of the grafted kidney are helpful in diagnosing active replication[30]. PCR also has an additional advantage over serological tests to differentiate A and B subtypes of HHV6.

Most respiratory viruses are diagnosed by quantitative PCR, viral culture or immunodiagnostic methods from samples such as nasopharyngeal aspirate or bronchoalveolar lavage. Adenovirus can be found in other specimens such as plasma and stools.

Diagnosis of HBV infection is with detection of Hepatitis B Surface antigen and antibodies to Hepatitis B core antigen. This should be followed up with quantification of viral load by PCR. Anti- HCV antibodies and quantitative PCR are used to diagnose Hepatitis C infection.

TREATMENT

Infections need vigorous and timely treatment to prevent severe complications in the immunocompromised transplant recipient. CMV infections are treated depend on the viral load and clinical symptoms (Table 3). Intravenous ganciclovir or oral valganciclovir are first line treatment and intravenous ganciclovir is preferred in the presence of severe infections, higher viral titers and poor gastrointestinal absorption. A minimum of two-week course is recommended and treatment should be guided by viral clearance and resolution of symptoms. Resistant CMV infection is diagnosed when either clinical symptoms or viraemia persists despite 2-wk course of ganciclovir[31]. Optimization of antiviral therapy and reduction in immunosuppression as necessary and deemed safe are also important in treating resistant CMV infections. Foscarnet is the drug of choice for those with mutations in *UL97* gene which is associated with higher resistance for conventional treatment[32]. It is recommended that antiviral therapy is continued until complete symptomatic recovery, virologic clearance and at least 2-wk course of anti-viral therapy is administered[33].

Early diagnosis and commencement of treatment is crucial in improving outcomes of patients with post-transplantation lymphoproliferative disorder following EBV infection. Persistent symptoms of lymphoproliferative syndrome or mononucleosis like syndrome should make the clinician suspect post-transplant lymphoproliferative disease (PTLD). However, it is recommended that histological diagnosis is made in order to determine the appropriate treatment regimen [34]. Widely accepted modalities of treatment of PTLD include reduction in immunosuppression, local irradiation or surgical excision and use of chemotherapy[26]. In life-threatening and extensive PTLD, abrupt reduction in immunosuppressive therapy is required to prevent mortality and this mainly involves discontinuation antimetabolite agents, calcineurin inhibitors and other non-corticosteroid immunosuppressive agents[34]. Rituximab is also considered standard therapy for CD 20 positive B cell post-transplantation lymphoproliferative disorder.

Polyomavirus associated nephropathy is primarily treated by either reduction or switching of the immunosuppressive regimen. Use of antiviral agents has not proven to be efficacious[35]. However, in the presence of rise of creatinine and renal dysfunction, the treatment should be guided by the renal biopsy findings. Widely used interventions for Polyomavirus associated nephropathy include stepwise reductions in doses of calcineurin inhibitors, antimetabolites and switching tacrolimus to cyclosporin A[36,37]. However, these practices may vary in different centers.

Successful treatment of Herpesvirus 6 has been achieved by use of either ganciclovir or foscarnet combined with reduction in immunosuppressive therapy as necessary[38]. However, treatment can be complicated in some children due to emergence of viral strains that are resistant to ganciclovir[39].

Treatment of choice for respiratory viruses following immunosuppression is Ribavirin[40,41]. However, it has proven efficacy only against respiratory syncytial viruses. There are reports of intravenous cidofovir being used successfully to treat adenoviral infections[42] and more evidence in this regard is necessary.

Treatment of HBV infection includes reduction of immunosuppression with the combination of at least one antiviral active against HBV infection. The lamivudine is the most common drug used at present. Other antivirals with activity against Hepatitis B include interferon (IFN), adefovir, entecavir and telbivudine should be used with caution due to potential for renal toxicity. With the emergence of effective antiviral agents, patients positive for HB surface antigen and antibodies for Hepatitis B core antigen are considered as renal transplant recipients provided that they are cleared of viremia after therapy. These recipients should undergo liver biopsy before and after transplantation to evaluate the extension of liver pathology[43].

Treatment of hepatitis C is usually consists of a combination of IFN and ribavirin. As Ribavirin is metabolized in the kidney, it should not be used in patients with a creatinine clearance less than 50. INF can be used in patients before transplantation to decrease viral load and it decreases the liver morbidity[44]. Although INF use is associated with acute graft rejection as studied in treatment of CMV infections in post renal transplant recipients[45], recent studies in post liver transplant recipients have not demonstrated significant rejection. Therefore, INF can be considered for treatment of

Table 3 Treatment of viral infections kidney transplant recipients

CMV	CMV load copy no < 500 - below quantifiable level - no action
	CMV load copy no 500-3000 - active CMV infection - repeat CMV in 1 week, consider treatment if clinically indicated
	CMV load copy no > 3000 - Active CMV infection - commence pre-emptive treatment
	Intravenous ganciclovir or oral valganciclovir
EBV	Immunosuppressive drug reduction
	Ganciclovir and valganciclovir have antiviral impact against EBV
BKPyV	Immunosuppressive drug reduction
	No specific antiviral therapy
HSV	Acyclovir
	Intravenous or oral
VZV	Intravenous acyclovir, while less severe infection can be treated with oral acyclovir
Hepatitis B & C	Immunosuppressive drug reduction
	Hepatitis B – Lamivudine
	Hepatitis C - IFN and ribavirin
Respiratory viruses	Reduce immunosuppressive drugs
	Supportive care and, in some cases, the use of antivirals

CMV: Cytomegalovirus, EBV: Epstein-Barr virus, BKPyV: Human BK polyomavirus, HSV: Herpes simplex viruses, VZV: Varicella zoster virus.

Hepatitis C in the renal transplant recipients[46].

PREVENTION

Cytomegalovirus infection is prevented mainly two strategies that involve either universal therapy or preemptive therapy (Table 4). Antiviral treatment is administered continuously during the peak of the post-transplantation immunosuppression period in universal therapy whilst they are administered according to thresholds of CMV anti-genemia or DNA titers in pre-emptive therapy[25]. Either intravenous ganciclovir or oral valganciclovir is used in prevention of cytomegalovirus infections in the transplant recipient. Universal therapy is generally associated with higher prevalence of side-effects and increased costs whereas preemptive therapy needs facilities for timely monitoring of viral kinetics to guide preventive treatment. Serostatus of the donor and the recipient is a key factor in determining the correct preventative approach[47]. High risk D+/R- kidney transplant recipients benefit from universal therapy with a longer 6-mo course of oral valganciclovir given at preventive doses [Dose (mg) = (7 × BSA × eGFR) once a day]. Universal therapy is also indicated for those R+ patients who were treated with lymphocyte depleting immunosuppressive therapy and a course with oral valganciclovir is recommended up to a duration of 6-mo. Preemptive therapy is mainly indicated for R+ recipients with weekly monitoring of the viral load to guide therapy and a 12-wk course is recommended for those who successfully respond. The routine use of preventative therapy is not recommended for D-/R- renal transplant recipients. D-/R- patients should be given either leukodepleted or CMV negative blood products to prevent CMV acquired thorough blood products.

Most important preventive measure against development of post-transplantation lymphoproliferative disorder in patients with increasing EBV viral loads is reduction in the immunosuppression in a step-wise manner. It is recommended that calcineurin inhibitors are maintained at an acceptable lower level to reduce the risk of development of PTLD [48]. However, it is critical that graft function is monitored to detect early graft rejection early during the phase of reduction in immunosuppression. Although some experts advocate treating patients with high viral loads with either ganciclovir or valganciclovir, the evidence base for this practice is not strong. Similarly, there is a wide variation in the practice of treating patients with higher EBV viral loads with rituximab in those who do not respond to reduction in immunosuppression alone[49].

Prevention of Polyomavirus BK associated nephropathy is achieved by early detection of viraemia and modification of immunosuppressive treatment. As children manifest nephropathy earlier than adults more frequent monitoring for viraemia is indicated in children following the period immediately following the kidney transplantation[35].

Intravenous palivizumab (an RSV-specific monoclonal antibody) prevents progression of respiratory infections in children with suppressed immunity[50]. Vaccination of patients is also important in preventing them from acquiring opportunistic viral and bacterial respiratory infections[51].

Table 4 Prevention of viral infections kidney transplant recipients

CMV	Valganciclovir
	Universal prophylaxis - Dose (mg) = (7 × BSA × eGFR) once a day
	Preemptive therapy - Dose (mg) = (7 × BSA × eGFR) bd
EBV	EBV viral load surveillance and preemptive therapy for EBV mismatched patients
BKPyV	BK viral load monitoring and early identification of BK viremia
HSV	Avoidance of visitors or health professionals who have HSV signs and symptoms
VZV	Avoidance of visitors or health professionals who have VZV signs and symptoms. Vaccination including family members
Hepatitis B & C	Hepatitis B vaccination and immunity verified with Hepatitis B surface antibody screening following completion of the vaccination series
Respiratory viruses	Avoidance of other individuals who have signs or symptoms of infection, hand hygiene, and use of droplet precautions for those suspected of having infection

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKPyV: Human BK polyomavirus; HSV: Herpes simplex viruses; VZV: Varicella zoster virus.

Hepatitis B infection can be prevented by vaccination of all nonimmune patients with ends stage renal disease with hepatitis B vaccine series. The post vaccine immunity should be verified with hepatitis B surface antibody levels. If antibody levels are below the recommended immunity level, a booster dose of vaccine is indicated. Screening of hepatitis C in children with ends stage renal failure may be confounded by the reduced serological sensitivity in this cohort. Thus, all hepatitis C seronegative transplant recipients with deranged transaminases and/or risk factors for hepatitis C should have quantification of viral load[52].

More frequent monitoring and preemptive treatment have resulted in better control of viral infections while reducing graft rejection due to undesirable reductions in immunosuppressive therapy. Monitoring of the viral loads according to the institutional protocol and evaluation of the immune status of the individual patient is therefore, crucial improving the outcomes of the transplant recipient children.

CONCLUSION

Paediatric renal transplant recipients are at high risk of acquiring virus-related complications due to immunological immaturity and the enhanced alloreactivity risk that led to maintenance of high immunosuppressive regimes. Herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, hepatitis B & C viruses, BK polyomavirus, and adenovirus are common in this cohort. These viruses can cause severe systemic diseases or allograft dysfunction affecting the clinical outcome.

More frequent monitoring and preemptive treatment have resulted in better control of viral infections while reducing graft rejection due to undesirable reductions in immunosuppressive therapy. Recent advances in technology and antiviral therapy with precise treatment in the immunocompromised host has result in significant impact on outcome.

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MINIREVIEWS

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Maurizio Salvadori, Giuseppina Rosso

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Abstract

Gut microbiota is often modified after kidney transplantation. This principally happens in the first period after transplantation. Antibiotics and, most of all, immunosuppressive drugs are the main responsible. The relationship between immunosuppressive drugs and the gut microbiota is bilateral. From one side immunosuppressive drugs modify the gut microbiota, often generating dysbiosis; from the other side microbiota may interfere with the immunosuppressant pharmacokinetics, producing products more or less active with respect to the original drug. These phenomena have influence over the graft outcomes and clinical consequences as rejections, infections, diarrhea may be caused by the dysbiotic condition. Corticosteroids, calcineurin inhibitors such as tacrolimus and cyclosporine, mycophenolate mofetil and mTOR inhibitors are the immunosuppressive drugs whose effect on the gut microbiota is better known. In contrast is well known how the gut microbiota may interfere with glucocorticoids, which may be transformed into androgens. Tacrolimus may be transformed by microbiota into a product called M1 that is 15-fold less active with respect to tacrolimus. The pro-drug mycophenolate mofetil is normally transformed in mycophenolic acid that according the presence or not of microbes producing the enzyme glucuronidase, may be transformed into the inactive product.

Key Words: Immunosuppressive therapy; Kidney transplantation; Gut microbiota; Dysbiosis; Pathobionts; Graft outcomes

Core Tip: Gut dysbiosis frequently occurs in the first period after kidney transplantation. Among the different causes, immunosuppressive drugs play a relevant role. There is a reciprocal effect between immunosuppressive drugs and the gut microbiota. Indeed, immunosuppressive drugs may change the gut microbiota composition causing dysbiosis as related side effects as rejection and infections. In contrast, the gut microbiota may alter the pharmacokinetic of immunosuppressive drugs determining modification in their metabolism and favoring the presence of substances with lower or higher immunosuppressant effect with respect to the original compound. Physicians should pay particular attention to these possibilities and carefully control both changes in the gut microbiota and the correct level of immunosuppressive drugs.

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INTRODUCTION

Among the different factors that influence the outcomes of a transplant, the gut microbiota plays a relevant role. Indeed, the relationship between the gut microbiota and the local or general immune system plays an important role in conditioning the transplant outcome. Due to this relationship, the gut microbiota may have different effects. On the one hand, the indigenous microbiota may favor the positive evolution of the graft due to, among other factors, the secretion of beneficial substances; on the other hand, the presence of pathobionts and pathogenic microbes may have deleterious effects on the graft outcomes, interfering with the metabolism of several immunosuppressant drugs.

A study from Lee *et al*[1] examined fecal specimens of five kidney transplant recipients, which provided fecal specimens prior to transplantation and 2 wk after transplantation. *Proteobacteria* were more abundant in the posttransplantation specimens as were *Erysipelotrichales* and *Enterobacteriales*.

Other studies on the gut microbiota after kidney transplantation (KT) reported a reduction in *Faecalibacterium*[2], reduction in *Actinobacteria* and *Faecalibacterium prausnizii*[3], reduction in *Ruminococcaceae*[4], and reduction in *Clostridiales* [5].

The influences of these modifications of the gut microbiota on the posttransplant settings are reported in Table 1[6-16].

Principally in the first period after transplantation, transplant recipients need to receive both immunosuppressive drugs to avoid rejection and antibiotic therapy to avoid infections.

These drugs principally influence the changes in the gut microbiota documented in the first period after transplantation. In addition, fecal metobolomic reveals distinct profiles of kidney transplant recipients and healthy controls [17].

The aim of this study was to analyze the relevance of immunosuppressive therapy on the modification of the gut microbiota composition. In addition, this study will analyze how the gut microbiota may influence the metabolism of immunosuppressive drugs.

BENEFICIAL EFFECTS IN HEALTHY CONDITIONS

In healthy conditions, the gut microbiota is principally composed of the indigenous microbiota.

The principal functions of the gut microbiota are metabolic, structural and protective. The metabolic function is exerted by metabolizing fermentable polysaccharides to produce several compounds, and to stimulate a thick intestinal mucus layer. The production of short-chain fatty acids (SCFAs), in addition to decreasing the intestinal pH and to providing further sources of energy by binding-to G protein coupled receptors, increases energy expenditure[18], reduces food intake[19] and improves glucose metabolism. In addition, the gut microbiota can contribute to drug efficacy by enzymatically transforming drug structure and altering drug bioavailability or toxicity. As we will describe, improved insight into the interaction between microbiota and drugs may optimize treatment efficacy[20].

Structural function is exerted by contributing to the integrity of the gut epithelium, do not allowing the cytokines present in the gut lumen to pass across the epithelium barrier.

Protective function. Several metabolites produced by the production of SCFAs contribute to the protective function of the gut microbiota. Butyrate by carbohydrate metabolism increases the intestinal barrier, and this function is due to *Clostridia* and *Faecalibacterium prausnizii*[21]. Propionate by carbohydrate metabolism suppresses colonic inflammation and decreases the innate immune response due to microbial stimulation. *Coprococcus catus* and *Roseburia*[22] favor this action. Indole by tryptophan metabolism increases the barrier function and modulates metabolism. *Lactobacillus* and *Bacteroides fragilis* favor this action[23]. Indole-3-propionic acid by tryptophan metabolism protects the intestinal barrier and increases the production of antioxidant products. *Clostridium sporogenes* provides this action[24]. Finally, the 10-hydroxy-cis-12-octadecoate by produced by *Lactobacillus* by lipid metabolism maintains the intestinal barrier function and decreases inflammation[25].

Table 1 Role of gut microbiota in kidney transplantation[6-16]

Post-transplant Setting	Study population	Gut bacteria involved	Outcome
TAC dosing	KTRs (*n* = 19)	↑*Faecalibacterium prausnizii*	Increased abundance positively correlated with increased TAC dose requirements
Rejection	KTRs (*n* = 55)	↑*Lactobacillales*; ↓*Clostridiales*; ↑*Enterococcus*; ↓*Barnesiellaceae*; ↑*Anaerofilum*; ↓*Paraprevotellaceae*; ↑*Clostridium*; ↓*Pasteurellaceae*; *Tertium*; ↓*Roseburia*; ↓*Haemophilus*; ↓*Faecalibacterium*	Gut microbiotra alterations associated with ABMR
TAC metabolism	*In vitro*	*Faecalibacterium prausnizii*; *Erysipelotricheles*; *Bacteroidales*	Taxa able to metabolize TAC into a less effective immunosuppressant metabolite
TAC metabolism	KTRs (*n* = 10)	Gut bacteria	Active metabolism of TAC by the gut bacteria. The gut microbiota could impact TAC trough variability
Infection	KTRs (*n* = 60)	↓*Clostridiales*; ↓*Mogibacterium*; ↓*Peptoniphilus*; ↓*Coriobacterineae*	Changes in the relative abundance associated with the development of infections after six months post transplantation
Infection	KTRs (*n* = 168)	↑*Escherichia*; ↑*Enterococcus*	Increased abundance associated with the development of *Escherichi*a and *Enterococcus* bacteriuria
Infection	KTRs (*n* = 168)	↑*Faecalibacterium*; ↑*Romboutsia*	Increased abundance associated with lower risk of Enterobacteriaceae bacteriuria and UTI
Infection	KTRs (*n* = 168)	Butyrate-producing bacteria	A relative abundance than 1% associated with lower risk of respiratory viral infection and CMV viremia
Diarrhea	KTRs (*n* = 64)	↑*Enterococcus*; ↓*Eubacterium*; ↑*Escherichia*; ↓*Anaerostipes*; ↑*Lachnoclostridium*; ↓*Coprococcus*; ↓*Romboutsia*; ↓*Ruminococcus*; ↓*Dorea*; ↓*Faecalibacterium*; ↓*Fusicatenibacter*; ↓*Oscillibacter*; ↓*Blautia*; ↓*Bifidobacterium*; ↓*Bacteroides*	Changes in the relative abundance associated with the development of diarrhea
Diarrhea	KTRs (*n* = 79)	↓*Eubacterium*; ↓*Anaerostipes*; ↓*Ruminococcus*; ↓*Dorea*; ↓*Fusicatenibacter*; ↓*Bifidobacterium*	Decreased relative abundance associated with the development of non.infectious diarrhea
NODAT	KTRs (*n* = 50)	↑*Lactobacillus*; ↓*Akkermansia muciniphila*	Changes in the relative abundance associated with the development of NODAT

TAC: Tacrolimus; KTR: Kidney transplant recipient; ABMR: Antibody mediated rejection; UTI: Urinary tract infection; CMV: Cytomegalovirus; NODAT: New onset diabetes after transplantation.

FACTORS MODIFYING THE GUT INDIGENOUS MICROBIOTA

Several factors can modify the aforementioned gut microbiota. Among these are age, diet, genetic factors of the host, and exercise and drugs.

Many of these factors affect the intestinal microbiota after KT. These can be divided into pharmacological factors, such as anti-infectious treatments[26], immunosuppressive drugs[27] and anesthetics[28], and nonpharmacological factors, such as the normalization of renal function and its associated metabolic abnormalities[29], the modification of dietary habits[30] and the discontinuation of chronic hemodialysis[31]. All these factors are shown in Figure 1.

In the case of solid organ transplantation (SOT), a particular effect on the gut microbiota is exerted by immunosuppressive treatment.

INTERRELATIONSHIP BETWEEN IMMUNOSUPPRESSIVE THERAPY AND GUT MICROBIOTA

There is a reciprocal effect between immunosuppressive drugs and microbiota. Indeed, immunosuppressive treatment may modify the gut microbiota composition. In contrast, the gut microbiota may alter the metabolism of immunosuppressive drugs.

Several studies have documented the modification of the gut microbiota after KT. Fricke *et al*[10] documented microbiota modification in all intestinal tracts after transplantation in 60 patients. Lee *et al*[1], in the aforementioned study, documented *Bacteroidetes* reduction and *Proteobacteria* increase. Shin *et al*[32] documented the presence of *Salmonellae* and *Escherichia coli* (*E. coli*) as signs of a pro-inflammatory condition. A recent and large study from Swarte *et al*[33] analyzed 1370 fecal specimens from 415 liver transplant and 672 kidney transplant subjects. In addition, they analyzed 1183 fecal specimens after 78 KT patients that were followed for two years. Overall, they found a reduction in indigenous microbiota, such as *Akkermansia muciniphila* and *Ruminococcus obeum,* and an increase in *Clostridium asparagiform* and

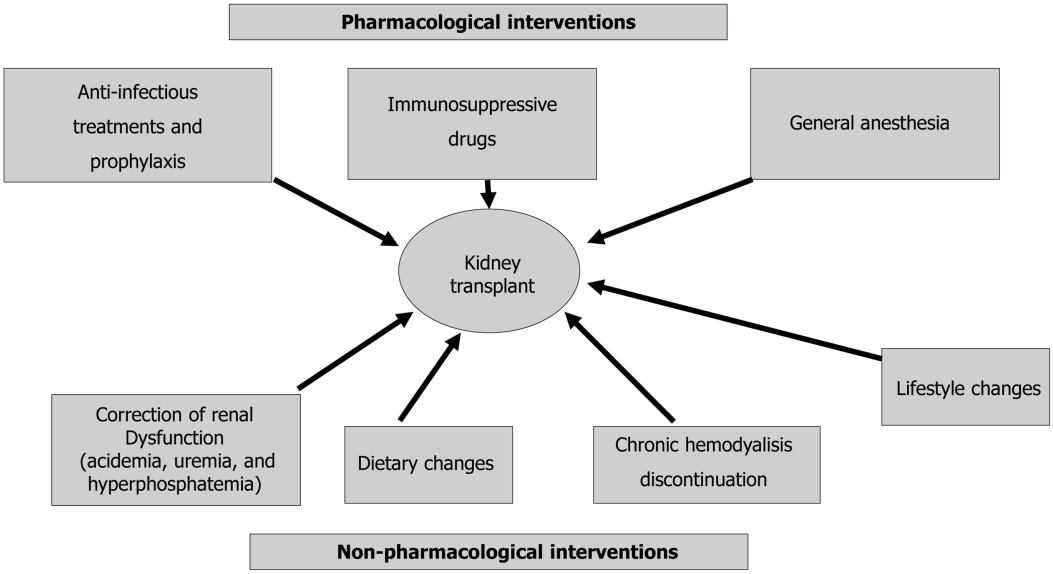

Figure 1 Factors affecting the intestinal microbiota after kidney transplantation.

Coprobacter fastidiosus. In addition, the authors found an increase in pathobionts, which could persist up to 20 years after transplantation.

A gut microbiota reduction in bacteria of the *Clostridiales* order is associated with rejection. The low production of SCFAs may have a role in this complication, as documented by the study of Koh *et al*[34].

Tourret *et al*[35] found that immunosuppressive treatment alters the secretion of iliac antimicrobial peptides and the gut microbiota and favors subsequent colonization by uropathogenic *E. coli*.

These gut microbiota modifications may cause several posttransplant events.

Different factors, including immunosuppression and antibiotic therapy, lifestyle and diet, may alter the microbiota and led to dysbiosis. Dysbiosis disrupts the gut epithelial barrier, causes loss of barrier integrity, and leads to overgrowth of pathogens. Leaky gut and increased permeability allow translocation of bacteria and their components into the inner environment. In this dysbiotic condition, the proinflammatory response triggers the elimination of pathogens by intestinal epithelial cells (IL-1, IL-6, and IL-18 secretion, dendritic cells[36], and macrophages[37], which induces the development of the effector $CD4^+$ T cells TH1 and TH17. These immune responses can preserve the activation of alloreactive T cells by cross-reacting with commensal organisms and molecular mimicry, leading to graft rejection. On the other hand, in the colon and liver, dysbiotic gut-derived uremic toxins are further metabolized to trimethylamine-N-oxide, p-cresyl sulfate (PCS) and indoxyl sulfate. The accumulation of PCS in the kidney generates reactive oxygen substances that lead to the production of inflammatory cytokines and profibrotic factors, resulting in cell injury.

On the one hand, almost all immunosuppressive drugs may determine modifications of the gut microbiota with the appearance of pathobionts and secondary dysbiosis. Their action is different according to the drugs. In contrast, the gut microbiota may modify the metabolism of immunosuppressive drugs.

GUT MICROBIOTA MODIFICATION INDUCED BY IMMUNOSUPPRESSIVE DRUGS

In a study from Gibson *et al*[38], the alteration of the gut microbiome by immunosuppressive agents used in SOT, has been well documented.

Corticosteroids

Glucocorticoids (GCs) inhibit the expression and synthesis of Muc2, the main component of colonic mucus[39]. GCs also alter gut immunity by downregulating the ileal expression of antimicrobial C-type lectins RegIII β and Reg III γ[40] *via* the inhibition of IL-22. In addition, GCs restrict the coating of bacteria by mucosal IgA[41]. On the other hand, GCs induce a retightening of TNF-α-induced tight junction relaxation by downregulating myosin light chain kinase (MLCK) synthesis and myosin light chain 2 (MLC2) phosphorylation, which is responsible for the contraction of the perijunctional actin-myosin filaments. Therefore, tight junction dysfunction is induced[42]. These modifications of the gut barrier may cause gut microbiome modification and facilitate a kinase back diffusion. Finally, the dysregulation of the circadian clock by exogenous GCs could also result in gut dysbiosis as documented by the study of Wu *et al*[43]. Figure 2 shows the corticosteroid action.

Tacrolimus

Tacrolimus pharmacokinetics is associated with gut microbiota diversity in kidney transplant patients as resulted from a pilot cross-sectional study by Degraeve *et al*[44].

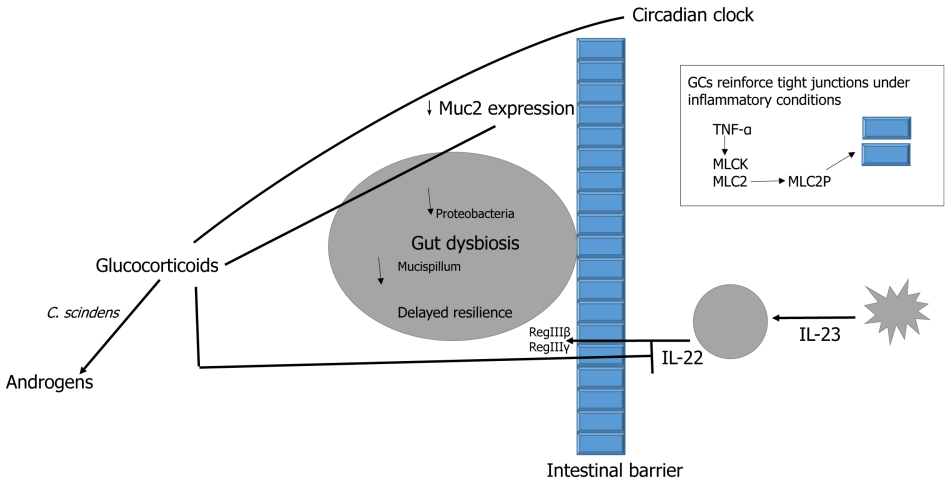

Figure 2 Impact of glucocorticoids on the gut microbiota. MUC: Mucin; RegIII: Regenerating protein; Muc2: Mucine 2; GC: Glucocorticoids; TNF-α: Tumor necrosis factor α; MLCK: Myosin light chain kinase; MLC2: Myosin light chain 2.

Tacrolimus confers immunosuppressive properties to the gut microbiota both locally and systemically by increasing the population of Treg lymphocytes. Moreover, tacrolimus is responsible for local immunosuppression in the gut by inhibiting T-lymphocyte and NK cell function[45]. Tacrolimus-induced gut microbiota alterations could also result in side effects, such as high blood pressure and diabetes[46]. This fact was confirmed by the PICRUST analysis that uses marker gene data[47] and by metagenomics analysis. Tacrolimus increases gut permeability and decreases iliac RegIIIβ levels, participating in dysbiosis[40].

In a large study conducted in liver transplant patients, tacrolimus decreased *Bifidobacterium*, *Lactobacillus* and *Faecalibacterium prausnizii* and increased *Enterobacteriaceae* and *Enterococcus*[48]. Another relevant variable in tacrolimus -induced gut microbiota changes is the administered dose. Even if based on liver transplant in rats, an intermediate dose (0.5 mg/kg) increased beneficial indigenous bacteria such as *Bifidobacterium* and *Faecalibacterium prausnizii*, while lower or higher doses resulted in different effects with an increase in pathobionts[49]. Figure 3 shows the reciprocal interference between tacrolimus and the gut microbiota.

Cyclosporine

Fewer data are available on the effect of cyclosporine (CsA) on the gut microbiota. In addition, studies have been conducted in rats and in mouse liver transplants. CsA is a calcineurin inhibitor similar to tacrolimus. According to these studies[50,51], CsA seems to have different effects with respect to tacrolimus increasing beneficial indigenous bacteria and decreasing pathobionts such as *Enterobacteriaceae* and *Clostridium*.

The major drawback of almost all these studies is that they are made on animals, mice overall. Recently, a study by O'Reilly *et al*[52] documented that encapsulated CsA does not change the composition of the human microbiota when assessed *ex vivo* and *in vivo* in humans. In particular, SWFCAs increased as well as butyrate and acetate in fecal samples.

In conclusion, it seems that CsA causes dysbiosis when given with other immunosuppressant drugs, but, when given alone, it preserves the indigenous bacteria.

Mycophenolate mofetil

Mycophenolate Mofetil (MMF) strips the diversity of the gut microbiota, increases the *Firmicutes*/*Bacteroidetes* ratio and favors *Clostridia*, *Bacteroides* and *Proteobacteria*, which include strains such as *Shigella* and *E. coli*. In contrast, *Akkermansia*, *Parabacteroides* and *Clostridium* are decreased[53]. This gut dysbiosis generates high fecal concentrations of lipopolysaccharides and colonic inflammation. In addition, mycophenolic acid (MPA), the active metabolite of MMF, perturbs tight junctions by upregulating MLCK and MLC2 phosphorylation. This is responsible for alteration of the gut barrier[54]. The resulting endotoxemia is responsible for a higher rate of cardiovascular events in KT recipients[55]. Finally, the abundance of *Bacteroides* correlates with a high level of activity of colonic bacterial β-glucuronidase, which converts the glucoronated form of MPA (MPAG) back to its active form. The addition of Vancomycin eliminates gut bacterial β-glucuronidase activity, decreasing *Bacteroides*. In this way, Vancomycin reduces MMF-induced gastrointestinal toxicity [56]. Figure 4 shows all the MMF activity at the gut level.

mTOR inhibitors

Few data are available on the interrelationship of mTOR inhibitors and gut microbiota. Almost all concern Rapamycin and the major limit is that all have been conducted on animals, rats in particular. Two actions should be distinguished: Modification of microbiota and alteration of the intestinal barrier. Clinically, one important drawback of rapamycin is its action on dyslipidemia and on glucose intolerance. In rat studies[57], the action of rapamycin was characterized by the enrichment of *Proteobacteria*, depletion of *Akkermansia*, and potential functional shifts to bacteria involved in lipid metabolism. In addition, rapamycin reduced the thickness of the intestinal barrier, increasing its permeability and

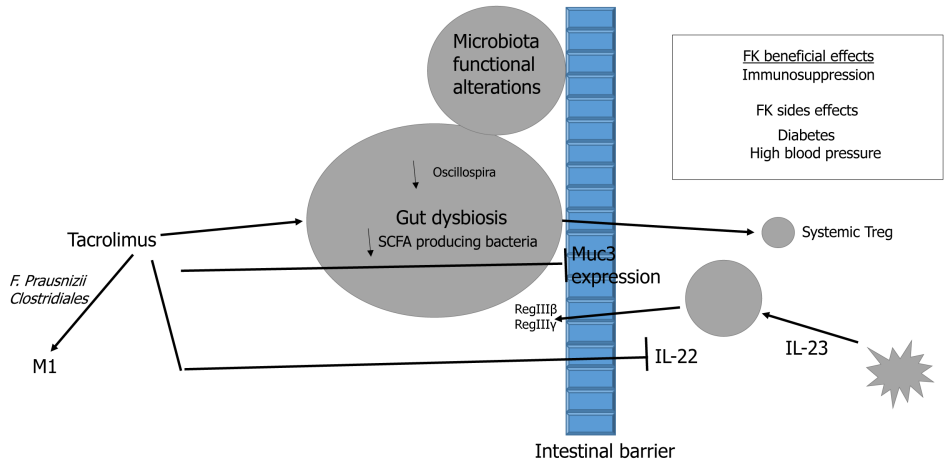

Figure 3 Impact of Tacrolimus on the gut microbiota. SCFA: Short chain fatty acids.

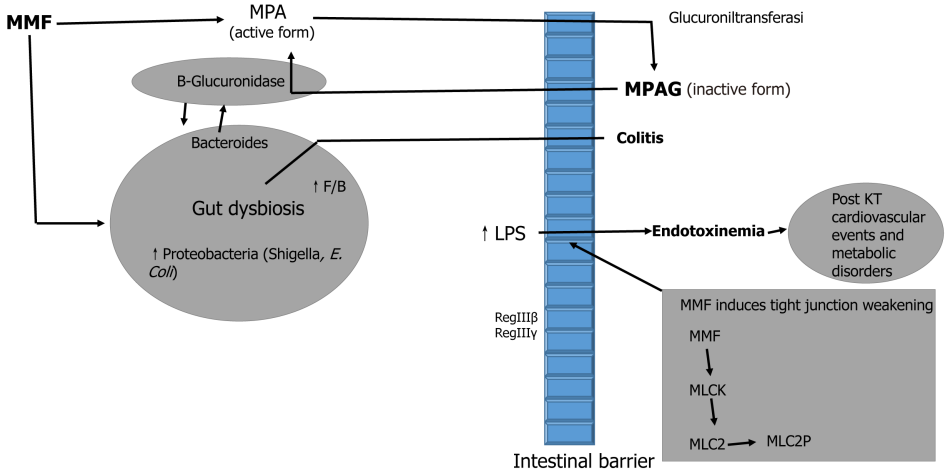

Figure 4 Impact of mycophenolate mofetil on the gut microbiota. MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; MPAG: Mycophenolic acid glucuronated; LPS: Lipopolysaccherides; MLCK: Myosin light chain kinase; MLC2: Myosin light chain 2; MLC2P: Myosin light chain 2 phosphorilated; KT: Kidney transplantation.

favoring the back diffusion of several cytokines that induce systemic inflammation. This is particularly related to the inhibition that rapamycin induces to enterocyte proliferation[58].

In conclusion, the main side effects related to rapamycin-induced dysbiosis are increased body weight, insulin resistance and altered fat metabolism[59].

INFLUENCE ON IMMUNOSUPPRESSIVE DRUG METABOLISM INDUCED BY GUT MICROBIOTA

The clinical response to classical immunosuppressant drugs is highly variable among individuals and this may be ascribed to the variety of gut microorganisms[60].

Zimmermann *et al*[61] conducted a large study on the drug metabolism modifications induced by the gut microbiota.

GCs

In particular, *Clostridium scindens* and *Propionimicrobium lymphophilum* are able to transform GCs into androgens. The consequence of this modification is a less immunosuppressive action, and it is hypothesized that a higher androgen concentration in the blood could lead to prostate cancer and mood changes[62].

Tacrolimus

Higher levels of Faecalibacterium prausnizii and Clostridiales are able to convert tacrolimus into a 15-fold less active compound called "M1"[63]. This study was confirmed by an *in vitro* study conducted by Guo *et al*[8]. This was further confirmed by a pilot study in KT patients who detected the presence of the "M1" compound in the blood after tacrolimus administration[9]. These findings could explain in part the intrapatient variability of tacrolimus trough levels. A very

recent study conducted on heart transplant patients documented a relationship between gut microbiota variability and the tacrolimus dose need[64]. Degraeve *et al*[65] documented that the gut microbiome modulates tacrolimus pharmacokinetics through the transcriptional regulation of ABCB1.

In addition, *Lactobacillus acidophilus* supplementation exerts a synergistic effect on tacrolimus efficacy by modulating Th17/Treg balance *via* the SIGNR3 pathway[66].

CsA

Fewer studies have been conducted on the influence of the gut microbiota on CsA metabolism. The enzymes CYP3A1, UGY1A1, and P-gp are relevant in the metabolism of CsA. In a recent study conducted in rats, Zhou *et al*[67] documented that the abundance of microbiota such as *Alloprevolleta* and *Oscillospiraceae* influences the expression of these enzymes and is positively related to CsA bioavailability. Studies in men and KT patients are still lacking.

Mycophenolate mofetil

MMF is associated with gastrointestinal side effects such as pain and diarrhea. An intact gut microbiota favors MMF-induced gastrointestinal toxicity. An explanation is that the abundance of Bacteroides, *Escherichia* and *Shigella*[53] favors the expansion of pathobionts. This correlates with a high level of activity of colonic bacterial β-glucuronidase, an enzyme that converts the MPAG back into its active form. Modulation of the gut microbiota with antibiotics[56] reduces β-glucuronidase activity, decreases colonic MPA levels, and ameliorates the digestive side effects of MMF. In a follow-up study in kidney transplant patients, Zhang *et al*[15] found a correlation between high levels of *Coprococcus* and *Subdoligranulum* and fecal β-glucuronidase activity in fecal samples. In addition, this correlated with long duration of diarrhea. Finally, in a recent study from Khan *et al*[68] fecal β-glucuronidase activity was different between KT patients and hematopoietic cell transplant patients. This fact could explain the different dose requirements of MMF between KT patients.

CLINICAL IMPLICATIONS OF DYSBIOSIS IN SOTS

Intestinal dysbiosis-associated with immunosuppressive therapy is a key factor in the pathogenesis of several post-transplant disease[69].

The principal clinical manifestations of dysbiosis in SOT are as follows: (1) Gut microbiota modification induced by immunosuppressive drugs; (2) influence on immunosuppressive drug metabolism induced by gut microbiota; (3) rejection; (4) infections; and (5) diarrhea.

The first two points have already been discussed. They, as aforementioned “per se”, may induce dysbiosis whose principal consequences are as follows.

Rejection

Studies on animals have documented that *Proteobacteria* induce graft rejection *via* a proinflammatory state, while *Bifidobacterium pseudolongum* decreases pro-inflammatory cytokines such as IL-6 and TNF-α and increases IL-10[70]. However, clinical studies in men are few. Pilot studies found an increase in the *Proteobacteria/Firmicutes* ratio during rejection episodes[71,72]. The pilot study of Lee *et al*[1] found a decrease in Bacteroidetes in kidney transplant rejection, but this finding was not confirmed by the study of Fricke *et al*[10].

In the aforementioned study of Wang *et al*[7], careful attention was given to identify the microbiota involved in kidney acute rejection in 53 patients. Significantly, higher levels with respect to controls were found for *Clostridiales* and *Lactobacillaceae,* while lower levels were found for *Clostridia* and *Faecalibacterium*. In the study of Fricke *et al*[10], a decreased relative abundance that correlated with future development of rejection events was found for *Anaerotruncus, Coprobacillus*, and *Coprococcus*.

The role of antibiotics in protecting or favoring acute rejection is still debated. The majority of these studies have been conducted on animals[73,74]. This is not surprising considering that some bacteria are protective and others are not protective.

Infections

A healthy microbiota protects against the development of infections. This protection is principally related to three factors: (1) The production of antimicrobial factors[75]; and (2) the induction of IgA production[76] and the reinforcement of the epithelial barrier[77]. In conditions of dysbiosis, some of these factors are lacking, and this fact may induce the colonization of pathobionts and generate infections in different organs, such as the urinary tract (UTI). Several studies have documented how the gut microbiota may favor infections. The study of Lee *et al*[1] documented that the increased abundance of *Enterococcus* is associated with the development of Enterococcus in UTIs. The study of Fricke *et al*[10] documented that the reduction of *Clostridiales, Peptoniphilus, Mogibacterium*, and *Coriobacterineae* is associated with the development of infections after six months posttransplantation. The study of Magruder *et al*[11] documented that the increased abundance in the gut of *E. coli* and *Enterococcus* is associated with bacteriuria of the same bacteria. Another study by Lee *et al*[13] documented that a relative abundance higher than 1% of butyrate-producing bacteria was associated with a lower risk of respiratory viral infection and CMV viremia. Finally, the dangerous emergence of multidrug resistant bacteria is related to dysbiosis, as documented by the study of Annavajhala *et al*[78].

Diarrhea

Diarrhea is another posttransplant complication that is often related to altered gut microbiota. Apart from the cases in which pathogens such as *Clostridium difficile* (*C. difficile*) are involved, diarrhea is often related to modifications in the gut microbiota and to the presence of pathobionts. Several studies that analyzed the gut microbiota comparing patients with or without posttransplant diarrhea confirmed that its modification is a frequent cause of posttransplant diarrhea. Lee *et al* [1] documented in a small group of kidney transplant recipients that a decreased abundance of bacteria such as *Bacteroides, Ruminococcus, Coprococcus*, and *Dorea* is associated with the development of posttransplant diarrhea. Nevertheless, Lee *et al*[14] in a further study, analyzed fecal specimens at three months post-transplantation in 64 KT recipients. Eighteen patients had diarrhea and 46 patients did not have diarrhea. In this study, they found that several bacteria with changes in relative abundance were associated with the development of diarrhea. These bacteria were *Eubacterium, Anaerostipes, Coprococcus, Romboutsia, Ruminococcus, Dorea, Faecalibacterium Oscillibacter, Ruminiclostridium, Blautia, Bifidobacterium*, *Fusicatenibacter,* and *Bacteroides*. With respect to the previous study, they found more bacteria responsible. This fact could be ascribed either to the higher number of patients studied or to the use of a more predictive technique. Indeed, in this study, they profiled the gut microbiota using 16S rRNA gene V4-V5 deep sequencing. In a different study, Zhang *et al*[15] analyzed the gut microbiota profiles and fecal beta-glucuronidase activity in kidney transplant recipients with and without posttransplant diarrhea. Bacteria, whose decreased relative abundance was associated with the development of non-infectious diarrhea, were similar to those found by the study of Lee *et al*[1]. In addition, in this study, the authors evaluated the microbiota whose relative abundance was associated with β-glucu-ronidase activity, which in turn is associated with prolonged diarrhea. These bacteria were *Subdoligranulum, Coprococcus, Tyzzerella*, and *Erysipelotrichaceae*. Clearly, this finding is related to the active form of MPA as a cause of diarrhea.

CONCLUSIONS

Our study has well documented that there is a reciprocal effect between immunosuppressive drugs and microbiota. Indeed, immunosuppressive treatment may modify the gut microbiota composition. In contrast, the gut microbiota may alter the metabolism of immunosuppressive drugs.

In addition, the clinical consequences of the dysbiosis are as follows: (1) Gut microbiota modification induced by immu -nosuppressive drugs; (2) influence on immunosuppressive drug metabolism induced by gut microbiota; (3) rejection; (4) infections; and (5) diarrhea.

A main problem without a definitive conclusion is the treatment of a severe dysbiosis. Indeed, few studies have been conducted in patients transplanted and most of them are still in phase II level.

Treatment of severe dysbiosis

The principal interventions for the treatment of gut dysbiosis are diet, fecal microbiota transplantation (FMT), prebiotics, probiotics, postbiotics and phages. Few studies have been conducted in SOT. The effect of diet is rather nonspecific, and the most serious phase II trials have been conducted in patients with hematopoietic stem cell transplantation[79].

FMT is the transfer of fecal material from a healthy subject to a patient affected by severe dysbiosis. The most frequent circumstance occurs for patients affected by recurrent *C. difficile* infections. The most important report of FMT in transplant patients is a multicenter study conducted on 94 SOT[80]. In addition, it is well documented that FMT mitigates intestinal barrier injury and gut dysbiosis induced by antibiotics and cyclophosphamide[81].

The use of probiotics and prebiotics is still the object of preclinical studies in the field of SOT, and preliminary data are available in the case of hematopoietic stem cell transplantation together with the use of microbiota-accessible carbohydrates[79].

Considering that, the argument of this review is the reciprocal interactions between the gut microbiota and the immunosuppressive drugs, the best treatment and prophylactic measure is the careful monitoring of the immunosuppressive drugs principally when a dysbiotic condition is suspected. This is principally recommended in the case of clinical manifestations often related to dysbiosis such as rejection, infection and diarrhea. Nevertheless, the use of the therapeutic measures aforementioned has the highlighted limitations.

In conclusion to date the gut microbiota in KT represents a target for a personalized therapy as documented by the studies of García-Martínez *et al*[82] and Nobakht *et al*[83].

FOOTNOTES

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MINIREVIEWS

Thrombotic microangiopathy after kidney transplantation: Expanding etiologic and pathogenetic spectra

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Abstract

Thrombotic microangiopathy (TMA) is an uncommon but serious complication that not only affects native kidneys but also transplanted kidneys. This review is specifically focused on post-transplant TMA (PT-TMA) involving kidney transplant recipients. Its reported prevalence in the latter population varies from 0.8% to 14% with adverse impacts on both graft and patient survival. It has many causes and associations, and the list of etiologic agents and associations is growing constantly. The pathogenesis is equally varied and a variety of pathogenetic pathways lead to the development of microvascular injury as the final common pathway. PT-TMA is categorized in many ways in order to facilitate its management. Ironically, more than one causes are contributory in PT-TMA and it is often difficult to pinpoint one particular cause in an individual case. Pathologically, the hallmark lesions are endothelial cell injury and intravascular thrombi affecting the microvasculature. Early diagnosis and classification of PT-TMA are imperative for optimal outcomes but are challenging for both clinicians and pathologists. The Banff classification has addressed this issue and has developed minimum diagnostic criteria for pathologic diagnosis of PT-TMA in the first phase. Management of the condition is also challenging and still largely empirical. It varies from simple maneuvers, such as plasmapheresis, drug withdrawal or modification, or dose reduction, to lifelong complement blockade, which is very expensive. A thorough understanding of the condition is imperative for an early diagnosis and quick treatment when the treatment is potentially effective. This review aims to increase the awareness of relevant stakeholders regarding this important, potentially treatable but under-recognized cause of kidney allograft dysfunction.

Key Words: Thrombotic microangiopathy; Microvascular injury; Anemia; Thrombocytopenia; Kidney allograft failure

Core Tip: Thrombotic microangiopathy (TMA) is a pattern of microvascular injury characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and multi-organ dysfunction. It is not a specific disease but rather a clinicopathological syndrome associated with numerous causes and conditions. It can also involve kidney allograft and can lead to graft dysfunction and loss. Posttransplant-TMA is distinct from native kidney TMA in certain respects and poses significant diagnostic and therapeutic challenges. A thorough understanding of the condition and the development of consensus-based diagnostic criteria are imperative for an early diagnosis and timely treatment to achieve best patient outcomes.

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INTRODUCTION

Thrombotic microangiopathy (TMA) is an uncommon but serious complication that not only affects native kidneys but can also kidney allografts, with resultant graft dysfunction and graft loss. Its reported prevalence in the latter setting varies from 0.8 to 14% of kidney transplant recipients (KTRs) with adverse impacts on both graft and patient survival[1,2]. It is a highly heterogeneous condition with equally heterogeneous outcomes. TMA is not a single disease entity but rather a morphologic pattern of microvascular occlusive injury that can be seen with a variety of disease states and conditions. It has many causes and associations, and the list of these is growing steadily as new cases are being reported [3-7]. The heterogeneous etiology is reflected in a multitude of pathogenetic pathways leading to the final common pathway of occlusive microvascular injury[8,9]. This review is directed at post-transplant TMA (PT-TMA) in KTRs, which is an important cause of kidney allograft injury and loss if not treated promptly and appropriately. The main focus will be on the expanding etiologic and pathogenetic spectra with some description devoted to the pathology and diagnosis of the condition. The management and prognosis will not be dealt with in detail in this review. TMA not only involves the native kidneys but also occurs in the transplanted kidneys. The condition has many similarities as well as some differences in the two settings. This review will be confined mainly to PT-TMA in kidney transplant setting. A thorough understanding of the condition is imperative for an early diagnosis and quick treatment when the treatment is potentially effective. This review aims to increase the awareness of relevant stakeholders regarding this important, potentially treatable but under-recognized cause of kidney allograft dysfunction.

DEFINITION AND CLASSIFICATION

TMA is a clinicopathological syndrome characterized by endothelial injury and the presence of thrombi in the microvasculature (arterioles and capillaries). Thrombus formation in the vascular lumina leads to platelet consumption, damage to the red blood cells, and occlusion of the lumina. The latter phenomenon leads to tissue ischemia and organ dysfunction, typically involving the kidneys but sometimes also other organs[10-14]. It is a potentially life-threatening condition. TMA is broadly categorized into two flagship clinical prototypes: Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The former is characterized by severe kidney disease manifested as oliguria and uremia, but few extra-renal manifestations[11-13]. In the second form, TTP, the kidney changes are similar but milder than in HUS. However, widespread systemic manifestations, particularly, central nervous system involvement, are highly prevalent [15,16]. TMA syndromes are an emerging field of research and discoveries in nephrology, hematology, and rheumatology disciplines. Although many developments have taken place, much work remains to be done in genetics, molecular biology, and therapeutics to disentangle the conundrum of the relationships and the apparent differences between the different subclasses of TMA syndromes[16-18].

The classification of the TMAs is not only challenging but is constantly evolving. Traditionally, these were classified on the basis of clinical findings: TTP for predominant neurologic involvement and HUS for kidney-dominant disease. TMA syndromes can also be classified according to the pathogenetic processes involved in endothelial injury[19-21]. However, the ideal approach to categorize TMA is that of etiology, which, however, may not be identified in each and every case of TMA. Broadly, TMA is labeled as primary when a genetic or acquired defect is identified [as in atypical HUS (aHUS) and TTP] and secondary when it occurs in the setting of another disease process, such as autoimmune disease, malignancy, infection, or drugs (Table 1). This subdivision is also not absolute because underlying genetic defects have been recognized in many cases of secondary TMA as well[21,22].

Table 1 Etiology and classification of thrombotic microangiopathies

Primary TMAs
Shiga toxin-producing *E. Coli*-associated HUS
Thrombotic thrombocytopenic purpura
Atypical HUS or complement-mediated
Secondary TMAs
Infections including viral, fungal, and bacterial
Drugs including immunosuppressants and chemotherapeutic agents
Autoimmune diseases
Malignant hypertension
Malignancy
Metabolic defects
Pregnancy
Transplantation, both hematopoietic stem cell transplantation and solid organ transplantation
Disseminated intravascular coagulation
Radiation

TMAs: Thrombotic microangiopathies.

PT-TMA

TMA not only involves the native kidneys but also the transplanted kidneys. Kidney transplantation poses a challenging scenario due to multiple potential inciting factors for the development of TMA[1,2,23-26]. PT-TMA has many similarities with native renal TMA as well as some differences necessitating its detailed review. Like native kidney TMA, PT-TMA is caused by endothelial injury in the vast majority of cases and manifests as thrombotic occlusion of the microcirculation resulting in often clinically unexplained allograft dysfunction[27]. The endothelial injury may be caused by a myriad of injurious agents including but not limited to immunologic, genetic, and hematologic disorders and drugs either alone or in various combinations[28-30]. A kidney transplant biopsy is required for a definitive diagnosis[31]. The histopathologic diagnosis of PT-TMA is based on the subjective interpretation of a large number of histopathologic lesions, whose nature, prevalence, and extent vary from case to case depending on many factors including the duration of the pathologic process. It also depends on the expertise and diagnostic insight of the pathologist[31]. Accurate diagnosis and classification are important for optimal treatment of the condition and favorable patient outcomes. The diagnosis can sometimes be challenging and delayed with consequent delay in the initiation of targeted treatment[32].

PT-TMA has been categorized in many ways. It can occur in a localized (L-TMA) form, limited to kidney allograft with resulting allograft dysfunction, or in a systemic form, with microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. In native kidneys, TMA is often part of the systemic illness, whereas in PT-TMA, it is often allograft kidney-limited. It can also be classified as recurrent or *de novo* PT-TMA; the latter being more common. Recurrent PT-TMA is almost invariably complement-mediated, whereas *de novo* PT-TMA may be complement-mediated or secondary to other inciting factors (Table 2). *De novo* TMA is reported in 0.8%-14% of KTRs, although the true frequency is unknown, and the incidence of a genetic complement abnormality may be underestimated[1,2]. Differentiating between a primary complement-mediated process and one caused by secondary factors is important to minimize allograft damage since the former is non-responsive to supportive therapy and has a high risk of recurrence. However, distinguishing between the two types can be difficult, given their overlap of clinical, laboratory, and pathological features. TMA syndromes can also be classified according to the pathogenetic processes involved in endothelial injury. However, the ideal approach to categorize TMA is that of etiology, which, however, may not be identified in every case of PT-TMA (Figure 1).

