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Contents

Monthly Volume 12 Number 8 August 18, 2022

REVIEW

211 Hypertension in kidney transplant recipients

Alexandrou ME, Ferro CJ, Boletis I, Papagianni A, Sarafidis P

MINIREVIEWS

223 Acute kidney injury and the compensation of kidney function after nephrectomy in living donation

Okumura K, Grace H, Sogawa H, Yamanaga S

231 Kidney disease in non-kidney solid organ transplantation

Swanson KJ

ORIGINAL ARTICLE

Retrospective Cohort Study

250 Emergency department visits and hospital admissions in kidney transplant recipients during the COVID-19 pandemic: A hospital-based study

Wongtanasarasin W, Phinyo P

Retrospective Study

259 Trends and outcomes of liver transplantation among older recipients in the United States

Okumura K, Lee JS, Dhand A, Sogawa H, Veillette G, John D, Misawa R, Bodin R, Wolf DC, Diflo T, Nishida S

SYSTEMATIC REVIEWS

268 Gastrointestinal manifestations, risk factors, and management in patients with post-transplant lymphoproliferative disorder: A systematic review

Reiche W, Tauseef A, Sabri A, Mirza M, Cantu D, Silberstein P, Chandan S

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Contents

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REVIEW

Hypertension in kidney transplant recipients

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Abstract

Kidney transplantation is considered the treatment of choice for end-stage kidney disease patients. However, the residual cardiovascular risk remains significantly higher in kidney transplant recipients (KTRs) than in the general population. Hypertension is highly prevalent in KTRs and represents a major modifiable risk factor associated with adverse cardiovascular outcomes and reduced patient and graft survival. Proper definition of hypertension and recognition of special phenotypes and abnormal diurnal blood pressure (BP) patterns is crucial for adequate BP control. Misclassification by office BP is commonly encountered in these patients, and a high proportion of masked and uncontrolled hypertension, as well as of white-coat hypertension, has been revealed in these patients with the use of ambulatory BP monitoring. The pathophysiology of hypertension in KTRs is multifactorial, involving traditional risk factors, factors related to chronic kidney disease and factors related to the transplantation procedure. In the absence of evidence from large-scale randomized controlled trials in this population, BP targets for hypertension management in KTR have been extrapolated from chronic kidney disease populations. The most recent Kidney Disease Improving Global Outcomes 2021 guidelines recommend lowering BP to less than 130/80 mmHg using standardized BP office measurements. Dihydropyridine calcium channel blockers and angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers have been established as the preferred first-line agents, on the basis of emphasis placed on their favorable outcomes on graft survival. The aim of this review is to provide previous and recent evidence on prevalence, accurate diagnosis, pathophysiology and treatment of hypertension in KTRs.

Key Words: Hypertension; Kidney transplantation; Epidemiology; Diagnosis; Physiopathology; Therapy

Core Tip: Kidney transplantation is considered the treatment of choice for end-stage kidney disease patients. However, the residual cardiovascular risk remains significantly higher in kidney transplant recipients than in the general population. This article summarizes available evidence on prevalence, abnormal blood pressure phenotypes and diurnal patterns as well as on the association of hypertension with target organ damage and clinical outcomes in kidney transplantation. The complex pathophysiology, treatment goals and recent data on therapeutic options for management of hypertension in kidney transplant recipients are also discussed.

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INTRODUCTION

Kidney transplantation is considered the optimal choice for renal replacement therapy in end-stage kidney disease due to improved survival and quality of life compared to dialysis modalities; this survival benefit has been attributed to kidney function improvement and delay of progression of cardiovascular disease[1]. Nevertheless, cardiovascular disease remains the leading cause of death in these patients in the early (< 10) post-transplant years[2]. Among traditional cardiovascular disease risk factors, hypertension represents the most prominent comorbidity post transplantation and a major cause of allograft dysfunction and adverse patient outcomes[3]. The diagnosis and treatment of hypertension in kidney transplantation has been traditionally based on office blood pressure (BP) measurements; BP control therefore remains suboptimal due to high rates of resistant and masked hypertension and abnormal diurnal BP patterns[4]. Controversies over BP targets and optimal antihypertensive regimen remain unresolved and should be further explored in well-designed randomized clinical trials (RCTs) in order to optimize hypertension management in this population.

