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REVIEW

Islet transplantation-immunological challenges and current perspectives

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Abstract

Pancreatic islet transplantation is a minimally invasive procedure aiming to reverse the effects of insulin deficiency in patients with type 1 diabetes (T1D) by transplanting pancreatic beta cells. Overall, pancreatic islet transplantation has improved to a great extent, and cellular replacement will likely become the mainstay treatment. We review pancreatic islet transplantation as a treatment for T1D and the immunological challenges faced. Published data demonstrated that the time for islet cell transfusion varied between 2 and 10 h. Approximately 54% of the patients gained insulin independence at the end of the first year, while only 20% remained insulin-free at the end of the second year. Eventually, most transplanted patients return to using some form of exogenous insulin within a few years after the transplantation, which imposed the need to improve immunological factors before transplantation. We also discuss the immunosuppressive regimens, apoptotic donor lymphocytes, anti-TIM-1 antibodies, mixed chimerism-based tolerance induction, induction of antigen-specific tolerance utilizing ethylene carbodiimide-fixed splenocytes, pretransplant infusions of donor apoptotic cells, B cell depletion, preconditioning of isolated islets, inducing local immunotolerance, cell encapsulation and immunoisolation, using of biomaterials, immunomodulatory cells, *etc.*

Key Words: Islet transplantation; Type 1 diabetes; Diabetes mellitus; Immune tolerance; Graft rejection; T regulatory cells; B regulatory cells

Core Tip: Type 1 diabetes (T1D) is associated with loss of beta-cell mass and insulin secretion. Regardless of its nature, autoimmune or idiopathic, the loss of own insulin secretion is a hallmark dysfunction in T1D mellitus; thus, therapeutic options are aimed at either replacing the missing insulin or restoring physiological insulin secretion to achieve normoglycemia and postponing micro- and macrovascular complications. Nevertheless, the need to completely replace the depleted pancreatic secretion also leads to the emergence of new therapeutic horizons, including pancreas and islet cell transplantation. However, this approach also meets several immunological challenges-cellular and antibody-mediated rejection and loss of function. To improve the outcomes, several approaches are performed: Immunosuppression, apoptotic donor lymphocytes, anti-TIM-1 antibodies, mixed chimerism-based tolerance induction, induction of antigen-specific tolerance utilizing ethylene carbodiimide-fixed splenocytes, infusion of donor apoptotic cells before transplantation, combined with anti-CD40L antibodies and rapamycin, preconditioning of isolated islets, inducing local immunotolerance, cell encapsulation and immunoisolation, using of biomaterials, immunomodulatory cells, *etc.* mesenchymal stem cells, as an adjunct therapy to islet transplantation, can promote long-term graft survival, possibly by reducing inflammation and enhancing immune tolerance.

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INTRODUCTION

Pancreatic islet transplantation is a minimally invasive procedure aiming to reverse the effects of insulin deficiency by transplanting pancreatic beta cells[1]. Pancreatic islet transplantation can be done with autologous and allogeneic islets. While autologous islet transplantation has the advantage of being derived from the same patient, eliminating the risk of immune rejection, its widespread utilization is limited due to several drawbacks, including the need for pancreatectomy, which may have associated surgical risks, and the limited availability of functional islets from a single organ in patients with advanced disease. On the other hand, allogeneic islets are taken from different individuals of the same species, usually for treating type 1 diabetes (T1D), with followed immunological response complications [2].

Typical for T1D is the continuing pancreatic beta cell destruction, which could be autoimmune (Type 1A) or non-autoimmune (Type 1B), resulting in decreased or absent insulin production. As a result, it increases in incidence yearly and is associated with severe hypoglycemia, ketoacidosis, and vascular

complications[3]. Although exogenous insulin analogs are considered the primary treatment option for managing T1D in response to hyperglycemia, they cannot accurately resemble the timing and dosing of physiological insulin secretion. Moreover, exogenous insulin therapy is associated with an increased risk of severe side effects such as hypoglycemia, weight gain, lipodystrophy, *etc.*[4]. Therefore, there is an ongoing effort to improve the treatment options[5]. Among them, pancreatic islet transplantation is promising to become the mainstay in the treatment process[6].

As a minimally invasive procedure, islet transplantation is ideal for high-risk surgical patients burdened with cardiovascular disease[7]. It does not follow the significant complications of vascularized pancreas transplantation, and with minimal intra-operational complications, such as bleeding and portal vein thrombosis, the mortality is negligible. On the negative side, multiple donors for a single patient are needed, while the alternative whole pancreatic transplantation treatment needs 1 and rarely 2 pancreases. This makes it a rather wasteful procedure[8]. An adequate islet number must be transplanted for patients to become insulin-independent. A single transplantation is often insufficient; several sequential transplantations are needed for satisfactory glycaemic and insulin results[9]. Early attempts had been made as early as 1893. Still, the milestone that grabbed the scientific community's attention was the ground-breaking Edmonton protocol, with its non-corticosteroid immunosuppressive treatment[9] and the other studies regarding the benefits of islet transplantation on glucose metabolism improvement[10,11]. Studies have shown that 5-year insulin independence has increased manifold[12-14].

Overall, pancreatic islet transplantation has improved to a great extent, and cellular replacement will likely become the mainstay treatment. Our goal was to review pancreatic islet transplantation as a treatment for T1D and the immunological challenges faced. To prepare this narrative review, we search the main databases, Medline, PubMed, and Scopus, in conformity with the principles of writing a narrative review[15].

ISLET TRANSPLANTATION PROCEDURE

The main procedural steps are pre-transplant assessment, pancreas procurement, islet isolation, tissue culture, transplantation, and post-transplant evaluation[8].

In pre-transplant assessment, eligible patients are chosen. Strong indications include recurrent severe hypoglycemic shocks, impaired awareness of hypoglycemia, undetectable C-peptide, age between 18-65, and a diagnosis of more than five years[16]. Additionally, previous kidney transplantation has been shown to impact the outcomes of islet transplantation positively. Studies have reported that patients who have undergone a kidney transplant before islet transplantation have higher graft survival rates, improved glycemic control, and reduced insulin requirements compared to those without a prior kidney transplant. This may be attributed to the immunosuppressive regimen used for kidney transplantation, which may enhance the success of islet transplantation by preventing the rejection of the transplanted islets[17]. Exclusion criteria include poorly controlled hypertension, heart disease, macroalbuminuria, glomerular filtration rate < 80 mL/min/1.73 m^2 and potential contraindications for immunosuppression. Current indications do not include the pediatric population[18]. In the transplantation of allogeneic pancreatic beta cells, ABO and human leucocyte antigen histocompatibility have to be assessed. The number of islet donors is generally limited, but new xenografts with islets from other species, typically porcine islets, and stem cell technologies could tackle this critical problem[19].

In the stage of pancreas procurement, the pancreas is removed from donors and preserved in the University of Wisconsin solution for up to 24 h. Important in this stage is the capsule to be kept intact. The pancreas is delivered to the islet isolation center when procurement is ready[20]. The islet isolation process involves the preparation of the pancreas, which is carefully cleaned of surrounding tissues and dissected to expose the islets of Langerhans. The pancreas is then cannulated and perfused with a collagenase enzyme solution for 10 min, which distends the pancreas to facilitate the separation of the islets from the surrounding stroma. Next, the distended pancreas is cut and set into the Ricordi Chamber, an automated device designed to facilitate the islet isolation process. The chamber employs a series of automatic steps to separate the islets from the exocrine tissue, including filtration and density gradient centrifugation. Finally, the isolated islets are processed using a COBE 2991 cell processor, which further separates the islets from any residual exocrine tissue, and the purified islets are then cultured for transplantation[21,22].

In the hands of the proper expert, the tissue culture stage of islet isolation represents a critical step in preparing isolated islets for transplantation. This stage allows the islets to recover from the stress induced by the previous steps of the isolation procedure, during which they may have been subjected to mechanical and enzymatic stress. The tissue culture stage typically involves the placement of the purified islets into a nutrient-rich media in a controlled environment, where they are allowed to recover for several hours to several days. During this time, the islets are carefully monitored for signs of viability and function, including assessment of insulin secretion and glucose-stimulated insulin release. This stage also allows for flexibility in scheduling the subsequent transplant procedure, as the islets can be stored under optimal conditions until the transplant recipient is ready to receive them. The success of

the tissue culture stage is highly dependent on the expertise of the individual performing the procedure, as optimal conditions must be maintained to ensure the viability and function of the isolated islets[23].

Before transplantation begins, the final transplantation islet site has to be decided. The liver is considered preferable for transplantation, although different places are being tested for better islet survival and function[24]. Upon islet infusion, an "instant blood-mediated inflammatory reaction" is described with platelet consumption, activation of coagulation, and the complement system[25].

The post-transplant period following islet transplantation is characterized by a prolonged period of recovery during which insulin independence may not be immediately achieved. The transplanted islets may take months to years to fully integrate into the recipient's body[6] and establish a functional vascular supply. During this period, the transplanted islets are subject to immunological attacks from the recipient's immune system, which can compromise their function and survival. A combination of induction, maintenance, and antirejection immunosuppressive drugs are typically used to prevent rejection of the transplanted islets. However, a notable irony is that many of these immunosuppressive drugs have diabetogenic properties, which can exacerbate preexisting metabolic abnormalities in transplant recipients. As such, these drugs must be carefully balanced against the need to maintain optimal islet function and prevent rejection[26].

Recent advances in islet transplantation have focused on immunoisolation, which involves the encapsulation of transplanted islets in a protective membrane to prevent their recognition and subsequent destruction by the recipient's immune system. Encapsulation of islets for immunoisolation involves using biocompatible materials that allow for efficient nutrient and oxygen exchange while preventing immune cells from accessing the transplanted islets. Several biomaterials have been studied for this purpose, including alginate, agarose, and polyethylene glycol hydrogels[27,28]. The techniques for improving islet cell survival by encapsulation are presented in Figure 1A.

For example, alginate hydrogels are commonly used due to their biocompatibility, ease of fabrication, and ability to protect transplanted islets from the immune system. While early studies in small animal models have shown promising results, with sustained islet function and reduced immunosuppressive drug requirements, translation to larger animals and humans has been less successful, with limited long-term success and significant technical challenges in maintaining membrane integrity and permeability. Using traditional immunosuppressive regimens remains a crucial component of current islet transplantation protocols, albeit with the recognized risks of diabetogenicity and other adverse effects[11].

T1D AND THE NEED FOR ISLET TRANSPLANTATION

Type 1 diabetes mellitus (T1DM) is a metabolic disease distinct by hyperglycemia, insulin deficiency, and a lifelong need for exogenous insulin replacement treatment[3,29]. T1DM is an autoimmune disease that develops in genetically predisposed individuals under the influence of environmental factors, which triggers autoimmunity to pancreatic beta cells. Although it is defined as "diabetes of young age", T1DM can also affect adults[30]. In general, T1DM is divided into two subtypes, 1A and 1B[31]. While T1ADM is associated with autoantibodies against islet cells [glutamic acid decarboxylase (anti-GAD65), tyrosine phosphatases islet antigen 2 (IA-2), IA-2β insulin, or zinc transporter 8[32], also observed in patients with T2D[33], T1BDM, in turn, is a relatively small subtype that is not mediated by the immune system and has an unclear genesis.

T1DM is related to other autoimmune conditions such as celiac disease[34,35], Hashimoto thyroiditis, Addison's disease, pernicious anemia, *etc*.[36]. Moreover, patients with diabetes may have a compromised immune system, leading to a more complicated course of infections, including coronavirus disease 2019[37]. Some of the immune defects described in patients with diabetes are decreased cellular response *in vitro*, low complement factor 4, diminished cytokine response after stimulation, reduced chemotaxis, phagocytosis, and killing of polymorphonuclear cells and macrophages[38].

Regardless of the subtype, the loss of insulin secretion is a hallmark dysfunction in T1DM, and therapeutic options aim to replace the missing insulin or restore physiological insulin secretion to achieve normoglycemia and prevent micro- and macrovascular complications. Within the last few years, we have seen a rapid evolution in the therapy of T1DM[39]. First, tangible progress marked the discovery of insulin in 1921-22 by Banding and Macleod, saving from certain death children with diabetes. The subsequent development of new analog insulins with a better therapeutic and safety profile results in better control of hyperglycemia and a reduced risk of hypoglycemia, respectively. The introduction of insulin pumps with continuous subcutaneous insulin administration[40] and the implementation of modern technologies in diabetes control with continuous glucose monitoring systems combined with glucose prediction algorithms enabling the development of artificial pancreas delivery systems[41] marks extraordinary progress in managing T1DM.

Nevertheless, the need to completely replace the depleted pancreatic secretion also leads to the emergence of new therapeutic horizons, including pancreas and islet cell transplantation. They allow not only to achieve independence from exogenous insulin administration and the need to monitor blood sugar but also successfully to afford counterregulatory hormone secretion and pancreatic exocrine

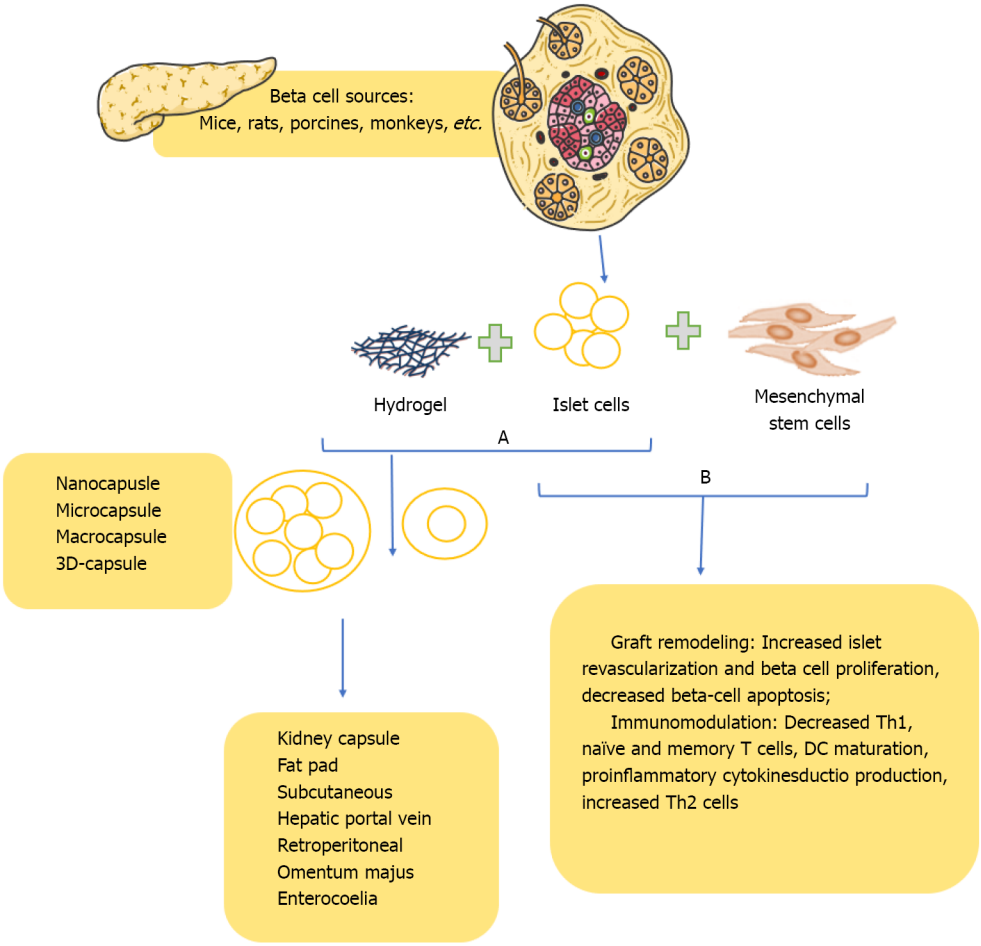

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Figure 1 Techniques for improving graft survival. A: Islet cell encapsulation (after isolation of islets by density gradient centrifugation), islets are capsuled with different hydrogel types to obtain various sizes of capsules. Then the capsules are transplanted into the body; B: Mesenchymal stem cells modulate graft and immune responses and support the islet cell survival after transplantation. Parts of the figure were drawn using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/Licenses/by/3.0/).

function[42].

IMMUNOLOGICAL ALTERATIONS IN T1D

T1DM was thought to be a T cell-mediated autoimmune illness for many decades. This belief persists, but multiple recent discoveries hint at a role for beta cells beyond being a non-provoking victim of an autoimmune onslaught[38].

The interaction between genetic vulnerability and probable triggers is likely to begin at a young age, gradually leading to the loss of tolerance to self and, eventually, the development of clinical symptoms. The result is determined by genetic predisposition, decreased removal of the apoptotic cell remains, altered immune regulation, and environmental triggers (*i.e.*, viral infections). In addition, autoreactivity may exist under physiological settings, and illness may arise if the integrity of the complicated regulatory process is compromised[43].

The beta cells are destroyed by islet-infiltrating cells (*i.e.*, CD8+ cytotoxic lymphocytes and macrophages), resulting in insulitis. In addition, macrophages release cytokines that are harmful to beta cells. Secondary considerations are autoantibodies, which serve as the foundation for clinical diagnosis [43].

Initially, B lymphocytes are known to play a secondary role in T1DM that even occurs in severe congenital B-lymphocyte immunodeficiency[44]. Xiu *et al*[45] considerably delayed disease development in NOD mice by depleting B-lymphocytes using an anti-CD20 antibody. They concluded that this was not due to T effector cell reduction or T regulatory (Tregs) induction but rather to a decrease in the development of autoreactive T cells[45].

However, autoreactive T cells are part of the typical T cell repertoire. In T1D, beta cells live in an inflammatory environment and participate in their destruction. Additionally, metabolic activity is what causes beta cell malfunction and destruction. Insulitis is characterized by inflammation, associated with substantial metabolic, epigenetic, and autoantigenic alterations that expose beta cells to the immune system[46]. In line with this, immunotherapy may be insufficient to treat T1D, although beta cell therapy may help reduce beta cell immunogenicity and islet autoimmunity[47].

It was demonstrated recently that innate immunity components might play a role in T1D pathogenesis, such as pattern recognition receptors and proinflammatory cytokines[47]. Nevertheless, the accompanying inflammation of the islets leads to damaged beta cells and loss of insulin production.

Animal studies (*i.e.*, non-obese diabetic mice) and human studies in T1D revealed defects in thymic selection, expansion of effector T cells, impaired homeostasis and FoxP3+ Tregs[48]. However, even if we accept the immune system's role in the development of T1D, science cannot assume that the disease is entirely a result of dysfunctional immunity, *i.e.*, autoreactive T cells. Recent research focuses on the participation of the peripheral immune system in the targeted tissue and the role of beta cells in the autoimmune process[49,50].

Indeed, when we accept this conception, it was demonstrated that T1D is usually characterized by less beta-cell mass, functional capacity and inability to control glycemia. Usually, beta cells undergo metabolic stress, inflammatory environment and other factors that increase the expression of specific adhesion molecules and other receptors, making them prone to immune attacks[46].

Islet transplantation has been considered a potential cure for T1D by replacing the damaged beta cells. However, its effectiveness is dependent on the underlying cause of the disease. For example, if T1D results from a pancreatic dysfunction leading to the loss of beta cells, then islet transplantation may be a viable option. However, if T1D is viewed as an autoimmune disorder, the presence of autoreactive T and B cells can lead to the disease's recurrence and limit the transplantation's efficacy[47]. In such cases, alternative approaches such as immunomodulatory therapies, co-transplantation with immune cells, or encapsulation of islets can be explored to improve the success rate of islet transplantation.

RESULTS ON DIABETES CONTROL AND AVOIDING DIABETES COMPLICATIONS AFTER ISLET TRANSPLANTATION

Patients with T1D or pancreatogenic (type 3c) diabetes (also known as insulin-deficient) may benefit from islet isolation from a deceased donor followed by transplantation of allogeneic islets in the liver. This can help alleviate hypoglycemia while stabilizing glycemic lability, and maintaining glycemic control, ultimately improving quality of life and frequently eliminating the need for insulin therapy. Replacement of islet function by transplantation addresses the underlying pathophysiology of long-standing T1D with sub-total annihilation of islet alpha-cells and the associated loss of the alpha-cell response to hypoglycemia[19]. This allows for the avoidance of hypoglycemia and stabilization of glycemic lability, which would otherwise contribute to impaired awareness of hypoglycemic states. Patients with T1D uncontrolled hyperglycemia, demonstrated by the recurring episodes of diabetes-associated ketoacidosis or quickly progressing severe complications related to the disease, might also benefit from islet transplantation[51,52].

Patients with T1D complicated by an allergy or resistance to insulin that is administered subcutaneously are a rare but essential indication for this treatment[53]. Finally, alloislets (from a viable allograft pancreatectomy) re-transplantation has been successfully executed in a patient with T1D who was initially given the pancreas transplant for hypoglycemia unawareness. Similarly, a T1D patient received simultaneous pancreas/kidney transplantation complicated by pancreas graft arterial anastomosis bleeding[54]. Notably, the degree of glycemic control achieved within the first five days after surgery determines the chances of accomplishing long-term insulin independence[55].

We analyzed the literature data published on islet transplantation focusing on the clinical outcomes [55-60]. Our results have been summarized in Table 1. The total number of included patients was 372. We established that the time for islet cell transfusion varied between 2 and 10 h. Approximately 54% of the patients gained insulin independence at the end of the first year, while only 20% remained insulin-free at the end of the second year. Most patients have received islet cells in the liver, and only 38 patients have IC harvested in the spleen. Another interesting fact we discovered was the high percentage of opioid-free patients after this intervention.

Unfortunately, the Collaborative Islet Transplant Registry reported 71% insulin independence in the first year and 24% in the third from the islet transplant centers[61]. Eventually, most transplanted patients need exogenous insulin within a few years after the transplantation[62].

Some additional factors can also improve the outcomes after islet transplantation. For example, experiments in mice and rats with Vitamin D show promising results on glycemia and tumor necrosis factor-α (TNF-α) production in islet transplantation[63]. In addition, analogs of vitamin D3 are shown to prevent the autoimmune destruction of transplanted islets in non-obese mice[64]. This is a promising direction for research on humans due to the well-known anti-inflammatory effects of vitamin D3 *in vivo* [65,66].

Table 1 Islet transplantation protocols

Ref.	Patients (*n*)	Time of infusion of islets (h)	HbA1c, 1-yr, median (%)	HbA1c, 2-yr, median (%)	Insulin independence 1-yr, median (%)	Insulin independence 2-yr, median (%)	IEQ harvested/g pancreas, median (range)	IEQ transplanted/g pancreas, median (range)	Opioid and pain-relieving	Organ placement
Sutherland *et al*[56]	173	2-7	NR	NR	32	24	< 1000 IE/kg	(> 5000, 2500-5000 and < 2500 IE/kg)	NR	173 liver
Ahmad *et al*[57]	45	7-10	NR	NR	40	NR	NR	297889 ± 49480	72%	45 liver
Rodriguez Rilo *et al*[58]	22	9	NR	NR	41	NR	245457 (range 20850 to 607466-175234)	350428 (range 31500 to 1164000-299321	82%	22 liver
Webb *et al*[59]	46	NR	7	6.7	12	5	1876 (249-12271)	I130029 (24332-958078)	NR	42 liver; 2 spleen; 2 both
Garcea *et al*[60]	50	NR	Approximately 6	Approximately 6	24	10	NR	NR	60%	85 liver
Johnston *et al*[55]	36	8-9	NR	6.8	50	33	358959 (45000–672000)	4308 (769–9942)	30%	36 spleen

HbA1c: Hemoglobin A1c; IEQ: Indoor environmental quality. NR: Not reported.

IMMUNOLOGICAL CHALLENGES OF ISLET TRANSPLANTATION-CELLULAR IMMUNE RESPONSE, INDUCTION OF TOLERANCE, REJECTION

At this point, the main complication after allogeneic islet transplantation is the chronic rejection conducted by activated T cells. This is also the main barrier to accomplishing long-term engraftment. One of the ways to maintain immune tolerance to the allograft is to administer immunosuppression[67].

However, this could be toxic for the islet grafts, leading to worsening long-term function of the islets, increased risk of infections, development of cardiovascular and renal diseases, *de novo* diabetes, neurotoxicity and malignancies[68].

The ultimate goal of islet transplantation is to achieve donor-specific immune tolerance. A recently proposed method for tolerance induction using apoptotic donor lymphocytes (ADLs) in animal models (*i.e.*, non-human primates)[69]. ADLs employ clonal depletion, anergy, expansion of Treg cells, regulatory B cells (Bregs), *etc.* Usually, these mechanisms act together to induce and maintain tolerance. However, this approach also meets several challenges.

Initially, the immune rejection after transplantation starts with innate immune cells infiltration into the islet grafts (*i.e.*, macrophages), followed by donor-specific lymphocyte response, consisting of T cells (CD4+ and CD8+) and B cells. In line with this, the protocol comprised of T cell depletion and anti-TNF agents may enhance short-term graft survival[67]. However, this protocol has a significant drawback-it cannot modulate antibody-mediated rejection[70,71].

Targeting Bregs (*i.e.*, low-affinity antibodies against TIM-1, essential for Breg development) results in considerably longer islet cell survival (about 30% of mice attained engraftment over 3 mo)[72]. Surprisingly, anti-TIM-1 treatment of B cell-depleted recipients significantly increased interferon-γ and prevented the typically seen rise in Th2 cytokines[72].

Furthermore, in a mouse islet transplant model, a combination of anti-CD45RB and anti-TIM-1 antibodies synergized in establishing tolerance in all recipients. Depending on the presence of interleukin (IL)-10-producing B cells in the recipient, the combined antibody therapy significantly increased the regulatory lymphocytes[73]. Furthermore, the study implied that B cells expressing CD19 and TIM-1 are part of tolerance development and maintenance. These results might clarify why B cell reduction decreased the effectiveness of dual antibody therapy.

Cross-reactive memory T and B cells could substantially impede immunological tolerance in animals and humans after transplantation. However, tolerance development in non-human models or humans would be more complex than in rat models, owing to cross-reactive memory immune cells. Yet, a few hopeful treatments exist, such as mixed chimerism through hematopoietic cell transplantation[74,75] or ADL exposure[76], which have led us to anticipate that immune tolerance can eventually be attained in people.

Oura *et al*[77] published the results of a non-human islet transplantation model where a nonmyeloablative condition regimen induced the mixed chimerism-based tolerance. The latter consisted of total

body irradiation, and administration of horse anti-thymocyte globulin, monoclonal antibodies (*i.e.*, anti-CD154, anti-CD8, *etc*.), or cyclosporine (the so-called calcineurin inhibitor-free regimen)[77]. As a result, temporary chimerism did not prompt tolerance to increase the islet graft survival. Eventually, the islet stopped functioning shortly after chimerism disappeared[77]. Oura *et al*[77] also found that islet recipients had greater levels of inflammatory cytokines (*i.e.*, TNF-α and IL-17) in blood circulation than kidney recipients[77]. This study implies that excessive levels of inflammatory mediators following islet transplantation may impede islet graft tolerance induction. Since isolated islet grafts could induce a significant systemic inflammatory response, this should be the focus of future research to improve tolerance development and graft survival.

Induction of immune tolerance utilizing ethylene carbodiimide (ECDI)-fixed splenocytes in combination with particular antigens or peptides is a method used in transplantation models, including islet transplantation. Kheradmand *et al*[78] demonstrated various mechanisms (*i.e.*, anergy, clonal depletion, employment of Tregs, *etc*.) *via* donor ECDI-fixed splenocytes administration. These splenocytes possess direct and indirect allospecificities that target allogeneic host responses. These mechanisms act synergistically to cause tolerance after transplantation[78]. In addition, Tregs and myeloid-derived cells that exert immunosuppression are activated and increased in number in the case of ECDI-fixed splenocytes infusion[79].

Allotransplantation in sensitized patients with pre-formed donor-specific memory lymphocytes and antibodies increases the risk of allograft rejection. Dangi *et al*[80] showed that administration of donor apoptotic cells, anti-CD40L antibodies, and rapamycin before transplantation resulted in a considerable extension of islet graft in allosensitized patients (median survival time, 35 d)[80]. Sato and Marubashi [69] confirmed that invading B lymphocytes play an essential part in the chronic rejection of the islet graft by stimulating local T cells. Therefore, ECDI-fixed splenocytes from the donor infused into sensitized recipients efficiently reduced alloreactive B cells. However, the latter could be switched by contemporary B cell invasion into the graft. As a result, in B cell-depleted patients, a method to regulate concurrent B cell invasion is required[69].

Moreover, islet grafts might be more resistant to immunological tolerance induction. Compared to kidney grafts, the considerably increased immunogenicity of islet grafts may impede tolerance induction in islet transplantation[77]. Islet grafts have relatively strong cytokine secretion activity because pancreatic islets are endocrine cells. Furthermore, cell stressors during the isolation process cause islet inflammation, increasing the immunogenicity of the islet graft before transplantation.

These conclusions imply that the stress during the separation method activates the proinflammatory gene program. Islet isolation entails many steps, including pancreatic distention, digesting with collagenase, and purification. Therefore, the islets should be injured throughout each phase by hypoxia and heated ischemia, production of activated proteolytic enzymes by acinar cells, and oxidative and mechanical stress[69].

According to estimates, around half of the transplanted islets are irreparably destroyed around the transplantation period (from hours to days). In addition, more than a quarter of islet grafts are known to be lost shortly after the portal vein infusion[81]. Therefore, the initial inflammatory response is crucial in instant transplanted islet loss due to immediate blood-mediated inflammatory reaction (IBMIR). During IBMIR, coagulation pathways are activated, proinflammatory cytokines are produced, and innate immune cells infiltrate the graft[82], all contributing to the islet's acute cell-mediated damage. Additionally, IBMIR is distinguished by coagulation and complement systems activation, fast activation and binding of platelets and leukocyte recruitment and infiltration[83].

Preconditioning isolated islets with sublethal genotoxic stress may be a potential technique for lowering islet immunogenicity and extending islet transplant life. It is reasonable to believe that preconditioning therapy for reducing graft immunogenicity will synergistically impact tolerance induction therapy, including the ADL regimen[69].

Applying the cellular treatment is a novel approach to induce local immunotolerance and avoid islet rejection. In addition, the administration of stem cell-derived beta cells during islet transplantation improves graft performance while reducing the negative consequences of systemic immunosuppression. Recent advances in T1D cell replacement treatments (*i.e.*, non-encapsulation and local immunomodulatory techniques) are addressed in this concise review[84]. They include alteration of islet/cell, use of biomaterials that provide immunomodulation, and immunomodulatory cell co-transplantation.

Co-transplantation of pancreatic islets with mesenchymal stem cells (MSCs) is one such approach that has attracted attention. Studies have shown that using MSCs as an adjunct therapy to islet transplantation can promote long-term graft survival, possibly by reducing inflammation and enhancing immune tolerance[85]. For instance, co-transplantation of adipose tissue-derived MSCs and pancreatic islets improved glycemic control and regulation of the Th17/Treg function streptozotocin-induced diabetic mice model[86]. Encapsulation, on the other hand, is another technique that has been extensively studied for its potential to protect transplanted islets from immune rejection while allowing for efficient nutrient and oxygen exchange. In addition, Vegas *et al*[87] demonstrated that beta cells derived from human stem cells, when implanted into mice with preserved immune competence, resulted in long-term glycemic control[87]. Thus, further investigation into these novel strategies for T1D cell replacement therapies may provide new insights and solutions to the ongoing challenges in this field.

Therefore, methods for immunoisolation or beta cell encapsulation are one approach to improving graft performance. Still, it has its own set of obstacles, which causes a loss in cell viability over time (Figure 1B). Although altering human islets in clinical applications is implausible, creating universal cells from pluripotent stem cells that can elude immune identification offers enormous promise in diabetic cell treatments. However, despite these breakthroughs, critical problems like the persistence of genomic and epigenetic modifications and cell phenotypes stability remain unanswered. Additionally, although these cells are hypoimmunogenic, their safety should be carefully maintained because cells that elude the immune system are intrinsically dangerous.

Similarly, undifferentiated stem cells can potentially develop into teratomas *in vivo* because it is well-known that both embryonic and induced pluripotent stem cells can differentiate into all three germ layers. Therefore, they can form teratomas if not fully differentiated[88]. Theoretically, the presence of a few remaining undifferentiated pluripotent stem cells can cause undesirable teratomas after transplantation. Although "suicide genes" could be incorporated into stem cells for increased safety[89], it is still uncertain how these cells would behave in people over time, necessitating additional research.

Biomaterials combined with immunomodulation give multiple instruments for locally modulating immune responses and are an intriguing way to assist cell transplantation. This technique has apparent advantages, including safety as "nonliving" materials. Furthermore, biomaterials are generally simple to mass-produce. In contrast, cell modification or immunomodulatory cell preparation is sometimes difficult, in addition to the necessity of good manufacturing processes that must fulfill clinical requirements. Yet, given the restricted ligands and the eventual exhaustion of coated reagents, the long-term durability of biomaterials and delivery techniques remains challenging. Hence, there is a need for new approaches for the retention or restocking of the supplied reagents in the future[84].

Interestingly, immunomodulatory cells operate as "living" medicine repositories and, if engrafted, may boost functional stability by producing cytokines continuously or expressing surface markers to affect the immune system. Improvements in these immunoregulatory cells' acquisition, retention, stability, potency and localization are required to increase their effectiveness and safety. As we create T1D therapies and cures, a functioning resolution will likely need a multi-modal methodology involving several immuno-modalities and tissue engineering methods. The strategy for the 3D-engineered biomaterial tissue construct coupled with both invisible to the immune response cells and accessory cells that exert could be employed to provide long-term effective and safe cell treatments for T1D. Examining the disease's heterogeneity and customizing therapy procedures is critical to reaching the best possible outcomes[84].

Additionally, because transplanted islets are isolated from deceased donors who are not human leukocyte antigen (HLA)-matched to recipients, the use of multiple donors and the potential need to discontinue immunosuppression in the case of a clinically failed islet-alone graft increases the risk of HLA sensitization in islet transplant recipients. Most transplant patients currently have an unexplained slow loss of islet graft function may be partly caused by allograft rejection. However, discovering anti-HLA antibodies during graft deterioration remains uncommon[90].

FUTURE PERSPECTIVES ON ISLET TRANSPLANTATION

Future pathways for improving the outcomes of islet transplantation include obtaining alternative sources of insulin-secreting cells, attempts to improve the immune protection and revascularization of the transplanted tissue, and methods for enhancing viability[91].

Islets obtained from human embryonic stem cells (hESC) are in early-phase clinical trials[92]. hESC islets should theoretically not require immunosuppression or HLA silencing, which would allow the treatment of children. However, alternative strategies, such as xenogeneic sources of islets and human-induced pluripotent stem cells[93], are also being researched.

Several therapeutical approaches to improve islet survivability are currently in the preclinical phase of research. These include cellular therapies such as MSCs[94], regulatory T-cells[95], as well as modulators of the liver niche with anti-inflammatory agents[96] and growth factors[97]. MSCs appear promising as their anti-inflammatory and immunomodulatory properties have been used in humans for other conditions and could, in theory, enable them to reduce the immunosuppression dose[98]. In addition, improving vascularity through gene therapy[99] of the transplant has also been a sought-after strategy for future development.

Last but not least, various scaffolding methods, as well as alternative implant sites, are undergoing research to enhance the viability of the grafts. For example, dexamethasone-loaded microplate-enriched collagen-coated polydimethylsiloxane scaffolds have improved transplant outcomes and survival[100]. While the liver currently remains the localization of choice for islet transplantation, several other sites are being investigated, such as intramuscular[101], gastric submucosa[102], thymus, testes and the eyes [103].

CONCLUSION

T1DM is an immune-associated metabolic disease characterized by hyperglycemia, absolute insulin deficiency, and a lifelong need for exogenous insulin replacement treatment. The implementation of modern technologies in diabetes control with continuous glucose monitoring systems combined with glucose prediction algorithms enables the development of artificial pancreas delivery systems. Nevertheless, the need to completely replace the depleted pancreatic secretion also leads to the emergence of new therapeutic horizons, including pancreas and islet cell transplantation. They allow not only to achieve independence from exogenous insulin administration and the need to monitor blood sugar but also successfully to afford counterregulatory hormone secretion and pancreatic exocrine function. At this point, the main complication after allogeneic islet transplantation is the chronic rejection conducted by activated T cells and autobodies-mediated rejection, the main barrier to accomplishing long-term engraftment. To improve the outcomes, several approaches are performed: Immunosuppression, ADLs, anti-TIM-1 antibodies, mixed chimerism-based tolerance induction, induction of antigen-specific tolerance utilizing ECDI-fixed splenocytes, infusion of donor apoptotic cells before transplantation, therapy with anti-CD40L antibodies and rapamycin, preconditioning of isolated islets, inducing local immunotolerance, cell encapsulation and immunoisolation, using of biomaterials, immunomodulatory cells, *etc*.

FOOTNOTES

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REFERENCES

1 **Shapiro AM**, Pokrywczynska M, Ricordi C. Clinical pancreatic islet transplantation. *Nat Rev Endocrinol* 2017; **13**: 268-277 [PMID: 27834384 DOI: 10.1038/nrendo.2016.178]
2 **Khan K**, Desai CS. Islet Transplantation in Children. *Curr Gastroenterol Rep* 2019; **21**: 26 [PMID: 31025126 DOI: 10.1007/s11894-019-0693-6]
3 **Atkinson MA**, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet* 2014; **383**: 69-82 [PMID: 23890997 DOI: 10.1016/S0140-6736(13)60591-7]
4 **Ku HT**, Zhang N, Kubo A, O'Connor R, Mao M, Keller G, Bromberg JS. Committing embryonic stem cells to early endocrine pancreas in vitro. *Stem Cells* 2004; **22**: 1205-1217 [PMID: 15579640 DOI: 10.1634/stemcells.2004-0027]
5 **Akil AA**, Yassin E, Al-Maraghi A, Aliyev E, Al-Malki K, Fakhro KA. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. *J Transl Med* 2021; **19**: 137 [PMID: 33794915 DOI: 10.1186/s12967-021-02778-6]

6 **Miller KM**, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, Maahs DM, Tamborlane WV; T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care* 2015; **38**: 971-978 [PMID: 25998289 DOI: 10.2337/dc15-0078]

7 **Maffi P**, Secchi A. Islet Transplantation Alone Versus Solitary Pancreas Transplantation: an Outcome-Driven Choice? *Curr Diab Rep* 2019; **19**: 26 [PMID: 31025188 DOI: 10.1007/s11892-019-1145-2]

8 **Johnson PR**, Jones KE. Pancreatic islet transplantation. *Semin Pediatr Surg* 2012; **21**: 272-280 [PMID: 22800980 DOI: 10.1053/j.sempedsurg.2012.05.012]

9 **Ryan EA**, Lakey JR, Rajotte RV, Korbutt GS, Kin T, Imes S, Rabinovitch A, Elliott JF, Bigam D, Kneteman NM, Warnock GL, Larsen I, Shapiro AM. Clinical outcomes and insulin secretion after islet transplantation with the Edmonton protocol. *Diabetes* 2001; **50**: 710-719 [PMID: 11289033 DOI: 10.2337/diabetes.50.4.710]

10 **Digon BJ 3rd**. History of islet transplantation. *Curr Diab Rep* 2009; **9**: 312-316 [PMID: 19640345 DOI: 10.1007/s11892-009-0048-z]

11 **Farney AC**, Sutherland DE, Opara EC. Evolution of Islet Transplantation for the Last 30 Years. *Pancreas* 2016; **45**: 8-20 [PMID: 26658037 DOI: 10.1097/MPA.0000000000000391]

12 **Ryan EA**, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JR, Shapiro AM. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005; **54**: 2060-2069 [PMID: 15983207 DOI: 10.2337/diabetes.54.7.2060]

13 **Qi M**, Kinzer K, Danielson KK, Martellotto J, Barbaro B, Wang Y, Bui JT, Gaba RC, Knuttinen G, Garcia-Roca R, Tzvetanov I, Heitman A, Davis M, McGarrigle JJ, Benedetti E, Oberholzer J. Five-year follow-up of patients with type 1 diabetes transplanted with allogeneic islets: the UIC experience. *Acta Diabetol* 2014; **51**: 833-843 [PMID: 25034311 DOI: 10.1007/s00592-014-0627-6]

14 **Lablanche S**, Borot S, Wojtusciszyn A, Bayle F, Tétaz R, Badet L, Thivolet C, Morelon E, Frimat L, Penfornis A, Kessler L, Brault C, Colin C, Tauveron I, Bosco D, Berney T, Benhamou PY; GRAGIL Network. Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network. *Diabetes Care* 2015; **38**: 1714-1722 [PMID: 26068866 DOI: 10.2337/dc15-0094]

15 **Gasparyan AY**, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. *Rheumatol Int* 2011; **31**: 1409-1417 [PMID: 21800117 DOI: 10.1007/s00296-011-1999-3]

16 **Othonos N**, Choudhary P. Who Should Be Considered for Islet Transplantation Alone? *Curr Diab Rep* 2017; **17**: 23 [PMID: 28293906 DOI: 10.1007/s11892-017-0847-6]

17 **Chetboun M**, Jannin A, Kerr-Conte J, Pattou F, Vantyghem MC. 1921-2021: From insulin discovery to islet transplantation in type 1 diabetes. *Ann Endocrinol (Paris)* 2021; **82**: 74-77 [PMID: 33839122 DOI: 10.1016/j.ando.2021.03.006]

18 **McCall M**, Shapiro AM. Islet cell transplantation. *Semin Pediatr Surg* 2014; **23**: 83-90 [PMID: 24931353 DOI: 10.1053/j.sempedsurg.2014.03.006]

19 **Rickels MR**, Robertson RP. Pancreatic Islet Transplantation in Humans: Recent Progress and Future Directions. *Endocr Rev* 2019; **40**: 631-668 [PMID: 30541144 DOI: 10.1210/er.2018-00154]

20 **Tsujimura T**, Kuroda Y, Kin T, Avila JG, Rajotte RV, Korbutt GS, Ryan EA, Shapiro AM, Lakey JR. Human islet transplantation from pancreases with prolonged cold ischemia using additional preservation by the two-layer (UW solution/perfluorochemical) cold-storage method. *Transplantation* 2002; **74**: 1687-1691 [PMID: 12499881 DOI: 10.1097/00007890-200212270-00007]

21 **Ricordi C**, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. *Diabetes* 1988; **37**: 413-420 [PMID: 3288530 DOI: 10.2337/diab.37.4.413]

22 **Gamble A**, Pepper AR, Bruni A, Shapiro AMJ. The journey of islet cell transplantation and future development. *Islets* 2018; **10**: 80-94 [PMID: 29394145 DOI: 10.1080/19382014.2018.1428511]

23 **Vantyghem MC**, de Koning EJP, Pattou F, Rickels MR. Advances in β-cell replacement therapy for the treatment of type 1 diabetes. *Lancet* 2019; **394**: 1274-1285 [PMID: 31533905 DOI: 10.1016/S0140-6736(19)31334-0]

24 **Cayabyab F**, Nih LR, Yoshihara E. Advances in Pancreatic Islet Transplantation Sites for the Treatment of Diabetes. *Front Endocrinol (Lausanne)* 2021; **12**: 732431 [PMID: 34589059 DOI: 10.3389/fendo.2021.732431]

25 **Bennet W**, Groth CG, Larsson R, Nilsson B, Korsgren O. Isolated human islets trigger an instant blood mediated inflammatory reaction: implications for intraportal islet transplantation as a treatment for patients with type 1 diabetes. *Ups J Med Sci* 2000; **105**: 125-133 [PMID: 11095109 DOI: 10.1517/03009734000000059]

26 **Stratta RJ**, Farney AC, Rogers J, Orlando G. Immunosuppression for pancreas transplantation with an emphasis on antibody induction strategies: review and perspective. *Expert Rev Clin Immunol* 2014; **10**: 117-132 [PMID: 24236648 DOI: 10.1586/1744666X.2014.853616]

27 **Ghasemi A**, Akbari E, Imani R. An Overview of Engineered Hydrogel-Based Biomaterials for Improved β-Cell Survival and Insulin Secretion. *Front Bioeng Biotechnol* 2021; **9**: 662084 [PMID: 34513805 DOI: 10.3389/fbioe.2021.662084]

28 **Zhang Q**, Gonelle-Gispert C, Li Y, Geng Z, Gerber-Lemaire S, Wang Y, Buhler L. Islet Encapsulation: New Developments for the Treatment of Type 1 Diabetes. *Front Immunol* 2022; **13**: 869984 [PMID: 35493496 DOI: 10.3389/fimmu.2022.869984]

29 **Todd JA**. Etiology of type 1 diabetes. *Immunity* 2010; **32**: 457-467 [PMID: 20412756 DOI: 10.1016/j.immuni.2010.04.001]

30 **Leslie RD**, Kolb H, Schloot NC, Buzzetti R, Mauricio D, De Leiva A, Yderstraede K, Sarti C, Thivolet C, Hadden D, Hunter S, Schernthaner G, Scherbaum W, Williams R, Pozzilli P. Diabetes classification: grey zones, sound and smoke: Action LADA 1. *Diabetes Metab Res Rev* 2008; **24**: 511-519 [PMID: 18615859 DOI: 10.1002/dmrr.877]

31 **American Diabetes Association**. Standards of Medical Care in Diabetes-2022 Abridged for Primary Care Providers. *Clin Diabetes* 2022; **40**: 10-38 [PMID: 35221470 DOI: 10.2337/cd22-as01]

32 **Ziegler AG**, Nepom GT. Prediction and pathogenesis in type 1 diabetes. *Immunity* 2010; **32**: 468-478 [PMID: 20412757 DOI: 10.1016/j.immuni.2010.03.018]

33 **Zaharieva ET**, Velikova TV, Tsakova AD, Kamenov ZA. Prevalence of Positive Diabetes-Associated Autoantibodies among Type 2 Diabetes and Related Metabolic and Inflammatory Differences in a Sample of the Bulgarian Population. *J*

Diabetes Res 2017; **2017**: 9016148 [PMID: 28573146 DOI: 10.1155/2017/9016148]

34 **Bao F**, Yu L, Babu S, Wang T, Hoffenberg EJ, Rewers M, Eisenbarth GS. One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase autoantibodies. *J Autoimmun* 1999; **13**: 143-148 [PMID: 10441179 DOI: 10.1006/jaut.1999.0303]

35 **Hoffenberg EJ**, Bao F, Eisenbarth GS, Uhlhorn C, Haas JE, Sokol RJ, Rewers M. Transglutaminase antibodies in children with a genetic risk for celiac disease. *J Pediatr* 2000; **137**: 356-360 [PMID: 10969260 DOI: 10.1067/mpd.2000.107582]

36 **Triolo TM**, Armstrong TK, McFann K, Yu L, Rewers MJ, Klingensmith GJ, Eisenbarth GS, Barker JM. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011; **34**: 1211-1213 [PMID: 21430083 DOI: 10.2337/dc10-1756]

37 **Vasilev G**, Kabakchieva P, Miteva D, Batselova H, Velikova T. Effectiveness and safety of COVID-19 vaccines in patients with diabetes as a factor for vaccine hesitancy. *World J Diabetes* 2022; **13**: 738-751 [PMID: 36188150 DOI: 10.4239/wjd.v13.i9.738]

38 **Geerlings SE**, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol* 1999; **26**: 259-265 [PMID: 10575137 DOI: 10.1111/j.1574-695X.1999.tb01397.x]

