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REVIEW

Cardiac risk stratification of the liver transplant candidate: A comprehensive review

Sanjana Nagraj, Spyros Peppas, Maria Gabriela Rubianes Guerrero, Damianos G Kokkinidis, Felipe I Contreras-Yametti, Sandhya Murthy, Ulrich P Jorde

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Abstract

Cardiovascular diseases (CVD) form a principal consideration in patients with end-stage liver disease (ESLD) undergoing evaluation for liver transplant (LT) with prognostic implications in the peri- and post-transplant periods. As the predominant etiology of ESLD continues to evolve, addressing CVD in these patients has become increasingly relevant. Likewise, as the number of LTs increase by the year, the proportion of older adults on the waiting list with competing comorbidities increase, and the demographics of LT candidates evolve with parallel increases in their CVD risk profiles. The primary goal of cardiac risk assessment is to preemptively reduce the risk of cardiovascular morbidity and mortality that may arise from hemodynamic stress in the peri- and post-transplant periods. The complex hemodynamics shared by ESLD patients in the pre-transplant period with adverse cardiovascular events occurring in only some of these recipients continue to challenge currently available guidelines and their uniform applicability. This review focusses on cardiac assessment of LT candidates in a stepwise manner with special emphasis on preoperative patient optimization. We hope that this will reinforce the importance of cardiovascular optimization prior to LT, prevent futile LT in those with advanced CVD beyond the stage of optimization, and thereby use the finite resources prudently.

Key Words: Cardiovascular risk; Liver transplantation; End stage liver disease; Liver cirrhosis; Cardiovascular diseases; Cardiovascular diagnostic techniques

Core Tip: Liver transplantation is high-risk invasive procedure with an increased likelihood of cardiovascular mortality in the perioperative and postoperative periods. As the predominant etiology of end-stage liver disease and attributes of transplant candidates continue to evolve, cardiac risk stratification of these patients is becoming increasingly relevant. This review aims to reach providers seeking to learn about the current state of cardiac assessment of liver transplant candidates, commonly encountered cardiovascular conditions, preoperative diagnostic testing, and patient optimization. We also highlight areas requiring further investigation.

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INTRODUCTION

Patients with end-stage liver disease (ESLD) often have multiple comorbidities, of which cardiovascular diseases (CVD) form a principal consideration with prognostic implications in the peri- and post-transplant periods[1]. Nearly 36000 liver transplants (LTs) per million population were performed globally in 2019, a 5% increase since 2018, and an additional 13000 patients were added to the waiting list[2]. CVD which is a well-established risk factor of increased mortality in both the early and late periods after LT, accounts for > 40% of deaths in the first 30 d after transplant[3-5]. Additionally, CVD is the leading cause of death at 1-yr follow-up[3-5].

As the predominant etiology of ESLD continues to shift towards non-alcoholic steatohepatitis (NASH) with corroborating increases in obesity (body mass index ≥ 30 kg/m^2 in 40% of LT recipients) and diabetes mellitus (30% of LT recipients), addressing CVD in these patients has become increasingly relevant[6-9]. Likewise, as the number of LTs increase by the year, the proportion of older adults (age ≥ 65 years old) on the waiting list with competing comorbidities increase, and the demographics of LT candidates evolve, they parallel increases in their CVD risk profiles. Therefore, cardiac risk stratification and timely management of CVD is important to ensure favorable outcomes in LT candidates.

The primary goal of cardiac risk assessment in patients awaiting LT is to preemptively reduce the risk of cardiovascular morbidity and mortality that may arise from hemodynamic stress in the peri- and post-transplant periods. Currently, there exist no validated models to predict cardiovascular mortality in LT recipients. The complex hemodynamics shared by ESLD patients in the pre-transplant period with adverse cardiovascular events occurring in only some of these recipients continue to challenge currently available guidelines and their uniform applicability[8]. Moreover, there is a paucity of guidelines for adverse cardiac events unrelated to perioperative myocardial ischemia in LT recipients[10]. Recognizing these limitations, this review aims to reach providers seeking to learn about the current state of cardiac assessment of LT candidates. We hope that this will reinforce the importance of cardiovascular optimization prior to LT, prevent futile LT in those with advanced CVD beyond the stage of optimization, and thereby use the finite resources prudently.

HEMODYNAMIC CHANGES DURING LT

Significant hemodynamic alterations occur during the LT procedure and invasive hemodynamic monitoring is necessary to guide intraoperative management[11]. The most significant periods of hemodynamic instability arise while clamping the portal vein and inferior vena cava (IVC) during the anhepatic stage, and again at the time of reperfusion of the donor graft called the neohepatic stage[12, 13]. During the anhepatic stage, an abrupt cessation of blood flow to the native liver results in a significant reduction in the preload and subsequently, in the cardiac output predisposing to cardiac dysfunction[12]. In anticipation of this complication, intravenous administration of fluids is recommended prior to vessel clamping to prevent sudden reductions in intravascular volume. Alternative options include partially occluding the IVC or creating a temporary portocaval shunt[11,14].

During the neohepatic stage, reperfusion of the donor graft predisposes to post-reperfusion syndrome (PRS), defined as a > 30% decline in mean arterial pressure that lasts for at least 1 min and occurs within 5 min of reperfusion of the donor liver[15]. PRS complicates 8%-30% of LT and manifests as dramatic reductions in the heart rate, cardiac output and systemic vascular resistance, leading to systemic hypotension, and in some cases dysrhythmias or even cardiac arrest[16]. Although the pathogenesis of PRS remains unclear, different mechanisms have been implicated with most important being the rapid release of vasoactive substances and pro-inflammatory cytokines [tumor necrosis factor (TNF)-1α, interleukin (IL)-6] from both the donor graft and the recipient's immune system[16,17].

A subset of patients undergoing LT develop an abnormal cardiac response characterized by a decrease in stroke work despite an increase in preload[18]. This is associated with a longer post-operative intubation time and poor surgical outcomes[18,19]. Although these cardiovascular complications can be anticipated, the cardiac response during LT tends to vary significantly between individuals depending on competing comorbidities and presence of preexisting cardiomyopathy[20]. Therefore, careful monitoring of hemodynamic parameters during LT is essential to lower the risk of perioperative adverse outcomes and increase the likelihood of graft survival. Similarly, recognition of underlying CVD and optimization prior to LT is imperative in reducing the risk of perioperative complications and mortality. A comprehensive review of CVD encountered in LT candidates, including their pathophysiology, pretransplant evaluation, and management is detailed below and outlined in Table 1.

CLINICAL ENTITIES

Coronary artery disease

Epidemiology: Patients with ESLD and concomitant coronary artery disease (CAD) undergoing LT have higher morbidity and mortality rates compared to recipients without CAD[21,22]. The incidence of CAD in LT candidates varies widely, ranging 2%-38% depending on the etiology of ESLD, investigation modality used for diagnosis, criteria for significant CAD used in different studies (defined as either ≥ 50% diameter stenosis of ≥ 1 major epicardial vessels *vs* ≥ 70% stenosis), and heterogeneity of the surveyed populations[4,10,21,23]. Among ESLD patients without symptoms of CAD, prevalence of obstructive CAD (defined as ≥ 50% diameter stenosis of ≥ 1 major epicardial vessels) is similar to that of the general population[24]. Besides the well-established implications of obstructive CAD, nonobstructive CAD plays an important role in LT candidates. Patients with ESLD have a significantly higher prevalence of silent nonobstructive CAD in comparison with matched subjects without liver disease[21,24]. This is relevant as any degree of CAD, obstructive or non-obstructive, has been associated with a significantly higher risk of major adverse cardiac events (MACE) after transplant[21,24,25]. Additionally, the prevalence of CAD in ESLD from NASH/cryptogenic etiology is higher compared to other etiologies of ESLD and parallels the increased risk of postoperative myocardial ischemia in this subset of transplant recipients[4].

Pathophysiology: Patients with ESLD may not manifest symptoms of CAD due to the mal-adaptive hemodynamic changes that occur in liver disease[26]. Splanchnic vasodilation in response to high portal pressures reduce the peripheral vascular resistance and increases the cardiac output. The resulting hyperdynamic circulation leads to increased blood flow through systemic and pulmonary circulations [26]. Therefore, in the presence of a reduced afterload from a low peripheral vascular resistance, both CAD and cirrhotic cardiomyopathy may remain silent for prolonged durations. As described previously, intraoperative hemodynamic changes during LTs are significant and impose immense stress on the cardiovascular system, wherein a sudden reduction in preload, precipitated by acute blood loss or clamping of the portal vein and IVC, a reduction in the cardiac output, and an increase in systemic vascular resistance can rapidly precipitate overt myocardial ischemia in patients with preexisting CAD [23].

Pre-operative evaluation: The rationale behind screening for CAD in LT candidates is to determine the ability of the cardiovascular system to handle hemodynamic stress peri- and post-transplant without sustaining ischemic damage. Therefore, screening helps with cardiac risk stratification and identification of those patients who would benefit from pre-operative optimization, including revascularization of their CAD[27]. Considering the high prevalence of CAD in these patients, basic cardiac workup consisting of an electrocardiogram (ECG), chest X-ray, and transthoracic echocardiogram should be obtained routinely in all LT candidates, with further workup pursued on a case-specific basis[28]. As per American Heart Association (AHA) guidelines, screening for CAD should be pursued only if diagnosis would change management with a discernable improvement in patient outcomes[8]. Specifically, screening asymptomatic individuals should take into consideration patient eligibility for downstream intervention(s) if indicated, cost of the screening procedure and intervention, and the likelihood of preventing adverse cardiac events in the context of LT. However, decision to screen and treat asymptomatic patients is often challenging as predicting which subset will develop intraoperative or postoperative complications is difficult. Therefore, a detailed history and examination that explore

Table 1 Preoperative assessment of common cardiac diseases and relationship with liver transplant outcomes

	Pretransplant	During transplant	Post-transplant
Coronary artery disease	Prevalence 2%-38%. Screening: DSE (high NPV), SPECT myocardial perfusion, conventional coronary angiography (gold standard)		Cumulative 3-yr post-LT MACE incidence: 37.5%. All-cause mortality: 13%
Cirrhotic cardiomyopathy	Prevalence 40%-50%. TTE is the preferred method for the diagnosis of systolic or diastolic dysfunction preoperatively	23% abnormal cardiac response	Pretransplant diastolic dysfunction increase the risk for acute graft rejection or failure, and all-cause mortality
Valvular heart disease	27.5% with cardiac valve dysfunction. Routine TTE screening is recommended prior to LT	Severe aortic stenosis associated with 31% risk of perioperative complications	Pretransplant AV replacement or AS increase the likelihood for significant cardiac complications 1-3 yr post-LT
Portopulmonary hypertension	Prevalence 5%-8.5%. Preoperative screening with TTE is recommended to all LT candidates. Patients with RVSP > 45 mm Hg needs confirmation with RHC	MPAP > 50 mm Hg: 100% mortality. MPAP 35-50 mm Hg: Increased morbidity and mortality. MPAP < 35 mm Hg and MPAP > 35 mm Hg due to volume overload or hyperdynamic state: No increase in mortality	
Conduction abnormalities	Routine ECG should be performed in all LT candidates independently of a cardiac abnormality history		AF is the most common MACE in the first 90 d post-transplant (-43%). AF is an independent risk factor for MACE 30- and 90-d after LT
QTc prolongation	Common ECG finding in ESLD patients with CCM; no sex-based differences exist as in general population. Reversible causes of QTc prolongation should be identified and corrected preoperatively		Conflicting data exist regarding QTc prolongation as an independent predictor of mortality and its reversibility post-LT

LT: Liver transplantation; DSE: Dobutamine stress echocardiogram; NPV: Negative predictive value; SPECT: Single-photon emission computerized tomography; MACE: Major adverse cardiac events; TTE: Transthoracic echocardiogram; AV: Aortic valve; AS: Aortic stenosis; RVSP: Right ventricular systolic pressure; RHC: Right heart catheterization; MPAP: Mean pulmonary arterial pressure; ECG: Electrocardiogram; AF: Atrial fibrillation; ESLD: End-stage liver disease; CCM: Cirrhotic cardiomyopathy; QTc: Corrected QT.

the presence of both traditional and non-traditional risk factors of CAD, and presence of CAD equivalents such as peripheral artery disease should be obtained in all patients to determine the need of screening and the choice of investigation. Presence of ≥ 1 risk factors of CAD has been found to be highly predictive of angiographically significant stenosis and can be used to guide decision-making[24,25]. Similarly, the absence of CAD risk factors serves as a reliable clinical marker in ruling out significant CAD[24]. Specifically, age > 60 years, hypertension, left ventricular hypertrophy, diabetes, smoking, dyslipidemia, prior history of CAD, and high model for ESLD scores have been identified as significant risk factors of CAD in LT candidates[4,8]. Non-traditional risk factors of CAD pertinent to LT candidates should also be identified and integrated into decision-making. These include familial amyloid polyneuropathy, hereditary hemochromatosis, and NASH, each of which is associated with CAD apart from causing ESLD[29,30].

Despite studies reporting the presence one or more risk factors of CAD to be highly predictive of angiographically significant stenosis, there is a lack of consensus between guidelines on the number of risk factors needed to pursue noninvasive testing and the role of functional status in determining the need for screening for CAD. The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend noninvasive testing in the presence of more than two risk factors of CAD and poor functional capacity while the AHA/American College of Cardiology (ACC) guidelines consider three or more risk factors to warrant testing irrespective of patients' functional status[8,31]. Generally, candidates should be perceived as high risk in the presence of a prior history of CAD, diabetes mellitus or ≥ 2 risk factors of CAD.

Noninvasive testing: Noninvasive testing which has a well-established role in detecting CAD in the general population is unfortunately suboptimal in patients with ESLD who tend to have a higher pre-test probability. In these patients, noninvasive tests are further limited by the hemodynamic changes of liver disease, poor coronary flow reserve, microvascular dysfunction, and carry a poor sensitivity[32-34]. However, they have been found to accurately predict development of adverse cardiac events in the post-transplant period[32-34]. Patients with nondiagnostic or abnormal noninvasive testing should undergo coronary angiography (CAG) to corroborate findings, determine the need for intervention, and whether revascularization will improve LT outcomes on an individual basis.

Noninvasive testing with stress echocardiography, typically dobutamine stress echocardiography (DSE) is a class 1B recommendation of the American Society of Transplantation for routine evaluation of CAD in all LT candidates[27]. Cardiac catheterization is recommended if DSE is nondiagnostic or abnormal. Over the years, conflicting data regarding the sensitivity and predictive value of noninvasive stress tests have been reported. In a meta-analysis evaluating the diagnostic accuracy of DSE for detecting CAD in ESLD patients awaiting LT, DSE demonstrated a poor sensitivity (32%) but excellent negative predictive value (NPV) (98%) for perioperative and long-term cardiac events[33]. Multiple other studies have found DSE to have a low sensitivity and positive predictive values and intermediate to high NPVs[4,34-36]. A frequently encountered limitation of DSE in patients with ESLD is the inability to achieve target heart rates and thereby rate-pressure products.

Myocardial perfusion imaging with single positron emission tomography (SPECT) is another modality with established role in diagnosing CAD in the general population. However, its diagnostic accuracy in ESLD patients is unclear due to conflicting results reported by different studies[28,37,38]. A high number of false positives may be secondary to the chronic vasodilatory state characteristic of ESLD and a low coronary flow due to microvascular dysfunction rather than epicardial vessel stenosis, encountered frequently in patients with NASH cirrhosis[28,37,38].

Coronary computed tomography (CT) is another option with excellent diagnostic accuracy for detect significant CAD in the general population and can serve as a viable option in ESLD patients as well[39]. Considering the questionable sensitivity of stress tests and specificity of perfusion testing such as SPECT, coronary CT can serve as an accurate and noninvasive alternative. However, there are limitations associated with it just like any other test. As per the 2018 American Society of Transplantation Liver and Intestinal and Thoracic and Critical Care Community of Practice guidelines, coronary CT maybe considered as an alternative to CAG in patients with ESLD who are able to tolerate lying flat, do not have severely impaired renal function, have low heart rates without irregularities in the rhythm, although newer gating techniques allow interpretation of coronary CT even in patients with atrial fibrillation (AF)[40,41].

Invasive testing: CAG is the gold standard diagnostic modality for detecting coronary artery stenosis and is relatively safe in patients with ESLD[28,40]. It is indicated in patients with a prior history of CAD, myocardial infarction, or a coronary intervention, in those with high pre-test probability of CAD, and in patients with abnormal or nondiagnostic noninvasive test results. On detecting significant stenosis, the decision to revascularize should be guided by whether it will improve transplant outcomes. Notably, the study conducted by Snipelisky *et al*[42] showed that patients with severe CAD continued to have an elevated cardiac mortality after LT despite revascularization preoperatively, thus questioning the benefit of pre-transplant coronary interventions. However, revascularization should be pursued if obstructive CAD is the primary precluding factor for LT[28,43]. Studies investigating the feasibility of percutaneous coronary intervention and stenting in LT candidates have found it to be feasible with a preference for bare metal stents considering the shorter dual antiplatelet therapy compared to drug eluting stents[44,45].

Cirrhotic cardiomyopathy

Epidemiology: Impaired cardiac contractility secondary to sympathetic stress and altered diastolic function in patients with ESLD is termed cirrhotic cardiomyopathy[26,46,47]. Although there are limited data citing the prevalence of cirrhotic cardiomyopathy, attributable in part to the indolent nature of the disease, nearly 40%-50% of ESLD patients have cardiac changes consistent with cardiomyopathy[48,49]. This is relevant as nearly 20% of mortality in LT recipients over a 20 years post-transplant follow up period and 40% of early postoperative deaths after LT are cardiovascular-related[50].

Pathophysiology: Cirrhotic cardiomyopathy predisposes to reduced survival, and complications such as renal failure and hepatorenal syndrome in patients undergoing LT[47]. Cardiac dysfunction in ESLD occurs secondary to maladaptive alterations in the systemic and splanchnic circulations leading to an increased cardiac output and heart rate[51,52]. Pooling of blood in the splanchnic vascular bed leads to a lower central blood volume termed “central” or “effective” hypovolemia. This results in baroreceptor-induced activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS)[47]. SNS stimulation leads to overactivation of the β-adrenergic system resulting in receptor desensitization and cardiac dysfunction[53].

Systolic dysfunction: At rest, systolic dysfunction in patients with ESLD remains subclinical due to a reduced afterload and low systemic vascular resistance. However, it manifests overtly when the cardiovascular system is challenged with stressors such us LT, TIPS, and exercise[26,46,47,53]. Four possible mechanisms have been proposed to explain the systolic dysfunction in patients with ESLD: (1) Impaired beta-adrenergic receptor signaling secondary to sympathetic hyperactivity, which has also been shown to cause direct myocyte damage; (2) Decreased cardiac contractility and increased cardiomyocyte apoptosis mediated by endocannabinoids, levels of which have been shown to be increased in murine cirrhotic hearts; (3) The presence of cardio-depressant substances such as nitric oxide and carbon monoxide; and (4) Abnormalities of the sodium/calcium (Na/Ca) exchanger that result in the excess Ca influx leading to cardiomyocyte apoptosis[26,53].

Diastolic dysfunction: Diastolic dysfunction in patients with ESLD occurs due to an increased stiffness of the myocardial wall from a combination of myocardial hypertrophy, fibrosis and subendothelial edema. Activation of RAAS has been implicated in myocardial hypertrophy, myocardial fibrosis and development of diastolic heart failure in patients with portal hypertension irrespective of the presence of cirrhosis[54]. Additionally, increased levels of plasma aldosterone, a byproduct of RAAS activation have been associated with a reduced ratio of early to late (atrial) phases of ventricular filling (E:A ratio) in ESLD[54]. Therefore, it is likely that activation of RAAS leads to diastolic dysfunction by multiple direct and indirect pathophysiologic mechanisms[55-58]. Other proposed mechanisms for diastolic dysfunction in ESLD involve alteration in collagen configuration and sodium retention[59,60].

Pretransplant evaluation: Patients with ESLD can be screened for cirrhotic cardiomyopathy through biological markers and imaging modalities, wherein they supplement data obtained from history and physical examination[61]. Imaging appears to provide maximum diagnostic value when used in the appropriate clinical context.

Biological markers: Biomarkers for subclinical and clinical heart failure (HF) include brain natriuretic peptide (BNP), propeptide, N-terminal pro-BNP (NT-proBNP), and cardiac troponins[53,62,63]. BNP and NT-proBNP have been associated with the severity of ESLD and portal hypertension. Henriksen *et al*[64] demonstrated a significant correlation between proBNP and BNP levels and Child score. Moreover, they reflect the severity of diastolic and systolic cardiac abnormalities as well as mortality in clinical HF and in cirrhotic cardiomyopathy (CCM)[63,65,66]. A major consideration and limitation to setting cut-off values for any biomarker including BNP and NT-proBNP is the heterogeneity in assays used across institutions, timing of measurement, and the different thresholds/cut-offs used by individual labs. Therefore, at this time there are no cut-off points for biomarkers indicating that the patient should be removed from the transplant waiting list.

Cardiac remodeling may be measured by levels of galectin-3 and soluble suppression of tumorgenicity-2 (ST-2), member of the IL-1 family, directly interacting with cardioprotective IL-33. These markers have been shown to reflect cardiac inflammatory and fibrotic remodeling[67,68]. However, galectin-3, and soluble ST-2 are also markers for liver inflammation and fibrosis, which may limit their applicability to CCM[69]. In addition to highly sensitive C-reactive protein associated with cardiac disease (and other inflammatory conditions), other inflammatory markers have been studied in HF and CCM including IL-6, IL-8, TNF-α, lipopolysaccharide binding protein, vascular endothelial growth factor, and soluble urokinase-type plasminogen activator receptor, some of which may worsen the circulatory dysfunction of portal hypertension[47,53,61,63].

Imaging

Transthoracic echocardiography: Transthoracic echocardiography (TTE) is the preferred imaging modality although cirrhotic cardiomyopathy is largely a clinical diagnosis and there are no specific TTE features distinguishing a cirrhotic etiology[47]. Systolic dysfunction is characterized by either left ventricular ejection fraction (LVEF) ≤ 50% or global longitudinal strain (GLS) < 18% even in the presence of a normal LVEF[47,53]. Some studies have recommended a higher a cut-off value of LVEF 55%-60% in patients with ESLD due to the decreased afterload and increased preload, which could falsely normalize the LVEF in this subset[61]. GLS is particularly useful as the longitudinally oriented subendocardial fibers are highly susceptible to damage making longitudinal left ventricular function the first manifestation of cardiac impairment[53]. Diastolic dysfunction characterized by TTE should meet three or more of the following diagnostic criteria: (1) Diastolic tissue velocity of mitral annulus (septal E′ velocity) < 7 cm/s; (2) Ratio of velocity of the left ventricle inflow during early, rapid passive filling (E wave) compared to E′ (E/E′ ratio) ≥ 15. E:E′ ratio has been found to reflect left ventricular filling pressure, and this ratio increases as diastolic function worsens; (3) Left atrial volume index > 34 mL/m^2; and (4) Tricuspid regurgitation velocity > 2.8 m/s[47,53,61]. Tissue doppler imaging is a well validated imaging technique for diastolic dysfunction evaluation[61].

Cardiac magnetic resonance imaging: Structural changes in cirrhotic cardiomyopathy as seen on cardiac magnetic resonance imaging (MRI) appear similar to those of myocarditis with a non-specific patchy distribution[70]. Considering the non-specific changes, the practical applicability of cardiac MRI for diagnosing cirrhotic cardiomyopathy is low[61]. However, it can be used to visualize edema and myocardial fibrosis seen as late gadolinium enhancement, especially pronounced in patients with alcoholic liver cirrhosis, to measure LVEF and chamber volumes[39,61,71,72].

Management and prognosis: Currently there exist no guidelines for the diagnosis and treatment of cirrhotic cardiomyopathy. Management of heart failure in patients with ESLD is built on principles similar to that of non-cirrhotic patients, consisting of strict sodium and fluid restriction, use of diuretics to decongest, and afterload reduction[26]. However, afterload reduction in patients with ESLD can be challenging as they have arterial hypotension at baseline[26]. Additionally, the benefit of beta-blockers in ESLD patients is not as clear as in other groups. While nonselective beta-blockers can help improve electromechanical coupling, data from clinical trial report a reduction in cardiac output which can have

detrimental consequences during periods of stress such as infection[73].

LT remains the gold standard treatment as it normalizes hepatic metabolism and reduces the adverse effects of hyperdynamic circulation, thus improving cardiac function[53,74]. Despite undergoing LT, recipients seldom remain complication free as the presence of cirrhotic cardiomyopathy increases their likelihood of acute graft rejection and mortality. This unfavorable effect of cirrhotic cardiomyopathy on post-transplant outcomes was illustrated in a study by Mittal *et al*[75] of 970 LT recipients evaluated over a mean duration of 5.3 years. Patients with diastolic dysfunction pretransplant had a significantly higher risk of acute cellular rejection [hazard ratio (HR) = 10.56; P = 0.0001)], graft failure (HR = 2.09; P = 0.007), and all-cause mortality (HR = 1.52; P = 0.01) compared to recipients without cardiac dysfunction. Notably, the risk of complications increased with worsening diastolic dysfunction. Although point-based scoring systems such as the cardiovascular risk in orthotopic liver transplantation score to predict adverse cardiovascular events after LT have been proposed, till date there exist no validated and standardized models to quantitatively risk-stratify patients based on their risk of developing perioperative cardiac complications[76].

Portopulmonary hypertension

Epidemiology and pathophysiology: Portopulmonary hypertension (PoPH) is the presence of pulmonary arterial hypertension associated with portal hypertension of hepatic or extrahepatic origin and is currently classified as World Health Organization group 1 PH[77,78]. Prospective studies evaluating PoPH have reported a prevalence of 5 to 8.5% in patients awaiting LT[78-80]. No specific etiology of portal hypertension or chronic liver disease is associated consistently with the development of PoPH[81,82]. Similarly, the severity of liver disease has not been found to be predictive of PoPH[81,82]. However, presence of severe PoPH has been associated with a worse prognosis in patients undergoing LT compared to recipients without PoPH[83,84]. Although the pathophysiology of PoPH remains unclear, the most widely accepted mechanism is an imbalance of vasoconstrictive and vasodilatory mediators, wherein humoral substances such as endothelin-1 bypass hepatic metabolism and reach the pulmonary circulation through portosystemic shunts, leading to pulmonary arterial hypertension[85,86].

Preoperative evaluation and management: PoPH most commonly presents with exertional dyspnea but symptoms may be absent or subtle in the initial stages[87,88]. Currently, the ESC and ERS recommend echocardiographic assessment for PH in symptomatic patients with chronic liver disease or portal hypertension and in all LT candidates (Class I/Grade B)[89]. Screening with TTE is geared at estimating the right ventricular systolic pressure (RVSP). Additional information obtained from TTE include right ventricular dilatation or dysfunction and presence and severity of tricuspid regurgitation[90,91]. Patients with RVSP > 45-50 mmHg should be evaluated further with right heart catheterization (RHC) which is the gold standard investigation for diagnosing PoPH. The updated RHC criteria for diagnosing PoPH are: Mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary vascular resistance (PVR) ≥ 240 dyne $s^{-1} \cdot cm^{-5}$ or 3 Wood Units (WU) and pulmonary capillary wedge pressure ≤ 15 mmHg[92]. Importantly, PoPH with severe hemodynamic impairment (*i.e.*, mPAP > 45-50 mmHg or PVR > 3 WU) is associated with excessive mortality and is considered an absolute contraindication for LT[93,94]. Patients with mPAP ranging from 35-50 mmHg should be referred to a PoPH specialist for pulmonary arterial hypertension-specific-therapy with the goal of lowering mPAP to < 35 mmHg and becoming eligible for LT in the future[93,94]. It is important to note that mPAP may be elevated in conditions other than PoPH such as volume overload and a hyperdynamic state encountered in ESLD patients. Therefore, optimization of volume status is important and a complete assessment during RHC to ensure PVR is > 3 WU is necessary to diagnose PoPH[95,96].

Hypertension: Systemic hypertension is not a common finding among patients with ESLD who most often have low arterial blood pressure (BP), pathognomonic of splanchnic vasodilation and portal hypertension in liver cirrhosis[97,98]. The release of vasodilators and SNS-mediated vasodilation of splanchnic vessels lead to reductions in the afterload and systemic vascular resistance[97,99]. Also, patients with ESLD have a blunted response to vasopressors, and an increased arterial compliance, all of which result in low systemic BPs[99]. Often, patients with arterial hypertension become "normotensive" during the course of developing chronic liver disease. In clinical practice, determining the etiology of an inappropriately normal BP should take into consideration secondary causes of hypertension such as severe renovascular disease, a previous history of arterial hypertension, and mechanisms counteracting vasodilation. In ESLD, release of nitric oxide, calcitonin gene-related peptide, and adrenomedullin results in splanchnic vasodilation, while counteractive activation of renin angiotensin aldosterone system leads to vasoconstriction and an increase in BP[97,98]. Additionally, these counteractive mechanisms are influenced by agents such as beta blockers and aldosterone antagonists which are often used in these patients to mitigate other manifestations of ESLD and also provide antihypertensive effects.

Valvular diseases: The prevalence of valvular heart disease in patients with ESLD is currently unknown and there is a paucity of literature and guidelines about management of structural heart disease in LT

candidates[100]. The presence of valvular diseases such as severe aortic stenosis can pose a prohibitive risk to live transplant due to an increased risk of intraoperative complications and a risk of perioperative mortality greater than 30%[101,102]. Similarly, the hemodynamics of ESLD can preclude candidacy for valve surgery making these patients extremely high-risk for both procedures[101]. Additionally, the severity of aortic stenosis has been found to correspond with perioperative mortality in patients undergoing noncardiac surgery[102]. Additionally, patients with uncorrected severe aortic stenosis undergoing LT have been found to have a higher rate of cardiac complications, including cardiac death, myocardial infarction, and requirement of aortic valve replacement in the post-transplant period compared to patients without valvular disease[101,103]. As per the AHA/ACC 2014 guidelines, elevated-risk elective noncardiac surgery is reasonable to perform in patients with either severe asymptomatic aortic stenosis, mitral regurgitation, or severe asymptomatic aortic regurgitation with normal LVEF[104]. Since exercise tolerance is often poor in patients with ESLD, assessment of severity of valvular heart disease is primarily made based on imaging. However, a detailed history of symptoms of valvular heart disease or heart failure, clinical examination including cardiac examination for murmurs, and transthoracic echocardiogram is recommended routinely in all LT candidates to detect ESLD valvular heart disease, determine its severity, and assess left ventricular function[100,104,105]. This allows for risk stratification and timely planning of valvular intervention if indicated based on clinical or radiological findings.

Conduction abnormalities: A routine 12-lead ECG should be performed irrespective of a history of cardiac disease in all patients undergoing evaluation for LT[8,27].

AF: AF has a prevalence of around 10% in patients with ESLD and is the most common arrhythmia after liver transplantation[106]. It has been found to be associated with a poor prognosis, especially higher in-hospital mortality, length of hospital stay, increased perioperative cardiac complications, and MACE after liver transplantation[106-109]. Presence of AF in the pre-transplant period is a strong independent predictor of MACE at both 30- and 90-d after LT. In LT recipients, it is also the most common major adverse cardiac event in the first 90 d after transplant and constitutes nearly half of MACE (43%) in these patients[107]. Therefore, detection of AF with 12-lead ECG, telemetry monitoring, or ambulatory monitoring devices in those with a suspicion of paroxysmal AF is important as a part of cardiac evaluation of LT candidates.

QT interval prolongation: QT interval prolongation, considered a hallmark of cirrhotic cardiomyopathy, occurs in 30%-50% of patients with ESLD[110-112]. The mechanism for QT prolongation in ESLD can be multifactorial but only the Child-Pugh score has been found to be an independent predictor, with changes in plasma norepinephrine contributing to corrected QT (QTc) interval variability[110,113]. Individual components of the Child-Pugh score have not been found to prolong QTc interval significantly[110,112]. Sex-specific differences in the duration of QT interval which are well-established in the general population do not exist in patients with ESLD, whereby a QTc ≥ 440 ms is considered elevated in both women and men[112,113]. The lack of sex-based differences in the duration of QTc interval in patients with ESLD persists in the post-transplant period[113]. Although men with ESLD have a relative androgen deficiency, levels of sex hormones have not been found to correlate with durations of QTc interval in men and women in the pre-transplant period[113]. Assessment and management of prolonged QTc interval is important as it has been associated with an increased risk of mortality, especially in alcoholic liver cirrhosis, and in Child-Pugh Class A patients with any etiology of ESLD[110,114]. However, conflicting data have been reported on the effect of prolonged QT interval on mortality and its reversibility with LT[110,112,114]. Ko *et al*[112] their study of LT candidates did not find an association between QTc interval prolongation and mortality or complications in the post-transplant period. In this study, patients who underwent LT demonstrated a significant rise in QTc intervals in the early-post transplant period followed by a significant reduction within the first six months of LT. On the contrary, Kim *et al*[114] did not find significant reversibility of the QTc interval after LT, and rather found it to be an independent predictor of mortality. Also, the threshold value set for usually defined in the general population and the investigators found male sex to be an independent predictor of prolongation. This is contrary to the study by Adigun *et al*[113] who found no sex-based differences in QTc prolongation among patients with ESLD and did not find male gender to be independently associated with the duration of the QT interval.

A QT interval of ≥ 500 ms has been found to be associated with a greater risk of developing torsade de pointes in the general population but there exists no established cut-off threshold below which a prolonged QT interval confers freedom from a risk of arrhythmias in both LT recipients and the general population[115]. There is also a lack of consensus on the cut-off threshold warranting drug discontinuation in drug-induced QT prolongation[115]. Beta blockers which are frequently used in patients with ESLD have been found to shorten the QT-interval in those with prolonged durations and increase the duration of QT-interval without prolonging it in those with normal values at baseline[116,117]. Although prolonged QTc interval is prevalent in LT candidates, reversible causes such as QT-interval prolonging medications and electrolyte abnormalities should be sought and corrected promptly due to the possibility of life-threatening ventricular arrhythmias. Also, a prolonged QTc interval is not a

contraindication to LT.

Pericardial diseases

Pericardial effusion: Pericardial effusions can occur both before and after LT and require careful evaluation to detect tamponade. Hepatitis C infection with or without cryoglobulinemia has been associated with pericardial effusions both in patients with ESLD and in transplant recipients[118-120]. Although cryoglobulinemia is a well-established complication of hepatitis C infection, pericardial effusions and myopericarditis occurring as a multiorgan manifestations of cryoglobulinemia are rare with only a few reported cases worldwide[120]. Physical examination and bedside TTE should be performed to exclude tamponade. Presence of tamponade or significant pericardial effusion requires timely pericardiocentesis or pericardial window prior to LT and follow-up with repeat echocardiogram to evaluate for recurrence[28].

Constrictive pericarditis: In the context of patients with ESLD awaiting LT, constrictive pericarditis occurs as an etiology of chronic liver disease whereby longstanding hepatic congestion can lead to cardiac cirrhosis. A high degree of clinical suspicion is required as symptoms of constrictive pericarditis such as ascites, hepatomegaly and peripheral edema are often misdiagnosed as primary chronic liver disease[121]. TTE with doppler is the initial recommended test which may reveal characteristics suggestive of constrictive pericarditis such as ventricular septal shift with respiration, variation in mitral annular inflow velocity, a thickened pericardium, and rapid early diastolic filling[122]. Cardiac MRI and cardiac catheterization provide additional information to aid with diagnosis. Management involves pericardiectomy but cannot reverse ESLD, which in turn renders this procedure very high risk due to coagulopathy[123].

CONCLUSION

Comprehensive and yet patient-directed cardiovascular assessment consisting of risk factor evaluation, clinical examination, diagnostic testing with laboratory parameters, imaging, and invasive testing when medically indicated is essential for risk stratifying patients being considered for LT. Considering the high-risk nature of this invasive procedure, limited number of donor grafts available, and the high likelihood of cardiovascular mortality in the postoperative period, identifying those at highest risk of adverse events who will also benefit from preoperative optimization is imperative. This will help maximize the chances of a successful LT and avoid futile transplants in those with severe CVD not amenable to mitigation or repair. Routine cardiac workup consisting of basic tests is indicated in all LT candidates. Further workup should be guided by clinical judgement and results of the preliminary workup. Despite the high prevalence of CVD among patients with ESLD, current guidelines fall short of meeting clinical need. Areas of future research include developing validated predictive models for cardiac risk stratification in patients with ESLD, improving the diagnostic accuracy of noninvasive tests for evaluation of CAD, and development of standardized guidelines for nonischemic CVD in patients with ESLD.