ETIOLOGY OF PT-TMAs

The etiologic spectrum of PT-TMA is expanding and evolving with ever-increasing transplant activity. The etiology of PT-TMA not only includes all those causes that are seen in native kidney disease but also many additional causes unique to the transplant setting (Figure 1). The presence of a causal factor in isolation, such as ADAMTS13 deficiency or a complement mutation (the first hit), may not manifest clinically until a condition, such as an inflammatory disorder, surgery, or pregnancy (the second hit), precipitates an acute TMA episode. In fact, in PT-TMA, often more than one acquired factors are implicated in the causation of the disorder, leading to a proposal by some researchers of three-hit mechanism. It is important to identify all the predisposing factors in order to optimally treat the condition[33-38]. It is,

Table 2 Etiology of post-transplant thrombotic microangiopathies

Recurrent TMA, rare (5%-10% of cases)
Mutations in complement regulatory factor genes [*e.g.*, factor H, factor I, membrane cofactor protein, *etc.*]
Mutations in complement genes (*e.g.*, C3)
TMA associated with autoantibodies (anti-factor H antibodies, anti-ADAMTS13 antibodies, antiphospholipid antibodies)
TMA associated with autoimmune diseases (scleroderma and systemic lupus erythematosus)
***De-novo* TMA, common (90%-95% of cases)**
Associated with the type of donor and organ procurement procedure, *e.g.* Ischemia reperfusion injury
Drugs
I: Calcineurin inhibitors-associated TMA
II: Mammalian target of rapamycin inhibitors-associated TMA
Antibody-mediated rejection associated TMA
Infection-associated TMA
I: Viral, *e.g.* hepatitis C virus, parvovirus B19, and cytomegalovirus)
II: Fungal
III: Bacterial
Other rare causes, such as malignancy, other drugs, and pregnancy

ADAMTS13: A disintegrin-like and metalloprotease with thrombospondin type 1 motif, 13; TMA: Thrombotic microangiopathy.

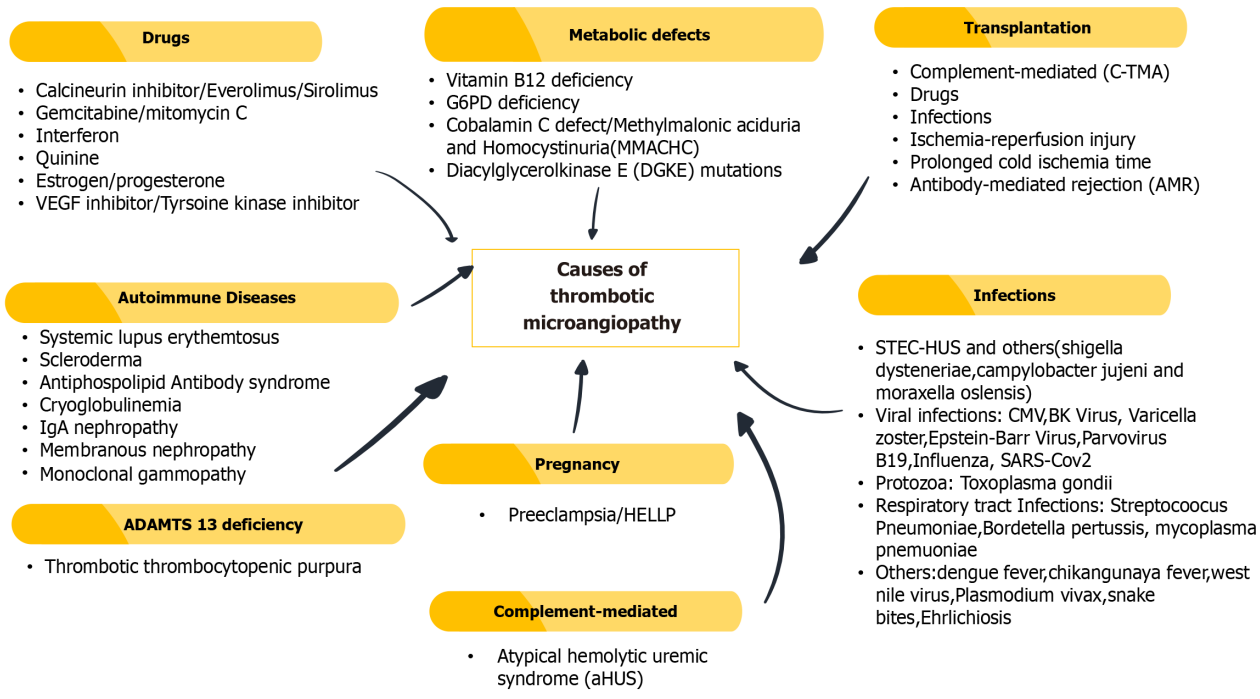

Figure 1 Common causes of thrombotic microangiopathies.

however, often impossible to pinpoint to a single etiologic factor in an individual patient.

The role of immunosuppressant drugs posttransplantation in the development of PT-TMA deserves some attention. The two main groups of immunosuppressants used in all forms of transplantation, *i.e.*, calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors (mTORi) such as sirolimus, can both trigger the development of PT-TMA[39,40]. The etiologic role of CNIs in causing PT-TMA is well established. However, the role of mTOR inhibitors is still largely controversial[40]. In vitro studies have suggested that sirolimus causes endothelial cell (EC) injury only when used in combination with tacrolimus. When used as single-agent, it does not lead to EC injury[41]. In clinical studies too, there is increasing evidence showing that sirolimus and everolimus, either alone or in combination with cyclosporine-can

be associated with the pathogenesis of de novo PT-TMA. Some studies suggest that the impact of mTORi may be even higher in the development of TMA than that of CNIs. A USRDS-based study has demonstrated that there is a higher incidence of TMA in patients on initial maintenance therapy with sirolimus (18.1 episodes/1000 person-years) compared with those on CNIs (5.0 episodes/1000 patient- years)[42]. Some other studies have shown that replacing tacrolimus with rapamycin may improve PT-TMA. Thus, the exact mechanisms and roles of immusuppressant drugs are still largely incompletely understood and need further research.

PATHOGENESIS

The pathogenesis of TMA is understandably as diverse as its etiological spectrum. The final common pathway in all forms of injury is endothelial damage with resultant activation of the thrombosis cascade. Within the TMA syndromes, two principal mechanisms participate: (1) Endothelial injury and activation; and (2) excessive platelet aggregation and activation. Among these, the endothelial injuries take precedence in HUS, whereas platelet aggregation and activation appear to be the main driving event in the TTP. Many different etiological precipitating factors have been described for the development of PT-TMA, such as ischemia-reperfusion-injury, use of immunosuppressive drugs, infections, and many more[43,44].

Endothelial injury

A variable degree of EC injury and activation is the hallmark of all TMA syndromes and in many TMA syndromes, constitutes the final common pathway of microvascular injury. The endothelium is a highly active and dynamic tissue responsible in part for regulating vascular tone, coagulation, and inflammation[45,46].

All types of TMA are characterized by a common phenotype of activated, prothrombotic ECs. This EC phenotype arises from various distinct types of injurious agents: complement activation, autoimmune diseases, infections, drug toxicity, or malignancy. For most types of TMAs, the exact intracellular mechanisms of EC injury are not well understood.

In typical or classic HUS, the initiating factor for endothelial injury and activation is usually a Shiga-like toxin, whereas, for atypical and inherited forms of HUS, excessive or inappropriate activation of complement is the main triggering event. Many other injurious agents and conditions can sometimes precipitate a HUS-like condition, probably also by damaging the endothelial layer. The EC injury in HUS causes platelet activation, aggregation, and thrombus formation within the lumina of the microvasculature. Previous research has found that reduced production of prostaglandin I_2 and nitric oxide by ECs contributes to intraluminal thrombosis. The reduced production of the above two factors and increased production of EC-derived endothelin also promote vasoconstriction, accentuating the hypoperfusion of organs[47-49].

Platelet aggregation

This is the second main pathogenetic pathway of thrombus formation in TMA syndromes, manifesting clinically as TTP. In this scenario, endothelial structure and function are relatively intact. In this pathway, the initiating event is the platelet aggregation induced by ultra-large multimers of vWF, which accumulate to a deficiency of ADAMTS13, a plasma protease that degrades vWF multimers into smaller fragments. The deficiency of ADAMTS13 is most often functional caused by autoantibodies that inhibit its function. This form of TTP is referred to as acquired or immune TTP and accounts for 95% of cases. Rarely, an inherited deficiency of ADAMTS13 Leads to a chronic relapsing and remitting form of TTP. This pattern of disease is labeled as inherited or congenital TTP and is rare[48-50].

PATHOLOGY OF PT-TMAs

A large variety of morphological lesions can be found on kidney allograft biopsies in cases of PT-TMA. The lesions may involve glomeruli, arterioles, and rarely small arteries in variable combinations and with varying degrees of severity (Table 3). Their nature varies according to the duration of the disease process and may be categorized as acute, chronic, or acute-on-chronic[51-55]. The morphological features in various types of TMA syndromes are indistinguishable and vary mainly according to the age of the lesion than the cause of TMA. The glomeruli in active disease may show many non-specific changes such as marked congestion, bloodless appearance, capillary collapse, mild to moderate cellular proliferation, crescent formation, and rarely, complete infarction. Disruption of the mesangial matrix and damage to the mesangial cells may result in mesangiolysis and aneurysmal dilatation of the capillary loops. More specific features include the thickening of the capillary walls by expansion of the subendothelial zones, intraluminal thrombi, and the presence of red cell fragmentation and extravasation into vessel walls (Figure 2). The glomerular lesions vary from case to case and from glomerulus to glomerulus.

The arterioles and small arteries in acute PT-TMA show intraluminal thrombosis and subendothelial edema resulting in marked narrowing of the lumina. Red blood cell fragmentation and extravasation in the walls of arterioles may be observed. Medial necrosis, fibrinoid necrosis, and intramural thrombosis may be seen in severe cases.

Chronic TMA lesions are commonly observed in patients with aHUS and manifest as lesions emanating from continued endothelial injury and attempts at repair. The glomeruli are mildly hypercellular and show thickened capillary walls with double contours or tram-tracking, producing mesangiocapillary pattern of injury. The double contours result from reduplication and formation of neobasement membrane because of persistent injury to the endothelium. In vessels,

Table 3 Morphological features of thrombotic microangiopathies

Active lesions
1 Glomerular lesions (Light microscopy):
Intraluminal thrombi
Endothelial swelling or denudation
Endothelial swelling or denudation
Subendothelial space widening (bloodless glomeruli)
Mesangiolysis
Microaneurysms
2 Arteriolar lesions:
Intraluminal thrombi
Endothelial swelling or denudation
Intramural fibrin
Fragmented red blood cells
3 Arterial lesions:
Intraluminal thrombi
Intimal edema
Myxoid intimal swelling
Myocyte necrosis
Intramural fibrin
Fragmentation of red blood cells
Chronic lesions
1 Glomerular lesions (Light microscopy):
Double contours of peripheral capillary walls, with variable mesangial interposition
2 Arteriolar lesions:
Hyaline deposits
3 Arterial lesions:
Fibrous intimal thickening with concentric lamination (onion-skining)

medial hypertrophy (onion-skining) may be seen in lesions of longer duration. Mucinous intimal thickening with marked narrowing of lumina is characteristically observed in chronic TMA lesions involving the arterioles and small arteries (Figure 3).

Immunoflourescence shows deposits of fibrin in glomeruli and arterioles. There may be weak nonspecific positivity of IgM in the glomeruli and arterioles with less frequent C3 and IgG. Fibrin is invariably present in the fibrin thrombi.

Electron microscopy shows separation of the endothelium from the underlying glomerular basement membrane (GBM) by electron-lucent zone filled with fluffy electron-lucent material during early phase of the disease. Within this space also lie scattered fine fibrils, occasional stands of fibrin, fragments of red blood cells and platelets and cytoplasmic processes of mesangial and endothelial cells. No electron dense deposits are found. A newly formed basement membrane is found below the endothelial layer. Mesangial changes may be marked on ultrastructural level[51-55].

Till recent past, the diagnostic criteria were not standardized for the clinical or pathological diagnosis of PT-TMA. Moreover, the histopathologic diagnosis is a subjective task. The Banff Working Group (BWG) on TMA was formed in 2016 under the auspices of the Banff Foundation for Allograft Pathology, with the aim of standardizing the diagnostic criteria of TMA and formulating recommendations[31]. A survey conducted in January 2016 among the BWG participants, showed considerable heterogeneity among pathologists, using a variety of known TMA features with imprecise or subjective definitions. Therefore, the first objective of the BWG was to provide the nephropathology community with a standardized set of minimum diagnostic criteria (MDC) for PT-TMA. A secondary objective, identified during the study, was to scrutinize specific lesions that could potentially determine specific etiologies of PT-TMA. Diagnosis of TMA in the renal allograft is not merely a morphologic task; clinical and laboratory information is also critical for diagnosis and needs to be standardized in phase II of the study. The Delphi approach was used by the BWG, for the first time in the Banff classification, to generate consensus, among an expert panel[31]. The group generated consensus on 24 criteria, provided a list of eight differential diagnoses, and identified areas of diagnostic difficulty.

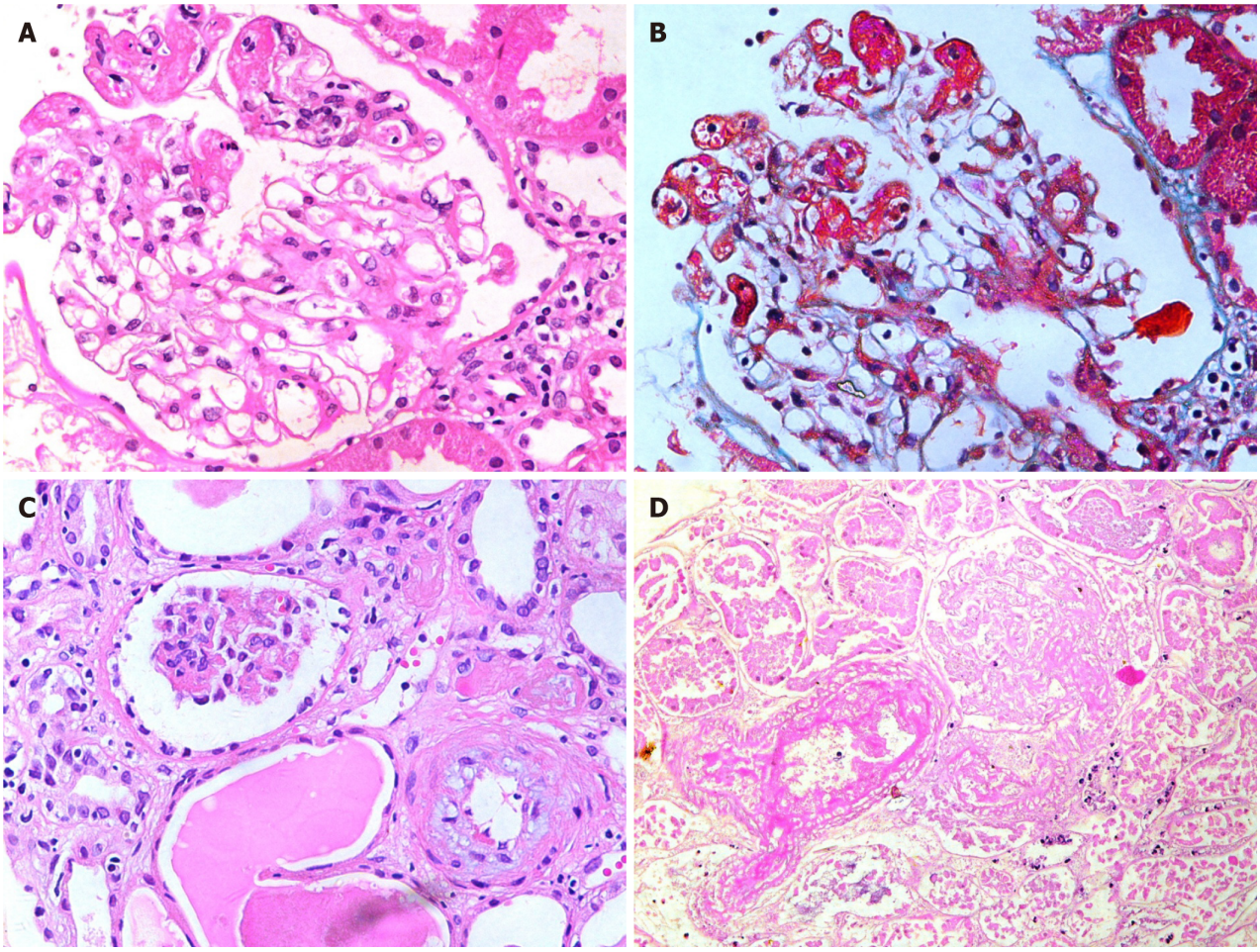

Figure 2 Glomerular lesions in thrombotic microangiopathies. A: High-power view showing a glomerulus containing fibrin thrombi in dilated capillaries at 9 to 12'O clock position (H&E, × 400); B: The same glomerulus on trichrome staining showing fibrin thrombi staining red with this stain (Masson's Trichrome, × 400); C: Medium-power view showing one ischemic glomerulus and an arteriole exhibiting mucinous intimal thickening (H&E, × 200); D: Medium-power view showing completely infarcted glomerulus and an adjacent infarcted arteriole containing intraluminal fibrin thrombus. (H&E, × 200).

According to the authors this work is a starting point in the process of diagnosing PT-TMA in KTRs[31].

DIAGNOSIS OF PT-TMAs

Overall, there is a lack of international consensus criteria for the diagnosis of PT-TMA. Moreover, the clinical and laboratory features of the condition are non-specific and protean. This is reflected in the wide variation in the reported incidence of PT-TMA. An algorithmic approach to diagnosis, classification and treatment is presented in Figure 4. Recently, the BWG on TMA has published the results of phase I of the consensus process for MDC for the pathologic diagnosis PT-TMA in KTRs. The other main group of PT-TMA relates to patients undergoing hematopoietic stem cell transplantation. Different diagnostic criteria are used in the hematology discipline. There is no uniformity in the approach to diagnosis and investigation in these two broad groups of PT-TMA. There is a clear need for unified, objective, and organ-specific criteria to help in the timely diagnosis of TMA in clinical practice and for use in future clinical trials.

MANAGEMENT AND PROGNOSIS

Management of the condition is challenging and still largely empirical. It varies from simple maneuvers, such as plasmapheresis, drug withdrawal or modification, or dose reduction, to lifelong complement blockade by eculizumab, which is very expensive approach (Figure 5). Careful donor selection and proper recipient preparation, including complete genetic screening, would be a more rational approach. Novel targeted therapies are being actively researched but are still in the experimental phase and are not yet available in clinical practice[56-59].

The prognosis of *de novo* or recurrent TMA in kidney allografts is generally guarded and varies according to underlying causes[60-68]. With better understanding and characterization of the disease, the patient and allograft outcomes are improving steadily.

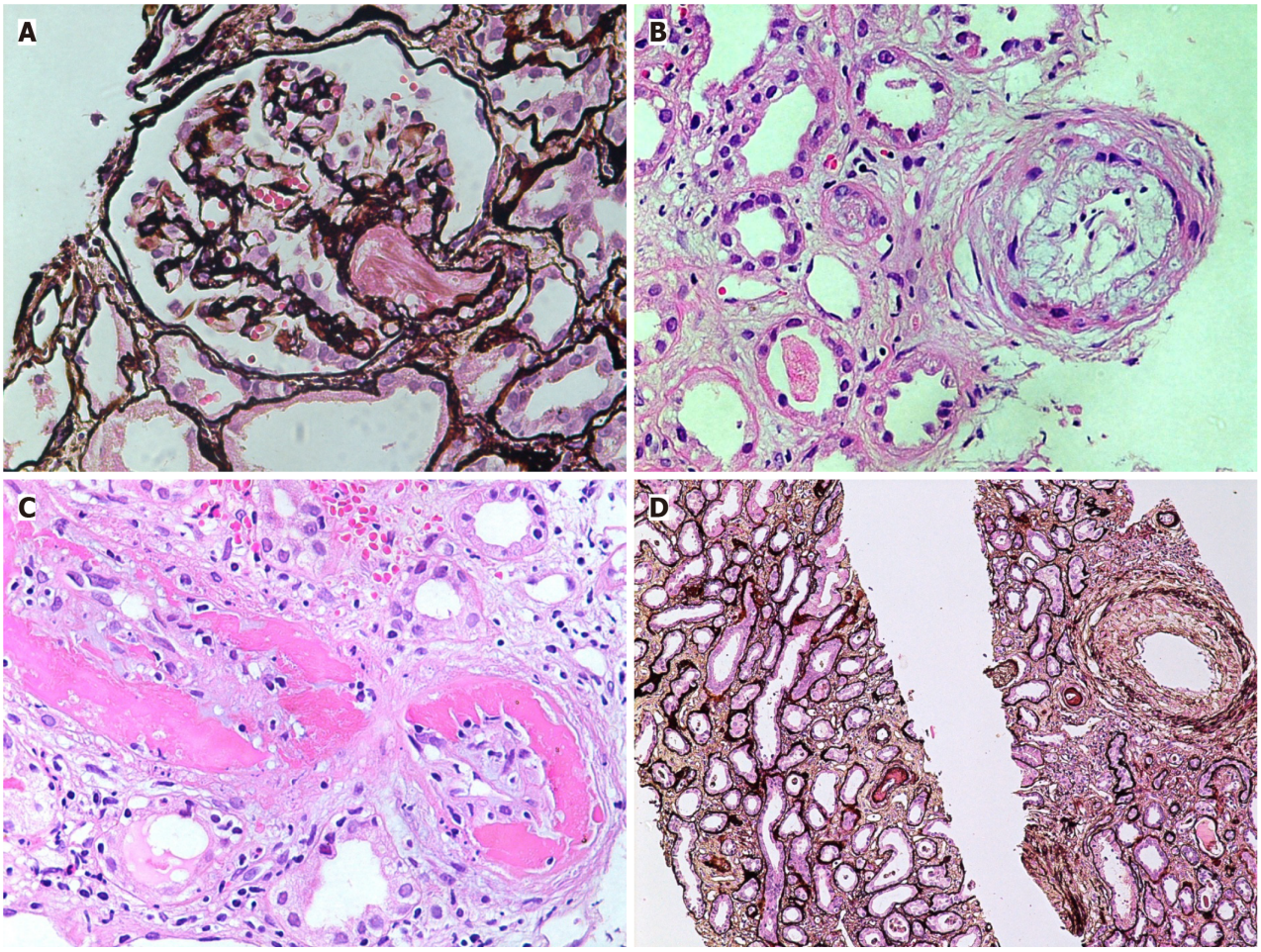

Figure 3 Vascular lesions in thrombotic microangiopathies. A: Medium-power view showing a glomerulus with an arteriole containing fibrin thrombi in acute phase of thrombotic microangiopathies (TMAs) (H&E, × 200); B: High-power view showing an arteriole with endothelial swelling and complete occlusion of the lumen. An adjacent small artery shows marked mucinous thickening of the intima with narrowing of the lumen (H&E, × 400); C: High-power view showing a small artery with fibrinoid necrosis of the vessel wall and intimal proliferation (H&E, × 400); D: Medium-power view showing fibrointimal thickening of an interlobular size artery in chronic phase of TMA. Mild tubular atrophy is seen in the background (Silver stain, × 200).

PREVENTIVE/PROPHYLAXIS MEASURES

These measures or strategies can only be applied in cases of aHUS for possible risk of recurrence after kidney transplantation (Figure 5). The risk of recurrence depends on the type of mutation in complement regulatory proteins and can be calculated before transplantation. Recurrence usually occurs very early in the posttransplant period and may be precipitated quickly by an ischemia-reperfusion–induced endothelial injury. However, the time between kidney transplantation and aHUS recurrence varies considerably. Due to the severity of aHUS recurrences and the unpredictable time of onset, the KDIGO workgroup recommends the prophylactic use of eculizumab for KTRs who are at high risk of recurrence based on the patient's genetic background. Eculizumab has been used both before and after transplantation. An analysis of the Global aHUS Registry showed that pretransplant use of eculizumab resulted in better allograft function than posttransplant initiation. Other preventive measures include pretransplant plasma exchange (PE), use of induction therapy and low doses of CNIs. For some complement regulatory gene mutations, use of liver-kidney transplantation has been used successfully[69]. This procedure is controversial because of potentially severe postoperative complications but the use of PE or a single dose of eculizumab until graft liver function is adequate greatly improved outcomes for the patient. However, this type of transplant should only be performed in centers with proven expertise, after a careful risk-benefit analysis.

CONCLUSION

PT-TMA is an important but underestimated cause of kidney allograft dysfunction and loss. Its etiologic spectrum and associated pathogenetic pathways are expanding steadily. Its early diagnosis and treatment are challenging. Recently attempts have been made to standardize the pathologic diagnostic criteria for its accurate diagnosis so as to optimize treatment approaches. There is a need to adopt a unified and international consensus-based approach across all the relevant specialties involved for standardizing and optimizing TMA diagnosis and management.

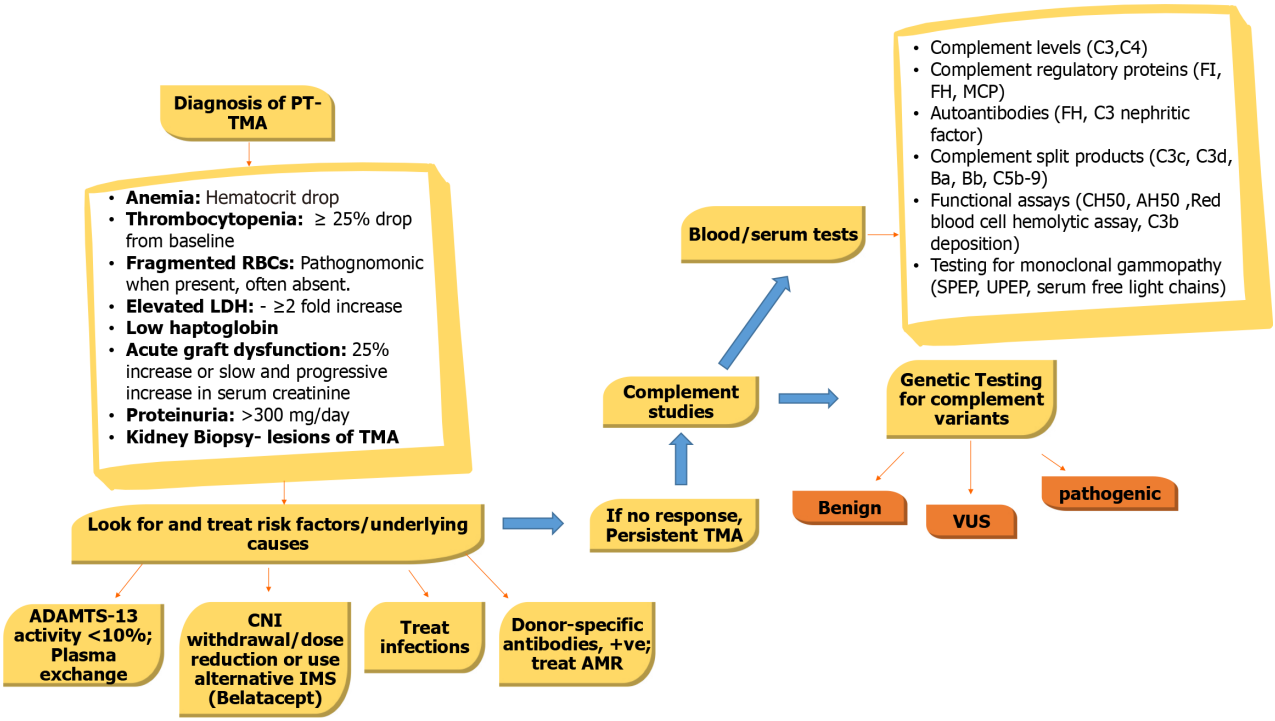

Figure 4 An algorithmic approach to diagnosis, classification and treatment of posttransplant thrombotic microangiopathy. ADAMTS13: A disintegrin-like and metalloprotease with thrombospondin type 1 motif, 13; AMR: Antibody-mediated rejection; IMS: Immunosuppression; LDH: Lactate dehydrogenase; MCP: Membrane cofactor protein; PT-TMA: Posttransplant thrombotic microangiopathy; SPEP: Serum protein electrophoresis; TMA: Thrombotic microangiopathy; UPEP: Urine protein electrophoresis; VUS: Variant of unknown significance.

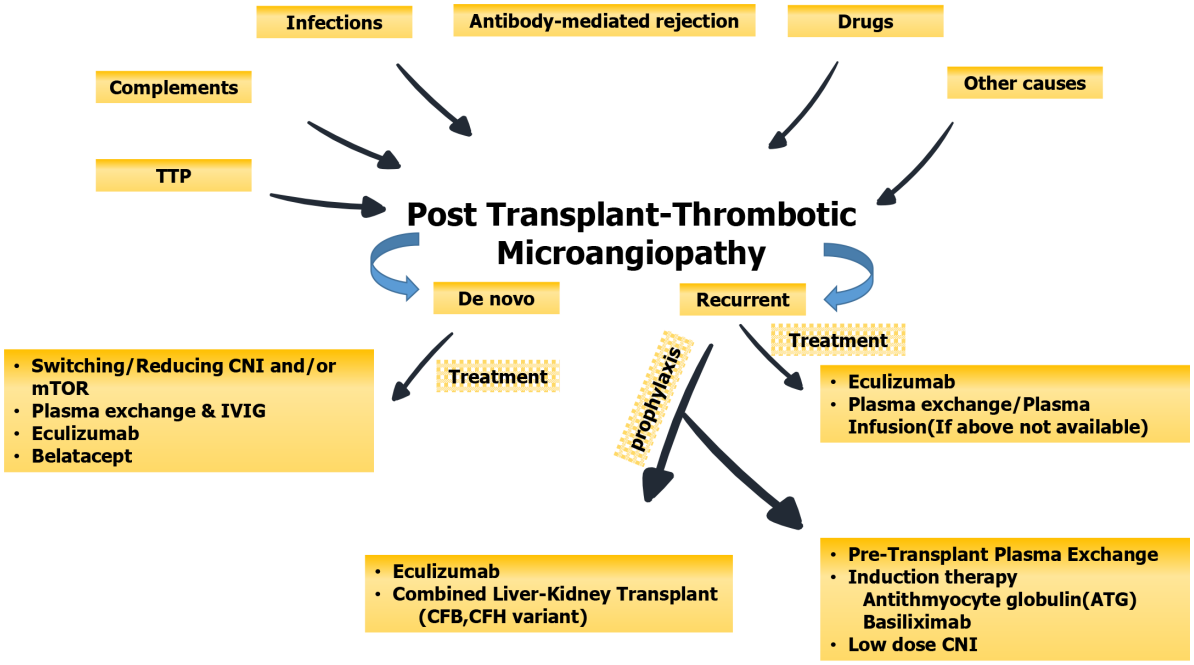

Figure 5 Summary of the main etiologic agents and types of posttransplant thrombotic microangiopathy and their treatment and preventive strategies. CFB: Complement factor B; CFH: Complement factor H; CNI: Calcineurin inhibitor; IVIG: Intravenous immunoglobulin; mTOR: Mammalian target of rapamycin; TTP: Thrombotic thrombocytopenic purpura.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Pediatric and adult liver transplantation in Bahrain: The experiences in a country with no available liver transplant facilities

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Abstract

BACKGROUND

Liver transplantation (LT) is a life-saving procedure for patients with end-stage liver disease and has become the standard and most effective treatment method for these patients. There are many indications for LT that vary between countries and settings. The outcome of LT depends on the available facilities and surgical expertise, as well as the types of liver graft donors available.

AIM

To assess the clinical characteristics of patients from Bahrain who underwent LT overseas, and analyze factors affecting their survival.

METHODS

In this retrospective cohort study, we reviewed the medical records and overseas committee registry information of all pediatric and adult patients who were sent overseas to undergo LT by the Pediatric and Medical Departments of Salmaniya Medical Complex and Bahrain Defence Force Hospital *via* the Overseas Treatment Office, Ministry of Health, Kingdom of Bahrain, between 1997 and 2023. Demographic data, LT indication, donor-recipient relationship, overseas LT center, graft type, post-LT medications, and LT complications, were collected. Outcomes

measured included the overall and 5-year LT survival rate. Fisher's exact, Pearson χ^2, and Mann-Whitney *U* tests were used to compare the pediatric and the adults' group in terms of clinical characteristics, donor-recipient relationship, medication, complications, and outcome. Survival analysis was estimated *via* the Kaplan-Meier's method. Univariate and multivariate analyses were used to detect predictors of survival.

RESULTS

Of the 208 eligible patients, 170 (81.7%) were sent overseas to undergo LT while 38 (18.3%) remained on the waiting list. Of the 170 patients, 167 (80.3%) underwent LT and were included in the study. The majority of the patients were Bahraini (91.0%), and most were males (57.5%). One-hundred-and-twenty (71.8%) were adults and 47 (28.3%) were children. The median age at transplant was 50.0 [interquartile range (IQR): 14.9–58.4] years. The main indication for pediatric LT was biliary atresia (31.9%), while that of adult LT was hepatitis C-related cirrhosis (35.0%). Six (3.6%) patients required re-transplantation. Most patients received a living-related liver graft (82%). Pediatric patients received more living and related grafts than adults (P = 0.038 and P = 0.041, respectively), while adult patients received more cadaveric and unrelated grafts. Most patients required long-term immunosuppressive therapy after LT (94.7%), of which tacrolimus was the most prescribed (84.0%), followed by prednisolone (50.7%), which was prescribed more frequently for pediatric patients (P = 0.001). Most patients developed complications (62.4%) with infectious episodes being the most common (38.9%), followed by biliary stricture (19.5%). Tonsilitis and sepsis (n = 12, 8.1% for each) were the most frequent infections. Pediatric patients experienced higher rates of infection, rejection, and early poor graft function than adult patients (P < 0.001, P = 0.003, and P = 0.025, respectively). The median follow-up time was 6.5 (IQR: 2.6–10.6) years. The overall survival rate was 84.4%, the 5-year survival rate, 86.2%, and the mortality rate, 15.6%. Younger patients had significantly better odds of survival (P = 0.019) and patients who survived had significantly longer follow-up periods (P < 0.001).

CONCLUSION

Patients with end-stage liver disease in Bahrain shared characteristics with those from other countries. Since LT facilities are not available, an overseas LT has offered them great hope.

Key Words: Overseas liver transplantation; End-stage liver disease; Liver transplant facilities; Liver donor; Biliary atresia; Hepatitis C

Core Tip: The clinical characteristics, management, and outcomes of patients from Bahrain with end-stage liver disease who underwent an overseas liver transplantation (LT) have not been studied previously. In this retrospective cohort study, we found that biliary atresia in children and hepatitis C infection in adults were the main indications. This was comparable to literature from neighboring countries and worldwide. Most patients received living-related grafts. The overall survival rate was 84.4% and was significantly better in younger patients. Therefore, in countries where LT facilities are not available, an overseas LT can offer great hope for this group of patients.

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INTRODUCTION

The first successful human liver transplantation (LT) in the world took place in 1967 by Starzl *et al*[1]; after which LT became a standard treatment for patients with acute or chronic hepatic failure of various etiologies.

There are many indications for LT. In children, the most common indication for LT is biliary atresia, while in adults, the hepatitis C virus (HCV) infection is the most common[2]. Yet, LT indications can vary between countries and settings [3,4].

The outcome of LT depends on the available facilities, surgical expertise as well as the types of liver graft donor[3,4]. The improvement in surgical techniques as well as immunosuppression have improved patient survival and their overall quality of life[3,4].

LT is an essential surgical service that should be available in all countries that have the capabilities. In most of the developed countries, LT centers are available and providing LT services to their patients[3,4]. However, some small and developing countries are lacking LT facilities. Patients in these countries either die from the complications of acute and chronic liver failure, or if a suitable donor is found, they are sent overseas to undergo an expensive LT. The Kingdom of

Bahrain is an example for the latter. Since the 90s, the Overseas Treatment Office of the Ministry of Health in Bahrain sends pediatric and adult patients with end-stage liver failure overseas to undergo LT when a suitable liver donor is found. Referral for LT may be emergent, urgent, or anticipatory, as the time of referral varies depending on the patient's clinical circumstances and donor availability.

Many countries have built respectable reputations and experience in LT, including Turkey and India[5,6]. Moreover, some Gulf Cooperation Council countries and neighboring countries, including Saudi Arabia and Iran, have provided this surgical service for the public for many years[9-7]. Other countries have recently started developing their capabilities to provide LT services, such as Kuwait and Oman[10,11]. In Bahrain, an arrangement was made with multiple overseas LT centers from countries including Turkey, India, and Saudi Arabia, whereby they agreed to take care of patients from Bahrain.

Multiple reports about LT experiences have been published from several countries worldwide[3,4,7]. However, there are no reports studying the details of patients from Bahrain who went overseas for LT. The aim of this study was to review the clinical characteristics, indications, medical therapies, complications, and outcomes of pediatric and adult patients from Bahrain requiring LT, and assess the possible predictors of survival following overseas LT.

MATERIALS AND METHODS

Study design, setting, and population

A retrospective review was conducted of medical records of all pediatric and adult patients who were listed for an overseas LT by the Department of Pediatrics and the Department of Medicine at Salmaniya Medical Complex and Bahrain Defense Force Hospital *via* the Overseas Treatment Office, Supreme Committee for Treatment Abroad, Ministry of Health, Manama, Kingdom of Bahrain, between January 1, 1997 and August 1, 2023. All patients who underwent LT were included in the study while those who died before LT, those who remained on the waiting list, and those with missing relevant data, were excluded. Prior to LT, patients with end-stage liver failure were evaluated by their pediatric or adult gastroenterology consultant and the parents/guardians or the patient were asked to provide one or more LT donors.

Donor preparation

According to our protocol, a dedicated LT nurse meets the donors, checks their body mass index, orders the basic laboratory tests and radiological imaging (vascular imaging to assess the hepatic arterial anatomy), and fills the donor check list. Following a satisfactory medical and psychological examination by the caring physicians, the donor's results and the check list are reviewed and approved for donation fitness. The acceptance of a potential donor requires the following: Donors should be 18-55 years of age, have a compatible blood type with the recipient, normal or only slightly altered liver function tests, and hemodynamic stability. Once the donor is ready, a request letter along with a detailed patient medical report are sent to the Head of the Overseas Treatment Office who communicates with multiple overseas LT centers to get their approval. After approval, the patient, the donor, and two direct family members are sent to the overseas LT center by airplane. A senior doctor and a nurse escort sick patients. If more than one center accepts the patient, the choice of center will be based on the patient/guardian's preference and the quoted cost of the LT.

Data collection

Patients' data were collected by reviewing paper-based and electronic medical records along with the overseas committee registry. Important missing data were retrieved by direct contact with the adult patient or the patient's parents/guardians in case of a child or *via* telephone calls. Demographic data including sex, nationality, area of residence, age at LT, weight and height at LT, presence of associated diseases, any previous surgeries, and family history of liver diseases were collected.

The underlying liver disease that led to liver failure requiring LT were reviewed. The LT indications included but were not limited to the following causes: (1) Extrahepatic cholestasis: Biliary atresia and choledochal cyst; (2) Intra-hepatic cholestasis: Primary sclerosing cholangitis, Alagille's syndrome, and progressive familial intrahepatic cholestasis; (3) Infections: Intrauterine viral hepatitis, and viral hepatitis B and C; (4) Metabolic diseases: Wilson's disease, Crigler-Najjar syndrome, inborn error of bile acid metabolism, tyrosinemia, galactosemia, disorders of the urea cycle, organic acidemia, and disorders of carbohydrate metabolism; (5) Acute liver failure; and (6) Other: Autoimmune hepatitis, primary liver tumor, hepatocellular carcinoma (HCC), cystic fibrosis, nonalcoholic steatohepatitis, and alcoholic liver disease.

The donor-recipient relationship, the type of graft (living or cadaveric), the LT center, and the surgical approach were also gathered. Based on the availability of a deceased donor, the LT team might select a cadaveric graft in the absence of a suitable living-related donor or if an early poor graft function developed after the first LT. In the latter case, the patient's name is moved to the top of the LT waiting list.

Post-LT medical therapy was also reviewed. The use of immunosuppressive medications such as tacrolimus, prednisolone, mycophenolic acid, cyclosporine A, azathioprine, and baziliximab, was noted. Use of antibiotics *e.g.*, aminoglycoside, azithromycin, and trimethoprim/sulfamethoxazole; antifungals *e.g.*, fluconazole and amphotericin B; and antivirals *e.g.*, valganciclovir was also recognized. Information regarding dietary supplementations *e.g.*, calcium, vitamin D, magnesium oxide, multivitamins, folic acid, ferrous sulphate, biotin, and carnitine was collected, as well as use of other medications *e.g.*, proton pumps inhibitors, ursodeoxycholic acid, N-acetylcysteine (NAC), and aspirin.

Development of LT-related complications like bleeding, hypovolemia, post-LT dialysis, early poor graft function, need for re-transplantation, hepatic surgical complications, infections, rejection, surgical wound complications, hepatic artery, or portal vein thrombosis, *etc.* were collected.

Follow-up duration was measured from the date of LT until death or the study end date. The patient outcomes were assessed based on the overall survival rate, 5-year survival rate, and mortality rate. The LT cost was presented in United States dollars (USD).

Statistical analysis

Patients' data were analyzed using the Statistical Package for Social Sciences program (SPSS) version 21 (IBM Corp., Armonk, NY, United States). The patients were divided into pediatric and adult groups and compared in terms of clinical characteristics, LT indications, donor-recipient relationship, medications used, complications, and outcome. The frequencies and percentages were calculated for cate-gorical variables while continuous variables were presented as the median and interquartile range (IQR). The Fisher's exact or Pearson's χ^2 tests were used to compare categorical variables. The Mann-Whitney *U* test was used to compare group means. Survival analysis based on age group (pediatric or adult) and graft type (living and cadaveric) was estimated *via* the Kaplan-Meier method. Both univariate and multivariate analyses of binary logistic regression were performed to exhibit the predictors of LT outcome. Confidence interval was set at 95%. *P* values < 0.05 were considered significant.

RESULTS

Until August 2023, a total of 208 pediatric and adult patients were listed for possible LT, and 170 (81.7%) were sent overseas to undergo LT surgery. Of the latter, 167 (80.3%) patients underwent LT, and were included in the study, while 38 (18.3%) were excluded (Figure 1). Most patients were adults (adult: *n* = 120, 71.8%; pediatric: *n* = 47, 28.3%). Clinical characteristics of the included patients are shown in Table 1. Ninety-six (57.5%) patients were males. The majority were Bahraini (*n* = 152, 91.0%) while of the remaining 15 (9.0%), four were from Yemen, two from each of Sudan, Syria, Iran, and India, and one patient from each of Qatar, Egypt, and Pakistan. The median age at transplant was 50.0 (IQR: 14.9–58.4) years. There was no significant difference between males and females in terms of the median age at LT (*P* = 0.793) or age groups (*P* = 0.515).

Most of the patients presented with chronic liver disease (*n* = 164, 98.2%), while three (1.8%) patients had acute liver failure. In patients with chronic liver diseases, 117 (71.3%) were adults while 47 (28.7%) were children, and all patients with acute liver failure were adults (*n* = 3, 2.5%). There was no significant difference between pediatric and adult patients in terms of disease onset (acute or chronic) (*P* = 0.560). Forty-one (24.6%) patients had documented liver cirrhosis prior to the LT with no difference between adult patients (*n* = 33, 19.8%) and children (*n* = 8, 17.0%) (*P* = 0.230).

The main indication for pediatric LT was biliary atresia (*n* = 15, 31.9%), followed by progressive familial intrahepatic cholestasis (*n* = 9, 19.1%), while the main indication for adult LT was HCV-related cirrhosis (*n* = 42, 35.0%), followed by nonalcoholic steatohepatitis (*n* = 19, 15.8%) (Table 2).

Six (3.6%) patients required re-transplantation, of whom four (3.3%) were adults and two were children (4.3%) (*P* = 0.674). Two of the four adults were re-transplanted after three years from the first LT, while one underwent re-transplantation after four years, and another after nine years. One pediatric patient was re-transplanted after one week and the other after one month. The indications for re-transplantation in adults were early cirrhosis due to reinfection with HCV (*n* = 2), recurrence of primary sclerosing cholangitis (*n* = 1), and liver failure due to ductopenic chronic rejection (*n* = 1), while in the two pediatric patients the indication was early allograft dysfunction.

Of 173 LT surgeries, donor type data was available in 150 (86.7%) [144 (96%) single LT surgeries and the six (4%) re-transplantations]. The donor-recipient relationships are shown in Table 3. Most patients received a living-related liver graft (*n* = 123/150, 82%). Pediatric patients received more living grafts than adults [47/48 (97.9%) *vs* 88/102 (86.3%), respectively] while adult patients received more cadaveric [14/102 (13.7%) *vs* 1/48 (2.1%), respectively], (*P* = 0.038). Pediatric patients received more related grafts than adults [44/48 (91.7%) *vs* 79/102 (76.5%), respectively] while adult patients received more unrelated grafts [23/102 (23.5%) *vs* 4/48 (8.3%), respectively], (*P* = 0.041). The median hospitalization duration was 30 (IQR: 14–60) days.

The main countries receiving patients from Bahrain for LT are shown in Figure 2. Most of the patients underwent LT in Turkey (*n* = 70/171, 40.9%), followed by India (*n* = 52/171, 30.4%), then Saudi Arabia (*n* = 22/171, 12.9%). There was no significant difference between the pediatric and adult patients in terms of LT center location (*P* = 0.481).

Of 173 LT surgeries, data about the surgical approach was available for 145 surgeries. The Mercedes incisions was the most common approach (*n* = 100, 69.0%) followed by the L-shaped (*n* = 24, 16.6%) and transverse incisions (*n* = 21, 14.5%). In pediatric patients, most incisions were either transverse or Mercedes (*n* = 20/44, 45.5% each), followed by L-shaped (*n* = 4/44, 9.0%) while in adult patients, most were Mercedes incisions (*n* = 80/101, 79.2%), followed by L-shaped (*n* = 20/101, 19.8%) and transverse (*n* = 1/101, 0.9%). This difference was statistically significant (*P* < 0.001). Of six patients who underwent re-transplantation, five (83.3%) had the same Mercedes incision while one (16.7%) patient had a transverse followed by an L-shaped incisional approach.

Medications used after LT surgery are shown in Table 4. Most patients required long-term immunosuppressive therapy (*n* = 142, 94.7%). Tacrolimus was the most prescribed (*n* = 126, 84.0%) followed by prednisolone (*n* = 76, 50.7%) which was significantly prescribed more for pediatric patients (*P* = 0.001). None of the patients received NAC prior to the LT. Ninety-three (62.4%) patients developed complications during or after LT. Infections were the most common complications (*n* = 58, 38.9%), followed by biliary stricture (*n* = 29, 19.5%) (Table 5). In general, pediatric patients had a higher rate

Table 1 Clinical characteristics of patients underwent liver transplantation

Patient demography	Total, *n* = 167 (100)	Pediatric, *n* = 47 (28.1)	Adult, *n* = 120 (71.8)	*P* value
Sex				0.492[a]
Male	96 (57.5)	25 (53.2)	71 (59.7)	
Female	71 (42.5)	22 (46.8)	49 (40.8)	
Nationality				**< 0.001**[a]
Bahraini	152 (91.0)	36 (76.6)	116 (96.7)	
Non-Bahraini	15 (9.0)	11 (23.4)	4 (3.3)	
Governorate				0.369[b]
Northern	73 (43.7)	21 (44.7)	52 (43.3)	
Capital	35 (20.9)	6 (12.8)	29 (24.2)	
Southern	34 (20.4)	12 (25.5)	22 (18.3)	
Muharraq	25 (15.0)	8 (17.0)	17 (14.2)	
Age at transplant (yr)	50.0 (14.9-58.4)	3.7 (1.0-9.0)	55.2 (48.4-60.5)	**< 0.001**[c]
Weight at transplant (kg), (*n* = 83)	52 (15.0-70.0)	11.0 (7-23)	69 (52-80)	**< 0.001**[c]
Height at transplant (cm), (*n* = 75)	163 (138-169)	82.0 (69-120)	167 (159-172)	**< 0.001**[c]
Presence of associated diseases[1]	130/162 (80.3)	25 (53.2)	105/115 (91.3)	**< 0.001**[a]
Previous liver biopsy	67/145 (46.2)	20/46 (43.5)	47/99 (47.5)	0.722[a]
Previous surgeries	52/145 (35.9)	17/46 (37.0)	35/99 (35.4)	0.855[a]
Kasai procedure	11/145 (7.6)	10/46 (21.7)	1/99 (1.0)	**< 0.001**[a]
Other surgeries	45/145 (31.0)	10/46 (21.7)	35/99 (35.4)	0.124[a]
Family history of liver disease	38/145 (26.2)	17/46 (37)	21/99 (21.2)	0.067[a]
Follow up duration (yr)	6.5 (2.6-10.6)	8.1 (1.3-10.6)	6.1 (3.3-10.3)	0.976[c]
Number of overseas visits	3 (2.0-8.0)	4 (2.0-10.0)	3 (2.0-6.0)	0.299[c]

[a]Fisher's exact test.
[b]Pearson's χ^2 test.
[c]Mann-Whitney *U* test.
[1]Supplementary Table 1. Data are presented as number and percentage or median and interquartile range. Boldface indicates a statistically significant difference with $P < 0.05$.

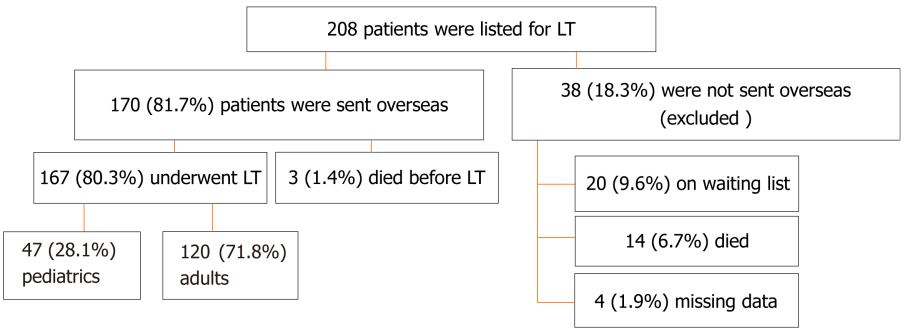

Figure 1 Flow charts of patients who underwent an overseas liver transplantation, Kingdom of Bahrain, 1997-2023. LT: Liver transplantation.

of complications (*n* = 33/46, 71.7%) than adult patients (*n* = 60/103, 58.3%) but this difference was not statistically significant ($P = 0.144$). However, pediatric patients showed a significantly higher rate of infectious episodes, rejection, and early poor graft function than adult patients ($P < 0.001$, $P = 0.003$, and $P = 0.025$, respectively). Pediatric patients had significantly more tonsilitis and acute gastroenteritis than adults ($P < 0.001$ and $P = 0.035$, respectively) who had more septic episodes but with no significant difference ($P = 0.755$). None of the patients developed hypovolemia or bowel perforation.

Table 2 Indications of liver transplantation in pediatrics and adults in Bahrain

Indications of liver transplantation[a]	Total, *n* (%)
Pediatric indications	47 (28.1)
Biliary atresia	15 (31.9)
Progressive familial intrahepatic cholestasis	9 (19.1)
Metabolic diseases[b]	7 (14.9)
Alagille's syndrome	3 (6.4)
Autoimmune hepatitis	3 (6.4)
Primary sclerosing cholangitis	3 (6.4)
Cystic fibrosis liver disease	2 (4.3)
Hepatocellular carcinoma	2 (4.3)
Cytomegalovirus hepatitis	2 (4.3)
Others[c]	8 (17.0)
Adult indications	120 (71.9)
Hepatitis C-related cirrhosis	42 (35.0)
Nonalcoholic steatohepatitis	19 (15.8)
Hepatocellular carcinoma	18 (15.0)
Primary sclerosing cholangitis	17 (14.2)
Hepatitis B virus	15 (12.5)
Cryptogenic cirrhosis	13 (10.8)
Autoimmune hepatitis	9 (7.5)
Alcoholic liver cirrhosis	4 (3.3)
Others[d]	5 (4.2)

[a]Some patients had more than one indication for liver transplantation. Data are presented as number and percentage.
[b]Urea cycle defect (*n* = 3) [argininosuccinic aciduria type 1 (*n* = 2) and ornithine transcarbamylase deficiency (*n* = 1)], propionic academia (*n* = 2), tyrosinemia, and Wilson's disease (*n* = 1 each).
[c]Choledocal cyst type 4 (*n* = 2), hereditary hemorrhagic telangiectasia, neonatal hepatitis, liver metastasis due to Wilms tumor, cryptogenic, Crigler Najjar syndrome type 1, and neonatal hemochromatosis (*n* = 1 each).
[d]Cholangiocarcinoma, hereditary hemorrhagic telangectasia, bilharzial liver disease, biliary atresia, and unspecified viral hepatitis (*n* = 1 each).