39 **Hirsch IB**, Juneja R, Beals JM, Antalis CJ, Wright EE. The Evolution of Insulin and How it Informs Therapy and Treatment Choices. *Endocr Rev* 2020; **41**: 733-755 [PMID: 32396624 DOI: 10.1210/endrev/bnaa015]

40 **Bergenstal RM**, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, Willi SM, Wood MA; STAR 3 Study Group. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010; **363**: 311-320 [PMID: 20587585 DOI: 10.1056/NEJMoa1002853]

41 **Breton M**, Farret A, Bruttomesso D, Anderson S, Magni L, Patek S, Dalla Man C, Place J, Demartini S, Del Favero S, Toffanin C, Hughes-Karvetski C, Dassau E, Zisser H, Doyle FJ 3rd, De Nicolao G, Avogaro A, Cobelli C, Renard E, Kovatchev B; International Artificial Pancreas Study Group. Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. *Diabetes* 2012; **61**: 2230-2237 [PMID: 22688340 DOI: 10.2337/db11-1445]

42 **Fridell JA**, Stratta RJ, Gruessner AC. Pancreas Transplantation: Current Challenges, Considerations, and Controversies. *J Clin Endocrinol Metab* 2023; **108**: 614-623 [PMID: 36377963 DOI: 10.1210/clinem/dgac644]

43 **Zóka A**, Műzes G, Somogyi A, Varga T, Szémán B, Al-Aissa Z, Hadarits O, Firneisz G. Altered immune regulation in type 1 diabetes. *Clin Dev Immunol* 2013; **2013**: 254874 [PMID: 24285974 DOI: 10.1155/2013/254874]

44 **Martin S**, Wolf-Eichbaum D, Duinkerken G, Scherbaum WA, Kolb H, Noordzij JG, Roep BO. Development of type 1 diabetes despite severe hereditary B-cell deficiency. *N Engl J Med* 2001; **345**: 1036-1040 [PMID: 11586956 DOI: 10.1056/NEJMoa010465]

45 **Xiu Y**, Wong CP, Bouaziz JD, Hamaguchi Y, Wang Y, Pop SM, Tisch RM, Tedder TF. B lymphocyte depletion by CD20 monoclonal antibody prevents diabetes in nonobese diabetic mice despite isotype-specific differences in Fc gamma R effector functions. *J Immunol* 2008; **180**: 2863-2875 [PMID: 18292508 DOI: 10.4049/jimmunol.180.5.2863]

46 **Roep BO**, Thomaidou S, van Tienhoven R, Zaldumbide A. Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?). *Nat Rev Endocrinol* 2021; **17**: 150-161 [PMID: 33293704 DOI: 10.1038/s41574-020-00443-4]

47 **Pino SC**, Kruger AJ, Bortell R. The role of innate immune pathways in type 1 diabetes pathogenesis. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 126-130 [PMID: 20125005 DOI: 10.1097/MED.0b013e3283372819]

48 **Clark M**, Kroger CJ, Tisch RM. Type 1 Diabetes: A Chronic Anti-Self-Inflammatory Response. *Front Immunol* 2017; **8**: 1898 [PMID: 29312356 DOI: 10.3389/fimmu.2017.01898]

49 **Culina S**, Lalanne AI, Afonso G, Cerosaletti K, Pinto S, Sebastiani G, Kuranda K, Nigi L, Eugster A, Østerbye T, Maugein A, McLaren JE, Ladell K, Larger E, Beressi JP, Lissina A, Appay V, Davidson HW, Buus S, Price DA, Kuhn M, Bonifacio E, Battaglia M, Caillat-Zucman S, Dotta F, Scharfmann R, Kyewski B, Mallone R; ImMaDiab Study Group. Islet-reactive CD8(+) T cell frequencies in the pancreas, but not in blood, distinguish type 1 diabetic patients from healthy donors. *Sci Immunol* 2018; **3** [PMID: 29429978 DOI: 10.1126/sciimmunol.aao4013]

50 **Bottazzo GF**. Lawrence lecture. Death of a beta cell: homicide or suicide? *Diabet Med* 1986; **3**: 119-130 [PMID: 2951152 DOI: 10.1111/j.1464-5491.1986.tb00722.x]

51 **Rickels MR**, Stock PG, de Koning EJP, Piemonti L, Pratschke J, Alejandro R, Bellin MD, Berney T, Choudhary P, Johnson PR, Kandaswamy R, Kay TWH, Keymeulen B, Kudva YC, Latres E, Langer RM, Lehmann R, Ludwig B, Markmann JF, Marinac M, Odorico JS, Pattou F, Senior PA, Shaw JAM, Vantyghem MC, White S. Defining outcomes for β-cell replacement therapy in the treatment of diabetes: a consensus report on the Igls criteria from the IPITA/EPITA opinion leaders workshop. *Transpl Int* 2018; **31**: 343-352 [PMID: 29453879 DOI: 10.1111/tri.13138]

52 **Rickels MR**, Stock PG, de Koning EJP, Piemonti L, Pratschke J, Alejandro R, Bellin MD, Berney T, Choudhary P, Johnson PR, Kandaswamy R, Kay TWH, Keymeulen B, Kudva YC, Latres E, Langer RM, Lehmann R, Ludwig B, Markmann JF, Marinac M, Odorico JS, Pattou F, Senior PA, Shaw JAM, Vantyghem MC, White S. Defining Outcomes for β-cell Replacement Therapy in the Treatment of Diabetes: A Consensus Report on the Igls Criteria From the IPITA/EPITA Opinion Leaders Workshop. *Transplantation* 2018; **102**: 1479-1486 [PMID: 29528967 DOI: 10.1097/TP.0000000000002158]

53 **Gillard P**, Ling Z, Lannoo M, Maes B, Maleux G, Pipeleers D, Keymeulen B, Mathieu C. Beta-cell transplantation restores metabolic control and quality of life in a patient with subcutaneous insulin resistance. *Diabetes Care* 2004; **27**: 2243-2244 [PMID: 15333492 DOI: 10.2337/diacare.27.9.2243]

54 **Nijhoff MF**, Dubbeld J, van Erkel AR, van der Boog PJM, Rabelink TJ, Engelse MA, de Koning EJP. Islet alloautotransplantation: Allogeneic pancreas transplantation followed by transplant pancreatectomy and islet transplantation. *Am J Transplant* 2018; **18**: 1016-1019 [PMID: 29160954 DOI: 10.1111/ajt.14593]

55 **Johnston PC**, Lin YK, Walsh RM, Bottino R, Stevens TK, Trucco M, Bena J, Faiman C, Hatipoglu BA. Factors associated with islet yield and insulin independence after total pancreatectomy and islet cell autotransplantation in patients with chronic pancreatitis utilizing off-site islet isolation: Cleveland Clinic experience. *J Clin Endocrinol Metab* 2015; **100**: 1765-1770 [PMID: 25781357 DOI: 10.1210/jc.2014-4298]

56 **Sutherland DER**, Radosevich DM, Bellin MD, Hering BJ, Beilman GJ, Dunn TB, Chinnakotla S, Vickers SM, Bland B, Balamurugan AN, Freeman ML, Pruett TL. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg* 2012; **214**: 409-424

57 **Ahmad SA**, Lowy AM, Wray CJ, D'Alessio D, Choe KA, James LE, Gelrud A, Matthews JB, Rilo HL. Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. *J Am Coll Surg* 2005; **201**: 680-687 [PMID: 16256909 DOI: 10.1016/j.jamcollsurg.2005.06.268]

58 **Rodriguez Rilo HL**, Ahmad SA, D'Alessio D, Iwanaga Y, Kim J, Choe KA, Moulton JS, Martin J, Pennington LJ, Soldano DA, Biliter J, Martin SP, Ulrich CD, Somogyi L, Welge J, Matthews JB, Lowy AM. Total pancreatectomy and autologous islet cell transplantation as a means to treat severe chronic pancreatitis. *J Gastrointest Surg* 2003; **7**: 978-989 [PMID: 14675707 DOI: 10.1016/j.gassur.2003.09.008]

59 **Webb MA**, Illouz SC, Pollard CA, Gregory R, Mayberry JF, Tordoff SG, Bone M, Cordle CJ, Berry DP, Nicholson ML, Musto PP, Dennison AR. Islet auto transplantation following total pancreatectomy: a long-term assessment of graft function. *Pancreas* 2008; **37**: 282-287 [PMID: 18815550 DOI: 10.1097/mpa.0b013e31816fd7b6]

60 **Garcea G**, Weaver J, Phillips J, Pollard CA, Ilouz SC, Webb MA, Berry DP, Dennison AR. Total pancreatectomy with and without islet cell transplantation for chronic pancreatitis: a series of 85 consecutive patients. *Pancreas* 2009; **38**: 1-7 [PMID: 18665009 DOI: 10.1097/MPA.0b013e3181825c00]

61 **Alejandro R**, Barton FB, Hering BJ, Wease S; Collaborative Islet Transplant Registry Investigators. 2008 Update from the Collaborative Islet Transplant Registry. *Transplantation* 2008; **86**: 1783-1788 [PMID: 19104422 DOI: 10.1097/TP.0b013e3181913f6a]

62 **Shapiro AM**, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, Lakey JR. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med* 2006; **355**: 1318-1330 [PMID: 17005949 DOI: 10.1056/NEJMoa061267]

63 **Gurol AO**, Okten-Kursun A, Kasapoglu P, Suzergoz F, Kucuksezer UC, Cevik A, Tutuncu Y, Yentur SP, Gurol SD, Kucuk M, Yilmaz MT. The synergistic effect of ω3 and Vit D3 on glycemia and TNF-α in islet transplantation. *Cell Mol Biol (Noisy-le-grand)* 2016; **62**: 90-98 [PMID: 26828994]

64 **Casteels K**, Waer M, Laureys J, Valckx D, Depovere J, Bouillon R, Mathieu C. Prevention of autoimmune destruction of syngeneic islet grafts in spontaneously diabetic nonobese diabetic mice by a combination of a vitamin D3 analog and cyclosporine. *Transplantation* 1998; **65**: 1225-1232 [PMID: 9603172 DOI: 10.1097/00007890-199805150-00014]

65 **Infante M**, Ricordi C, Sanchez J, Clare-Salzler MJ, Padilla N, Fuenmayor V, Chavez C, Alvarez A, Baidal D, Alejandro R, Caprio M, Fabbri A. Influence of Vitamin D on Islet Autoimmunity and Beta-Cell Function in Type 1 Diabetes. *Nutrients* 2019; **11** [PMID: 31514368 DOI: 10.3390/nu11092185]

66 **Szymczak-Pajor I**, Śliwińska A. Analysis of Association between Vitamin D Deficiency and Insulin Resistance. *Nutrients* 2019; **11** [PMID: 30959886 DOI: 10.3390/nu11040794]

67 **Bellin MD**, Barton FB, Heitman A, Harmon JV, Kandaswamy R, Balamurugan AN, Sutherland DE, Alejandro R, Hering BJ. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. *Am J Transplant* 2012; **12**: 1576-1583 [PMID: 22494609 DOI: 10.1111/j.1600-6143.2011.03977.x]

68 **Vallabhajosyula P**, Hirakata A, Shimizu A, Okumi M, Tchipashvili V, Hong H, Yamada K, Sachs DH. Assessing the effect of immunosuppression on engraftment of pancreatic islets. *Transplantation* 2013; **96**: 372-378 [PMID: 23883972 DOI: 10.1097/TP.0b013e31829f7515]

69 **Sato N**, Marubashi S. Induction of Immune Tolerance in Islet Transplantation Using Apoptotic Donor Leukocytes. *J Clin Med* 2021; **10** [PMID: 34830586 DOI: 10.3390/jcm10225306]

70 **Johnson PRV**. Islet Transplantation in the UK. *CellR4 Repair Replace Regen Reprogram* 2019; **7** [PMID: 34527761 DOI: 10.32113/cellr4_201911_2788]

71 **UK Guidelines on Pancreas and Islet Transplantation**. British Transplantation Society. Available from: https://bts.org.uk/wp-content/uploads/2019/09/FINAL-Pancreas-guidelines-FINAL-version-following-consultation.-Sept-2019.pdf

72 **Ding Q**, Yeung M, Camirand G, Zeng Q, Akiba H, Yagita H, Chalasani G, Sayegh MH, Najafian N, Rothstein DM. Regulatory B cells are identified by expression of TIM-1 and can be induced through TIM-1 ligation to promote tolerance in mice. *J Clin Invest* 2011; **121**: 3645-3656 [PMID: 21821911 DOI: 10.1172/JCI46274]

73 **Lee KM**, Kim JI, Stott R, Soohoo J, O'Connor MR, Yeh H, Zhao G, Eliades P, Fox C, Cheng N, Deng S, Markmann JF. Anti-CD45RB/anti-TIM-1-induced tolerance requires regulatory B cells. *Am J Transplant* 2012; **12**: 2072-2078 [PMID: 22494812 DOI: 10.1111/j.1600-6143.2012.04055.x]

74 **Kawai T**, Sogawa H, Boskovic S, Abrahamian G, Smith RN, Wee SL, Andrews D, Nadazdin O, Koyama I, Sykes M, Winn HJ, Colvin RB, Sachs DH, Cosimi AB. CD154 blockade for induction of mixed chimerism and prolonged renal allograft survival in nonhuman primates. *Am J Transplant* 2004; **4**: 1391-1398 [PMID: 15307826 DOI: 10.1111/j.1600-6143.2004.00523.x]

75 **Kawai T**, Cosimi AB, Spitzer TR, Tolkoff-Rubin N, Suthanthiran M, Saidman SL, Shaffer J, Preffer FI, Ding R, Sharma V, Fishman JA, Dey B, Ko DS, Hertl M, Goes NB, Wong W, Williams WW Jr, Colvin RB, Sykes M, Sachs DH. HLA-mismatched renal transplantation without maintenance immunosuppression. *N Engl J Med* 2008; **358**: 353-361 [PMID: 18216355 DOI: 10.1056/NEJMoa071074]

76 **Singh A**, Ramachandran S, Graham ML, Daneshmandi S, Heller D, Suarez-Pinzon WL, Balamurugan AN, Ansite JD, Wilhelm JJ, Yang A, Zhang Y, Palani NP, Abrahante JE, Burlak C, Miller SD, Luo X, Hering BJ. Long-term tolerance of islet allografts in nonhuman primates induced by apoptotic donor leukocytes. *Nat Commun* 2019; **10**: 3495 [PMID: 31375697 DOI: 10.1038/s41467-019-11338-y]

77 **Oura T**, Ko DS, Boskovic S, O'Neil JJ, Chipashvili V, Koulmanda M, Hotta K, Kawai K, Nadazdin O, Smith RN, Cosimi AB, Kawai T. Kidney Versus Islet Allograft Survival After Induction of Mixed Chimerism With Combined Donor Bone Marrow Transplantation. *Cell Transplant* 2016; **25**: 1331-1341 [PMID: 26337731 DOI: 10.3727/096368915X688966]

78 **Kheradmand T**, Wang S, Bryant J, Tasch JJ, Lerret N, Pothoven KL, Houlihan JL, Miller SD, Zhang ZJ, Luo X. Ethylenecarbodiimide-fixed donor splenocyte infusions differentially target direct and indirect pathways of allorecognition for induction of transplant tolerance. *J Immunol* 2012; **189**: 804-812 [PMID: 22696445 DOI: 10.4049/jimmunol.1103705]

79 **Bryant J**, Lerret NM, Wang JJ, Kang HK, Tasch J, Zhang Z, Luo X. Preemptive donor apoptotic cell infusions induce IFN-γ-producing myeloid-derived suppressor cells for cardiac allograft protection. *J Immunol* 2014; **192**: 6092-6101 [PMID: 24808363 DOI: 10.4049/jimmunol.1302771]

80 **Dangi A**, Yu S, Lee FT, Burnette M, Knechtle S, Kwun J, Luo X. Donor apoptotic cell-based therapy for effective inhibition of donor-specific memory T and B cells to promote long-term allograft survival in allosensitized recipients. *Am J Transplant* 2020; **20**: 2728-2739 [PMID: 32275799 DOI: 10.1111/ajt.15878]

81 **Eriksson O**, Eich T, Sundin A, Tibell A, Tufveson G, Andersson H, Felldin M, Foss A, Kyllönen L, Langstrom B, Nilsson B, Korsgren O, Lundgren T. Positron emission tomography in clinical islet transplantation. *Am J Transplant* 2009; **9**: 2816-2824 [PMID: 19845588 DOI: 10.1111/j.1600-6143.2009.02844.x]

82 **Nilsson B**, Ekdahl KN, Korsgren O. Control of instant blood-mediated inflammatory reaction to improve islets of Langerhans engraftment. *Curr Opin Organ Transplant* 2011; **16**: 620-626 [PMID: 21971510 DOI: 10.1097/MOT.0b013e32834c2393]

83 **Hu M**, Hawthorne WJ, Yi S, O'Connell PJ. Cellular Immune Responses in Islet Xenograft Rejection. *Front Immunol* 2022; **13**: 893985 [PMID: 35874735 DOI: 10.3389/fimmu.2022.893985]

84 **Wang X**, Brown NK, Wang B, Shariati K, Wang K, Fuchs S, Melero-Martin JM, Ma M. Local Immunomodulatory Strategies to Prevent Allo-Rejection in Transplantation of Insulin-Producing Cells. *Adv Sci (Weinh)* 2021; **8**: e2003708 [PMID: 34258870 DOI: 10.1002/advs.202003708]

85 **Scuteri A**, Donzelli E, Rodriguez-Menendez V, Ravasi M, Monfrini M, Bonandrini B, Figliuzzi M, Remuzzi A, Tredici G. A double mechanism for the mesenchymal stem cells' positive effect on pancreatic islets. *PLoS One* 2014; **9**: e84309 [PMID: 24416216 DOI: 10.1371/journal.pone.0084309]

86 **Rahavi H**, Hashemi SM, Soleimani M, Mohammadi J, Tajik N. Adipose tissue-derived mesenchymal stem cells exert in vitro immunomodulatory and beta cell protective functions in streptozotocin-induced diabetic mice model. *J Diabetes Res* 2015; **2015**: 878535 [PMID: 25893202 DOI: 10.1155/2015/878535]

87 **Vegas AJ**, Veiseh O, Gürtler M, Millman JR, Pagliuca FW, Bader AR, Doloff JC, Li J, Chen M, Olejnik K, Tam HH, Jhunjhunwala S, Langan E, Aresta-Dasilva S, Gandham S, McGarrigle JJ, Bochenek MA, Hollister-Lock J, Oberholzer J, Greiner DL, Weir GC, Melton DA, Langer R, Anderson DG. Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice. *Nat Med* 2016; **22**: 306-311 [PMID: 26808346 DOI: 10.1038/nm.4030]

88 **Prokhorova TA**, Harkness LM, Frandsen U, Ditzel N, Schrøder HD, Burns JS, Kassem M. Teratoma formation by human embryonic stem cells is site dependent and enhanced by the presence of Matrigel. *Stem Cells Dev* 2009; **18**: 47-54 [PMID: 18393673 DOI: 10.1089/scd.2007.0266]

89 **Harding J**, Vintersten-Nagy K, Shutova M, Yang H, Tang J, Massumi M, Izadifar M, Izadifar Z, Zhang P, Li C, Nagy A. Induction of long-term allogeneic cell acceptance and formation of immune privileged tissue in immunocompetent hosts. 2019 Preprint. Available from: BioRxiv:716571 [DOI: 10.1101/716571]

90 **Rickels MR**, Kearns J, Markmann E, Palanjian M, Markmann JF, Naji A, Kamoun M. HLA sensitization in islet transplantation. *Clin Transpl* 2006; 413-420 [PMID: 18365398]

91 **Paget MB**, Murray HE, Bailey CJ, Downing R. From insulin injections to islet transplantation: An overview of the journey. *Diabetes Obes Metab* 2022; **24** Suppl 1: 5-16 [PMID: 34431589 DOI: 10.1111/dom.14526]

92 **Siehler J**, Blöchinger AK, Meier M, Lickert H. Engineering islets from stem cells for advanced therapies of diabetes. *Nat Rev Drug Discov* 2021; **20**: 920-940 [PMID: 34376833 DOI: 10.1038/s41573-021-00262-w]

93 **Coe TM**, Markmann JF, Rickert CG. Current status of porcine islet xenotransplantation. *Curr Opin Organ Transplant* 2020; **25**: 449-456 [PMID: 32773503 DOI: 10.1097/MOT.0000000000000794]

94 **Hubber EL**, Rackham CL, Jones PM. Protecting islet functional viability using mesenchymal stromal cells. *Stem Cells Transl Med* 2021; **10**: 674-680 [PMID: 33544449 DOI: 10.1002/sctm.20-0466]

95 **Harden PN**, Game DS, Sawitzki B, Van der Net JB, Hester J, Bushell A, Issa F, Brook MO, Alzhrani A, Schlickeiser S, Scotta C, Petchey W, Streitz M, Blancho G, Tang Q, Markmann J, Lechler RI, Roberts ISD, Friend PJ, Hilton R, Geissler EK, Wood KJ, Lombardi G. Feasibility, long-term safety, and immune monitoring of regulatory T cell therapy in living donor kidney transplant recipients. *Am J Transplant* 2021; **21**: 1603-1611 [PMID: 33171020 DOI: 10.1111/ajt.16395]

96 **Kuppan P**, Kelly S, Polishevska K, Hojanepesov O, Seeberger K, Korbutt GS, Pepper AR. Co-localized immune protection using dexamethasone-eluting micelles in a murine islet allograft model. *Am J Transplant* 2020; **20**: 714-725 [PMID: 31650674 DOI: 10.1111/ajt.15662]

97 **Alwahsh SM**, Qutachi O, Starkey Lewis PJ, Bond A, Noble J, Burgoyne P, Morton N, Carter R, Mann J, Ferreira-Gonzalez S, Alvarez-Paino M, Forbes SJ, Shakesheff KM, Forbes S. Fibroblast growth factor 7 releasing particles enhance islet engraftment and improve metabolic control following islet transplantation in mice with diabetes. *Am J Transplant* 2021; **21**: 2950-2963 [PMID: 33428803 DOI: 10.1111/ajt.16488]

98 **Vandermeulen M**, Erpicum P, Weekers L, Briquet A, Lechanteur C, Detry O, Beguin Y, Jouret F. Mesenchymal Stromal Cells in Solid Organ Transplantation. *Transplantation* 2020; **104**: 923-936 [PMID: 31929427 DOI: 10.1097/TP.0000000000003077]

99 **Staels W**, Verdonck Y, Heremans Y, Leuckx G, De Groef S, Heirman C, de Koning E, Gysemans C, Thielemans K, Baeyens L, Heimberg H, De Leu N. Vegf-A mRNA transfection as a novel approach to improve mouse and human islet graft revascularisation. *Diabetologia* 2018; **61**: 1804-1810 [PMID: 29789879 DOI: 10.1007/s00125-018-4646-7]

100 **Primavera R**, Razavi M, Kevadiya BD, Wang J, Vykunta A, Di Mascolo D, Decuzzi P, Thakor AS. Enhancing islet transplantation using a biocompatible collagen-PDMS bioscaffold enriched with dexamethasone-microplates. *Biofabrication* 2021; **13** [PMID: 33455953 DOI: 10.1088/1758-5090/abdcac]

101 **Bertuzzi F**, Colussi G, Lauterio A, De Carlis L. Intramuscular islet allotransplantation in type 1 diabetes mellitus. *Eur Rev Med Pharmacol Sci* 2018; **22**: 1731-1736 [PMID: 29630119 DOI: 10.26355/eurrev_201803_14588]

102 **Yin Z**, Li J, Zheng Y, Wang S, Wang X. Gastric submucosal alleviated pro-inflammation cytokines mediated initial dysfunction of islets allografts. *Transpl Immunol* 2021; **65**: 101292 [PMID: 32302641 DOI: 10.1016/j.trim.2020.101292]

103 **Addison P**, Fatakhova K, Rodriguez Rilo HL. Considerations for an Alternative Site of Islet Cell Transplantation. *J Diabetes Sci Technol* 2020; **14**: 338-344 [PMID: 31394934 DOI: 10.1177/1932296819868495]

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MINIREVIEWS

Intracranial pressure monitoring in the perioperative period of patients with acute liver failure undergoing orthotopic liver transplantation

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Abstract

Acute liver failure (ALF) may result in severe neurological complications caused by cerebral edema and elevated intracranial pressure (ICP). Multiple pathogenic mechanisms explain the elevated ICP, and newer hypotheses have been described. While invasive ICP monitoring (ICPM) may have a role in ALF management, these patients are typically coagulopathic and at risk for intracranial hemorrhage. ICPM is the subject of much debate, and significant heterogeneity exists in clinical practice regarding its use. Contemporary ICPM techniques and coagulopathy reversal strategies may be associated with a lower risk of hemor-rhage; however, most of the evidence is limited by its retrospective nature and relatively small sample size.

Key Words: Acute liver failure; Liver transplant; Hepatic encephalopathy; Intracranial hypertension; Brain edema

Core Tip: Despite its rare occurrence, acute liver failure generates academic interest from multiple disciplines because of its multiorgan involvement and high morbidity and mortality. Severe neurological complications may arise, requiring invasive monitoring with the potential risk of fatal intracranial bleeding. Newer strategies could decrease the risks while keeping the benefits.

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INTRODUCTION

Definition and incidence

Acute liver failure (ALF) is a rare syndrome caused by abrupt hepatocyte injury that can progress to a fatal outcome in days to weeks. The most widely accepted definition of ALF includes evidence of coagulopathy and any degree of mental alteration (*i.e.*, encephalopathy) within 26 wk in a patient without preexisting liver disease[1]. Classification according to etiology highlights associated prognostic value and disease-specific treatment. An alternative classification quantifies the interval between symptom onset and development of encephalopathy; hyperacute (0–7 d), acute (8–28 d), and subacute (1–3 mo)[2]. The incidence of ALF in the United States of America is thought to be close to 3000 cases per year[3].

Despite its rare occurrence, ALF generates academic interest from multiple disciplines because of its multiorgan involvement and high morbidity and mortality. The survival from ALF has improved in recent years through better knowledge of pathophysiology, advances in critical care management, and access to emergency liver transplantation (LT)[4].

Etiology, pathophysiology and multiorgan involvement

The pathophysiological process that leads to hepatocyte injury causes either direct toxic necrosis or immune apoptotic injury; the predominant cause for direct injury is acetaminophen toxicity, developing from hours to days[5]. The immune apoptotic injury is a slower injury process, led by hepatitis B infection/reactivation, autoimmune hepatitis, and drug-induced liver injury[6,7]. ALF is characterized by the development of hepatic encephalopathy (HE), and the loss of synthetic dysfunction in the form of coagulopathy. An elevated prothrombin time is a marker of synthetic dysfunction that occurs from the decrease in the vitamin K-dependent coagulation factors (II, VII, IX, X); prolongation of the INR more than 1.5 is considered a poor prognostic sign and a cornerstone of ALF diagnostic criteria.

The pathophysiology of ALF can be divided into primary liver injury specific to etiology and secondary multiorgan failure. The primary liver insult of acetaminophen-induced ALF has the best understood mechanism, namely glutathione depletion. The secondary multiorgan failure, severe systemic inflammation and microcirculatory alterations contribute to a clinical picture comparable to a distributive shock[8]. The vascular tone of the brain and kidneys are most vulnerable, leading to cerebral edema, encephalopathy, and functional renal failure[9].

NEUROLOGICAL DYSFUNCTION IN ALF

The central place of HE in the definition of ALF reflects its key prognostic impact, and its development reflects severely impaired liver function. A multiaxial definition of the syndromes of HE was developed for chronic liver disease by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism based on the type of underlying hepatic abnormality, the time course, and severity of neurological manifestations[10]. The American and European Associations for the Study of Liver Diseases practice guidelines highlights the distinct features of HE in ALF and the association of HE with increased intracranial pressure (ICP)[11].

Cerebral edema and resulting intracranial hypertension (ICH) are the most severe neurological clinical manifestations in patients with ALF. In the past, cerebral edema was presumed to occur in up to 80% of patients with ALF. However, recent data from developed countries estimates a drop in the incidence to 20%-30%, probably due to earlier diagnosis and improved management[12].

Pathogenesis of brain edema in ALF

The pathogenesis of cerebral edema in ALF is complex and only partially understood, and its occurrence is related to the severity of encephalopathy. Cerebral edema is occasionally observed in patients with grade I-II encephalopathy; moreover,the risk of edema increases to 25% to 35% with progression to grade III, and 65% to 75% or more in patients reaching grade IV coma[13].

Potential contributing factors include cytotoxicity due to osmotic effects of ammonia, glutamine, and proinflammatory cytokines, vasogenic edema due to disruption of the blood-brain barrier with the rapid accumulation of low molecular substances, and the loss of the cerebral blood flow autoregulation.

Multiple studies support astrocyte swelling and cytotoxic edema as major contributors to cerebral edema in ALF[12,14,15]; the evidence is most compelling in the central role of ammonia causing astrocyte swelling. The ammonia-glutamine hypothesis has persisted over years, describing an excess of ammonia in the brain which is converted to glutamine with resulting osmotic effects on astrocytes. New studies have challenged this hypothesis, concluding that astrocyte swelling may not be the result of glutamine's direct osmotic effect; instead, a "Trojan horse" hypothesis is proposed in which glutamine may function as a carrier of ammonia into the mitochondria where its accumulation can lead to oxidative stress and ultimately cellular swelling[16]. Oxidative stress has been implicated as an important factor in the pathophysiology of ammonia-induced neurotoxicity through the formation of free radicals which may result in mitochondrial permeability transition[17].

Other studies have suggested that neuroinflammatory mediators, particularly proinflammatory cytokines such as the interleukins (IL)-1β and IL-6 and tumor necrosis factor-α, play an essential role in the development of brain edema and ICH[18,19]. Neuroinflammation is now widely considered the result of a direct interaction between microglia and ammonia. The released proinflammatory cytokines from activated microglia cells and ammonia appear to act synergistically to induce cytotoxic cerebral edema in which the blood-brain barrier is preserved.

Research combining brain imaging in the context of ALF demonstrates evidence of interstitial brain edema in addition to cytotoxic brain edema, implying the presence of vasogenic edema, in which the blood-brain barrier would be compromised[20,21]. Although a generalized breakdown of the blood-brain barrier cannot be demonstrated, some studies propose the "leaky" theory, in which there are subtle changes in the integrity of the tight junctions of the blood-brain barrier. The exact mechanism of how cytotoxic, vasogenic, and neuroinflammation interact to bring brain edema in ALF remains unknown.

The role of ICP monitoring in ALF

The Brain Trauma Foundation guidelines explicitly recommend ICP monitoring (ICPM) for patients with severe traumatic brain injury to minimize mortality[22]; however, recommendations for ICPM in patients with non-traumatic brain injury are lacking. The rationale for using monitors to measure the pressure inside the cranium in ALF considers the potential benefit of early identification and management of ICH. In addition, continuous ICP measurements contribute to the decision-making process for emergency LT; intraoperative ICPM facilitates active neurological management in the setting of rapid fluid shifts and hemodynamic instability.

Invasive ICPM remains the gold standard for the measurement of ICP[23], which may reveal occult elevations in ICP in comatose patients with ALF[24]. Despite the proposed benefits, invasive ICPM in this unique patient population raises concern due to the risk of life-threatening intracranial hemorrhage in the setting of coagulopathy.

Noninvasive ICPMs offer an alternative solution in this specific group of patients, employing techniques of optic nerve ultrasound and transcranial doppler. However, current evidence does not support its use to accurately identify patients with ICH. One study evaluated noninvasive ICPM techniques in comparison to the gold standard of invasive ICPM; the authors concluded that neither optic nerve ultrasound nor transcranial doppler pulsatility index correlated with the gold standard[25]. Another standard noninvasive option is cerebral computerized tomography, yet, evidence demonstrates this method's failure to consistently detect brain edema in patients with elevated ICP[23]. In addition, the complexity of intrahospital transport for critically ill patients should not be underestimated.

With invasive ICPMs identified as the most accurate modality to identify ICH in patients with ALF, several invasive options exist. Transducers may be placed in the brain parenchyma, ventricular system, epidural or subdural spaces. Epidural devices have lower complication rates than subdural or intraparenchymal monitors[26]. A ventricular system has the potential to be diagnostic and therapeutic as cerebrovascular fluid can be drained; however, intraventricular placement may be associated with severe and potentially fatal hemorrhage.

LT in ALF

With high-grade HE identified as an independent predictor of mortality in patients with ALF, LT is a potentially life-saving intervention[27]. Access to emergency LT has improved survival rates for patients that fulfill criteria for a poor prognosis. The King's College Criteria remains the most clinically useful prediction tool, with disease-specific modeling for paracetamol and non-paracetamol categories[28]. Post-LT outcomes in this population are high with one- and three-year patient survival rates reported as 91% and 90% respectively[28].

Consensus guidelines for ICP monitor use

A review of the current literature highlights the lack of consensus regarding the use of ICPM in patients with ALF. The Acute Liver Failure Study Group guidelines does not recommend the use of external ventricular devices to monitor ICP for all patients with ALF; however, they recognize that most centers will place ICPM in patients with advanced encephalopathy[29,30]. A survey of 24 centers in the United States of America demonstrated that a minority (approximately 30%) of centers utilized ICPM[31].

Invasive ICPM use in Europe is more prevalent with 55% of centers surveyed reporting use of this monitoring modality[26]. In both surveys, invasive ICPM was reserved for patients with advanced encephalopathy according to The West Haven criteria; the type of invasive monitor use was not specified. The American Association for the Study of the Liver recommends invasive ICPM in patients with ALF awaiting LT and in centers with expertise[28]; The European Association for the Study of the Liver recommends monitoring only in a select group of patients including those with advanced encephalopathy at risk of ICH, hyperammonemia, and renal or vasopressor support[32]. Table 1 summarizes the current large-society recommendations.

Robust data regarding the impact on long-term neurological consequences of cerebral edema and ICH in patients with ALF is scarce. Similarly, evidence reporting outcomes associated with the use of ICPM in this patient population is also lacking. Karvellas *et al*[33] reported a multicenter retrospective cohort study involving 140 patients managed with ICPM *vs* 489 controls without ICPM; the mortality at 21 d was not significantly different[33].

The incidence of spontaneous intracranial hemorrhage in ALF

The estimated risk of spontaneous intracranial hemorrhage in overt encephalopathy grade III and IV is 25%-35% and 65%-75% respectively[34]. The incidence of intracranial hemorrhage has decreased over many years. Bernal *et al*[4] reported a series of 3300 patients, in which intracranial hemorrhage occurred in more than 70% of patients on initial analysis with a dramatic reduction in incidence to only 20%, with a corresponding reduction in mortality, 20 years later[4]. The same author reported 29% incidence of intracranial hemorrhage in a series of more than 160 patients with overt encephalopathy[14]. The risk factors for intracranial hemorrhage include hyperacute presentation, younger age, and requirements of vasopressors or renal replacement therapy[14,35].

Risk of bleeding and outcomes from the use of invasive ICPM in ALF

The general incidence of hemorrhagic complications from ICPM is approximately 10%-20% with fatal hemorrhage reported in 1%-5% of patients[31,36]. The risk of intracranial bleeding is related to the type of device and location of the ICPM placement. Some authors claim a reduction in bleeding risk by a meticulous insertion technique and targeted peri-procedural transfusion (*e.g.*, recombinant factor VIIa prior to the placement of the ICPM)[37]. A literature search from 1992 to 2017 shows eleven studies reporting the use of ICPM in ALF;only four of these studies described an institutional protocol to correct the coagulopathy prior to the insertion of ICPM. Variable use of peri-procedural blood product transfusion was observed.

Another potential complication associated with ICPM insertion is infection. The general risk of infection is approximately 1%-20%[38]. To our knowledge, ALF patients have no associated increase in infection risk; however, data is limited. Multiple small case series demonstrated a low incidence of ICPM-related infections[24,37,39]. Reported rates of infection ranged from 0%-7%. A common practice to reduce infection risk is the administration of prophylactic intravenous antibiotics to cover the typical skin flora prior to ICPM placement.

TECHNICAL ASPECTS FOR ICPM

It is important to acknowledge that regardless of the transducer selected, the management of ICP should be guided by the cerebral perfusion pressure. The cerebral perfusion is estimated by the difference between the mean cerebral arterial pressure and the ICP. To ensure accurate measurement of cerebral arterial pressure, it is recommended that the arterial line transducer should be positioned at the external auditory meatus, level with the middle cranial fossa[40].

Interventions for managing brain edema and ICH in ALF are out of the scope of this article. However, standard measures are to maintain adequate sedation, head elevation at 30 degrees, target plasma sodium levels of 145 to 155 mEq/L, maintain normocapnia with a CO_2 of 35 mmHg, a plasma osmolarity of 320 mOsml/L, a mean arterial blood pressure of 75-80 mmHg, and temperature between 32-34 °C for 10-14 h in candidates for LT[41].

SINGLE-CENTER EXPERIENCE

Using the limited evidence and large-society guidelines, a protocol was developed and implemented to guide management of severe neurological consequences of ALF in our center. Integral to this document is the recommendation for the use of invasive ICPM in carefully selected patients. Protocol development engaged representatives from all multidisciplinary stakeholders including hepatology, anesthesia, critical care, and surgery. Explicit clinical criteria outlined patients appropriate for invasive ICPM use.

As outlined in this protocol, patients with high-grade HE (grade III and IV) in the context of ALF, with the possibility of recovery from medical intervention and/or LT, warrant ICPM insertion.

Table 1 Summary of recommendations for intracranial pressure monitor in patients with acute liver failure

Society	Recommendation	Quality of evidence
AASLD 2005[1]	ICPM is mainly considered for patients who are listed for transplantation. In the absence of ICPM, frequent evaluation for signs of intracranial hypertension is needed to identify early evidence of uncal herniation	Evidence level III
AASLD Revised 2011[28]	The use of recombinant factor rVIIa may be considered	NA
ALSFG 2007[30]	Insufficient data to recommend ICPM placement in all patients with ALF. However, most members of the ALFSG place ICPM in patients with advanced (stage III/IV) hepatic encephalopathy	NA
EASL 2017 [32]	ICPM should be considered in a highly selected subgroup of patients, who have progressed to grade 3 or 4 coma, are intubated and ventilated and deemed at high risk of intracranial hemorrhage, based on the presence of more than one of the following variables: (1) Young patients with hyperacute or acute presentations; (2) ammonia level over 150–200 lmol/L that does not drop with initial treatment interventions (RRT and fluids); (3) renal impairment; and (4) vasopressor support (> 0.1 lg/kg/min)	(Evidence level II-3, grade of Recommendation 1)

AASLD: American Association for the Study of Liver Diseases; ALSFG: United States Acute Liver Failure Study Group; EASL: European Association for the study of the Liver; ICPM: Intracranial pressure monitor; RRT: Renal replacement therapy; ALF: Acute liver failure; rFVIIa: Recombinant factor VIIa; NA: Not available.

Due to the risk of severe brain edema, eventually obliterating the ventricles, our neurosurgical team is reluctant to use external ventricular devices, in addition to the increased risk of periprocedural hemorrhage. In our protocol, we use the Codman Microsensor™ intraparenchymal monitor, which measures ICP *via* a strain gauge microchipat the catheter's tip. Pressure is reflected as an electrical voltage transmitted to the proximal end of the catheter through nylon-encapsulated copper wires. The proximal end of the catheter is connected to the Codman Express™ monitor, which displays the ICP value. Following baseline brain imaging andbefore insertion, the ICPMis zeroed at atmospheric pressure; after insertion, opening pressure is determined, and real-time display and longitudinal recordings are obtained.

To minimize the risk of ICPM-associated hemorrhage, coagulation correction is frequently undertaken prior to device insertion. It is generally accepted that conventional coagulation tests (*e.g.*, INR and platelet count) provide a limited perspective of *in vivo* clot formation in patients with liver disease. With the growing popularity of viscoelastic testing (VET) to guide coagulation management during LT, VET has been proposed as a more comprehensive tool to facilitate invasive procedures such as ICPM insertion. Our protocol utilizes a combined approach of VET and conventional laboratory testing. In our early institutional experience, directed administration of recombinant factor VIIa, fibrinogen, platelets, and desmopressin has enabled intraparenchymal monitor insertion, maintenance, and removal without hemorrhagic complications.

CONCLUSION

Future prospective studies are necessary to address the existing gaps in knowledge outlined in this review. Given the rarity of ALF, and the broad spectrum of presentation, it is unlikely that single-center studies will provide robust evidence. Most of the protocols currently in place, including the one used in our center, are derived from retrospective observational and expert consensus statements. It is paramount to define the specific population of patients in which insertion of ICPMs changes outcomes and standardized transfusion protocols to minimize the associated risk of bleeding.

FOOTNOTES

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REFERENCES

1 **Polson J**, Lee WM; American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology* 2005; **41**: 1179-1197 [PMID: 15841455 DOI: 10.1002/hep.20703]
2 **O'Grady JG**, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet* 1993; **342**: 273-275 [PMID: 8101303 DOI: 10.1016/0140-6736(93)91818-7]
3 **Wijdicks EFM**. Hepatic Encephalopathy. *N Engl J Med* 2017; **376**: 186 [PMID: 28076712 DOI: 10.1056/NEJMc1614962]
4 **Bernal W**, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, Williams R. Lessons from look-back in acute liver failure? *J Hepatol* 2013; **59**: 74-80 [PMID: 23439263 DOI: 10.1016/j.jhep.2013.02.010]
5 **Bailey B**, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. *Crit Care Med* 2003; **31**: 299-305 [PMID: 12545033 DOI: 10.1097/00003246-200301000-00048]
6 **Jayakumar S**, Chowdhury R, Ye C, Karvellas CJ. Fulminant viral hepatitis. *Crit Care Clin* 2013; **29**: 677-697 [PMID: 23830658 DOI: 10.1016/j.ccc.2013.03.013]
7 **Wang K**. Molecular mechanisms of hepatic apoptosis. *Cell Death Dis* 2014; **5**: e996 [PMID: 24434519 DOI: 10.1038/cddis.2013.499]
8 **Zoubek ME**, Lucena MI, Andrade RJ, Stephens C. Systematic review: ibuprofen-induced liver injury. *Aliment Pharmacol Ther* 2020; **51**: 603-611 [PMID: 31984540 DOI: 10.1111/apt.15645]
9 **Dong V**, Nanchal R, Karvellas CJ. Pathophysiology of Acute Liver Failure. *Nutr Clin Pract* 2020; **35**: 24-29 [PMID: 31840297 DOI: 10.1002/ncp.10459]
10 **Munk Lauridsen M**, Vilstrup H. Diagnosing covert hepatic encephalopathy. *Clin Liver Dis (Hoboken)* 2015; **5**: 71-74 [PMID: 31040954 DOI: 10.1002/cld.451]
11 **Vilstrup H**, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014; **60**: 715-735 [PMID: 25042402 DOI: 10.1002/hep.27210]
12 **Scott TR**, Kronsten VT, Hughes RD, Shawcross DL. Pathophysiology of cerebral oedema in acute liver failure. *World J Gastroenterol* 2013; **19**: 9240-9255 [PMID: 24409052 DOI: 10.3748/wjg.v19.i48.9240]
13 **Muñoz SJ**. Difficult management problems in fulminant hepatic failure. *Semin Liver Dis* 1993; **13**: 395-413 [PMID: 8303321 DOI: 10.1055/s-2007-1007368]
14 **Bernal W**, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology* 2007; **46**: 1844-1852 [PMID: 17685471 DOI: 10.1002/hep.21838]
15 **Vaquero J**, Chung C, Blei AT. Brain edema in acute liver failure. A window to the pathogenesis of hepatic encephalopathy. *Ann Hepatol* 2003; **2**: 12-22 [PMID: 15094701]
16 **Albrecht J**, Norenberg MD. Glutamine: a Trojan horse in ammonia neurotoxicity. *Hepatology* 2006; **44**: 788-794 [PMID: 17006913 DOI: 10.1002/hep.21357]
17 **Schliess F**, Görg B, Häussinger D. Pathogenetic interplay between osmotic and oxidative stress: the hepatic encephalopathy paradigm. *Biol Chem* 2006; **387**: 1363-1370 [PMID: 17081108 DOI: 10.1515/BC.2006.171]
18 **Rodrigo R**, Cauli O, Gomez-Pinedo U, Agusti A, Hernandez-Rabaza V, Garcia-Verdugo JM, Felipo V. Hyperammonemia induces neuroinflammation that contributes to cognitive impairment in rats with hepatic encephalopathy. *Gastroenterology* 2010; **139**: 675-684 [PMID: 20303348 DOI: 10.1053/j.gastro.2010.03.040]
19 **Zemtsova I**, Görg B, Keitel V, Bidmon HJ, Schrör K, Häussinger D. Microglia activation in hepatic encephalopathy in rats and humans. *Hepatology* 2011; **54**: 204-215 [PMID: 21452284 DOI: 10.1002/hep.24326]
20 **Rai V**, Nath K, Saraswat VA, Purwar A, Rathore RK, Gupta RK. Measurement of cytotoxic and interstitial components of cerebral edema in acute hepatic failure by diffusion tensor imaging. *J Magn Reson Imaging* 2008; **28**: 334-341 [PMID: 18626948 DOI: 10.1002/jmri.21438]
21 **Kale RA**, Gupta RK, Saraswat VA, Hasan KM, Trivedi R, Mishra AM, Ranjan P, Pandey CM, Narayana PA. Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. *Hepatology* 2006; **43**: 698-706 [PMID: 16557540 DOI: 10.1002/hep.21114]
22 **Kolias AG**, Rubiano AM, Figaji A, Servadei F, Hutchinson PJ. Traumatic brain injury: global collaboration for a global challenge. *Lancet Neurol* 2019; **18**: 136-137 [PMID: 30663604 DOI: 10.1016/S1474-4422(18)30494-0]
23 **Raghavan M**, Marik PE. Therapy of intracranial hypertension in patients with fulminant hepatic failure. *Neurocrit Care* 2006; **4**: 179-189 [PMID: 16627910 DOI: 10.1385/NCC:4:2:179]
24 **Rajajee V**, Fontana RJ, Courey AJ, Patil PG. Protocol based invasive intracranial pressure monitoring in acute liver failure: feasibility, safety and impact on management. *Crit Care* 2017; **21**: 178 [PMID: 28693567 DOI:

10.1186/s13054-017-1762-6]
25 **Rajajee V**, Williamson CA, Fontana RJ, Courey AJ, Patil PG. Noninvasive Intracranial Pressure Assessment in Acute Liver Failure. *Neurocrit Care* 2018; **29**: 280-290 [PMID: 29948998 DOI: 10.1007/s12028-018-0540-x]
26 **Rabinowich L**, Wendon J, Bernal W, Shibolet O. Clinical management of acute liver failure: Results of an international multi-center survey. *World J Gastroenterol* 2016; **22**: 7595-7603 [PMID: 27672280 DOI: 10.3748/wjg.v22.i33.7595]
27 **Karvellas CJ**, Leventhal TM, Rakela JL, Zhang J, Durkalski V, Reddy KR, Fontana RJ, Stravitz RT, Lake JR, Lee WM, Parekh JR. Outcomes of patients with acute liver failure listed for liver transplantation: A multicenter prospective cohort analysis. *Liver Transpl* 2023; **29**: 318-330 [PMID: 35980605 DOI: 10.1002/lt.26563]
28 **Lee WM**, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology* 2012; **55**: 965-967 [PMID: 22213561 DOI: 10.1002/hep.25551]
29 **Keays RT**, Alexander GJ, Williams R. The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. *J Hepatol* 1993; **18**: 205-209 [PMID: 8409336 DOI: 10.1016/s0168-8278(05)80247-8]
30 **Stravitz RT**, Kramer AH, Davern T, Shaikh AO, Caldwell SH, Mehta RL, Blei AT, Fontana RJ, McGuire BM, Rossaro L, Smith AD, Lee WM; Acute Liver Failure Study Group. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med* 2007; **35**: 2498-2508 [PMID: 17901832 DOI: 10.1097/01.CCM.0000287592.94554.5F]
31 **Vaquero J**, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, Han S, Harrison ME, Stravitz TR, Muñoz S, Brown R, Lee WM, Blei AT. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl* 2005; **11**: 1581-1589 [PMID: 16315300 DOI: 10.1002/Lt.20625]
32 **European Association for the Study of the Liver**; Clinical practice guidelines panel, Wendon, J; Panel members, Cordoba J, Dhawan A, Larsen FS, Manns M, Samuel D, Simpson KJ, Yaron I; EASL Governing Board representative, Bernardi M. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol* 2017; **66**: 1047-1081 [PMID: 28417882 DOI: 10.1016/j.jhep.2016.12.003]
33 **Karvellas CJ**, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM; U S Acute Liver Failure Study Group. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. *Crit Care Med* 2014; **42**: 1157-1167 [PMID: 24351370 DOI: 10.1097/CCM.0000000000000144]
34 **Jalan R**. Intracranial hypertension in acute liver failure: pathophysiological basis of rational management. *Semin Liver Dis* 2003; **23**: 271-282 [PMID: 14523680 DOI: 10.1055/s-2003-42645]
35 **Raschke RA**, Curry SC, Rempe S, Gerkin R, Little E, Manch R, Wong M, Ramos A, Leibowitz AI. Results of a protocol for the management of patients with fulminant liver failure. *Crit Care Med* 2008; **36**: 2244-2248 [PMID: 18664779 DOI: 10.1097/CCM.0b013e31818029a3]
36 **Blei AT**, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993; **341**: 157-158 [PMID: 8093756 DOI: 10.1016/0140-6736(93)90016-a]
37 **Jinadasa SP**, Ruan QZ, Bayoumi AB, Sharma SV, Boone MD, Malik R, Chen CC, Kasper EM. Hemorrhagic Complications of Invasive Intracranial Pressure Monitor Placement in Acute Liver Failure: Outcomes of a Single-Center Protocol and Comprehensive Literature Review. *Neurocrit Care* 2021; **35**: 87-102 [PMID: 33205356 DOI: 10.1007/s12028-020-01143-7]
38 **Nag DS**, Sahu S, Swain A, Kant S. Intracranial pressure monitoring: Gold standard and recent innovations. *World J Clin Cases* 2019; **7**: 1535-1553 [PMID: 31367614 DOI: 10.12998/wjcc.v7.i13.1535]
39 **Maloney PR**, Mallory GW, Atkinson JL, Wijdicks EF, Rabinstein AA, Van Gompel JJ. Intracranial Pressure Monitoring in Acute Liver Failure: Institutional Case Series. *Neurocrit Care* 2016; **25**: 86-93 [PMID: 26966022 DOI: 10.1007/s12028-016-0261-y]
40 **Thomas E**; NACCS, Czosnyka M, Hutchinson P; SBNS. Calculation of cerebral perfusion pressure in the management of traumatic brain injury: joint position statement by the councils of the Neuroanaesthesia and Critical Care Society of Great Britain and Ireland (NACCS) and the Society of British Neurological Surgeons (SBNS). *Br J Anaesth* 2015; **115**: 487-488 [PMID: 26187435 DOI: 10.1093/bja/aev233]
41 **Gasco J**, Rangel-Castilla L, Franklin B, Thomas PG, Patterson JT. State-of-the-art management and monitoring of brain edema and intracranial hypertension in fulminant hepatic failure. A proposed algorithm. *Acta Neurochir Suppl* 2010; **106**: 311-314 [PMID: 19812970 DOI: 10.1007/978-3-211-98811-4_58]

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MINIREVIEWS

Women's health issues in solid organ transplantation: Breast and gynecologic cancers in the post-transplant population

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Abstract

The success of solid organ transplant has steadily improved which has led to a unique set of post-transplant issues. The rates of *de novo* cancer in the solid organ transplant recipient population are higher than those in the general population. There is growing evidence that breast and gynecologic cancers may have a higher mortality rate in post-transplant patients. Cervical and vulvovaginal cancers specifically have a significantly higher mortality in this population. Despite this increased mortality risk, there is currently no consistent standard in screening and identifying these cancers in post-transplant patients. Breast, ovarian and endometrial cancers do not appear to have significantly increased incidence. However, the data on these cancers remains limited. Further studies are needed to determine if more aggressive screening strategies would be of benefit for these cancers. Here we review the cancer incidence, mortality risk and current screening methods associated with breast and gynecologic cancers in the post-solid organ transplant population.

