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EVIDENCE REVIEW

Simultaneous pancreas-kidney transplantation for end-stage renal failure in type 1 diabetes mellitus: Current perspectives

Lakshmi Nagendra, Cornelius James Fernandez, Joseph M Pappachan

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Abstract

Type 1 diabetes mellitus (T1DM) is one of the important causes of chronic kidney disease (CKD) and end-stage renal failure (ESRF). Even with the best available treatment options, management of T1DM poses significant challenges for clinicians across the world, especially when associated with CKD and ESRF. Substantial increases in morbidity and mortality along with marked rise in treatment costs and marked reduction of quality of life are the usual consequences of onset of CKD and progression to ESRF in patients with T1DM. Simultaneous pancreas-kidney transplant (SPK) is an attractive and promising treatment option for patients with advanced CKD/ESRF and T1DM for potential cure of these diseases and possibly several complications. However, limited availability of the organs for transplantation, the need for long-term immunosuppression to prevent rejection, peri- and post-operative complications of SPK, lack of resources and the expertise for the procedure in many centers, and the cost implications related to the surgery and postoperative care of these patients are major issues faced by clinicians across the globe. This clinical update review compiles the latest evidence and current recommendations of SPK for patients with T1DM and advanced CKD/ESRF to enable clinicians to care for these diseases.

Key Words: Type 1 diabetes mellitus; Chronic kidney disease; End-stage renal failure; Simultaneous pancreas-kidney transplantation; Perioperative complications; Immunosuppression

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Core Tip: Simultaneous pancreas-kidney transplant (SPKT) is a promising management option for patients with advanced chronic kidney disease or end-stage renal failure (CKD/ESRF) and type 1 diabetes mellitus (T1DM) for probable cure of these diseases and possibly some of their complications. However, limited availability of these organs, need for long-term immunosuppression, the surgical complications, lack of availability of this procedure in most centers, and the cost implications related to SPKT are major challenges across the world. This clinical update review is to enable clinicians with the best evidence and current recommendations of SPKT for managing their patients with T1DM and advanced CKD/ESRF.

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INTRODUCTION

Diabetes mellitus is one of the most common causes of chronic kidney disease (CKD) and end-stage renal failure (ESRF). Type 1 diabetes mellitus (T1DM), though less common when compared to type 2 diabetes, is associated with considerable morbidity and mortality secondary to microvascular and macrovascular complications including CKD. ESRF is a leading cause of death in patients with T1DM[1]. Although there has been considerable progress in the development of insulin delivery devices, newer insulin molecules, and glucose monitoring systems in recent years, there is still a significant negative impact on the quality of life in relation to disease management among T1DM patients[2]. Furthermore, these are not useful in reversing end-stage complications of diabetes such as ESRF. Despite extensive research, stem cell therapies in T1DM are still in the infantile stages[3]. Simultaneous pancreas-kidney transplant (SPK) is an attractive modality that fills this treatment gap in the management of T1DM and ESRF. Lack of wide availability, high cost, infections, and immunological problems following SPK have long been the challenges precluding the widespread use of SPK. However, advanced surgical techniques and newer immunosuppressive drug regimens in recent years have resulted in dramatic improvement in SPK outcomes. We describe the current perspectives on SPK for individuals with T1DM and ESRF, with the latest evidence on indications, perioperative care, immediate and long-term complications, and clinical outcomes through this comprehensive review.

HISTORY OF SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

Kelly *et al*[4] from the University of Minnesota conducted the first pancreatic transplant in 1966 in combination with a kidney transplant to treat a 28-year-old uremic patient with T1DM. The patient was insulin-free for six days before needing exogenous insulin, which was brought on by the large dosages of steroids that were administered to avoid rejection. However, the patient developed graft pancreatitis, which was most likely caused by duct ligation and the transplantation procedure had to be reversed. Unfortunately, 13 days after the excision of the rejected pancreas and kidney transplant, the patient passed away from a pulmonary embolism[2]. Surgical difficulties, wound infections, and graft rejection were all prevalent issues with pancreatic transplantation in this initial example, which persisted for the next 20 years. Despite difficulties, the Minnesota team demonstrated the technical feasibility of SPK[4].

The first documented effective use of cyclosporine A in two pancreatic transplants was by Calne *et al*[5] in 1979. This heralded an exciting new era of effective immunosuppressive regimens which eventually led to the more widespread use of SPK. Triple immunosuppression (maintenance therapy with cyclosporine A, azathioprine, and steroids) soon gained popularity all over the world after the introduction of cyclosporine A[6]. In 1989 Starzl *et al*[7] used tacrolimus as an immunosuppressive agent. This was followed by the development of induction therapy initially using anti-thymocyte globulin such as thymoglobulin and later (1997) by a recombinant DNA-derived humanised anti-CD52 lymphocyte depleting monoclonal antibody known as Alemtuzumab. Certain centres explored steroid-free regimens in the late 1990s and early 2000s which showed improvement in metabolic outcomes[6].

The initial pancreas transplant was done with ligation of the pancreatic duct[7]. Montefiore used the pancreatic duct to ureter anastomosis as a method of exocrine secretion drainage; however, it was complicated with anastomosis leakage. Bewick developed the open pancreatic duct drainage of exocrine secretions; however, it was complicated by peritonitis and ascites. Sollinger *et al*[8] developed pancreas-to-bladder anastomosis for exocrine secretion drainage; however, it was complicated with urinary tract infections, chronic cystitis, reflux pancreatitis, metabolic acidosis, and haematuria. Currently, enteric drainage is widely used for exocrine drainage with anastomosis between transplanted duodenum and

recipient ileum, jejunum, and duodenum, with drainage into a jejunal loop being the most used technique using techniques including Roux-en-Y reconstruction[9].

There are many types of pancreas and islet transplantations as depicted in Figure 1. The number of pancreas transplants (especially SPK) increased steadily in the US and worldwide since 1984. However, the number of pancreas transplants has shown a 20% decline between 2005 and 2014, with a nadir reaching in 2015. This decline in pancreas transplants is due to various reasons including the availability of advanced alternative treatment options like sensors, pumps, and hybrid closed loops resulting in fewer referrals to the pancreas transplantation waiting list, diabetic complications like ESRF occurring at a later age group, worsening donor organ quality related to body mass index (BMI) among organ donors (BMI > 35 kg/m^2 associated with fatty infiltration of the pancreas), and high post-operative complication burden (> 50%) associated with the pancreas transplants[9].

Thereafter, though the pancreas transplant volume started to increase, there was a further decline to coincide with the beginning of the coronavirus disease 2019 (COVID-19) pandemic where the number of SPKs in the US dropped from 872 in 2019 to 827 in 2020[10]. The number of pancreas transplants and the trends in pancreas transplants in the US between 1966 and 2021 are shown in Figures 2 and 3[11,12]. This decline likely reflects the unwillingness of many transplant programs to move forward with pancreatic transplants due to COVID-19 limiting the resources. The pancreas after kidney (PAK) and pancreas transplant alone (PTA) increased marginally to compensate for the drop in SPK, as shown in Figure 3[10].

INDICATIONS FOR SPK

Typically, patients with T1DM who have low or absent C-peptide levels are eligible for the SPK. Candidates could also have severe nephropathy or ESRF, as well as comorbidities such as hypoglycemia unawareness, recurrent hospitalisation for diabetic ketoacidosis, progressive retinopathy, enteropathy, and neuropathy. The current indications for SPK in T1DM are outlined in the Table 1[13,14].

In patients with stage 4/5 chronic kidney disease, preemptive SPK is described as the transplantation of both the pancreas and kidney before the patient is initiated on dialysis. Preemptive SPK has been shown to be related to better results when compared to SPK carried out in patients undergoing dialysis, according to several retrospective investigations, including registry analysis. In SPK patients, time spent on dialysis also has a poor prognostic significance[15,16].

CONTRAINDICATIONS

The absolute and relative contraindications for SPK in patients with T1DM are given in Table 1[17].

Obesity alone is not an absolute contraindication to SPK, given that positive outcomes have been documented[18]. However, obese patients may experience a greater risk of early complications when compared to non-obese recipients [19]. Additionally, the significance of BMI < 18.5 kg/m^2 as a risk factor for long-term mortality needs to be emphasized [18].

Previous history of limb amputation and presence of coronary heart disease are risk factors for worse outcomes, but neither is considered an absolute contraindication to SPK[20]. Pre-SPK limb amputation often indicates worse transplant results because it raises the risk of cardiovascular disease[21]. The risk of serious adverse cardiovascular events following transplantation is further increased by a history of coronary artery disease before transplantation[22]. If medically treated and revascularized by accepted standards, coronary artery disease, however, does not pose a significantly higher risk for death.

SURGICAL TECHNIQUES

Most of the pancreas grafts are retrieved from heart-beating brain-dead donors, with an increasing number from non-heart-beating donors after circulatory death[17]. The retrieval involves the removal of the pancreas en-bloc with the donor duodenum and spleen, with the spleen removed before implantation. In SPK, both kidney and pancreas grafts are taken from the same deceased donor. The donor pancreas has two arteries (superior mesenteric artery and splenic artery), and these are joined with a 'Y' graft utilizing the donor common iliac artery and its bifurcation to create a single arterial inflow which is anastomosed to the recipient's right common iliac artery. The donor portal vein is anastomosed to the recipient's right common iliac vein or inferior vena cava. Finally, the donor duodenal conduit is anastomosed to the recipient's small bowel or urinary bladder. A pancreas transplant alone takes approximately 3-4 h, whereas a simultaneous pancreas and kidney transplant takes approximately 4-6 h[17,23].

Diverse and institution-specific procedures are employed for SPK. The intra-peritoneal technique is used by most transplant facilities for graft insertion. The kidney is transplanted to the left iliac fossa, the pancreas is generally placed in the right iliac fossa. The native pancreas and kidney remain in place. The peripancreatic fluid accumulations and wound complications are reduced because of this strategy. Extraperitoneal and ipsilateral insertion of both grafts constitute an alternate strategy[17,24].

Most pancreatic transplants use either enteric or bladder drainage. Comparing bladder and intestinal drainage of exocrine secretions in pancreas transplantation has been extensively studied. Compared to enteric drainage, bladder

Table 1 Current indications and contraindications for simultaneous pancreas-kidney in type 1 diabetes mellitus[11,12,15]

Current indications for SPK in T1DM
Confirmed diabetic nephropathy with low or absent C-peptide, on insulin treatment
Creatinine clearance < 15 mL/min or on dialysis
Presence of other microvascular or macrovascular complications of T1DM
Ability to withstand immunosuppression and surgery
History of compliance with medical advice and treatment
Absolute contraindications for SPK in T1DM
Significant cardiovascular disease with severe or non-correctable coronary artery disease
Cardiac ejection fraction < 50%
Recent myocardial infarction
Non-curable malignancy except localized skin cancer
Active sepsis
Active peptic ulcer disease
Severe mental health conditions that can lead to non-compliance
Inability to survive surgery or immunosuppression due to significant comorbidity
Relative contraindications for SPK in T1DM
Cerebrovascular event with long-standing impairment
Human immunodeficiency virus, hepatitis B and C virus infections
BMI > 30 kg/m^2
Age > 60 yrs
Extensive vascular, aortic, and renal artery disease (making surgery high-risk)
Excessive need for insulin > 1.5 U/kg/d
Continuous use of alcohol, smoking, and other drugs

T1DM: Type 1 diabetes mellitus; SPK: Simultaneous pancreas-kidney.

drainage increases late reintervention rates (primarily for enteric conversion), but it has no acute surgical risks[17]. In a recent study by Riad *et al*[25], at 10 years posttransplant, 44.3% of simultaneous pancreas-kidney transplant recipients had undergone enteric conversion. The enteric conversion was associated with an 85% increased risk of acute rejection but was not associated with graft loss or mortality. Additionally, bladder drainage is linked to long-term urologic problems such as bladder calculi, haemorrhagic cystitis, and recurrent urinary tract infections, as well as metabolic disturbances like acidosis and dehydration[26]. These factors have contributed to a drop in the use of bladder drainage over time.

PERIOPERATIVE CARE

Insulin regimens

Perioperative plasma glucose monitoring is crucial. The metabolic reaction to stress and the impact of corticosteroids contribute to the frequent occurrence of intraoperative hyperglycemia. As uncontrolled glucose levels are linked to impaired immune function and an increased risk of infection, insulin infusion should be started before unclamping of the pancreas transplant. Plasma glucose must be closely monitored after unclamping since glucose levels might dangerously plummet[27].

Heparin thromboprophylaxis

Thrombosis, which has a reported prevalence of 4%–20%, is a common complication associated with pancreatic transplantation. One of the main factors contributing to pancreatic transplant failure and graft loss has been identified as thrombosis. Despite this, the effectiveness of preventive anticoagulation is still debatable, with some trials finding positive results from anticoagulation and other trials reporting no benefit[28,29]. Pancreas transplant centers have various internal policies and practices, and there is still no standardised thromboprophylaxis approach for this procedure. According to a recent meta-analysis that included 11 studies and 1122 patients in the heparin group and 236 patients in

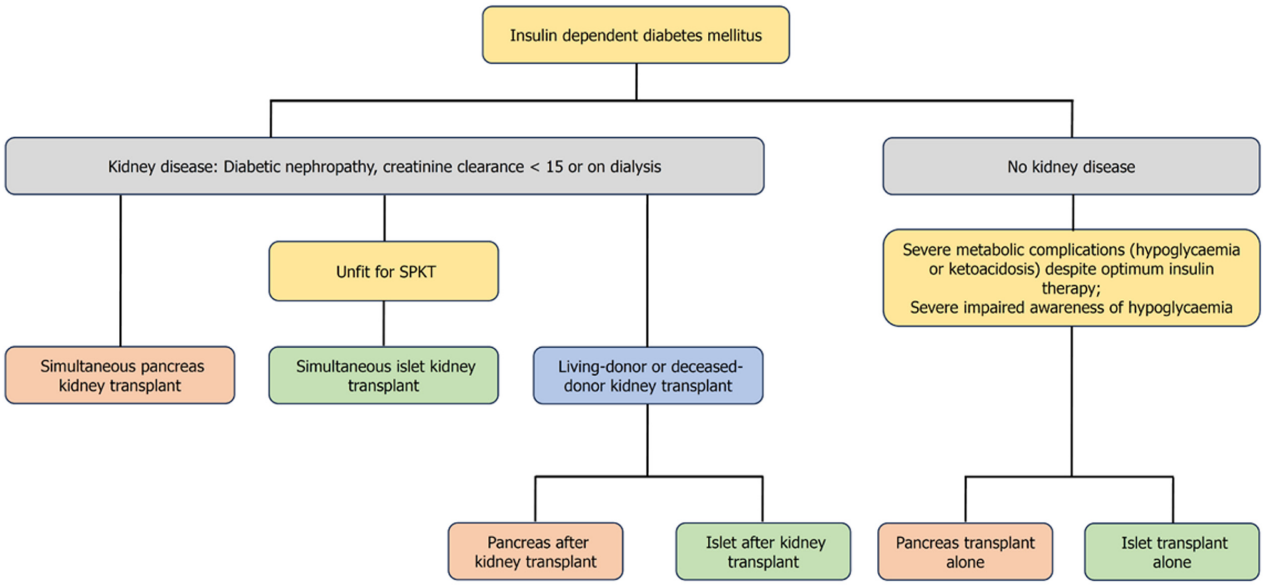

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Figure 1 Various types of pancreas (red box) and islet (green box) transplantation[7]. SPKT: Simultaneous pancreas-kidney transplant.

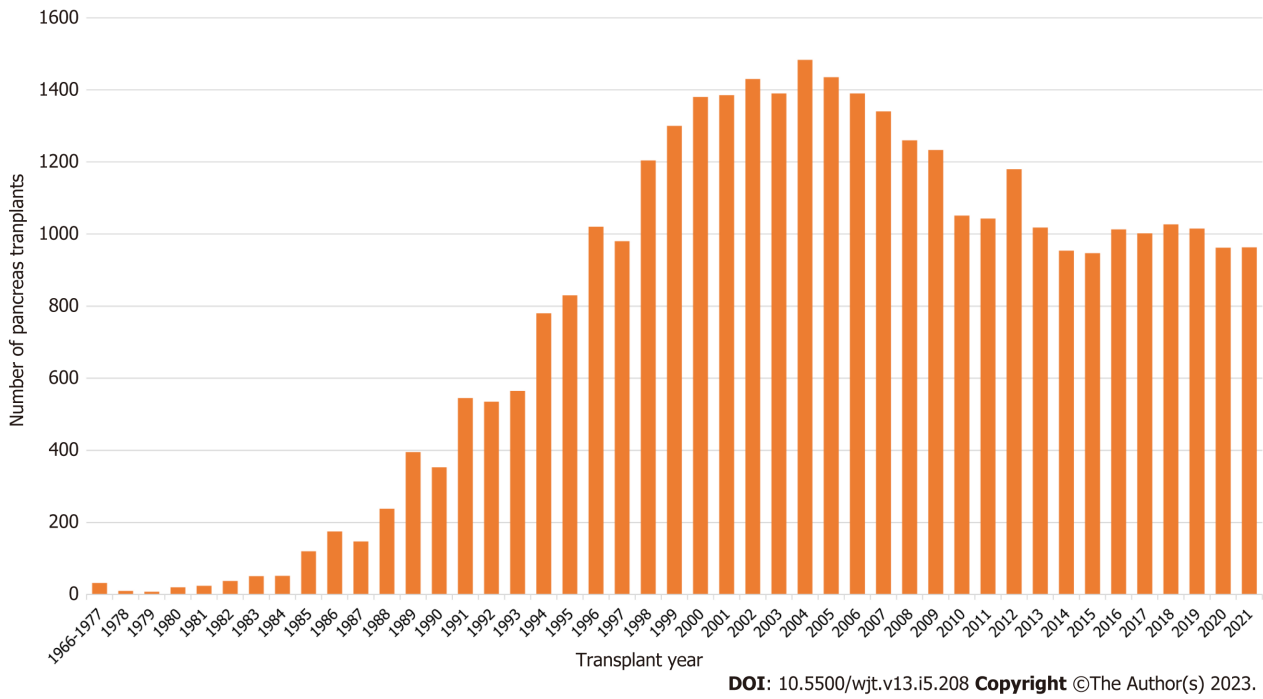

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Figure 2 Number of pancreas transplants in the United States between 1966 and 2021[9,10].

the no-heparin group, prophylactic heparinization significantly reduced the risk of early pancreas thrombosis and pancreas loss for SPK without increasing the incidence of bleeding or acute return to the operating room when compared to the no-heparin control[30]. In the included studies, intraoperative intravenous heparin 30-70 IU/kg was administered when heparin thromboprophylaxis was not contraindicated. Heparin was administered intravenously 200-1000 IU/h for 1-14 d or subcutaneously 3000-5000 IU 1-2 times daily during the postoperative period. Following this, aspirin 81-325 mg per day was used for maintenance[30].

IMMUNOSUPPRESSION

The accepted practice in modern immunosuppression is to combine numerous drugs with various mechanisms of action for maintenance therapy and to employ biologic medicines for induction. These regimens achieve the main objectives of

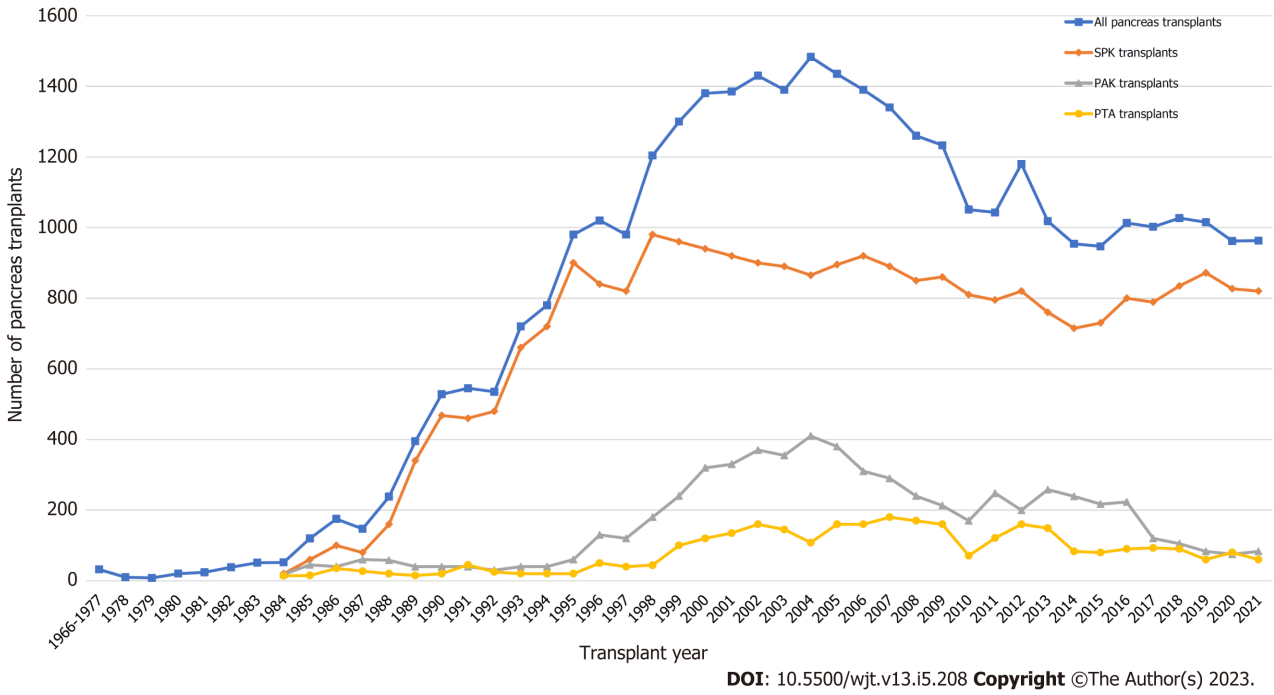

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Figure 3 Trends in pancreas transplants in the United States between 1966 and 2021[9,10]. SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone.

immunosuppression, which are to effectively manage acute rejection while reducing risks to the patient's safety and tolerability and damage to the allograft(s).

Induction immunosuppression

Early rejection and graft loss from combined pancreas-kidney transplants have been lower with the use of induction immunosuppression. Of the induction therapies, lymphocyte-depleting agents (alemtuzumab and anti-thymocyte globulin) and nondepleting agents [basiliximab and daclizumab (anti–interleukin 2 (anti–IL-2) receptor monoclonal antibody)] have been used in SPKs. Ninety percent of pancreatic transplant patients get a lympho-depleting drug during induction treatment, reflecting the widespread observation of greater rejection rates following pancreas transplant[10].

A recent meta-analysis studied 536 SPK participants in 7 randomised clinical trials that reported 5 induction methods. Antithymocyte globulin (97 patients), alemtuzumab (42 patients), 2 or 5 doses of daclizumab (113 patients), and no induction treatment (120 patients) were included in these regimens. A regimen containing 2 doses of daclizumab ranked highest for patient survival as well as kidney and pancreas transplant survival in the network meta-analysis. In contrast, alemtuzumab was ranked best for the prevention of acute renal and pancreatic rejection[31].

In patients at low immunologic risk, there isn't any conclusive proof that induction with depleting *vs* nondepleting antibodies leads to better immunologic outcomes. When compared with the use of nondepleting antibodies or no induction therapy, induction with depleting antibodies is associated with cytokine release syndrome requiring premedication and with an increased incidence of early posttransplant infections, especially cytomegalovirus (CMV) viremia (that do not result in inferior patient and graft survival). There is no conclusive evidence that induction treatment with depleting antibodies increases the risk of oncologic problems in pancreatic transplant patients, despite data on renal transplantation to the contrary[20].

Maintenance Immunosuppression

Modern immunosuppressive protocols for all types of pancreatic transplantation include tacrolimus, mycophenolate, and steroids for the purpose of maintenance of immunosuppression. Tacrolimus has been the preferred calcineurin inhibitor (CNI) for more than ten years, despite the risks of beta cell toxicity and renal damage linked to it. Results of a 3-year single-center, prospective, randomized comparison of the two calcineurin inhibitors in the setting of mycophenolate mofetil (MMF)-based immunosuppression in 47 SPK patients did not show superiority of tacrolimus over cyclosporin [32]. However, a larger study in 205 SPK recipients confirmed the superiority of tacrolimus over cyclosporine in preventing moderate or severe kidney or pancreas rejection and pancreatic thrombosis[33]. Tacrolimus is available as an immediate-release formulation (IR-Tac) which is traditionally given twice daily. Extended-release tacrolimus (ER-Tac) given once daily was later explored with the expectation of improved medication adherence. Falconer *et al*[34] reported that stable SPK recipients can safely be converted from IR-Tac to ER-Tac, with no clinical impact on the transplant function.

MMF continues to be the preferred antiproliferative drug for maintenance therapy. Following induction therapy, a review found that using mycophenolate mofetil in conjunction with CNI and steroids was linked to a 40% decrease in the risk of acute rejection one year following pancreatic transplantation[35]. When combined with tacrolimus or cyclosporine,

retrospective studies have shown that mycophenolate mofetil, as opposed to azathioprine, improves the immunologic outcome of pancreas transplantation, but at the cost of more gastrointestinal side effects that frequently necessitate dose reduction[36,37].

Total avoidance of steroid immunosuppression is referred to as "steroid avoidance." Early avoidance is defined as steroid therapy for fewer than 14 d following transplantation, while late avoidance is defined as steroid withdrawal after 14 d[38]. Though steroids form the cornerstone of immunosuppression therapy, steroid discontinuation is being explored and could lead to better metabolic outcomes over time. Although it fell from 27.2% in 2019 to 25.8% in 2020, the percentage of patients kept on a tacrolimus/MMF steroid-free therapy was mostly steady. Steroid withdrawal between 6-12 mo after transplantation was successful and safe in most patients without an increase in immune events. Additionally, the patients had a low prevalence of hypertension, dyslipidemia, and obesity[39].

Compared to the 12.4% reported in 2010, the percentage of pancreatic transplant patients in the "other" maintenance therapy regimens has reduced to 2.6%. This slow decline shows that co-stimulation blockade or mammalian target-of-rapamycin (mTOR) inhibitors have not been frequently used as alternate maintenance regimen components[9,20]. Though mTOR inhibitors show non-inferior immunological outcomes, the side effect profile of this group of drugs precludes its widespread use[40,41].

COMPLICATIONS

When compared to patients of kidney transplantation alone (KTA), those who received SPK typically have more severe and frequent complications in the first year after transplant. These complications are typically caused by either the more extensive surgical procedure or the necessary immunosuppression. Greater morbidity and early death are related to SPK than KTA because of perioperative problems. This difference is evidenced by longer initial hospital stays, higher rates of rehospitalization in the first 30 d, more serious infections necessitating rehospitalization, and higher perioperative mortality risk[42]. Khubutia *et al*[43] reported surgical complications in 37.5% of SPK patients. Asymptomatic para-pancreatic fluid collection (52.5%) was the most common surgical complication followed by superior mesenteric artery thrombosis (12.5%). Surgical site infections after pancreas transplantation in the Swiss Transplant Cohort Study were seen in 14% of patients[44].

Following a pancreatic transplant, technical failure rates might reach 8%. Graft thrombosis, graft pancreatitis, anastomotic leak, and infection are some causes of failure[45,46]. In a recent retrospective, single-center analysis, 114 adult patients who received an SPK between 2005 and 2018 were included. There was an 85.1% pancreas transplant survival rate at 3 mo. Early pancreatic transplant loss was mostly due to pancreatitis (2.6%), necrosis (2.6%), and thrombosis (6.1%). In contrast to patients with a functional pancreas, early pancreatic transplant loss was not linked to a lower chance of survival (P = 0.168) or severe adverse cerebral or cardiovascular events during a 10-year period[47]. Most postoperative problems in the SPK population that necessitate surgical re-exploration are pancreas-related. In a recent study on SPK patients, while 28.2% of patients experienced a major kidney complication, the rate for major pancreas-related complications was 43.6%[48].

Even though SPK outcomes have improved dramatically, infectious complications continue to be the leading cause of morbidity and death. Michalak *et al*[49] reported 102 infections among 51 SPK patients during the posttransplant period. A total of 73 bacterial infections (systemic 13, pulmonary 13, intestinal 8, wound 23), 21 episodes of CMV infection (systemic 20, duodenal site 1), 73 fungal infections (central nervous system 5, gastrointestinal tract 3), and 8 bacterial infections (systemic 13, pulmonary 13, intestinal 8, wound 23) were reported. Some individuals had multiple infections. The overall mortality rate in the study cohort was 24.5%. Most deaths (77%) were due to infectious complications, which included systemic infection (38.5%) and CNS infection (38.5%). The majority of systemic illnesses had a bacterial aetiology and CNS infections had a fungal aetiology.

Metabolic complications are also a frequent cause of morbidity post-SPK. Within the first six months, transient hyperglycemia may develop because of acute or chronic rejection, pancreatitis, or a significant rise in insulin resistance brought on by weight gain. Post-transplant hyperglycemia has also been associated with immunosuppressant drug side effects, including steroids, calcineurin inhibitors (particularly tacrolimus), sirolimus, and mycophenolate. About 60 to 80% of patients receiving immunosuppressive medication develop hyperlipidemia following solid organ transplantation. Two of the most significant lipid abnormalities seen are high triglyceride levels and low-density lipoprotein cholesterol concentrations. Combined hyperlipidemia is also typical. Many risk factors, including advanced age, obesity, post-transplant weight gain, pre-transplant dyslipidemia, male gender, graft malfunction, proteinuria, newly diagnosed diabetes mellitus, prednisone dose, and the kind of immunosuppressive regimen, might contribute to the development of dyslipidemia following pancreatic transplant. Although tacrolimus and cyclosporine similarly negatively impact lipid metabolism, sirolimus has been linked to larger elevations in triglycerides and cholesterol[50]. The common complications of SPK are displayed in Figure 4.

OUTCOMES

Survival benefit

For transplants performed in 2018-2019, one-year patient mortality remained low at 2.6%. Ten-year mortality rates among 2010-11 transplant recipients were 20.9% likely reflecting cardiovascular comorbidities in the population. Five-year

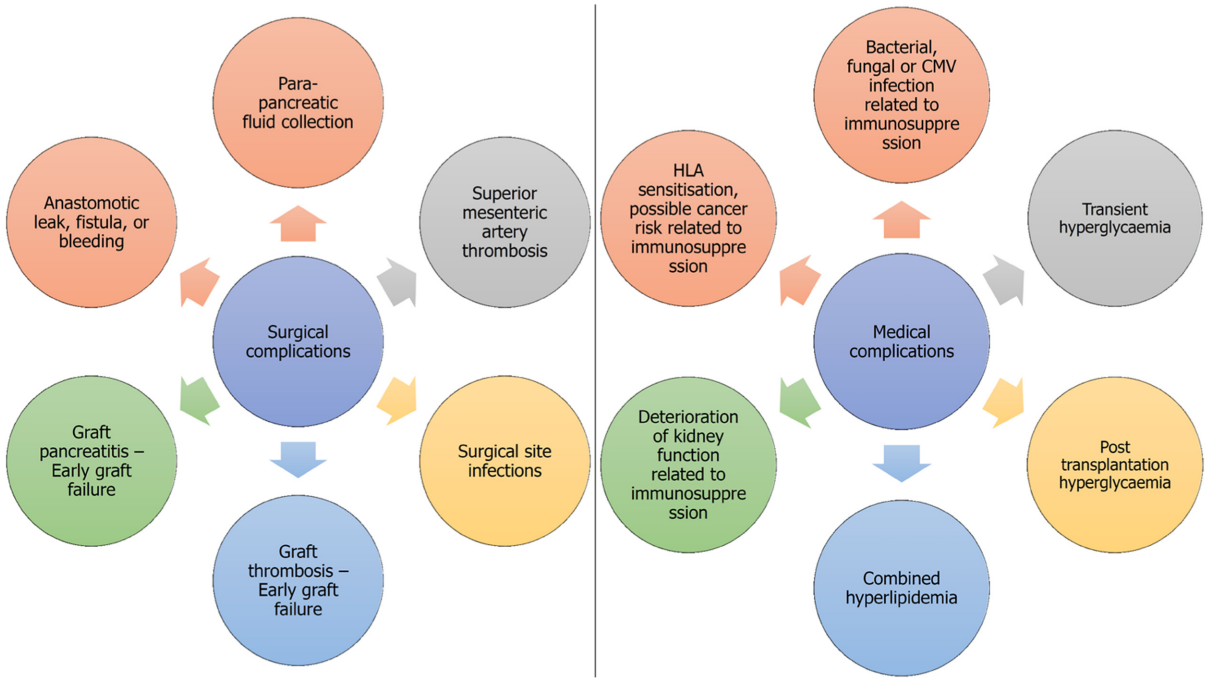

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Figure 4 Common complications of simultaneous pancreas-kidney. CMV: Cytomegalovirus; HLA: Human leukocyte antigen.

survival rate was 92.7%[10].