Patients were seen at the liver clinic in Bahrain within two weeks of their overseas LT, with close follow-up in the first three months. Afterward, regular follow-up visits continued at every three months in the first year and every six months in the second year. The median follow-up time was 6.5 (IQR: 2.6–10.6) years and the median number of overseas follow-up visits was three (IQR: 2–8). Most patients were sent back to the overseas LT center for follow-up every six months during the first-year post LT.

The results of post-LT survival analysis using the Kaplan-Meier method are shown in Figure 3. The overall survival rate was 84.4% (*n* = 141/167), 5-year survival rate was 86.2%, and the mortality rate was 15.6% (26 patients died; 21 adults and five children). Pediatric patients had better survival outcomes (*n* = 42, 89.4%) compared to adult patients (*n* = 99, 82.5%). However, this difference was not statistically significant (*P* = 0.346). The median survival age was 57.1 (IQR: 26–65.2) years; 11.1 (IQR: 7.4–17.5) years for pediatric patients and 61.6 (IQR: 54.9–67.6) years for adults. Younger patients had better survival outcome (*P* = 0.019) (Table 6). Patients who survived had a significantly longer period of follow up compared to those who died (*P* < 0.001). None of the other variables such as sex, nationality, area of residency, weight and height at LT, presence of associated diseases (Supplementary Table 1), type of graft, donor-recipient relationship, indication for LT, intra- and post-LT complications, and the location of the LT center had a statistically significant impact on survival. On comparing the main three centers regarding the patient outcomes, the overall survival was 100% in Saudi Arabia, 88.2% in India, and 76.1% in Turkey and this difference was statistically significant (*P* = 0.021). On comparing the survival between pediatric and adult patients according to the LT center, after excluding Iran (81.8% survival) as they transplanted adult patients only, the ranking was in favor of Saudi Arabia, followed by India, then Turkey with no difference between pediatric and adult patients (Supplementary Table 2). In univariate and multivariate analyses, none of the selected variables were found to be significant predictors of LT outcome (Table 7).

The LT cost varied between centers. The average cost of LT surgery was 60000 USD per patient, ranging from 42500 USD to 84000 USD. For the donor preparation, the cost ranged from 10000 USD to 20000 USD.

Table 3 Donor-recipient relationship of patients underwent liver transplantation

Donor	Total LT, *n* = 150/173 (86.7)	Pediatrics, *n* = 48/49 (98.0)	Adults, *n* = 102/124 (82.3)	*P* value
Related living donors	123 (82)	44 (91.7)	79 (76.5)	**0.041**[a]
1st degree	65 (52.8)	29 (65.9)	36 (45.6)	**0.020**[b]
2nd degree	19 (15.5)	3 (6.8)	16 (20.3)	
3rd degree	21 (17.1)	10 (22.7)	11 (13.9)	
4th degree	17 (13.8)	2 (4.5)	15 (18.9)	
Unspecified relation	1 (0.8)	0 (0.0)	1 (1.3)	
Unrelated donors	27 (18)	4 (8.3)	23 (22.5)	**0.041**[a]
Living	12 (8.0)	3 (6.3)	9 (8.8)	0.753[a]
Cadaveric	15 (10.0)	1 (2.1)	14 (13.7)	**0.038**[a]

[a]Fisher's exact test.
[b]Pearson's χ^2 test.
Data are presented as number and percentage. Boldface indicates a statistically significant difference with $P < 0.05$. The six patients who underwent re-transplantation surgery had different donor types. LT: Liver transplantation.

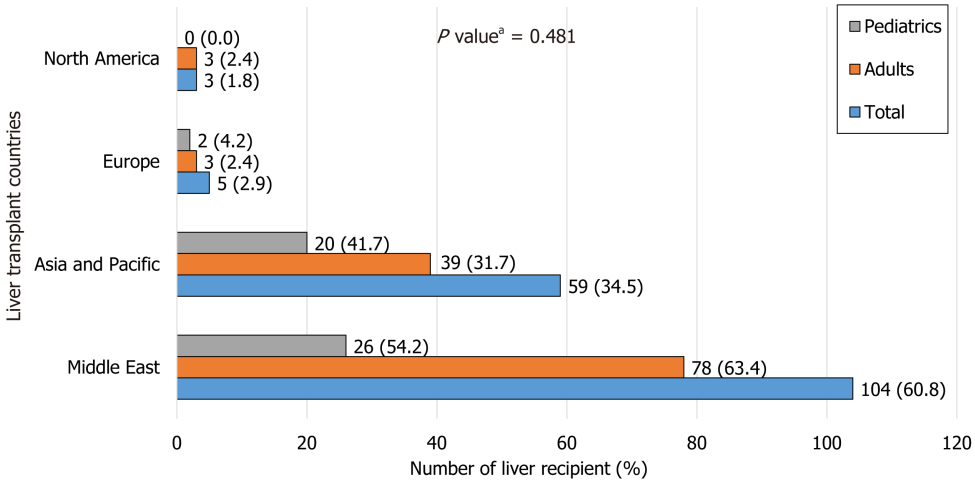

Figure 2 The main countries where Kingdom of Bahrain is sending pediatric and adult patients overseas to underwent liver transplantation. Middle East countries included Turkey (*n* = 70, 40.9%), Saudi Arabia (*n* = 22, 12.9%), Iran (*n* = 11, 6.4%), and Egypt (*n* = 2, 1.2%); Asia and Pacific countries included India (*n* = 52, 30.4%), China (*n* = 3, 1.8%), Singapore (*n* = 3, 1.8%), and Japan (*n* = 1, 0.6%); European countries included Germany (*n* = 2, 1.2%), United Kingdom (*n* = 2, 1.2%), and North America countries included United states (*n* = 3, 1.7%). [a]Pearson's χ^2 test.

DISCUSSION

This study found that most patients who required LT were adults (71.8%). Similarly, several studies reported that a higher number of adult patients underwent LT than pediatric patients[2,7,12,13]. The reason behind this finding might be related to the fact that most centers started LT services in adults first, followed by the pediatric population. Subsequently, the adult LT programs are predominant compared to those for pediatric patients[4]. Moreover, the rapid rise in the prevalence of nonalcoholic steatohepatitis in adults makes them more likely to require LT[4].

In the present study, most of the LT patients were males (57.5%). This is similar to several other studies where a male predominance ranged from 52.8% to 85.0%[2,8-10,12,14-17]. This male predominance might be attributed to the risky behaviors of males, such as alcohol consumption, tobacco smoking, and addiction to intravenous drug use which may increase their risk of becoming infected with HCV[18]. Moreover, HCC is approximately three times more prevalent in males than females, attributed to their hormonal pattern[19]. Furthermore, males have a higher prevalence of obesity and metabolic dysfunction-associated fatty liver disease[4]. In contrary to our study, three studies from Korea and one study from the United States reported that most of the patients were females[20-23].

In the current study, the median age at transplant was 50.0 (IQR: 14.9–58.4) years. However, multiple studies reported that most of the patients underwent LT at a younger age, ranging from 17.6 to 43 years[8,12,15,22]. Moreover, many studies reported LT among pediatric patients alone[5,9,20,23,24]. This can be related to the study population, design, and setting.

Table 4 Medications used after liver transplantation

Medications[a]	Total, *n* = 150/167 (89.8)	Pediatrics, *n* = 44/47 (93.6)	Adults, *n* = 106/120 (88.3)	*P* value[b]
Immunosuppressive medications	142 (94.7)	40 (90.9)	102 (96.2)	0.234
Tacrolimus	126 (84.0)	38 (86.4)	88 (83.0)	0.807
Prednisolone	76 (50.7)	32 (72.7)	44 (41.5)	**0.001**
Mycophenolic acid	73 (48.7)	14 (31.8)	59 (55.7)	**0.012**
Cyclosporine A	13 (8.7)	4 (9.1)	9 (8.5)	1.000
Azathioprine	8 (5.3)	5 (11.4)	3 (2.8)	**0.048**
Everolimus	7 (4.7)	0 (0.0)	7 (6.6)	0.106
Baziliximab	1 (0.7)	1 (2.3)	0 (0.0)	0.293
Dietary supplementations	109 (72.7)	37 (84.1)	72 (67.9)	**0.046**
Calcium	77 (51.3)	18 (40.9)	59 (55.7)	0.110
Vitamin D	63 (42.0)	22 (50.0)	41 (38.7)	0.210
Magnesium	35 (23.3)	20 (45.5)	15 (14.2)	**< 0.001**
Multivitamin	32 (21.3)	27 (61.4)	5 (4.7)	**< 0.001**
Folic acid	30 (20.0)	14 (31.8)	16 (15.1)	**0.026**
Iron	22 (14.7)	11 (25.0)	11 (10.4)	**0.040**
Biotin	4 (2.7)	4 (9.1)	0 (0.0)	**0.007**
Carnitine	2 (1.3)	2 (4.5)	0 (0.0)	0.085
Antiviral (valganciclovir)	23 (15.3)	20 (45.5)	3 (2.8)	**< 0.001**
Antibiotics	20 (13.3)	18 (40.9)	2 (1.9)	**< 0.001**
Aminoglycosides	15 (10.0)	15 (34.1)	0 (0.0)	**< 0.001**
Co-trimoxazole	12 (8.0)	10 (22.7)	2 (1.9)	**< 0.001**
Antifungal medications	9 (6.0)	8 (18.2)	1 (0.9)	**< 0.001**
Fluconazole	7 (4.7)	6 (13.6)	1 (0.9)	**0.003**
Amphotericin B	2 (1.3)	2 (4.5)	0 (0.0)	0.085
Other medications	135 (90.0)	38 (86.4)	97 (91.5)	0.375
Proton pump inhibitors	96 (64.0)	21 (47.7)	75 (70.8)	**0.009**
Urosodeoxycholic acid	91 (60.7)	27 (61.4)	64 (60.4)	1.000
N-acetylcysteine	66/118 (55.9)	10/29 (34.5)	56/89 (62.9)	**0.010**
Aspirin	57 (38.0)	22 (50.0)	35 (33.0)	0.065

[a]Some patients received more than one medication.
[b]Fisher's exact test.
Data are presented as number and percentage. Boldface indicates a statistically significant difference with $P < 0.05$.

In this study, biliary atresia was the main indication for LT in pediatric patients (31.9%). Comparably, many published studies reported that biliary atresia was the most common indication for LT among the pediatric population, but with a higher percentage, ranging from 43% to 66.1%[2,3,13,20,25-27]. The reason behind this finding might be that most children with biliary atresia underwent the Kasai procedure that failed to re-establish effective biliary flow, which causes rapid evolution to secondary biliary cirrhosis[28]. In contrast, a Turkish study reported that Wilson disease was the main indication for LT in pediatric patients (16.3%) rather than biliary atresia (14.5%)[5].

HCV-related cirrhosis was the main LT indication in adult patients in this study (35%). This is comparable to other published studies from Argentina, the United States, and Saudi Arabia, where HCV was the most common LT indication in adult patients and represented 35%, 37.4%, and 38% of their patients, respectively[2,7,17]. However, the European Liver Transplant Registry reported a lower percentage of HCV-related cirrhosis (13%) among their population[3]. This variation might be related to the differences in the HCV infection prevalence between countries. The overall prevalence of HCV in Bahrain was 1.7% (1.0%–1.9%) in 2011 and reduced to 0.99% in 2014[29,30]. This prevalence is considered relatively low when compared to the total global HCV prevalence (2.5%)[31]. The reason behind the high incidence of

Table 5 Complications during or after liver transplantation

Complications[a]	Total, *n* = 93/149 (62.4)	Pediatrics, *n* = 33/46 (71.7)	Adults, *n* = 60/103 (58.3)	*P* value[b]
Infection episodes	58 (38.9)	29 (63.0)	29 (28.2)	**< 0.001**
Tonsillitis	12 (8.1)	10 (21.7)	2 (1.9)	**< 0.001**
Sepsis	12 (8.1)	3 (6.5)	9 (8.7)	0.755
Acute gastroenteritis	11 (7.4)	7 (15.2)	4 (3.9)	**0.035**
Cytomegalovirus	7 (4.7)	7 (15.2)	0 (0.0)	**< 0.001**
Fever of unclear cause	7 (4.7)	1 (2.2)	6 (5.8)	0.437
Pneumonia	7 (4.7)	5 (10.9)	2 (1.9)	**0.029**
Other infections[1]	31 (20.8)	16 (34.8)	15 (14.6)	**0.016**
Biliary stricture	29 (19.5)	5 (10.9)	24 (23.3)	0.115
Rejection	15 (10.1)	10 (21.7)	5 (4.9)	**0.003**
Early poor graft function	9 (6.0)	6 (13.0)	3 (2.9)	**0.025**
Incisional hernia	9 (6.0)	3 (6.5)	6 (5.8)	1.000
Surgical wound complications	8 (5.4)	2 (4.3)	6 (5.8)	1.000
Bleeding	4 (2.7)	2 (4.3)	2 (1.9)	0.587
Hepatic artery complications	2 (1.3)	1 (2.2)	1 (0.9)	0.524
Portal vein thrombosis	2 (1.3)	1 (2.2)	1 (0.9)	0.524
Gastric perforation	2 (1.3)	2 (4.3)	0 (0.0)	0.094
Chylous ascites	2 (1.3)	1 (2.2)	1 (0.9)	0.524
Other complications[2]	9 (6.0)	3 (6.5)	6 (5.6)	1.000

[a]Some patients had more than one complication.
[b]Fisher's exact test.
Data are presented as number and percentage. Boldface indicates a statistically significant difference with $P < 0.05$.
[1]In pediatrics: Herpetic gingivostomatitis (n = 3), herpes zoster infection and septic shock (n = 2 each), bronchitis, chickenpox, conjunctivitis, atopic dermatitis, candidal stomatitis, Epstein-Barr virus infection, hepatitis, lymphadenitis, colitis, cholangitis, and viremia (n = 1 each). In adults: Lymphadenitis (n = 3), septic shock and cellulitis (n = 2 each), bronchitis, candidiasis, peritonitis, pulmonary tuberculosis, hepatic abscess, and herpes zoster infection (n = 1 each).
[2]In pediatrics: Post liver transplant lymphoproliferative disorder, pancreatitis, and diabetes mellitus (n = 1 each). In adults: Post liver transplant lymphoproliferative disorder and myoglobulinemia of unknown significance (n = 2 each), post-transplant dialysis and pleural effusion (n = 1 each).

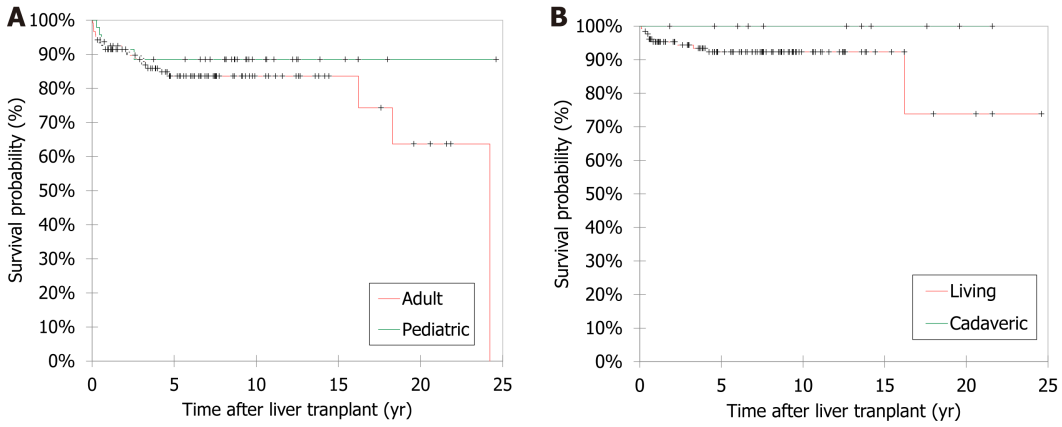

Figure 3 Survival analysis in patients post liver transplantation using the Kaplan-Meier method. A: Survival analysis based on patients' age group; B: Survival analysis based on liver graft type.

Table 6 Analysis of outcome in pediatric and adult liver transplantation

Variable	Survived, *n* = 141 (84.4)	Died, *n* = 26 (15.6)	*P* value
Sex			0.130[a]
Male	85 (60.3)	11 (42.3)	
Female	56 (39.7)	15 (57.7)	
Nationality			0.471[a]
Bahraini	127 (90.1)	25 (96.2)	
Non-Bahraini	14 (9.9)	1 (3.8)	
Area of residency			0.118[b]
Northern	63 (44.7)	10 (38.5)	
Capital	29 (20.6)	6 (23.1)	
Southern	25 (17.7)	9 (34.6)	
Muharraq	24 (17.0)	1 (3.8)	
Age at liver transplant (yr)	48.8 (13.2-58.0)	57.5 (47.9-65.2)	**0.019**[c]
Age group			0.346[a]
Pediatric	42 (29.8)	5 (19.2)	
Adult	99 (70.2)	21 (80.8)	
Weight at transplant (kg), (*n* = 83)	52.0 (20.0-70.0)	8.0 (5.0-46.0)	0.144[c]
Height at transplant (cm), (*n* = 76)	163.0 (149.0-169.0)	138.0 (74.0-149.0)	0.101[c]
Presence of associated diseases	139 (98.6)	23 (88.5)	0.255[a]
Yes	109 (78.4)	21 (91.3)	
No	30 (21.6)	2 (8.7)	
Type of graft (*n* = 150)	137 (97.2)	13 (50.0)	0.364[a]
Living	122 (89.1)	13 (100)	
Cadaveric	15 (10.9)	0 (0.0)	
Donor-recipient relationship (*n* = 150)	137 (97.2)	13 (50.0)	0.704[a]
Related donors	113 (82.5)	10 (76.9)	
Unrelated donors	24 (17.5)	3 (23.1)	
Indications of liver transplantation			
Hepatitis C virus	37 (26.2)	5 (19.2)	0.623[a]
Primary sclerosing cholangitis	18 (12.8)	2 (7.7)	0.743[a]
Nonalcoholic steatohepatitis	15 (10.6)	4 (15.4)	0.503[a]
Hepatic cellular carcinoma	14 (9.9)	6 (23.1)	0.092[a]
Biliary atresia	13 (9.2)	3 (11.5)	0.718[a]
Hepatitis B virus	13 (9.2)	2 (7.7)	1.000[a]
Autoimmune hepatitis	11 (7.8)	1 (3.8)	0.694[a]
Metabolic diseases	7 (5.0)	0 (0.0)	0.597[a]
Intra- or post-LT complications (*n* = 150)	138 (97.9)	11 (42.3)	0.537[a]
Yes	85 (61.6)	8 (72.7)	
No	53 (38.4)	3 (27.7)	
Post-LT N-acetylcysteine use	50/66 (75.8)	46/52 (88.5)	0.098
Liver transplant countries			0.582[b]
Middle East	86 (61.0)	19 (73.1)	

Asia & Pacific	51 (36.2)	8 (30.7)	
Europe	4 (2.8)	0 (0.0)	
North America	3 (2.1)	0 (0.0)	
Follow-up duration (yr)	7.5 (3.9-10.6)	1.5 (0.3-3.2)	**< 0.001**[c]

[a]Fisher's exact test.
[b]Pearson's χ^2 test.
[c]Mann-Whitney *U* test.
Data are presented as number and percentage or median and interquartile range. Boldface indicates a statistically significant difference with $P < 0.05$. LT: Liver transplantation.

Table 7 Univariate and multivariate analysis of the selected predictors of outcome of liver transplantation

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Male sex	0.483 (0.207-1.128)	0.093	0.617 (0.127-2.999)	0.549
Bahraini nationality	0.363 (0.046-2.886)	0.338	2.001 (0.124-32.414)	0.625
Governorate (Northern *vs* others)	0.774 (0.328-1.823)	0.558	0.912 (0.179-4.652)	0.912
Age at LT (yr)	0.980 (0.960-1.001)	0.059	1.047 (0.955-1.148)	0.329
Age group (pediatrics *vs* adults)	0.561 (0.198-1.588)	0.276	0.073 (0.001-8.750)	0.284
Weight at LT (kg)	1.009 (0.990-1.029)	0.362	1.047 (0.965-1.136)	0.268
Height at LT (cm)	1.007 (0.994-1.022)	0.293	1.000 (0.969-1.032)	0.989
Presence of associated diseases	0.346 (0.077-1.560)	0.167	1.131 (0.136-9.415)	0.909
Related versus unrelated donor	1.865 (0.225-15.447)	0.563	1.979 (0.149-26.338)	0.605
Hepatitis C virus	1.494 (0.526-4.249)	0.451	0.275 (0.026-2.914)	0.284
Biliary atresia	0.779 (0.206-2.949)	0.713	1.474 (0.124-17.462)	0.759
Presence of complications	0.601 (0.153-2.368)	0.467	0.222 (0.020-2.458)	0.220
LT countries (Middle East versus others)	2.096 (0.784-5.602)	0.140	2.699 (0.383-19.017)	0.319

CI: Confidence interval; LT: Liver transplant.

HCV in adults is the history of blood transfusion (35%) which is a major risk factor in patients with thalassemia and sickle cell anemia, which are common in Bahrain[32]. Other reasons include intravenous drug use (16.9%), tattoos (4.9%), extramarital sexual contact (3.3%), hemodialysis for chronic renal failure (3.3%), previous surgery (1.6%), and bleeding disorders (1.6%)[32].

The difficulty in finding deceased donors is a serious universal problem especially in Asia for social, religious, and cultural reasons[10,16]. Religious beliefs may either reject or limit organ donation from deceased individuals[10]. Moreover, procurement of organs is considered as an act of body mutilation in some cultures[10]. In the current study, most patients received a living-related liver graft (82%). This figure was comparable to that reported from Korea (84.6%)[20]. However, two studies from Canada and Turkey reported a lower percentage (45% and 32%) of patients received liver allografts from living donors[5,24]. In contrast, most reported patients from Saudi Arabia received a cadaveric graft due to the difficulty in finding living donors who can fulfill all the required criteria for liver donation[12]. Nonetheless, a Korean study reported no significant difference between emergency LT with a deceased donor and elective LT with a living donor[22], which was also observed in our study. In the current study, pediatric patients received more related grafts (91.7%) than adults (76.5%) ($P = 0.041$). Similarly, a study from Japan stated that the parents were the main donors for pediatric cases (95%)[33]. Moreover, a study from Korea found that haplo-matched donors were predominant among pediatric patients, while unrelated donors were predominant among the adult group ($P = 0.006$)[22].

Most patients in the current study received long-term immunosuppressive therapy post-LT ($n = 142$, 94.7%). Tacrolimus-based immunosuppression was the most frequently prescribed (84.0%). Similarly, Kim *et al*[20] and Ng *et al*[26] reported that most LT recipients received tacrolimus as immunosuppressive therapy (94.4% and 68%, respectively). Tacrolimus is the most effective immunosuppressive medication used after LT, as it helps prevent organ rejection and, therefore, increases the survival rate[34,35]. Tacrolimus had become the standard immunosuppressive medication used after LT in adults and pediatric patients[2,26]. Adequate immunosuppression is needed to support graft function but must be balanced against the risks of side effects and potential over immunosuppression[35]. Tacrolimus and cyclo-

sporine have been compared in large multicenter trials that showed similar 1-year patient and graft survival, with a significantly reduced incidence of acute rejection as well as steroid-resistant rejection in children treated with tacrolimus [28]. Moreover, liver support medications such as NAC have shown beneficial effects in both acetaminophen-induced and non-acetaminophen acute liver failure due to its anti-inflammatory and antioxidant effects[36]. NAC also showed a protective effect against LT-induced ischemia–reperfusion injury[37]. In this study, 55.9% of our patients had received NAC post-LT.

In the current study, many patients developed LT-related complications (62.4%). Comparably, two studies reported a post-operative complication rate of 72.4% and 58.4%[9,21]. Infectious episodes were the most common complications in our study (38.9%). Similarly, Busuttil *et al*[2] found that infections were the most common complication after LT but with a lower percentage (13.7%). Early infectious complications tend to be related to surgical manipulations, technical complications of the surgery, catheters, and other foreign bodies[38]. Development of infection after LT may be related to the immunosuppressive drugs used to prevent rejection, which inhibit the activation of T lymphocytes, medullar cell proliferation, and macrophage functions[28]. This can create an optimal environment for development of infections[28]. Infectious complications had become the most common cause of morbidity and mortality after transplantation[28]. In the current study, tonsilitis and sepsis were the most frequent infectious complications (8.1% each) followed by acute gastroenteritis (7.4%). Bacteria are the main infectious agents in the first weeks after LT, with enterococci and gram-negative bacteria in the abdomen being the most frequent[39]. Signs of infection can vary from laboratory abnormalities without clinical manifestations to irreversible fulminant septic shock[39]. Septic shock was found in four (2.4%) patients in this study. Fever of unknown origin was found in seven (4.7%) patients, and the presence of fever may indicate the development of systemic inflammatory response syndrome or a hidden infection which requires blood or urine sampling for culture and further investigations to detect the focus of infection[39]. Moreover, immediate administration of either specific or broad-spectrum antibiotics is important[39]. Upon literature review, most of the studies focused on cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections post-LT. One review article reported that viral infections usually occur during the first month post-LT, with CMV being the most frequent infectious agent[39]. Another two studies reported that EBV infection was the most common type of infection after LT, followed by CMV[20,21]. EBV infection was documented in 0.7% (one of 149 patients) in the current study, while CMV infection was found in 4.7% of the patients. Campbell *et al*[35] stated that treatment of CMV with intravenous ganciclovir is recommended as initial therapy and can dramatically improve the outcomes. All our patients had received valganciclovir as a prophylactic measure initially as per the protocol but only 15.3% of them had documented valganciclovir therapy in their medical records either as treatment for active CMV infection or as a continuation of the prophylactic use.

Biliary stricture was the second most frequent complication (19.5%) in this study and the most common surgical problem. A study from Korea also reported that bile duct complications were the most frequent in the surgical aspect (17.1%)[21]. However, another study reported a lower rate of biliary stricture (11%) in their pediatric patients who underwent LT[5]. The majority of stenoses can be treated with dilation by percutaneous transhepatic cholangiography, which involves inserting a bile drain to shape the anastomosis for approximately six months[39].

Follow-up duration of patients post LT varies between studies based on the time of establishing the LT services, patients' general condition, development of complications, and survival rate. The median follow-up time in this study was 6.5 (IQR, 2.6–10.6) years. Similarly, Busuttil *et al*[2] reported a median follow-up time of 6.7 (range, 0–20) years. However, other studies reported shorter mean/median follow-up period ranging 2–5.9 years[12,17,20,22]. In contrast, Thammana *et al*[23] reported longer median follow-up time (8.3 years).

The overall survival rate was 84.4% in the patients who underwent LT in the present study. Comparably, Al-Sebayel *et al*[12] reported a survival rate of 90% despite a shorter follow-up period of 736 days. In the current study, pediatric patients had better survival rate (89.4%) compared to adult patients (82.5%). Adam *et al*[3] also found that the 5-year survival rate in pediatric patients was significantly better than adult patients, 79% *vs* 70%, respectively ($P < 0.0001$). Many studies reported a higher survival rate among pediatric patients after LT[2,5,20,25]. One study reported that the overall survival rate within five years was 97% after pediatric orthotopic LT[25]. Another study reported that 1-year and 5-year survival rates of their pediatric patients were 87% and 84%, respectively[5]. On the other hand, a study from Korea[22] reported that there were no significant differences between pediatric and adult patients in terms of outcomes when the etiology was the same and the same surgical techniques were used at a single medical center. Nonetheless, LT outcomes are improving, and the number of candidates listed for transplantation has increased dramatically over the years[40].

In this study, a younger age at LT and longer follow-up duration appeared to have a positive effect on survival ($P = 0.019$ and $P < 0.001$, respectively). Similarly, Haseli *et al*[9] found patient age to be one of the effective factors on patient survival in the univariate analysis. However, children below one year old had the lowest survival rate compared to the other age groups[9]. In terms of the effect of LT center on patient survival, we found a significant variation between the main three centers ($P = 0.021$), which may lead us to recommend a LT center from Saudi Arabia for both pediatric and adult patients from Bahrain. This variation in the outcome might be attributed to the proximity of the center to our country which is the case for centers in Saudi Arabia, and the length of LT surgical experience, as for the centers in India and Turkey. In addition, Haseli *et al*[9] found that weight at LT, initial diagnosis, pediatric end-stage liver disease/model for end-stage liver disease score, type of graft, existence of post-LT complications, and year of LT were effective factors on patient survival. Busuttil *et al*[2] found that recipient survival was affected by operative parameters and the etiology of end-stage liver disease. Moreover, recipients of younger organs appeared to exhibit long-term survival advantage over recipients of older donors[2]. In comparison between living and cadaveric grafts recipients, two studies reported no significant difference between the two groups in graft and patient survival after long-term follow-up[12,22], which was similar to the findings of our study. Furthermore, the use of liver support medications such as NAC have shown better overall and post LT survival[36]. However, on analyzing the effect of NAC on the overall survival, we found no significant difference between patients who received it and those who did not ($P = 0.098$). Yet, this finding should be

interpreted with caution especially as the data was available from only two centers, each with different NAC prescription protocols.

Like most of other retrospective studies, this study has limitations, such as missing patient data, including anthropometric data at the time of LT, previous surgical history, the donor-recipient relationship, medications used, and complications. Another limitation is that our study did not focus on those patients who died while on the waiting list for LT. Likewise, patients who could not afford to bring a suitable donor were not listed and were not accounted for in this study. This may underestimate the magnitude of the mortality related to end-stage liver disease in Bahrain. Moreover, the details of the cost of the overseas LT including donor preparation work-up, transportation, surgery, post-LT care, and follow-up visits were not analyzed in this study. Furthermore, compared to bacterial infections, viral infections were less documented in our study as viral serology was limited to CMV and EBV infections. In addition, upon an extensive literature search, we could not find published studies from countries lacking LT facilities to compare with our study. Despite these limitations, the findings of this study are important, being the first study focusing on patients from Bahrain undergoing LT. Our study included both pediatric and adult patients from the main two centers in Bahrain that send patients overseas for LT which makes our sample highly representative of the general population. This study is contributing to the body of literature, highlighting the effectiveness of pediatric and adult LT in improving the survival of patients with acute or chronic liver failure. The findings of this study might benefit centers in which LT facilities are not available. They can direct targeted ranking of patients at risk of liver failure and help implementing new interventional strategies in these high-risk groups.

LT remains a complex and costly procedure and initiating a LT program in any country can present several challenges including: (1) The availability of infrastructure and resources; (2) establishing effective organ procurement mechanisms; (3) recruiting and training healthcare professionals to formulate a multidisciplinary team; (4) navigating various regulatory and legal requirements; (5) careful financial planning; and (6) collaboration and networking with other transplant centers. Nonetheless, these challenges are not insurmountable, and many countries have successfully established LT programs. On January 19, 2020, the Health Minister for Bahrain announced that the preparations are underway to perform the first ever LT[41]. Recently, the Royal Medical Services (RMS) at King Hamad University Hospital initiated the Organ Transplantation Program in co-operation with the Supreme Committee for Treatment Abroad, Bahrain and King Fahad Specialist Hospital, Dammam, Saudi Arabia. On November 15, 2023, the RMS transplant team announced that they have successfully performed the first-of-it-kind living-related LT in Bahrain on a patient in his twenties[42].

CONCLUSION

Acute and chronic liver failure are conditions that carry a high mortality rate in both pediatric and adult populations. This study found that patients with end-stage liver disease in Bahrain shared comparable clinical characteristics to those published in reports from neighboring countries and worldwide. In a developing country like Bahrain, where LT facilities are not available, an overseas LT can offer great hope to patients with an end-stage liver disease, assuming the presence of a suitable donor. Greater attention must be made to identify patients at increased risk of developing liver failure and establishing strategies for early overseas LT is crucial. A multicenter prospective study is required to investigate the cost-effectiveness of the overseas LT in countries lacking this important facility.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) is a life-saving procedure for patients with end-stage liver disease and has become the standard and most effective way of treatment for these patients. There are many indications for LT that vary between countries and settings. The outcome of LT depends on the available facilities and surgical expertise, as well as the types of liver graft donors available.

Research motivation

Multiple reports about LT experiences have been published from several countries worldwide. However, there are no reports studying the details of patients from Bahrain who went overseas for LT. This gap of knowledge motivated us to study the experience of an overseas LT in our country.

Research objectives

To assess the clinical characteristics of patients from Bahrain who underwent LT overseas, and analyze factors affecting their survival.

Research methods

We retrospectively reviewed the medical records and overseas committee registry information of all pediatric and adult patients who were sent overseas to undergo LT by the Pediatric and Medical Departments of Salmaniya Medical Complex and Bahrain Defence Force Hospital *via* the Overseas Treatment Office, Ministry of Health, Kingdom of Bahrain,

between 1997 and 2023. Pediatric and adult patients were compared in terms of demographic data, LT indication, donor-recipient relationship, overseas LT center, graft type, post-LT medications, LT complications, and outcomes. Survival analysis was estimated, and predictors of survival were analyzed.

Research results

Up to August 2023, of the 208 listed patients, 170 (81.7%) were sent overseas to undergo LT. Of the latter, 167 (80.3%) underwent LT and were included. The majority were Bahraini (91.0%), and most were males (57.5%). One-hundred-and-twenty (71.8%) were adults and 47 (28.3%) were children. The median age at transplant was 50.0 [interquartile range (IQR): 14.9–58.4] years. The main indication for pediatric LT was biliary atresia (31.9%), while that of adult LT was hepatitis C-related cirrhosis (35.0%). Six (3.6%) patients required re-transplantation. Most patients received a living-related liver graft (82%). Pediatric patients received more living and related grafts than adults ($P = 0.038$ and $P = 0.041$, respectively), while adult patients received more cadaveric and unrelated grafts. Most patients required long-term immunosuppressive therapy after LT (94.7%), of which tacrolimus was the most prescribed (84.0%), followed by prednisolone (50.7%), which was prescribed more frequently for pediatric patients ($P = 0.001$). Most patients developed complications (62.4%) with infectious episodes being the most common (38.9%), followed by biliary stricture (19.5%). Tonsilitis and sepsis ($n = 12$, 8.1% for each) were the most frequent infections. Pediatric patients experienced higher rates of infection, rejection, and early poor graft function than adult patients ($P < 0.001$, $P = 0.003$, and $P = 0.025$, respectively). The median follow-up time was 6.5 (IQR: 2.6–10.6) years. The overall survival rate was 84.4%, the 5-year survival rate, 86.2%, and the mortality rate, 15.6%. Younger patients had significantly better odds of survival ($P = 0.019$) and patients who survived had significantly longer follow-up periods ($P < 0.001$).

Research conclusions

Acute and chronic liver failure are conditions that carry a high mortality rate in both pediatric and adult populations. This study found that patients with end-stage liver disease in Bahrain shared comparable clinical characteristics to those published in reports from neighboring countries and worldwide. In a developing country like Bahrain, where LT facilities are not available, an overseas LT can offer great hope to patients with an end-stage liver disease, assuming the presence of a suitable donor.

Research perspectives

Greater attention must be made to identify patients at increased risk of developing liver failure and establishing strategies for early overseas LT is crucial. A multicenter prospective study is required to investigate the cost-effectiveness of the overseas LT in countries lacking this important facility.

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FOOTNOTES

Author contributions: Isa HM was the main contributor in study design, literature review, data analysis, drafting manuscript, and oversight for all phases of the project and the final approval of the version to be published; Alkharsi FA was responsible for literature review, data collection, data analysis, drafting and revising manuscript; Khamis JK, Hasan SA, and Naser ZA were responsible for literature review, data collection, drafting and revising manuscript; Mohamed ZN was responsible for data collection, drafting and revising manuscript; Mohamed AM and Altamimi SA were responsible for data collection and revising manuscript; All the authors have read and approved the final manuscript.

Institutional review board statement: The study was conducted in accordance with the principles of Helsinki Declaration of 1975 (revised 2013), and it was ethically approved by the Research and Research Ethics Committee, Salmaniya Medical Complex, Government hospitals, Kingdom of Bahrain (IRB number: 87151122, November 15, 2022).

Informed consent statement: Consent was not needed as the study was retrospective without exposure to the patients' data.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Primary liver transplantation *vs* transplant after Kasai portoenterostomy in children with biliary atresia: A retrospective Brazilian single-center cohort

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Abstract

BACKGROUND

Biliary atresia (BA) is the most common indication for pediatric liver transplantation, although portoenterostomy is usually performed first. However, due to the high failure rate of portoenterostomy, liver transplantation has been advocated as the primary procedure for patients with BA. It is still unclear if a previous portoenterostomy has a negative impact on liver transplantation outcomes.

AIM

To investigate the effect of prior portoenterostomy in infants un-dergoing liver transplantation for BA.

METHODS

This was a retrospective cohort study of 42 pediatric patients with BA who underwent primary liver transplantation from 2013 to 2023 at a single tertiary center in Brazil. Patients with BA were divided into two groups: Those undergoing primary liver transplantation without portoenterostomy and those undergoing liver transplantation with prior portoenterostomy. Continuous variables were compared using the Student's *t*-test or the Kruskal-Wallis test, and

categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate. Multivariable Cox regression analysis was performed to determine risk factors for portal vein thrombosis. Patient and graft survival analyses were conducted with the Kaplan–Meier product-limit estimator, and patient subgroups were compared using the two-sided log-rank test.

RESULTS

Forty-two patients were included in the study (25 [60%] girls), 23 undergoing liver transplantation without prior portoenterostomy, and 19 undergoing liver transplantation with prior portoenterostomy. Patients with prior portoenterostomy were older (12 *vs* 8 months; $P = 0.02$) at the time of liver transplantation and had lower Pediatric End-Stage Liver Disease scores (13.2 *vs* 21.4; $P = 0.01$). The majority of the patients (35/42, 83%) underwent living-donor liver transplantation. The group of patients without prior portoenterostomy appeared to have a higher incidence of portal vein thrombosis (39 *vs* 11%), but this result did not reach statistical significance. Prior portoenterostomy was not a protective factor against portal vein thrombosis in the multivariable analysis after adjusting for age at liver transplantation, graft-to-recipient weight ratio, and use of vascular grafts. Finally, the groups did not significantly differ in terms of post-transplant survival.

CONCLUSION

In our study, prior portoenterostomy did not significantly affect the outcomes of liver transplantation.

Key Words: Hepatic portoenterostomy; Biliary atresia; Liver transplantation; Patient outcome assessment; Portal vein; Survival

Core Tip: Children with biliary atresia comprise the majority of patients undergoing liver transplantation worldwide. Timely portoenterostomy can postpone or even remove the need for liver transplantation. Current data are not conclusive regarding whether performing a portoenterostomy negatively affects the transplantation procedure. In this study, we compared the outcomes of liver transplantation in patients with biliary atresia with or without prior portoenterostomy in a single center. Our results indicate that it does not affect the outcomes.

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INTRODUCTION

Biliary atresia (BA) is a progressive fibroinflammatory process that leads to obstruction of the biliary tree and cirrhosis if left untreated. It affects people worldwide across ethnicities. BA is the most common cause of pediatric liver-related death and the leading indication for pediatric liver transplantation (LT)[1]. Symptoms are usually present in the 1st weeks of life, with a pattern of obstructive jaundice and abnormal liver function test results. Early diagnosis and portoenterostomy (PE) are essential for adequate bile flow, clearance of jaundice, and normalization of the serum bilirubin concentration.

Kasai PE is the standard initial procedure for BA, followed by LT for patients in whom PE fails or the condition progresses to liver cirrhosis. Less than 50% of patients with BA undergoing the Kasai PE procedure gain 10 years of transplant-free survival[2]. However, successful PE can increase the life of the native liver, thus postponing the need for LT[3].

Advances in pediatric LT have improved outcomes. A subset of patients with BA benefit from primary LT without first undergoing PE, especially those who are diagnosed at a later stage[4]. PE before 60 d of life is associated with a higher native liver survival rate than PE after 60 d[5]. However, whether prior PE negatively affects LT outcomes in patients with BA remains unclear[6-11].

Here, we aim to add further data on this issue by comparing the outcomes of children with BA who underwent LT without previous PE with those who underwent PE before LT at our institution.

MATERIALS AND METHODS

Population

This was a retrospective, single-center cohort study of patients who underwent LT for BA at Santa Casa de Porto Alegre, Brazil, a tertiary center. Data were extracted from a database of children who underwent LT at our center from 2013 to

2023. Only recipients of primary LT with a diagnosis of BA were selected and divided into two groups: BA without prior PE (no-PE) and BA with prior PE (PE). Demographic and perioperative variables such as sex, age at LT, Pediatric End-Stage Liver Disease (PELD) score, Model for End Stage Liver Disease score, and weight were included in the analysis. Post-LT outcomes, such as vascular and biliary complications, hospital and intensive care unit (ICU) stay, and acute and chronic rejection, were also evaluated. The hospital's ethics committee approved this study.

Liver transplant procedure and follow-up

ABO blood group compatibility determined recipient and donor selection, and no incompatible blood type transplantations were performed during the study period. The grafts were orthotopically implanted using a "piggyback technique." The graft's portal vein was anastomosed in an end-to-end fashion, either to the recipient's portal vein trunk or by interposition of the vascular grafts. In all cases, the hepatic artery was reconstructed using microvascular techniques with 9-0 or 10-0 nylon sutures (Ethicon, Edinburgh, United Kingdom). Biliary anastomosis was performed by Roux-en-Y bilioenteric reconstruction.

Tacrolimus (FK 506, Prograf) and steroids were used for immunosuppression in the majority of recipients. Basiliximab (Simulect; Novartis, Basel, Switzerland) was used to induce immunosuppression in the majority of the recipients. Doppler ultrasound was routinely performed on the 1st postoperative day, and thereafter, according to the clinician's discretion upon clinical assessment. Vascular or biliary alterations upon Doppler ultrasound were confirmed by contrast imaging, either computed tomography or magnetic resonance imaging.

Statistical analyses

Means ± standard deviations and medians (interquartile ranges) were calculated to summarize continuous variables, and the results were compared using the Student's *t*-test or the Kruskal-Wallis test as non-parametric test when distributional assumptions were in doubt. Categorical variables are expressed as numbers and percentages. Differences between groups were assessed using the χ^2 or Fisher's exact test, as appropriate. Patient and graft survival analyses were conducted with the Kaplan-Meier product-limit estimator, and patient subgroups were compared using the two-sided log-rank test. Multivariable Cox regression analysis was performed, adjusting for risk factors. Variables with $P < 0.1$ during univariate analysis and those deemed clinically significant were included in the model. The study was reviewed by our expert biostatistician, Gabriele Dell'Era, MD.

RESULTS

In summary, prior PE did not significantly affect post-LT outcomes in our study. The apparent trend for more portal vein thrombosis (PVT) events in the no-PE group was probably due to the smaller size and younger age of patients in this group. The post-LT survival did not differ between the groups. Larger multicenter studies are required to confirm our results.

DISCUSSION

LT is primarily indicated for patients with BA in whom initial PE fails or who present with advanced, progressive liver disease at the time of diagnosis. The reported impact of prior PE on LT outcomes differ between studies. A meta-analysis conducted by Wang *et al*[12] did not reveal statistically significant differences in major outcomes, overall survival, and complications between patients undergoing LT with prior PE and those undergoing LT without prior PE. Subsequent studies have not resolved the question[13-16]. Our study did not reveal in survival between the groups.

Kasai PE is performed in an attempt to salvage the native liver and reestablish biliary flow. It yields 10-year LT-free survival in more than 50% of patients with BA. Although the procedure is effective in most cases, adequate biliary drainage is not achieved in approximately 30% of patients, requiring another surgical procedure or LT. Moreover, many long-term complications, such as recurrent cholangitis, portal hypertension, ascites, infections, gastrointestinal bleeding, and failure to thrive, are observed in those who live with their native liver[17,18].

The present study revealed interesting results in the subgroup of patients who underwent LT without prior PE, including a higher incidence of PVT than in the group who had previously undergone PE. In accordance with the literature, patients with BA who underwent LT without prior PE were younger and smaller in this study. This combination, especially in the setting of living donor LT (LDLT), which was the most common in our cohort, usually results in a higher graft-to-recipient weight ratio (GRWR), although this difference was not statistically significant in our study. A higher GRWR can lead to large-for-size syndrome, which, in turn, increases the risk of PVT. Patients with BA who undergo LT usually present with sclerotic portal veins that can be replaced with vascular grafts during LDLT to ensure adequate portal flow. However, these same vascular grafts have been associated with PVT after pediatric LDLT[19]. In our cohort, venous grafts were used in 10 (24%) recipients. Similar to the results reported by Neto *et al*[19], these grafts were used in a seemingly higher proportion of recipients in the group that developed PVT in our study, although this result was not statistically significant. The PVT subgroup analysis was exploratory in this study and requires vali-dation in larger cohorts.

Excellent outcomes have been reported with LDLT for BA[20,21]. LDLT is considered the first-choice graft in various centers for children with BA, particularly in Asian countries. In accordance with other high-volume centers in Brazil[7],

Table 1 Pre and intra-operative variables in biliary atresia recipients who underwent liver transplantation with and without previous portoenterostomy, *n* (%)

Parameter	No-PE, *n* = 23	PE, *n* = 19	*P* value
Sex, female	13 (56.5)	12 (63.2)	0.75
Age at LT, months	8 (6-10)	12 (7-23)	0.02
Weight at LT, kg, median (IQR)	6.5 (5.7-7.4)	7 (6.4-13.5)	0.15
PELD/MELD, mean ± SD	21.4 ± 9.5	13.2 ± 8.9	0.01
Living donor	19 (82.6)	16 (84.2)	1
Deceased donor	4 (17.4)	3 (15.8)	
GRWR, mean ± SD	4.0 ± 1.3	3.7 ± 1.7	0.4
RCBT in mL/kg, mean ± SD	2.4 ± 0.9	1.6 ± 1.3	0.15
CIT in min, median (IQR)	81 (61-140)	105 (73-189)	0.24
WIT in min, mean ± SD	39.4 ± 12.5	33.8 ± 8.4	0.11
Time to extubate in d, median (IQR)	1 (0-2)	0 (0-1)	0.55
ICU stay in d, median (IQR)	12 (6-17)	8 (5-14)	0.4
Hospital stay in d, median (IQR)	21 (16-37)	23 (15-30)	0.25

Data are *n* (%). CIT: Cold ischemia time; GRWR: Graft-to-recipient-weight-ratio; ICU: Intensive care unit; IQR: Interquartile range; LT: Liver transplant; PE: Portoenterostomy; RCBT: Red cell blood transfusion; SD: Standard deviation; WIT: Warm ischemia time.

our cohort was mainly composed of children undergoing LDLT (83%). In contrast to Asian countries, deceased donations are widely accepted in Brazil. However, pediatric and adult donors suitable for graft reduction or splitting are scarce, and LDLT is a safe alternative for enlisted patients[22,23].

The early BA diagnosis and the timing to perform the Kasai procedure also influences the decision to indicate a primary LT for BA. A recent European cohort study in BA patients compared early Kasai, late Kasai and primary LT. As expected, native liver survival in 5-y was under 50% (47% early, 30% late Kasai, and 4% for those without a portoenterostomy). Overall 5-y survival, however, was quite comparable among the same groups (91, 83 and 80%, respectively). This study raises an important question as to whether age alone should limit the indication to perform a Kasai procedure [24].

Lemoine *et al*[25] documented their cohort of 113 patients with BA who underwent LT. Notably, only 14 individuals (12%) in their study underwent primary LT. By contrast, our findings indicate that 54.7% of BA patients in our report underwent primary LT. This observation could suggest the influence of delayed BA diagnosis, preventing the implementation of the Kasai procedure in developing countries, such as Brazil.

Limitations of the study

The retrospective nature of the study and relatively small sample are acknowledged as drawbacks. However, survival and post-transplant complication rates in this study were in accordance with those of large transplant centers[19]. Our study might have been underpowered due to the small size of the cohort. The impact of PE on the outcome of LT remains debatable, and center expertise, especially with LDLT, plays an important role in the outcomes of children with BA. Larger, multicenter studies could help in answering this question.

CONCLUSION

Of the forty-two recipients with BA, twenty-five (60%) were girls. LDLT was the main LT modality (83% of patients). Twenty-three patients were in the no-PE group and nineteen in the PE group. Patients in the no-PE group were significantly younger than those in the PE group (8 *vs* 12 months; $P = 0.02$). Patients in the no-PE group had higher PELD scores than those in the PE group (21.4 ± 9.5 *vs* 13.2 ± 8.9; $P = 0.01$). The groups did not differ in terms of ischemia times, blood transfusion volume, or hospital and ICU stay (Table 1).

The no-PE group had a seemingly higher incidence of PVT (39% *vs* 11%; $P = 0.07$) (Table 2). Although this difference was not statistically significant, we conducted a subgroup analysis on patients with PVT as it might have been clinically significant.

The PVT and no-PVT groups did not reach statistically significant difference in terms of age (8 *vs* 10 months; $P = 0.06$) or mean GRWR (4.38 + -1.20 *vs* 3.75 + -1.56; $P = 0.08$). The use of vascular grafts as substitutes for the portal vein (cryopreserved deceased-donor iliac vein or living-donor inferior mesenteric vein) also did not reach statistically significant difference between these subgroups (45% *vs* 16%; $P = 0.09$) (Table 3).

Table 2 Outcomes in biliary atresia recipients who underwent liver transplantation with and without previous portoenterostomy

Parameter	No-PE, *n* = 23	PE, *n* = 19	*P* value
HAT	2 (8.7)	4 (21.1)	0.38
PVT	9 (39.1)	2 (10.5)	0.07
PVS	4 (17.4)	4 (21.1)	1
Biliary fistula	9 (39.1)	6 (31.6)	0.75
Biliary stricture	5 (21.7)	8 (42.1)	0.19
Reoperation	7 (30.4)	2 (10.5)	0.14
Acute rejection	5 (21.7)	3 (15.8)	0.7
Chronic rejection	2 (8.7)	0	0.49
EBV infection	14 (60.9)	9 (47.4)	0.5
CMV infection	19 (82.6)	13 (68.4)	0.46

Data are *n* (%). CMV: Cytomegalovirus; EBV: Epstein Barr virus; HAT: Hepatic artery thrombosis; LT: Liver transplant; PE: Portoenterostomy; PVS: Portal vein stenosis; PVT: Portal vein thrombosis.

Table 3 Pre and intra-operative variables in biliary atresia recipients who underwent liver transplantation who developed portal vein thrombosis comparing with those who did not develop portal vein thrombosis

Parameter	No-PVT, *n* = 31	PVT, *n* = 11	*P* value
Age at LT, months, median (IQR)	10 (6-15)	8 (5-8)	0.06
Weight at LT, kg, median (IQR)	7 (6.2-10)	6.4 (5.7-7.3)	0.2
PE	17 (54.8)	2 (18.2)	0.07
PELD/MELD, mean ± SD	16.1 ± 10.3	22 ± 8	0.12
Living donor	26 (83.9)	9 (81.8)	1
Deceased donor	5 (16.1)	2 (18.2)	1
Portal vein graft	5 (16.1)	5 (45.5)	0.09
GRWR, mean ± SD	3.75 ± 1.56	4.38 ± 1.2	0.08
RCBT in mL/kg, mean + SD	1.8 ± 1.3	2.5 ± 0.9	0.14
CIT in min, median (IQR)	95 (66-163.5)	88 (68-127)	0.8
WIT in min, mean ± SD	36.1 ± 9.9	39 ± 14.1	0.7

Data are *n* (%). BA: Biliary atresia; CIT: Cold ischemia time; GRWR: Graft-to-recipient-weight-ratio; LT: Liver transplant; PE: Portoenterostomy; PVT: Portal vein thrombosis; RCBT: Red cell blood transfusion; SD: Standard deviation; WIT: Warm ischemia time.

Table 4 Logistic regression analysis for portal vein thrombosis

Parameter	OR	95%CI	*P* value
PE	0.35	0.05-2.27	0.27
GRWR	1.03	0.52-2.02	0.92
Age at LT	0.84	0.63-1.12	0.24
Portal vein graft	2.87	0.54-15.1	0.21

CI: Confidence interval; GRWR: Graft-to-recipient-weight-ratio; LT: Liver transplant; OR: Odds ratio; PE: Portoenterostomy; PVT: Portal vein thrombosis.