Key Words: Cancer screening; Solid organ transplant; Female-specific cancer

Core Tip: Survival after solid organ transplant is continually improving. Because of this, patients are living longer and are requiring long-term monitoring for malignancies. There is growing evidence that breast and gynecologic cancers (specifically cervical and vulvovaginal cancers) may have a higher mortality rate in post-transplant patients. Despite this increased mortality risk, there is currently no consistent standard among transplant societies for screening and identifying these cancers in post-transplant patients. Ultimately, data are not robust and further studies are needed to determine if more aggressive screening strategies would be of benefit for these cancers.

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INTRODUCTION

Overall, survival following solid organ transplant (SOT) has improved considerably since the first successful kidney transplant was performed in 1954. The female post-transplant population is growing as well; with women constituting 38% of liver transplant recipients in 2021 *vs* 35% in 2011[1]. Improvement in post-transplant survival, along with the growing female transplant recipient population presents unique concerns with regards to post-transplant sex-specific cancer screening. There are currently no American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Kidney Disease: Improving Global Outcomes (KDIGO) or International Society for Heart and Lung Transplantation (ISHLT) guidelines regarding post-transplant specific screening methods for gynecologic or breast cancers following liver, kidney, heart, or lung transplantation[2-6]. Here we will review the incidence and current screening standards for breast and gynecologic (particularly cervical, ovarian, uterine, and vulvovaginal) cancers following SOT. The data included in this paper is extracted from studies including solid organ transplant recipients (SOTRs). It is challenged to define the rates and true causality of *de novo* cancers in the post-SOT population. There is a growing body of evidence suggesting that cancer diagnosis and cancer-related mortality are increased in post-transplant patients as compared to the general population. Here, we will review the incidence and mortality data available for breast and gynecologic cancers as well as the current screening recommendations for the general population in comparison to the post-transplant population. Although these cancers affect a small proportion of all SOTRs, they bear significance as their mortality rates appear to be considerably higher than in the general population.

CANCER RISK FOLLOWING TRANSPLANTATION

Analysis from SOTRs registries suggests there is a higher incidence of cancers in the post-transplant population as compared to the general population[7]. Most studies analyze the incidence of cancer post-transplant utilizing the standardized incidence ratio (SIR), which depicts the relationship between the observed and expected cancer cases among post-transplant patients compared to the general population. A Swedish study conducted in 2003 demonstrated SIR of 4.0 for developing a first cancer post renal, hepatic or other organs from 1970 to 1997[8]. Watt *et al*[9] found that malignancy was responsible for 22% of deaths greater than one year after liver transplant in a population of 798 patients [9]. Although the cancer risk post-transplant remains high, incidence of *de novo* malignancy following transplantation is improving over time. In a Nordic cohort of greater than 4000 post-liver transplant patients followed over three decades, there was a noted era-dependent decrease in SIR[10]. The SIR for all cancers in this population decreased each decade from the 1980s to the early 2000s, however cancer incidence remained elevated compared to the general population. These findings were attributed to changes in immunosuppression regimens as well as changes in cancer screening protocols and patient follow up. The majority of *de novo* cancers following transplantation are cutaneous and lymphoid, and have been previously linked to the degree of immunosuppression[11-13]. However, there is also a large category of viral infection-related cancers, including cervical, vulvar and vaginal cancers which affect women in particular. 12805 kidney transplant recipients registered in the Netherlands Organ Transplant Registry were followed for a total of 89651 person-years with an incidence of cancer of 7.1 percent as well as a survival reduction of nearly 5 years despite 69 percent dying with a functioning renal graft. The authors also highlighted that 62% of patients diagnosed with *de novo* breast cancer and 64% of patients diagnosed with gynecologic cancers died from their respective cancer; both mortality rates are considerably higher than the general population[14]. This increase in cancer-related mortality is striking and begs the question of its true relationship to SOT or immunosuppression. But the mortality rates

urge those managing post-transplant patients to explore perhaps more aggressive cancer screening strategies.

Cervical cancer

Cervical cancer is primarily caused by the oncogenic human papillomavirus (HPV) infection[15,16]. Although the incidence and mortality of cervical cancer has decreased since the adoption of routine screening with Papanicolaou (Pap) smear, cervical cancer continues to have a considerable impact on the United States population[17]. Cervical cancer had an incidence rate of 7.5 in the general population in 2019[18]. There is varying data on the incidence of cervical cancer in post-transplant populations. However, several studies showed an increased risk of cervical cancer, particularly in the younger post-transplant population[8,19-21]. In a study published by Madeleine *et al*[19] in 2013, there was a SIR of 3.3 for *in situ* cervical carcinoma in SOTRs, and a SIR of 1.0 for invasive cervical cancer[19]. After adjustment for age, this study found that younger recipients (18–34 years old) had a higher incidence of *in situ* cervical cancer. Using incidence rate ratio (IRR), which compares between subgroups of the transplant population (in this case, age), an IRR of 4.7 for *in situ* cervical cancer and an IRR of 2.4 for invasive cervical cancer in the younger transplant recipients was noted compared to older transplant recipients. Another study found a statistically non-significant mild increase in cervical cancer post-SOT with SIR of 2.6 [95% confidence interval (CI): 0.1-15][20]. Adami *et al*[8] found cervical carcinoma *in situ* SIR of 1.3 (95%CI: 1.0-1.8) among patients transplanted with kidney, liver or other organs[8]. A separate study published from data utilizing Swedish and Danish SOTR registries discovered a significantly increased incidence of cervical cancer compared to the general population with SIR 2.6 (95%CI: 1.6–4.5) [21]. Although the rate of cervical cancers varied between these studies, they illustrate a concern for increased risk for cervical cancers in the SOTR. These studies again highlight the concern for a significant change in incidence of cancer post transplantation. These studies also do not clearly delineate the rates of cervical cancer screening in post-transplant patients. But given the incidence, continued diligence seems necessary. Particularly when considering the increased mortality risk related to gynecologic cancers.

Breast cancer

Breast cancer is the most commonly diagnosed cancer among women in the United States and was the second leading cause of cancer-related deaths in 2021[18,22]. The etiology is thought to be multifactorial due to the presence of proliferative breast disease, reproductive factors and genetics and is impacted by several factors such as demographics and environmental exposures[22]. Given the incidence of breast cancer in the general population, most transplant centers require breast cancer screening prior to transplant listing. Several studies have shown a decreased risk of breast cancer which is likely a consequence of pre-transplant screening methods[23-25]. In one study of 1000 post-liver transplant patients, 57 of whom developed cancer after transplantation, the SIR for breast cancer was 0.74 (95%CI: 0.15-2.16, $P > 0.05$)[23]. Another study by Oruc *et al*[24] found the incidence rates of *de novo* breast cancer following liver transplant at the University of Pittsburgh were similar to incidence of breast cancer in the general population with incidence rate of 523.6 per 100000 women in the post-transplant population. Though it is worth noting the incidence rate of breast cancer in the general population at the time was a bit lower than that observed in post-transplant patients, this was not found to be statistically significant [24]. Engels *et al*[25] found a significantly decreased SIR in breast cancer. Among 1700 SOTRs, there was a SIR of 0.85 (95%CI: 0.77-0.93). The authors attribute this significant decrease in risk to pre-transplant cancer screening[25].

Ovarian and endometrial cancer

Ovarian cancer is the second most common gynecologic cancer and the most common cause of gynecologic cancer-related death in the United States[26]. The most common histopathologic type is epithelial ovarian cancer. There are many risk factors for epithelial ovarian cancer; increased age, polycystic ovarian syndrome, endometriosis, infertility, and genetic predisposition (particularly presence of BRCA 1 or 2 mutation and Lynch Syndrome)[26]. Most studies in SOTRs found the SIR for ovarian cancer did not have a statistically significant increase compared to the general population, with a range of 1.2-2[8,9,21,27]. One study did find an increased incidence of *de novo* ovarian cancer arising in patients with a prior breast cancer diagnosis with an incidence of one in 6.5 women *vs* one in 385 for the rest of the study population[28]. Most studies show a statistically non-significant increase in SIR for ovarian cancer One study did show a very mildly decreased SIR of 0.95 for ovarian cancer following SOT, however this was not statistically significant (95%CI: 0.7-1.24)[25]. There is little evidence for ovarian cancer-related mortality within the SOTR population. However, one Korean study found the standardized mortality rate (a comparison in mortality due to the cancer between the transplant population and the general population) for ovarian cancer was 4.0 (95%CI: 2.1-6.5) in female kidney transplant recipients[29]. This study had a higher incidence of ovarian, gynecologic and breast cancer as compared to SOTR studies within North America. The reason for this difference is not clearly elucidated in this paper. The authors postulate the difference may be due to a focus on a later transplant epoch in the Korean population, higher proportion of female transplant recipients (43% *vs* 36%), genetic predis-

position, possible unique environmental exposure of the Korean population, different immunosuppression regimens or different screening and surveillance protocols[11,29].

Endometrial cancer develops in about 3 percent of females in the United States[30]. The more common type 1 endometrial cancer tends to present at an earlier stage and has a better prognosis than type 2 for the general population. Risk factors for type 1 endometrial cancer include excess estrogen unopposed by progestin, genetic predisposition (Lynch Syndrome), obesity, nulliparity, hypertension and diabetes[30]. In most post-SOT studies published, there does not seem to be a statistically significant increase in risk for development of endometrial cancer. Multiple studies have demonstrated SIR ranging from 0.86 to 1.4 without statistical significance[20,21,25]. However one study utilizing data from the Australian and New Zealand SOT registry did find a significant increase in uterine cancer with SIR 1.85 (95%CI: 1.16-2.93)[27,31]. The difference in incidence in this study appears to be anomalous compared to other post-SOT studies.

Vulvar and vaginal cancer

Vulvovaginal cancers are less common in the United States compared to the rest of the world. The incidence of vulvar cancer was 2.5 in 100000 women in 2019; the true incidence of vaginal cancer is unknown, however the estimated incidence of vaginal carcinoma *in situ* is 0.1 in 100000[18,32,33]. Most cases of vaginal cancer in the United States are linked to HPV infection, similar to cervical cancer. Risk factors include multiple lifetime sexual partners, current cigarette smoking, early age at first intercourse [32,33]. Vulvar cancer is less common than the other gynecologic malignancies in the United States, and tends to be diagnosed at earlier stages. Similar to cervical and vaginal cancer, it is also linked to HPV infection. Other risk factors include prior history of cervical cancer or intraepithelial neoplasia, current cigarette smoking, vulvar lichen sclerosis, immunodeficiency syndromes and northern European descent[32]. Most studies found a dramatic increase in rates of vulvar, vaginal or combination of the two malignancies in post-transplant patients which is postulated to be due to viral infection with HPV[34, 35]. In a retrospective study of female renal transplant patients over the age of 40 years, Meeuwis *et al* [36] found 92% of cervical and vulvovaginal cancers were associated with HPV, specifically HPV 16 in 53.8% of cases[36]. In most studies, there was a statistically significant increase in vulvar and vaginal cancers, with SIR ranging from two to forty-five-fold increase compared to the general population[8,19, 20,25,27]. One study found a higher incidence of *in situ* vulvar cancer in younger SOT patients (age 18-34 years) with an increase in IRR to 4.1 (95%CI: 3.0-5.6) for vulvar cancer compared to women transplanted over the age of 35. This study found that younger age at transplant, older immunosuppressive regimens containing azathioprine and cyclosporine, and increased time since transplant were associated with a higher incidence of *in situ* vulvar cancer. Additionally, they found higher incidence of *in situ* rather than invasive genital cancers; potentially due to diagnosis of cancer at earlier stages with screening, or owing to the nature of vulvovaginal cancers being symptomatic, even at early stages[19, 30]. There is sparse data regarding mortality specifically due to vulvar or vaginal cancer across SOTR studies. This may be due to diagnosis at earlier stages and consequently higher rates of remission after treatment.

CURRENT SCREENING STANDARDS

More aggressive cancer screening methods are known to improve detection of cancer and in to thus improve cancer-related mortality rates. Finkenstedt *et al*[37] introduced an intensified surveillance protocol in their post-liver transplant patients and were able to improve the detection of *de novo* cancers from 4.9% to 13%. They also observed more *de novo* malignancies diagnosed in earlier stages[37]. Despite studies such as this, there is no SOTR-specific guideline or guidance for breast or gynecologic cancers aside from cervical cancer surveillance. The ISHLT recommends employing the same general malignancy screening and surveillance methods used for the general population in pre- and post-heart and lung transplant patients with respect to breast and gynecologic cancers[5,38]. The American Society of Transplantation (AST) recommends annual pelvic exam with Pap smear for post-kidney transplant patients[39]. The KDIGO recommends age-appropriate cancer screening in pre- and post-transplant patients in their latest guidance statement, however no specific screening for ovarian, endometrial or vulvovaginal cancers[6,40]. Thusly, the screening strategies included below are those suggested for the general population and, if available, those recommended for the SOTR population (Table 1).

Breast cancer screening: Breast cancer screening, like many other cancer screenings relies heavily upon risk designation of the individual being screened. Screening modality, time at which to start screening and risk-reducing measures differ from the average risk population for women who are considered moderate or high risk. Currently, immunosuppression and transplant status are not considered to increase risk and thus average risk breast cancer screening strategies should be applied to these groups. Screening is recommended by most United States government-sponsored groups and medical societies for average risk women beginning at age 50 with mammography every 1-2 years, with interval frequency based on imaging findings. For women age 40-49 years, it is recommended a conversation

Table 1 Breast and gynecologic cancer screening recommendations and incidence rates as compared to the general population

Cancer type	Current standard guidelines	SOTR specific recommendations	Rates of malignancy in SOTR: Increased (+), Same (=), or Less (-) than general population
Breast cancer	Mammography every 1-2 yr in women > 50 years old (for average risk). Discussion for screening beginning at age 40 yr	Mammography prior to transplantation if > 50 yr; otherwise, same screening interval as the general population	-
Cervical cancer	Women 21 to 29 years old should have a Pap test alone every 3 yr. HPV testing alone can be considered for women who are 25 to 29 years old, but Pap tests are preferred	Pap if younger than 30 years old at transplant, co-testing with Pap and HPV is preferred beginning at age 30 yr but annual Pap is considered adequate	+
	Women who are 30 to 65 years old have three options for testing: Pap and HPV (co-testing) every 5 yr. Pap alone every 3 yr. Or they can have HPV testing alone every 5 yr	If performing co-testing with HPV and Pap: If results of baseline Pap and HPV testing are normal, co-testing can be performed every 3 yr. If the patient is transplanted prior to age 21, it is recommended screening begin within 1 yr of initial engagement of sexual activity	
Vulvar and vaginal cancer	No current screening strategy for the general population, however recommended annual pelvic exam in patients with HIV	AST recommends annual pelvic exam for kidney transplant patients; otherwise, no consistent guidance across societies	+
Endometrial cancer	No current screening strategy	No current screening strategy	=/-
Ovarian cancer	No current screening strategy	No current screening strategy	=/-

SOTR: Solid organ transplant recipient; Pap: Papanicolaou smear; HIV: Human immunodeficiency virus; AST: American Society of Transplantation.

regarding screening is initiated, but screening itself has not shown mortality benefit in this population [41,42].

Cervical cancer screening and prevention: There is considerable data for women post-transplant supporting a more aggressive screening approach than for the general population[13,19]. There is a consensus statement published in 2019 by the American Society for Colposcopy and Cervical Pathology recommending the following: Cervical cytology if the patient is younger than 30 years at transplant, co-testing with cytology and HPV is preferred beginning at age 30 years but cytology is considered adequate. If only performing cytology, annual cytology is recommended; if 3 consecutive cytology results are normal, the interval frequency may be increased to cytology every 3 years. If performing co-testing with HPV and cytology: If results of baseline cytology and HPV testing are normal, co-testing can be performed every 3 years. If the patient is transplanted prior to age 21, it is recommended screening begin within 1 year of initial engagement of sexual activity. Continuation of screening throughout the patient's lifetime is recommended. A discussion regarding quality and duration of life should be pursued prior to discontinuation of screening[43]. There is currently guidance regarding HPV vaccination in pre-transplant populations. Currently, it is recommended by the AASLD to administer the quadrivalent HPV vaccine prior to listing for transplant in women up to the age of 45 years[44]. There is evidence that the HPV vaccine is safe in the immunocompromised population, including SOTRs[45]. However, it is worth noting the immunogenicity of the vaccine is lower in certain circumstances: Lung transplant recipients (57.1% response rate 7 mo after vaccination), high doses of tacrolimus, and vaccination in the early post-transplant period[46]. Further studies are required to assess the benefit of repeating the vaccine series to improve response rates and the effect of this on decreasing vulvovaginal and cervical cancers in the SOTR population.

Vulvovaginal cancer screening: There are currently no screening strategies for vulvovaginal cancer other than pelvic exam. The AST recommends annual pelvic exam in post-kidney transplant patients, however most other SOT societies lack guidance in this area[39]. Diagnosis of vulvovaginal cancers rely upon visual assessment with histopathologic confirmation. The American College of Obstetricians and Gynecologists (ACOG) primarily focuses on methods of prevention including administration of the quadrivalent or nonavalent HPV vaccine[47]. There is growing evidence of increased risk for vulvovaginal cancers among HIV patients due to immunosuppression and concomitant HPV infection. Because of this, annual pelvic exam with close attention paid to visual inspection is recommended in this population[48]. Although the means of immunocompromise/immunosuppression differ between the HIV-infected population and the post-transplant population, the dramatic increased incidence of

vulvovaginal cancers in the HIV-infected population could serve as evidence for more aggressive screening methods in other immunocompromised (or immunosuppressed, in this case) populations. Although there are not specific recommendations regarding screening for vulvovaginal cancers, they are by default screened for by means of pelvic exam during cervical cancer screening-which does have recommendations by transplant societies and the ACOG[2,4-6,13,43]. In one recent review of gynecologic malignancies post-liver transplant, annual pelvic exam is recommended[49]. It is possible that as vulvovaginal cancers are diagnosed in early stages, the mortality rate is relatively low. However, treatment can potentially include chemotherapy, radiation and excision (depending on the stage); all of which have considerable risk and cost to the patient[50].

Ovarian cancer screening: There is currently no recommended screening strategy for ovarian cancer in women of low or average risk within the general population. Furthermore, there is no screening test leading to the early detection of ovarian cancer that reduces ovarian cancer mortality, regardless of risk [51]. One study found an incidence of 1 in 6.5 cases of ovarian cancer in pts with a prior history of breast cancer suggesting closer follow up/screening for this population[28]. Obtaining a detailed family history to identify high risk patients is essential. Patients with family history of breast or ovarian cancer, patients of Ashkenazi Jewish descent, and patients with known hereditary syndromes such a BRCA 1 or 2 mutation or Lynch Syndrome (among others) are identified as high-risk for developing ovarian cancer and should be considered for referral to genetic counseling. Patients with the presence of high-risk genes may benefit from risk-reducing techniques such as bilateral salpingo-oopherectomy[52].

Endometrial cancer screening: Current screening strategies for endometrial cancer rely upon presence of clinical signs/symptoms (such as uterine bleeding) in both average and high-risk patients. It is recommended patients with a genetic predisposition such as Lynch Syndrome or Cowden Syndrome potentially undergo endometrial tissue sampling every 1-2 years starting at age 30-35 years and risk-reducing hysterectomy[53,54].

CONCLUSION

While overall survival and incidence of cancer post-SOT are improving, cancer-related mortality across all cancers remains considerably higher in the post-transplant populations that have been studied as compared to the general population. Despite limited series, cervical and vulvovaginal cancers appear to be the highest risk of incidence of the gynecologic cancers following SOT. Breast cancer does not appear to have a higher incidence following transplantation, and screening methods used in the general population should be sufficient. Ovarian and endometrial cancer rates vary among post-SOT populations[8,9,21,27]. For the most part, they are not significantly increased with exception of patients with a genetic predisposition[28]. Careful history-taking with particular attention to familial cancer syndromes is key in identifying this population.

The lack of uniform gynecologic cancer screening recommendations post-SOT may be due to the small amount of existing evidence. Many studies either combine ovarian, uterine, cervical and vulvovaginal cancers together into a "gynecologic cancer" group or fail to mention vulvovaginal cancers entirely. The incidence of these cancers appears to be small when compared to other cancers. Data regarding mortality from breast and gynecologic cancers is also lacking in these patients. The existing data does appear to indicate a substantially higher mortality rate for SOTRs with breast and gynecologic cancers.

Despite these limitations, there are certain modifiable risk factors to which all Physicians managing the post-transplant population should be aware. As the most common risk factor for vulvovaginal and cervical cancer is infection with HPV, efforts should be focused on prevention (with HPV vaccination in those less than 45) as well as screening in order to decrease the associated morbidity and mortality of these malignancies.

Further studies regarding breast and gynecologic cancer in SOTRs is required to assess the respective incidence and mortality in order to direct screening and surveillance of these cancers. The decreasing age at transplant, growing female transplant population and improved survival post-transplant necessitate improved guidance regarding screening and surveillance of breast and gynecologic cancers among SOTRs.

FOOTNOTES

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REFERENCES

1 **National data-OPTN**. Organ Procurement and Transplantation Network. [cited November 3, 2022]. Available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/
2 **Lucey M**, Terrault N, Ojo L. Long-term management of the adult liver transplant. AASLD.org. [cited November 1, 2022]. Available from: https://www.aasld.org/practice-guidelines/Long-term-management-adult-liver-transplant
3 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol* 2016; **64**: 433-485 [PMID: 26597456 DOI: 10.1016/j.jhep.2015.10.006]
4 **Adegunsoye A**, Strek ME, Garrity E, Guzy R, Bag R. Comprehensive Care of the Lung Transplant Patient. *Chest* 2017; **152**: 150-164 [PMID: 27729262 DOI: 10.1016/j.chest.2016.10.001]
5 **Velleca A**, Shullo MA, Dhital K, Azeka E, Colvin M, DePasquale E, Farrero M, García-Guereta L, Jamero G, Khush K, Lavee J, Pouch S, Patel J, Michaud CJ, Schubert S, Angelini A, Carlos L, Mirabet S, Pham M, Urschel S, Kim KH, Miyamoto S, Chih S, Daly K, Grossi P, Jennings DL, Kim IC, Lim HS, Miller T, Potena L, Velleca A, Eisen H, Bellumkonda L, Danziger-Isakov L, Dobbels F, Harkess M, Kim D, Lyster H, Peled Y, Reinhardt Z. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2023; **42**: e1-e141 [PMID: 37080658 DOI: 10.1016/j.healun.2022.10.015]
6 **Kasiske BL**, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, Green MD, Jha V, Josephson MA, Kiberd BA, Kreis HA, McDonald RA, Newmann JM, Obrador GT, Vincenti FG, Cheung M, Earley A, Raman G, Abariga S, Wagner M, Balk EM; Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int* 2010; **77**: 299-311 [PMID: 19847156 DOI: 10.1038/ki.2009.377]
7 **Brennan DC**, Rodeheffer RJ, Ambinder RF. Malignancy after solid organ transplantation. UpToDate.com. [cited October 11, 2022]. Available from: https://www.uptodate.com/contents/malignancy-after-solid-organ-transplantation#!
8 **Adami J**, Gäbel H, Lindelöf B, Ekström K, Rydh B, Glimelius B, Ekbom A, Adami HO, Granath F. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer* 2003; **89**: 1221-1227 [PMID: 14520450 DOI: 10.1038/sj.bjc.6601219]
9 **Watt KD**, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010; **10**: 1420-1427 [PMID: 20486907 DOI: 10.1111/j.1600-6143.2010.03126.x]
10 **Nordin A**, Åberg F, Pukkala E, Pedersen CR, Storm HH, Rasmussen A, Bennet W, Olausson M, Wilczek H, Ericzon BG, Tretli S, Line PD, Karlsen TH, Boberg KM, Isoniemi H. Decreasing incidence of cancer after liver transplantation-A Nordic population-based study over 3 decades. *Am J Transplant* 2018; **18**: 952-963 [PMID: 28925583 DOI: 10.1111/ajt.14507]
11 **Acuna SA**, Fernandes KA, Daly C, Hicks LK, Sutradhar R, Kim SJ, Baxter NN. Cancer Mortality Among Recipients of Solid-Organ Transplantation in Ontario, Canada. *JAMA Oncol* 2016; **2**: 463-469 [PMID: 26746479 DOI: 10.1001/jamaoncol.2015.5137]
12 **Ajithkumar TV**, Parkinson CA, Butler A, Hatcher HM. Management of solid tumours in organ-transplant recipients. *Lancet Oncol* 2007; **8**: 921-932 [PMID: 17913661 DOI: 10.1016/S1470-2045(07)70315-7]
13 **Busnach G**, Piselli P, Arbustini E, Baccarani U, Burra P, Carrieri MP, Citterio F, De Juli E, Bellelli S, Pradier C, Rezza G, Serraino D; Immunosuppression and Cancer Study Group. Immunosuppression and cancer: A comparison of risks in recipients of organ transplants and in HIV-positive individuals. *Transplant Proc* 2006; **38**: 3533-3535 [PMID: 17175324 DOI: 10.1016/j.transproceed.2006.10.144]
14 **van de Wetering J**, Roodnat JI, Hemke AC, Hoitsma AJ, Weimar W. Patient survival after the diagnosis of cancer in renal transplant recipients: a nested case-control study. *Transplantation* 2010; **90**: 1542-1546 [PMID: 21076383 DOI: 10.1097/TP.0b013e3181ff1458]
15 **Schiffman M**, Doorbar J, Wentzensen N, de Sanjosé S, Fakhry C, Monk BJ, Stanley MA, Franceschi S. Carcinogenic human papillomavirus infection. *Nat Rev Dis Primers* 2016; **2**: 16086 [PMID: 27905473 DOI: 10.1038/nrdp.2016.86]
16 **Guan P**, Howell-Jones R, Li N, Bruni L, de Sanjosé S, Franceschi S, Clifford GM. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *Int J Cancer* 2012; **131**: 2349-2359 [PMID: 22323075 DOI: 10.1002/ijc.27485]
17 **Yang DX**, Soulos PR, Davis B, Gross CP, Yu JB. Impact of Widespread Cervical Cancer Screening: Number of Cancers Prevented and Changes in Race-specific Incidence. *Am J Clin Oncol* 2018; **41**: 289-294 [PMID: 26808257 DOI: 10.1097/COC.0000000000000264]

18 **U. S. Cancer Statistics Working Group**. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. [cited November 2022]. Available from: https://www.cdc.gov/cancer/dataviz

19 **Madeleine MM**, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-related cancers after solid organ transplantation in the United States. *Am J Transplant* 2013; **13**: 3202-3209 [PMID: 24119294 DOI: 10.1111/ajt.12472]

20 **Krynitz B**, Edgren G, Lindelöf B, Baecklund E, Brattström C, Wilczek H, Smedby KE. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008--a Swedish population-based study. *Int J Cancer* 2013; **132**: 1429-1438 [PMID: 22886725 DOI: 10.1002/ijc.27765]

21 **Hortlund M**, Arroyo Mühr LS, Storm H, Engholm G, Dillner J, Bzhalava D. Cancer risks after solid organ transplantation and after long-term dialysis. *Int J Cancer* 2017; **140**: 1091-1101 [PMID: 27870055 DOI: 10.1002/ijc.30531]

22 **Chlebowski R**. Factors that modify breast cancer risk in women. UpToDate.com. [cited October 20, 2022]. Available from: https://www.uptodate.com/contents/factors-that-modify-breast-cancer-risk-in-women#!

23 **Jain AB**, Yee LD, Nalesnik MA, Youk A, Marsh G, Reyes J, Zak M, Rakela J, Irish W, Fung JJ. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. *Transplantation* 1998; **66**: 1193-1200 [PMID: 9825817 DOI: 10.1097/00007890-199811150-00014]

24 **Oruc MT**, Soran A, Jain AK, Wilson JW, Fung J. De novo breast cancer in patients with liver transplantation: University of Pittsburgh's experience and review of the literature. *Liver Transpl* 2004; **10**: 1-6 [PMID: 14755771 DOI: 10.1002/Lt.20025]

25 **Engels EA**, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, Wolfe RA, Goodrich NP, Bayakly AR, Clarke CA, Copeland G, Finch JL, Fleissner L, Goodman MT, Kahn A, Kock L, Lynch CF, Madeleine MM, Pawlish K, Rao C, Williams MA, Castenson D, Curry M, Parsons R, Fant G, Lin M. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* 2011; **306**: 1891-1901 [PMID: 22045767 DOI: 10.1001/jama.2011.1592]

26 **Rendi MH**. Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum. UpToDate. [cited November 23, 2022]. Available from: https://www.uptodate.com/contents/epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum-histopathology#!

27 **Buell JF**, Gross TG, Woodle ES. Malignancy after transplantation. *Transplantation* 2005; **80**: S254-S264 [PMID: 16251858 DOI: 10.1097/01.tp.0000186382.81130.ba]

28 **Molmenti EP**, Molmenti H, Weinstein J, Elliott EE, Fasola CG, Orr D, Blum J, Savino D, Hamilton WM, Goldstein RM, Levy MF, Klintmalm GB. Syndromic incidence of ovarian carcinoma after liver transplantation, with special reference to anteceding breast cancer. *Dig Dis Sci* 2003; **48**: 187-189 [PMID: 12645808 DOI: 10.1023/a:1021715305407]

29 **Jeong S**, Lee HS, Kong SG, Kim DJ, Lee S, Park MJ, Song W, Rim JH, Kim HJ. Incidence of malignancy and related mortality after kidney transplantation: a nationwide, population-based cohort study in Korea. *Sci Rep* 2020; **10**: 21398 [PMID: 33293655 DOI: 10.1038/s41598-020-78283-5]

30 **Plaxe SC**, Mundt AJ. Overview of endometrial carcinoma. UpToDate. [cited November 20, 2022]. Available from: https://www.uptodate.com/contents/overview-of-endometrial-carcinoma?search=endometrial+cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

31 **Chapman J**, Webster AC. Cancer report: ANZDATA registry 2004 report. Adelaide, Australia: Australia and New Zealand Dialysis and Transplant Registry

32 **Berek JS**, Karam A. Vulvar cancer: Epidemiology, diagnosis, histopathology, and treatment. UpToDate.com. [cited December 1, 2022]. Available from: https://www.uptodate.com/contents/vulvar-cancer-epidemiology-diagnosis-histopathology-and-treatment#!

33 **Karam A**, Berek JS. Vaginal cancer. UpToDate.com. [cited December 1, 2022]. Available from: https://www.uptodate.com/contents/vaginal-cancer

34 **Sinno AK**, Saraiya M, Thompson TD, Hernandez BY, Goodman MT, Steinau M, Lynch CF, Cozen W, Saber MS, Peters ES, Wilkinson EJ, Copeland G, Hopenhayn C, Watson M, Lyu C, Unger ER. Human papillomavirus genotype prevalence in invasive vaginal cancer from a registry-based population. *Obstet Gynecol* 2014; **123**: 817-821 [PMID: 24785610 DOI: 10.1097/AOG.0000000000000171]

35 **Rakislova N**, Saco A, Sierra A, Del Pino M, Ordi J. Role of Human Papillomavirus in Vulvar Cancer. *Adv Anat Pathol* 2017; **24**: 201-214 [PMID: 28590952 DOI: 10.1097/PAP.0000000000000155]

36 **Meeuwis KA**, Melchers WJ, Bouten H, van de Kerkhof PC, Hinten F, Quint WG, Massuger LF, Hoitsma AJ, van Rossum MM, de Hullu JA. Anogenital malignancies in women after renal transplantation over 40 years in a single center. *Transplantation* 2012; **93**: 914-922 [PMID: 22377788 DOI: 10.1097/TP.0b013e318249b13d]

37 **Finkenstedt A**, Graziadei IW, Oberaigner W, Hilbe W, Nachbaur K, Mark W, Margreiter R, Vogel W. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. *Am J Transplant* 2009; **9**: 2355-2361 [PMID: 19663894 DOI: 10.1111/j.1600-6143.2009.02766.x]

38 **Leard LE**, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, Campos SV, Christon LM, Cypel M, Dellgren G, Hartwig MG, Kapnadak SG, Kolaitis NA, Kotloff RM, Patterson CM, Shlobin OA, Smith PJ, Solé A, Solomon M, Weill D, Wijsenbeek MS, Willemse BWM, Arcasoy SM, Ramos KJ. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2021; **40**: 1349-1379 [PMID: 34419372 DOI: 10.1016/j.healun.2021.07.005]

39 **American Society of Transplantation**. Guidelines for post-kidney transplant management in the community setting. 2017. [cited December 22, 2022]. Available from: https://www.myast.org/guidelines-post-kidney-transplant-management-community-setting

40 **Chadban SJ**, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, Kumar D, Oberbauer R, Pascual J, Pilmore HL, Rodrigue JR, Segev DL, Sheerin NS, Tinckam KJ, Wong G, Balk EM, Gordon CE, Earley A, Rofeberg V, Knoll GA. Summary of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. *Transplantation* 2020; **104**: 708-714 [PMID: 32224812 DOI: 10.1097/TP.0000000000003137]

41 Practice Bulletin Number 179: Breast Cancer Risk Assessment and Screening in Average-Risk Women. *Obstet Gynecol* 2017; **130**: e1-e16 [PMID: 28644335 DOI: 10.1097/AOG.0000000000002158]

42 **Elmore JG**, Lee CI. Screening for breast cancer: Strategies and recommendations. UpToDate. [cited December 5, 2022]. Available from: https://www.uptodate.com/contents/screening-for-breast-cancer-strategies-and-recommendations#!

43 **Moscicki AB**, Flowers L, Huchko MJ, Long ME, MacLaughlin KL, Murphy J, Spiryda LB, Gold MA. Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection. *J Low Genit Tract Dis* 2019; **23**: 87-101 [PMID: 30907775 DOI: 10.1097/LGT.0000000000000468]

44 **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]

45 **Garland SM**, Brotherton JML, Moscicki AB, Kaufmann AM, Stanley M, Bhatla N, Sankaranarayanan R, de Sanjosé S, Palefsky JM; IPVS. HPV vaccination of immunocompromised hosts. *Papillomavirus Res* 2017; **4**: 35-38 [PMID: 29179867 DOI: 10.1016/j.pvr.2017.06.002]

46 **Kumar D**, Unger ER, Panicker G, Medvedev P, Wilson L, Humar A. Immunogenicity of quadrivalent human papillomavirus vaccine in organ transplant recipients. *Am J Transplant* 2013; **13**: 2411-2417 [PMID: 23837399 DOI: 10.1111/ajt.12329]

47 Committee Opinion No.675: Management of Vulvar Intraepithelial Neoplasia. *Obstet Gynecol* 2016; **128**: e178-e182 [PMID: 27661656 DOI: 10.1097/AOG.0000000000001713]

48 **Robinson W**. Vulvar and vaginal intraepithelial neoplasia in patients with HIV infection. UpToDate.com. [cited December 4, 2022]. Available from: https://www.uptodate.com/contents/vulvar-and-vaginal-intraepithelial-neoplasia-in-patients-with-hiv-infection#!

49 **Liao JB**, Fisher CE, Madeleine MM. Gynecologic cancers and solid organ transplantation. *Am J Transplant* 2019; **19**: 1266-1277 [PMID: 30725527 DOI: 10.1111/ajt.15292]

50 **Karam A**, Berek JS, Russo AL. Squamous cell carcinoma of the vulva: Staging and surgical treatment. UpToDate. [cited December 23, 2022]. Available from: https://www.uptodate.com/contents/squamous-cell-carcinoma-of-the-vulva-staging-and-surgical-treatment?topicRef=3237&source=see_link

51 Committee Opinion No. 716: The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk. *Obstet Gynecol* 2017; **130**: e146-e149 [PMID: 28832487 DOI: 10.1097/AOG.0000000000002299]

52 **Peshkin BN**, Isaacs C. Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes. UpToDate.com. [cited December 6, 2022]. Available from: https://www.uptodate.com/contents/genetic-testing-and-management-of-individuals-at-risk-of-hereditary-breast-and-ovarian-cancer-syndromes

53 **Chen LM**, Berek JS. Endometrial carcinoma: Clinical features, diagnosis, prognosis, and screening. UpToDate.com. [cited December 6, 2022]. Available from: https://www.uptodate.com/contents/endometrial-carcinoma-clinical-features-diagnosis-prognosis-and-screening#!

54 ACOG Practice Bulletin No. 147: Lynch syndrome. *Obstet Gynecol* 2014; **124**: 1042-1054 [PMID: 25437740 DOI: 10.1097/01.AOG.0000456325.50739.72]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Pre-Lung transplant reflux testing demonstrates high prevalence of gastroesophageal reflux in cystic fibrosis and reduces chronic rejection risk

Wai-Kit Lo, Ryan Flanagan, Nirmal Sharma, Hilary J Goldberg, Walter W Chan

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Peer-review model: Single blind

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Abstract

BACKGROUND

Gastroesophageal reflux (GER) has been associated with poor outcomes after lung transplantation for chronic lung disease, including increased risk of chronic rejection. GER is common in cystic fibrosis (CF), but factors influencing the likelihood of pre-transplant pH testing, and the impact of testing on clinical management and transplant outcomes in patients with CF are unknown.

AIM

To evaluate the role of pre-transplant reflux testing in the evaluation of lung transplant candidates with CF.

METHODS

This was a retrospective study from 2007-2019 at a tertiary medical center that included all patients with CF undergoing lung transplant. Patients with pre-transplant anti-reflux surgery were excluded. Baseline characteristics (age at transplantation, gender, race, body mass index), self-reported GER symptoms prior to transplantation, and pre-transplant cardiopulmonary testing results, were recorded. Reflux testing consisted of either 24-h pH- or combined multichannel intraluminal impedance and pH monitoring. Post-transplant care included a standard immunosuppressive regimen, and regular surveillance bronchoscopy and pulmonary spirometry in accordance with institutional practice as well as in symptomatic patients. The primary outcome of chronic lung allograft dysfunction (CLAD) was defined clinically and histologically per International Society of

Heart and Lung Transplantation criteria. Statistical analysis was performed with Fisher's exact test to assess differences between cohorts, and time-to-event Cox proportional hazards modeling.

RESULTS

After applying inclusion and exclusion criteria, a total of 60 patients were included in the study. Among all CF patients, 41 (68.3%) completed reflux monitoring as part of pre-lung transplant evaluation. Objective evidence of pathologic reflux, defined as acid exposure time > 4%, was found in 24 subjects, representing 58% of the tested group. CF patients with pre-transplant reflux testing were older (35.8 *vs* 30.1 years, $P = 0.01$) and more commonly reported typical esophageal reflux symptoms (53.7% *vs* 26.3%, $P = 0.06$) compared to those without reflux testing. Other patient demographics and baseline cardiopulmonary function did not significantly differ between CF subjects with and without pre-transplant reflux testing. Patients with CF were less likely to undergo pre-transplant reflux testing compared to other pulmonary diagnoses (68% *vs* 85%, $P = 0.003$). There was a decreased risk of CLAD in patients with CF who underwent reflux testing compared to those who did not, after controlling for confounders (Cox Hazard Ratio 0.26; 95%CI: 0.08-0.92).

CONCLUSION

Pre-transplant reflux testing revealed high prevalence of pathologic reflux in CF patients and was associated with decreased risk of CLAD. Systematic reflux testing may enhance outcomes in this patient population.

Key Words: Cystic fibrosis; Gastroesophageal reflux; Lung transplantation; pH monitoring

Core Tip: This study found that objective evidence of gastroesophageal reflux disease was present in > 50% of lung transplant candidates with cystic fibrosis (CF). However, CF patients were less likely than those with other pulmonary diagnoses to undergo pre-transplantation reflux testing. CF patients who underwent objective reflux testing were less likely to develop chronic lung allograft dysfunction, as those tested positive were more likely to undergo anti-reflux surgery. Our findings provided evidence for the association of routine peri-transplant reflux testing with improved lung transplant outcomes in CF patients, and the importance of timely identification of reflux to allow early intervention.

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INTRODUCTION

Gastroesophageal reflux (GER) has been associated with poor outcomes after lung transplantation including early rehospitalization[1], early allograft injury[2], and chronic allograft rejection[3]. The proposed mechanism for this involves the increased risk of post-transplant aspiration, which may lead to an inflammatory cascade resulting in recurrent allograft injury and ultimately rejection. GER has been recognized as a common condition associated with cystic fibrosis (CF), with a reported prevalence of 67%-90% in adult CF patients[4-8]. Since CF is a common indication for lung transplantation, the detection and treatment of GER in this population may potentially reduce multiple preventable post-lung transplant complications[9].

Unfortunately, despite the high prevalence of GER in CF patients and the association between GER and worse lung transplant outcomes, the testing and management of GER in these patients remain inconsistent across lung transplant centers. For instance, some centers have selectively pursued objective GER testing and treatment in patients with restrictive lung disorders such as idiopathic pulmonary fibrosis (IPF) rather than all chronic lung diseases, likely due to a correlation between GER and IPF in several early studies[10-13]. However, the factors that influence whether patients with CF undergo testing for GER prior to lung transplant are unknown. Additionally, the long-term outcomes and effects of pre-lung transplant GER testing and management for patients with CF have not been evaluated.

In this study, we aimed to assess the differences between CF patients with and without GER on reflux testing during pre-lung transplant assessment, as well as the relationship between reflux test performance and chronic rejection in this cohort. We hypothesized that GER symptoms and demographic factors would influence the likelihood of undergoing pre-transplant reflux testing, and that performance of pre-transplant reflux testing to identify candidates for reflux interventions would decrease the risk of post-transplant allograft rejection in this patient population.

MATERIALS AND METHODS

This was a retrospective cohort study of lung transplant recipients at a tertiary care center from 2007-2019. All patients above the age of 18 who underwent lung transplant for a primary indication of CF were included in the primary analysis; all transplant recipients of any indication were included to calculate differences in the rates of reflux test performance between CF and non-CF patients. Patients with pre-transplant anti-reflux surgery were excluded. Baseline characteristics [age at transplantation, gender, race, body mass index (BMI)], self-reported GER symptoms prior to transplantation, and pre-transplant cardiopulmonary testing results, including echocardiogram, right heart catheterization, and spirometry, were recorded. ABO compatibility was assured for all donors and recipients prior to transplantation.