EPIDEMIOLOGY OF HYPERTENSION IN KIDNEY TRANSPLANT RECIPIENTS

Prevalence of hypertension and abnormal BP phenotypes by the various metrics and definitions

The prevalence of hypertension is particularly high among kidney transplant recipients (KTRs) with previously reported rates between 70%-90%[5] and more recently even exceeding 95% of this population [6]. The source of variability in estimates of prevalence, control and different phenotypes of hypertension among KTRs is attributed to differences in the definitions used for hypertension diagnosis and in the type of BP measurement used (in office *vs* out-of-office setting) across various studies. Defining the diagnostic threshold for hypertension based on office and ambulatory BP measurements has been a matter of intense debate in chronic kidney disease (CKD) patients and more specifically in KTRs[7], with the two major existing hypertension guidelines producing confusion[8].

The cutoff values for hypertension diagnosis proposed by the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for office and ambulatory BP monitoring (ABPM) measurements were ≥ 130/80 mmHg and ≥ 125/75 mmHg, respectively[9] (Table 1), while those proposed by the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines were office BP ≥ 140/90 mmHg and ABPM ≥ 130/80 mmHg[10]. In the more recent 2021 Kidney Disease Improving Global Outcomes BP guidelines (Table 1), hypertension was defined as office BP ≥ 130/80 mmHg and ABPM ≥ 125/75 mmHg[11], in agreement with the 2017 ACC/AHA guidelines.

Taking into consideration all the above, studies assessing the epidemiology of hypertension have previously reported the presence of this disease in > 80.0% of patients based on the office 140/90 mmHg cutoff value[12] and in 89.5% based on the office 130/80 mmHg cutoff value, with control rates among hypertensive subjects at 45.5%[13]. The prevalence of resistant hypertension in this population (office BP ≥ 130/80 mmHg) has been previously reported in 17.5%[13] and 23.5%[14] of patients, despite intake of ≥ 1 and ≥ 3 antihypertensive drugs, respectively.

Recent guidelines recommend the use of out-of-office BP measurements as a complementary tool for improving the management of hypertension. In KTRs the wider use of ABPM has led to the recognition of abnormal diurnal BP patterns and BP phenotypes[11,15]. The rates of non-dipping status have been reported to range between 36%-95%[16-18] and that of nocturnal hypertension between 69%-77%

Table 1 Summary of guidelines for the management of hypertension in kidney transplant recipients

Ref.	Threshold for pharmacological treatment	Target blood pressure	Recommendations on 24-h ABPM	Recommendations for KTRs
Whelton *et al*[9], 2018	≥ 130/80 mmHg for primary prevention if estimated 10-yr ASCVD risk ≥ 10% and for secondary prevention if known CVD; ≥ 140/90 mmHg for primary prevention if no history of CVD and estimated 10-yr ASCVD risk < 10%	< 130/80 mmHg	Advised to exclude white coat and masked hypertension	In the absence of trials comparing different BP targets in KTRs, treatment targets for BP should probably be similar to the general CKD population; CCBs recommended as first line therapy on the basis of improved GFR and kidney survival; RAASi reserved for subset of patients with other comorbidities (proteinuria or heart failure)
KDIGO Blood Pressure Work Group[11], 2021	≥ 130/80 mmHg using standardized office BP measurement	< 130/80 mmHg using standardized office BP measurement	Out-of-office BP measurements with ABPM or home BP monitoring recommended to complement standardized office BP readings (2B)	Use of a dihydropyridine CCB or an ARB recommended as the first-line antihypertensive agent in adult KTRs (1C)

ABPM: Ambulatory blood pressure monitoring; ARB: Angiotensin receptor blocker; ASCVD: Atherosclerotic cardiovascular disease; BP: Blood pressure; CCB: Calcium channel blocker; CKD: Chronic kidney disease; CVD: Cardiovascular disease; GFR: Glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes; KTRs: Kidney transplant recipients; RAASi: Renin-angiotensin-aldosterone system inhibitor.