FOOTNOTES

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REFERENCES

1 **De Gasperi A**, Spagnolin G, Ornaghi M, Petrò L, Biancofiore G. Preoperative cardiac assessment in liver transplant candidates. *Best Pract Res Clin Anaesthesiol* 2020; **34**: 51-68 [PMID: 32334787 DOI: 10.1016/j.bpa.2020.02.002]
2 **Kwong AJ**, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Foutz J, Booker SE, Cafarella M, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2019 Annual Data Report: Liver. *Am J Transplant* 2021; **21** Suppl 2: 208-315 [PMID: 33595192 DOI: 10.1111/ajt.16494]
3 **Tovikkai C**, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. *BMJ Open* 2015; **5**: e006971 [PMID: 25976762 DOI: 10.1136/bmjopen-2014-006971]
4 **Główczyńska R**, Galas M, Witkowska A, Ołdakowska-Jedynak U, Raszeja-Wyszomirska J, Krasuski K, Milkiewicz P, Krawczyk M, Zieniewicz K, Opolski G. The Pre-Transplant Profile of Cardiovascular Risk Factors and Its Impact on Long-Term Mortality After Liver Transplantation. *Ann Transplant* 2018; **23**: 591-597 [PMID: 30127335 DOI: 10.12659/AOT.908771]
5 **VanWagner LB**, Lapin B, Levitsky J, Wilkins JT, Abecassis MM, Skaro AI, Lloyd-Jones DM. High early cardiovascular mortality after liver transplantation. *Liver Transpl* 2014; **20**: 1306-1316 [PMID: 25044256 DOI: 10.1002/lt.23950]
6 **Targher G**, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010; **363**: 1341-1350 [PMID: 20879883 DOI: 10.1056/NEJMra0912063]
7 **Rawshani A**, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjörnsdottir S. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2018; **379**: 633-644 [PMID: 30110583 DOI: 10.1056/NEJMoa1800256]
8 **Lentine KL**, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, Carithers RL, Ragosta M, Bolton K, Auerbach AD, Eagle KA; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Peripheral Vascular Disease; American Heart Association; American College of Cardiology Foundation. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. *Circulation* 2012; **126**: 617-663 [PMID: 22753303 DOI: 10.1161/CIR.0b013e31823eb07a]
9 **Chahal D**, Marquez V, Hussaini T, Kim P, Chung SW, Segedi M, Chartier-Plante S, Scudamore CH, Erb SR, Salh B, Yoshida EM. End stage liver disease etiology & transplantation referral outcomes of major ethnic groups in British Columbia, Canada: A cohort study. *Medicine (Baltimore)* 2021; **100**: e27436 [PMID: 34678872 DOI: 10.1097/MD.0000000000027436]
10 **Sandal S**, Chen T, Cantarovich M. The Challenges With the Cardiac Evaluation of Liver and Kidney Transplant Candidates. *Transplantation* 2020; **104**: 251-258 [PMID: 31490188 DOI: 10.1097/TP.0000000000002951]
11 **Rudnick MR**, Marchi LD, Plotkin JS. Hemodynamic monitoring during liver transplantation: A state of the art review. *World J Hepatol* 2015; **7**: 1302-1311 [PMID: 26052376 DOI: 10.4254/wjh.v7.i10.1302]
12 **Ozier Y**, Klinck JR. Anesthetic management of hepatic transplantation. *Curr Opin Anaesthesiol* 2008; **21**: 391-400 [PMID: 18458561 DOI: 10.1097/ACO.0b013e3282ff85f4]
13 **Bukowicka B**, Akar RA, Olszewska A, Smoter P, Krawczyk M. The occurrence of postreperfusion syndrome in orthotopic liver transplantation and its significance in terms of complications and short-term survival. *Ann Transplant* 2011; **16**: 26-30 [PMID: 21716182 DOI: 10.12659/aot.881861]
14 **Schumann R**. Intraoperative resource utilization in anesthesia for liver transplantation in the United States: a survey. *Anesth Analg* 2003; **97**: 21-28, table of contents [PMID: 12818937 DOI: 10.1213/01.ane.0000068483.91464.2b]
15 **Aggarwal S**, Kang Y, Freeman JA, Fortunato FL Jr, Pinsky MR. Postreperfusion syndrome: hypotension after reperfusion of the transplanted liver. *J Crit Care* 1993; **8**: 154-160 [PMID: 8275160 DOI: 10.1016/0883-9441(93)90021-c]
16 **Manning MW**, Kumar PA, Maheshwari K, Arora H. Post-Reperfusion Syndrome in Liver Transplantation-An Overview. *J Cardiothorac Vasc Anesth* 2020; **34**: 501-511 [PMID: 31084991 DOI: 10.1053/j.jvca.2019.02.050]
17 **Bodys-Pelka A**, Kusztal M, Raszeja-Wyszomirska J, Główczyńska R, Grabowski M. What's New in Cirrhotic Cardiomyopathy? *J Pers Med* 2021; **11** [PMID: 34945757 DOI: 10.3390/jpm11121285]
18 **Escobar B**, Taurá P, Martínez-Palli G, Fondevila C, Balust J, Beltrán J, Fernández J, García-Pagán JC, García-Valdecasas JC. Stroke volume response to liver graft reperfusion stress in cirrhotic patients. *World J Surg* 2014; **38**: 927-935 [PMID: 24132825 DOI: 10.1007/s00268-013-2289-x]
19 **Reich DL**, Wood RK Jr, Emre S, Bodian CA, Hossain S, Krol M, Feierman D. Association of intraoperative hypotension and pulmonary hypertension with adverse outcomes after orthotopic liver transplantation. *J Cardiothorac Vasc Anesth* 2003; **17**: 699-702 [PMID: 14689408 DOI: 10.1053/j.jvca.2003.09.010]
20 **Feng AC**, Fan HL, Chen TW, Hsieh CB. Hepatic hemodynamic changes during liver transplantation: a review. *World J Gastroenterol* 2014; **20**: 11131-11141 [PMID: 25170200 DOI: 10.3748/wjg.v20.i32.11131]
21 **Hughes DL**, Rice JD, Burton JR, Jin Y, Peterson RA, Ambardekar AV, Pomposelli JJ, Pomfret EA, Kriss MS. Presence of any degree of coronary artery disease among liver transplant candidates is associated with increased rate of post-transplant major adverse cardiac events. *Clin Transplant* 2020; **34**: e14077 [PMID: 32939833 DOI: 10.1111/ctr.14077]
22 **Diedrich DA**, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant Proc* 2008; **40**: 3554-3557 [PMID: 19100436 DOI: 10.1016/j.transproceed.2008.08.129]
23 **Moody WE**, Holloway B, Arumugam P, Gill S, Wahid YS, Boivin CM, Thomson LE, Berman DS, Armstrong MJ,

Ferguson J, Steeds RP. Prognostic value of coronary risk factors, exercise capacity and single photon emission computed tomography in liver transplantation candidates: A 5-year follow-up study. *J Nucl Cardiol* 2021; **28**: 2876-2891 [PMID: 32394403 DOI: 10.1007/s12350-020-02126-z]

24 **Patel S**, Kiefer TL, Ahmed A, Ali ZA, Tremmel JA, Lee DP, Yeung AC, Fearon WF. Comparison of the frequency of coronary artery disease in alcohol-related versus non-alcohol-related endstage liver disease. *Am J Cardiol* 2011; **108**: 1552-1555 [PMID: 21890080 DOI: 10.1016/j.amjcard.2011.07.013]

25 **Kalaitzakis E**, Rosengren A, Skommevik T, Björnsson E. Coronary artery disease in patients with liver cirrhosis. *Dig Dis Sci* 2010; **55**: 467-475 [PMID: 19242795 DOI: 10.1007/s10620-009-0738-z]

26 **Chayanupatkul M**, Liangpunsakul S. Cirrhotic cardiomyopathy: review of pathophysiology and treatment. *Hepatol Int* 2014; **8**: 308-315 [PMID: 25221635 DOI: 10.1007/s12072-014-9531-y]

27 **Martin P**, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; **59**: 1144-1165 [PMID: 24716201 DOI: 10.1002/hep.26972]

28 **Raval Z**, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, Fix OK, Kay N, Abecassis MI, Gheorghiade M, Flaherty JD. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol* 2011; **58**: 223-231 [PMID: 21737011 DOI: 10.1016/j.jacc.2011.03.026]

29 **Johnston SD**, Morris JK, Cramb R, Gunson BK, Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. *Transplantation* 2002; **73**: 901-906 [PMID: 11923689 DOI: 10.1097/00007890-200203270-00012]

30 **Ye C**, Saincher M, Tandon P, Meeberg G, Williams R, Burak KW, Bain VG. Cardiac work-up protocol for liver transplant candidates: experience from a single liver transplant centre. *Can J Gastroenterol* 2012; **26**: 806-810 [PMID: 23166904 DOI: 10.1155/2012/857063]

31 **Kristensen SD**, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C; Authors/Task Force Members. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014; **35**: 2383-2431 [PMID: 25086026 DOI: 10.1093/eurheartj/ehu282]

32 **Bhutani S**, Tobis J, Gevorgyan R, Sinha A, Suh W, Honda HM, Vorobiof G, Packard RR, Steadman R, Wray C, Busuttil R, Tseng CH. Accuracy of stress myocardial perfusion imaging to diagnose coronary artery disease in end stage liver disease patients. *Am J Cardiol* 2013; **111**: 1057-1061 [PMID: 23337839 DOI: 10.1016/j.amjcard.2012.12.023]

33 **Nguyen P**, Plotkin J, Fishbein TM, Laurin JM, Satoskar R, Shetty K, Taylor AJ. Dobutamine stress echocardiography in patients undergoing orthotopic liver transplantation: a pooled analysis of accuracy, perioperative and long term cardiovascular prognosis. *Int J Cardiovasc Imaging* 2013; **29**: 1741-1748 [PMID: 23974907 DOI: 10.1007/s10554-013-0275-x]

34 **Harinstein ME**, Flaherty JD, Ansari AH, Robin J, Davidson CJ, Rossi JS, Flamm SL, Blei AT, Bonow RO, Abecassis M, Gheorghiade M. Predictive value of dobutamine stress echocardiography for coronary artery disease detection in liver transplant candidates. *Am J Transplant* 2008; **8**: 1523-1528 [PMID: 18510630 DOI: 10.1111/j.1600-6143.2008.02276.x]

35 **Doytchinova AT**, Feigenbaum TD, Pondicherry-Harish RC, Sepanski P, Green-Hess D, Feigenbaum H, Sawada SG. Diagnostic Performance of Dobutamine Stress Echocardiography in End-Stage Liver Disease. *JACC Cardiovasc Imaging* 2019; **12**: 2115-2122 [PMID: 30660519 DOI: 10.1016/j.jcmg.2018.10.031]

36 **Safadi A**, Homsi M, Maskoun W, Lane KA, Singh I, Sawada SG, Mahenthiran J. Perioperative risk predictors of cardiac outcomes in patients undergoing liver transplantation surgery. *Circulation* 2009; **120**: 1189-1194 [PMID: 19752326 DOI: 10.1161/CIRCULATIONAHA.108.847178]

37 **Abele JT**, Raubenheimer M, Bain VG, Wandzilak G, AlHulaimi N, Coulden R, deKemp RA, Klein R, Williams RG, Warshawski RS, Lalonde LD. Quantitative blood flow evaluation of vasodilation-stress compared with dobutamine-stress in patients with end-stage liver disease using ^{82}Rb PET/CT. *J Nucl Cardiol* 2020; **27**: 2048-2059 [PMID: 30456495 DOI: 10.1007/s12350-018-01516-8]

38 **Yilmaz Y**, Kurt R, Yonal O, Polat N, Celikel CA, Gurdal A, Oflaz H, Ozdogan O, Imeryuz N, Kalayci C, Avsar E. Coronary flow reserve is impaired in patients with nonalcoholic fatty liver disease: association with liver fibrosis. *Atherosclerosis* 2010; **211**: 182-186 [PMID: 20181335 DOI: 10.1016/j.atherosclerosis.2010.01.049]

39 **Wiese S**, Hove JD, Møller S. Cardiac imaging in patients with chronic liver disease. *Clin Physiol Funct Imaging* 2017; **37**: 347-356 [PMID: 26541640 DOI: 10.1111/cpf.12311]

40 **Aghaulor B**, VanWagner LB. Cardiac and Pulmonary Vascular Risk Stratification in Liver Transplantation. *Clin Liver Dis* 2021; **25**: 157-177 [PMID: 33978576 DOI: 10.1016/j.cld.2020.08.008]

41 **Tiwari N**, Nagraj S, Tzoumas A, Arfaras-Melainis A, Katamreddy A, Sohal S, Palaiodimos L. Diagnostic accuracy of coronary computed tomography angiography in ischemic workup of heart failure: a meta-analysis. *Future Cardiol* 2022; **18**: 325-335 [PMID: 35118872 DOI: 10.2217/fca-2021-0108]

42 **Snipelisky DF**, McRee C, Seeger K, Levy M, Shapiro BP. Coronary Interventions before Liver Transplantation Might Not Avert Postoperative Cardiovascular Events. *Tex Heart Inst J* 2015; **42**: 438-442 [PMID: 26504436 DOI: 10.14503/THIJ-14-4738]

43 **Bonou M**, Mavrogeni S, Kapelios CJ, Skouloudi M, Aggeli C, Cholongitas E, Papatheodoridis G, Barbetseas J. Preoperative Evaluation of Coronary Artery Disease in Liver Transplant Candidates: Many Unanswered Questions in Clinical Practice. *Diagnostics (Basel)* 2021; **11** [PMID: 33466478 DOI: 10.3390/diagnostics11010075]

44 **Lu DY**, Saybolt MD, Kiss DH, Matthai WH, Forde KA, Giri J, Wilensky RL. One-Year Outcomes of Percutaneous Coronary Intervention in Patients with End-Stage Liver Disease. *Clin Med Insights Cardiol* 2020; **14**: 1179546820901491 [PMID: 32030068 DOI: 10.1177/1179546820901491]

45 **Russo MW**, Pierson J, Narang T, Montegudo A, Eskind L, Gulati S. Coronary artery stents and antiplatelet therapy in patients with cirrhosis. *J Clin Gastroenterol* 2012; **46**: 339-344 [PMID: 22105182 DOI: 10.1097/MCG.0b013e3182371258]

46 **Correale M**, Tarantino N, Petrucci R, Tricarico L, Laonigro I, Di Biase M, Brunetti ND. Liver disease and heart failure: Back and forth. *Eur J Intern Med* 2018; **48**: 25-34 [PMID: 29100896 DOI: 10.1016/j.ejim.2017.10.016]

47 **Wiese S**, Hove JD, Bendtsen F, Møller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 177-186 [PMID: 24217347 DOI: 10.1038/nrgastro.2013.210]

48 **Kazankov K**, Holland-Fischer P, Andersen NH, Torp P, Sloth E, Aagaard NK, Vilstrup H. Resting myocardial dysfunction in cirrhosis quantified by tissue Doppler imaging. *Liver Int* 2011; **31**: 534-540 [PMID: 21382164 DOI: 10.1111/j.1478-3231.2011.02468.x]

49 **Nazar A**, Guevara M, Sitges M, Terra C, Solà E, Guigou C, Arroyo V, Ginès P. LEFT ventricular function assessed by echocardiography in cirrhosis: relationship to systemic hemodynamics and renal dysfunction. *J Hepatol* 2013; **58**: 51-57 [PMID: 22989573 DOI: 10.1016/j.jhep.2012.08.027]

50 **Koshy AN**, Gow PJ, Han HC, Teh AW, Jones R, Testro A, Lim HS, McCaughan G, Jeffrey GP, Crawford M, Macdonald G, Fawcett J, Wigg A, Chen JWC, Gane EJ, Munn SR, Clark DJ, Yudi MB, Farouque O. Cardiovascular mortality following liver transplantation: predictors and temporal trends over 30 years. *Eur Heart J Qual Care Clin Outcomes* 2020; **6**: 243-253 [PMID: 32011663 DOI: 10.1093/ehjqcco/qcaa009]

51 **Kowalski HJ**, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. *J Clin Invest* 1953; **32**: 1025-1033 [PMID: 13096569 DOI: 10.1172/jci102813]

52 **Møller S**, Henriksen JH. Cardiovascular complications of cirrhosis. *Postgrad Med J* 2009; **85**: 44-54 [PMID: 19240290 DOI: 10.1136/gut.2006.112177]

53 **Yoon KT**, Liu H, Lee SS. Cirrhotic Cardiomyopathy. *Curr Gastroenterol Rep* 2020; **22**: 45 [PMID: 32651721 DOI: 10.1007/s11894-020-00783-1]

54 **De BK**, Majumdar D, Das D, Biswas PK, Mandal SK, Ray S, Bandopadhyay K, Das TK, Dasgupta S, Guru S. Cardiac dysfunction in portal hypertension among patients with cirrhosis and non-cirrhotic portal fibrosis. *J Hepatol* 2003; **39**: 315-319 [PMID: 12927915 DOI: 10.1016/s0168-8278(03)00271-x]

55 **Morrey C**, Brazin J, Seyedi N, Corti F, Silver RB, Levi R. Interaction between sensory C-fibers and cardiac mast cells in ischemia/reperfusion: activation of a local renin-angiotensin system culminating in severe arrhythmic dysfunction. *J Pharmacol Exp Ther* 2010; **335**: 76-84 [PMID: 20668055 DOI: 10.1124/jpet.110.172262]

56 **Fields NG**, Yuan BX, Leenen FH. Sodium-induced cardiac hypertrophy. Cardiac sympathetic activity versus volume load. *Circ Res* 1991; **68**: 745-755 [PMID: 1835910 DOI: 10.1161/01.res.68.3.745]

57 **Okumura K**, Jin D, Takai S, Miyazaki M. Beneficial effects of angiotensin-converting enzyme inhibition in adriamycin-induced cardiomyopathy in hamsters. *Jpn J Pharmacol* 2002; **88**: 183-188 [PMID: 11928719 DOI: 10.1254/jjp.88.183]

58 **Ames MK**, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. *J Vet Intern Med* 2019; **33**: 363-382 [PMID: 30806496 DOI: 10.1111/jvim.15454]

59 **Takeda Y**, Yoneda T, Demura M, Miyamori I, Mabuchi H. Sodium-induced cardiac aldosterone synthesis causes cardiac hypertrophy. *Endocrinology* 2000; **141**: 1901-1904 [PMID: 10803602 DOI: 10.1210/endo.141.5.7529]

60 **Wong F**. Cirrhotic cardiomyopathy. *Hepatol Int* 2009; **3**: 294-304 [PMID: 19669380 DOI: 10.1007/s12072-008-9109-7]

61 **Rimbaș RC**, Rimbas M, Chitroceanu AM, Luchian LM, Pop C, Vinereanu D. Cirrhotic Cardiomyopathy in the Era of Liver Transplantation: Time for Precise Stepwise Evaluation. *J Gastrointestin Liver Dis* 2020; **29**: 665-675 [PMID: 33331343 DOI: 10.15403/jgld-3137]

62 **Henning RJ**. Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction. *World J Cardiol* 2020; **12**: 7-25 [PMID: 31984124 DOI: 10.4330/wjc.v12.i1.7]

63 **Izzy M**, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, Watt KD, Lee SS; Cirrhotic Cardiomyopathy Consortium. Redefining Cirrhotic Cardiomyopathy for the Modern Era. *Hepatology* 2020; **71**: 334-345 [PMID: 31342529 DOI: 10.1002/hep.30875]

64 **Henriksen JH**, Gøtze JP, Fuglsang S, Christensen E, Bendtsen F, Møller S. Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: relation to cardiovascular dysfunction and severity of disease. *Gut* 2003; **52**: 1511-1517 [PMID: 12970147 DOI: 10.1136/gut.52.10.1511]

65 **Farr M**, Schulze PC. Recent advances in the diagnosis and management of cirrhosis-associated cardiomyopathy in liver transplant candidates: advanced echo imaging, cardiac biomarkers, and advanced heart failure therapies. *Clin Med Insights Cardiol* 2014; **8**: 67-74 [PMID: 25657603 DOI: 10.4137/CMC.S15722]

66 **Wiese S**, Mortensen C, Gøtze JP, Christensen E, Andersen O, Bendtsen F, Møller S. Cardiac and proinflammatory markers predict prognosis in cirrhosis. *Liver Int* 2014; **34**: e19-e30 [PMID: 24313898 DOI: 10.1111/liv.12428]

67 **Shah RV**, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure. *Eur J Heart Fail* 2010; **12**: 826-832 [PMID: 20525986 DOI: 10.1093/eurjhf/hfq091]

68 **Emdin M**, Aimo A, Vergaro G, Bayes-Genis A, Lupón J, Latini R, Meessen J, Anand IS, Cohn JN, Gravning J, Gullestad L, Broch K, Ueland T, Nymo SH, Brunner-La Rocca HP, de Boer RA, Gaggin HK, Ripoli A, Passino C, Januzzi JL Jr. sST2 Predicts Outcome in Chronic Heart Failure Beyond NT-proBNP and High-Sensitivity Troponin T. *J Am Coll Cardiol* 2018; **72**: 2309-2320 [PMID: 30384887 DOI: 10.1016/j.jacc.2018.08.2165]

69 **Pejnovic N**, Jeftic I, Jovicic N, Arsenijevic N, Lukic ML. Galectin-3 and IL-33/ST2 axis roles and interplay in diet-induced steatohepatitis. *World J Gastroenterol* 2016; **22**: 9706-9717 [PMID: 27956794 DOI: 10.3748/wjg.v22.i44.9706]

70 **Lossnitzer D**, Steen H, Zahn A, Lehrke S, Weiss C, Weiss KH, Giannitsis E, Stremmel W, Sauer P, Katus HA, Gotthardt DN. Myocardial late gadolinium enhancement cardiovascular magnetic resonance in patients with cirrhosis. *J Cardiovasc Magn Reson* 2010; **12**: 47 [PMID: 20704762 DOI: 10.1186/1532-429X-12-47]

71 **To AC**, Dhillon A, Desai MY. Cardiac magnetic resonance in hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging* 2011; **4**: 1123-1137 [PMID: 21999873 DOI: 10.1016/j.jcmg.2011.06.022]

72 **Lawton JS**, Cupps BP, Knutsen AK, Ma N, Brady BD, Reynolds LM, Pasque MK. Magnetic resonance imaging detects significant sex differences in human myocardial strain. *Biomed Eng Online* 2011; **10**: 76 [PMID: 21859466 DOI: 10.1186/1475-925X-10-76]

73 **Pozzi M**, Grassi G, Ratti L, Favini G, Dell'Oro R, Redaelli E, Calchera I, Boari G, Mancia G. Cardiac, neuroadrenergic, and portal hemodynamic effects of prolonged aldosterone blockade in postviral child A cirrhosis. *Am J Gastroenterol* 2005; **100**: 1110-1116 [PMID: 15842586 DOI: 10.1111/j.1572-0241.2005.41060.x]

74 **Fouad TR**, Abdel-Razek WM, Burak KW, Bain VG, Lee SS. Prediction of cardiac complications after liver transplantation. *Transplantation* 2009; **87**: 763-770 [PMID: 19295324 DOI: 10.1097/TP.0b013e318198d734]

75 **Mittal C**, Qureshi W, Singla S, Ahmad U, Huang MA. Pre-transplant left ventricular diastolic dysfunction is associated with post transplant acute graft rejection and graft failure. *Dig Dis Sci* 2014; **59**: 674-680 [PMID: 24323177 DOI: 10.1007/s10620-013-2955-8]

76 **VanWagner LB**, Ning H, Whitsett M, Levitsky J, Uttal S, Wilkins JT, Abecassis MM, Ladner DP, Skaro AI, Lloyd-Jones DM. A point-based prediction model for cardiovascular risk in orthotopic liver transplantation: The CAR-OLT score. *Hepatology* 2017; **66**: 1968-1979 [PMID: 28703300 DOI: 10.1002/hep.29329]

77 **Rodríguez-Roisin R**, Krowka MJ, Hervé P, Fallon MB; ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-Hepatic vascular Disorders (PHD). *Eur Respir J* 2004; **24**: 861-880 [PMID: 15516683 DOI: 10.1183/09031936.04.00010904]

78 **Krowka MJ**. Portopulmonary hypertension. *Semin Respir Crit Care Med* 2012; **33**: 17-25 [PMID: 22447257 DOI: 10.1055/s-0032-1301731]

79 **Ramsay MA**, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl Surg* 1997; **3**: 494-500 [PMID: 9346791 DOI: 10.1002/Lt.500030503]

80 **Li J**, Zhuang Q, Zhang X, Zheng Y, Qiao Z, Zhang J, Shen X, Shen J. Prevalence and Prognosis of Portopulmonary Hypertension in 223 Liver Transplant Recipients. *Can Respir J* 2018; **2018**: 9629570 [PMID: 30319722 DOI: 10.1155/2018/9629570]

81 **Le Pavec J**, Souza R, Herve P, Lebrec D, Savale L, Tcherakian C, Jaïs X, Yaïci A, Humbert M, Simonneau G, Sitbon O. Portopulmonary hypertension: survival and prognostic factors. *Am J Respir Crit Care Med* 2008; **178**: 637-643 [PMID: 18617641 DOI: 10.1164/rccm.200804-613OC]

82 **Chen HS**, Xing SR, Xu WG, Yang F, Qi XL, Wang LM, Yang CQ. Portopulmonary hypertension in cirrhotic patients: Prevalence, clinical features and risk factors. *Exp Ther Med* 2013; **5**: 819-824 [PMID: 23403613 DOI: 10.3892/etm.2013.918]

83 **DuBrock HM**, Runo JR, Sadd CJ, Burger CD, Cartin-Ceba R, Rosen CB, Taner T, Nyberg SL, Heimbach JK, Findlay JY, Krowka MJ. Outcomes of Liver Transplantation in Treated Portopulmonary Hypertension Patients With a Mean Pulmonary Arterial Pressure ≥35 mm Hg. *Transplant Direct* 2020; **6**: e630 [PMID: 33204828 DOI: 10.1097/TXD.0000000000001085]

84 **Krowka MJ**, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C, Pardo M Jr, Marotta P, Uemoto S, Stoffel MP, Benson JT. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl* 2004; **10**: 174-182 [PMID: 14762853 DOI: 10.1002/Lt.20016]

85 **Panos RJ**, Baker SK. Mediators, cytokines, and growth factors in liver-lung interactions. *Clin Chest Med* 1996; **17**: 151-169 [PMID: 8665787 DOI: 10.1016/s0272-5231(05)70305-1]

86 **Huertas A**, Guignabert C, Barberà JA, Bärtsch P, Bhattacharya J, Bhattacharya S, Bonsignore MR, Dewachter L, Dinh-Xuan AT, Dorfmüller P, Gladwin MT, Humbert M, Kotsimbos T, Vassilakopoulos T, Sanchez O, Savale L, Testa U, Wilkins MR. Pulmonary vascular endothelium: the orchestra conductor in respiratory diseases: Highlights from basic research to therapy. *Eur Respir J* 2018; **51** [PMID: 29545281 DOI: 10.1183/13993003.00745-2017]

87 **Robalino BD**, Moodie DS. Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. *J Am Coll Cardiol* 1991; **17**: 492-498 [PMID: 1991908 DOI: 10.1016/s0735-1097(10)80121-4]

88 **Yang YY**, Lin HC, Lee WC, Hou MC, Lee FY, Chang FY, Lee SD. Portopulmonary hypertension: distinctive hemodynamic and clinical manifestations. *J Gastroenterol* 2001; **36**: 181-186 [PMID: 11291881 DOI: 10.1007/s005350170126]

89 **Galiè N**, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; **37**: 67-119 [PMID: 26320113 DOI: 10.1093/eurheartj/ehv317]

90 **Raevens S**, Colle I, Reyntjens K, Geerts A, Berrevoet F, Rogiers X, Troisi RI, Van Vlierberghe H, De Pauw M. Echocardiography for the detection of portopulmonary hypertension in liver transplant candidates: an analysis of cutoff values. *Liver Transpl* 2013; **19**: 602-610 [PMID: 23584902 DOI: 10.1002/lt.23649]

91 **Cartin-Ceba R**, Krowka MJ. Pulmonary Complications of Portal Hypertension. *Clin Liver Dis* 2019; **23**: 683-711 [PMID: 31563218 DOI: 10.1016/j.cld.2019.06.003]

92 **Simonneau G**, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; **53** [PMID: 30545968 DOI: 10.1183/13993003.01913-2018]

93 **Thomas C**, Glinskii V, de Jesus Perez V, Sahay S. Portopulmonary Hypertension: From Bench to Bedside. *Front Med (Lausanne)* 2020; **7**: 569413 [PMID: 33224960 DOI: 10.3389/fmed.2020.569413]

94 **Krowka MJ**, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MA, Sitbon O, Sokol RJ. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. *Transplantation* 2016; **100**: 1440-1452 [PMID: 27326810 DOI: 10.1097/TP.0000000000001229]

95 **Krowka MJ**. Hepatopulmonary Syndrome and Portopulmonary Hypertension: The Pulmonary Vascular Enigmas of Liver Disease. *Clin Liver Dis (Hoboken)* 2020; **15**: S13-S24 [PMID: 32140210 DOI: 10.1002/cld.846]

96 **Cartin-Ceba R**, Krowka MJ. Portopulmonary hypertension. *Clin Liver Dis* 2014; **18**: 421-438 [PMID: 24679504 DOI:

10.1016/j.cld.2014.01.004]
97 **Henriksen JH**, Moller S. Liver cirrhosis and arterial hypertension. *World J Gastroenterol* 2006; **12**: 678-685 [PMID: 16521178 DOI: 10.3748/wjg.v12.i5.678]
98 **El Hadi H**, Di Vincenzo A, Vettor R, Rossato M. Relationship between Heart Disease and Liver Disease: A Two-Way Street. *Cells* 2020; **9** [PMID: 32121065 DOI: 10.3390/cells9030567]
99 **Martell M**, Coll M, Ezkurdia N, Raurell I, Genescà J. Physiopathology of splanchnic vasodilation in portal hypertension. *World J Hepatol* 2010; **2**: 208-220 [PMID: 21160999 DOI: 10.4254/wjh.v2.i6.208]
100 **Martinez-Palli G**, Cárdenas A. Pre operative cardio pulmonary assessment of the liver transplant candidate. *Ann Hepatol* 2011; **10**: 421-433 [PMID: 21911881 DOI: 10.1016/S1665-2681(19)31508-X]
101 **Coverstone E**, Korenblat K, Crippin JS, Chapman WC, Kates AM, Zajarias A. Aortic balloon valvuloplasty prior to orthotopic liver transplantation: a novel approach to aortic stenosis and end-stage liver disease. *Case Rep Cardiol* 2014; **2014**: 325136 [PMID: 25431682 DOI: 10.1155/2014/325136]
102 **Kertai MD**, Bountioukos M, Boersma E, Bax JJ, Thomson IR, Sozzi F, Klein J, Roelandt JR, Poldermans D. Aortic stenosis: an underestimated risk factor for perioperative complications in patients undergoing noncardiac surgery. *Am J Med* 2004; **116**: 8-13 [PMID: 14706659 DOI: 10.1016/j.amjmed.2003.07.012]
103 **Nicolau-Raducu R**, Marshall T, Patel H, Ural K, Koveleskie J, Smith S, Ganier D, Evans B, Fish B, Daly W, Cohen AJ, Loss G, Bokhari A, Nossaman B. Long-Term Cardiac Morbidity and Mortality in Patients With Aortic Valve Disease Following Liver Transplantation: A Case Matching Study. *Semin Cardiothorac Vasc Anesth* 2017; **21**: 345-351 [PMID: 28486870 DOI: 10.1177/1089253217708034]
104 **Fleisher LA**, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **130**: 2215-2245 [PMID: 25085962 DOI: 10.1161/CIR.0000000000000105]
105 **Hulselmans M**, Vandermeulen E, Herregods MC. Risk assessment in patients with heart valve disease facing non-cardiac surgery. *Acta Cardiol* 2009; **64**: 151-155 [PMID: 19476105 DOI: 10.2143/ac.64.2.2035337]
106 **Han H**, Qin Y, Yu Y, Wei X, Guo H, Ruan Y, Cao Y, He J. Atrial fibrillation in hospitalized patients with end-stage liver disease: temporal trends in prevalence and outcomes. *Liver Int* 2020; **40**: 674-684 [PMID: 31705572 DOI: 10.1111/liv.14291]
107 **VanWagner LB**, Serper M, Kang R, Levitsky J, Hohmann S, Abecassis M, Skaro A, Lloyd-Jones DM. Factors Associated With Major Adverse Cardiovascular Events After Liver Transplantation Among a National Sample. *Am J Transplant* 2016; **16**: 2684-2694 [PMID: 26946333 DOI: 10.1111/ajt.13779]
108 **Darrat YH**, Smer A, Elayi CS, Morales GX, Alqahtani F, Alkhouli M, Catanzaro J, Shah J, Salih M. Mortality and morbidity in patients with atrial fibrillation and liver cirrhosis. *World J Cardiol* 2020; **12**: 342-350 [PMID: 32843936 DOI: 10.4330/wjc.v12.i7.342]
109 **Tzoumas A**, Nagraj S, Tasoudis P, Arfaras-Melainis A, Palaiodimos L, Kokkinidis DG, Kampaktsis PN. Atrial fibrillation following coronary artery bypass graft: Where do we stand? *Cardiovasc Revasc Med* 2021 [PMID: 34949543 DOI: 10.1016/j.carrev.2021.12.006]
110 **Główczyńska R**, Galas M, Ołdakowska-Jedynak U, Peller M, Tomaniak M, Raszeja-Wyszomirska J, Milkiewicz P, Krawczyk M, Zieniewicz K, Opolski G. Pretransplant QT Interval: The Relationship with Severity and Etiology of Liver Disease and Prognostic Value After Liver Transplantation. *Ann Transplant* 2018; **23**: 622-630 [PMID: 30177675 DOI: 10.12659/AOT.908769]
111 **Bernardi M**, Maggioli C, Dibra V, Zaccherini G. QT interval prolongation in liver cirrhosis: innocent bystander or serious threat? *Expert Rev Gastroenterol Hepatol* 2012; **6**: 57-66 [PMID: 22149582 DOI: 10.1586/egh.11.86]
112 **Ko J**, Koshy AN, Han HC, Weinberg L, Gow P, Testro A, Lim HS, Farouque O, Teh AW. Effect of liver transplantation on QT-interval prolongation and impact on mortality. *Int J Cardiol* 2021; **326**: 158-163 [PMID: 33186663 DOI: 10.1016/j.ijcard.2020.11.017]
113 **Adigun AQ**, Pinto AG, Flockhart DA, Gorski JC, Li L, Hall SD, Chalasani N. Effect of cirrhosis and liver transplantation on the gender difference in QT interval. *Am J Cardiol* 2005; **95**: 691-694 [PMID: 15721125 DOI: 10.1016/j.amjcard.2004.10.054]
114 **Kim SM**, George B, Alcivar-Franco D, Campbell CL, Charnigo R, Delisle B, Hundley J, Darrat Y, Morales G, Elayi SC, Bailey AL. QT prolongation is associated with increased mortality in end stage liver disease. *World J Cardiol* 2017; **9**: 347-354 [PMID: 28515853 DOI: 10.4330/wjc.v9.i4.347]
115 **Al-Khatib SM**, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA* 2003; **289**: 2120-2127 [PMID: 12709470 DOI: 10.1001/jama.289.16.2120]
116 **Lagerström PO**. Ion-pair chromatography of phenylacetic acid derivatives and other hydrophilic carboxylic acids of physiological importance on micro silica particles. *Acta Pharm Suec* 1976; **13**: 213-228 [PMID: 181948 DOI: 10.1016/j.jhep.2007.11.012]
117 **Țieranu E**, Donoiu I, Istrătoaie O, Găman AE, Țieranu LM, Gheonea DI, Ciurea T. Q-T Interval Prolongation in Patients with Liver Cirrhosis. *Curr Health Sci J* 2018; **44**: 274-279 [PMID: 30647948 DOI: 10.12865/CHSJ.44.03.11]
118 **Nikolaidis LA**, Azzouz M, Friedlander L, Van Thiel DH, Gradman AH. Hepatitis C virus-associated pericardial effusion and tamponade in a liver transplant recipient. *Can J Cardiol* 2004; **20**: 719-721 [PMID: 15197425]
119 **Safadi R**, Ilan Y, Ashur Y, Shouval D. Hepatitis C-associated cryoglobulinemia presenting with pericardial effusion. *Am J Gastroenterol* 1997; **92**: 710-712 [PMID: 9128336]
120 **Ali MA**, Kayani WZ, Linzie BM, Punjabi GV, Wetmore JB. Myopericarditis in a patient with hepatitis C and cryoglobulinemic renal disease. *Clin Case Rep* 2017; **5**: 616-620 [PMID: 28469862 DOI: 10.1002/ccr3.788]
121 **Kamio T**, Hiraoka E, Obunai K, Watanabe H. Constrictive Pericarditis as a Long-term Undetermined Etiology of Ascites and Edema. *Intern Med* 2018; **57**: 1487-1491 [PMID: 29321423 DOI: 10.2169/internalmedicine.9455-17]

122 **Welch TD**, Ling LH, Espinosa RE, Anavekar NS, Wiste HJ, Lahr BD, Schaff HV, Oh JK. Echocardiographic diagnosis of constrictive pericarditis: Mayo Clinic criteria. *Circ Cardiovasc Imaging* 2014; **7**: 526-534 [PMID: 24633783 DOI: 10.1161/CIRCIMAGING.113.001613]

123 **Miranda WR**, Oh JK. Constrictive Pericarditis: A Practical Clinical Approach. *Prog Cardiovasc Dis* 2017; **59**: 369-379 [PMID: 28062267 DOI: 10.1016/j.pcad.2016.12.008]

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MINIREVIEWS

Gut microbiome dysbiosis in the setting of solid organ transplantation: What we have gleaned from human and animal studies

Aparna Sharma, Emmanouil Giorgakis

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Abstract

The human gut microbiome refers to all of the microorganisms present throughout the length of the gastrointestinal tract. Gut flora influence host metabolic and immune processes in myriad ways. They also play an important role in maturation and modulation of the immune system. Dysbiosis or a pathologic alteration in gut flora has been implicated in a number of diseases ranging from metabolic, autoimmune and degenerative. Whether dysbiosis has similar implications in organ transplant has been the focus of a number of pre-clinical and clinical studies. Researchers have observed significant microbiome changes after solid organ transplantation in humans that have been associated with clinical outcomes such as post-transplant urinary tract infections and diarrhea. In this article, we will discuss the available data regarding pathologic alterations in gut microbiome (dysbiosis) in solid organ transplant recipients as well as some of challenges in this field. We will also discuss animal studies focusing on mouse models of transplantation that shed light on the underlying mechanisms that explain these findings.