Reflux testing consisted of either 24-h pH- or combined multichannel intraluminal impedance and pH monitoring (Sandhill Scientific Inc, Highland Ranch, CO, United States) performed off acid suppression medications prior to transplantation. The reflux monitoring systems included a catheter with one or two pH sensor(s) which was introduced transnasally and positioned in the esophagus with the distal sensor localized to 5 cm above the lower esophageal sphincter, as well as a portable electronic datalogger. During the 24-h study, subjects remained upright during the day and recumbent at night, maintaining their normal scheduled activities. Meal periods, as documented by the patients using the datalogger, were excluded from analysis. Reflux monitoring results were analyzed with the assistance of a dedicated software package (Bioview Analysis, version 5.6.3.0, Sandhill Scientific Inc, Highland Ranch, CO, United States). Parameters of interest included acid exposure time [(AET) percentage of total study time with pH < 4 at the distal pH sensor] and the DeMeester score, a composite measure of acid reflux severity[14]. Standard normative cutoffs were employed in determining abnormal reflux[15,16].

Following transplantation, patients were prescribed a standard immunosuppressive regimen with azathioprine or mycophenolate, a calcineurin inhibitor, and methylprednisolone[17]. Routine surveillance bronchoscopy and pulmonary spirometry were performed at regular intervals according to institutional practice, and reflexively in symptomatic patients to evaluate for complications. The primary outcome was chronic rejection manifesting as chronic lung allograft dysfunction (CLAD), which was defined clinically and histologically per International Society of Heart and Lung Transplantation criteria[18].

Of note, post-transplant proton pump inhibitor (PPI) use was not part of the established clinical protocol. However, the threshold to initiate such medication was low with any reflux-associated symptoms or based on evidence of objective reflux on pre-transplant testing.

Statistical analyses were performed using χ^2 test or student's *t*-test for comparison of baseline characteristics between patient groups. Time-to-event analysis was performed for chronic rejection outcome using Cox proportional hazards model. Subjects not meeting the outcome were censored at time of post-transplant anti-reflux surgery, last clinic visit, or death, whichever was earliest. Potential confounders adjusted for in the multivariable Cox regression model were selected based on univariate analyses, and included presence of typical GER symptoms pre-transplant, forced expiratory volume in 1 s on pulmonary function testing prior to transplant, BMI, and age at transplant. All statistical analysis was performed using SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, United States).

The study was approved by the Mass General Brigham Healthcare Institutional Review Board (2011P001563) prior to inception.

RESULTS

Of the 368 patients who underwent lung transplant during the study period, 60 subjects with CF met inclusion criteria for the study, with 50% male, a mean age of 34 years, and a total follow-up of 254 person-years. Among all CF patients, 41 (68.3%) completed reflux monitoring as part of pre-lung transplant assessment. Overall, objective evidence of increased acid reflux, defined as AET > 4%, was found in 24 (58.4%) subjects. Of the subgroup of 22 (53.7%) patients reporting typical esophageal symptoms of GER, including heartburn, regurgitation, and chest pain, 14 (63.4%) demonstrated increased acid reflux on pH-monitoring.

Patients with CF were less likely to undergo reflux testing during pre-lung transplant assessment compared to those with other pulmonary diagnoses (68% *vs* 85%, $P = 0.003$). CF patients with pre-transplant reflux testing were older (35.8 years *vs* 30.1 years, $P = 0.01$) and more commonly reported

typical esophageal symptoms of GER (53.7% *vs* 26.3%, P = 0.06) compared to those without reflux testing. Conditions that may affect reflux, including major esophageal motility disorders (achalasia, absent contractility) and gastroparesis, were not noted in our study cohort during the pre-transplant period, likely because many patients with known history of these conditions were not transplanted. Other patient demographics and baseline cardiopulmonary function did not significantly differ between CF subjects with and without pre-transplant reflux testing. All CF patients underwent bilateral lung transplant, and none received lung allografts from donors with risk factors for blood-borne disease transmission. Post-transplant infection rates were similar between subjects who did and did not undergo pre-transplant reflux testing, and were relatively high across both groups as is commonly seen in this patient population (Table 1).

A significantly lower proportion of patients in the pre-transplant reflux testing group developed CLAD compared to the no reflux testing group (21.9% *vs* 63.1%, P = 0.02). The risk of acute rejection did not differ significantly between groups. Both all-cause and pulmonary mortality were higher among those who did not undergo pre-transplant reflux testing, although statistical significance was not reached (42.1% *vs* 19.5%, P = 0.11 and 31.6% *vs* 12.2%, P = 0.09, respectively). Post-transplant PPI use was very common in both groups, including 83.9% in the pre-transplant testing group compared with 89.5% in the no testing group (P = 0.70), and higher than pre-transplant PPI use in both groups. One third (8/24) of patients who were found to have objective evidence of acid reflux on pre-transplant testing proceeded to anti-reflux surgery in the post-transplant follow-up period, while none of the patients in the no reflux testing group underwent anti-reflux surgery.

Multivariable time-to-event analysis, summarized in Table 2, similarly demonstrated a decreased risk of CLAD in patients with CF who underwent reflux testing during pre-lung transplant assessment compared to those who did not, even after controlling for confounders [Cox Hazard Ratio (HR) 0.26; 95%CI: 0.08-0.92, P = 0.03]. In the Cox multivariable regression model, reports of typical reflux symptoms also significantly predicted development of CLAD (HR 3.13; 95%CI: 1.03-9.54, P = 0.04). On subgroup analysis of patients who underwent pre-transplant reflux testing, those with abnormal reflux had a trend of increased risk of CLAD compared to those with normal reflux burden, although statistical significance was not reached (HR 4.09; 95%CI: 0.74-35.2, P = 0.20).

DISCUSSION

GER has been suggested to represent a potentially modifiable risk-factor for the development of chronic allograft rejection in lung transplant patients, given the potential role of reflux and aspiration in the risk of allograft injury[2,3,19,20]. Moreover, both medical and surgical anti-reflux therapies have been associated with improved allograft function and transplantation outcome among those with GER[21-26]. The prevalence of GER in CF patients is particularly high as reported in prior studies as well as in our cohort, where 58.4% of patients tested showed objective acid reflux on pH testing. Despite these findings, reflux testing remains non-standardized in the evaluation of lung transplant candidates across transplant centers and in the management of chronic lung diseases including CF. Traditionally, objective reflux testing is more commonly obtained for patients with restrictive lung diseases, particularly those with IPF, as prior evidence suggests a higher prevalence of and more severe reflux among those with restrictive *vs* obstructive lung disease[27,28]. Data for lung transplant candidates with CF, characterized by both restrictive and obstructive features, remains more limited. Our study demonstrated that transplant patients with CF less likely underwent reflux testing as part of pre-transplant assessment. However, completing pre-transplant reflux testing was an independent predictor for lower risk of developing CLAD, after adjusting for severity of lung disease, possibly due to more timely GER treatment. Among the subgroup who underwent reflux testing, abnormal reflux was associated with a trend for increased risk for CLAD.

In addition to poor standardization of reflux evaluation and management in lung transplantation, there are several other reasons why CF patients may undergo reflux testing less frequently than patients with other chronic lung diseases. While GER can be present at any age, the risk of GER increases as one gets older[29]. Since most CF patients present for clinical evaluation at a younger age, clinicians may be less likely to consider GER as a contributor to clinical symptoms and pulmonary function decline. This may, in part, explain the finding in our data that CF patients without reflux testing were significantly younger than those who did undergo reflux testing.

Another possible explanation for why some CF patients were less likely to undergo reflux testing was that these patients may have had more severe clinical disease, requiring urgent transplantation without time for additional evaluation. In this scenario, these non-testing patients may have more severe pulmonary disease before transplant and may be at higher risk for complications and poor outcomes following transplant regardless of gastroesophageal reflux disease. Reassuringly, the pre-transplant pulmonary function test measures were similar between CF patients who did and did not undergo pre-transplant reflux testing, suggesting similar baseline lung function prior to transplantation between both groups, although this may not fully reflect the speed of pulmonary decline or clinical severity that may occasionally drive the urgency of lung transplantation.

Table 1 Differences in demographics, transplant risk, reflux parameters, and post-transplant management between cystic fibrosis subjects receiving and not receiving pre-transplant gastroesophageal reflux evaluation, *n* (%)

Covariate	CF patients with pre-transplant reflux testing (*n* = 41)	CF patients without pre-transplant reflux testing (*n* = 19)	*P* value
Male gender	21 (51.2)	9 (47.4)	1.00
Age at lung transplant	35.8 ± 8.21	30.1 ± 7.89	0.01
Body mass index	20.4 ± 2.51	19.4 ± 1.97	0.11
Caucasian race	41 (100)	19 (100)	1.00
FEV1 before transplant	0.84 ± 0.36)	0.75 ± 0.22	0.24
LVEF before transplant	0.60 ± 0.05	0.59 ± 0.05	0.52
Bilateral lung transplant	41 (100)	19 (100)	1.00
CMV mismatch	15 (36.6)	6 (31.6)	0.78
High-risk donor	0	0	1.00
GER symptoms before transplant	22 (53.7)	5 (26.3)	0.06
Pre-transplant PPI use	27 (65.8)	16 (84.2)	0.22
Abnormal testing/Acid reflux	24 (58.4)	-	
Post-transplant PPI use	34 (82.9)	17 (89.5)	0.70
Post-transplant Nissen fundoplication	8 (19.5)	0 (0)	**0.05**
Any infection	35 (85.4)	17 (89.5)	1.00
Acute rejection	12 (29.3)	7 (36.8)	0.56
Chronic rejection/CLAD	9 (21.9)	12 (63.1)	**0.02**
Death (All-cause)	8 (19.5)	8 (42.1)	0.11
Death (Pulmonary)	5 (12.2)	6 (31.6)	0.09

CF: Cystic fibrosis; FEV1: Forced expiratory volume in 1 second; LVEF: Left ventricular cardiac ejection volume; CMV: Cytomegalovirus; GER: Gastroesophageal reflux; PPI: Proton pump inhibitor; CLAD: Chronic lung allograft dysfunction.

Table 2 Cox multivariate time-to-event analysis demonstrating the association between pre-transplant reflux testing and reduction in chronic rejection (chronic lung allograft dysfunction) in cystic fibrosis patients, after controlling for confounders, suggesting that reflux testing and timely treatment may reduce rejection in this patient cohort

Covariate	Cox multivariate analysis hazard ratios for chronic lung allograft dysfunction	*P*
Pre-transplant reflux testing	0.26 (0.08-0.92)	0.03
Gastroesophageal reflux symptoms before transplant	3.13 (1.03-9.54)	0.04
Forced expiratory volume in 1 second before transplant	3.17 (0.61-16.4)	0.17
Body mass index	0.98 (0.75-1.28)	0.88
Age at transplant	0.98 (0.90-1.05)	0.54

In our study, reflux testing was also associated with a significantly reduced risk of chronic rejection, independent of baseline pulmonary function and patient-reported GER symptoms. The is notable as symptomatic patients may be more likely to get tested and our multivariable model also found GER symptoms to be associated with increased risk for CLAD, thereby potentially biasing the pre-transplant reflux testing group towards development of CLAD. Our observation that completing reflux testing correlated with lower risk of CLAD despite this potential selection bias further strengthens our results. The possible mechanism by which reflux testing reduced risk of CLAD was likely related to the increased early detection of pathologic acid reflux leading to consideration of anti-reflux therapy. In our cohort, one-third of patients with pre-transplant reflux testing eventually underwent anti-reflux surgery, compared to none in the no reflux testing group. Since most patients in both groups received

PPI therapy post-transplant, anti-reflux surgery represented the major difference in clinical anti-reflux management between patient cohorts. Thus, the difference in CLAD risk between groups could be due, in part, to increased and earlier diagnosis of GER with more timely and aggressive management, through appropriate application of anti-reflux surgery when indicated.

Despite prior evidence demonstrating the potential deleterious effect of GER on lung allografts[2,3,19,20,30,31] and the protective effect of both medical and surgical anti-reflux therapy[21,22,24-26,32-35], the value and optimal strategy for reflux assessment among lung transplant patients remain debated and inconsistent across centers. In particular, timely or early anti-reflux therapy, often defined in prior studies as within 6 mo of transplantation, has been associated with improved outcomes compared to late or no reflux treatment among lung transplant patients with GER[23,36]. Therefore, accurate and prompt detection of abnormal reflux among lung transplant patients may play a role in reducing allograft dysfunction and improving outcomes. Currently, testing strategies employed by lung transplant centers may include: No esophageal assessment; selective testing based on presence of esophageal symptoms; selective testing based on underlying lung disease diagnosis; routine testing for all patients. Furthermore, the testing modality obtained may include barium esophagram, upper endoscopy, or objective reflux testing such as pH-monitoring. However, prior studies have found that esophageal symptoms are often absent among chronic lung disease patients with abnormal reflux and may not be adequate in guiding reflux testing, and that barium esophagram may not be sufficiently sensitive for detection of abnormal reflux[37]. As discussed above, some centers routinely perform reflux testing for patients with restrictive lung disease due to the higher reflux burden often observed in this population. However, our study provides evidence that routine reflux testing should also be advocated for CF patients undergoing lung transplant, especially given the high prevalence of reflux and mixed restrictive and obstructive property of the condition.

The limitations of our study include its retrospective nature, which makes it difficult to assign causality. Another limitation is the modest sample size, which reduces the statistical power, particularly in subgroup analyses such as that of patients with reflux testing showing abnormal reflux. Additionally, the sample size and retrospective design also limit the ability to perform more comprehensive analyses of other potential factors that may be associated with performance of reflux testing. Despite these limitations, our study would add to the current scarce data on the impact of objective reflux testing on post-transplant outcomes in patients with CF.

CONCLUSION

Given that patients with CF have favorable outcomes compared to the general lung transplant population, the judicious use of pre-transplant pH testing and appropriate management of GER is crucial to reducing CLAD[38]. Our findings suggest that while lung transplant patients with CF are less likely to undergo reflux testing compared to patients with other chronic lung diseases, they would likely benefit from more routine use of reflux testing to inform prompt and effective management of GER, including anti-reflux surgery when indicated. Thus, standardized reflux testing followed by timely reflux management should be adopted systematically in the care of patients undergoing lung transplant to improve post-transplant outcomes, especially among patients with CF.

ARTICLE HIGHLIGHTS

Research background

Gastroesophageal reflux is prevalent in chronic lung disease and can negatively impact lung transplant outcomes. However, the impact of pre-transplant reflux testing is not established in the cystic fibrosis (CF) population.

Research motivation

Routine reflux evaluation remains poorly standardized in lung transplantation, and this work contributes to the growing literature on the utility of reflux testing and timely management in lung transplant patients, especially those with CF.

Research objectives

To evaluate the impact of pre-transplant reflux testing on transplant outcomes in CF, as well as determining the prevalence of reflux in this patient population.

Research methods

This was a retrospective cohort study of CF patients that underwent lung transplantation at a tertiary referral center.

Research results

Lung transplant candidates with CF were less likely than those with other chronic lung diseases to undergo reflux testing. Pre-transplant reflux testing identified high prevalence of pathologic reflux in CF. Reflux testing was associated with decreased risk of chronic rejection.

Research conclusions

Pre-transplant reflux testing revealed high prevalence of pathologic reflux in CF patients and was associated with decreased risk of chronic lung allograft dysfunction.

Research perspectives

Systemic reflux testing may improve lung transplant outcomes in the CF population. Future research should focus on the implementation of standardized reflux evaluation and timely reflux management in lung transplantation, and its impact on transplant outcomes, particularly in patients with CF.

FOOTNOTES

Author contributions: Chan WW and Lo WK initiated study concepts and design; Lo WK, Goldberg HJ, and Chan WW contributed to acquisition of data; Chan WW, Lo WK, Flanagan R, Goldberg HJ, and Sharma N performed analysis and interpretation of data; Lo WK, Flanagan R, and Chan WW drafted the manuscript; Chan WW, Lo WK, Flanagan R, Goldberg HJ, and Sharma N contributed to critical revision of manuscript for important intellectual content; Chan WW and Lo WK performed statistical analyses; and Chan WW provided administrative support and overall study supervision.

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REFERENCES

1 **Lo WK**, Goldberg HJ, Burakoff R, Feldman N, Chan WW. Increased proximal acid reflux is associated with early readmission following lung transplantation. *Neurogastroenterol Motil* 2016; **28**: 251-259 [PMID: 26568193 DOI: 10.1111/nmo.12720]
2 **Lo WK**, Burakoff R, Goldberg HJ, Feldman N, Chan WW. Pre-transplant impedance measures of reflux are associated with early allograft injury after lung transplantation. *J Heart Lung Transplant* 2015; **34**: 26-35 [PMID: 25444368 DOI: 10.1016/j.healun.2014.09.005]
3 **Lo WK**, Moniodis A, Goldberg HJ, Feldman N, Chan WW. Increased Acid Exposure on Pretransplant Impedance-pH Testing Is Associated With Chronic Rejection After Lung Transplantation. *J Clin Gastroenterol* 2020; **54**: 517-521 [PMID: 32091450 DOI: 10.1097/MCG.0000000000001331]
4 **Ledson MJ**, Tran J, Walshaw MJ. Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients. *J R Soc Med* 1998; **91**: 7-9 [PMID: 9536132 DOI: 10.1177/014107689809100103]
5 **Pauwels A**, Blondeau K, Mertens V, Farre R, Verbeke K, Dupont LJ, Sifrim D. Gastric emptying and different types of reflux in adult patients with cystic fibrosis. *Aliment Pharmacol Ther* 2011; **34**: 799-807 [PMID: 21793864 DOI: 10.1111/j.1365-2036.2011.04786.x]
6 **Blondeau K**, Dupont LJ, Mertens V, Verleden G, Malfroot A, Vandenplas Y, Hauser B, Sifrim D. Gastro-oesophageal reflux and aspiration of gastric contents in adult patients with cystic fibrosis. *Gut* 2008; **57**: 1049-1055 [PMID: 18372497

DOI: 10.1136/gut.2007.146134]
7 **Bongiovanni A**, Manti S, Parisi GF, Papale M, Mulè E, Rotolo N, Leonardi S. Focus on gastroesophageal reflux disease in patients with cystic fibrosis. *World J Gastroenterol* 2020; **26**: 6322-6334 [PMID: 33244195 DOI: 10.3748/wjg.v26.i41.6322]
8 **Mendez BM**, Davis CS, Weber C, Joehl RJ, Fisichella PM. Gastroesophageal reflux disease in lung transplant patients with cystic fibrosis. *Am J Surg* 2012; **204**: e21-e26 [PMID: 22921151 DOI: 10.1016/j.amjsurg.2012.07.019]
9 **Yeung JC**, Machuca TN, Chaparro C, Cypel M, Stephenson AL, Solomon M, Saito T, Binnie M, Chow CW, Grasemann H, Pierre AF, Yasufuku K, de Perrot M, Donahoe LL, Tikkanen J, Martinu T, Waddell TK, Tullis E, Singer LG, Keshavjee S. Lung transplantation for cystic fibrosis. *J Heart Lung Transplant* 2020; **39**: 553-560 [PMID: 32147452 DOI: 10.1016/j.healun.2020.02.010]
10 **Tobin RW**, Pope CE 2nd, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998; **158**: 1804-1808 [PMID: 9847271 DOI: 10.1164/ajrccm.158.6.9804105]
11 **Raghu G**, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, Sillery JK, Pope CE 2nd, Pellegrini CA. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J* 2006; **27**: 136-142 [PMID: 16387946 DOI: 10.1183/09031936.06.00037005]
12 **Savarino E**, Carbone R, Marabotto E, Furnari M, Sconfienza L, Ghio M, Zentilin P, Savarino V. Gastro-oesophageal reflux and gastric aspiration in idiopathic pulmonary fibrosis patients. *Eur Respir J* 2013; **42**: 1322-1331 [PMID: 23471347 DOI: 10.1183/09031936.00101212]
13 **Gavini S**, Finn RT, Lo WK, Goldberg HJ, Burakoff R, Feldman N, Chan WW. Idiopathic pulmonary fibrosis is associated with increased impedance measures of reflux compared to non-fibrotic disease among pre-lung transplant patients. *Neurogastroenterol Motil* 2015; **27**: 1326-1332 [PMID: 26176338 DOI: 10.1111/nmo.12627]
14 **Johnson LF**, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. *Am J Gastroenterol* 1974; **62**: 325-332 [PMID: 4432845]
15 **Zerbib F**, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, Lepicard P, Mion F; Groupe Français De Neuro-Gastroentérologie. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clin Gastroenterol Hepatol* 2013; **11**: 366-372 [PMID: 23142603 DOI: 10.1016/j.cgh.2012.10.041]
16 **Hirano I**, Richter JE; Practice Parameters Committee of the American College of Gastroenterology. ACG practice guidelines: esophageal reflux testing. *Am J Gastroenterol* 2007; **102**: 668-685 [PMID: 17335450 DOI: 10.1111/j.1572-0241.2006.00936.x]
17 **Knoop C**, Haverich A, Fischer S. Immunosuppressive therapy after human lung transplantation. *Eur Respir J* 2004; **23**: 159-171 [PMID: 14738248 DOI: 10.1183/09031936.03.00039203]
18 **Parulekar AD**, Kao CC. Detection, classification, and management of rejection after lung transplantation. *J Thorac Dis* 2019; **11**: S1732-S1739 [PMID: 31632750 DOI: 10.21037/jtd.2019.03.83]
19 **D'Ovidio F**, Mura M, Tsang M, Waddell TK, Hutcheon MA, Singer LG, Hadjiliadis D, Chaparro C, Gutierrez C, Pierre A, Darling G, Liu M, Keshavjee S. Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. *J Thorac Cardiovasc Surg* 2005; **129**: 1144-1152 [PMID: 15867792 DOI: 10.1016/j.jtcvs.2004.10.035]
20 **Blondeau K**, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, Sifrim D, Dupont LJ. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. *Eur Respir J* 2008; **31**: 707-713 [PMID: 18057058 DOI: 10.1183/09031936.00064807]
21 **Lo WK**, Goldberg HJ, Boukedes S, Burakoff R, Chan WW. Proton Pump Inhibitors Independently Protect Against Early Allograft Injury or Chronic Rejection After Lung Transplantation. *Dig Dis Sci* 2018; **63**: 403-410 [PMID: 29094310 DOI: 10.1007/s10620-017-4827-0]
22 **Hoppo T**, Jarido V, Pennathur A, Morrell M, Crespo M, Shigemura N, Bermudez C, Hunter JG, Toyoda Y, Pilewski J, Luketich JD, Jobe BA. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. *Arch Surg* 2011; **146**: 1041-1047 [PMID: 21931001 DOI: 10.1001/archsurg.2011.216]
23 **Lo WK**, Goldberg HJ, Wee J, Fisichella PM, Chan WW. Both Pre-Transplant and Early Post-Transplant Antireflux Surgery Prevent Development of Early Allograft Injury After Lung Transplantation. *J Gastrointest Surg* 2016; **20**: 111-8; discussion 118 [PMID: 26493975 DOI: 10.1007/s11605-015-2983-0]
24 **Hartwig MG**, Anderson DJ, Onaitis MW, Reddy S, Snyder LD, Lin SS, Davis RD. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. *Ann Thorac Surg* 2011; **92**: 462-8; discussion; 468 [PMID: 21801907 DOI: 10.1016/j.athoracsur.2011.04.035]
25 **Davis RD Jr**, Lau CL, Eubanks S, Messier RH, Hadjiliadis D, Steele MP, Palmer SM. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg* 2003; **125**: 533-542 [PMID: 12658195 DOI: 10.1067/mtc.2003.166]
26 **Abbassi-Ghadi N**, Kumar S, Cheung B, McDermott A, Knaggs A, Zacharakis E, Moorthy K, Carby M, Hanna GB. Anti-reflux surgery for lung transplant recipients in the presence of impedance-detected duodenogastroesophageal reflux and bronchiolitis obliterans syndrome: a study of efficacy and safety. *J Heart Lung Transplant* 2013; **32**: 588-595 [PMID: 23540400 DOI: 10.1016/j.healun.2013.02.009]
27 **Masuda T**, Mittal SK, Kovács B, Smith MA, Walia R, Huang JL, Bremner RM. Foregut function before and after lung transplant. *J Thorac Cardiovasc Surg* 2019; **158**: 619-629 [PMID: 31084982 DOI: 10.1016/j.jtcvs.2019.02.128]
28 **Masuda T**, Mittal SK, Kovacs B, Smith M, Walia R, Huang J, Bremner RM. Thoracoabdominal pressure gradient and gastroesophageal reflux: insights from lung transplant candidates. *Dis Esophagus* 2018; **31** [PMID: 29617746 DOI: 10.1093/dote/doy025]
29 **Nirwan JS**, Hasan SS, Babar ZU, Conway BR, Ghori MU. Global Prevalence and Risk Factors of Gastro-oesophageal Reflux Disease (GORD): Systematic Review with Meta-analysis. *Sci Rep* 2020; **10**: 5814 [PMID: 32242117 DOI: 10.1038/s41598-020-62795-1]

30 **Murthy SC**, Nowicki ER, Mason DP, Budev MM, Nunez AI, Thuita L, Chapman JT, McCurry KR, Pettersson GB, Blackstone EH. Pretransplant gastroesophageal reflux compromises early outcomes after lung transplantation. *J Thorac Cardiovasc Surg* 2011; **142**: 47-52.e3 [PMID: 21683838 DOI: 10.1016/j.jtcvs.2011.04.028]

31 **Shah N**, Force SD, Mitchell PO, Lin E, Lawrence EC, Easley K, Qian J, Ramirez A, Neujahr DC, Gal A, Leeper K, Pelaez A. Gastroesophageal reflux disease is associated with an increased rate of acute rejection in lung transplant allografts. *Transplant Proc* 2010; **42**: 2702-2706 [PMID: 20832573 DOI: 10.1016/j.transproceed.2010.05.155]

32 **Fisichella PM**, Davis CS, Gagermeier J, Dilling D, Alex CG, Dorfmeister JA, Kovacs EJ, Love RB, Gamelli RL. Laparoscopic antireflux surgery for gastroesophageal reflux disease after lung transplantation. *J Surg Res* 2011; **170**: e279-e286 [PMID: 21816422 DOI: 10.1016/j.jss.2011.05.038]

33 **Fisichella PM**, Davis CS, Lowery E, Pittman M, Gagermeier J, Love RB, Kovacs EJ. Pulmonary immune changes early after laparoscopic antireflux surgery in lung transplant patients with gastroesophageal reflux disease. *J Surg Res* 2012; **177**: e65-e73 [PMID: 22537841 DOI: 10.1016/j.jss.2012.03.066]

34 **Fisichella PM**, Davis CS, Lundberg PW, Lowery E, Burnham EL, Alex CG, Ramirez L, Pelletiere K, Love RB, Kuo PC, Kovacs EJ. The protective role of laparoscopic antireflux surgery against aspiration of pepsin after lung transplantation. *Surgery* 2011; **150**: 598-606 [PMID: 22000170 DOI: 10.1016/j.surg.2011.07.053]

35 **Gasper WJ**, Sweet MP, Hoopes C, Leard LE, Kleinhenz ME, Hays SR, Golden JA, Patti MG. Antireflux surgery for patients with end-stage lung disease before and after lung transplantation. *Surg Endosc* 2008; **22**: 495-500 [PMID: 17704875 DOI: 10.1007/s00464-007-9494-3]

36 **Biswas Roy S**, Elnahas S, Serrone R, Haworth C, Olson MT, Kang P, Smith MA, Bremner RM, Huang JL. Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease. *J Thorac Cardiovasc Surg* 2018; **155**: 2762-2771.e1 [PMID: 29572022 DOI: 10.1016/j.jtcvs.2018.02.009]

37 **Posner S**, Zheng J, Wood RK, Shimpi RA, Hartwig MG, Chow SC, Leiman DA. Gastroesophageal reflux symptoms are not sufficient to guide esophageal function testing in lung transplant candidates. *Dis Esophagus* 2018; **31** [PMID: 29444329 DOI: 10.1093/dote/dox157]

38 **Lynch JP 3rd**, Sayah DM, Belperio JA, Weigt SS. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Semin Respir Crit Care Med* 2015; **36**: 299-320 [PMID: 25826595 DOI: 10.1055/s-0035-1547347]

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ORIGINAL ARTICLE

Retrospective Study

Mortality assessment for pancreas transplants in the United States over the decade 2008-2018

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Abstract

BACKGROUND

Pancreas transplant is the only treatment that establishes normal glucose levels for patients diagnosed with diabetes. However, since 2005, no comprehensive analysis has compared survival outcomes of: (1) Simultaneous pancreas-kidney (SPK) transplant; (2) Pancreas after kidney (PAK) transplant; and (3) Pancreas transplant alone (PTA) to waitlist survival.

AIM

To explore the outcomes of pancreas transplants in the United States during the decade 2008-2018.

METHODS

Our study utilized the United Network for Organ Sharing Standard Transplant Analysis and Research file. Pre- and post-transplant recipient and waitlist characteristics and the most recent recipient transplant and mortality status were used. We included all patients with type I diabetes listed for pancreas or kidney-pancreas transplant between May 31, 2008 and May 31, 2018. Patients were grouped into one of three transplant types: SPK, PAK, or PTA.

RESULTS

The adjusted Cox proportional hazards models comparing survival between transplanted and non-transplanted patients in each transplant type group showed that patients who underwent an SPK transplant exhibited a significantly reduced hazard of mortality [hazard ratio (HR) = 0.21, 95% confidence intervals (CI): 0.19-0.25] compared to those not transplanted. Neither PAK transplanted patients (HR = 1.68, 95%CI: 0.99-2.87) nor PTA patients (HR = 1.01, 95%CI: 0.53-1.95) experienced significantly different hazards of mortality compared to patients who did not receive a transplant.

CONCLUSION
When assessing each of the three transplant types, only SPK transplant offered a survival advantage compared to patients on the waiting list. PKA and PTA transplanted patients demonstrated no significant differences compared to patients who did not receive a transplant.

Key Words: Pancreas transplant; Simultaneous pancreas-kidney transplant; Pancreas after kidney transplant; Survival; Diabetes mellitus; Insulin

Core Tip: The total number of pancreas transplants has been in the decline in United States since 2003/2004. This study aimed to show acceptable survival outcome for diabetic patients receiving pancreas transplant as a cure therapeutic approach.

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INTRODUCTION

The Diabetes Control and Complications Trial demonstrated the advantage of intensive diabetes therapy in delaying the development of macro/microvascular diabetic-related complications and decreasing the overall mortality rate of diabetic patients[1-4]. It is clear, however, from follow-up studies that the risk of developing secondary diabetic complications is not eliminated, and the incidence of hypoglycemic episodes increases over time[5,6]. As a result, pancreas transplant is the only treatment that restores normal glucose metabolism in insulin-dependent diabetic patients[7,8].

Pancreas transplants, in relation to kidney function, fall into three different categories: (1) Simultaneous pancreas-kidney (SPK) transplant in patients with end-stage kidney disease (ESKD); (2) Pancreas after kidney (PAK) transplant; and (3) Pancreas transplant alone (PTA) in patients with no kidney disease[9]. Recipient and graft survival rates and the total number of pancreas transplants had improved in all three categories since the introduction of the procedures. However, around 2003, the number of pancreas transplants started to decline[10]. Multiple events and factors could explain the paradoxical relationship between declining transplants despite improving outcomes[10]. One contributing factor was that during the period, two major studies conducted by Venstrom *et al*[11] in 2003 and Gruessner *et al*[12] in 2005 showed inconsistency in reported outcomes of patients and grafts after a pancreas transplant. Subsequently, the overall number of active pancreas transplant centers fell. By 2016, only 11 centers in the United States performed more than 20 pancreas transplants a year, and most centers performed less than 5 transplants annually[10,13]. Consequently, fewer surgeons are adequately trained in pancreas donor recovery and transplant[14,15]. Since the 2003 and 2005 studies, no comprehensive analysis has compared the outcomes of the three categories of pancreas transplant and waitlist survival. To remedy this gap in our understanding, the present study analyzed the mortality of transplanted *vs* wait-listed patients in all three pancreas recipient categories using United Network for Organ Sharing (UNOS)/IPTR data from May 31, 2008 through May 31, 2018. We hypothesized that since 2005, survival for each type of transplant will have improved. Specifically:

Hypothesis 1: PTA patients will have improved survival compared to those not transplanted.
Hypothesis 2: PAK patients will have improved survival compared to those not transplanted.
Hypothesis 3: SPK patients will have improved survival compared to those not transplanted.

MATERIALS AND METHODS

Data source and measures

Our study utilized the UNOS Standard Transplant Analysis and Research file[16]. This database contains clinical and follow-up data for all transplants in the United States. Pre- and post-transplant recipient and waitlist characteristics and the most recent recipient transplant and mortality status were used. We included all patients with type I diabetes listed for pancreas or kidney-pancreas transplant between May 31, 2008 and May 31, 2018. Any patients listed for pancreas or pancreas-kidney transplant for the first time before or after those dates were excluded. Patients listed for any organ other than a

pancreas, pancreas-kidney simultaneously, or were listed before May 31, 2008, were excluded. Patients under 18 years of age were also removed, as were patients with missing waitlist ID or registration dates.

Patients were grouped into one of three transplant types: SPK, PAK, or PTA. Patients listed for pancreas and kidney transplants at the same time (with overlapping waitlist times) or receiving a pancreas and kidney transplant together were included in the SPK group. Patients listed for their first pancreas transplant on or after May 31, 2008, and with a kidney or kidney-pancreas transplant record before their listing for a pancreas transplant and those receiving a pancreas transplant after having a kidney transplant were included in the PAK group. Finally, patients listed for or who received only a pancreas transplant, having never been listed for or received a kidney transplant, were considered in the PTA group. Patients were considered to have a pancreas transplant if they had a pancreas transplant ID code and date. Patient death was defined as having a death date in the UNOS record, and patients were censored at removal from the waiting list or at the date of the last follow-up unless a death date was present. Waitlist times were calculated as the difference between first registration (INIT_DATE) and waitlist removal date (END_DATE), death date (COMPOSITE_DEATH_DATE), or transplant date (TX_DATE). If a patient was listed at multiple locations or had multiple entries, we determined the unique days between first registration and the removal date, death date, or transplant date. If a candidate was removed for being too sick to undergo their transplant and had a death date after being removed, the time between removal and death was added to the waitlist time. Time from transplant to death or loss to follow-up was calculated as the difference between the transplant date and death or last follow-up date (PX_STAT_DATE).

Statistical analysis

Descriptive statistics were calculated for transplanted and non-transplanted waitlist patients for each transplant type group. Means, standard deviations, and ranges are used to describe continuous variables. Categorical variables are described by frequency and percentages. Cox regression models comparing transplanted to non-transplanted patients used transplant as a time-dependent covariate, with time on the waitlist as time interval one and time from transplant to death or last follow-up as time interval two for transplanted patients. Adjustment variables included age at waitlist registration, gender, race (white, black, or other), duration of diabetes (years from the date of diabetes onset to date of waitlist registration), body mass index (BMI), Karnofsky functional status score, and presence of peripheral vascular disease (yes or no). BMI and functional status were divided into common clinically relevant groups operationalized into categorical variables. Adjustment variables were not considered as time-varying. Adjusted Cox models comparing survival after transplant between transplant-type groups only included transplanted patients and time from transplant to death or censoring. Additional models for up to 90 d post-transplant, 91 to 365 d post-transplant, and over 1 year post-transplant were also performed to compare survival within each period between transplant-type groups. These models were adjusted for the same variables as the previous set of models, with the addition of years on the waitlist. Hazard ratio (HR) and 95% confidence interval (CI) are reported[17]. All statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic and clinical characteristics

There were 9498 patients listed for SPK transplant, 1111 Listed for PAK transplant, and 939 Listed for PTA between May 31, 2008 and May 31, 2018. Of those, 6883 (59.6%) were transplanted, and 926 (8.0%) died on the waitlist. The mean age at listing was 40.6 years (range: 18-73 years), and 6539 (56.6%) patients were male. The majority of patients (7695, 66.6%) were white, 2187 (18.9%) were black, and 1666 (14.4%) were of other races. Almost 12 percent of patients were of Hispanic/Latino ethnicity. Most patients (6931, 62.4%) had a high Karnofsky functional status score, 5347 (46.7%) had a normal BMI, 10217 (90.0%) did not have peripheral vascular disease, and the mean duration of diabetes before registration was 26.5 years (Table 1).

Survival

Kaplan-Meier curves for each transplant type *vs* the wait list over 8 years of follow-up are shown in Figure 1. When considering SPK transplant, there was a significant difference in the survival of the transplanted *vs* non-transplanted group, starting immediately and growing as time progressed. However, for PAK transplant and PTA, there was no separation between the groups over time, identifying no survival differences.

Results of adjusted Cox proportional hazards models comparing survival between transplanted and non-transplanted patients in each transplant type group are shown in Table 2. SPK transplanted patients exhibited a significantly reduced hazard of mortality (HR = 0.21, 95%CI: 0.19-0.25) compared to those not transplanted. Neither PAK transplanted patients (HR = 1.68, 95%CI: 0.99-2.87) nor PTA patients (HR = 1.01, 95%CI: 0.53-1.95) experienced significantly different hazards of mortality compared to patients who did not receive a transplant. Associations of adjustment variables with mortality varied by

Table 1 Demographic and clinical characteristics of patients listed for a pancreas transplant by transplant status and transplant type (May 31, 2008–May 31, 2018)

	SPK			PAK			PTA		
	Transplant (*n* = 5834)	Waitlist (*n* = 3664)	*P* value	Transplant (*n* = 430)	Waitlist (*n* = 681)	*P* value	Transplant (*n* = 619)	Waitlist (*n* = 320)	*P* value
Age at registration (yr)			< 0.001			0.04			0.68
mean (SD)	40.1 (8.7)	41.0 (9.3)		40.6 (8.9)	41.8 (9.5)		41.7 (10.6)	41.4 (10.8)	
Range	18.0 - 69.0	18.0 - 73.0		22.0 - 67.0	18.0 - 66.0		18.0 - 68.0	20.0 - 70.0	
Gender			< 0.001			0.026			0.49
Female	2284 (39.1%)	1663 (45.4%)		174 (40.5%)	322 (47.3%)		378 (61.1%)	188 (58.8%)	
Male	3550 (60.9%)	2001 (54.6%)		256 (59.5%)	359 (52.7%)		241 (38.9%)	132 (41.2%)	
Race			0.3			0.08			< 0.001
White	3732 (64.0%)	2295 (62.6%)		336 (78.1%)	502 (73.7%)		567 (91.6%)	263 (82.2%)	
Black	1229 (21.1%)	781 (21.3%)		37 (8.6%)	88 (12.9%)		25 (4.0%)	27 (8.4%)	
Other	873 (15.0%)	588 (16.0%)		57 (13.3%)	91 (13.4%)		27 (4.4%)	30 (9.4%)	
Ethnicity			0.22			0.7			0.012
Hispanic/Latino	714 (12.2%)	480 (13.1%)		46 (10.7%)	78 (11.5%)		23 (3.7%)	24 (7.5%)	
Non-Hispanic/Non-Latino	5120 (87.8%)	3184 (86.9%)		384 (89.3%)	603 (88.5%)		596 (96.3%)	296 (92.5%)	
Karnofsky score at registration			0.34			0.46			0.013
High	3441 (60.7%)	2151 (61.9%)		291 (70.3%)	427 (66.6%)		392 (64.9%)	229 (74.1%)	
Middle	2108 (37.2%)	1259 (36.3%)		114 (27.5%)	199 (31.0%)		195 (32.3%)	76 (24.6%)	
Low	121 (2.1%)	63 (1.8%)		9 (2.2%)	15 (2.3%)		17 (2.8%)	4 (1.3%)	
BMI at registration			< 0.001			0.038			0.82
Normal	2847 (49.1%)	1640 (45.2%)		200 (46.9%)	287 (42.5%)		240 (40.1%)	133 (41.8%)	
Underweight	95 (1.6%)	60 (1.7%)		5 (1.2%)	8 (1.2%)		11 (1.8%)	4 (1.3%)	
Overweight	2180 (37.6%)	1311 (36.2%)		172 (40.4%)	259 (38.4%)		231 (38.6%)	116 (36.5%)	
Obese	674 (11.6%)	615 (17.0%)		49 (11.5%)	121 (17.9%)		117 (19.5%)	65 (20.4%)	
Duration of diabetes (yr)			0.064			0.052			0.28
mean (SD)	26.3 (9.0)	26.6 (9.2)		26.9 (8.6)	28.0 (9.5)		26.6 (11.4)	25.8 (11.7)	
Range	0.0 - 59.0	0.0 - 60.0		3.0 - 49.0	2.0 - 55.0		0.0 - 58.0	1.0 - 57.0	
Peripheral vascular disease at registration			< 0.001			0.96			0.78
No	5253 (91.5%)	3136 (87.4%)		384 (91.0%)	613 (91.1%)		545 (89.1%)	286 (89.7%)	
Yes	488 (8.5%)	453 (12.6%)		38 (9.0%)	60 (8.9%)		67 (10.9%)	33 (10.3%)	
Time on waitlist (yr)			< 0.001			< 0.001			< 0.001
mean (SD)	0.9 (1.0)	1.8 (1.7)		1.2 (1.1)	2.5 (2.0)		0.6 (0.8)	1.9 (1.9)	
Range	0.0 - 7.4	0.0 - 10.3		0.0 - 5.9	0.0 - 9.9		0.0 - 6.7	0.0 - 10.0	
Follow-up time after transplant (yr)									
mean (SD)	3.7 (2.5)	NA		3.4 (2.6)	NA		3.3 (2.5)	NA	
Range	0.0 - 10.1	NA		0.0 - 9.1	NA		0.0 - 9.1	NA	

Continuous variables are presented as the mean and standard deviation (SD), and categorical variables are presented as frequency and percentage. SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone; NA: Not available.

Table 2 Adjusted Cox proportional hazards models comparing transplanted to non-transplanted patients within each transplant group

	SPK		PAK		PTA	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Transplanted (No)	Reference	Reference	Reference	Reference	Reference	Reference
Transplanted (Yes)	0.21 (0.19, 0.25)	< 0.001	1.68 (0.99, 2.87)	0.06	1.01 (0.53, 1.95)	0.97
Age at registration	1.01 (1.00, 1.02)	0.04	1.03 (1.00, 1.06)	0.02	1.03 (1.00, 1.06)	0.03
Gender (F)	Reference	Reference	Reference	Reference	Reference	Reference
Gender (M)	0.97 (0.86, 1.08)	0.55	0.55 (0.35, 0.88)	0.01	1.46 (0.90, 2.37)	0.13
Race (White)	Reference	Reference	Reference	Reference	Reference	Reference
Race (Black)	1.05 (0.91, 1.22)	0.47	1.82 (0.89, 3.71)	0.1	0.34 (0.05, 2.54)	0.29
Race (Other)	0.74 (0.62, 0.89)	0.001	0.77 (0.34, 1.74)	0.53	1.27 (0.45, 3.61)	0.66
BMI (Normal)	Reference	Reference	Reference	Reference	Reference	Reference
BMI (Obese)	0.76 (0.63, 0.90)	0	0.46 (0.21, 1.04)	0.06	0.80 (0.39, 1.65)	0.54
BMI (Overweight)	0.87 (0.77, 0.99)	0.03	0.66 (0.40, 1.10)	0.11	0.85 (0.50, 1.46)	0.57
BMI (Underweight)	1.16 (0.77, 1.75)	0.48	3.15 (0.90, 10.96)	0.07	1.76 (0.41, 7.64)	0.45
Duration of diabetes (yr)	1.00 (0.99, 1.01)	0.96	0.99 (0.96, 1.02)	0.62	0.98 (0.96, 1.01)	0.21
Karnofsky score (High)	Reference	Reference	Reference	Reference	Reference	Reference
Karnofsky score (Low)	0.98 (0.60, 1.60)	0.94	2.77 (0.96, 7.95)	0.06	3.07 (0.39, 24.14)	0.29
Karnofsky score (Middle)	1.42 (1.26, 1.60)	< 0.001	0.89 (0.52, 1.52)	0.66	2.22 (1.35, 3.64)	0
Peripheral vascular disease (No)	Reference	Reference	Reference	Reference	Reference	Reference
Peripheral vascular disease (Yes)	1.40 (1.19, 1.66)	< 0.001	0.98 (0.44, 2.16)	0.95	0.99 (0.47, 2.12)	0.99

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; HR: Hazard ratios; CI: Confidence intervals; PTA: Pancreas transplant alone. Hazard ratios and 95% confidence intervals result from multivariate Cox proportional hazards models using transplant as a time-dependent covariate.

transplant type.

Results of adjusted Cox proportional hazards models comparing post-transplant survival between the transplant-type groups are shown in Table 3. In the model that utilized all post-transplant follow-up time, PAK transplant recipients showed a significantly increased mortality hazard compared to SPK transplant recipients (HR = 1.46, 95%CI: 1.07-2.01). In the model using only up to 90 d of follow-up, PTA recipients showed a significantly reduced hazard compared to SPK transplant recipients (HR = 0.21, 95%CI: 0.05-0.88). Patients in the PAK group also showed a reduced hazard in the 90 d after transplant compared to those in the SPK group, although the association was not significant (HR = 0.25, 95%CI: 0.06-1.03). In the model using 91-365 d of follow-up, no significant differences in mortality hazard were observed between the three groups. In the model using over one year of follow-up time, the PAK transplanted group exhibited a significantly increased hazard compared to the SPK group (HR = 1.59, 95%CI: 1.11-0.30), and the PTA group showed a higher hazard than the SPK group, though the association was not statistically significant (HR = 1.36, 95%CI: 0.96-1.92).

DISCUSSION

Solid organ pancreas transplant is a complex procedure for which significant progress, in terms of immunosuppressive and surgical advancement, has been made over the past 5 decades. However, despite the advancement in immunomodulatory medications and surgical techniques, the number of pancreas transplants in the United States has declined significantly since 2003/2004[18,19]. The current study found that simultaneous pancreas-kidney transplant offered a survival advantage compared to patients on the waiting list. PAK transplant and PTA patients demonstrated no significant differences compared to patients who did not receive a transplant. As mentioned, two milestone studies demonstrated divergent results regarding pancreas transplant outcomes that are important to consider in light of the current results. The 2005 study conducted by Gruessner *et al*[12] showed survival results to be improved, while the 2003 study conducted by Venstrom *et al*[11] showed negative survival

Table 3 Cox proportional hazards models comparing survival after transplant between transplant types

	Overall		Up to 90 d post-transplant		91-365 d post-transplant		Greater than 1 yr post-transplant	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Transplant type (SPK)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Transplant type (PAK)	1.46 (1.07, 2.01)	0.02	0.25 (0.06, 1.03)	0.06	1.89 (0.89, 4.02)	0.1	1.59 (1.11, 2.30)	0.01
Transplant type (PTA)	1.22 (0.91, 1.65)	0.19	0.21 (0.05, 0.88)	0.03	1.31 (0.64, 2.68)	0.46	1.36 (0.96, 1.92)	0.08

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone; CI: Confidence intervals; HR: Hazard ratios. Hazard ratios and 95% confidence intervals result from multivariate Cox proportional hazards models predicting survival after transplant among only transplanted patients and excluding time on the waiting list.