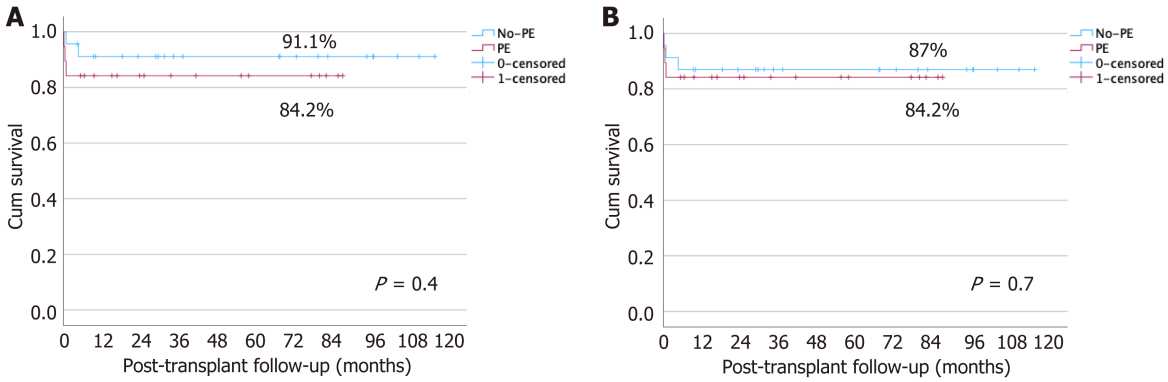

Figure 1 Comparison of patients with and without a portoenterostomy before liver transplantation. A: Post-transplant patient survival; B: Post-transplant graft survival.

Multivariable Cox regression analysis was performed to evaluate factors associated with PVT. After adjusting for age at LT, GRWR, and vascular grafting, the protective effect of PE was attenuated (Table 4). The 1-year patient and graft survival did not differ between the no-PE and PE groups (91% *vs* 84%; $P = 0.4$ and 87% *vs* 84%; $P = 0.7$, respectively) (Figure 1).

ARTICLE HIGHLIGHTS

Research background

Biliary atresia (BA) is the most common indication for pediatric liver transplantation, although portoenterostomy is usually performed first. However, due to the high failure rate of portoenterostomy, liver transplantation has been advocated as the primary procedure for patients with BA. It is still unclear if a previous portoenterostomy has a negative impact on liver transplantation outcomes.

Research motivation

Is there a negative impact of a prior portoenterostomy on liver transplantation outcomes?

Research objectives

To analyze the post-transplant complications and survival in children with BA with or without a previous portoenterostomy.

Research methods

This was a retrospective cohort study of 42 pediatric patients with BA who underwent primary liver transplantation from 2013 to 2023 at a single tertiary center in Brazil. Patients with BA were divided into two groups: Those undergoing primary liver transplantation without portoenterostomy and those undergoing liver transplantation with prior portoenterostomy.

Research results

In our study, prior portoenterostomy did not significantly affect the outcomes of liver transplantation.

Research conclusion

There are no survival differences in patients transplanted with or without a prior portoenterostomy. There is a trend for more portal vein complications in the group of patients transplanted without a portoenterostomy.

Research perspectives

Larger studies, also multicenter studies would be important to better address this issue.

FOOTNOTES

Author contributions: Sanha V, Melere M, and Feier FH designed the research study; Sanha V, Melere M, Farina M, and Feier FH wrote the manuscript; Nader L, Trein C, and Soares C collected and evaluated the data and wrote the manuscript; Ferreira C, Kalil NA, and Lucchese A wrote the manuscript and critically evaluated the final version; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Impact of sex on the outcomes of deceased donor liver transplantation

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Abstract

BACKGROUND

Data examining the impact of sex on liver transplant (LT) outcomes are limited. It is clear that further research into sex-related differences in transplant patients is necessary to identify areas for improvement. Elucidation of these differences may help to identify specific areas of focus to improve on the organ matching process, as well as the peri- and post-operative care of these patients.

AIM

To utilize data from a high-volume Eurotransplant center to compare characteristics of male and female patients undergoing liver transplant and assess association between sex-specific variables with short- and long-term post-transplant outcomes.

METHODS

A retrospective review of the University of Essen's transplant database was performed with collection of baseline patient characteristics, transplant-related data, and short-term outcomes. Comparisons of these data were made with Shapiro-Wilk, Mann-Whitney *U*, χ^2 and Bonferroni tests applied where appropriate. A *P* value of < 0.05 was accepted as statistically significant.

RESULTS

Of the total 779 LT recipients, 261 (33.5%) were female. Female patients suffered higher incidences of acute liver failure and lower incidences of alcohol-related or viremic liver disease ($P = 0.001$). Female patients were more likely to have received an organ from a female donor with a higher donor risk index score, and as a high urgency offer (all $P < 0.05$). Baseline characteristics of male and female recipients were also significantly different. In multivariate hazard regression analysis, recipient lab-Model for End-Stage Liver Disease score and donor cause of death were associated with long-term outcomes in females. Pre-operative diagnosis of hepatocellular carcinoma, age at time of listing, duration of surgery, and units transfused during surgery, were associated with long-term outcomes in males. Severity of complications was associated with long-term outcomes in both groups. Overall survival was similar in both males and females; however, when stratified by age, females < 50 years of age had the best survival.

CONCLUSION

Female and male LT recipients have different baseline and transplant-related characteristics, with sex-specific variables which are associated with long-term outcomes. Female recipients < 50 years of age demonstrated the best long-term outcomes. Pre- and post-transplant practices should be individualized based on sex-specific variables to optimize long-term outcomes.

Key Words: Liver transplant; Outcomes; Survival; Peri- and post-operative care

Core Tip: Within this retrospective review, we evaluated baseline and transplant-related features of both male and female liver transplant recipients. Our results identify several sex-specific variables that affect long-term outcomes of liver transplantation, including statistically significant survival outcomes seen in females under the age of 50.

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INTRODUCTION

Since the advent of liver transplantation in 1967, significant efforts have been made by the transplant community to refine not only the technical aspects of the procedure and medical management of patients, but also the equity of graft allocation. The current system prioritizes patients based on severity of disease, with a major landmark in its evolution being the adoption of the Model for End-stage Liver Disease (MELD; 2002) as a way to predict individual pre-transplant mortality. This was quickly recognized as a potential way to stratify patients according to medical urgency of liver transplant (LT) and has been noted to have a significant impact on waitlist mortality and number of transplants performed per year[1]. However, in recent years it has been suggested that the current graft allocation system may unintentionally bias against female candidates[2,3].

As of 2020, 60.9% of patients on the liver transplant waitlist were male, as were 63.2% of recipients[4]. Females are known to be disadvantaged due to certain MELD components, namely creatinine and sodium[2,5,6]. Females also experience longer waitlist times and higher pre-transplant mortality as well as impaired access to transplant[2,3,5,7,8]. Renal transplant data has shown that female patients are less likely to be referred for transplant and that there may be biases in their evaluation for fitness to undergo surgery, which may contribute to this[9-11]. Females are generally considered to be disadvantaged in all aspects of the process, including referrals for evaluation qualification for transplant and receipt of a matched organ[12]. MELD 3.0, which is pending adoption by UNOS, aims to reduce this discrepancy and has been shown to afford females a significantly higher chance of transplant[13].

Female liver transplant recipients demonstrate comparable, if not better, outcomes than males across a number of etiologies; however, as their access to liver transplant is limited, female patients are getting progressively sicker while waiting and risk being removed from the transplant list while their male counterparts undergo successful transplant[14-18]. It is clear that more research into sex-related differences in transplant patients is needed to identify areas for improvement. Elucidation of these differences may help to identify specific areas of focus to improve on the organ matching process, as well as the peri- and post-operative care of these patients.

The aim of this study was to utilize data from a high-volume Eurotransplant center to compare characteristics of male and female patients undergoing liver transplant and assess association between sex-specific variables with short- and long-term post-transplant outcomes.

MATERIALS AND METHODS

We performed a retrospective review of the University of Essen's transplant database, which included pre-collected and deidentified data. All adult liver transplant recipients between January 2010 and December 2020 were included. We reviewed patient baseline characteristics including sex, age, body mass index (BMI), and underlying etiology of liver disease. These were categorized as acute liver failure (ALF), alcohol-related liver disease (ALD), hepatitis B- or hepatitis C-related liver disease, non-alcoholic steatohepatitis (NASH) and primary sclerosing cholangitis (PSC). We also collected data on additional risk factors including: Smoking history, medical comorbidities such as chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, coronary artery disease, diagnosis of hepatocellular carcinoma (HCC) and MELD score[19]. Waitlist times were reported in the form of days from listing until transplant. Transplant-related characteristics including donor age, high urgency transplant status, donor risk index (DRI), operative time cold and warm ischemic times (WIT), intraoperative transfusion requirements and perioperative death were reviewed[20]. Short-term postoperative outcomes were assessed in terms of both intensive care unit (ICU) stay and overall length of hospital stay in days. The comprehensive complication index (CCI) was used to assess and record the severity of post-operative complications[21]. Finally, overall survival was also recorded to a limit of 140 mo post-operatively.

Statistical analyses

The normality of all data was tested using the Shapiro-Wilk test. Non-normally distributed data were compared using the Mann-Whitney *U* test. χ^2 and Bonferroni tests were applied to draw comparisons between categorical data points. Relationships between numerical variables were assessed using Spearman's rank correlation. Mean and median survival times and overall survival rates were estimated using the Kaplan Meier method. The Log-rank test was then applied to compare overall survival rates between groups. For determination of risk factor-association with overall survival, multivariate cox proportional hazard regression analysis was performed, and hazard ratios (HRs) and 95% confidence intervals (CIs) were assigned to each independent variable. For determination of risk factors for perioperative death, a multivariate binary logistic regression model was built, and odds ratios (ORs) and 95%CIs were generated for each independent variable. For length of hospital stay, ICU stay, waitlist time, CCI, and MELD score at time of transplantation, generalized linear models were applied, and Beta coefficients and 95%CIs were derived for each independent variable. Multi-collinearity was confirmed by calculating variance inflation factor (VIF) scores. Collinear variables (VIF scores > 2) were not included in multivariate analysis to avoid problems with multi-collinearity. Des-criptive statistic parameters were presented as frequency, percentage (%) and mean ± SD, and median and inter-quartile ranges were given. All statistical analyses were performed using SPSS for Windows (version 24.0), and P values < 0.05 were accepted as statistically significant.

Study approval and ethical conduct

This study was deemed exempt by the Institutional Review Board of Essen University. All research referenced in this manuscript was conducted in accordance with institutional processes as well as both the Declarations of Helsinki and Istanbul.

RESULTS

Data from 779 LT recipients was collected. 518 (66.5%) patients were male, and 261 (33.5%) were female. Female patients were on average younger at the time of transplant (median 52 *vs* 54 years, $P = 0.04$) and had lower BMI (median 24.38 *vs* 26.3, $P = 0.001$) compared to males. Lab- and match-MELD scores were similar between females and males. Female patients overall had fewer comorbidities at baseline compared to male LT recipients (Table 1). Female recipients had higher incidences of acute liver failure and lower incidences of alcohol-related or viremic liver disease ($P = 0.001$). Female patients were more likely to have received an organ from a female donor, with a higher donor risk index score (1.71 *vs* 1.84), and as a high urgency offer (all $P < 0.05$). Median wait time was similar between 2 groups (Tables 1 and 2).

Regarding intra- and post-operative data, females had shorter WIT and shorter duration surgery; however, length of ICU or total stay, complication indexes and perioperative death rates were similar between males and females (Tables 1 and 2). On multivariate hazard regression analysis, higher lab-MELD score of the recipient and donor cause of death were associated with differences in long-term outcomes for female patients. A pre-operative diagnosis of HCC, increased age at time of listing, high urgency status of transplant, longer duration of surgery, and a higher number of units transfused during surgery were all associated with differences in long-term outcomes for males. Complication index grade was associated with differences in long-term outcomes for both groups (Table 3). One-, 3- and 5-year patient survival rates were similar between females and males [80.2%, 74.4% and 70% for females and 76.1%, 70.5% and 65.3% for males, ($P = 0.12$)] (Figure 1). When we performed sub-group analyses according to sex and age-related categorization, female patients younger than 50 had the best overall survival ($P = 0.003$) (Figure 2).

DISCUSSION

Overall, characteristics of our study population were similar to known demographics of transplant patients in Germany. Proportions of male and female transplant recipients (66.5% *vs* 33.5%) were consistent with what is generally seen

Table 1 Descriptive variables stratified by recipient sex, *n* (%)

	Male	Female	*P* value
	518 (66.5)	261 (33.5)	
Donor sex			0.001
Male	326 (62.9)	59 (22.6)	
Female	192 (37.1)	202 (77.4)	
Etiology			0.001
Acute liver failure	18 (3.5)	34 (13.0)	
Alcohol	149 (28.8)	46 (17.6)	
HBV/HCV	160 (30.9)	53 (20.3)	
HCC	152 (29.3)	45 (17.2)	0.001
NASH	58 (11.2)	20 (7.7)	
PSC	53 (10.2)	12 (4.6)	
Others[1]	80 (15.4)	96 (36.8)	
Milan criteria			
HCC within Milan	132 (86.8)	39 (86.7)	0.9756
HCC beyond Milan	20 (13.2)	6 (13.3)	
Comorbidities	364 (70.3)	162 (62.1)	0.021
Coronary artery disease	83 (16.0)	25 (9.6)	0.014
Diabetes	140 (27.0)	41 (15.7)	0.001
Peripheral vascular disease	5 (1.0)	2 (0.8)	0.781
COPD	75 (14.5)	33 (12.6)	0.484
Smoker	131 (25.3)	49 (18.8)	0.042
High urgency transplant	25 (4.8)	41 (15.7)	0.001
Intraoperative blood transfusion	217 (41.9)	115 (44.1)	0.563
Perioperative death	89 (17.2)	39 (14.9)	0.426

[1]Hepatopulmonary syndrome, hyperoxaluria, polycystic liver disease, hepatoblastoma, Budd Chiari, neuroendocrine tumor, Wilson's disease, primary biliary cirrhosis, autoimmune hepatitis, cryptogenic. COPD: Chronic obstructive pulmonary disease; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; PSC: Primary sclerosing cholangitis.

throughout the region[22]. Differences in the etiology of chronic liver disease according to sex in our study were also consistent with known predominance of ALD, viral hepatitis, NASH and PSC in males[23,24]. In our study, we report that significantly larger number of transplants for ALF were performed in female patients, which is in accordance with existing literature[25,26]. Females are known to be more susceptible to certain causes of ALF than males, including acetaminophen overdose and other drug toxicities, as well as acute-on-chronic liver failure associated with alcohol use [27-29]. It is possible that our findings represent selection bias associated with use of single-institution data; however, we suspect that our findings may demonstrate increasing incidences of alcohol-related liver disease, particularly in females [30]. This is a trend which has especially been seen in relation to the recent pandemic[31]. Unfortunately, we did not have data for the underlying etiology of ALF in our cohort. As a result, further information would be required to make solid conclusions.

The baseline characteristics of our study cohort are similar to those previously reported[15]. In our study, females were on average younger than males both at time of listing and at time of transplant. They also had significantly lower BMIs. Interestingly, although previous studies have suggested that higher BMIs in male recipients may contribute to worse survival in these patients, the impact of BMI on overall survival was not found to be significant in our multivariate analysis[32]. Male patients had significantly higher overall rates of comorbidity consistent with previous data[33]. However, we found that the comorbidity index was associated with long-term survival in both male and female transplant patients, as expected. Consideration of pre-transplant comorbidities during listing and allocation is crucial, and pre-operative risk should be managed, where possible, to maximize chances of the best possible outcome. Currently there is no specific risk calculator for transplant surgery, and the only surgical risk calculator which considers sex is the ACS Surgical risk calculator[34].

Table 2 Numerical variables stratified by recipient sex

	Male	Female	*P* value
	Median [25%-75%]	Median [25%-75%]	
Age at time of listing	54 [47-59]	51 [43-59]	0.019
BMI (kg/m²)	26.3 [23.46-29.41]	24.38 [21.72-28.7]	0.001
Comorbidity Index	33.5 [0-63.8]	33.5 [0-58.1]	0.84
Lab MELD	15 [11-21]	16 [12-24]	0.052
Wait list time (d)	78 [23-206]	61 [7-220]	0.094
Match MELD	25 [22-28]	25 [22-28]	0.598
Age at time of transplant	54 [48-60]	52 [44-59]	0.039
Donor age	58 [49-70]	61 [46-73]	0.781
DRI	1.706 [1.432-1.962]	1.837 [1.528-2.078]	0.001
CIT (min)	450 [370-530]	445 [382-521]	0.741
WIT (min)	30 [26-36]	28 [25-32]	0.001
Duration of surgery (min)	249 [209-302]	229 [190-286]	0.001
ICU stay (d)	5 [3-10]	5 [3-9]	0.571
Hospital stay (d)	19 [15-26]	19 [15-29]	0.317

BMI: Body mass index; CIT: Cold ischemic time; DRI: Donor risk index; ICU: Intensive care unit; MELD: Model for End-stage Liver Disease; WIT: Warm ischemic time.

Table 3 Multivariate analysis of variables associated with overall survival according to recipient sex

	Male		Female	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
HCC	1.6 (1.11-2.3)	0.011	1.71 (0.81-3.64)	0.161
Age at time of listing	1.02 (1-1.04)	0.014	1.02 (0.99-1.05)	0.116
Comorbidity Index	1.04 (1.03-1.04)	0.001	1.04 (1.03-1.05)	0.001
Lab MELD	1.01 (0.99-1.04)	0.302	1.05 (1.02-1.08)	0.004
High urgency	2.87 (1.48-5.57)	0.002	0.84 (0.39-1.8)	0.656
Trauma (cause of death, donor)	1.32 (0.71-2.45)	0.384	3.05 (1.05-8.85)	0.04
Duration of surgery (min)	1 (1-1)	0.013	1 (1-1.01)	0.2
Units transfused	1.04 (1-1.09)	0.043	1.04 (0.95-1.13)	0.439

HCC: Hepatocellular carcinoma; MELD: Model for End-stage Liver Disease.

Despite recent concerns that MELD may significantly disadvantage females in terms of waitlist times and pre-transplant mortality, in our study, we saw that waiting times were similar between males and females, with a trend towards shorter waitlist times for females[2,3]. Though the female patients in our cohort did not experience longer waitlist times, the fact that this pattern has been demonstrated in a number of other recent studies is concerning. MELD is thought to underestimate the severity of liver disease and its complications in females, in part due to sex-related differences in muscle mass (female patients typically demonstrate a lower glomerular filtration rate per given creatinine level)[3,5]. In our report, female patients had higher lab-MELD scores, although this was not statistically significant. We believe this finding is still important to mention because it requires a more severe disease process to reach the same or higher MELD scores in female patients as male patients. This may be reflected in the increased number of females receiving high-urgency transplants as compared to males in our study, which is almost double that of similar database studies[35]. High-urgency transplants are considered to have comparable outcomes to those performed in patients who have demonstrated more stable disease[36]. However, this does not eliminate the fact that female patients are placed at higher risk of pre-transplant mortality by the current system[2]. Furthermore, in this study, lab-MELD was found to

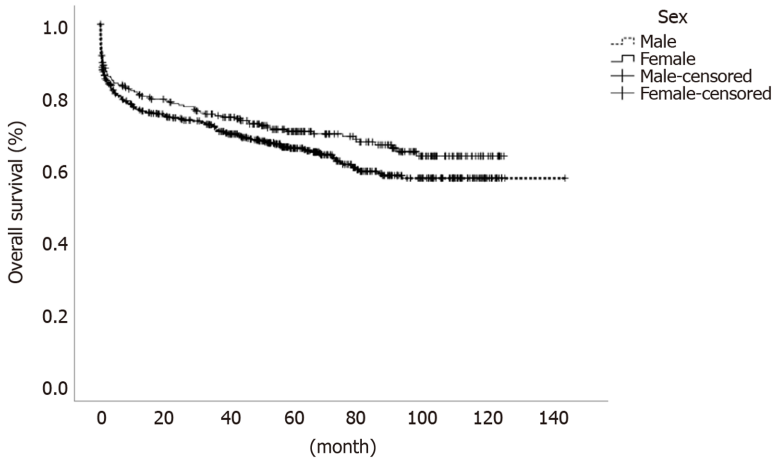

Figure 1 Overall survival of transplant recipients according to sex.

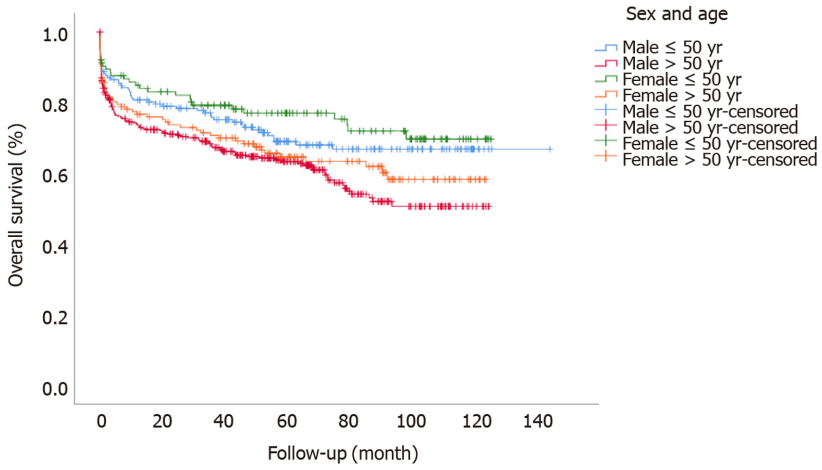

Figure 2 Overall survival of transplant recipients stratified by age and sex.

differentially impact the overall survival of female patients after liver transplant. Taken together, sex-specific adjustments to scoring as well as allocation systems are necessary.

Male patients were also statistically more likely to have HCC, which correlates with larger database studies[5]. This translates into sex bias in transplant prioritization, as exception points are awarded to patients with HCC after 6 mo on the waitlist. In our study, transplant in the setting of known HCC in male patients was found to be associated with poorer outcomes, but not for female patients. This may partially reflect the fact that male patients with HCC demonstrate poorer long-term survival independent of transplantation[37]. However, it has also been shown through a retrospective analysis of the UNOS database that females have a 25% lower recurrence rate after transplant. Lastly, some literature suggested donor/recipient sex match may also play a role in HCC recurrence after LT[38,39]. Unfortunately we had limited data on tumor-specific variables in our study; for instance, we did not have tumor grade, AFP levels, or downstage data. However, we report similar numbers of within and beyond Milan criteria HCC in both groups. We were also not able to analyze interactions between donor sex and HCC-specific outcomes due to the small sample size. Regardless, we believe our findings merit attention that sex-specific factors may impact LT outcomes, specifically for HCC. Further analysis is necessary regarding the impact of sex on LT after HCC.

Whether there are sex differences in post-transplant survival remains controversial based on underlying disease and/or age classification or MELD scores[35,40,41]. In this study, we report similar overall survival rates between male and female patients; however, we found significantly better survival for females younger than 50 years of age as compared to all other groups[42]. Given the retrospective nature of our study, limited sample size, and existing donor differences in both groups, we agree that prospective randomized studies with more granular data would be necessary to determine the impact of sex on LT outcomes.

It is well known that females experience more problems with donor-recipient matching than males. Part of this issue is due to concerns for large-for-size transplants in smaller female patients. Aside from just technical difficulty associated with transplanting a size-mismatched organ, it is thought that large discrepancies in this area can lead to increased risk of graft failure[43]. Donor mismatch is often cited as one of the top causes of offer denial[44]. Our study showed significantly higher DRI scores for female patients, which is likely due to limitations in which grafts are deemed appropriate for them, with the number one reason being size restrictions. Despite being transplanted with higher DRI scores, female

recipients had similar long-term outcomes compared to males; in fact, younger females had even better outcomes, similar to other reports[35,45]. Large-for-size liver transplantation is associated with elevated morbidity and mortality and represents a major limiting factor in organ matching to female transplant candidates[46]. On the other hand, the higher DRI scores seen in female recipients may also represent an institutional pattern in accepting earlier offers despite higher risk donors. This could explain why females in our study did not have longer waitlist times. It is well known that higher DRI scores are also associated with worse outcomes; however, this was not seen in our study[47,48]. This could very well be due to small sample size or the retrospective nature and inherent non-randomization of our study. Regardless, based on the results of our study, when balancing the risks of a less ideal graft in female patients, it may be important to prioritize other factors over perceived graft quality. Females have specifically been noted to have an approximately 25% increase in likelihood of pre-transplant mortality with one or more offer refusals[44]. Further assessment of the comparative impact of accepting earlier offers in female patients *vs* waiting for a better perceived match should also be performed.

Limitations of our study are largely related to the fact that this is a single-institution, retrospective study, and therefore assessment of baseline characteristics of patients is not generalizable to the wider population. However, variables identified in multivariate analysis, which are associated with worse outcomes according to sex, remain translatable to other population groups. We also have limited baseline data on our HCC patients, making it difficult to ascertain the exact impact of cancer on outcomes. Our study included a small transplant population and was underpowered to detect smaller differences that may still be clinically significant. Lastly, due to a lack of anatomical data, we are not able to make conclusions based on WIT or duration of surgery.

CONCLUSION

Overall, female and male transplant candidates demonstrate different characteristics, which have a complex interplay to influence access to liver transplant as well as transplant outcomes. Despite global improvements in the allocation and technique of liver transplantation over recent years, female patients are still significantly disadvantaged in terms of access to transplant, underscored disease severity, longer wait times, more difficulty to have proper or timely organ offers and longer hospital stay in the post-operative period as described in the literature. Herein, we demonstrate sex-based differences in disease etiology, comorbidity profile and donor characteristics. In addition, we demonstrated specific factors with differential impact on the survival of each sex after liver transplant. These should be considered as tools to improve the system, and adjustments to the allocation process could reduce the disparities between males and females. Lastly, perioperative care of females with chronic liver disease may differ from males. Thus, management and follow up of liver transplant patients should be individualized, with consideration of sex-specific variables. This may further optimize long-term outcomes, and further prospective studies are warranted.

ARTICLE HIGHLIGHTS

Research background

Female liver transplant recipients generally demonstrate comparable, if not better, outcomes than males across a number of etiologies. However, due to lack of access, female patients are getting progressively sicker while waiting and risk being removed from the transplant list while their male counterparts undergo successful transplant (14-18). Further research into sex-based differences in transplant patients is paramount in identifying areas of improvement. Defining these differences may lead to focused improvement on the organ-matching process and more specific management of peri- and post-operative care of male and female recipients.

Research motivation

Female and male transplant candidates demonstrate different characteristics, which have a complex interplay to influence access to liver transplant as well as transplant outcomes. Herein, we demonstrate sex-based differences in disease etiology, comorbidity profile and donor characteristics. In addition, we demonstrated specific factors with differential impact on the survival of each sex after liver transplant. These should be considered as tools to improve the system, and adjustments to the allocation process could reduce the disparities between males and females.

Research objectives

The aim of this study was to utilize data from a high-volume Eurotransplant center to compare characteristics of male and female patients undergoing liver transplant and assess association between sex-specific variables with short- and long-term post-transplant outcomes.

Research methods

A retrospective review of the University of Essen's transplant database was performed with collection of baseline patient characteristics, transplant-related data, and short-term outcomes. Comparisons of these data were made with Shapiro-Wilk, Mann-Whitney *U*, χ^2 and Bonferroni tests applied where appropriate. A P value of < 0.05 was accepted as statistically significant.

Research results

There were significant differences in baseline characteristics between male and female recipients. Female patients suffered more from acute liver failure and less from alcohol-related or viremic liver disease ($P = 0.001$). Female patients were more likely to receive an organ from a female donor, with a higher donor risk index score, and as a high urgency offer (all $P < 0.05$). On multivariate hazard regression analysis, patient lab-MELD score and donor cause of death were associated with differences in long-term outcomes for females. A pre-operative diagnosis of hepatocellular carcinoma, increased age at time of listing, high urgency status of transplant, duration of surgery, and higher number of units transfused during surgery were all associated with differences in long-term outcomes for males.

Research conclusions

Through this retrospective review, we have demonstrated sex-based differences in disease etiology, comorbidity profile and donor characteristics as well as specific factors with differential impact on the survival of each sex after liver transplant. These should be considered as tools to improve the system, and adjustments to the allocation process could reduce the disparities between males and females. Lastly, perioperative care of females with chronic liver disease may differ from males. Thus, management and follow up of liver transplant patients should be individualized, with consideration of sex-specific variables.

Research perspectives

Further research should aim to focus to optimize long-term outcomes between male and female liver transplant recipients.

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FOOTNOTES

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Association of donor hepatectomy time with liver transplantation outcomes: A multicenter retrospective study

Geisiane Custodio, Andrew Maykon Massutti, Aline Caramori, Taynara Gonçalves Pereira, Augusto Dalazen, Gabriela Scheidt, Ludmilla Thomazini, Cristiane Bauermann Leitão, Tatiana Helena Rech

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Abstract

BACKGROUND

Prolonged donor hepatectomy time may be implicated in early and late complications of liver transplantation.

AIM

To evaluate the impact of donor hepatectomy time on outcomes of liver transplant recipients, mainly early allograft dysfunction.

METHODS

This multicenter retrospective study included brain-dead donors and adult liver graft recipients. Donor-recipient matching was obtained through a crossover list. Clinical and laboratory data were recorded for both donors and recipients. Donor hepatectomy, cold ischemia, and warm ischemia times were recorded. Primary

outcome was early allograft dysfunction. Secondary outcomes included need for retransplantation, length of intensive care unit and hospital stay, and patient and graft survival at 12 months.

RESULTS

From January 2019 to December 2021, a total of 243 patients underwent a liver transplant from a brain-dead donor. Of these, 57 (25%) developed early allograft dysfunction. The median donor hepatectomy time was 29 (23–40) min. Patients with early allograft dysfunction had a median hepatectomy time of 25 (22–38) min, whereas those without it had a median time of 30 (24–40) min (P = 0.126).

CONCLUSION

Donor hepatectomy time was not associated with early allograft dysfunction, graft survival, or patient survival following liver transplantation.

Key Words: Brain death; Hepatectomy; Liver transplantation; Early allograft dysfunction; Graft survival

Core Tip: This study aims to evaluate the impact of donor hepatectomy time on outcomes of liver transplant recipients. This is a multicenter retrospective study that included brain-dead donors and adult liver graft recipients. A total of 243 patients underwent liver transplantation form brain-dead donors. The median duration of donor hepatectomy was 29 (23–40) min. Patients with early allograft dysfunction had a median hepatectomy time of 25 (22-38) min, while those without had a median time of 30 (24–40) min (P = 0.126). Duration of donor hepatectomy was not associated with early allograft dysfunction, graft survival, or patient survival following liver transplantation.

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INTRODUCTION

The main source of livers for transplantation is brain-dead donors[1]. During liver harvesting and storage processes, the organs are exposed to numerous cellular insults[2]. As a result, transplantation becomes a race against time. In order to mitigate the negative effects of ischemia, efforts have focused on organ preservation by reducing cold ischemia time and implementing different organ perfusion techniques[3,4].

However, a novel concept has emerged regarding the development of early allograft dysfunction: Donor hepatectomy time, also referred to as donor warm ischemia time[5,6]. Hepatectomy time is defined as the interval from aortic cross-clamping to placing the liver at low temperatures. Despite the brief duration of donor warm ischemia (minutes) in contrast to the long duration of cold ischemia (hours), in the warm phase the organs are maintained at relatively high temperatures and at high metabolic demands[5,7].

Despite the significant role of donor hepatectomy time in graft outcomes, it has received insufficient attention[6,8]. Recently, Gilbo *et al*[5] demonstrated an association between longer hepatectomy times and early surgical complications [5]. They showed that a 10-min increase in donor hepatectomy time produced a similar effect of 1-h increase in cold ischemia time. Similarly, Adelmann *et al*[8] demonstrated that hepatectomy time was independently associated with early allograft dysfunction[8].

To address the shortage of organs and improve liver transplantation outcomes, it is crucial to continuously explore opportunities to enhance donor, graft, and recipient care. One such method involves reducing the duration of ischemic phases, which has been demonstrated to be of great importance. Therefore, our study aimed to evaluate the impact of donor hepatectomy time on outcomes of liver transplant recipients.

MATERIALS AND METHODS

This is a multicenter retrospective study. The study was approved by the reference Ethics Committee at the Universidade Federal Rio Grande do Sul (PROPESQ UFRGS, project No. 5.526.176), Brazil. The study adheres to the guidelines set forth by the Helsinki Declaration, as well as to local standards and Brazilian legislation[9]. The Ethics Committee did not require informed consent due to the retrospective design and the anonymization of donors and recipients prior to analysis.

Study population

This study included brain-dead donors from 19 regional centers in the state of Santa Catarina, Brazil, and adult liver transplant recipients from brain-dead donors at Hospital Santa Isabel, a general hospital in the city of Blumenau, state of Santa Catarina, Brazil, from January 2019 to December 2021. In order to be eligible, patients had to be over 18 years of age and have received a liver transplant in the Liver Transplantation Center at Hospital Santa Isabel. Exclusion criteria were retransplantation, grafts from living-related donors, split liver grafts, and intraoperative death.

Donor-recipient matching was obtained through a crossover list provided by the regional organ distribution center of the state of Santa Catarina. Clinical and laboratory data were recorded for both donors and recipients, and the donor risk index (DRI) was calculated to assess organ quality[10]. The DRI considers 8 donor characteristics, namely age, height, ethnicity, cause of death, donation after circulatory death, donor hospital location, split liver graft, and cold ischemia time. The DRI assesses the risk of graft loss in comparison to an ideal donor[10,11]. A DRI score ≥ 1.4 predicts graft failure [11]. Model for end-stage liver disease (MELD) scores were calculated for recipients. The MELD score is a prospectively developed and validated scoring system for assessing the severity of chronic liver disease that uses patients' laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict 3-month survival[12].

Donor hepatectomy time as well as cold and warm ischemia times were analyzed. Donor hepatectomy time, also known as donor warm ischemia time, is the interval from the start of aortic cold flush in the donor to the completion of donor hepatectomy, during which the liver is transferred to ice-cold preservation solution on the back table[7]. Cold ischemia time refers to the interval from the start of cold flush (both aortic and portal) in the donor to the moment the liver is removed from ice storage and placed in the recipient abdomen for implantation[7]. Warm ischemia time in the recipient is the interval between the removal of the liver from the cold solution and organ reperfusion in the recipient[5, 7].

The criteria for early allograft dysfunction were defined as the presence of any of the following postoperative laboratory findings: (1) Serum bilirubin > 10 mg/dL on day 7 after transplant; (2) INR > 1.6 on day 7 after transplant; and (3) Alanine or aspartate aminotransferase levels > 2000 IU/L within the first 7 d after transplant[13]. Graft survival was defined as the time from liver transplantation to either retransplantation or death from any cause[14]. Patient survival was defined as the time from transplantation to death from any cause. Graft and patient survival were evaluated at 12 mo. Patients were followed up until their last visit to the Liver Transplantation Center at Hospital Santa Isabel.

Primary outcome was early allograft dysfunction. Secondary outcomes included need for retransplantation, length of intensive care unit (ICU) and hospital stay, and patient and graft survival at 12 months.

Organ procurement and transplantation

Livers were procured regionally at 19 centers in the state of Santa Catarina, Brazil. The procedure involved isolating the liver and extracting it after dissection of the biliary duct, portal vein, and hepatic artery, along with *en-bloc* resection of the celiac trunk and aortic patch. The liver was then flushed and cooled through both the abdominal aorta and portal vein and immersed in ice-cold preservation solution (Institute George Lopez 1 solution). Skilled senior staff members performed all liver transplants, with most recipients receiving an inferior vena cava-sparing piggyback anastomosis, although some required replacement of the inferior vena cava. The portal vein was reconstructed in a standard end-to-end fashion. An end-to-end hepatic artery anastomosis was performed, with multiple anastomoses performed in cases of abnormal donor or recipient hepatic artery anatomy. Sequential portal and arterial reperfusion were employed. A standard triple immunosuppression regimen consisting of a calcineurin inhibitor, steroids, and an antimetabolite was administered to all patients[15].

Statistical analysis

Categorical variables were expressed as percentages. Continuous data were presented as mean (SD) if normally distributed, or median (interquartile range) if not. Patients with and without early allograft dysfunction were compared using Student's *t* test, Mann-Whitney U test, or χ^2 test, as appropriate. Correlations between variables were calculated using Spearman's test. For patient and graft survival analyses, Kaplan-Meier survival curves with the log-rank test were constructed while censoring graft survival for death with a functioning graft to account for competing events. The discriminative power of donor hepatectomy time to predict the outcome was determined by analyzing receiver operating characteristic (ROC) curves, and patients were divided into two groups: Below and above the cutoff. Values were statistically significant if $P < 0.05$. Statistical analyses were conducted using SPSS 21.0 (Chicago, IL, United States).

RESULTS

Patient characteristics

Between January 2019 and December 2021, a total of 243 patients underwent a liver transplant from a brain-dead donor. Table 1 presents the main baseline characteristics of donors, recipients, and surgical procedures. The donors were predominantly male (*n* = 150, 62%), with a mean age of 41 (SD, 14) years. Stroke was the leading cause of brain death (*n* = 118, 48.6%), followed by traumatic brain injury (*n* = 96, 39.5%) and anoxic encephalopathy (*n* = 19, 7.8%). The median DRI was 1.3 (1.1–1.6). The recipients were mostly male (*n* = 175, 72%), with a mean age of 56 (SD, 11) years and a body mass index (BMI) of 27.8 (SD, 4.8) kg/m^2. The primary indications for liver transplantation were viral hepatitis (*n* = 78, 32%), alcoholic liver disease (*n* = 63, 26%), and non-alcoholic fatty liver disease (*n* = 29, 12%).

Table 1 Baseline characteristics of the donors, recipients, and surgical procedures, *n* (%)

Donor characteristics	**Values**
Demographics	
Age (yr)	41 ± 14
Men	150 (62)
BMI (kg/m^2)	25.5 ± 3.5
Cause of death	
Stroke	118 (48.6)
Traumatic brain injury	96 (39.5)
Anoxic encephalopathy	19 (7.8)
Others	10 (4.1)
Organ Procurement	
Regional	215 (88.5)
Local	28 (11.5)
Disease severity	
Time on MV before donation (d)	4 (3-7)
Presence of sepsis	125 (51.4)
Need for vasopressors	201 (82.7)
Cardiac arrest	48 (19.8)
Biochemical measurements	
ALT (U/L)	29 (19-62)
AST (U/L)	40 (24-70)
Bilirubin (mg/dL)	0.5 (0.3-0.8)
Creatinine (mg/dL)	1 (0.7-1.4)
Sodium (mEq/L)	148 ± 10
Platelets (10^3/mm^3)	158 (106-212)
Blood glucose (mg/dL)	243 ± 91
Recipients' characteristics	**Values**
Demographics	
Age (yr)	56 ± 11
Men	175 (72)
BMI (kg/m^2)	27.8 ± 4.8
Blood group	
O	89 (36.6)
A	108 (44.5)
B	34 (14)
AB	11 (4.5)
Indications for liver transplantation	
Viral hepatitis	78 (32)
Alcoholic liver disease	63 (26)
Non-alcoholic steatohepatitis	29 (12)
Cryptogenic	23 (9.5)
Others	50 (20.5)

Disease severity	
MELD score	20 ± 8
Presence of HCC	92 (38)
Previous abdominal surgery	88 (36.2)
Previous decompensation	153 (63)
Biochemical measurements	
ALT (U/L)	611 (375-1041)
AST (U/L)	1055 (580-1829)
Bilirubin (mg/dL)	4 (2.3-6.2)
Creatinine (mg/dL)	0.9 (0.7-1.2)
Platelets (10^3/mm^3)	105 (67-142)
INR	2.1 (1.7-2.7)
Albumin (g/dL)	2.6 (2.3-2.9)
Surgical procedures	
Cold ischemia time (min)	405 (329-492)
Warm ischemia time (min)	34 (30-37)
Donor hepatectomy time (min)	29 (23-40)
Need for thrombectomy	33 (13.6)
Need for arterial reconstruction	31 (12.8)

BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MELD: Model of end-stage liver disease; MV: Mechanical ventilation; HCC: Hepatocellular carcinoma; INR: International normalized ratio. Values are mean ± SD or median and interquartile range.

Donor hepatectomy time ranged from 15 to 93 min, with a median of 29 (23–40) min. There was a difference in hepatectomy time between local and regional organ procurement centers [22 (25–46) *vs* 30 (24–41) min, respectively, $P \leq 0.001$]. Donor BMI was associated with hepatectomy time. For donors with BMI < 30 kg/m^2, the median hepatectomy time was 28 (23–38) min, whereas for donors with BMI ≥ 30 kg/m^2, it was 35 (25–46) min ($P = 0.031$). Regarding ischemia times, the median cold ischemia time was 405 (329–492) min, while the median warm ischemia time was 34 (30–37) min.

Primary outcome

Early allograft dysfunction was observed in 57 patients (25%). The median donor hepatectomy time had no impact on the development of early allograft dysfunction. Patients with early allograft dysfunction had a median donor hepatectomy time of 25 (22–38) min, whereas those without it had a median time of 30 (24–40) min ($P = 0.126$) (Table 2). Similarly, other surgical times were not associated with early allograft dysfunction (Table 2).

When each of the 3 criteria for early allograft dysfunction was analyzed separately, no significant correlation was found between donor hepatectomy time and postoperative markers of liver graft function on ICU admission, day 1, or day 7 (Table 3).

Secondary outcomes

Donor hepatectomy time did not differ significantly between survivors and non-survivors [29 (24–38) *vs* 26 (21–42) min, $P = 0.787$], patients with and without graft survival at 12 months [29 (24–38) *vs* 27 (21–45) min, $P = 0.893$], or patients requiring and not requiring retransplantation [30 (24–42) *vs* 29 (24–40) min, $P = 0.951$].

To better understand the impact of donor hepatectomy time, we categorized patients based on the discriminative power of hepatectomy time to predict the outcome determined by the ROC curve, which was set at 23 min. The effects of hepatectomy time below and above this cutoff are detailed in Table 4. Figure 1 illustrates the survival analysis for grafts (Figure 1A) and for patients (Figure 1B) according to hepatectomy times below and above the cutoff value (23 min).

Exploratory outcomes

Arterial anatomy type was not associated with donor hepatectomy time. The median procedure duration was 29 (23–38) min for donors with standard arterial anatomy and 28 (24–41) min for donors with unusual arterial anatomy ($P = 0.688$).

Donors with hepatectomy time < 23 min were receiving vasopressors in a similar number to those with hepatectomy time > 23 min [$n = 55$ (90.2%) *vs* $n = 146$ (80.2%), respectively, $P = 0.075$]. Likewise, donors who had hepatectomy times either above or below the cutoff (23 min) required similar doses of preoperative vasopressors. The dose administered was 0.12 (0.04–0.22) mcg/kg/min for donors above the cutoff and 0.13 (0.05–0.26) mcg/kg/min for donors below the cutoff ($P = 0.507$).

Table 2 Association between donor, recipients, and surgical procedures with the development of early allograft dysfunction, *n* (%)

	All patients (*n* = 228)	With EAD (*n* = 57)	Without EAD (*n* = 171)	*P* value
Donors' characteristics				
Age (yr)	41 ± 14	43 ± 14	40 ± 14	0.186
BMI (kg/m^2)	25.5 ± 3.6	26 ± 4.1	25.3 ± 3.5	0.286
Need for vasopressors	187 (82)	44 (77.2)	143 (8.6)	0.273
Time on MV before donation (d)	4 (3-7)	5 (4-11)	4 (3-7)	0.001
Cardiac arrest	41 (18)	14 (24.6)	27 (15.8)	0.135
DRI score	1.3 (1.1-1.6)	1.3 (1.1-1.5)	1.4 (1.1-1.7)	0.224
Recipients' characteristics				
Age (yr)	56 ± 11	53 ± 13	58 ± 10	0.021
BMI (kg/m^2)	27.7 ± 4.8	28.9 ± 5.9	27.4 ± 4.1	0.112
Indication for transplantation				0.079
Alcoholic liver disease	62 (27.2)	13 (22.8)	49 (28.7)	
Viral hepatitis	74 (32.4)	16 (28.1)	58 (33.9)	
Non-alcoholic steatohepatitis	26 (11.4)	8 (14)	18 (10.5)	
Cryptogenic	21 (9.2)	4 (7.0)	17 (9.9)	
Others	45 (19.7)	16 (28.1)	29 (17)	
MELD score	19 (14-24)	20 (13-25)	18 (12-23)	0.047
Biochemistry at ICU admission				
Albumin (g/dL)	2.6 (2.3-2.9)	2.5 (2.3-1.7)	2.7 (2.3-2.9)	0.314
Creatinine (mg/dL)	0.9 (0.7-1.2)	0.9 (0.7-1.3)	0.8 (0.7-1.1)	0.009
Platelets (10^3/mm^3)	105 (67-142)	104 (74-143)	108 (82-157)	0.057
AST (U/L)	1055 (580-1829)	1370 (739-3174)	1003 (561-1434)	< 0.001
ALT (U/L)	611 (375-1041)	799 (435-1583)	488 (289-826)	< 0.001
INR	2.1 (1.7-2.7)	2.7 (1.9-3.7)	2.1 (1.7-2.7)	< 0.001
Bilirubin (mg/dL)	4 (2.3-6.2)	6.5 (4.1-8.8)	3.7 (2.5-5.3)	0.077
Surgical procedures				
Donor hepatectomy time (min)	29 (23-40)	30 (23-39)		0.126
Cold ischemia time (min)	405 (329-492)	388 (311-495)	407 (334-483)	0.291
Warm ischemia time (min)	34 (30-37)	35 (30-39)	34 (3037)	0.079

Values are mean ± SD or median and interquartile range. Student's *t* test, Mann-Whitney U test or χ^2 test was used as appropriate. *P* value was considered significant at $P < 0.05$. AD: Early allograft dysfunction; BMI: Body mass index; MV: Mechanical ventilation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MELD: Model of end-stage liver disease; DRI: Donor Risk Index; ICU: Intensive care unit; INR: International normalized ratio.

DISCUSSION

In this multicenter retrospective study involving liver recipients from brain-dead donors, we did not find any evidence of an association between donor hepatectomy time and the development of early allograft dysfunction. Furthermore, our findings indicate that longer hepatectomy times did not affect either graft or patient survival.

Previous literature reports donor hepatectomy time ranging from 32 to 51 min, with a median of 40 min[5,16]. Two single-center retrospective studies investigated whether donor hepatectomy and implantation time increased the incidence of early allograft dysfunction, but their results were inconclusive[5,8]. Adelmann *et al*[8] suggested that prolonged donor hepatectomy time increased the risk of early allograft dysfunction, but no adjustment was made for confounders, such as cold ischemia time[8]. Conversely, Gilbo *et al*[5] showed that the risk of developing early allograft dysfunction was not influenced by donor hepatectomy time but rather by implantation time, which had a linear effect on the development of early allograft dysfunction, increasing the risk by 15% for every 10-min increase in time[5]. Our findings align with these results, as we showed that donor hepatectomy time was not associated with an increased risk of

Table 3 Correlation between donor hepatectomy time and postoperative liver function markers

Hepatectomy time	r	*P* value
Graft function markers		
At admission		
AST (IU/L)	-0.017	0.797
ALT (IU/L)	0.005	0.943
INR	0.033	0.617
Bilirubin (mg/dL)	0.069	0.287
At day 1		
AST (IU/L)	-0.083	0.213
ALT (IU/L)	0.041	0.541
INR	-0.051	0.449
Bilirubin (mg/dL)	0.054	0.419
At day 7		
AST (IU/L)	-0.026	0.717
ALT (IU/L)	0.068	0.336
INR	-0.055	0.443
Bilirubin (mg/dL)	0.087	0.234

Correlations between variables were calculated using Spearman's test. *P* value was considered significant at $P < 0.05$. AST: Alanine transferase; ALT: Aspartate transferase; INR: International normalized radio.

Table 4 Effects of donor hepatectomy time below and above the median value (23 min) on liver transplantation outcomes

Outcomes	All patients (*n* = 243)	Patients with hepatectomy time < 23 min (*n* = 61)	Patients with hepatectomy time ≥ 23 min (*n* = 182)	*P* value
Early allograft dysfunction[1]	57 (25)	19 (33.9)	38 (22.1)	0.076
Need for retransplantation	13 (5.3)	4 (6.6)	9 (4.9)	0.628
Graft survival[2]	166 (81.8)	37 (75.5)	129 (83.8)	0.192
Patient survival	167 (68.7)	37 (60.7)	130 (71.4)	0.116
LOS, hospital (d)	10 (8-14)	10 (7-16)	10 (8-13)	0.790
LOS, ICU (d)	4 (3-6)	4 (3-6.5)	4 (3-5)	0.417

[1]*n* = 228 (56; 172).
[2]*n* = 203 (49; 154).
LOS: Length of stay; ICU: Intensive care unit.

early allograft dysfunction. It is reasonable to conceive that hepatectomy times in our province are sufficiently short (11 min below the median time reported in the literature) to allow for reduced risk of early allograft dysfunction or other clinical outcomes.

Although consensus on the optimal donor hepatectomy time remains inconclusive, studies have suggested that minimizing ischemia times[7,17], especially cold ischemia time[18,19], is associated with better outcomes and fewer early surgical complications, including non-anastomotic biliary strictures[5,20]. However, the impact of donor hepatectomy time, which is relatively brief compared to other ischemia times, on clinical outcomes has received limited attention. In this study, we showed that donor hepatectomy time was not associated with graft or patient survival, need for retransplantation, or length of ICU or hospital stay. Probably, other donor, recipient, and surgical procedure characteristics, such as previous comorbidities[21], age[22], underlying disease[19], and bleeding volume[23,24], are better determinants of these outcomes than hepatectomy time itself. For instance, liver grafts recovered from donors after cardiac death undergo distinct ischemic insults during procurement, exhibiting differences in nature and severity of injury. Using the Euro-

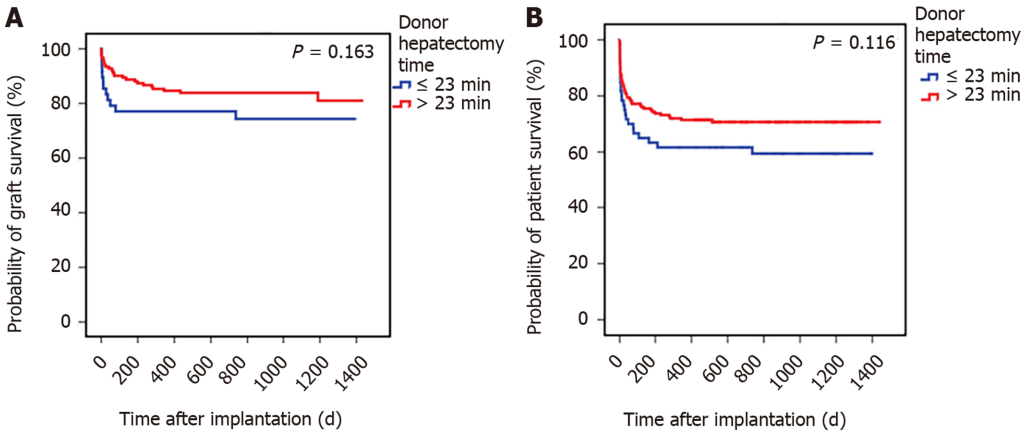

Figure 1 Kaplan-Meir curve illustrating the probability of graft and patient survival after liver transplantation according to donor hepatectomy time. A: Kaplan-Meir curve illustrating the probability of graft; B: Patient survival after liver transplantation according to donor hepatectomy time.

transplant Registry data, Jochmans *et al*[6] reported that the impact of donor hepatectomy time is more pronounced in livers from donors after cardiac death than in those after brain death[6]. In donors after cardiac death, cold preservation follows a prolonged period of warm ischemia during treatment withdrawal, progression to asystole, and hepatectomy itself, making these grafts more vulnerable to insults. Recently, a retrospective study using the United States national data including 3810 Liver transplants from donors after cardiac death demonstrated that prolonged donor hepatectomy time significantly increased the risk of 1-year graft loss and patient mortality. This study showed that prolonged donor hepatectomy time, defined as ≥ 42 min, is a significant risk factor impacting short-term outcomes, along with the receptor age and MELD score[25]. We believe that the exceptionally short median donor hepatectomy time of < 29 min in our study, along with the absence of prolonged warm ischemia typical of donors after cardiac death, explains the lack of association between donor hepatectomy time and outcomes in our cohort of brain-dead donors.

Unstable patients and those with unusual arterial anatomy may have prolonged hepatectomy times. In our study, the presence of unusual arterial anatomy or vasopressor dose had no significant impact on donor hepatectomy time, although this result should be considered exploratory.