Key Words: Dysbiosis; Gut microbiome; Innate immunity; Short chain fatty acids; Toll like receptors; Tolerance

Core Tip: The human gut microbiome refers to all of the microorganisms present throughout the length of the gastrointestinal tract. Gut flora influence host metabolic and immune processes in myriad ways. Gut microbiota alterations have been described in solid organ recipients. In this review we discuss available human studies about changes in gut flora in solid organ transplant such as kidney, liver and small bowel.

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INTRODUCTION

The human gut microbiota refers to all of the microorganisms present throughout the length of the gastrointestinal tract and include bacteria, viruses, protozoa, and fungi. The term microbiome is used to describe these microorganisms along with their collective genetic material. In this article, the terms microbiome/microbiota will be used interchangeably. We now know that there are over 100 trillion microbes in the human gut alone, with the majority being found in the colon[1].

Most of these microorganisms consist of bacteria, along with smaller numbers of viruses, fungi, and protozoa. Previous studies of gut microbiota relied heavily on culture methods and could reliably detect only a small minority of organisms. Advances in molecular technology with methods such culture independent RNA and meta-genomic sequencing have revolutionized our understanding of the composition and function of gut flora and ways they influence host metabolism, immunity and inflammation.

The importance of gut flora in maintaining a healthy physiologic state cannot be understated. Research studies have shed light on the fact that a multitude of host processes depend on microbial function. These include maintaining the integrity of gut epithelial cells and thereby the epithelial barrier, modulation of immune system[2], nutrient processing and regulating systemic inflammation and metabolism through production of chemical messengers[3,4]. One example of these messengers are short chain fatty acids (SCFAs) that are produced by bacterial fermentation of dietary fiber in the gut lumen and circulate in the bloodstream with resultant downstream organ effects[5]. Due to their enormous contribution to the host, researchers have referred to the gut microbiome as the "second human genome". Dysbiosis is defined as a pathologic alteration in the microbiota that has adverse consequences for the host. This could manifest either as bloom of pathogenic organisms, loss of commensals or loss of diversity. Both animal and human studies have described the association between dysbiosis and diseases as diverse as such as coronary artery disease, chronic kidney disease[6], liver cirrhosis, diabetes mellitus and autoimmune conditions like systemic lupus erythematosus and rheumatoid arthritis[7-9].

The advent of modern immunosuppressive drugs has revolutionized transplant outcomes in the short term due to a dramatic reduction in the incidence of acute rejection. However long-term allograft survival remains sub-optimal[10]. It has been noted that allograft outcomes vary according to the type of organ transplanted. For instance, lung and intestine grafts that are considered colonized with microorganisms have poorer graft outcomes than heart and kidney grafts (not colonized)[11]. Gut bacteria play an important role in maturation and "setting the tone" of the host immune system[2]. Given their pivotal role in shaping immunologic responses, gut microbiome can possibly affect graft outcomes in transplantation. In this review we discuss the available data regarding pathologic alterations in gut microbiome (dysbiosis) in solid organ transplant recipients. We will also explore data from preclinical studies on mouse models of transplantation that shed light on the possible mechanisms behind these findings.

METHODOLOGY

Literature search was conducted on PubMed using Mesh database for papers until March 2021. We also cite high-quality articles in Reference Citation Analysis (https://www.referencecitationanalysis.com). Only studies published in English were considered. Search terms on Mesh database consisted of "Dysbiosis", "Gut microbiome", "Kidney transplantation", "Liver transplantation", "heart transplantation", "Heart lung transplantation" and "Lung transplantation".

Organ transplantation is associated with changes in gut microbiome

Solid organ transplant recipients are exposed to a variety of factors that can affect gut flora. These include, but are not limited to, antibiotics used for treatment or prophylaxis of infections, immunosup-

pressive medications as well as other classes of medications such as antihypertensives. Numerous studies have shed light on gut microbiome changes in hematopoietic stem cell transplant recipients. In regards to the setting of solid organ transplantation, these studies are still limited and consist mostly of cross-sectional or longitudinal observational correlation studies.

Studies in liver transplant recipients

Bajaj *et al*[12] looked at liver transplant recipients and noted that they have increase in microbial diversity and decrease in endotoxin levels compared to pre-transplant cirrhotic levels. Pathogenic genera such as *Enterobacteriaceae* (*Escherichia*, *Shigella*, *Salmonella*) were decreased compared to baseline cirrhotic state while relative abundance of potentially beneficial commensals *Lachnospiraceae* and *Ruminococcaceae* were increased. Kato *et al*[13] looked at liver transplant patients and found that *Enterobacteriaceae*, *Streptococcaceae* and *Bifidobacteriaceae* were increased whereas *Enterococcaceae*, *Lactobacillaceae*, *Clostridiaceae*, *Ruminococcaceae,* and *Peptostreptococcaceae* were decreased in patients with allograft rejection. A study by Sun *et al*[14] showed that microbiota of cirrhotic patients awaiting liver transplant surgery was significantly different than controls, however in this study no significant difference was noted between post-transplant and control groups. A similar study showed that compared to healthy controls, liver transplantation was associated with decrease beneficial bacteria such as bifibacteria and lactobacillus and increased pathogenic bacteria such as *Enterobacteriaceae*[15].

Studies in kidney transplant recipients

The phylum bacteroides is dominant in normal humans as shown by the human microbiome project. In a study of kidney transplant recipients, Swarte *et al*[16] found that gut microbiome composition was significantly different from that of healthy controls, and had a lower diversity. Use of mycophenolate mofetil (MMF) correlated to a lower diversity of gut flora as well. Lee *et al*[17] in a study looking at 26 kidney transplant recipients found that instead of bacteroides the dominant phylum was *firmicutes*. The same group also showed significant differences in gut bacteria between kidney transplant patients that had post-transplant complications such as diarrhea, acute rejection and *Enterococcal* urinary tract infections *vs* those that did not. Similar findings were noted in pediatric kidney transplant recipients [18].

In a study of intestinal transplant patients, ileal microbial diversity as measured by Shannon indices were not different between patients with and without allograft rejection however patients with acute graft rejection had significantly higher relative abundance of *Proteobacteria* and lower abundance of *firmicutes*[19]. In a study by Yuzefpolskaya *et al*[20], stool samples of patients who had received a heart transplant within the past 6 mo showed a decrease in microbial diversity.

Metabolic changes after solid organ transplant and changes in gut microbiome: New onset diabetes after transplant

New onset Diabetes after transplant (NODAT) is a frequent complication in solid organ transplant recipients. Microbiota changes have been described in these patients that were non diabetic pre transplant. In a study of kidney transplant recipients, the relative abundance of *Akkermansia muciniphila* decreased significantly after transplant in NODAT and in initially diabetic patients but not in controls [21].

Viral infections after transplant

In a study of 168 kidney transplant recipients, Lee *et al*[22] showed that patients with high levels of butyrate producing gut (BPG) bacteria in their stool had a significantly decreased risk for development of respiratory viral infections such as rhinoviral and coronavirus infections and influenza at 6 mo, 1 year and 2 years post transplantation. It was also noted in the study that the higher BPG bacteria group had a decreased risk for development of cytomegalovirus viremia at 1 year post kidney transplantation.

The above-described studies have a number of limitations. These include small sample size and patient heterogeneity. The timing of sample collection after transplant also varied between studies. Hence the pivotal question of whether dysbiosis is merely associated with rather than directly causing post-transplant adverse outcomes remains unanswered.

Evidence from animal models of transplantation

Mice with allogenic skin grafts have been studied to understand immune processes during transplantation. It has been shown that considerable immune defects are detectable in germ-free mice that lack gut flora[23]. In these mice, smaller Peyer's patches are noted and the number of $CD4^+$ T cells and immunoglobulin A producing plasma cells are found to be reduced. This highlights the important role that gut microorganisms play in maturation and development of host immunity. In a landmark study, Lei *et al*[24] found that both germ-free and antibiotic-pre-treated mice exhibit decreased allo-immunity and had increase in survival of skin grafts. This phenomenon was associated with reduction in type I interferon and nuclear factor-κB pathway activation in dendritic cells. In the same study when these germ-free mice had gastric inoculation of gut bacteria from conventional mice, accelerated skin graft rejection occurred.

Pre-clinical studies show that both innate and adaptive immune responses are affected by gut flora [25,26]. Intestinal epithelial cells express surface toll-like receptors on their surface and these are activated by binding to microbial ligands also called microbe associated molecular patterns MAMP. This binding suppresses the inflammatory response and promotes tolerance to normal microbiota components by the host immune cells. Gut flora also stimulates Treg cells which are known to play a role in graft tolerance. Depending on whether gut flora prime or quiesce the immune system of a mouse model, changes in allograft outcomes can be seen. If gut bacteria activate inflammatory pathways, this can hasten allograft rejection. On the other hand, induction of inhibitory pathways can dampen the immune response and induce tolerance. A study by Emal *et al*[27] showed that microbiome inflammation and acute kidney injury after ischemia-reperfusion *via* maturation of macrophages. Conversely, depletion of the microbes significantly attenuated renal damage, dysfunction, and remote organ injury and maintained tubular integrity after ischemia-reperfusion.

A number of chemical messengers are produced in the gut lumen by microbial activity. These include SCFAs comprising butyrate, acetate, and propionate. Butyrate has been found to induce Tregs and increase interleukin-10 production and decrease proinflammatory cytokine production by colonic macrophages[28]. In a mouse study, antibiotics to alter gut microbiota increased rate of acute rejection of skin grafts[29]. This indicates that disruption of the gut microbiota during early life development may have persistent effects on immune regulation.

The concept of molecular mimicry

Infections occurring prior to transplant can result in several T cell receptors (TCRs) that can cross-react with donor self-peptides/allo-major histocompatibility complex. In other words, microbial antigens can mimic allo-antigens from the graft. These have the potential to generate memory T cells that can subsequently cause injury to the transplanted organ. Infections contracted after transplantation can influence ongoing allo-immunity by influencing both native and memory alloreactive T cells independently of TCR cross-reactivity. This can lead to Th1 differentiation and heralds the onset of acute rejection[30].

Therapeutic trials of modifying microbiome in a mouse model seem promising. Supplementation with the SCFAs sodium acetate or sodium butyrate decreased dysbiosis and afforded protection against allograft rejection. This protection was dependent on the G protein-coupled receptor GPR43 and T regulatory cells. This study could prompt future clinical trials exploring prebiotic and dietary modifications in solid organ transplant recipients as a means to facilitate better long-term graft survival[31].

Microbiome and immunosuppressive drugs: A bidirectional relationship

The gut microbiome can influence pharmacokinetics of immunosuppressive medications causing either activation or inactivation of the drug[32,33]. Drug elimination can also be impacted by interference in the enterohepatic circulation by de-conjugation of liver-produced drug metabolites. Studies have shown that human gut bacteria are capable of metabolizing tacrolimus and MMF, the two most commonly used medications in solid organ transplantation. Additionally, Guo *et al*[34] showed that bacterial species belonging to the *Clostridiales* order convert tacrolimus into a less active metabolite. The same research group found that *Faecalibacterium prausnitzii*, a member of the *Clostridiales* order, was found in greater levels in the gut of 5 kidney transplant patients in need of higher tacrolimus doses. Gut microbes can also alter the expression of metabolic liver enzymes (*e.g.*, cytochrome P450s). It is a commonly seen phenomenon that diarrhea in transplant patients can elevate tacrolimus levels. This effect is thought to be related to downregulation of intestinal cytochrome P4503A4 and P-glycoprotein activity.

Discussion

Both animal and human studies conducted thus far indicate an association between gut microbiome changes and distinct clinical consequences in solid organ transplant recipients. However, association does not imply causation and further studies are needed in this direction. The complex crosstalk between gut flora and immune cells of solid organ transplant recipients needs to be better elucidated in order to develop newer and better therapeutic strategies to improve long term graft outcomes. There remain challenges in designing and executing methodologically rigorous microbiome studies including patient heterogeneity, financial cost and distinguishing between cause, effect, and coincidental association.

CONCLUSION

It is clear from both animal and human studies conducted thus far that gut microbiome changes are associated with distinct clinical consequences in solid organ transplant recipients. The complex crosstalk between gut flora and immune cells of solid organ transplant recipients needs to be better elucidated in order to develop newer and better therapeutic strategies to improve long term graft outcomes. There remain significant challenges in designing and executing methodologically rigorous microbiome studies due to patient heterogeneity, financial cost and distinguishing between cause, effect, and coincidental

association.

FOOTNOTES

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REFERENCES

1 **Ley RE**, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* 2006; **124**: 837-848 [PMID: 16497592 DOI: 10.1016/j.cell.2006.02.017]
2 **Hooper LV**, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012; **336**: 1268-1273 [PMID: 22674334 DOI: 10.1126/science.1223490]
3 **Rowland I**, Gibson G, Heinken A, Scott K, Swann J, Thiele I, Tuohy K. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr* 2018; **57**: 1-24 [PMID: 28393285 DOI: 10.1007/s00394-017-1445-8]
4 **Morrison DJ**, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* 2016; **7**: 189-200 [PMID: 26963409 DOI: 10.1080/19490976.2015.1134082]
5 **Kasubuchi M**, Hasegawa S, Hiramatsu T, Ichimura A, Kimura I. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. *Nutrients* 2015; **7**: 2839-2849 [PMID: 25875123 DOI: 10.3390/nu7042839]
6 **Ramezani A**, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol* 2014; **25**: 657-670 [PMID: 24231662 DOI: 10.1681/ASN.2013080905]
7 **Singer-Englar T**, Barlow G, Mathur R. Obesity, diabetes, and the gut microbiome: an updated review. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 3-15 [PMID: 30791839 DOI: 10.1080/17474124.2019.1543023]
8 **Katz-Agranov N**, Zandman-Goddard G. The microbiome and systemic lupus erythematosus. *Immunol Res* 2017; **65**: 432-437 [PMID: 28233089 DOI: 10.1007/s12026-017-8906-2]
9 **De Luca F**, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol* 2019; **195**: 74-85 [PMID: 29920643 DOI: 10.1111/cei.13158]
10 **Lamb KE**, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant* 2011; **11**: 450-462 [PMID: 20973913 DOI: 10.1111/j.1600-6143.2010.03283.x]
11 Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients 2010 data report. *Am J Transplant* 2012; **12** Suppl 1: 1-156 [PMID: 22107249 DOI: 10.1111/j.1600-6143.2011.03886.x]
12 **Bajaj JS**, Kakiyama G, Cox IJ, Nittono H, Takei H, White M, Fagan A, Gavis EA, Heuman DM, Gilles HC, Hylemon P, Taylor-Robinson SD, Legido-Quigley C, Kim M, Xu J, Williams R, Sikaroodi M, Pandak WM, Gillevet PM. Alterations in gut microbial function following liver transplant. *Liver Transpl* 2018; **24**: 752-761 [PMID: 29500907 DOI: 10.1002/lt.25046]
13 **Kato K**, Nagao M, Miyamoto K, Oka K, Takahashi M, Yamamoto M, Matsumura Y, Kaido T, Uemoto S, Ichiyama S. Longitudinal Analysis of the Intestinal Microbiota in Liver Transplantation. *Transplant Direct* 2017; **3**: e144 [PMID: 28405600 DOI: 10.1097/TXD.0000000000000661]
14 **Sun LY**, Yang YS, Qu W, Zhu ZJ, Wei L, Ye ZS, Zhang JR, Sun XY, Zeng ZG. Gut microbiota of liver transplantation recipients. *Sci Rep* 2017; **7**: 3762 [PMID: 28630433 DOI: 10.1038/s41598-017-03476-4]
15 **Wu ZW**, Ling ZX, Lu HF, Zuo J, Sheng JF, Zheng SS, Li LJ. Changes of gut bacteria and immune parameters in liver transplant recipients. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 40-50 [PMID: 22251469 DOI: 10.1016/s1499-3872(11)60124-0]
16 **Swarte JC**, Douwes RM, Hu S, Vich Vila A, Eisenga MF, van Londen M, Gomes-Neto AW, Weersma RK, Harmsen HJM, Bakker SJL. Characteristics and Dysbiosis of the Gut Microbiome in Renal Transplant Recipients. *J Clin Med* 2020; **9** [PMID: 32024079 DOI: 10.3390/jcm9020386]
17 **Lee JR**, Muthukumar T, Dadhania D, Toussaint NC, Ling L, Pamer E, Suthanthiran M. Gut microbial community structure and complications after kidney transplantation: a pilot study. *Transplantation* 2014; **98**: 697-705 [PMID: 25289916 DOI: 10.1097/TP.0000000000000370]

18 **Crespo-Salgado J**, Vehaskari VM, Stewart T, Ferris M, Zhang Q, Wang G, Blanchard EE, Taylor CM, Kallash M, Greenbaum LA, Aviles DH. Intestinal microbiota in pediatric patients with end stage renal disease: a Midwest Pediatric Nephrology Consortium study. *Microbiome* 2016; **4**: 50 [PMID: 27640125 DOI: 10.1186/s40168-016-0195-9]

19 **Oh PL**, Martínez I, Sun Y, Walter J, Peterson DA, Mercer DF. Characterization of the ileal microbiota in rejecting and nonrejecting recipients of small bowel transplants. *Am J Transplant* 2012; **12**: 753-762 [PMID: 22152019 DOI: 10.1111/j.1600-6143.2011.03860.x]

20 **Yuzefpolskaya M**, Bohn B, Nasiri M, Zuver AM, Onat DD, Royzman EA, Nwokocha J, Mabasa M, Pinsino A, Brunjes D, Gaudig A, Clemons A, Trinh P, Stump S, Giddins MJ, Topkara VK, Garan AR, Takeda K, Takayama H, Naka Y, Farr MA, Nandakumar R, Uhlemann AC, Colombo PC, Demmer RT. Gut microbiota, endotoxemia, inflammation, and oxidative stress in patients with heart failure, left ventricular assist device, and transplant. *J Heart Lung Transplant* 2020; **39**: 880-890 [PMID: 32139154 DOI: 10.1016/j.healun.2020.02.004]

21 **Lecronier M**, Tashk P, Tamzali Y, Tenaillon O, Denamur E, Barrou B, Aron-Wisnewsky J, Tourret J. Gut microbiota composition alterations are associated with the onset of diabetes in kidney transplant recipients. *PLoS One* 2020; **15**: e0227373 [PMID: 31910227 DOI: 10.1371/journal.pone.0227373]

22 **Lee JR**, Huang J, Magruder M, Zhang LT, Gong C, Sholi AN, Albakry S, Edusei E, Muthukumar T, Lubetzky M, Dadhania DM, Taur Y, Pamer EG, Suthanthiran M. Butyrate-producing gut bacteria and viral infections in kidney transplant recipients: A pilot study. *Transpl Infect Dis* 2019; **21**: e13180 [PMID: 31544324 DOI: 10.1111/tid.13180]

23 **Bauer H**, Horowitz RE, Levenson SM, Popper H. The response of the lymphatic tissue to the microbial flora. Studies on germfree mice. *Am J Pathol* 1963; **42**: 471-483 [PMID: 13966929]

24 **Lei YM**, Chen L, Wang Y, Stefka AT, Molinero LL, Theriault B, Aquino-Michaels K, Sivan AS, Nagler CR, Gajewski TF, Chong AS, Bartman C, Alegre ML. The composition of the microbiota modulates allograft rejection. *J Clin Invest* 2016; **126**: 2736-2744 [PMID: 27322054 DOI: 10.1172/JCI85295]

25 **Belkaid Y**, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; **157**: 121-141 [PMID: 24679531 DOI: 10.1016/j.cell.2014.03.011]

26 **Gensollen T**, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. *Science* 2016; **352**: 539-544 [PMID: 27126036 DOI: 10.1126/science.aad9378]

27 **Emal D**, Rampanelli E, Stroo I, Butter LM, Teske GJ, Claessen N, Stokman G, Florquin S, Leemans JC, Dessing MC. Depletion of Gut Microbiota Protects against Renal Ischemia-Reperfusion Injury. *J Am Soc Nephrol* 2017; **28**: 1450-1461 [PMID: 27927779 DOI: 10.1681/ASN.2016030255]

28 **Arpaia N**, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, Liu H, Cross JR, Pfeffer K, Coffer PJ, Rudensky AY. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 2013; **504**: 451-455 [PMID: 24226773 DOI: 10.1038/nature12726]

29 **Rey K**, Manku S, Enns W, Van Rossum T, Bushell K, Morin RD, Brinkman FSL, Choy JC. Disruption of the Gut Microbiota With Antibiotics Exacerbates Acute Vascular Rejection. *Transplantation* 2018; **102**: 1085-1095 [PMID: 29538261 DOI: 10.1097/TP.0000000000002169]

30 **Ahmed EB**, Wang T, Daniels M, Alegre ML, Chong AS. IL-6 induced by Staphylococcus aureus infection prevents the induction of skin allograft acceptance in mice. *Am J Transplant* 2011; **11**: 936-946 [PMID: 21449942 DOI: 10.1111/j.1600-6143.2011.03476.x]

31 **Wu H**, Singer J, Kwan TK, Loh YW, Wang C, Tan J, Li YJ, Lai SWC, Macia L, Alexander SI, Chadban SJ. Gut Microbial Metabolites Induce Donor-Specific Tolerance of Kidney Allografts through Induction of T Regulatory Cells by Short-Chain Fatty Acids. *J Am Soc Nephrol* 2020; **31**: 1445-1461 [PMID: 32482686 DOI: 10.1681/ASN.2019080852]

32 **Wilson ID**, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl Res* 2017; **179**: 204-222 [PMID: 27591027 DOI: 10.1016/j.trsl.2016.08.002]

33 **Dempsey JL**, Cui JY. Microbiome is a functional modifier of P450 drug metabolism. *Curr Pharmacol Rep* 2019; **5**: 481-490 [PMID: 33312848 DOI: 10.1007/s40495-019-00200-w]

34 **Guo Y**, Crnkovic CM, Won KJ, Yang X, Lee JR, Orjala J, Lee H, Jeong H. Commensal Gut Bacteria Convert the Immunosuppressant Tacrolimus to Less Potent Metabolites. *Drug Metab Dispos* 2019; **47**: 194-202 [PMID: 30598508 DOI: 10.1124/dmd.118.084772]

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MINIREVIEWS

Robot-assisted kidney transplantation: Is it getting ready for prime time?

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Abstract

Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease, providing a better survival rate and quality of life compared to dialysis. Despite the progress in the medical management of KT patients, from a purely surgical standpoint, KT has resisted innovations during the last 50 years. Recently, robot-assisted KT (RAKT) has been proposed as an alternative approach to open surgery, especially due to its potential benefits for fragile and immuno-compromised recipients. It was not until 2014 that the role of RAKT has found value thanks to the pioneering Vattikuti Urology Institute-Medanta collaboration that conceptualized and developed a new surgical technique for RAKT following the Idea, Development, Exploration, Assessment, Long-term follow-up recommendations for introducing surgical innovations into real-life practice. During the last years, mirroring the Vattikuti-Medanta technique, several centers developed RAKT program worldwide, providing strong evidence about the safety and the feasibility of this procedure. However, the majority of RAKT are still performed in the living donor setting, as an "eligible" procedure, while only a few centers have realized KT through a robotic approach in the challenging scenario of cadaver donation. In addition, despite the spread of minimally-invasive (predominantly robotic) surgery worldwide, many KTs are still performed in an

open fashion. Regardless of the type of incision employed by surgeons, open KT may lead to non-negligible risks of wound complications, especially among obese patients. Particularly, the assessment for KT should consider not only the added surgical technical challenges but also the higher risk of postoperative complications. In this context, robotic surgery could offer several benefits, including providing a better exposure of the surgical field and better instrument maneuverability, as well as the possibility to integrate other technological nuances, such as the use of intraoperative fluorescence vascular imaging with indocyanine green to assess the ureteral vascularization before the uretero-vesical anastomosis. Therefore, our review aims to report the more significant experiences regarding RAKT, focusing on the results and future perspectives.

Key Words: Deceased donors; Living donors; Kidney transplantation; Minimally invasive surgery; Robotics

Core Tip: Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease, providing a better survival rate and quality of life compared to dialysis. Despite the progress in the medical management of KT patients, from a purely surgical standpoint KT has resisted innovations during the last 50 years. Recently, robot-assisted KT (RAKT) has been proposed as an alternative approach to open surgery especially thanks to its potential benefits for fragile and immunocompromised recipients. Therefore, our review aims to report the more significant experiences regarding RAKT, focusing on the results and future perspectives.

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INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease, providing a better survival rate and quality of life compared to dialysis[1]. Despite the progress in the medical management of KT patients, from a purely surgical standpoint, KT has resisted innovations during the last 50 years[2]. Indeed, open surgery remains the gold standard approach for KT according to the latest European Association of Urology (EAU) guidelines[3]. Recently, minimally invasive surgery (MIS) [and in particular robot-assisted KT (RAKT)] has been proposed as an alternative approach to open surgery, particularly due to its potential benefits for fragile and immunocompromised recipients in terms of peri- and postoperative outcomes, length of hospital stay, postoperative pain, wound infection rate, and cosmetic results[4]. While the spread of a pure laparoscopic approach was limited by the complexity of the procedure and by long learning curves, robotic surgery in this setting helps overcome these limitations thanks to the three-dimensional vision, high magnification, elimination of hand tremor, and the opportunity to take advantage from the Endo-wrist technology.

In 2021, RAKT has become a reality at selected referral centers worldwide in the setting of KT from living donors (LD), with several reports showing favorable outcomes at a short- and mid-term follow-up. Yet, expanding the indications for RAKT from deceased donors (DD) is still challenging due to specific technical and logistical issues[5]. Herein we provide a comprehensive overview of the history of RAKT, focusing on the evolution of the techniques proposed by different groups worldwide, as well as on the specific challenges associated with the expansion of this approach for KT from DDs.

RAKT: A HISTORICAL PERSPECTIVE

During the last decades, selected referral centers have implemented MIS in the field of KT from LDs. As such, a pure laparoscopic approach and subsequently RAKT were performed as progressive steps to minimize the surgical morbidity of KT while ensuring favorable functional and perioperative outcomes. Rosales *et al*[6] reported their first experience with a pure laparoscopic approach, introducing the kidney through a Pfannenstiel incision and using topical ice slush and cold saline to keep a low graft temperature. KT was completed with a median overall operative time of 240 min (53 min for vascular sutures), with a blood loss of 300 cm^3 and a hospital stay of 14 d. No surgical complications were reported.

Then, Modi *et al*[7] published a larger experience of 72 patients treated with laparoscopic KT from LDs. The authors described the use of a Pfannenstiel incision and four left-sided abdominal ports, and compared laparoscopic KT to open KT. The authors found that laparoscopic KT was associated with a longer overall operative time [223.8 min *vs* 175.7 min (P = 0.07), respectively] and a similar estimated glomerular filtration rate (eGFR) value at 3, 6, 12, and 18 mo. The mean wound length was 5.5 and 17.8 cm (P = 0.0001) and the analgesic requirement was 1.4 and 3.2 mg morphine equivalent in first 24 h (P = 0.005) in the laparoscopic KT and open KT groups, respectively. While other groups have attempted to use a laparoscopic approach to perform KT from LDs, the spread of a pure laparoscopic approach among transplant centers was limited by several issues, such as the prolonged rewarming time (that could negatively impact graft outcomes), the complexity of surgical procedure, and the longer learning curve for surgeons, which represents a barrier to the widespread adoption of the technique across centers.

Therefore, thanks to the progressive spread of robotic surgery for the treatment of urological diseases [8], and given the persistence of the unmet clinical need of introducing MIS in the field of KT, the technique of RAKT was progressively codified and developed by selected centers in United States, India, and Europe[9-13] as shown in Table 1. In particular, Hoznek *et al*[14] performed the first KT assisted by a robot using an open incision and taking advantage of the robotic arms to perform the vascular anastomoses. For the first time, this experience demonstrated that vascular anastomoses for KT could be performed through the robotic platform.

While the first preliminary experience with a purely robotic KT was reported by Giulianotti *et al*[15], it was not until 2014 that the role of RAKT has been valued thanks to the pioneering Vattikuti Urology Institute-Medanta collaboration that conceptualized and developed a new surgical technique for RAKT following the Idea, Development, Exploration, Assessment, Long-term (IDEAL) follow-up recommendations for introducing surgical innovations into real-life practice[9-11,16].

Such a technique, described in detail in the following sections of the review, allowed to overcome the main limitations of a pure laparoscopic approach (*i.e.*, long exposure of the graft to high temperatures during vascular anastomosis; technical challenges associated with performance of anastomoses laparoscopically leading to long learning curves, *etc*). This experience provided robust evidence showing the advantages of the robotic technology for minimally-invasive KT, and the foundation for the spread of a structured step-by-step technique for robotic KT to other referral KT centers worldwide[9,10].

A further major step in this direction was made by the EAU Robotic Urology Section (ERUS), which created a specific working group to prospectively collect data from patients undergoing RAKT from LDs at several European Institutions[12]. Breda *et al*[12] reported the results of a large multicenter prospective study by the ERUS-RAKT working group, confirming the feasibility and safety of RAKT and highlighting the reproducibility of the procedure by multiple surgeons with experience in both open KT and robotic urologic surgery. In this study, excellent perioperative and functional outcomes of RAKT were reported. An updated analysis from the ERUS-RAKT prospective registry including almost 300 patients provided evidence on the favorable mid-term outcomes of RAKT from LDs[17]. Lastly, the feasibility and safety of RAKT from DDs were explored by the team of the University of Florence[5]. This preliminary experience raised the bar for RAKT and led to a renowned enthusiasm for this technique also in the broader setting of DDs. In fact, the University of Florence experience confirmed that RAKT can be successfully performed in the complex setting of DDs despite specific logistical and technical challenges. Of note, expanding the indications for RAKT to DDs is a key unmet need for the transplant community, aiming to increase the number of recipients who may benefit from MIS.

SURGICAL TECHNIQUE FOR RAKT

The Vattikuti-Medanta technique RAKT from LDs

IDEAL phase 0-1: The introduction of the Vattikuti-Medanta technique for RAKT with regional hypothermia following the IDEAL recommendations represents a milestone for the development and spread of RAKT worldwide[16]. The IDEAL phase 0-1 involved the preliminary ideation of a new procedure/technique that could provide benefits for patients. After this, authors could use animal models or cadavers to evaluate and modify the initial procedure to optimize results during real clinical cases[9].

First, to reduce the exposure of the graft to longer ischemia time, the authors tested a new technique to keep the graft temperature low within the pelvis, introducing 240-300 mL of ice slush in the abdomen during > 300 robot-assisted laparoscopic radical prostatectomies. In addition, based on previous experiences in robot-assisted laparoscopic radical prostatectomy and robotic partial nephrectomy, they employed the GelPOINT® device (Applied Medical Resources Corp, Rancho Santa Margarita, CA, United States) to provide an easy access to the intraperitoneal environment, allowing safe positioning of the graft into the surgical field, as well as of the ice slush to achieve renal hypothermia[18]. Later, to simulate a real procedure, four autotransplantations with such a robotic approach were performed in two cadavers. During the first procedure, the authors replicated the Giulianotti technique, highlighting relevant difficulties in performing the ureterovesical anastomosis without undocking the robot platform

Table 1 Overview of the main steps for development and implementation of robot-assisted kidney transplantation programs worldwide

Ref.	Topic
Hoznek *et al* [14], 2002	First procedure performed through da Vinci robot (Intuitive Surgical, Inc., Mountain View, California) to complete vascular dissection and anastomosis as well as ureterovesical anastomosis
Rosales *et al* [6], 2010	First laparoscopic transplantation of a kidney from a living, related donor, performed April 16, 2009
Boggi *et al* [13], 2011	First European robotic kidney transplantation
Giulianotti *et al*[15], 2010	First robotic kidney transplant in a morbidly obese patient
Menon *et al* [9], 2014	First standardization of RAKT according to IDEAL principals. Phase 0 (simulation) studies included the establishment of techniques for pelvic cooling, graft placement in a robotic prostatectomy model, and simulation of the robotic kidney transplantation procedure in a cadaveric model. Phase 1 (innovation) studies began in January 2013 and involved treatment of a highly selective small group of patients (n = 7), using the principles utilized in the phase 0 studies, at a tertiary referral center
Menon *et al* [10], 2014	Prospective study of 50 consecutive patients who underwent live-donor RAKT at Medanta Hospital following a 3-yr planning/simulation phase at the Vattikuti Urology Institute according to IDEAL principals
Sood *et al*[11], 2014	Monitoring patient safety during the learning phase of RAKT and determine when it could be considered learned using the techniques of statistical process control
Breda *et al* [12], 2018	First multicenter prospective observational study performed by the ERUS RAKT working group
Vignolini *et al* [5], 2019	Report of the development of the first RAKT program from deceased donors
Territo *et al* [29], 2018	Update of the multicenter prospective observational study performed by the ERUS RAKT working group
Campi *et al* [26], 2019	Report of a monocentric RAKT experience with extraperitonelization of the graft according to the Vattikuti-Medanta technique, allowing a safe access for diagnostic and therapeutic percutaneous procedures during the postoperative period
Gallioli *et al* [19], 2020	Analyse of the learning curve for RAKT. At least 35 cases are needed to achieve reproducibility in terms of timing, complications, and functional results
Vignolini *et al* [25], 2019	First preliminary experience with 6 patients operated from January 2017 to April 2018 using indocyanine green fluorescence videography to assess graft and ureteral reperfusion
Musquera *et al*[17], 2021	The results of the RAKT experience performed in 10 European centers by members of the ERUS-RAKT group

ERUS: European Robotic Urology Section; IDEAL: Idea, Development, Exploration, Assessment, Long-term; RAKT: Robot-assisted kidney transplantation.

[15]. As such, for the following procedures, the cadaver was placed in a lithotomic position with a 15°-20° Trendelenburg tilt, and the robot was positioned between the patient's legs mirroring the configuration for robot-assisted laparoscopic radical prostatectomy[9].

IDEAL phase 2A: Patient and trocar positioning: The ideal phase 2A aimed to evaluate the safety and the efficacy of the new procedure in a few patients in a small prospective study[16]. The absolute contraindications were the presence of significant atherosclerosis plaques at the level of the iliac vessels, prior bilateral KTs, previous major abdominal surgery, second transplant, simultaneous dual or multiple organ transplant, and second transplantation. After confirming the feasibility of RAKT in a cadaver model with the introduction of specific technical nuances, Menon *et al*[10] reported their first experience with RAKT from LDs in carefully selected patients.

In particular, the recipient was positioned as previously described[9]. A 4-5 cm periumbilical incision was performed for the GelPOINT® device. The port configuration included: (1) One 12-mm port for the camera and one 8-mm port for the assistant, placed within the GelPOINT device (to minimize the abdominal incisions); (2) Three 8-mm ports for the robotic arms; and (3) One 12-mm assistant port placed in the right iliac fossa. The da Vinci robotic platform (Intuitive Surgical, Sunnyvale, CA, United States) was docked between the patient's legs. After skeletonization of external iliac vessels, the surgeon created an extraperitoneal pouch over the psoas muscle to allocate the graft after completion of the vascular anastomoses. The graft was placed in a gauze jacket filled with ice and then introduced into the pelvis using the GelPOINT device. Subsequently, 180-240 mL of ice slush were introduced in the pelvis through modified Toomey syringes to achieve adequate regional hypothermia.