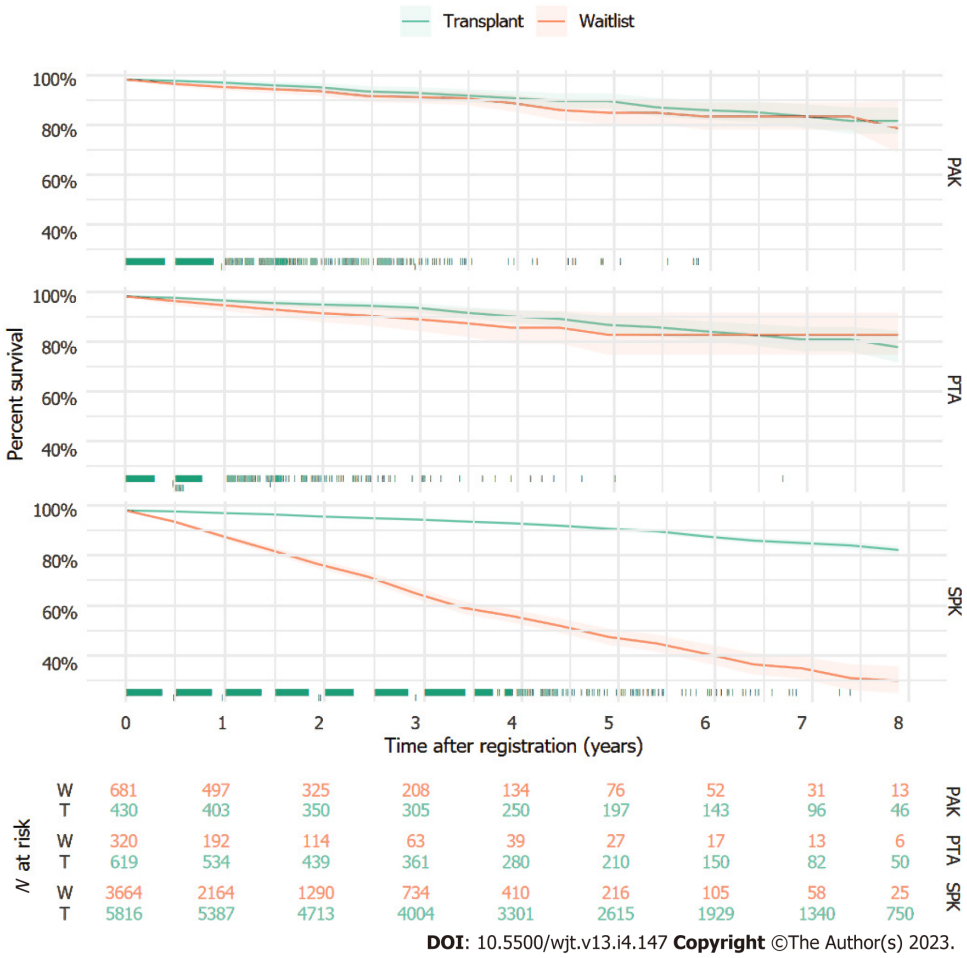

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Figure 1 Kaplan-Meier curves for each transplant type: Pancreas after kidney (PAK), pancreas transplant alone (PTA), and simultaneous pancreas and kidney transplant (SPK). The 8-year survival rate for PAK and PTA showed no separation between the transplanted and wait-listed groups over time. Simultaneous pancreas and kidney transplanted patients showed a significant difference in survival compared to the wait-listed group, starting immediately and growing as time progressed. PTA: Pancreas transplant alone; PAK: Pancreas after kidney; SPK: Simultaneous pancreas and kidney.

benefits.

In the category of PTA, the Gruessner study showed that the overall hazard ratio was 0.66 (95%CI: 0.39–1.12), favoring transplantation, while the Venstrom study showed the overall hazard ratio was 1.57 (95%CI: 0.98-2.53) favoring a no transplantation strategy. In our study, we analyzed data from the decade 2008-2018, and found recipients of PTA to have better survival results compared to the previous analysis conducted by Venstrom *et al*[11] and offered non-inferior outcomes when compared to patients on the waiting list (HR = 1.01, 95%CI: 0.53-1.95). As a result, there is mixed support for hypothesis 1, as

survival has improved compared to the Venstrom study but has not improved compared to the Grussner study. For PAK transplanted patients, Gruessner and colleagues found no overall difference for transplant (HR = 0.92, 95%CI: 0.69-1.12), but Venstrom *et al*[11] (HR = 1.42, 95%CI: 1.03-1.94) found a worse outcome. Our results, however, showed PAK transplanted patients to have an increased but not significant risk of death after transplant compared to waiting list patients (HR = 1.68, 95%CI: 0.99-2.87). As a result, there is also mixed support for hypothesis 2 as we found worse survival outcomes than Gruessner *et al*[12], but better survival than the Venstrom study. Finally, previous studies and ours favored transplantation in the SPK transplant category. Specifically, the Gruessner study identified an HR of 0.29 (95%CI: 0.27-0.33), and the Venstrom study identified an HR of 0.43 (95%CI: 0.39-0.48). Compared to patients on the waiting list, the mortality HR for SPK transplant recipients in the current study was 0.21 (95%CI: 0.19-0.25). As a result, there is support for hypothesis 3 as our results indicate improved survival compared to the previous studies.

When we considered the SPK transplant recipients' category as the analysis reference and broke down the follow-up period to: (1) Up to 90 d post-transplant; (2) 91 to 365 d post-transplant; and (3) Greater than 1 year post-transplant, we found an increased mortality risk among patients with PTA; however, the result was not significant (HR = 1.22, 95%CI: 0.91-1.65) (P = 0.19). The increased mortality risk was significant among patients in the PAK category (HR = 1.46, 95%CI: 1.07- 2.01) (P = 0.02). However, it is unclear why PAK transplant offers less survival benefit when compared to SPK transplant and the waiting list. This is more puzzling, especially if the expected sequence of PAK transplant is to receive a kidney from a living donor first, followed by a pancreas from a deceased donor. This sequence of events should offer a better survival than our results and previously published ones. Therefore, more analysis is needed to dissect all characteristics and conditions associated with the PAK category.

In relation to diseases that could influence poor outcomes, we also reviewed the impact of peripheral vascular disease (PVD) on the survival of the study patients. Patients diagnosed with PVD have a 3-fold increased risk of dying from all causes and a 6-fold increased risk of dying from cardiovascular disease within 10 years compared with patients without PVD[20-22]. Diabetic patients with PVD and those younger than 75 years have a 23% increase in mortality rate *vs* 7% among the control group[23]. We found patients from the SPK category group to have a lower incidence of PVD (8.5%) when compared to waitlist patients (12.6%) (P = 0.001). In the adjusted Cox proportional hazards models comparing transplanted to non-transplanted patients within each transplant category, SPK transplanted patients with PVD showed a significantly increased mortality risk compared to wait-listed patients (HR = 1.40, 95%CI: 1.19-1.66, P = 0.001). This could add a biased survival advantage when patients with less PVD are selected to proceed with SKP transplants after bypassing patients with more PVD on the waiting list. When reviewing the impact of BMI on the survival of the study patients, we found a paradoxical benefit of obesity among transplanted patients compared to wait-listed patients. This association was significant in the SPK category (HR = 0.76, 95%CI: 0.63-0.90) (P = 0.00) but was not significant in the PAK and PTA categories. The controversial advantage of obesity among patients with ESKD was shown before. Abbott *et al*[24] performed a retrospective analysis of the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Wave II Study patients who started dialysis in 1996 and were followed until October 31, 2001. They concluded that BMI ≥ 30 kg/m^2 was associated with improved survival in hemodialysis patients.

These results, in total, could be seen as an advancement in the field of transplantation and diabetic care in general. When we consider the consensus of the previous two studies and ours in favoring survival among patients who received SPK transplant, we are likely seeing a result of the remarkably high mortality rate among patients with end-stage kidney disease[25]. As a result, the benefit after an SPK transplant would appear to be more a consequence of resolving the kidney disease[25]. On the other hand, the lack of differences identified in the PAK and PTA groups, despite improved surgical and medical management techniques, likely points to similar progress in diabetic care in terms of medical technology, which improved the survival of diabetic patients with standard insulin therapy [26]. Patients with advanced diabetic disease may most benefit from PAK transplant or PTA. Previous studies have shown improved cost-effectiveness and quality of life for these groups compared to diabetic management through insulin alone[27].

CONCLUSION

Our study showed the survival advantage of SKP transplants compared to patients on the waiting list over the last decade. However, PAK transplant and PTA demonstrated no significant differences compared to patients who did not receive a transplant.

ARTICLE HIGHLIGHTS

Research background

Pancreas transplant is the only treatment that establishes normal glucose levels for patients diagnosed with diabetes. A significant advancement in management of diabetes associated with significant improvement in diabetic patients outcome has been achieved within the last decade. During the same period of time, there has been a noticeable decline in pancreas transplant procedures in the United States. In order to outline the importance of pancreas transplant as the only incurable treatment available for diabetes that could lead to normal glycemic status of these patients, we analyzed the outcome of pancreas transplant *vs* diabetic standard of care in the United States from 2008 to 2018.

Research motivation

A noticeable and significant decline of pancreas transplantation in the United States since 2004 has led to a decrease in the number of transplant centers that perform such procedure. This decline has led to a significant limitation among transplant surgeons and transplant physicians that are caring for patients receiving pancreas transplant. This study was to highlight the benefit of pancreas transplant in curing diabetes and to emphasize the potential benefit of pancreas transplantation in order to increase the number of diabetic patients that could receive this curative therapy.

Research objectives

The objective of this study was to bring pancreas transplant as a curative treatment, that could achieve glycemic control among diabetic patients, to the attention of transplant and endocrinology stakeholders. With the current technological advancement in treatment of diabetes, still a significant number of patients suffer from acute hyper and hypoglycemic events in addition to the chronic complications of diabetes. We hope that our research will at the current body of knowledge that supports pancreas transplant as a definitive treatment for diabetes and will encourage more clinical trials to compare standard of care for diabetes *vs* organ transplantation.

Research methods

Our study utilized the United Network for Organ Sharing Standard Transplant Analysis and Research file. This database contains clinical and follow-up data for all transplants in the United States since 1988. We included all patients with type I diabetes listed for pancreas or kidney-pancreas transplant between May 31, 2008 and May 31, 2018 and compared their outcome with the patients that had type 1 diabetes and were being listed and waiting for an organ transplant.

Research results

The adjusted Cox proportional hazards models comparing survival between transplanted and non-transplanted patients in each transplant type group showed simultaneous pancreas and kidney transplant patients to exhibit a significantly reduced hazard of mortality [hazard ratio (HR) = 0.21, 95% confidence interval (CI): 0.19-0.25] compared to those not transplanted. Neither transplanted patients (HR = 8, 95%CI: 0.99-2.87) nor pancreas transplant alone patients (HR = 1.01, 95%CI: 0.53-1.95) experienced significantly different hazards of mortality compared to patients who did not receive a transplant.

Research conclusions

Our study showed the survival advantage of simultaneous kidney and pancreas transplants compared to patients on the waiting list over the last decade. Patients who underwent pancreas transplant alone demonstrated no significant differences compared to patients who did not receive a transplant, which could highlight the importance of pancreas transplant alone despite the advancement in the technology of insulin delivery and diabetic management over the last decade.

Research perspectives

We hope that our study will encourage future clinical trials to randomize patients between diabetic standard of care *vs* transplantation. Meanwhile, we are conducting further studies to address disparities among patients who are receiving pancreas transplant *vs* remaining on the waiting list. We are aiming to identify any barriers among minorities that could prevent their access to transplant evaluation and to receive an organ transplantation.

FOOTNOTES

Author contributions: Jarmi T and Spaulding A designed the study and wrote the paper; Clendenon J wrote the paper; Brennan ER and Spaulding A collected and analyzed the data and wrote the paper.

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REFERENCES

1 **Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial**. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int* 1995; **47**: 1703-1720 [PMID: 7643540 DOI: 10.1038/ki.1995.236]
2 **Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group**. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003; **290**: 2159-2167 [PMID: 14570951 DOI: 10.1001/jama.290.16.2159]
3 **Diabetes Control and Complications Trial Research Group**, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977-986 [PMID: 8366922 DOI: 10.1056/NEJM199309303291401]
4 Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol* 1998; **116**: 874-886 [PMID: 9682700 DOI: 10.1001/archopht.116.7.874]
5 **Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group**. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002; **287**: 2563-2569 [PMID: 12020338 DOI: 10.1001/jama.287.19.2563]
6 **The effect of intensive diabetes therapy on the development and progression of neuropathy**. The Diabetes Control and Complications Trial Research Group. *Ann Intern Med* 1995; **122**: 561-568 [PMID: 7887548 DOI: 10.7326/0003-4819-122-8-199504150-00001]
7 **Aref A**, Zayan T, Pararajasingam R, Sharma A, Halawa A. Pancreatic transplantation: Brief review of the current evidence. *World J Transplant* 2019; **9**: 81-93 [PMID: 31523630 DOI: 10.5500/wjt.v9.i4.81]
8 **Dean PG**, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. *BMJ* 2017; **357**: j1321 [PMID: 28373161 DOI: 10.1136/bmj.j1321]
9 **White SA**, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet* 2009; **373**: 1808-1817 [PMID: 19465236 DOI: 10.1016/S0140-6736(09)60609-7]
10 **Stratta RJ**, Fridell JA, Gruessner AC, Odorico JS, Gruessner RW. Pancreas transplantation: a decade of decline. *Curr Opin Organ Transplant* 2016; **21**: 386-392 [PMID: 27096564 DOI: 10.1097/MOT.0000000000000319]
11 **Venstrom JM**, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. *JAMA* 2003; **290**: 2817-2823 [PMID: 14657065 DOI: 10.1001/jama.290.21.2817]
12 **Gruessner RW**, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. *Am J Transplant* 2004; **4**: 2018-2026 [PMID: 15575904 DOI: 10.1111/j.1600-6143.2004.00667.x]
13 **Kandaswamy R**, Skeans MA, Gustafson SK, Carrico RJ, Tyler KH, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2013 Annual Data Report: pancreas. *Am J Transplant* 2015; **15** Suppl 2: 1-20 [PMID: 25626343 DOI: 10.1111/ajt.13196]
14 **Fridell JA**, Rogers J, Stratta RJ. The pancreas allograft donor: current status, controversies, and challenges for the future. *Clin Transplant* 2010; **24**: 433-449 [PMID: 20384731 DOI: 10.1111/j.1399-0012.2010.01253.x]
15 **Marang-van de Mheen PJ**, Hilling DE, Dirkes MC, Baranski AG. Surgical injuries of pancreatic allografts during procurement. *Clin Transplant* 2011; **25**: 737-743 [PMID: 20973826 DOI: 10.1111/j.1399-0012.2010.01335.x]

16 **Organ Procurement and Transplantation Network**. Sharing UNfO. Data request instructions: STAR FILES. Available from: https://optn.transplant.hrsa.gov/data/request-data/data-request-instructions/

17 **Therneau TM**. Lumley T, Elizabeth A, Cynthia C. Survival Analysis. 2013. Available from: https://cran.r-project.org/web/packages/survival/survival.pdf

18 **Benjamens S**, Leemkuil M, Margreiter C, Huurman VA, Leuvenink HG, Pol RA. A steady decline in pancreas transplantation rates. *Pancreatology* 2019; **19**: 31-38 [PMID: 30448085 DOI: 10.1016/j.pan.2018.11.003]

19 **Boggi U**, Vistoli F, Andres A, Arbogast HP, Badet L, Baronti W, Bartlett ST, Benedetti E, Branchereau J, Burke GW 3rd, Buron F, Caldara R, Cardillo M, Casanova D, Cipriani F, Cooper M, Cupisti A, Davide J, Drachenberg C, de Koning EJP, Ettorre GM, Fernandez Cruz L, Fridell JA, Friend PJ, Furian L, Gaber OA, Gruessner AC, Gruessner RWG, Gunton JE, Han DJ, Iacopi S, Kauffmann EF, Kaufman D, Kenmochi T, Khambalia HA, Lai Q, Langer RM, Maffi P, Marselli L, Menichetti F, Miccoli M, Mittal S, Morelon E, Napoli N, Neri F, Oberholzer J, Odorico JS, Öllinger R, Oniscu G, Orlando G, Ortenzi M, Perosa M, Perrone VG, Pleass H, Redfield RR, Ricci C, Rigotti P, Paul Robertson R, Ross LF, Rossi M, Saudek F, Scalea JR, Schenker P, Secchi A, Socci C, Sousa Silva D, Squifflet JP, Stock PG, Stratta RJ, Terrenzio C, Uva P, Watson CJE, White SA, Marchetti P, Kandaswamy R, Berney T. First World Consensus Conference on pancreas transplantation: Part II - recommendations. *Am J Transplant* 2021; **21** Suppl 3: 17-59 [PMID: 34245223 DOI: 10.1111/ajt.16750]

20 **Criqui MH**, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; **326**: 381-386 [PMID: 1729621 DOI: 10.1056/NEJM199202063260605]

21 **Mohler ER 3rd**. Peripheral arterial disease: identification and implications. *Arch Intern Med* 2003; **163**: 2306-2314 [PMID: 14581250 DOI: 10.1001/archinte.163.19.2306]

22 **Belch JJ**, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, Creager MA, Easton JD, Gavin JR 3rd, Greenland P, Hankey G, Hanrath P, Hirsch AT, Meyer J, Smith SC, Sullivan F, Weber MA; Prevention of Atherothrombotic Disease Network. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med* 2003; **163**: 884-892 [PMID: 12719196 DOI: 10.1001/archinte.163.8.884]

23 **Mueller T**, Hinterreiter F, Luft C, Poelz W, Haltmayer M, Dieplinger B. Mortality rates and mortality predictors in patients with symptomatic peripheral artery disease stratified according to age and diabetes. *J Vasc Surg* 2014; **59**: 1291-1299 [PMID: 24393280 DOI: 10.1016/j.jvs.2013.11.063]

24 **Abbott KC**, Glanton CW, Trespalacios FC, Oliver DK, Ortiz MI, Agodoa LY, Cruess DF, Kimmel PL. Body mass index, dialysis modality, and survival: analysis of the United States Renal Data System Dialysis Morbidity and Mortality Wave II Study. *Kidney Int* 2004; **65**: 597-605 [PMID: 14717930 DOI: 10.1111/j.1523-1755.2004.00385.x]

25 **Foster BJ**, Mitsnefes MM, Dahhou M, Zhang X, Laskin BL. Changes in Excess Mortality from End Stage Renal Disease in the United States from 1995 to 2013. *Clin J Am Soc Nephrol* 2018; **13**: 91-99 [PMID: 29242373 DOI: 10.2215/CJN.04330417]

26 **Zimmerman C**, Albanese-O'Neill A, Haller MJ. Advances in Type 1 Diabetes Technology Over the Last Decade. *Eur Endocrinol* 2019; **15**: 70-76 [PMID: 31616496 DOI: 10.17925/EE.2019.15.2.70]

27 **Jarmi T**, Thao V, Borah BJ, Brennan E, Moriarty JP, Spaulding AC. Comparing Outcomes and Cost Between Pancreas Transplant and Standard of Care in Patients With Type 1 Diabetes. *Pancreas* 2022; **51**: 483-489 [PMID: 35835120 DOI: 10.1097/MPA.0000000000002053]

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ORIGINAL ARTICLE

Retrospective Study

Is peri-transplant blood transfusion associated with worse transplant outcomes? A retrospective study

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Abstract

BACKGROUND

Blood transfusion is common during the peri-transplantation period. The incidence of immunological reactions to blood transfusion after kidney transplantation and their consequences on graft outcomes have not been extensively studied.

AIM

To examine the risk of graft rejection and loss in patients who received blood transfusion in the immediate peri-transplantation period.

METHODS

We conducted a single-center retrospective cohort study of 105 kidney recipients, among them 54 patients received leukodepleted blood transfusion at our center between January 2017 and March 2020.

RESULTS

This study included 105 kidney recipients, of which 80% kidneys were from living-related donors, 14% from living-unrelated donors, and 6% from deceased donors. Living-related donors were mostly first-degree relatives (74.5%), while the rest were second-degree relatives. The patients were divided into transfusion (

n = 54) and non-transfusion (*n* = 51) groups. The average hemoglobin level at which blood transfusion was commenced was 7.4 ± 0.9 mg/dL. There were no differences between the groups in terms of rejection rates, graft loss, or death. During the study period, there was no significant difference in creatinine level progression between the two groups. Delayed graft function was higher in the transfusion group; however, this finding was not statistically significant. A high number of transfused packed red blood cells was significantly associated with increased creatinine levels at the end of the study.

CONCLUSION
Leukodepleted blood transfusion was not associated with a higher risk of rejection, graft loss, or death in kidney transplant recipients.

Key Words: Transplantation; Transfusion; Rejection; Graft survival

Core Tip: Blood transpfusion in patient undergoing kidney transplantation has long been avoided for the fear for the potential risk of reciepient's immunization and potential rejection. This study addresses the risks of peri-transplantation outcomes of blood transfusion.

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INTRODUCTION

Anemia is common in the early post-kidney transplant period[1-3]. The causes of this anemia are multiple and may include blood loss during the surgical operation, erythropoietin deficiency, iron deficiency as a result of previous end-stage renal disease along with delayed graft function (DGF), and adverse reactions to immunosuppressive agents. In some cases, blood transfusion is an essential life-saving practice. Blood transfusion is widely used in the early post-transplantation period following surgery[2].

However, blood transfusion is not without risks. Exposure to non-self human leukocyte antigens (HLAs) can lead to the formation of anti-HLA antibodies or allosensitization[2-4]. Donor-specific antibodies (DSAs) can develop in kidney recipients after receiving a blood transfusion[2]. HLA sensitization may have negative clinical impacts, including, an increased risk of rejection, and graft loss. Despite these risks, clinical guidelines do not provide specific recommendations for blood transfusion during the perioperative period[4]. This uncertainty could be due to the assumption that post-kidney transplant patients receive immunosuppressive agents, which could reduce the possibility of allosensitization[4,5].

The incidence of immunological reactions to blood transfusion after kidney transplantation and their consequences on graft outcomes have not been extensively studied. Our study aimed to examine the risk of graft rejection and graft loss in patients who receive a blood transfusion in the immediate post-transplantation period and those who were on immunosuppressive therapy.

MATERIALS AND METHODS

Study design

This was a single-center retrospective cohort study of kidney transplantation recipients who received either deceased or living-donor kidneys at Al-Hada Armed Forces Hospital, Taif, Saudi Arabia between January 2017 and March 2020. No other solid-organ transplantation or spontaneous kidney-pancreas transplantation was performed at our center during the study period.

We surveyed kidney transplant recipients who received a blood transfusion in the peri-transplant period (one week prior to transplantation and one month after the surgery). The control group included patients who underwent kidney transplantation during the same period but did not require blood transfusion. At our institution, only leukodepleted blood products are administered to kidney

transplant candidates and kidney transplant recipients; this applied to the kidney recipients enrolled in this study. Data were obtained from the patients' electronic files in the hospital. However, blood product type (leuko-depleted *vs* non-leuko-depleted) was confirmed from the blood bank records. We excluded recipients who were < 18 years of age, those with previous organ transplantation, those who required desensitization prior to transplantation, those on a calcineurin inhibitors (CNIs) avoidance protocol, and those who required permanent withdrawal of one or more of their immunosuppressive therapies.

During the study period, Immunosuppression protocol in our hospital consisted of induction therapy with either antithymocyte globulin (cumulative dose of 4-6 mg/kg) or basiliximab (two intravenous doses of 20 mg on post-op days 0 and 4) and maintenance immunosuppression with tacrolimus (targeting a tacrolimus level of 8-10 ng/mL in the first three months then 4-6 ng/mL), an antimetabolite (mycophenolate mofetil 1 gm twice daily) and prednisone (tapered to a maintenance dose of 5 mg daily).

Outcomes

Primary outcomes were biopsy-proven rejection, DGF, graft loss within the first 18 mo post-transplantation and death of any cause during the same time period. Post-transplant kidney biopsy and DSA identification were not performed routinely in this cohort but rather on a for-cause basis. Secondary outcomes were changes in creatinine levels during the study period, infections, and urological complications. Both cellular and antibody-mediated rejections were accounted for. Graft loss was defined as the need for another renal replacement therapy. Identification of DSAs was performed using a Luminex single-bead antigen solid-phase assay with a cutoff of 1000 mean fluorescence intensity.

Statistical analysis

All analyses were performed using SPSS version 26 (IBM, Armonk, NY, United States). Continuous variables are denoted as mean ± SD for normally distributed variables or median (interquartile range) for non-normally distributed variables. The Shapiro-Wilk test was used to assess the normality of continuous variables to guide the selection of a parametric or nonparametric test for the comparison of variables. The variables were compared using the Welch's *t*-test, Student's *t*-test, and Mann-Whitney-U test. Categorical variables were presented as frequencies and percentages and were compared using the χ^2 or Fisher's exact tests as appropriate. All independent variables from the univariate linear regression analysis with $P < 0.05$ were entered into a multivariate linear regression model to examine their association with creatinine changes. All reported P values were two-sided and P values < 0.05 were considered to indicate a statistical significance.

RESULTS

A total of 124 kidney transplant surgeries were performed at Al-Hada Armed Forces Hospital during the study period (between January 2017 and March 2020). Nineteen patients were excluded they were < 18 years (three recipients), had a previous kidney transplant (five recipients), required desensitization prior to surgery (nine recipients), had ABO incompatibility (1 recipient), and lacked sufficient information (one recipient). The final analysis included data from 105 recipients. The patients were divided into two groups: Blood transfusion (54 recipients) and non-transfusion (51 recipients) groups (Table 1). The transplant recipients in our cohort had a higher prevalence of male sex (77 recipients: 73%), and most kidney transplantations were from living-related (84 recipients, 80%) than living-unrelated (15 recipients, 14%) donors or from deceased-donor kidney transplantation (six recipients; 6%). The median number of HLA mismatches was three in both groups. Basiliximab was the most commonly used agent for induction (62 recipients; 59%). All the recipients in our cohort received a tacrolimus-based regimen with an average tacrolimus level during the study time of 7 ng/mL (6-8 ng/mL).

Approximately 85 (69%) recipients in our cohort had anemia [hemoglobin (Hb) of < 12 g/dL]; however, only 57 (54%) recipients received blood transfusions. Among the 57 recipients who received blood transfusion 31 recipients (54%) received only 1 unit, 15 (26%) received two units, 7 (12%) received three units, 3 (5%) received four units, and only 1 (2%) received nine units of blood. The average Hb at the time of transplantation was significantly higher in the non-transfusion group (11.2 mg/dL *vs* 9.8 mg/dL, $P < 0.001$) (Table 2). In the transfusion group, the average Hb level at which blood transfusion was initiated was 7.4 ± 0.9 mg/dL. There were no significant differences in infectious and non-infectious complications between the two groups (Table 3). Additionally, there was no significant difference in graft loss or all-cause death between the two groups (Table 4, Figures 1 and 2). There was no significant difference in creatinine level progression between the two groups during the study period (Figure 3).

Rejection occurred in five recipients in our cohort; three had cellular rejection and two had antibody-mediated rejections (Table 5). All rejection episodes were biopsy-proven, and three occurred in the transfusion group; nevertheless, there was no significant difference in the rate of rejection between the

Table 1 Baseline characteristics of both the transfusion and non-transfusion groups, *n* (%)

	Total cohort, 105	Non-transfusion, 51 (48.6%)	Transfusion, 54 (51.4%)	*P* value
Age (mean ± SD)	39.7 ± 14.5	40.5 ± 13.9	38.9 ± 15.1	0.583
Gender				
Female	28 (26.7)	10 (19.6)	18 (33.3)	0.127
Male	77 (73.3)	41 (80.4)	36 (66.7)	
Type of transplantation				
LRKTx	84 (80)	43 (84.3)	41 (75.9)	0.566
LURKTx	15 (14.3)	6 (11.8)	9 (16.7)	
DDKTx	6 (5.7)	2 (3.9)	4 (7.4)	
HLA mismatch	3 (1-4)	3 (0-4)	3 (2-4)	0.152
Cause of ESRD				
Diabetes	18 (17.1)	7 (13.7)	11 (20.4)	0.331
GN	26 (24.8)	11 (21.6)	15 (27.8)	
Hypertension	18 (17.1)	12 (23.5)	6 (11.1)	
PCKD	1 (1)	1 (2)	0 (0)	
Urological	7 (6.7)	2 (3.9)	5 (9.3)	
Other	35 (33.3)	18 (35.3)	17 (31.5)	
Donor's age	33 ± 8.6	32.4 ± 8.4	33.5 ± 8.8	0.562
Induction therapy				
ATG	42 (40)	21 (41.2)	21 (38.9)	1
Basiliximab	62 (59)	30 (58.8)	32 (59.3)	
No induction	1 (1)	0 (0)	1 (1.9)	
Maintenance immunosuppression				
CNI used tacrolimus	105 (100)	51 (100)	54 (100)	
Average CNI level	7 (6-8)	7 (6-8)	7 (6-8)	0.743
Antimetabolite used (MMF)	105 (100)	51 (100)	54 (100)	

LRKTX: Living-related kidney transplantation; LURKTx: Living non-related kidney transplantation; DDKTX: Deceased-donor kidney transplantation; HLA: Human leucocyte antigen; ESRD: End-stage renal disease; GN: Glomerulonephritis; PCKD: Polycystic kidney disease; ATG: Antithymocyte globulin; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil.

Table 2 Blood transfusion information

	Total, 105	Non-transfused, 51 (48.6%)	Transfused, 54 (51.4%)	*P* value
Hemoglobin at transplantation	10.5 ± 1.7	11.2 ± 1.6	9.8 ± 1.6	< 0.001
Hemoglobin at blood transfusion			7.4 ± 0.9	
Hemoglobin after transfusion			9.2 ± 1.1	
Number of blood transfusion units given	1 (0-1.5)		1 (0-1.5)	

two groups. Additionally, during the study period, there was an improvement in serum creatinine levels in all the patients with rejection in both groups. None of the recipients with allograft rejection lost their grafts during the study period. However, one of the recipients died due to coronavirus disease 2019 pneumonia with a functioning graft. There were no statistically significant differences in age, sex, type of transplantation, HLA mismatch, induction therapy, or CNI levels between patients who developed rejection and those who did not.

Table 3 Infectious and non-infectious complications among the two groups, *n* (%)

	Total, 105	Non-transfusion, 51 (48.6%)	Transfusion, 54 (51.4%)	*P* value
No. of infections	0 (0-1)	1 (0-1)	0 (0-1.25)	0.554
Types of infections				
none	55 (52.4)	25 (49)	30 (55.6)	0.745
UTI	30 (28.6)	14 (27.5)	16 (29.6)	0.832
Pnemonia	1 (1)	1 (2)	0 (0)	0.486
TB	1 (1)	0 (0)	1 (1.9)	1
BK	7 (6.7)	5 (9.8)	2 (3.7)	0.261
Bactremia	4 (3.8)	1 (2)	3 (5.6)	0.618
Epidediymo-orchitis	2 (1.9)	1 (2)	1 (1.9)	1
Gastroenteritis	2 (1.9)	2 (3.9)	0 (0)	0.234
Herpes zoster	1 (1)	0 (0)	1 (1.9)	1
Infected AVF	1 (1)	1 (2)	0 (0)	0.486
Perianal abcess	1 (1)	1 (2)	0 (0)	0.486
COVID-19	9 (8.6)	6 (11.8)	3 (5.6)	0.311
URTI	2 (1.9)	1 (2)	1 (1.9)	1
CMV	12 (11.4)	6 (11.8)	6 (11.1)	1
Urological complications				
None	95 (90.5)	49 (96.1)	46 (85.2)	0.484
Allograft artery stenosis	1 (1)	0 (0)	1 (1.9)	
Collection	3 (2.9)	1 (2)	2 (3.7)	
Lymphocele	1 (1)	0 (0)	1 (1.9)	
Obstrctive uropathy	1 (1)	0 (0)	1 (1.9)	
Perinephric collection and ureteric stricture	2 (1.9)	0 (0)	2 (3.7)	
Unrogenic bladder	1 (1)	0 (0)	1 (1.9)	
Urinary leak	1 (1)	1 (2)	0 (0)	
Urological complications				
No	95 (90.5)	49 (96.1)	46 (85.2)	0.094
Yes	10 (9.5)	2 (3.9)	8 (14.8)	
CNI withdrawal	1 (1)	0 (0)	1 (1.9)	1
Duration from Tx	3 d			
MMF withdrawal	1 (1)	0 (0)	1 (1.9)	1
Duration from Tx	3 d			
Steroids withdrawal	0 (0)	0 (0)	0 (0)	

UTI: Urinary tract infection; TB: Tuberculosis; AVF: Arterio-venous fistula; COVID-19: Coronavirus disease 2019; URTI: Upper respiratory tract infection; CMV: Cytomegalovirus; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil.

The incidence of DGF was higher in the transfusion group; however, this difference was not statistically significant. In contrast, analysis of the predictors of DGF using multivariate logistic regression showed that age [adjusted odds ratio, 1.06, 95% confidence interval (CI): 1.012-1.111; P = 0.014] and blood transfusion (adjusted odds ratio 5.649, 95%CI: 1.106-28.848; P = 0.037) were significant independent risk factors for DGF. There were no significant differences in graft loss or all-cause death mortality between the two groups.

Table 4 Comparison in Outcomes of transplantation between the two groups, *n* (%)

	Total, 105	Non-transfusion, 51 (48.6%)	Transfusion, 54 (51.4%)	*P* value
Rejection	5 (4.8)	2 (3.9)	3 (5.6)	1
Rejection type				
ABMR	2 (40)	1 (50)	1 (33.3)	1
Cellular	3 (60)	1 (50)	2 (66.7)	
Graft loss	4 (3.8)	1 (2)	3 (5.6)	0.618
Death	2 (1.9)	1 (2)	1 (1.9)	1
DGF	11 (10.5)	2 (3.9)	9 (16.7)	0.053
Serum creatinine				
At discharge	141 ± 124.1	123 ± 56.7	158 ± 163	0.770
6 mo	108 ± 40.7	107.1 ± 28	108.9 ± 50.4	0.825
12 mo	109.1 ± 51.3	101.9 ± 22.9	117 ± 69.8	0.182
18 mo	126 ± 168.7	106.2 ± 26.5	147.4 ± 241.5	0.735
Creatinine difference: At 18 mo-at discharge		-19.4 ± 61.5	12.3 ± 253.8	0.439

ABMR: Antibody-mediated rejection; DGF: Delayed-graft function.

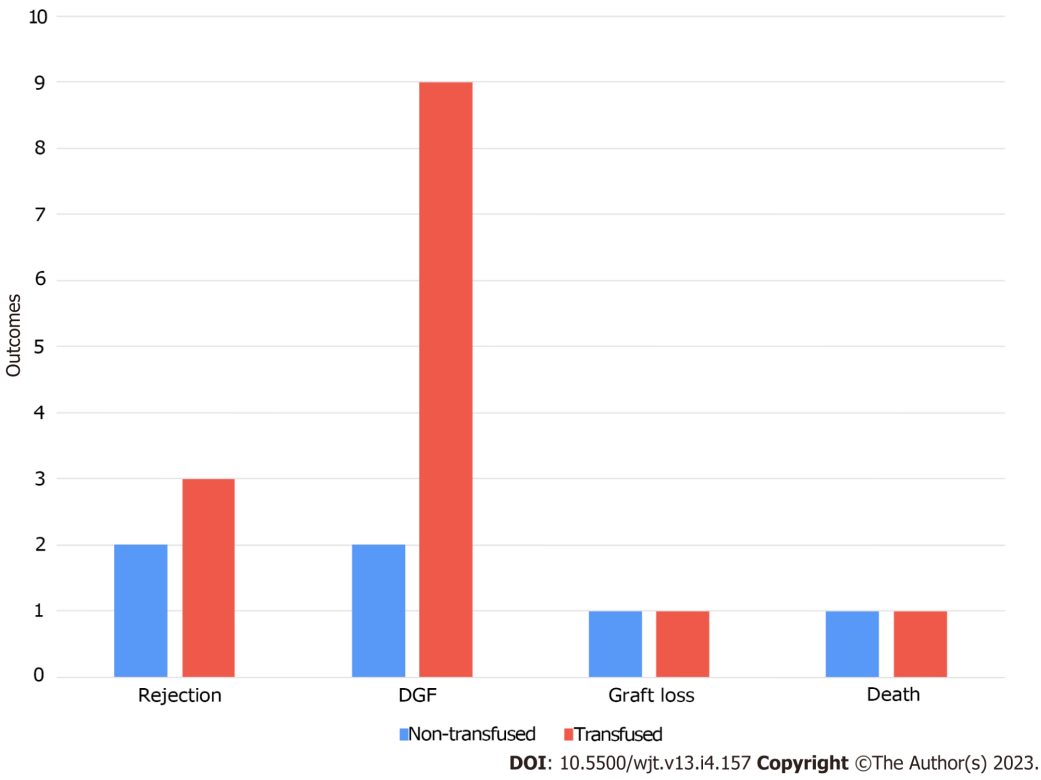

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Figure 1 Comparison in the outcomes between the blood transfusion *vs* non-blood transfusion groups. DGF: Delayed graft function.

We conducted a multiple linear regression analysis to examine the association between creatinine change (the difference between creatinine at the end of the study and baseline creatinine) as a dependent variable and eligible study variables as independent variables. We found that a higher number of transfused packed red blood cells was significantly associated with increased creatinine levels at the end of the study (B = 20.14; SE = 6.99; P = 0.004), whereas a higher creatinine level at discharge was associated with milder creatinine increase over the study period (B = -0.79; SE = 0.12; P < 0.001) (Table 6).

Table 5 Characteristics of rejection developers *vs* non-rejection developers among the study cohort, *n* (%)

	Non-rejection, 100	Rejection, 5	*P* value
Age (mean ± SD)	36.5 (28.25-51.75)	36 (21-46.5)	0.383
Gender			
Female	28 (28)	0 (0)	0.321
Male	72 (72)	5 (100)	
Type of transplantation			
LRKTx	81 (81)	3 (60)	0.172
LURKTx	13 (13)	2 (40)	
DDKTx	6 (6)	0 (0)	
HLA mismatch	3 (1-4)	3 (1-4)	0.729
Cause of ESRD			
Diabetes	18 (18)	0 (0)	0.199
GN	23 (23)	3 (60)	
Hypertension	18 (18)	0 (0)	
PCKD	1 (1)	0 (0)	
Urological	6 (6)	1 (20)	
Other	34 (34)	1 (20)	
Donor's age	32 (26-39)	28 (25.5-43.5)	0.981
Induction therapy			
ATG	41 (41)	1 (20)	0.438
Basiliximab	58 (58)	4 (80)	
No induction	1 (1)	0 (0)	
Average CNI level	7 (6-8)	8 (6.5-9)	0.311
Hb at transplantation	10.65 (9.025-11.3)	10.7 (9.05-12.45)	0.792
Hb at blood transfusion	7.4 (6.8-8)	7.8[1]	0.138
Hb after transfusion	8.9 (8.4-10)	10[1]	0.382
No of blood transfusion unites given	1 (0-1)	1 (0-3)	0.491
Serum creatinine			
At discharge	111 (83.25-142.75)	151 (113.5-222.5)	0.096
6 mo	102.5 (80.5-123)	120 (80-156)	0.420
12 mo	99.5 (81.75-119.25)	124.5 (92.5-140.75)	0.201
18 mo	105 (84.25-119)	107 (72-)	0.894
Death	1 (1)	1 (20)	0.093
DGF	9 (9)	2 (40)	0.084
No. of infections	0 (0-1)	1 (0-2)	0.651
Types of infections			
None	53 (53)	2 (40)	0.188
UTI	30 (28.6)	29 (29)	1
Pnemonia	1 (1)	1 (1)	1
TB	1 (1)	1 (1)	1
BK	7 (6.7)	7 (7)	1
Bactremia	4 (3.8)	4 (4)	1

Epidediymo-orchitis	2 (1.9)	2 (2)	1
Gastroenteritis	2 (1.9)	1 (1)	0.093
Herpes zoster	1 (1)	1 (1)	1
Infected AVF	1 (1)	1 (1)	1
Perianal abcess	1 (1)	1 (1)	1
COVID-19	9 (8.6)	8 (8)	0.367
URTI	2 (1.9)	1 (1)	0.093
CMV	11 (11)	1 (20)	0.462
Urological complications			
None	90 (90)	5 (100)	1
Allograft artery stenosis	1 (1)	0 (0)	
Collection	3 (3)	0 (0)	
Lymphocele	1 (1)	0 (0)	
Obstrctive uropathy	1 (1)	0 (0)	
Perinephric collection and ureteric stricture	2 (2)	0 (0)	
Unrogenic bladder	1 (1)	0 (0)	
Urinary leak	1 (1)	0 (0)	
Urological complications			
No	90 (90)	5 (100)	1
Yes	10 (10)	0 (0)	

[1]Interquartile range could not be calculated due to small number of patients for this outcome.
COVID-19: Coronavirus disease 2019; LRKTX: Living-related kidney transplantation; LURKTx: Living non-related kidney transplantation; DDKTX: Deceased-donor kidney transplantation; HLA: Human leucocyte antigen; ESRD: End-stage renal disease; GN: Glomerulonephritis; PCKD: polycystic kidney disease; ATG: Antithymocyte globulin; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil; Hb: Hemoglobin; DGF: Delayed-graft function; UTI: Urinary tract infection; TB: Tuberculosis; AVF: Arterio-venous fistula; URTI: Upper respiratory tract infection; CMV: Cytomegalovirus.

Table 6 Multiple linear regression analysis of the association between creatinine change and eligible study variables

	B	SE	95%CI	*P* value
(Intercept)	70.23	18.72	33.54 to 106.92	< 0.001
Male *vs* female	-1.74	18.59	-38.17 to 34.69	0.925
No. of PRBCs	20.14	6.99	6.45 to 33.84	0.004
Creatinine at discharge	-0.79	0.12	-1.03 to -0.54	< 0.001

CI: Confidence interval; PRBC: Packed red blood cell.

DISCUSSION

Anemia is a common condition during the peri-transplantation period. The rate of anemia during this period varies significantly. In a retrospective cohort study, Vanrenterghem *et al*[1] reported an anemia rate of 38% in a transplant population[1]. However, in a recent prospective study, 64% of the study cohort had anemia that requiring blood transfusion in the first month after transplantation[2]. The transfusion rate post-transplantation has been repeatedly reported to be between 37%-75%[4,6-8]. This high prevalence of transfusion has also been observed in pediatric populations. For instance, Richards *et al*[7] reported that the prevalence of transfusion was approximately 50% with a higher prevalence in younger children[7]. In our study, the anemia rate was toward the higher end of the above mentioned range at 69% however, only 54% of our cohort required blood transfusion.

Anemia carries significant risk in kidney transplant recipients. A drop of Hb level > 30% of its pre-transplant level was reported to be associated with higher all-cause graft failure and longer length of hospital stay, with a greater risk in those who required blood transfusion of > 3 units and those with

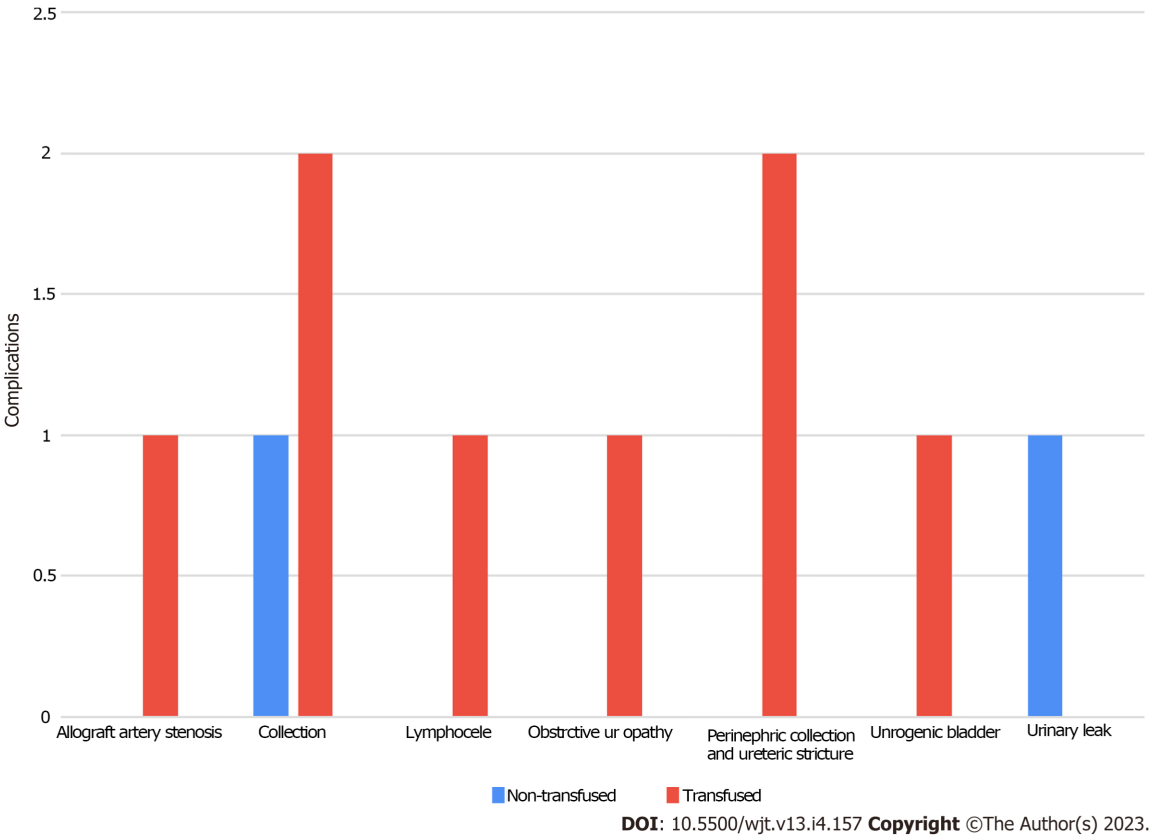

Figure 2 Progression of the mean creatinine between the blood transfusion *vs* non-blood transfusion groups.

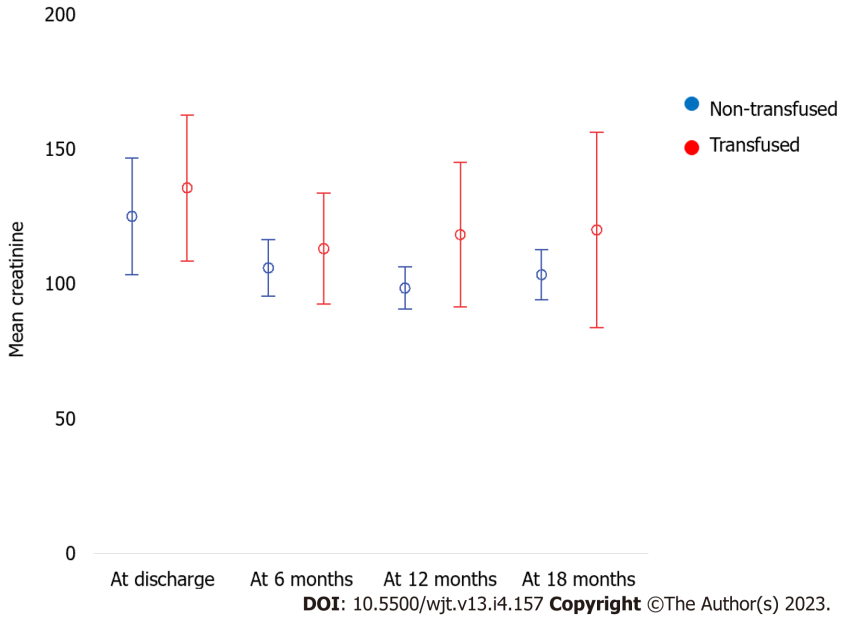

Figure 3 Progression of the mean creatinine between the blood transfusion *vs* non-blood transfusion groups. Total patients in non-transplantation group are 51. Total patients in transplantation group are 54 patients.

longer cold ischemia time[9]. However, the effect of peri-transplantation blood transfusion on graft outcome have not been well established. For instance, in a study by Daloul *et al*[4], blood transfusion was not associated with a greater risk of worse graft outcomes[4]; however, Massicotte-Azarniouch *et al*[6] revealed that blood transfusion is associated with a greater risk of graft loss[6]. This is also supported by the findings form a recent study that included more than 1000 recipients, which showed that early blood transfusion post-transplantation didn't lead to de novo DSAs formation[10]. Our study did not find any association between blood transfusion and graft loss or mortality. The link between blood

transfusion and graft or patient loss might be a cofounding factor because patients with advanced allograft dysfunction are commonly anemic. Similarly, sick patients with multiple comorbidities are usually anemic and may require blood transfusions.