Our study is one of the few studies that have been specifically designed to investigate the association between donor hepatectomy time and the development of early allograft dysfunction. Nevertheless, given the multicenter nature of the study, it is essential to acknowledge some limitations. First, although this study represents the largest dataset to test this hypothesis, it is still underpowered. Based on the 5-min difference that we found in median hepatectomy time between patients with and without early allograft dysfunction, our results have a power of 71%. However, it is highly unlikely that an increment in sample size would change results, as a very short hepatectomy time was observed overall. Second, since donor hepatectomy time is not considered crucial, surgeons may have provided less accurate information in this regard, but data were collected from patients' medical records. Third, the retrospective nature of the study resulted in some missing information, including 15 patients without the primary outcome. Fourth, unfortunately we do not have data on the impact of donor hepatectomy time after cardiac death, as well described[26], because this type of donation is not currently available in Brazil.

CONCLUSION

In conclusion, donor hepatectomy time was not associated with early allograft dysfunction, graft survival, or patient survival following liver transplantation. While there is a need for policies and interventions to enhance post-transplant outcomes, it appears that the current donor hepatectomy time is already sufficiently short to further mitigate risks. We suggest that future research efforts should focus on exploring alternative strategies other than further reducing donor hepatectomy time.

ARTICLE HIGHLIGHTS

Research background

To address the shortage of organs and improve liver transplantation outcomes, it is crucial to explore opportunities to enhance donor, graft, and recipient care. One such method involves reducing the duration of ischemic phases, which has been demonstrated to be of great importance.

Research motivation

There is a need for policies and interventions to improve post-transplant results, it appears that the donor's hepatectomy time may be a factor contributing to this improvement.

Research objectives

This study aimed to evaluate the impact of donor hepatectomy timing on outcomes in liver transplant recipients, particularly early allograft dysfunction. We know that transplantation is a race against time, and better understanding the importance of these times is essential for a more accurate strategy.

Research methods

This is a multicenter retrospective study. The study included brain-dead donors from 19 regional centers in the state of Santa Catarina, Brazil, and adult liver transplant recipients from brain-dead donors at Hospital Santa Isabel, a general hospital in the city of Blumenau, state of Santa Catarina, Brazil, from January 2019 to December 2021. The discriminative power of donor hepatectomy time to predict the outcome was determined by analyzing receiver operating characteristic curves, and patients were divided into two groups: Below and above the cutoff.

Research results

In this multicenter retrospective study involving liver recipients from brain-dead donors, we did not find any evidence of an association between donor hepatectomy time and the development of early allograft dysfunction. Furthermore, our findings indicate that longer hepatectomy times did not affect either graft or patient survival. We believe that the exceptionally short median donor hepatectomy time of < 29 min in our study, along with the absence of prolonged warm ischemia typical of donors after cardiac death, explains the lack of association between donor hepatectomy time and outcomes in our cohort of brain-dead donors.

Research conclusions

Donor hepatectomy times did not affect either graft or patient survival. The new methods that this study proposed was to evaluate hepatectomy time in centers where this time is already reduced in relation to other centers already studied.

Research perspectives

While there is a need for policies and interventions to enhance post-transplant outcomes, it appears that the current donor hepatectomy time is already sufficiently short to further mitigate risks. We suggest that future research efforts should focus on exploring alternative strategies other than further reducing donor hepatectomy times.

FOOTNOTES

Author contributions: Custodio G participated in the study design, collection and interpretation of data, statistical analysis, and drafting of the manuscript; Massutti AM and Caramori A performed all liver transplantations; Pereira TG, Dalazen A, Scheidt G, and Thomazini L were involved in data collection; Leitão CB participated in the study conception and design, interpretation of data, and statistical analysis; Rech T contributed to the study conception and design, interpretation of data, statistical analysis, and drafting the manuscript; All authors reviewed and edited the manuscript. Rech TH is the guarantor of this work and, as such, had complete access to all data, with full responsibility for the integrity of the data and accuracy of analysis.

Institutional review board statement: The study was approved by the reference Ethics Committee at the Universidade Federal Rio Grande do Sul (PROPESQ UFRGS, project No. 5.526.176), Brazil. The study adheres to the guidelines set forth by the Helsinki Declaration, as well as to local standards and Brazilian legislation.

Informed consent statement: The Ethics Committee did not require informed consent due to the retrospective design and the anonymization of donors and recipients prior to analysis.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Observational Study

Liver transplantation for hepatocellular carcinoma in India: Are we ready for 2040?

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Abstract

BACKGROUND

Liver transplantation (LT) for hepatocellular carcinoma (HCC) has been widely researched and is well established worldwide. The cornerstone of this treatment lies in the various criteria formulated by expert consensus and experience. The variations among the criteria are staggering, and the short- and long-term outcomes are controversial.

AIM

To study the differences in the current practices of LT for HCC at different centers in India and discuss their clinical implications in the future.

METHODS

We conducted a survey of major centers in India that performed LT in December 2022. A total of 23 responses were received. The centers were classified as high- and low-volume, and the current trend of care for patients undergoing LT for HCC was noted.

RESULTS

Of the 23 centers, 35% were high volume center (> 500 Liver transplants) while 52% were high-volume centers that performed more than 50 transplants/year. Approximately 39% of centers had performed > 50 LT for HCC while the percent distribution for HCC in LT patients was 5%–15% in approximately 73% of the patients. Barring a few, most centers were divided equally between University of California, San Francisco (UCSF) and center-specific criteria when choosing patients with HCC for LT, and most (65%) did not have separate transplant criteria for deceased donor LT and living donor LT (LDLT). Most centers (56%) preferred surgical resection over LT for a Child A cirrhosis patient with a resectable 4 cm HCC lesion. Positron-emission tomography-computed tomography (CT) was the modality of choice for metastatic workup in the majority of centers (74%). Downstaging was the preferred option for over 90% of the centers and included transarterial chemoembolization, transarterial radioembolization, stereotactic body radiotherapy and atezolizumab/bevacizumab with varied indications. The alpha-fetoprotein (AFP) cut-off was used by 74% of centers to decide on transplantation as well as to downstage tumors, even if they met the criteria. The criteria for successful downstaging varied, but most centers conformed to the UCSF or their center-specific criteria for LT, along with the AFP cutoff values. The wait time for LT from downstaging was at least 4–6 wk in all centers. Contrast-enhanced CT was the preferred imaging modality for post-LT surveillance in 52% of the centers. Approximately 65% of the centers preferred to start everolimus between 1 and 3 months post-LT.

CONCLUSION

The current predicted 5-year survival rate of HCC patients in India is less than 15%. The aim of transplantation is to achieve at least a 60% 5-year disease free survival rate, which will provide relief to the prediction of an HCC surge over the next 20 years. The current worldwide criteria (Milan/UCSF) may have a higher 5-year survival (> 70%); however, the majority of patients still do not fit these criteria and are dependent on other suboptimal modes of treatment, with much lower survival rates. To make predictions for 2040, we must prepare to arm ourselves with less stringent selection criteria to widen the pool of patients who may undergo transplantation and have a chance of a better outcome. With more advanced technology and better donor outcomes, LDLT will provide a cutting edge in the fight against liver cancer over the next two decades.

Key Words: Hepatocellular carcinoma; Liver transplant; India; Downstaging; Survey; Milan; University of California, San Francisco; Portal vein tumor thrombus; Expanded criteria

Core Tip: The current predicted 5-year survival rate of hepatocellular carcinoma (HCC) patients in India is less than 15%. The aim of transplantation is to achieve at least a 60% 5-year disease free survival which will truly provide a relief to the predictions of HCC surge over the next 20 years. The current worldwide criteria (Milan/University of California, San Francisco) may have a higher 5-year survival (> 70%) but the majority of patients still do not fit these criteria and are dependent on other sub-optimal modes of treatment with much lower survival rates. In order to face predictions for 2040, we must prepare to arm ourselves with less stringent selection criteria to widen the pool of patients who may avail transplant and have a chance at a better outcome.

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INTRODUCTION

Hepatocellular carcinoma (HCC) comprises for approximately 75%–80% of all liver cancer types in most countries[1]. HCC is the sixth most common cancer worldwide, comprising approximately 5% of the total cancer incidence, and causes approximately six deaths per 100000 people annually[2,3]. In 2020, liver cancer was the third most common cause of cancer-related deaths worldwide (830000)[4]. There is a lack of statistical data from India, with the number of deaths estimated to be approximately 6.8 per 100000 people, with a total of approximately 14000 deaths annually in 2010[5,6].

The burden of HCC has been increasing worldwide, and India is no exception[7,8]. Asian countries have reported the highest global liver cancer incidence (73%) and liver cancer deaths in 2020[9]. Between 1978 and 2012, there was a steady increase in the number of HCC cases in India[10,11]. In the United States, a recent study predicted a continued increase in HCC rates through 2030[12]. At present, India contributes to approximately 18% of the incidence and 4% of the mortality. By 2040, the global burden of new cases and deaths from liver cancer may increase by up to 55% (an estimated 1.3 million cases and 1.4 million deaths)[13,14]. However, India still has a low 5-year survival rate for HCC (< 15%) despite the advancement of curative and palliative treatment options over the last two decades[15,16].

Liver transplantation (LT) for HCC in patients with cirrhosis has been widely researched and is now well established worldwide[17-19]. The cornerstone of this treatment lies in the various criteria formulated by expert consensus and experience over the years. The Milan criteria was established by Mazzaferro *et al*[20] in 1996 to improve the outcomes of LT for HCC in the initial aftermath of low survival and high recurrence rates[20]. Subsequent studies by Yao *et al*[21] and Mazzaferro *et al*[22] indicated the restrictive nature of these criteria, and slightly more liberal criteria, called the University of California, San Francisco (UCSF) criteria, were introduced in 2001[21,22]. These mainly included the number and size of HCC nodules, vascular invasion, and extrahepatic spread. Since then, several other criteria have been introduced, each with its own justification and outcomes. The variations among the criteria are staggering, and the short- and long-term outcomes are controversial[19,23,24]. Another factor is the evolution of living donor LT (LDLT) as a treatment option, which has led us to accept less stringent guidelines for LT in patients with HCC, as it does not affect the LT waitlist. However, the survival of HCC-LT recipients outside the standard criteria must be comparable to that of the expanded criteria to mitigate the additional risks to live donors. The incorporation of tumor markers into downstaging protocols has also contributed to improved outcomes and overall survival rates. We aimed to study the differences in the current practices of LT for HCC at different centers in India and discuss their clinical implications in the future.

MATERIALS AND METHODS

We created an electronic survey form using Google Docs. It included several multiple-choice and short-answer questions to elaborate on specific choices or topics. Data were collected regarding the name of each center, their overall experience, and their LT practices with respect to HCC. In total, 54 questions were included (Supplementary Figure 1). The survey was reviewed and acknowledged as exempt from the Institutional Review Board at Medicover Hospitals, Navi Mumbai.

The survey was conducted in 42 transplant centers in India. Each center communicated *via* a transplant surgeon or physician. Responses were obtained over a 3-month period between January 2023 and April 2023. No incentives or honorariums were provided for completing the survey. Participation in the study was voluntary. Any duplicate or doubtful responses were clarified by the concerned center, and only one complete response was included in the final assessment. Eventually, 23 responses were received, which were tabulated and analyzed using standard software.

RESULTS

Overall, 23 of 41 (56%) transplant centers across India responded voluntarily to our survey. Almost all centers perform LDLT rather than deceased donor LT (DDLT). High-volume centers were defined as those that had performed more than 50 Liver transplants/year in the last 3 years, whereas low-volume centers were defined as those that had performed less than 50 Liver transplants/year in the last 3 years. Centers with more than 500 Liver transplants were referred to as experienced centers for discussion. Among the 23 centers, eight centers (34.8%) were identified as experienced LT centers, with two centers performing more than 2000 Liver transplants to date. More than 50% (12/23) of the centers were high-volume centers (Figure 1). Approximately 39% (nine centers) of the centers had performed over 50 cases of liver transplant for patients with HCC (Figure 2).

Among the centers, the majority (17/23) responded that HCC was present in 5%–15% of LT recipients (Figure 2). Only one center followed the Milan criteria for LT, whereas the remaining centers were equally divided (11 each) between the UCSF and center-specific criteria for the eligibility of patients with HCC for LT. Apart from one center, all other centers (21/22 responses; 95%) replied that the percentage of patients with HCC within the Milan criteria undergoing LT was < 5%. Thirteen out of 23 centers (56.5%) preferred surgical resection in a 43 year-old Child A cirrhosis patient with a 4 cm solitary HCC and good performance status over LT directly. Nine centers specified the criteria for liver transplant in patients with HCC. The different center-specific criteria at the time of transplantation (either primary or after down-staging) used by various institutes are outlined in Table 1.

The majority of centers (17/23; 74%) preferred positron-emission tomography (PET)-computed tomography (CT) as their modality of choice for metastatic work-up in HCC patients with chronic liver disease (CLD) planned for LT. The remaining centers (26%) opted for a combination of contrast-enhanced CT (CECT) of the abdomen and pelvis, chest CT, and bone scan (Figure 3). Approximately 65% of the centers did not have different criteria for LDLT and DDLT with respect to HCC–CLD patients. Six of the eight centers that had different criteria explained that they would list patients only under the UCSF criteria for DDLT, while they would opt for center-specific criteria to proceed with LDLT. One center mentioned that downstaged portal vein tumor thrombus (PVTT) with transarterial radioembolization (TARE) or stereotactic body radiotherapy (SBRT) would not be a candidate for DDLT at their center but would be a candidate for LDLT.

Table 1 Various center-specific criteria for hepatocellular carcinoma used at the time of liver transplantation across India

No. of centers	Center-specific criteria			
	Size/No. of tumor	Invasion	Extrahepatic	AFP/markers
4	Any size/any No.	No macrovascular	No	Any
2	Any size/any No.	No macrovascular	No	< 1000
1	Encapsulated, any size, < 10	No macrovascular	No	< 400
1	Within UCSF size/No.	Vp1-vp3 invasion	No	< 400
1	Any size/any No.	Vp1-vp2 invasion	No	Any

UCSF: University of California, San Francisco criteria; AFP: Alpha-fetoprotein.

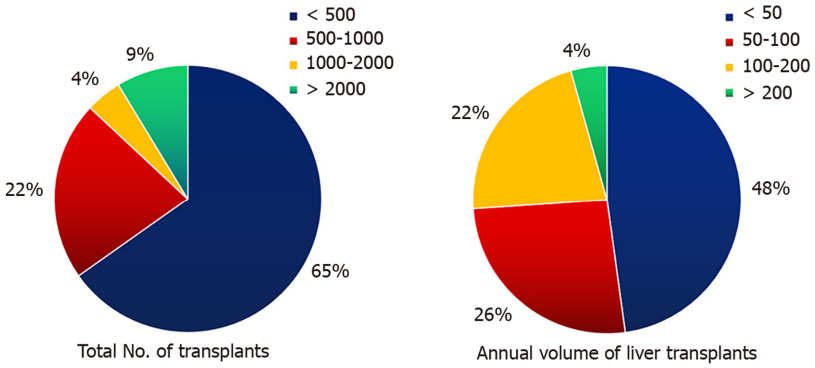

Figure 1 Total number and yearly volume of liver transplants at the participating centers.

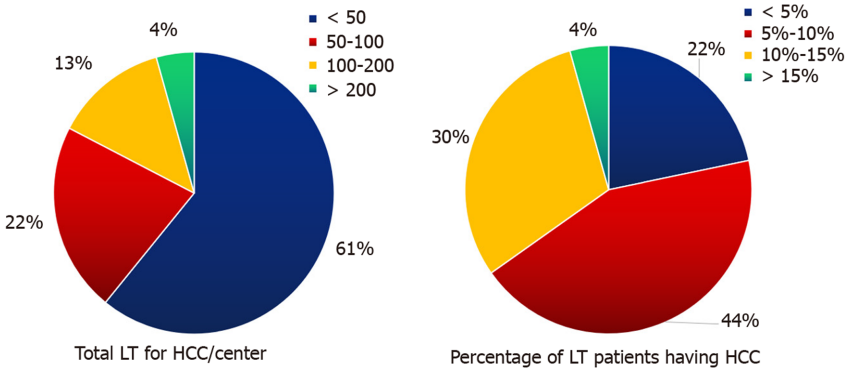

Figure 2 Total number of liver transplants performed in patients with hepatocellular carcinoma (center-wise) and percentage of transplant patients with hepatocellular carcinoma. HCC: Hepatocellular carcinoma; LT: Liver transplantation.

Most of the centers (21/23; 91%) used downstaging as a bridge to LT when the center-specific criteria were not fulfilled, but there was no absolute contraindication to LT. Of them, 18 centers (overall 18/23; 78%) would consider branch PVTT for downstaging prior to transplantation. Transarterial chemoembolization (TACE), TARE, and SBRT are common modalities used to downstage tumors for various indications. The indications for TACE, TARE, and/or SBRT as downstaging tools received eight responses, as outlined in Table 2. TARE was preferred over TACE in the presence of PVTT (12 responses), large or multiple tumors (six responses), and in all cases, when financially feasible (three responses), with some overlap in the responses. TACE was preferred mostly for large tumors without PVTT, in cases of financial restrictions, and when TARE was unavailable in some centers. The use of atezolizumab/bevacizumab combination in HCC patients awaiting transplantation was advocated by six centers, of which five would use it universally and one would use it when TACE/TARE was not feasible. Six other centers responded that they had no experience using atezolizumab or bevacizumab as part of the downstaging protocol.

Alpha-fetoprotein (AFP) was used as a marker for downstaging at most centers (17/23; 74%). The cut-off AFP value for transplant was 1000 ng/mL in most (10/17; 59%) centers, 400 ng/mL in four centers, and 2000, 500, and 200 ng/mL in one center each. All 17 centers considered AFP as a criterion for downstaging based on their set cut-off levels. Sixteen

Table 2 Indications of transarterial chemoembolization, transarterial radioembolization and stereotactic body radiotherapy in hepatocellular carcinoma–chronic liver disease patients awaiting liver transplantation

Modality	TACE	TARE	SBRT
Indications (No. Of centers preferred)	HCC patients on waitlist[12]	PVTT[12]	Vp1-3 PVTT[12]
	> Milan[4]	Large/multiple HCC[6]	Vp2 PVTT[2]
	> UCSF[2]	All affordable cases[3]	TACE/TARE not possible[4]
	Large tumor size[13]		Exophytic HCC[1]
	Awaiting donor fitness/logistical delay in transplant[2]		Diaphragm involved or local infiltration[1]
	High AFP[5]		Presence of shunt[1]
	Absence of PVTT[2]		Not preferred[3]
	TARE unaffordable/unavailable[4]		

There is overlap among the respondents for the indications of either modalities. HCC: Hepatocellular carcinoma; PVTT: Portal vein tumor thrombosis; UCSF: University of California, San Francisco criteria; TACE: Trans-arterial chemo embolization; TARE: Trans-arterial radio embolization; SBRT: Stereotactic body radiotherapy; AFP: Alpha fetoprotein.

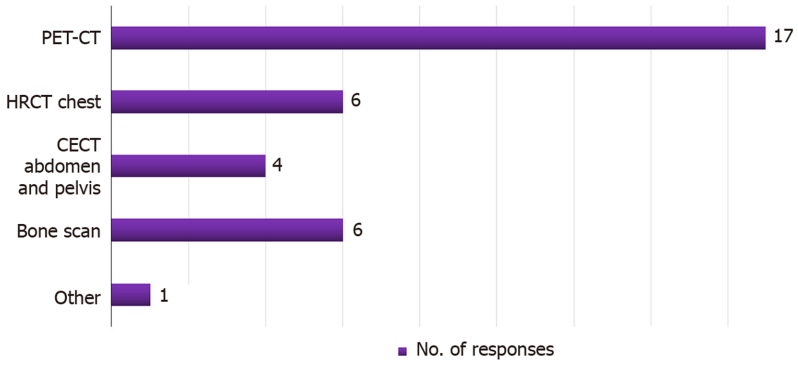

Figure 3 Preferred metastatic work-up imaging modality in patients with hepatocellular carcinoma planned for transplant. PET: Positron-emission tomography; CT: Computed tomography; HRCT: High resolution computed tomography; CECT: Contrast-enhanced computed tomography.

centers (70%) used protein induced by vitamin K absence or antagonist II (PIVKA-II) as a biomarker for HCC surveillance. All centers (19 responses) considered successful downstaging when their center-specific criteria or transplant listing criteria, including the AFP cutoff, were met. The most common determinants were decreased tumor size, clearance of PVTT, reduced AFP/PIVKA-II, loss of PET avidity or CT enhancement, and non-progression of tumor status. Opinions were divided among centers regarding when transplants should be performed after downstaging. Nine centers (9/23; 39%) thought it should be more than 6 wk, whereas six (26%) and seven centers (30%) thought it should be 4 wk and 6 wk, respectively. For post-operative surveillance, CECT-abdomen was the preferred imaging of choice (52%), followed by PET-CT (35%). The remaining few centers opted for CT + Bone Scan on follow-up (Figure 4). Everolimus was preferred by 22 of the 23 centers at different times post-transplant, with only one center not using it routinely (Figure 4).

DISCUSSION

This survey covered a wide range of transplant centers across India, with an overall experience of over 8000 Liver transplants. Based on these results, we derived an idea of the distinct practices around the country regarding HCC leading to LT and its subsequent follow-up. Despite certain clear-cut agreements, many corresponding answers have highlighted gray areas where judgments and opinions differ and are of utmost importance in different settings.

Selection criteria for HCC

The selection criteria for HCC in LT have always been debated. From the early days of the Milan criteria to UCSF and, more recently, the Expanded Selection Criteria, it has been well established that cancer-free survival is dependent largely on extrahepatic spread and the level of vascular invasion, as compared to that on the size and number of tumors[20,21,25]. There is increasing evidence that outcomes outside the age-old criteria, such as the Milan criteria, are near-equivalent or at least good, as shown in Table 3[21,25-33]. In a country like India, where the burden of cirrhosis patients is huge and

Table 3 Different criteria for liver transplantation in hepatocellular carcinoma patients

Criteria name (yr)	Size of tumor (cm)	No. of tumors	Additional criteria	Overall 5-year survival
Milan criteria (1996)	≤ 5; ≤ 3	1; 3	None	75%
UCSF criteria (2001)	6.5; ≤ 4.5 (total ≤ 8)	1; 3	None	75.2%
Up-to-7 criteria (2001)	Size (cm) + No. ≤ 7		None	
Navarro criteria (2001)	≤ 6; ≤ 5	1; 3	None	79%
Tokyo criteria (2007)	≤ 5	≤ 5	None	75%
Asan criteria (2008)	≤ 5	≤ 6	None	82%
Hangzhou criteria (2008)	< 8 (total)	Any No.	AFP < 400 ng/mL	72%
Chang Gung criteria (2008)	≤ 6.5; ≤ 4.5	1; ≤ 3	None	90%
Hong Kong criteria (2008)	≤ 6.5; ≤ 4.5	1; ≤ 3	None	66%
Kyushu criteria (2009)	≤ 5	Any No.	PIVKA-II < 300 mAU/mL	83%
Kyoto criteria (2010)	≤ 5	≤ 10	PIVKA-II < 400 mAU/mL	87%
Toronto criteria (2011)	Any Size	Any No.	Poorly differentiated HCC excluded	72%
Japanese National Expanded criteria (2019)	≤ 5	≤ 5	AFP < 500 ng/mL	75.8%

All the criteria exclude any vascular invasion or any extra-hepatic spread[25-33]. HCC: Hepatocellular carcinoma.

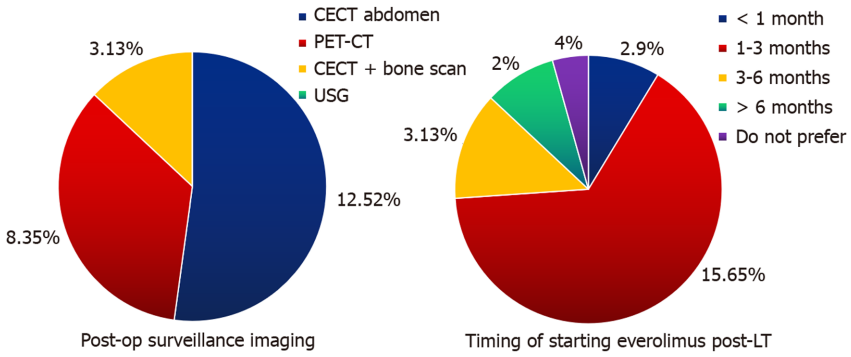

Figure 4 Post-operative imaging and everolimus use preference in centers across India. PET: Positron-emission tomography; CT: Computed tomography; HRCT: High resolution computed tomography; CECT: Contrast-enhanced computed tomography; LT: Liver transplantation.

most patients are from the lower socioeconomic status, it is most usual for HCC to present in a late-stage with a background of CLD where they are often beyond Milan or UCSF criteria[10,11,15,16]. The diagnosis of these patients is often delayed owing to the unavailability of facilities or a lack of awareness in rural/semi-urban centers. The 5-year survival rate of these patients is extremely low[15,16]. In this situation, external criteria from predominantly Western or other developed countries may not be suitable for Indian patients in the current scenario. The availability and use of direct-acting antivirals did not have any impact on the incidence or recurrence of HCC; however, extensive data are lacking in this regard[34-36].

In our survey, 5%-15% of patients undergoing LT in India were diagnosed with HCC annually. Of these, only 5% belonged to the Milan category. Since the advent of the Milan criteria, advancements in radiological techniques have made it possible to achieve extremely accurate staging. LDLT, with a high degree of donor safety, has mitigated organ availability issues. Hence, the expansion of recipient criteria has become possible with LDLT, even with slightly inferior outcomes compared to those in Milan[37]. In our opinion, any treatment that offers at least a chance of 60% 5-year disease-free survival should be acceptable and offered to a patient and their donor for LDLT and should not be outrightly rejected[38].

Regarding the listing of patients with HCC–CLD, there has been considerable debate on whether the same criteria used for LDLT are applicable for DDLT. More recently, expanded criteria have been shown to have comparable outcomes, and this dilemma has intensified. In general, DDLT listing has been reserved for those patients who have a similar 5 year survival as compared to non HCC patients (*e.g.*, Milan or UCSF criteria)[37,38]. This reservation is due to the potential impact of this listing on other patients on the liver waitlist. It has also been suggested that DDLT listings should be subject to regional listing criteria for patients with HCC, whereas LDLT can be pursued with more liberal center-specific criteria, providing a full disclosure of risks and outcome benefits[37]. Our survey sheds light on the fact that up to 65% of

centers preferred to use the same criteria for LDLT and DDLT listing. Of the eight experienced centers, three opted for separate listing criteria, while five opted for the same criteria.

Metastatic work-up

The current diagnostic tools for HCC include ultrasonography, CT, magnetic resonance imaging (MRI), and biopsy[39]. Biopsy confirmation is usually not required for a diagnosis[40]. Triple CT or MRI is the best imaging modality to diagnose HCC in patients with CLD. Current literature on the best imaging method for the evaluation of HCC metastasis is scarce. CT is the most accurate technique; however, it has limitations with respect to bone lesions, small vascular tumors, and difficulty in distinguishing between scarring and metastases[41-43]. The 18-Fluoro-deoxy-glucose-PET-CT has become increasingly established for the evaluation and treatment of metastatic HCC, with an average sensitivity of 60%–80% in most studies[44-46]. Other programs use a combination of dynamic CECT or MRI, chest CT and bone scintigraphy[47]. In our survey, 74% of centers chose PET-CT, whereas the remaining opted for the latter as a metastatic work-up prior to transplantation. AFP is considered an important biomarker for the diagnosis, treatment, and follow-up of patients with HCC before and after treatment[48]. It has also been implicated in the development and progression of HCC along with drug resistance in HCC cells[49]. However, only 60%–70% of HCC cases show elevated AFP levels, while 30%–40% of patients have normal values[50,51]. Newer biomarkers and models such as lens culinaris agglutinin-reactive fraction of AFP, des-carboxy-prothrombin, and GALAD scores (gender, age, AFP-L3, AFP, and DCP) are being increasingly used by various centers around the world[52,53]. In our study, AFP was universally followed, whereas PIVKA II was followed up in nearly 70% of the centers.

Downstaging for HCC

In our survey, more than 90% of the centers considered downstaging of HCC either as a bridge to transplantation or to fit the respective listing criteria or center-specific criteria for LDLT. The various indications mentioned by the surveyed participants, along with their corresponding modalities, are listed in Table 3. TACE and TARE were the most popular choices depending on availability and feasibility, whereas SBRT was mostly reserved for branch PVTT. A recent meta-analysis found that down-staged HCC–CLD patients who were initially beyond the listing criteria and who underwent transplantation had much better 3- and 5-year survival rates than non-transplanted patients[54]. They also noted that patients with downstaged HCC–CLD did not have inferior outcomes to transplant recipients who met the listing criteria [54]. Although the current European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines suggest LT for downstaging to the Milan criteria, while the United Network for Organ Sharing (UNOS) adopted the UCSF criteria, the Indian perspective is different from the point of view of its socio-economics, advanced stage at diagnosis, and overall poor 5-year survival[55-57]. Mazzaferro *et al*[58] demonstrated that patients with downstaged HCC–CLD (to Milan) had a 77% 5-year overall survival rate compared to that of 31% with conventional anticancer therapies[58]. In this survey, TARE was preferred in many centers when available and affordable, especially in the presence of PVTT or multifocal HCC. An international systematic review of TARE as a downstaging tool before LT in 178 patients concluded that TARE is safer and better than TACE, with a 79% success rate[59]. Radunz *et al*[60] performed TARE downstaging in 40 pre-transplant patients and demonstrated an 87% tumor response (both complete and partial) [60]. However, another comparative meta-analysis indicated that TACE may have a better overall outcome than TARE when indicated with an approximately 60% tumor response[61-63]. Soin *et al*[64] demonstrated that after successful downstaging of PVTT (Vp1-3), a 5-year overall survival rate of 57% was obtained, which was comparable to that of patients without PVTT (65%)[64]. Regardless of the preference, downstaging with TACE or TARE is widely used throughout the country, with comparable results to those within the respective criteria for LDLT or DDLT.

SBRT is less frequently used but has been established as a safe alternative to conventional bridging therapies such as radiofrequency ablation (RFA), TACE, and TARE[64-67]. Patients with contraindications to TACE, especially those with PVTT, may receive SBRT[68]. Compared to other forms of treatment for PVTT like 3D-chemoradiation therapy, hepatic artery infusion chemotherapy, and molecular targeted drugs for HCC, SBRT offers a higher biologically effective dose in a shorter duration[69]. Retrospective studies of SBRT as a downstaging tool have indicated a good response and overall 5-year survival post-LT. In India, most centers select SBRT when TACE/TARE is not feasible or in the presence of branch PVTT (Vp1-2). However, the use of AFP in downstaging protocols remains controversial. There is no consensus among centers around the globe regarding the incorporation of biological (tumor markers, such as AFP) and morphological features for downstaging prior to transplantation. When adopting the UCSF criteria, the UNOS also suggested that a significant drop in AFP (< 500 ng/mL) along with stable disease at 6 months would be acceptable for DDLT listing[21, 57]. Other studies have proposed various cutoffs for initial listing and downstaging endpoints ranging from < 100 to < 1000 ng/mL, while a few criteria have no cutoff and would accept any AFP if morphological variables were acceptable [25,30,48,70]. In our study, the majority of centers used 1000 ng/mL as a cut-off for AFP either at primary listing or after downstaging to proceed with LT. It is universally agreed that higher AFP levels impact the risk of recurrence and have worse outcomes than lower AFP levels. Finally, a combination of atezolizumab and bevacizumab was used by six centers as a bridge to transplantation. Several worldwide reports have suggested successful downstaging of advanced HCC with combination immunotherapy[71-72]. There is significant concern regarding the safety of using immunotherapy in patients with HCC who may later undergo liver transplant, especially given the risk of immune-related adverse events. In the IMBrave 150 trial, grade 3 to 4 toxicities were reported in 38% of patients receiving combination therapy with atezolizumab and bevacizumab[73]. In our study, many other centers did not use it because of a lack of experience, controversial nature or affordability issues.

The downstaging criteria for most centers were similar to their respective criteria for LT. The overall goal of downstaging is to give the opportunity for higher survival through LT to patients with HCC–CLD who would otherwise not fall into the LT criteria. Clavien *et al*[37] recommended that downstaging should only be performed when the 5-year

survival rate after LT is comparable to those that fit the criteria without downstaging[37]. Our survey provided varying opinions on this aspect. Morphological and biological tumor responses were the main aspects, while the non-progression of tumors was also an important factor to consider. The modified Response Evaluation Criteria in Solid Tumors was also used by several centers[74,75]. Notably, all transplant centers waited at least 4 wk, with nearly 70% preferring to wait 6 wk after successful downstaging to ensure disease stability.

Post-operative care and follow-up

There is no international consensus on the post-transplant surveillance of HCC patients. The National Comprehensive Cancer Network guidelines suggest imaging and AFP every 3–6 months initially, followed annually thereafter[76]. We have a similar protocol for HCC surveillance after LT. Patients with hepatitis B usually continue antiviral therapy. In this survey, more than 50% respondents opted for CECT abdomen alone as their imaging of choice, while the remaining picked PET-CT or CECT abdomen with bone scintigraphy. Many pre-transplant factors are implicated in the risk of HCC recurrence, such as the number and size of nodules, vascular invasion, AFP level, neutrophil-to-lymphocyte ratio, bridging therapy prior to transplantation, presence of metabolic syndrome, viral infections, and time to transplant[77]. In the post-transplant period, immunosuppression with calcineurin inhibitors at higher levels has been implicated in recurrence but has not yet been established[78]. However, it is well established that most HCC recurrences occur within 2 years post-LT[79-81]. Regardless of the type of imaging or cause of recurrence, early diagnosis and treatment by RFA or resection offer the only hope for long-term survival. The use of mammalian target of rapamycin inhibitors in post-transplant period is not routinely recommended according to International Liver Transplant Society guidelines[78]. However, in the current context, everolimus was routinely used by 22 of the 23 centers listed in this study.

Expansion of current criteria

HCC is one of the leading causes of cancer-related deaths worldwide, with an annual global mortality rate of more than 800000[4]. An increase of up to 55% in the global burden of HCC is expected by 2040 (an estimated 1.3 million cases and 1.4 million deaths)[12-14]. LT offers hope to patients with HCC–CLD without extrahepatic disease for a better chance of survival[15-19]. It has already been established as the best treatment option for patients, with the highest survival rate. However, for long, LT was not considered an option for patients with HCC–CLD. This was followed by an era in which stringent criteria for sufficiently good outcomes were used to justify the use of deceased donor livers for other patients on waitlists[20,21,37]. Over the years, this has been accepted as the benchmark for new and upcoming guidelines and their corresponding results. The use of living donor grafts has mitigated the concern of the use of deceased donor livers for HCC patients; however, it has raised issues over overall survival rates compared to the risk of living liver donation. The benchmark of survival is highly debatable, but in a country like India, where the non-transplant survival of HCC–CLD patients is extremely low, any chance of a 5-year success beyond 50% warrants sufficient discussion[37,64]. Markov models and other recent downstaging studies suggest that a 5-year survival rate of 60% is worth the minimal risk of living donations and deceased donor candidacy[38]. However, other guidelines have suggested deceased donor candidacy at outcomes comparable to those of patients with CLD without HCC, whereas LDLT can be pursued with lower outcomes in the setting of full disclosure of risks and benefits[37].

Summary

Based on our survey, we summarize the following trends across liver transplant programs in India:

(1) Approximately 10% of CLD patients in India undergoing LT are diagnosed with HCC; however, only 5% of these patients fall within Milan criteria;

(2) Most centers follow the expanded center-specific criteria for LDLT, with comparable outcomes to those who fall within the Milan criteria. However, further validation is required through national collaborations and multicenter studies;

(3) PET-CT is the most preferred modality of metastatic work-up in HCC–CLD patients. AFP is the biological marker of choice; however, many centers opt for PIVKA-II surveillance;

(4) All centers opted for downstaging as a bridge to LT or to fit center-specific criteria if no extrahepatic metastasis or major vascular invasion was present. TACE, TARE, and SBRT are the therapies of choice with varying indications, whereas atezolizumab/bevacizumab combination immunotherapy is infrequently used. Downstaging was confirmed using both morphological and biological markers according to either international or center-specific guidelines;

And (5) Post-transplant surveillance was mostly guided by CECT abdomen and tumor markers, while some centers opted for PET-CT or CECT and bone scintigraphy. Despite the lack of concrete evidence, almost all centers started administering everolimus in the post-transplant period for HCC–LT patients.

CONCLUSION

The current predicted 5-year survival rate of HCC patients in India is less than 15%. The aim of transplantation is to achieve at least a 60% 5-year disease free survival rate, which will provide relief to the prediction of an HCC surge over the next 20 years. The current worldwide criteria (Milan/UCSF) may have a higher 5-year survival (> 70%); however, the majority of patients still do not fit these criteria and are dependent on other suboptimal modes of treatment, with much lower survival rates. To make predictions for 2040, we must prepare to arm ourselves with less stringent selection criteria to widen the pool of patients who may undergo transplantation and have a chance of a better outcome. With more advanced technology and better donor outcomes, LDLT will provide a cutting edge in the fight against liver cancer over

the next two decades.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) with chronic liver disease (CLD) is an indication for liver transplantation (LT). However, the overall survival for this condition is low in India, especially due to late presentation.

Research motivation

The various criteria that are established worldwide may lead to comparable outcomes compared to non-HCC patients, but significantly limit the number of patients that can avail this treatment option.

Research objectives

The aim of our study was to establish the current trends and give our opinion as to how to improve the donor pool or increase the access of patients to this life saving treatment option by relaxing stringent criteria while maintaining at least significant survival benefit.

Research methods

We conducted a survey to see the current trend of practices in India with regards to HCC-CLD patients undergoing LT.

Research results

In this survey, we were able to ascertain trends of practice in HCC-CLD patients with respect to LT. We were also able to identify possible pathways to improve access of LT to these patients and improve the overall survival rates of HCC patients in India to make it comparable to other cancers.

Research conclusions

This study shows that majority of patients are still dependent on sub optimal modes of treatment, and less stringent criteria may need to be followed with acceptable outcomes so that we may be able to match the increasing burden on HCC predicted over next 2 decades.

Research perspectives

To make predictions for 2040, we must prepare to arm ourselves with less stringent selection criteria to widen the pool of patients who may undergo transplantation and have a chance of a better outcome.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Comparison of resistive index and shear-wave elastography in the evaluation of chronic kidney allograft dysfunction

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Abstract

BACKGROUND

Detection of early chronic changes in the kidney allograft is important for timely intervention and long-term survival. Conventional and novel ultrasound-based investigations are being increasingly used for this purpose with variable results.

AIM

To compare the diagnostic performance of resistive index (RI) and shear wave elastography (SWE) in the diagnosis of chronic fibrosing changes of kidney allograft with histopathological results.

METHODS

This is a cross-sectional and comparative study. A total of 154 kidney transplant recipients were included in this study, which was conducted at the Departments of Transplantation and Radiology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan, from August 2022 to February 2023. All consecutive patients with increased serum creatinine levels and reduced glomerular filtration rate (GFR) after three months of transplantation were enrolled in this study. SWE and RI were performed and the findings of these were evaluated against the kidney allograft biopsy results to determine their diagnostic utility.

RESULTS

The mean age of all patients was 35.32 ± 11.08 years. Among these, 126 (81.8%) were males and 28 (18.2%) were females. The mean serum creatinine in all patients was 2.86 ± 1.68 mg/dL and the mean estimated GFR was 35.38 ± 17.27 mL/min/1.73 m^2. Kidney allograft biopsy results showed chronic changes in 55 (37.66%) biopsies. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SWE for the detection of chronic allograft damage were 93.10%, 96.87%%, 94.73%, and 95.87%, respectively, and the diagnostic accuracy was 95.45%. For RI, the sensitivity, specificity, PPV, and NPV were 76.92%, 83.33%, 70.17%, and 87.62%, respectively, and the diagnostic accuracy was 81.16%.

CONCLUSION

The results from this study show that SWE is more sensitive and specific as compared to RI in the evaluation of chronic allograft damage. It can be of great help during the routine follow-up of kidney transplant recipients for screening and early detection of chronic changes and selecting patients for allograft biopsy.

Key Words: Shear wave; Sonoelastography; Resistive index; Chronic allograft changes; Biopsy; Histopathology

Core Tip: Kidney transplantation is the treatment of choice for patients with end-stage kidney disease. Although short-term outcomes have improved markedly, chronic allograft damage remains a formidable challenge. Early detection of chronic changes is crucial for the optimal well-being of the graft. Biopsy is the gold standard but is invasive, and prone to sampling error and interobserver variation. The resistive index on Doppler is routinely used for the assessment of renal allograft status but its value in chronic renal allograft dysfunction is unclear. Shear wave sonoelastography is a novel imaging technique that has shown promising results in a number of studies.

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INTRODUCTION

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease. However, the recipients of kidney transplants have to be continually monitored both clinically and by radiological and laboratory tests to ensure the proper functioning of the allograft and to detect any damage to the allograft at an early and reversible stage. In this regard, it is to be noted that allograft dysfunction can occur at any time post-transplantation. It is variously categorized as acute and chronic allograft dysfunction and the causes vary accordingly. An early and accurate diagnosis of the underlying causes is essential for optimal management and better long-term outcomes. Any damage to the graft parenchyma may result in chronic sclerosing changes in the parenchyma if not treated promptly. In spite of a comprehensive approach toward the allograft's well-being adopted in most transplantation centers, kidney graft damage often sets in and goes undiagnosed as early abnormalities are either undetected or the laboratory or radiological investigations and clinical presentation are insensitive to early changes in the graft parenchyma[1-3].

A number of diagnostic modalities including imaging and laboratory-based tools are used in practice to detect graft damage at an early stage. Conventionally, structural assessment of the allografts is done by the greyscale and Doppler ultrasounds (US), computed tomography scans, and magnetic resonance imaging, some of which, now provide added information regarding the function of the allograft[4-9]. US is a very useful and often the first-line non-invasive tool for the early diagnosis of reversible surgical complications and is used routinely during the follow-up of kidney transplant recipients (KTRs). The role of Doppler US in the assessment of vascular pathologies in transplanted kidneys can not be overemphasized[6,7]. Currently, several transplantation centers utilize the intrarenal resistive index (RI), which is calculated using Doppler ultrasonography, to evaluate the functional status of the renal allografts, particularly in the early post-transplant period. The RI is a hemodynamic index commonly used to measure blood flow resistance in organs to assess vascular disease[6]. Several studies have reported that an increased RI is diagnostic of acute transplant dysfunction. Naesens *et al*[7] in their seminal paper studied the usefulness of RI in protocol and graft dysfunction settings in 321 KTRs[7]. A total of 1124 kidney allograft RI measurements were included in the analysis. At protocol-specified biopsy time points, the RI was not associated with kidney allograft histologic features. Older recipient age was the strongest determinant of a higher RI. However, the RI was significantly higher in cases of antibody-mediated rejection or acute tubular necrosis, as compared with normal biopsy results, in allograft biopsies performed because of graft dysfunction[7]. They concluded that the routinely performed RI at pre-specified time points after transplantation reflects characteristics of recipient but not those of the graft[7]. Radermacher and Haller commented on the study by Naesens *et al* [7] and noted that the findings of their study differ from most previous studies, in which an increase in RI was associated

with graft deterioration[8]. They suggested possible explanations for these discrepant results. Naesens *et al*[7] studied interlobar arteries, whereas the previous studies investigated segmental arteries, and RI values are lower in the former arteries. The use of a lower cutoff value for the RI (*i.e.*, one considered abnormal) might have been more accurate in the study by Naesens *et al*[7] In addition, peripheral vessels are more prone to sampling bias, and the Doppler signal quality is poorer[8]. Timing of RI measurement was also a minor factor. The length of follow-up period is also a contributory factor to the discrepant results. According to Radermacher and Haller, a consensus on a single vessel area for study might provide a single cutoff value for the RI. This should allow an assessment of whether the RI predicts graft loss, recipient death, or both, and the results of which would define the role of the RI in the assessment of transplant patients[8]. The usefulness of the RI after kidney transplantation, particularly in chronic allograft dysfunction, remains controversial. RI as an investigation suffers from certain pitfalls, particularly in extended criteria donors or old recipients. Most importantly, its assessment is not uniformly standardized. It is a non-specific prognostic marker of vascular diseases that affect the kidney. The RI is thought to reflect central hemodynamic (cardiac or aortic) characteristics rather than properties of the kidney or kidney allograft. There is little correlation between the RIs and the quantitative extent of kidney allograft dysfunction.

More recently, another emerging technology of US, *i.e.*, sonoelastography, is increasingly being used to assess and visually display tissue stiffness by US probes[10-14]. Elasticity imaging or elastography is an imaging modality based on tissue stiffness or hardness, rather than anatomy. US elastography can be considered the imaging equivalent of palpation, being able to quantify the stiffness of a lesion, which was previously judged only subjectively by physical examination[10, 11]. Palpation has been used to evaluate malignancy for a very long time. Sonoelastography has mainly been used in the diagnosis of cancers in both superficial and deep organs like the breast, thyroid, and prostate gland[15-21].

Recent studies have suggested that quantitative elastography is a reliable non-invasive tool to assess chronic fibrosing changes in organs like the liver[22-26] and kidney[27-32] at early stages. A few studies have investigated the usefulness of sonoelastography in the assessment of chronic fibrosing changes in the kidney allograft[33-36]. In the first clinical pilot study by Arndt *et al*[33], parenchymal stiffness measured by sonoelastography was found to be suitable for assessing the progression of kidney allograft fibrosis. They concluded that a longitudinal assessment of parenchymal stiffness might be a powerful tool to identify patients with chronic allograft damage who benefit from biopsy and consequent adaptation of the immunosuppressive treatment[33]. Subsequently, many more studies have reported the diagnostic utility of sonoelastography in the assessment of chronic kidney allograft dysfunction[34-36]. However, only a few studies have compared the diagnostic performance of RI *vs* shear-wave elastography (SWE) in the assessment of chronic sclerosing changes in the kidney allograft. The aim of this study was to compare the diagnostic performance of RI and SWE in the early detection of chronic fibrosing changes in kidney allograft against the findings of renal allograft biopsy.

MATERIALS AND METHODS

This cross-sectional, observational study was conducted at the Radiology, Histopathology, and Transplantation departments, Sindh Institute of Urology and Transplantation, Karachi, Pakistan from August 2022 to February 2023. A formal approval was sought from the research and ethical committees of the institution before starting the study. All consecutive adult KTRs who fulfilled the inclusion criteria were included. The inclusion criteria included patients presenting with kidney allograft dysfunction occurring any time after the first three months of transplantation and manifesting as a rise in serum creatinine > 20% from the baseline or reduced estimated glomerular filtration rate (eGFR) < 50 mL/min, as determined by Cockcroft-Gault (C-G) formula and a normal allograft size (≥ 9 cm). Kidney transplant patients with a skin-to-allograft distance of > 3 cm, cortex thickness < 1 cm, kidney allograft dysfunction within first three months after transplantation, small graft size (< 9 cm), and perigraft fluid collection were excluded.

Written informed consent was taken from all eligible patients. The patients were either referred from the outpatient department of transplant services or they were admitted in the transplant ward. All patients participating in this study received kidney transplants from a living-related donor.

All consecutive adult patients (≥ 20 years) of either gender were investigated by all three methods, *i.e.*, Doppler US, SWE, and kidney allograft biopsy.

All US assessments including SWE measurements were performed by the two experienced radiologists with > 10 years of experience in the abdominal US, including 5 years of experience with SWE and Doppler sonography. One of these performed RI measurements first on all included patients independently followed by the other radiologist, who performed SWE and allograft biopsy, also independently, such that no duplicate measurements of the radiological tests were performed. Both were blinded to the patient data and each other's sonographic findings. A "check" US examination was performed first to assess the morphologic characteristics of the allograft and its vascularity, perigraft collection, and skin-to-allograft distance. SWE measurements were then undertaken with the patient lying in a supine position. The sampling for point-based SWE was performed with the patient holding his or her breath. A total of six measurements of SWE (US systems (CANON; APLIO i800) in kPa were made with two measurements each from the upper pole, lower pole, and mid-polar regions. The mean of these six values of parenchymal stiffness was calculated for each patient and was analyzed. The representative SWE visual displays and the quantitative parameters in a case of stable graft function and another case with chronic allograft changes are shown in Figure 1. In Figure 1B and D, the elastography demonstrates the non-homogeneous color coding of the area in renal allograft with multiple colors with red color predominating which represents a significant loss of elasticity and increased stiffness of the renal allograft parenchyma. In addition, both the speed and elasticity columns are very heterogeneous in Figure 1B and D, reflecting patchy distribution of early fibrosis. Most severely affected area was chosen for sampling for the allograft biopsy. The sonoelastography findings were

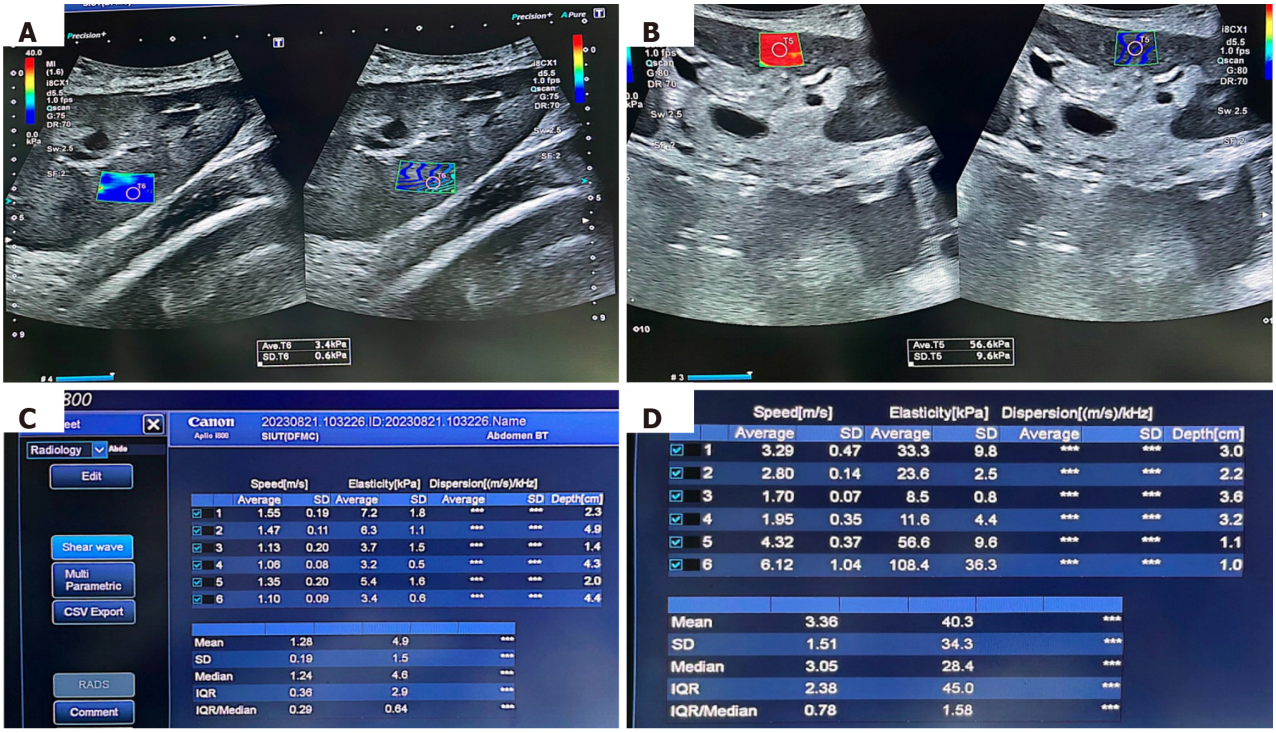

Figure 1 Shear wave elastography results from a case of stable graft function and with chronic kidney allograft dysfunction. A: Shear wave elastography of the kidney graft parenchyma. Tissue elasticity is determined within the selected one region of interest and visually displayed as blue color; B: Shear wave elastography of the kidney graft parenchyma in this case is showing red colour which denotes increased tissue stiffness of the parenchyma; C: Quantitative report in kPa. The mean of the elasticity is 4.9 kPa, which is within the normal range; D: The quantitative value in kPa in this case is 40.3 kPa, which is clearly increased.

correlated with histopathology of the same renal allografts showing variable degrees of chronic changes (Figure 2). Kidney allograft biopsies were interpreted according to the updated Banff classifications. Two cores of kidney allograft biopsies were performed routinely and processed according to standard guidelines. As noted above, the most abnormal area of allograft parenchyma on SWE was selected for biopsy purpose.

The same procedure was repeated for measuring the RI on the same US system as was used for SWE. A single reading was recorded for each pole and the mean value was calculated for each patient.

The findings of the SWE and RI were then compared with the histopathological findings of the allografts on renal allograft biopsy in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. The results of histopathology were considered the gold standard for this purpose. The average of the semi-quantitative scores of chronic changes affecting the two cores were considered for final analysis.