Compared with living or deceased-donor kidney transplantation, SPK was associated with improved patient survival, especially in recipients with a long-term functioning pancreatic graft, and resulted in an almost 50% reduction 10-year mortality rate[51].

Glycemic control

Following a solid-organ pancreas transplant, the great majority of patients attain total insulin independence in both the short and long terms. Glycemic control outperforms that attained with insulin pumps or islet-cell transplants by a wide margin[52]. A recent study evaluated CGM-derived time in range and glucose variability in 43 patients with SPK. Time in range (TIR) at 5-12 years follow-up was 97.5%. Time above range (TAR) and time below range (TBR) were 2.5% and 3.5% respectively. Thus patients with functional pancreatic grafts exhibit very high TIR and low GV following SPK[53]. In the immediate post-transplant period at 6 wk, Dadlani *et al*[54] reported a TIR, TAR and TBR of 92%, 7.9% and 0.3% respectively in SPK patients.

Diabetes-related complications

Diabetic retinopathy: A feared side effect of pancreatic transplantation is the worsening of diabetic retinopathy brought on by abrupt glucose normalisation. There have been conflicting results on retinopathy outcomes after SPK. Chow *et al* [55] reported a high prevalence of severe proliferative diabetic retinopathy (DR) and blindness at the time of presentation for SPK. This was subsequently stabilised to inactive proliferative DR by appropriate laser therapy followed by metabolic control achieved by SPK. Voglová *et al*[56] studied 43 pancreatic and kidney recipients for a 12-mo composite endpoint that included the requirement for fresh laser therapy, newly discovered proliferation, macular edema, deteriorating vision, and blindness. This primary goal was attained by 37% of patients, however, the severity was only moderately high. Visual acuity remained constant. The absolute glycated haemoglobin, age, and duration of diabetes mellitus did not significantly differ between patients who met and did not achieve the primary goal, while a greater percentage of patients with deterioration had recently undergone laser therapy. 62.8% of individuals had stable retinal disease. In 26% of cases, visual acuity was noticeably improved. Even though retinal deterioration was observed in more than one-third of individuals, the progression of the condition was unrelated to the degree of metabolic alteration and instead followed the predicted normal course of retinopathy[56].

Diabetic neuropathy: Cardiac autonomic neuropathy is a dreaded complication of long-standing uncontrolled diabetes. Argente-Pla *et al*[57] reported improved cardiac autonomic neuropathy post SPK as evidenced by an improved Valsalva ratio. SPK is been shown to be beneficial for diabetic polyneuropathy in earlier studies. Kennedy *et al*[58] used muscle action potential and indices of nerve conduction velocity to examine how pancreatic transplantation affected peripheral motor, sensory, and autonomic nerve function. They discovered a notable improvement in motor and sensory indices during a 12-mo follow-up. Martinenghi *et al*[59] demonstrated that even in the presence of severe polyneuropathy, a persistent normoglycemic condition can enhance nerve function.

Diabetic nephropathy: For most patients with type 1 DM and ESRF, SPK restores normal renal function. According to Fioretto *et al*[60], characteristics of diabetic nephropathy were restored after 10 years of sustained normoglycemia post-transplant. It greatly decreased the thickness of the mesangial matrix and glomerular basement membrane, and it significantly improved glomerular and tubular lesions. Additionally, a decline in the rate of urine albumin excretion (20 mg/d *vs* 103 mg/d) was seen, demonstrating improved renal function. Diabetic nephropathy is reported to alter circulating long noncoding RNA levels that normalize following SPK[61].

Macrovascular complications: Microvascular diabetic problems are stabilised more frequently following effective SPK, although macrovascular diabetic sequelae and diabetic Charcot neuro-osteoarthropathy have been traditionally thought to progress. Duration of hemodialysis is an important risk factor for adverse cardiac events[62]. However, a recent study showed significant improvements in left ventricular systolic parameters during follow-up in SPK recipients[63]. Another recent study concluded that SPK favorably slows down the development and progression of peripheral vascular disease by maintaining a superior metabolic vascular risk profile[21].

Quality of life: When compared to KTA, it has been demonstrated that SPK improves quality of life (QoL). In addition to avoiding hypoglycemia spells and insulin injections, pancreas transplantation also lowers the risk of developing microvascular and macrovascular complications of diabetes and eliminates the need for glucose monitoring. After correcting for QoL, SPK outperformed KTA or dialysis in terms of cost-effectiveness over five years in a trial on individuals with T1DM and ESRF[64]. The outcomes of SPK are summarised in Figure 5.

Future perspectives of SPK in the context of islet transplantation

Pancreas transplantation is the best treatment to provide insulin-independence, excellent metabolic control, and an improvement in QoL. Additionally, it may be able to avoid, ameliorate, or even reverse most of the diabetic complications. The technique of pancreas transplantation has shown improvement over time. The factors playing their part in this improvement include intestinal drainage of pancreatic juices, the introduction of calcineurin inhibitors and T-cell depleting agents, and improvements in maintenance immunosuppression with tacrolimus and mycophenolate mofetil. Though the sirolimus-based protocols showed initial promise, their use subsequently declined significantly.

PTA and PAK are more difficult to monitor. Hence, they carry a high risk of immunological rejection and have less favourable outcomes in comparison to SPK. PAK is effective in those who have had KTA in the past and are now having trouble with achieving glycaemic control and/or management of diabetes-related complications. Thus, PAK is a therapeutic option as a life-preserving procedure that avoids long-term dialysis and mortality on the waitlist and provides the time to find a good pancreas graft after the kidney transplant. On the other hand, PTA is a treatment option for patients with brittle diabetes who suffer from hypoglycaemia unawareness impairing QoL or have difficulty adhering to insulin injection requirements, but with a normal or near-normal renal function. It provides the best one-year patient survival among all whole organ transplants[65].

Careful selection of recipients and donors, improvement in surgical techniques, and refinement in immunosuppressive protocols have provided excellent outcomes after pancreas transplantation. Additionally, early detection of postoperative complications through careful observation, and regular imaging, and prophylactic use of antimicrobial agents are possible strategies that would reduce postoperative morbidity/mortality and thereby favour the expansion of existing pancreas transplant programs. Islets constitute only 1%-2% of the pancreas. Therefore, a less invasive procedure with lower procedural morbidity, islet transplantation, involving percutaneous intra-portal infusion of the islets is considered another alternative[17].

No trials are comparing the outcomes of islet transplantation (SIK or IAK) *vs* SPK[17]. Pancreas transplantation is a more acceptable treatment option for patients with ESRF, who are already undergoing a kidney transplantation. On the other hand, islet transplantation is preferred in elderly, frail, and morbid patients who are unfit for pancreas transplantation and in patients with a preference for a less invasive procedure. These two procedures have comparable results in glucose control, avoidance of severe hypoglycaemia, and recovery from hypoglycaemia unawareness. However, the insulin independence rates are 'slow and low' with islet transplants in comparison to pancreas transplants depending on the number of islet transplants and the success of engraftments. Multiple donors are needed in islet transplantation, thereby increasing the waiting list. Contrary to pancreas transplantation, obesity in the donor is not a contraindication for islet transplantation[65].

CONCLUSION

For individuals with T1DM and ESRF, simultaneous pancreas and kidney transplantation has become the gold standard of care. In terms of patient survival, graft survival, diabetes complications, and QoL, there is a substantial body of evidence from clinical research that supports the procedure. Only carefully chosen individuals should undergo simultaneous pancreas and kidney transplantation since it is a technically challenging treatment that is linked with serious short-term and long-term complications. The wider adoption of this therapeutic paradigm can be made possible with patient education initiatives and public outreach to foster a charitable culture of organ donation.

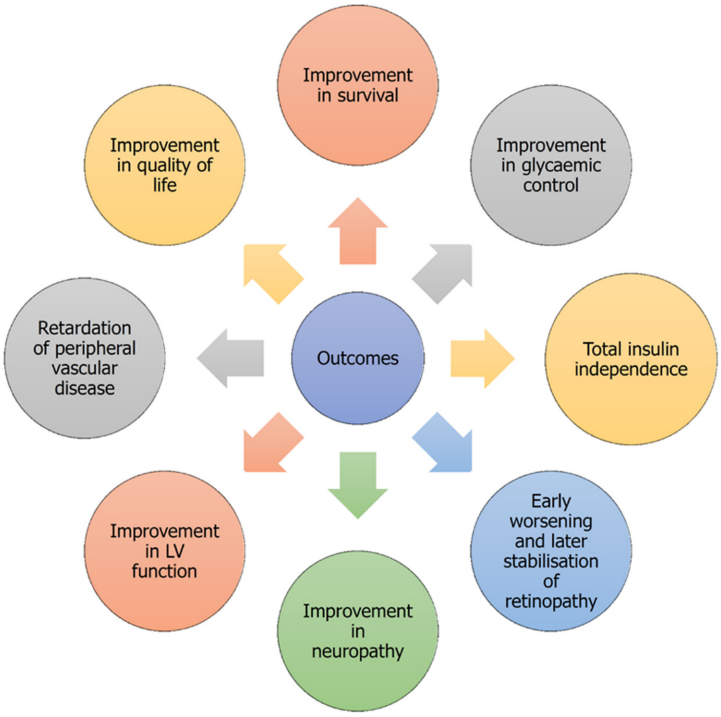

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Figure 5 The outcomes of simultaneous pancreas-kidney. LV: Left ventricular.

FOOTNOTES

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REVIEW

Evolution of human kidney allograft pathology diagnostics through 30 years of the Banff classification process

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Abstract

The second half of the previous century witnessed a tremendous rise in the number of clinical kidney transplants worldwide. This activity was, however, accompanied by many issues and challenges. An accurate diagnosis and appropriate management of causes of graft dysfunction were and still are, a big challenge. Kidney allograft biopsy played a vital role in addressing the above challenge. However, its interpretation was not standardized for many years until, in 1991, the Banff process was started to fill this void. Thereafter, regular Banff meetings took place every 2 years for the past 30 years. Marked changes have taken place in the interpretation of kidney allograft biopsies, diagnosis, and classification of rejection and other non-rejection pathologies from the original Banff 93 classification. This review attempts to summarize those changes for increasing the awareness and understanding of kidney allograft pathology through the eyes of the Banff process. It will interest the transplant surgeons, physicians, pathologists, and allied professionals associated with the care of kidney transplant patients.

Key Words: Banff process; Rejection; Kidney allograft biopsy; Transplant pathology; Review

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Core Tip: The efforts to standardize the nomenclature, classification, and reporting of kidney allograft biopsies were initiated in 1991 by a small group of renal pathologists, transplant physicians, and surgeons at a meeting in Banff, Alberta, Canada. Thereafter, regular meetings of the now ever-expanding, multidisciplinary, and international Banff community have been held every 2 years at different places around the world to revise, update and refine the classification. Major and frequent changes have occurred in the classification over the three decades of its evolution, making it extremely complex and difficult to comprehend, particularly for beginners in the field. The classification has essentially changed from pathology-based to pathogenesis-based classification and has become clinician-friendly and treatment-friendly. This review is an attempt to summarize the changes in the classification in an easily understandable manner and describe the rationale behind these changes for easy assimilation by both neophytes and practicing renal pathologists, transplant physicians, surgeons, and other relevant stakeholders.

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INTRODUCTION

Kidney transplantation is the preferred type of treatment for end-stage kidney disease patients throughout the world. Advancements in surgical techniques, immunosuppressive regimens, and infection control during the second half of the previous century markedly improved the short- and medium-term outcomes of kidney allografts. However, the long-term results are still poor and little progress has been made in this area[1,2]. Although highly effective, kidney transplantation is not completely immune to complications. Kidney allograft dysfunction can occur at any time after transplantation. It has been reported that kidney allograft dysfunction occurs in 50%-60% of cases after transplantation and there are many causes. Among the most important and prevalent causes of kidney allograft dysfunction are rejection, infection, and drug toxicity[3].

The Banff classification schema for kidney allograft pathology was developed in 1991 and is an ongoing process with an international approach[4-9]. The first Banff meeting was held at the small town of Banff in Alberta, Canada in August 1991, which was attended by a group of 12 nephropathologists and transplant clinicians with a common interest in kidney transplantation with the goal of standardizing the reporting of kidney allograft biopsies[10]. The objectives were two-fold: To guide therapy and to establish an objective endpoint for clinical trials. The first report in full paper form was published in 1993 after several cross-consultations and follow-up discussions[10]. These meetings have subsequently taken place biennially, initially at Banff and later on, in other parts of the world but have been named the Banff meetings after their original place of meeting to revisit, revise and update the Banff classification. Our understanding of kidney transplant pathology, and particularly, rejections has grown and improved with discourses and publications emerging out of these meetings[4-6,9]. At the same time, the classification has become more complex and difficult to assimilate, particularly for novices in the field.

The Banff schema is distinctive as the classification criteria are developed based on a consensus approach. Although the original Banff classification was developed based on expert opinion, its subsequent revisions and refinements have been made based on published sound scientific studies, multicenter studies by the Banff working groups (BWGs) on problematic areas, and consensus among the experts[6]. In this review, we summarize the major changes in the Banff classification and the rationale behind these changes. This will help the neophytes and practicing nephropathologists, nephrologists, and other stakeholders to better understand this classification.

TECHNICAL CONSIDERATIONS AND TISSUE ADEQUACY

For a kidney allograft biopsy to fulfill its role as the gold standard for accurate diagnosis, it needs to be adequate and as representative as possible of the whole kidney allograft and be prepared according to recommended protocols. With the evolution in the diagnostic criteria of the Banff categories, changes have also taken place in the tissue adequacy criteria, technical preparation guidelines, and the extent of the workup of kidney allograft biopsies (Table 1). In the first Banff meeting, the biopsy adequacy criteria were less stringent, particularly with regard to the number of blood vessels required. The first major change in adequacy criteria was made in 1997 when two cylinders of kidney allograft parenchyma including both cortex and medulla with 10 glomeruli and two arteries were recommended to fulfill adequacy criteria[11]. As the process of rejection is often focal and patchy in distribution, particularly during the early phase, a generous sampling of the kidney cortex from different areas is desirable for an accurate diagnosis, necessitating the recommendation for two cores of allograft tissue. During the first decade of the Banff process, the study of kidney allograft biopsy was based only on morphologic evaluation, *i.e.* light microscopy (LM). From the 2001 meeting onwards, a piece of frozen tissue for C4d was made mandatory for the complete evaluation of allograft pathologic lesions[12,13]. C4d staining should be done on all kidney allograft biopsies, preferably by immunofluorescence (IF), or by immunohisto-

Table 1 Adequacy criteria of renal allograft biopsies for an accurate pathologic diagnosis

Parameters/investigations	Requirements
Number of cores	Two (these should be divided to procure tissue for IF and EM studies, if necessary)
Components of graft parenchyma	Both cortex and medulla
For the light microscopic study	A significant amount of cortex containing up to: (1) 10 glomeruli; and (2) 2 arteries
For the immunofluorescence study	Cortex with up to 3 glomeruli
For the electron microscopic study	Cortex with 1 glomerulus

EM: Electron microscopy; IF: Immunofluorescence.

chemistry (IHC) technique, if the former is not available[13]. The threshold of C4d staining intensity is one grade level lower with the IHC technique. In the Banff 2013 meeting, conditional use of electron microscopy (EM) was recommended in certain situations[14-16]. EM study is not done routinely on all kidney allograft biopsies at all centers, but is performed in the case of suspected recurrent or *de novo* glomerulonephritis, persistent significant but unexplained proteinuria, and for the diagnosis of early chronic changes of allograft rejection such as transplant glomerulopathy and sometimes peritubular capillaries (PTCs). Tissue fixed in 2.5% glutaraldehyde provides optimum results for transmission EM. Standard techniques are employed for the preparation and interpretation of EM. For the above-mentioned ancillary investigations, the biopsy needs to be divided in such a manner that a minimum number of glomeruli and/or PTCs be present in specimens apportioned for IF and EM to maximize their utility. Ideally, this should be done in the biopsy suite under the dissection microscope while the specimen is fresh. Tissue samples should then be placed in appropriate fixatives for respective studies. Although not mandatory, IHC for polyomavirus is recommended on all renal allograft biopsies to help detect early viral lesions. In brief, the pathologic evaluation of kidney allograft biopsies has evolved from pure LM to ancillary techniques of IHC, IF, EM, and more recently, molecular studies to accurately diagnose transplant pathology lesions.

COMPONENTS OF THE BANFF CLASSIFICATION SYSTEM

The foundation of the Banff classification system is centered on the morphological evaluation of kidney allograft tissue comprising four basic components. Each of these components can be involved in either the acute or chronic disease processes, particularly the rejection process. The Banff process identified and defined the lesions of the allograft parenchyma in a systemic and semi-quantitative way (Table 2). Thus, the components of the Banff classification system can conveniently be grouped as: (1) Definitions of various components or lesions; (2) Diagnostic lesions; (3) Semi-quantitative scoring of the lesions; (4) Additional diagnostic features; and (5) The diagnostic categories (Figure 1). None of the individual lesions, in isolation, except possibly for intimal arteritis, is diagnostic of the rejection process. A combination of the lesions along with scores above some threshold value is needed to make a specific diagnosis. It is important to be thoroughly familiar with all these components of the Banff classification in order to reliably and precisely apply it in clinical or research settings[9]. Some important diagnostic lesions are illustrated in Figures 2-4.

TIMELINE OF THE EVOLUTIONARY CHANGES IN THE BANFF CLASSIFICATION

The year 2021 marked the 30th anniversary of the beginning of the Banff classification process for standardized reporting of renal allograft pathological lesions. However, XVth biennial Banff meeting that was to be held that year was postponed and held in 2022 due to the coronavirus disease 2019 situation[6]. It is befitting to review the evolution of the Banff classification, its strengths and limitations, future prospects, and opportunities. It will be more convenient if we divide the evolution of the Banff classification into three decade-wise eras, as below.

FIRST DECADE: DEVELOPMENT AND RECONCILIATION

The first decade may be called the decade of development and reconciliation/integration of the Banff classification, the latter with a rival classification developed in the United States called the Collaborative Clinical Trials in Transplantation (CCTT) modification of the classification[17]. This merger was the most significant achievement during the first decade as it paved the way for a single uniformly agreed-upon international classification for renal allograft pathology[6]. Three main and full papers on the classification were published during this decade, two of which became popular, the first was published in 1993 and the second in 1999. During this decade, the main focus of classification schema was on the cellular part of the rejection[18-20]. In fact, this category was named acute rejection without further qualification. Later on, it was changed to acute/active cellular and still later, acute/active T-cell mediated rejection (TCMR). The role of antibodies

Table 2 Banff reporting standardization template according to the Banff 2019 meeting

Components of the allograft	Acute lesions	Scoring as 0, 1, 2, 3	Chronic lesions	Scoring as 0, 1, 2, 3	Acute & chronic lesions	Scoring as 0, 1, 2, 3
Glomeruli	g	-	cg	-		
Interstitium	i	-	ci	-	ti, i-IFTA	-
Tubules	t	-	ct	-	t-IFTA	-
Vessels	v	-	cv	-		
Peritubular capillaries	ptc	-	ptcml	-		
C4d	C4d	-				

C4d: Linear staining in peritubular capillaries or medullary vasa recta either by immunofluorescence on frozen sections of fresh frozen tissue or immunohistochemistry on formalin-fixed, paraffin-embedded tissue; cg: Chronic glomerulopathy (transplant glomerulopathy); ci: Interstitial fibrosis involving the cortex; ct: Tubular atrophy in the cortex; cv: Arterial intimal fibrosis (fibrointimal thickening); g: Glomerulitis; i: Inflammation in the non-scarred cortex; i-IFTA: Inflammation in the scarred cortex; ptc: Peritubular capillaritis; ptcml: Peritubular capillary basement membrane multilayering (requires EM for detection); t: Tubulitis in cortical tubules within the non-scarred cortex; ti: Total cortical inflammation, including scarred and non-scarred cortex; t-IFTA: Tubulitis in mildly to moderately atrophic tubules within the scarred cortex; v: Arteritis (intimal to transmural arteritis).

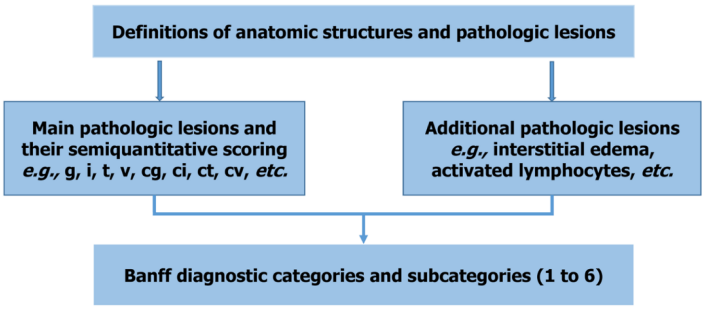

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Figure 1 Basic components and construct of the Banff classification system. The content of the Banff classification can be cataloged into definitions, pathologic lesions, their semi-quantitative scoring, and a combination of these lesions to construct the diagnostic categories.

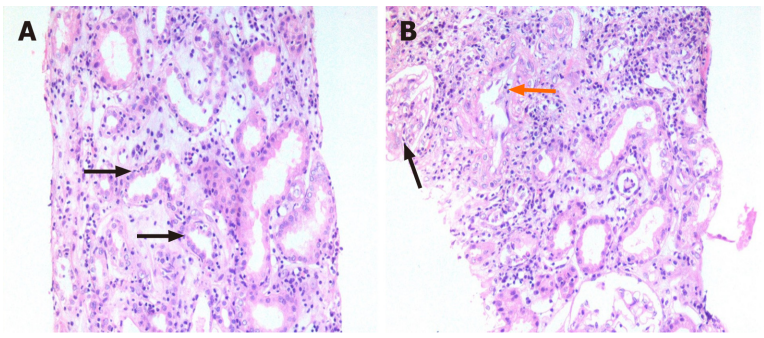

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Figure 2 Representative acute Banff diagnostic lesions for rejection and their scores. A: There is diffuse interstitial inflammation (i3) along with interstitial edema. The later lesion, although important when present, is not formally included in the Banff classification system. Foci of mild tubulitis (t1) are also seen (arrows). These are better visualized on Period acid-Schiff stain [hematoxylin and eosin (H&E), × 200]; B: This field shows glomerulitis (g1) (black arrow) and intimal arteritis (v1) (orange arrow) in addition to i3 and interstitial edema. Such findings raise the suspicion of mixed antibody-mediated and T cell-mediated rejection (H&E, × 200).

beyond the immediate post-transplant period was not formally recognized during this decade, although studies were going on this subject. The workup of renal allograft biopsy was based on morphologic examination alone. The adequacy criteria for renal allograft biopsy were made more stringent in Banff 1997 classification but were still limited to the morphological study of the biopsy material.

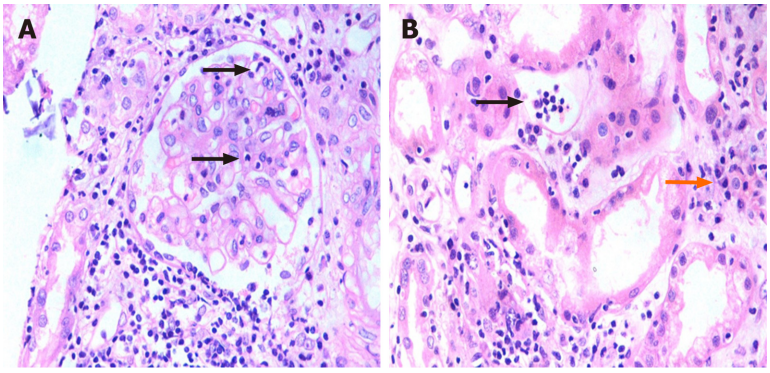

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Figure 3 Acute Banff diagnostic lesions of microvascular inflammation. A: There is segmental glomerulitis (g1) (arrows) along with diffuse interstitial inflammation (i3) in the background [hematoxylin and eosin (H&E), × 400]; B: Peritubular capillaritis (ptc) score ptc 2 (black arrow). ptc is one of the key lesions of antibody-mediated rejection. Patchy interstitial edema, and inflammation with a few plasma cells (orange arrows) are seen in the background (H&E, × 400).

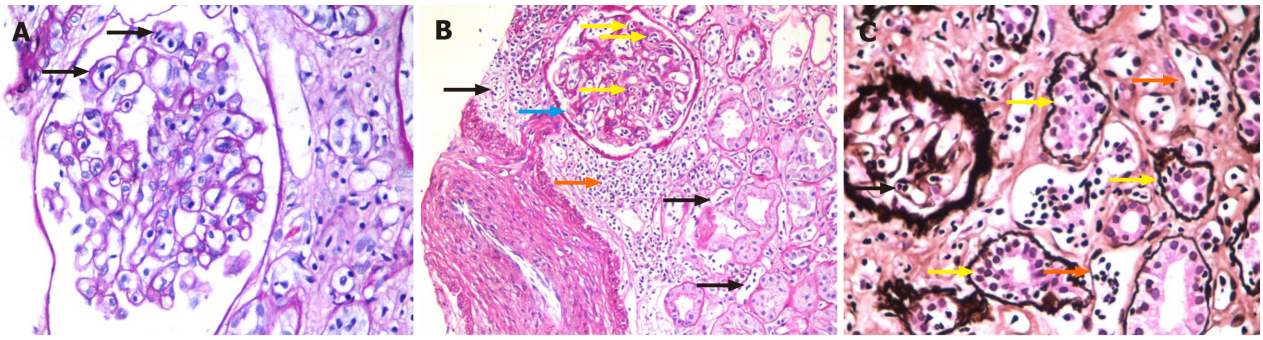

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Figure 4 Diagnostic lesions. A: Acute Banff lesion of glomerulitis. There is segmental glomerulitis (g1) (arrows) characterized by mononuclear inflammatory cell infiltration and endothelial cell enlargement resulting in partial to complete occlusion of capillary lumena. Glomerulitis is one of the key lesions of antibody-mediated rejection. (Period acid-Schiff, ×400); B Morphologic features of mixed antibody-mediated and T cell-mediated rejection with both acute and chronic lesions. There is almost global glomerulitis (yellow arrows) with segmental foci of glomerular basement membrane thickening (blue arrows) suggestive of early transplant glomerulopathy along with diffuse interstitial inflammation (i3) (orange arrows) and peritubular capillaritis (black arrows). An artery included shows severe intimal fibrous thickening (neo-intima formation) without duplication of elastica, (Period acid-Schiff, × 200); C: Mixed acute and chronic Banff diagnostic lesions of rejection. There is segmental glomerulitis (black arrow), peritubular capillaritis (orange arrows), and foci of tubulitis in mildly to moderately atrophic tubules within the scarred cortex (yellow arrows) (Jones Methenamine Silver, × 400).

SECOND DECADE: ANTIBODY-MEDIATED REJECTION

During this decade, the focus of the Banff classification was shifted to the development of the pathologic criteria and their refinement for a conclusive diagnosis of antibody-mediated rejection (AMR) beyond the immediate post-transplant period. Starting from the 2001 Banff meeting, the attention of the transplant community was shifted to the increasing recognition of the role of alloantibodies in causing allograft rejection. During the 2001 Banff meeting, pathologic criteria were formulated for the first time for a definitive diagnosis of AMR in the acute setting, *i.e.* beyond the immediate post-transplant period[12]. These included not only the morphologic criteria but also immunopathologic and serologic criteria. This led to the evolution of the Banff classification to a multidisciplinary schema. The adequacy of tissue was expanded to a portion of tissue for C4d staining and an optional tissue sample for EM study. In the 2005 Banff meeting, criteria for the diagnosis of chronic active AMR were formulated, thus recognizing the full spectrum of antibody-mediated injury[21]. With the widespread application of these criteria in clinical practice, it became obvious that not all forms of AMR are C4d positive. Hence, the need arose for a subtype of AMR to be introduced in the Banff classification, *i.e.* C4d-negative AMR, which was introduced in the Banff 2009 meeting[22]. From Banff 2001 to Banff 2011 meetings, only diffuse C4d staining (C4d3), involving more than 50% of PTCs, was recognized as fulfilling the immunopathologic criterion for AMR[23]. In the Banff 2013 meeting, focal (c4d2: 10%-50%) staining of PTCs for C4d was also accepted, as it was also associated with donor-specific antibodies (DSAs) and reduced allograft survival[14]. BWGs were also created during the 2009 Banff meeting for addressing the problematic areas of the Banff classification for evidence-based investigations and solutions [22].

THIRD DECADE: REFINEMENTS AND INTEGRATIONS

During this decade, further clarifications and refinements were made in the diagnostic criteria and classification of chronic active AMR and TCMR[14,24-27]. The thresholds of some of the lesions were re-defined[14]. Integrations of ancillary techniques of IHC, EM, and molecular studies were recommended for an accurate diagnosis and classification of rejection processes. Digital pathology (DP) and artificial intelligence (AI) tools were explored for their possible role in predicting, diagnosing, and prognosticating kidney allograft pathology[25,26].

Following a brief overview of the decade-wise evolution of the overall classification schema, it is now appropriate to discuss the evolutionary changes of the Banff classification according to individual diagnostic categories in some detail. The names of categories have changed many times. Here, we use the most representative name of the category, which may not be necessarily the same as in the latest Banff classification, the 2019 Banff classification.

Banff category 1: Normal biopsy or nonspecific changes

This is the first category of the original Banff construct and is still so. The definition of this category is self-explanatory. In fact, this category is a diagnosis of exclusion, which implies that not only the graft parenchyma should be free of inflammatory cell infiltration, but it should also show no features of acute tubular injury (ATI) or acute tubular necrosis. Taken at its face value, this category appears superfluous. The rationale behind using and retaining this category seems to be the unavoidable consequence of an overenthusiastic biopsy approach. In some centers, allograft biopsies are performed too quickly or for transient rises in serum creatinine, such that the morphological lesions are either not fully expressed or there is a cause of allograft dysfunction outside of the graft parenchyma. In some instances, sampling error may account for the normal appearances of the sampled cores, especially when the rise in serum creatinine is of an appreciable degree. This is the only category of the Banff classification that cannot be diagnosed in concurrence with any other category.

No significant changes have occurred in this category except for a name change from the "Normal" in the 1993 report through to the 2013 paper to the "Normal biopsy or nonspecific changes" in the 2015 Banff report[10,23,24]. The prevalence of this category in renal allograft biopsies should ideally be low.

Banff category 2: Antibody-mediated changes

Although the founders of the Banff classification recognized the importance of alloantibodies in causing allograft injury right from the beginning of the development of the classification and category 2 was devoted to alloantibodies in the original classification, their full scope was not fully known at that time[28-31]. The role of antibodies was initially thought to be limited only to the immediate post-transplant period[10,11]. With increasing experience and the resulting accumulating evidence, this notion proved to be incorrect and this category has undergone dramatic changes including its nomenclature during the three decades of the evolution of the Banff classification (Figure 5A).