A distal bulldog clamp followed by a proximal clamp was placed on the external iliac vein. Then, a longitudinal venotomy with cold scissors was performed, and an end-to-side anastomosis between the graft renal vein and the external iliac vein was completed in an end-to-side fashion using a running ePTFE suture (Gore-Tex CV-6; W. L. Gore & Associates Inc, Flagstaff, AZ, United States)[10]. Before the

suture had been finished, the lumen of the external iliac vein was flushed with heparinized solution through a 4.8 Fr ureteric catheter introduced through the assistant port. In the end, the graft vein was clamped, and the previously placed bulldog clamps were released and positioned proximally and then distally on the external iliac artery. Initially, the arteriotomy was made with cold scissors; thereafter, a laparoscopic aortic punch (Teleflex-Medical Inc, Research Triangle Park, NC, United States) was employed to create a circular hole. A continuous end-to-side anastomosis was realized between the external iliac and the graft artery using the Gore-Tex CV-6 suture.

At completion of the arterial anastomosis, the graft renal vessels were clamped and the external iliac artery declamped. If no signs of bleeding were observed, all clamps were removed to revascularize the graft. The graft was inspected for color, turgor, and on-table diuresis, and gently placed in the extraperitoneal pouch (closed by approximating the previously prepared peritoneal flaps) taking care not to stretch the vascular anastomoses. Lastly, the uretero-vesical anastomosis was performed according to a modified Lich-Gregoire technique using a 4-0 polydiaxone suture (Ethicon Inc, Cincinnati, OH, United States). A 6 Fr, 16-cm double-J stent, introduced through the assistant port, was placed into the ureter before completing the anastomosis. During this phase, developing an adequate detrusor tunnel was relevant to provide an anti-reflux mechanism. The stent was generally removed 3 wk after RAKT in the outpatient clinic.

ERUS-RAKT technique for RAKT from LDs

In 2018 the ERUS RAKT working group reported their first multicenter prospective study on RAKT from LD enrolling 120 enrolled patients[12]. All European centers followed a standardized operative protocol based on the Vattikuti-Medanta experience with the introduction of a few technical nuances. The patient was placed in a lithotomy position with a 20°-30° Trendelenburg tilt. After the introduction of the GelPOINT through a linear periumbilical incision of 6 cm, the other four ports were placed, in the same position reported by Menon *et al*[10]. However, in 4 female recipients, the introduction of the graft was provided through a transvaginal GelPOINT. In all cases, a 2 cm incision of the GelPOINT cap was made to guarantee the introduction of ice slush with a modified Toomey tip syringe. After placing the clamp on the external iliac vein and the realization of the venotomy using Potts scissors, an end-to-side anastomosis between the graft vein and the external iliac vein was made with a 6/0 Gore-Tex® CV-6 TTc-9 or THc-12 needle. The suture was tied to secure the posterior wall of the anastomosis at the proximal angle and then it was completed until the distal to avoid stenosis. For the artery, the bulldog clamps placement on the external iliac artery were finalized to perform a preliminary incision with cold scissors, completed using a laparoscopic aortic punch. In the beginning, both vascular anastomoses require passing the needle in the external iliac vessel in an outside-inside direction and then inside-outside through the graft vessel. However, while during the venous anastomosis the knot was tied immediately, and only then the needle was passed outside-inside through the renal vein to start the running suture, during the artery anastomosis, the knot was created to a loop left outside after the passage of the needle through the graft vessel outside-inside. Finally, the vesicoureteral anastomosis was realized following the principles of the Lich-Gregoir technique over a pre-placed 4.8-Fr, 12-cm double-J stent[12].

During the procedure, an adequate management of vascular anastomosis was mandatory to reduce the risk of severe postoperative complications. In particular, avoiding intimal injury through a careful manipulation of graft vessels was a key step during RAKT. In addition, as suggested by Gallioli *et al* [19], a complete learning curve could be useful to achieve reproducible intra- and postoperative outcomes. Finally, the exclusion criteria to perform RAKT have been modified during the last years, but the main issues are currently represented by severe calcification at the level of the iliac vessels and previous bilateral KT[17].

Technical nuances for RAKT from DD: The University of Florence experience

After the development of RAKT from LD, some centers tried to widen the indications for RAKT, including grafts from DDs[20]. The main contraindications in these series were: (1) The presence of atherosclerotic plaques at the level of the iliac vessels; (2) Previous multiple major abdominal surgery; (3) Absolute contraindications for robotic surgery; and (4) Previous bilateral KT. In this context, the transplant multidisciplinary team must deal with specific issues from both organizational and technical standpoints due to the "emergency scenario" and the time-dependent nature of the intervention. To the best of our knowledge, the largest experience of RAKT from DD was reported by our group proposing specific technical nuances to improve surgical technique while ensuring maximal patient and graft safety[5,19].

Bench surgery

The harvesting procedure is performed according to established protocol[21]. In case of grafts from donors after circulatory death, a hypothermic machine perfusion device is employed for graft preservation before RAKT. During the bench surgery, the graft is perfused with Celsior® solution. Then, the anterior margin of the vein is shaped by cutting a small part of venous tissue to provide better visualization of its posterior margin. In addition, if a right-sided graft is available, increasing the length of the

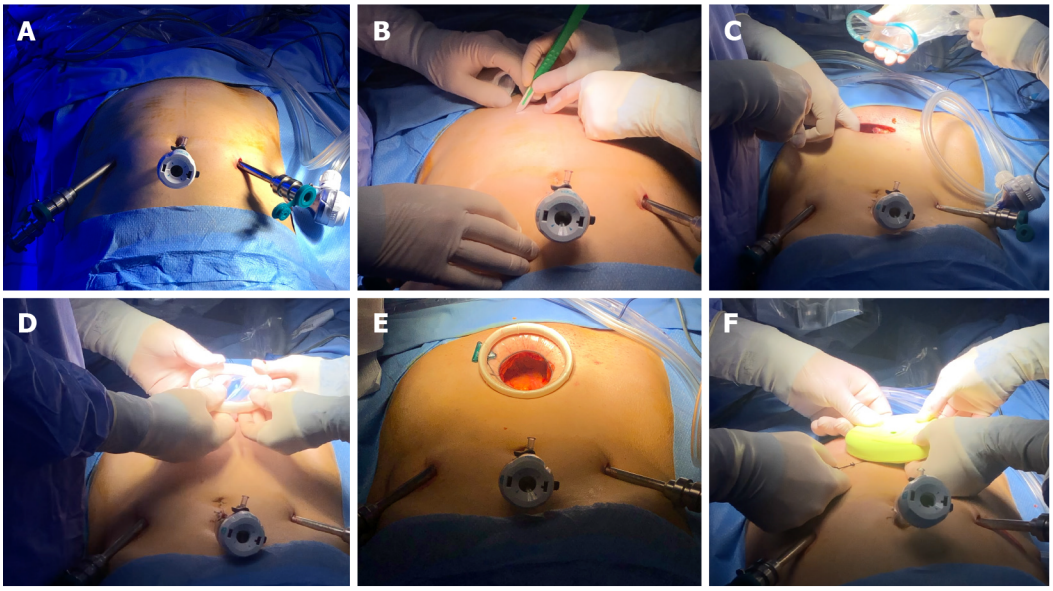

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Figure 1 Overview of the main steps for Alexis® Wound Protectors/Retractors placement through Pfannestiel incision according to the University of Florence technique for robot-assisted kidney transplantation. A: After ports placement; B and C: A Pfannestiel incision is performed; D-F: The Alexis® device is placed through Pfannestiel incision.

right vein using an inferior vena cava patch is always considered; yet, RAKT using right-sided grafts from DDs appears feasible even without a caval patch thanks to the advantages of the robotic platform, as demonstrated for RAKT in LD setting[22].

Of note, if severe atherosclerotic plaques are observed at the level of the aortic Carrel's patch, the surgeon may remove them, realizing the arterial anastomosis without the patch. In case of multiple vessels, the surgeon usually reconstructs them to perform a single anastomosis (*i.e.*, using a side-to-side anastomosis between two renal arteries in a "pantaloon" fashion), as shown in several experiences[23, 24]; alternatively, a small polar artery can be anastomosed to the inferior epigastric artery with a separate arterial anastomosis[10]. When the kidney is prepared, it is placed into a gauze jacket filled with ice to provide less traumatic handling and to maintain graft hypothermia. Finally, a 5-Fr, 12-cm double-J stent is routinely pre-placed into the ureter during bench surgery to facilitate the subsequent uretero-vesical anastomosis.

Surgical technique for RAKT from DDs

At our institution, all RAKTs followed the principles of the Vattikuti-Medanta technique with the progressive introduction of specific nuances during the learning curve[10]. Specifically: (1) A Pfannestiel rather than a periumbilical incision is used for the GelPOINT® (or the Alexis® Wound Protectors/Retractors, Applied Medical Resources Corp, United States) placement improving the aesthetic results and providing closer access to the iliac vessels (Figure 1); (2) The GelPOINT® device is placed only after adequate preparation of iliac vessels, bladder, and extraperitoneal pouch to reduce the potential risk of bladder injury; (3) The venotomy is realized with curve scissors and then a two-continuous suture is completed for the posterior and anterior plate of the venous anastomosis. First, the anterior part is performed from 12 to 6 o'clock position knotting at 6 o'clock, and then the posterior one is completed from 6 to 12 o'clock position; and (4) The arteriotomy is realized with cold scissors without the use of a laparoscopic aortic punch. In addition, considering the higher risk of atherosclerotic plaques at the level of the external iliac arteries for recipient in DD setting, the anastomosis is performed using two running sutures (in Gore-Tex 5/0 instead of 6/0). After the realization of the posterior plate using a running suture from 12 to 6 o'clock position, without knotting at the end, the anterior wall is completed with another running suture from 6 to 12 o'clock position. Then, the two ends are tied together at 6 o'clock. This technique establishes the correct tension of the anastomosis considering the characteristics of both the graft and iliac vessels. If the Carrel's patch is suitable, it can be removed, mirroring the anastomosis during RAKT in LD setting.

Regarding the assessment of graft and ureter reperfusion, our group proposed the use of intraoperative indocyanine green fluorescence videography to complement the intraoperative visual and ultrasound-based evaluation of the graft after completion of the vascular anastomoses[25]. In any case, the graft is allocated in the previously prepared extraperitoneal pouch by reapproximating the two peritoneal flaps prepared at the beginning of the procedure (Figure 2): This step has been shown to offer a safe access for diagnostic and therapeutic percutaneous procedures during the postoperative period,

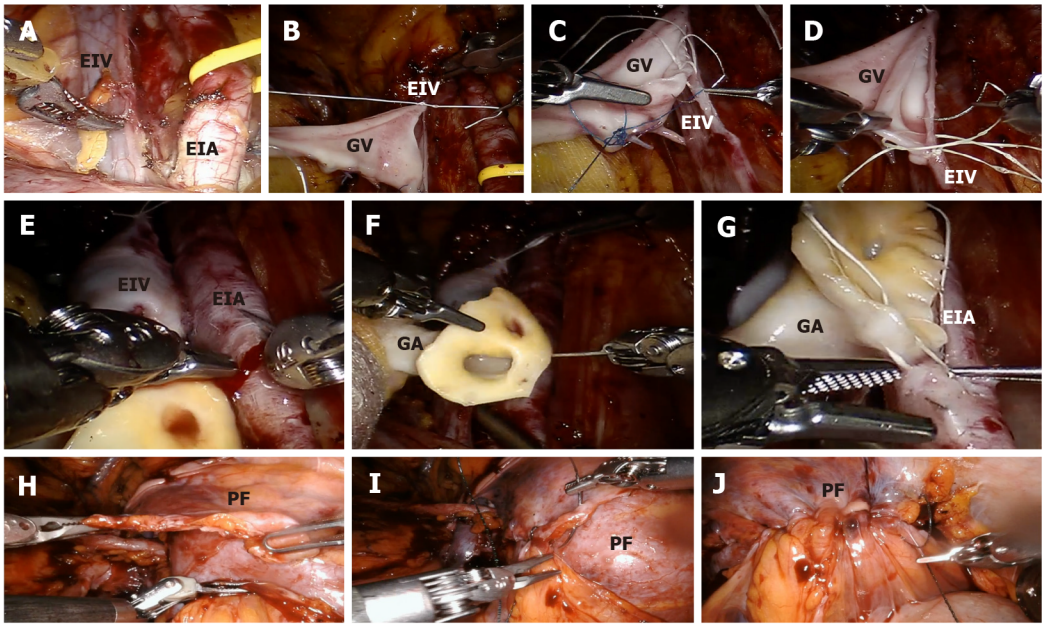

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Figure 2 Intraoperative snapshots showing the main phases of isolation of the vascular and uretero-vesical anastomoses during robot-assisted kidney transplantation from deceased donors. A: After skeletonization of external iliac vessels, the surgeon created an extraperitoneal pouch over the psoas muscle to allocate the graft after completion of the vascular anastomoses. A distal bulldog clamp followed by a proximal clamp was placed on the external iliac vein; B-D: A longitudinal venotomy with cold scissors was performed, and an end-to-side anastomosis between the graft renal vein and the external iliac vein was completed in an end-to-side fashion using a running suture; E: The previously placed bulldog clamps were released and positioned proximally and then distally on the external iliac artery. After the realization of the arteriotomy; F and G: A continuous end-to-side anastomosis was performed between the external iliac and the graft artery. Subsequently, the uretero-vesical anastomosis was performed according to a modified Lich-Gregoire technique; H-J: The graft is allocated in the previously prepared extraperitoneal pouch by reapproximating the two peritoneal flaps prepared at the beginning of the procedure. EIA: External iliac artery; EIV: External iliac vein; GA: Graft artery; GV: Graft vein; PF: Peritoneal flap.

as reported by Campi *et al*[26] without any type of postprocedural complications.

OUTCOMES OF RAKT FROM LD SETTING

During the last 10 years, several studies have been reported showing the feasibility and safety of RAKT in the LD setting. Menon *et al*[10] published their experience of the first 25 RAKTs, reporting a mean console, warm ischemia, arterial, and venous anastomotic times of 135 min, 2.4 min, 12 min, and 13.4 min, respectively. In addition, no delayed graft function (DGF) or early surgical postoperative complications were observed, while at 6 mo of follow-up two patients underwent re-exploration, and one patient died of congestive heart failure. Subsequently, Sood *et al*[27] published a preliminary comparison of 50 and 175 patients who had undergone RAKT and open KT, respectively. No difference in terms of early postoperative functional outcomes was reported (median creatinine 1.2 and 1.3 mg/dL, in RAKT and open KT group, respectively). No DGF was observed, while one patient in the RAKT group and four in the open KT underwent post-transplant dialysis. In addition, during the early follow-up, three deaths were observed (one in the RAKT group and two in the open KT, respectively). Recently, the final results of this experience (IDEAL phase 2B) have been published[28]. Particularly, 126 patients undergone RAKT and 378 open KT (1:3 matched cohort) were included, reporting a lower rate of wound infections (0% *vs* 4%, $P = 0.023$), symptomatic lymphoceles at 36 mo (0% *vs* 7%, $P = 0.003$), DGF (0% *vs* 2.3%, $P = 0.081$), and reduced postoperative pain with the robotic approach. At a median follow-up of 24.7 and 23.2 mo, for RAKT and open KT group respectively, no differences in terms of graft survival were observed {95.2% [95% confidence interval (CI): 86-99.3] *vs* 96.3% (95%CI: 93.1-99.4), $P = 0.266$}.

Another relevant experience was reported by Breda *et al*[12], presenting the preliminary results of ERUS RAKT working group from 120 patients who underwent RAKT. In this multicenter prospective observational study, the median operative and vascular suture time was 250 and 38 min, respectively. The median estimated blood loss was 150 mL and no major intraoperative complications were reported. Two patients needed open conversion and in five cases (4.2%), surgical management was requested for intraperitoneal hematoma. The median eGFR was 58.0 mL/min on postoperative day 30. Territo *et al*[29] updated this study, reporting the results of 291 RAKTs from LD and highlighting a shorter operative time after the first 120 cases (265 min *vs* 230 min, $P = 0.005$). The mean overall surgical and re-warming

time was 244 (70.5) and 53.16 (15.27) min, respectively. In all, five (2%) were lost due to thrombosis and one due to acute rejection. Two patients had arterial stenosis, three had incisional hernias, six had ureteric stenosis, and nine had lymphoceles. Finally, Musquera *et al*[17] described the mid-terms outcomes of 291 RAKT from LDs procedures. Overall, 22 cases of early major postoperative complications (defined as Clavien-Dindo Complication > 2) were recorded, while after more than 90 d from RAKT, 16 cases of major postoperative complications were observed, including one patient who died for pulmonary thromboembolism, two cases of arterial stenosis, three of incisional hernias, two of ureteric stenosis, one of angioplasty, and seven of lymphoceles. However, regarding the functional outcomes, the authors reported a progressive improvement of the eGFR (60 mL/min/1.73 m^2 at last follow-up). The median hospital stay ranged between 7 and 14 d[12,17], but it could be influenced by several items, such as hospital policies and patient-related factors. Despite the favorable results, several issues still limit the spread of RAKT from living (and deceased) donors worldwide, including the technical and logistical complexity of the procedure, as well as limited evidence regarding its learning curve. Sood *et al*[11] analyzed the learning curve of RAKTs with regional hypothermia from LDs, stratifying the recipients into three groups according to the robotic and open KT experience of the surgeons. Of note, they observed that the learning curve for RAKT was minimal for surgeons who had prior robotic and KT experience. These results were confirmed by Ahlawat *et al*[30] who described a short learning curve in RAKT for experienced surgeons in KT and robotic surgery, achieving optimal skills within ten cases. However, the authors suggested that further improvements could be observed for the first 20-25 cases.

Later, Gallioli *et al*[19] published the results of a multicenter study, including the five highest-volume centers of the ERUS RAKT working group. They demonstrated that the Trifecta, defined as no major intra/postoperative complications, no delayed graft function, and rewarming time < mean + 2 SD (= 48.6 min), was achieved in 75% of cases after a minimum of 35 procedures. Notably, all graft losses took place during the first ten RAKTs, raising concerns regarding potential technical errors during the very first cases of the robotic series, and highlighting the need of proper modular training for surgeons wishing to start their experience with RAKT. In brief, the authors suggested that at least 35 procedures could be necessary to achieve reproducibility in surgical time, complications rate, and functional results. In conclusion, while further prospective studies are needed to define the differences in the learning curve of open and robotic KT (adjusting for all patient- and provider-specific factors), centers that are interested in developing RAKT programs may benefit from existing courses on RAKT (*i.e.*, Orsi Academy, Belgium) and from the expertise gained by multicenter collaborations such as the ERUS-RAKT working group. Standardized proficiency-based training curricula are warranted.

RAKT FROM DECEASED-DONORS: CHALLENGES AND PRELIMINARY RESULTS

Since its inception, RAKTs has been primarily developed as an "elective" procedure in the LD setting. Considering the limited available evidence, as well as several logistical challenges, many teams might have concerns regarding the feasibility and safety of RAKT in a more complex scenario, such as that of DDs. Indeed, RAKT from DDs is a challenging procedure, demanding great efforts from organizational standpoints and with only few preliminary experiences worldwide[15,17,19,31-33]. Particularly, Vignolini *et al*[5] published the results of their structured RAKT program, based on a previous solid experience in open KT and RAKT from LDs.

The authors defined 5 essential phases to determine the technical and logistical feasibility of performing RAKT in case of DDs. Initially, the availability of the dedicated surgical team must be ensure, while the recipient is admitted to the Nephrology Unit to perform careful anesthesiologic and preoperative work-up. Then, the availability of the robotic operating room must be verified, aiming to start RAKT within 16 h from the organ procurement surgery, in order to keep the overall ischemia time < 24 h[34]. Finally, a careful graft evaluation on the bench is critical to individualize the indication for RAKT (*i.e.*, open KT is preferred in case of multiple vessels which cannot be reconstructed to perform a single vascular robotic anastomosis).

Despite these specific challenges, preliminary experiences coming from selected referral centers worldwide provided the proof of the concept that RAKT (in experienced hands) can be safely perform from DDs, with favorable short- and mid-term outcomes, even during the pandemic[5,19,35,36]. To the best of our knowledge, our experience represents the largest series so far on RAKT from unselected DDs [19,37]. At a median follow-up of 16 mo [interquartile range (IQR): 7-22], recipients showed good functional results with a median eGFR of 57 mL/min/1.73 m^2 (IQR: 45-76); only two patients needed dialysis treatment at the last follow-up. The safety profile of RAKT from DDs in terms of major (Clavien-Dindo grade ≥ 3) surgical complications was also promising. These favorable preliminary findings were confirmed by an updated analysis comparing RAKT and open KT from DDs at our center [37]. Overall, there were no significant differences between the RAKT and open KT cohorts in terms of baseline donor-, graft- and recipient-related characteristics, except for a significantly higher proportion of pre-emptive recipients in the RAKT cohort (40.0% *vs* 4.9%, $P = 0.0001$), a significantly lower American Society of Anesthesiologists score among patients undergoing RAKT (2 *vs* 3, $P = 0.033$). The re-warming and the vascular anastomosis time did not significantly differ between RAKT and open KT (47 min *vs* 28

min, P = 0.2; 15 min *vs* 18 min, P = 0.2, respectively).

There were no significant differences between RAKT and open KT in terms of median hospital stay (13 d) as well as the major postoperative complication rate. However, the RAKT group was associated with a significantly lower blood transfusion rate (14.3% *vs* 22.2%, P = 0.008). At the last follow-up, no differences were observed between the two groups in terms of mid-term graft function. Despite lack of randomization, our experience provides further evidence supporting the non-inferiority of RAKT as compared to open KT from DDs, provided careful patient selection, adequate surgical training, and availability of a framework allowing performance of RAKT even in "non-elective" conditions (*i.e.*, weekends, night, *etc*). However, our technique is not devoid of limitations. In particular, all candidates for RAKT are evaluated with a computed tomography (CT) scan before surgery to identify atherosclerotic plaques at the level of the external iliac vessels; that remains an absolute contraindication for the procedure. In addition, in case of atherosclerotic lesions of the renal vessels, the characteristics of polypropylene needle could provide advantages compared to Gore-Tex, but it is not suitable for robotic surgery. For these reasons, a carefully preoperative evaluation of patients is needed to tailor the surgical approach taking into consideration the patients' characteristics, especially when the procedure will be carried out as an emergency.

DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES

Despite the development and spread of minimally invasive (predominantly robotic) surgery worldwide, many KTs are still performed in an open fashion. Regardless of the type of incision employed by surgeons, open KT may lead to non-negligible risks of wound complications[38], especially among obese patients. In addition, considering the fragility of KT recipients, there is certainly a window of opportunity for new surgical techniques to minimize the morbidity of KT allowing faster recover and better patient-reported outcomes[39]. As such, RAKT has the potential to reduce specific KT-related surgical complications, such as wound dehiscence/infection, symptomatic lymphoceles, postoperative pain, as well as to minimize the length of hospitalization. RAKT might also improve the cosmetic result of KT. All these potential advantages of RAKT are most promising for overweight/obese recipients[40], who represent a patient population at a higher risk of postoperative adverse events. As universally known, the obese "pandemic" is nowadays spread in developed countries, affecting a large part of the population. Although obesity is not considered an absolute contraindication for KT, European and United States data have shown that this condition is associated with a reduced chance of receiving transplantation[12]. The assessment of obese recipients for KT should consider not only the added surgical technical challenges but also the higher risk of postoperative complications, while remaining the best treatment option[41,42]. In this context, robotic surgery could offer several benefits, providing a better exposure of the surgical field and a better instrument maneuverability.

However, the optimal indications as well as the ideal body mass index (BMI) to perform RAKT is still under debate. Recently, some experiences regarding the outcomes for obese patients and morbidity obese ones (BMI ≥ 30 and 35 kg/m^2, respectively) have been reported, highlighting benefits in terms of postoperative wound infection if compared to open KT[40-43]. In addition, Spaggiari *et al*[44] have recently published the results about the simultaneous realization of RAKT and sleeve-gastrectomy, improving the patients' compliance and outcomes. The available evidence suggests potential advantages, even in terms of learning curve. As previously reported, a surgeon's background has a limited impact on his ability to perform RAKT; what really matter is the previous surgeons' exposure to robotic surgery and open KT[11]. However, considering the major exposure to minimally invasive surgery and expertise in ureteral diseases, urologists may have advantages, if compared to other specialties (*e.g.*, general surgeons, transplant surgeons), as well as the skills to manage significant postoperative complications (*e.g.*, ureteral stricture).

On this regard, while Musquera *et al*[17] reported two patients treated through open ureteral reimplantation for stenosis, Campi *et al*[37] reported two cases of endoscopic management for ureteral complications in a DD setting. Therefore, the best surgical approach to treat urological complications should be evaluated in light of patients' and related-problems characteristics (endoscopic, minimally invasive surgery, or an open approach). Despite the fact that the development of a RAKT program from DD could be extremely challenging from both a technical and organizational standpoint, Campi *et al*[37] proposed the realization of a dedicated pathway, avoiding any impact on donors' management from both a clinical and organizational standpoint, even in the DD setting. To move the field forward, specific challenges of RAKT (especially in the DD setting) must be overcome. These include the need of a dedicated, highly qualified surgical team (trained in robotic surgery), and higher direct costs as compared to open KT. While an estimated increased cost of 15000 USD per RAKT has been reported if compared to open approach[31], the higher availability of platforms will hopefully reduce the costs of robotic technology, mitigating the financial downside of RAKT in the future. This might potentially allow a more significant penetrance of the robotic technology among KT centers in Europe and worldwide.

CONCLUSION

In conclusion, the vast majority of RAKTs so far have been performed using grafts from LDs in carefully selected recipients and have been shown to achieve optimal early and mid-term outcomes (which are at least non-inferior to those of open KT based on the current literature). Yet, to date, no randomized controlled trial has been conducted comparing RAKT to the gold-standard open approach. As such, several clinical and research questions (such as the reproducibility of RAKT outside referral high-volume centers) remain unanswered. In addition, only a few preliminary experiences have been reported on the outcomes of RAKT from DDs. In this scenario, critical steps need to be taken to implement the technique and the logistics aiming to increase the number of recipients who may benefit from minimally invasive surgery and "making RAKT ready for the prime time". Large randomized prospective multicenter studies are eagerly warranted to address these unmet clinical needs, defining the best indications and limits of robotic surgery for KT.

FOOTNOTES

Author contributions: Li Marzi V and Campi R conceptualized and designed the study; Gallo ML collected data; Pecoraro A and Campi R wrote the manuscript and made the figures and table; Serni S, Vignolini G, Li Marzi V, Peris A, and Caroti L revised the manuscript for important intellectual content.

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REFERENCES

1 **Hariharan S**, Israni AK, Danovitch G. Long-Term Survival after Kidney Transplantation. *N Engl J Med* 2021; **385**: 729-743 [PMID: 34407344 DOI: 10.1056/NEJMra2014530]
2 **Alcaraz A**, Peri L, Izquierdo L, Musquera M. Is Robotic Kidney Transplant the Near Future? *Eur Urol* 2017; **72**: 218-219 [PMID: 28343721 DOI: 10.1016/j.eururo.2017.03.018]
3 **Breda A**, Budde K, Figueiredo A, Lledó García E, Olsburgh J, Regele H, Boissier R, Hevia V, Rodríguez Faba O, Zakri RH. EAU Guidelines on Renal Transplantation. Proceedings of the EAU Annual Congress; 2021 Jul 8-12; Leeds, Milan. Arnhem: EAU Guidelines Office, 2021: 484-505
4 **Herrell SD**, Smith JA Jr. Laparoscopic and robotic radical prostatectomy: what are the real advantages? *BJU Int* 2005; **95**: 3-4 [PMID: 15638882 DOI: 10.1111/j.1464-410X.2005.05235.x]
5 **Vignolini G**, Campi R, Sessa F, Greco I, Larti A, Giancane S, Sebastianelli A, Gacci M, Peris A, Li Marzi V, Breda A, Siena G, Serni S. Development of a robot-assisted kidney transplantation programme from deceased donors in a referral academic centre: technical nuances and preliminary results. *BJU Int* 2019; **123**: 474-484 [PMID: 30311992 DOI: 10.1111/bju.14588]
6 **Rosales A**, Salvador JT, Urdaneta G, Patiño D, Montlleó M, Esquena S, Caffaratti J, Ponce de León J, Guirado L, Villavicencio H. Laparoscopic kidney transplantation. *Eur Urol* 2010; **57**: 164-167 [PMID: 19592155 DOI: 10.1016/j.eururo.2009.06.035]
7 **Modi P**, Pal B, Modi J, Singla S, Patel C, Patel R, Padhy S, T K, Patel K, Rizvi J, Sharma S, Sharma V, Modi M, Shah VR, Trivedi HL. Retroperitoneoscopic living-donor nephrectomy and laparoscopic kidney transplantation: experience of initial 72 cases. *Transplantation* 2013; **95**: 100-105 [PMID: 23202533 DOI: 10.1097/TP.0b013e3182795bee]
8 **Rassweiler JJ**, Autorino R, Klein J, Mottrie A, Goezen AS, Stolzenburg JU, Rha KH, Schurr M, Kaouk J, Patel V, Dasgupta P, Liatsikos E. Future of robotic surgery in urology. *BJU Int* 2017; **120**: 822-841 [PMID: 28319324 DOI: 10.1111/bju.13851]
9 **Menon M**, Abaza R, Sood A, Ahlawat R, Ghani KR, Jeong W, Kher V, Kumar RK, Bhandari M. Robotic kidney transplantation with regional hypothermia: evolution of a novel procedure utilizing the IDEAL guidelines (IDEAL phase 0

and 1). *Eur Urol* 2014; **65**: 1001-1009 [PMID: 24287316 DOI: 10.1016/j.eururo.2013.11.011]
10 **Menon M**, Sood A, Bhandari M, Kher V, Ghosh P, Abaza R, Jeong W, Ghani KR, Kumar RK, Modi P, Ahlawat R. Robotic kidney transplantation with regional hypothermia: a step-by-step description of the Vattikuti Urology Institute-Medanta technique (IDEAL phase 2a). *Eur Urol* 2014; **65**: 991-1000 [PMID: 24388099 DOI: 10.1016/j.eururo.2013.12.006]
11 **Sood A**, Ghani KR, Ahlawat R, Modi P, Abaza R, Jeong W, Sammon JD, Diaz M, Kher V, Menon M, Bhandari M. Application of the statistical process control method for prospective patient safety monitoring during the learning phase: robotic kidney transplantation with regional hypothermia (IDEAL phase 2a-b). *Eur Urol* 2014; **66**: 371-378 [PMID: 24631408 DOI: 10.1016/j.eururo.2014.02.055]
12 **Breda A**, Territo A, Gausa L, Tuğcu V, Alcaraz A, Musquera M, Decaestecker K, Desender L, Stockle M, Janssen M, Fornara P, Mohammed N, Siena G, Serni S, Guirado L, Facundo C, Doumerc N. Robot-assisted Kidney Transplantation: The European Experience. *Eur Urol* 2018; **73**: 273-281 [PMID: 28916408 DOI: 10.1016/j.eururo.2017.08.028]
13 **Boggi U**, Vistoli F, Signori S, D'Imporzano S, Amorese G, Consani G, Guarracino F, Melfi F, Mussi A, Mosca F. Robotic renal transplantation: first European case. *Transpl Int* 2011; **24**: 213-218 [PMID: 21091963 DOI: 10.1111/j.1432-2277.2010.01191.x]
14 **Hoznek A**, Zaki SK, Samadi DB, Salomon L, Lobontiu A, Lang P, Abbou CC. Robotic assisted kidney transplantation: an initial experience. *J Urol* 2002; **167**: 1604-1606 [PMID: 11912372]
15 **Giulianotti P**, Gorodner V, Sbrana F, Tzvetanov I, Jeon H, Bianco F, Kinzer K, Oberholzer J, Benedetti E. Robotic transabdominal kidney transplantation in a morbidly obese patient. *Am J Transplant* 2010; **10**: 1478-1482 [PMID: 20486912 DOI: 10.1111/j.1600-6143.2010.03116.x]
16 **McCulloch P**, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, Nicholl J; Balliol Collaboration, Aronson JK, Barkun JS, Blazeby JM, Boutron IC, Campbell WB, Clavien PA, Cook JA, Ergina PL, Feldman LS, Flum DR, Maddern GJ, Nicholl J, Reeves BC, Seiler CM, Strasberg SM, Meakins JL, Ashby D, Black N, Bunker J, Burton M, Campbell M, Chalkidou K, Chalmers I, de Leval M, Deeks J, Ergina PL, Grant A, Gray M, Greenhalgh R, Jenicek M, Kehoe S, Lilford R, Littlejohns P, Loke Y, Madhock R, McPherson K, Meakins J, Rothwell P, Summerskill B, Taggart D, Tekkis P, Thompson M, Treasure T, Trohler U, Vandenbroucke J. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009; **374**: 1105-1112 [PMID: 19782876 DOI: 10.1016/S0140-6736(09)61116-8]
17 **Musquera M**, Peri L, Ajami T, Campi R, Tugcu V, Decaestecker K, Stockle M, Fornara P, Doumerc N, Vigues F, Barod R, Desender L, Territo A, Serni S, Vignolini G, Sahin S, Zeuschner P, Banga N, Breda A, Alcaraz A. Robot-assisted kidney transplantation: update from the European Robotic Urology Section (ERUS) series. *BJU Int* 2021; **127**: 222-228 [PMID: 32770633 DOI: 10.1111/bju.15199]
18 **Rogers CG**, Ghani KR, Kumar RK, Jeong W, Menon M. Robotic partial nephrectomy with cold ischemia and on-clamp tumor extraction: recapitulating the open approach. *Eur Urol* 2013; **63**: 573-578 [PMID: 23183196 DOI: 10.1016/j.eururo.2012.11.029]
19 **Gallioli A**, Territo A, Boissier R, Campi R, Vignolini G, Musquera M, Alcaraz A, Decaestecker K, Tugcu V, Vanacore D, Serni S, Breda A. Learning Curve in Robot-assisted Kidney Transplantation: Results from the European Robotic Urological Society Working Group. *Eur Urol* 2020; **78**: 239-247 [PMID: 31928760 DOI: 10.1016/j.eururo.2019.12.008]
20 **Vignolini G**, Greco I, Sessa F, Gemma L, Pecoraro A, Barzaghi P, Grosso A, Corti F, Mormile N, Martiriggiano M, Berni A, Firenzuoli N, Gacci M, Giancane S, Sebastianelli A, Li Marzi V, Serni S, Campi R. The University of Florence Technique for Robot-Assisted Kidney Transplantation: 3-Year Experience. *Front Surg* 2020; **7**: 583798 [PMID: 33262999 DOI: 10.3389/fsurg.2020.583798]
21 **Peris A**, Lazzeri C, Cianchi G, Bonizzoli M, Batacchi S, Franci A, Rugna M, De Vito L, Ticali PF, Li Marzi V, Migliaccio ML. Implementing a donation after circulatory death program in a setting of donation after brain death activity. *Minerva Anestesiol* 2018; **84**: 1387-1392 [PMID: 29808973 DOI: 10.23736/S0375-9393.18.12635-6]
22 **Serni S**, Pecoraro A, Sessa F, Gemma L, Greco I, Barzaghi P, Grosso AA, Corti F, Mormile N, Spatafora P, Caroassai S, Berni A, Gacci M, Giancane S, Tuccio A, Sebastianelli A, Li Marzi V, Vignolini G, Campi R. Robot-Assisted Laparoscopic Living Donor Nephrectomy: The University of Florence Technique. *Front Surg* 2020; **7**: 588215 [PMID: 33521044 DOI: 10.3389/fsurg.2020.588215]
23 **Siena G**, Campi R, Decaestecker K, Tuğcu V, Sahin S, Alcaraz A, Musquera M, Territo A, Gausa L, Randon C, Stockle M, Janssen M, Fornara P, Mohammed N, Guirado L, Facundo C, Doumerc N, Vignolini G, Breda A, Serni S. Robot-assisted Kidney Transplantation with Regional Hypothermia Using Grafts with Multiple Vessels After Extracorporeal Vascular Reconstruction: Results from the European Association of Urology Robotic Urology Section Working Group. *Eur Urol Focus* 2018; **4**: 175-184 [PMID: 30049659 DOI: 10.1016/j.euf.2018.07.022]
24 **Nataraj SA**, Zafar FA, Ghosh P, Ahlawat R. Feasibility and Functional Outcome of Robotic Assisted Kidney Transplantation Using Grafts With Multiple Vessels: Comparison to Propensity Matched Contemporary Open Kidney Transplants Cohort. *Front Surg* 2020; **7**: 51 [PMID: 33195380 DOI: 10.3389/fsurg.2020.00051]
25 **Vignolini G**, Sessa F, Greco I, Cito G, Vanacore D, Cocci A, Sessa M, Grandi V, Pili A, Giancane S, Gacci M, Sebastianelli A, Li Marzi V, Breda A, Campi R, Serni S. Intraoperative assessment of ureteral and graft reperfusion during robotic kidney transplantation with indocyanine green fluorescence videography. *Minerva Urol Nefrol* 2019; **71**: 79-84 [PMID: 30421596 DOI: 10.23736/S0393-2249.18.03278-2]
26 **Campi R**, Vignolini G, Savi E, Sessa F, Agostini S, Serni S. Robotic kidney transplantation allows safe access for transplant renal biopsy and percutaneous procedures. *Transpl Int* 2019; **32**: 1333-1335 [PMID: 31483897 DOI: 10.1111/tri.13517]
27 **Sood A**, Ghosh P, Jeong W, Bhandari M, Ahlawat R, Menon M. 715 Robotic kidney transplantation with regional hypothermia: Results from a prospective two-arm non-randomized controlled trial (Ideal phase 2b). *Eur Urol Suppl* 2016; **15**: e715 [DOI: 10.1016/S1569-9056(16)60717-0]
28 **Ahlawat R**, Sood A, Jeong W, Ghosh P, Keeley J, Abdollah F, Kher V, Olson P, Farah G, Wurst H, Bhandari M, Menon M. Robotic Kidney Transplantation with Regional Hypothermia versus Open Kidney Transplantation for Patients with End Stage Renal Disease: An Ideal Stage 2B Study. *J Urol* 2021; **205**: 595-602 [PMID: 32941100 DOI:

10.1097/JU.0000000000001368]
29 **Territo A**, Gausa L, Alcaraz A, Musquera M, Doumerc N, Decaestecker K, Desender L, Stockle M, Janssen M, Fornara P, Mohammed N, Siena G, Serni S, Sahin S, Tuğcu V, Basile G, Breda A. European experience of robot-assisted kidney transplantation: minimum of 1-year follow-up. *BJU Int* 2018; **122**: 255-262 [PMID: 29645355 DOI: 10.1111/bju.14247]
30 **Ahlawat RK**, Tugcu V, Arora S, Wong P, Sood A, Jeong W, Bhandari M, Menon M. Learning Curves and Timing of Surgical Trials: Robotic Kidney Transplantation with Regional Hypothermia. *J Endourol* 2018; **32**: 1160-1165 [PMID: 29587531 DOI: 10.1089/end.2017.0697]
31 **Oberholzer J**, Giulianotti P, Danielson KK, Spaggiari M, Bejarano-Pineda L, Bianco F, Tzvetanov I, Ayloo S, Jeon H, Garcia-Roca R, Thielke J, Tang I, Akkina S, Becker B, Kinzer K, Patel A, Benedetti E. Minimally invasive robotic kidney transplantation for obese patients previously denied access to transplantation. *Am J Transplant* 2013; **13**: 721-728 [PMID: 23437881 DOI: 10.1111/ajt.12078]
32 **Tsai MK**, Lee CY, Yang CY, Yeh CC, Hu RH, Lai HS. Robot-assisted renal transplantation in the retroperitoneum. *Transpl Int* 2014; **27**: 452-457 [PMID: 24471482 DOI: 10.1111/tri.12279]
33 **Doumerc N**, Beauval JB, Rostaing L, Sallusto F. A new surgical area opened in renal transplantation: a pure robot-assisted approach for both living donor nephrectomy and kidney transplantation using transvaginal route. *Transpl Int* 2016; **29**: 122-123 [PMID: 26332034 DOI: 10.1111/tri.12678]
34 **Delsuc C**, Faure A, Berthiller J, Dorez D, Matillon X, Meas-Yedid V, Floccard B, Marcotte G, Labeye V, Rabeyrin M, Codas R, Chauvet C, Robinson P, Morelon E, Badet L, Hanf W, Rimmelé T. Uncontrolled donation after circulatory death: comparison of two kidney preservation protocols on graft outcomes. *BMC Nephrol* 2018; **19**: 3 [PMID: 29310591 DOI: 10.1186/s12882-017-0805-1]
35 **Tzvetanov IG**, Spaggiari M, Tulla KA, Di Bella C, Okoye O, Di Cocco P, Jeon H, Oberholzer J, Cristoforo Giulianotti P, Benedetti E. Robotic kidney transplantation in the obese patient: 10-year experience from a single center. *Am J Transplant* 2020; **20**: 430-440 [PMID: 31571369 DOI: 10.1111/ajt.15626]
36 **Li Marzi V**, Campi R, Pecoraro A, Peris A, Serni S. Feasibility and Safety of Kidney Transplantation from Deceased Donors during the COVID-19 Pandemic: Insights from an Italian Academic Centre. *Actas Urol Esp (Engl Ed)* 2020; **44**: 708-712 [PMID: 33077290 DOI: 10.1016/j.acuro.2020.08.011]
37 **Campi R**, Pecoraro A, Li Marzi V, Tuccio A, Giancane S, Peris A, Cirami CL, Breda A, Vignolini G, Serni S. Robotic Versus Open Kidney Transplantation from Deceased Donors: A Prospective Observational Study. *Eur Urol Open Sci* 2022; **39**: 36-46 [PMID: 35528789 DOI: 10.1016/j.euros.2022.03.007]
38 **Nanni G**, Tondolo V, Citterio F, Romagnoli J, Borgetti M, Boldrini G, Castagneto M. Comparison of oblique versus hockey-stick surgical incision for kidney transplantation. *Transplant Proc* 2005; **37**: 2479-2481 [PMID: 16182716 DOI: 10.1016/j.transproceed.2005.06.055]
39 **Wagenaar S**, Nederhoed JH, Hoksbergen AWJ, Bonjer HJ, Wisselink W, van Ramshorst GH. Minimally Invasive, Laparoscopic, and Robotic-assisted Techniques Versus Open Techniques for Kidney Transplant Recipients: A Systematic Review. *Eur Urol* 2017; **72**: 205-217 [PMID: 28262412 DOI: 10.1016/j.eururo.2017.02.020]
40 **Prudhomme T**, Beauval JB, Lesourd M, Roumiguié M, Decaestecker K, Vignolini G, Campi R, Serni S, Territo A, Gausa L, Tugcu V, Sahin S, Alcaraz A, Musquera M, Stockle M, Janssen M, Fornara P, Mohammed N, Del Bello A, Kamar N, Sallusto F, Breda A, Doumerc N. Robotic-assisted kidney transplantation in obese recipients compared to non-obese recipients: the European experience. *World J Urol* 2021; **39**: 1287-1298 [PMID: 32562044 DOI: 10.1007/s00345-020-03309-6]
41 **Kim SD**, Kim JI, Moon IS, Park SC. Comparison of Minimal Skin Incision Technique in Living Kidney Transplantation and Conventional Kidney Transplantation. *Chin Med J (Engl)* 2016; **129**: 917-921 [PMID: 27064035 DOI: 10.4103/0366-6999.179800]
42 **Malinka T**, Banz VM, Wagner J, Candinas D, Inderbitzin D. Incision length for kidney transplantation does not influence short- or long-term outcome: a prospective randomized controlled trial. *Clin Transplant* 2013; **27**: E538-E545 [PMID: 23924205 DOI: 10.1111/ctr.12209]
43 **Spaggiari M**, Lendacki FR, Di Bella C, Giulianotti PC, Benedetti E, Oberholzer J, Tzvetanov I. Minimally invasive, robot-assisted procedure for kidney transplantation among morbidly obese: Positive outcomes at 5 years post-transplant. *Clin Transplant* 2018; **32**: e13404 [PMID: 30216555 DOI: 10.1111/ctr.13404]
44 **Spaggiari M**, Di Cocco P, Tulla K, Kaylan KB, Masrur MA, Hassan C, Alvarez JA, Benedetti E, Tzvetanov I. Simultaneous robotic kidney transplantation and bariatric surgery for morbidly obese patients with end-stage renal failure. *Am J Transplant* 2021; **21**: 1525-1534 [PMID: 32976702 DOI: 10.1111/ajt.16322]

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MINIREVIEWS

How and when of eyelid reconstruction using autologous transplantation

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Abstract

Reconstructive surgery of the eyelid after tumor excision, trauma or other causes can be challenging, especially due to the complexities of the anatomic structures and to the necessity of both functional and aesthetic successful outcomes. The aim of this minireview was to investigate the use of tissue transplantation in eyelid reconstruction. Surgical procedures are various, based on the use of both flaps, pedicled or free, and grafts, in order to guarantee adequate tissue reconstruction and blood supply, which are necessary for correct healing. Common techniques normally include the use of local tissues, combining non-vascularized grafts with a vascularized flap for the two lamellae repair, to attempt a reconstruction similar to the original anatomy. When defects are too wide, vast, deep, and complex or when no adjacent healthy tissues are available, distant area tissues need to be recruited as free flaps or grafts and paired with mucosal layer reconstruction. With regards to the anterior lamella, full thickness skin grafts are commonly preferred. With regards to the reconstruction of posterior lamella, there are different graft options, which include conjunctival or tarsoconjunctival, mucosal or palatal or cartilaginous grafts usually combined with local flaps. Free flap transplantation, normally reserved for rare select cases, include the use of the radial forearm and anterolateral flaps combined with mucosal grafts, which are surgical options currently reported in the literature.

Key Words: Eyelid reconstruction; Graft transplantation; Flap transplantation; Eyelid lamella grafts; Cartilage grafts; Dermis grafts; Mucosa grafts

Core Tip: Transplantation tends to be a viable option in eyelid reconstruction surgery. The most commonly used technique involves the use of grafts for the reconstruction of one or both eyelid structures. The use of free flaps are seldom used and are reserved for cases of extensive tissue lost. In these cases, favorable flaps considered are those that are anatomically thin and pliable.

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INTRODUCTION

Eyelid reconstruction tends to be complex and difficult and can be needed after oncological surgery or trauma. There are also cases, which are not frequent, in which reconstructive surgery is needed to repair damage caused by aesthetic surgery, such as lagophthalmos post-blepharoplasty or scarring eyelid retraction. In patients with invasive and relatively large eyelid tumors, the need to perform complete oncologic excision with margins adapted to tumor type may result in the removal of an important part of this anatomical structure that encompasses both aesthetic and functional properties[1].

The eyelid consists of an anterior and posterior lamella. The anterior portion of the lid is composed of skin and orbicularis muscles, while the posterior portion includes the posterior tarsal plate, retractors (in the lower eyelid), and conjunctiva[2]. In most eyelid reconstruction surgical procedures, both lamellae need to be replaced. At least one lamella needs to include a functioning blood supply and therefore has to be pediculated, otherwise the reconstructed tissue cannot properly grow and heal, resulting in poor and/or no wound closure[3].

Several surgical techniques are currently available for lower eyelid reconstruction; the choice of the technique and postoperative results mainly depend on the preference and experience of the surgeon and on the etiology of the eyelid defect. Most surgical techniques combine different flaps and grafts in order to reconstruct both lamellae. The most commonly used reconstructive techniques are based on local flaps, which are widely described in the literature[4-6], and possible grafts to complete lid reconstruction. The main objectives of surgery include obtaining postsurgical outcomes that reflect the normal eyelid in terms of anatomy, aesthetics, and function. The aim of our minireview was to present a brief overview of reconstructive techniques based on autologous tissue transplantation for eyelid reconstruction surgery, including the use of grafts and/or free flaps, which have been reported in the literature in the past 10 years.

MATERIALS AND METHODS

We conducted a search of the literature published between January 1, 2011 to November 1, 2021 using MEDLINE (PubMed). The database was first searched using the key words "eyelid reconstruction, eyelid reconstruction AND grafts, free flaps, tissue transplantation, autologous grafts, autologous tissues". We considered only studies in English and those referring to humans and with an abstract, thus reducing the count to 1473 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. The research of articles was preformed using PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (https://www.referencecitation-analysis.com).

Only articles with an abstract were considered. After excluding all works in which only local flaps were used for reconstruction, 63 studies were analyzed. A quality score was calculated for each article using a check list from the American Society of Plastic Surgeons guideline for therapeutic studies[7]. Each study was independently assessed by at least two reviewers (Miotti G and Zeppieri M), and rating decisions were based on the consensus of the reviewing authors. The results of the most relevant studies are shown in Table 1.

GENERAL NOTIONS REGARDING RECONSTRUCTIVE EYELID SURGERY

The particular eyelid anatomy must always be considered when reconstructing it. In doing so, we must always remember the presence of two lamellae that constitute the two eyelids. Full thickness defects larger than a third of the eyelid should be reconstructed in two planes, which correspond to the posterior and anterior lamellae. In order to avoid necrosis of the reconstruction, at least one lamella

Table 1 Studies in literature regarding reconstructive eyelid surgery

What	Where	Type of tissue transplant	Ref.	Conclusions
Grafts	Bilamellar reconstruction	Skin graft + tarsoconjunctival graft with orbicularis oculi muscle advancement	Doxanas[11], 1986, Kakizaki *et al*[10], 2009	Orbital part muscle mobilization allows full thickness eyelid reconstruction using two grafts due to its vascular support
		Skin graft + tarsal graft	Bortz *et al*[12], 2020	Reconstruction of lower eyelid defects with a free tarsal graft and overlying free skin graft resulted in an acceptable functional and aesthetic lower eyelid suggesting that retention of or provision of vascular support in either the anterior or posterior lamella may not be necessary
	Anterior lamella	Skin graft	Alghoul *et al*[9], 2013	Anterior lamellar defects can be reconstructed with a full-thickness skin graft. Split-thickness skin grafts should not be used
		Skin graft	Shorr *et al*[14], 2003	Upper eyelid skin grafting can be performed with good cosmetic results to address corneal decompensation in patients who have acquired lagophthalmos from anterior lamellar insufficiency
	Posterior lamella	Tarsoconjunctival graft	Hawes *et al*[17], 2011	Essential component of eyelid reconstruction as it provides an anatomically similar tissue for the inner layer of reconstructed eyelids. Patients receiving a free tarsoconjunctival graft were less likely to require surgery to repair eyelid margin erythema than those receiving a Hughes tarsoconjunctival flap
			Yazici *et al*[23], 2020	Lateral periorbital bilobed flap with tarsoconjunctival graft can be a good alternative for the single-stage reconstruction of large upper eyelid defects
			Bengoa-González *et al*[24], 2019	Reconstruction of upper eyelid defects secondary to malignant tumors with a newly modified Cutler-Beard technique with tarsoconjunctival graft gives stability to the new upper eyelid, avoiding retraction caused by scarring
		Hard-palate mucoperiosteal	Yue *et al*[26], 2020, Ito *et al*[27], 2007	HPM may be considered the optimal choice for reconstructing the posterior lamella of the eyelids because it has similar histological composition and texture to the tarsoconjunctiva
			Hendriks *et al*[28], 2020	The use in upper eyelid reconstruction is controversial because hard-palate mucosa is composed of keratinized, stratified squamous epithelium, which can irritate the cornea. Despite this, excellent results were reported for its use in upper eyelid posterior lamellar reconstruction
		Chondromucosal graft	Yamamoto *et al*[33], 2017	Ear cartilage is useful because it is easy to harvest and fabricate, has suitable flexibility, and provides adequate support. Chondromucosal grafts from the nasal septum consist of highly supportable tissue. It lacks softness and flexibility, and harvesting is limited
			Suga *et al*[34], 2016	Ear cartilage fits well to bulbar surface. It has lower complication rate, while in the nose septal perforation and more bleeding can occur
			Hendriks *et al*[28], 2020	The use of alar or triangular cartilage provides a thinner but smaller sized sample, with good adaptability in eyelid reconstruction but raised the problem of donor site morbidity
		Scapha chondrocutaneous graft	Uemura *et al*[36], 2016	The scapha cartilage graft with small skin, round and soft with a shape similar to that of the lower lid, affords a good fit to the eye globe
		Dermis fat graft	Kuzmanović Elabjer *et al*[39], 2018	Provides stiffness, additional surface area, and a scaffold. Helps with vascularization and decreases fat tissue atrophy. It can be flat or domed
		Venous graft	Barbera *et al*[40], 2008	VGs obtained by propulsive venous vessels are the most suitable for this reconstruction because of their thinness, texture, and anatomical structure
			Tomassini *et al*[41], 2012	By properties of elasticity, smoothness, and concavity, the VG conforms to the globe without inducing a chronic inflammatory reaction on the bulbar conjunctiva or on the cornea
			Scevola *et al*[42], 2015	Safe, fast, and easily reproducible compared with chondroseptal graft
		Galea or pericranium graft	Ibáñez-Flores *et al*[43], 2019	Pericranial graft provides enough tissue to cover large defects, with an appropriate volume and a non-painful postoperative period
		Buccal mucosa graft	Grixti and Malhotra[44], 2018, Jin and Cao[45], 2021	It lacks structural integrity. It is too weak and small to support the lower eyelid, shrinking substantially during the postoperative period, so it should be used in combination with cartilage
Flaps	Bilamellar reconstruction	Neurovascular free flap from the first web space of the foot	Chait *et al*[46], 1980	

Free flap based on the second metacarpal artery	Yap *et al*[47], 1997	
Free dorsalis pedis flap	Thai *et al*[48], 1999	Free flap used for outer lamella and conjunctival flap for inner lamella
Free forearm flap	Kushima *et al*[49], 2003	Entire upper eyelid reconstruction and a hard palate graft for the posterior one
	Ghadiali *et al*[50], 2016	Upper and lower eyelid total reconstruction where an extensive tissue loss of the ipsilateral forehead and temple. Tarsal plate of the eyelids was rebuilt by palmaris tenon grafts
	Iwanaga *et al*[51], 2019	2 cases of functional upper eyelid defect reconstruction. They used a free flap elevated with palmaris longus tenon split into two strips: One fixed to the frontalis muscle to achieve the opening function and the second to the medial palpebral ligament and the lateral orbicularis muscle to achieve the closing function
ALT flap	Rubino *et al*[52], 2008	Upper and lower eyelid unilateral full thickness reconstruction with ALT free flap in a patient with no available adjacent tissues, involved in extended burns, and no possibility of using RFF

ALT: Anterolateral; HPM: Hard-palate mucoperiosteal; RFF: Radial forearm flap; VGs: Venous grafts.

should have an intact blood supply. The association of two grafts is therefore not recommended. The two planes must thus consist of the association of either two flaps or a flap and a graft[1]. Most studies reported in the literature follow this common idea; however, some authors have also proposed the use of only grafts.

The association of two flaps is the safest combination regarding vascular supply and postoperative recovery. However, the use of two flaps can lead to a thick reconstructed eyelid, which can be limited if each flap is comprised exclusively of the exact missing layer. For this reason, the use of a flap and a graft is the best option for satisfactory aesthetic result. The final choice of the surgical technique depends on several factors, which include the preference and experience of the surgeon, etiology of the eyelid defect, and the availability of flaps and grafts[8]. The quality of local tissues can also modify this choice. History of radiotherapy, previous or planned in the postoperative period, can guide the reconstruction. By determining a reduction of the vascularization of the treated tissues, well vascularized tissue are preferred to repair the defects[3,5]. Local flaps certainly represent a common reconstructive choice and are preferable to grafts, especially for previously irradiated sites. The aim of our study, however, was to assess a narrower and more specific field of literature, to concentrate on studies regarding eyelid reconstruction surgery based on tissue transplantation, to include grafts or free flaps.

GRAFT TRANSPLANTATION

Graft transplantation in eyelid reconstruction is perhaps the most commonly used procedure in routine clinical settings. Various tissues can be transplanted to complete the eyelid reconstruction. Both lamellae can be restored with grafts; however, the anterior lamella is the most common segment that tends to be repaired. As a basic rule, grafts should be used when there is an adequate vascular bed to enhance post-transplanted survival. Grafts can also be used in irradiated tissues when needed; however, these types of grafts generally need to be associated with local flaps to enhance the vascularization and guarantee graft survival. Radiotherapy on engrafted areas could cause ulceration or delay the wound healing[9]. Commonly used techniques combine a non-vascularized graft for one lamella with a vascularized flap for the other[9].

As mentioned above, usually only one lamella can be reconstructed with a graft, but techniques to reconstruct both have also been described. Kakizaki *et al*[10] reported bilamellar graft reconstruction with orbicularis muscle mobilization between grafted areas ("sandwich flap"), first described by Doxanas[11] in 1986. The orbicularis oculi muscle provides an excellent blood supply to grafted tissues in these cases, in addition to enhancing the mobility of the reconstructed lid. In 2020, Bortz *et al*[12] published a clinical series in which full-thickness lid defects were restored using free tarsal grafts for the posterior lamella and free skin grafts for the anterior lamella. The authors reported this method as an alternative to the "classic" Hughes flap for lower eyelid reconstruction, especially when the occlusion of the eye could be a problem (vision deficit, elderly patients, *etc*). The evidence reported by Tenland *et al*[13] led the authors to propose this type of reconstruction. The study showed that tarsoconjunctival (TC) tissue survival does not seem to be dependent on a conjunctival flap, and thus free TC grafts or composite grafts might be considered as viable alternatives.

Anterior lamella grafts

Anterior lamella is often reconstructed with a full-thickness skin graft[10-14]. Other possibilities of

tissue transplantation include tissue cultured autograft, tissue cultured allograft, skin bank allograft, acellular dermal replacement, and xenograft[15]. Ideal donor sites include upper and lower eyelid skin and posterior auricular, preauricular, or supraclavicular skin. Split-thickness skin grafts should not be used, with the exception of cases of extensive burns in which the donor site is limited[9].

Posterior lamella grafts

Grafts or flaps are viable options for posterior lamellar reconstruction[10]. Grafts include conjunctival or TC grafts, hard palate (or palate) graft, cartilage (auricular or nasal septal) grafts, mucoperichondrium grafts, dermis fat grafts (DFGs), venous grafts (VGs), galea or pericranium grafts, mucosal membrane (buccal or labial) grafts, and temporalis fascia grafts. For lower eyelid reconstruction, for example, single or tandem composite skin muscle TC eyelid grafts from the upper lids or contralateral lower lid may be an option[10].

TC grafts: TC grafts are an excellent choice for posterior lamellar reconstruction considering that this structure reflects the features of a normal eyelid[9]. Tarsal grafts alone, taken from the healthy eyelid, can be used in association with local flaps for anterior lamella reconstruction[16]. TC grafts and flaps are essential components of eyelid reconstruction since these alternatives provide anatomically similar tissues for the inner layer of reconstructed eyelids[17]. First described in 1918 by Blaskovics[18] for lower eyelid reconstruction, autogenous TC grafts have found widespread use, as described by Hughes [19], Leone *et al*[20], and several others in the literature[21,22]. Hawes *et al*[17] proposed guidelines for the use of TC flaps and grafts to repair lower eyelid defects.

Free grafts are preferred in most cases in which the defect is from one-third to three-quarters of the eyelid length. TC flaps are advantageous when the defects are large (entire lower eyelid loss) and when poor healing can be expected. Usually, this type of reconstruction is completed by a local flap for the anterior lamella and is not limited only to the lower eyelid. Yazici *et al*[23] recently described the association of a TC graft with a bilobed local flap for the upper eyelid. Bengoa-González *et al*[24] described the use of the graft to complete and modify the Cutler-Beard technique for the upper eyelid. The TC graft gives stability to the new upper eyelid, avoiding retraction caused by scarring. From a technical point of view, it is fundamental to also avoid complications in the donor site, which usually heals spontaneously by secondary intention[9]. Almost 3-4 mm of tarsus must be maintained to allow donor eyelid stability, and Müller's muscle should be conserved. To avoid entropion or ectropion to reconstructed eyelid, the tarsal graft should be snug and no wider than the smallest dimension of the defect[17]. Figure 1 shows an example of our patient that underwent left lower eyelid reconstruction after tumor excision using a TC graft (from the left upper eyelid) for the posterior lamella and a local flap for the anterior one.

Hard-palate mucoperiosteal grafts: Hard-palate mucoperiosteal (HPM) grafts, described for the first time by Siegel[25] in 1985, can be used to replace the posterior lamella due to the ability of this graft to provide structural support and mucosal lining[9]. HPM may be considered the optimal choice for reconstructing the posterior lamella of the eyelids because it has similar histological composition and texture to the tarsoconjunctiva, and an adequately sized graft can easily be acquired[26,27]. HPM tends to be one of the preferred choices for most lower eyelid reconstructions in routine clinical settings[26]. The use of HPM in upper eyelid reconstruction is controversial because hard-palate mucosa is composed of keratinized, stratified squamous epithelium, which can irritate the cornea, especially when the defect is adjacent to the middle part of the cornea[9,28]. Despite this, excellent results without complications have been reported in studies when used in upper eyelid posterior lamellar reconstruction[28,29].

The reconstruction of the anterior lamella requires the use of flaps. Palatal mucosal grafts provide good structural support to the eyelid. This is essential for the inferior eyelid, especially when the graft is combined with a heavy flap such as the Mustardé or the orbito-nasogenien flap. The graft is and remains stiff. The shrinkage is minimal, thus providing a stable, free eyelid margin and limiting ectropion or entropion[28]. Limits of this technique, in addition to the aforementioned corneal irritation, are the described pain and delayed healing at the donor site observed when periosteum is included in the graft[30].

Auricular and nasoseptal cartilage grafts: Auricular and nasoseptal cartilage can also be useful alternatives when considering graft tissues for reconstructive surgery[28,31,32]. In some cases, this graft may prove to be too thick and too stiff to match with the eye convexity, thus needing to be thinned without compromising the supportive strength. Ear cartilage is useful because it is easy to harvest and fabricate, has suitable flexibility, and provides adequate support[33]. The spherical surface fits well with the shape of the external bulbar surface[34]. Chondromucosal grafts from the nasal septum consist of highly supportable tissue. Caution must be taken when harvesting a chondroseptal graft to avoid damage to the remaining mucosa surrounding the vast perforation. Considering this tissue is composed of hyaline cartilage, it lacks softness and flexibility. This may result in difficulty with fabrication and unsuitable contact with the bulbar conjunctiva. In addition, the harvestable size is limited[33]. The use of alar or triangular cartilage provides a thinner but smaller sized sample, with good adaptability in eyelid reconstruction but raises the problem of donor site morbidity[28]. Suga *et al*[34] published in 2016 a

comparison between ear and nasal septum grafts. The study reported that both tissues provide good options for reconstructing an inner layer of the lower eyelid. The authors stressed that the main difference lies on postoperative outcomes at the donor site. Ear cartilage tends to have lower complication rates, while harvesting nose grafts can cause important septal perforation and vast bleeding.

Another option for cartilaginous reconstruction of the posterior lamella of the lower eyelid is a scapha chondrocutaneous graft, first proposed by Yanaga and Mori[35]. Further studies reported by Uemura *et al*[36] described interesting results with the use of this graft combined with a local propeller flap. The scapha cartilage graft is an interesting alternative because it has a thin coat of skin and is round and soft with a shape similar to that of the lower lid. This tissue can provide a good fit with the eye globe and can be harvested quickly without severe complications.

DFGs: DFGs can provide useful replacement tissue for eyelid and orbit reconstruction. The DFG is composed of a dermis button, obtained by removing the overlying epidermis with the underlying subcutaneous fat. The dermis provides stiffness, additional surface area, and a scaffold. Moreover, the dermis helps with vascularization and decreases fat tissue atrophy. This tissue can be flat or domed shaped[37]. This graft option tends to be considered primarily for socket reconstruction in the context of anophthalmia, either congenital or acquired[38]. Secondary indications are eyelid reconstruction, socket contraction, eyelid contraction (used as spacer[39]), or implant exposure.

VGs: Barbera *et al*[40] first proposed VGs as a reconstructive possibility in 2008. The study reported that VGs obtained by propulsive venous vessels are the most suitable for this type of surgical reconstruction because of the tissue thinness, texture, and anatomical structure. Moreover, due to the properties of elasticity, smoothness, and concavity, the venous graft conforms to the globe without inducing a chronic inflammatory reaction on the bulbar conjunctiva or on the cornea[41]. Scevola *et al*[42] showed that VG is a good technique for palpebral reconstruction because it is safe, fast, and easily reproducible when compared with a chondroseptal graft.

Galea and pericranium grafts: Galea and pericranium grafts represent a secondary choice in eyelid reconstruction. These tissues represent a reconstructive possibility in cases of severe periocular trauma, wide tumor resections, or in socket reconstruction[35]. Ibáñez-Flores *et al*[43] published a series of cases in which pericranium grafts were used. The authors concluded that pericranial grafts provided a sufficient amount of tissue to cover large defects, thus providing appropriate substitutional volume without painful postoperative healing.

Buccal mucosa graft: Buccal mucosa graft is a good lining option[9]. Oral mucosa has similar biological properties to conjunctiva, thus making it a viable alternative to restore the ocular surface[44]. This tissue, however, lacks structural integrity and tends to be too weak and small to support the lower eyelid. Moreover, postoperative shrinking can be substantial during the follow-up period, thus it should be used in combination with cartilage[43,45]. It is important to note that buccal mucosa graft harvesting and postoperative healing tend to be rather painful for most patients.

FLAP TRANSPLANTATIONS FROM DISTANT SITES

When defects are too complex to be reconstructed with local flaps or grafts or when no adjacent tissues are available, the operation is challenging, and transplantation of tissues from distant areas is necessary. Mechanical support and mobility for reconstructive surgery can seldom be found in tissues from a distant region, combining thin and pliable skin with mucosal layer reconstruction. The flap needs to provide characteristics that are appropriate both from a functional and an aesthetic prospective. Free flaps are normally not frequently considered in reconstructive surgery. In addition, reconstructions with free flaps have several possible complications. The effect of possible radiotherapy on the recipient site (which is frequent in advanced tumors) is one of the elements that can determine the failure of autologous microsurgical reconstruction. The harmful effects on tissues and blood vessels are well known. There are only a few studies reported in the literature that are based on this surgical option for complete or partial eyelid reconstruction.

One of the first attempts of periocular region reconstruction using free flaps was described by Chait *et al*[46] who used a neurovascular free flap from the first web space of the foot after exenteration. An alternative distant surgical flap was described in a case report by Yap *et al*[47] in 1997 in which the eyelids were rebuilt using a free flap based on the second metacarpal artery. Thai *et al*[48] proposed a free dorsalis pedis flap for the outer lamella and a local conjunctival flap for the inner one for total eyelid surgical reconstruction after deep facial burn in a study published in 1999.

One of the main problems in periocular region reconstruction is represented by the extreme thinness of the tissues that compose it. This represents a limit for the reconstructive techniques due to the thickness of the tissues generally used to cover the defects. This limit is highlighted when the reconstructive choice is a free flap. For this reason, it is quite difficult to find a viable flap that can

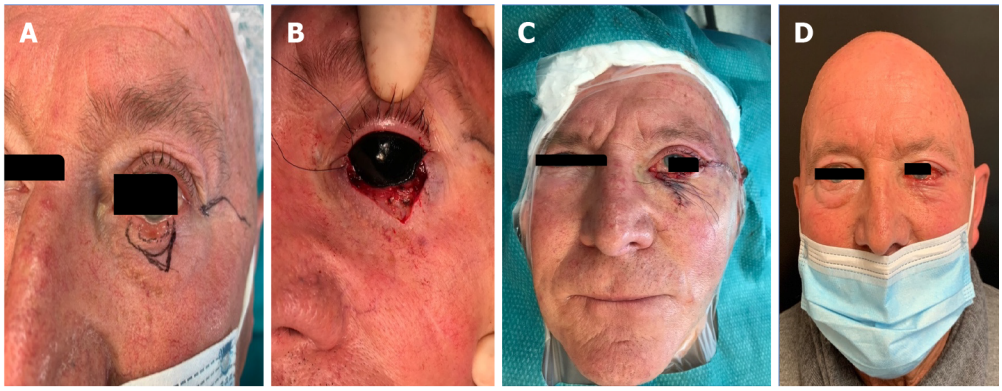

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Figure 1 A patient that underwent left lower eyelid reconstruction after tumor excision using a tarsoconjunctival graft (from the left upper eyelid) for the posterior lamella and a local flap for the anterior one. A: Basal cell carcinoma of left lower eyelid with preoperative markings; B: Lid after surgical removal; C: Postoperative reconstruction with Tenzel flap + tarsoconjunctival graft from the left upper eyelid; D: Clinical presentation 2 wk after surgery.

provide satisfactory surgical reconstruction outcomes. Kushima *et al*[49] described an entire upper eyelid reconstruction using a free radial forearm flap for the anterior lamella and a hard palate graft for the posterior one. This flap, thanks to its flexibility and thinness, is considered the ideal solution.

The same flap has been used by Ghadiali *et al*[50] in a case of upper and lower eyelid total reconstruction in which the patient had extensive tissue loss of the ipsilateral forehead and temple. In this specific case, there were no local tissues available for reconstruction. The authors used a 5 cm × 11 cm radial flap to reconstruct the entire area, followed by a fenestration of the flap 4 mo later. The tarsal plate of the eyelids was rebuilt by palmaris tenon grafts. As a result, the patient obtained a visually useful eye, which remained intact after the trauma[50]. Radial forearm flap was also used by Iwanaga *et al*[51] in 2 cases of functional upper eyelid defect reconstruction surgeries. The authors used a free flap elevated with palmaris longus tenon in a fascinating way. The palmaris longus tenon was split into two strips, in which one strip was fixed to the frontalis muscle to achieve the opening function and the second to the medial palpebral ligament and the lateral orbicularis muscle to achieve functioning closing lids.

Another feasible free flap, especially in thin or super-thin forms, is the anterolateral flap. In 2008, Rubino *et al*[52] described a case of upper and lower eyelid unilateral full thickness reconstruction with anterolateral free flap in a patient with no available adjacent tissues, who had extensive burns and no possibility of using a radial forearm flap. In this patient, the blepharoraphy was opened after 3 mo from the first surgery, obtaining good skin coverage but incomplete closure of the eye.

CONCLUSION

Eyelid reconstruction remains extremely complex and fascinating, especially considering that the main aims of surgery include re-establishing the anatomy, providing protection of the eye globe, favoring the sight, and guaranteeing the aesthetics of the face. It is clear that each surgical procedure requires experience, careful planning, and personalized surgical options tailored for each patient. From the analysis of the current literature in this field, it appears significantly advantageous to exploit periocular tissues when possible. However, other options including non-traditional flaps and grafts can prove to be viable alternatives in specific cases, especially when there is extensive damage to the lids and/or neighboring tissues are scarce and not feasible options. Stem cell harvesting and new transplanted autologous tissues can pave the way to future surgical techniques in reconstructive lid surgery.