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS 21.0). Descriptive statistics were applied. Mean ± SD was computed for the quantitative variables distributed normally, *i.e.* age of patients and serum creatinine. For non-normally distributed data, such as posttransplant duration of biopsies, median ± interquartile range (IQR) were used. Frequencies and percentages were calculated for qualitative variables, *i.e.*, presenting complaints and histopathological findings.

Taking histopathological findings as the gold standard, all statistical parameters (sensitivity, specificity, PPV, NPV) were calculated to obtain diagnostic accuracy of SWE and RI.

RESULTS

In this study, a total of 154 KTRs of both genders were included. The mean age of all patients was 35.32 ± 11.08 years (range: 20-60 years). Among these, 126 (81.8%) were males and 28 (18.2%) were females. The US-based investigations and allograft biopsies were performed at a median posttransplant duration of 24 months (IQR: 7 to 61.5 months). Around 50% of biopsies were performed within 24 months after transplantation. The mean serum creatinine at the time of biopsy was 2.86 ± 1.68 mg/dL and the mean eGFR was 35.38 ± 17.27 mL/min/1.73 m^2. Histopathological confirmation of chronic allograft changes was obtained in 55 (37.66%) biopsies. However, SWE results were positive for chronic changes in 57 (37.01%) of cases, as shown in Table 1. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SWE for the detection of chronic changes were 93.10%, 96.87%, 94.73%, and 95.87% and the overall diagnostic accuracy was 95.45% (Table 1). On the other hand, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of RI for the detection of chronic changes were 76.92%, 83.33%, 70.17%, 87.62%, and the diagnostic accuracy 81.16% (Table 2).

Table 1 Diagnostic performance of shear-wave elastography in chronic renal allograft dysfunction, *n* (%)

Shear-wave elastography results	Histopathological results		Total
	Positive	Negative	
Positive	54 (TP)	3 (FP)	57 (37.01)
Negative	4 (FN)	93 (TN)	97 (62.98)
Total	58 (37.66)	96 (62.33)	154 (100)
Sensitivity	54/58	93.10	
Specificity	93/96	96.87	
Positive predictive value	54/57	94.73	
Negative predictive value	93/97	95.87	
Diagnostic accuracy	(54 + 93)/154	95.45	

TP: True positive; FP: False positive; FN: False negative; TN: True negative.

Table 2 Diagnostic performance of resistive index on Doppler ultrasound in chronic kidney allograft dysfunction, *n* (%)

Resistive index results	Histopathological results		Total
	Positive	Negative	
Positive	40 (TP)	17 (FP)	57 (37.01)
Negative	12 (FN)	85 (TN)	97 (62.98)
Total	52 (33.76)	102 (66.23)	154 (100)
Sensitivity	40/52	76.92	
Specificity	85/102	83.33	
Positive predictive value	40/57	70.17	
Negative predictive value	85/97	87.62	
Diagnostic accuracy	(40 + 85)/154	81.16	

TP: True positive; FP: False positive; FN: False negative; TN: True negative.

The sonoelastography clearly performed better than RI in predicting the chronic allograft changes with superior sensitivity, specificity, and positive and NPV as shown in Table 2.

DISCUSSION

Chronic sclerosing changes in kidney allografts have been categorized in different ways. In the pre-Banff era, these were labeled as "chronic rejection" irrespective of the underlying etiopathogenesis. The Banff classification introduced the term chronic allograft nephropathy (CAN)[37]. In 2005, the term CAN was replaced by interstitial fibrosis/tubular atrophy (IFTA). The changes of IFTA are highly prevalent in kidney allografts. A study by Nankivell *et al*[38] found chronic changes in 24.7% of renal transplant recipients 1 year post-transplant and the percentage increased to 89.9% in recipients after 10 years of a kidney transplant making CAN the most frequent reason for kidney graft failure[38]. The chronic changes are thought to be the result of chronic subclinical injury, either immune-mediated or non-immune, that progresses to kidney allograft failure[39].

An early and accurate diagnosis of chronic changes is imperative for salvaging the kidney allograft from failure. Protocol biopsies represent the gold standard for detecting chronic changes in the allograft parenchyma at an early stage. However, these are associated with certain complications and drawbacks related to the invasive nature, sampling error, and subjectivity of their interpretation[40]. The current approaches for diagnosis of suspected IFTA include serum creatinine and eGFR measurements and vascular perfusion assessment by RI using Doppler US. When abnormalities are detected in the above-mentioned parameters, the next step in evaluation is kidney allograft biopsy for tissue diagnosis[41, 42]. Various formulas are used for calculating eGFR in the kidney transplant patients and all give comparable results[43, 44]. Hence, we used C-G formula in our study, as it is relatively straightforward in calculation.

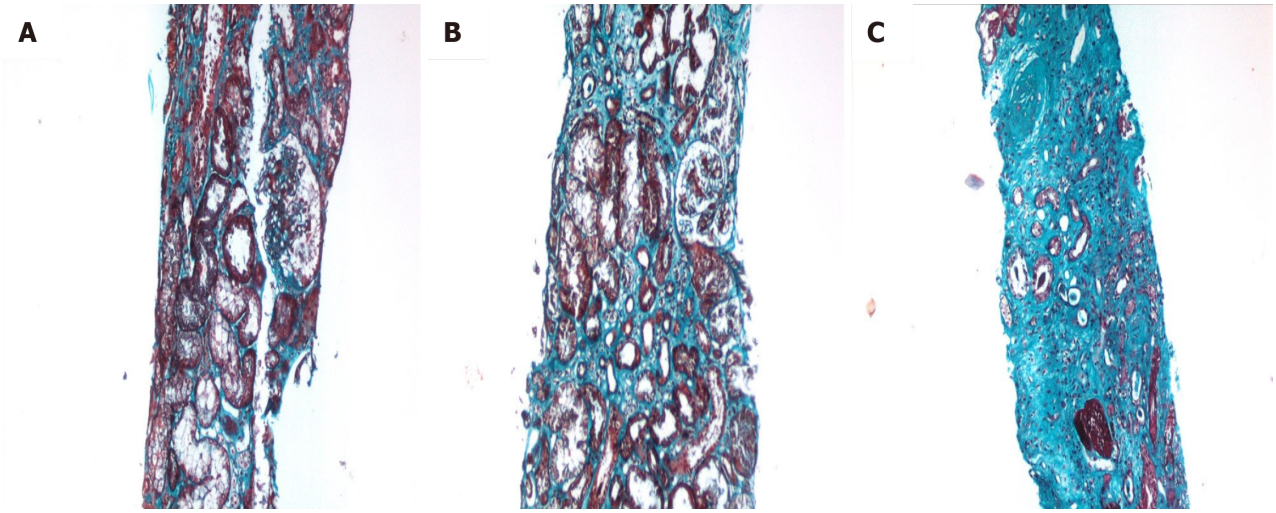

Figure 2 Histopathology results from allograft biopsies. A: In this case, there is early deposition of blue collagen in between the tubules, which are showing only mild atrophy. One glomerulus included is intact (Trichrome stain, × 200); B: In this example, there is moderate amount of fibrous tissue in the graft parenchyma and moderate tubular atrophy. One glomerulus included is intact (Trichrome stain, × 200); C: In this case, there is severe tubular atrophy associated with severe interstitial fibrosis. The included glomerulus is globally sclerosed (Trichrome stain, × 200).

Very few studies are available in the literature on the detection of early fibrosing changes in transplanted kidneys using sonoelastography, which assesses stiffness as a measure of fibrosis[34-36,45-50]. A large number of studies are available for superficial organs like the breast and thyroid gland[15-26]. The native kidneys are deep-seated and hence, have been little investigated by this technique[27-32]. In a study done to determine the elasticity of various tissues, Arda *et al*[45] studied normal elasticity values within the kidney cortex along with many other internal organs in 127 healthy volunteers aged 17-63 years. The mean elasticity values were 5.2 ± 2.9 kPa (range: 1-13 kPa) in men and 4.9 ± 2.9 kPa (range: 1-26 kPa) in women of renal cortex[45]. Some studies conducted previously have reported that renal parenchymal elasticity values differ with anisotropy, and vascular and urinary pressures[46]. According to these authors, intrarenal elasticity values fluctuate with tissue anisotropy and, with vascular and urinary pressure levels. These parameters must be taken into account for the interpretation of tissue changes[47].

Exploiting the superficial location of the kidney allograft, several studies have been conducted to determine the diagnostic utility of SWE in the evaluation of kidney allograft dysfunction and compared it with various clinical, laboratory, or imaging parameters[34-36,48-55]. The mean parenchymal stiffness on SWE was 24.5 + 7.34 kPa (range: 17-32 kPa) in patients with allograft dysfunction in this study. Parenchymal stiffness showed a positive correlation with serum creatinine level (r = 0.714; P < 0.001) and a negative correlation with eGFR (r = 20.725; P < 0.001). Lukenda *et al*[48] studied transient elastography (TE) in 52 KTRs and reported a highly significant negative correlation of kidney allograft stiffness on SWE with eGFR in 52 KTRs (r = -0.640; P < 0.0001). The kidney allograft stiffness showed a positive correlation with allograft fibrosis on biopsy (r = 0.727; P = 0.0001). They concluded that parenchymal stiffness obtained by elastography reflects interstitial fibrosis[48]. Therefore, elastography provides the opportunity for noninvasive screening of CAN. Similarly, Ozkan *et al*[47] studied 42 patients by real-time sonoelastography to investigate the relationship of tissue stiffness with RI and eGFR. Allograft parenchymal stiffness demonstrated a significant positive correlation with RI (r: 0.41, P = 0.007). They did not find a significant correlation between parenchymal stiffness and eGFR (P = 0.42). Interobserver agreement, expressed as intraclass correlation coefficient, was fair at 0.47 (95%CI: 0.05- 0.70). They concluded that parenchymal stiffness showed a significant positive correlation with RI but sonoelastography has also a wide range of intra- and low interobserver agreement in kidney transplants warranting further studies[47].

Arndt *et al*[33] studied TE in 57 KTRs and found that parenchymal stiffness was significantly and positively correlated to the extent of interstitial fibrosis (r = 0.67, P = 0.002) and inversely related to eGFR (r = 0.47, P = 0.0003). Parenchymal stiffness values of patients with an eGFR > 50 mL/min were significantly lower than in patients with an eGFR 50 mL/min (22.2 ± 11.0 *vs* 37.1 ± 14.2 kPa, P = 0.0005). The parenchymal stiffness values of Chronic allograft injury Banff grades 0-1 differed significantly from grade 2 (P = 0.008) and grade 3 (P = 0.046). Parenchymal stiffness measured by TE reflects interstitial fibrosis in kidney allografts. They concluded that a longitudinal assessment of parenchymal stiffness might be a potent tool to identify patients with chronic allograft changes who benefit from biopsy and consequent alteration of the immunosuppressive regime[33].

More recently, Barsoum *et al*[54] studied 36 KTRs with SWE with biopsy-proven CAN. All patients underwent a B-mode US examination followed by US SWE in the same sitting, as in our study. They compared the results of SWE measurements with the histopathological results. They found that the mean parenchymal stiffness was directly correlated with time post-transplantation. With a longer post-transplantation period, parenchymal stiffness and IF/TA percentages increased with r = 0.72, 0.90, and P value < 0.001. Antero-posterior (AP) diameter of the kidney allograft was significantly correlated with mean parenchymal stiffness as the larger the AP diameter, the higher the mean parenchymal stiffness with r = 0.47, 0.73, and P value 0.001. Sensitivity analysis showed that US SWE can significantly predict moderate Banff score of renal fibrosis using a cutoff value of 28.67 kPa with sensitivity of 87.5%, specificity of 90%, area under the curve

(AUC) of 0.91, and *P* value < 0.001. SWE may be useful for the prediction of fibrosis in KTRs, especially in the case of a moderate Banff score, where the accuracy reached 87.5% using a cutoff value of 28.67 kPa. They concluded that US SWE may be of great help in the regular follow-up of KTRs. It can act as a screening tool to identify patients with early parenchymal fibrosis, eventually helping in the early diagnosis and management and helping in selecting patients who are candidates for biopsy and in avoiding repeated unnecessary biopsies for others[54].

We found a sensitivity of 93.10% and specificity of 96.87% of SWE for the detection of chronic fibrosing changes in the allograft biopsy. These results are marginally better than RI on Doppler studies. Our results are also slighter better as compared to those of Barsoum *et al*[54] in terms of overall sensitivity and specificity[54]. In our study, the parenchymal stiffness measurement correlated with histopathological diagnosis.

Although histopathology is considered the gold standard for the detection of chronic renal allograft changes, there are a few drawbacks related to this invasive method. These drawbacks include sampling errors, traumatic complications, and interobserver variations among histopathologists. Hence, a search for non-invasive techniques for the early diagnosis of kidney allograft damage has always been a dream of researchers. The best attribute of sonoelastography as a modality is its noninvasive nature making it a safe screening tool for serial evaluation of kidney allograft. In addition to being non-invasive, SWE enables us to assess a much larger area of the tissue under study as compared to biopsy. On the basis of the results of the present study, it would not be wrong to state that this study will help in building confidence among clinicians regarding non-invasive modalities for the diagnosis of chronic allograft dysfunction. However, we do recognize that allograft biopsy will retain the status of the gold standard in cases with equivocal or ambiguous findings, or in synchrony with sonoelastography. In addition, if used judicially, this technique will help in decreasing the bulk of invasive procedures making the investigative process less risky for the patients.

There are certain limitations to this study. Firstly, it is a single-center study. No follow-up data was collected for this study. We did not calculate the AUC for SWE regarding its diagnostic utility. There is a need for multicenter studies to add more strength to the observations made in this study. Certain artifacts are associated with increased thickness of the patient which renders it appropriate in patients of a certain body habitus.

CONCLUSION

In conclusion, SWE is more sensitive and specific as compared with RI and can serve as a reliable noninvasive imaging modality for the detection of early chronic changes in the kidney allograft. On the basis of these results, we propose to use SWE routinely for serial evaluation of kidney allograft during follow-up for early detection of chronic changes and selecting patients for allograft biopsy.

ARTICLE HIGHLIGHTS

Research background

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease. Although, short-term outcomes have improved but long-term graft survival remains a formidable challenge. Detection of early chronic changes in the kidney allograft is important for timely intervention and long-term survival. Conventional and novel ultrasound (US)-based investigations are being increasingly used for this purpose with variable results. This study aims to compare the diagnostic performance of two US-based tests with biopsy results.

Research motivation

The main aim is to determine the diagnostic performance of a non-invasive US-based investigation in the assessment of early chronic changes in the kidney allograft. This will help avoid or minimize the invasive procedure of kidney allograft biopsy.

Research objectives

The main objective was to assess the diagnositc performance of shear-wave elastography (SWE) on US of the allograft kidney for detection of early chronic changes in the kidney allograft. It was found that SWE performs better than resistive index (RI) and this can be a useful addition to the diagnostic armamenterium for post-transplant follow-up.

Research methods

All consecutive kidney transplant patients with increased serum creatinine levels and reduced glomerular filtration rate three months after transplantation were assessed by SWE and RI tools and the findings of these were analyzed against the kidney allograft biopsy results to determine their diagnostic performance.

Research results

The sensitivity, specificity, positive predictive value, and negative predictive value of SWE for the detection of chronic allograft damage were better as compared to RI results. These results indicate that SWE test is more sensitive for the detection of early chronic changes in the kidney allograft and this should be routinely used in the assessment of kidney allograft during post-transplant follow-up.

Research conclusions

Novel US-based techniques offer promising new tools for non-invasive monitoring of early chronic kidney allograft damage. These can be used for screening the kidney transplant patients during routine follow-up visits followed by biopsies.

Research perspectives

Further improvements in US-based techniques for non-invasive monitoring of kidney allograft status are needed.

FOOTNOTES

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SYSTEMATIC REVIEWS

Use of machine learning models for the prognostication of liver transplantation: A systematic review

Gidion Chongo, Jonathan Soldera

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Abstract

BACKGROUND

Liver transplantation (LT) is a life-saving intervention for patients with end-stage liver disease. However, the equitable allocation of scarce donor organs remains a formidable challenge. Prognostic tools are pivotal in identifying the most suitable transplant candidates. Traditionally, scoring systems like the model for end-stage liver disease have been instrumental in this process. Nevertheless, the landscape of prognostication is undergoing a transformation with the integration of machine learning (ML) and artificial intelligence models.

AIM

To assess the utility of ML models in prognostication for LT, comparing their performance and reliability to established traditional scoring systems.

METHODS

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines, we conducted a thorough and standardized literature search using the PubMed/MEDLINE database. Our search imposed no restrictions on publication year, age, or gender. Exclusion criteria encompassed non-English studies, review articles, case reports, conference papers, studies with missing data, or those exhibiting evident methodological flaws.

RESULTS

Our search yielded a total of 64 articles, with 23 meeting the inclusion criteria. Among the selected studies, 60.8% originated from the United States and China combined. Only one pediatric study met the criteria. Notably, 91% of the studies were published within the past five years. ML models consistently demonstrated satisfactory to excellent area under the receiver operating characteristic curve values (ranging from 0.6 to 1) across all studies, surpassing the performance of traditional scoring systems. Random forest exhibited superior predictive capabilities for 90-d mortality following LT, sepsis, and acute kidney injury (AKI). In contrast, gradient boosting excelled in predicting the risk of graft-versus-host

disease, pneumonia, and AKI.

CONCLUSION
This study underscores the potential of ML models in guiding decisions related to allograft allocation and LT, marking a significant evolution in the field of prognostication.

Key Words: Liver transplantation; Machine learning models; Prognostication; Allograft allocation; Artificial intelligence

Core Tip: This systematic review highlights the promising role of machine learning (ML) models in improving prognostication for liver transplantation (LT). ML models consistently outperformed traditional scoring systems, demonstrating excellent predictive capabilities for various post-transplant complications, including mortality, sepsis, and acute kidney injury. The findings underscore the potential of ML in enhancing decision-making related to organ allocation and LT, representing a substantial advancement in prognostication methods.

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INTRODUCTION

Liver transplantation (LT) has long been a transformative intervention for individuals afflicted with acute and chronic-end-stage liver ailments. In addition to restoring patients' health, LT can enhance their overall well-being and potentially extend their lifespan by up to 15 years[1]. This treatment approach is firmly established as a last resort when alternative methods and therapies have proven ineffective. According to the Scientific Registry of Transplant Recipients in the United States, the survival rates for patients after deceased donor LT are commendable, standing at approximately 90% at one year and 77% at five years post-LT[2]. Nevertheless, the field of LT confronts a range of challenges, encompassing can-didate selection, organ allocation, and a scarcity of donor organs.

The persistent scarcity of donor organs has emerged as a critical and ongoing concern. While living donation has bolstered liver transplant numbers in some regions, in others, the field has stagnated. Consequently, there has been a concerted effort over the past decade to augment the pool of deceased donors. This endeavor has led to increased utilization of liver allografts obtained after cardiac death (DCD), as well as those from marginal and extended donor criteria[3]. Despite these improvements, a notable number of DCD livers remain unused due to suboptimal allograft function and unacceptable donor parameters. This predicament has given rise to the concept of mechanical perfusion for solid organ transplantation, aiming to expand the available organ pool, particularly for liver allografts, further underscoring the significant scarcity of this vital resource for transplantation[4].

A recent study emphasized the multifaceted challenges inherent to LT. In 2017, the United States recorded a waiting list of 14360 candidates eagerly awaiting LT[5]. Furthermore, the study reported an average hospital expenditure exceeding $490000 per patient associated with LT in 2011[5]. Evidently, there is an escalating demand for a more efficient system of liver organ allocation to optimize outcomes within a society grappling with diminishing liver organ donations and escalating expenditures linked to the care of end-stage liver disease patients.

The allocation of liver allografts to patients in need has relied on various scoring tools. Initially, Child-Turcotte-Pugh (CTP) score served this purpose, but the Model for End-stage Liver Disease (MELD) has now become the preferred score for organ allocation. Additionally, several other scoring systems, such as survival outcomes following LT (SOFT), balance of risk (BAR), donor risk index (DRI), age, bilirubin, international normalized ratio (INR), and creatinine (ABIC), chronic liver failure (CLIF)-Consortium Organ Failure scoreC OFs (CLIF-C OFs), CLIF-Consortium score for Acute on Chronic Liver Failure (CLIF-C ACLFs), and CLIF-Sequential Organ Failure Assessment score (SOFA), have been employed in this context.

The CTP score, initially validated for predicting postoperative mortality in cirrhotic patients, incorporates clinical and biochemical data, including serum albumin, serum bilirubin, INR or prothrombin time, ascites, and encephalopathy, to assess the prognosis of end-stage liver disease. The total Child-Pugh (CP) score is calculated by assigning points to each variable, with a maximum score of 15 points (Supplementary Table 1). CP class A corresponds to a score of 5-6 points, with a 10% mortality rate. CP class B corresponds to a score of 7-9 points, with a 30% mortality rate, while CP class C repre-sents a score of 10-15 points, associated with a poorer prognosis, including a 50% mortality rate at one-to-five years and sometimes as high as 70%-80%[6-8].

However, the use of CTP for liver transplant allocation had significant limitations. It relied on subjective assessments of ascites and encephalopathy, lacked an evaluation of renal function, and had a limited scoring range, making it challenging to differentiate patients based on disease severity. This limitation was evident when patients with different

INR and bilirubin levels were assigned the same CTP score, potentially leading to misleading prioritization[9]. Other drawbacks of the CTP score include the empirical selection of variables and the interdependence of some variables, such as coagulation and albumin, which could result in an imbalance in their influence within the score.

The CTP score's arbitrary cutoffs for quantitative variables lack evidence of optimality in defining hepatic changes and mortality risk, hindering its reliability in predicting prognosis in liver cirrhosis and post-LT[10]. Conversely, MELD score, originally designed for predicting survival after trans-jugular intrahepatic Porto-systemic shunt procedures, has been extended to assess prognosis in liver cirrhosis and serves as a tool for liver organ allocation[11]. MELD score's has a good reliability in predicting 1-year and 5-year survival across diverse liver diseases, including alcoholic cirrhosis and hepatitis [12]. Additionally, MELD score has prognostic value in conditions like spontaneous bacterial peritonitis, variceal bleeding, and hepatorenal syndrome (HRS)[13]. In cases of variceal bleeding, the MELD score's predictive ability was comparable to the CTP score. Concerning HRS, a high MELD score (> 20) has been linked to a median survival of just 1 mo for type 1 HRS, while type 2 HRS patients' survival correlated with their MELD score, with a median survival of 3 mo for MELD > 20 and 11 mo for MELD < 20[14]. To enhance its predictive power, the MELD score has evolved into multiple versions, including MELD sodium (MELD NA) and Delta MELD (D-MELD).

MELD NA, developed due to the observation of dilutional hyponatremia in cirrhotic patients, stems from systemic arterial vasodilation-induced antidiuretic hormone release, which was linked to portal hypertension severity[15]. Hyponatremia indirectly contributes to portal hypertension, leading to complications like ascites, HRS, and liver-related mortality[16]. Neurologic dysfunction, refractory ascites, HRS, and liver disease-related death are also associated with hyponatremia[17]. Numerous studies affirm hyponatremia as an independent predictor of early mortality, with the most pronounced impact between sodium concentrations of 120 to 135 mEq/L. A 1 mEq/L decrease corresponds to a 12% reduction in 3-month survival probability. Adding sodium to the MELD score enhances its predictive accuracy, especially for lower MELD scores. However, this addition doesn't significantly improve survival prediction at 3 and 12 mo and has its limitations due to fluctuating serum sodium levels influenced by various factors[18,19].

The D-MELD was introduced to address the limitation of a single MELD score at a specific time. While it is useful in predicting survival in cirrhotic patients awaiting transplantation, conflicting evidence exists. The potential bias in frequent laboratory testing for acutely worsening patients also complicates its use[20,21]. In summary, all versions of the MELD score have limitations, including susceptibility to therapeutic interventions, empirical variable selection, limited predictive ability for post-transplant mortality, and the need for on-site computation[10].

To improve the prediction of post-liver transplant mortality, various prediction tools have been explored, including the DRI, eurotransplant-donor risk Index (ET-DRI), SOFT, pre-allocation SOFT (p-SOFT), BAR, ABIC, CLIF C OFs, CLIF-C ACLFs, and the CLIF-SOFA. The DRI, predating the MELD score, was initially considered as an independent predictor of allograft failure across different MELD categories. However, numerous studies have revealed its limited association with outcomes[22]. The DRI's limitations include its validation in the pre-MELD era, the absence of recipient-related risk factors as the fact that is impractical for predicting morbidity and graft failure due to its poor predictive ability, inclusion of irrelevant factors (*e.g.*, ethnicity), and omission of relevant factors[23].

The ET-DRI replaces ethnicity and height risk factors with parameters like the latest gamma-glutamyl transferase and rescue offer in the Eurotransplant context. Although it has been shown to be potentially useful for liver allocation, studies have consistently shown its limited predictive ability for early post-transplant outcomes[22-26]. Overall, the ET-DRI is consistently considered an unreliable tool for predicting morbidity and mortality after LT.

Various prediction tools have been explored to enhance post-liver transplant prognostication. The SOFT score (Supplementary Table 2) has been tested for predicting 90-d post-transplant mortality[22,27]. A derivative of SOFT, the p-SOFT score (Supplementary Table 3), exhibited promising predictive accuracy[22]. However, the complexity of these scores, which involve multiple subjective and semi-quantitative variables, hampers their prompt clinical assessment and decision-making. Furthermore, their predictive ability for major morbidity at 3 mo appears limited[22,28].

The BAR score (Supplementary Table 4) offers promise by evaluating both recipient and donor factors for severe complications and 90-d mortality[22,28]. This tool has shown robustness in various patient populations, including pediatric, adolescent, and living donor liver transplant recipients[29,30]. However, in specific patient subgroups, BAR's accuracy in assessing short-term outcomes, including major complications, 90-d mortality, and ICU and hospital stay length, may be suboptimal[22].

The ABIC score (Supplementary material) aim to predict outcomes in patients with alcoholic hepatitis. While it has shown potential, its validation has been inconsistent, and it may not be widely applicable. Additionally, it primarily assesses the risk of wait-time mortality, making it unsuitable for post-liver transplant mortality assessment[31,32].

The CLIF-SOFA score (Supplementary Table 5), a modified version of the SOFA, is tailored for end-stage liver disease patients. This adaptation replaces platelet count and Glasgow coma scale with INR and hepatic encephalopathy, respectively. Additionally, it incorporates terlipressin and renal replacement therapy into cardiovascular and renal parameters, respectively, and includes SpO_2/FiO_2 as an alternative respiratory parameter for patients without an arterial line[33].

In a study published in 2014, the CLIF-SOFA score proved to be a significant predictor of 1-year post-LT mortality, surpassing the SOFA score in discriminatory power on several post-transplant days[34]. CLIF-SOFA score exhibited greater numerical differences between 1-year survivor and non-survivor groups, especially post-LT. Furthermore, CLIF-SOFA score trends reflected patients' responses to therapeutic strategies, with a CLIF-SOFA score > 8 on post-transplant day 7 indicating delayed recovery from multiple organ dysfunction, associated with higher acute rejection rates and poorer 1-year survival rates.

The CLIF-C OFs, a simplified version of CLIF-SOFA, uses a 3-point range per organ system and performs similarly to CLIF-SOFA, outperforming SOFA[35]. This score has proven to be an excellent prognostic tool for short-term outcomes in LT. Another variation, the CLIF-C ACLFs (Supplementary material), designed for acute-on-chronic liver failure (ACLF)

patients, includes the CLIF-SOFA score, age, and white-cell count. Jalan *et al*[35] demonstrated the superiority of the CLIF-ACLF score in terms of performance compared to CLIF-SOFA and CLIF-C OFs scores. However, inferior performance of CLIF-ACLF compared to CLIF-SOFA has been reported[34]. Results of CLIF-SOFA, CLIF-C[36-39] and ACLF classification[40-43] has been conflicting[7].

In response to the limitations of existing prognostic scores, there is a growing interest in harnessing machine learning (ML) models and algorithms to enhance the prediction of outcomes in LT. ML models serve as a bridge between organ allocation and achieving optimal results, capitalizing on the increasing use of artificial intelligence (AI) in medicine over the past decade (Figure 1). ML algorithms, as illustrated in Figure 2, rely on various types of input data, including structured, semi-structured, and unstructured data. Structured data, characterized by well-defined formats and adherence to specific data models, is organized in a tabular fashion and includes information like names, dates, and addresses. Semi-structured data, found in NoSQL databases, JSON documents, HTML, and XML, possesses organizational properties that enable analysis. On the other hand, unstructured data, comprising text and multimedia materials from sources like emails, sensor data, and web pages, lacks predefined formats, making it more challenging to process and analyze. To extract valuable insights from data for building intelligent applications in specific problem domains, various ML techniques are applied based on their learning capabilities[44]. Mohammed *et al*[45] categorized ML algorithms into four main groups: Supervised, unsupervised, semi-supervised, and reinforcement learning (Supplementary Table 6). Supervised learning involves mapping input to output based on labeled training data, typically used for tasks like classification and regression. Unsupervised learning, on the other hand, analyzes unlabeled datasets without human intervention and is employed for tasks such as clustering and dimensionality reduction, focusing on extracting generative features and identifying meaningful trends.

In the realm of ML, several techniques are employed to enhance predictive models for various applications, including LT prognostication. One such technique is semi-supervised learning, which effectively leverages both labeled and unlabeled data to achieve improved prediction outcomes, especially when labeled data is limited. This approach plays a crucial role in bridging the gap between supervised and unsupervised learning methods, finding utility in domains such as machine translation, data labeling, and text classification[46].

Reinforcement learning, on the other hand, offers a distinct approach by focusing on environment-driven algorithms that enable software agents and machines to autonomously evaluate optimal behavior within specific contexts. This methodology relies on the concept of rewards and penalties, aiming to utilize insights gained from interactions with the environment to maximize rewards or minimize risks. While reinforcement learning possesses significant potential in training AI models, it is better suited for complex scenarios rather than straightforward problems[47].

Within the realm of classification algorithms, several notable methods find application in health-related domains. Logistic regression (LR) stands as a commonly used technique, relying on logistic functions to estimate probabilities. While LR can excel in linearly separable datasets, it may suffer from overfitting in high-dimensional scenarios. Regularization techniques like L1 and L2 regularization are often employed to mitigate this issue[46].

Support vector machine (SVM) is another prominent classification method with applications in health data. SVM operates in high-dimensional spaces by constructing hyperplanes that maximize the margin between data points in different classes. The choice of kernel functions, such as polynomial, linear, radial basis function, and sigmoid, significantly influences SVM's performance. However, SVM's efficacy can diminish in the presence of noisy datasets and overlapping target classes[46].

Random forest (RF) offers a distinct ensemble classification technique, widely used in ML and data science applications. RF employs parallel ensembling, training multiple decision tree classifiers on different data subsets and combining their outcomes through averaging or majority voting. This approach effectively addresses overfitting concerns and enhances prediction accuracy, making it suitable for both continuous and categorical data in classification and regression problems[40].

Additionally, Adaptive Boosting (AdaBoost) serves as a valuable classification algorithm in the realm of health data. It adopts a sequential ensembling approach to improve the performance of weak classifiers by learning from their errors. By combining multiple underperforming classifiers, AdaBoost creates a robust classifier with high accuracy, boosting the performance of decision trees, base estimators, and binary classification tasks. However, it's essential to note that AdaBoost can be susceptible to overfitting and sensitivity to noisy data and outliers[48].

These various ML techniques have been instrumental in addressing complex problems in health-related domains, including LT prognostication. However, they also come with their own set of challenges, such as overfitting and interpretability issues. Therefore, periodic reviews are crucial to evaluate their performance and reliability compared to traditional scoring methods. This study aims to conduct a systematic review of observational studies, assessing the effectiveness of ML models in LT prognostication and comparing their performance with established scoring systems.

Extreme gradient boosting (XGBoost) stands out as a prominent classifier, belonging to the ensemble learning algorithm family, akin to RF. XGBoost represents a specific variant of gradient boosting that intricately considers detailed approximations when determining the optimal model. It effectively addresses overfitting concerns by minimizing the loss function and employing advanced regularization techniques, including L1 and L2 regularization. These regularization methods are implemented through the computation of second-order gradients of the loss function, resulting in enhanced model generalization and performance[48].

In the domain of ML, artificial neural networks (ANN) and deep learning techniques hold significant sway. Deep learning, a subset of ANN-based approaches, encompasses representation learning and comprises multiple layers, including input, hidden, and output layers. These layers collaboratively facilitate learning from data, giving rise to a computational architecture that excels, particularly when dealing with large datasets. Notable deep learning algorithms encompass multilayer perceptron, long short-term memory recurrent neural network, convolutional neural network, and ConvNet, among others[49].

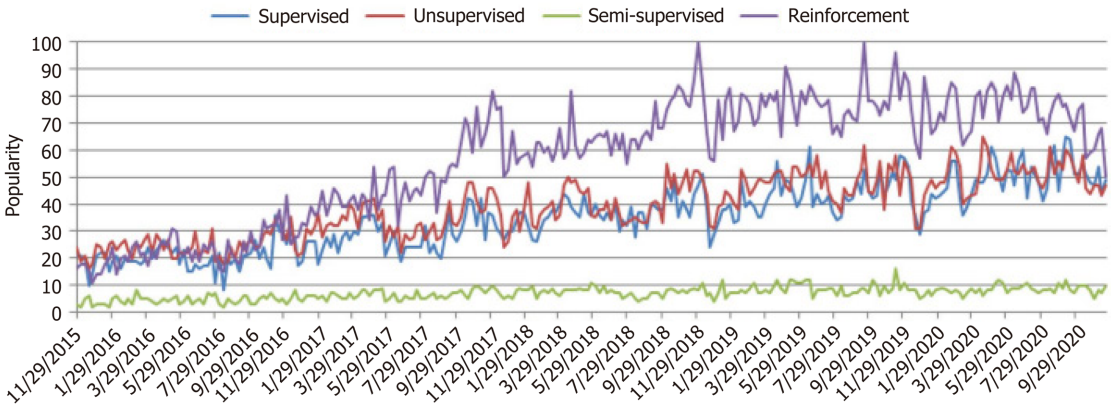

Figure 1 Machine learning popularity: Worldwide popularity score of different types of machine learning algorithms. Popularity scores range from 0 (minimum) to 100 (maximum) and are plotted against the timestamp information on the x-axis. The y-axis represents the corresponding popularity score[44]. Citation: Sarker IH. Machine Learning: Algorithms, Real-World Applications and Research Directions. SN Comput Sci 2021; 2: 160. Copyright ©The Author(s) 2021. Published by Springer Nature.

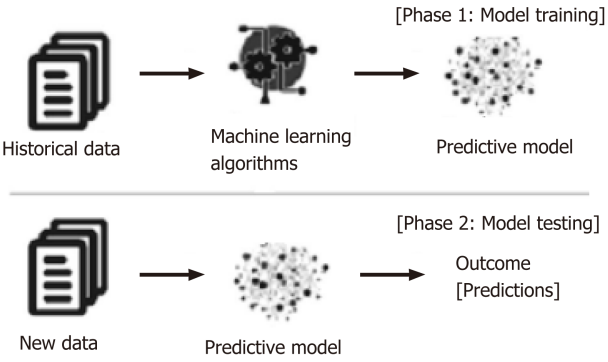

Figure 2 Basic machine learning model: Process of training and testing in machine learning[44]. Citation: Sarker IH. Machine Learning: Algorithms, Real-World Applications and Research Directions. SN Comput Sci 2021; 2: 160. Copyright ©The Author(s) 2021. Published by Springer Nature.

ML demonstrates versatility by not only addressing diagnostic challenges but also serving as a valuable tool in prognostic applications. It proves beneficial in disease prediction, data pattern identification, extraction of medical insights, and patient management[50]. Nevertheless, ML models are not without their limitations, as highlighted earlier. Concerns encompass overfitting, interference phenomena, where new data may disrupt previous learning, and the black box dilemma, which pertains to the challenge of explaining model results[51].

Within the context of LT, ML models have garnered increasing attention, underscoring the need for periodic assessments of their reliability and performance compared to conventional scoring systems. To this end, this study endeavors to conduct a systematic review of observational studies. The objective is to comprehensively evaluate the evidence concerning the deployment of ML models for prognostication in LT. This evaluation encompasses an assessment of their performance and reliability, juxtaposed with the array of traditional scoring systems currently available.

MATERIALS AND METHODS

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines to ensure a standardized approach[52].

Search strategy

A comprehensive literature search was conducted using the PubMed/MEDLINE search engine by one researcher. The search strategy included the following terms: ("ML" OR "AI") AND ("LT" OR "Allograft liver") AND ("Prognosis" OR "Mortality" OR "Prognostication"). A reference manager tool, Zotero, was utilized for sorting and managing references.

Study selection

All observational studies discussing ML models and prognosis of LT, regardless of the year of publication, age, or sex, were included. Studies written in English were considered. Additionally, studies examining ML models and the risk of post-transplant complications were included, as these complications often contribute to transplant failure or mortality. Exclusion criteria encompassed non-English papers, review articles, case reports, conference articles, studies with missing data, or studies with evident methodological flaws.

Data extraction and synthesis

The systematic search was conducted by one reviewer, who screened the potential studies based on their titles and abstracts. Full-text versions of eligible studies were obtained and thoroughly analyzed for content and methodology.

A summary of the included studies was created, providing a narrative overview of each paper's objectives, methods, results, and conclusions. After reviewing the full papers, data on various elements was extracted including; study type, population studied and year of study, purpose of the study, setting of the study, its methods and results, conclusion, limitations and strengths of the study as well as a summary of the study. Additionally, if reported by the studies, a comparison was made between traditional scores and algorithms *vs* ML models. This analysis aimed to explore the performance and effectiveness of ML approaches in prognosing LT outcomes.

By systematically extracting relevant information from the selected studies, a comprehensive understanding of the role of AI in LT prognosis was obtained. The data synthesis process involved organizing and presenting the findings in a coherent manner, allowing for a comprehensive evaluation of the current literature in this field.

This approach enabled to examine the various methodologies employed in the studies, identify key trends, and evaluate the potential benefits and limitations of using ML models for prognostication in LT. The synthesized data from the included studies will contribute to providing valuable insights into the current state of research on the role of AI in predicting outcomes in LT.

RESULTS

Using the predetermined search strategy, a total of 64 references were initially identified. Among these, 7 references were excluded as they were conference articles or review papers. Additionally, 1 duplicate article was removed, and 8 articles were excluded as they were abstracts only and could not be accessed for full-text reading. Subsequently, a thorough evaluation of the remaining 48 articles was conducted through full-text reading and content analysis. Following the comprehensive assessment, 23 studies met the inclusion criteria and were included in the final analysis. The selection process and reasons for exclusion of certain studies are visually represented in Figure 3, which depicts the flowchart illustrating the search strategy employed. Table 1, summarizes the findings of every study included[53-74].

Quality assessment

The majority of the included studies were considered to be of good quality, despite being observational in nature and not appraised using any specific quality assessment tool. Many of these studies incorporated validation sets in their analyses, which contributes to the robustness of their findings.

Study outcomes: The studies assessed in this systematic review covered a range of transplantation reasons, including ACLF from various causes, primary sclerosing cholangitis (PSC), and hepatocellular carcinoma (HCC). Among the 23 studies analyzed, the highest number (8 studies, accounting for 34.8%) were conducted in America, followed by 6 studies (26%) from China. Additionally, 2 studies (8.7%) were from Korea, while the remaining studies originated from Spain, Australia, Portugal, Taiwan, Iran, and Brazil, each contributing 1 study (4.3%). Furthermore, there was one multinational study involving participants from the United States, Canada, and the United Kingdom, which represented 4.3% of the total sample as depicted by Figure 4.

The studies analyzed in this review spanned from 2014 to 2023. Notably, the highest proportion of studies (26%, 6 studies) were published in 2021, followed by 5 studies (21.7%) from 2022. Studies from 2019, 2020, 2018, and 2023 accounted for 13% (3 studies) each, while 2014 and 2015 each contributed 1 study (4.3%) as shown in Figure 5. Regarding the age of participants, one study involved individuals under 18 years old, while the remaining 22 studies focused on adults aged 18.

Primary outcomes and findings

The primary outcomes of interest in the included studies were mortality and the emergence of complications post liver transplant. Most of the studies reported the receiver operating characteristic (ROC) curve and used the area under the ROC curve (AUROC) as a measure of predictive performance. AUROC values were categorized as excellent (0.9-1), very good (0.8-0.9), good (0.7-0.8), satisfactory (0.6-0.7), and unsatisfactory (0.5-0.6) based on previous classification[75].

Across all the studies, ML algorithms and models were developed using pre-transplant donor and/or recipient variables. Short-term mortality predictions were typically up to 90 d, while long-term predictions extended up to 5 years. Analysis of AUROC demonstrated that ML models consistently yielded satisfactory to excellent results in predicting short and long-term mortality or the risk of complications post liver transplant.

Furthermore, the AUROC analysis revealed that ML models outperformed traditional models and scoring systems, including commonly used models such as MELD, D-MELD, SOFT, P-SOFT, BAR, DRI score, ABIC, CLIF-C OFs, CLIF-C ACLFs, and CLIF SOFA. Additionally, ML models showed superiority over models based on Cox and LR. Detailed

Table 1 Summary table of included studies

Ref.	Context	Aim	Methods	Results	Conclusion
Briceño *et al*[53], 2014	A Spanish study using a two-fold ANN model which included, the positive survival and the negative loss models were implored to predict 3 mo graft survival post LT	To test the accuracy of ANN inpredicting post-transplant outcomes and compare with other conventional models	Sixty-four donor and recipient variables from a set of 1003 LT from a multicenter study including 11 Spanish centers were included. For each D-R pair, common statistics (simple and multiple regression models) and ANN formulae for two non-complementary probability-models of 3-months graft-survival and -loss were calculated: a positive-survival (NN-CCR) and a negative-loss (NN-MS) model. The NN models were obtained by using the Neural Net Evolutionary Programming (NNEP) algorithm. Additionally, receiver-operating curves (ROC) were performed to validate ANN against other scores	Optimal results for NN-CCR and NN-MS models were obtained, with the best performance in predicting the probability of graft-survival (90.79%) and -loss (71.42%) for each D-R pair, significantly improving results from multiple regressions. ROC curves for 3- months graft-survival and –loss predictions were significantly more accurate for ANN than for other scores in both NN-CCR (AUROC-ANN = 0.80 *vs* –MELD = 0.50; -D-MELD = 0.54; -P- 5 SOFT = 0.54; -SOFT = 0.55; –BAR = 0.67 and -DRI = 0.42) and NN-MS (AUROC-ANN = 0.82 *vs* – MELD = 0.41; -D-MELD = 0.47; -P-SOFT = 0.43; -SOFT = 0.57, -BAR = 0.61 and -DRI = 0.48)	ANN maybe considered a powerful decision-making technology for this dataset, optimizing the principles of justice, efficiency and equity. This may be a useful tool for predicting 3-months outcome and a potential research area for future D-R matching models
Ershoff *et al*[54], 2020	An American study in which DNN was trained on pre transplant data and compared with the BAR and SOFT scores in predicting 90-d mortality post LT	The primary aim of the study was to classify recipients with 90-d post-liver transplant mortality using DNNs	In this study, we trained a DNN to predict 90-d post -transplant mortality using preoperative variables and compared the performance to that of the Survival Outcomes Following Liver Transplantation (SOFT) and Balance of Risk (BAR) scores, using United Network of Organ Sharing data on adult patients who received a deceased donor liver transplant between 2005 and 2015 (n = 57544). The DNN was trained using 202 features, and the best DNN's architecture consisted of 5 hidden layers with 110 neurons each	The area under the receiver operating characteristics curve (AUC) of the best DNN model was 0.703 (95%CI: 0.682-0.726) as compared to 0.655 (95%CI: 0.633-0.678) and 0.688 (95%CI: 0.667-0.711) for the BAR score and SOFT score, respectively	Despite the complexity of DNN, it did not achieve a significantly higher discriminative performance than the SOFT score. Future risk models will likely benefit from the inclusion of other data sources, including high-resolution clinical features for which DNNs are particularly apt to outperform conventional statistical methods
Lau *et al*[55], 2015	An Australian study proposing an algorithm made from 15 donor, recipient and transplant factors selected by ML predicting mortality within 30 days after LT	To evaluate the utility of machine-learning algorithms, such as random forests and artificial neural networks, to predict outcome based on donor and recipient variables which are known before organ allocation	Liver transplant data from the Austin Hospital, Melbourne, Australia, from 2010 to 2013 has been included in the study. The top 15 donor, recipient, and transplant factors influencing the outcome of graft failure within 30 days were selected using a machine learning methodology. An algorithm predicting the outcome of interest was developed using those factors	Donor risk index predicts the outcome with an area under the receiver operating characteristic curve (AUC-ROC) value of 0.680 (95%CI: 0.669-0.690). The combination of the factors used in donor risk index with the model for end-stage liver disease score yields an AUC-ROC of 0.764 (95%CI: 0.756-0.771), whereas survival outcomes after liver transplantation (LT) score obtains an AUC-ROC of 0.638 (95%CI: 0.632-0.645). The top 15 donor and recipient characteristics	This study confirms that machine-learning algorithms based on donor and recipient variables which are known before organ allocation can be utilized to predict transplant outcomes

				within random forests results in an AUC-ROC of 0.818 (95%CI: 0.812-0.824)	
Liu *et al*[56], 2020	A Chinese study using ML to predict 30 d survival after LT	To use data-driven technique to develop a predictive model using ML to predict postoperative survival within 30 days for the patients who have undergone LT	We use random forest (RF) to select important features, including clinically used features and new features discovered from physiological measurement values. Moreover, we propose a new imputation method to deal with the problem of missing values and the results show that it outperforms the other alternatives. In the predictive model, we use patients' blood test data within 1–9 d before surgery to construct the model to predict postoperative patients' survival	The experimental results on a real data set indicate that RF outperforms the other alternatives. The experimental results on the temporal validation set show that our proposed model achieves AUC of 0.771 and specificity of 0.815	ML can detect the high risk patients in early phase after LT, and discover important factors that are essential in LT
Yang *et al*[57], 2022	A Chinese study in which conventional Scoring systems were compared with ML models in predicting 90 day survival in ACLF patients following LT	To compare the predictive value of conventional models and ML models for predicting 90-d post-transplant survival of ACLF patients based on preoperative variables	Preoperative data of 132 ACLF patients receiving LT at our center were investigated retrospectively. Cox regression was performed to determine the risk factors for short-term survival among ACLF patients following LT. Five conventional score systems (the MELD score, ABIC, CLIF-C OFs, CLIF-SOFAs and CLIF-C ACLFs) in forecasting short term survival were estimated through the ROC. Four machine-learning (ML) models, including support vector machine (SVM), logistic regression (LR), multi-layer perceptron (MLP) and random forest (RF), were also established for short-term survival prediction	Cox regression analysis demonstrated that creatinine (Cr) and international normalized ratio (INR) were the two independent predictors for short-term survival among ACLF patients following LT. The ROC curves showed that the AUC ML models was much larger than that of conventional models in predicting short term survival. Among conventional models the model for end stage liver disease (MELD) score had the highest AUC (0.704), while among ML models the RF model yielded the largest AUC (0.940). (AUROC) of MELDs (AUROC: 0.704) was higher than those of ABIC (AUROC: 0.607), CLIF-C OFs (AUROC: 0.606), CLIF-C ACLFs (AUROC: 0.653), and CLIF-SOFAs (AUROC: 0.633) for prediction of the 90-d outcome in ACLF patients following LT	Compared with the traditional methods, the ML models showed good performance in the prediction of short-term prognosis among ACLF patients following LT and the RF model perform the best
Andres *et al*[58], 2018	A United States study using ML to construct a prediction tool called PSSP using SRTR data to predict survival following LT for PSC and compared with cox regression in survival analysis	To develop ML models to predict individual survival after LT for Primary Sclerosing Cholangitis (PSC)	We applied a software tool, PSSP, to adult patients in the Scientific Registry of Transplant Recipients (n = 2769) who received a LT for PSC between 2002 and 2013; this produced a model for predicting individual survival distributions for novel patients. We also developed an appropriate evaluation measure, D-calibration, to validate this model	The learned PSSP model showed an excellent D-calibration (P = 1.0), and passed the single-time calibration test (Hosmer-Lemeshow P value of over 0.05) at 0.25, 1, 5 and 10 yr. In contrast, the model based on traditional Cox regression showed worse calibration on long-term survival and failed at 10 yr (Hosmer-Lemeshow P value = 0.027). The overall KM survival curve at 0.25, 1, 3, 5 and 10-yr showed survival probabilities of: 95.6%, 93%,	Our empiricalresults show that the individual survival distributions produced by these models are well calibrated, which means they can be used for this screening task of deciding whether a candidateshould be added to the LT waiting list as they can help predict the survival of a possible recipient (or of a donor/recipient pair)