A number of factors contributed to this increased focus on AMR: (1) Increased recognition of the condition as a result of identification of a highly sensitive and equally specific biomarker of AMR, *i.e.* C4d and subsequently some relatively specific pathological features of AMR; (2) A better understanding of the roles and techniques for the detection of anti-donor antibodies; (3) Increasing numbers of re-transplants, *i.e.* second or third transplants; and (4) Increased rates of transplantations across ABO and other immunologic barriers as a result of a shortage of donor organs.

Before discussing the changes in the Banff category of AMR at length, it seems prudent to discuss briefly the pathophysiology of AMR. The main target of AMR is the endothelial cell lining the vascular system, most notably those lining the microcirculation (glomeruli and PTCs in the kidney), but larger arteries may also be targeted. This is comprehensible as the alloantibodies are found in the bloodstream and they first encounter the endothelium of the blood vessels and interact with it. The intensity and nature of the subsequent pathological lesions are variable and depend on many factors including antibody type[32].

The terminology of the category has changed many times, as depicted in Table 3. These changes were necessitated by changing knowledge and accumulating evidence of the role of antibodies in causing allograft injury. In the Banff 93 classification, the category was named hyperacute rejection (HAR). The reason behind this was that, at that time, antibodies were thought to be responsible for causing only this particular type of rejection. In the Banff 97 classification, the category was renamed "antibody-mediated rejection" and divided on clinical grounds into two categories depending on their presentation, as shown in Table 3. HAR and accelerated acute rejections have fortunately become exceedingly rare nowadays. As a result, the Banff classification dropped these terms from the subsequent revised versions. In contrast to cellular rejection, antibodies themselves are not easily visualized in the kidney allograft biopsy tissue. Hence, identification of their role beyond the immediate post-transplant period required the discovery and use of some biomarkers of antibody action. The discovery of C4d in 1993 was such a transformative marker, which prompted research into the role of alloantibodies in allograft rejection[33-39]. In the Banff 2001 meeting, the role of antibodies was recognized in acute settings also, *i.e.* beyond the immediate post-transplant period[12]. In this meeting, for the first time, the pathological criteria were developed for the diagnosis of acute AMR and types of AMR were described. This marked the debut of not only the ancillary technique of C4d staining but also incorporated serology in the Banff classification system, making it a multidisciplinary classification[12]. In the Banff 2005 meeting, diagnostic criteria were developed for chronic AMR including the lesions of transplant glomerulopathy (cg), PTC basement membrane multilayering (ptcml), and transplant arteriopathy (cv)[21]. From the Banff 2007 meeting onwards, the name of this category was changed to antibody-mediated changes, instead of AMR, as it had been shown in experimental studies that not all antibodies cause rejection but some of the antibodies may be involved in accommodation and the full spectrum of antibody actions and outcome on graft tissue was being explored[40,41]. Thus, the present terminology reflects the broad spectrum of actions that can be mediated by antibodies in the graft, many of which still remain to be explored.

Table 3 Main changes in the nomenclature and classification of antibody-mediated rejection in the Banff classification over three decades of evolution (1991 to 2019)

Meeting reports, year	Category 2: Antibody-mediated rejection[1]
Banff, 1993	Hyperacute rejection
Banff, 1997	AMR[3]
	Hyperacute
	Accelerated acute[3]
Banff, 1997 update (2001)	Diagnostic criteria for acute antibody-mediated rejection were developed. Three types were described as: (1) Types I: ATN-like[3]; (2) Types II: Capillary[3]; and (3) Type III: Arterial[3]
Banff, 2005	Diagnostic criteria for chronic antibody-mediated rejection were developed
Banff, 2007	Antibody-mediated changes[2,3]
	C4d deposition without rejection[3]
	Acute antibody-mediated rejection
	Chronic active[3] antibody-mediated rejection
Banff, 2013	Antibody-mediated changes
	Acute/active antibody-mediated rejection
	Chronic active antibody-mediated rejection
	C4d-negative antibody[3]-mediated rejection
Banff, 2015	Antibody-mediated changes
	Acute/active[3] antibody-mediated rejection
	Chronic active antibody-mediated rejection
	C4d staining without evidence of rejection
	Transplant arteriopathy may be seen in chronic AMR
Banff, 2017	Antibody-mediated changes
	Active[3] AMR
	Chronic active AMR
	C4d staining without evidence of rejection
	3 criteria for AMR diagnosis remain but C4d can substitute for DSA
	DSA testing still advised
	Suspicious for AMR eliminated
Banff, 2019	Category 2: Antibody-mediated changes
	Active AMR
	Chronic active AMR
	Chronic (inactive) AMR[3]
	C4d staining without evidence of rejection

[1]May coincide with categories 3, 4 and 5 and 6;
[2]With the identification of c4d positivity without rejection, the category name was changed from rejection to changes);
[3]Changes in the nomenclature or criteria. AMR: Antibody-mediated rejection; ATN: Acute tubular necrosis; DSA: Donor-specific antibody.

With extensive use of c4d in clinical practice, particularly in the protocol biopsies, it was observed that a small number of graft biopsies show c4d positivity in the absence of morphological or clinical features of acute or chronic AMR. Thus, a new subcategory of "C4d deposition without morphologic evidence of active rejection" was added to the Banff classification in 2007[40,41]. Two new lesions of C4d and PTC were also introduced and presented at the 2007 Banff meeting for validation and future incorporation[42].

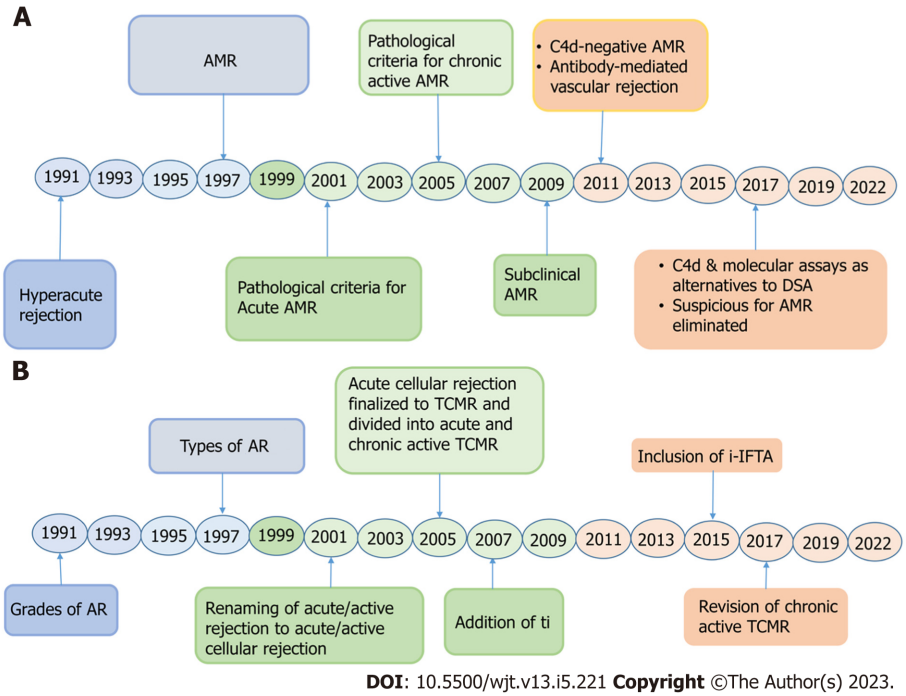

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Figure 5 Diagram depicting the main changes with the timeline. A: In the category of antibody-mediated rejection (AMR); B: In the category of T cell-mediated rejection (TCMR). DSA: Donor-specific antibody; i-IFTA: Inflammation in the scarred cortex.

From Banff 2001 to Banff 2011, only diffuse C4d staining (c4d3) on IF, involving more than 50% of PTCs, was recognized as fulfilling the immunopathologic requirement for AMR, which was amended in the Banff 2013 meeting to accept focal (c4d2: Staining 10%-50% of PTCs) PTC staining as it was shown to correlate with DSA and decreased allograft survival[14].

The second major modification in the AMR category took place in the Banff 2013 meeting[13]. Any degree of v (v > 0) was incorporated in the morphologic criteria for active AMR in contrast to the previous requirement of v3 in light of new studies[43,44]. The absolute condition (criterion 2) for PTC C4d staining for the definite diagnosis of active and chronic active AMR, was supplanted by the criterion of "Evidence of the recent/current interaction of alloantibody with the microvascular endothelium", the latter including C4d but alternatively a minimum of moderate microvascular inflammation (g + ptc ≥ 2) or amplified expression of validated gene transcripts in the biopsy material suggestive of endothelial injury[45-50]. This signaled the first incorporation of molecular diagnostics into the Banff classification[13]. With these additional criteria, many studies showed that a substantial number of AMR cases were C4d negative[51,52]. Thus, the subcategory of C4d-negative AMR was included in the classification at this meeting. The significance of this change can be judged by the fact that this inclusion was incorporated in the title of the paper of the 2013 Banff meeting[13]. In addition, at the Banff 2013 meeting, the minimum thresholds for glomerulitis score (g1) and chronic glomerulopathy by LM (cg1) were revisited based on results of BWG data showing better interobserver reproducibility with the revised criteria. The potential role of EM in the diagnostic evaluation of kidney allograft biopsies was also emphasized, with the inclusion of precise criteria for ptcml to augment the specificity of this pattern for chronic AMR and the inclusion of a new subtype of cg by EM exclusively (cg1a)[53,54].

In the Banff 2019 meeting, a subtype of chronic AMR, *i.e.* chronic inactive AMR was also introduced, as it could be diagnosed on kidney allograft biopsies[26]. Of note, there is no category of chronic (inactive) in TCMR. There is no provision for borderline changes (BCs) in the AMR category, but diagnostic thresholds do apply. The diagnosis of "suspicious for AMR (sAMR)" was finally removed from the Banff 2017 classification.

In summary, considerable progress has been made in the category of AMR. Molecular studies have been officially incorporated in the Banff classification for diagnosis of this category only. The absolute requirement for C4d its diagnosis has been eliminated. The requirement of DSA is also not absolute. sAMR has been removed from the classification.

Banff category 3: BCs

The original Banff classification recognized a category of BCs in reporting the renal allograft pathological lesions and the category is still there even after 30 years of refinements and evolution of the classification. This category encompasses only the tubulointerstitial type of rejection and is used when there is mild (i1) to severe (i3) interstitial inflammation but the tubulitis is of mild degree only (t1) or vice versa and no arteritis is present (v0). The true clinical significance of this lesion is still contentious and is largely determined by the clinical context of the case[55-62]. Some of the factors that may determine its clinical relevance include the source of the donor organ, time post-transplant, and the indication and timing of kidney allograft biopsies. Most of the studies on this category have been carried out in deceased donor transplantation programs[56-62]. Only a few studies are available on the clinical relevance of this finding in the live-related renal transplant setting[63,64].

The criteria for the diagnosis of BCs have changed little over time and essentially consist of any combination of interstitial inflammation (i) and tubulitis (t) scores below the threshold level required for the diagnosis of rejection, *i.e.* "i2, t2". The original criteria for the borderline category were developed at the Banff 1991 meeting, describing it as a "very mild" form of acute rejection lacking intimal arteritis (v0) and having only mild to moderate patchy mononuclear interstitial inflammatory cell infiltration (i1 or i2) with foci of mild tubulitis (t1; 1 to 4 mononuclear cells per tubular cross-section). In this initial classification, "no treatment" was suggested[10]. In 2005, the Banff group suggested the expansion of the "BC" category to include lesions with minimal interstitial inflammatory cell infiltration (i0) to i3 with t0 or t1 or t2, t3 with i0, i1[21]. This was further confirmed in the Banff 2007 meeting[42]. However, the minimum threshold of BC was restored to "i1, t1" in the Banff 2019 meeting, as longitudinal studies by Nankivell *et al*[65] showed no effect of isolated "t" on allograft survival.

The reported frequency of this category varies widely and ranges from 46% to 74 % on dysfunctional kidney allograft biopsies performed at different time points after transplantation[66,67]. This category is also most problematic from the point of view of the treatment. In reality, this category does not represent a true pathophysiological phenomenon. It represents a heterogeneous category of lesions encompassing pathophysiological processes with minimal, nonspecific, insignificant inflammation to clinically important TCMR, capable of immune-mediated allograft injury resulting in poor immunological, functional, and histological outcomes if not treated[55-58]. This category has been created primarily because of varying clinical criteria and the timing of kidney allograft biopsies. In an ideal world, an allograft biopsy should be categorized as rejection or no rejection, but in practice, it is not always so clear-cut. As the biological process of rejection is a gradual and patchy process, it takes time to develop full-blown features of rejection. If a biopsy is performed very early during the development of rejection, the pathological lesions will not have reached the threshold of diagnosis of rejection, and will inevitably be classified as a BC category. It is hoped that in near future this category will be eliminated with the incorporation of better diagnostic markers, particularly, molecular markers.

Banff category 4: Acute rejection (acute/active TCMR)

The spectrum of TCMR, as it is now officially called, was defined from the origin of the classification as the Banff diagnostic category 4 and now includes acute TCMR, grades IA, IB, IIA, IIB, and III, and chronic active TCMR (CA TCMR), grades IA, IB and II. There are no subgrades of grade II and no grade III in CA TCMR[26]. In addition, there is no subtype of chronic (inactive) in the category of TCMR, as is true for AMR. Category 4 is separated from category 3 by a threshold of i2, t2 and any v. Banff diagnostic categories 3 and 4 are mutually exclusive but can be diagnosed concurrently with other lesions from categories 2, 5, and 6.

In the previous iterations of the Banff schema, the main emphasis was on the diagnosis and classification of acute rejection, which essentially implied TCMR. This focus on cellular rejection dominated the transplant pathology field and subdued the recognition and characterization of AMR for quite some time during the earlier period of the Banff classification. On the other contrary, the category of cellular rejection lagged behind AMR in undergoing modifications till the very recent past. The most important changes in this category took place during the 1997 Banff meeting (Table 4). Thereafter, this category remained fairly stable and immune to changes except for minor nomenclature changes. More recent Banff updates have made some modifications to the morphological criteria and subdivision of this category (Figure 5B).

As alluded to earlier, the main emphasis of the first Banff classification was on the accurate diagnosis and classification of acute rejection, which essentially included acute cellular rejection. As this type of rejection is characterized by the infiltration of mononuclear cells into the allograft parenchyma, its diagnosis was relatively easy and obvious in most cases. The main targets of cellular rejection are the tubules, interstitium, and larger blood vessels. Microcirculation inflammation is rarely observed in this type of rejection[10,11,68-75]. The Banff classification introduced for the first time a minimum threshold (*i.e.* i2, t2) for the definitive diagnosis of acute cellular rejection of tubulointerstitial type or type I rejection. This separated it from the category of BCs in the cellular alloimmune lesions. There is no BC category for vascular or type II and type III rejections and the presence of even one lymphocyte in the intima is sufficient to diagnose vascular rejection. Early Banff classifications also emphasized the importance of the topographic location of the inflammatory cell infiltrate in the biopsy[10,11].

The nomenclature of this category has changed from acute rejection to acute cellular rejection to TCMR over the years reciprocating the changes in category 2 of AMR, as shown in Table 4 and Figure 3. With regard to the classification of TCMR, the first Banff classification divided acute rejection into three "grades" based on the increasing severity of the allograft damage, as shown in Table 4. These were: Grade I (mild), grade II (moderate), and grade III (severe) (Table 4). This classification lumped together both the tubulointerstitial and vascular rejections in grade II. It may be noted that this subdivision was based purely on a morphological or pathological basis with little consideration of the underlying pathogenetic basis of rejection. As mentioned earlier, the first main change in this category was effected in the Banff 97 meeting, when pathologists using the original Banff 93 classification and its CCTT modification got together and merged the two classifications to develop a unified and international consensus-based Banff 97 classification with substantial input from the CCTT classification, which stressed the pathogenetic foundation for the categorization of cellular rejection [4,5,10,11]. The Banff 97 classification divided acute/active rejection into "types" and subtypes rather than grades (Table 4). The main modifications in the Banff 97 classification included the segregation of type I (tubulointerstitial) rejection from vascular (type II) rejection. Type III rejection was categorized separately as in the Banff 93 classification (Table 4). This merger signified the adaptability of the Banff group to incorporate the observations of pathologists using CCTT modification and also embrace the emerging evidence from newer investigations showing that vasculitis per se has significant consequences for the response to treatment and/or graft survival[35,36].

Table 4 Main changes in the nomenclature and classification of T cell-mediated rejection in the Banff classification over three decades of evolution (1991 to 2019)

Meeting reports, year	Category 4: T cell-mediated rejection[1]
Banff, 1993	Acute rejection, grades I, II, III
Banff, 1997	Acute/ active cellular rejection
	Types[2] I A/B, II A/B, III
Banff, 1997 update (2001)	Acute/ active cellular rejection
	Types I A/B, II A/B, III
Banff, 2005	TCMR[2]
	Acute, types[2] I A/B, II A/B, III
	Chronic active[2] (includes only transplant arteriopathy)
Banff, 2007	TCMR
	Acute
	Chronic active (includes only transplant arteriopathy)
Banff, 2013	TCMR
	Acute
	Chronic active (includes only transplant arteriopathy)
Banff, 2015	TCMR
	Acute
	Chronic active TCMR may have tubulointerstitial changes[2]
Banff, 2017	TCMR
	Acute
	Chronic active TCMR grades I A/B and II defined
Banff, 2019	i-IF/TA and t-IF/TA included in criteria[2] (inflammation and tubulitis in areas of scarring)
	In chronic active TCMR with i >1, diagnosis to be combined chronic active and acute TCMR[2]

[1]May coincide with categories 3, 4 and 5 and 6;
[2]Changes in the nomenclature or criteria. i-IFTA: Inflammation in the scarred cortex; TCMR: T cell mediated rejection; t-IFTA: Tubulitis in mildly to moderately atrophic tubules within the scarred cortex.

In the Banff 97-update published in 2003 (from the Banff 2001 meeting), with profound and far-reaching changes in the category of AMR, the category of acute/active rejection was rechristened as acute/active cellular rejection (ACR), to underscore its distinction from AMR. Its types and subtypes, however, remained unchanged from the Banff 97 classification. The name of the category was again changed to TCMR in the Banff 2005 update (Table 4). On this occasion, it was further categorized into acute TCMR, which now encompassed all the subtypes of ACR of the Banff 97-update, and CA TCMR. The latter was diagnosed by the presence of chronic allograft arteriopathy only till the 2017 Banff meeting, characterized by new-onset arterial fibrointimal thickening with mononuclear cell infiltration in fibrosis, and the creation of neo-intima. Compared to previous iterations of the Banff classification, the Banff 2007 classification added a new "i" lesion score, labeled as "ti" (total interstitial inflammation score) to the schema[34,76-81]. Not much was changed in the criteria for diagnosis or classification of cellular rejection during the Banff 2009, Banff 2011, and Banff 2013 meetings. In the Banff meeting of 2015, it was realized and acknowledged that CA TCMR may manifest itself with tubulointerstitial inflammation in the form of inflammation in areas of scarred cortex (i-IFTA) in addition to arterial lesions[24]. However, detailed criteria and formal inclusion of CA TCMR were not affected till the 2017 meeting[25]. In the 2019 meeting, tubulitis in mildly to moderately atrophic tubules within the scarred cortex (t-IFTA) was also added as the diagnostic criterion for CA TCMR in addition to i-IFTA and ti scores. Thus, CA TCMR was divided into two types, in contrast to three types in acute TCMR. These types were: Types IA and IB and type II. A provision was also made for the diagnosis of borderline CA TCMR if the diagnostic criteria of CA TCMR types IA and IB were not fulfilled[26]. Banff 2019 also allows concurrent diagnosis of acute and CA TCMR, especially in the presence of intimal arteritis in association with acute TCMR types IA and IB[6,26].

It is obvious from the above deliberations that the mainstay for the diagnosis and classification of cellular rejection has remained and is still so the LM evaluation of allograft biopsy material with little help from the ancillary techniques of IHC or EM. More recently, molecular markers have shown promising results for a conclusive diagnosis of acute cellular

rejection in single-center studies[82-84]. These need to be validated in large, multicenter trials and the methodology needs to be standardized before they can be used widely in clinical practice. These represent the current challenges for the Banff classification system. The molecular information may be integrated with the histomorphological findings in the Banff classification in the future to improve the accuracy of diagnosis and classification of rejection, particularly borderline and CA TCMR cases[85-93].

Banff category 5: Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology

This category of Banff classification of kidney allograft pathology was created to diagnose, classify, and grade (or stage) chronic fibrosing changes of kidney allografts resulting from a variety of causes[94]. Historically, many important changes took place in this category over the past three decades of the evolution of the Banff classification process. In the Banff 2019 meeting, this category has been replaced by polyomavirus nephropathy[26]. The rationale behind this change is that this category seems to be redundant in the absence of a plausible cause. The Banff schema stresses the need to determine the etiology of chronic changes whenever possible[21]. Moreover, chronic subtypes have been added to both types of rejection over the last two decades of evolution.

It seems appropriate to briefly summarize the evolution of the nomenclature and classification of chronic sclerosing lesions in the Banff schema, which are reflective of a continued and improved understanding of the pathophysiology of these lesions (Table 5). During the pre-Banff era, the term "chronic rejection" was utilized for all forms of chronic allograft dysfunction. This approach was an oversimplification, in that chronic changes in the allograft parenchyma are caused not only by alloimmune factors but also by non-immune factors and a distinction among these is important for tailored treatment. The Banff system put forward the nomenclature of "chronic allograft nephropathy (CAN)" in 1991 as a non-committal alternative to the then prevalent and confusing designation of "chronic rejection". The Banff 93 schema categorized CAN into three grades of increasing severity based on the degree of interstitial fibrosis and tubular atrophy (IFTA)[10]. No subdivision of the CAN grades was made and all etiologies of chronic changes were combined together in this unified category. In addition, many histomorphological patterns of, for example, chronic AMR, were not discovered at that time. In the Banff 1995 meeting, the chronic allograft damage index was merged with the CAN group to grade the severity of chronic changes. However, no subdivision of CAN was made in this update of the classification. In the Banff 97 meeting, an effort was made toward subclassifying chronic changes in the allograft and identifying and documenting the changes caused by the rejection processes. A subclassification of each of the grades of chronic changes into "a" and "b" categories was attempted depending on the absence or presence of obvious features associated with "chronic rejection", respectively. The 3-tier grading of the CAN entity remained the same as in previous classifications[11]. No modifications in the terminology or grading of CAN were attempted in the 97-update classification (Banff 2001 meeting) or the Banff 2003 meeting reports[12].

A significant modification in the category of chronic sclerosing changes was effected in the Banff 2005 meeting when the terminology of CAN was abolished and substituted by the term "interstitial fibrosis/tubular atrophy (IFTA)", with no evidence of specific etiology[21]. The etiologic groups of "a" subcategory of CAN in the previous classifications were relocated to the "other" category, while the chronic allo-immune causes were moved to the respective categories of AMR and TCMR as chronic active or chronic (inactive) types. Thus, category 5 in the Banff 2005 report and all succeeding updates (till 2019), included only those forms of chronic changes for which no specific etiological findings were found on the biopsy (Table 5). In the 2019 Banff classification, the category of IFTA has been eliminated and replaced by polyomavirus nephropathy, as shown in Table 5.

It is worth highlighting here that category 5 of the Banff classification can co-exist with any other types of renal allograft pathology, except category 1, which is normal. It is important to record and report both the acute and chronic pathological changes on the biopsies to guide therapy and determine the prognosis.

In summary, the nomenclature, categorization, and subcategorization of chronic changes have undergone substantial alterations over the past three decades of the Banff consensus classification. Of late, the focus was on identifying the early specific features relevant to causes of chronic allograft damage, so that their progression may be halted with intervention. This was somewhat facilitated by the ancillary techniques of IHC and EM. In the latest published 2019 Banff meeting report, this category has been eliminated altogether.

IMPLICATIONS OF ALLOGRAFT BIOPSY FOR CLINICIANS AND OTHER TRANSPLANT CARE TEAM MEMBERS

Renal allograft biopsy is a valuable diagnostic and prognostic tool in the hands of clinicians for evaluating the structural and functional status of the kidney allograft. It can provide important information about the underlying cause of graft dysfunction or rejection. Studies have shown that renal allograft biopsies change the clinical diagnosis in an average of 36% (24%-47%) of cases and treatment in 59% of cases. However, because only a tiny amount of kidney tissue is obtained during the biopsy, several limitations and shortcomings exist in the extent to which renal allograft biopsies can prove useful. A close liaison between the clinicians and nephropathology laboratory will go a long way in overcoming many of these shortcomings[13]. According to studies, the sensitivity of diagnosis of rejection is 90% with one core of tissue and it increases to 99% when two cores are obtained[95-102]. Apart from the above-mentioned inherent sampling error, it is well known that there can be interobserver variability among nephropathologists in interpreting renal allograft biopsies. It can arise due to variations in individual expertise, experience, training, and personal judgment. Many studies have documented the occurrence of interobserver variability in renal pathology, including the interpretation of allograft biopsies[103-112]. Sometimes, the biopsy has to be repeated in view of the above considerations, particularly when the

Table 5 Main changes in the nomenclature and classification of chronic changes of the allograft in the Banff classification over three decades of evolution (1991 to 2019)

Meeting reports, year	Category 5: Chronic allograft nephropathy
Banff, 1993	CAN, grades, I, II, III
Banff, 1997	CAN, grades, I, II, III, each divided into a and b subcategories[1]
Banff, 1997 update (2001)	CAN, grades, I, II, III, a and b
Banff, 2005	IFTA, of no specific etiology[1], grades I, II, III
Banff, 2007	IFTA of no specific etiology, grades I, II, III
Banff, 2013	IFTA of no specific etiology, grades I, II, III
Banff, 2015	IFTA of no specific etiology, grades I, II, III
Banff, 2017	IFTA of no specific etiology, grades I, II, III
Banff, 2019	Grading of polyoma viral nephropathy into classes 1, 2 and 3 (adequate sampling for scoring should include 2 cores with medulla)[1]

[1]Changes in the nomenclature or criteria. CAN: Chronic allograft nephropathy; IFTA: Interstitial fibrosis/tubular atrophy.

biopsy findings do not match the clinical picture. Furthermore, it is to be noted that the interobserver variability is not uniform for all the pathological lesions observed on renal allograft biopsies. For some lesions, the interobserver agreement is good, *e.g.*, ATI, interstitial fibrosis, and vascular changes are often more easily recognized and agreed upon by pathologists, leading to higher concordance in their interpretation. On the other hand, certain pathological patterns may be more challenging and prone to interobserver variability. For instance, the diagnosis and grading of TCMR, AMR, or BCs can sometimes be subjective and require expert judgment. These categories of pathological lesions often involve evaluating subtle changes in cellular infiltrates, glomerular lesions, or peritubular capillaritis, which can lead to differences in interpretation among pathologists.

It is important to recognize that considerable efforts have been made to minimize this variability. Quality control measures such as consensus conferences, panel discussions, and standardized reporting systems have been implemented to improve agreement among pathologists. For instance, the Banff classification system is widely used to grade and classify various pathological findings in renal allograft biopsies. This standardized approach helps in enhancing the reproducibility and consistency of pathological interpretations. In addition, advancements in ancillary diagnostic tests, morphometry, DP, and telepathology have allowed for remote consultation and collaboration among experts, further reducing the impact of interobserver variability[113,114].

While interobserver variability remains a consideration, renal allograft biopsy continues to be an essential diagnostic tool in clinical practice. It provides valuable information for guiding treatment decisions, assessing the severity of graft dysfunction, monitoring for rejection, and identifying other causes of kidney dysfunction. Collaborative efforts, standardized criteria, and ongoing advancements in the field aim to improve the reliability and credibility of renal allograft biopsy interpretations.

The turnaround time for reporting a renal allograft biopsy varies depending on several factors, including the urgency of the clinical situation, the workload of the pathology laboratory, and the complexity of the biopsy specimen. In general, the time frame for reporting renal allograft biopsies can range from a few hours to a few days. However, it's important to note that this is a general estimate and the actual turnaround time varies among different institutions and laboratories. In urgent or critical cases, such as suspected acute rejection or severe graft dysfunction, the pathology laboratory may prioritize the processing and reporting of the biopsy to expedite the diagnosis and facilitate prompt clinical decision-making. In such situations, the reporting time is typically shorter, ranging from a few hours (as short as 2-3 h) to 24-48 h, and is based on LM interpretation alone. In the authors' laboratory, LM findings of all renal allograft biopsies are reported within 4-8 h' time. For those cases, where there is no immediate need for urgent intervention, the reporting time is typically longer. This allows pathologists to carefully evaluate the biopsy specimen, conduct any necessary additional testing or staining such as IF, IHC, or EM, and provide a detailed and accurate report.

It is important to note that the clinical decision-making process based on renal allograft biopsy requires a multidisciplinary approach, involving nephrologists, transplant surgeons, pathologists, and other healthcare professionals. In particular, making a clinical decision based on renal allograft biopsy involves a comprehensive evaluation that integrates the pathological findings with clinical information and other relevant diagnostic tests such as imaging studies, drug levels, urine culture, and other laboratory tests. Collaboration and communication among the healthcare team members is the key to providing optimal patient care.

FUTURE DIRECTIONS

Although major advances have been made in understanding and categorizing kidney allograft pathology during the last

three decades, there are still many problematic areas that remain to be addressed. Issues of sampling errors, reproducibility, borderline category, subclinical rejection, global training and competence, and lack of sensitivity and specificity of morphological features are some such areas[115-118]. Many gaps remain from the diagnostic accuracy and precision point of view, *e.g.*, diagnostic thresholds and BCs. Focused research on molecular diagnostics, DP, AI, machine learning, and deep learning are some of the tools being actively investigated to address these problems[119-123]. Non-invasive serum and urinary molecular markers are also being actively sought for early and reliable identification of the rejection process right from the inception of the injury[124-127]. Integration of these with clinical, laboratory, and biopsy-based investigations may lead to a multimodal diagnostic algorithm for quick and accurate diagnosis for optimal treatment outcomes. Translation of the advancements in pathology diagnostics has yet not been realized into improved long-term graft outcomes.

CONCLUSION

The first 30 years of the Banff classification system have witnessed tremendous progress in understanding, streamlining, and classifying kidney allograft pathology, particularly the rejection. Essentially, the classification has changed from pathology-based to pathogenesis-based and has become clinician-friendly and treatment-friendly. However, many gaps remain from the diagnostic sensitivity point of view, *e.g.*, diagnostic thresholds and BCs. More sophisticated techniques and digital and computational approaches are being actively researched at present to further improve diagnostic accuracy and precision of the classification.

FOOTNOTES

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MINIREVIEWS

Sodium-glucose cotransporter-2 inhibitor use in kidney transplant recipients

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are novel oral hypoglycemic agents garnering much attention for their substantial benefits. These recent data have positioned SGLT2i at the forefront of diabetic chronic kidney disease (CKD) and heart failure management. SGLT2i use post-kidney transplant is an emerging area of research. Highlights from this mini review include the following: Empagliflozin is the most prescribed SGLT2i in kidney transplant recipients (KTRs), median time from transplant to initiation was 3 years (range: 0.88-9.6 years). Median baseline estimated glomerular filtration rate (eGFR) was 66.7 mL/min/1.73 m^2 (range: 50.4-75.8). Median glycohemoglobin (HgbA1c) at initiation was 7.7% (range: 6.9-9.3). SGLT2i were demonstrated to be effective short-term impacting HgbA1c, eGFR, hemoglobin/hematocrit, serum uric acid, and serum magnesium levels. They are shown to be safe in KTRs with low rates of infections, hypoglycemia, euglycemic diabetic ketoacidosis, and stable tacrolimus levels. More data is needed to demonstrate long-term outcomes. SGLT2i appear to be safe, effective medications for select KTRs. Our present literature, though limited, is founded on precedent robust research in CKD patients with diabetes. Concurrent research/utilization of SGLT2i is vital to not only identify long-term patient, graft and cardiovascular outcomes of these agents, but also to augment management in KTRs.