FOOTNOTES

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REFERENCES

1 **Lemaître S**, Lévy-Gabriel C, Desjardins L, González-Candial M, Gardrat S, Dendale R, Cassoux N, Couturaud B. Outcomes after surgical resection of lower eyelid tumors and reconstruction using a nasal chondromucosal graft and an upper eyelid myocutaneous flap. *J Fr Ophtalmol* 2018; **41**: 412-420 [PMID: 29778279 DOI: 10.1016/j.jfo.2017.10.008]
2 **Pfeiffer MJ**. Update on upper lid blepharoplasty. *Oculoplastics Orbit* 2006; 123-42 [DOI: 10.1007/3-540-29969-6_11]
3 **Frimmel S**, Kniestedt C, Chaloupka K. Eyelid Reconstruction: Pediculated versus Non-Pediculated. *Klin Monbl Augenheilkd* 2018; **235**: 398-403 [PMID: 29351708 DOI: 10.1055/s-0043-122736]
4 **Hughes WL**. Total lower lid reconstruction: technical details. *Trans Am Ophthalmol Soc* 1976; **74**: 321-329 [PMID: 867633]
5 **Tenzel RR**, Stewart WB. Eyelid reconstruction by the semicircle flap technique. *Ophthalmology* 1978; **85**: 1164-1169 [PMID: 733166 DOI: 10.1016/s0161-6420(78)35578-0]
6 **Mustardé JC**. The use of flaps in the orbital region. *Plast Reconstr Surg* 1970; **45**: 146-150 [PMID: 5411895]
7 **DePalma JA**. Evidence-based clinical practice guidelines. *Semin Perioper Nurs* 2000; **9**: 115-120 [PMID: 12029704]
8 **Karim A**, Schapiro D, Morax S. [Reconstruction of full-thickness lower eyelid defects]. *J Fr Ophtalmol* 2005; **28**: 675-680 [PMID: 16141935 DOI: 10.1016/s0181-5512(05)81114-3]
9 **Alghoul M**, Pacella SJ, McClellan WT, Codner MA. Eyelid reconstruction. *Plast Reconstr Surg* 2013; **132**: 288e-302e [PMID: 23897357 DOI: 10.1097/PRS.0b013e3182958e6b]
10 **Kakizaki H**, Madge SN, Mannor G, Selva D, Malhotra R. Oculoplastic surgery for lower eyelid reconstruction after periocular cutaneous carcinoma. *Int Ophthalmol Clin* 2009; **49**: 143-155 [PMID: 20348862 DOI: 10.1097/IIO.0b013e3181b806a4]
11 **Doxanas MT**. Orbicularis muscle mobilization in eyelid reconstruction. *Arch Ophthalmol* 1986; **104**: 910-914 [PMID: 3718317 DOI: 10.1001/archopht.1986.01050180144047]
12 **Bortz JG**, Al-Shweiki S. Free Tarsal Graft and Free Skin Graft for Lower Eyelid Reconstruction. *Ophthalmic Plast Reconstr Surg* 2020; **36**: 605-609 [PMID: 32732536 DOI: 10.1097/IOP.0000000000001680]
13 **Tenland K**, Memarzadeh K, Berggren J, Nguyen CD, Dahlstrand U, Hult J, Engelsberg K, Lindstedt S, Sheikh R, Malmsjö M. Perfusion Monitoring Shows Minimal Blood Flow From the Flap Pedicle to the Tarsoconjunctival Flap. *Ophthalmic Plast Reconstr Surg* 2019; **35**: 346-349 [PMID: 30383574 DOI: 10.1097/IOP.0000000000001250]
14 **Shorr N**, Goldberg RA, McCann JD, Hoenig JA, Li TG. Upper eyelid skin grafting: an effective treatment for lagophthalmos following blepharoplasty. *Plast Reconstr Surg* 2003; **112**: 1444-1448 [PMID: 14504530 DOI: 10.1097/01.PRS.0000081477.02812.C9]
15 **Merriam JC**. A Manual of Systematic Eyelid Surgery. *Arch Ophthalmology* 1991; **109**: 929 [DOI: 10.1001/archopht.1991.01080070041026]
16 **Toft PB**. Reconstruction of large upper eyelid defects with a free tarsal plate graft and a myocutaneous pedicle flap plus a free skin graft. *Orbit* 2016; **35**: 1-5 [PMID: 26636623 DOI: 10.3109/01676830.2015.1078372]
17 **Hawes MJ**, Grove AS Jr, Hink EM. Comparison of free tarsoconjunctival grafts and Hughes tarsoconjunctival grafts for lower eyelid reconstruction. *Ophthalmic Plast Reconstr Surg* 2011; **27**: 219-223 [PMID: 21562393 DOI: 10.1097/IOP.0b013e318217e194]
18 **Blaskovics LV**. III. über Totalplastik des unteren Lides. Bildung einer hinteren Lidplatte durch Transplantation eines Tarsus- und Bindehautstreifens aus dem Oberlide. *Ophthalmologica* 1918; **40**: 222-227 [DOI: 10.1159/000294462]
19 **Hughes WL**. Reconstructive surgery of the eyelids. *Adv Ophthalmic Plast Reconstr Surg* 1986; **5**: 25-87 [PMID: 3331907]
20 **Leone CR Jr**, Hand SI Jr. Reconstruction of the medial eyelid. *Am J Ophthalmol* 1979; **87**: 797-801 [PMID: 377974 DOI: 10.1016/0002-9394(79)90357-x]
21 **Beyer CK**, Bathrick ME. One-stage lower eyelid reconstruction. *Ophthalmic Surg* 1982; **13**: 551-554 [PMID: 7050807]
22 **Hawes MJ**. Free autogenous grafts in eyelid tarsoconjunctival reconstruction. *Ophthalmic Surg* 1987; **18**: 37-41 [PMID: 3561935]
23 **Yazici B**, Ozturker C, Cetin Efe A. Reconstruction of Large Upper Eyelid Defects With Bilobed Flap and Tarsoconjunctival Graft. *Ophthalmic Plast Reconstr Surg* 2020; **36**: 372-374 [PMID: 31809481 DOI: 10.1097/IOP.0000000000001557]
24 **Bengoa-González Á**, Laslău BM, Martín-Clavijo A, Mencía-Gutiérrez E, Lago-Llinás MD. Reconstruction of Upper Eyelid Defects Secondary to Malignant Tumors with a Newly Modified Cutler-Beard Technique with Tarsoconjunctival Graft. *J Ophthalmol* 2019; **2019**: 6838415 [PMID: 30944732 DOI: 10.1155/2019/6838415]

25 **Siegel RJ**. Palatal grafts for eyelid reconstruction. *Plast Reconstr Surg* 1985; **76**: 411-414 [PMID: 4034758 DOI: 10.1097/00006534-198509000-00013]

26 **Yue H**, Tian L, Bi Y, Qian J. Hard Palate Mucoperiosteal Transplantation for Defects of the Upper Eyelid: A Pilot Study and Evaluation. *Ophthalmic Plast Reconstr Surg* 2020; **36**: 469-474 [PMID: 32091481 DOI: 10.1097/IOP.0000000000001599]

27 **Ito R**, Fujiwara M, Nagasako R. Hard palate mucoperiosteal graft for posterior lamellar reconstruction of the upper eyelid: histologic rationale. *J Craniofac Surg* 2007; **18**: 684-690 [PMID: 17538339 DOI: 10.1097/scs.0b013e318053446d]

28 **Hendriks S**, Bruant-Rodier C, Lupon E, Zink S, Bodin F, Dissaux C. The palatal mucosal graft: The adequate posterior lamellar reconstruction in extensive full-thickness eyelid reconstruction. *Ann Chir Plast Esthet* 2020; **65**: 61-69 [PMID: 30795932 DOI: 10.1016/j.anplas.2019.01.007]

29 **Cohen MS**, Shorr N. Eyelid reconstruction with hard palate mucosa grafts. *Ophthalmic Plast Reconstr Surg* 1992; **8**: 183-195 [PMID: 1390426 DOI: 10.1097/00002341-199209000-00005]

30 **Pedlar J**. Healing following full thickness excision of human palatal mucosa. *Br J Plast Surg* 1985; **38**: 347-351 [PMID: 4016422 DOI: 10.1016/0007-1226(85)90240-1]

31 **Mehrotra ON**. Repairing defects of the lower eyelid with a free chondromucosal graft. *Plast Reconstr Surg* 1977; **59**: 689-693 [PMID: 322172 DOI: 10.1097/00006534-197705000-00011]

32 **Parodi PC**, Calligaris F, De Biasio F, De Maglio G, Miani F, Zeppieri M. Lower lid reconstruction utilizing auricular conchal chondral-perichondral tissue in patients with neoplastic lesions. *Biomed Res Int* 2013; **2013**: 837536 [PMID: 23865069 DOI: 10.1155/2013/837536]

33 **Yamamoto N**, Ogi H, Yanagibayashi S, Yoshida R, Takikawa M, Nishijima A, Kiyosawa T. Eyelid Reconstruction Using Oral Mucosa and Ear Cartilage Strips as Sandwich Grafting. *Plast Reconstr Surg Glob Open* 2017; **5**: e1301 [PMID: 28507862 DOI: 10.1097/GOX.0000000000001301]

34 **Suga H**, Ozaki M, Narita K, Kurita M, Shiraishi T, Ohura N, Takushima A, Harii K. Comparison of Nasal Septum and Ear Cartilage as a Graft for Lower Eyelid Reconstruction. *J Craniofac Surg* 2016; **27**: 305-307 [PMID: 26967067 DOI: 10.1097/SCS.0000000000002295]

35 **Yanaga H**, Mori S. Eyelids and eye socket reconstruction using the expanded forehead flap and scapha composite grafting. *Plast Reconstr Surg* 2001; **108**: 8-16 [PMID: 11420499 DOI: 10.1097/00006534-200107000-00003]

36 **Uemura T**, Watanabe H, Masumoto K, Kikuchi M, Satake Y, Yanai T, Harada Y, Ishihara Y, Yasuta M. Aesthetic Total Reconstruction of Lower Eyelid Using Scapha Cartilage Graft on a Vascularized Propeller Flap. *Plast Reconstr Surg Glob Open* 2016; **4**: e696 [PMID: 27200258 DOI: 10.1097/GOX.0000000000000604]

37 **Migliori ME**, Putterman AM. The domed dermis-fat graft orbital implant. *Ophthalmic Plast Reconstr Surg* 1991; **7**: 23-30 [PMID: 2018746 DOI: 10.1097/00002341-199103000-00003]

38 **Jovanovic N**, Carniciu AL, Russell WW, Jarocki A, Kahana A. Reconstruction of the Orbit and Anophthalmic Socket Using the Dermis Fat Graft: A Major Review. *Ophthalmic Plast Reconstr Surg* 2020; **36**: 529-539 [PMID: 32134765 DOI: 10.1097/IOP.0000000000001610]

39 **Kuzmanović Elabjer B**, Miletić D, Bušić M, Bišćan Tvrdi A, Bosnar D, Bjeloš M. Dermis-Fat Graft for Correction of Recurrent Severe Upper Eyelid Retraction in Graves' Orbitopathy. *Acta Clin Croat* 2018; **57**: 173-176 [PMID: 30256028 DOI: 10.20471/acc.2018.57.01.23]

40 **Barbera C**, Manzoni R, Dodaro L, Ferraro M, Pella P. Reconstruction of the tarsus-conjunctival layer using a venous wall graft. *Ophthalmic Plast Reconstr Surg* 2008; **24**: 352-356 [PMID: 18806653 DOI: 10.1097/IOP.0b013e3181863292]

41 **Tomassini GM**, Ansidei V, Ricci AL, Cagini C, Cencetti F, Simonetti S, Covarelli P. Venous graft for reconstruction of neoplastic and post-traumatic eyelid defects. *In Vivo* 2012; **26**: 447-451 [PMID: 22523297]

42 **Scevola A**, Sanna MP, Maxia S, Esposito S, Di Giulio S, Sartore L. Venous Graft for Full-thickness Palpebral Reconstruction. *Plast Reconstr Surg Glob Open* 2015; **3**: e344 [PMID: 26034651 DOI: 10.1097/GOX.0000000000000300]

43 **Ibáñez-Flores N**, Bruzual-Lezama C, Castellar-Cerpa JJ, Fernández-Montalvo L. Lower eyelid reconstruction with pericranium graft and Mustarde flap. *Arch Soc Esp Oftalmol (Engl Ed)* 2019; **94**: 514-517 [PMID: 31171387 DOI: 10.1016/j.oftal.2019.04.011]

44 **Grixti A**, Malhotra R. Oral mucosa grafting in periorbital reconstruction. *Orbit* 2018; **37**: 411-428 [PMID: 29405795 DOI: 10.1080/01676830.2018.1435693]

45 **Jin MJ**, Gao Y. Using Buccal Mucosa and Auricular Cartilage With a Local Flap for Full-Thickness Defect of Lower Eyelid. *J Craniofac Surg* 2021; **32**: e660-e661 [PMID: 34054082 DOI: 10.1097/SCS.0000000000007770]

46 **Chait LA**, Cort A, Braun S. Upper and lower eyelid reconstruction with a neurovascular free flap from the first web space of the foot. *Br J Plast Surg* 1980; **33**: 132-135 [PMID: 6989423 DOI: 10.1016/0007-1226(80)90070-3]

47 **Yap LH**, Earley MJ. The free 'V': a bipennate free flap for double eyelid resurfacing based on the second dorsal metacarpal artery. *Br J Plast Surg* 1997; **50**: 280-283 [PMID: 9215072 DOI: 10.1016/s0007-1226(97)91160-7]

48 **Thai KN**, Billmire DA, Yakuboff KP. Total eyelid reconstruction with free dorsalis pedis flap after deep facial burn. *Plast Reconstr Surg* 1999; **104**: 1048-1051 [PMID: 10654746 DOI: 10.1097/00006534-199909040-00022]

49 **Kushima H**, Yuzuriha S, Kondo S, Osada Y. Reconstruction of an inner layer defect of the upper eyelid with avulsion of the superior levator palpebrae muscle and orbital fat. *Ann Plast Surg* 2003; **51**: 321-324 [PMID: 12966248 DOI: 10.1097/01.SAP.0000054245.79994.9D]

50 **Ghadiali LK**, Patel P, Levine JP, Gold KG, Lisman RD. Microvascular Free Flap for Total Eyelid Reconstruction With a Visually Useful Eye. *Ophthalmic Plast Reconstr Surg* 2016; **32**: e109-e111 [PMID: 25299739 DOI: 10.1097/IOP.0000000000000288]

51 **Iwanaga H**, Nuri T, Okada M, Ueda K. Functional reconstruction of total upper eyelid defects with a composite radial forearm-palmaris longus tenocutaneous free flap: A report of two cases. *Microsurgery* 2019; **39**: 559-562 [PMID: 30666696 DOI: 10.1002/micr.30410]

52 **Rubino C**, Farace F, Puddu A, Canu V, Posadinu MA. Total upper and lower eyelid replacement following thermal burn using an ALT flap--a case report. *J Plast Reconstr Aesthet Surg* 2008; **61**: 578-581 [PMID: 17954041 DOI: 10.1016/j.bjps.2007.06.036]

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ORIGINAL ARTICLE

Randomized Controlled Trial

Metabolic and functional effects of exercise training in diabetic kidney transplant recipients

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Abstract

BACKGROUND

Physical activity levels are significantly lower in kidney transplant (KT) recipients compared to the general population. The effects of exercise training in KT recipients with diabetes mellitus remain unclear, and so little is known about the role of increased exercise on cardiovascular risk and metabolic profile of KT patients.

AIM

To investigate the effects of a 6-mo home-based exercise training program on functional capacity, glucose levels and lipid profile of diabetic KT patients.

METHODS

In total, 21 type II diabetic KT recipients were randomly assigned into two groups: Exercise (n = 11, aged 52.9 ± 10.1 years) and control (n = 10, aged 53.01 ± 9.5 years). All participants at baseline and the end of the study underwent biochemical tests for fasting plasma glucose levels, glycated hemoglobin and lipid profile and cardiopulmonary exercise testing for maximum oxygen uptake [$(VO_2)_{peak}$] estimation. The exercise group followed a 6-mo supervised home-based aerobic and progressive resistance exercise program of moderate intensity 3 times per week, while the control group continued to receive usual care.

RESULTS

At the end of the 6-mo study, the exercise group had significantly lower values in fasting plasma glucose by 13.4% (from 120.6 ± 28.9 mg/dL to 104.8 ± 21.9 mg/dL, P = 0.01), glycated hemoglobin by 1.5% (from 6.7% ± 0.4 to 6.6% ± 0.4, P = 0.01) and triglycerides by 8.5% (from 164.7 ± 14.8 mg/dL to 150.8 ± 11.6 mg/dL, P < 0.05) and higher values in high-density lipoprotein by 10.2% (from 51.4 ± 8.8

mg/dL to 57.2 ± 8.7 mg/dL, $P < 0.05$) and $(VO_2)_{peak}$ by 4.7% (from 22.7 ± 3.3 to 23.8 ± 4.2, $P = 0.02$) than the control group. There were statistically significant differences between the two groups at the end of the study for fasting plasma glucose (decreased by 9.6%, $P < 0.05$), triglycerides (decreased by 4.5%, $P = 0.04$) and $(VO_2)_{peak}$ (increased by 4.4%, $P = 0.01$). Finally, after training, there was a moderate, positive linear relationship between $(VO_2)_{peak}$ and glycated hemoglobin in the exercise group ($r = 0.408$, $P = 0.03$).

CONCLUSION

The results demonstrated that a 6-mo home-based mixed type exercise training program can improve the functional capacity, levels of glucose and lipid profile of diabetic KT recipients.

Key Words: Renal transplant recipients; Diabetes mellitus; exercise; Lipid profile; Glucose control; Functional capacity

Core Tip: Physical activity levels are significantly lower in kidney transplant (KT) recipients compared to the general population. The effects of exercise training in KT recipients with diabetes mellitus remain unclear, and so little is known about the role of increased exercise on cardiovascular risk and metabolic profile of KT patients. This randomized controlled trial aimed to investigate the effects of a 6-mo home-based exercise training program on functional capacity, glucose levels and lipid profile of diabetic KT patients. The results of the present study demonstrated that a long-term exercise training program is feasible and effective in diabetic KT recipients.

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INTRODUCTION

Renal transplantation is an effective treatment option for end-stage kidney disease patients and aims to improve quality of life and reduce mortality. Kidney transplant (KT) patients are dealing with many non- or modifiable risk factors after the transplantation surgery, especially due to the use of maintenance immunosuppression[1,2]. Dyslipidemia, abnormal glucose tolerance, hypertension, anemia and nephrotoxicity are common immunosuppressive therapy side effects in KT patients[2,3]. Unfavorable alterations in lipid and glucose profiles contribute to high cardiovascular risk[4], while low functional capacity due to comorbidities, corticosteroids and inactivity is common among these patients [5].

Diabetes mellitus incidence among the KT patient population is also high. Regular physical exercise can be an adjunct therapeutic modality for patients with diabetes mellitus, as it reduces the risk of cardiovascular disease, increases insulin sensitivity[5], leads to better glucose control and reduces lipid disorders[1]. High cardiovascular disease risk in KT patients is strongly associated with low physical activity levels[6-8]. Despite physical exercise benefiting KT patients' general health, only a few patients include physical activity in their daily routine[9]. This may be due to the non-normalized physical fitness after transplantation and comorbidities[10,11].

Although most of the studies on KT recipients have previously evaluated functional capacity and metabolic profile compared to healthy individuals, only a few studies have investigated the effects of structured exercise programs on glucose levels and lipid profile. Results from the few studies on functional capacity in KT recipients have shown that physical inactivity is a risk factor contributing to a patient's low physical fitness, which increases the risk of morbidity and mortality[5,9].

By increasing physical activity levels during their daily life KT recipients show favorable results, such as improvements in their cardiovascular fitness[6], even though the exact type, frequency or intensity recommended is not yet clear. Home-based exercise programs have previously largely been applied in hemodialysis and patients undergoing cardiovascular rehabilitation[4,12], while only two studies have so far provided home-based exercise rehabilitation programs for KT recipients[13,14]. This study aimed to examine the effects of a 6-mo home-based exercise training program on glycemic control, lipid profile and functional capacity of diabetic KT recipients.

MATERIALS AND METHODS

Patients

Twenty-eight adult KT recipients with type 2 diabetes (T2D) mellitus were recruited from the Transplant Surgery Clinic of the Hippokration General Hospital of Thessaloniki, Greece. Exclusion criteria included age older than 70 years, body mass index over 40 kg/m^2, presence of autoimmune disorders (such as systemic lupus erythematosus, multiple sclerosis, ulcerative colitis, Crohn's disease or rheumatoid arthritis), history of recent coronary heart disease (CHD) (myocardial infarction, unstable angina) within the previous 6 mo, serious musculoskeletal problems that may limit the patient's participation in this study, non-compliance with diabetes medication and previous participation in an exercise training program.

Study design

Initially, all patients who met the inclusion criteria underwent clinical examination {electrocardiography, hemodynamic [blood pressure and heart rate (HR)] and anthropometric (weight and height) measurements}, blood sampling and cardiorespiratory testing for their physical fitness estimation. After baseline measurements, patients were randomly assigned by simple randomization (drawing lots) to either an exercise group or a control group. Participants in the control group were asked to maintain their regular lifestyle and their current physical activity level during the study period. At the end of the 6-mo study, all patients underwent the same assessment. All tests were conducted by the same researcher, who was blinded to group allocation. Patients' medications were asked to remain unchanged during the study period. This randomized controlled trial protocol was approved by the Ethics Committee of the Aristotle University of Thessaloniki (Protocol number: 117461/2019). All participants received all the necessary study information before the enrollment and provided written informed consent. The clinical trial started in September 2019 and ended in February 2020.

Functional capacity assessment

To assess patient functional capacity, patients underwent a symptom-limited cardiopulmonary exercise testing on a treadmill using a Bruce protocol[15] during morning hours (9:00-11:00 am). Breath-by-breath gas exchange was measured by the Med Graphics Breeze Suite CPX Ultima (Medical Graphics Corp, MN, United States). The electrocardiogram was continuously monitored throughout each test, and the blood pressure was measured at every stage. The endpoint was set as the respiratory exchange ratio ≥ 1.10. From each test, the peak oxygen uptake [$(VO_2)_{peak}$], pulmonary ventilation, ventilatory equivalents for oxygen (pulmonary ventilation/VO_2), carbon dioxide (pulmonary ventilations/VCO_2) and the ratio between VO_2 and maximum HR (VO_2/HR_{max}) were measured.

Lipid and glucose profile assessment

At baseline and the end of the study, blood samples were taken from the brachial artery between 7:00-9:00 am, after a 12-h fast by the same blinded microbiologist at the Hippokration General Hospital of Thessaloniki. Blood samples were drawn from each group to determine by photometric method hematocrit, by computational method hemoglobin, by ion-selective electrode method serum concentrations of sodium, potassium, calcium, magnesium and electrolytes (potassium, sodium, calcium, phosphorus, magnesium), by enzymatic colorimetric method fasting plasma glucose (FPG) (mg/Dl), serum triglycerides (TG) and hemoglobin A1c (HbA1c) and by enzymatic method serum total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Results were analyzed through biochemical auto-analyzer devices.

Exercise program design

Participants in the exercise group received a home-based exercise program for 6 mo. The exercise program included aerobic exercise and muscle strengthening exercises, 3 times per week for 60-90 min, with moderate intensity, *i.e.*, 60%-80% of the maximum HR reached during cardiopulmonary exercise testing. Training intensity was increased gradually throughout the study according to each patient's capacity and adaptations. Each exercise session started with a 10-min warm-up and finished with a 10-min recovery (upper and lower limp stretching).

The aerobic part of each exercise session consisted of walking through going up and down stairs or cycling on a stationary bike, initially for 15 min, with a consequent gradual increase of time by 5 min every 2 wk, reaching 40 min in the last 2 wk before the end of the program. After a 5 min break, patients continued with the strengthening part of the exercise program. Patients were asked to perform six dynamic muscle strengthening exercises using just their body weight at the beginning. During the first week, each patient had three familiarization sessions with a physical education teacher experienced in exercise rehabilitation for patients with chronic disease, who also gave him/her an information booklet with exercise instruction images and a detailed description of the strengthening part of the program. Strengthening exercises were performed in 2 sets of 8-10 repetitions (with a 1-min passive break between the sets), in a progressive sequence from sitting to standing position. The exercise prescription included three strengthening exercises for the upper limbs (such as shoulder press, bicep curl and

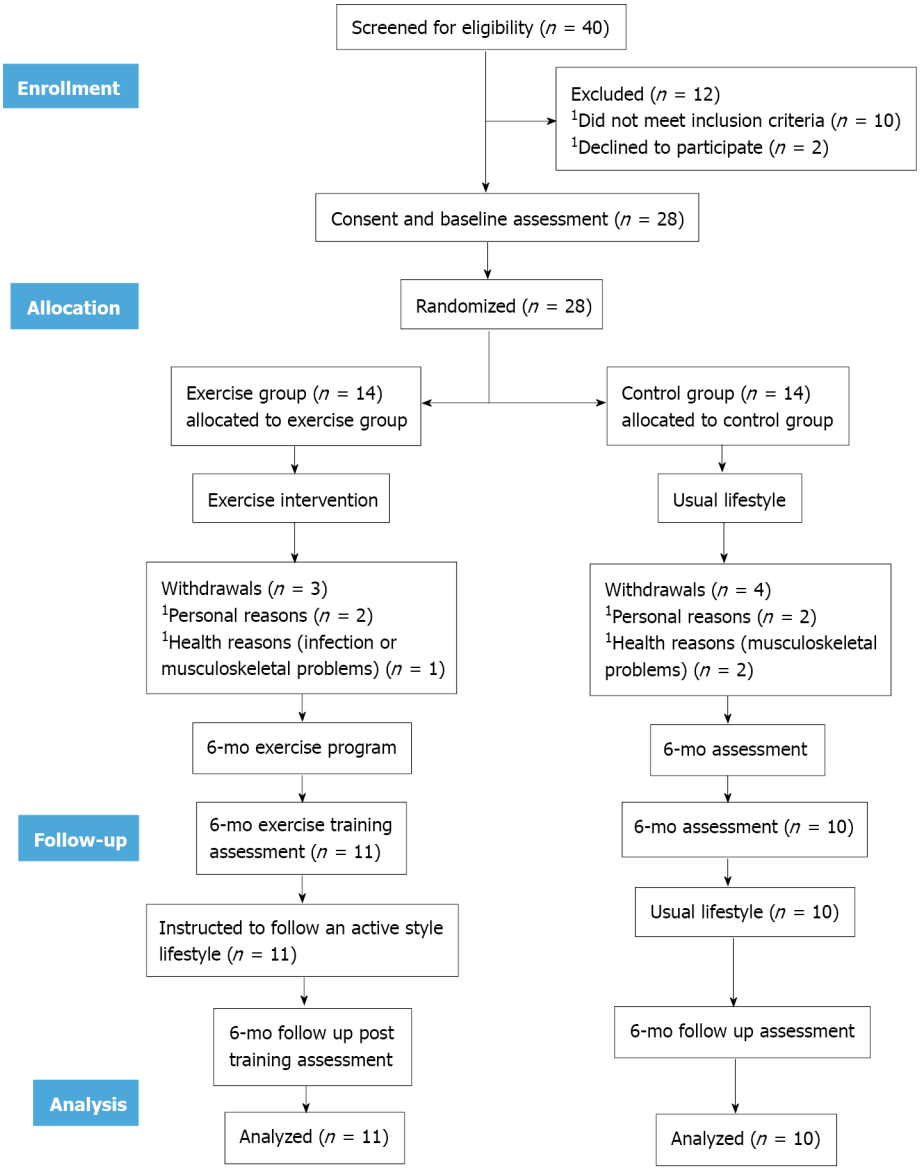

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Figure 1 Flow chart diagram of the study design. [1]Flowchart of participants was based on recommendations from the Consolidated Standards of Reporting Trials. EX: Exercise; C: Control.

triceps extension) and three for the lower limbs (such as leg flexion-extension). Progressively they were asked to perform the same exercises using rubber bands, balls and dumbbells (1 kg). Patients were advised to first perform 2 sets (8-10 repetitions) of upper limb strengthening exercise with balls and 2 sets with the 1 kg dumbbells (8-10 repetitions) in a sitting position. Second, patients were asked to place the rubber bands on their feet, tie them to the bottom of their bed or chair and do strengthening exercises in a sitting position (2 sets, 8-10 repetitions). Last, patients were asked to place the dumbbells on their feet in a standing position and move their legs back and forth, right and left of their torso, with hands placed in the middle of their body.

To ensure each patient's autonomy, the interventional 6-mo home-based exercise program was individualized, while the progress and adherence to the program were monitored by telephone every week and a home visit every month to control improvement and possible modification of the program by the researcher. To enhance compliance, participants were asked to fill in individual diaries, describing the type, frequency and duration of each exercise session and significant notes, which were collected every week through telephone communications. Moreover, researchers contacted patients for possible modifications or recommendations for exercise prescription.

Furthermore, it was essential for patients to measure before each exercise session (at least 30 min before) their blood glucose, blood pressure and HR levels and note the results in their diary. If glucose concentration was below 70 mg/dL or above 130 mg/dL, patients were advised to avoid starting exercise. Moreover, intake of a small number of carbohydrates (10-15 g) before exercise or having a carbohydrate snack available, in case of signs of hypoglycemia, was an important preventive measure.

Patients were also informed about the area of insulin injection that should be done in the abdominal cavity and not in the exercised limbs.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS 27.0 for Windows, Chicago, IL, United States) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to evaluate variables' normality of distribution. Mean differences within time and between the two groups were analyzed using two-way analysis of variance with repeated measures. Linear regression was used to study the association between variables that revealed statistically significant changes over time. Data were expressed as mean ± SD for normally distributed variables. The two-tailed *P*-values < 0.05 were considered statistically significant.

RESULTS

Patient demographic data and characteristics

At baseline, 40 KT patients were screened for eligibility; 28 were included in our study and randomized to either exercise or control group. During the 6 mo, 3 patients from the exercise group and 4 patients from the control group withdrew from the study due to health reasons (such as infection or musculoskeletal problems) or personal reasons (such as lack of time). Therefore, 21 patients completed the study (exercise group: $n = 11$; control group: $n = 10$). The flowchart of participants was based on recommendations from the Consolidated Standards of Reporting Trials (Figure 1). There was no statistically significant difference between the two groups' demographic and clinical data (Table 1). There were no exercise-induced musculoskeletal, cardiovascular, renal or other complications during the study.

Lipid and glucose profile results

After the 6-mo home-based exercise program, a statistically significant reduction of FPG by 13.4% ($P = 0.01$), TG by 8.5% ($P < 0.05$) and HbA1c by 1.5% ($P = 0.01$) as well as a significant increase in HDL by 10.2% ($P < 0.05$) compared to the baseline values in the exercise group was noted. In contrast, there was no statistically significant difference in any biochemical parameter studied in the control group at the end of the study (Table 2). Concerning changes between groups at the end of the study, the mean concentrations of FPG and TG were decreased by 9.6% ($P < 0.05$) and 4.5% ($P = 0.04$), respectively.

Functional capacity results

Exercise group results from the cardiopulmonary exercise testing revealed a statistically significant increase in $(VO_2)_{peak}$ by 4.7%, ($P = 0.02$) at the end of the study (Table 3). At baseline, there was no statistically significant difference between groups, but at the end of the study, there was only a significant intergroup difference in $(VO_2)_{peak}$, which was increased by 4.4% ($P = 0.01$) in the exercise group compared to controls.

Correlations

Lastly, linear regression analysis showed that there was a moderate, positive correlation only between $(VO_2)_{peak}$ and HbA1c after training in the exercise group ($r = 0.408$, $P = 0.03$) (Figure 2).

DISCUSSION

The results of the present study demonstrated that a home-based aerobic and strengthening exercise training program improved serum lipids by lowering the TG and increasing the HDL levels and glucose metabolism, as reflected by fasting glucose and HbA1c levels in diabetic KT patients. Moreover, the improved cardiorespiratory fitness observed in the exercise patients was found to be linearly related to the improved HbA1c.

Randomized controlled trials on exercise training programs in KT patients are few, and so little is known about their positive or negative effects or the type, frequency or intensity of exercise in this population. Painter *et al*[13] was the first that studied the clinical effects of exercise training on CHD risk profile through the first year of renal transplantation. Results showed that even though exercise led to a statistically significant increase in HDL and decreased high TC-HDL ratio, which categorized patients at high CHD risk, exercise as the only modifiable parameter did not significantly reduce CHD risk in KT patients. Pooranfar *et al*[16] showed that a 10-wk, non-pharmaceutical, aerobic (at 45%-65% of maximum HR) and resistance exercise program statistically decreased TG, TC and LDL, while HDL remained unchanged.

A few years ago Juskowa *et al*[17] assessed the effects of early rehabilitation on the musculoskeletal system and blood atheromatic indices and found that after daily 30 min of exercise, FPG and HDL levels were statistically improved in the exercise group, while TC-HDL ratio was unchanged. There was also a

Table 1 Patients' baseline demographic and clinical data

	Exercise group	Control group	*P* value
Sex (male/female)	8/3	8/2	0.52
Age (yr)	52.9 ± 9.5	53.0 ± 13.1	0.51
Height (cm)	1.6 ± 0.5	1.6 ± 0.0	0.34
Weight (kg)	70.8 ± 12.2	72.1 ± 6.7	0.77
BMI (kg/m^2)	24.4 ± 2.6	25.6 ± 2.0	0.23
Place of residence			
Rural area	27.2% (3/11)	40.0% (4/10)	0.69
Urban area	72.7% (8/11)	60.0% (6/10)	0.42
Education			
Primary education	54.5% (6/11)	40.0% (4/10)	0.33
Secondary education	18.1% (2/11)	10.0% (1/10)	0.68
Higher education	9.0% (1/11)	20.0% (2/10)	0.65
No education	18.1% (2/11)	30.0% (3/10)	0.70
Employment status			
Employed	18.1% (2/11)	10.0% (1/10)	0.71
Unemployed	54.5% (6/11)	40.0% (4/10)	0.53
Retired	27.2% (3/11)	50.0% (5/10)	0.38
Smoking	18.1% (2/11)	10.0% (1/10)	0.74
eGFR-CKD-EPI equation (mL/min)	61.0 ± 7.3	59.5 ± 8.2	0.53
Stage of diabetic nephropathy			
Stage 3	81.8% (9/11)	90.0% (9/10)	0.77
Stage 4	18.1% (2/11)	10.0% (1/10)	0.64
Time after KTx (mo)	47.4 ± 18.3	47.8 ± 18.1	0.68
Primary causes of ESKD			
Diabetes mellitus	54.5% (6/11)	50.0% (5/10)	0.64
Hypertension	27.2% (3/11)	20.0% (2/10)	0.56
Polycystic kidney disease	18.1% (2/11)	10.0% (1/10)	0.56
Glomerulonephritis	9.0% (1/11)	10.0% (1/10)	0.72
Nephrosclerosis	9.0% (1/11)	0.0% (0/10)	0.55
Reflux nephropathy	0.0% (0/11)	10.0% (1/10)	0.61
Others	0.0% (0/11)	10.0% (1/10)	0.59
Medication			
Statins	100.0% (11/11)	100.0% (10/10)	0.53
Calcium channel blockers	36.3% (4/11)	50.0% (5/10)	0.23
Oral antidiabetic drugs	18.1% (2/11)	30.0% (3/10)	0.51
Angiotensin II receptor blockers/angiotensin converting enzyme blockers	54.5% (6/11)	50.0% (5/10)	0.66
Slow and/or intermediate acting insulin	81.9% (9/11)	70.0% (7/10)	0.47
Immunosuppression therapy (corticosteroid, tacrolimus, mycophenolate mofetil)	100.0% (11/11)	100.0% (10/10)	0.74
Adherence to medication	90.9% (10/11)	100.0% (10/10)	0.82

Hematocrit (%)	42.1 ± 4.6	39.8 ± 4.5	0.63
Hemoglobin (g/dL)	14.1 ± 1.0	13.1 ± 1.6	0.16
Na^+ (mg/dL)	139.8 ± 2.5	140.3 ± 4.3	0.90
K^+ (mg/dL)	4.1 ± 0.3	4.3 ± 0.5	0.15
Ca^{2+} (mg/dL)	10.1 ± 0.5	9.7 ± 0.9	0.94
P (mg/dL)	2.9 ± 0.5	3.4 ± 0.4	0.09
Mg^+ (mg/dL)	1.6 ± 0.1	1.6 ± 0.3	0.50
Fe^+ (mg/dL)	89.8 ± 23.2	87.9 ± 16.6	0.54
Urea (mg/dL)	42.2 ± 8.7	48.1 ± 16.7	0.90
Creatinine (mg/dL)	1.1 ± 0.2	1.2 ± 0.5	0.16
Alkaline phosphatase (mg/dL)	72.1 ± 27.2	62.5 ± 10.4	0.17
Uric acid (mg/dL)	5.7 ± 1.1	5.9 ± 1.2	0.23
24-h urine albumin level (mg/dL)	106.4 ± 25.1	115.6 ± 20.9	0.25

Paired-sample *t*-test for continuous variables. Significant at the 0.05 level ($P < 0.05$). BMI: Body mass index; KTx: Kidney transplantation; eGFR: Estimated glomerular filtration rate; ESKD: End-stage kidney disease; CKD-EPI: Chronic kidney disease epidemiology collaboration equation; Na: Sodium; P: Potassium; Ca: Calcium; Mg: Magnesium; P: Phosphorus; Fe: Iron.

Table 2 Lipid and glucose profile at the beginning and the end of the 6-mo clinical trial

	Exercise group			Control group			Exercise *vs* control group	
	Baseline	After 6-mo	*P* value	Baseline	After 6-mo	*P* value	Pre	Post
FPG (mg/dL)	120.6 ± 28.9	104.8 ± 21.9	0.01	116.1 ± 33.2	115.4 ± 33.9	0.38	0.47	< 0.05
TC (mg/dL)	224.8 ± 30.4	224.0 ± 30.1	0.11	229.7 ± 28.8	230.8 ± 27.8	0.60	0.41	0.48
TG (mg/dL)	164.7 ± 14.8	150.8 ± 11.6	< 0.05	165.4 ± 19.0	165.2 ± 20.5	0.67	0.11	0.04
HDL (mg/dL)	51.4 ± 8.8	57.2 ± 8.7	< 0.05	51.1 ± 7.9	51.3 ± 12.6	0.43	0.56	0.06
LDL (mg/dL)	119.6 ± 11.4	119.4 ± 10.9	0.27	119.4 ± 17.0	119.5 ± 16.4	0.33	0.78	0.45
HbA1c (%)	6.7 ± 0.4	6.6 ± 0.4	0.01	6.5 ± 1.0	6.5 ± 1.1	0.25	0.20	0.36

Data are expressed as mean ± SD. $P > 0.05$: Baseline *vs* 6 mo follow-up; $P > 0.05$ and $P < 0.05$: Exercise *vs* control group. FPG: Fasting plasma glucose; TC: Total cholesterol; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HbA1c: Hemoglobin A1c.

positive correlation between improved graft function and muscle strength in the intervention group. The results of our study showed that a 6-mo mixed type exercise program led to a significant decrease in TG, FPG and HbA1c and an increase in HDL, without affecting the TC and LDL levels.