(according to the nighttime ABPM > 120/70 mmHg cutoff value for both)[18,19]. In an Italian cohort of 260 KTRs followed-up for 3.9 years, the agreement between 785 paired office and 24-h ABPM measurements was assessed, revealing significant discordance in 37% of all visits (κ-statistics = 0.25, indicating poor agreement)[19]. In 12% of all visits, patients were misclassified as hypertensive according to the office BP > 140/90 mmHg criterion while 24-h ABPM was normal according to the < 130/80 mmHg criterion (white-coat hypertension); in 25% of all visits patients were classified as normotensive according to the office criterion, while 24-h ABPM was > 130/80 mmHg (masked hypertension). In a cross-sectional study from Spain with 868 KTRs, the prevalence of white-coat and masked hypertension was 12% and 20%, respectively, applying similarly the ESC/ESH criteria[14]. Absence of systolic BP (SBP) dipping pattern was evidenced in 80% of patients. In a retrospective study, prevalence of white-coat and masked hypertension was estimated to be at 3% and 56%, respectively, with the office BP ≥ 130/80 mmHg and ABPM ≥ 125/75 mmHg thresholds[20].

In a recently published cross-sectional study with 205 KTRs[6], the prevalence of hypertension and the diagnostic performance of the two existing office BP thresholds for defining hypertension (adopted by the ESC/ESH and ACC/AHA guidelines mentioned above) was comparatively assessed. Prevalence of hypertension was 88.3% and 92.7% according to the ESC/ESH with ACC/AHA definitions for office BP measurements and 94.1% and 98.5% according to the respective ABPM thresholds. Moderate to fair agreement between office BP and 24-h ABPM was shown for both thresholds (κ-statistics = 0.52, P < 0.001; κ-statistics = 0.32, P < 0.001, respectively). Prevalence of white coat and masked hypertension was 6.7% and 39.5% using the office BP ≥ 140/90 mmHg and 5.9% and 31.7% using the office BP ≥ 130/80 mmHg threshold. Notably, ABPM revealed significantly lower control rates among hypertensive patients compared to office BP measurements using both definitions (69.6% for office *vs* 38.3% for ABPM measurements with the ESC/ESH thresholds; 43.7% *vs* 21.3% respectively with ACC/AHA thresholds).

In a sub-analysis of this study investigating presence of sex differences, the prevalence of hypertension was similar between the two genders with the office BP ≥ 130/80 mmHg threshold (93.4% for men *vs* 91.3% for women, P = 0.589) but significantly higher in men with the ABPM ≥ 125/75 criterion (100% *vs* 95.7%, P = 0.014, respectively). Prevalence of white-coat hypertension (5.1% *vs* 7.6%, P = 0.493) and masked hypertension (35.3% *vs* 24.2%, P = 0.113) did not differ significantly between men and women. The above findings underline the need for more extensive use of 24-h ABPM in KTRs, similarly to what is currently being increasingly recommended for the general population.

Association of hypertension with target organ damage

In KTRs, abnormal dipping status (non-dipping and reverse-dipping) independently predicts kidney function deterioration[21,22], while nighttime BP and night-day ratio are strongly associated with carotid-intimal media thickness[18]. Increased urinary albumin and protein excretion have been associated with hypertension in KTRs and are both independent predictors of graft loss[23-26]. Several longitudinal studies have reported an association of hypertension with left ventricular hypertrophy in KTRs, while significant reduction in left ventricular mass index (LVMI) and regression of left ventricular hypertrophy have been observed in the first 2-3 years following kidney transplantation[27,28]. However, this regression may be compromised by persistence of hypertension, high pulse pressure[27] and high sodium intake[28].