Key Words: Sodium glucose cotransporter-2; Sodium glucose cotransporter-2 inhibitor; Kidney transplantation; Diabetes; Post-transplant diabetes mellitus; New onset diabetes after transplant

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Core Tip: Multiple large trials have demonstrated sodium-glucose cotransporter-2 inhibitors (SGLT2i) associated kidney and cardiovascular benefits for chronic kidney disease patients with diabetes. Important considerations are critical to determine safety and efficacy of these medications after kidney transplantation. While evidence is limited, SGLT2i appear to be both safe and effective short-term. More robust research is needed to determine the long-term impacts of their use in kidney transplant recipients. Appropriate patient selection and monitoring are vital to clinical use and future research efforts of SGLT2i in kidney transplantation.

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INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) or "gliflozins", are oral hypoglycemics that work by inducing glucosuria. They are derived from phlorizin, a glucosuric compound found in apple tree root bark. As described by van Bommel *et al*[1], there are 2 clinically significant sodium-glucose transporters found in humans: SGLT1 Low-affinity high-capacity transport in the distal convoluted tubule and SGLT1 high-affinity low-capacity transporter in proximal convoluted tubule. As noted by Salvatore *et al*[2] and Sawaf *et al*[3], SGLT2i reduces the glucose excretion threshold to 2.2 mmol/L (40 mg/dL) from 10 mmol/L (180 mg/dL).Consequently, they have been shown to reduce glycohemoglobin (HgbA1c) by 0.6%-0.9% with glomerular filtration rate (GFR) > 60 mL/min and 0.3%-0.4% with GFR 30-59 mL/min[1]. SGLT2i also block the sodium/glucose symport channel in the proximal convoluted tubule leading to osmotic diuresis and natriuresis[3]. This excess sodium excretion is thought to induce afferent vasoconstriction through glomerular feedback thereby reducing hyperfiltration[1].

Data on SGLT2i have demonstrated great promise for their use in chronic kidney disease (CKD) patients with diabetes. In a recent meta-analysis, Zelniker *et al*[4] synthesized the findings of multiple landmark trials (EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI). They showed that SGLT2i reduced the risk of renal disease progression by 45% [hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.48-0.64, $P < 0.0001$], and cardiovascular death or heart failure hospitalization by 23% (HR = 0.77, 95%CI: 0.71-0.84, $P < 0.0001$) in patients with and without atherosclerotic heart disease.

These renoprotective benefits have been observed in patients with, as well as without, diabetes. Heerspink *et al*[5], *via* dapagliflozin (DAPA)-CKD, showed that DAPA in CKD patients with or without diabetes reduced the risk of a composite outcome of estimated GFR (eGFR) decline of at least 50%, end stage kidney disease (ESKD), or death from renal/cardiovascular cause (HR = 0.56, 95%CI: 0.45-0.68, $P < 0.001$) with a number needed to treat of 19 (95%CI: 15-27).

As shown by adoption of SGLT2i as first line therapies for CKD patients with diabetes by the 2022 Kidney Disease Improving Global Outcomes guidelines by Rossing *et al*[6], evidence for these agents is promising. Favorable outcomes owing to SGLT2is have led the transplant community to investigate their broader application.

Many dependent diabetic kidney transplant recipients (KTR) appear to be likely beneficiaries of SGLT2i therapy. As described by Chewcharat *et al*[7], 40% of waitlisted patients have diabetes mellitus (DM) and 15%-30% of non-diabetic patients develop post-transplant DM (PTDM)[7]. PTDM is associated with high rates of graft loss, cardiovascular disease, infectious complications, and mortality[7]. Inherent risks of kidney transplantation *e.g.*, urinary tract infection, concern for drug interactions *i.e.*, immunosuppression, and acute kidney injury/CKD risk, have raised safety and efficacy concerns of SGLT2i.

In this mini review, we aim to summarize recent literature describing SGLT2i usage in KTRs to: (1) Provide guidance for clinical use; (2) identify current limitations; and (3) highlight future directions. We hope this mini review will act as a reference for clinicians and researchers alike to advance clinical/translational research and characterize SGLT2i's role in diabetes management after kidney transplantation.

SEARCH STRATEGY

We conducted literature searches in PubMed, Cochrane, Google Scholar from January 2019 to January 2023 and reference lists of relevant studies and reviews. Key words utilized in our search included the following: "SGLT2 inhibitors, SGLT2i, KTRs, type 2 diabetes mellitus, post-transplant diabetes mellitus."

We limited our search to studies with available full text and English language. In this mini review, we selected studies of SGLT2i use in type 2 DM (T2DM) and/or PTDM in KTRs that were either: (1) Prospective randomized control trials; (2) prospective case series; and/or (3) retrospective case series with comparison groups. We limited study inclusion to those occurring in the last 4 years to highlight recent research.

For our analysis of the following outcomes: HgbA1c, eGFR, weight, blood pressure, Immunosuppression drug interactions, adverse events, we pooled studies that reported these data together. As descriptions of cost, novel findings, and long-term outcomes were limited to one or a few studies, these were simply discussed in context of specific studies.

Nine studies met our search criteria: 1 randomized controlled trial, 2 prospective observational studies, and 5 retrospective analyses, of which 2 had comparison groups. All nine studies occurred in the last 4 years.

FINDINGS

In this sample, empagliflozin (n = 241) was the most prescribed SGLT2i followed by DAPA (n = 85) and canagliflozin (n = 74). The median time from transplant for initiating SGLT2i was 3 years (range: 0.88-9.6 years post-transplant). Median baseline eGFR was 66.7 mL/min/1.73 m^2 (range: 50.4-75.8). Median HgbA1c at initiation was 7.7% (range: 6.9-9.3). The following results were seen and are summarized in Table 1.

HgbA1c

HgbA1c generally improved with changes between 0.2%-1% in the reported studies. Notably, in the study by AlKindi *et al*[8], which included a cohort with a mean HgbA1c of 9.3% at initiation as well as excellent allograft function, HgbA1c decreased by 2.3% at 12 mo. As is described by Halden *et al*[9], more robust impacts on glycemic control were observed in those with higher HgbA1c and eGFR.

eGFR

eGFR was preserved in most studies over a period of 6-12 mo[8-13]. Lim *et al*[13] observed a 10% eGFR dip in 15.6% of their cohort with SGLT2i initiation, though eGFR did recover from this and stabilize. After month 5, there was no significant difference in eGFR between dippers and non-dippers. At last follow up (8 mo post-SGLT2i initiation), eGFR in the dippers (67.9 ± 13.9, n = 24) was comparable to that of the non-dippers [67.9 ± 13.9 mL/min/1.73 m^2 (n = 24) *vs* 69.8 ± 19.0 mL/min/1.73 m^2 (n = 106), P = 0.358].

Though specific data on long term eGFR are lacking, Lim *et al*[13] did report a significant reduction in terms of SCr doubling in the SGLT2i cohort *vs* non-SGLT2i users in both unadjusted (HR = 0.49, 95%CI: 0.29-0.85) , adjusted (across multiple models: Adjusted HR (aHR) = 0.37-0.41, 95%CI: 0.22-0.90, all P < 0.05) , and propensity-score matching (aHR = 0.45, 95%CI: 0.23-0.88, P = 0.019) at 72 mo of follow up.

Proteinuria

Proteinuria was not assessed in these studies. As proteinuria is a major risk factor for and driver of progressive CKD, this is certainly an area that needs further studying.

Weight

Weight decreased in 8 studies with a median weight decrease of 1.95 kg (range: 0.7-3.2 kg)[8-10,12,14].

Blood pressure

Blood pressure changes were reported in 4 studies, with mixed results[8,9,11,12]. The magnitude of these changes was on the order of 7-9 mmHg, which are likely clinically significant. This is reaffirmed by findings in the ADVANCE trial, whereby Heerspink *et al*[15] showed that randomization to perindopril-indapamide compared to placebo in CKD ≥ 3 patients with diabetes for 5 years prevented 12 cardiovascular events with reductions in systolic blood pressure on the order of 4.5 mmHg.

Immunosuppression drug interactions

Though data on drug interactions with immunosuppression were limited, four studies did not observe clinically nor statistically significantly differences in drug trough levels after SGLT2i initiation[9-12].

Adverse events

Urinary tract infections (UTI) were the most common adverse event observed across the various studies. When reported, these ranged from none observed up to 36%. 4 studies reported rates between 13%-15%[8-10,14].

Genital infections (GI) occurred but less commonly than UTI in KTRs with only a few GI occurring in studies where it was distinctly described[9,14,16].

Graft function remained stable throughout these studies despite high angiotensin converting enzyme inhibitors (ACEi)/aldosterone receptor blockers (ARB) utilization and the observed eGFR dip at the 4-6 wk mark[10,12,13].

Leg amputation was not observed in any of the studies described. Schwaiger *et al*[16] reported on this in their study with empagliflozin. As is aptly described by Heyward *et al*[17] in their systematic review and meta-analysis, the risk for lower extremity amputation for SGLT2i use in the non-transplant population has only been observed with canagliflozin.

In these small studies, no episodes of euglycemic diabetic ketoacidosis were reported. Song *et al*[14] noted a wide range of insulin dose reductions post-SGLT2i incorporation. Hypoglycemia was noted infrequently in these studies (n = 2 per Lemke *et al*[10]). This risk for hypoglycemia is highest for those with well controlled diabetes (HgbA1c < 8) as well as those on insulin and/or sulfonylurea-class medications, as was the case in the Lemke *et al*'s study[10].

Cost

Lemke *et al*[10] identified cost as the highest reported reason for SGLT2i discontinuation (35%, n = 6). Over time, SGLT2i have become more affordable. Aggarwal *et al*[18] recently described out-of-pocket expenses for SGLT2i, noting that for

Table 1 Summary of studies on sodium-glucose cotransporter-2 inhibitor use in kidney transplant recipients

Ref.	Type, location	Follow up	Treatment arms	Inclusion/exclusion criteria	Baseline eGFR (mL/min/1.73 m^2), HgbA1c (%)	Time from transplant	Result	Adverse events/treatment discontinuation	Comments
Lemke *et al*[10], 2022	Retrospective, United States	12 mo; 27 pts ≥ 12 mo	Cana (*n* = 12); Dapa (*n* = 3); Empa (*n* = 24)	T2DM or PTDM; SGLT2i; 4/2013 to 10/2020; care solely in health system	eGFR, median (IQR) 69 (54-76); HgbA1c Median (IQR) 8.4 (7.8-9.2)	Median (IQR) 28 mo (16-60)	HbA1c↓ (8.4-7.5 at 3 mo; 7.5 at 12 mo; eGFR ↔/Cr ↔ at 3/12 mo; Wt ↓1.6 kg	UTI (*n* = 6; 3 required hospital stay; 1 ICU). Diabetic foot ulcer (*n* = 2). Hypoglycemia (*n* = 2; insulin *n* = 1, glipizide *n* = 1). No DKA, AKI dehydration requiring IVF, Fournier gangrene, Genital infection, fractures. Discontinued tx: *n* = 17 [d/c after a median (IQR) 244d (117-401)], *n* = 6 for cost, *n* = 4, eGFR, *n* = 3 infection, *n* = 1 poor wound healing, *n* = 1, hypoglycemia, *n* = 1 self d/c, *n* = 1, death unrelated to SGLT2i	38% on ACEi/ARB at initiation. Insufficient proteinuria data; Tac levels stable. 5/6 had prior UTI, 4/6 continued SGLT2i w/o recurrence
Lim *et al* [13], 2022	Retrospective, South Korea	62 mo ± 42 mo	Empa (*n* = 150). Dapa (*n* = 76) *vs* non-SGLT2i (*n* = 1857)	T2DM or PTDM Pancreas Transplant Prescribed SGLT2i < 90 from transplant	eGFR at 3 mo post-transplant 66.9 ± 17.7 *vs* 68.4 ± 20.1. HgbA1c at 3 mo post-transplant. Both 7.3 ± 1.4	Mean 3.8 yr ± 4.5	A risk primary outcome = composite outcome of all-cause mortality, DCGF, and SCr doubling: Multivariate [aHR (0.43; 95%CI = 0.24-0.78, *P* = 0.006) propensity score-matched; aHR (0.45; 95%CI = 0.24-0.85, *P* = 0.013)]. HbA1c = NR. eGFR stable at 8 mo. ↓SCr doubling significantly in unadjusted and adjusted models. Wt = NR	UTI/genital mycotic infection: (SGLT2i 4.5 events/100 patient-year *vs* non-SGLT2i 6.2/100 patient-year). No DKA. Discontinued txt: NR	15.6% eGFR dip over 10% during first month. eGFR recovered thereafter. 48.7% of the SGLT2i cohort was on ACEi/ARB. Composite all-cause mortality, DCGF, or SCr doubling in KTRs
Hisadome *et al*[12], 2021	Retrospective observational study, Japan	48 wk	SGLT2i (*n* = 29); Cana (*n* = 9); Empa (*n* = 4); Dapa (*n* = 3); Luseo (*n* = 5); Ipra (*n* = 7); Tofo (*n* = 1) *vs* Other oral glycemic agent (*n* = 60); DDP4i (*n* = 42); meglitinides (*n* = 9); metformin (*n* = 4); SU (*n* = 4) α-glucosidase	ESRD patients w/T2DM nephropathy pre-transplant PO hypoglycemic. Follow up at outside centers < 1 yr follow up. Missing data	eGFR mean ± SD: 50.4 ± 13.9; 47.5 ± 13.1. HgbA1c mean ± SD: 7.7 ± 0.9; 7.6 ± 1.1	NR	HgbA1c 7.7 -> 7.6 (same) *vs* 7.6 to 7.5. Wt -0.7 ± 5.1 kg *vs* 1.6 ± 4.5 kg. eGFR 50.4 -> 51.4 *vs* 47.5 to 46.3. BP went up (7 mmHg ± 20 *vs* -3 ± 24)	UTI 2:0; CV disease 0:2. BPAR 1:1. Discontinued txt: NR	71.2% of the SGLT2i group was also on ACEi/ARB. Stable tac levels (*P* = 0.755)
Song *et al* [14], 2021	Retrospective, United States	101 d	Empa (*n* = 43); Cana (*n* =6); Dapa (*n* = 1)	PTDM eGFR ≥ 30. AKI in prior ≤ 30 d. UTI in prior 6 mo	eGFR at initiation: Mean 66.7; 30-45 (*n* = 7; 14%) HbA1c mean ± SD: 7.1 ± 0.1	Median (IQR): 319.5 d (122-696). 40% within 200 d	ΔeGFR 3 mo: -1 mL/min; 6 mo: 1 mL/min. ΔHgbA1c 0.53%. Treated UTI 7 (14%). Approximately 20% typical rate. Change in insulin (-3.7 units ± 22.8). Wt (-2.95 kg ± 3.54, 95%CI 3.53-1.5). HgbA1c ↔; eGFR ↔; Wt↓. ΔMag2+ ↑ by 0.13	UTI (*n* = 7). D/C txt: *n* = 9 (5, UTI; 1 genital infection, 1; native disease; recurrence, 1 PTDM; resolution, 1; physician preference)	80% T2DM; 98% on prednisone; UTI rate comparable to KT population (14%)

AlKindi *et al*[8], 2020	Retrospective case series, United Arab Emirates	Range: 3 mo to 2 yr	Empa 10 mg *n* = 5; 25 mg *n* = 1. Dapa 25 mg *n* = 2	Diabetic KTRs; SGLT2i between 06/16-01/19	eGFR mean ± SD: 75.8 ± 13.4; HbA1c mean ± SD: 9.3 ± 1.4	mean ± SD: 9.6 yr ± 6.41	HgbA1c↓ (9.0 at 3 mo; 8.6 at 6 mo; 7.7 at 9 mo; 7.4 at 12 mo; eGFR ↔ median eGFR 72 (range 62-76) at 12 mo. Wt (mean wt 84.82 kg -> 82.87 at 3 mo -> 82.75 at 6 mo). BP not statistically significant though 9 pt difference	UTI + hospitalization (*n* = 1); pt w hx of UTI no UTI w ppx. Discontinuation rate: NR	2/8 T2DM; 6/8 PTDM; all LURKTx
Halden *et al*[9], 2019	Prospective, double blind, RCT Norway	6 mo	Cana 10 mg (*n* = 22). Placebo (*n* = 22)	≥ 18 yr; ≥ 1 yr post-transplant. PTDM only < 20% SCr deviation in last 2 mo. ≥ 3 mo stable immunosuppression. eGFR ≤ 30; Pregnant or nursing	eGFR Median (IQR) 66(57-68): 59 (52-72). HbA1c Median (IQR) 6.9 (6.5-8.2): 6.8 (6.1-7.2)	Median (IQR) 3 yr (1-16): 3 yr (1-15)	HbA1c↓ (6.9 to 6.7 *vs* 6.6 to 6.9); eGFR↓ (2 mo), ↔ (6 mo)-66 to 61 *vs* 59 to 59. Weight↓ (92 kg to 88.8 kg *vs* 84 to 85 kg). No real impact on BP. Hgb increase 13.9 to 14.5. ↓Uric acid. Tac/CSA/Siro levels stable	Urosepsis 1:0 (hx of recurrent UTI), UTI 3:3, genital infection 1:0, dizziness 2:0, hematuria 1:0. Discontinued txt: *n* = 2 (recurrent UTI, urosepsis): 3 (withdrew consent, colon cancer, no longer PTDM)	High DPP-4i use; most were not on additional therapy
Schwaiger *et al*[16], 2019	Prospective	1 mo (*n* = 14); 12 mo (*n* = 8)	Empagliflozin (*n* = 14). Reference (*n* = 24)	eGFR > 30; < 40 IU/d insulin. HgbA1c < 8.5. Adequately diagnosed PTDM	Baseline. eGFR 55.6. Baseline HgbA1c 6.5	Median 69.4 ± 57.2 mo	HgbA1c 6.5-> 6.6 at 4 wk (*P* > 0.05). eGFR 55.6 -> 47.5 at 4 wk (*P* > 0.05). Average TBW↓ 1.6 kg; Waist circ ↓4 cm. ECV/TBFV decreased	UTIs: 5:9. Genital infection: 1. AKI, DKA, Fournier's-NR	100% on steroids. Median onset of PTDM was 0.5 months. 100% on insulin
Shah *et al*[11], 2019	Prospective	6 mo	Canagliflozin (*n* = 25)	≥ 18 years old. CrCl (ml/min) > 60; HgbA1c > 6.5; T2DM; PTDM. Unstable Cr. ALT > 2 × ULN; TBili > 2 × ULN; Recent UTI/genital mycotic infection	Baseline Cr (mg/dL): 1.1 ± 0.2; Baseline HgbA1c: 8.5 ± 1.5	Mean duration of transplant = 2.7 yr (0.2-13.2)	HgbA1c: 8.5 ± 1.5 -> 7.6 ± 1. Cr: 1.1 ± 0.2 -> 1.1 ± 0.3. Weight: 78.6 ± 12.1 -> 76.1 ± 11.2 (*P* < 0.05). SBP (mmHg): 142 ± 21 -> 134 ± 17 (*P* < 0.05)	No increase in UTI/genital infections. No hypoglycemia or DKA. Fatigue (*n* = 3). Discontinued treatment (*n* = 1)	20 T2DM; 5 PTDM. Reduction of other hypoglycemics needed. 1 KTR self d/ced. Used fixed 100 mg dose. Stable tac doses

eGFR: Estimated glomerular filtration rate; pts: Patients; Cana: Canagliflozin; Dapa: Dapagliflozin; Empa: Empagliflozin; T2DM: Type 2 diabetes mellitus; PTDM: Post-transplant diabetes mellitus; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; IQR: Interquartile range; HgbA1c: Glycohemoglobin; Cr: Creatinine; Wt: Weight; UTI: Urinary tract infection; ICU: Intensive care unit; DKA: Diabetic ketoacidosis; AKI: Acute kidney injury; IVF: Intravenous fluids; txt: Treatment: d/c: Discontinued; ACEi: Angiotensin converting enzyme inhibitors; ARB: Aldosterone receptor blockers; tac: Tacrolimus; SCr: Serum creatinine; DCGF: Death censored graft failure; aHR: Adjusted hazard ratio; CI: Confidence interval; NR: Not reported; KTR: Kidney transplant recipient; Luseo: Luseogliflozin; Ipra: Ipragliflozin; Tofo: Tofogliflozin; DDP4i: Dipeptidyl peptidase 4 inhibitors; ESRD: End stage renal disease; PO: Oral; SD: Standard deviation; BP: Blood pressure; CV: Cardiovascular; BPAR: Biopsy proven acute rejection; Δ: Change in; Mag2+: Magnesium; KT: Kidney transplant; hx: History; ppx: Prophylaxis: LURKTx: Living unrelated kidney transplant; Hgb: Hemoglobin; CSA: Cyclosporine; siro: Sirolimus; IU: International units; TBW: Total body weight; circ: Circumference; ECV: Extracellular volume; TBFV: Total body fluid volume; CrCl: Creatinine clearance; ALT: Alanine transaminase; ULN: Upper limit of normal; TBili: Total bilirubin; SBP: Systolic blood pressure.

most insured patients, median cost for 30 d of SGLT2i therapy cost around $38.43 (range: $3.87-$49.42)[18].

Novel findings

In their comprehensive randomized controlled trial, Halden *et al*[9] observed increased hemoglobin/hematocrit and decreased uric acid levels with SGLT2i use. Song *et al*[14] observed an improvement in serum magnesium levels after SGLT2i initiation.

Long term outcomes

Lim *et al*[13] showed a significant reduction at five years in their composite outcome of all-cause mortality, death-

censored graft failure (DCGF), and serum creatinine doubling with SGLT2i use in both multivariate (aHR = 0.43; 95%CI: 0.24-0.78, *P* = 0.006] and propensity score-matched aHR (0.45; 95%CI: 0.24-0.85, *P* = 0.013). Otherwise, these studies lacked long term outcome data.

ANALYSIS

Though these studies are heterogenous and limited in terms of design and size, short term safety and efficacy outcomes of SGLT2i use in diabetic KTRs appear comparable to those observed in CKD patients with diabetes.

Glycemic control paralleled that seen in the non-transplant DM population with modest HgbA1c improvements. Though most studies included KTRs with adequate allograft function, Hisadome *et al*[12] and Song *et al*[14] included a substantial number of individuals with eGFR in the 30-45 range, which approximates to CKD stage 3b. Though there are potential differences between CKD and CKD after transplant as described by Djamali *et al*[19], evidence supporting safe, effective use of SGLT2i in KTRs with decreased allograft function is encouraging.

Remarkably, the eGFR decline, recovery and stabilization of kidney function that occurs in non-transplant diabetics was also observed in some KTRs without significant unfavorable impacts on long term graft function. This was in the setting of high reported concurrent ACEi/ARB use which are recommended as first line agents in diabetic kidney disease. This is exciting, as renin-angiotensin-aldosterone system (RAAS) blockade plays a vital role in diabetic CKD/cardiovascular management. Moreover, the major trials for SGLT2i, such as EMPA-REG OUTCOME by Wanner *et al*[20] reported RAAS blockade use between 80%-85% of those studied. In summary, the illustration of eGFR stability with simultaneous use of SGLT2i/RAAS blockade in KTRs across multiple studies will hopefully quell clinician fears regarding their concurrent use.

It is unfortunate that proteinuria was not an endpoint in any of the included studies. Results of studies in the general population, namely those by Jongs *et al*[21], Cherney *et al*[22], and Trujillo *et al*[23], in terms of SGLT2i effect on proteinuria, are both limited and mixed[21-23]. EMPA-REG OUTCOME by Wanner *et al*[20], CANVAS by Neal *et al*[24] and CREDENCE by Perkovic *et al*[25] and DAPA-CKD by Heerspink *et al*[5], suggested utility for these agents in reducing the geometric mean urinary albumin creatinine ratio, increasing the likelihood of regression in albuminuria stage and reducing the risk of macroalbuminuria progression[20,21]. Further investigations into whether or not SGLT2i impact proteinuria in KTRs will be important not only to better understand these medications, but also to help with agent selection if a difference *e.g.*, empagliflozin and canagliflozin *vs* DAPA, is observed between them in KTRs.

Weight loss occurred in almost every study, likely due to the osmotic diuresis caused by SGLT2i use. This is also occurring due to fat loss from caloric wasting *via* glucose. As the weight loss demonstrated for most patients is less than 5% total body weight, this likely has little bearing clinically.

That being said, perhaps weight loss can underscore future studies examining impacts on truncal obesity, waist size (as Schwaiger *et al*[16] remarked), cholesterol, uric acid levels, and other markers of obesity/metabolic syndrome and their impacts on kidney and cardiovascular outcomes.

Blood pressure outcomes were less clear across these studies, which is at least partly explained by the different mechanisms and influences on blood pressure in KTRs compared to CKD patients as described by Kasiske *et al*[26]. It is unlikely due to weight loss alone given the magnitude of weight loss as previously noted. As these medications are studied further in KTRs, perhaps novel mechanisms for how SGLT2i influence blood pressure will be elucidated.

While UTIs were observed in these studies, they did not appear to occur significantly more than in KTRs not on SGTL2i. As described by Brune *et al*[27], the prevalence of UTI after transplant varies significantly based on several factors (namely *via* definition, study, population, length of follow up). However, they state that a reasonable benchmark based on larger studies is a 1-year incidence rate around 30%. Lemke *et al*[10] reported continued use of SGLT2i after UTI, with one of those patients requiring hospitalization for treatment, but without recurrent disease. Long term impacts of SGLT2i use/glucosuria not only on UTI risk, but also asymptomatic bacteriuria, antibiotic use and associated complications are ongoing uncertainties. GI were observed but at a fairly low rate compared to UTI as described above.

Though limited, drug level data suggest that SGLT2i have little to no impact on calcineurin inhibitor (CNI) trough levels, nor were increased episodes of rejection observed. As Scheen[28] describes in his excellent review on the subject, SGLT2i metabolism minimally involves cytochrome CYP3A4, making SGLT2i-CNI drug interactions slight at best.

As described by Song *et al*[14], hypomagnesemia was improved in KTRs on SGLT2i. As hypomagnesemia is associated with increased risk of cardiovascular and infection-related mortality as noted by Panthofer *et al*[29] and Odler *et al*[30] and this is an important management target. Per Huang *et al*[31], there may be a role for pre-emptive SGLT2i use as hypomagnesemia itself has been shown to increase the risk of PTDM in KTRs. Additionally, hypomagnesemia treatment can be challenging as most magnesium formulations cause diarrhea. Therefore, SGLT2i may play a role obviate/minimize high magnesium supplementation needs.

Though not discussed thoroughly in the literature, Bilezikian *et al*[32] and Kohan *et al*[33] note that there are some concerns for SGLT2i and their impacts on bone health. Lemke *et al*[10] reported on fractures in their study, noting none occurred. Though this is a nascent area of research, Blau and Taylor[34] demonstrated a possible mechanism *via* the FGF23–1,25-dihydroxyvitamin D–parathyroid hormone axis. As impaired bone health is common in KTRs, seeing how this relationship bears out in longer, more robust studies will be important for patient selection and ongoing management. At the moment, there is insufficient data to attribute substantial fracture risk to SGLT2i use.

With SGLT2i being relatively new agents, there is a paucity of data on long-term kidney, cardiovascular, and survival outcomes. Determination of their impact on long-term outcomes will require larger, protracted investigations. This is illustrated in the EMPA-REG trial by Wanner *et al*[35], in which SGLT2i-mediated eGFR preservation was first seen

around 80 wk of therapy *vs* placebo.

Ideally, future retrospective studies, like that by Lim *et al*[13] and/or prospective analyses can describe these relationships going forward. These would be best achieved by multi-center, large trials analogous to their landmark predecessors.

In their comprehensive study review on the management of PTDM, Hecking *et al*[36] aptly summarize direct and indirect potential benefits of SGLT2i in kidney transplantation. Though some of this is extrapolated from non-KT research, novel impacts such as reduction in vascular rigidity as well as hypoxia-inducible factor-1, could be impactful in the kidney transplant population regarding cardio-/reno-/vascular health, anti-inflammatory properties and perhaps anemia management as described by Hecking *et al*[36], Gupta and Wish[37].

A key limitation of these studies is that they evaluated KTRs with diabetes alone. As this is a logical starting place for investigating the efficacy of SGLT2i, to suggest that these medications are limited only to KTRs with diabetes is too narrow a view. With kidney transplantation existing as a state of CKD as well as ESKD itself portending significant cardiovascular risk, we surmise (and hope) that the benefits of SGLT2i will extend to KTRs without diabetes as well. As was demonstrated in DAPA-CKD, a multicenter randomized controlled trial of 4304 patients in which 32.5% of the patients were non-diabetic, SGLT2i increased the likelihood of albuminuria regression and reduced the likelihood of progression to more severe stages of albuminuria in CKD patients with and without diabetes[5]. Therefore, KTRs without diabetes warrant investigation into the utility of SGLT2i use.

CLINICAL RECOMMENDATIONS

Though more research is needed, there appears to be a subset of non-insulin dependent diabetic KTRs who ought to benefit from SGLT2i therapy.

Identifying appropriate candidates is a critical step for implementing SGLT2i therapy routinely. Though questions remain presently regarding long term safety, the stalwart evidence from the CKD literature is compelling for the transplant community to press forward.

In their recent review, Patel *et al*[38] proposed an "ideal" KTR SGLT2i candidate. While this provides a nice general framework, we have additional characteristics to build on this model for identifying SGLT2i candidates.

At present, there does not appear to be substantial evidence on when post-transplant to initiate SGLT2i therapy. Earlier initiation *i.e.*, prior to 6- or 12-mo post-transplant may be beneficial for at least 3 reasons: (1) PTDM appears to be an early post-transplant complication. This is shown by Jenssen and Hartmann[39], in their review on PTDM, where they cite Porrini *et al*[40]. In their study, 32% of the cohort developed PTDM (215/672). Of these 215, 187 (87%) of these KTRs developed PTDM prior to 12 mo; (2) major benefits of SGLT2i therapy such as eGFR preservation may require long term medication use, as EMPA-REG showed[35]; and (3) as is aptly described by Wolfe *et al*[41] in their seminal study on mortality after deceased donor kidney transplant (DDKT), there is increased risk of death in the early post-transplant time period. Perhaps this will promote studies of initiating SGLT2i at the time of transplantation in select patients *e.g.*, DDKT with immediate graft function.

In the following section, we will put forth clinical recommendations for SGLT2i use in KTRs. These are based on the aforementioned results as well as inclusion/exclusion criteria in the studies reviewed. As this is an evolving science, these are solely recommendations *i.e.*, provider discretion remains crucial to using these medications. These are also summarized in Figure 1.

Based on the literature reviewed, we propose the following as good candidates for SGLT2i use: (1) KTRs with pre-transplant T2DM or PTDM; (2) at least 3 mo post-transplant; (3) stable allograft function preferably with eGFR of at ≥ 30 mL/min/1.73 m^2, ideally ≥ 60 mL/min/1.73 m^2 for the past 2 mo; (4) no rejection episodes within the past 3 mo; (5) at least 3 mo of stable immunosuppression; (6) stable ACEi/ARB doses; (7) patients at low risk for volume depletion *e.g.*, low risk for unstable diarrhea, vomiting; (8) patients at low risk for hypoglycemia *e.g.*, HgbA1c > 8 or < 8 and not on a sulfonylurea or insulin. If at risk for hypoglycemia, would consult diabetic specialist for regimen titration; (9) patients without significant UTI history or diabetic foot ulcers; (10) patients with low risk for acute kidney injury; and (11) patients who may benefit from novel aspects of SGLT2i: Hypomagnesemia, hyperuricemia, anemia.

In terms of pharmacologic therapy titration in the context of SGLT2i initiation, we recommend the following: (1) Insufficient data to support empiric adjustments to maintenance immunosuppression or to diabetic prescriptions; (2) can consider reducing diuretic doses; (3) advise diabetic specialist consultation for KTRs with well controlled diabetes (HgbA1c < 8) and other diabetic agents, particularly insulin or sulfonylureas, to help titrate their diabetic regimen to minimize the risk of hypo-glycemia; and (4) continued drug trough and blood glucose monitoring are key to titrate further.