Interestingly, a 6-mo combined exercise program in our diabetic KT recipients led to a significantly improved lipid and glucose profile, while their functional capacity was enhanced, too. These results are very important, as cardiovascular mortality in KT patients is almost 10 times higher than in the general population[18], and the T2D prevalence according to global estimates will increase by 3.0%-6.0% at the end of 2025, with approximately 3 million T2D patients[19]. According to our results, combined exercise training in diabetic patients seems to be the most dominant choice.

De Feyter *et al*[20] showed that after a 5-mo progressive resistance training with high-intensity interval training, T2D patients under regular diabetes medication, had lower FPG and HbA1c levels, while HDL, LDL and TG did not statistically improve. Furthermore, Yavari *et al*[21] in a 52-wk aerobic, resistance or combined training program in 80 T2D patients found that aerobic or combined exercise statistically reduced TG, but the long-term combined exercise was associated with higher reductions both in HbA1c and TG levels compared to the aerobic or resistance training groups. Similarly, Cauza *et al*[22] compared the effects of short-term (4 mo) and long-term (8 mo) strength and endurance training on glucose and lipid control in 20 T2D patients. Results showed that HbA1c, TC, LDL and TG were statistically decreased in the group of the 8-mo combined training program, while the group in the 4-mo exercise program developed after the end of the exercise training an atherogenic lipid profile and did not improve glycemic control compared to those who continued exercising.

Table 3 Functional capacity and respiratory responses at the beginning and the end of the 6-mo clinical trial

	Exercise group			Control group			Exercise *vs* control group	
	Baseline	After 6-mo	*P* value	Baseline	After 6-mo	*P* value	Pre	Post
$(VO_2)_{peak}$ (mL/kg/min)	22.7 ± 3.3	23.8 ± 4.2	0.02	21.9 ± 4.1	21.8 ± 3.2	0.34	0.43	0.01
RER_{max}	1.1 ± 0.0	1.2 ± 0.1	0.53	1.1 ± 0.0	1.1 ± 0.2	0.75	0.73	0.48
VO_2/HR_{max}	12.6 ± 3.3	13.0 ± 3.0	0.23	12.7 ± 2.9	12.8 ± 2.6	0.69	0.63	0.51
$VE/(VO_2)_{max}$	37.2 ± 5.0	36.3 ± 2.2	0.54	37.4 ± 4.8	37.3 ± 4.5	0.56	0.54	0.62
$VE/V(CO_2)_{max}$	33.0 ± 4.4	32.4 ± 4.3	0.60	32.9 ± 4.1	33.2 ± 3.8	0.33	0.38	0.43

Data are expressed as mean ± SD. $P > 0.05$: Baseline *vs* 6 mo follow-up; $P > 0.05$ and $P < 0.05$: Exercise *vs* control group. HR: Heart rate; RER: Respiratory exchange ratio; VO_2/HR_{max}: Ratio between VO_2 and maximum heart rate; VE: Pulmonary ventilation; $VE/(VO_2)_{max}$: Ventilatory equivalents for oxygen; $VE/V(CO_2)_{max}$: Ventilatory equivalents for carbon dioxide; $(VO_2)_{peak}$: Maximum oxygen consumption.

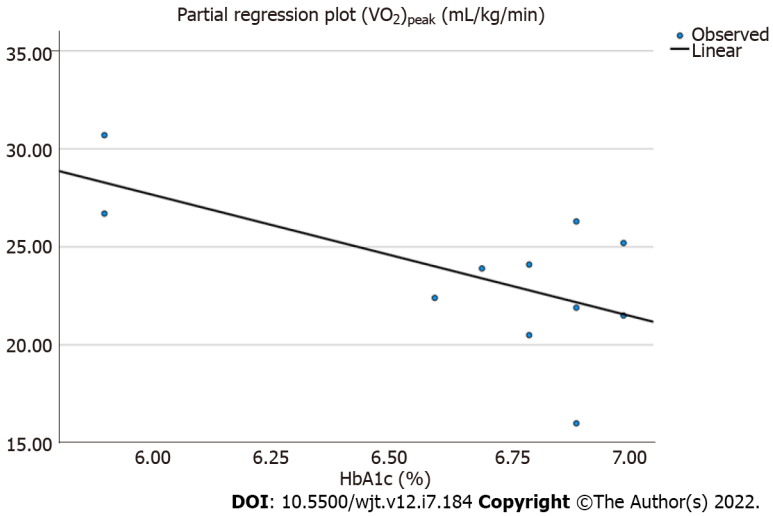

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Figure 2 Linear regression analysis between the peak oxygen uptake and glycated hemoglobin (%) after 6 mo in exercise group (r = 0.408, P = 0.03). HbA1c: Hemoglobin A1c; $(VO_2)_{peak}$: Maximum oxygen consumption.

Our study revealed statistical differences between groups after a 6-mo combined exercise program in FPG and TG levels under stable diabetic medication for both groups, similarly to the above-mentioned studies. Maintenance of diabetic medication therapy is important to understand glycemic control and lipid profile relationship and to exact results towards effects of exercise on dyslipidemia without the impact of drugs[23].

According to a recent systematic review[24], structured exercise programs for KT patients have shown short-term improvements in aerobic capacity and muscular strength, while De Smet and Van Craenenbroeck[1] mentioned that exercise towards long-term effects is only slightly investigated. Improving functional capacity is very important for KT patients, with or without diabetes. According to Calella *et al*[24], exercise training improves the cardiovascular fitness of KT patients. However, $(VO_2)_{peak}$ improvements were observed only after aerobic exercise training. In a recent randomized controlled trial, O'Connor *et al*[14] showed that $(VO_2)_{peak}$ values have notably increased after a 12-wk non-supervised moderate-intensity aerobic exercise program and that after a 9-mo follow up there were statistically significant differences in the $(VO_2)_{peak}$ values between the exercise and control groups.

On the contrary, Riess *et al*[25] showed that a supervised endurance and strength exercise program did not improve the cardiovascular disease score, although it improved the aerobic capacity and muscle strength of the KT recipients, who were taking statins and immunosuppression medication. Moreover, in a previous study of ours a 15.8% increase in $(VO_2)_{peak}$ after a 6-mo aerobic exercise training on KT patients was also noted[26]. At the end of the study, we found a statistically significant increase of 4.7% in $(VO_2)_{peak}$ of the exercise group and a significant intergroup difference in $(VO_2)_{peak}$.

This study has some limitations that need to be taken into consideration. Firstly, the sample size was small, which may decrease the power of our findings. However, this study included a 6-mo

intervention, which is a considerably long period for patients. Secondly, the biochemical tests were performed only at baseline and after 6 mo. Unfortunately, there was neither an assessment in the middle of the study nor a follow-up. Thus, larger randomized controlled trials should be implemented in the specific population to confirm the favorable effects of exercise on their metabolic profile.

CONCLUSION

In conclusion, long-term aerobic and strengthening exercise training in diabetic KT patients was found to have many beneficial effects on patients' metabolic profiles and functional capacities. The results of the present study demonstrated that a long-term exercise training program is feasible and effective in diabetic KT recipients. It is a major challenge to change their daily routine into active living to sustain their physical fitness and the benefits achieved by systemic exercise training.

ARTICLE HIGHLIGHTS

Research background

According to the existing literature, kidney transplant (KT) recipients with diabetes mellitus seem to have low physical activity levels, while dyslipidemia and abnormal glucose profile are common cardiovascular risk factors.

Research motivation

As little is known about the effects of systematic exercise on the metabolic profile and cardiovascular risk of KT patients, we believe that this study will positively contribute to the literature gap.

Research objectives

This study aimed to investigate the effects of a mixed type 6-mo exercise program on functional capacity, glucose and lipid profile of KT patients with diabetes mellitus.

Research methods

KT patients were randomly divided into two groups. Both exercise and control groups underwent biochemical blood analysis, in order to determine lipid and glucose levels, at baseline and at the end of the study. Cardiopulmonary exercise testing was also done to assess functional capacity.

Research results

At the end of the 6-mo study, fasting plasma glucose, glycated hemoglobin, triglycerides, high-density lipoprotein and the peak oxygen uptake [$(VO_2)_{peak}$] were statistically improved in the exercise group, while a positive linear relationship between peak oxygen uptake and glycated hemoglobin was also found (r = 0.408, P = 0.03).

Research conclusions

According to the results, a 6-mo home-based mixed type exercise training program can significantly improve the metabolic profile and functional capacity of diabetic KT recipients.

Research perspectives

It is crucial for future larger randomized controlled trials to explore the side effects of exercise on the metabolic profile and respiratory responses of diabetic KT recipients.

FOOTNOTES

Author contributions: Michou V designed this study and collected and analyzed the data; Michou V, Koudi E and Deligiannis A drafted the manuscript and gave final approval of the version to be published; Michou V and Koudi E took part in this study as cardiopulmonary exercise testing operators or assistants; Nikodimopoulou M recruited diabetic kidney transplant recipients to participate to the study.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Aristotle University of Thessaloniki (Protocol number:117461/2019).

Clinical trial registration statement: This study is registered at Laboratory of Sports Medicine, Aristotle University of Thessaloniki, TEFAA.

Informed consent statement: All study participant received all the necessary study information before the study enrollment and provided written informed consent.

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

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REFERENCES

1 **De Smet S**, Van Craenenbroeck AH. Exercise training in patients after kidney transplantation. *Clin Kidney J* 2021; **14**: ii15-ii24 [PMID: 33981416 DOI: 10.1093/ckj/sfab022]
2 **Rysz J**, Franczyk B, Radek M, Ciałkowska-Rysz A, Gluba-Brzózka A. Diabetes and Cardiovascular Risk in Renal Transplant Patients. *Int J Mol Sci* 2021; **22** [PMID: 33810367 DOI: 10.3390/ijms22073422]
3 **Halloran PF**. Immunosuppressive drugs for kidney transplantation. *N Engl J Med* 2004; **351**: 2715-2729 [PMID: 15616206 DOI: 10.1056/NEJMra033540]
4 **Imran HM**, Baig M, Erqou S, Taveira TH, Shah NR, Morrison A, Choudhary G, Wu WC. Home-Based Cardiac Rehabilitation Alone and Hybrid With Center-Based Cardiac Rehabilitation in Heart Failure: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2019; **8**: e012779 [PMID: 31423874 DOI: 10.1161/JAHA.119.012779]
5 **Ponticelli C**, Favi E. Physical Inactivity: A Modifiable Risk Factor for Morbidity and Mortality in Kidney Transplantation. *J Pers Med* 2021; **11** [PMID: 34575704 DOI: 10.3390/jpm11090927]
6 **Armstrong K**, Rakhit D, Jeffriess L, Johnson D, Leano R, Prins J, Garske L, Marwick T, Isbel N. Cardiorespiratory fitness is related to physical inactivity, metabolic risk factors, and atherosclerotic burden in glucose-intolerant renal transplant recipients. *Clin J Am Soc Nephrol* 2006; **1**: 1275-1283 [PMID: 17699359 DOI: 10.2215/CJN.00210106]
7 **Zelle DM**, Corpeleijn E, Stolk RP, de Greef MH, Gans RO, van der Heide JJ, Navis G, Bakker SJ. Low physical activity and risk of cardiovascular and all-cause mortality in renal transplant recipients. *Clin J Am Soc Nephrol* 2011; **6**: 898-905 [PMID: 21372213 DOI: 10.2215/CJN.03340410]
8 **Kang AW**, Garber CE, Eaton CB, Risica PM, Bostom AG. Physical Activity and Cardiovascular Risk among Kidney Transplant Patients. *Med Sci Sports Exerc* 2019; **51**: 1154-1161 [PMID: 30629045 DOI: 10.1249/MSS.0000000000001886]
9 **Bellizzi V**, Cupisti A, Capitanini A, Calella P, D'Alessandro C. Physical activity and renal transplantation. *Kidney Blood Press Res* 2014; **39**: 212-219 [PMID: 25118089 DOI: 10.1159/000355799]
10 **Williams TJ**, McKenna MJ. Exercise limitation following transplantation. *Compr Physiol* 2012; **2**: 1937-1979 [PMID: 23723030 DOI: 10.1002/cphy.c110021]
11 **Zanotto T**, Gobbo S, Bullo V, Vendramin B, Roma E, Duregon F, Bocalini DS, Di Blasio A, Cugusi L, Furian L, Di Bella C, Neunhaeuserer D, Battista F, Bergamin M, Ermolao A. Postural balance, muscle strength, and history of falls in end-stage renal disease patients living with a kidney transplant: A cross-sectional study. *Gait Posture* 2020; **76**: 358-363 [PMID: 31901763 DOI: 10.1016/j.gaitpost.2019.12.031]
12 **Baggetta R**, D'Arrigo G, Torino C, ElHafeez SA, Manfredini F, Mallamaci F, Zoccali C, Tripepi G; EXCITE Working group. Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: a secondary analysis of the EXCITE trial. *BMC Geriatr* 2018; **18**: 248 [PMID: 30342464 DOI: 10.1186/s12877-018-0938-5]
13 **Painter PL**, Hector L, Ray K, Lynes L, Paul SM, Dodd M, Tomlanovich SL, Ascher NL. Effects of exercise training on coronary heart disease risk factors in renal transplant recipients. *Am J Kidney Dis* 2003; **42**: 362-369 [PMID: 12900820 DOI: 10.1016/s0272-6386(03)00673-5]
14 **O'Connor EM**, Koufaki P, Mercer TH, Lindup H, Nugent E, Goldsmith D, Macdougall IC, Greenwood SA. Long-term pulse wave velocity outcomes with aerobic and resistance training in kidney transplant recipients - A pilot randomised controlled trial. *PLoS One* 2017; **12**: e0171063 [PMID: 28158243 DOI: 10.1371/journal.pone.0171063]
15 **Nerlekar N**, Mulley W, Rehmani H, Ramkumar S, Cheng K, Vasanthakumar SA, Rashid H, Barton T, Nasis A, Meredith

IT, Moir S, Mottram PM. Feasibility of exercise stress echocardiography for cardiac risk assessment in chronic kidney disease patients prior to renal transplantation. *Clin Transplant* 2016; **30**: 1209-1215 [PMID: 27327660 DOI: 10.1111/ctr.12796]

16 **Pooranfar S**, Shakoor E, Shafahi M, Salesi M, Karimi M, Roozbeh J, Hasheminasab M. The effect of exercise training on quality and quantity of sleep and lipid profile in renal transplant patients: a randomized clinical trial. *Int J Organ Transplant Med* 2014; **5**: 157-165 [PMID: 25426284]

17 **Juskowa J**, Lewandowska M, Bartłomiejczyk I, Foroncewicz B, Korabiewska I, Niewczas M, Sierdziński J. Physical rehabilitation and risk of atherosclerosis after successful kidney transplantation. *Transplant Proc* 2006; **38**: 157-160 [PMID: 16504691 DOI: 10.1016/j.transproceed.2005.12.077]

18 **Neale J**, Smith AC. Cardiovascular risk factors following renal transplant. *World J Transplant* 2015; **5**: 183-195 [PMID: 26722646 DOI: 10.5500/wjt.v5.i4.183]

19 **Wild S**, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047-1053 [PMID: 15111519 DOI: 10.2337/diacare.27.5.1047]

20 **De Feyter HM**, Praet SF, van den Broek NM, Kuipers H, Stehouwer CD, Nicolay K, Prompers JJ, van Loon LJ. Exercise training improves glycemic control in long-standing insulin-treated type 2 diabetic patients. *Diabetes Care* 2007; **30**: 2511-2513 [PMID: 17626892 DOI: 10.2337/dc07-0183]

21 **Yavari A**, Najafipoor F, Aliasgharzadeh A, Niafar M, Mobasseri M. Effect of aerobic exercise, resistance training or combined training on glycaemic control and cardiovascular risk factors in patients with type 2 diabetes. *Biology Sport* 2012; **29**: 135-143 [DOI: 10.5604/20831862.990466]

22 **Cauza E**, Hanusch-Enserer U, Strasser B, Kostner K, Dunky A, Haber P. The metabolic effects of long term exercise in Type 2 Diabetes patients. *Wien Med Wochenschr* 2006; **156**: 515-519 [PMID: 17041809 DOI: 10.1007/s10354-006-0337-y]

23 **Wang S**, Ji X, Zhang Z, Xue F. Relationship between Lipid Profiles and Glycemic Control Among Patients with Type 2 Diabetes in Qingdao, China. *Int J Environ Res Public Health* 2020; **17** [PMID: 32718055 DOI: 10.3390/ijerph17155317]

24 **Calella P**, Hernández-Sánchez S, Garofalo C, Ruiz JR, Carrero JJ, Bellizzi V. Exercise training in kidney transplant recipients: a systematic review. *J Nephrol* 2019; **32**: 567-579 [PMID: 30649716 DOI: 10.1007/s40620-019-00583-5]

25 **Riess KJ**, Haykowsky M, Lawrance R, Tomczak CR, Welsh R, Lewanczuk R, Tymchak W, Haennel RG, Gourishankar S. Exercise training improves aerobic capacity, muscle strength, and quality of life in renal transplant recipients. *Appl Physiol Nutr Metab* 2014; **39**: 566-571 [PMID: 24766239 DOI: 10.1139/apnm-2013-0449]

26 **Kouidi E**, Vergoulas G, Anifanti M, Deligiannis A. A randomized controlled trial of exercise training on cardiovascular and autonomic function among renal transplant recipients. *Nephrol Dial Transplant* 2013; **28**: 1294-1305 [PMID: 23129823 DOI: 10.1093/ndt/gfs455]

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SYSTEMATIC REVIEWS

Enhanced recovery after surgery in liver transplantation: Challenges and feasibility

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Abstract

BACKGROUND

Enhanced recovery after surgery (ERAS) started a revolution that changed age-old surgical stereotypical practices regarding the overall management of the surgical patient. In the last decade, ERAS has gained significant acceptance in the community of general surgery, in addition to several other surgical specialties, as the evidence of its advantages continues to grow. One of the last remaining fields, given its significant complexity and intricate nature, is liver transplantation (LT).

AIM

To investigate the existing efforts at implementing ERAS in LT.

METHODS

We conducted a systematic review of the existing studies that evaluate ERAS in orthotopic LT, with a multimodal approach and focusing on measurable clinical

primary endpoints, namely length of hospital stay.

RESULTS
All studies demonstrated a considerable decrease in length of hospital stay, with no readmission or negative impact of the ERAS protocol applied to the postoperative course.

CONCLUSIONS
ERAS is a well-validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT.

Key Words: Enhanced recovery; Enhanced recovery after surgery; Recovery; Liver transplantation; Liver

Core Tip: Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. The benefits of ERAS in liver transplantation seem promising, and further studies should be conducted to validate its application in properly selected patients.

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INTRODUCTION

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery[1]. Since its introduction in 1997 by Kehlet *et al*[2], initially destined for and subsequently established in colorectal surgery, the concept of ERAS was validated and has since evolved and spread to a multitude of surgical disciplines[3] including solid organ transplantation[4].

Although the concept of enhanced recovery was explored in liver transplantation (LT) before its official introduction by Kehlet *et al*[2] as early as 1990 in the form of early extubation yielding encouraging results[5], it was done so without the classic multimodal approach, focusing and highlighting on the importance of anesthesia management in these patients[6]. Over the years, independent studies have validated the significance and efficiency of other classic ERAS parameters such as preoperative nutrition, early mobilization, early feeding, and optimal analgesia of patients undergoing LT. Nevertheless, the medical literature is scarce in studies that combine all of the above parameters in a classic large-scale ERAS approach specific for LT. This narrative review paper will investigate existing efforts at implementing ERAS in LT, as well as try to identify the existing challenges and future potential developments in the field.

This review paper investigates existing efforts at implementing ERAS in LT and identifies the existing challenges and future potential developments in the field.

MATERIALS AND METHODS

Our goal was to identify the existing studies that evaluate ERAS in orthotopic LT, with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stay. Medline, Embase, OVID, and the Cochrane library were searched in the English language using the search terms (ERAS OR "enhanced recovery" OR "fast track" AND "liver transplantation") from years 1990 to 2021 and after independent assessment from three reviewers, three articles were selected. PRISMA flow chart is presented in Figure 1.

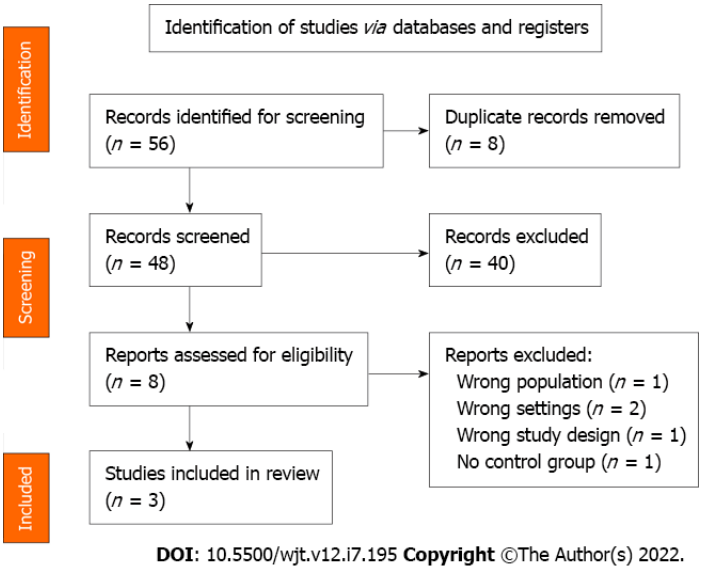

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Figure 1 PRISMA flowchart.

RESULTS

There was a small number of studies identified, which were limited scale non-randomized single-center observational studies, with the exception of the work of Rao *et al*[7], who presented a prospective single-blinded randomized study including 128 patients divided in two groups: ERAS (n = 54) and control (n = 74). The ERAS group was analyzed by logistic stepwise regression analysis and displayed a decreased intensive care unit and hospital stay, without significant difference in the postoperative complication rate between the two groups and no readmissions or postoperative mortality during the follow-up period. Brustia *et al*[8] conducted a small-scale feasibility study with 10 patients treated prospectively with an ERAS protocol who were compared with 20 matched patients treated by the same team in previous years. They designed an elaborate 26-point ERAS protocol and observed a 47% reduction in the total length of stay compared to the control arm. There were no readmissions or postoperative mortality during the follow-up period.

Xu *et al*[9] reported a cohort of 93 patients, 40 in the ERAS group and 53 in the control group, and found a significant reduction of postoperative hospital stay in favor of the ERAS group (14.5 *vs* 16 d; P < 0.001). No difference in postoperative complication rate between the two groups and no readmissions or postoperative mortality were noted.

Common inclusion criteria used in the aforementioned studies are presented in Table 1. As expected, patients' Model for End-Stage Liver Disease (MELD) scores were low in all four studies, as they reflect patient status[10]. All studies included patients with a MELD score well below 25. Patients with no previous history of LT were also selected for the ERAS group in all three studies. A considerable number of patients for ERAS LT had a hepatocellular carcinoma (HCC)-related indication in all three studies (Brustia 90%, Xu 42.5%, Rao 33.3%).

Given the lack of a standardized ERAS protocol, each team designed its own protocols, based on previous experience from existing literature on other surgical fields. Table 2 depicts a comparison of the preoperative, intraoperative and post-operative characteristics between the three studies. All of the studies applied multimodal measures in the three distinct phases of classic ERAS protocols: preoperative, intraoperative and postoperative phase. In Table 3, measures applied by all three authors are depicted in capital letters. Of the 26 points proposed by Brustia *et al*[8], 11 (42.3%) were observed by all three authors.

All three studies demonstrated a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocol applied in the postoperative course (Table 2). From the above-mentioned publications, we meta-analyzed the primary endpoint, postoperative hospital stay. The variable was continuous, and the results were summarized using median and 25%-75% values (because the data were skewed). The sample mean and standard deviations were calculated using the formula of Wan *et al*[11]. The random-effects model was applied for the meta-analysis, as high heterogeneity was expected among the studies with regard to study populations and diagnostic procedures. The presence of between-study heterogeneity was quantitatively reflected with the I^2 index, considering I^2 of > 50%, indicative of statistically significant heterogeneity. R studio version 4.0.2 software was used to perform all of the statistical analyses, employing the packages "meta" and "metaphor." A comparison of total hospital stay showed a statistically significant difference in both groups (n = 251; MD- 5.79; 95% confidence interval (CI), 10.89 to 0.69; I^2 = 89%; P < 0.01). Nevertheless,

Table 1 Common inclusion criteria (with incorporation of exclusion criteria)

Inclusion criteria	Brustia *et al*[8]	Xu *et al*[9]	Rao *et al*[7]
Meld score < 25	√	[1]	[1]
HCC	√	√	√
The first liver transplantation	√	√	√
Age > 18	√	> 16	> 16

[1]All patients included in the three studies had a MELD score < 25. HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease.

great heterogeneity was observed between the samples (Figure 2). A similar meta-analysis of the MELD score showed that there was no statistically significant difference in both groups (n = 251, MD -0.25, 95%CI, -1.36 to 0.85; I^2 0%; P = 0.62) (Figure 3). As aforementioned, all patients were low MELD patients with a mean MELD well below 20.

DISCUSSION

The scarcity of strong evidence in the widespread application of ERAS programs in LT may reflect the reluctance of teams to implicate such protocols in a cohort of patients that are generally perceived as a frail, high-risk group, undergoing a major surgical procedure of a life-threatening nature. The evolution of LT on the other hand, is a successful story, evolving from an experimental and innovative procedure to a more "standard" one over the last several decades, and especially when performed in high volume centers with experienced multidisciplinary teams. Throughout the years, LT has proved its life saving nature as an operation and the morbidity and mortality plummeted, offering patients excellent survival and quality of life[12]. The major incentives in applying ERAS in LT came from the successful application of Enhanced Recovery Programs in Liver Surgery[13] and the subsequent publication of suggested guidelines for ERAS in Liver Surgery[14]. Although ERAS with its multimodal approach pattern did not appear in the literature until recently, the concept of multimodal clinical pathways in LT was raised as early as 2011 by Pavlakis *et al* of the Beth Israel Deaconess Medical Center team[15], characterizing the transplantation domain as an "*ideal forum for successful implementation of clinical pathways*" and highlighting their importance and potential in reducing length of stay, morbidity, costs, as well as improving patient satisfaction. Piñero *et al*[16] introduced in 2015 the concept of the early discharge from hospital following LT focusing on healthcare costs and proposed an early discharge prediction model based on MELD points (exception MELD points were deemed a favorable prognostic factor), length of surgery (time < 4 h), transfusion of less than 5 units of packed red blood cells, and early respirator weaning. The author concluded that early discharge from the hospital following LT is feasible, without a negative impact on patient or graft survival, nor did it increase short-term rehospitalization. A recent publication of Brustia *et al*[18] in Paris reinforced the basis for further developing ERAS in LT. Although it is a small-scale single-center observational study, the authors reported a 47% reduction of length of hospital stay with no safety issues in a small but well-designed protocol. This conclusion was corroborated by all three publications mentioned above, demonstrating that ERAS in LT could be possible in a larger scale and should be further studied. Rodríguez-Laiz *et al*[17] presented a cohort of 236 patients who were treated with a comprehensive multistep ERAS protocol that is the product of lessons and experiences emanating from liver surgery and other disciplines aiming to evaluate its value as a proof-of-concept. In this study, the authors identified 133 patients who were discharged early and they retrospectively defined them as the ERAS group. However, their study, with extremely short lengths of stay, was inherently flawed, as the authors pointed out, by a lack of a traditional control group; for this reason, their article was not included in our final selection. In 2021 Brustia *et al*[18] drafted the "*Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Society Recommendations,*" after a systematic review by a wide international panel of experts and the application of the Delphi method. The authors of the manuscript recognized the lack of current strong evidence in ERAS in LT but laid a solid foundation and precious scaffold, which can serve as the basis for large studies in the definitive validation of ERAS in LT.

ERAS is a well-validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT. The majority of studies analyzing ERAS in LT use a cohort of low MELD highly selected patients that might not represent the majority of patients that benefit from LT; an issue that has to be addressed. The overall majority of patients in the three studies analyzed were low MELD HCC patients, and this type of selection might harbor an inherent bias in evaluating ERAS in LT. However it is a first step and understandably first steps must be careful. The encouraging results

Table 2 Preoperative, intraoperative, and post-operative characteristics

Preoperative	Brustia *et al*[8]		Xu *et al*[9]		Rao *et al*[7]	
	ERAS group, *n* = 10	CONTROL group, *n* = 20	ERAS group, *n* = 40	CONTROL group, *n* = 53	ERAS group, *n* = 54	CONTROL group, *n* = 74
Gender						
Male	8	17	35	46	40	58
Female	2	3	5	7	1	16
Age, yr	60.1 (52.5-66.1)	58.2 (52.6-65.3)	49.5 (40-56.8)	53 (47-59)	52.4 + 15.2	55.8 + 14.3
Primary cause						
Alcohol	7 (70%)	9 (45%)	7	3	6 (11.1)	10 (13.5)
Viral cirrhosis	7 (70%)	10 (50%)	11	16	30 (55.6)	40 (54.1)
HBV	2 (20%)	4 (20%)	NA	NA	NA	NA
HCV	6 (60%)	8 (40%)	NA	NA	NA	NA
Metabolic syndrome	2 (20%)	4 (20%)	NA	NA	NA	NA
Biliary disease	0	3 (15%)	NA	NA	NA	NA
HCC	9 (90%)	9 (45%)	17	24	18 (33.3)	24 (32.4)
MELD score	7 (6-10)	7 (6-9)	14 (9-22)	17 (14-19)	7.7 + 3.2	7.9 + 4.6
Intraoperative						
Operative time	6.0 (5.9-8.4) h	6.7 (5.7-8.2) h	443.7 + 85.3min	453.5 + 62.3min	265 (215-360) min	325 (275-455) min
Anhepatic period	NA	NA	44.3 + 5.2 min	42.7 + 4.2 min	45 (35-70) min	60 (50-75) min
Blood loss	NA	NA	775 (525-1000) mL	800 (600-1000) mL	1100 (300-4200) mL	2900 (1600-7000) mL
Hypothermia during the operation (*n*, %)	NA	NA	0	12%	0	0
Postoperative						
Early extubation (h)	2 (0-2)	7.5 (4.5-13.0)	0	6 (5.5-8)	NA	NA
ICU stay (d)	3 (2-4)	4.5 (3.0-8.3)	2 (2-3)	4 (4-5)	2 (1-7)	5 (3-15)
Complications (*n*, %)	5 (50%)	16 (80%)	9 (22.5%)	26 (49.1%)	10 (18.5%)	20 (27%)
Pain score after operation	3 (1.0-4.0) POD	4.5 (2.7-6.) POD	2.45+ 0.54	3.02+0.44	NA	NA
Postoperative hospital stay (d)	9.5 (9.0-10.5)	18 (14.3-24.3)	14.5 (12-17)	16 (15-18)	18 (15-32)	28 (23-35)
Readmission within 30 d after discharge	NA	NA	0	0	0	0

Categorical variables are reported using percentages; continuous variables are summarized using median and 25%-75% percentiles. ERAS: Enhanced recovery after Surgery; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; ICU: Intensive care unit; MELD: Model for end-stage liver disease.

presented, along with the observed benefit of a well-designed ERAS protocol in these patients mandates further exploration and expansion of inclusion criteria in these types of protocols. After all, an earlier discharge might be the result of a better overall patient management in all aspects of their journey through the hospital and not necessarily the primary endpoint.

One of the key factors in implementing ERAS protocols is the understanding of the philosophy behind ERAS by both patients and caregivers and although this might seem simple or a given, studies indicate that this might not be the case[19,20]. As ERAS is new to the field of LT, similar issues are expected to occur. In the first years of the implementation of ERAS in colorectal surgery, many issues arose concerning patient and physician capability of correctly implementing and accepting what proved to be a validated protocol for better patient recovery[21,22] including the complexity of these multimodal pathways[23], the need for teamwork along with the difficulty of eradicating old surgical stereotypes of traditional care. Agrafiotis *et al*[24], along with the first author of the present review, have

Table 3 Experimental "fast trans" protocol items

Preoperative	Brustia *et al*[8]	Xu *et al*[9]	Rao *et al*[7]
1 Outpatient counseling and information	√	√	√
2 Preoperative carbohydrate loading	√	√	√
3 Absence of preanesthetic medication (anxiolytic)	√		
Intraoperative			
4 Antimicrobial prophylaxis and skin preparation	√		
5 Prevention of intraoperative hypothermia	√	√	
6 Incision	√		
7 Adapted IV filling	√	√	√
8 Temporary portocaval anastomosis	√		
9 No prophylactic nasogastric intubation	√		√
10 No prophylactic abdominal drainage	√		√
11 Prevention of postoperative nausea and vomiting	√		
12 Antithrombotic prophylaxis and/oranti-aggregation	√	√	
13 Early extubation (< 6 h after the endof lt)	√	√	√
Postoperative			
14 Early mobilization (POD1)	√	√	√
15 Patient-controlled analgesia	√	√	
16 Gastric probe removal POD1	√	√	
17 Clear liquid per OS POD1	√	√	√
18 Enteral feeding per OS POD1	√	√	√
19 Stop IV fluids POD1	√	√	
20 Per OS analgesia (POD2)	√	√	
21 Abdominal drain removal POD2	√		
22 Urinary probe removal POD2	√	√	√
23 Stop IV analgesia POD3	√	√	
24 Independent mobilization POD3	√	√	√
25 Daily revision of discharge criteria	√	√	√
26 Audit	√	√	√

ICU: Intensive care unit; IV: Intravenous; LT: Liver transplantation; POD: Post-operative day; PONV: Post-operative nausea and vomiting.

explored in 2013 the efficacy of a "soft" non-strict fast-track protocol in a cohort of 92 patients undergoing colorectal surgery. The conclusion was that even without a strict ERAS protocol, enhanced recovery and accelerated safe patient discharge are possible, pointing out among others[25] that *"length of stay should not be an aim in itself within an enhanced recovery protocol. The main object of these programs ought to be the enhancement of patient recovery and not earlier discharge."* This statement is endorsed by our team, in the Transplantation Department of a public Medical School part of a public healthcare system with significant challenges, who tried to evaluate the implementation of a non-strict ERAS protocol in selected LT patients in a small cohort of patients trying to replicate the results of Brustia *et al*[8]. In a small feasibility and safety study, we observed a 56% decrease in hospital stay in the ERAS group without any safety issues (unpublished data). These encouraging results might indicate that ERAS, when implemented in the right way, can be beneficial to patients even in small volume transplant centers and their implementation should be encouraged. We also noted the lack of estimation of the importance of every point in the proposed ERAS protocols towards the final endpoint, which hinders the simplification of these protocols, as we do not currently know which one of the steps – if any - could be omitted without a significant compromise in the outcome.

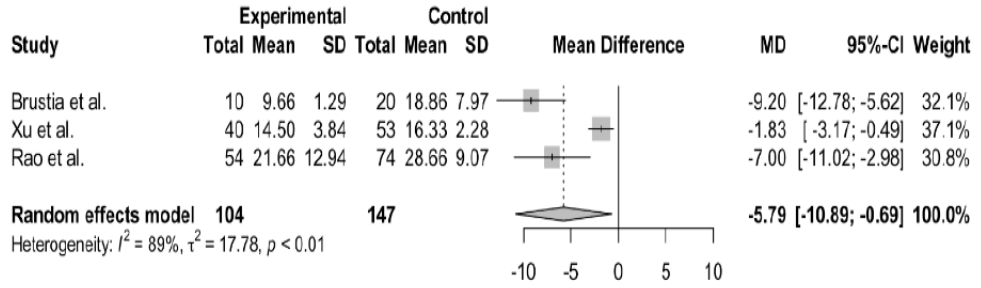

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Figure 2 Forest plot of postoperative hospital stay in days.