Moreover, reversal of uremic cardiomyopathy has been recently questioned according to the results of a recent meta-analysis where no difference in LVMI was detected following kidney transplantation after pooling data from four studies with 236 participants [standardized mean difference = 0.07, 95% confidence interval (CI): 0.41-0.26][29]. Masked or sustained hypertension were independent predictors for left ventricular hypertrophy in a cohort of 221 children and young adults with kidney transplant [30]. A negative association between brachial flow-mediated dilation, a marker of endothelial function, with 24-h BP and indices of BP variability has also been reported[31]. In a recently published meta-analysis pooling data from 22 studies (2078 participants), 24-h ABPM was found to be a stronger predictor of renal function decline and outperformed office BP with regards to LVMI, carotid-intimal media thickness and endothelial dysfunction markers[32]. Abnormal dipping status also identified a subgroup of KTRs at risk for target organ damage.

Prognostic impact of hypertension for adverse clinical outcomes

Hypertension in KTRs has been consistently shown to be associated with a higher incidence of kidney function decline, poor graft survival[33-38] and worse patient survival[3,34,38,39]. In the Collaborative Transplant Study, a retrospective cohort that evaluated the impact of hypertension on long-term kidney function in 29751 KTRs, a strong graded relationship between post-transplant BP and subsequent graft failure, even when patient death was censored, was reported for the first time[35]. In a subsequent sub-analysis of the Collaborative Transplant Study with data from 24404 patients, the same authors showed that SBP values consistently lower than 140 mmHg during the first 3 years post transplantation were associated with the best 10-year graft and patient outcomes; moreover successfully lowering SBP to ≤ 140 mmHg even by the 3rd year was associated with better 10-year graft and death-censored survival (but not with total patient survival) compared to persistently uncontrolled BP[3].

With regards to different causes of death, changes in SBP were significantly associated with the risk of cardiovascular death only in the subgroup of patients < 50-years-old but not in older KTRs. In another retrospective cohort of 1666 patients, each rise in SBP by 10 mmHg was associated with a 12% higher risk for graft failure [relative risk (RR) = 1.12, 95%CI: 1.08-1.15], a 17% higher risk for death-censored graft failure (RR = 1.17, 95%CI: 1.12-1.22) and an 18% higher risk for death (RR = 1.18, 95%CI: 1.12-1.23), even after adjusting for acute rejection and decreased kidney failure that were previously reported to trigger BP increases and therefore further supported the independent beneficial effect of BP control[34]. Microalbuminuria and macroalbuminuria, both markers of target organ damage associated with hypertension, have been similarly shown to be independent predictors of death compared to normoalbuminuria [odds ratio (OR) = 5.55, 95%CI: 2.43-12.66; OR = 4.12, 95%CI: 1.65-10.29, respectively] [25].

With regards to specific cardiovascular events in KTRs, their burden remains high; a fact that is partly attributed to accumulation of traditional cardiovascular risk factors[40]. In a French retrospective cohort of 17526 KTRs and 3288857 non-transplanted non-dialysis participants with a 5-year follow-up, an increased incidence of myocardial infarction in the former compared to the latter (5.8% *vs* 2.8%) was shown [hazard ratio (HR) = 1.45, 95%CI: 1.35-1.55][41]. KTRs experiencing an myocardial infarction were more likely to be hypertensive than their non-KTR counterparts (76.0% *vs* 48.1%, $P < 0.0001$). Hypertension is an independent predictor of death from ischemic heart disease and major ischemic heart events, with a reported increase by 20% in the risk for death from ischemic heart disease per 10 mmHg SBP increments, during a follow-up of 5 years[39].

PATHOPHYSIOLOGY OF HYPERTENSION IN KTRS

The underlying mechanisms for development of hypertension in KTR include: (1) Traditional risk factors; (2) Those that are associated with kidney function decline; and (3) Those that are related to the kidney transplantation procedure.

Traditional risk factors

Factors considered to be associated with an increased risk of hypertension in the general population, including age, male sex, smoking status, obesity, insulin resistance and syndrome of obstructive sleep apneas, are also present in patients undergoing kidney transplantation and may be aggravated, further contributing to new-onset or worsening hypertension[42-46].