In terms of monitoring parameters, we recommend the following: (1) Renal function assessment at least every 3 mo at a minimum. Can consider more frequent monitoring with initiation/dose adjustments; (2) if applicable (on CNI or mammalian target of rapamycin inhibitor therapy), serial immunosuppression trough levels per provider's discretion. Can consider more frequent monitoring with initiation/dose adjustments; (3) routine monitoring for volume status, risk factors for diabetic ketoacidosis, hypoglycemia; and (4) routine monitoring for signs and symptoms of UTI, diabetic foot ulcers.

It is somewhat challenging to put forth contraindications to use at this time, particularly when the evidence for use is so persuasive. Assuredly there are patients in whom SGLT2i use poses greater risk of harm than benefit *e.g.*, a KTR with a history of DKA, at risk for or experiencing recurrent transplant pyelonephritis, and/or chronic osteomyelitis and/or active diabetic foot wounds. Ultimately, the determination of benefit *vs* risk requires clinical reasoning, evaluation and

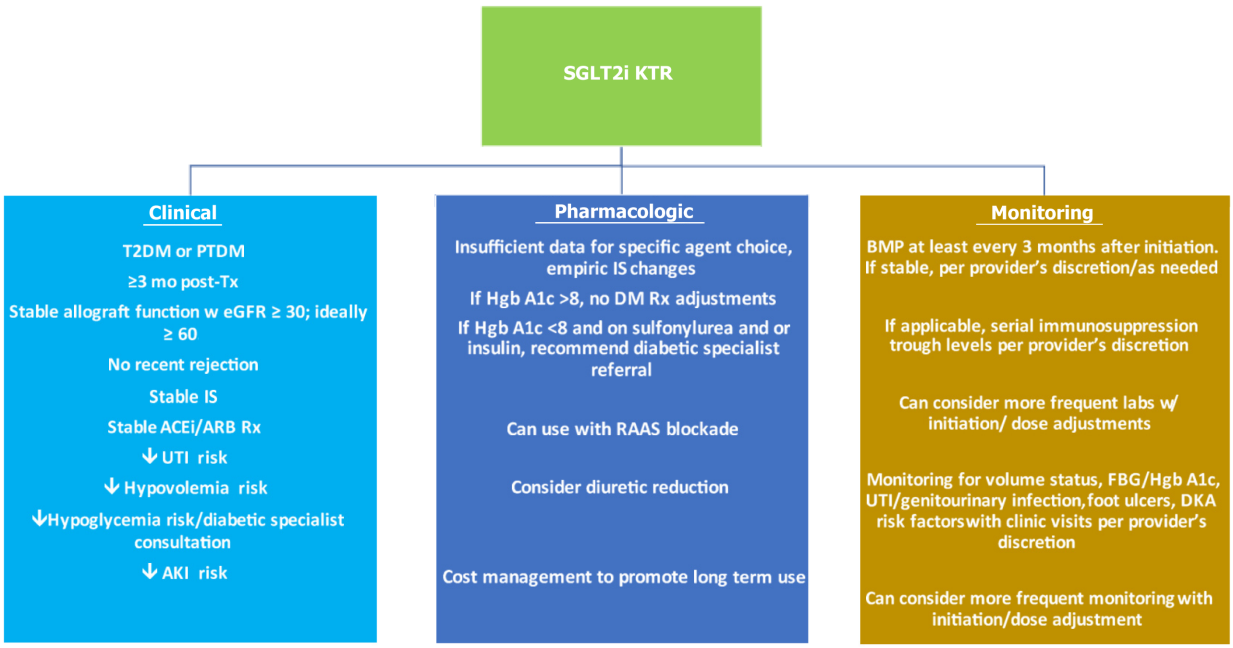

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Figure 1 Clinical, pharmacologic and monitoring parameters for sodium glucose cotransporter-2 inhibitor use in a kidney transplant recipient. Clinical criteria, pharmacologic and monitoring strategies are essential to selecting and managing kidney transplant recipient (KTRs) for sodium-glucose cotransporter-2 inhibitor (SGLT2i) use. Stable KTRs with an appropriate diabetes diagnosis, clinical stability and low risk for adverse events is key. Little data exists for empiric medication changes, though diuretic dose reduction ought to be considered. Strategies for cost management beyond insurance ought to be explored to maximize possible long-term benefit from SGLT2i administration. Laboratory and clinical monitoring more frequently with initiation/dose adjustments is critical to identifying adverse events. SGLT2i: Sodium-glucose cotransporter-2 inhibitors; KTR: Kidney transplant recipient; T2DM: Type 2 diabetes mellitus; PTDM: Post-transplant diabetes mellitus; Tx: Transplant; w: With; eGFR: Estimated glomerular filtration rate; IS: Immunosuppression; ACEi: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; Rx: Prescription; UTI: Urinary tract infection; AKI: Acute kidney injury; Hgb: Hemoglobin; DM: Diabetes mellitus; RAAS: Renin-angiotensin-aldosterone system; FBG: Fasting blood glucose; DKA: Diabetic ketoacidosis.

patient-provider dialogue on whether SGLT2i use is in the patient's best interest.

Notably, guidance exists in the literature regarding patient handout communications when initiating SGLT2i therapy. Lam *et al*[42] provide an excellent version that is generally applicable to KTRs.

LIMITATIONS

Though early data on SGLT2i implementation in KTRs is promising, it is albeit limited.

There are 3 main limitations in the data on the use of SGLT2i in KTRs. Longitudinal studies with large enrollment volume are absent. The longest follow up was around 8.5 years with most having far less. This leaves cardiovascular, graft and mortality outcomes unexplored. Rare adverse events like euglycemic DKA or osteoporosis are also not explored. RCTs are necessary to establish causality and bolster clinical practice recommendations. Most of the studies in SGLT2i are limited to retrospective, observational design or case series.

The SGLT2i story is one that is well underway. There appears to be substantial evidence supporting their use in terms of safety and short-term efficacy based on the studies we described and their antecedents. What lies ahead regarding long-term SGLT2i therapy is unknown. With SGLT2i, we are not working *ab initio* (from the beginning). Rather, as is precedent in some of the greatest epics and sagas (*i.e.*, the *Mahābhārata,* Homer's *Iliad* and *Odyssey*, Virgil's *Aeneid,* Dante's *Divine Comedy*) as noted by Lochtefeld[43], Murray[44] and Raffa[45], we can and ought to forge ahead into the unknown *in medias res*-into the middle of things.

FUTURE DIRECTIONS

While the current literature gives insight into short-term outcomes of SGLT2i use in KTRs, more research is needed to identify the long-term impacts of SGLT2i use in this population.

Currently, there are 2 actively recruiting clinical trials (NCT04965935 aka INFINITI2019 and NCT04906213 aka CREST-KT).

INFINITI2019 is a double-blind, placebo-controlled trial aimed at comparing DAPA to placebo in 52 KTRs. The primary outcome is blood pressure reduction in addition to fasting blood glucose, HgbA1c, continuous home glucose

monitoring, arterial stiffness, systemic vascular resistance, change in baseline measured GFR, change in eGFR, proximal tubular natriuresis, albuminuria, change in baseline urinary and plasma oxidative stress markers, change in tubule interstitial hypoxia, CNI levels, and adverse events.

CREST-KT is a single-center, double-blinded randomized controlled trial of empagliflozin therapy in 72 KTRS with (36) and without (36) diabetes. After dividing by diabetes diagnosis, the groups will be randomized 2:1 to empagliflozin 10 mg *vs* placebo *i.e.*, 48 KTRs will be on empagliflozin and 24 KTRS will be on placebo. Study time is planned to be 18 mo.

Primary outcomes include: Change in eGFR, change in albuminuria, change in cardiac structure by 3D echocardiogram, change in blood insulin level, change in fasting blood sugar, # of UTIs and # of GI.

Secondary outcomes include: Change in kidney biopsy from time zero to 6 mo and change in HgbA1c as well as AEs.

In addition to these studies, hopefully future randomized controlled trials examining long term renal outcomes as well as cardiovascular outcomes, particularly in patients with known heart failure, will help guide appropriate SGLT2i use and influence guidelines and practice patterns for SGLT2i in KTRs.

CONCLUSION

SGLT2i appear to be safe, effective medications in the arsenal of post-transplant therapies for select KTRs. Our present literature, though somewhat limited, is founded on preceding strong research in CKD patients with diabetes. Concurrent research and utilization of SGLT2i is vital to not only identify long-term patient, graft and cardiovascular outcomes of these agents, but also to augment diabetic, CKD, and cardiovascular management in KTRs *in media res*.

FOOTNOTES

Author contributions: Ramakrishnan P wrote and drafted the article, performed critical revision of the article and approved the article; Garg N, Pabich S and Mandelbrot DA provided critical revisions and approval of the article; Swanson KJ provided concept/design, article drafting, critical revision and approval of the article; All authors have read and approve the final manuscript.

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MINIREVIEWS

Renal allograft procurement from living unrelated donors in Iran: What falls under the eclipse

Saeed Taheri

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Abstract

Renal transplantation is the treatment of choice for end stage kidney disease. However, despite all the efforts to expand the donor pool, the shortage of donors is increasing and as a consequence, there has been a significant increase in the number of patients on transplant waiting lists globally. Societies worldwide have employed different methods to address this, each with specific ethical concerns surrounding them. Over three decades ago, a governmentally regulated program of kidney transplantation from living unrelated donors was introduced in Iran and since practiced which has been the subject of hot debate in the literature. Nevertheless, despite all these extensive discussions and publications, several key aspects of the program have still not been properly elucidated and addressed. In this article, the author aims to illuminate some dark corners related to this issue that have largely escaped the notice of ethicists.

Key Words: Allograft procurement; Renal transplantation; Living unrelated donor; Organ market; Iran

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Core Tip: Iran's living unrelated kidney transplantation program has several limitations by its definition, but what is already in practice goes far beyond that and is actually a government legislated and regulated kidney market in which the laws and supports all essentially best serve the interests of brokers and financial agencies, and result in exploitation of the poor on either the recipient or donor.

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INTRODUCTION

Conventionally called "the Iranian Model of Kidney Transplantation", the practice of kidney allograft transplantation procured from living unrelated (LUR) donors in Iran has been highly controversial, and for that reason as well as the unclear origins of the idea when it was introduced into the Iranian medical society, this terminology was avoided in this commentary. Although this topic has been widely tackled in the past by its proponents, opponents, and health-authorities [1-3], there are still several major aspects of the practice that have not been very well addressed. In this paper, I intend to discuss some of these complexities.

According to the latest report by the Iranian Society of Nephrology, 76.3% of all the kidney transplantations performed in Iran are from living donors[4], 86% of which has been reportedly from LUR donors[5]. With such a large share of the transplantation volume, rather extensive claims have been made in the literature as to the merits of LUR transplantation in eliminating the kidney transplant waiting lists; although in real practice, there are already two simultaneous waiting lists in Iran: One for recipients and the other for donors. To be precise, they are not actual waiting lists, as you do not need to wait a moment if you have enough money to pay.

KIDNEY FOR SALE

"Kidney for sale with the blood-group of AB from Tehran. Urgent need for money! Also ready to sell bone marrow, liver or any other part of the body that could be sold (for money) anyway!" This is one of the huge number of advertisements that have been submitted to the Iranian Online Associations for Kidney Donation website[6] which provides free rooms to people who would want to get to the market, as kidney sellers, buyers or even brokers. Examples of advertisements from this website and other unofficial websites are provided in Table 1. A look at the advertisements reveals that kidney sellers likely concentrate on the price, while the buyers usually focus on the age (usually < 30 years), gender (male), overall health and the readily available laboratory reports which are supposed to be primarily paid and provided by the kidney sellers, as a prerequisite for finding a potential recipient.

A BRIEF INTRODUCTION

Upon its introduction to the Iranian health system, the LUR renal transplantation program had implemented some legal measures that were supposed to eliminate ethical concerns. In brief, renal patients as well as the potential LUR donors would separately contact a governmental regulation center which identifies suitable donor-recipient couplets and introduces them to transplantation centers (without them knowing each other prior to transplantation). All the expenses associated with the transplantation procedure and hospital costs would be fully covered by the government. After the procedure, the LUR donors would receive government-funded financial compensation and health insurance for one year, and "a majority" of them would also receive a gift from the recipient or charitable organizations. There would be no role for brokers or agencies in the process, and the program runs under the close scrutiny and surveillance of the Iranian Society for Organ Transplantation[1].

Whether or not the above-mentioned model sounds ethical, there are large practical deviations from the pronounced guidelines. During the past decades, the governmental "rewarding gift" to the LUR donors has shrunk from about 3000 United States dollar (USD) equivalent in local currency to less than 800 USD, with expectations to plunge even more due to the ongoing economic decline. Therefore, the government's financial participation in donor compensation is rapidly becoming smaller, driving the recipients to provide the largest share of the payment. In other words, only wealthy patients could be sure of obtaining an allograft whenever they need to, and the less-resourceful individuals would be driven to sacrifice their last possessions (*e.g.*, selling their family home) for this purpose; and finally the poorest people would have no chance in this market, meaning that even the limited governmental support would inevitably escape those who could not manage to provide the (much larger) remaining bulk of the payment, and the graft would go exclusively to the relatively more resourceful patients.

PREREQUISITES AND CONSEQUENCES OF INSTITUTING SUCH A PROGRAM

According to the above-mentioned evidence, what had been initially proclaimed to be a governmentally regulated and compensated altruistic organ donation is a myth now, and the only thing that one needs to get to the kidney market is simply finding a partner (a donor or a recipient) who would fulfill his/her (mainly financial) expectations, with apparent roles for brokers and agencies and no authoritarian surveillance. The burden of such a market could go far beyond what was mentioned above. Recently there was news about a father who was trying to sell his 19 mo-old child's organs in Alborz Province and was arrested after the baby's demise due to methadone overdose. This is probably not an exception and similar events have supposedly been taking place without finding a way to the media. Even in the legal practice, almost no one gets to the market in this country and it is about gaining higher standards of living, for example, buying a better house or indulging in an extraordinary ambition or anything other than the urgency of escaping a catastrophic collapse or securing the least living requirements. However, all societies and governments are obligated to provide appropriate environments for people to achieve fruitful livelihoods and prospects through ethical and constructive

Table 1 Examples of advertisements from kidney sellers and buyers on an official website in Iran[6]

Buyers' advertisements	Sellers' advertisements
Kidney buyer; blood group O+; man or woman; please only people with HLA reports contact; otherwise let's not waste each other's time (Tehran)	Kidney for sale; 42 yr old; blood group B+; due to financial crisis; no tobacco; no alcohol; bicycling each day for hours; and body works as infallible as a watch (East Azerbaijan)
Kidney buyer; blood group O; our patient is under dialysis and medical conditions is rapidly deteriorating; unemployed; lives in a renting house; some people promised helping; let's help for God's sake and his wife and children (Markazi)	Kidney for sale; 35 yr old man; blood group O+; me and my wife (blood group B+) both are ready to sell our kidneys; HLA testing ready for both; only recipients contact not dealers (brokers) (Tehran)
Kidney buyer; blood group O; I am under dialysis with complications; for God's sake help me to get free of dialysis; I also have financial problems; the seller preferably a man less than 35 (West Azerbaijan)	Kidney for sale; 39 yr old man; HLA and ultrasonography tests are ready; no history of any disease; family consent ready; I need money for my kid's illness; price would be fair and just (Kurdistan)
Kidney buyer; blood group AB; please don't give "mind blowing" price so I can prepare it (East Azerbaijan)	Kidney for sale; 24 yr old woman; married; family consent ready; all tests and HLA report ready; ultrasonography report ready; weight; no tobacco; healthy in every aspect (Tehran)
Kidney buyer; blood group O+; applicants must have HLA report and family consent ready; age less than 30; I'd pay the hospital costs and tests would be paid after the procedure; (Mazandaran)	Kidney for sale; 32 yr old; all tests (HLA, CTA, United States, & cardiologist letter) ready; hospital costs and labs should be covered by the buyer; price fair & with mutual consent (Mazandaran)
Kidney buyer; blood group A+; urgent need for a kidney; seller should have all the tests ready; age less than 30; powerful body; no user of tobacco; alcohol or other junks; preferably from Tehran (Khuzestan)	Kidney, liver and all other purchasable organs for sale; 40 yr old man; blood group A+; HLA test ready; at service wherever on the earth for the procedure; people with financial problems please don't contact! (Tehran)
I am highly experienced in kidney transplantation; ready to give consultation services to both buyers and sellers; contact me! (Tehran)	Kidney for sale; blood group AB; 31 yr old; I am in debt and can't pay for my house renting; please contact (West Azerbaijan)

Although in the introduction of the living unrelated kidney transplantation in Iran it is declared that all the hospital costs would be totally paid by the government[1], yet in the advertisements, the kidney sellers and buyers are talking about who should pay for the hospital costs. HLA: Human leukocyte antigen; CTA: Computed tomography angiography.

endeavors.

Such an organ procurement program as is already underway in Iran would not survive if the country managed to provide stable, productive and predictable economic conditions that offer people acceptable levels of livelihood in reasonable ways and time. In other words, there should be a constant state of "struggle for existence" to save the current organ market in Iran from collapse, and therefore any attempt at improving the country's economy could be considered a threat to the practice that betrays the donor pool. This would definitely not be good news, but the solution is certainly not to sustain the country in a collapsing state: *i.e.*, to force people into the organ market, *e.g.*, to rent a house for a while or pay for a life-saving medical procedure.

The penetration of brokers and agencies into the practice has further complicated the already-controversial program exponentially. As conventionally only people with high political connections can intervene in such businesses, any attempt to change the existing order into states that sound more ethical would be expected to receive serious backlashes. They even seem to consider renal graft procurement from deceased donors as a threat to their business. In a popular TV show, a person who happened to be a member of the health care system told his story of being in coma (for several weeks), and claimed that his family were under pressure to permit the donation of his organs for transplantation. However, it was only due to his father's heroic resistance against all the pressures that saved his life. It is not only in Iran but also in other parts of the world, that only brain-dead subjects, and not the comatose, who would be considered for organ donation.

SAFETY DATA AND RESEARCH

Despite decades of LUR kidney transplantation practice in Iran, some key aspects of concern have been hidden from the public and scientific literature. In fact there seems to be some undeclared red-lines that nobody could manage to cross. For example, despite overwhelming studies indicating the advantages of LUR transplantations, there are no data on the (particularly long-term) physical and/or psychological burden of the procedure on the donors. I had a not-so-good experience in a research attempt on donors' motivations and psychological burdens associated with LUR kidney transplantation, which was blocked suddenly and prematurely[7]. Moreover, the rationale behind some of the laboratory tests that are legally required for the procedure is unclear. For example, the introduction of potent immunosuppressive drugs and the shortage of available organs has eliminated the necessity for human leukocyte antigen (HLA) matching between the donors and recipients[1]. Actually the transplantation teams in Iran do not even look at the HLA test reports, yet it is still a mandatory part of the practice. Theoretically at least, the HLA reports could be used to find the best HLA matched donors only in exceptional cases, which offers no foundation to the large majority of donors or recipients to pay for this very important person service.

CONCLUSION

In conclusion, the LUR transplantation practice in Iran is associated with profound ethical concerns including discrimination, abuse, withholding information, and potential safety concerns. Should the practice persist, there would be a need for a major revision of the program in almost every aspect, in order to properly address all the issues of concern. Attempts at renovation of the practice should also warrant development of the country towards a more fruitful and prosperous economy and would not adversely affect transplantation.

FOOTNOTES

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MINIREVIEWS

Impact of tacrolimus intra-patient variability in adverse outcomes after organ transplantation

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Abstract

Tacrolimus (Tac) is currently the most common calcineurin-inhibitor employed in solid organ transplantation. High intra-patient variability (IPV) of Tac (Tac IPV) has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation. Few data are available concerning the impact of high Tac IPV in non-kidney transplants. However, even in kidney transplantation, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in those reports published up to now in the literature. Little is also known about the influence of high Tac IPV in the development of other untoward adverse events, update of the current knowledge regarding the impact of Tac IPV in different outcomes following kidney, liver, heart, lung, and pancreas tran-splantation to better evaluate its use in clinical practice.

Key Words: Tacrolimus; Intra-patient variability; Rejection; Organ transplantation; Graft survival; Outcomes

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Core Tip: Tacrolimus is widely used after solid organ transplantation. High intra-patient variability of tacrolimus (Tac IPV) has been associated with poor graft and patient survival. This review summarizes current evidence regarding the impact of high Tac IPV in several outcomes after kidney, liver, heart, lung and pancreas transplantation.

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INTRODUCTION

Tacrolimus (Tac) is nowadays the most common immunosuppressive drug employed in solid organ transplantation and has replaced cyclosporin as the most common calcineurin inhibitor used worldwide in immunosuppressive regimens[1, 2]. Tac exhibits a peculiar pharmacokinetic profile with large inter-patient and intra-patient variability (IPV) of whole blood drug levels over time, even when doses remain unchanged. This is usually ascribed to overlapping factors, such as ethnicity, pharmacogenomics, food-drug and drug-drug interactions, non-adherence, enhanced Tac absorption or impaired drug excretion due to either diarrhea or cholestasis, assays variability for Tac levels determinations or even alternate use of Tac compounds or its generic formulations[3-5]. Due to its narrow therapeutic window, therapeutic drug monitoring of trough levels (Cmin) is required to attain target levels of immunosuppression over time, as well as avoidance of undesired Tac side effects such as infections, neurotoxicity and nephrotoxicity, which are usually related to higher drug exposure[1].

High Tac IPV or time in the therapeutic range (TTR) of Tac has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation (KT)[5,6]. Few data are available concerning the impact of high Tac IPV in non-kidney transplants[7]. However, even in KT, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival[5,6]. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in the reports published up to now. Little is also known about the influence of high Tac IPV in the development of other harmful adverse events associated with immunosuppression, such as infections, chronic kidney disease, type 2 diabetes, metabolic syndrome and *de novo* or recurrent cancer. The purpose of this review is to provide an update of current knowledge regarding the impact of Tac IPV in different outcomes following KT, liver (LT), heart (HT), lung, kidney/pancreas and bone marrow (BMT) transplantation to better evaluate its use in clinical practice.

STUDY SELECTION

To identify and select studies for this review, research was made in the MedLine/PubMed database, using the following terms: Tacrolimus; intra-patient; variability; transplant; transplantation; rejection; and graft loss. These terms were obtained from Medical Subject Headings (MeSH), using the Booleans "AND" and "OR", from various search algorithms in PubMed.

Search 1: ((“tacrolimus”[MeSH Terms] OR “tacrolimus”[All Fields]) AND “intra”[All Fields] AND (“patient s”[All Fields] OR “patients”[MeSH Terms] OR “patients”[All Fields] OR “patient”[All Fields] OR “patients s”[All Fields]) AND (“variabilities”[All Fields] OR “variability”[All Fields] OR “variable”[All Fields] OR “variable s”[All Fields] OR “variables”[All Fields] OR “variably”[All Fields])) AND (y_10[Filter]). Search 2: ((((((tacrolimus[Title/Abstract]) AND (variability[Title/Abstract])) OR (intrapatient variability[Title/Abstract])) AND (transplant[Title/Abstract])) OR (transplantation[Title/Abstract])) AND (rejection[Title/Abstract])) OR (graft loss[Title/Abstract]).

Subsequently, an active manual search of studies was carried out through carefully selected articles in gray literature.

The research was completed on May 17th, 2023. A total of 43 articles were included in the present study, 376 studies were found in PubMed database, and after careful reading of abstracts, 15 were included in our final review (references No. 3, 7, 24, 31, 33, 37, 38, 57, 60, 62, 65-67, 69, and 70). The excluded works did not satisfactorily meet the theme proposed for the present work. Furthermore, 28 studies different from the ones previously selected in PubMed database were identified in our active manual research in gray literature, all of which were included in this review.

METHODS USED TO ASSESS TAC IPV

Intra-patient variability of Tac over time has been calculated using different methods, particularly[5-7]: Mean levels and standard deviation (SD) of Tac whole-blood Cmin levels, also expressed as the medication level variability index (MLVI).

Mean absolute deviation (MAD), based on the formula MAD (%) = {[(Xmean - X1) + (Xmean - X2)… + (Xmean - Xn)]/n of Cmin results}, where X is the Tac Cmin level.

Coefficient of variation (CV), calculated according to the formula CV (%) = σ/μ, where σ is the standard deviation, and μ is the mean Tac Cmin levels of all available samples of the individual. CV may be corrected or not by the corresponding Tac dose (C0/D) or defined as time-weighted coefficient of variability using time-weighted standard deviation divided by the mean drug levels.

Tac TTR, calculated by the Rosendaal method[8]. Standard deviation or MLVI are expressed as numbers, classes, or dichotomized intervals, whereas CV and TTR are expressed as percentages, tertiles and dichotomized intervals usually at the median split. There are no universally accepted recommended target levels for each one of those parameters used to assess Tac IPV. It is important to highlight that target levels of Tac Cmin usually vary over time according to the type of organ transplant, donor and recipient risk factors for rejection, comorbidity, occurrence of side effects and local immunosuppression protocols. The TTR may also vary sharply according to adopted Tac Cmin thresholds used by distinct centers in different time frames after organ transplantation[5-7].

FACTORS INFLUENCING TAC IPV

Interpatient variability of Tac has been attributed to interindividual pharmacokinetics variability which may be induced by several factors including drug-food and drug-drug interactions, concurrent clinical events such as diarrhea, cholestasis or liver dysfunction, ethnicity and pharmacogenetics[3,9-13]. In this regard, polymorphisms in CYP3A5, CYP3A4, and SLC and ABC transporter encoding genes have been shown to influence the area under the curve of tacrolimus, leading either to rejection or even toxicity in transplant recipients[4,13].

Tac IPV, on the other hand, has been additionally ascribed to non-adherence after organ transplantation, pre-analytical and analytical variables to measure Cmin in different commercially available biochemical assays and administration of different Tac formulations, including generic substitutions[3,5-7]. However, non-adherence is a common reason reported in medical literature to explain the observed deleterious effect of Tac IPV on patient and graft survival in organ transplantation by some[14-19], but not all authors[20,21].

Several approaches have been proposed to assess IPV, with most studies being retrospective, with different methodologies, considering pediatric and adult populations, with no organ-specific approach. Despite these limitations, IPV provides a sign that patients are at risk.

TAC IPV IN HEART TRANSPLANTATION

Four studies evaluating the influence of Tac IPV on HT outcomes were performed in adult patients using Tac CV[22-24] and Tac TTR[25], and in pediatric subjects using Tac SD/MLVI[26,27].

Concerning pediatric LT, Pollock-Barziv *et al*[26] associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study. Sirota *et al*[27] found similar results for rejection, but the authors also linked Tac SD/MLVI, particularly when higher than 3, to cardiac allograft vasculopathy and patient survival. In adults, Gueta *et al*[22] described an association of Tac IPV in the first year after HT with rejection after 12 but not between three and 12 mo after HT. On the other hand, Shuker *et al*[23] found no increase in the frequency of either early or late acute rejection or even cardiac allograft vasculopathy in heart transplant recipients. Both authors ascribed the lack of association of Tac IPV with early acute rejection[20] and overall rejection[23] to a higher immunosuppression exposure frequently observed in those heart transplant recipients. González-Vílchez *et al*[24] studied the largest cohort up to now. The authors found an effect of Tac IPV, assessed between four to 12 mo after HT, on the frequency of rejection after one year. Using Tac TTR, Baker *et al*[25] found no effect of Tac IPV on acute rejection within the first 30 d after HT. None of those studies in adults reported other outcomes such as mortality or Tac-related adverse events in association with Tac IPV[22-25]. The main findings related to HT are depicted in Table 1[22-27].

TAC IPV IN LUNG TRANSPLANTATION

Four studies have investigated the impact of Tac IPV in the frequency of acute and chronic rejection or chronic lung allograft dysfunction (CLAD) after lung transplantation in adults using Tac SD/MLVI[28], Tac CV[29] and Tac TTR[29-31]. Gallagher *et al*[28] demonstrated that higher Tac SD/MLVI between 6-12 mo after lung transplantation was associated with development of CLAD with an adverse impact on survival. Acute rejection, on the other hand was not associated with Tac SD/MLVI[28]. Ensor *et al*[30] evaluated retrospectively the role of Tac TTR in 292 Lung transplant recipients the development of acute and chronic rejection. Tac TTR was measured in the first year after lung transplantation. The authors observed a lower likelihood for acute rejection and CLAD whenever Tac TTR was increased by 10%. Lower rates of infection and mortality was also linked to high Tac TTR. Other authors failed to demonstrate higher frequency of acute rejection after lung transplantation when Tac IPV was assessed by either Tac CV or Tac TTR in the first 6 mo after surgery[29]. On the other hand, more recently Japanese investigators disclosed an association of acute rejection with Tac TTR calculated in the first six month after lung transplantation[31]. The main findings related to lung transplantation are depicted in Table 2.

Table 1 Tacrolimus intra-patient variability in heart transplantation: Main findings

Heart transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV, assessment**	**Outcome**
Gueta *et al*[22], 2018	72	Deceased	CV	High trough level variability is associated with higher rates of graft rejection, and trough level variability during the first year is associated with increased risk of rejection after HT
Shuker *et al*[23], 2018	86	Deceased	MAD	A high IPV was not associated with the development and progression of cardiac allograft vasculopathy or development of acute cellular rejection
González-Vílchez *et al*[24], 2022	1581	Deceased	CV	IPV levels had limited influence on mid-term outcomes in heart transplant, however high IPV may predispose to rejection in initially stable patients
Baker *et al*[25], 2019	67	Deceased	TTR	Higher TTR was not associated with a lower rate of Acute Cellular Rejection within the first 30 d after heart transplant
Pollock-Barziv *et al*[26], 2010	144	Deceased	SD	Associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study
Sirota *et al*[27], 2021	118	Deceased	SD	SD ≥ 3 is associated with increased risk of poor outcomes

CV: Coefficient of variability; HT: Heart transplant; MAD: Mean absolute deviation; TTR: Time in therapeutic range; SD: Standard deviation.

Table 2 Tacrolimus intra-patient variability in lung transplantation: main findings

Lung transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV assessment**	**Outcome**
Gallagher *et al*[28], 2015	110	Non specified	SD	Patients with highly variable trough tacrolimus levels in the second half of the first post-transplant year will likely have similar variability in the second year and are at high risk for subsequent chronic lung allograft dysfunction and death
Kao *et al*[29], 2021	157	Non specified	CV and TTR	The results suggest that tacrolimus TTR, time in therapeutic range, and variability are not related to the presence of ACR in LTRs
Ensor *et al*[30], 2018	292	Non specified	TTR	Tacrolimus TTR was predictive of clinical outcomes of ACR, CLAD, infection, and death in lung transplant recipients at 1 yr in this investigation after adjusting for potential confounders
Katada *et al*[31], 2022	90	Living and deceased	TTR	A lower tacrolimus TTR is a predictor of late acute rejection

SD: Standard deviation; TTR: Time in therapeutic range; ACR: Acute cellular rejection; LTR: Lung transplant rejection; CLAD: Chronic lung allograft dysfunction.

TAC IPV IN LIVER TRANSPLANTATION

Impact of Tac IPV on different outcomes after LT, including allograft rejection, postoperative complications and survival was evaluated in pediatric[26,32-35] and adult[36-42] transplant recipients using SD/MLVI[26,32-34], CV[35-41], and TTR [42].

Most studies performed in children associated higher SD/MLVI to biopsy-proven acute rejection (BPAR) at least six months after LT[42-34]. Defrancq *et al*[35] found similar results in another cohort of children using Tac CV one year after surgery. The authors reported an association between high Tac CV and BPAR and correlated Tac CV with albumin and bilirubin levels in different time frames after LT as well as with missed outpatient consultations, possibly reflecting immunosuppression adherence[33]. Decreased survival was also related to high Tac IPV in just one of those reports including few patients submitted to LT[26].