				87.6%, 84.1% and 72%	
Kong *et al*[59], 2020	A Chinese study in which Logistic regression and artificial neural network(ANN) analysis were used to determine the preoperative independent risk factors and protective factors for the survival or death of patients90 days after surgery	To develop a simple ML model for quick prediction of the short-term survival ofpatients after LT in the event that the donor's information is not available in advance	A total of 1495 adult patients underwent LT in the present study. Three-quarters of recipients were randomly selected into the test set (n = 1121), while the remaining 25% formed the validation set (n = 374). Univariate and multivariate analysis and machine-learning techniques were applied to evaluate possible influencing factors. To further simplify the model, a weighted-scoring system was designed considering each influencing factor and its importance in an ANN	In the test set, multivariate analysis identified creatinine, age, and total bilirubin as independent risk factors, while albumin was an independent protective factor. Logistic regression analysis showed the C-statistic to be 0.650, while ANN indicated this to be 0.698. We simplified the model to obtain the final scoring model, for which the C-statistic was 0.636, and defined four risk grades. The 90-d mortality rates corresponding to the four risk levels were 6.2%, 11.8%, 24.0%, and 34.9%, respectively. In the validation set, the C-statistic value of the original model was 0.668 and that of the simplified model was 0.647	We demonstrated that the postoperative 90-d mortality follow-ingadult LT can be predicted using a scoring system based on recipients' preoperative characteristics
Bertsimas *et al*[60], 2019	An American study using Optimized prediction of mortality (OPOM) utilizing machine-learning optimal classification tree models trained to predict a candidate's 3-months waitlist mortality or removal using the standard transplant analysis andresearch (STAR) dataset	To utilize a state-of-the-art machine-learning method-termed optimal classification trees (OCTs)-to generatea more accurate prediction of a liver candidate's 3-months wait-list mortality or removal	An OPOM was developed (http://www.opom.online) utilizing machine-learning optimal classi-fication tree models trained to predict a candidate's 3-months waitlist mortality or removal utilizing the STAR dataset. The Liver Simulated Allocation Model (LSAM) was then used to compare OPOM to MELD-based allocation. Out-of-sample area under the curve (AUC) was also calculated for candidate groups of increasing disease severity	OPOM considerably outperformed both MELD variants when predicting the 3-months probability of dying or becoming unsuitable for transplant for all patients (0.859 *vs* 0.841 for MELD-Na, and 0.823for Match MELD) and across all exception statuses. In addition, analysis of out-of-sample AUC for OPOM, Match MELD and MELD-Na, for subpopulations of patients with increasing dis-ease severity, revealed a notable decline in predictive power for Match MELD and MELD-Na as disease severity increased, whereas OPOM's predictive power was maintained. The largest divergence in predictive power between OPOM and MELD was at the higher disease severity brackets, with OPOM outperforming Match MELD by up to 16%	OPOM more accurately and objectively prioritizes candidates for LT based on disease severity, allowing for more equitable allocation of livers with a resultant sig- nificant number of additional lives saved every year. These data demonstrate the potential of machine learning technology to help guide clinical practice, and potentially guide national policy
He *et al*[61], 2021	An American study using image omics and multi-network based deep learning model that converts expertise in LT, full-slide image digitization, and deep machine learning, and integrates multimodality data of quantitative image features with relevant clinical data to identify pre-clinical and biological markers for predicting good post-transplant outcomes, regardless of size	To develop a convergent artificial intelligence (AI) model that combines transient clinical data with quantitative histologic and radiomic features for more objective risk assessment of LT for HCC patient	Patients who received a LT for HCC between 2008-2019 were eligible for inclusion in the analysis. All patients with post-LT recurrence were included, and those without recurrence were randomly selected for inclusion in the deep learning model. Pre- and post-transplant magnetic resonance imaging (MRI) scans and reports were compressed using Caps Net networks and natural language processing,	A total of 109 patients were included (87 in the training group, 22 in the testing group), of which 20 were positive for cancer recurrence. Seven models (AUC; F-1 score) were generated, including clinical features only (0.55; 0.52), MRI only (0.64; 0.61), pathological images only (0.64; 0.61), MRI plus pathology (0.68; 0.65), MRI plus clinical (0.78, 0.75), pathology plus clinical (0.77; 0.73), and a combination of clinical, MRI,	We validated that the deep learning model combining clinical features and multi scale histopathologic and radiomic image features can be used to discover risk factors for recurrence beyond tumor size and biomarker analysis

			respectively, as input for a multiple feature radial basis function network. We applied a histological image analysis algorithm to detect pathologic areas of interest from explant tissue of patients who recurred. The multilayer perceptron was designed as a feed forward, supervised neural network topology, with the final assessment of recurrence risk. We used AUC and F-1 score to assess the predictability of different network combinations	and pathology features (0.87; 0.84). The final combined model showed 80% recall and 89% precision. The total accuracy of the implemented model was 82%	
Pinto-Marques *et al*[62], 2022	A Portuguese study in which the ML model, Hepato-Predict was constructed on retrospective LT data for HCC based on the assessment of a gene expression signature plus clinical variables	To propose a new decision algorithm combining biomarkers measured in a tumor biopsy with clinical variables, to predict recurrence after LT	A literature systematic review singled out candidate biomarkers whose RNA levels were assessed by quantitative PCR in tumor tissue from 138 HCC patients submitted to LT (> 5 yr follow up, 32% beyond Milan criteria). The resulting 4 gene signature was combined with clinical variables to develop a decision algorithm using machine learning approaches. The method was named HepatoPredict	HepatoPredict identifies 99% disease-free patients (> 5 yr) including many outside clinical criteria (16%-24%). Has increased positive predictive value (88.5%-94.4%) without any loss of long-term overall survival or recurrence rates for patients deemed eligible by HepatoPredict; those deemed ineligible display marked reduction of survival and increased recurrence in the short and long term	HepatoPredict outperforms conventional clinical-pathologic selection criteria (Milan, UCSF), providing superior prognostic information
Lai *et al*[63], 2023	A Taiwanese study in which the ML model ResNet-18 was trained on FDG-PET-CT images to predict outcomes in HCC patients undergoing LT	To evaluate the performance of deep learning from 18F-FDG PET-CT images to predict overall survival in HCC patients before LT	We retrospectively included 304 patients with HCC who underwent 18F-FDG PET/CT before LT between January 2010 and December 2016. The hepatic areas of 273 of the patients were segmented by software, while the other 31 were delineated manually. We analyzed the predictive value of the deep learning model from both FDG PET/CT images and CT images alone	The results of the developed prognostic model were obtained by combining FDG PET-CT images and combining FDG CT images (0.807 AUC *vs* 0.743 AUC). The model based on FDG PET-CT images achieved somewhat better sensitivity than the model based on CT images alone (0.571 SEN *vs* 0.432 SEN)	Our retrospective study indicated that an automated 3D ResNet-18 convolutional neural network with FDG-PET-CT has promise for predicting clinical outcomes in patientswith HCC undergoing LDLT and that Automatic liver segmentation from 18F-FDG PET-CT images is feasible and can be utilized to train deep-learning models
Kazemi *et al*[64], 2019	Iranian study aimed at modelling patient survival after LT using machine-learning methods to investigate influential factors and compare the performance of these methods with a classic statistic method, cox regression	To Identify effective factors for patient survival after LT using ML techniques	Our study included 902 adults who received livers from deceased donors from March 2011 to March 2014 at the Shiraz Organ Transplant Center (Shiraz, Iran). In a 3-step feature selection method, effective features of 6-month survival were extracted by: (1) F statistics, Pearson chi-square, and likelihood ratio chi-square; (2) 5 machine earning techniques. To evaluate the performance of the machine-learning techniques, Cox regression was applied to the data set. Evaluations were based on the area under the receiver operating characteristic	The model predicted survival based on 26 identified effective factors. In the following order, graft failure, Aspergillus infection, acute renal failure and vascular complications after transplant, as well as graft failure diagnosis interval, previous diabetes mellitus, Model for End-Stage Liver Disease score, donor inotropic support, units of packed cell received, and previous recipient dialysis, were found to be predictive factors in patient survival. The area under the receiver operating characteristic curve and model sensitivity were 0.90 and 0.81, respectively	Data mining analyses can help identify effective features of patient survival after livertransplant and build models with equal or higher performance than Cox regression. The order ofinfluential factors identified with the machine learning model was close to clinical experiments

			curve and sensitivity of models; and (3) We also constructed a model using all factors identified in the previous step		
Nitski *et al*[65], 2021	An American study that examined retrospective data of transplant recipients from the SRTR and UHN to assess the role of deep learning algorithms to predict complications resulting in death after liver transplant over multiple time frames in comparison with logistic regression	To assess the ability of deep learning algorithms of longitudinal data from two prospective cohorts to predict complications resulting in death after LT over multiple timeframes, compared with logistic regression models	In this machine learning analysis, model development was done on a set of 42 146 liver transplant recipients [mean age 48.6 yr (SD 17.3); 17 196 (40.8%) women] from the Scientific Registry of Transplant Recipients (SRTR) in the United States. Transferability of the model was further evaluated by fine-tuning on a dataset from the UHN in Canada [n = 3269; mean age 52.5 yr (11.1); 1079 (33.0%) women]. The primary outcome was cause of death, as recorded in the databases, due to cardiovascular causes, infection, graft failure, or cancer, within 1 yr and 5 yr of each follow-up examination after transplantation. We compared the performance of four deep learning models against logistic regression, assessing performance using the AUROC	In both datasets, deep learning models outperformed logistic regression, with the Transformer model achieving the highest AUROCs in both datasets (P < 0.0001). The AUROC for the Transformer model across all outcomes in the SRTR dataset was 0.804 (99%CI: 0.795-0.854) for 1-yr predictions and 0.733 (0.729-0.769) for 5-yr predictions. In the UHN dataset, the AUROC for the top-performing deep learning model was 0.807 (0.795-0.842) for 1-yr predictions and 0.722 (0.705–0.764) for 5-yr predictions. AUROCs ranged from 0.695 (0.680–0.713) for prediction of death from infection within 5 yr to 0.859 (0.847-0.871) for prediction of death by graft failure within 1 yr	Deep learning algorithms can incorporate longitudinal information to continuously predict long-term outcomes after LT, outperforming logistic regression models
Ivanics *et al*[66], 2022	A multinational study of ML models assessing their 90-d predictive value post LT across United States, Canada and	To evaluate the feasibility of developing MLA-based models to predict 90-d post-LT mortality using 3 large nationaltransplant registries and to evaluate the external validity of the models across countries	We used data from 3 national registries and developed machine learning algorithm (MLA)–based models to predict 90-d post-LT mortality within and across countries. Predictive performance and external validity of each model were assessed. Prospectively collected data of adult patients (aged ≥ 18 yr) who underwent primary LTs between January 2008 and December 2018 from the Canadian Organ Replacement Registry (Canada), National Health Service Blood and Transplantation (United Kingdom), and United Network for Organ Sharing (United States) were used to develop MLA models to predict 90-d post-LT mortality. Models were developed using each registry individually (based on variables inherent to the individual databases) and using all 3 registries combined (variables in common between the registries [harmonized]). The model performance was evaluated using AUROC curve. The number of patients included was as follows:	The best performing MLA-based model was ridge regression across both individual registries and harmonized data sets. Model performance diminished from individualized to the harmonized registries, especially in Canada (individualized ridge: AUROC, 0.74; range, 0.73-0.74; harmonized: AUROC, 0.68; range, 0.50-0.73) and US (individualized ridge: AUROC, 0.71; range, 0.70-0.71; harmonized: AUROC, 0.66; range, 0.66-0.66) data sets. External model performance across countries was poor overall	External model performance across countries was poor overall. MLA-based models yield a fair discriminatory potential when used within individual databases. However, the external validity of these models is poor when applied across countries

			Canada, *n* = 1214; the United Kingdom, *n* = 5287; and the United States, *n* = 59558		
Cheong *et al*[67], 2021	A Korean study assessing the role of pre LT hyperlactatemia in early mortality post LT	To study important variables for pre-LT hyperlactatemia and examine the impact of preoperative hyperlactatemia on 30 and 90 d mortality after LT	A total of 2002 patients from LT registry between January 2008 and February 2019 were analyzed. Six organ failures (liver, kidney, brain, coagulation, circulation, and lung) were defined by criteria of EASL-CLIF ACLF Consortium. Variable importance of pre-operative hyperlactatemia was examined by machine learning using random survival forest (RSF). Kaplan-Meier Survival curve analysis was performed to assess 90-d mortality	Median lactate level was 1.9 mmol/L (interquartile range: 1.4, 2.4 mmol/L) and 107 (5.3%) patients showed > 4.0 mmol/L. RSF analysis revealed that the four most important variables for hyperlactatemia were MELD score, circulatory failure, hemoglobin, and respiratory failure. The 30-d and 90-d mortality rates were 2.7% and 5.1%, whereas patients with lactate > 4.0 mmol/L showed increased rate of 15.0% and 19.6%, respectively	Pre-LT lactate > 4.0 mmol/L was associated with increased early post-LT mortality. Our results suggest that future study of correcting modifiable risk factors may play a role in preventing hyperlactatemia and lowering early mortality after LT
Kulkarni *et al*[68], 2021	An American study using Random Forest approach to identify key predictors of outcomes in pediatric candidates less than 2 yr of age undergoing LT	To identify key predictors of LT outcomes in Pediatric candidates less than 2 yr of age using random forest approach	SRTR database was queried for children < 2 yr listed for initial LT during 2002-17 (*n* = 4973). Subjects were divided into three outcome groups; bad (death or removal for too sick to transplant), good (spontaneous improvement) and transplant. Demographic, clinical, listing history and laboratory variables at the time of listing (baseline variables), and changes in variables between listing and prior to outcome (trajectory variables) were analyzed using random forest analysis	81.5% candidates underwent LT, 12.3% had bad outcome. RF model including both baseline and trajectory variables improved prediction compared to model using baseline variables alone. RF analyses identified change in serum creatinine and listing status as the most predictive variables. 80% of subjects listed with a PELD score at time of listing and outcome underwent LT, while 70% of subjects in both bad and good outcome groups were listed with either Status 1 (A or B) prior to an outcome, regardless of initial listing status. Increase in creatinine on LT waitlist was predictive of bad outcome. Longer time spent on WL was predictive of good outcome. Subjects with biliary atresia, liver tumors and metabolic disease had LT rate > 85%; while > 20% of subjects with acute liver failure had a bad outcome	Change in creatinine, listing status, need for RRT, time spent on LT waitlist and diagnoses were the most predictive variables
Molinari *et al*[69], 2019	An American study using ML techniques to identify predictors of short and long term mortality post cadaveric LT	To develop a scoring system using ML that could stratify patients by their risk of death after LT based only on preoperative variables. Secondary aims were to assess whether the model could also predict 1- and 5-yr patient survival	The study population was represented by 30458 adults who underwent LT in the United States between January 2002 and June 2013. Machine learning techniques identified recipient age, Model for End-Stage Liver Disease score, body mass index, diabetes, and dialysis before LT as the strongest predictors for 90-d postoperative mortality. A weighted scoring system (minimum of 0 to a maximum of 6 points) was subsequently developed	Recipients with 0, 1, 2, 3, 4, 5, and 6 points had an observed 90-d mortality of 6.0%, 8.7%, 10.4%, 11.9%, 15.7%, 16.0%, and 19.7%, respectively ($P \leq 0.001$). One-year mortality was 9.8%, 13.4%, 15.8%, 17.2%, 23.0%, 25.2%, and 35.8% ($P \leq 0.001$) and five-year survival was 78%, 73%, 72%, 71%, 65%, 59%, and 48%, respectively ($P = 0.001$). The mean 90-d mortality for the cohort was 9%. The area under the curve of the model was 0.952 for the discrim-	Short- and long-term outcomes of patients undergoing cadaveric LT can be predicted using a scoring system based on recipients' preoperative characteristics

				ination of patients with 90-day mortality risk ≥ 10%	
Cooper *et al*[70], 2022	A United States study predicting the risk of GVHD among patients undergoing OLT using ML models	To develop ML algorithms for predicting the risk of GVHD among patients undergoing OLT	To develop a predictive model, we retrospectively evaluated the clinical features of 1938 donor-recipient pairs at the time they underwent OLT at our center; 19 (1.0%) of these recipients developed GVHD. This population was divided into training (70%) and test (30%) sets. A total of 7 machine-learning classification algorithms were built based on the training data set to identify patients at high risk for GVHD	The C5.0, heterogeneous ensemble, and generalized gradient boosting machine (GGBM) algorithms predicted that 21% to 28% of the recipients in the test data set were at high risk for developing GVHD, with an AUROC of 0.83 to 0.86. The 7 algorithms were then evaluated in a validation data set of 75 more recent donor-recipient pairs who underwent OLT at our center; 2 of these recipients developed GVHD. The logistic regression, hetero-geneous ensemble, and GGBM algorithms predicted that 9% to 11% of the validation recipients were at high risk for developing GVHD, with an AUROC of 0.93 to 0.96 that included the 2 recipients who developed GVHD	we show that a machine-learning approach can predict which recipients are at high risk for developing GVHD after OLT based on factors known or measurable at the time of transplantation
He *et al*[71], 2021	A Chinese study comparing the predicting power of ML models and logistic regression for AKI among patients undergoing DCDLT	To compare the performance of ML algorithms to that of a logistic regression model for predicting AKI after LT using preoperative and intraoperative data	A total of 493 patients with donation after cardiac death LT (DCDLT) were enrolled. AKI was defined according to the clinical practice guidelines of kidney disease: improving global outcomes (KDIGO). The clinical data of patients with AKI (AKI group) and without AKI (non-AKI group) were compared. With logistic regression analysis as a conventional model, four predictive machine learning models were developed using the following algorithms: Random forest, support vector machine, classical decision tree, and conditional inference tree. The predictive power of these models was then evaluated using the AUC	The incidence of AKI was 35.7% (176/493) during the follow-up period. Compared with the non AKI group, the AKI group showed a remarkably lower survival rate (P < 0.001). The random forest model demonstrated the highest prediction accuracy of 0.79 with AUC of 0.850 (95%CI: 0.794-0.905), which was significantly higher than the AUCs of the other machine learning algorithms and logistic regression models (P < 0.001)	The random forest model based on machine learning algorithms for predicting AKI occurring after DCDLT demonstrated stronger predictive power than other models in our study
Chen *et al*[72], 2023	A Chinese study predicting the risk of sepsis within 7 days post LT	Our study aimed to develop and validate a predictive model for postoperative sepsis within 7 days in LT recipients using ML technology	Data of 786 patients who received LT from January 2015 to January 2020 was retrospectively extracted from the big data platform of Third Affiliated Hospital of Sun Yat-sen University. Seven ML models were developed to predict postoperative sepsis. The AUC, sensitivity, specificity, accuracy, and f1-score were evaluated as the model performances. The model with the best performance was validated in an independent dataset involving 118	After excluding 109 patients according to the exclusion criteria, 677 patients who underwent LT were finally included in the analysis. Among them, 216 (31.9%) were diagnosed with sepsis after LT, which were related to more periop-erative complications, increased postoperative hospital stay and mortality after LT (all P < 0.05). Our results revealed that a larger volume of red blood cell infusion, ascitic removal, blood loss and gastric	The random forest classifier model showed the best overall performance to predict sepsis after LT

			adult LT cases from February 2020 to April 2021. The postoperative sepsis-associated outcomes were also explored in the study	drainage, less volume of crystalloid infusion and urine, longer anesthesia time, higher level of preoperative TBIL were the top 8 important variables contributing to the prediction of post-LT sepsis. The RF model showed the best overall performance to predict sepsis after LT among the seven ML models developed in the study, with an AUC of 0.731, an accuracy of 71.6%, the sensitivity of 62.1%, and specificity of 76.1% in the internal validation set, and a comparable AUC of 0.755 in the external validation set	
Lee *et al*[73], 2018	A Korean study comparing the predicting power for AKI post LT of ML models and logistic regression	To compare the performance of machine learning approaches with that of logistic regression analysis to predict AKI after LT	We reviewed 1211 patients and preoperative and intraoperative anesthesia and surgery-related variables were obtained. The primary outcome was postoperative AKI defined by acute kidney injury network criteria. The following machine learning techniques were used: decision tree, random forest, gradient boosting machine, support vector machine, naïve Bayes, multilayer perceptron, and deep belief networks. These techniques were compared with logistic regression analysis regarding the AUROC	AKI developed in 365 patients (30.1%). The performance in terms of AUROC was best in gradient boosting machine among all analyses to predict AKI of all stages (0.90, 95%CI: 0.86-0.93) or stage 2 or 3 AKI. The AUROC of logistic regression analysis was 0.61 (95%CI: 0.56-0.66). Decision tree and random forest techniques showed moderate performance (AUROC 0.86 and 0.85, respectively)	In our comparison of seven machine learning approaches with logistic regression analysis, the gradient boosting machine showed the best performance with the highest AUROC
Bredt *et al*[74], 2022	A Brazilian study investigating risk factors of AKI post DDLT using ML and Logistic regression	To identify the risk factors of AKI after deceased-donor LT (DDLT) and compare the prediction performance of ANN with that of LR for this complication	Adult patients with no evidence of end-stage kidney dysfunction (KD) who underwent the first DDLT according to model for end-stage liver disease (MELD) score allocation system were evaluated. AKI was defined according to the International Club of Ascites criteria, and potential predictors of postoperative AKI were identified by LR. The prediction performance of both ANN and LR was tested	The incidence of AKI was 60.6% (n = 88/145) and the following predictors were identified by LR: MELD score > 25 (OR = 1.999), preoperative kidney dysfunction (OR = 1.279), extended criteria donors (OR = 1.191), intraoperative arterial hypotension (OR = 1.935), intraoperative massive blood transfusion (MBT) (OR = 1.830), and postoperative serum lactate (SL) (OR = 2.001). The area under the receiver-operating characteristic curve was best for ANN (0.81, 95%CI: 0.75-0.83) than for LR (0.71, 95%CI: 0.67-0.76). The root-mean-square error and mean absolute error in the ANN model were 0.47 and 0.38, respectively	The severity of liver disease, pre-existing kidney dysfunction, marginal grafts, hemodynamic instability, MBT, and SL are predictors of postoperative AKI, and ANN has better prediction performance than LR in this scenario

ANN: Artificial neural network; DRI: Donor risk index; D-R: Donor-recipient; LT: Liver transplantation; MELD: Model of end-stage liver disease; NN-CCR: Neural network for correct classification rate; NN-MS: Neural network for minimum sensitivity; SOFT: Survival outcomes following liver transplantation score; ROC: Receiver-operating curves; BAR: Balance of risk score; DNN: Deep neural network; ML: Machine Learning; ACLF: Acute-on-chronic liver

failure; CLIF-C OFs: Chronic liver failure consortium organ failure scores: CLIF-SOFAs: CLIF sequential organ failure assessment scores; CLIF-C ACLFs: CLIF consortium ACLF scores; RF: Random forest; SRTR: Scientific registry of transplant recipients; PSSP: Patient-specific survival prediction; PSC: Primary sclerosing cholangitis; KM: Kaplan meier; OPOM: Optimized prediction of mortality; STAR: transplant analysis and research; HCC: Hepatocellular carcinoma; Milan-UCSF: Milan-University of California San Francisco criteria; 18F-FDG: 18F-fluorodeoxyglucose; PET-CT: Positron emission tomography and computed tomography; LDLT: Live donor liver transplantation; DDLT: Deceased donor liver transplant; EASL-CLIF ACLF Consortium: European Association for the Study of the Liver-CLIF ACLF; PELD: Pediatric end stage liver disease; WL: Wait list; GVHD: Graft-versus-host disease; OLT: Orthotropic liver transplant.

comparisons and findings are presented in Table 1.

Sub-analysis: In terms of predicting 90-d mortality, the RF model demonstrated the highest area under the curve (AUC) value of 0.940 compared to other ML models. Additionally, among the six studies identified in the literature search that discussed the prediction of complications post liver transplant using ML models, an analysis of the AUC values indicated that the 'gradient boosting machine' model performed better than other ML models in predicting the risk of graft-versus-host disease (GVHD), pneumonia, and acute kidney injury (AKI). On the other hand, the RF model showed better performance in predicting the risk of sepsis and AKI post liver transplant. Detailed results and comparisons are provided in Table 1.

This sub-analysis highlights the specific performance of ML models in predicting 90-d mortality and the risk of complications following LT. The RF model exhibited superior predictive capability for mortality within the 90-d timeframe.

Furthermore, when examining the prediction of post-transplant complications, the 'gradient boosting machine' model demonstrated better performance in predicting GVHD, pneumonia, and AKI, while the RF model showed greater effectiveness in predicting the risk of sepsis and AKI. These findings emphasize the potential of ML techniques in enhancing prognostic accuracy and tailoring clinical management strategies in LT.

DISCUSSION

The review highlights a limited number of studies, just 64, that have explored the application of ML models in the context of LT. This scarcity of research, despite an unrestricted search, indicates a historical lack of emphasis on the potential of ML models in the realm of prognosis and transplant decision-making. Factors contributing to this limited attention include lingering perceptions of ML models as associated with science fiction and concerns regarding potential errors and patient harm. However, it's noteworthy that ML models have advanced in sophistication and have implemented strategies to address challenges like overfitting. Their effectiveness is contingent upon access to substantial datasets for continuous learning and refinement[76].

In recent years, there has been a notable surge in research at the intersection of ML and LT, particularly within the last five years. Among the 23 studies reviewed, a substantial majority (91%) were conducted between 2018 and 2023, signifying a burgeoning interest in this field[77]. Additionally, a significant proportion of these studies (61%) originated from the United States and China. A multinational study involving participants from the United States, United Kingdom, and Canada stands out, as it evaluated the 90-d predictive capacity of ML models post-LT across these countries, utilizing transplant registries. Notably, the study revealed that ML model performance varied when applied across countries, indicating limited external validity. Therefore, it is suggested that ML algorithms should be tailored to each country's specific transplant registry data for enhanced reliability. The underrepresentation of other countries in these studies underscores the importance of more diverse ML research to benefit liver transplant patients worldwide.

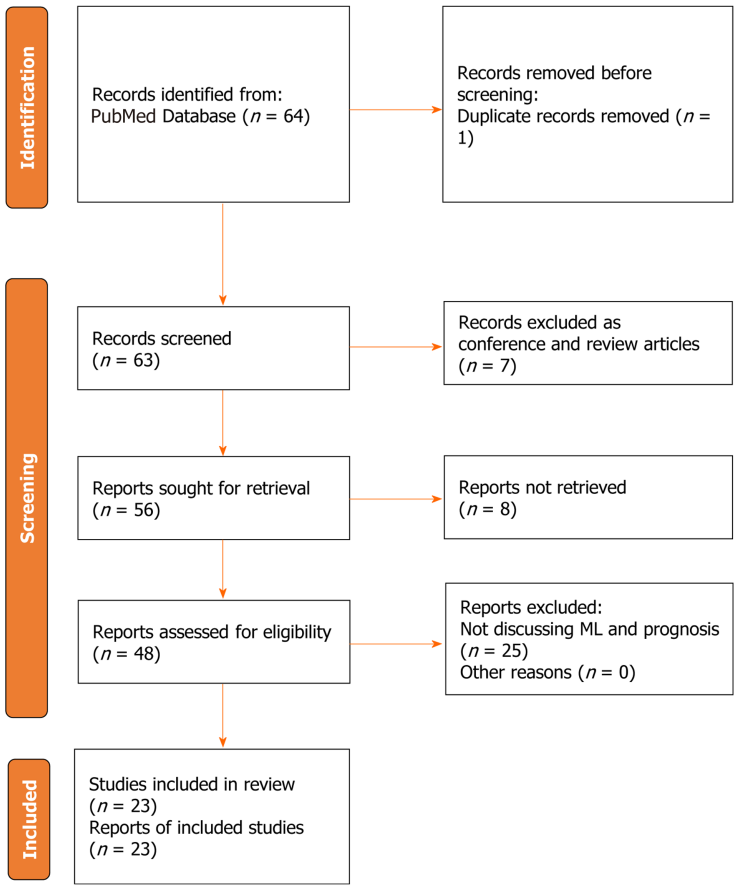

Figure 3 PRISMA flow chart of the selection process.

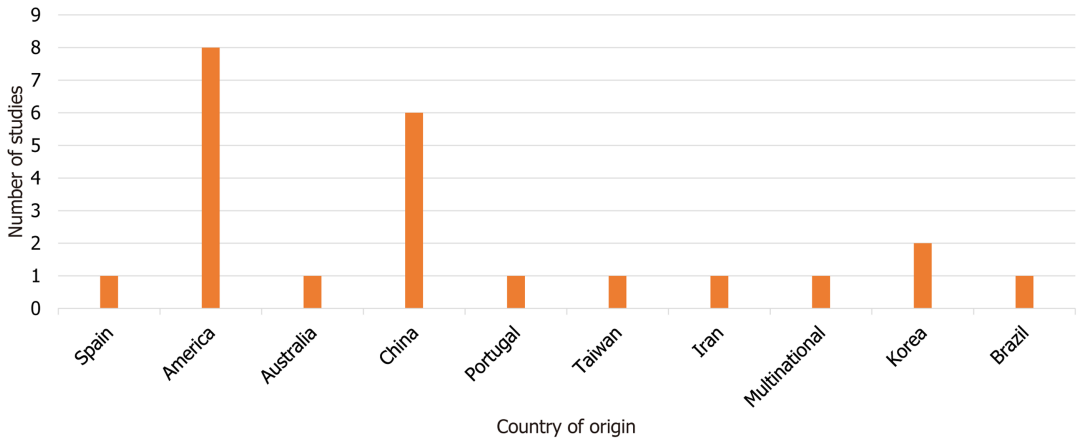

Figure 4 Countries that published machine learning studies related to liver transplantation and prognosis extracted from literature over the study period.

Crucially, ML methods employed for the allocation of orthotopic liver transplants, whether from living donors, deceased donors, or cadaveric sources, should be rooted in population-specific parameters pertaining to the recipient. This individualized approach is essential to ensure post-transplant longevity and minimize the risk of complications. The utilization of ML models that take into account an individual's unique population parameters or variables to assess the risk of mortality prior to transplantation holds the potential to prevent unnecessary mortality and morbidity associated with high-risk transplantations[78].

Concerning the underlying reasons for transplantation, factors such as ACLF, PSC, and HCC have been prominent considerations. Existing studies have demonstrated the pivotal role of LT as a life-saving intervention for ACLF patients [79]. ACLF can manifest at any stage of chronic liver disease, leading to a rapid deterioration in liver function and a high mortality rate within a short timeframe[80], as it is noticeable a high mortality rate for non-transplanted ACLF patients within 28 and 90 d[81,82].

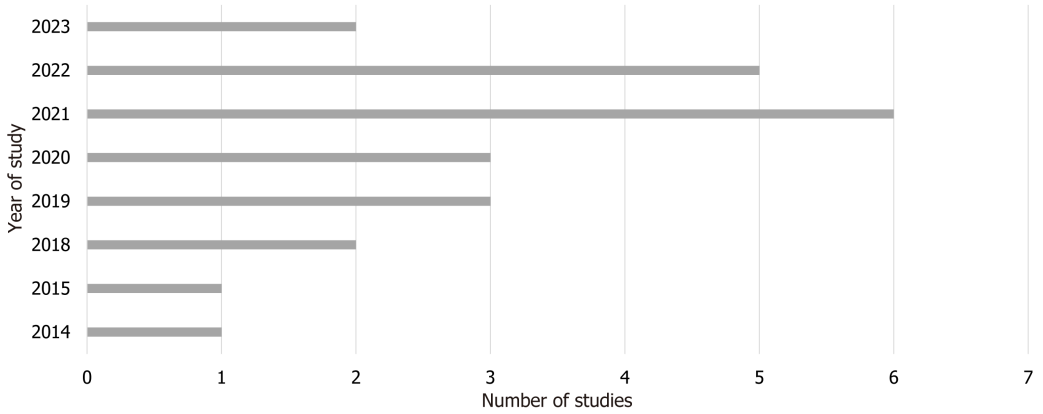

Figure 5 Increase in machine learning studies related to liver transplantation and prognosis in the past 5 years.

LT is a critical treatment option for various liver-related conditions, including ACLF, PSC, and HCC. However, the efficacy of LT in ACLF patients remains debated, with conflicting findings suggesting no significant survival advantage over non-transplanted patients[83]. ML models have the potential to improve the assessment of short-term mortality risk in ACLF patients post-transplantation, thereby aiding in the allocation of liver allografts and potentially enhancing outcomes[79]. It is imperative to expand the scope of research on ML models in LT to encompass diverse patient populations, thereby increasing the external validity of these models. Customizing ML algorithms to specific transplant registries and incorporating population-specific parameters can enhance the accuracy and effectiveness of prognosis and decision-making in LT.

PSC is a chronic liver disease characterized by progressive bile duct inflammation, cholestasis, and fibrosis. LT is the primary treatment for end-stage PSC, yielding generally favorable outcomes, although complications like cholangiocarcinoma, recurrent disease, worsening of inflammatory bowel disease, and an elevated risk of colonic cancer pose challenges[84]. Cholangiocarcinoma develops in 8%-18% of long-standing PSC patients[85], and PSC recurrence post-transplantation is observed in some cases[86]. Increased dysplasia and colon cancer risk are also associated with colitis patients having coexisting PSC[87,88]. Consequently, accurate evaluation and allocation of liver allografts in PSC patients are critical, with ML algorithms incorporating pertinent variables from PSC patients facilitating informed and precise decision-making[86-89].

HCC is a common indication for LT, ranking fifth among the most prevalent malignancies and being the third leading cause of cancer-related mortality worldwide[90-92]. LT offers a promising therapeutic option for long-term survival in HCC cases by addressing both advanced liver disease and HCC itself[93,94]. However, the risk of HCC recurrence post-transplantation underscores the necessity for careful patient selection. HCC recurrence occurs most frequently among liver transplant recipients compared to other liver diseases, estimated at 8%-20%[95]. Guidelines recommend active post-transplant surveillance for HCC patients, such as regular liver imaging tests within the first postoperative year and subsequent monitoring to detect lung metastases[96]. Tumor recurrence in HCC patients after transplantation is often attributed to advanced tumor burden and unclear tumor biology[97].

The Milan criteria, comprising specific size and number requirements for liver lesions along with the absence of vascular invasion or extra-hepatic metastases, were established to guide LTs for HCC[98]. Transplantations adhering to these criteria have demonstrated comparable survival outcomes to those performed for cirrhosis. However, criticism of the Milan criteria centers on their strictness in terms of lesion size and number, with some studies suggesting successful transplantation outcomes for HCC patients beyond these criteria. Additionally, the Milan criteria do not account for tumor biology, potentially limiting their applicability[99].

Down-staging, a strategy involving loco-regional therapy to reduce tumor burden and bring lesions outside the transplant criteria within the criteria, has shown promise in achieving favorable long-term outcomes for HCC patients beyond the Milan criteria. Nevertheless, tumor recurrence remains a concern, occurring in 8%-20% of transplanted HCC patients, typically within 2 years post-transplantation, with a median survival of 1 year following recurrence diagnosis [100].

To address the risk of tumor recurrence, various prognostic scores have been developed, such as the Risk Estimation of Tumor REcurrence After Transplant (RETREAT) score. This score considers three factors associated with post-transplant HCC recurrence: explant liver tumor burden, microvascular invasion evidence, and alpha-fetoprotein levels at the time of transplant. The RETREAT score ranges from 0 to 8, with higher scores indicating an elevated risk of recurrence. A score of 0 corresponds to a 1% recurrence rate at 1 year and a 2.9% recurrence rate at 5 years. Conversely, RETREAT scores of 5 or higher are associated with 1- and 5-year HCC recurrence rates of 39.3% and 75.2%, respectively[101]. Deep learning models can be used for diagnosis of HCC[102,103].

The RETREAT score, while valuable for post-transplant management, has limitations as it relies on factors that assess explant tissue biology and anatomy. This restricts its utility to assessing transplant failure risk after transplantation. ML models, utilizing pre-transplant data in HCC patients, can effectively allocate liver allografts before transplantation, thereby enhancing long-term survival prospects[101].

Although ML is gaining traction in various medical disciplines, this review reveals a dearth of pediatric studies among the 23 studies discussing ML and LT. This shortage reflects the limited interest in applying ML in pediatric patients, aligning with trends in other pediatric disciplines where ML adoption has been low. Consequently, there's a clear need for more research on ML in pediatric LT to assess its impact in this domain[104]. Furthermore, the high mortality rate in pediatric acute liver failure underscores the importance of robust criteria, including ML models, to inform decision-making in this patient group[105].

Evaluating ML model performance involves various metrics like accuracy, precision, confusion matrix, recall, specificity, precision-recall curve, F1 score, and ROC curve. The use of ROC values in this study for assessing different ML models across studies is justified and reliable.

The utilization of ML algorithms in LT prognostication is a significant advancement. These models are primarily based on pre-transplant donor and recipient data, allowing for accurate predictions before transplantation. Considering that crucial decisions regarding LT must be made pre-procedure, ML models hold promise in addressing the complex challenge of allocating allografts to the most suitable recipients[101].

Numerous studies reviewed consistently indicate that ML models provide satisfactory to excellent predictions for both short- and long-term mortality or complication risks[106]. Additionally, emerging evidence suggests that AI can surpass traditional tools in predicting cardiac events post LT[107] and mortality related to esophageal variceal bleeding[108,109]. Accurate predictions of short- and long-term complications following LT are crucial, as they inform the need for additional surveillance or even potential halting of the transplantation process for patients at higher risk of mortality. Long-term complications post LT remain a significant concern, with limited improvement in survival rates over the years[110].

Long-term survivors face increased risks of comorbidities like metabolic syndrome, renal dysfunction, cardiovascular disease, and extrahepatic malignancies, necessitating multidisciplinary management strategies to prevent medical complications and their associated cost implications[111,112]. Metabolic syndrome, in particular, is prevalent among liver transplant recipients and is associated with chronic liver disease progression and increased cardiovascular risk[110]. Sustained transient post-transplant diabetes significantly elevates the long-term risk of major adverse cardiac events and mortality[113]. Therefore, precise prognostication of patients at risk of long-term complications is essential, and AI algorithms offer promise in enhancing risk assessment and improving patient outcomes.

Furthermore, ML models consistently outperform traditional scoring systems, including MELD, D-MELD, SOFT, p-SOFT, BAR, DRI score, ABIC, CLIF-C OFs, CLIF-C ACLFs, and CLIF SOFA, as well as models based on Cox and LR. This finding is particularly significant given the limitations of traditional scoring systems in predicting post-transplant outcomes[101]. The incorporation of ML algorithms in organ allocation can enhance efficiency by preventing unnecessary transplantations and allocating allografts to patients with a higher likelihood of success. This optimization helps manage the associated costs of transplant failure and complications, especially considering the limited availability of donor organs. Regarding short and long-term mortality prediction (90-d), the RF model consistently exhibits the highest AUC [114,115].

ML models provide numerous advantages, such as managing large datasets, objectivity, and assisting in cases with similar probabilities. In LT, ANNs and RF classifiers are the commonly used AI models. ANNs excel at identifying complex patterns beyond human capability and can yield near-perfect predictions, reaching up to 95% accuracy in 3-months graft survival. However, ANNs lack transparency regarding the variables they consider. In contrast, RF models offer better confidence in utilizing marginal organs, resulting in improved post-transplantation outcomes[114].

RF models exhibit superiority when predicting the risk of sepsis and AKI. Although overall survival post-LT has improved, post-transplantation infections remain a significant challenge, contributing to morbidity and mortality. Studies reveal that 35%-55% of liver transplant recipients experience infection-related complications, including bacterial, fungal, and multidrug-resistant infections. Most of these infections occur within the first six months after transplantation and are responsible for a significant portion of early post-transplant deaths[116-119].

AKI and chronic renal dysfunction are common complications following LT. Contributing factors include long-term exposure to immunosuppressive medications like calcineurin inhibitors, preoperative kidney dysfunction, perioperative AKI/hypertension, diabetes mellitus (DM), and atherosclerosis pre- and/or post-transplantation. Long-term data indicates that kidney failure, defined as a glomerular filtration rate of 29 mL/min/1.73 m² or less or the development of end-stage renal disease, occurs in 18% at 5 years and 25% at 10 years post-transplantation[120]. Factors significantly associated with worse survival in patients with renal dysfunction include higher age at transplantation, increased creatinine levels, post-transplant DM, and transplantation in the pre-MELD era. Consequently, serum creatinine was incorporated into the MELD score to prioritize donor livers for transplant candidates with renal dysfunction[121,122]. AKI immediately following LT is linked to increased morbidity and mortality, with an incidence ranging from 25% to 60%[95].

The use of ML models in predicting the risk of sepsis and AKI is vital to enhance post-liver transplant outcomes. Post-transplant infections and AKI are associated with increased healthcare costs, prolonged hospital stays, and adverse effects on both allograft and patient survival[116,119]. Also, ML models have been used for the diagnosis of appendicitis and heart disease[123,124]. Employing ML models for predicting and managing these complications holds the potential to yield improved patient outcomes, reduced healthcare expenditures, and an overall better quality of life.

Despite the demonstrated superiority of ML models in the review, certain limitations must be acknowledged. Many studies relied on retrospective designs, which can introduce biases and impact result generalizability. Prospective studies with larger sample sizes and more diverse populations are necessary to validate ML model performance across different contexts and patient groups.

Another limitation stems from the lack of standardization and consistency in data collection and reporting of LT-related variables across various centers and studies. Data collection disparities can result in inconsistencies and hinder accurate comparisons of different ML models. Efforts should be made to standardize data collection practices in LT research to enhance the reliability and general applicability of ML models.

The underrepresentation of pediatric LT in the reviewed studies underscores a research gap. Pediatric patients have unique considerations and challenges in LT, and developing ML models tailored to this population could significantly enhance their outcomes.

Ethical considerations are paramount when implementing ML models in clinical decision-making. These models must be transparent, explainable, and accountable to ensure that clinicians and patients comprehend the rationale behind predictions, enabling informed decisions. Furthermore, addressing the black box dilemma of AI models for prognostication is imperative, as ensuring transparency and interpretability in these models is essential to uphold ethical standards in healthcare decision-making.

CONCLUSION

This study reveals a significant surge in interest in the application of ML for liver transplant prognostication, with the majority of the studies emerging within the past five years. Notably, the United States and China stand out as the frontrunners in this field. This research also emphasizes that the performance of ML models exhibits variability when applied across different countries, underscoring limited external validity. Consequently, ML algorithms tailored to each country's unique transplant registry data demonstrate greater reliability.

Furthermore, the study highlights the superior predictive accuracy of ML models built on pre-transplant data in comparison to established scoring systems like MELD, irrespective of the underlying cause of hepatic failure, including HCC. Additionally, the study suggests that when selecting an ML model for predicting the risk of sepsis and AKI post-LT, the RF model may be the most suitable choice.

Overall, the use of ML models in LT has the potential to optimize organ allocation, improve patient outcomes, and reduce healthcare costs. However, more prospective studies with larger and diverse populations are needed to validate ML model performance and standardize data collection practices in LT research. Additionally, the inclusion of pediatric patients in ML research is crucial to address their unique needs. With continued research and advancements in ML techniques, ML models are poised to play an increasingly pivotal role in LT in the coming years.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) is a life-saving procedure for individuals with end-stage liver disease, offering not only health restoration but also a potential 15-year extension of life. However, the equitable allocation of donor organs remains a challenge due to donor scarcity. While the survival rates post-transplant are commendable, the shortage of donor organs persists, pushing the field towards utilizing less conventional donors. An efficient system of liver organ allocation is essential as there's a growing demand, leading to escalating healthcare costs. Traditional scoring systems like Child-Turcotte-Pugh and model for end-stage liver disease (MELD) have been employed for organ allocation, but they have limitations, such as empirical variable selection and limited predictive ability.

Research motivation

The primary challenge in LT is optimizing organ allocation. The scarcity of donor organs necessitates accurate prognostication for organ allocation and transplant success. While traditional scoring systems have been useful, they are not without limitations. Therefore, there's a need to explore more reliable and predictive methods. In this context, machine learning (ML) models present a promising avenue. ML algorithms can analyze various data types, from structured to unstructured, and offer a new dimension in predictive accuracy. Their ability to handle complex datasets and discover intricate patterns makes them suitable for enhancing prog-nostication in LT. Given the critical importance of optimizing organ allocation and predicting transplant outcomes, evaluating the utility of ML models is a significant step towards improving the LT process.

Research objectives

The primary objectives of this study are to comprehensively assess the effectiveness of ML models in LT prognostication and to compare their performance and reliability with traditional scoring systems. This evaluation involves a systematic review of observational studies to determine the real-world utility of ML models in predicting transplant outcomes. Realizing these objectives is crucial for advancing the field of LT and ensuring that patients receive the most suitable organs, ultimately improving survival rates and healthcare resource allocation. Moreover, the study aims to bridge the gap between ML and traditional scoring systems, shedding light on the potential of ML models to revolutionize prognostication in LT.

Research methods

This systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines and conducted a comprehensive literature search on PubMed/MEDLINE using specific terms related to ML, artificial intelligence (AI), LT, and prognosis. It included all relevant observational studies without restrictions on publication year, age, or gender, focusing on ML models for LT prognosis and post-transplant complications. Exclusion criteria covered

non-English papers, review articles, case reports, conference papers, studies with missing data, or methodological flaws. A single reviewer screened and analyzed eligible studies, summarizing their objectives, methods, results, and conclusions. Data extraction included study type, population, year, purpose, setting, methods, results, and strengths/limitations. The review also compared ML models to traditional scoring systems. This systematic approach synthesized information, offering a comprehensive understanding of artificial intelligence's role in LT prognosis and identified trends and potential benefits and limitations. It provides valuable insights into the current state of research in predicting LT outcomes with AI.

Research results

In this systematic review, an initial pool of 64 references was identified and refined through a selection process. After excluding conference articles, review papers, and duplicates, 23 studies were included for analysis. These studies spanned from 2014 to 2023 and covered various transplantation reasons, with the majority conducted in the United States (34.8%), followed by China (26%). The primary outcomes assessed were mortality and post-transplant complications, with ML models consistently outperforming traditional models and scoring systems. The receiver operating characteristic curve analysis demonstrated ML models' excellent predictive performance for both short-term and long-term outcomes. Notably, the Random forest (RF) model excelled in predicting 90-d mortality, while the 'gradient boosting machine' model showed proficiency in forecasting complications like graft-versus-host disease, pneumonia, and acute kidney injury (AKI). The RF model was particularly adept at predicting sepsis and AKI. These findings highlight the potential of ML to enhance prognostic accuracy and inform clinical management in LT.

Research conclusions

This study underscores the growing interest in applying ML to liver transplant prognostication, with a surge in research within the last five years. Notably, the United States and China have been leaders in this field. The research emphasizes the need for customized ML algorithms, adapted to each country's unique transplant registry data, to enhance the reliability of predictions. ML models, based on pre-transplant data, consistently outperform established scoring systems like MELD, regardless of the underlying cause of hepatic failure, including hepatocellular carcinoma. Additionally, when selecting an ML model for predicting the risk of sepsis and AKI post-LT, the RF model appears to be a promising choice. These findings point to the potential of ML models in optimizing organ allocation, improving patient outcomes, and reducing healthcare costs in LT.

Research perspectives

The future of research in this field should focus on conducting more prospective studies with larger and diverse patient populations to validate the performance of ML models and enhance their generalizability. Standardizing data collection practices in LT research is crucial to ensure consistency and facilitate accurate comparisons of different ML models. Furthermore, there is a pressing need to include pediatric patients in ML research to address their unique requirements and challenges in LT. Ethical considerations should remain paramount, with a focus on ensuring transparency, explainability, and accountability in ML models to uphold ethical standards in healthcare decision-making. Continued advancements in ML techniques and the expansion of research efforts are expected to play an increasingly pivotal role in LT, offering the potential to further enhance patient care and clinical decision-making in the coming years.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Current status and future perspectives on stem cell transplantation for spinal cord injury

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Abstract

BACKGROUND

Previous assessments of stem cell therapy for spinal cord injuries (SCI) have encountered challenges and constraints. Current research primarily emphasizes safety in early-phase clinical trials, while systematic reviews prioritize effectiveness, often overlooking safety and translational feasibility. This situation prompts inquiries regarding the readiness for clinical adoption.

AIM

To offer an up-to-date systematic literature review of clinical trial results concerning stem cell therapy for SCI.

METHODS

A systematic search was conducted across major medical databases [PubMed, Embase, Reference Citation Analysis (RCA), and Cochrane Library] up to October 14, 2023. The search strategy utilized relevant Medical Subject Heading (MeSH) terms and keywords related to "spinal cord", "injury", "clinical trials", "stem cells", "functional outcomes", and "adverse events". Studies included in this review consisted of randomized controlled trials and non-randomized controlled trials reporting on the use of stem cell therapies for the treatment of SCI.

RESULTS

In a comprehensive review of 66 studies on stem cell therapies for SCI, 496 papers were initially identified, with 237 chosen for full-text analysis. Among them, 236 were deemed eligible after excluding 170 for various reasons. These studies encompassed 1086 patients with varying SCI levels, with cervical injuries being the most common (42.2%). Bone marrow stem cells were the predominant stem cell type used (71.1%), with various administration methods. Follow-up durations averaged around 84.4 months. The 32.7% of patients showed functional improvement from American spinal injury association Impairment Scale (AIS) A to B, 40.8% from AIS A to C, 5.3% from AIS A to D, and 2.1% from AIS B to C. Sensory improvements were observed in 30.9% of patients. A relatively small number of adverse events were recorded, including fever (15.1%), headaches (4.3%), muscle tension (3.1%), and dizziness (2.6%), highlighting the potential for SCI recovery with stem cell therapy.

CONCLUSION

In the realm of SCI treatment, stem cell-based therapies show promise, but clinical trials reveal potential adverse events and limitations, underscoring the need for meticulous optimization of transplantation conditions and parameters, caution against swift clinical implementation, a deeper understanding of SCI pathophysiology, and addressing ethical, tumorigenicity, immunogenicity, and immunotoxicity concerns before gradual and careful adoption in clinical practice.

Key Words: Spinal cord injury; Stem cell therapy; Adverse events; Functional outcomes; Systematic review

Core Tip: In the context of spinal cord injury (SCI) treatment, stem cell-based therapies exhibit promise, as demonstrated in this systematic review of 66 studies. However, the research reveals potential adverse events and limitations, emphasizing the importance of optimizing transplantation conditions, cautious clinical implementation, a deeper understanding of SCI pathophysiology, and addressing ethical, tumorigenicity, immunogenicity, and immunotoxicity concerns before a gradual and careful adoption of stem cell therapy in clinical practice. This underscores the need for further research to ensure the safety and effectiveness of these therapies for SCI patients, while acknowledging their potential for improving functional outcomes.

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INTRODUCTION

Each year, approximately half a million fresh cases of spinal cord injury (SCI) emerge on a global scale. These instances are predominantly triggered by trauma stemming from car accidents, slips, firearm incidents, or medical/surgical complications. Given the nature of these causative factors, SCI primarily affects younger individuals[1].

The intricate and time-sensitive pathophysiology of SCI renders the exploration of therapeutic targets exceedingly challenging. Following the initial mechanical injury, a cascade of secondary events exacerbates patients' conditions. These events include the inflammatory response, gliosis hyperplasia, the creation of inhibitory environments, and the formation of scars, all of which hinder axonal regeneration and limit the effectiveness of various treatment approaches[2]. These pathophysiological consequences often lead to enduring neurological impairments, including the loss of motor and sensory functions below the injury level, as well as autonomic dysfunction[3].

Present-day clinical approaches prioritize prompt surgical decompression and mechanical stabilization at the location of SCI, bolstered by pharmaceutical measures encompassing methylprednisolone, nimodipine, naloxone, and various others. Subsequent to this crucial stage, patients engage in rehabilitative initiatives geared towards reinstating functionality and self-sufficiency. Regrettably, these endeavors yield unsatisfactory results concerning the safeguarding of neural structures, the rejuvenation of nervous tissue, and the recuperation of bodily functions. The primary cause of this dearth of achievement can be attributed to the intricate pathophysiological processes inherent to SCI, culminating in irreversible harm within the neural microenvironment at the site of injury[4,5].

In recent decades, stem cell therapy has emerged as a highly promising avenue within the realm of SCI. After a series of encouraging experimental treatments using diverse stem cell types in animals of various species, clinical trials involving human SCI patients became a reality in the early 2000s[3,5].

While prior evaluations of stem cell therapy for SCI have occurred, they have encountered specific challenges and restrictions. Most current investigations consist of single-arm, early-phase clinical trials primarily aimed at gauging the safety of stem cell treatments. In contrast, established systematic appraisals have exclusively featured randomized

controlled trials, concentrating solely on the effectiveness of stem cells. Consequently, they have encompassed a limited range of studies and do not provide a comprehensive scrutiny of available data. Furthermore, they overlook critical facets such as the safety and feasibility of translating stem cell therapy from laboratory research to clinical application. Consequently, the question of whether we have amassed enough substantiation to justify an immediate clinical adoption of stem cell therapy remains open[6,7].

This review, in turn, delves into the pathophysiological intricacies of SCI, exploring the potential mechanisms through which various stem cells contribute to the restoration of the spinal cord, and it presents the fundamental characteristics and results of the pertinent clinical trials published.

MATERIALS AND METHODS

Literature review

The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[8]. Two authors (E.A. and A.P.) performed a systematically comprehensive literature search of the databases PubMed, Web of Science, Cochrane, Embase databases, and Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). The first literature search was performed on August 30, 2023, and the search was updated on October 14, 2023. A combination of keyword searches was performed to generate a search strategy. The search keywords, including "spinal cord", "injury", "clinical trials", "stem cells", "functional outcomes", and "adverse events", were used in both AND and OR combinations. Studies were retrieved using the following Medical Subject Heading (MeSH) terms and Boolean operators: ("spinal injury" OR "spinal cord injury") AND ("stem cells" OR "staminal cells") AND ("clinical trials" OR "clinical studies"). Other pertinent articles were identified through reference analysis of selected papers. A search filter was set to show only publications over the designated period, 2010–2023.

Inclusion and exclusion criteria

The studies were chosen according to the below inclusion criteria: (1) The use of English; (2) clinical trials, such as randomized controlled or non-randomized controlled trials, single-arm or double-arm studies; (3) research on the use of stem cells to treat spinal cord injuries; and (4) research with adverse occurrences or functional results. The subsequent criteria for exclusion were utilized: (1) Publications such as editorials, case reports, case series, cohort studies, literature reviews, and meta-analyses; (2) research with vague methodology and/or findings; (3) research that omits information on adverse occurrences or functional results; (4) study that has been published several times; (5) the complete text is not available; and (6) patients with various significant conditions are included. Duplicates were eliminated from the list of recognized studies before importing it into Endnote X9. E.A. and P.P.P., two independent researchers, examined the data in accordance with the inclusion and exclusion criteria. All differences were settled by M.Z., the third reviewer. After that, full-text screening was applied to the qualifying articles.

Collecting data

We extracted the following data for each study: Authors, year, stage of the clinical trial, number of patients, degree of damage, neurological status prior to treatment, type and origin of stem cells, dosage and mode of administration, duration of follow-up, and clinical results.

Outcomes

Our primary outcomes were: (1) Clinical improvement, evaluated by the American Spinal Cord Injury Association Impairment Scale (ASIA) improvement scale (AIS) (Table 1), or, if not available, with other spinal cord injury scales or reported descriptive clinical data; and (2) adverse events (AEs) pertaining to many systems such as the cardiovascular, neurological, digestive, and musculoskeletal systems.

Assessment of bias risk

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale[9]. By evaluating the study's comparability, outcome evaluation, and selection criteria, quality assessment was carried out. Nine was the optimal score. Better study quality was reflected by higher ratings. Research that scored seven or above were deemed to be of excellent quality. Independently, E.A. and P.P.P. conducted the quality evaluation. The third author reexamined publications when inconsistencies emerged (Figure 1).

Analytical statistics

Ranges and percentages were included in the descriptive statistics that were provided. The R statistical software, version 3.4.1, was used for all statistical analyses (http://www.r-project.org).

RESULTS

Literature review

After duplicates were eliminated, 496 papers in total were found. 237 articles were found for full-text analysis after title

Table 1 American Spinal Cord Injury Association Impairment Scale improvement scale

A = Complete	No sensory or motor function is preserved in the sacral segments S4–S5
B = Sensory incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch or pin-prick at S4–S5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body
C = Motor incomplete	Motor function is preserved below the neurological level AND more than half of the key muscle functions below the neurological level of injury have a muscle grade less than 3 (grades 0–2)
D = Motor incomplete	Motor function is preserved below the neurological level AND at least half (half or more) of the key muscle functions below the neurological level of injury have a muscle grade ≥ 3
E = Normal	If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments AND the patient has prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade

Time from injury: Immediate: 0-2 h after the injury; acute: Early acute phase: 2-48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 mo; chronic phase: > 6 mo.
AIS: American spinal injury association Impairment Scale; ISNCSCI: International Standards for Neurological Classification of SCI.