Factors associated with impaired kidney function

The same risk factors that are present in CKD populations and that are inherent to kidney function decline are also applicable in KTRs. Among those, impaired homeostatic mechanisms handling sodium and water excretion are considered a hallmark of CKD, leading to extracellular volume accumulation, hypervolemia and increased BP[5,47]. Renal sodium retention may be worsened by the use of immunosuppressive regimens, mainly corticosteroids[48] and calcineurin inhibitors (CNIs)[49] as well as during episodes of acute rejection, probably indicating ischemic allograft damage[50]. Dysregulation of the renin-angiotensin-aldosterone system[51] and sympathetic nerve overactivity, driven in the early

post transplantation period by the native kidneys (since the graft is initially denervated before becoming later re-innervated[52]), also lead to increased peripheral vascular resistance and development of hypertension[5,53,54]. Increased arterial stiffness, endothelial dysfunction and imbalance between vasoconstrictive and vasodilating agents are also pertinent to CKD and further contribute to increased BP[55,56].

Factors associated with kidney transplantation

Immunosuppressive regimens: Most current protocols for prevention of transplant rejection include as maintenance therapy a combination of a CNI (cyclosporine or tacrolimus) with either a purine pathway inhibitor that subsequently blocks lymphocyte proliferation (mycophenolate mofetil or azathioprine) or a mammalian target of rapamycin inhibitor (everolimus or sirolimus), with or without corticosteroids [57]. While mycophenolate mofetil and mammalian target of rapamycin inhibitors are considered low risk agents, corticosteroids and CNIs potentially trigger hypertension and other major comorbidities in KTRs[58,57].

The burden of long-term corticosteroid exposure on corticosteroid-related adverse events and healthcare economic costs has been previously explored in the general population, as well as in KTRs, with prevalence of corticosteroid-induced hypertension estimated to exceed 30% of the total population [59] and hospitalization costs to be 2.2-fold higher in the steroid-maintenance group than in the steroid-free group 1-year post living-donor kidney transplantation[60]. According to the results of a meta-analysis (34 studies, 5637 patients), complete steroid avoidance or withdrawal reduces the risk of incident hypertension and diabetes with no significant effect on graft or patient survival[61]. The main cause of corticosteroid-induced hypertension is associated with partial activation of mineralocorticoid receptors by cortisol causing urinary sodium and water retention and therefore volume expansion[5]. This mechanism has been however called into question, and a similarly important role of glucocorticoid receptors in vascular smooth cells has been proposed[62], leading to an increase in peripheral vascular resistance through attenuation of vascular response to vasodilators (nitric oxide) and upregulation of the angiotensin II receptor[48].

The mechanisms of CNI-induced hypertension are multifactorial and involve impaired sodium and water excretion, upregulation of vasoconstrictive agents (prostaglandins, thromboxane, endothelin-1), downregulation of vasodilating prostaglandins and alterations in regulation of intracellular calcium ions, leading to vasoconstriction of afferent arteriole, a decrease in glomerular filtration rate (GFR) and an increase in peripheral vascular resistance[49,63-66]. Tacrolimus has been associated with a lower incidence of hypertension[67,68] but a higher risk for new-onset diabetes compared to cyclosporine[69, 70].

After complete withdrawal of CNIs was abandoned due to an increased risk of biopsy-proven acute rejection episodes[71], reduction of their dose was explored in an attempt to minimize their toxic effects. In an open-label RCT, 1645 KTRs were randomly allocated to receive standard-dose cyclosporine (target trough level 150-300 ng/mL for the first 3 mo; 100-200 ng/mL thereafter), low-dose cyclosporine (target trough level 50-100 ng/mL throughout the study), low-dose tacrolimus (target trough level 3-7 ng/mL throughout the study) or low-dose sirolimus (target trough level 4-8 ng/mL throughout the study) for 12 mo[72]. Patients in all treatment groups received mycophenolate mofetil and corticosteroids; those randomized to low-dose regimens followed a 2-mo induction treatment with daclizumab. At study-end, patients in the low-dose tacrolimus group had the highest estimated GFR (65.4 mL/min) and highest rates of allograft survival (94.2%), followed by low-dose cyclosporine (93.1%), standard-dose cyclosporine (89.3%) and low-dose sirolimus (89.3%) (P = 0.02), therefore providing further evidence in favor of low-dose tacrolimus regimens.