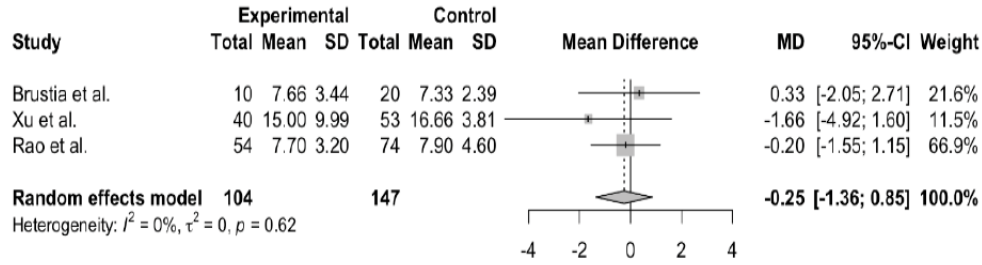

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Figure 3 Forest plot of model for end-stage liver disease scores.

Henric Kehlet pointed out the delay of the development of ERAS: "*there is an urgent need for better implementation of the current established scientific evidence for ERAS practices in order to fill the still very present gap between knowing and doing*" and has been advocating for many years the concept of "stress free, pain free" operations[26], which might seem an impossible task for operations of the magnitude of a LT. However, as the term "fast-track" was gradually replaced by the more correct term "enhanced recovery," the concept of "*first better, then faster*" had to be reappraised[27,28].

CONCLUSION

Enhanced recovery means better recovery and its value should be further exploited for liver transplant patients. After all, ERAS is not about the type of operation; ERAS is about the patient.

ARTICLE HIGHLIGHTS

Research background

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery.

Research motivation

In the last decade, ERAS has gained significant acceptance in the community of general surgery, in addition to several other surgical specialties, as the evidence of its advantages continues to grow. Orthotopic Liver Transplantation (LT) remains one of the last frontiers in the application of ERAS.

Research objectives

To evaluate existing data on the use of ERAS in orthotopic LT.

Research methods

We conducted a systematic review of the existing studies that evaluate ERAS in orthotopic LT with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stay.

Research results

All studies demonstrated a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocols in the postoperative period.

Research conclusions

Enhanced recovery can be safely applied in selected LT patients and its value should be further exploited.

Research perspectives

The future widespread use of ERAS in selected LT patients seems promising.

FOOTNOTES

Author contributions: Katsanos G, Karakasi KE, and Tsoulfas G wrote the manuscript; Morsi-Yeroyannis A and Sinakos E conducted the statistics; Goulis I, Giouleme O, and Vasileiadou S, reviewed the articles; Oikonomou IM and Mochailidou E proofread the manuscript; Tsoulfas G, Katsanos G, and Mouloudi E designed the review; Antoniadis N, Massa E, Tsakiris G, and Evlavis G conducted the bibliographic research and analyzed the results; All authors read and approved the final manuscript.

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REFERENCES

1 **ERAS Society**. [cited 2 June 2021]. Available from: https://erassociety.org/ [DOI: 10.5040/9781472542182.0010]
2 **Kehlet H**, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. *Br J Surg* 1999; **86**: 227-230 [PMID: 10100792 DOI: 10.1046/j.1365-2168.1999.01023.x]
3 **Zhang X**, Yang J, Chen X, Du L, Li K, Zhou Y. Enhanced recovery after surgery on multiple clinical outcomes: Umbrella review of systematic reviews and meta-analyses. *Medicine (Baltimore)* 2020; **99**: e20983 [PMID: 32702839 DOI: 10.1097/MD.0000000000020983]
4 **Golder HJ**, Papalois V. Enhanced Recovery after Surgery: History, Key Advancements and Developments in Transplant Surgery. *J Clin Med* 2021; **10** [PMID: 33921433 DOI: 10.3390/jcm10081634]
5 **Rossaint R**, Slama K, Jaeger M, Konrad M, Pappert D, Bechstein W, Blumhardt G, Neuhaus P, Falke KJ. Fluid restriction and early extubation for successful liver transplantation. *Transplant Proc* 1990; **22**: 1533-1534 [PMID: 2389392]
6 **Biancofiore G**, Bindi ML, Romanelli AM, Boldrini A, Bisà M, Esposito M, Urbani L, Catalano G, Mosca F, Filipponi F. Fast track in liver transplantation: 5 years' experience. *Eur J Anaesthesiol* 2005; **22**: 584-590 [PMID: 16119594 DOI: 10.1017/s0265021505000980]
7 **Rao JH**, Zhang F, Lu H, Dai X Z, Zhang CY, Qian XF, Wang XH, Lu L. Effects of multimodal fast-track surgery on liver transplantation outcomes. Hepatobiliary & pancreatic diseases international: HBPD INT 2017; 16: 364–369 [DOI:

10.1016/s1499-3872(17)60020-1]
8 **Brustia R**, Monsel A, Conti F, Savier E, Rousseau G, Perdigao F, Bernard D, Eyraud D, Loncar Y, Langeron O, Scatton O. Enhanced Recovery in Liver Transplantation: A Feasibility Study. *World J Surg* 2019; **43**: 230-241 [PMID: 30094639 DOI: 10.1007/s00268-018-4747-y]
9 **Xu Q**, Zhu M, Li Z, Zhu J, Xiao F, Liu F, Wang Y, Liu C. Enhanced recovery after surgery protocols in patients undergoing liver transplantation: A retrospective comparative cohort study. *Int J Surg* 2020; **78**: 108-112 [PMID: 32304897 DOI: 10.1016/j.ijsu.2020.03.081]
10 **Samuel D**, Coilly A. Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. *BMC Med* 2018; **16**: 113 [PMID: 30064414 DOI: 10.1186/s12916-018-1110-y]
11 **Wan X**, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14**: 135 [PMID: 25524443 DOI: 10.1186/1471-2288-14-135]
12 **Adam R**, McMaster P, O'Grady JG, Castaing D, Klempnauer JL, Jamieson N, Neuhaus P, Lerut J, Salizzoni M, Pollard S, Muhlbacher F, Rogiers X, Garcia Valdecasas JC, Berenguer J, Jaeck D, Moreno Gonzalez E; European Liver Transplant Association. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. *Liver Transpl* 2003; **9**: 1231-1243 [PMID: 14625822 DOI: 10.1016/j.lts.2003.09.018]
13 **Coolsen MM**, Wong-Lun-Hing EM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH. A systematic review of outcomes in patients undergoing liver surgery in an enhanced recovery after surgery pathways. *HPB (Oxford)* 2013; **15**: 245-251 [PMID: 23458424 DOI: 10.1111/j.1477-2574.2012.00572.x]
14 **Melloul E**, Hübner M, Scott M, Snowden C, Prentis J, Dejong CH, Garden OJ, Farges O, Kokudo N, Vauthey JN, Clavien PA, Demartines N. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J Surg* 2016; **40**: 2425-2440 [PMID: 27549599 DOI: 10.1007/s00268-016-3700-1]
15 **Pavlakis M**, Hanto DW. Clinical pathways in transplantation: a review and examples from Beth Israel Deaconess Medical Center. *Clin Transplant* 2012; **26**: 382-386 [PMID: 22136467 DOI: 10.1111/j.1399-0012.2011.01564.x]
16 **Piñero F**, Fauda M, Quiros R, Mendizabal M, González-Campaña A, Czerwonko D, Barreiro M, Montal S, Silberman E, Coronel M, Cacheiro F, Raffa P, Andriani O, Silva M, Podestá LG. Predicting early discharge from hospital after liver transplantation (ERDALT) at a single center: a new model. *Ann Hepatol* 2015; **14**: 845-855 [PMID: 26436356 DOI: 10.5604/16652681.1171770]
17 **Rodríguez-Laiz GP**, Melgar-Requena P, Alcázar-López CF, Franco-Campello M, Villodre-Tudela C, Pascual-Bartolomé S, Bellot-García P, Rodríguez-Soler M, Miralles-Maciá CF, Más-Serrano P, Navarro-Martínez JA, Martínez-Adsuar FJ, Gómez-Salinas L, Jaime-Sánchez FA, Perdiguero-Gil M, Díaz-Cuevas M, Palazón-Azorín JM, Such-Ronda J, Lluís-Casajuana F, Ramia-Ángel JM. Fast-Track Liver Transplantation: Six-year Prospective Cohort Study with an Enhanced Recovery After Surgery (ERAS) Protocol. *World J Surg* 2021; **45**: 1262-1271 [PMID: 33620540 DOI: 10.1007/s00268-021-05963-2]
18 **Brustia R**, Monsel A, Skurzak S, Schiffer E, Carrier FM, Patrono D, Kaba A, Detry O, Malbouisson L, Andraus W, Vandenbroucke-Menu F, Biancofiore G, Kaido T, Compagnon P, Uemoto S, Rodriguez Laiz G, De Boer M, Orloff S, Melgar P, Buis C, Zeillemaker-Hoekstra M, Usher H, Reyntjens K, Baird E, Demartines N, Wigmore S, Scatton O. Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Recommendations. *Transplantation* 2022; **106**: 552-561 [PMID: 33966024 DOI: 10.1097/TP.0000000000003808]
19 **Herbert G**, Sutton E, Burden S, Lewis S, Thomas S, Ness A, Atkinson C. Healthcare professionals' views of the enhanced recovery after surgery programme: a qualitative investigation. *BMC Health Serv Res* 2017; **17**: 617 [PMID: 28859687 DOI: 10.1186/s12913-017-2547-y]
20 **Alawadi ZM**, Leal I, Phatak UR, Flores-Gonzalez JR, Holihan JL, Karanjawala BE, Millas SG, Kao LS. Facilitators and barriers of implementing enhanced recovery in colorectal surgery at a safety net hospital: A provider and patient perspective. *Surgery* 2016; **159**: 700-712 [PMID: 26435444 DOI: 10.1016/j.surg.2015.08.025]
21 **Maessen J**, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, Kessels AG, Revhaug A, Kehlet H, Ljungqvist O, Fearon KC, von Meyenfeldt MF. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg* 2007; **94**: 224-231 [PMID: 17205493 DOI: 10.1002/bjs.5468]
22 **Kahokehr A**, Sammour T, Zargar-Shoshtari K, Thompson L, Hill AG. Implementation of ERAS and how to overcome the barriers. *Int J Surg* 2009; **7**: 16-19 [PMID: 19110478 DOI: 10.1016/j.ijsu.2008.11.004]
23 **Feroci F**, Lenzi E, Baraghini M, Garzi A, Vannucchi A, Cantafio S, Scatizzi M. Fast-track colorectal surgery: protocol adherence influences postoperative outcomes. *Int J Colorectal Dis* 2013; **28**: 103-109 [PMID: 22941115 DOI: 10.1007/s00384-012-1569-5]
24 **Agrafiotis AC**, Corbeau M, Buggenhout A, Katsanos G, Ickx B, Van de Stadt J. Enhanced recovery after elective colorectal resection outside a strict fast-track protocol. A single centre experience. *Int J Colorectal Dis* 2014; **29**: 99-104 [PMID: 23982426 DOI: 10.1007/s00384-013-1767-9]
25 **Wind J**, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT, Gouma DJ, Bemelman WA; Laparoscopy and/or Fast Track Multimodal Management Versus Standard Care (LAFA) Study Group; Enhanced Recovery after Surgery (ERAS) Group. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* 2006; **93**: 800-809 [PMID: 16775831 DOI: 10.1002/bjs.5384]
26 **Kehlet H**. Enhanced Recovery After Surgery (ERAS): good for now, but what about the future? *Can J Anaesth* 2015; **62**: 99-104 [PMID: 25391731 DOI: 10.1007/s12630-014-0261-3]
27 **Vehmeijer SBW**, Husted H, Kehlet H. Outpatient total hip and knee arthroplasty. *Acta Orthop* 2018; **89**: 141-144 [PMID: 29202644 DOI: 10.1080/17453674.2017.1410958]
28 **Kehlet H**. Enhanced postoperative recovery: good from afar, but far from good? *Anaesthesia* 2020; **75** Suppl 1: e54-e61 [DOI: 10.1111/anae.14860]

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CASE REPORT

Portal vein-variceal anastomosis for portal vein inflow reconstruction in orthotopic liver transplantation: A case report and review of literature

Aviad Gravetz

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Abstract

BACKGROUND

Portal vein thrombosis (PVT) is a frequent complication occurring in 5% to 26% of cirrhotic patients candidates for liver transplantation (LT). In cases of extensive portal and or mesenteric vein thrombosis, complex vascular reconstruction of the portal inflow may become necessary for a successful orthotopic LT (OLT).

CASE SUMMARY

A 54-year-old male with history of cirrhosis secondary to schistosomiasis complicated with extensive portal and mesenteric vein thrombosis and severe portal hypertension who underwent OLT with portal vein-left gastric vein anastomosis.

CONCLUSION

We review the various types of PVT, the portal venous inflow reconstruction techniques.

Key Words: Portal vein thrombosis; Portal inflow reconstruction; Orthotopic liver transplantation; Splanchnic varices; Left gastric varix; Case report

Core Tip: The portal vein-variceal anastomosis is a challenging physiological non-anatomical technique of portal vein inflow reconstruction used and described rarely. Herein we review the various types of portal vein thrombosis, the portal venous inflow reconstruction techniques and describe an extraordinary case of portal vein-left gastric vein anastomosis for the portal inflow reconstruction during orthotopic liver transplantation.

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INTRODUCTION

Portal vein thrombosis (PVT) is a frequent and serious complication in patients with cirrhosis, with a prevalence ranging from 5% to 26%[1-4]. Patients with PV and/or mesenteric vein thrombosis while awaiting liver transplantation (LT) pose a significant surgical challenge for the reconstruction of the liver portal inflow, an essential step for successful orthotopic LT (OLT)[5-6]. While an end-to-end donor to recipient portal vein anastomosis is fashioned in the majority of liver transplant recipients, approximately 2% of recipients will require a complex vascular reconstruction due to inadequate recipient portal vein inflow[7,8].

The portal vein-variceal anastomosis is a challenging physiological non-anatomical technique of portal vein inflow reconstruction used and described rarely. Herein we review the various types of PVT, the portal venous inflow reconstruction techniques and describe an extraordinary case of portal vein-left gastric vein (LGV) anastomosis for the portal inflow reconstruction during OLT.

CASE PRESENTATION

Chief complaints

A 54-year-old male of Ethiopian origin who presented back in 1993 with variceal bleeding leading to a subsequent diagnosis of non-cirrhotic portal hypertension with splenomegaly and PVT with cavernous transformation.

History of present illness

The presence of granulomas and periportal fibrosis with preserved hepatic architecture on liver biopsy, together with positive serologic tests for antischistosomal antibodies and the patient origin suggested the diagnosis of hepatosplenic schistosomiasis. Further work up revealed protein C deficiency. Whether the patient received anthelmintic therapy upon diagnosis is unclear, however, prior to transplant no specific prophylactic treatment was administered as there was no evidence of active hepatic or systemic disease.

History of past illness

The patient in 1993 with variceal bleeding leading to a subsequent diagnosis of non-cirrhotic portal hypertension with splenomegaly and PVT with cavernous transformation.

Personal and family history

The patient has none personal and family history.

Physical examination

Medical management of portal hypertension complications included diuretics, beta-blockers and periodic upper endoscopy with sclerotherapy and esophageal varices ligation. The patient eventually presented with severe decompensation and model for end-stage liver disease score of 25 necessitating LT.

Laboratory examinations

His physical examination revealed signs of cachexia, jaundice, abdominal distention, umbilical hernia, caput medusa and impression of moderate to large volume ascites. Laboratory results showed total white blood cell count of 2.67 × 10^9/L, hemoglobin levels of 8 g/dL, platelet count of 33 × 10^9/L, international normalized ratio 2.43, total bilirubin of 7.5 mg/dL (and direct bilirubin of 3.6 mg/dL), serum

sodium 140 mEq/L, serum creatinine 1.1 mg/dL and albumin levels of 2.5 gr/dL.

Imaging examinations

Preoperative esophagogastroduodenoscopy showed grade III esophageal varices and portal hypertensive gastropathy. Imaging revealed liver cirrhosis, extensive portal and mesenteric vein thrombosis with cavernous transformation, splenomegaly, with the spleen measuring 20 cm in diameter, and splanchnic varices comprising a large left gastric varix (Figure 1).

FINAL DIAGNOSIS

Over the years the patient gradually developed compensated liver fibrosis and cirrhosis as seen on various imaging modalities and worsening liver synthetic function.

TREATMENT

The patient underwent OLT on April 2021 with piggyback venous outflow reconstruction and a portal vein-left gastric varix anastomosis for portal inflow. During the procedure the LGV was carefully dissected cephalad at the level of the mid lesser curvature of the stomach. Adequate venous flow was confirmed prior to creation of end-to-side porto-LGV anastomosis performed using polypropylene 5-0 suture (Figure 2A). Postoperative Doppler sonography documented patent anastomosis with adequate flow (Figure 2B), a finding which was confirmed by a contrast abdominal computed tomography performed on postoperative day 16 (Figure 2C).

OUTCOME AND FOLLOW-UP

The patient had a relatively benign postoperative course characterized by mild to moderate ascites, as anticipated, controlled initially with drainage and medical treatment and eventually resolved prior to discharge. Ten months post-operatively the patient is doing well with excellent liver function.

DISCUSSION

Schistosomiasis (bilharzia) is a chronic parasitic entero-pathogenic disease caused by a genus of trematodes commonly known as blood flukes[1]. Hepatic schistosomiasis represents the best known form of chronic disease and represents the most important cause of non-cirrhotic portal hypertension in Latin America, Africa, and Asia[2]. The pathogenesis of schistosomiasis is related to the host cellular immune response. This leads to granuloma formation and neo-angiogenesis with subsequent irreversible periportal fibrosis and, consequently, severe portal hypertension manifesting with splenomegaly and esophageal varices[3,4]. Traditionally the diagnosis of Schistosoma infection is based upon demonstration of parasite eggs in patient secretions or tissues. However, in the case of liver disease, detection of ova often fails and the diagnosis is established using serologic tests along with DNA amplification techniques and characteristic liver biopsy findings[5-7]. Praziquantel is the drug of choice to treat laboratory-proven Schistosoma infection[8]. The effect of antischistosomal treatment on disease manifestations varies by stage. Early liver involvement is known to resolve after anthelmintic therapy, but late manifestations, such as fibrosis, do not change and treatment is focused on tempering portal hypertension manifestations[9]. LT represents a curative option for patients who develop severe hepatic fibrosis and portal hypertension secondary to hepatic schistosomiasis[10], and no specific treatment is indicated for the recipients[11].

PVT is a frequent and serious complication in patients with cirrhosis, with a prevalence ranging from 5% to 26%[12-17]. Patients with cirrhosis presenting with or developing PV and/or superior mesenteric vein (SMV) thrombosis while awaiting LT pose a significant surgical challenge for the reconstruction of the liver portal inflow, an essential step for successful OLT[18,19]. Although PVT has long been considered an absolute contraindication to OLT, it is currently regarded as a relative contraindication, depending on the patient clinical status, type of PVT and collateral venous flow, and the surgeon's experience[20,21]. While an end-to-end donor to recipient portal vein anastomosis is fashioned in the majority of liver transplant recipients, approximately 2% of recipients will require a complex vascular reconstruction due to inadequate recipient portal vein inflow[22,23].

The type of PVT is classified according to the nature of the occlusion (complete *vs* partial) and the extension in the portal vein, the venous confluence and its contributories - the SMV and the splenic vein (SV). Various classification systems of PVT have been proposed with the Yerdel classification being

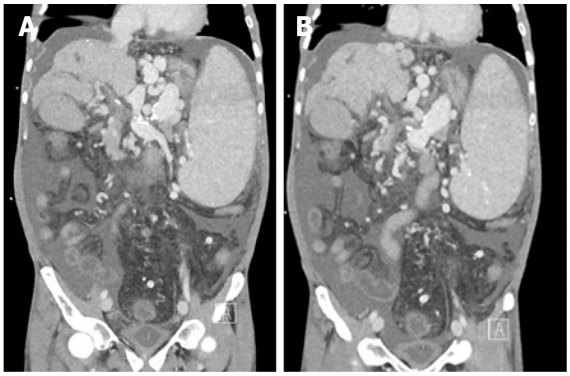

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Figure 1 Preoperative abdominal computed tomography. A: Extensive portal vein thrombosis; B: Superior mesenteric vein thrombosis.

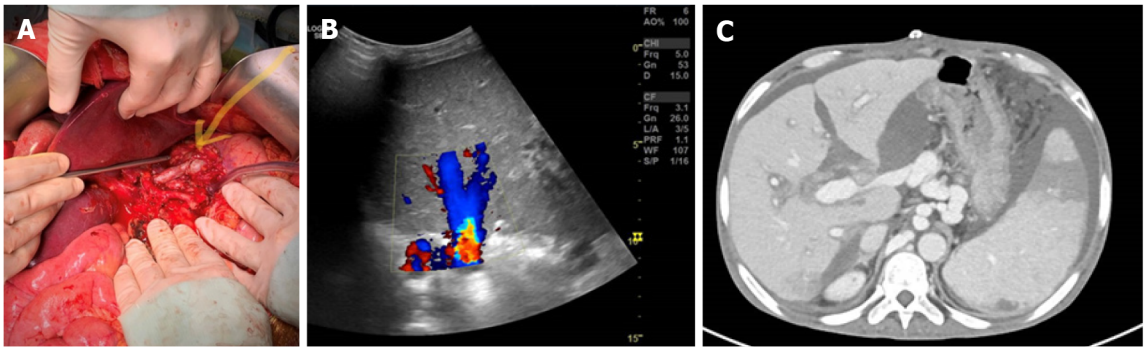

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Figure 2 Treatment imaging. A: End-to-side portal vein-left gastric vein anastomosis upon completion; B: Postoperative Doppler sonography documenting patent anastomosis with adequate flow; C: Abdominal computed tomography showing patent portal vein-left gastric vein anastomosis.

widely used because it correlates thrombus extent and surgical management[24-28]. Yerdel's classification defines grade I as partial PVT (< 50% of the lumen) with or without minimal extension into the SMV, grade II as partial PVT (> 50% of the lumen), grade III - complete thrombosis of both PV and proximal SMV and grade IV with complete PV and both proximal and distal SMV.

For the reconstruction of the liver portal inflow in the presence of PV-SMV thrombosis there are 3 main strategies: Anatomical (and physiological), physiological (non-anatomical) and non-physiological [19,29]. For Yerdel grades I to III, an anatomical reconstruction may be achieved; operative techniques include thrombectomy, whether the thrombus is removed *en-bloc* with the liver or through an intraoperative PV/SMV thrombectomy, followed by direct porto-portal anastomosis or indirect using an interposition venous graft.

For more complex cases of complete occlusion or proximal extension of the thrombus, such as in Yerdel's grade IV and some grade III cases, alternative approaches should be used to redirect the portal venous flow into the graft[29,30]. Some of those extraordinary cases of extensive thrombosis may be considered as a contraindication to transplant. However, when evaluated by highly experienced transplant centers, a complex vascular reconstruction may be attempted or else, a multivisceral transplant may be considered. That is, for Yerdel's grade IV and some grade III cases, a physiological (non-anatomical) or non-physiological (inflow achieved by reno-portal anastomosis, cavo-portal hemitransposition or portal vein arterialization), approach may be used.

The portal vein-variceal anastomosis is a challenging physiological non-anatomical technique of portal vein inflow reconstruction used and described rarely. In those procedures, enlarged splanchnic varices[31-34], LGV[35-38], or pericholedochal varix[39,40] is used. Use of a splanchnic varix such as a dilated LGV necessitates a meticulous and very careful dissection in a hostile surrounding of other dilated fragile varices. Furthermore, length of the donor's liver portal vein should be sufficient or else an interposition venous graft may be used for the anastomosis. From the functional standpoint, adequate portal flow should be assessed, using direct (needle- transducer) or indirect (ultrasound Doppler) method. In the occurrence of slow venous flow, proximal ligation of the varix may be considered in order to divert splanchnic venous drainage towards the neo-liver and to avoid the siphon effect of the peri-gastric varices and SV. In cases of extensive SMV thrombosis there is also a concern for inadequate venous intestinal drainage, despite a successful and functional anastomosis, and a as result refractory ascites.

Although challenging, good outcomes are possible in patients with extensive PV/SMV thrombosis undergoing LT. Meticulous patient selection, preoperative imaging planning and highly experienced surgical team are crucial for a successful transplantation and reconstruction of the portal inflow in those complex clinical scenarios. This case shows the feasibility of this unusual approach, using a dilated left gastric varix for the reconstruction of the liver portal inflow, giving a patient in an extreme condition access to life-saving LT.

CONCLUSION

Although challenging, good outcomes are possible in patients with extensive PV/SMV thrombosis undergoing LT. Meticulous patient selection, preoperative imaging planning and highly experienced surgical team are crucial for a successful transplantation and reconstruction of the portal inflow in those complex clinical scenarios. This case shows the feasibility of this unusual approach, using a dilated left gastric varix for the reconstruction of the liver portal inflow, giving a patient in an extreme condition access to life-saving LT.

FOOTNOTES

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REFERENCES

1 **Ross AG**, Olds GR, Cripps AW, Farrar JJ, McManus DP. Enteropathogens and chronic illness in returning travelers. *N Engl J Med* 2013; **368**: 1817-1825 [PMID: 23656647 DOI: 10.1056/NEJMra1207777]
2 **Bodh V**, Chawla Y. Noncirrhotic intrahepatic portal hypertension. *Clin Liver Dis (Hoboken)* 2014; **3**: 129-132 [PMID: 30992906 DOI: 10.1002/cld.344]
3 **Elbaz T**, Esmat G. Hepatic and intestinal schistosomiasis: review. *J Adv Res* 2013; **4**: 445-452 [PMID: 25685451 DOI: 10.1016/j.jare.2012.12.001]
4 **Andrade ZA**. Schistosomiasis and liver fibrosis. *Parasite Immunol* 2009; **31**: 656-663 [PMID: 19825105 DOI: 10.1111/j.1365-3024.2009.01157.x]
5 **Guimarães Cavalcanti M**, Marcello de Araujo-Neto J, Mauro Peralta J. Schistosomiasis: Clinical management of liver disease. *Clin Liver Dis (Hoboken)* 2015; **6**: 59-62 [PMID: 31040989 DOI: 10.1002/cld.495]
6 **Tamarozzi F**, Fittipaldo VA, Orth HM, Richter J, Buonfrate D, Riccardi N, Gobbi FG. Diagnosis and clinical management of hepatosplenic schistosomiasis: A scoping review of the literature. *PLoS Negl Trop Dis* 2021; **15**: e0009191 [PMID: 33764979 DOI: 10.1371/journal.pntd.0009191]
7 **Weerakoon KG**, Gordon CA, McManus DP. DNA Diagnostics for Schistosomiasis Control. *Trop Med Infect Dis* 2018; **3** [PMID: 30274477 DOI: 10.3390/tropicalmed3030081]
8 **Vale N**, Gouveia MJ, Rinaldi G, Brindley PJ, Gärtner F, Correia da Costa JM. Praziquantel for Schistosomiasis: Single-Drug Metabolism Revisited, Mode of Action, and Resistance. *Antimicrob Agents Chemother* 2017; **61** [PMID: 28264841 DOI: 10.1128/AAC.02582-16]

9 **Deng WC**, Li JX, Pan K, Kong GQ, He YK, Li YS. [Recommendation of a new clinical classification of advanced schistosomiasis]. *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi* 2012; **24**: 235-236 [PMID: 22799179]

10 **El Moghazy W**, Kashkoush S, O'hali W, Abdallah K. Long-term outcome after liver transplantation for hepatic schistosomiasis: a single-center experience over 15 years. *Liver Transpl* 2015; **21**: 96-100 [PMID: 25262935 DOI: 10.1002/lt.24010]

11 **Vincenzi R**, Neto JS, Fonseca EA, Pugliese V, Leite KR, Benavides MR, Cândido HL, Porta G, Miura IK, Pugliese R, Danesi VB, Guimarães TC, Porta A, Kondo M, Carone E, Chapchap P. Schistosoma mansoni infection in the liver graft: The impact on donor and recipient outcomes after transplantation. *Liver Transpl* 2011; **17**: 1299-1303 [PMID: 21504049 DOI: 10.1002/lt.22316]

12 **Garcia-Pagan JC**, Valla DC. Portal vein thrombosis: a predictable milestone in cirrhosis? *J Hepatol* 2009; **51**: 632-634 [PMID: 19660824 DOI: 10.1016/j.jhep.2009.06.009]

13 **Tao YF**, Teng F, Wang ZX, Guo WY, Shi XM, Wang GH, Ding GS, Fu ZR. Liver transplant recipients with portal vein thrombosis: a single center retrospective study. *Hepatobiliary Pancreat Dis Int* 2009; **8**: 34-39 [PMID: 19208512]

14 **Nery F**, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology* 2015; **61**: 660-667 [PMID: 25284616 DOI: 10.1002/hep.27546]

15 **Ponziani FR**, Zocco MA, Senzolo M, Pompili M, Gasbarrini A, Avolio AW. Portal vein thrombosis and liver transplantation: implications for waiting list period, surgical approach, early and late follow-up. *Transplant Rev (Orlando)* 2014; **28**: 92-101 [PMID: 24582320 DOI: 10.1016/j.trre.2014.01.003]

16 **Francoz C**, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. *J Hepatol* 2012; **57**: 203-212 [PMID: 22446690 DOI: 10.1016/j.jhep.2011.12.034]

17 **Ravaioli M**, Zanello M, Grazi GL, Ercolani G, Cescon M, Del Gaudio M, Cucchetti A, Pinna AD. Portal vein thrombosis and liver transplantation: evolution during 10 years of experience at the University of Bologna. *Ann Surg* 2011; **253**: 378-384 [PMID: 21183851 DOI: 10.1097/SLA.0b013e318206818b]

18 **Harding DJ**, Perera MT, Chen F, Olliff S, Tripathi D. Portal vein thrombosis in cirrhosis: Controversies and latest developments. *World J Gastroenterol* 2015; **21**: 6769-6784 [PMID: 26078553 DOI: 10.3748/wjg.v21.i22.6769]

19 **Hibi T**, Nishida S, Levi DM, Selvaggi G, Tekin A, Fan J, Ruiz P, Tzakis AG. When and why portal vein thrombosis matters in liver transplantation: a critical audit of 174 cases. *Ann Surg* 2014; **259**: 760-766 [PMID: 24299686 DOI: 10.1097/SLA.0000000000000252]

20 **Qi X**, Dai J, Jia J, Ren W, Yang M, Li H, Fan D, Guo X. Association between portal vein thrombosis and survival of liver transplant recipients: a systematic review and meta-analysis of observational studies. *J Gastrointestin Liver Dis* 2015; **24**: 51-59, 4 p following 59 [PMID: 25822434 DOI: 10.15403/jgld.2014.1121.qix]

21 **Kotsifa E**, Kykalos S, Machairas N, Nikiteas N, Sotiropoulos GC. Management of portal vein thrombosis in cirrhotic patients enlisted for liver transplantation: From diagnosis to treatment (Review). *Biomed Rep* 2021; **15**: 94 [PMID: 34631049 DOI: 10.3892/br.2021.1470]

22 **Alexopoulos SP**, Thomas E, Berry E, Whang G, Matsuoka L. The portal vein-variceal anastomosis: an important technique for establishing portal vein inflow. *Clin Transplant* 2014; **28**: 52-57 [PMID: 24261456 DOI: 10.1111/ctr.12278]

23 **Singh N**, Washburn K, Black S, Schenk A. Techniques for Management of Portal Vein Thrombosis during Liver Transplantation. *Case Rep Transplant* 2020; **2020**: 8875196 [PMID: 32908775 DOI: 10.1155/2020/8875196]

24 **Sarin SK**, Philips CA, Kamath PS, Choudhury A, Maruyama H, Nery FG, Valla DC. Toward a Comprehensive New Classification of Portal Vein Thrombosis in Patients With Cirrhosis. *Gastroenterology* 2016; **151**: 574-577.e3 [PMID: 27575821 DOI: 10.1053/j.gastro.2016.08.033]

25 **Jamieson NV**. Changing perspectives in portal vein thrombosis and liver transplantation. *Transplantation* 2000; **69**: 1772-1774 [PMID: 10830208 DOI: 10.1097/00007890-200005150-00006]

26 **Charco R**, Fuster J, Fondevila C, Ferrer J, Mans E, García-Valdecasas JC. Portal vein thrombosis in liver transplantation. *Transplant Proc* 2005; **37**: 3904-3905 [PMID: 16386579 DOI: 10.1016/j.transproceed.2005.09.120]

27 **Ma J**, Yan Z, Luo J, Liu Q, Wang J, Qiu S. Rational classification of portal vein thrombosis and its clinical significance. *PLoS One* 2014; **9**: e112501 [PMID: 25393320 DOI: 10.1371/journal.pone.0112501]

28 **Yerdel MA**, Gunson B, Mirza D, Karayalçin K, Olliff S, Buckels J, Mayer D, McMaster P, Pirenne J. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation* 2000; **69**: 1873-1881 [PMID: 10830225 DOI: 10.1097/00007890-200005150-00023]

29 **Bhangui P**, Lim C, Levesque E, Salloum C, Lahat E, Feray C, Azoulay D. Novel classification of non-malignant portal vein thrombosis: A guide to surgical decision-making during liver transplantation. *J Hepatol* 2019; **71**: 1038-1050 [PMID: 31442476 DOI: 10.1016/j.jhep.2019.08.012]

30 **Bhangui P**, Fernandes ESM, Di Benedetto F, Joo DJ, Nadalin S. Current management of portal vein thrombosis in liver transplantation. *Int J Surg* 2020; **82S**: 122-127 [PMID: 32387201 DOI: 10.1016/j.ijsu.2020.04.068]

31 **Lacerda CM**, de Melo PS, Amorim A, Carvalho G, Pereira LB. The left gastric vein as an alternative to portal reconstruction in orthotopic liver transplantation. *Transplant Proc* 2002; **34**: 1216-1217 [PMID: 12072319 DOI: 10.1016/s0041-1345(02)02743-4]

32 **Teixeira UF**, Machry MC, Goldoni MB, Kruse C, Diedrich JA, Rodrigues PD, Giacomazzi CB, Negri EA, Koop M, Gomes CG, Sampaio JA, Fontes PR, Waechter FL. Use of Left Gastric Vein as an Alternative for Portal Flow Reconstruction in Liver Transplantation. *Case Rep Surg* 2016; **2016**: 8289045 [PMID: 27595034 DOI: 10.1155/2016/8289045]

33 **Ravaioli M**, Prosperi E, Pinna A, Siniscalchi A, Fallani G, Frascaroli G, Maroni L, Odaldi F, Serenari M, Cescon M. Restoration of portal flow with varix in liver transplantation for patients with total portal vein thrombosis: An effective strategy in the largest center experience. *Clin Transplant* 2021; **35**: e14303 [PMID: 33797802 DOI: 10.1111/ctr.14303]

34 **Pinheiro RS**, Cruz RJ Jr, Nacif LS, Vane MF, D'Albuquerque LA. Successful liver allograft inflow reconstruction with the right gastroepiploic vein. *Hepatobiliary Pancreat Dis Int* 2016; **15**: 106-107 [PMID: 26818551 DOI:

10.1016/s1499-3872(15)60369-1]
35 **Czerniak A**, Badger I, Sherlock D, Buckels J. Orthotopic liver transplantation in a patient with thrombosis of the hepatic portal and superior mesenteric veins. *Transplantation* 1990; **50**: 334-336 [PMID: 2382299 DOI: 10.1097/00007890-198909000-00037]
36 **Wu TH**, Chou HS, Pan KT, Lee CS, Wu TJ, Chu SY, Chen MF, Lee WC. Application of cryopreserved vein grafts as a conduit between the coronary vein and liver graft to reconstruct portal flow in adult living liver transplantation. *Clin Transplant* 2009; **23**: 751-755 [PMID: 19659513 DOI: 10.1111/j.1399-0012.2009.01045.x]
37 **Wang Z**, Yang L. Gastric coronary vein to portal vein reconstruction in liver transplant: case report. *Exp Clin Transplant* 2014; **12**: 562-564 [PMID: 24918690 DOI: 10.6002/ect.2013.0186]
38 **Safwan M**, Nagai S, Abouljoud MS. Portal Vein Inflow From Enlarged Coronary Vein in Liver Transplantation: Surgical Approach and Technical Tips: A Case Report. *Transplant Proc* 2016; **48**: 3070-3072 [PMID: 27932149 DOI: 10.1016/j.transproceed.2016.05.001]
39 **Lee S**, Kim DJ, Kim IG, Jeon JY, Jung JP, Choi GS, Kim JS. Use of pericholedochal plexus for portal flow reconstruction in diffuse portal vein thrombosis: case report. *Transplant Proc* 2014; **46**: 977-979 [PMID: 24767395 DOI: 10.1016/j.transproceed.2014.02.001]
40 **Kim JD**, Choi DL, Han YS. The paracholedochal vein: a feasible option as portal inflow in living donor liver transplantation. *Ann Surg Treat Res* 2014; **87**: 47-50 [PMID: 25025028 DOI: 10.4174/astr.2014.87.1.47]

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