Up to now, seven reports were published in the medical literature concerning the effect of Tac IPV on post-LT outcomes in adults. In this regard, Christina *et al*[36] disclosed an association between Tac SD/MLVI and BPAR in patients submitted to LT. Similar findings were reported by Del Bello *et al*[37] who reported higher Tac CV measured just after LT discharge with BPAR, as well as with the occurrence of *de novo* anti-donor specific antibodies (*dn*DSA). No impact was seen in patient survival[37]. Van der Veer *et al*[39] evaluated the influence of Tac CV measured between six to 18 mo after LT in adult subjects. The authors were unable to disclose any association between Tac CV and immune mediated graft injury. Rayar *et al*[38] investigated the influence of Tac CV measured in the first 30 d after LT on postoperative outcomes. The authors found an increased frequency of acute kidney injury as well as cardiovascular and

Table 3 Tacrolimus intra-patient variability and liver transplantation: Main findings

Liver transplantation				
Ref.	**Sample size**	**Donor**	**Tac-IPV assessment**	**Outcome**
Lieber *et al*[18], 2013	988	Not specified	SD	Non-adherence among liver transplant recipients is associated with increased risk of graft failure
Stuber *et al*[19], 2008	96	Not specified	SD	The SD has utility of monitoring routine tac blood levels in pediatric recipients for detecting non-adherence prior to clinical rejection
Venkat *et al*[32], 2008	101	Not specified	SD	Variations in tac blood levels is associated with an increased risk of late allograft rejection in pediatric recipients
Shemesh *et al* [33], 2017	400	Both living and deceased donor	SD; MLVI	MLVI predicts late acute rejection in pediatric liver transplantation recipients
de Oliveira *et al* [34], 2017	50	Both living and deceased donor	SD; MLVI	MLVI may be a nice indicator of the risk of medication non-adherence in child-age
Defrancq *et al* [35], 2019	41	Both living and deceased donor	CV	High Tac IPV may be associated with adverse patient outcomes. Also, there is some impact of biological factors on IPV and therapy adherence
Christina *et al* [36], 2014	150	Not specified	SD; MLVI	The MLVI is associated with and can predict rejection, possibly related to non-adherence in adult recipients
Del Bello *et al* [37], 2018	116	Deceased donor only	CV	Tac IPV could be useful to identify patients with a greater risk of graft rejection and pf developing *de novo* DSA after liver transplantation
Rayar *et al*[38], 2018	812	Deceased donor only	CV	High CV of Tac concentrations was found to be predictive of Tac-related toxicity and poorer survival
van der Veer *et al* [39], 2019	326	Both living and deceased donor	CV	High IPV in Tac exposure beyond 6 mo after liver transplantation was not associated with imune-mediated graft injury
Dopazo *et al*[40], 2022	140	Deceased donor only	CV	High IPV between the third and sixth months appears to be an early and independent predictor of poorer liver transplant outcomes
Kim *et al*[41], 2022	636	Both living and deceased donor	CV	High Tac IPV was associated with increased risks of overall mortality and HCC recurrence in liver transplantation recipients with HCC

SD: Standard deviation; CV: Coefficient of variation; MLVI: Medication level variability index; DSA: Donor-specific antibodies; HCC: Hepatocellular carcinoma.

neurologic complications in patients with higher Tac CV. Most importantly, shortened graft and patient survival rates were also associated with Tac IPV[38]. Other authors investigated whether Tac CV, assessed between three to six months after LT, could be associated with worse graft and patient long-term outcomes[40]. In this study, lower long-term survival and poorer renal function were similarly observed in those subjects with high Tac CV. Another group of investigators also linked higher Tac IPV using CV with hepatocellular carcinoma (HCC) recurrence after LT[41]. Only one study up to now assessed the impact of Tac IPV after LT employing TTR[42]. The authors found that lower TTR in those subjects, irrespectively of Tac CV, was associated with a higher risk for *dn*DSA and long-term death-censored graft loss. The main findings related to LT are depicted in Table 3.

TAC IPV IN KIDNEY TRANSPLANTATION

Most of the studies published thus far demonstrated an adverse impact of Tac IPV on KT outcomes (Table 4)[43-68]. Most of them were performed in adult recipients using MLVI/SD[44], MAD[45-48,62,66], CV[49-60,63,64,67-68], TTR[61] or other methods[65]. In this regard, several authors have associated higher Tac IPV, usually measured more than 6 mo after KT, with BPAR[44-46], long-term graft loss or dysfunction[47-55,58,59,68] as well as with lower survival[50,51]. In some, but not all reports[62], higher Tac IPV was associated with the development of *dn*DSA[53,67], chronic active antibody mediated rejection[47] and chronic histological lesions in kidney grafts[54,56]. Most authors attributed those Tac IPV-related outcomes to non-adherence[43] and some[57-59] but not others[60] to genetic predisposition. Two other reports compared TTR[61] and a novel Tac variability score (TVS)[64] to conventional IPV measures and found that both were more reliable in their ability to predict worse outcomes after KT.

Concerning pediatric transplant recipients, Pollock-Barziv *et al*[26] were one of the first authors to show a significant association of higher Tac IPV and late graft rejection or loss. Similar findings were subsequently reported by other investigators who reported and association of higher Tac IPV with BPAR and graft loss beyond one year in children and adolescents submitted to KT[66-68].

Table 4 Tacrolimus intra-patient variability and kidney transplantation: Main findings

Kidney transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV assessment**	**Outcomes**
Borra *et al*[47], 2010	297	Both living and deceased donor	MAD	Significant relationship between high Tac-IPV and long-term graft failure
Ro *et al*[45], 2012	249	Both living and deceased donor	MAD	TAC IPV had a significant impact on rejection-free survival. The effect was influenced by CYP3A5 polymorphism
Sapir-Pichhadze *et al*[44], 2014	356	Both living and deceased donor	MLVI/SD	Increased time-dependent TAC SD may be an independent risk factor for adverse kidney transplant outcomes
O'Regan *et al*[49], 2016	394	Both living and deceased donor	CV	Inferior renal allograft survival was observed in recipients with higher Tac-IPV
Rodrigo *et al*[53], 2016	310	Deceased donor only	CV	Tacrolimus level variability is a strong risk factor for dnDSA development and death-censored graft loss
Whalen *et al*[46], 2017	376	Both living and deceased donor	MAD	Highly variable tacrolimus levels predict worse out- comes postrenal transplantation
Shuker *et al*[48], 2016	808	Both living and deceased donor	MAD	A high tacrolimus IPV is an independent risk factor for adverse kidney transplant outcomes that can be used as an easy monitoring tool to help identify high-risk RTRs
Vanhove *et al*[56], 2016	220	Both living and deceased donor	CV	High IPV is related to accelerated progression of chronic histologic lesions before any evidence of renal dysfunction
Rozen-Zvi *et al*[51], 2017	803	Both living and deceased donor	CV	The combination of high CV and exposure to low drug levels might identify high-risk patients in the early post-transplantation period
Goodall *et al*[50], 2017	688	Both living and deceased donor	CV	High tacrolimus IPV and clinic nonattendance are associated with inferior allograft survival
Sablik *et al*[62], 2018	248	Both living and deceased donor	MAD	A high Tac IPV per se does not predispose to the development of chronic active antibody mediated rejection (c-aABMR) but is associated with inferior graft survival once c-aABMR is diagnosed
Seibert *et al*[57], 2018	1472	Both living and deceased donor	CV	High variability of TAC dose increases risk of acute rejection. High variability of TAC trough increases risk of graft failure
Mo *et al*[54], 2019	671	Both living and deceased donor	CV	High IPV of Tac is associated with early deterioration of chronic histologic lesions as well as poorer long-term outcomes
Song *et al*[61], 2019	1241	Living donor only	TTR	Increasing the TTR of tacrolimus in the first year was associated with improved long-term outcomes in living kidney transplants, and TTR may be a novel valuable strategy to monitor tacrolimus exposure
Süsal *et al*[55], 2019	6638	Deceased donor only	CV	Even in patients with good outcome during the first 3 post-transplant years, a high IPV was associated with inferior graft survival, indicating that a fluctuating tacrolimus trough level at years 1, 2 and 3 post-transplant is a major problem in kidney transplantation
Rahamimov *et al*[52], 2019	878	Both living and deceased donor	CV	Monitoring CV can help detect the high-risk patients
Gold *et al*[66], 2020	1419	Deceased donor only	MAD	A more intense and less variable exposure to tacrolimus could improve graft survival strongly in patients with high TAC IPV
Stefanović *et al*[58], 2020	104	Both living and deceased donor	CV	Combined assessment of tacrolimus IPV and tacrolimus C0/D may categorize patients towards risk of graft deterioration in the long-term post-transplantation period
Stefanović *et al*[59], 2021	103	Both living and deceased donor	CV	Simultaneous assessment of Tac IPV, C0/D, and CYP3A5 genotype may identify patients at risk of deterioration of graft function in the long-term post-transplantation period
Kim *et al*[65], 2021	1080	Both living and deceased donor	CV	High tacrolimus IPV significantly increases the risk of graft failure and antibody mediated rejection in patients with high immunological risk
Park *et al*[63], 2021	1143	Both living and deceased donor	CV	TAC-IPV can significantly affect allograft outcomes even with a high mean TAC-C0
Yin *et al*[64], 2022	1343	Living donor only	CV	Tac variability score is a novel measure of Tac IPV with higher correlation with graft survival and more convenience in clinical use than CV after kidney transplantation
Baghai Arassi *et al*[67], 2022	48	Both living and deceased donor	CV	High Tac IPV is associated with an increased risk of dnDSA development and rejection episodes > year 1 posttransplant even in patients with low immunological risk profile

Nuchjumroon *et al* [60], 2022	188	Both living and deceased donor	CV	No evidence that the CYP3A5 polymorphisms significantly influence tacrolimus IPV during the 6 to 12 mo after kidney transplantation

SD: Standard deviation; CV: Coefficient of variation; MLVI: Medication level variability index; DSA: Donor-specific antibodies; TTR: Time in therapeutic range.

TAC IPV IN KIDNEY AND PANCREAS, AND BONE MARROW TRANSPLANTATION

Two studies have evaluated the impact of Tac IPV in the frequency of *dn*DSA, BPAR and graft loss in adult kidney and pancreas recipients[69,70] and in the occurrence of graft *vs* host disease after bone marrow transplantation[70]. The first report failed to disclose an association of Tac IPV with BPAR in adult recipients of kidney and pancreas transplants, but the main purpose of the study was to compare Tac IPV and graft function in groups of patients receiving two different Tac formulations[69]. Davis *et al*[38] on the other hand, demonstrated that Tac TTR was associated to a very high risk of *dn*DSA and a 4-fold risk of graft loss by five years, independently of Tac CV.

In respect to bone marrow transplant recipients, Marco *et al*[70] correlated high Tac IPV, measured by CV, with the occurrence of acute graft *vs* host disease in the first month after BMT (Table 5).

CONCLUSION

Altogether, available data up to now suggest that Tac IPV, possibly due to non-adherence and/or genetic, pharmacologic, or clinically significant factors, is associated with adverse outcomes after organ transplantation, particularly KT. The heterogeneity observed in the results obtained in the reports thus far are probably due to the retrospective design of most studies, the distinct methods used to assess Tac IPV, utilization of different immunosuppression protocols, distinct observation time frames and endpoints. Refinement or combination of different scores may improve usage of Tac IPV in clinical practice in the future.

Table 5 Tacrolimus intra-patient variability in pancreas and bone marrow transplantation: Main findings

Kidney and pancreas, and bone marrow transplant				
Ref.	**Sample size**	**Donor type**	**Tac-IPV Assessment**	**Outcome**
Torabi *et al* [69], 2020	39	Both living and deceased donor	CV	The once daily LCPT dosing may facilitate medication adherence and result in improved long-term outcomes
Marco *et al* [70], 2022	128	Living donor only	CV	Determination of Tac IPV soon after alloHSCT could be useful in identifying greater risks of aGVHD

CV: Coefficient of variation; LCPT: LCP-tacrolimus; alloHSCT: Allogeneic stem cell transplantation; aGVHD: Acute graft-vesus-host disease.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Invasive aspergillosis in liver transplant recipients, an infectious complication with low incidence but significant mortality

Azam Farahani, Fereshteh Ghiasvand, Setareh Davoudi, Zahra Ahmadinejad

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Abstract

BACKGROUND

Infections, including invasive fungal infections (IFIs), are among the leading causes of mortality in liver transplant recipients during the first year post-transplantation.

AIM

To investigate the epidemiology, clinical manifestations, risk factors, treatment outcomes, and mortality rate of post-liver transplantation invasive aspergillosis (IA).

METHODS

In this case-control study, 22 patients with IA were identified by reviewing the archived and electronic medical records of 850 patients who received liver transplants at the Imam Khomeini Hospital complex in Tehran, Iran, between 2014 and 2019. The control group comprised 38 patients without IA infection matched for age and sex. The information obtained included the baseline characteristics of liver transplant patients, operative reports, post-transplantation characteristics of both groups and information about the fungal infection of the patient group.

RESULTS

The prevalence rate of IA among liver transplant recipients at Imam Khomeini Hospital was 2.7%. The risk factors of IA among studied patients included high serum creatinine levels before and post-transplant, renal replacement therapy, antithymocyte globulin induction therapy, post-transplant bile leakage, post-transplant hepatic artery thrombosis, repeated surgery within 30 d after the

transplant, bacterial pneumonia before the aspergillosis diagnosis, receiving systemic antibiotics before the aspergillus infection, cytomegalovirus infection, and duration of post-transplant hospitalization in the intensive care unit. The most prevalent form of infection was invasive pulmonary aspergillosis, and the most common chest computed tomography scan findings were nodules, pleural effusion, and the halo sign. In the case group, prophylactic antifungal therapy was administered more frequently than in the control group. The antifungal therapy response rate at 12 wk was 63.7%. The 3- and 12- mo mortality rates of the patients with IA were 36.4% and 45.4%, respectively (compared with the mortality rate of the control group in 12 mo, which was zero).

CONCLUSION

In this study, the prevalence of IA among liver transplant recipients was relatively low. However, it was one of the leading causes of mortality following liver transplantation. Targeted antifungal therapy may be a factor in the low incidence of infections at our facility. Identifying the risk factors of IFIs, maintaining an elevated level of clinical suspicion, and initiating early antifungal treatment may significantly improve the prognosis and reduce the mortality rate of liver transplant recipients.

Key Words: Aspergillosis; Cytomegalovirus infection; Immunosuppression therapy; Liver transplantation; Risk factors; Fungal infections; Fungal pneumonia

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Core Tip: In our center, invasive aspergillosis had a low incidence but a high mortality rate among liver transplant recipients. Invasive pulmonary aspergillosis was the most prevalent form of infection. Nodules, pleural effusion, and halo signs were the most commonly observed findings on chest computed tomography scans. Antifungal prophylaxis was more prevalent in the case group than in the control group. At week 6 of antifungal treatment, more than 60% of patients experienced complete recovery or relative response to therapy.

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INTRODUCTION

Invasive aspergillosis (IA) is one of the most common invasive fungal infections (IFIs) following solid organ transplants (SOT) and the leading cause of mortality and morbidity among transplant recipients. Several studies have reported rates of IA in organ transplant recipients between 1% and 15%[1-4]. In the TRANSNET study, an extensive cohort study on the prevalence of IFI in SOT recipients, the annual incidence rate of IA was 0.65%, second only to candidiasis[5].

IA typically develops 1 to 3 mo after a transplant[6]. However, delayed IA (6 mo after transplant) has recently been reported[7]. In a Swiss Transplant cohort study, the incidence of IA among liver transplant recipients was significantly lower than among recipients of other organ transplants[8]. In immunocompromised hosts, Aspergillus can infect every organ; however, sinopulmonary involvements are more common. Involvement of the central nervous system (CNS) and multiple organs is more prevalent in liver transplants than in other SOT[9].

The mortality rate of IA among recipients of liver transplants has not fallen over the past 15 years (compared with other SOTs). The 90-day mortality rate of liver transplant recipients with IA is higher than that of recipients of other organ transplants (85.7% *vs* 15.9%)[8,10].

Early diagnosis and proper treatment of IA are associated with a more favorable prognosis. Noninvasive modalities (such as imaging and antigen detection) aid in antifungal treatment initiation and duration. However, aggressive diagnostic approaches, such as bronchoalveolar lavage (BAL), should be considered for patients with imaging findings suggestive of IA[11,12].

Investigations revealed that BAL culture has a sensitivity of 50% in focal pulmonary lesions[13]. In such instances, a definitive diagnosis necessitates aggressive procedures, such as a thoracoscopic biopsy. Invasive diseases are strongly predicted by isolating Aspergillus species from sputum or BAL samples[14]. In the early stages of IA, single or multiple nodules are the most frequent finding on computed tomography (CT) scans[15]. Halo sign with peri-nodular haziness is a reliable indicator of IA[16]. In serial CT scan studies, the halo sign decreases during the first week, while the air crescent sign (another radiologic marker of pulmonary IA) increases[17]. Despite the clinical response to antifungal therapy, pulmonary lesions increase in size during the first week of treatment.

Positive serum and BAL galactomannan (GM), in conjunction with IA predisposing factors of the host, clinical and imaging findings consistent with IA, eliminate the need for invasive procedures in diagnosing IA[18]. The GM sensitivity decreases in the case of simultaneous use of active antimold agents[19]. Historically, Piperacillin-Tazobactam has been

linked to false positive GM results[20]. Blood[21,22] and BAL[23,24] Aspergillus PCR are used for initial IA diagnosis. However, further prospective studies are required to investigate the combination of diagnostic modalities in the early IA stages.

Voriconazole is more effective than amphotericin B in the early treatment of IA and significantly improves survival (71% *vs* 58%)[25]. Voriconazole improved the prognosis of CNS involvements[26], which in most cases resulted in high mortality rates[27]. Accordingly, it is recommended as the treatment of choice for IA. There are no clinical trials involving echinocandins as a first-line treatment for IA. Recent attention has been drawn to a combination of echinocandin and amphotericin B or azoles, and *in vitro*, studies have confirmed the synergistic effect of this combination[28,29].

In probable aspergillus cases, a combination of echinocandin with amphotericin B was associated with 40%-60% prognosis improvement[30,31]. Marr *et al*[32] reported survival improvement by combining voriconazole and echinocandin (compared with voriconazole alone). However, further studies are required to investigate the advantages of combination therapy in IA. Patients who recovered a single episode of IA are at higher risk of re-infection during immunosuppressive therapy. Therefore, effective antifungal prophylaxis is recommended, particularly in the hematopoietic stem cell transplant (HSCT) group[33,34].

This study examined the prevalence, epidemiology, clinical manifestations, risk factors, antifungal therapy response, and prognosis of IA infection in liver transplant recipients.

MATERIALS AND METHODS

The study population consisted of liver transplant recipients in the Imam Khomeini Hospital complex between 2014 and 2019. This hospital is a major referral and educational hospital and the second-largest center of liver transplants in Iran, with over 100 transplants per year.

Inclusion criteria

The study included all patients who received a liver transplant between 2014 and 2019 and were diagnosed with probable/proven IA.

Exclusion criteria

Multi-organ transplant recipients were excluded from the study.

Control group

Patients without IFI after the liver transplant. The following formula was utilized to determine the sample size of the control group:

Z tests-Correlations: Two independent Pearson r's; Analysis: A priori: Compute required sample size; Input: Tail (s) = One; Effect size q = 0.84; α err probability = 0.05; Power (1-β err probability) = 0.90; Allocation ratio N2/N1 = 2.

Output

Critical z = 1.6448536; Sample size group 1 (case) = 21; Sample size group 2 (control) = 42; Total sample size = 63; Actual power = 0.9037178.

A questionnaire containing the necessary information was created and filled out using data from liver transplant recipients' electronic and non-electronic medical records. The pre-transplant information included: Age, sex, underlying diseases, the Model for End-Stage Liver Disease (MELD) score, intensive care unit (ICU) hospitalization before the transplant, ventilator support during the week before the transplant, fungal colonization or infection within three months before the transplant, dialysis within the month before the transplant, diabetes mellitus, bacteremia within a month before the transplant, bacterial peritonitis before the transplant, cytomegalovirus (CMV) serology, and creatinine level before the transplant.

The peri-transplant information included: The date of transplant, transplant type (from deceased or living donor), type of anastomosis (duct to duct or Roux-en-Y), cold ischemia time (measured by minutes), and the number of transfused blood units (packed cells) during the operation.

The post-transplant information of the patients included: Induction therapy, type of antifungal prophylaxis after transplant, repeated surgery within 30 d after the transplant, ICU admission duration, mechanical ventilation after the transplant, bacteremia and pneumonia within 2 wk before IA diagnosis, creatinine level at the time of diagnosis, CMV viremia or disease within one month before the diagnosis, transplant rejection requiring treatment within three months before the diagnosis of IA.

Aspergillus information included: The time of infection, proven or probable diagnosis, the involved organ, the result of fungus culture, GM, pathology, PCR, radiologic findings, type of antifungal treatment, response to treatment at weeks 6 and 12, death within 12 mo of diagnosis, repeated transplant within 3 mo of diagnosis, and transplant rejection requiring treatment within three months of diagnosis. Proven and probable diagnoses of IA were defined according to the European Organisation for Research and Treatment of Cancer (EORTC) criteria[35].

The surgical methods, preventative measures, and immunosuppressive regimen utilized at our center are described in another article[36]. However, since 2018, the antifungal prophylaxis method has been changed from universal to targeted prophylaxis, and since 2020, the diagnosis of CMV infection has been based on PCR rather than CMVPP65 Ag detection.

Ethical considerations

The Institutional Review Board of the Tehran University of Medical Sciences approved the study with the file number (IR.TUMS.MEDICINE.REC.1399.874). The patients' information was registered anonymously in questionnaires. Due to the study's retrospective nature, no written consent was obtained from the patients.

Data analysis

The data was analyzed using SPSS version 26. The data was expressed as mean ± standard deviation (SD) to present quantitative variables with normal distribution and frequency (%) for qualitative variables. The qualitative variables were analyzed by chi-squared test, and continuous quantitative variables with normal distribution were analyzed with Student's *t*-test. *P* values < 0.05 were considered statistically significant. Multiple logistic regression analyses (both multivariate and bivariate) were performed.

RESULTS

Between 2014 and 2019, 850 patients received a liver transplant at the Imam Khomeini Hospital Complex in Tehran, Iran. Investigations of these patients' medical records revealed 22 cases of IA. To examine the risk factors of IA, 38 liver transplant recipients without a history of IA who matched the case group regarding age and sex were selected as the control group and enrolled in the study. Table 1 summarizes both groups' demographic and pretransplant information (cases and controls).

Of 22 patients with IA infection, 18 (81.8%) were male, and 4 (18.2%) were female. The mean ± SD age of the patients was 45.27 ± 14.85 years. In the control group, 31 (81.6%) were male, and the mean age of the control group was 47.21 (SD = 12.03). The mean number of MELD scores in the case and control groups was similar (21.05 *vs* 20.24). The blood creatinine level in the case group before the transplant was significantly higher than in the control group [1.74 mg/dL *vs* 1.22 mg/dL, *P* value 0.04, odds ratio (OR): 0.34; confidence interval (CI): 0.13-0.87)]. There were no statistically significant differences between the proportions of fulminant hepatic failure (FHF) patients in the patient and control groups [*P* value = 0.18; 27.3% (*n* = 6) and 5.3% (*n* = 2), respectively]. A higher percentage of IA patients were re-transplants [22.7% (*n* = 5) *vs* 7.9% (*n* = 3), *P* = 0.13], but the difference was not statistically significant. The mean time between liver transplantation and occurrence of IA was 313 ± 337.64 d (range 15-1350 d).

The most prevalent symptom of IA was pulmonary aspergillosis. Of the 22 cases of IA, nine patients had confirmed IA, and 13 had probable IA. Amphotericin B was the primary antifungal treatment (empirical therapy) for 72.6% of the patients. Nodular lesions and halo signs were the most common radiographic findings among the patients (50% and 45.5%, respectively). At week 6 of antifungal therapy, complete recovery and response to treatment were observed in 10 patients (45.5%), and relative response to treatment was observed in 4 patients (18.2%). The mortality rate after the study period was 36.4%. (8 patients). Table 2 presents the patients' information regarding IA.

Among the variables related to the peritransplant period, four variables, including induction therapy with antithymocyte globulin (ATG) [case no = 8 (36.4%), control no = 6 (15.8%), *P* value < 0.001, OR: 0.08, CI: 0.02-0.41] biliary leakage (case no = 9 [40.9%], control no = 0, *P* value < 0.001]), reoperation within 30 d of the transplant [case no = 12 (54.5%), control no = 5 (13.2%), *P* value < 0.001, OR = 7.92, CI: 2.25-27.94], and hepatic artery thrombosis [case no = 8 (36.4%), control no = 1 (2.6%), OR = 21.14, CI: 2.42-184.79], were significantly higher among patients with IA (Table 3).

Within 2 wk before the IA diagnosis, the immunosuppressive regimen included tacrolimus and mycophenolate in over 80% of patients and the control group. Nineteen patients in the case group (86.4%) and 18 patients in the control group (47.4%) received antifungal prophylaxis (40.9% of the patients' group and 13.1% of the control group received voriconazole). Bacterial pneumonia was diagnosed in 13 individuals in the case group (59.1%) and four individuals in the control group (10.5%) within 2 wk of the fungal infection diagnosis (*P* value < 0.001).

During the 2 wk preceding the infection, 16 patients (72.7%) received antibiotics, whereas 39% (no = 15) of patients in the control group received antibiotics during the same period (*P* value < 0.01). The maximum creatinine level at the time of IA diagnosis was 1.87 mg/dL (SD = 1.1) in the case group *vs* 1.21 (SD = 1.43) in the control group. CMV viremia was significantly higher in IA patients [case no = 9 (40.9%), control no = 4 (10.5%), *P* value=0.009]. Transplant rejection requiring treatment within 3 mo before the IA diagnosis occurred in 13 patients in the case group (59.1%) and 10 patients in the control group (26.3%) (*P* value = 0.01; OR: 4.04; CI: 1.33-12.34).

The mean lengths of stay in the ICU at the time of transplantation were 4.1 d for the case group and 1.8 d for the control group (*P* value = 0.008). The number of patients in the IA group who underwent dialysis was greater [7 (31.8%) cases *vs* 4 (10.5%)] controls; *P* value = 0.08), but the difference was not statistically significant. The results pertaining to post-transplant factors are summarized in Tables 4 and 5.

The case group had a significantly lower 12-month survival rate than the control group (56.4% *vs* 100%) (*P* value < 0.001) (Tables 1 and 2).

DISCUSSION

The epidemiology of IFIs (including aspergillosis) among transplant recipients has changed during the last two decades. The incidence rate of IA has significantly reduced (from 40% to less than 10%), and most cases now occur more than 90 d after the transplant[37].

Table 1 Demographic information and background factors before transplantation of the study population

Covariate	Case	Control	*P* value	OR (95%CI)
Gender (Male)	18 (81.8%)	31 (81.6%)	0.9	-
Gender (Female)	4 (18.2%)	7 (18.4%)	0.9	-
Age mean (SD)	45.27 (14.85)	47.21 (12.03)	0.58	-
MELD score (SD)	21.05 (6.78)	20.24 (5.54)	0.62	-
Pretransplant ICU stay	1.95 (0.22)	1.97 (0.16)	0.9	-
Duration of pretransplant ICU stay	2 (1)	1 (0)	0.27	-
Pretransplant creatinine	1.74 (1.03)	1.22 (0.47)	0.04	0.34 (0.13-0.87)
Pretransplant ventilator within 1 wk	-	1 (2.6%)	0.9	-
Pretransplant dialysis within 1 mo	-	1 (2.6%)	0.9	-
Pretransplant diabetes mellitus	12 (54.5%)	15 (39.5%)	0.26	-
Fulminant hepatic failure	6 (27.3%)	2 (5.3%)	0.18	-
Immunosuppressive agents (steroids)	2 (9.1%)	6 (15.8%)	0.08	-
Immunosuppressive agent (antimetabolites)	1 (4.5%)	1 (2.6%)	0.08	-
Immunosuppressive agent (steroids & antimetabolites)	1 (4.5%)	0	0.08	-
Immunosuppressive agent (steroids & calcineurin inhibitors)	1 (4.5%)	0	0.08	-
Immunosuppressive agent (no)	12 (54.5%)	31 (81.6%)	0.08	-
The pretransplant episode of documented bacterial peritonitis	3 (13.6%)	5 (13.2%)	0.9	-
Previous systemic antibiotic use of more than 14 consecutive days	5 (22.7%)	6 (15.8%)	0.51	-
Re transplantation	5 (22.7%)	3 (7.9%)	0.13	-

CI: Confidence interval; ICU: Intensive care unit; OR: Odds ratio; SD: Standard deviation.

The prevalence of IA in liver transplant recipients was 2.7% in the present study. Other studies have reported incidence rates between 1% and 8%[4,38]. The lower incidence of IA is attributable to several factors, including improvements in surgical techniques, immunosuppressive regimens, and targeted antifungal prophylaxis in patients at moderate to high risk for fungal infection[37]. There was no significant difference between the two groups' underlying liver disease and MELD scores (case and control groups). In earlier studies, however, a MELD score greater than 30 was associated with an increased risk of fungal infection[38].

Several studies have investigated the risk factors associated with IA in transplant recipients. Among the identified risk factors are longer duration of surgery, severe blood loss during the operation, reoperation, steroid-resistant rejection, renal failure (especially when dialysis is required), CMV infection, diabetes, and long-term use of broad-spectrum antibiotics[39-41]. Fortún *et al*[40] (2002) found that positive GM, in addition to reoperation and post-transplant dialysis, was a risk factor for aspergillus infection in 13 patients with IA and 38 patients without IA (control group).

Due to epidemiological changes in IFIs among liver transplant recipients, antifungal prophylaxis for the low-risk group is no longer recommended. The American Society of Transplantation and Infectious Diseases Society of America (IDSA) reserves antifungal prophylaxis against candidiasis in moderate-risk patients (patients with complicated surgeries, anastomosis of choledochojejunostomy and candida colonization before transplantation), and anti-mold prophylaxis for high-risk patients (repeated liver transplant, repeating the surgery, and post-transplant renal replacement therapy)[42-44].

Our facility has also implemented a targeted prevention strategy since 2018. In our study, over 80% of patients with IA received antifungal prophylaxis, compared to less than 50% of patients in the control group.

ATG induction therapy was more common among patients with IA than the control group. Given that administering this medication as induction therapy in our facility is primarily reserved for patients with renal dysfunction, renal function may influence this relationship. However, the immunosuppressive therapy type is a known risk factor for IA[45, 46]. CMV reactivation, an additional risk factor for delayed IA, is one of the most common side effects of anti-thymocyte globulin therapy. In addition, an increased dose of immunosuppressives for the treatment of rejection episodes (such as administration of corticosteroid pulses) was more prevalent in the case group than in the control group (59.1% *vs* 26.3%)[46-49].

In the case group, post-transplant ICU stays were significantly longer than in the control group (4.1 *vs* 1.8). This statistically significant difference in ICU admission length reflects the critical illness of the case group (which requires intensive care) and their increased susceptibility to opportunistic infections[45].