Accordingly, it is usually recommended to use minimal dosages of steroids (for example, 5 mg per day dose of prednisone) to achieve long-term immunosuppression in organ transplant patients without increasing the risk for hypertension[42]. Belatacept is another biologic immunosuppressive agent that acts by inhibiting T cell co-stimulation, approved by the United States Food and Drug Administration since 2011 on the basis of evidence of non-inferiority in preventing acute rejection in KTRs provided from three RCTs comparing belatacept to cyclosporine[69,73,74]. According to a meta-analysis (5 studies, 1535 participants), use of belatacept has been associated with lower BP levels and reduced incidence of chronic kidney scarring compared to CNIs[75].

Donor/recipient factors: Donor's age represents a major risk factor for development of post-transplant hypertension[23], along with considerable discrepancies in somatometric characteristics between donors and graft recipients (female to male transplantation, pediatric to adult transplantation, low donor/recipient body weight ratio), leading to a phenomenon of "underdosing" due to reduced donor nephron mass compared to recipient needs[76,77]. These differences result in hyperfiltration, glomerular hypertrophy and increased intraglomerular pressure.

Pre-existing donor hypertension is also associated with an increased risk for post transplantation hypertension and allograft dysfunction[23,78]. Transplant recipients from donors with a family history of hypertension face a 10-fold higher risk of requiring antihypertensive treatment compared to recipients from a normotensive family[79]. Recipients of transplants from expanded criteria donors (age > 60 or 50-59 with two of the following: History of hypertension; serum creatinine > 1.5 mg/dL;

cerebrovascular death) also experience a higher risk for hypertension post transplantation[80].

Other factors related to donors, predisposing to delayed graft function and increased nephrotoxicity, that could be possibly associated with development of hypertension in KTRs include the presence of genetic variants that affect the expression of cytochrome P450 3A5, apolipoprotein L1, P-glycoprotein and multidrug resistance protein 2[81-83]. With regards to recipient factors, the presence of native kidneys may further contribute to BP increments probably due to renin secretion[84]. Moreover, longstanding hypertension may be present in many recipients before transplantation, as progression of CKD is associated with atheromatosis of middle-sized conduit arteries and most importantly with reduced compliance and arterial stiffness of the aorta and the large arteries[85]. This vascular remodeling may not be fully reversible after kidney transplantation.

Transplant renal artery stenosis: Prevalence of transplant renal artery stenosis (TRAS) reportedly ranged in the past between 1%-23%, with a significant increase noted in diagnosed cases with the use of non-invasive imaging techniques[86]. Refractory hypertension and worsening kidney function are the main clinical manifestations of TRAS, which usually develops 3-24 mo post transplantation and is associated with an increased risk of graft loss[84].

With regards to the anatomic site, the stenosis can be: (1) Anastomotic (due to vascular damage at the time of surgery); (2) Proximal (due to recipient's atherosclerosis); and (3) Distal (with a non-fully elucidated pathogenesis related to mechanical and immunological factors)[87]. Since the recipient's iliac artery and not the abdominal aorta is the most common site of donor renal artery anastomosis, this connection between smaller arteries is prone to narrowing and subsequent development of TRAS pathophysiology, involving impediment of blood flow, renal hypoperfusion and activation of the renin-angiotensin-aldosterone system[84].

Immunological factors leading to TRAS include immune-mediated vascular endothelial injury[88] and development of *de novo* class II donor-specific antibodies[89]. The association between TRAS and cytomegalovirus infection[90], as well as ischemia/reperfusion injury, has also been reported[91]. In the absence of an RCT comparing endovascular angioplasty with or without stenting *vs* surgical vascularization in KTRs, angioplasty is the preferred treatment of TRAS with reported rates of clinical success (improvements in BP or kidney function) between 65.5%-94.0% and of technical success > 90%[92].

Acute and chronic kidney dysfunction: Kidney function decline, whether in the context of an episode of acute cellular and antibody rejection or due to chronic allograft nephropathy, has been associated with new or worsening hypertension, with the evidence of a cause-effect relationship still inconclusive [42,84,93,94]. Acute rejection may trigger new-onset hypertension, probably *via* activation of the renin-angiotensin system according to the patient's volume status. In this case, treatment of rejection is accompanied by improvement in BP levels, whereas hypertension that is not associated to acute rejection would be further deteriorated with modifications in doses of immunosuppression[94].