HLA molecules in the blood products are known to cause HLA allosensitization for blood transfusion recipients[11-13]. Various strategies have been attempted to avoid HLA allosensitization after blood transfusion, including leuko-reduced (leuko-depleted) blood products[11,14], HLA-selected blood products[15], and autologous blood transfusion[16]. However, the protective effects of these strategies are not well established[11,14-19]. In our study, we decided to account only for leuko-depleted blood products because this is a widely used technique in our blood bank.

The effect of blood transfusion on DSA formation and antibody-mediated rejection are not well understood. Few studies have examined the development of de-novo HLA antibodies after blood transfusions in transplant populations. While some studies found that *de-novo* HLA antibodies and DSAs have a negative impact on the transplant[2,20], other studies have doubted the significance of HLA antibody development in the setting of immunosuppression therapy[3,8,11]. For instance, In Ferrandiz *et al*[2] reported that antibody-mediated rejection occurred in 6% of kidney transplant recipients who required blood transfusion post-surgery compared with 1.4% in a non-transfusion group (P = 0.04)[2]. In contrast, in a study by Jalalonmuhali *et al*[3] involving 699 patients, there was no differences in the development of HLA antibodies or de-novo HLA-DSA and rejection between the transfusion and none transfusion groups[3]. Similarly in our study, the rejection rate in the transfusion group was approximately 5%, with no difference between the two groups.

Multiple factors are associated with an increased risk of poor transplant outcomes after blood transfusion. In a previous prospective observational study, worse transplantation outcomes were linked to the number of transfusion episodes (pre and post-transplantation), regardless of the total number of transfusion units[20]. In another study, poor transplantation outcomes were linked to the number of transfusion units (> 3 units)[9]. In our study, creatinine levels tended to increase toward the end of the follow-up period in the transfusion group, but this finding was not statistically significant.

It is noteworthy that maintenance immunosuppression therapy in studies that found a significant increase in rejection risk after transfusion was cyclosporine-based[2,20] while studies in which the maintenance immunosuppression regimen was tacrolimus-based showed no significant increase in rejection rate between transfusion and non-transfusion groups[3,8]. Our study is consistent with this observation as rejection rate was not significantly different between the two groups in our tacrolimus-based study cohort.

Although blood transfusion after kidney transplantation did not have an impact on patient survival, a cross-sectional study of 1198 liver transplant recipients showed a significant increase in mortality rate in patients who received a large number of blood transfusion units. Average blood transfusion units in expired patients was 5.92 ± 5.91 compared to 3.74 ± 4.23 in alive patients (95%CI: 1.47–2.88)[21].

In this study, there was a tendency toward higher DGF rates in the transfusion group. Although this finding was not statistically significant, it was in line with that of MacIsaac *et al*[9], in which the rate of DGF in transplant patients was up to 26%[9]. Similarly, in a retrospective cohort study on 1258 kidney transplant recipients who were followed for a median of 1405 d, DGF was as high as 41% in a transfusion group *vs* 15% in a non-transfusion group (P < 0.0001)[6]. In a study by Fidler *et al*[20], DGF was associated with a higher risk of combined patient and graft loss at a hazard ratio of 2.5 (1.5-4.5) on univariate analysis; However, this difference disappeared on multivariate analysis. It's difficult to determine whether DGF is a cause, or a result of blood transfusion based on the available literature.

This study has limitations. This was a single-center retrospective cohort study. The lack of routine DSA and allograft biopsy restricted the inclusion of clinically insignificant DSAs and non-apparent rejections. Moreover, our cohort was predominantly males, which limits the generalizability of our findings.

CONCLUSION

Leukodepleted blood transfusion in the peri-transplantation period was not associated with a higher risk of rejection, graft loss, or patient loss. Further investigations are needed to address the link between peri-transplantation blood transfusions, DGF and DSA formation.

ARTICLE HIGHLIGHTS

Research background

Blood transfusion is common during the peri-transplantation period. The incidence of immunological reactions to blood transfusion after kidney transplantation and their consequences on graft outcomes have not been extensively studied.

Research motivation
Blood transfusion during the peri-transplantation period is very common and its safety need to be studied.

Research objectives
To examine the risk of graft rejection and loss in patients who received blood transfusion in the immediate peri-transplantation period.

Research methods
A retrospective cohort study of 105 kidney recipients who received leukodepleted blood transfusions at our center between January 2017 and March 2020.

Research results
Of 105 kidney recipients were divided into transfusion (n = 54) and non-transfusion (n = 51) groups. There were no differences between the two groups in terms of rejection rates, graft loss, or death. There was no significant difference in creatinine level progression between the two groups. A high number of transfused packed red blood cells was significantly associated with increased creatinine levels at the end of the study.

Research conclusions
Leukodepleted blood transfusion was not associated with a higher risk of rejection, graft loss, or death in kidney transplant recipients.

Research perspectives
Leukodepleted blood transfusion in the peri-transplantation period is likely safe.

FOOTNOTES

Author contributions: All the co-authors contributed in data collection, writing, editing, literature review and designing the study.

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Informed consent statement: Signed informed consent wasn't required for this manuscript.

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

Data sharing statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

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REFERENCES

1 **Vanrenterghem Y**, Ponticelli C, Morales JM, Abramowicz D, Baboolal K, Eklund B, Kliem V, Legendre C, Morais Sarmento AL, Vincenti F. Prevalence and management of anemia in renal transplant recipients: a European survey. *Am J Transplant* 2003; **3**: 835-845 [PMID: 12814475 DOI: 10.1034/j.1600-6143.2003.00133.x]

2 **Ferrandiz I**, Congy-Jolivet N, Del Bello A, Debiol B, Trébern-Launay K, Esposito L, Milongo D, Dörr G, Rostaing L, Kamar N. Impact of Early Blood Transfusion After Kidney Transplantation on the Incidence of Donor-Specific Anti-HLA

Antibodies. *Am J Transplant* 2016; **16**: 2661-2669 [PMID: 26998676 DOI: 10.1111/ajt.13795]
3 **Jalalonmuhali M**, Carroll RP, Tsiopelas E, Clayton P, Coates PT. Development of de novo HLA donor specific antibodies (HLA-DSA), HLA antibodies (HLA-Ab) and allograft rejection post blood transfusion in kidney transplant recipients. *Hum Immunol* 2020; **81**: 323-329 [PMID: 32327243 DOI: 10.1016/j.humimm.2020.04.002]
4 **Daloul R**, Braga JR, Diez A, Logan A, Pesavento T. Early Posttransplant Blood Transfusion and Risk for Worse Graft Outcomes. *Kidney Int Rep* 2021; **6**: 986-994 [PMID: 33912748 DOI: 10.1016/j.ekir.2020.12.038]
5 **Scornik JC**, Meier-Kriesche HU. Blood transfusions in organ transplant patients: mechanisms of sensitization and implications for prevention. *Am J Transplant* 2011; **11**: 1785-1791 [PMID: 21883910 DOI: 10.1111/j.1600-6143.2011.03705.x]
6 **Massicotte-Azarniouch D**, Sood MM, Fergusson DA, Chassé M, Tinmouth A, Knoll GA. Blood Transfusion and Adverse Graft-related Events in Kidney Transplant Patients. *Kidney Int Rep* 2021; **6**: 1041-1049 [PMID: 33912754 DOI: 10.1016/j.ekir.2021.01.015]
7 **Richards KM**, Spicer RA, Craig E, Kennedy SE. Prevalence and predictors of blood transfusion after pediatric kidney transplantation. *Pediatr Nephrol* 2018; **33**: 2177-2184 [PMID: 30006835 DOI: 10.1007/s00467-018-4017-0]
8 **Bynum JP**, Zachary A, Ness PM, Luo X, Bagnasco S, King KE, Segev DL, Orandi BJ, Warren DS, Fuller A, Ciappi A, Montgomery R, Tobian AAR. Transfusion of leukoreduced blood products and risk of antibody-mediated rejection of renal allografts. *Transfusion* 2018; **58**: 1951-1957 [PMID: 30171817 DOI: 10.1111/trf.14800]
9 **MacIsaac S**, Ramanakumar AV, Saw C, Naessens V, Saberi N, Cantarovich M, Baran D, Paraskevas S, Tchervenkov J, Chaudhury P, Sandal S. Relative decrease in hemoglobin and outcomes in patients undergoing kidney transplantation surgery: A retrospective cohort study. *Am J Surg* 2021; **222**: 825-831 [PMID: 33707078 DOI: 10.1016/j.amjsurg.2021.03.002]
10 **Jouve T**, Noble J, Naciri-Bennani H, Dard C, Masson D, Fiard G, Malvezzi P, Rostaing L. Early Blood Transfusion After Kidney Transplantation Does Not Lead to dnDSA Development: The BloodIm Study. *Front Immunol* 2022; **13**: 852079 [PMID: 35432350 DOI: 10.3389/fimmu.2022.852079]
11 **Scornik JC**, Ireland JE, Howard RJ, Fennell RS 3rd, Pfaff WW. Role of regular and leukocyte-free blood transfusions in the generation of broad sensitization. *Transplantation* 1984; **38**: 594-598 [PMID: 6390819 DOI: 10.1097/00007890-198412000-00009]
12 **Terasaki PI**, Cai J. Humoral theory of transplantation: further evidence. *Curr Opin Immunol* 2005; **17**: 541-545 [PMID: 16098722 DOI: 10.1016/j.coi.2005.07.018]
13 **Vaidya S**. Synthesis of new and memory HLA antibodies from acute and chronic rejections versus pregnancies and blood transfusions. *Transplant Proc* 2005; **37**: 648-649 [PMID: 15848488 DOI: 10.1016/j.transproceed.2005.01.067]
14 **Karpinski M**, Pochinco D, Dembinski I, Laidlaw W, Zacharias J, Nickerson P. Leukocyte reduction of red blood cell transfusions does not decrease allosensitization rates in potential kidney transplant candidates. *J Am Soc Nephrol* 2004; **15**: 818-824 [PMID: 14978185 DOI: 10.1097/01.asn.0000115399.80913.b1]
15 **Magee BA**, Martin J, Cole MP, Morris KG, Courtney AE. Effects of HLA-matched blood transfusion for patients awaiting renal transplantation. *Transplantation* 2012; **94**: 1111-1116 [PMID: 23111496 DOI: 10.1097/TP.0b013e318271d776]
16 **Sasaki H**, Chikaraishi T, Furuhata S, Tsutsumi H, Miyano S, Nakazawa R, Nakano T, Kudo H, Kitajima K, Takahashi T, Satoh Y, Kimura K. Autologous blood transfusion for kidney transplant recipients. *Transplant Proc* 2008; **40**: 1371-1372 [PMID: 18589108 DOI: 10.1016/j.transproceed.2008.03.136]
17 **van de Watering L**, Hermans J, Witvliet M, Versteegh M, Brand A. HLA and RBC immunization after filtered and buffy coat-depleted blood transfusion in cardiac surgery: a randomized controlled trial. *Transfusion* 2003; **43**: 765-771 [PMID: 12757528 DOI: 10.1046/j.1537-2995.2003.00390.x]
18 **Ohto H**, Nomizu T, Kuroda F, Hoshi T, Rokkaku Y. HLA alloimmunization of surgical patients by transfusion with bedside leukoreduced blood components. *Fukushima J Med Sci* 2003; **49**: 45-54 [PMID: 14603951 DOI: 10.5387/fms.49.45]
19 **Sanfilippo FP**, Bollinger RR, MacQueen JM, Brooks BJ, Koepke JA. A randomized study comparing leukocyte-depleted versus packed red cell transfusions in prospective cadaver renal allograft recipients. *Transfusion* 1985; **25**: 116-119 [PMID: 3885483 DOI: 10.1046/j.1537-2995.1985.25285169200.x]
20 **Fidler S**, Swaminathan R, Lim W, Ferrari P, Witt C, Christiansen FT, D'Orsogna LJ, Irish AB. Peri-operative third party red blood cell transfusion in renal transplantation and the risk of antibody-mediated rejection and graft loss. *Transpl Immunol* 2013; **29**: 22-27 [PMID: 24090807 DOI: 10.1016/j.trim.2013.09.008]
21 **Kasraian L**, Nikeghbalian S, Karimi MH. Blood Product Transfusion in Liver Transplantation and its Impact on Short-term Survival. *Int J Organ Transplant Med* 2018; **9**: 105-111 [PMID: 30487957]

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ORIGINAL ARTICLE

Retrospective Study

Delayed referral for liver transplant evaluation worsens outcomes in chronic liver disease patients requiring inpatient transplant evaluation

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Abstract

BACKGROUND

Indications to refer patients with cirrhosis for liver transplant evaluation (LTE) include hepatic decompensation or a model for end stage liver disease (MELD-Na) score ≥ 15. Few studies have evaluated how delaying referral beyond these criteria affects patient outcomes.

AIM

To evaluate clinical characteristics of patients undergoing inpatient LTE and to assess the effects of delayed LTE on patient outcomes (death, transplantation).

METHODS

This is a single center retrospective cohort study assessing all patients undergoing inpatient LTE (n = 159) at a large quaternary care and liver transplant center between 10/23/2017-7/31/2021. Delayed referral was defined as having prior indication (decompensation, MELD-Na ≥ 15) for LTE without referral. Early referral was defined as referrals made within 3 mo of having an indication based on practice guidelines. Logistic regression and Cox Hazard Regression were used to evaluate the relationship between delayed referral and patient outcomes.

RESULTS

Many patients who require expedited inpatient LTE had delayed referrals. Misconceptions regarding transplant candidacy were a leading cause of delayed referral. Ultimately, delayed referrals negatively affected overall patient outcome and an independent predictor of both death and not receiving a transplant. Delayed referral was associated with a 2.5 hazard risk of death.

CONCLUSION
Beyond initial access to an liver transplant (LT) center, delaying LTE increases risk of death and reduces risk of LT in patients with chronic liver disease. There is substantial opportunity to increase the percentage of patients undergoing LTE when first clinically indicated. It is crucial for providers to remain informed about the latest guidelines on liver transplant candidacy and the transplant referral process.

Key Words: Liver transplantation; Liver transplant evaluation; Liver transplant referral; Patient access; Equity; Patient outcomes

Core Tip: There are many system and provider-level barriers to liver transplant evaluation. However, the effect of late transplant evaluations remains unclear. We demonstrate delayed liver transplant evaluation is independently associated with death prior to transplant in patients undergoing liver transplant evaluation.

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INTRODUCTION

The global impact of chronic liver disease is increasing. Liver transplantation is the only definitive treatment for decompensated cirrhosis. Guideline recommended indications to refer patients with cirrhosis for liver transplant evaluation (LTE) include hepatic decompensation or a Model for End Stage Liver Disease score (MELD) ≥ 15[1,2]. While the progression cirrhosis usually occurs over multiple years [3], many patients go un-diagnosed prior to overt hepatic decompensation[3,4]. Thus, many patients have progressed disease when they begin receiving care[5]. Further delays entering the transplant care pathway can result in delayed referral and need for expedited LTE in the setting of acute decompensation. While there is emerging literature on what qualifies as late referral or urgent transplant evaluation[6,7], there is little data regarding the influence of delayed transplant evaluation on outcomes. In this retrospective analysis, we evaluate clinical characteristics of patients undergoing inpatient LTE to identify risk factors for delayed LTE and assess the effect of delayed LTE on patient outcomes.

MATERIALS AND METHODS

Study design and definitions

This is a single center retrospective cohort study analyzing patients undergoing LTE at a large quaternary care and liver transplant center. Medical records were obtained for patients with a transplant evaluation encounter between October 2017 and July 2021 using our center's liver transplant database. Patients with diagnosis of cirrhosis who underwent LTE for chronic liver disease (CLD) as an inpatient in this time period were identified as potential subjects. Patients were excluded if they: (1) Were undergoing re-transplantation; (2) being evaluated for acute liver failure; and (3) were completing evaluation in the outpatient setting. Patients with hepatocellular carcinoma were also excluded due to differences in candidacy and referral criteria[8]. Study data were collected and managed using a 255-field form with an electronic data capture tool hosted at UMass Chan Medical School. Research Electronic Data Capture (REDCap) is a secure, web-based software platform designed to support data capture for research studies, providing: (1) An intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources[9,10].

All clinical and laboratory data including Model for End Stage Liver Disease -Sodium (MELD-Na) score were collected at the time of LTE. Available clinical documentation collected during LTE was closely reviewed and evaluated. Cirrhosis etiologies included chronic alcohol (ETOH) associated liver disease, non-alcoholic steatohepatitis (NASH), Hepatitis C (HCV), cholestatic liver disease (primary sclerosing cholangitis, primary biliary cirrhosis), inherited/genetic disease (hereditary hemochromatosis, alpha-1 anti-trypsin deficiency), and cryptogenic/other. Clinical decompensations included hepatic encephalopathy, jaundice, ascites, hepato-renal syndrome, spontaneous bacterial peritonitis (SBP), and variceal bleed[2,11]. Patients were considered to have a cardiac diagnosis if their past medical history included diagnosis or treatment of a cardiac arrhythmia, coronary artery disease, or cardiomyopathy with heart failure. Malnutrition was diagnosed by registered dieticians on the multidisciplinary transplant team using the ASPEN criteria[12]. Cause of death was recorded when available.

Transplant evaluation indications were defined using the American Association for the Study of Liver Disease (AASLD) guidelines and included: (1) Hepatic decompensation OR; and (2) MELD ≥ 15 AND (3) absence of active alcohol or illicit drug use[13]. Time for sobriety required for evaluation at our institution is 3 mo. Subjects were dichotomized to either "delayed referral" or "early referral." "Delayed referral" indicated that subjects had an indication for transplant evaluation but were not referred within three months, while "early referral" meant that subjects were referred within three months of having an indication for transplant evaluation. Three months was chosen as this is the timeline of clinical improvement in patients expected to recover once cirrhosis trigger is withdrawn (*e.g.*, alcohol cessation) [14]. In terms of transplant outcomes, there are multiple potential outcomes of LTE and many of these can occur interchangeably. For example, patients can be approved but not yet listed, or listed but inactive on the wait list. For analytical simplicity, our selected outcomes included: not approved, died on waitlist, off list, on list, and transplanted. For statistical analysis, subjects were further dichotomized as "approved" or "not approved, "dead" or "not dead," and "transplanted" or "not transplanted" at the time of data collection.

Endpoints and data analysis

Normally distributed continuous data is reported as "mean (standard deviation)" and were compared with two-sample *t*-test. Non-normally distributed continuous data is reported as "median [inter-quartile range]" and were compared using Wilcoxon rank sum tests. Categorical variables are reported as "percentage" and were compared using pair-wise z testing. Correlations are reported using Pearson's bivariate correlation coefficient. Associations are reported as odds ratios with 95% confidence intervals and were evaluated with logistic regression.

Demographic, psychosocial, and clinical variables were compared between delayed and early referral (Tables 1-3). Comparisons were also made between: (1) Dead and not dead; and (2) transplanted and not transplanted within the delayed referral group to identify potential markers of mortality within this cohort (Supplementary Table 1).

Backward logistic regression modeling was used to identify risk factors for delayed referral with the following starting variables: Age, race, sex, ethnicity, time since diagnosis (months), malnutrition (as defined by ASPEN guidelines), depression, trauma history, number of prior hospitalizations, sobriety period, smoking history, lives with family, married/stable partner, stable housing, employed within 1 year, military service history, non-English first language, education, proximity to transplant center, regular outside gastroenterologist, regular outpatient labs.

Backward logistic regression was also used to evaluate if delayed referral was an independent predictor of transplant status and death amongst other relevant clinical markers (for full list see Tables 4 and 5, respectively). We created a multi-variable logistic regression model utilizing this data and other variables known to affect outcomes in the liver transplantation pathway including but not limited to sex [15], age[16], height[17], acute on chronic liver failure (ACLF) grade[18], and laboratory markers that comprise MELD-Na and represent hepatic function. The final model was created to optimize goodness of fit using the Hosmer and Lemeshow test.

Cox proportional hazard regression modeling was used to evaluate the impact of delayed referral on risk of dead in patients undergoing inpatient LTE. Participants were censored on the day of transplant and the last known well if lost to follow up. An unadjusted model was performed using "delayed" as the sole independent variable; the adjusted model incorporated the following additional variables: age, sex, ethnicity, etiology, MELD-Na, and blood type. Data is reported as hazard ratios (HRs) with 95% confidence intervals.

The threshold for statistical significance was set at $P < 0.05$. For all backward logistic regression model threshold to enter was 0.05 and threshold to remove was 0.10. All statistical analysis was conducted using SPSS version 29. This study was reviewed and approved by the institutional review board at our medical center.

RESULTS

We identified 160 patients undergoing inpatient LTE for cirrhosis (49% delayed referral and 51% early

Table 1 Baseline and demographics, %

Characteristic	Delayed referral (*n* = 78)	Early referral (*n* = 82)	*P* value
Portion of sample	49	51	-
Age (yr)	59 (10)	57 (9)	0.19
Distance to center (miles)	43.0 [20.5–59.5]	43.5 [19.3–67.3]	0.74
Time since diagnosis (mo)	30 [12.3–60]	11 [3.75–55.5]	< 0.01
Gender			0.59
Female	39.7	43.9	
Male	60.3	56.1	
Race			0.49
Asian	1.3	3.7	
Black or African American	1.3	1.2	
Other/Unknown	17.9	12.2	
White	79.5	82.9	
Ethnicity			0.11
Hispanic/other	19.2	9.8	
Non-Hispanic	80.8	90.1	
Etiology			0.88
Autoimmune	5.1	4.9	
Alcohol	43.6	53.7	
Cryptogenic/cholestatic	5.1	6.1	
Genetic	7.7	4.9	
Hepatitis C	11.5	9.8	
NASH	26.9	20.7	
Blood type			0.36
A	37.2	27.2	
B	16.7	19.8	
AB	1.3	4.9	
O	44.9	48.1	

Demographic and clinical data for delayed referral (left) versus early referral (right) patients undergoing inpatient liver transplant evaluation. Data reported as percentages of total group for categorical data; as average (standard deviation) for normally distributed continuous data, and as median [IQR] for non-normally distributed continuous data. NASH: Non-alcoholic steatohepatitis.

referral). Participants were predominately a male, white, and non-Hispanic with a mean age of 58 +/- 10. Over half of subjects had a high school level education or less (50.7% early *vs* 62.7% delayed, P = 0.14). The most common etiologies of cirrhosis were ETOH, NASH, and HCV. Subjects with delayed referral had been diagnosed with liver disease more months on average than those with early referral (P < 0.01). Subjects with early referral were diagnosed within the preceding year more often than subjects with delayed referral (50.7% *vs* 30.8%, P = 0.02) (See Table 1 for summary of demographics).

Laboratory evaluation collected at time of LTE did not differ between groups (Supplementary Table 2). Most subjects had MELD-Na scores between 25-34 with an average score of 27 in each group (P = 0.91). A similar proportion of subjects had Grade 1, Grade 2, and Grade 3 ACLF (P = 0.56). The mean number clinical decompensations present during LTE was 4 and the number decompensations positively correlated with MELD-Na score (r(157) = 0.390, P < 0.01). One third of subjects were diagnosed with malnutrition during LTE (23.1% delayed referral *vs* 43.9% early referral, $P \leq 0.001$). Infection was recorded 40% of patients (42.3% delayed *vs* 35.4% early, P = 0.39) and blood pressure support occurred in 30% of patients (34.6% delayed *vs* 26.8% early, P = 0.29). About half the subjects in each group (48%) required an intensive care unit (ICU) stay during LTE with no differences in days of ICU stay (P = 0.44). Trans-jugular intrahepatic portosystemic shunt during admission was 2.3 times

Table 2 Liver transplant evaluation data, %

	Delayed	Early	*P* value
Transferred to center	48.7	51.2	0.75
MELD-Na (points)	27.2 (7)	27.0 (9)	0.87
TIPS placed	15.4	7.3	0.22
ICU stay	51.3	43.9	0.35
ICU d (#)	10 (9)	8 (7)	0.44
Pressor support	34.6	26.8	0.29
Declined for LT listing	17.9	15.9	0.72
Reasons declined			
Psychosocial	30.0	12.5	0.38
Medical	20.0	25.0	
Death	30.0	12.5	
Other	20.0	50.0	
Decompensations			
Ascites	94.9	96.3	0.65
Jaundice	64.1	72.0	0.29
EVB	21.8	24.4	0.70
HE	70.7	70.5	0.98
HRS	59.8	62.8	0.69
HHT	21.8	14.6	0.24
SBP	21.8	18.3	0.58
ACLF grade			
Grade 1	34.6	42.7	0.56
Grade 2	50.0	42.7	
Grade 3	15.4	14.6	
ACLF bilirubin			
< 15 mg/dL	82.1	76.8	0.28
15-25 mg/dL	9.0	17.1	
> 25 mg/dL	9.0	6.1	
ACLF INR			
< 1.8	62.8	62.2	0.78
1.8-2.5	28.2	25.6	
> 2.5	9	12.2	
ACLF lactate			
< 1.5 mmol/L	73.1	80.5	0.16
1.5-2.5 mmol/L	15.4	6.1	
> 2.5 mmol/L	11.5	13.4	
ACLF creatinine			
< 0.7 mg/dL	7.3	7.3	0.64
0.7-1.5 mg/dL	32.9	32.9	
> 1.5 mg/dL	52.6	59.8	

Clinical data from index admission and liver transplant evaluation. Data reported as percentages of group for categorical data; as average (standard deviation) for normally distributed continuous data. Comparisons were made using students T tests and comparison of proportions test. ACLF: Acute on chronic liver failure; LT: Liver transplant; ICU: Intensive care unit; MELD: Model for end stage liver disease; TIPS: Trans-jugular intrahepatic portosystemic shunt; EVB: Esophagogastric variceal bleeding; HRS: Hepatorenal syndrome; HHT: Hepatic hydrothorax; SBP: Spontaneous bacterial peritonitis; LTE: Liver transplant evaluation; INR: International normalized ratio; HE: Hepatic encephalopathy.

more common in delayed referrals (95%CI: 0.92-8.25, P = 0.11). Most subjects (83%) were accepted as candidates for liver transplant with no differences between groups (P = 0.78). However, it took 6-8 d longer to complete LTE for subjects with delayed referral compared to early referral (P = 0.07) (See Table 2 for summary of clinical data).

Pre-LTE: Identifying risk factors for delayed referral

Psychosocial factors: A similar proportion of participants resided with family (P = 0.75) and had stable housing in each group (P = 0.68). Interestingly more subjects with delayed referral had an established partner compared to early referral (P = 0.05). Slightly more subjects with a delayed referral reported English as a second language, though this failed to meet statistical significance 20.5% *vs* 13.6%, P = 0.24). In terms of education, almost two thirds of the delayed referral group had a high school education or less compared to one half of the early referral group (P = 0.14) Employment within the last year (P < 0.01) and having an identifiable source of income (P = 0.01) were more common in subjects with early referral. Smoking history (P = 0.15) and alcohol use history was similar in each group (P = 0.12). However, for those patients who reported prior regular alcohol consumption, early referral subjects were closer to their last drink compared to delayed referral (P < 0.01). Specifically, more patients in the early group were evaluated with sobriety of 3-6 mo (39.3% early *vs* 22.4% delayed, P = 0.05) while more patents in the delayed group were referred with sobriety of 1-2 years (30.6% delayed *vs* 8.2% early, P < 0.01) (See Table 3 for summary of psychosocial factors).

Clinical care- outpatient providers, medication, and gastrointestinal provider notes: There were no significant differences in pre-LTE hepatic decompensations between groups (Table 3). Average body mass index was slightly higher in missed group (32.5 +/-10 *vs* 30.1 +/- 8; P = 0.09). Malnutrition was more common amongst early referrals and was associated with a 2/3 Lower chance of having a delayed referral (OR: 0.34, CI: 0.14-0.78, P = 0.01). The number of patients receiving routine medications for ascites and hepatic encephalopathy when applicable based on decompensation history did not differ between groups. Interestingly, of the 35.6% of patients with known diabetes, insulin use was more common in delayed referrals, but not to a statistically significant degree (33.3% delayed *vs* 16.7%, P = 0.15). Of patients with regular laboratory evaluation available, previously documented hypercoagulability and transaminitis was noted between groups; hypoalbuminemia was slightly more common amongst those with delayed referral (Table 3). Considering only patients with outside documentation from gastroenterologist, there were no differences in proportion of patients with low albumin, elevated international normalized ratio, or abnormal liver enzymes between early and delayed referral (data not shown) (See Table 3 for summary of outpatient care factors).

Risk factors for delayed referrals: Backward logistic regression model using 20 psychosocial or demographical variables identified female sex and trauma history to be predictors of delayed referral while malnutrition, work within the prior year, and prior smoking history were predictors of early referral (Supplementary Table 3). The most common theme identified in clinical documentation leading to delayed referral was poor understanding about indications for transplant referral, which was identified in 20% of the subjects with delayed referrals. Specifically, outpatient providers cited inaccurate contraindications to transplant, such as age or weight, or incorrect sobriety periods required for referral. Other frequently identified themes included failure to obtain or calculate MELD-Na labs (10%), lack of care continuity (18%), insurance or financial barriers (9%), or patient reluctance to pursue transplant (10%). However, one in three patients had no clear reason for lack of referral.

Effects of referral time on patient outcomes

Primary outcome measures differed between those with delayed compared to early referral. Delayed referrals were transplanted less often (28% *vs* 48%) and died prior to transplant more often those with early referral (42% *vs* 21%). Predictors of transplant identified on backward logistic regression include age, ACLF grade, platelets, neutrophil-lymphocyte ratio, albumin, sex, months since diagnosis, weight, blood type, and delayed referral. On a multivariable regression model created using clinical data optimized for goodness of fit, early referral was associated with 2.3 increased odds of receiving a transplant (95%CI: 1.02-4.57; P = 0.045) (Supplementary Table 4). Of those transplanted, over 80% of each group was one year post transplant at the time of data collection, and about 50% were two years post-transplant. There were no differences in survival at either the one-year (P = 0.650), or two-year (P = 1.000) time points (data not shown).

Table 3 Pre-transplant clinical and demographic factors, %

	Delayed	Early	*P* value
Education			0.14
Highschool or less	62.6	50.7	
College degree or more	14.7	23.4	
Substance use			
Smoking history	55.1	57.3	0.15
Drinking history	62.8	74.3	0.12
Sobriety period			< 0.01
< 6 mo	22.4	59.0	
6 mo – 2 yrs	53.0	26.2	
> 2 yrs	23.6	14.8	
Psychosocial factors			
Depression history	39.7	28.0	0.12
Trauma history	9.0	2.4	0.07
Public insurance	50.0	50.0	1.00
Non-English first language	20.5	13.6	0.24
Lives with family	78.2	80.2	0.75
Married/stable partner	67.5	52.4	0.05
Unstable housing	6.4	4.9	0.68
Military service history	3.8	8.6	0.21
Worked within 1 mo	7.7	22.2	<0.01
Worked within 1 yr	24.4	49.4	<0.01
Clinical care			
Outpatient GI documentation	83.3	78.0%	
Ascites on diuretics	90.7	90.3	0.94
Ascites with regular paracentesis	32.0	25.0	0.35
On lactulose/rifaximin	85.0	90.5	0.39
Midodrine	42.9	46.0	0.81
Regular labs	*n* = 59	*n* = 40	
Low albumin	89.8	77.5	0.09
High ALT/AST	93.2	87.5	0.31
High INR	84.7	72.5	0.14
Prior decompensations			
Ascites	96.2	87.8	0.05
Jaundice	66.7	68.3	0.83
Variceal bleed	35.9	29.3	0.37
Hepatic encephalopathy	78.2	64.2	0.06
Hepatorenal syndrome	35.9	31.7	0.58
Hepatic hydrothorax	11.5	9.8	0.72
Spontaneous bacterial peritonitis	21.8	24.4	0.68

Comparison of psychosocial and clinical data from prior to liver transplant evaluation (LTE) in patients with delayed compared to early LTE. Psychiatric

comorbidities including depression and trauma occurred more in delayed LTE. Working history was strongly associated with timely referral. Data reported as percentages of group for categorical data; as average (standard deviation) for normally distributed continuous data. Comparisons were made using students T tests and comparison of proportions test. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GI: Gastrointestinal; INR: International normalized ratio.

Predictors of death on backward logistic regression include Age, hematocrit, neutrophil to lymphocyte ratio, albumin, months since diagnosis, weight, decompensation number, and delayed referral (Table 5). Within the delayed LTE cohort patients who died were older (P = 0.04), had an outpatient gastrointestinal (GI) provider less often (P = 0.03), had SBP more often (P = 0.04) and required an ICU stay and blood pressure support more often (< 0.01) (Supplementary Table 1). On univariable Cox Regression, the HR of death was 2.2 (95%CI: 1.2–2.9) in for delayed referral compared to early referral over average follow up period of 269 d. When adjusting for age, sex, ethnicity etiology, and MELD-Na, the HR for increased to 2.5 (95%CI: 1.3–4.7) for delayed referral compared to early referral (Figure 1).

DISCUSSION

Our study assessed clinical characteristics of patients with decompensated cirrhosis undergoing inpatient LTE and examined the effect of delayed referral on patient outcomes. We observed that a significant proportion of patients could have been referred earlier and built on this notion by demonstrated delayed LTE was associated with worse patient outcomes in patients already undergoing urgent LTE. These relationships persisted when controlling for key variables and backward logistic regression identified delayed referral as an independent risk factor for death and not receiving a liver transplant. We identified risk factors for death within the patients who had a delayed LTE to identify the most vulnerable cohorts and found death to be most common in patients with delayed referral and (1) Had no regular documentation from an outside GI provider; and (2) were critically ill in the ICU with SBP and requiring blood pressor support.

The high proportion of patients with delayed referrals is consistent with previous studies that report poor adherence to liver transplant referral guidelines in patients with cirrhosis[19]. We sought to identify demographical risk factors for delayed LTE but observed no differences in basic demographics between cohorts in our study. Patients in our study resided within similar proximity to the transplant center, which is inconsistent with previous literature reporting that increased distance from a transplant site is a barrier to transplant related care[20]. However, we believe this suggests distance may be more related to the ability to attend health care appointments and not play a role in the referral decision itself. For example, a recent study that identified LTE within 30 d of LT referral was associated with better outcomes and that distance from the transplant center reduced odds of completing LTE within the 30-d window[21]. While we anticipated group differences in health insurance[6,22,23], we observed approximately 50% of each cohort having publicly funding insurance. It is possible that this is due to the robust public health and insurance funding in Massachusetts.

There were notable psychosocial differences between cohorts including education and employment status. Lower education attainment and lack of employment within the preceding year were more common in patients with delayed referral. This data supports that lower degrees of financial stability and health literacy may act as barriers to early evaluation. Identifying patients with limited health literacy could reduce the number of delayed evaluations by improving patients' understanding of their disease[24]. In addition, we found that being married or having a stable partner was more common in patients with delayed referrals but did not affect transplant or death. We found this point interesting as typically psychosocial support is associated with improved outcomes in the transplant pathway; it remains unclear the role of having a spouse or stable partner on referral and care seeking in this population.

We utilized clinical history and provider written medical documentation to inform understanding of barriers to access to liver transplantation referral and evaluation. First, specific hepatic decompensations did not differ between groups, which is consistent with recent research reporting that clinical manifestations of CLD may be poor markers of the timeliness of transplant evaluation[7]. Conversely, malnutrition was protective against of delayed evaluation which may suggest that frailty is a conspicuous manifestation of CLD that is more readily recognized compared to more obscure manifestations of CLD, such as mild hepatic encephalopathy, or that physicians associate frailty with poor outcomes and are more likely to refer. Differences in time from diagnosis to transplant evaluation may reflect this as well, as data suggests providers have different thresholds for referral. Conversely it may be explained by lack of care continuity amongst patients with delayed referrals. Care continuity may reflect poor understanding of disease severity, and it is possible that targeting patient understanding of liver disease may improve the follow up rate in this cohort.

Table 4 Predictors of transplant

	Initial multivariate regression				Backward logistic regression			
	Wald	*P* value	OR	95%CI	Wald	*P* value	OR	95%CI
Age (yr)	3.45	0.06	0.94	0.9-1.0	4.62	0.03	0.95	0.9-1.0
Education (HS)	2.41	0.12	1.49	0.9-2.5	-	-	-	-
ICU stay (+)	1.12	0.29	0.38	0.1-2.3	-	-	-	-
ACLF grade (G3)	2.67	0.10	2.76	0.8-9.3	4.75	0.03	2.13	1.1-4.2
MELD (points)	0.58	0.45	1.07	0.9-1.3	-	-	-	-
Creatinine (mg/dL)	0.08	0.78	0.90	0.4-1.9	-	-	-	-
Sodium (mmol/L)	1.28	0.26	0.90	0.8-1.0	-	-	-	-
Bilirubin (mg/dL)	1.06	0.30	1.05	1.1-1.1	-	-	-	-
INR	1.28	0.26	0.42	0.1-1.9	-	-	-	-
WBC ($\times 10^9$/L)	0.03	0.86	0.99	0.8-1.2	-	-	-	-
Hematocrit (%)	1.34	0.25	0.94	0.9-1.0	-	-	-	-
Platelets ($\times 10^9$/L)	1.73	0.19	0.99	1.0-1.0	5.50	0.02	0.99	1.0-1.0
N-L ratio	3.65	0.06	0.89	0.8-1.0	5.15	0.02	0.90	0.8-1.0
Albumin (g/dL)	6.79	< 0.01	3.58	1.4-9.4	9.04	< 0.01	3.32	1.5-7.3
Malnutrition (+)	0.30	0.59	1.39	0.4-4.6	-	-	-	-
Cardiac dx (+)	0.06	0.82	0.83	0.2-3.9	-	-	-	-
Sex (Male)	7.29	< 0.01	14.8	2.1-105	3.02	0.08	2.38	0.9-6.3
Race (White)	1.24	0.27	0.42	0.1-1.9	-	-	-	-
Depression (+)	4.17	0.04	4.24	1.1-17	-	-	-	-
Time since dx (mo)	2.44	0.12	1.01	1.0-1.0	2.69	0.10	1.01	1.0-1.0
Pressor need (+)	0.28	0.60	0.56	0.1-4.8	-	-	-	-
Height (cm)	2.37	0.12	0.94	0.9-1.0	-	-	-	-
Weight (kg)	1.22	0.27	0.99	1.0-1.0	4.72	0.03	0.98	1.0-1.0
Transferred (+)	0.00	1.0	1.00	0.3-3.5	-	-	-	-
Refer to LTE (d)	0.04	0.85	1.00	1.0-1.0	-	-	-	-
Delayed referral (+)	2.67	0.10	0.32	0.1-1.2	3.51	0.06	0.40	0.2-1.0
Decompensations (#)	0.11	0.73	0.91	0.5-1.6	-	-	-	-
Etiology (ETOH)	0.00	0.98	1.00	0.7-1.5	-	-	-	-
TIPS (+)	1.36	0.24	0.52	0.2-1.6	-	-	-	-
Blood type (A)	2.50	0.11	0.62	0.3-1.1	2.71	0.01	0.65	0.4-1.1
Constant	3.26	0.07	5000	-	0.745	0.38	6.54	-

Multivariable logistic model with backward logistic regression to identify predictors of receiving transplant in patients undergoing inpatient liver transplant evaluation (LTE). Starting with 30 potential variables that may predict hepatic encephalopathy, backward regression identified 10 potential independent predictors for transplant including age, ACLF grade, platelets, N-L ratio, serum albumin, sex, time since diagnosis, weight blood type, and having a delayed LTE. Regression complete din SPSS using backward regression conditional model; probability to enter 0.05 and probability to remove 0.10. Units recorded in parenthesis for continuous variables; reference variable recorded in parenthesis for categorical variables where "+" indicates the variable is present in the patient. ACLF: Acute on chronic liver failure; ICU: Intensive care unit; WBC: White blood cell count; MELD: Model for end stage liver disease; INR: International normalized ratio; N-L ratio: Neutrophil to lymphocyte ratio; dx: Diagnosis; TIPS: Trans-jugular intrahepatic portosystemic shunt.

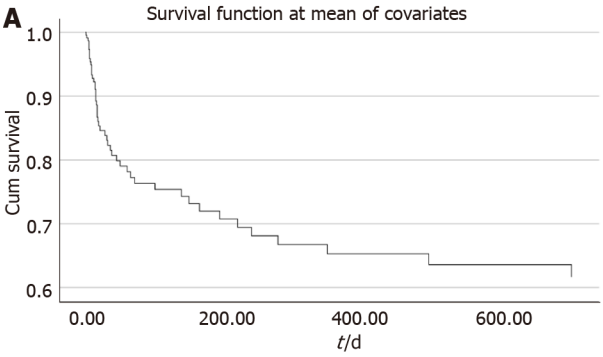
Documentation for 1 in 5 patients with delayed referral included misconceptions about candidacy and referenced inaccurate contraindications to transplant. This was especially evident in subjects with alcohol use disorder, where providers noted longer sobriety periods than truly required to enter the transplant care pathway. These findings are consistent with literature showing provider level factors

Table 5 Predictors of death

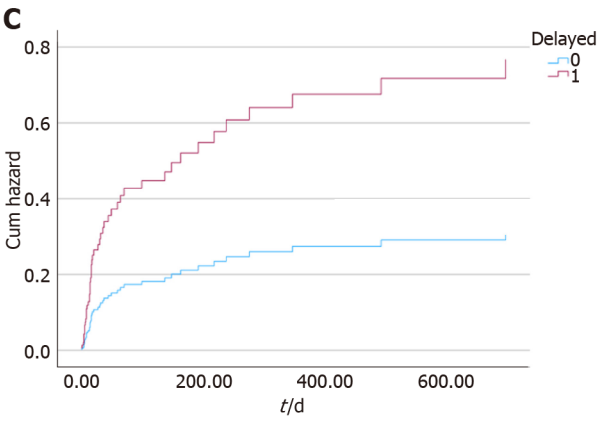
	Initial multivariate regression				Backward logistic regression			
	Wald	*P* value	OR	95%CI	Wald	*P* value	OR	95%CI
Age (yrs)	5.51	0.02	1.12	1.0-1.2	6.24	0.01	1.10	1.0-1.1
Education (HS)	0.72	0.40	0.75	0.4-1.5	-	-	-	-
ICU stay (+)	0.03	0.86	0.84	0.1-5.8	-	-	-	-
ACLF grade (G3)	0.06	0.81	1.19	0.3-4.9	-	-	-	-
MELD (points)	4.58	0.03	0.73	0.5-1.0	-	-	-	-
Creatinine (mg/dL)	2.85	0.09	2.46	0.9-7.0	-	-	-	-
Sodium (mmol/L)	5.25	0.02	0.82	0.7-1.0	-	-	-	-
Bilirubin (mg/dL)	0.04	0.84	0.99	0.9-1.1	-	-	-	-
INR	3.06	0.08	8.85	0.8-101	-	-	-	-
WBC ($\times 10^9$/L)	0.02	0.88	1.02	0.8-1.3	-	-	-	-
Hematocrit (%)	1.57	0.21	1.11	0.9-1.3	2.67	0.10	1.09	1.0-1.2
Platelets ($\times 10^9$/L)	0.09	0.76	1.00	1.0-1.0	-	-	-	-
N-L ratio	5.90	0.02	1.22	1.0-1.4	5.47	0.02	1.11	1.0-1.2
Albumin (g/dL)	5.07	0.02	0.18	0.0-0.8	2.67	0.10	0.49	0.2-1.2
Malnutrition (+)	0.04	0.85	0.84	0.1-5.1	-	-	-	-
Cardiac dx (+)	1.71	0.19	3.53	0.5-23	-	-	-	-
Sex (Male)	4.43	0.04	0.08	0.0-0.8	-	-	-	-
Race (White)	1.06	0.30	0.32	0.0-2.8	-	-	-	-
Depression (+)	1.72	0.19	3.07	0.6-16	-	-	-	-
Time since dx (mo)	5.84	0.02	0.97	1.0-1.0	3.52	0.06	0.99	1.0-1.0
Pressor need (+)	0.36	0.55	0.44	0.0-6.5	-	-	-	-
Height (cm)	4.04	0.05	1.13	1.0-1.3	-	-	-	-
Weight (kg)	3.83	0.05	1.04	1.0-1.1	7.01	< 0.01	1.02	1.0-1.0
Transferred (+)	1.53	0.22	0.36	0.1-1.8	-	-	-	-
Refer to LTE (d)	0.65	0.42	0.99	1.0-1.0	-	-	-	-
Delayed referral (+)	6.75	0.01	8.40	1.7- 42	7.27	< 0.01	4.51	1.5-14
Decompensations (#)	3.61	0.06	2.08	1.0-4.4	6.33	0.01	1.49	1.1-2.0
Etiology (ETOH)	1.22	0.27	1.30	0.8-2.1	-	-	-	-
Blood type (A)	4.98	0.03	3.01	1.1-7.9	-	-	-	-
TIPS (+)	0.44	0.51	1.45	0.5-4.4	-	-	-	-
Constant	0.09	0.76	0.02	-	0.75	0.38	6.54	-

Multivariable logistic model with backward logistic regression to identify predictors of receiving transplant in patients undergoing inpatient liver transplant evaluation (LTE). Starting with 30 potential variables that may predict hepatic encephalopathy, backward regression identified 8 potential independent predictors for transplant including age, Hematocrit, N-L ratio, serum albumin, sex, time since diagnosis, weight, number of decompensations, and having a delayed LTE. Regression complete din SPSS using backward regression conditional model; probability to enter 0.05 and probability to remove 0.10. Units recorded in parenthesis for continuous variables; reference variable recorded in parenthesis for categorical variables where "+" indicates the variable is present in the patient. ACLF: Acute on chronic liver failure; ICU: Intensive care unit; WBC: White blood cell count; MELD: Model for end stage liver disease; INR: International normalized ratio; N-L ratio: Neutrophil to lymphocyte ratio; dx: Diagnosis; TIPS: Trans-jugular intrahepatic portosystemic shunt.

affect LT access[19,25] and may suggest bias has a negative impact on referral. Patients in our study who were referred within the first year of sobriety had improved outcomes. Patients in the delayed evaluation were more likely to have 1-2 years of sobriety than early referral. Patients who have continued hepatic decompensation after 3 mo of sobriety are less likely to recompensate and our data



B	Exp (B)	95%CI	*P* value
***Delayed**	2.46	1.30-4.66	0.005
***Age**	1.04	1.01-1.08	0.017
Ethnicity	1.36	0.58-3.21	0.479
Sex	1.20	0.64-2.26	0.576
***MELD**	1.07	1.03-1.12	0.002
Blood type	1.21	0.87-1.67	0.263
Etiology			0.601
ETOH	0.62	0.12-3.21	0.565
NASH	0.88	0.17-4.64	0.876
HCV	1.25	0.21-7.42	0.804
AIH	2.18	0.17-27.8	0.548
Genetic	1.60	0.21-12.0	0.647
Cholestatic	0.74	0.11-5.10	0.756



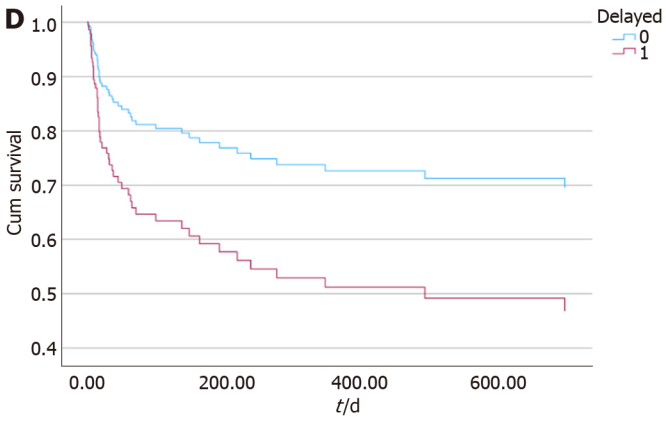


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Figure 1 Multivariable Cox regression model assessing the effect of delayed referral on death when accounting for age, ethnicity, patient sex, MELD score, and disease etiology. Patients were censored if lost to follow up or at the time of transplant. A: Total survival curve for patients undergoing inpatient liver transplant evaluation (LTE); B: Cox hazard regression output with hazard ratio (HR) with 95% CI and p values are reported from multivariate analysis. (*) indicates variables that are significant with $P < 0.05$; C: Hazard function plotted for risk of death since time of LTE start where "0" is early LTE and "1" is delayed LTE; D: Cumulative survival function since time of LTE start where "0" is early LTE and "1" is delayed LTE. Delayed LTE was associated with increased mortality amongst patients undergoing inpatient LTE.

supports the growing trend for early LTE referral in patients with alcohol liver disease. Our results demonstrate that providers need have increased awareness of patients who have not been referred to a transplant center at this point in sobriety as they may be at increased risk of precipitous decompensation and require urgent LTE. Beyond alcohol, reducing bias toward cirrhosis in general may help as almost one-third of patients did not have an identifiable reason for delayed referral. Further research is needed to characterize referral patterns for LTE. While nationwide and database research can help improve this, there is also the need for regionally based research given practices and attitudes likely vary by geographic location.