Table 2 Clinical and laboratory information of patients with invasive aspergillus infection[1]

Covariate	Number (percent)
Diagnosis (proven)	9 (40.9%)
Diagnosis (probable)	13 (59.1%)
Site of diagnosis (isolated pulmonary)	19 (86.4%)
Site of diagnosis (isolated sinusitis)	2 (9.1%)
Site of diagnosis (peritonitis)	1 (4.5%)
Positive galactomannan (serum)	5 (22.7%)
Positive galactomannan (BAL)	8 (36.4%)
Positive galactomannan (N/A)	9 (40.9%)
PCR (positive)	8 (36.4%)
PCR (negative)	3 (13.6%)
PCR (N/A)	11 (50%)
Pathology (positive)	2 (9.1%)
Pathology (negative)	4 (18.2%)
Pathology (N/A)	16 (72.7%)
Fungal culture (positive)	10 (45.5%)
Fungal culture (negative)	2 (9.1%)
Fungal culture (N/A)	10 (45.5%)
Site of positive culture (sputum)	2 (9.1%)
Site of positive culture (BAL)	6 (27.3%)
Site of positive culture (sinus biopsy)	4 (18.2%)
Site of positive culture (pulmonary biopsy)	1 (4.5%)
Site of positive culture (peritonitis)	1 (4.5%)
CT scan findings (nodules)	11 (50%)
CT scan findings (ground glass opacity)	2 (9.1%)
CT scan findings (halo sign)	10 (45.5%)
CT scan findings (consolidation)	5 (22.7%)
CT scan findings (cavity)	3 (13.6%)
CT scan findings (pleural effusion)	7 (31.8%)
Treatment response at 6 & 12 wk (cure)	10 (45.5%)
Treatment response at 6 & 12 wk (partial response)	4 (18.2%)
Treatment response at 6 & 12 wk (stable)	-
Treatment response at 6 & 12 wk (progression)	-
Treatment response at 6 & 12 wk (death)	8 (36.4%)
12- month mortality	10 (4.45%)

[1]Cases information are attached.
BAL: Bronchoalveolar lavage; CT: Computed tomography; PCR: Polymerase chain reaction; N/A: Not applicable.

A creatinine level equal to or higher than 2 mg/dL is suggested as a risk factor for IA[5]. Renal dysfunction, renal replacement therapy, and dialysis after transplantation are known factors associated with the incidence of IFIs in organ transplant recipients[2,8,40,46]. In the current study, most patients with IA underwent dialysis; however, the difference was not statistically significant, which may be due to the low sample size and lower mean creatinine level before IA diagnosis.

Table 3 Comparison of factors related to the transplant of the study population

Covariate	Case	Control	*P* value	OR (95%CI)
Type of anastomosis (duct to duct)	16 (72.7%)	30 (78.9%)	0.53	-
Type of anastomosis (Roux-en-Y)	6 (27.3%)	8 (21.1%)	0.53	-
Cold ischemic time (h)	283.95 (66.58)	300.37 (58.39)	0.32	-
Underlying disease (NASH)	6 (27.3%)	6 (15.8%)	0.74	-
Underlying disease (PSC)	3 (13.6%)	8 (21.1%)	0.74	-
Underlying disease (HBV)	3 (13.6%)	5 (13.2%)	0.74	-
Underlying disease (HCV)	2 (9.1%)	1 (2.6%)	0.74	-
Underlying disease (AIH)	1 (4.5%)	3 (7.9%)	0.74	-
Underlying disease (AIH & HCC)	1 (4.5%)	1 (2.6%)	0.74	-
Underlying disease (HCV & NASH)	1 (4.5%)	-	0.74	-
Underlying disease (PBC)	1 (4.5%)	-	0.74	-
Underlying disease (Others)	4 (18.1%)	5 (13.2%)	0.74	-
Underlying disease (ASH)	-	2 (5.3%)	0.74	-
Underlying disease (HCV & HCC)	-	2 (5.3%)	0.74	-
Underlying disease (NASH & HCC)	-	2 (5.3%)	0.74	-
Underlying disease (NASH & PSC)	-	1 (2.6%)	-	-
Underlying disease (HBV & HCC)	-	1 (2.6%)	-	-
Underlying disease (Wilson)	-	1 (2.6%)	-	-
Intraoperative blood transfusion	3.45 (3.05)	2.5 (2.57)	0.2	-
Induction therapy (ATG)	8 (36.4%)	6 (15.8%)	< 0.001	0.08 (0.02-0.41)
Induction therapy (methyl prednisolon)	14 (63.6%)	32 (84.2%)	< 0.001	0.05 (0.01-0.25)
Biliary leak post-transplant	9 (40.9%)	-	< 0.001	-
Reoperation within 30 d of transplant	12 (54.5%)	5 (13.2%)	< 0.001	7.92 (2.25-27.94)
Hepatic artery thrombosis post-transplant	8 (36.4%)	1 (2.6%)	< 0.001	21.14 (2.42-184.79)

AIH: Autoimmune Hepatitis; ASH: Alcoholic Steatohepatitis; ATG: Antithymocyte Globulin; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; NASH: Nonalcoholic Steatohepatitis; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; CI: Confidence interval; OR: Odds ratio.

According to previous studies[8,46] and the current investigation, any local or systemic infection requiring IV antibiotics for more than 3-14 d is associated with further disruption of the normal microbial flora, the predominance of opportunistic pathogens, and an increased risk of IA. The incidence of bacterial pneumonia was significantly higher in IA cases two weeks before diagnosis (59.1% in the case group compared with 10.5% in the control group). The proportion of IA patients receiving systemic antibiotics two weeks before diagnosis was also greater than that of the control group (P = 0.01).

CMV is one of the immunosuppressive viruses known to cause various complications in organ transplant recipients due to cytokine dysregulation. CMV infection has been associated with increased susceptibility to IFIs due to dysfunction of the host's neutrophils and macrophages, which play a crucial role in aspergillosis defense. According to our study, CMV viremia was four times higher in IA patients than in the control group (40.9% *vs* 10.5%). Previous research shows CMV viremia is one of the most prominent predictors of IA (mostly the late form of IA)[10,40].

According to previous studies[47,49,50], type of anastomosis (Roux-en-y choledochojejunostomy), repeated transplant, FHF, antibiotics, and immunosuppressive medications before the transplant are among the reported risk factors for post-liver transplant aspergillosis. However, our study did not observe a significant difference between the two groups regarding these factors, which may be due to the low sample size of the present study.

In the past two decades, the rate of late IA (more than 90 d after transplant) has increased with intervals ranging from 22 to 1117 d[9,10,40,46]. An average of 313 d elapsed between the time of liver transplantation and the occurrence of IA, according to the present study (range 15-810 d). This shift in the onset of IA infection may be attributable to improvements in the early management of high-risk patients, advances in surgical techniques, or delayed risk factors (including CMV infection).

Table 4 Comparison of the post-transplant factors in the study population

Covariate	Case	Control	*P* value	OR (95%CI)
Antifungal prophylaxis after transplant (Fluconazole)	10 (45.5%)	13 (34.2%)	0.003	0.20 (0.05-0.85)
Antifungal prophylaxis after transplant (voriconazole)	9 (40.9%)	5 (13.1%)		0.08 (0.02-0.43)
Antifungal prophylaxis after transplant (no)	3 (13.6%)	20 (52.7%)		-
Bacteremia within 2 wk before diagnosis	3 (13.6%)	4 (10.5%)	0.70	-
Pneumonia within 2 wk before diagnosis	13 (59.1%)	4 (10.5%)	< 0.001	0.08 (0.02-0.31)
Systemic antibacterial within 2 wk before diagnosis	16 (72.7%)	15 (39.5%)	< 0.001	4.09 (1.31-12.81)
Dialysis requirement	7 (31.8%)	4 (10.5%)	0.08	
CMV viremia before diagnosis	9 (40.9%)	4 (10.5%)	0.009	5.89 (1.54-22.47)
CMV diseases before diagnosis	3 (13.6%)	2 (5.3%)	0.35	
Length of ICU stay at the time of transplant	4.05 (3.59)	1.75 (1.20)	0.008	0.56 (0.38-0.82)
Duration of mechanical ventilation at the time of transplant	1.25 (0.55)	1.12 (0.41)	0.34	
Creatinine at the day of diagnosis (highest value)	1/87 (SD:1/1)	1/21 (SD:1/43)	-	-

CI: Confidence interval; CMV: Cytomegalovirus; ICU: Intensive care unit; OR: Odds ratio; SD: Standard deviation.

Table 5 Rejection before and after diagnosis of invasive aspergillosis

Covariate	Case	Control	*P* value	OR (95%CI)
Rejection requiring treatment within 3 mo before diagnosis	13 (59.1%)	10 (26.3%)	0.01	4.04 (1.33-12.34)
Rejection required treatment after diagnosis	4 (18.2%)	4 (10.5%)	0.45	-

CI: Confidence interval; OR: Odds ratio.

Statistically significant differences were also observed between patients with IA and controls regarding biliary leakage after transplant (40.9% *vs* 0%) and hepatic artery thrombosis (36.4% *vs* 2.6%). It is necessary to consider these factors when determining the risk of IFIs. However, no similar findings were reported in the published literature.

Lungs were this study's most common site of IA (86.4%). This finding was consistent with other studies, which indicated that pulmonary aspergillosis (66% to 79%) was the most prevalent form of IA[4,46]. Environmental exposure to Aspergillus and inhalation of spores will result in airway colonization, which can progress to infection and disease development following transplant-induced immunodeficiency[4,46]. Elevated GM levels at any time after transplantation are an independent factor associated with aspergillosis, which may be a suitable predictor of IA prognosis[40]. In addition to a positive culture or positive PCR of secretions, GM serum antigen > 0.5 or BAL GM > 1 with a sensitivity of 22% and specificity of 84% aids in the diagnosis of IA[51].

In our study, GM was detected in 59.1% of cases, most of which were in the BAL. This finding is consistent with previous research indicating that BAL GM is more sensitive[18,52]. Due to the absence of GM measurement in the control group, the sensitivity and specificity of this test for IA diagnosis cannot be calculated.

In the present study, the most common CT scan findings were lung nodules (50%), halo sign (45.5%), and pleural effusion (31.8%). According to previous research, imaging-specific findings are ground glass opacities, cavities, and the nodule (with or without a halo sign)[15-17]. Halo sign, a typical and early finding of IA in HSCT and neutropenic patients, is rarely observed in SOT patients[53,54]. The high frequency of halo signs in the present study may be due to early diagnosis of this infection and conducting lung CT scan in our center as a primary diagnostic action for each patient with changes in general conditions, with or without pulmonary symptoms.

According to the most recent IDSA guidelines, voriconazole is the drug of choice for IA[55]. Isavuconazole and liposomal amphotericin B are alternatives. In our study, liposomal amphotericin B was administered to most patients with a high probability of fungal infection. After the diagnosis was confirmed, the treatment was changed to voriconazole. Those who received voriconazole had a higher recovery and survival rate than those who received amphotericin B[25]. In our study, the response to treatment, defined as complete and partial recovery within 12 wk of initiating antifungal treatment, was 45.5% and 18.2%, respectively. The overall treatment response rate of 63.7% was consistent with previous studies[9,42].

Overall, 16.9% of the mortality during the first year post-transplant is due to IA. The highest mortality rate is observed in CNS involvements and disseminated aspergillosis[10]. However, due to the increased rate of late-onset IA, the mortality has been reduced from 65%-92% to 22% (the higher mortality rate was related to the studies before 2000)[56].

Nevertheless, the mortality rate of IA in liver transplant patients remains high[8]. According to our study, the 12-week mortality rate was 36.4%. A study by Nagao *et al*[7] (2016) on five IA patients reported a mortality rate of 80%. The one-year survival rate of aspergillosis patients in this study was 54.6%. In contrast, the entire control group population survived one year after the transplant. A study by Barchiesi *et al*[4] revealed a 35% one-year survival rate. After the year 2000, the survival of patients who received voriconazole improved in the absence of renal failure.

Considering the study's retrospective nature, it was impossible to investigate several factors (including the role of GM and β-d-glucan in the IA diagnosis). In addition, due to the absence of invasive diagnostic procedures, most IA patients were not diagnosed.

CONCLUSION

Despite the significant decline in the incidence of IA at our center, this disease has a negative impact on the survival of transplant recipients. Early diagnosis based on clinical symptoms and imaging modalities, as well as identification of factors related to the incidence of IA, is of significant importance. The imaging findings of aspergillosis, including nodule and halo signs, continue to play a crucial role in diagnosing this lethal invasive infection.

Furthermore, according to our study, the level of creatinine before the transplant, the creatinine level after the transplant, or patients who require renal replacement therapies after transplantation, induction therapy with ATG, ICU length of stay after the transplant, pneumonia 2 wk before the IA diagnosis, CMV viremia within one month before the IA diagnosis, receiving systemic antibiotics more than three days within the two weeks before the IA diagnosis, treatment-required transplant rejection within three months before the IA diagnosis, repeated surgery within 30 d after the transplant were the risk factors associated with increased risk of IA. We also hypothesize that biliary leakage and hepatic artery thrombosis after the transplant are two potential risk factors for IA.

ARTICLE HIGHLIGHTS

Research background

During the past two decades, the incidence rate and onset time of invasive fungal infections (IFIs), such as aspergillosis, have changed in liver transplant recipients.

Research motivation

Determining the new risk factors and treatment outcomes of early and late-onset invasive aspergillosis (IA) in high-volume centers for liver transplants is essential. It may have a key role in improving the prognosis of these patients.

Research objectives

This study sought to determine the prevalence, risk factors, treatment outcomes, and prognosis of IA infection among liver transplant recipients at our institution. We also investigated the study patients' major clinical, laboratory, and radiologic manifestations of IA.

Research methods

To determine the prevalence of IA, we analyzed the data of 850 patients who received a liver transplant at the Imam Khomeini Hospital Complex in Tehran, Iran, between 2014 and 2019, and recorded the study variables for patients with an IA diagnosis. In addition, we devised a case-control study to identify the risk factors for IA and compare the prognoses of patients with and without IA.

Research results

Our center's IA rate was 2.7%. Pulmonary aspergillosis was the most common presentation of the patients with IA. In most of our patients, imaging findings indicative of aspergillosis, including nodule and halo signs, were detected. The high level of creatinine before and after the transplant, renal replacement therapy after transplantation, induction therapy with antithymocyte globulin, longer duration of intensive care unit admission after the transplant, pneumonia 2 wk before the IA diagnosis, cytomegalovirus viremia within 1 mo before the IA diagnosis, receiving systemic antibiotics for more than three days within the 2 wk before the IA diagnosis, treatment-required transplant rejection within three months before the IA diagnosis, receiving systemic antibiotics for longer than three months before the IA diagnosis, repeated surgery within 30 d after the transplant, biliary leakage after the transplant and hepatic artery thrombosis were the risk factors associated with increased risk of IA.

Research conclusions

In this study, the prevalence of IA among liver transplant recipients was relatively low. However, it was one of the leading causes of mortality following liver transplantation. Identifying and addressing risk factors for IA, early diagnosis and prompt treatment of this fatal disease may improve the prognosis and decrease the mortality rate of liver transplant recipients.

Research perspectives

The primary risk factors of IA in liver transplant recipients should be determined through a large, multicenter study. Moreover, we must investigate the role of noninvasive and rapid diagnostic tests in diagnosing patients suspected of IFI early.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Reasons and effects of the decline of willing related potential living kidney donors

Rabea Ahmed Gadelkareem, Amr Mostafa Abdelgawad, Nasreldin Mohammed, Ahmed Reda, Nashwa Mostafa Azoz, Mohammed Ali Zarzour, Hisham Mokhtar Hammouda, Mahmoud Khalil

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Abstract

BACKGROUND

Although the availability of related living donors (LDs) provides a better chance for receiving kidney transplantation (KT), the evaluation protocols for LD selection remain a safeguard for the LD's safety. These protocols are variable from one center to another, resulting in variable rates of decline of the potential LDs (PLDs). The decline of willing PLDs may occur at any stage of evaluation, starting from the initial contact and counseling to the day of operation.

AIM

To identify the causes of the decline of PLDs, the predictors of PLD candidacy, and the effect on achieving LDKT.

METHODS

A retrospective study was performed on the willing PLDs who attended our outpatient clinic for kidney donation to their related potential recipients between October 2015 and December 2022. The variables influencing their candidacy rate and the fate of their potential recipients were studied. Two groups of PLDs were compared: Candidate PLDs after a completed evaluation *vs* non-candidate PLDs with a complete or incomplete evaluation. A multivariate logistic regression was performed to assess the factors contributing to the achievement of PLD candidacy.

RESULTS

Of 321 willing PLDs, 257 PLDs (80.1%) accessed the evaluation to variable extents for 212 potential recipients, with a mean age (range) of 40.5 ± 10.4 (18-65) years,

including 169 females (65.8%). The remaining 64 PLDs (19.9%) did not access the evaluation. Only 58 PLDs (18.1%) succeeded in donating, but 199 PDLs (62.0%) were declined; exclusion occurred in 144 PLDs (56.0%) for immunological causes (37.5%), medical causes (54.9%), combined causes (9.7%), and financial causes (2.1%). Regression and release occurred in 55 PLDs (17.1%). The potential recipients with candidate PLDs were not significantly different from those with non-candidate PLDs, except in age (P = 0.041), rates of completed evaluation, and exclusion of PLDs (P < 0.001). There were no factors that independently influenced the rate of PLD candidacy. Most patients who failed to have KT after the decline of their PLDs remained on hemodialysis for 6 mo to 6 years.

CONCLUSION

The rate of decline of willing related PLDs was high due to medical or immunological contraindications, release, or regression of PLDs. It reduced the chances of high percentages of potential recipients in LDKT.

Key Words: Donor decline; Donor evaluation; Donor exclusion; Kidney transplantation; Living kidney donors; Related living donors

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Core Tip: The rate of decline of willing related potential living kidney donors (PLDs) was high (82%). The causes of decline included exclusion by the transplant team due to contraindications of donation, release after disqualification of the potential recipients, and regression due to withdrawal of the decision by the PLD. PLD exclusion was the commonest form of decline due to medical or immunological contraindications. The high rate of PLD decline resulted in the loss of chances of kidney transplantation for high percentages of potential recipients who were left on dialysis for variably long periods, who died, or who were lost to an unknown fate.

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INTRODUCTION

Living donor kidney transplantation (LDKT) is the optimal form of renal replacement therapy. It shortens the waiting times and provides better survival rates. Hence, it is recommended as the first choice of treatment for each candidate patient with end-stage renal disease (ESRD), especially with the availability of related potential LDs (PLDs)[1,2]. However, it is not easy to find a willing and suitable LD. In addition, the preparation of a potential donor-recipient pair for KT is a complex sequential process[3,4]. Relative to the variability of assessment protocols, the reported acceptance rate of LDs is variable at 8.0%-18.4%[4,5]. This variability in acceptance of LDs is significant among countries, medical societies, health organizations, and KT units[3,6].

A large proportion of those PLDs may initially be declined for demographic issues, such as unsuitable age and genetic unrelatedness, or excluded later during preparation due to different medical reasons[5,7,8]. Although the exclusion of a willing potential LD may negatively reflect on the potential recipients by reducing their chances of transplantation, it is still a paramount principle not to violate the donor's safety for the recipient's benefit[3-5]. In our center, the maintenance of this narrow-margin principle between the donor's safety and the recipient's benefit through the assessment process was the motivator for the conduct of the current study. The aim was to assess the reasons for the decline of PLDs and their effects on the fate of potential recipients.

MATERIALS AND METHODS

Study design

A retrospective study was carried out by reviewing the data of the PLDs of ESRD patients who presented to our center seeking KT from October 2015 to December 2022. The inclusion criteria were a related PLD presenting to our center for donation to a related, intended patient with ESRD. Exclusion criteria included an initial failure to confirm the willingness to donate a kidney (Figure 1).

The flow of PLD evaluation

In our policy, the process of PLD evaluation is differentiated into six phases, from the initial contact to the achievement of a donation (Figure 2). Owing to the unavailability of a national waitlisting program and the nature of related living

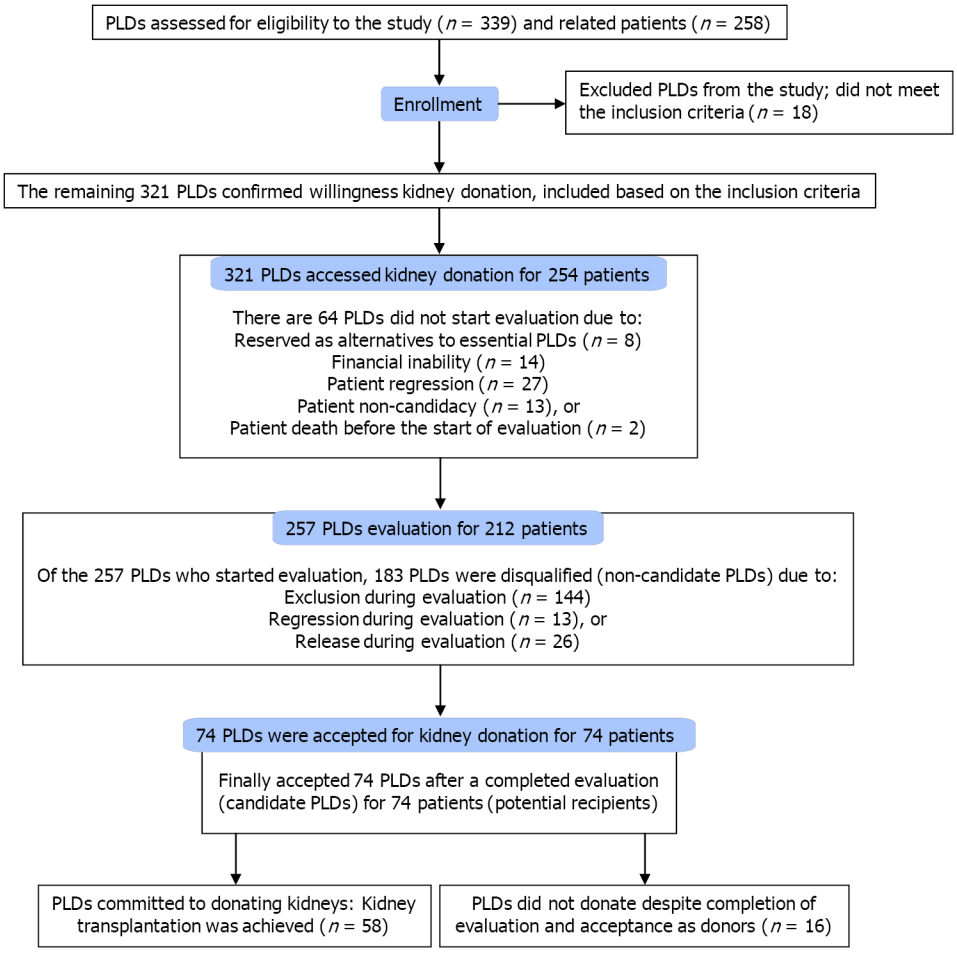

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Figure 1 Flowchart of the potential living kidney donors and their intended recipients showing the levels of decline of the potential donors from the stage of access to the kidney transplantation center to the achievement of kidney transplantation. PLD: Protentional living donor.

kidney donation (LKD), PLDs directly present with their intended recipients at the KT center. The initial two phases consist of contact with the KT center, confirmation of willingness to donate a kidney to an intended related potential recipient, counseling about KT, sociodemographic evaluation (age, familial relationships, and financial issues), and blood group matching. Initial history taking is usually performed at the first contact or counseling session, excluding previously known systemic diseases, financial issues, and factors violating the integrity of volunteer donation.

The third and fourth phases are multidisciplinary steps, including medical and immunological evaluations. The medical evaluation consists of detailed medical history, physical examinations, laboratory workups, and imaging workups. Kidney function was evaluated using the Technetium 99-diethylenetriamine pentaacetate renography for measurement of the total and split glomerular filtration rates in all PLDs. However, the anatomical features were evaluated by abdominal ultrasonography and contrast-enhanced computed tomography with renal angiography. In addition, psychosocial assessment was a routine workup to evaluate the mental status of the PLDs, motives for donation, cognitive capacity, expectations after donation, and exclude any psychogenic drive for self-harm. Furthermore, evaluation and exclusion of drug addiction was performed. The immunological workups include crossmatching, human leukocytic antigen (HLA) typing, and panel reactive antibody tests.

The fifth phase includes medicolegal permissions, determination of the date of surgery, and revision of the important tests. The sixth phase is the donation achievement.

Study outcomes and variables

The primary outcome of this study was the rate of PLD candidacy. It was defined as the percentage of PLDs with complete preparation for LKD and acceptance for donation, either when the transplantation was performed or it was cancelled due to causes related to the patient. Because the relevant characteristics of the intended patients were significant for the identification of the causes of decline of PLDs and their fates, these characteristics of those intended patients and their distribution per the outcomes of evaluation of their PLDs were studied. Each patient's file was examined for relevant demographic and clinical characteristics and related PLDs. The studied characteristics included the number, age, relatedness form and degree, decline form (exclusion, release, or regression), and causes of the decline of PLDs. In addition, the fate of PLDs and patients with declined PLDs was studied. Here, the relatedness was presented relative to

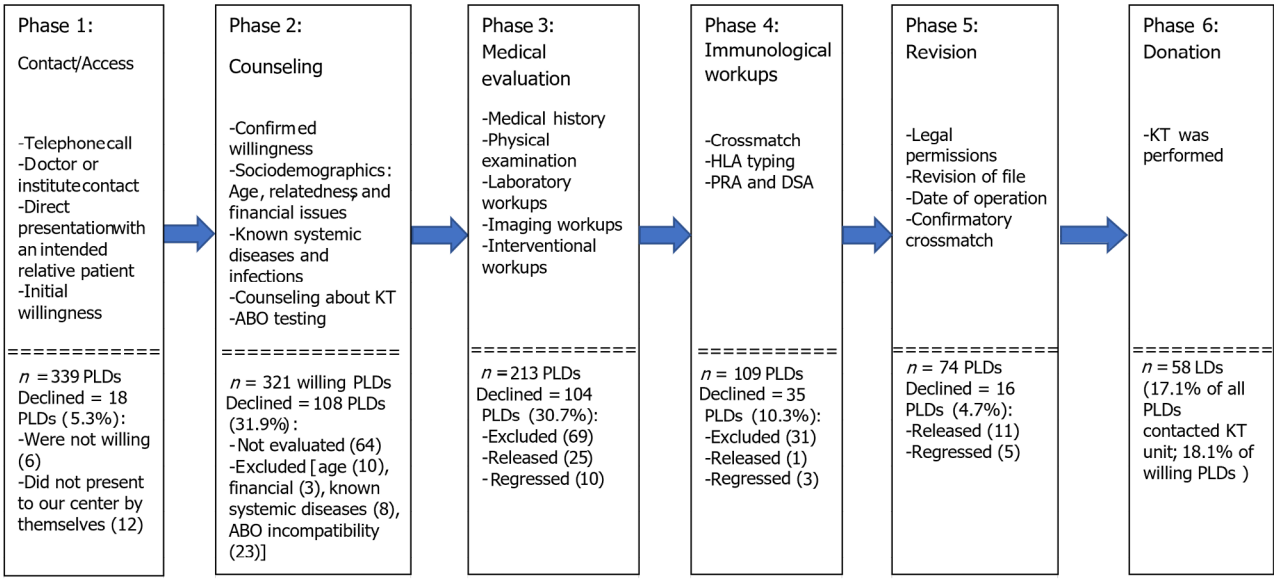

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Figure 2 Diagram of the different phases of the evaluation of the potential living kidney donors, showing the essential workups, percentages of declined donors, and causes of decline in each phase. DSA: Donor-specific antigens test; HLA: Human leukocytic antigen; KT: Kidney transplantation; PLD: Protentional living donor; PRA: Panel reactive antibodies test.

the genetic relatedness degrees (ABO-relatedness).

According to the primary outcome, the PLDs were differentiated into two groups. The first group was the candidate donors, including the finally accepted donors with a completed evaluation and preparation for donation. The second group was the non-candidate donors, including the remaining donors who were disqualified as PLDs, either with or without initial acceptance or a completed evaluation. The characteristics of both groups were compared with each other. The secondary outcomes were the rate of PLD decline in each phase of evaluation and the fate of patients with declined PLDs.

Sociodemographic definitions and documentation of donor-recipient relatedness

Throughout the process of LKD, the different statuses of the PLD were distinguished from each other as well-defined clinical events. They were defined to describe the events of PLD evaluation, from access to the achievement of LKD (Table 1). Based on these definitions, the outcomes of the study were estimated.

Official documents from the Civil Registry Office were requested to document the degree of genetic relatedness between the PLD and the intended recipient. Routinely, the birth certificates and national identity numbers for all PLDs and their intended recipients were the basic documents. In our center, the first and second degrees of genetic relatedness of PLDs were routinely allowed, based on these routine documents. If there was difficulty finding a PLD, the third and fourth degrees were allowed after investigations, and they were mostly processed similarly to the unrelated PLDs. In the latter instances, further documentation was warranted, such as a family genealogy tree from the Civil Registry Office and consent registered in the Real Estate Publicity Department and Documentation Office.

The processes employed to investigate the transparency of kidney donation

The transparency of the donation as an unpaid act was verified *via* multiple processes to identify and exclude any financial agreements in these cases: (1) Direct confrontation of the PLD and intended recipient with this issue during counseling and warning them that KT would not be done if there was any violation to the moral donation principle; (2) The KT ethical committee, which is composed of three medical professors who do not belong to the KT team, has the authority to investigate and revise the process of preparation, including the soundness of donation principles; (3) Each patient with a PLD of more than the second degree genetic relatedness had to introduce the proofs (official papers or documents) of the relatedness to his PLD from the Civil Registry Office; (4) As mentioned above, each PLD accepted for donation of his kidney had to sign a consent that the donation was for free without any financial or non-financial rewards from the intended recipient or from other relatives. This consent was documented by the Real Estate Publicity Department and Documentation Office; and (5) The Egyptian Supreme Committee of Organ Transplantation revises all these files and documents to prove the family tree and degree of relatedness between each candidate PLD and the intended recipient, with a special attention to exclude any financial agreements.

Ethical approval

This study was conducted as part of a research project on the outcomes of LDKT performed in our center. The institutional review board number is 17200148/2017.

Table 1 Definitions of terms used to describe the living donors at different stages of kidney donation including access, counseling, evaluation, acceptance, candidacy, and donation with kidney transplantation of related intended patients

Term	Definition
PLD	An individual who confirmed his willingness to donate a kidney to an intended patient at the initial counseling settings and was ready to start the evaluation for kidney donation, regardless of the commencement of the evaluation
Related PLD	PLD who had a relative intended patient with end-stage renal disease up to the 4th degree of genetic relatedness. Regardless of their genetic relatedness, the wife or husband of a recipient was considered a related PLD
Excluded PLD	PLD who was disqualified as a kidney donor and excluded from the process of kidney donation by KT team due to causes that disqualify candidacy to donate a kidney, such as medical, immunological, or financial causes
Regressed PLD	PLD who withdrew his decision of kidney donation at any stage after an initial confirmation of the donation decision and before the operation
Released PLD[1]	PLD who was still willing and completed or was still continuing the evaluation, but the related intended patient was withdrawn from KT preparation due to any cause
Candidate PLD	PLD who completed all the steps of evaluation and was finally accepted by the KT team for kidney donation, regardless of the later regression or release from donation
Accepted PLD	PLD who completed the evaluation without exclusion from kidney donation and was accepted for donation without release or regression from his willingness
LD	PLD becomes a LD when he succeeds in donating a kidney to his/her intended patient, which also means KT was achieved
Relatedness degrees and forms[2]	First degree: father, mother, son, daughter, wife, and husband. Second degree: brother, sister, grandfather, grandmother, grandson, and granddaughter. Third degree: nephew, uncle and aunt. Fourth degree: cousins

[1]In this study, release of the donor meant that the donor became free from any commitment to donating a kidney because his relative intended patient was excluded, regressed, or died. In addition, the donor would not be allocated to another patient, as he/she was willing to donate to his intended relative only.
[2]Husband-wife couples were processed as first-degree related potential living donors when donations were planned between each couple. However, they may be genetically related or unrelated, relative to their premarriage relatedness. KT: Kidney transplantation; LD: Living donor; PLD: Potential living donor.