Recurrence of the primary glomerular disease, tubular atrophy, interstitial fibrosis, chronic antibody-mediated organ rejection, development of non-HLA agonistic anti-angiotensin-II type 1 receptor antibodies and thrombotic microangiopathy are the major contributors to chronic allograft injury leading to sudden rises of BP[5,84,94,95]. Patients with positive angiotensin-II type 1 receptor antibodies represent a subset of those with antibody-mediated rejection in whom kidney dysfunction is associated with malignant hypertension and acute vascular lesions on biopsy. A clinicopathological entity including seizures on top of malignant hypertension and vasculopathy has also been described, bearing resemblance to pre-eclamptic syndromes where angiotensin-II type 1 receptor antibodies have been previously reported[95].

HYPERTENSION TREATMENT IN KTRS

Targets of BP therapy

Historically, no universal agreement has been achieved with regards to BP targets in CKD and more particularly in kidney transplantation, similarly to the heterogeneity observed in different BP thresholds used for diagnosis of hypertension[7-11]. In the absence of specific focus on KTRs, the BP targets of CKD population were expected to be endorsed; according to the 2018 ESC/ESH guidelines in patients with CKD the respective recommendation was lowering BP to < 140/90 mmHg and towards 130/80 mmHg [10]. However in the latest 2017 ACC/AHA and 2021 Kidney Disease Improving Global Outcomes guidelines specific recommendations targeting BP less than 130/80 mmHg have been provided for KTRs[9,11].

Non-pharmacological measures

In the absence of evidence focused on KTRs, lifestyle modifications should be adopted as a first-line approach on the basis of recommendations applied in the general population since these interventions provide general health benefits that extend beyond BP control[96]. Low sodium intake (< 2 g/d), moderate-intensity physical activity (≥ 150 min/wk), adoption of a balanced diet and maintenance of

body mass index and waist circumference within normal range (18.5 and 24.9 kg/m^2 and < 102 cm, respectively), reduction in alcohol consumption and smoking cessation are encompassed by most hypertension guidelines[5,9-11,97].

Pharmacological measures

In CKD populations, use of an angiotensin-converting enzyme inhibitors (ACEi) or an angiotensin receptor blocker (ARB) has been established as first-line treatment, followed by combinations with a calcium channel blocker (CCB) and/or diuretic[98]. In KTRs, the use of a dihydropyridine CCB is commonly advocated notably in the early post transplantation period because of their demonstrated efficacy in improving graft function and minimizing the vasoconstrictive effects of CNIs[15,93,99]. To support this choice, CCBs have been uniformly associated with improved patient and graft outcomes in several studies[99-103]. In contrast, the use of ACEis/ARBs in KTRs was considered a source of controversy for many years[4]. Treatment with an ACEi/ARB led to impressively better patient (HR = 0.57; 95%CI: 0.40-0.81) and graft (HR = 0.56; 95%CI: 0.40-0.78) survival rates in a retrospective cohort with 2031 KTRs[104] but not in a subsequent analysis of data from 17208 KTRs[105].

According to the results of an RCT with 154 hypertensive KTRs allocated to receive nifedipine 30 mg or lisinopril 10 mg 3 wk post transplantation, no differences were noted in BP control. Nevertheless, a significant increase was observed in measured GFR for nifedipine compared to lisinopril (mean between-group difference 9.6 mL/min, 95%CI: 5.5-13.7 mL/min) at 1 year, an improvement that was maintained at 2 years[106]. The results of a 2009 Cochrane systematic review claimed that patients receiving ACEis were exposed to a higher risk of hyperkalemia and anemia and that in direct comparison with CCBs their use was associated with worse kidney function (mean between-group difference for estimated GFR -11.48 mL/min, 95%CI: -15.75 to -7.21).