We believe our paper has multiple strengths. To our knowledge, this is the first study stratifying inpatient liver transplant candidates based on presence or absence of previously missed opportunities for transplant evaluation and compared outcomes. Study staff had full access to the electronic medical record and were able to conduct a comprehensive chart review that included both discrete/categorical data and more qualitative information from clinical documentation. This offers advantages compared to large databases studies which can analyze large amounts of data, but do not consider the clinical context in which medical decisions are taken. Statistically, we used a variety of modeling methods and used backward logistic regression to demonstrate delayed LTE is an independent predictor of death. This was further supported with Cox regression to demonstrate the strength of this relationship over time.

There are also limitations to our study. Its retrospective and single center nature with a small sample limits the elimination of biases and statistical analysis. Our study population is predominantly white and non-Hispanic which limited our ability to control for the effect of race and ethnicity[26] without disrupting the statistical strength of our models. In effort to account for this, we incorporated language status into the model which improved overall representation of our data. This study included evaluations performed during the SARS-2 Coronavirus pandemic, which universally impacted organ transplantation. However, overall patient outcomes did not differ before and after the onset of the pandemic in our study population (data not shown).

In this paper we build on existing literature that demonstrates many patients experience delays in access to LTE care and demonstrate that delayed referral for LTE has a negative impact on patient survival and transplant outcomes even in patients receiving expedited and high-level care at a tertiary

liver transplant center. There is substantial opportunity to increase the percentage of patients undergoing transplant evaluation when first clinically indicated. Providers should aim to consistently adhering to referral guidelines to limit provider bias and allow determinations about candidacy to be made by dedicated transplant center. For this to occur, providers need to remain up to date on guidelines regarding liver transplant candidacy, the transplant referral process, and routine work up in patients with CLD. Efforts to increase awareness of this information is critical in general gastroenterology and primary care providers. In future studies, we hope to strengthen the understanding of these phenomena by studying patients who are evaluated through routine outpatient visits.

CONCLUSION

Delayed LTE negatively impacts patient care. There are both provider and patient level factors that contribute to delayed LTE and may act as actionable targets to improve patient outcomes.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation is the only definitive treatment for end stage liver disease, which has an increasing prevalence world wide. Despite this, there are many barriers to accessing liver transplant related care.

Research motivation

Barriers to timely liver transplant evaluation (LTE) are poorly understood and likely differ by geographic location.

Research objectives

We sought to perform a granular assessment of patients who completed inpatient LTE at our center and to identify risk factors for delayed LTE.

Research methods

We performed a single center retrospective cohort study analyzing patients with cirrhosis who completed LTE over 4 years. Patients were categorized as early or delayed LTE based on their clinical history. The electronic medical record was extensively reviewed to identify risk factors for delayed evaluation. Logistic regression was utilized to determine the effect of delayed evaluation on patient outcomes and to identify risk factors for delayed LTE.

Research results

Delayed referral increased the risk of death and decreased the odds of receiving a liver transplant. Female sex and trauma history to be predictors of delayed referral while malnutrition, work within the prior year, and prior smoking history were predictors of early referral. Documentation for 1 in 5 patients with delayed referral included misconceptions about candidacy and referenced inaccurate contraindications to transplant.

Research conclusions

Many patients undergo delayed LT which is associated with poor patient outcomes. Provider bias and patient psycho-social circumstances are both affect the timeliness of LTE and are targets for interventions aiming to improve access to liver transplantation.

Research perspectives

The use of granular data may improve the ability to identify patients at risk at individual centers.

FOOTNOTES

Author contributions: Cooper KM, Colletta A, Hathaway NJ, and Devuni D contributed to analysis and interpretation of data; Cooper KM, Talat A, and Devuni D contributed to study concept and design; Cooper KM, Colletta A, Liu D, Gonzalez D, Barry C, Krishnarao A, Mehta S, Movahedi B, and Martins PN contributed to acquisition of data; Cooper KM and Colletta A contributed to drafting of the manuscript; Cooper KM, Martins PN, and Devuni D contributed to critical revision of the manuscript for important intellectual content; Cooper KM and Hathaway NJ contributed to statistical analysis; Barry C, Krishnarao A, Mehta S, Movahedi B, and Martins PN contributed to material support; Devuni D contributed to study supervision.

Institutional review board statement: This study was reviewed and approved by the institutional review board at our medical center (IRB Docket: Study00000016, approved 10/24/21).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed care with informed consent. This study received a Health Insurance Portability and Accountability Act (HIPAA) waiver for informed consent at our institution through the IRB review process.

Conflict-of-interest statement: All authors have no conflicts of interest related to this study to report.

Data sharing statement: This study was reviewed and approved by the institutional review board at our medical center with a waiver of consent due to the retrospective nature of this study.

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REFERENCES

1 **Murray KF**, Carithers RL Jr; AASLD. AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology* 2005; **41**: 1407-1432 [PMID: 15880505 DOI: 10.1002/hep.20704]
2 **D'Amico G**, Bernardi M, Angeli P. Towards a new definition of decompensated cirrhosis. *J Hepatol* 2022; **76**: 202-207 [PMID: 34157322 DOI: 10.1016/j.jhep.2021.06.018]
3 **Nyberg LM**, Cheetham TC, Patton HM, Yang SJ, Chiang KM, Caparosa SL, Stern JA, Nyberg AH. The Natural History of NAFLD, a Community-Based Study at a Large Health Care Delivery System in the United States. *Hepatol Commun* 2021; **5**: 83-96 [PMID: 33437903 DOI: 10.1002/hep4.1625]
4 **Blais P**, Husain N, Kramer JR, Kowalkowski M, El-Serag H, Kanwal F. Nonalcoholic fatty liver disease is underrecognized in the primary care setting. *Am J Gastroenterol* 2015; **110**: 10-14 [PMID: 24890441 DOI: 10.1038/ajg.2014.134]
5 **Kwong A**, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Foutz J, Miller E, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Liver. *Am J Transplant* 2020; **20** Suppl 1: 193-299 [PMID: 31898413 DOI: 10.1111/ajt.15674]
6 **Alshuwaykh O**, Kwong A, Goel A, Cheung A, Dhanasekaran R, Ahmed A, Daugherty T, Dronamraju D, Kumari R, Kim WR, Nguyen MH, Esquivel CO, Concepcion W, Melcher M, Bonham A, Pham T, Gallo A, Kwo PY. Predictors of Outcomes of Patients Referred to a Transplant Center for Urgent Liver Transplantation Evaluation. *Hepatol Commun* 2021; **5**: 516-525 [PMID: 33681683 DOI: 10.1002/hep4.1644]
7 **Burke L**, Appleby V, Rowe I, Parker R, Jones R. P177 Identifying missed opportunities for transplant assessment: a review of referrals to a liver transplant centre. *BMJ Publishing Group* 2021
8 **Heimbach JK**. Overview of the Updated AASLD Guidelines for the Management of HCC. *Gastroenterol Hepatol (N Y)* 2017; **13**: 751-753 [PMID: 29339953]
9 **Harris PA**, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377-381 [PMID: 18929686 DOI: 10.1016/j.jbi.2008.08.010]
10 **Harris PA**, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; **95**: 103208 [PMID: 31078660 DOI: 10.1016/j.jbi.2019.103208]
11 **Passi NN**, McPhail MJ. The patient with cirrhosis in the intensive care unit and the management of acute-on-chronic liver failure. *JICS* 2020; **23** [DOI: 10.1177/1751143720978849]
12 **McClave SA**, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the

Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016; **40**: 159-211 [PMID: 26773077 DOI: 10.1177/0148607115621863]

13 **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]

14 **Sberna AL**, Bouillet B, Rouland A, Brindisi MC, Nguyen A, Mouillot T, Duvillard L, Denimal D, Loffroy R, Vergès B, Hillon P, Petit JM. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes. *Diabet Med* 2018; **35**: 368-375 [PMID: 29247558 DOI: 10.1111/dme.13565]

15 **Moylan CA**, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. *JAMA* 2008; **300**: 2371-2378 [PMID: 19033587 DOI: 10.1001/jama.2008.720]

16 **Su F**, Yu L, Berry K, Liou IW, Landis CS, Rayhill SC, Reyes JD, Ioannou GN. Aging of Liver Transplant Registrants and Recipients: Trends and Impact on Waitlist Outcomes, Post-Transplantation Outcomes, and Transplant-Related Survival Benefit. *Gastroenterology* 2016; **150**: 441-53.e6; quiz e16 [PMID: 26522262 DOI: 10.1053/j.gastro.2015.10.043]

17 **Sawinski D**, Lai JC, Pinney S, Gray AL, Jackson AM, Stewart D, Levine DJ, Locke JE, Pomposelli JJ, Hartwig MG, Hall SA, Dadhania DM, Cogswell R, Perez RV, Schold JD, Turgeon NA, Kobashigawa J, Kukreja J, Magee JC, Friedewald J, Gill JS, Loor G, Heimbach JK, Verna EC, Walsh MN, Terrault N, Testa G, Diamond JM, Reese PP, Brown K, Orloff S, Farr MA, Olthoff KM, Siegler M, Ascher N, Feng S, Kaplan B, Pomfret E. Addressing sex-based disparities in solid organ transplantation in the United States - a conference report. *Am J Transplant* 2023; **23**: 316-325 [PMID: 36906294 DOI: 10.1016/j.ajt.2022.11.008]

18 **Finkenstedt A**, Nachbaur K, Zoller H, Joannidis M, Pratschke J, Graziadei IW, Vogel W. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. *Liver Transpl* 2013; **19**: 879-886 [PMID: 23696006 DOI: 10.1002/lt.23678]

19 **Julapalli VR**, Kramer JR, El-Serag HB; American Association for the Study of Liver Diseases. Evaluation for liver transplantation: adherence to AASLD referral guidelines in a large Veterans Affairs center. *Liver Transpl* 2005; **11**: 1370-1378 [PMID: 16184521 DOI: 10.1002/Lt.20434]

20 **Webb GJ**, Hodson J, Chauhan A, O'Grady J, Neuberger JM, Hirschfield GM, Ferguson JW. Proximity to transplant center and outcome among liver transplant patients. *Am J Transplant* 2019; **19**: 208-220 [PMID: 29981195 DOI: 10.1111/ajt.15004]

21 **John BV**, Schwartz K, Scheinberg AR, Dahman B, Spector S, Deng Y, Goldberg D, Martin P, Taddei TH, Kaplan DE. Evaluation Within 30 Days of Referral for Liver Transplantation is Associated with Reduced Mortality: A Multicenter Analysis of Patients Referred Within the VA Health System. *Transplantation* 2022; **106**: 72-84 [PMID: 33587434 DOI: 10.1097/TP.0000000000003615]

22 **Bryce CL**, Angus DC, Arnold RM, Chang CC, Farrell MH, Manzarbeitia C, Marino IR, Roberts MS. Sociodemographic differences in early access to liver transplantation services. *Am J Transplant* 2009; **9**: 2092-2101 [PMID: 19645706 DOI: 10.1111/j.1600-6143.2009.02737.x]

23 **Bryce CL**, Chang CC, Angus DC, Arnold RM, Farrell M, Roberts MS. The Effect of Race, Sex, and Insurance Status on Time-to-Listing Decisions for Liver Transplantation. *J Transplant* 2010; **2010**: 467976 [PMID: 21234099 DOI: 10.1155/2010/467976]

24 **Patzer RE**, Adler JT, Harding JL, Huml A, Kim I, Ladin K, Martins PN, Mohan S, Ross-Driscoll K, Pastan SO. A Population Health Approach to Transplant Access: Challenging the Status Quo. *Am J Kidney Dis* 2022; **80**: 406-415 [PMID: 35227824 DOI: 10.1053/j.ajkd.2022.01.422]

25 **M Loy V**, Rzepczynski A, Joyce C, Bello S, Lu A. Disparity in Transplant Referral Patterns for Alcohol-Related Liver Disease Based on Physician-Dependent Variables. *Transplant Proc* 2020; **52**: 900-904 [PMID: 32151390 DOI: 10.1016/j.transproceed.2020.01.015]

26 **McClinton A**, Gullo J, Martins PN, Serrano OK. Access to liver transplantation for minority populations in the United States. *Curr Opin Organ Transplant* 2021; **26**: 508-512 [PMID: 34354000 DOI: 10.1097/MOT.0000000000000904]

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ORIGINAL ARTICLE

Observational Study

Haemodynamic management in brain death donors: Influence of aetiology of brain death

Chiara Lazzeri, Manuela Bonizzoli, Stefano Batacchi, Cristiana Guetti, Walter Vessella, Alessandra Valletta, Alessandra Ottaviano, Adriano Peris

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Abstract

BACKGROUND

In brain death donors (BDDs), donor management is the key in the complex donation process. Donor management goals, which are standards of care or clinical parameters, have been considered an acceptable barometer of successful donor management.

AIM

To test the hypothesis that aetiology of brain death could influence haemodynamic management in BDDs.

METHODS

Haemodynamic data (blood pressure, heart rate, central venous pressure, lactate, urine output, and vasoactive drugs) of BDDs were recorded on intensive care unit (ICU) admission and during the 6-h observation period (Time 1 at the beginning; Time 2 at the end).

RESULTS

The study population was divided into three groups according to the aetiology of brain death: Stroke (n = 71), traumatic brain injury (n = 48), and postanoxic encephalopathy (n = 19). On ICU admission, BDDs with postanoxic encephalopathy showed the lowest values of systolic and diastolic blood pressure associated with higher values of heart rate and lactate and a higher need of norepinephrine and other vasoactive drugs. At the beginning of the 6-h period (Time 1), BDDs with postanoxic encephalopathy showed higher values of heart rate, lactate, and central venous pressure together with a higher need of other vasoactive drugs.

CONCLUSION

According to our data, haemodynamic management of BDDs is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy have higher requirements for norepinephrine and other vasoactive drugs.

Key Words: Brain death donor; Postanoxic encephalopathy; Stroke; Acute traumatic injury; Haemodynamic management; Utilization rate

Core Tip: In our single centre observational study including 138 brain death donors (BDDs), haemodynamic management is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy had higher requirements for norepinephrine and other vasoactive drugs.

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INTRODUCTION

Management of potential organ donors is the key in the complex donation process, considering that haemodynamic instability may be responsible for the loss of organs of brain death donors (BDDs)[1-8]. Changes in epidemiologic characteristics of BDDs, becoming older and with more comorbidities[9], do make haemodynamic management more challenging[10].

Donor management goals, which are standards of care or clinical parameters, have been considered an acceptable barometer of successful donor management[9,10]. Meeting donor management goals has been associated with an increased number of retrieved organs per donor[1,11-13] and, more recently, a reduced incidence of delayed graft function[14,15].

We hypothesized that aetiology of brain death could influence haemodynamic management in BDDs. In the present study, we tested this hypothesis in 138 BDDs consecutively admitted to our intensive care unit (ICU).

MATERIALS AND METHODS

In the present single centre observational study, we enrolled 138 BDDs consecutively admitted to our ICU from January 1, 2018 to October 31, 2022. The study was approved by the Institutional Review Board of Regional Authority for Transplantation and performed in accordance with the Helsinki Declaration of 1975.

Study population

Diagnosis of death was confirmed by strict adherence to standardized clinical, neurologic, and electroencephalogram criteria in accordance with the Italian law and related guidelines. According to the Italian law, death by neurologic criteria is certificated after a 6-h observation period. Time 1 refers to the beginning of this period, and time 2 to the end of this period.

Clinical data included age, risk factors (hypertension, diabetes mellitus, and known previous coronary artery disease). Data were prospectively recorded and retrospectively analysed. The study population was divided into three groups according to the aetiology of brain death: Stroke (n = 71), traumatic brain injury (n = 48), and postanoxic encephalophy (n = 19).

Donor management

All potential donors were managed as previously described[8,10]. Management goals were as follows: Mean arterial pressure > 70 mmHg, central venous pressure of 6 to 10 mmHg, urine output of 1.2 mL/kg/h, and haemoglobin levels to ≥ 10 g/dL. Ventilatory management was aimed to reach the target partial pressure of oxygen ≥ 90 mmHg[6,8,13]. Haemodynamic management also included replacement therapy with cortisone and thyroid hormone (T3). Antidiuretic hormone and intravenous insulin (target glucose values < 180 mg/dL) were considered on a case-by-case basis.

The following parameters were recorded on ICU admission and during the 6-h observation period (Time 1 at the beginning; Time 2 at the end): Systolic (SBP) and diastolic (DBP) blood pressure (mmHg), heart rate (bpm), central venous pressure (CVP) (cmH_2O), lactate (mg/dL), and urine output (mL/h).

Statistical analysis

Data were analysed with the use of SPSS 20 statistical software (SPSS Inc, Chicago, IL, United States). A two-tailed *P* value < 0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages, and continuous variables are reported as the mean ± SD or median [and 25^{th}-75^{th} interquartile range (IQR)]. For continuous variables, between-group comparisons were made using analysis of variance (followed by Bonferroni posttests if the overall *P* value was significant) or by means of Kruskal-Wallis *H* test. Categorical variables were compared by chi-square tests.

RESULTS

The study population included 138 consecutive BDDs. Stroke was the most frequent aetiology (51%). Table 1 shows the comparisons between the three subgroups. BDDs with postanoxic encephalopathy were the youngest (aged 59 ± 19 yr). No differences were detectable among the three subgroups in risk factors and refusal rates. In BDDs with postanoxic encephalopathy, the utilization rate showed a trend towards lower values, which did not reach statistical significance.

Haemodynamic data are depicted in Table 2, recorded at ICU admission and Time 1 and Time 2, respectively.

On ICU admission, BDDs with postanoxic encephalopathy showed the lowest values of SBP and DBP (98 ± 33 and 77 ± 22 mmHg, respectively) associated with higher values of heart rate and lactate and a higher need of norepinephrine and other vasoactive drugs. Urine output and CVP were comparable among the three subgroups.

At the beginning of the 6-h period (Time 1), SBP and DBP were comparable among the three subgroups, as well as urine output and norepinephrine use. BDDs with postanoxic encephalopathy showed higher values of heart rate, lactate, and CVP together with a higher need of other vasoactive drugs.

At the end of the 6-h period (Time 2), no significant differences in haemodynamic data were detectable among the threegroups except higher value of CVP in BDDs with postanoxic encephalopathy.

Other vasoactive drugs were vasopressin in all cases except dobutamine used in one BDD.

DISCUSSION

Our investigation, performed in 138 consecutive BDDs managed with the same donor management protocol, documented that haemodynamic management in BDDs is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy require an aggressive treatment, that is, a higher need of norepinephrine and other vasoactive drugs. Utilization rates did not differ among the BDDs with different aetiologies of brain death, probably due to a strict haemodynamic monitoring and donor haemodynamic management.

Brain death has been reported to occur in about one-sixth of patients after successfully resuscitated cardiac arrest[16], thus creating opportunities for organ donation. In a recent review by Sandroni *et al* [17], kidneys, livers, hearts, and intestines retrieved from BDDs with postanoxic encephalopathy showed survival rates comparable to organs transplanted from BDDs from other aetiolgies. No data are so far available on haemodynamic management in these donors.

In our investigation, we specifically addressed haemodynamic management in BDDs from postanoxic encephalopathy upon ICU admission and after brain death developed. Haemodynamic management in these donors is more challenging since norepinephrine administration is more frequently needed to reach and maintain donor management goals and, in about one third of cases, another vasoactive drug is required. This phenomenon may be attributed to post-cardiac resuscitation syndrome. Higher values of heart rate can be related to reduced cardiac function (as a compensatory mechanism), as indicated by higher values of CVP. Despite the achievement of donor management goals, lactate values were the highest in BDDs from postanoxic encephalopathy but urine output (an indirect index of systemic perfusion) was maintained.

The utilization rate in BDDs with postanoxic encephalopathy did not differ from that of BDDs with stroke and traumatic brain injury. This may be related to the strict haemodynamic monitoring and haemodynamic donor management, performed at our centre.

Our data underscore the utility of the relevant data on potential organ donors being reported to a national registry and how this can be used to drive practice improvement and eventually to develop consensus statements.

Table 1 Study population, *n* (%)

	Stroke	Traumatic brain injury	Postanoxic encelophaphy	
Number	71	48	19	
Age (yr, mean ± SD)	79 ± 14	68 ± 20	59 ± 19	0.0007[a]
Males	34 (48)	31 (65)	10 (53)	0.197[b]
Risk factors				0.673[b]
Hypertension	51	10	24	
Diabetes	24	9	16	
Heart disease	6	2	5	
Refusals to donation	13	10	2	0.613[b]
Utilized donors (*n*)	54	35	15	0.808[b]
Utilization rate (%)	93	92	89	

[a]One way analysis of variance.
[b]χ^2.

Table 2 Haemodynamic data, *n* (%)

	Stroke	Traumatic brain injury	Postanoxic encephalopathy	
Number	71 (51)	48 (35)	19 (14)	
ICU admission				
SBP (mmHg), mean ± SD	112 ± 44	123 ± 34	98 ± 33	0.002[a]
DBP (mmHg), mean ± SD	74 ± 21	74 ± 18	77 ± 22	0.001[a]
HR (bpm), mean ± SD	75 ± 22	77 ± 34	82 ± 35	0.015[a]
CVP (cmH_2O), mean ± SD	10 ± 3	11 ± 4	10 ± 3	0.819[a]
Norepinephrine	31 (44)	29 (60)	14 (74)	0.03[b]
Other vasoactive drugs	5 (7)	9 (18)	6 (32)	0.015[b]
Urine output, median (IQR)	200 (125-393)	261 (124-408)	287 (186-440)	0.279[a]
Lactate (mg/dL), median (IQR)	1.5 (1-2.6)	2.1 (1.3-3.1)	1.8 (0.8-4.6)	0.033[a]
Time 1				
SBP (mmHg), mean ± SD	123 ± 19	125 ± 23	122 ± 21	0.818[a]
DBP (mmHg), mean ± SD	63 ± 13	65 ± 14	68 ± 17	0.497[a]
HR (bpm), mean ± SD	86 ± 16	92 ± 17	94 ± 22	0.037[a]
Norepinephrine	56 (78)	43 (89)	18 (95)	0.120[b]
CVP (cmH_2O), mean ± SD	10 ± 3	11 ± 5	12 ± 7	0.001[a]
Other vasoactive drugs	7 (9.8)	10 (20)	5 (26)	0.113[b]
Urine output, median (IQR)	113 (57-210)	115 (85-285)	110 (65 220)	0.374[a]
Lactate (mg/dL), median (IQR)	1.2 (0.9-1.7)	1.4 (1-3.1)	1.7 (1.3-3.1)	0.006[a]
Time 2				
SBP (mmHg), mean ± SD	133 ± 25	131 ± 22	126 ± 27	0.510[a]
DBP (mmHg), mean ± SD	66 ± 14	65 ± 12	70 ± 17	0.784[a]
HR (bpm), mean ± SD	94 ± 19	95 ± 15	99 ± 25	0.760[a]
Norepinephrine	57	43	18	0.172[b]
Other vasoactive drugs	8 (11)	6 (12)	5 (26)	0.227[b]

CVP (cmH_2O), mean ± SD	10 ± 4	12 ± 4 (12)	13 ± 4	0.040[a]
Urine output, median (IQR)	143 (79-240)	160 (95-250)	200 (92-250)	0.785[a]

[a]One-way analysis of variance.
[b]χ^2.
IQR: Interquartile range; ICU: Intensive care unit; CVP: Central venous pressure, SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

This study has several limitations. It is a single-centre study, and the number of enrolled BDDs is quite small. However, they were managed with the same donor management protocol.

CONCLUSION

According to our data, haemodynamic management in BDDs is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy have higher requirements for norepinephrine and other vasoactive drugs.

ARTICLE HIGHLIGHTS

Research background

In brain death donors (BDDs), donor management is the key in the complex donation process. Donor management goals, which are standards of care or clinical parameters, have been considered an acceptable barometer of successful donor management.

Research motivation

Meeting donor management goals has been associated with an increased number of retrieved organs per donor and, more recently, a reduced incidence of delayed graft function.

Research objectives

To test the hypothesis that aetiology of brain death could influence haemodynamic management in BDDs.

Research methods

Haemodynamic data (blood pressure, heart rate, central venous pressure, lactate, urine output, and vasoactive drugs) were recorded on intensive care unit (ICU) admission and during the 6-h observation period (Time 1 at the beginning; Time 2 at the end).

Research results

The study population was divided three groups according to aetiology of brain death: Stroke (n = 71), traumatic brain injury (n = 48), and postanoxic encephalopathy (n = 19). On ICU admission, BDDs with postanoxic encephalopathy showed the lowest values of SBP and DBP associated with higher values of heart rate and lactate and a higher need of norepinephrine and other vasoactive drugs. At the beginning of the 6-h period (Time 1), BDDs with postanoxic encephalopathy showed higher values of heart rate, lactate, and central venous pressure together with a higher need of other vasoactive drugs.

Research conclusions

According to our data, haemodynamic donor management is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy have higher requirements for norepinephrine and other vasoactive drugs.

Research perspectives

Our data underscore the utility of the relevant data on potential organ donors being reported to a national registry and how this can be used to drive practice improvement and eventually to develop consensus statements.

FOOTNOTES

Author contributions: Lazzeri C, Bonizzoli M, and Peris A designed the research study; Guetti C, Batacchi S, and Ottaviano A performed the research; Valletta A and Vessella W analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: The study protocol was approved by our Internal Editorial Board.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data.

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REFERENCES

1 **Patel MS**, De La Cruz S, Sally MB, Groat T, Malinoski DJ. Active Donor Management During the Hospital Phase of Care Is Associated with More Organs Transplanted per Donor. *J Am Coll Surg* 2017; **225**: 525-531 [PMID: 28739153 DOI: 10.1016/j.jamcollsurg.2017.06.014]
2 **Greer DM**, Shemie SD, Lewis A et al Determination of brain death/death by neurologic criteria. The World Brain Death Project. JAMA 2020; 324(11): 1078-1097 [DOI: 10.3410/f.738423716.793581021]
3 **Thet MS**, Verzelloni Sef A, Sef D. Can adequate hemodynamic management of brain-dead donors improve donor organ procurement? *World J Transplant* 2022; **12**: 79-82 [PMID: 35633852 DOI: 10.5500/wjt.v12.i4.79]
4 **McKeown DW**, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. *Br J Anaesth* 2012; **108** Suppl 1: i96-107 [PMID: 22194439 DOI: 10.1093/bja/aer351]
5 **Frenette AJ**, Williamson D, Weiss MJ, Rochwerg B, Ball I, Brindamour D, Serri K, D'Aragon F, Meade MO, Charbonney E. Worldwide management of donors after neurological death: a systematic review and narrative synthesis of guidelines. *Can J Anaesth* 2020; **67**: 1839-1857 [PMID: 32949008 DOI: 10.1007/s12630-020-01815-0]
6 **Meyfroidt G**, Gunst J, Martin-Loeches I, Smith M, Robba C, Taccone FS, Citerio G. Management of the brain-dead donor in the ICU: general and specific therapy to improve transplantable organ quality. *Intensive Care Med* 2019; **45**: 343-353 [PMID: 30741327 DOI: 10.1007/s00134-019-05551-y]
7 **Patel MS**, Zatarain J, De La Cruz S, Sally MB, Ewing T, Crutchfield M, Enestvedt CK, Malinoski DJ. The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor: a prospective study from the UNOS Region 5 Donor Management Goals Workgroup. *JAMA Surg* 2014; **149**: 969-975 [PMID: 25054379 DOI: 10.1001/jamasurg.2014.967]
8 **Lazzeri C**, Bonizzoli M, Guetti C, Fulceri GE, Peris A. Hemodynamic management in brain dead donors. *World J Transplant* 2021; **11**: 410-420 [PMID: 34722170 DOI: 10.5500/wjt.v11.i10.410]
9 **Nozary Heshmati B**, Ahmadi F, Azimi P, Tirgar N, Barzi F, Gatmiri SM. Hemodynamic factors affecting the suitability of the donated heart and kidney for transplantation. *Int J Organ Transplant Med* 2013; **4**: 150-154 [PMID: 25013668]
10 **Peris A**, Lazzeri C, D'Antonio L, Bombardi M, Bonizzoli M, Guetti C, Maccherini M, Migliaccio ML. Epidemiological changes in potential heart donors after brain death: a retrospective 15 year cohort study. *Intern Emerg Med* 2019; **14**: 371-375 [PMID: 29943077 DOI: 10.1007/s11739-018-1897-8]
11 **McKeown DW**, Ball J. Treating the donor. *Curr Opin Organ Transplant* 2014; **19**: 85-91 [PMID: 24553498 DOI: 10.1097/MOT.0000000000000059]
12 **Franklin GA**, Santos AP, Smith JW, Galbraith S, Harbrecht BG, Garrison RN. Optimization of donor management goals yields increased organ use. *Am Surg* 2010; **76**: 587-594 [PMID: 20583513 DOI: 10.1177/000313481007600621]
13 **Bera KD**, Shah A, English MR, Harvey D, Ploeg RJ. Optimisation of the organ donor and effects on transplanted organs: a narrative review on current practice and future directions. *Anaesthesia* 2020; **75**: 1191-1204 [PMID: 32430910 DOI:

10.1111/anae.15037]

14 **Kothari R**, Tolles J, Adelmann D, Lewis RJ, Malinoski DJ, Niemann CU. Organ donor management goals and delayed graft function in adult kidney transplant recipients. *Clin Transplant* 2022; **36**: e14528 [PMID: 34739731 DOI: 10.1111/ctr.14528]

15 **Malinoski DJ**, Patel MS, Ahmed O, Daly MC, Mooney S, Graybill CO, Foster CE, Salim A; United Network for Organ Sharing (UNOS) Region 5 Donor Management Goals (DMG) Workgroup. The impact of meeting donor management goals on the development of delayed graft function in kidney transplant recipients. *Am J Transplant* 2013; **13**: 993-1000 [PMID: 23406284 DOI: 10.1111/ajt.12090]

16 **Adrie C**, Haouache H, Saleh M, Memain N, Laurent I, Thuong M, Darques L, Guerrini P, Monchi M. An underrecognized source of organ donors: patients with brain death after successfully resuscitated cardiac arrest. *Intensive Care Med* 2008; **34**: 132-137 [PMID: 17932649 DOI: 10.1007/s00134-007-0885-7]

17 **Sandroni C**, Adrie C, Cavallaro F, Marano C, Monchi M, Sanna T, Antonelli M. Are patients brain-dead after successful resuscitation from cardiac arrest suitable as organ donors? A systematic review. *Resuscitation* 2010; **81**: 1609-1614 [PMID: 20932627 DOI: 10.1016/j.resuscitation.2010.08.037]

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ORIGINAL ARTICLE

Observational Study

Randomized intervention to assess the effectiveness of an educational video on organ donation intent among Hispanics in the New York metropolitan area

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Abstract

BACKGROUND

The Hispanic community has a high demand for organ donation but a shortage of donors. Studies investigating factors that could promote or hinder organ donation have examined emotional video interventions. Factors acting as barriers to organ donation registration have been classified as: (1) Bodily integrity; (2) medical mistrust; (3) "ick"-feelings of disgust towards organ donation; and (4) "jinx"-fear that registration may result in one dying due to premeditated plans. We predict that by providing necessary information and education about the donation process *via* a short video, individuals will be more willing to register as organ donors.

AIM

To determine perceptions and attitudes regarding barriers and facilitators to organ donation intention among Hispanic residents in the New York metropolitan area.

METHODS

This study was approved by the Institutional Review Board at Northwell Health. The approval reference number is No. 19-0009 (as presented in Supplementary material). Eligible participants included Hispanic New York City (NYC) residents, 18 years of age and above, who were recruited voluntarily through Cloud Research and participated in a larger randomized survey study of NYC residents.

The survey an 85-item Redcap survey measured participant demographics, attitudes, and knowledge of organ donation as well as the intention to register as an organ donor. Attention checks were implemented throughout the survey, and responses were excluded for those who did fail. Participants were randomly assigned two-between subject conditions: To view a short video on organ donation and then proceed to complete the survey (*i.e.*, video first) and view the same video at the end of the survey (video last). No intra-group activities were conducted. This study utilized an evidenced-based emotive educational intervention (video) which was previously utilized and was shown to increase organ donation registration rates at the Ohio Department of Motor Vehicles. Results were analyzed using Jamovi statistical software. Three hundred sixty-five Hispanic individuals were included in the analysis. Once consent was obtained and participants entered the survey (the survey sample is presented in Supplementary material), participants were asked to report on demographic variables and their general impression of organ donation after death. The video depicted stories regarding organ donation after death from various viewpoints, including from the loved ones of a deceased person who died waiting for a transplant; from the loved ones of a deceased person whose organs were donated upon death; and, from those who were currently waiting for a transplant.

RESULTS

Using a binomial logistic regression, the analysis provides information about the relationship between the effects of an emotive video and the intention to donate among Hispanic participants who were not already registered as donors. The willingness to go back and register was found to be significantly more probable for those who watched the emotive video before being asked about their organ donation opinions (odds ratio: 2.05, 95% confidence interval: 1.06-3.97). Motivations for participation in organ donation were also captured with many stating the importance of messages coming from "people like me" and a message that highlights "the welfare of those in need". Overall, the findings suggest that using an emotive video that addresses organ donation barriers to prompt organ donation intentions can be effective among the Hispanic populous. Future studies should explore using targeted messaging that resonates with specific cultural groups, highlighting the welfare of others.

CONCLUSION

This study suggests that an emotive educational intervention is likely to be effective in improving organ donation registration intent among the Hispanic population residing in NYC.

Key Words: Community engagement and health; Health equity; Diversity and inclusion; Health policy; Kidney donation; Minority health and disparities; Organ transplant

Core Tip: The Hispanic community has a high demand for organ donation but a shortage of donors. A study conducted in New York City found that providing an emotive educational video on organ donation before taking a survey significantly increased the odds of organ donation intent among Hispanic individuals. By providing necessary information and education about the donation process, Hispanic residents can be just as willing to become organ donors as their non-Hispanic counterparts.

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INTRODUCTION

As of March 2022, more than 105800 men, women, and children were on the United States national transplant waiting list, while just over 40000 organ transplants were performed in 2021, creating a deficit in which 17 people die each day while waiting for an organ transplant[1]. This issue can be viewed from many different perspectives, such as allocation systems, registration processes, cultural barriers, and even geographic considerations. Our goal is to highlight barriers and possible solutions to the dearth of organ donation registration in the State of New York, which has the lowest organ donation

rate in the country[2]. Specifically, the primary objective of this study is to test the effectiveness of a best practice educational video intervention to improve registration amongst Hispanic residents of the New York metropolitan area. Specifically, we will examine a representative sample of Hispanic respondents randomized to this best practice intervention, a subset of a previously published large study of New York residents, to focus on the Hispanic population to elucidate possible solutions to this significant and unfortunate shortage of lifesaving organs.

The organ donation process has a long legislative history that is not common knowledge nor without controversy[3]. In 1968, the United States passed the Uniform Anatomical Gift Act, creating a national organ transplantation policy[4]. Currently, the United Network for Organ Sharing maintains the organ procurement and transplantation network, a system established by the National Organ Transplant Act of 1984[4]. The goal of nationalizing the organ donation process and creating supporting networks was to create an effective and efficient organ-sharing system organized into 11 geographic regions[4]. Following the nationalization in 1998, the Former DHHS Secretary Donna Shalala issued the Final Rule policy to process organs more equitably[4]. The purpose of the policy is to match donors and recipients based on statistical consideration of both clinical parameters and proximity to the location of the organ donor. Before these rulings, states with larger donation banks benefited from distribution systems that favored locality, but allocation systems have now incorporated national needs. New York has explicitly unique difficulties that benefit from such policies, as they make up for 10% of the national organ transplant waiting list, yet they have the lowest donation rates[2]. NYS organ donation rate is a meager 35%, compared to the national average of 58%, and the highest-ranking state of Colorado, with a donation rate of 69%[5,6]. As a result, nearly 10000 New Yorkers are currently waiting for an organ[7].

Legislative initiatives intended to improve transplant systems have been effective, but literature reviews on improving donation rates at the individual level have taken on a human factor approach[3, 8]. This angle is of critical importance given the donation rates among racial/ethnic minority populations. The national transplant waiting list stands at 105464 people; 60.0% of those waiting represent racial and ethnic minorities[9]. Hispanics alone comprise 20.5% of the transplant waiting list [10]. Targeting organ donation initiatives to populations that are most at risk is vitally important in NYS, as increased diversity in donor populations can lead to increased access to transplantation and a better chance of finding close matches in terms of shared genetic background[4]. Hence, increasing registration rates among immigrant populations, of which NYS currently holds the second-largest ranking in the country, is key[11]. Donation trends by underrepresented minorities have always been historically low when compared to white individuals[12]. There is some encouraging news regarding donation rates. Specifically, the standardized donation ratio for Hispanic/Latino groups increased from 1.92% in 1999 to 3.35% in 2017[12]. While this increase is noteworthy, it was not significantly different than the increase seen in non-Hispanic/Latino individuals. Despite the benefits of a more diverse donor pool, there is still much to be done to motivate efforts to increase donation rates among Hispanic communities.

Given the great need to improve organ donation in NYS, we seek to identify effective interventions in Hispanic communities. Research looking at hindering factors to donor rates among Hispanic communities identifies factors such as mistrust of healthcare systems, literacy rates, and cultural barriers. For example, Hispanic donors are more likely to develop Clavien grade IV or higher surgical complications (not limited to nervous system complications), conversion to open nephrectomy, intensive care unit stays, and death[13]. Coupled with already existing health disparities such as kidney disease, higher prevalence of incidence of type 2 diabetes, and development of end-stage kidney disease, may add to the negative experiences and mistrust of the healthcare system[14-21]. Other factors that have been reported include insufficient levels of health literacy which has been found to impact organ donation registration and consent from family members[22-26]. Therefore, targeted educational messaging about organ donation is crucial to increase awareness and understanding among individuals. This is especially true when considering individuals' willingness to disseminate sociocultural tailored content that is shared by existing social ties[27]. Hence, targeted messaging that resonates with specific cultural groups and is shared through existing social connections may be more effective in increasing donation rates.

Educational interventions may include different settings such as schools, departments of motor vehicle (DMV), primary care, and other local community locations[8]. Approaches have included educational sessions and videos, leveraging peer leaders in the community, DMV staff training, messaging, and priming[8]. Other interventions include testing "opt-out" policies, which is a presumed consent model as opposed to the standard "opt-in" policy that exists in the United States[28-32]. Although the "opt-out" model has reported positive results such a policy is not expected to become imminently approved in the United States, suggesting further research into motivations behind organ donation. Our larger study 33 was built around an existing video message directly addressing some of the documented barriers to organ donation. The video was found to be successful in improving registration rates by addressing barriers such as: (1) Bodily integrity; (2) medical skepticism; (3) "ick"-described as a discomfort towards the process; and (4) "jinx"-superstitious around the process of preparing for one's death[33].

Table 1 Methodology

	Video first condition	Video last condition
Participants	192	173
IV	5 min 25 s emotive video addressing common barriers to organ donation	
DV	An 85-item Redcap survey measured participant demographics, attitudes, and knowledge of organ donation as well as intention to register as an organ donor	
Procedure	A human intelligence task, informed consent was required, random assignment was implemented	

The emotional video messaging used in the Thornton study[34] (as presented in Supplementary material) was effective in increasing organ donation registrations at the Ohio Bureau of Motor Vehicles (BMV). Our previous study[32] was also successful in increasing organ donation intent in NYS. While Thornton's study was conducted at 12 branches of the Ohio BMV, our larger study used a Sample of Amazon MTurk participants located in NYS with randomized exposure to the emotional video. We observed a significant increase in the proportion of respondents who were motivated to register as organ donors among those who were exposed to the emotional movie (randomized to the movie First condition) compared to those randomized to the Video Last condition. Of note, the original video did not use content specific to any particular culture. This paper aims to build on the larger study 32 by focusing on the effects of the video on the Hispanic demographic who viewed the video before ("first" group) administration of a survey of attitudes toward and knowledge of organ donation *vs* those who did not view the video until after survey participation ("last" group).

MATERIALS AND METHODS

The study adheres to the principles outlined in the Declaration of Helsinki and all participants provided informed consent before they participated in the study. As described in Table 1, participants (n = 365) were enrolled in part of a larger randomized survey study conducted with New York City residents who were recruited *via* a crowdsourcing online platform and were randomized to one of two groups, with exposure to viewing: (1) An educational video before completing an 81-question survey on organ donation ("video first" condition); or (2) after completing the survey ("video last" condition). The survey instrument was investigator-developed in the absence of existing validated tools. Interviews with subject matter experts and a review of the literature were utilized to ensure the topic of the survey is relevant to the population of interest during item creation. Logistic regression analysis compared organ donation intent (*i.e.*, "How likely are you to become an organ donor") between the two groups. Additional variables related to organ donation (*e.g.*, religious beliefs, financial incentives) were also evaluated between the two groups. Analyses were adjusted for organ donation registration status. Data were analyzed using Jamovi (version 2.3.19), a software package that runs in tandem with R Statistical Software. Frequencies and percentages were used for categorical data. Summary statistics were utilized to describe sample characteristics. To determine parameters that might predict the likelihood of organ donation registration and to assess the effects of the video intervention, we used binomial logistic regression analysis. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Participants

Table 2 presents Hispanic participant characteristics for the total sample by registration status (registered organ donor, non-registered organ donor, and those who did not specify). More than a quarter (35%) of participants identified as White or Caucasian, less than a quarter (15%) as Black or African American, and 18% as multiracial. The majority of participants were female. Seventy-two percent of the sample participants said they were between the ages of 19 and 39; 60% of them reported being single or never married; and 67% said they were employed either full- or part-time. Thirty-eight percent of the sample as a whole had organ donation records after passing away 40% and 38%, respectively, of those who described themselves as spiritual or religious had registered as organ donors. Additionally, 28% of participants with degrees of 2 years or less were registered as organ donors, compared to 45% of participants with graduate degrees or 4-year degrees.

Table 2 Hispanic participant characteristics and test of proportions, *n* (%)

Total (*n* = 365)		*n* = 1905	
		Registered (*n* = 137)	Not registered (*n* = 228)
Gender			
Female	236 (65)	87 (37)	149 (63)
Male	126 (34)	48 (38)	78 (62)
Other/prefer not to say	3 (1)	2 (67)	1 (33)
Age (yr)			
≤ 39	263 (72)	105 (40)	158 (60)
40-69	97 (27)	31 (32)	66 (68)
≥ 70	5 (1)	1 (20)	4 (80)
Race			
White/Caucasian	130 (36)	60 (46)	70 (54)
Black/African American	54 (15)	20 (37)	34 (63)
Asian	4 (1)	3 (75)	1 (25)
Multiracial	63 (17)	23 (37)	40 (63)
Other	101 (28)	29 (29)	72 (71)
Native American or Alaskan Native	5 (1)	1 (20)	4 (80)
Native Hawaiian or Other Pacific, Islander	3 (1)	0	3 (100)
Prefer not to say	5 (1)	1 (20)	4 (80)
Spirituality			
Yes	252 (69)	106 (42)	146 (58)
No	99 (27)	28 (28)	71 (72)
Prefer not to say	14 (4)	3 (21)	11 (79)
Religiosity			
Yes	162 (44)	64 (40)	98 (60)
No	189 (52)	70 (37)	119 (63)
Prefer not to say	14 (4)	3 (21)	11 (79)
Religious denomination			
Christian	198 (54)	77 (39)	121 (61)
Jewish	3 (1)	2 (67)	1 (33)
Muslim	6(2)	3 (50)	3 (50)
Buddhist	2 (1)	2 (100)	0
Non-religious	103 (28)	41 (40)	62 (60)
Other	41 (11)	10 (24)	31 (76)
Prefer not to say	12 (3)	2 (17)	10 (83)
Marital status			
Single/never married	219 (60)	77 (35)	142 (65)
Married/living as married	123 (34)	52 (42)	71 (58)
Divorced/separated	17 (5)	6 (35)	11 (65)
Widowed	4 (1)	1 (25)	3 (75)
Prefer not to say	2 (1)	1 (50)	1 (50)
Level of education			

2-year associate degree or less	216 (59)	63 (29)	153 (71)
4-year college degree (*e.g.*, Bachelor)	121 (33)	56 (46)	65 (54)
Graduate degree (*e.g.*, Master, MD, PhD)	28 (8)	18 (64)	10 (36)
Employment status			
Full time or part time	182 (50)	86 (47)	96 (53)
Unemployed	116 (32)	33 (28)	83 (72)
Prefer not to say	4 (1)	0	4 (100)
Self-employed			
Yes, *n* (%)	59 (16)	28 (47)	31 (53)
No, *n* (%)	306 (84)	109 (36)	197 (64)
Annual income			
< $30000	108 (30)	33 (31)	75 (69)
$30001-$60000	113 (31)	41 (36)	72 (64)
$60001-$100000	88 (24)	43 (49)	45 (51)
> $100000	36 (10)	19 (53)	17 (47)
Prefer not to say	20 (5)	1 (5)	19 (95)
Insurance			
Medicaid or medicare	167 (46)	43 (26)	124 (74)
Employer	139 (38)	71 (51)	68 (49)
	27 (7)	15 (56)	12 (44)
Out of pocket			
Other	15 (4)	5 (33)	10 (67)
Prefer not to say	15 (4)	2 (13)	13 (87)

Fifty participants did not indicate their registration status.