Modified Newcastle-Ottawa Quality Assessment Scale

Selection

(1) Representativeness of the exposed cohort
  (a) Consecutive eligible participants were selected, participants were randomly selected, or all participants were invited to participate from the source population,
  (b) Not satisfying requirements in part (a), or not stated.

(2) Selection of the non-exposed cohort
  (a) Selected from the same source population,
  (b) Selected from a different source population,
  (c) No description.

(3) Ascertainment of exposure
  (a) Medical record,
  (b) Structured interview,
  (c) No description.

(4) Demonstration that outcome of interest was not present at the start of the study
  (a) Yes,
  (b) No or not explicitly stated.

Comparability

(1) Were there clearly defined inclusion and exclusion criteria?
  (a) Yes,
  (b) No or not explicitly stated.

Outcome

(1) Assessment of outcome
  (a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records,
  (b) Record linkage (*e.g.*, identified through ICD codes on database records),
  (c) Self-report with no reference to original structured injury data or imaging,
  (d) No description.

(2) Was follow-up long enough for outcomes to occur?
  (a) Yes (≥ 12 months),
  (b) No (< 3 months).

(3) Adequacy of follow up
  (a) Complete follow up – all participants accounted for,
  (b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up or description provided of those lost),
  (c) Follow up rate < 85% and no description of those lost provided,
  (d) No statement.

Figure 1 Modified Newcastle-Ottawa Scale.

and abstract analysis. It was determined who was eligible for 236 articles. The following criteria led to the exclusion of the remaining 169 articles: (1) Unrelated to the study topic (164 articles); (2) lacking methodological and/or outcome information (2 articles); and (3) a systematic review or meta-analysis of the literature (3 articles). For each of the patient groups under consideration, at least one or more outcome measures were available for all of the studies that were part of the analysis. The PRISMA statement's flow chart is depicted in Figure 2. The PRISMA checklist is offered as additional content.

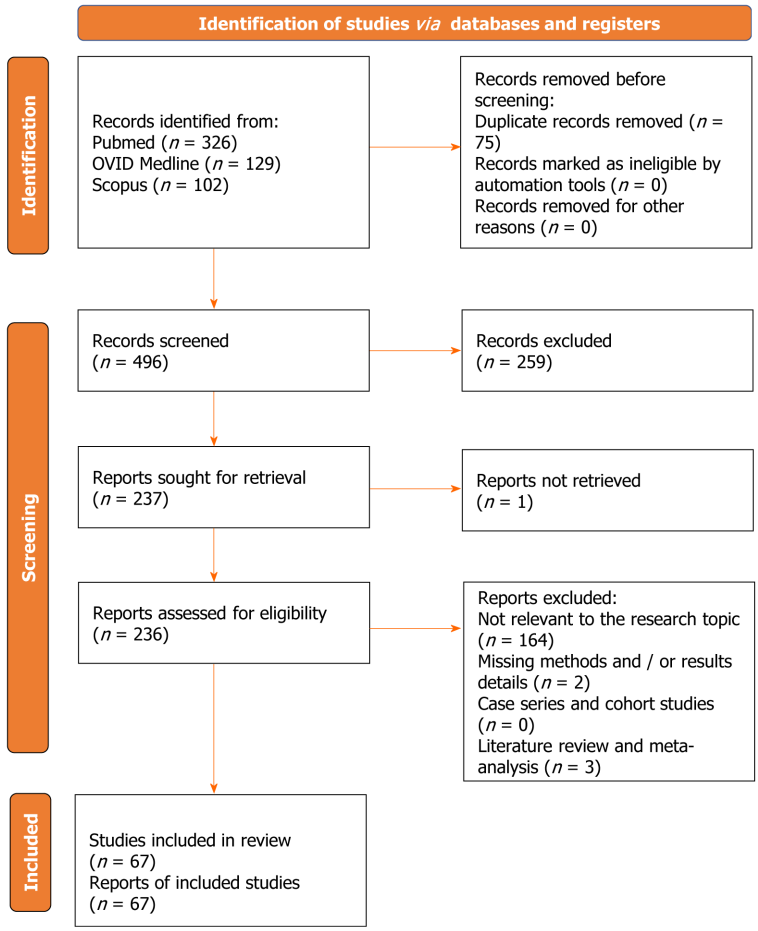

Figure 2 Flow chart according to the PRISMA statement.

Data analysis

This table presents data from a comprehensive collection of 67 studies that explored the use of stem cell therapies for spinal cord injuries. In total, these studies encompassed 1086 patients with varying injury levels. Cervical injuries were the most prevalent (42.2%), followed by thoracic injuries (32.3%), and lumbar injuries (8.6%). The specific stem cell types used varied across the studies, with bone marrow stem cells (BMSC) being the most common (71.1%), followed by umbilical cord tissue stem cells (UCMSC) in 16%, and others. The treatment approaches included intrathecal administration (61.3%), intramedullary (29.3%), and intravenous or intravenous plus intralesional methods (9.7%).

The follow-up periods for these studies ranged from acute to chronic stages, with an average follow-up duration of approximately 84.4 mo. The outcomes of these treatments were generally positive, with 32.7% of patients showing functional improvement from AIS A to B, 40.8% from AIS A to C, 5.3% from AIS A to D, and 2.1% from AIS B to C. A small percentage (1.3%) experienced improvement in AIS B to D, and AIS B to E (1.3%). Furthermore, sensory improvements were observed in 30.9% of patients. In terms of AEs, the studies consistently reported a low occurrence, with only mild and transient issues. Fever was experienced by 15.1% of patients, while 4.3% reported headaches, 3.1% experienced a transient increase in muscle tension, and 2.6% had dizziness. These findings collectively highlight the potential for functional recovery in spinal cord injury patients through stem cell therapies while underscoring their relatively safe profile (Tables 2-6).

DISCUSSION

The number of clinical trials involving stem cells has significantly increased in the last few years. Thousands of registered trials claim to use stem cells in their experimental treatments across the globe[2,4,7,10]. This could imply that stem cell therapy has a strong and established track record in clinical practice. But in actuality, even with some noteworthy breakthroughs, the application of stem cells in medicine is still relatively new.12, 15 Phase I clinical trials, case series, and case reports make up the majority of stem cell clinical research conducted today[2,4,5]. Good randomized controlled trials are hard to come by, and even simple controlled trials are difficult to find. It is therefore difficult to assess the efficacy of stem cells through head-to-head comparisons using meta-analysis. Furthermore, even while differences in patient age, the degree of spinal cord injury, cell kinds, sources, culture conditions, and other variables might make inter-study comparisons more difficult, they are nevertheless essential[5,8,9,11-15].

Table 2 Summary of the studies included in the systematic literature review focusing on bone marrow derived stem cells (*i.e.*, BMSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from Injury		Functional improvement	Adverse effects
Park *et al*[37], 2005	N/A	6	Cervical	AIS A	Autologous (iliac bone marrow)	BMSC	1.98×10^{10}	Intralesional	N/A	6-18	AIS A→C 4, AIS A→B: 1, AIS A=A: 1	No serious adverse effects
Sykova *et al* [11], 2006	N/A	20	Cervical and thoracic	AIS A: 15; AIS B: 4; AIS C: 1	Autologous (iliac bone marrow)	BMSC	$104.0 \pm 55.3 \times 10^8$	Intravenous + Intraarterial	Subacute or chronic	24	AIS A→B: 1, AIS B→D: 1, AIS=: 15	No serious adverse effects
Chernykh *et al* [12], 2007	N/A	18	Cervical, Thoracic, Lumbar	N/A	Autologous (iliac bone marrow)	BMSC	N/A	Intralesional+ Intravenous	Chronic	9.4 ± 4.6	ASIA scale: significant increase in total sensitivity and motor activity score	No serious adverse effects
Yoon *et al* [13], 2007	I/II	35	Cervical (4) and thoracic (4)	N/A	Autologous iliac bone marrow	BMSC	1×10^8	Intralesional	Intermediate	10.4	AIS grade increased in 30.4% of the acute and subacute treated patients (AIS A→B or A→C)	No serious adverse effects
Geffner *et al* [14], 2008	N/A	8	Thoracic	AIS A: 5, AIS B: 1, AIS C: 2	Autologous iliac bone marrow	BMSC	1.2×10^6/kg	Intrathecal	4 acute and 4 chronic (average 114 months)	24	AIS A→C: 4, AIS B→C: 1, AIS C→D: 1 AIS =: 2	No serious adverse effects
Adel *et al*[38], 2009	N/A	43	Cervical and thoracic	AIS A: 40, AIS C: 3	Autologous iliac bone marrow	BMSC	$5\text{-}10 \times 10^6$	Intrathecal	Chronic (average 43.2 months)	6	AIS A→B: 11; AIS A→C: 1; AIS B→C: 3; AIS =: 28	ADEM: 1/43; Marked increased spasticity: 4/43; Neuropathic pain: 24/43
Kumar *et al* [39], 2009	I/II	297	N/A	AIS A: 249, AIS B: 12, AIS C: 34, AIS D: 2	Autologous iliac bone marrow	BMSC	N/A	Intrathecal	N/A	18.4-20.5	32.7% of the ASIA-classified patients showed improvement, in sensory and motor scale	No serious adverse effects. Mild-to-moderate neuropathic pain in few patients
Pal *et al*[40], 2009	N/A	30	Cervical and thoracic	AIS A: 24, AIS C: 6	Autologous iliac bone marrow	BMSC	1×10^6/kg	Intrathecal	< 6 months: 20, > 6 months: 30	12-36	No changes in the ASIA scale, SSEP, MEP and NCV	No serious adverse effects. Neuropathic pain in two patients
Abdelaziz *et al*[41], 2010	N/A	20	Thoracic	AIS A: 10, AIS B: 5, AIS C: 5	Autologous iliac bone marrow	BMSC	5×10^6/kg	Intrathecal + Intralesional	Chronic (> 6 months)	12	AIS A→B: 1, AIS A→C: 2, AIS B→C: 3; AIS=: 14	No serious adverse effects.Headache (12) and fever (3)
Bhanot *et al* [30], 2011	N/A	13	Cervical and thoracic	AIS A	Autologous	BMSC	$3\text{-}6\text{-}8 \times 10^6$/kg	Intrathecal	Intermediate and chronic (3-132 months, average 28)	6-38	AIS A→B: 1, Patchy improvement in sensations below the injured level: 2, Patient subjectively felt	No serious adverse effects. Transient increase in spasticity in the lower limbs (50%)

											improved sense of bladder filling: 1	
Park *et al*[35], 2012	N/A	10	Cervical	AIS A: 4, AIS B: 6	Autologous iliac bone marrow	BMSC	8×10^6 (intralesional) + 4×10^7 (subdural)	Intralesional + Subdural	> 1 months	6-62	Improvements in ADL, SSEP, MEP (3/10, all AIS B)	No serious adverse effects
Karamouzian *et al*[18], 2012	I/II	11	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	$0.7\text{-}1.2 \times 10^6$	Intrathecal	Acute and intermediate/chronic (max 1.5 months)	12-33	AIS A→C: 5, AIS=: 0	No serious adverse effects
Dai *et al*[28], 2013	N/A	20	Cervical	AIS A, ASIA score: 31.6 ± 9.82	Autologous iliac bone marrow	BMSC	2×10^7	Intralesional	Chronic (51.9 ± 18.3)	6	AIS A→B: 9, ASIA score: 43.1 ± 19.32	No serious adverse effects. Fever (2), Headache and dizziness (1), pain and numbness in spinal cord dominant area (2)
Jiang *et al*[19], 2013	N/A	20	Cervical (4), thoracic (11) and lumbar (5)	AIS A: 8, AIS B: 4, AIS C: 8	Autologous iliac bone marrow	BMSC	1×10^8	Intrathecal	Intermediate and chronic (3-120 months)	1	AIS A→B: 3, AIS A→C: 1, →AIS C→D: 8	No serious adverse effects. Fever and headache
Yazdani *et al*[42], 2013	I	8	Cervical (1) and thoracic (7)	AIS A	Autologous iliac bone marrow	BMSC	1×10^6	Intralesional	Chronic (13-63 months)	26-43	Although some improvement in light touch and pinprick sensation was observed, no improvement in ASIA classification was seen	No serious adverse effects
Amr *et al*[43], 2014	N/A	14	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	N/A	Scaffold	Intermediate and chronic (5-84 months, average 23 months)	24	AIS A→B: 2, AIS A→C: 12	Haematoma formation (2), Seroma formation (2)
Suzuki *et al*[44], 2014	N/A	10	Cervical and thoracic	AIS A: 5, AIS B:5	Autologous iliac bone marrow	BMSC	$2.03\text{-}8.44 \times 10^8$	Intrathecal	Intermediate and chronic (3 wk-12 months)	6	AIS A→B: 1, AIS B→C: 2, AIS B→D: 1; AIS=: 6	No serious adverse effects. Transient anemia after aspiration of bone-marrow cells (2)
Goni *et al*[45], 2014	N/A	9	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	N/A	Intrathecal	Chronic	24	No significant difference in the ASIA score. Statistically significant differences in the Functional Independence Measure and Modified Ashworth Scale	No serious adverse effects. Postoperative temporary neuropathic pain (2)
El-kheir *et al*[10], 2014	I/II	50	Cervical (10) and thoracic (40)	AIS A: 15, AIS B: 35	Autologous iliac bone marrow	BMSC	2×10^6/kg	Intrathecal	Chronic (12-36 months, average 18.3 ± 5)	18	AIS A→B: 12, AIS A→C: 4, AIS B→C: 18; AIS=: 16	Temporary mild side effects: Headache, neuropathic pain (30%). No long-term side effects
Mendonca *et*	I	14	Thoracic and	AIS A	Autologous	BMSC	5×10^6	Intralesional	Chronic (18-180	6	AIS A→B: 6, AIS A→C:	One subject developed a

al[46], 2014			lumbar		iliac bone marrow				months)		1; AIS=: 5; Improvements in urologic function (9) and changes in SSEP (1)	postoperatory complication, evolving a cerebrospinal fluid leak that was treated by an additional surgical procedure
Shin *et al*[47], 2015	I/IIa	19	Cervical	AIS A: 17, AIS B: 2	Human fetal brain	NSC	1×10^8	Intralesional	Acute and intermediate	12	AIS A→C: 2, AIS A→B: 1, AIS B→D: 2; AIS=: 14. Positive response in SSEP (35.3%) and MEP (58.8%) activities of AIS-A patients below the level of injury	No serious adverse effects
Chhabra *et al* [48], 2016	I/II	7	Thoracic	AIS A, ISCIS total score: 162.6 ± 3.1	Autologous iliac bone marrow	BMSC	3.6×10^8	Intrathecal	Acute	12	ISCIS total score: 134.9 ± 2.5	Liver abscess (1)
Oraee-Yazdani *et al* [49], 2016	I	6	Cervical (1) and thoracic (5)	AIS A	Autologous iliac bone marrow	BMSC	2×10^6	Intrathecal	Chronic (38.1 ± 15.3 months average)	25-36	AIS A→B: 1. Improvement in sensory level (2), improvement in UDS, especially bladder compliance (1)	No serious adverse effects
Oh *et al*[32], 2016	III	16	Cervical	AIS B	Autologous iliac bone marrow	BMSC	4.8×10^7	Subdural	Chronic (24-181 months)	6	SEP improvement (4), MEP improvement (6), improvement in motor grade (2)	No serious adverse effects. 8 patients developed mild adverse effects (muscle rigidity, worsened symptoms of tingling sense)
Thakkar *et al* [33], 2016	N/A	10	Thoracic and lumbar	AIS A	Autologous bone marrow + abdominal adipose tissue	BMSC	1.82×10^8	Intrathecal	Chronic (30-64.8 months)	34	AIS A→B: 6, AIS A→C: 3, AIS A→D: 1	No serious adverse effects
Vaquero *et al* [27], 2016	I/II	12	Thoracic	AIS A, ASIA score: 165.92 ± 22.83	Autologous bone marrow	BMSC	100×10^6 - 230×10^6	Intralesional	Chronic (38.0-321 months, average 166.3)	12	AIS→B: 3, AIS A→C: 1, ASIA score: 213.25 ± 37.19	22 adverse events of minor (79.1%) or moderate (20.9%) intensity.
Kakabadze *et al*[25], 2016	I	18	Cervical and thoracic	AIS A: 10, AIS B: 5, AIS C: 3	Autologous iliac bone marrow	BMSC	$405\text{-}964 \times 10^6$	Intrathecal	Intermediate and chronic (max 20 months)	12	ASIA scale improvement by one grade: 7/9 (78%) Improvement by two grades: 2/9 (22%)	No serious adverse effects. Transient fever and headache
Xiao *et al*[50], 2016	N/A	5	Cervical (1) and thoracic (4)	AIS A	Autologous iliac bone marrow	BMSC	1×10^9	Scaffold	Intermediate and chronic (max 32 months)	12	AIS A No improvement also in MEP and SSEP	No serious adverse effects.
Chhabra *et al* [51], 2017	I/II	7	Thoracic	AIS A, ISCIS total score: 172.2 ± 2.3	Autologous iliac bone marrow	BMSC	2×10^8	Intralesional	Acute	12	ISCIS total score: 141.7 ± 2.5	Liver abscess (1)

Vaquero *et al* [52], 2017	II	10	Cervical, thoracic and lumbar	AIS B: 5, AIS C: 5, ASIA total score: 118.2 ±60	Autologous	BMSC	30 × 10^6 × 4 doses	Intratechal	Chronic (29.2-415.1 months, mean 170.5 ± 118.6)	12	ASIA total score: 235.5 ± 49.35. Motor and sensory scores, bladder, bowel and sexual functions improved. Spasms (2) and neuropathic pain (2) improved	No serious adverse effects. Transient headache and pain in the area of the lumbar puncture
Larocca *et al* [21], 2017	I/II	5	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	2 × 10^7	Subcutaneous	Chronic (25-111 months)	6	AIS A→B: 1, AIS A=: 5; One patient improved AIS A→B but reversed at 6 months. Improvements in SCIM III and FIM scale scores	No serious adverse effects
Vaquero *et al* [20], 2018	II	11	Cervical (4), thoracic (4) and lumbar (3)	AIS A: 3, AIS B: 4, AIS C: 3, AIS D: 1	Autologous	BMSC	100 × 10^6 × 3 doses	Intrathecal	Chronic (mean 163.8 ± 177.5 months)	10	AIS improvement in 27% of patients. AIS A→B: 1, AIS B→C: 1; AIS C→D: 1	No serious adverse effects. Transitory sciatic pain (37.5%), headaches and pain in the area of lumbar puncture
Guadalajara *et al*[53], 2018	Case report	1	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	300 × 10^6 × 3 doses (1/months)	Intrathecal	Chronic	6	Improvement in functionality and especially in Krogh's; Neurogenic Bowel Dysfunction scale	No serious adverse effects
Srivastava *et al*[54], 2019	I	70	Thoracic and lumbar	AIS A	Autologous iliac bone marrow	BMSC	2,41 ± 1,198 × 10^6	Intrathecal	Acute and intermediate	12	AIS A→B: 21, AIS A→C: 29, AIS A→D: 5; AIS=: 15	No serious adverse effects
Phedy *et al* [55], 2019	Case report	1	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	10 − 17 × 10^6 (× 7 times)	Intrathecal ×1 + Intravenous ×6	Chronic	60	AIS A→C. Increase in AIS score: 10→30. Increase in MRC score for L1 and L2 innervated muscles: 0/5→3/5	No serious adverse effects
Chen *et al* [56], 2020	I	7	Thoracic	AIS A	Autologous iliac bone marrow	BMSC	> 1 × 10^9	Scaffold	Acute or intermediate	36	All patients showed significant improvements in the FIM and ADL score. No obvious improvement in the ASIA grade, ASIA motor score, motor function, SSEPs, or MEPs was observed	Stress ulcer and lung infection (1), transient hyperthermia (1), shallow wound (1), spasm (4), paraplegic neuralgia (3), pressure ulcers (1), and lower limb amyotrophy (1)
Sharma *et al* [57], 2020	N/A	180	Cervical (63), thoracic and lumbar (117)	AIS A: 138, AIS B: 28, AIS C: 10, AIS D: 3	Autologous iliac bone marrow	BMSC	1.06 × 10^8	Intrathecal	Intermediate or chronic	2-16	FIM and WISCI showed statistically significant improvement	No serious adverse effects
Song *et al*[58], 2020	N/A	18	Cervical, thoracic and lumbar	ASIA score: 59.75 ± 5.22, SCIM-III score: 40.83 ±	Autologous iliac bone marrow	BMSC	1 × 10^7	Intrathecal	N/A	12	ASIA score: 81.1 ± 3.8, SCIM-III score: 72.5 ± 4.3	No serious adverse effects

				6.58								
Oraee-Yazdani *et al* [36], 2021	I/II	6	Cervical (1) and thoracic (5)	AIS A, SCIM III score: 28.9 ± 13	Autologous iliac bone marrow	BMSC	1×10^6	Intrathecal	Chronic (max 12 months)	30	SCIM III score: 43.1 ± 25.8. Sensory and/or motor improvement was evident in 9 patients according to the AIS assessment	Mild adverse effects: Increase in spasticity, numbness, or tingling sensation, and neuropathic pain
Honmou *et al* [59], 2021	II	13	Cervical	AIS A: 6, AIS B: 2, AIS C: 5	Autologous	BMSC (auto-serum expanded)	$84–150 \times 10^6$	Intravenous	Subacute	6	AIS A→B (3/6 patients), A→C (2/6), B→C (1/2), B→D (1/2), C→D (5/5)	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; ASIA: American Spinal Injury Association; BMSC: Bone Marrow Mesenchymal Stromal Cells; N/A: Not available; NSC: Neural stem cells.

Our review reveals a general enhancement in patient functionality, encompassing both motor and sensory perspectives. Notably, 32.7% of patients exhibited functional improvement, transitioning from AIS A to B, and 40.8% from AIS A to C. Sensory improvements were observed in 30.9% of patients. However, these improvements represent only modest progress in sensory and motor function, falling short of the anticipated levels required for walking and daily activities. It's important to highlight that the assessment of sensory and motor function, based on the ASIA score, depends on subjective evaluations by both the assessor and the patient, which introduces a degree of result variability[16,17]. Although the high effectiveness rates seem encouraging, the lack of control groups in the majority of trials allows for the possibility that the therapeutic improvements after stem cell transplantation might be influenced by spinal cord decompression or spontaneous healing. Consequently, stem cells cannot be fully blamed for the therapeutic benefits. Therefore, thorough investigation into the true therapeutic effects of stem cells is necessary using standardized controlled trials that follow pertinent regulations[17-21].

The potential benefits of stem cell therapy for patients remain uncertain, compounded by suboptimal design and execution of clinical trials[12,22]. Rigorously conducted randomized controlled trials, featuring double-blind methodologies and placebo groups, offer the most precise and dependable data, surpassing observational studies or case reports in reliability. Nonetheless, the majority of ongoing investigations consist of observational studies, case series, and similar approaches[15,21]. Clinical trials often suffer from issues such as limited sample sizes and subpar quality[22,23]. Furthermore, a considerable portion of the studies reviewed were phase I clinical trials, typically focused on evaluating stem cell safety. Intriguingly, all of these studies primarily explored and reported on the effectiveness of stem cells while neglecting to document AEs. Consequently, the safety profile of stem cells could potentially be inaccurately elevated[17].

The utmost priority should always be the safety of patients. The safety of stem cell therapy and the occurrence of AEs primarily hinge on the inherent traits of the transplanted stem cells and the transplantation procedure[16,17]. Our review of the studies did not reveal any severe AEs, such as the formation of tumors, further reinforcing the claims of these studies regarding the safety of stem cell therapy. Nevertheless, it's crucial to recognize that the absence of serious AEs doesn't definitively establish the therapy's safety. Many AEs were documented in the 66 research that we looked at. These included effects on the neurological, musculoskeletal, digestive, and cardiovascular systems. Following the proper medical measures, the majority of these AEs were moderate, and the patients recovered well. It would be premature, nevertheless, to declare stem cell treatment safe in all cases. By doing thus, it might unintentionally encourage unjustified trust in the therapy and jeopardize the scientific assessment of its safety and efficacy. Furthermore, Aspinall *et al*'s

Table 3 Summary of the studies included in the systematic literature review focusing on peripheral blood stem cells (*i.e.*, HSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from Injury		Functional improvement	Adverse effects
Deda *et al*[60], 2008	N/A	9	Cervical (6) and thoracic (3)	AIS A: 9	Autologous peripheral blood	HSC	5×10^6	Intrathecal	Chronic (6-51 months)	12	AIS A→B: 2, AIS A→C: 7	No serious adverse effects
Hammadi *et al* [61], 2012	N/A	277	Cervical (69) and thoracic (208)	N/A	Autologous peripheral blood	HSC	$1\text{-}8 \times 10^8$	Intrathecal	Chronic (6-104 months, average 34.5)	24	AIS A→B: 88, AIS A→C: 32, AIS = 157. A subgroup (12 patients) with lesion < 12 months had the best outcome: the percentage improvement reached 50%	No serious adverse effects. Backache and meningism (90%)
Al-Zoubi *et al* [62], 2014	N/A	19	Thoracic	AIS A	Autologous peripheral blood	HSC	7.6×10^7	Intrathecal	Chronic (12-48 months)	60	AIS A→B: 7. AIS A→C: 2, AIS =: 10	No serious adverse effects
Bryukhovetskiy *et al*[63], 2015	I/II	202	Cervical (98), thoracic (93) and lumbar (11)	N/A	Autologous peripheral blood	HSC	5.8×10^6	Intrathecal	Chronic (> 12 months)	144	Restoration of neurologic deficit (54.7%); Repair of the urinary system (47.7%). ASIA score improvement in 23 cases	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; HSC: Hematopoietic stem cells.

analysis revealed that only thirty percent of clinical trials sufficiently recorded different AEs during the clinical trial[24]. Consequently, it's plausible that a sizable percentage of studies may have failed to disclose or ignored AEs in an effort to make stem cell treatment appear safer than it actually is.

Among the myriad safety concerns associated with stem cell transplantation, the specter of tumorigenesis looms larger and more ominous than the comparatively milder fever and neuropathic pain stemming from immune or allergic reactions[17,22,23,25]. Stem cell products bear the highest potential for tumorigenesis due to the presence of lingering undifferentiated stem cells, cells carrying malignant transformations or mutations, and genetic instability[26]. Moreover, the expression of foreign genes, such as different growth factors, might result in oncogenic activation, and the danger of

Table 4 Summary of the studies included in the systematic literature review focusing on adipose tissue derived stem cells (*i.e.*, ADMSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from injury		Functional improvement	Adverse effects
Hur *et al*[26], 2016	I	14	Cervical (6), thoracic (7) and lumbar (1)	AIS A: 12, AIS B: 1, AIS D: 1	Autologous subcutaneous fat	ADMSC	9×10^7	Intrathecal	Intermediate and chronic (max 28 months)	8	Improvements in ASIA motor scores (5), voluntary anal contraction (2), ASIA sensory score (10), although degeneration was seen in 1. SSEP median nerve improvement (1)	No serious adverse effects. Transient headache, nausea and vomiting
Tien *et al*[64], 2019	N/A	31	Thoracic	AIS A, Barthel ADL: 3.35 ± 1.35	Autologous adipose tissue	ADMSC	$> 1 \times 10^8$	Intrathecal	Acute	12	AIS A→B: 10, AIS A→C: 1, AIS A→D: 2; AIS =: 16 Barthel ADL: 6.48 ± 2.14	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. ADL: Activities of Daily Living; ADMSC: Adipose-derived mesenchymal stem cells; AIS: American spinal injury association Impairment Scale.

insertional mutagenesis in stem cells is introduced by genetically modified viral vectors, such as lentiviruses and retroviruses. It's worth noting that there exists no consensus on a global scale regarding risk assessment strategies for evaluating the tumorigenicity and oncogenicity of stem cells. Curiously, there have been no reports of severe adverse events, including tumorigenesis, in clinical trials thus far. However, this absence of reports might be attributed to the relatively brief follow-up period[16,17,24].

While preclinical studies have indeed established a solid groundwork for stem cell therapy, its translation to clinical practice has encountered significant challenges. The number of newly initiated phase I and II clinical trials experienced steady growth between 2006 and 2012 but has since shown signs of stagnation and decline as of 2018[1-4,17,27]. This trend can be attributed primarily to the underwhelming efficacy of stem cell therapy. The stark contrast between animal studies and patient outcomes is a key contributor to this disparity[28,29]. The goal of animal research is to reduce the number of experimental variables as much as possible, such as the animals' initial features and the precise location and severity of their injuries. But spinal cord injury patients are highly heterogeneous; they include differences in rehabilitation regimens, age, gender, comorbid problems, and the location and degree of the damage[10,12,17,30,31]. Consequently, the observed treatment efficacy in patients often falls markedly below that observed in animal models.

Table 5 Summary of the studies included in the systematic literature review focusing on nervous tissue derived stem cells (*i.e.*, NSC, huCNSSC, OEC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from injury		Functional improvement	Adverse effects
Shin *et al*[47], 2015	I/IIa	19	Cervical	AIS A: 17, AIS B: 2	Human fetal brain	NSC	1×10^8	Intralesional	Acute and intermediate	12	AIS A→C: 2, AIS A→B: 1, AIS B→D: 2; AIS=: 14. Positive response in SSEP (35.3%) and MEP (58.8%) activities of AIS-A patients below the level of injury	No serious adverse effects
Ghobrial *et al* [65], 2017	II	5	Cervical	AIS A: 1, AIS B: 4	Allogeneic fetus	huCNSSC®	$15\text{-}40 \times 10^6$	Intrathecal	Chronic	12	AIS A→B: 1, AIS B→A: 1, AIS=: 3, GRASSP score mean improvement: 14.8 ± 7.8, ISNCSCI score mean improvement: 17.3 ± 16.8	No serious adverse effects
Anderson *et al* [66], 2017	I	6	Thoracic	N/A	Autologous (sural nerve)	SC	$5, 10 \text{ or } 15 \times 10^6$	Intramedullary	Subacute	12	AIS A→B: 1. Improvement in FIM and SCIM III scores	No serious adverse effects
Levi *et al*[67], 2018	I/II	29	Cervical: 17 (Cohort I: 6, Cohort II: 11) Thoracic: 12	AIS A: 11, AIS B: 18	Allogeneic (Stemcells Inc.)	huCNSSC®	$15 - 40 \times 10^6$	Intramedullary	Subacute	Up to 56	Improvement in AIS motor scores	15 serious adverse effects in cervical group and 4 in thoracic
Curtis *et al*[68], 2018	I	4	Thoracic	AIS A	Allogeneic (human-spinal-cord-derived neural stem cell)	NSI-566®	6 injections (Mean number)	Intramedullary	Chronic	60	Improved AIS scores, neurological levels and EMG findings. No improvement in QoL	No serious adverse effects
Levi *et al*[69],	I/II	17 Cohort I: 6,	Cervical	AIS A, B	Allogeneic	huCNSSC®	15 + 30 + 40 ×	Intramedullary	Intermediate or	12	Improvement	No serious

2019		Cohort II: 11 6/11 monitored			(Stemcells Inc.)		10^6 (Coh.I) 40 × 10^6 (Coh.II)		Chronic (max 24 months)		in UEMS score	adverse effects
Curt *et al*[70], 2020	I/IIa	12	Thoracic	AIS A: 7, AIS B: 5	Allogeneic (Stemcells Inc.)	huCNSSC®	20×10^6	Intramedullary	Intermediate or chronic (max 24 months)	72	Sensory improvements in 5 out of 12 patients. No motor improvements were observed	N No serious adverse effects
Zamani *et al* [71], 2021	I	3	Thoracic	AIS A	Autologous	OEC+ BMSC	15×10^6, OEC/BMSC = 1/1	Intrathecal	Chronic	24	AIS A→B: 1 and 6 points improvement in SCIM	Mild adverse effects
Gant *et al*[72], 2022	I	8	Cervical: 4; Thoracic: 4	N/A	Autologous (sural nerve)	SC	$50 - 200 \times 10^6$	Intramedullary	Chronic	60	The neurological level improved by 1 level in 1 patient. Improvement in Sensory score in all patients with thoracic and in 2 patients with cervical lesion	No serious adverse effects

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; BMSC: Bone Marrow Mesenchymal Stromal Cells; EMG: Electromyography; MSC; Mesenchimal stem cell; NSC: Neural stem cells; OEC: Olfactory ensheathing cell; SC: Stem cell; SCIM: Spinal cord independence measure.

Moreover, clinically recruited patients feature significant variations in their inclusion and exclusion criteria, coupled with disparities in injury location, severity, and timing. This diversity complicates the formation of a homogeneous patient cohort, even in well-designed randomized controlled trials, consequently clouding the interpretation of treatment efficacy and rendering it less precise and reliable[27,30,32-34].

The advancements made in stem cell clinical trials have been nothing short of captivating. However, it's essential to note that the majority of these studies are still situated in the early phase I/II stages, with ongoing data collection[17]. At this juncture, confirming the substantial therapeutic impact of stem cells remains premature. Across various clinical trials, a multitude of disparities and uncertainties surface, spanning the selection of patients, types of cells utilized, timing of intervention, and the dosages and routes employed for stem cell transplantation[35,36]. This necessitates a closer synergy between the preclinical and clinical dimensions of research. Improving trial safety, effectiveness, and repeatability; determining ideal transplant parameters; carefully weighing the advantages and disadvantages of stem cell treatment; and strengthening oversight practices in this area are among the urgent goals[16,17].

Table 6 Summary of the studies included in the systematic literature review focusing on nervous tissue derived stem cells (*i.e.*, UCMSC, HUCBC, HESC, WJ-MSC)

Ref.	Phase of clinical trial	Patients (*n*)	Localization of injury	Pre-treatment AIS classification or level of injury	Stem cells		Treatment			Follow up (months)	Outcomes	
					Origin	Type	Dose	Administration route	Time from injury		Functional improvement	Adverse effects
Dai *et al*[29], 2013	N/A	18	Cervical and thoracic	AIS A: 12, AIS B: 4, AIS C: 2	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^7	Intralesional	Chronic (18.67 ± 7.6 months)	6	AIS A→B: 7, AIS B→C: 3, AIS=: 8; MEP improvements	No serious adverse effects
Liu *et al*[73], 2013	N/A	22	Cervical (4), cervical + thoracic (2), thoracic + lumbar (2) and lumbar (7)	Motor function: 58.1 ± 22.2. Algesia: 73.2 ± 25.1. Sensory function: 74.2 ± 26.7. ADL: 29.5 ± 12.5	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^6/kg	Intrathecal	Intermediate and chronic (2-204 months)	> 12	Motor function: 61.5 ± 23.9. Algesia: 77.2 ± 26.1. Sensory function: 77.3 ± 26.1. ADL: 32.7 ± 12.4	Fever, lumbago, headache, dizziness and other adverse reactions were observed
Cheng *et al*[74], 2014	N/A	10	Thoracic and lumbar	AIS A, Barthel Index: 33.50 ± 6.69	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^7	Intralesional	Chronic (12-72 months)	6	Barthel Index: 41.40 ± 6.42; Muscle strength increased. Muscle tension decreased. Increase in maximum bladder capacity and decrease in maximum detrusor pressure	No serious adverse effects
Shroff *et al*[34], 2016	N/A	226	Cervical and thoracic	AIS A: 153, AIS B: 32, AIS C: 36, AIS D: 5	Pre-implantation stage fertilized ovum	HESC	1.6×10^7 + 1-5 × 1.6×10^7	Intravenous + intralesional	Intermediate and chronic	6-18	AIS A: 98, AIS B: 67, AIS C: 126, AIS D: 9, AIS E: 3	No serious adverse effects. Transient fever and headache
Shroff *et al*[75], 2017	N/A	15	Cervical and thoracic	AIS A: 13, AIS B: 2	Pre-implantation stage fertilized ovum taken during natural IVF process	HESC	1.6×10^7 + 1-5 × $1,6 \times 10^7$	Intravenous + intralesional	Acute, intermediate and chronic (6-15 months)	9	AIS A: 10, AIS B: 2, AIS C: 3	No serious adverse effects
Zhao *et al*[76], 2017	N/A	8	Cervical (4) and thoracic (4)	AIS A	Allogeneic neonatal umbilical cord tissue	UCMSC	4×10^7	Scaffold	Intermediate and chronic (max 36 months)	12	Expansion of sensation level (62.5%) and expansion of the MEP-responsive area	No serious adverse effects

											(87.5%) but AIS=	
Xiao *et al*[77], 2018	I	2	Cervical and thoracic	AIS A	Allogeneic	UCMSC+ Scaffold	40×10^6	Intramedullary	Acute	12	AIS A→C in both patients	No serious adverse effects
Deng *et al*[72], 2020	I	20	Cervical	AIS A	Allogeneic	UCMSC+ Scaffold	40×10^6 (Collagen scaffold)	Intramedullary	Acute	12	AIS A→B (9 patients), AIS A→C (2 patients). Improvement in ADL scores. Improvement in bowel and bladder function	No serious adverse effects
Albu *et al*[31], 2021	I/IIa	10	Thoracic	AIS A	Allogeneic	WJ-MSC	10×10^6	Intrathecal	Chronic	6	Significant improvement in pinprick sensation in compared with placebo group. No changes in motor function, independence, QoL, SEPs, MEPs, spasticity or bowel function	No serious adverse effects
Yang *et al*[23], 2021	I/II	102	Cervical, thoracic and lumbar	ASIA score: 158.15 ± 70.93, IANR-SCIFRS total score: 24.54 ± 9.82	Allogeneic neonatal umbilical cord tissue	UCMSC	1×10^6/kg	Intrathecal	Intermediate and chronic (max 240 months)	12	ASIA score: 183.88 ± 69.76, IANR-SCIFRS total score: 29.49 ± 10.47	No serious adverse effects. Fever (14.1%), headache (4.2%), transient increase in muscle tension (1.6%) and dizziness (1.3%)
Zhao *et al*[78], 2021	N/A	7	Cervical (3) and thoracic (4)	ASIA pin prick: 55.00 ± 28.46, ASIA light touch: 55.00 ± 28.46, ASIA motor score: 42.00 ± 28.19	Allogeneic neonatal umbilical cord tissue	UCMSC	5×10^4	Intrathecal	Intermediate and chronic (max 60 months)	6	ASIA pin prick: 57.06 ± 30.01, ASIA light touch: 58.20 ± 29.36, ASIA motor score: 44.13±27.23	No serious adverse effects
Smirnov *et al* [16], 2022	I/IIa	10	Cervical, thoracic and lumbar	AIS A: 6, AIS B: 4	Allogeneic	HUCBC	14.8×10^6/kg (Total cell number for 4 infusions)	Intravenous	Acute	12	AIS A→C: 3, AIS B→D: 2, AIS B→E: 2, AIS A→D: 1	No serious adverse effects related to therapy

Time from injury: Immediate: 0 - 2 h after the injury; acute: Early acute phase: 2 - 48 h; subacute: 2 d - 2 wk; intermediate: 2 wk - 6 months; chronic phase: > 6 months. AIS: American spinal injury association Impairment Scale; HESC: Human embryonic stem cells; HUCBC: human umbilical cord blood mononuclear cells; UCMSC: Umbilical cord derived mesenchymal stem cells; WJ-MSC: Wharton's jelly-Mesenchymal stem cells.

CONCLUSION

Within the realm of SCI treatment, stem cell-based therapies exhibit substantial promise. While rodent models indisputably illustrate the efficacy of stem cells, our exhaustive analysis of clinical trials uncovers a paradox: Despite the considerable potential of stem cells in improving neurological function among SCI patients, their transplantation carries the potential for numerous AEs. Ongoing clinical trials grapple with limitations, encompassing small sample sizes, subpar quality, and the absence of control groups, which collectively hinder the conclusive establishment of stem cell therapy's safety. It is, therefore, imperative to meticulously identify the optimal conditions and parameters for stem cell transplantation to optimize therapeutic outcomes.

Our findings highlight the lack of evidence currently available to justify the broad use of stem cell treatment for spinal cord injury and strongly advise against its immediate introduction into clinical practice. A deeper understanding of the pathophysiological mechanisms at play in SCI is imperative for the creation of treatments that surpass those presently in the investigative stage. Additionally, a range of concerns, encompassing ethical considerations and the assessment of tumorigenicity, immunogenicity, and immunotoxicity associated with diverse stem cell types, demand attention and resolution. The introduction of stem cell therapy into clinical practice should advance gradually and cautiously until well-structured animal experiments and high-caliber clinical studies are executed.

ARTICLE HIGHLIGHTS

Research background

Previous assessments of stem cell therapy for spinal cord injuries (SCI) have encountered challenges and constraints. Current research primarily emphasizes safety in early-phase clinical trials, while systematic reviews prioritize effectiveness, often overlooking safety and translational feasibility.

Research motivation

Current research primarily emphasizes safety in early-phase clinical trials, while systematic reviews prioritize effectiveness, often overlooking safety and translational feasibility.

Research objectives

This study seeks to offer an up-to-date systematic literature review of clinical trial results concerning stem cell therapy for SCI.

Research methods

A systematic search was conducted across major medical databases.

Research results

In a comprehensive review of 66 studies on stem cell therapies for SCI, 496 papers were initially identified, with 237 chosen for full-text analysis. Among them, 236 were deemed eligible after excluding 170 for various reasons.

Research conclusions

In the realm of SCI treatment, stem cell-based therapies show promise, but clinical trials reveal potential adverse events and limitations, underscoring the need for meticulous optimization of transplantation conditions and parameters, caution against swift clinical implementation, a deeper understanding of SCI pathophysiology, and addressing ethical, tumorigenicity, immunogenicity, and immunotoxicity concerns before gradual and careful adoption in clinical practice.

Research perspectives

There is a need for further research to ensure the safety and effectiveness of these therapies for SCI patients, while acknowledging their potential for improving functional outcomes.

FOOTNOTES

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CASE REPORT

New therapeutic strategy with extracorporeal membrane oxygenation for refractory hepatopulmonary syndrome after liver transplant: A case report

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Abstract

BACKGROUND

Due to the lack of published literature about treatment of refractory hepatopulmonary syndrome (HPS) after liver transplant (LT), this case adds information and experience on this issue along with a treatment with positive outcomes. HPS is a complication of end-stage liver disease, with a 10%-30% incidence in cirrhotic patients. LT can reverse the physiopathology of this process and restore normal oxygenation. However, in some cases, refractory hypoxemia persists, and extracorporeal membrane oxygenation (ECMO) can be used as a rescue therapy with good results.

CASE SUMMARY

A 59-year-old patient with alcohol-related liver cirrhosis and portal hypertension was included in the LT waiting list for HPS. He had good liver function (Model for End-Stage Liver Disease score 12, Child-Pugh class B7). He had pulmonary fibrosis and a mild restrictive respiratory pattern with a basal oxygen saturation of 82%. The macroaggregated albumin test result was > 30. Spirometry demonstrated a forced expiratory volume in one second (FEV1) of 78%, forced vital capacity (FVC) of 74%, FEV1/FVC ratio of 81%, diffusion capacity for carbon monoxide of 42%, and carbon monoxide transfer coefficient of 57%. He required domiciliary oxygen at 2 L/min (16 h/d). The patient was admitted to the intensive care unit (ICU) and extubated in the first 24 h, needing high-flow therapy and non-invasive ventilation and inhaled nitric oxide afterwards. Reintubation was needed after 72 h. Due to the non-response to supportive therapies, installation of

ECMO was decided with progressive recovery after 9 d. Extubation was possible on the tenth day, maintaining a high-flow nasal cannula and de-escalating to conventional oxygen therapy after 48 h. He was discharged from ICU on postoperative day (POD) 20 with a 90%-92% oxygen saturation. Steroid recycling was needed twice for acute rejection. The patient was discharged from hospital on POD 27 with no symptoms, with an 89%-90% oxygen saturation.

CONCLUSION
Due to the favorable results observed, ECMO could become the central axis of treatment of HPS and refractory hypoxemia after LT.

Key Words: Liver transplantation; Hepatopulmonary syndrome; Refractory hypoxemia; Treatment; Extracorporeal membrane oxygenation; Case report

Core Tip: Extracorporeal membrane oxygenation (ECMO) has been used as a rescue therapy in refractory hypoxemia after liver transplant (LT) in hepatopulmonary syndrome (HPS), with positive results. We present a patient with HPS who underwent LT and developed refractory hypoxemia requiring postoperative ECMO support. The literature demonstrates an 80% survival rate with an acceptable morbi-mortality. ECMO can become the central axis in the treatment of patients with HPS which present with refractory hypoxemia after LT.

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INTRODUCTION

In recent years, extracorporeal membrane oxygenation (ECMO) has become the gold-standard method for the treatment of severe pulmonary/cardiac dysfunction or insufficiency in the peritransplant period in liver recipients unresponsive to previous therapies[1,2]. Conditions that can be treated by ECMO include hepatopulmonary syndrome (HPS), porto-pulmonary hypertension, and pulmonary arterial hypertension[3].

HPS is characterized by the triad of liver disease, intrapulmonary vascular dilatation, and arterial hypoxemia. Although HPS is most frequently associated with liver cirrhosis, it may be related to any acute/chronic terminal liver disease, with or without associated portal hypertension[4]. Around 10%-30% of cirrhotic patients develop HPS[4]. Liver transplant (LT) may reverse the physiopathology of this process and restore normal oxygenation. However, in some cases, refractory hypoxemia persists despite support therapy. It is in this scenario where ECMO gives the necessary time to revert pulmonary arteriovenous shunts and reduce morbimortality.

This is a case report and literature review of adult liver recipients that received ECMO therapy for HPS during the peritransplant period.

CASE PRESENTATION

Chief complaints

We report the case of a 59-year-old male patient included in the LT waiting list for HPS in March 2022.

History of present illness

The patient had good liver function, with a Model for End-Stage Liver Disease score of 12 and a Child-Pugh class of B7. The patient had concomitant chronic respiratory failure, with a mild restrictive ventilatory defect and bronchial hyperreactivity (with a previous positive bronchodilator test). The patient also had HPS and slow progressive pulmonary fibrosis.

History of past illness

The patient had a history of alcohol-related liver cirrhosis and pulmonary hypertension.

Personal and family history
There was no familial history of interest.

Physical examination
The patient used home oxygen at 2 L/min for at least 16 h a day and a portable oxygen concentrator for walking. His baseline oxygen saturation (O_2Sat) was 82%.

Laboratory examinations
The macroaggregated albumin test result was > 30. Spirometry demonstrated a forced expiratory volume in one second (FEV1) of 78%, forced vital capacity (FVC) of 74%, FEV1/FVC ratio of 81%, diffusion capacity for carbon monoxide of 42%, and carbon monoxide transfer coefficient of 57%.

Imaging examinations
No imaging examinations relevant to this case.

FINAL DIAGNOSIS
Refractory hypoxemia.

TREATMENT
LT was performed with a matched cadaveric donor. A temporary porto-cava shunt and piggy-back technique were used. The patient was admitted to the intensive care unit (ICU). Extubation was performed within the first 24 post-transplant hours, and the patient immediately needed a high-flow nasal tube, which was escalated to noninvasive mechanical ventilation plus inhaled nitric oxide. At 72 h, reintubation was required due to severe hypoxemia. Protective mechanical ventilation with a high fraction of inspiration O_2 was initiated. Inhaled nitric oxide and support with inhaled ilioprost were maintained to reach an O_2Sat of 88%-92%. As the patient was unresponsive to support therapies, veno-venous ECMO (VV ECMO) was initiated. Anticoagulation by continuous perfusion of heparin sodium was also started to reach an activated clotting time of 140 s.

OUTCOME AND FOLLOW-UP
ECMO was maintained for 9 d, with progressive improvement of right-to-left shunt lesions and hypoxemia. The patient was extubated after 10 d on high-flow ventilation. The clinical course was excellent, with successful de-escalation to a conventional nasal tube in 48 h. The patient was discharged from the ICU at postoperative day (POD) 20 with an O_2Sat of 90%-92%. In relation to liver function, the patient required steroid recycling two times, due to acute cellular rejection in the ICU. The patient was discharged at POD 27 without any respiratory symptoms, with a constant O_2Sat of 89%-90% and very good tolerance.

Respiratory symptoms have disappeared since transplantation, and the patient showed good liver graft function. Lung function has improved with respect to pre-transplant status, with a basal O_2Sat of 98%. The patient no longer needs home oxygen therapy.

DISCUSSION
In the last decades, HPS has gone from being a contraindication to becoming an indication for transplant. This has been made possible by our better understanding of the physiopathology of the disease, in addition to constant improvements in support therapies. However, in liver recipients with severe oxygenation deficit [severe hypoxemia: Arterial partial pressure of oxygen (PaO_2) < 50 mmHg], post-transplant mortality remains high, with a higher occurrence in the immediate postoperative period[5]. VV ECMO removes non-oxygenated blood, transfers it through devices that add oxygen to the blood, and returns it to the venous system. By this technique, arterial oxygen is controlled to ensure optimal oxygenation and support tissue metabolism[6] in the presence of standard cardiac output. This technique provides the time necessary to reverse lung disease.

VV ECMO had never been used before in our hospital to treat HPS, since LT had always been effective. However, as this patient developed refractory hypoxemia, the multidisciplinary team decided to use VV ECMO, despite the little scientific evidence available on the use of this support therapy in HPS. Ten cases have been reported (ours included) in the literature on adult liver recipients who received VV ECMO during the peritransplant period as a treatment for HPS (Table 1). In 80% of cases, ECMO was used to treat post-transplant refractory hypoxemia[5,7-10], intraoperatively in 20% [3,8,11], and as bridge-to-transplant therapy in 10%[12]. In all cases, the indication for ECMO was hypoxemia refractory to mechanical ventilation combined with conventional measures. Measured pretransplant PaO_2 was 48.12 mmHg (range:

Table 1 Review of extracorporeal membrane oxygenation in hepatopulmonary syndrome

Ref.	Age	Gender	MELD score	Etiology of liver disease	Pre-LT PaO_2 (mmHg)	ECMO initiation	ECMO duration	ICU stay (d)	Days to discharge	State
Monsel *et al* [12]	51	M	N/D	OH	51	- 5	5	36	48	Alive
Auzinger *et al* [10]	44	N/D	N/D	OH	35	13	21	27	N/D	Alive
Sharma *et al* [5]	60	F	22	NASH	50	11	13	N/D	N/D	Alive
Braun *et al*[9]	50	M	25	OH	No	12	49	61	61	Dead
Braun *et al*[9]	28	M	31	Non-cirrhotic PH	No	5	10	58	58	Dead
Goussous *et al*[8]	52	F	26	HCV	No	1	10	N/D	N/D	Alive
Herden *et al* [7]	62	F	12	Idiopathic	No	7	6	N/D	N/D	Alive
Hogen *et al* [11]	42	F	N/D	N/D	52	Intraoperative	12	N/D	N/D	Alive
Laici *et al*[3]	45	F	31	OH	50	Intraoperative	36 h	N/D	42	Alive
This report	59	M	12	OH	57	3	9	N/D	28	Alive

M: Male; F: Female; MELD: Model for End-Stage Liver Disease; OH: Enolic; PH: Portal hypertension; N/D: Not described; LT: Liver transplant; PaO_2: Arterial partial pressure of oxygen; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; NASH: Nonalcoholic steatohepatitis; HCV: Hepatitis C virus.

35-57 mmHg). Mortality in these patients is high, with 60% of the series having required kidney replacement therapy, and 70% a tracheostomy. Complications included hepatic infarction/hematoma secondary to migration of the cannula[7] and hemothorax that required reintervention[8].

Despite the use of anticoagulation in this setting, no hemorrhages or hematomas were reported, as described previously[7,8], which we explain by good graft function at that moment (international normalized ratio: 1.31; caogulation factor V: 98%; prothrombine time: 68%). In total, 80% of our patients were discharged. Two patients (20%) died; one patient had multiorgan failure, and the other had hepatic infarction followed by a biliary fistula and sepsis with multiorgan failure, which occurred after withdrawal of ECMO therapy. The mean time to initiation and mean duration of ECMO therapy were 7 d and 13.7 d, respectively. Early initiation of ECMO has been reported to reduce therapy duration, thereby decreasing the occurrence of associated complications and increasing survival[13].

CONCLUSION

ECMO therapy emerges as a cornerstone of perioperative support that improves survival in patients with HPS undergoing LT. In the light of the growing evidence available and good outcomes reported, ECMO will certainly become the gold standard treatment for severe pulmonary dysfunction/insufficiency in liver recipients during the peritransplant period.

FOOTNOTES

Author contributions: Sánchez Pérez B wrote the manuscript; Santoyo-Santoyo J, Perez Reyes M, and Santoyo Villalba J performed the research; Aranda Narvaez J and Sánchez Pérez B performed the surgery; Perez Daga JA analyzed the data; Sanchez-Gonzalez C translated and submitted the manuscript.

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