Statistical analysis

Statistical analysis was performed with EasyMedStat software (version 3.21.4; www.easymedstat.com). The continuous data were presented as mean ± standard deviation and range. The categorical data were presented as frequency and percentage for each category. Two groups of PLDs were compared: candidate PLDs after a completed evaluation *vs* non-candidate PLDs with a complete or incomplete evaluation. Normality and hetereoskedasticity of continuous data were assessed with the White test (or Shapiro-Wilk in multivariate analysis) and Levene's test, respectively. Continuous outcomes were compared with the unpaired Student *t*-test, Welch *t*-test, or Mann-Whitney *U* test according to the data distribution. Categorical outcomes were compared with the *chi-squared* or Fisher's exact test. A multivariate logistic regression was performed to assess the factors contributing to the achievement of PLD candidacy. The data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 302 patients were referred to our center for related LDKT during the time frame of this study. The mean age (range) was 32.0 ± 11.7 (12-66) years. Of them, 44 patients (14.6%) did not have PLDs at presentation. The remaining 258 patients (85.4%) had 1-3 PLDs, constituting a total of 339 related PLDs. Eighteen PLDs (5.3%) were considered unwilling to donate a kidney as they could not confirm their willingness at the initial contact and presentation and were excluded from the study. However, the remaining 321 PLDs (94.7%) confirmed their initial willingness to donate to 254 relative patients and were included in the study (Figures 1 and 2). The mean (range) age of all the willing PLDs was 39.7 ± 10.4 (18-65) years, and they included 116 males (36.1%) and 205 females (63.9%).

Despite the confirmed willingness, 64 of 321 PLDs (19.9%) did not start the evaluation. The causes included financial inability in 14 PLDs (21.9%), serving as reserve donors in 8 PLDs (12.5%), patient non-candidacy to KT in 13 PLDs (20.3%), patient regression from KT in 27 PLDs (42.2%), and patient death in 2 PLDs (3.1%).

The remaining 257 PLDs (80.1%) were relatives of 212 patients (83.5%) (Tables 2-5). At the different levels of evaluation and preparation for the final acceptance as LDs (Figure 2), these 257 PLDs variably passed these levels of evaluation with two main outcomes. The first outcome was the completion of the evaluation with candidacy in 74 PLDs (28.8%). The second outcome was the failure to achieve the candidacy outcome in 183 PLDs (71.8%) (Table 5). The causes of the latter outcome were PLD exclusion in 144 PLDs (72.4%), regression from the donation decision in 18 PLDs (9%), and release after the disqualification of their potential recipients in 37 PLDs (18.6%) (Tables 3 and 4). In PLDs with candidacy for donation, 16 PLDs (21.6%) did not commit to donation. Accordingly, only 58 LDs (78.4%) succeeded in committing to

Table 2 Demographic and clinical characteristics of patients and related potential living donors presented as total patients (*n* = 212) and as a comparison between patients with candidate (*n* = 74) and patients with non-candidate (*n* = 138) potential living donors

Characteristics	Total patients, *n* = 212	Patients with candidate PLDs, *n* = 74	Patients with non-candidate PLDs, *n* = 138	*P* value
	mean ± SD (range)/number (%)			
Mean age in yr	31.2 ± 10.6 (13-66)	29.1 ± 9.6 (13-57)	32.9 ± 12.0 (14-66)	0.041
Sex, *n* = 212				
Males	173 (81.6%)	67 (90.5%)	106 (76.8%)	0.087
Females	39 (18.4%)	7 (9.5%)	32 (23.2%)	
Status of dialysis at presentation, *n* = 212				
Preemptive	19 (9.0%)	5 (6.8%)	14 (10.1%)	0.462
On regular hemodialysis	193 (91.0%)	69 (93.2%)	124 (89.9%)	
Primary kidney disease, *n* = 212				
Unknown	167 (78.8%)	56 (75.7%)	111 (80.4%)	0.088
Systemic disease	14 (6.6%)	3 (2.7%)	11 (8.0%)	
Glomerulonephritis	6 (2.8%)	3 (4.0%)	3 (2.2%)	
Hereditary renal disease	5 (3.8%)	2 (2.7%)	3 (2.2%)	
Obstructive uropathy	11 (5.2%)	8 (10.8%)	3 (2.2%)	
Urolithiasis	9 (4.2%)	2 (2.7%)	7 (5.1%)	
Categories of primary kidney disease, *n* = 212				
Unknown	167 (78.8%)	56 (75.7%)	111 (80.4%)	0.154
Systemic disease	14 (6.6%)	3 (4.0%)	11 (8.0%)	
Local, renal/urinary	31 (14.6%)	15 (20.3%)	16 (11.6%)	
Patients per number of PLDs, *n* = 212				
Patients with one PLD	165 (77.8%)	53 (71.6%)	112 (81.2%)	0.265
Patients with two PLDs	39 (18.4%)	17 (23.0%)	22 (15.9%)	
Patients with three PLDs	8 (3.8%)	4 (5.4%)	4 (2.9%)	

PLD: Potential living donor; SD: Standard deviation.

donating a kidney to their related recipients, representing 18.1% of the total 321 PLDs (Figures 1 and 2; Table 4). Single and multiple PLDs were found to be related to 165 patients (77.8%) and 47 patients (22.2%), respectively. The respective percentages of achieved donations (26.7% *vs* 29.8%) were not significantly different ($P = 0.674$).

In the 144 excluded PLDs, the causes of exclusion were immunological incompatibilities in 54 PLDs (37.5%), medical abnormalities in 79 PLDs (54.9%), and financial inability in 3 PLDs (2.1%). Combined immunological and medical causes occurred in 14 PLDs (9.7%). In addition, the exclusion was distributed per intended patient (Tables 3 and 4). Exclusion occurred before or after completion of the evaluation in 109 PLDs (75.7%) and 35 PLDs (24.3%), respectively.

A comparison was performed between patients with candidate PLDs and patients with non-candidate PLDs. Their characteristics and PLD-related distributions were not significantly different, except in the mean age, which was lower in patients with candidate PLDs ($P = 0.041$). During a variable follow-up period, patients with declined PLDs mostly remained on dialysis for 6 mo to 6 years (Tables 2-4).

Also, a comparison was performed between the candidate and non-candidate PLDs. Their characteristics were not significantly different, except in the degree of relatedness to their potential recipients ($P = 0.020$) and the time spent in the evaluation of PLDs. The latter was lower in patients with non-candidate PLDs ($P < 0.001$) (Table 5).

A multivariate logistic regression analysis of factors influencing the candidacy of PLDs was carried out. It revealed that the on-dialysis potential recipient ($P = 0.451$), younger age PLDs ($P = 0.925$), male PLDs ($P = 0.940$), second or higher degrees of relatedness to the recipient *vs* the first degree ($P = 0.834$), and multiplicity of PLDs ($P = 0.123$) were not significantly associated with the rate of candidacy of PLDs for LKD after completion of preparation (Table 6).

Table 3 Patient characteristics distributed per extent and outcome of evaluation of their potential living donors presented as total patients (*n* = 212) and as a comparison between patients with candidate (*n* = 74) and patients with non-candidate (*n* = 138) potential living donors.

Characteristics	Total patients, *n* = 212	Patients with candidate PLDs, *n* = 74	Patients with non-candidate PLDs, *n* = 138	*P* value
	mean ± SD (range)/number (%)			
Patients per extent of evaluation of their PLDs[1], *n* = 212				
Completed 1	71 (33.5%)	54 (73%)	17 (12.3%)	< 0.001
Completed 1/incomplete 1	15 (7.1%)	7 (9.5%)	8 (5.8%)	
Completed 1/incomplete 2	2 (0.9%)	2 (2.7%)	0 (0%)	
Completed 1/not evaluated 1	7 (3.3%)	6 (8.1%)	1 (0.7%)	
Completed 2	3 (1.4%)	3 (4.1%)	0 (0%)	
Completed 2/incomplete 1	1 (0.5%)	0 (0%)	1 (0.7%)	
Completed 3	2 (0.9%)	2 (2.7%)	0 (0%)	
Incomplete 1	94 (44.3%)	0 (0%)	94 (68.1%)	
Incomplete 1/not evaluated 1	1 (0.5%)	0 (0%)	1 (0.7%)	
Incomplete 1/not evaluated 2	1 (0.5%)	0 (0%)	1 (0.7%)	
Incomplete 2	13 (6.1%)	0 (0%)	13 (9.4%)	
Incomplete 3	2 (0.9%)	0 (0%)	2 (1.5%)	
Patients per acceptance of their PLDs[1], *n* = 212				
Accepted 1	44 (20.6%)	44 (59.5%)	0 (0%)	< 0.001
Accepted 1/excluded 1	8 (3.8%)	8 (10.8%)	0 (0%)	
Accepted 1/excluded 2	2 (0.9%)	2 (2.7%)	0 (0%)	
Accepted 1/not evaluated 1	4 (1.9%)	4 (5.4%)	0 (0%)	
Excluded 1	81 (38.2%)	0 (0%)	81 (0%)	
Excluded 2	14 (6.6%)	0 (0%)	14 (10.1%)	
Excluded 3	2 (0.9%)	0 (0%)	2 (1.5%)	
Excluded 1/released 1	5 (2.4%)	1 (1.4%)	4 (2.9%)	
Excluded 1/regressed 1	3 (1.4%)	1 (1.4%)	2 (1.5%)	
Excluded 1/not evaluated 1	2 (0.9%)	0 (0%)	2 (1.5%)	
Excluded 1/not evaluated 2	1 (0.5%)	0 (0%)	1 (0.7%)	
Excluded 2/released 1	2 (0.9%)	1 (1.4%)	1 (0.7%)	
Excluded 2/regressed 1	1 (0.5%)	1 (1.4%)	0 (0%)	
Released 1	28 (13.2%)	7 (9.5%)	21 (15.2%)	
Released 1/not evaluated 1	2 (0.9%)	2 (2.7%)	0 (0%)	
Regressed 1	12 (5.7%)	3 (4.1%)	9 (6.5%)	
Regressed 2	1 (0.5%)	0 (0%)	1 (0.7%)	

[1]The numbers here refer to the number of potential living donors who had this characteristic. In addition, it included 10 potential donors who were not evaluated, and they presented here as part of the combined donors to the same patients with evaluated donors. PLD: Potential living donor; SD: Standard deviation.

DISCUSSION

The state of the decline of PLDs is related to the availability of PLDs, the balance between the donor's safety and the recipient's benefit, and the achievement of LDKT as the optimal outcome of all these issues[5,6,8]. The decline of PLDs is the backbone of the failure to maintain the availability of PLDs for the majority of patients[6]. Its burden extends between and reflects on the medical and psychosocial integrities of the PLDs and their intended recipients. However, the current literature is still insufficient to resolve this problem because the rates of acceptance of LDs are still variably low[5]. Hence, the current situation mandates further study of the two main aspects of the process of evaluating PLDs. First, the root causes of the failure of high proportions of those PLDs to achieve the task of donating a kidney represent a major topic, despite the limited current literature. Many studies addressed the identification of these causes to help reduce their effects on the process of LKD[5,6,8]. Second, the fate of the intended recipients who had their PLDs lost is the other aspect that may be more critical in the process because those potential recipients may have their all chances for KT permanently lost also[5,6,9,10].

The availability of a related LD provides a better chance for receiving KT, and it represents the only source of grafts in many countries and programs[2,9]. This fact may raise caution to try to decrease the rate of decline of PLDs in those programs to afford the needs of the increasing pool of potential recipients over time. However, the evaluation protocols for suitable LD selection remain a safeguard against violations of donor safety, implementing a complex evaluation process[2,9,10]. According to this process, KT centers usually evaluate LD acceptance and exclusion processes in the context of the principle of non-violation of the donor's safety[3,11]. Our center implements only the LDKT strategy; hence, we evaluated the rate of candidacy and acceptance of LDs, the causes of declined PLDs, and the fate of potential recipients with declined PLDs.

Although the current rate of successful candidacy of PLDs is similar to other reported values from other centers, it is relatively hard to expect the exact percentage of PLDs who ultimately succeed in committing to LKD. This uncertainty in the acceptance rates can be attributed to the variability in the assessment protocols and stages from one center to another and from one country to another[5,8]. The stages of evaluation in our center may be different from those in other centers, due to socioeconomic factors and different policies of donation[5,9]. We considered HLA-typing at the late stage of evaluation due to sociodemographic reasons. Immunological tests for HLA typing and crossmatching are costly. However, other routine and multidisciplinary laboratory evaluations can be individualized into separate steps to catch any abnormalities in medical and laboratory workups with relatively low costs. In addition, related PLDs have higher chances of being HLA-matched with their intended recipients. On the other hand, this latter characteristic may be the reason why the mean age of the potential recipients was significantly lower than that of the PLDs. First-degree and second-degree relatedness between the PLDs and their potential recipients provided high proportions of parents and older sisters or brothers as PLDs for their relatives.

The efficiency of the evaluation of PLDs should consider the needs of the PLD, the intended recipient, and the qualifications of the healthcare system. The timing of the evaluation of multiple PLDs is an important issue[12]. In the current study, only the early stages of evaluation, including counseling and blood group (ABO) compatibility testing, can be carried out simultaneously due to financial causes. In addition, high proportions of PLD decline occur in the early stages of evaluation[5]. Similarly, the current results showed that more than two-thirds of PLDs were declined during the early evaluation phases.

The causes of the decline of PLDs are various and can be classified into PLD-related and patient-related causes[13]. In the current study, the major PLD-related causes included medical, immunological, and sociodemographic factors or combinations of them. ABO and HLA incompatibilities were responsible for high percentages of excluded PLDs. Trials to expand the pool of LDs may need novel strategies, such as accepting LDs with abnormalities that are not accepted in the standard criteria for LDs. The variability of the causes of decline mandates the variability of these strategies. Hence, this practice should be implemented under strict control in LDKT programs because it may have impacts on preserving full safety issues[3,4,11]. On the same principle, such policies have not been permitted in our center protocols to avoid the violation of donor safety.

About half of the evaluated PLDs in the current study were excluded due to immunological causes, including both ABO and HLA incompatibilities. These immunological barriers can be managed by strategies such as incompatible LDKT and paired or exchange LKD (PKD)[14]. The former strategy is certainly not acceptable due to the relatively inferior outcomes compared to the matched ABO-compatible or HLA-compatible patients and the potential higher costs for desensitization[15]. However, PKD or kidney-sharing programs seem to be more effective for the KT programs that are based on the LDKT strategy due to their low costs and high efficiency. They are currently recommended to reduce the decline rate of PLDs, which may increase the acceptance rate of PLDs to more than 50% and provide better chances of finding high-quality donors for those who already have matched PLDs. They overcome considerable proportions of ABO-incompatible and HLA-incompatible PLDs. Unfortunately, these programs have not been established in our country so far, allowing a high rate of PLD loss. However, it has gradually become the focus of some interested researchers in our KT community[16,17].

The PLDs could be disqualified from donation for different medical contraindications. These reasons vary from one program to another program[3,5]. In the current study, medical contraindications were found in more than 60% of the causes of the decline of PLDs, similar to previously reported experiences[5]. They included several clinical forms, such as systemic diseases, infections, urolithiasis, and primary kidney diseases with hereditary or familial patterns. These reasons may benefit from the relaxation of the standard criteria for donation, such as accepting those PLDs with mild hypertension, obesity, proteinuria, sporadic urolithiasis, or microscopic hematuria[3,18].

Table 4 Patients distributed per characteristics of exclusion of their potential living donors presented as total patients (*n* = 212) and as a comparison between patients with candidate (*n* = 74) and patients with non-candidate (*n* = 138) potential living donors.

Characteristics	Total patients, *n* = 212	Patients with candidate PLDs, *n* = 74	Patients with non-candidate PLDs, *n* = 138	*P* value
	mean ± SD (range)/number (%)			
Patients per number of excluded PLDs, *n* = 121				
Patients with one excluded PLD	100 (82.6%)	10 (71.4%)	90 (84.1%)	0.764
Patients with two excluded PLDs	19 (15.7%)	4 (28.6%)	15 (14.0%)	
Patients with three excluded PLDs	2 (1.7%)	0 (0%)	2 (1.9%)	
Patients per causes of exclusion of their PLDs, *n* = 121[1]				
Combined immunological and medical causes	14 (11.6%)	3 (21.4%)	11 (10.3%)	0.680
HLA-incompatibility	24 (19.8%)	3 (21.4%)	21 (19.6%)	
ABO-incompatibility	20 (16.5%)	1 (7.1%)	19 (17.8%)	
ABO and HLA-incompatibility	2 (1.7%)	0 (0%)	2 (1.9%)	
Age	8 (6.6%)	0 (0%)	8 (7.5%)	
Diabetes mellitus	4 (3.3%)	0 (0%)	4 (3.7%)	
HCV positive	5 (4.1%)	2 (14.3%)	3 (2.8%)	
Hypertension	11 (9.1%)	4 (28.6%)	7 (6.5%)	
Leprosy	1 (0.8%)	0 (0%)	1 (0.9%)	
Low GFR	4 (3.3%)	1 (7.1%)	3 (2.8%)	
High potential recurrence of primary kidney disease	6 (5.0%)	0 (0%)	6 (5.6%)	
Proteinuria	12 (9.9%)	0 (0%)	12 (11.2%)	
Psoriasis	1 (0.8%)	0 (0%)	1 (0.9%)	
Rheumatoid arthritis	1 (0.8%)	0 (0%)	1 (0.9%)	
Urolithiasis	5 (4.1%)	0 (0%)	5 (4.7%)	
Financial causes	3 (2.5%)	0 (0%)	3 (2.8%)	
Patients per main category of causes of exclusion of their PLDs, *n* = 121				
Combined immunological and medical causes	14 (11.6%)	3 (21.4%)	11 (10.3%)	0.866
Immunologic mismatches	46 (38%)	4 (28.6%)	42 (39.3%)	
Medical causes	58 (47.9%)	7 (50.0%)	51 (47.7%)	
Financial causes	3 (2.5%)	0 (0%)	3 (2.8%)	
Patients per timing of PLDs regression, *n* = 18				
During evaluation	13 (72.2%)	0 (0%)	13 (100.0%)	NA
After evaluation	5 (27.8%)	5 (100.0%)	0 (0%)	
Patients per cause of release of PLDs, *n* = 37				
Patient death	4 (10.8%)	3 (27.3%)	1 (3.9%)	0.186
Patient regression	22 (59.5%)	6 (54.5%)	16 (61.5%)	
Patient non-candidacy	11 (29.7%)	2 (18.2%)	9 (34.6%)	
Patients per timing of release of PLDs,				

n = 37				
During evaluation	26 (70.3%)	0 (0%)	26 (100.0%)	NA
After evaluation	11 (29.7%)	11 (100.0%)	0 (0%)	
Fate of patients with evaluated PLDs, *n* = 212				
Transplantation in our center	58 (27.4%)	58 (78.4%)	0 (0%)	NA
Transplantation in another center	14 (6.6%)	1 (1.4%)	13 (9.4%)	0.024
On hemodialysis	122 (57.6%)	12 (16.2%)	110 (79.7%)	< 0.001
Death	9 (4.2%)	3 (4.1%)	6 (4.4%)	0.920
Unknown	9 (4.2%)	0 (0%)	9 (6.5%)	0.024

[1]Regarding the exclusion due to anatomical abnormalities, they included ectopic pelvic kidney, solitary kidney, and hypoplastic kidney in 3 patients. They were included in donors with a low split glomerular filtration rate. However, kidneys with unilateral simple cysts in 2 patients and three renal arteries in 2 patients were not the cause of exclusion. In the former, the cysts were treated by marsupialization after perfusion and before implantation in the recipients. In the latter, the contralateral kidneys were donated. GFR: Glomerular filtration rate; HCV: Hepatitis C virus; HLA: Human leukocytic antigen; NA: Not available; PLD: Potential living donor; SD: Standard deviation.

Another right for PLD is autonomy, which provides the full capacity to preserve the ability to withdraw at any stage of preparation up to the date of surgery[19]. This right may contribute to the decline of PLDs due to withdrawal or regression from the decision to donate. In our study, 18 PLDs (7%) regressed from donation after confirmed initial willingness due to fear of health concerns, and 5 PLDs withdrew their decision after completion of the evaluation. Their potential recipients failed to find other suitable donors and remained on hemodialysis. Although it is disappointing to the potential recipients, PLD regression usually occurs in a small percentage of PLDs. However, it warrants the help of the team to support the PLDs in their decision and communicate with the potential recipient to deliver the decision[19]. Connaughton *et al*[5] reported that 15.5% of PLDs withdrew from donation during evaluation. A study by Liu *et al*[20] reported self-ranking health conditions, insufficient support in decision-making, value clarity, and conflicts in the decisions as factors of withdrawal.

For a PLD, withdrawal or being withdrawn indicates more time for finding another PLD. In our study, some patients found suitable donors after many trials among relatives. There is no doubt that this process was time-consuming, and the patients waited on dialysis for years. Also, some of them died while they were waiting for a donor. Moreover, the majority of the potential recipients are now still waiting on regular dialysis or have been transplanted in other places that mostly adopt the unrelated LDKT. The latter policy may predispose to such an unfavorable act of paid LKD. Hence, we preserved this policy for limited indications, such as cases of hereditary or familial primary renal diseases, including polycystic kidney disease. However, the in-depth discussion of the point of paid LKD is beyond the scope of this study.

Patient-related causes of the decline of PLDs included patient withdrawal from KT, non-candidacy, and death during preparation. We defined those PLDs as released because the intended recipients were disqualified. In an interview study by Pronk *et al*[21], patients expressed moral causes for regression from accepting related PLDs, such as reluctance to accept a kidney from close relatives and fear of being considered selfish.

The duration of PLD evaluation is variable and may be lengthy for repeating or confirmatory workups. Understanding the reasons that may prolong the evaluation may help reduce unnecessary delays[12]. The duration of evaluation in this study varied from 2 wk to 6 mo, with an average of 2.2 mo. This variation was due to the consideration of all PLDs with incomplete or complete evaluations.

Most of the potential recipients with declined PLDs remained on hemodialysis for variable periods ranging from 6 mo to 6 years. This means that the chances of achieving LDKT were reduced for those potential recipients when their PLDs were declined. Only 14 patients (6.6%) with declined PLDs succeeded in having LDKT in other centers, representing low chances of having LDKT similar to the results of previous studies[5,8,13]. In addition, patients with multiple PLDs did not significantly have higher chances of achieving KT. This might be attributed to the healthcare system implemented in our country, where most patients sought medical consultations in private clinics, and their PLDs had initial evaluations with their private physicians before the presentation to our center. PLDs with known systemic diseases and ABO typing can easily be excluded. In turn, this may be an explanation for the presentation of a single PLD in 77.8% of patients.

The outcomes of the current study should attract attention to the formulation of efficient plans to reduce the rates of decline of PLDs and promote LKD through the introduction of strategies such as PKD to our national program. Also, national initiatives for the education of the public, patients, and general practitioners about the advantages of LDKT and LKD may help reduce the decline of PLDs caused by the reluctance and low medical literacy of those individuals.

To the best of our knowledge, the current study is the first from Egypt that specifically addressed the topic of the decline of PLDs among related PLDs and recipients. This is a very important step in the development of an integrated national KT program, which has only been dependent on LKD until now. The current study may encourage other centers to conduct similar studies to provide better evidence of the problem and formulate a plan to overcome the causes of the decline of PLDs. In addition, the aim, rationale, and outcomes of this study were parallel to many studies from different countries[3,5,6,8,13], which may strengthen the effect of its outcomes on the improvement of our practice and healthcare

Table 5 Characteristics of potential living donors presented as total (*n* = 257) and as a comparison between the candidate (*n* = 74) and non-candidate (*n* = 183) groups of donors

Characteristics	Total PLDs, *n* = 257	Candidate PLDs, *n* = 74	Non-candidate PLDs, *n* = 183	*P* value
	mean ± SD (range)/number (%)			
Mean age in yr	40.5 ± 10.4 (18-65)	41.0 ± 10.5 (21-60)	40.4 ± 10.5 (18-65)	0.498
Sex				
Female	169 (65.8%)	49 (66.2%)	120 (65.6%)	> 0.999
Male	88 (34.2%)	25 (33.8%)	63 (34.4%)	
Form of relatedness[1]				
Aunt	4 (1.6%)	4 (5.4%)	0 (0%)	0.286
Brother	51 (19.8%)	14 (18.9%)	37 (20.2%)	
Cousin	4 (1.6%)	0 (0%)	4 (2.2%)	
Daughter	4 (1.6%)	1 (1.4%)	3 (1.6%)	
Father	23 (8.9%)	7 (9.5%)	16 (8.7%)	
Husband	6 (2.3%)	2 (2.7%)	4 (2.2%)	
Mother	76 (29.6%)	23 (31.1%)	53 (29%)	
Nephew	1 (0.4%)	0 (0%)	1 (0.6%)	
Sister	53 (20.6%)	13 (17.6%)	40 (21.9%)	
Son	4 (1.6%)	1 (1.4%)	3 (1.6%)	
Uncle	1 (0.4%)	1 (1.4%)	0 (0%)	
Wife	30 (11.7%)	8 (10.8%)	22 (12.0%)	
Degree of relatedness				
First	143 (55.6%)	42 (56.8%)	101 (55.2%)	0.020
Second	104 (40.5%)	27 (36.5%)	77 (42.1%)	
Third	6 (2.3%)	5 (6.8%)	1 (0.6%)	
Fourth	4 (1.6%)	0 (0%)	4 (2.2%)	
Extent of evaluation				
Complete	109 (42.4%)	74 (100.0%)	35 (19.1%)	NA
Incomplete	148 (57.6%)	0 (0%)	148 (80.9%)	
Fate of PLDs				
Donated	58 (22.6%)	58 (78.4%)	0 (0%)	NA
Excluded	144 (56.0%)	0 (0%)	144 (78.7%)	NA
Regressed[2]	18 (7.0%)	5 (6.8%)	13 (31.6%)	
During evaluation	13 (72.2%)	0 (0%)	13 (100.0%)	NA
After evaluation	5 (27.8%)	5 (100%)	0 (0%)	
Released	37 (14.4%)	11 (14.9%)	26 (68.4%)	
Causes of donor release				
Patient death	4 (10.8%)	3 (27.3%)	1 (3.9%)	0.186
Patient regression	22 (59.5%)	6 (54.5%)	16 (61.5%)	
Patient non-candidacy	11 (29.7%)	2 (18.2%)	9 (34.6%)	
Timing of PLDs release				
During evaluation	26 (70.3%)	0 (0%)	26 (100.0%)	NA
After evaluation	11 (29.7%)	11 (100.0%)	0 (0%)	

Time spent in PLDs evaluation in mo	2.2 ± 1.5 (0.5-6.0)	4.0 ± 0.9 (1-6)	1.5 ± 1.2 (0.5-5.0)	< 0.001

[1]Among the 6 husband and 30 wife potential living donors (PLDs), only 13 of them were genetically related PLDs to their intended recipients (due to consanguineous marriage);
[2]The reason of regression was the fear of health drawbacks from donation in all PLDs. NA: Not available; PLD: Potential living donor; SD: Standard deviation.

Table 6 Multivariate logistic regression of the potential variables influencing the candidacy of potential living donors with a completed preparation

Variables	Modality	Odds ratio	*P* value
Dialysis status	Preemptive *vs* on dialysis	0.66 (0.23-1.94)	0.451
Number of potential donors	Single *vs* multiple	1.69 (0.87-3.28)	0.123
Donor age	Increasing age	1.0 (0.97-1.03)	0.925
Donor sex	Men *vs* women	1.02 (0.55-1.92)	0.940
Relatedness degree	First *vs* more than first	1.07 (0.55-2.1)	0.834

system management.

The limitations of this study included the retrospective nature of the methods. The retrospective nature may be the reason that the regression of PLDs and their recipients was not reported in detail. It is unknown whether these events were due to improper counseling, sociodemographic characteristics, or the low integrity of the healthcare system. In addition, a relatively short follow-up period limited the evaluation of the long-term effect of the decline of PLDs on the fate of some intended recipients. Moreover, it was a single-center experience, which warrants further national or multicenter studies for the generalizability of these results. However, most of the available literature comes from retrospective single-center studies[3,5,8,13].

CONCLUSION

The willing, related PLDs have a mean age higher than their potential recipients due to relatedness; most of them were parents or older relatives. Also, their potential recipients had primary kidney diseases that typically affect young people. The rate of decline of the willing, related PLDs was high, reaching about 82%. The causes could be classified as PLD-related or potential recipient-related, depending on the side of the cause. In addition, they could be differentiated into exclusion due to contraindications, release after disqualification of the potential recipients, and regression due to withdrawal of the decision by the PLDs, based on the autonomy of decision-making. PLD exclusion was the commonest form during or after the completion of the evaluation due to medical or immunological contraindications. These high percentages of PLD decline resulted in the loss of the chance to obtain LDKT for a high percentage of potential recipients who were left on dialysis for variably long periods, who died, or who were lost to an unknown fate. In our country, this study represents an initial scientific step in the evidence-based evaluation of the situation of LD selection and its deficits. The high rate of decline of PLDs reported here may draw attention to implementing more research on this topic.

ARTICLE HIGHLIGHTS

Research background

The evaluation protocols for living kidney donor (LD) selection are usually strict but remain a safeguard against violations of LD safety. Hence, the decline of willing potential living donors (PLDs) may occur at any stage of evaluation due to different causes, resulting in variable rates of decline of PLDs.

Research motivation

The rate of decline of willing related LDs seems to be a modifiable variable for improving LD kidney transplantation (LDKT).

Research objectives

To identify the causes of the decline of PLDs, the predictors of PLD candidacy, and the effect on achieving LDKT.

Research methods
A retrospective study was performed on willing PLDs who attended our outpatient clinic for kidney donation to their related potential recipients between October 2015 and December 2022. Two groups of PLDs were compared: Candidate PLDs after a completed evaluation *vs* non-candidate PLDs with a complete or incomplete evaluation. A multivariate logistic regression was performed to assess the factors contributing to the achievement of PLD candidacy.

Research results
Of 321 willing PLDs, 257 (80.1%) accessed the evaluation to variable extents for 212 potential recipients, with a mean age (range) of 40.5 ± 10.4 (18-65) years. The remaining 64 PLDs (19.9%) did not access the evaluation due to serving as alternatives to essential PLDs, financial causes, and patient-related factors. Only 58 PLDs (18.1%) achieved donation, but 199 PDLs (62.0%) were declined. Exclusion occurred in 144 PLDs (56%) for immunological causes (37.5%), medical causes (54.9%), combined causes (9.7%), and financial causes (2.1%), but regression and release occurred in 55 PLDs (17.1%). The number of potential recipients with candidate PLDs was not significantly different from that with non-candidate PLDs, except in age ($P = 0.041$), rates of completed evaluation, and exclusion of PLDs ($P < 0.001$). In the multivariate analysis, there were no independent factors that influenced the rate of PLD candidacy. Most patients who failed to have KT after the decline of their PLDs remained on hemodialysis for 6 mo to 6 years.

Research conclusions
Despite the availability of willing related PLDs for most potential recipients, their rate of decline was high. The causes were various, including medical or immunological contraindications, release, and regression of PLDs. Hence, the chances of LDKT were reduced or lost in a high percentage of potential recipients.

Research perspectives
Trials to reduce the rate of decline of PLDs should not be at the expense of LD safety. However, revision and identification of the causes of PLD decline may help increase the chances of patients for KT, especially with the application of strategies that overcome the immunological barriers of LDKT and low medical literacy.

FOOTNOTES

Author contributions: Gadelkareem RA, Abdelgawad AM, and Mohammed N designed the research, collected the data, and wrote the paper; Reda A, Azoz NM, and Zarzour MA contributed to statistical analysis, literature review, writing, and revision; Hammouda HM and Khalil M contributed to the literature review, writing, revision, and supervision of the work; All authors approved the paper.

Institutional review board statement: This study was conducted as part of a research project on the outcomes of living donor kidney transplantation performed in our center (Approval No. 17200148/2017).

Informed consent statement: This article is a retrospective study. Hence, the patients were not required to give informed consent to the study because the manipulated data were anonymous and were obtained after each patient, with their potential kidney donor(s), agreed to the plan of management.

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