RESULTS

Impact of emotional video

In the current study of Hispanic participants who were randomly assigned to the Video First condition who had not yet registered as organ donors, were found to be significantly more inclined to do so than those in the Video Last condition [odds ratio (OR): 2.05, 95% confidence interval (CI): 1.06-3.97], according to the results (Table 3). In comparison to those in the Video Last condition, participants in the Video First condition were less likely to be swayed by the donor's health [OR: 0.53, 95%CI: 0.31-0.90], more likely to be aware that they could sign up at the DMV [OR: 2.21, 95%CI: 1.22-4.03], and less in favor of an opt-out system [OR: 0.49, 95%CI: 0.25-0.96]. Contrasted with the bigger sample, it was discovered that Hispanics in the Video First condition was just as likely as those in the overall sample to express a willingness to register as donors among non-registered donors [OR: 1.64, 95%CI: 1.22-2.20].

Driving factors for organ donation

Table 4 lists reasons for participating in organ donation among the entire sample of participants. According to the findings, 35% of participants thought the message needed to come from a person similar to them, while 11% disagreed and 54% said it made no difference. A majority of participants (58%) said they would be inspired by a message that focused on the welfare of less fortunate people. However, the majority of participants did not have a preference for the demographics of the speaker promoting organ donation, such as their ethnic background or notoriety (44% and 38%, respectively).

DISCUSSION

Previous studies have considered the many hindrances that impede registering to be an organ donor, specifically in minority communities. One of the main reasons identified is a lack of awareness and

Table 3 Effects of the video among Hispanic participants not registered as organ donors

OR		95%CI	*P* value
Outcome			
Willingness to go back	2.05	1.06-3.97	0.03
Factors associated with OD			
Religious beliefs	1.54	0.64-3.72	0.34
Bodily integrity	0.89	0.50-1.58	0.69
Impact funeral proceedings	0.89	0.46-1.72	0.72
Treated differently by doctor	1.03	0.60-1.77	0.91
Recipient	0.89	0.49-1.62	0.70
Ick factor	1.65	0.82-3.32	0.16
Jinx factor	0.82	0.48-1.40	0.47
Health of donor	0.53	0.31-0.90	0.02
Age limit of donor	0.79	0.47-1.34	0.38
Treated differently by race	0.58	0.31-1.11	0.10
Notify relatives	1.13	0.60-2.10	0.71
Association with pain	0.58	0.22-1.55	0.28
Legal to buy an organ	0.60	0.33-1.12	0.11
Known where to sign up	1.11	0.66-1.86	0.70
Know process to sign up	1.08	0.62-1.85	0.79
Know can sign up at DMV	2.21	1.22-4.03	0.01
Know can sign up on online	0.97	0.55-1.71	0.91
Appropriate to be asked at DMV	0.74	0.43-1.25	0.26
Receive compensation	1.09	0.62-1.92	0.76
Receive funeral payment	1.02	0.60-1.72	0.10
Opt-out system	0.49	0.25-0.96	0.04

"OR" represents odds of selecting "Yes" to respective question for those in the Video First condition compared to those in the Video Last condition. OR: Odds ratio; CI: Confidence interval; DMV: Department of motor vehicle.

understanding about organ donation among minority communities. Many people in these communities may not be aware of the need for organ donation or may have misconceptions about the process. Additionally, there may be cultural and religious barriers to organ donation in some minority communities. Hence the importance of analyzing this subset of Hispanic participants to highlight some possible avenues of approach to overcome these hindrances using an effective educational intervention.

This analysis found that a previously established intervention had a significant effect on respondent willingness to register as donors. Participants who were not registered and exposed to the Video First condition were more likely to report their intention to register compared to those who were exposed to the Video Last condition. Additionally, our analysis indicates that participants not registered as donors knew they could register at the DMV and favored an opt-out system. When comparing these results with the results of our larger study. We see a similar level of willingness to donate after participating in the Video First condition. This indicates that Hispanic individuals are just as willing to become organ donors as their non-Hispanic counterparts when provided with the necessary information and education about the donation process.

Moreover, most Hispanic participants who indicated a preference were inclined to register when the messaging emphasized the needs of others and originated from a relatable person rather than a public figure. This suggests that delivering the message and the message communicates are essential. Interestingly, there were no preferences for ethnicity or race. This may be because of the cited confusion among respondents, particularly among Hispanics, regarding the classification of ethnicity and race [35]. Specifically, although more participants reported that they did want the message to come from someone like them, they may not identify with the traditional concepts of race and ethnicity. Further,

Table 4 Motives for organ donation among Hispanics, *n* (%)

	Total (*n* = 365)			Registered organ donor (*n* = 137)			Not registered organ donor (*n* = 228)		
	Yes	No	Doesn't matter	Yes	No	Doesn't matter	Yes	No	Doesn't matter
Receiving message from									
Someone like you	127 (35)	40 (11)	198 (54)	43 (31)	16 (12)	78 (57)	84 (37)	24 (11)	120 (53)
Same gender as you?	44 (12)	65 (18)	256 (70)	17 (12)	27 (20)	93 (68)	27 (12)	38 (17)	163 (71)
Same race as you?	45 (12)	64 (18)	256 (70)	19 (14)	27 (20)	91 (66)	26 (11)	37 (16)	165 (72)
Your community?	53 (14)	61 (17)	251 (69)	29 (21)	25 (18)	83 (61)	24 (11)	36 (16)	168 (74)
Economic status as you?	59 (16)	66 (18)	240 (66)	28 (20)	25 (18)	84 (61)	31 (14)	41 (18)	156 (68)
Own ethnic background?	44 (12)	66 (18)	255 (70)	15 (11)	29 (21)	93 (68)	29 (13)	37 (16)	162 (71)
Message of those in need?	139 (38)	60 (16)	166 (46)	50 (36)	23 (17)	64 (47)	89 (39)	37 (16)	102 (45)
A public figure?	38 (10)	90 (25)	237 (65)	17 (12)	35 (26)	85 (62)	21 (9)	55 (24)	152 (67)
Motivated by hearing from									
Relatives of organ donor	214 (56)	-	-	94 (44)	-	-	120 (56)		
Recipient of organ donation	183 (48)	-	-	82 (45)	-	-	101 (55)		
Family of recipient who died waiting	209 (55)	-	-	81 (39)	-	-	128 (61)		
Physician or provider	120 (32)	-	-	61 (51)	-	-	59 (49)		
Other	10 (3)			5 (50)	-	-	5 (50)		

Frequency of responses regarding motivation to participation in an organ donor program.

some Hispanics may identify with more than one race or ethnic category, therefore participants may not agree with the defined constructs by the federal administrative guidelines. Our findings also suggest that future interventions could be effectively implemented at the DMV, in primary care settings, or with a trusts and estate lawyer, especially when the messaging is tailored to sociocultural content.

Limitations

The study that served as the foundation for the current analysis concentrated more on participants' intentions to give organs than on their actual registration as donors. The transtheoretical model, however, proposes that analyzing intention is a crucial first step in boosting donor registration rates [36]. Therefore, by examining how knowledge, motivations, and attitudes concerning organ donation change as a result of the intervention, we sought to address the first two stages of the model (awareness and reflection). A comparable video intervention should be studied in more detail to see how it affects actual donor registration rates. The use of an online poll in this study is another potential weakness. Although we used attention checks to guarantee data quality and contact a variety of potential donors in New York City, future studies should utilize alternate settings to replicate our findings.

CONCLUSION

Overall, disparities in organ donation among minority groups are a significant problem that needs to be addressed. Increasing awareness and understanding about organ donation in minority communities, improving access to healthcare, and increasing representation on organ transplant messaging materials

are all steps that can help reduce these disparities and improve access to life-saving organ transplantation for minority communities.

ARTICLE HIGHLIGHTS

Research background

Research has documented barriers to organ donation, including: (1) Bodily integrity; (2) medical skepticism; (3) "ick"-discomfort toward the process; and (4) "jinx"-superstitions regarding preparations toward death. Furthermore, emotional video messaging is impactful in increasing the intention to register. While the emotional video messaging used in the present study was found to increase the intention to register among the Hispanic population.

Research motivation

Given the backdrop of shortages of organ donations and the benefits of a more diverse donor pool. In New York City (NYC), a place renowned for its diverse population, our goal was to evaluate the effects of a brief educational intervention meant to increase organ donation intentions. Additionally, we wanted to learn more about the attitudes and beliefs of Hispanic inhabitants of NYC toward organ donation as well as the predictors of it.

Research objectives

We hypothesized that an educational video addressing commonly cited barriers to organ donation would help ease resistance and change attitudes regarding intentions to donate.

Research methods

Data were collected using the online crowdsourcing platform CloudResearch targeting NYC residents. This study was approved by our Institutional IRB. Once consent was obtained and participants entered the survey, respondents were asked to report on demographic variables and their general impression of organ donation after death. Participants were then assigned at random to the video First condition, in which they saw a brief movie on organ donation before responding to the survey questions, or the Video Last condition, in which they answered the survey questions first and then watched the video. The five-minute intervention implemented was originally developed, tested, and found to significantly increase donation rates in a general population. The video presented a dialogue among twenty ethnically diverse individuals in terms of age and their experiences regarding organ donation, including donors, recipients, and loved ones of those who died while waiting for organ donation. Furthermore, the video has been found to elicit emotional responses and address concerns that are common barriers to donor registration.

Research results

Using a binomial logistic regression, the analysis provides information about the relationship between the effects of an emotive video and the intention to donate among Hispanic participants who were not already registered as donors. The willingness to go back and register was found to be significantly more probable for those who watched the emotive video before being asked about their organ donation opinions [OR: 2.05, 95%CI: 1.06-3.97] (as presented in Table 3). Motivations for participation in organ donation were also captured in Table 4, with many stating the importance of messages coming from "people like me" and a message that highlights "the welfare of those in need". Overall, the findings suggest that using an emotive video that addresses organ donation barriers to prompt organ donation intentions can be effective among the Hispanic populous. Future studies should explore using targeted messaging that resonates with specific cultural groups, highlighting the welfare of others.

Research conclusions

The wide variations in organ donation rates across the United States present both a problem and a chance. Our analysis has demonstrated that future campaigns must concentrate on densely populated, diversified locations with low donor rates if they are to boost organ donation registration. Educational initiatives that elicit strong emotions, address donor concerns, and take into account potential donors' preferences must be conducted to increase the overall registration rate. By implementing these actions, we have the potential to significantly alter the situation and save the lives of thousands of people who pass away each year while awaiting organ transplants.

Research perspectives

Future research should examine how video intervention affects actual donor registration to have a more thorough understanding of its effects. Although we used attention checks to confirm the accuracy of the data, it is advised that future research replicate our findings in various contexts.

FOOTNOTES

Author contributions: Pekmezaris R, Patel V, and Molmenti E designed and supervised the study; Cigaran E conducted data analysis and interpretation, and drafted the manuscript; Pekmezaris R, Patel V, Molmenti E, and Cigaran E conducted a literature review; Clement D contributed to data analysis and interpretation; Sardo Molmenti CL revised the manuscript critically for intellectual content; Molmenti E and Pekmezaris R approved the final version of the paper.

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REFERENCES

1 **Health Resources and Services Administration**. Organ Donation Statistics. United States Department of Health & Human Services. Organ Donation Statistics. November 17, 2018. [cited 20 April 2023]. Available from: https://www.organdonor.gov/statistics-stories/statistics.html#glance
2 **Cardon JH**, Holbrook JC, Showalter MH. Estimating the effect of focused donor registration efforts on the number of organ donors. *PLoS One* 2020; **15**: e0241672 [PMID: 33147294 DOI: 10.1371/journal.pone.0241672]
3 **Grantham DA**. Transforming transplantation: The effect of the health and human services final rule on the organ allocation system. *USFL Rev* 2000; **35**: 751
4 **Duda L**. National organ allocation policy: the final rule. *Virtual Mentor* 2005; **7** [PMID: 23253588 DOI: 10.1001/virtualmentor.2005.7.9.hlaw1-0509]
5 **CenterState CEO**. Rate of registered organ donors grows, but state and regional rates still lag national rate. January 24, 2023. [cited 20 April 2023]. Available from: https://centerstateceo.com/news-events/rate-registered-organ-donors-grows-state-and-regional-rates-still-lag-national-rate
6 **Nowakowski B**. Colorado is Number One in the nation for highest donor designation rate (DDR). Donate Life Colorado. December 20, 2022. [cited 20 April 2023]. Available from: https://www.donatelifecolorado.org/blog/colorado-is-now-number-one-in-the-nation-for-highest-donor-designation-rate
7 **Register to Become an Organ and Tissue Donor Today**. New York State Donate Life Registry. January 24, 2023. [cited 20 April 2023]. Available from: https://donatelife.ny.gov/about-donation/
8 **Li AH**, Lo M, Crawshaw JE, Dunnett AJ, Naylor KL, Garg AX, Presseau J. Interventions for increasing solid organ donor registration. *Cochrane Database Syst Rev* 2021; **4**: CD10829 [PMID: 35608942 DOI: 10.1002/14651858.CD010829.pub2]
9 **Donate Life America**. Does Race Matter in Organ Donation and Transplant? August 2, 2022. [cited 20 April 2023]. Available from: https://www.donatelife.net/race-ethnicity-and-donation/
10 **HHS gov**. Office of Minority Health (no date) Home Page-Office of Minority Health (OMH). December 13, 2022. [cited 20 April 2023]. Available from: https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4
11 **United States Census Bureau**. QuickFacts: United States. June 22, 2020. [cited 20 April 2023]. Available from: https://www.census.gov/quickfacts/NY
12 **Kernodle AB**, Zhang W, Motter JD, Doby B, Liyanage L, Garonzik-Wang J, Jackson KR, Boyarsky BJ, Massie AB,

Purnell TS, Segev DL. Examination of Racial and Ethnic Differences in Deceased Organ Donation Ratio Over Time in the US. *JAMA Surg* 2021; **156**: e207083 [PMID: 33566079 DOI: 10.1001/jamasurg.2020.7083]

13 **Alvarado F**, Cervantes CE, Crews DC, Blanck J, Al Ammary F, Ng DK, Purnell TS. Examining post-donation outcomes in Hispanic/Latinx living kidney donors in the United States: A systematic review. *Am J Transplant* 2022; **22**: 1737-1753 [PMID: 35258164 DOI: 10.1111/ajt.17017]

14 **Desai N**, Lora CM, Lash JP, Ricardo AC. CKD and ESRD in US Hispanics. *Am J Kidney Dis* 2019; **73**: 102-111 [PMID: 29661541 DOI: 10.1053/j.ajkd.2018.02.354]

15 **Hall YN**. Social Determinants of Health: Addressing Unmet Needs in Nephrology. *Am J Kidney Dis* 2018; **72**: 582-591 [PMID: 29548780 DOI: 10.1053/j.ajkd.2017.12.016]

16 **Crews DC**, Liu Y, Boulware LE. Disparities in the burden, outcomes, and care of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2014; **23**: 298-305 [PMID: 24662984 DOI: 10.1097/01.mnh.0000444822.25991.f6]

17 **Aguayo-Mazzucato C**, Diaque P, Hernandez S, Rosas S, Kostic A, Caballero AE. Understanding the growing epidemic of type 2 diabetes in the Hispanic population living in the United States. *Diabetes Metab Res Rev* 2019; **35**: e3097 [PMID: 30445663 DOI: 10.1002/dmrr.3097]

18 **Centers for Disease Control and Prevention**. National Diabetes Statistics Report, 2020. Centers for Disease Control and Prevention, United States Dept of Health and Human Services; 2020. October 5, 2021. [cited 20 April 2023]. Available from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

19 **U. S. Department of Health and Human Services**. USRD System 2020 USRDS Annual Data Report: epidemiology of kidney disease in the United States. 2020. [cited 20 April 2023]. Available from: https://adr.usrds.org/2020

20 **AlRuthia Y**, Sales I, Almalag H, Alwhaibi M, Almosabhi L, Albassam AA, Alharbi FA, Bashatah A, Asiri Y. The Relationship Between Health-Related Quality of Life and Trust in Primary Care Physicians Among Patients with Diabetes. *Clin Epidemiol* 2020; **12**: 143-151 [PMID: 32104098 DOI: 10.2147/CLEP.S236952]

21 **Alpers LM**. Distrust and patients in intercultural healthcare: A qualitative interview study. *Nurs Ethics* 2018; **25**: 313-323 [PMID: 27284017 DOI: 10.1177/0969733016652449]

22 **Berry LL**, Parish JT, Janakiraman R, Ogburn-Russell L, Couchman GR, Rayburn WL, Grisel J. Patients' commitment to their primary physician and why it matters. *Ann Fam Med* 2008; **6**: 6-13 [PMID: 18195309 DOI: 10.1370/afm.757]

23 **Nutbeam D**. Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. *Health Promot Int* 2000; **15**: 267 [DOI: 10.1093/heapro/15.3.259]

24 **Berkman ND**, Davis TC, McCormack L. Health literacy: what is it? *J Health Commun* 2010; **15** Suppl 2: 9-19 [PMID: 20845189 DOI: 10.1080/10810730.2010.499985]

25 **Hälleberg Nyman M**, Nilsson U, Dahlberg K, Jaensson M. Association Between Functional Health Literacy and Postoperative Recovery, Health Care Contacts, and Health-Related Quality of Life Among Patients Undergoing Day Surgery: Secondary Analysis of a Randomized Clinical Trial. *JAMA Surg* 2018; **153**: 738-745 [PMID: 29710226 DOI: 10.1001/jamasurg.2018.0672]

26 **Sewell AA**. Inequality: Live poor, die young. *Nature* 2017; **18** ; 545: 286-287 [DOI: 10.1038/545286a]

27 **Gordon EJ**, Shand J, Black A. Google analytics of a pilot mass and social media campaign targeting Hispanics about living kidney donation. *Internet Interv* 2016; **6**: 40-49 [PMID: 30135813 DOI: 10.1016/j.invent.2016.09.002]

28 **Murphy MD**, Pinheiro D, Iyengar R, Lim G, Menezes R, Cadeiras M. A Data-Driven Social Network Intervention for Improving Organ Donation Awareness Among Minorities: Analysis and Optimization of a Cross-Sectional Study. *J Med Internet Res* 2020; **22**: e14605 [PMID: 31934867 DOI: 10.2196/14605]

29 **English V**. Is presumed consent the answer to organ shortages? Yes. *BMJ* 2007; **334**: 1088 [PMID: 17525449 DOI: 10.1136/bmj.39199.475301.AD]

30 **Wright L**. Is presumed consent the answer to organ shortages? No. *BMJ* 2007; **334**: 1089 [PMID: 17525450 DOI: 10.1136/bmj.39199.492894.AD]

31 **Coppen R**, Friele RD, Marquet RL, Gevers SK. Opting-out systems: no guarantee for higher donation rates. *Transpl Int* 2005; **18**: 1275-1279 [PMID: 16221158 DOI: 10.1111/j.1432-2277.2005.00202.x]

32 **Rithalia A**, McDaid C, Suekarran S, Myers L, Sowden A. Impact of presumed consent for organ donation on donation rates: a systematic review. *BMJ* 2009; **338**: a3162 [PMID: 19147479 DOI: 10.1136/bmj.a3162]

33 **Molmenti EP**, Finuf KD, Patel VH, Molmenti CL, Thornton D, Pekmezaris R. A Randomized Intervention to Assess the Effectiveness of an Educational Video on Organ Donation Intent. *Kidney360* 2021; **2**: 1625-1632 [PMID: 35372974 DOI: 10.34067/KID.0001392021]

34 **Thornton JD**, Alejandro-Rodriguez M, León JB, Albert JM, Baldeon EL, De Jesus LM, Gallardo A, Hossain S, Perez EA, Martin JY, Lasalvia S, Wong KA, Allen MD, Robinson M, Heald C, Bowen G, Sehgal AR. Effect of an iPod video intervention on consent to donate organs: a randomized trial. *Ann Intern Med* 2012; **156**: 483-490 [PMID: 22473435 DOI: 10.7326/0003-4819-156-7-201204030-00004]

35 **Smith FD**, Woo M, Austin SB. 'I didn't feel like any of those things were me': results of a qualitative pilot study of race/ethnicity survey items with minority ethnic adolescents in the USA. *Ethn Health* 2010; **15**: 621-638 [PMID: 20799118 DOI: 10.1080/13557858.2010.503872]

36 **Prochaska JO**, Velicer WF. The transtheoretical model of health behavior change. *Am J Health Promot* 1997; **12**: 38-48 [PMID: 10170434 DOI: 10.4278/0890-1171-12.1.38]

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CASE REPORT

Efficacy and safety of local candida immunotherapy in recalcitrant warts in pediatric kidney transplantation: A case report

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Abstract

BACKGROUND

Warts are common in recipients of kidney transplantation (KT). Resistant warts which are not amenable to conventional therapies may lead to significant morbidity. Limited data exists on safety and efficacy of local immunotherapy among immunocompromised KT recipients.

CASE SUMMARY

We report a seven-year-old child who presented with recalcitrant plantar periungual warts in the early KT period. Immunosuppression consisted of tacrolimus, mycophenolate and steroid. Due to failure of conventional anti-wart therapies, he was treated with two sessions of intralesional (IL) candida immunotherapy along with liquid nitrogen cryotherapy leading to complete resolution of the warts. Interestingly, de novo BK viremia was seen about three weeks following the last candida immunotherapy. This required reduction of immunosuppression and other anti-BK viral therapies. Allograft function remained stable but there were donor specific antibodies detected. There also was elevated level of plasma donor derived cell-free DNA. A *pneumocystis jirovecii* pneumonia occurred ten months following completion of immunotherapy that was successfully treated with trimethoprim-sulfamethoxazole. During this ten-month follow-up period, there have been no recurrence of warts, and transplant kidney function has remained stable.

CONCLUSION

Stimulation of cell-mediated immunity against the human papilloma virus induced by the IL candida immunotherapy is thought to be a cause for wart resolution. With this therapy, whether it is necessary to augment the immunosuppression to prevent rejection is unclear as that may come with a risk of infectious complications. Larger, prospective studies in pediatric KT recipients are needed to

explore these important issues.

Key Words: Warts; Kidney transplantation; Candida; Immunotherapy; Pediatric; Case report

Core Tip: Warts are common after pediatric kidney transplantation. Given immunosuppressed status, most children are unable to clear the warts with conventional anti-wart therapies. Local immunotherapy has emerged as an excellent treatment modality for treatment of resistant warts following kidney transplantation. However, the safety of such agents needs careful consideration with longitudinal studies. Here, we studied the efficacy and safety of local candida immunotherapy in an immunocompromised child with kidney transplantation and recalcitrant plantar warts.

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INTRODUCTION

Cutaneous common warts (verruca vulgaris) are commonly seen after kidney transplantation (KT)[1-3]. In one study of 60 children and adolescents with KT, the incidence of warts was 28% with increased prevalence with time since KT. Plantar warts are the most common warts following KT[4]. The most common immunosuppressive regimen in these patients was tacrolimus and prednisone, in combination with either azathioprine or mycophenolate mofetil (MMF). The most commonly seen human papillomavirus (HPV) strains responsible for common warts are HPV-2, 27, 29, 34 and 57[5]. Painful warts can impair the quality of life and cause significant morbidity[6]. Unlike in non-immunocompromised individuals, warts in KT recipients may not undergo spontaneous resolution. Although the risk of cancerous conversion is primarily seen with genital warts, multiple verrucae (> 10 verrucae) may be associated with the development of actinic keratoses, invasive squamous cell carcinoma and basal cell carcinoma[7]. Some of the treatment options are topical keratolytics such as salicylate, cryotherapy with liquid nitrogen, electrofulguration or radiofrequency ablation, duct tape, pulsed dye or CO_2 laser, intralesional (IL) bleomycin, surgical removal with curettage or cautery, and IL immunotherapy[8]. Here we describe a seven-year-old KT recipient with recalcitrant plantar warts who had an excellent response to the IL candida immunotherapy with no recurrence in the short-term follow-up of ten months.

CASE PRESENTATION

Chief complaints

A seven-year-old Caucasian male presented with multiple wart-like lesions in the plantar aspect of both foot after KT.

History of present illness

The patient had received a pre-emptive first living unrelated donor KT with bilateral native nephrectomies one month prior to the onset of the skin warts. He sustained early loss of renal allograft secondary to transplant renal artery thrombosis. Transplant kidney biopsy showed coagulative necrosis and he was transitioned to chronic hemodialysis until receiving a second deceased donor KT two months later with excellent allograft function. Induction immunosuppression (IS) for both first and second KT consisted of three doses of 1.5 mg/kg/dose Thymoglobulin^R with steroid. Low dose tacrolimus and MMF were continued after the first failed KT. The first allograft was removed during the second KT. Maintenance IS for second KT consisted of tacrolimus, MMF and steroid. Serum trough tacrolimus level was maintained at the goal range.

History of past illness

The past medical history consisted of end stage renal disease secondary to posterior urethral valve. He however did not require dialysis given stable electrolytes and normal urine output. He had been immunized fully as per the routine childhood immunization schedule.

Personal and family history

The patient's personal and family history was otherwise unremarkable.

Physical examination

Physical examination of the patient showed normal vital signs and examination except for the abdomen with scar marks from prior surgeries and positive skin findings. Skin examination showed multiple verrucous papules and plaques on the anterior aspect of the plantar surface of foot bilaterally (Figures 1A and B), and some papular lesions in the left thumb. There were no warts seen in the genital region or the oropharynx region. The warts were extremely painful and would wake him throughout the night. The patient had difficulty ambulating and had to be carried to the clinic visits.

Laboratory examinations

Complete blood count was normal. Renal allograft function remained stable after second KT with serum creatinine of 0.5-0.6 mg/dL. C-reactive protein was normal. Serum trough tacrolimus level was at the goal of 9-11 ng/mL in the first month post KT, then 8-10 ng/mL in the second month, followed by 6-8 ng/mL from three to six months post KT. Urinalysis showed no proteinuria, hematuria or urinary tract infections. Given cytomegalovirus (CMV) mismatch, he received oral valganciclovir for six months post-KT. CMV, Epstein-Barr virus and BK virus polymerase chain reaction (PCR)s were all negative until six months post KT. HPV genotyping of the warts was not done.

Imaging examinations

Chest X-ray was negative for pneumonia or other viral processes. Renal allograft sonogram was normal.

FINAL DIAGNOSIS

Plantar warts in a child with kidney transplantation.

TREATMENT

He was evaluated by dermatologist and was treated with lidocaine ointment, WartPEEL (17% salicylic acid and 2% 5-fluorouracil), WartSTICK (40% salicylic acid), and Differin (0.3% Adapalene gel) under occlusion for several weeks without any clinical improvement of the signs and symptoms. Six months after the first KT, he was treated with a first dose of Candin^{R} (IL *Candida albicans* antigen) to the largest wart paired with liquid nitrogen cryotherapy. Second dose of IL Candin^{R} and liquid nitrogen was administered four weeks later.

OUTCOME AND FOLLOW-UP

The patient had a significant improvement with almost complete resolution of the warts after two Candin^{R} paired with liquid nitrogen cryotherapy. Complete resolution was indicated by complete disappearance of the hyperkeratosis and thickening of the skin. Due to the presence of few scattered lesions only, a third dose of liquid nitrogen cryotherapy was administered two months later without IL Candin^{R}. There were no side effects observed such as blister, infection, post-inflammatory altered pigmentation, scarring or anaphylaxis. During a ten-month follow-up period since the second and last Candin^{R} therapy, there have been no recurrences of the warts (Figure 1C).

Three weeks after the first Candin^{R} injection, a follow-up whole blood BK virus deoxyribonuclease (DNA) PCR showed BK viral load of 159000 copies/mL (ARUP laboratories, Salt Lake City, UT, United States). His immunosuppression regimen had been same as before and his allograft function was stable. Following this, his tacrolimus dose was reduced with a lower trough goal level of 3-5 ng/mL, mycophenolate was discontinued and leflunomide was started. Over the next one year, his BK virus DNA PCR showed persistent positivity with a peak viral load of 453000 copies/mL seven months post last Candin^{R} therapy. He then received two monthly intravenous (IV) immunoglobulin therapies and a course of IV cidofovir with the most recent BK virus load of 6280 copies/mL ten months after the last Candin^{R} therapy (Figure 2). The most recent immunosuppression regimen consists of tacrolimus 2 mg twice daily, prednisone 10 mg daily and leflunomide 20 mg daily.

Donor specific antibodies (DSA) were obtained monthly as a part of the transplant center's protocol. Four months after the last Candin^{R} injection, weak DSA to class I antigens [B58, C12; 2500 mean fluorescent intensity (MFI) for both] were observed. Subsequently, strong DSAs against class II antigen (DQ6, 10000 MFI) also started appearing a month later. However, the serum creatinine remained stable around 0.6-0.7 mg/dL. He was treated with intravenous immunoglobulin and a dose of Rituximab 375

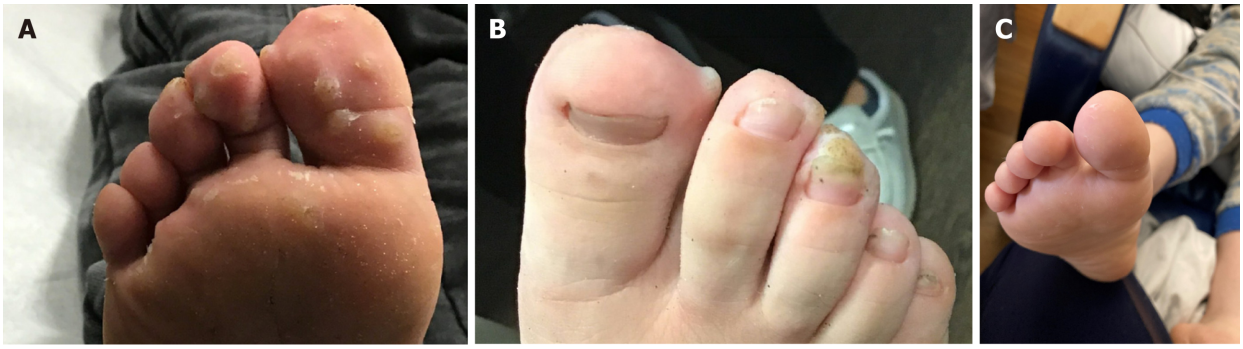

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Figure 1 Response to Candin^{R} treatment. A: Plantar warts before Candin^{R} treatment; B: Periungual plantar warts before Candin^{R} treatment; C: Resolution of plantar warts after Candin^{R} treatment.

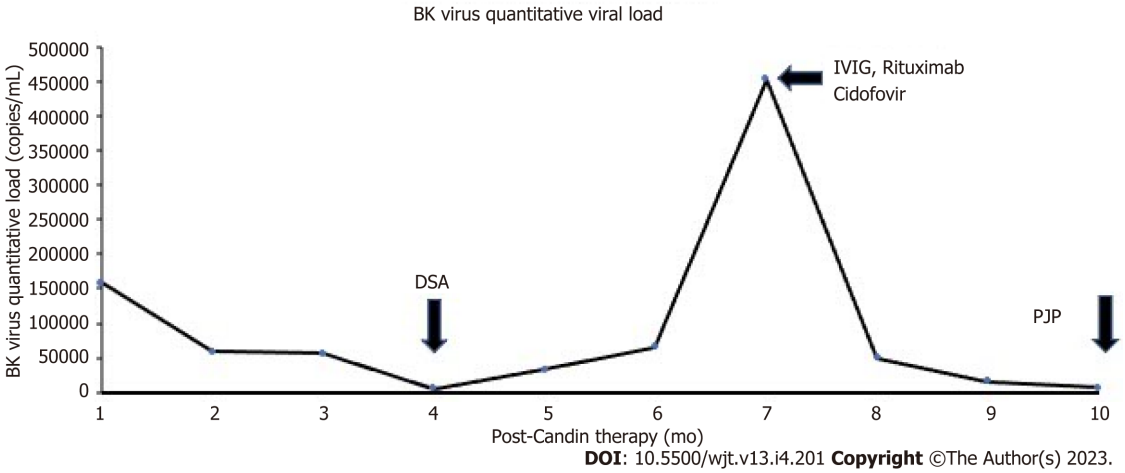

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Figure 2 Association of Candin^{R} treatment with BK viremia, donor specific antibodies and *pneumocystic carinii* pneumonia. DSA: Donor specific antibodies; IVIG: Intravenous immunoglobulin; PJP: *Pneumocystic carinii* pneumonia.

mg/m^2. A kidney transplant biopsy could not be obtained due to parental hesitation. However, a plasma donor-derived cell-free DNA (dd-cfDNA) test showed elevated value of 1.21% (reference range: < 0.7% dd-cfDNA, Viracor TRAC kidney dd-cfDNA, Eurofins Transplant Genomics, Framingham, MA, United States). A decision was made to serially follow the dd-cfDNA and DSA closely given stable serum creatinine.

Ten months after the last Candin^{R} therapy, he presented with hypoxia and respiratory distress with chest X-ray showing ground-glass opacities in the lungs. He underwent bronchoscopy; the PCR of the bronchoalveolar lavage was positive for *pneumocystis jirovecii* and diagnosed with *pneumocystis jirovecii* pneumonia (PJP). He was treated with trimethoprim-sulfamethoxazole with complete resolution of respiratory symptoms. Immunosuppression was kept the same with a goal trough tacrolimus level of 3-5 ng/mL.

DISCUSSION

In patients with cutaneous warts with suboptimal or no response to conventional anti-wart therapies, IL immunotherapy may be useful[9,10]. Various IL immunotherapy regimen have been described such as candida antigen, mumps antigen, measles mumps rubella vaccine, purified protein derivative and bacilli calmette-guerin vaccine[10]. One systematic review showed 68% cure-rate of local immunotherapy in plantar warts, as opposed to low cure rate with topical salicylic acid and cryotherapy[11]. A randomized placebo-controlled trial by Horn *et al*[12] showed excellent efficacy of IL candida, mumps or trichophyton skin test antigens. The possible mechanism of action of immunotherapy is the proliferation of HPV-specific peripheral blood mononuclear cells that possibly mediate an immunologic attack against the wart tissue[13].

Data on efficacy of IL candida in children is scarce[14]. Alikhan *et al*[15] reported a retrospective study of 100 adults and children with verruca vulgaris who were treated with IL purified candida antigen therapy with 39% complete response and 41% partial response rate. In their study, six out of seven patients who were immunocompromised demonstrated partial or complete response rate. The proposed mechanism is *via* stimulation of a cell-mediated immune response. Phillips *et al*[13] retrospectively reviewed adults and children who received monthly IL candida antigen with 72% complete resolution rate. Another retrospective study of 220 children with multiple and recalcitrant warts who received IL candida injections showed 71% and 17% complete and partial response rates respectively. There were no side effects reported except for some discomfort at the time of injection[16]. IL *Candida* immunotherapy has also been shown to be efficacious in treating the distant non-injected warts[17]. Whether the similar results are expected in immunocompromised individuals needs to be studied on a larger scale.

With regards to immunosuppressed patients, the prevalence of warts corresponds with the duration of immunosuppressive therapy, increasing to 50%-92% in patients who are more than 4-5 years after transplantation[3]. Our report is unique in that the onset of warts was fairly rapid following KT. In most HPV infections in immunocompetent individuals, the cellular and cytotoxic immunity provided by T cells and natural killer cells are sufficient to control the warts[18]; however, in immunocompromised patients, due to lack of cell-mediated immunity, the proliferation of virus occurs causing warts, sometimes in unusual locations such as bladder[19,20]. Indeed, a few studies have reported clearance of the warts with reduction or cessation of immunosuppression only in KT recipients[21,22]. Conversion to another anti-rejection agent may be useful as well. Nguyen *et al*[23] reported 4 children with warts and molluscum contagiosum who benefited from conversion from tacrolimus/mycophenolate to tacrolimus/Leflunomide. Conversion to sirolimus has been shown to be effective for recalcitrant cutaneous viral warts in liver transplant recipients[24,25]. There is not much data on the efficacy of the IL immunotherapy. In patients who do undergo local immunotherapy, it is not known whether immunosuppression decreases the efficacy of local immunotherapy such as IL candida. Immunosuppression usually is at the maximal level during the first few months of KT and it will be interesting to study the efficacy of these immunotherapies during this period of maximal immunosuppression. On the other hand, there are also potential safety concerns with stimulating cell-mediated immunity with IL Candida therapy leading to rejection[26]. Few studies done in the children on warts have not looked at these longitudinal issues[4]. In our patient, there was a temporal relationship between the onset of BK viremia and Candin^{R} therapy along with observation of DSA, elevated dd-cfDNA, and PJP a few months following the completion of Candin^{R}. However, we could not establish a direct cause and relationship between IL candida and these findings. Since dd-cfDNA has been shown to diagnose subclinical rejection even in the absence of deranged renal function, this test may be important in children who have underwent IL candida therapy for establishing an early diagnosis of rejection and possibly close monitoring and treatment[27]. In those with concurrent viral infections and elevated dd-cfDNA, it is challenging to decide the amount of immunosuppression, as in our case. Also, since children with current BK viremia have been shown to have significantly higher median plasma dd-cfDNA, the importance of elevated dd-cfDNA in this subset of children is uncertain[28]. Also, as seen in this report, there may be as association between BK virus and HPV as both belong to the human papovavirus family. These are important topics of discussion that will need to be studied in further larger studies.

CONCLUSION

A decision of whether to treat with immunotherapy such as IL candida in immunocompromised transplant recipients is challenging due to concerns with efficacy and the possibility of rejection, and perhaps infections. Well-designed prospective studies are needed in the future to determine the efficacy and safety of this potentially curative treatment for the recalcitrant warts.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design, writing; Acharya R, Bush R, and Johns F were involved in the acquisition of the clinical data, analysis, and interpretation; Upadhyay K was involved in the critical revision.

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REFERENCES

1 **Oliveira WRP**, Tirico MCCP, Souza AAV, Codarin FR, Silva LLC, Festa Neto C. Skin lesions in organ transplant recipients: a study of 177 consecutive Brazilian patients. *Int J Dermatol* 2019; **58**: 440-448 [PMID: 30565651 DOI: 10.1111/ijd.14285]
2 **Oh CC**, Lee HY, Tan BK, Assam PN, Kee TYS, Pang SM. Dermatological conditions seen in renal transplant recipients in a Singapore tertiary hospital. *Singapore Med J* 2018; **59**: 519-523 [PMID: 30386860 DOI: 10.11622/smedj.2018126]
3 **Dyall-Smith D**, Trowell H, Dyall-Smith ML. Benign human papillomavirus infection in renal transplant recipients. *Int J Dermatol* 1991; **30**: 785-789 [PMID: 1661712 DOI: 10.1111/j.1365-4362.1991.tb04787.x]
4 **Lunn A**, Ravenscroft J, Watson AR. Cutaneous warts in children before and after renal transplantation. *Pediatr Nephrol* 2010; **25**: 941-946 [PMID: 20024587 DOI: 10.1007/s00467-009-1390-8]
5 **Martelli-Marzagão F**, Yamashiro AS, Ogawa MM, Santos GF Jr, Tomimori J, Porro AM. Clinical and histopathological characterization and typing of the human papillomavirus in common warts of kidney transplant recipients. *An Bras Dermatol* 2010; **85**: 743-746 [PMID: 21152808 DOI: 10.1590/s0365-05962010000500027]
6 **Moloney FJ**, Keane S, O'Kelly P, Conlon PJ, Murphy GM. The impact of skin disease following renal transplantation on quality of life. *Br J Dermatol* 2005; **153**: 574-578 [PMID: 16120145 DOI: 10.1111/j.1365-2133.2005.06699.x]
7 **Cho CY**, Lo YC, Hung MC, Lai CC, Chen CJ, Wu KG. Risk of cancer in patients with genital warts: A nationwide, population-based cohort study in Taiwan. *PLoS One* 2017; **12**: e0183183 [PMID: 28806741 DOI: 10.1371/journal.pone.0183183]
8 **Gibbs S**, Harvey I. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev* 2006; CD001781 [PMID: 16855978 DOI: 10.1002/14651858.CD001781.pub2]
9 **Bhalala KB**, Poojary S, Shah KS. Comparative Study of Efficacy of Intralesional Purified Protein Derivative (PPD) Versus Intralesional Measles, Mumps, and Rubella (MMR) Vaccine in Management of Multiple Viral Warts. *J Cutan Aesthet Surg* 2021; **14**: 397-403 [PMID: 35283602 DOI: 10.4103/JCAS.JCAS_166_19]
10 **Fields JR**, Saikaly SK, Schoch JJ. Intralesional immunotherapy for pediatric warts: A review. *Pediatr Dermatol* 2020; **37**: 265-271 [PMID: 31930595 DOI: 10.1111/pde.14094]
11 **García-Oreja S**, Álvaro-Afonso FJ, García-Álvarez Y, García-Morales E, Sanz-Corbalán I, Lázaro Martínez JL. Topical treatment for plantar warts: A systematic review. *Dermatol Ther* 2021; **34**: e14621 [PMID: 33263934 DOI: 10.1111/dth.14621]
12 **Horn TD**, Johnson SM, Helm RM, Roberson PK. Intralesional immunotherapy of warts with mumps, Candida, and Trichophyton skin test antigens: a single-blinded, randomized, and controlled trial. *Arch Dermatol* 2005; **141**: 589-594 [PMID: 15897380 DOI: 10.1001/archderm.141.5.589]
13 **Phillips RC**, Ruhl TS, Pfenninger JL, Garber MR. Treatment of warts with Candida antigen injection. *Arch Dermatol* 2000; **136**: 1274-1275 [PMID: 11030787 DOI: 10.1001/archderm.136.10.1274-a]
14 **Majid I**, Imran S. Immunotherapy with intralesional Candida albicans antigen in resistant or recurrent warts: a study. *Indian J Dermatol* 2013; **58**: 360-365 [PMID: 24082180 DOI: 10.4103/0019-5154.117301]
15 **Alikhan A**, Griffin JR, Newman CC. Use of Candida antigen injections for the treatment of verruca vulgaris: A two-year mayo clinic experience. *J Dermatolog Treat* 2016; **27**: 355-358 [PMID: 26558635 DOI: 10.3109/09546634.2015.1106436]
16 **Muñoz Garza FZ**, Roé Crespo E, Torres Pradilla M, Aguilera Peirò P, Baltà Cruz S, Hernández Ruiz ME, Baselga Torres E. Intralesional Candida Antigen Immunotherapy for the Treatment of Recalcitrant and Multiple Warts in Children. *Pediatr Dermatol* 2015; **32**: 797-801 [PMID: 26584692 DOI: 10.1111/pde.12667]
17 **Maronn M**, Salm C, Lyon V, Galbraith S. One-year experience with candida antigen immunotherapy for warts and molluscum. *Pediatr Dermatol* 2008; **25**: 189-192 [PMID: 18429776 DOI: 10.1111/j.1525-1470.2008.00630.x]
18 **McBride AA**. Human papillomaviruses: diversity, infection and host interactions. *Nat Rev Microbiol* 2022; **20**: 95-108 [PMID: 34522050 DOI: 10.1038/s41579-021-00617-5]
19 **Leiding JW**, Holland SM. Warts and all: human papillomavirus in primary immunodeficiencies. *J Allergy Clin Immunol* 2012; **130**: 1030-1048 [PMID: 23036745 DOI: 10.1016/j.jaci.2012.07.049]
20 **Sarier M**, Ozel E, Duman I, Yuksel Y, Demirbas A. HPV type 45-positive condyloma acuminata of the bladder in a renal

transplant recipient. *Transpl Infect Dis* 2017; **19** [PMID: 28100036 DOI: 10.1111/tid.12667]

21 **Maor D**, Brennand S, Goh MSY, Chong AH. Recalcitrant hyperkeratotic verrucae in a renal transplant recipient clearing with cessation of immunosuppression. *JAAD Case Rep* 2018; **4**: 471-473 [PMID: 29984286 DOI: 10.1016/j.jdcr.2017.09.025]

22 **Ash MM**, Jolly PS. A Case Report of the Resolution of Multiple Recalcitrant Verrucae in a Renal Transplant Recipient After a Mycophenolate Mofetil Dose Reduction. *Transplant Proc* 2017; **49**: 213-215 [PMID: 28104140 DOI: 10.1016/j.transproceed.2016.11.030]

23 **Nguyen L**, McClellan RB, Chaudhuri A, Alexander SR, Chen SF, Concepcion W, Grimm P. Conversion from tacrolimus/mycophenolic acid to tacrolimus/Leflunomide to treat cutaneous warts in a series of four pediatric renal allograft recipients. *Transplantation* 2012; **94**: 450-455 [PMID: 22960763 DOI: 10.1097/TP.0b013e318264351e]

24 **Dharancy S**, Catteau B, Mortier L, Boleslawski E, Declerck N, Canva V, Piette F, Mathurin P, Pruvot FR. Conversion to sirolimus: a useful strategy for recalcitrant cutaneous viral warts in liver transplant recipient. *Liver Transpl* 2006; **12**: 1883-1887 [PMID: 17133572 DOI: 10.1002/Lt.20927]

25 **Shahidi S**, Moeinzadeh F, Mohammadi M, Gholamrezaei A. Sirolimus-based immunosuppression for treatment of cutaneous warts in kidney transplant recipients. *Iran J Kidney Dis* 2011; **5**: 351-353 [PMID: 21876315]

26 **Kawashima S**, Joachim K, Abdelrahim M, Abudayyeh A, Jhaveri KD, Murakami N. Immune checkpoint inhibitors for solid organ transplant recipients: clinical updates. *Korean J Transplant* 2022; **36**: 82-98 [PMID: 35919193 DOI: 10.4285/kjt.22.0013]

27 **Park S**, Guo K, Heilman RL, Poggio ED, Taber DJ, Marsh CL, Kurian SM, Kleiboeker S, Weems J, Holman J, Zhao L, Sinha R, Brietigam S, Rebello C, Abecassis MM, Friedewald JJ. Combining Blood Gene Expression and Cellfree DNA to Diagnose Subclinical Rejection in Kidney Transplant Recipients. *Clin J Am Soc Nephrol* 2021; **16**: 1539-1551 [PMID: 34620649 DOI: 10.2215/CJN.05530421]

28 **Dandamudi R**, Gu H, Goss CW, Walther L, Dharnidharka VR. Longitudinal Evaluation of Donor-Derived Cellfree DNA in Pediatric Kidney Transplantation. *Clin J Am Soc Nephrol* 2022; **17**: 1646-1655 [PMID: 36302566 DOI: 10.2215/CJN.03840322]

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