Data on graft loss were available from only one study showing no significant differences (RR = 7.37, 95%CI: 0.39-140.35)[100]. Among the main limitations of this meta-analysis was the fact that data for head-to-head comparisons were pooled from six studies with only 296 participants; four of them had a follow-up between 4 wk and 6 mo[25,107-109], two of them were published after the year 2000[25,106], and no one compared ARBs to CCBs directly. In a more recent meta-analysis conducted by Pisano *et al* [99] pooling data from 71 RCTs and providing evidence on both ACEis and ARBs, a significant reduction in the risk for graft loss was observed by 42% with CCBs (16 studies, 1327 participants) and by 38% with ACEi/ARBs (9 studies, 1246 participants).

When pooling results from head-to-head comparisons between CCBs and ACEis/ARBs, an increase in GFR (11.07 mL/min, 95%CI: 6.04-16.09) was noted for CCBs, along with a reduction in serum potassium levels (-0.24 mEq/L, 95%CI: -0.38 to -0.10). In the 2021 Kidney Disease Improving Global Outcomes guidelines, use of a dihydropyridine CCB or an ARB has received a grade 1C recommendation for first-line treatment in KTRs, with potential benefits on graft survival (RR for graft loss compared to placebo: Dihydropyridine CCBs 0.62, 95%CI: 0.43-0.90; ARBs: 0.35, 95%CI: 0.15-0.84) outweighing side effects related to each class of agent[11]. No significant effect on mortality or cardiovascular events was detected with either of these classes.

CONCLUSION

The accurate diagnosis of hypertension and adequate BP control in KTRs remains an area of controversy among different guidelines, with BP thresholds and treatment goals mostly extrapolated from CKD populations. The diagnostic performance of office measurements has been recently questioned, with more recent studies using ABPM suggesting a higher prevalence of uncontrolled, masked and nocturnal hypertension in KTRs than previously believed that is further increased when the new lower BP thresholds are applied. Recent analyses provide evidence that 24-h ABPM outperforms office BP measurements with regards to markers of target organ damage, including LVMI, carotid-intimal media thickness and flow-mediated dilation, and represents an independent predictor of kidney function decline and graft loss.

Except from pre-existing or *de novo* traditional risk factors and factors associated with CKD, immunosuppressive drugs, donor-recipient mismatches, TRAS, recurrence of primary glomerular disease, presence of native kidneys as well as episodes of acute and chronic allograft injury contribute to development of hypertension post transplantation. Recent guidelines recommend the use of dihydropyridine CCBs[15], as they exhibit a favorable profile due to their vasodilatory effects counteracting vasoconstriction induced by CNIs and their favorable effects on outcomes, or ARBs due to their favorable effects on graft survival, despite previously reported undesirable effects on risk of hyperkalemia and anemia. High-quality large-scale RCTs comparatively assessing the effect of different antihypertensive agents on mortality and major cardiovascular events are warranted to provide definite evidence.

FOOTNOTES

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MINIREVIEWS

Acute kidney injury and the compensation of kidney function after nephrectomy in living donation

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Abstract

Acute kidney injury (AKI) incidence is growing rapidly, and AKI is one of the predictors of inpatient mortality. After nephrectomy, all the patients have decreased kidney function with AKI and recover from AKI. However, the characteristic and behavior of AKI is different from usual AKI and compensatory kidney function has been well known in the postoperative setting, especially in living donors. In this review, we have focused on the compensation of kidney function after nephrectomy in living donors. We discuss factors that have been identified as being associated with kidney recovery in donors including age, sex, body mass index, remnant kidney volume, estimated glomerular filtration rate, and various comorbidities.

Key Words: Acute kidney injury; Kidney transplant donor; Compensation; Kidney function

Core Tip: Acute kidney injury (AKI) incidence is growing rapidly, and AKI is one of the predictors of inpatient mortality. The characteristic and behavior of AKI is different from usual AKI and compensatory kidney function has been well known in the postoperative setting, especially in living donors. In this review, we have focused on the compensation of kidney function after nephrectomy in living donors. We discuss factors of compensation of kidney function after nephrectomy.

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INTRODUCTION

The incidence of acute kidney injury (AKI) is growing rapidly in many situations[1]. Despite advances in medical care, AKI remains an independent predictor of in-hospital mortality[2]. While the nature of kidney is the organ to recover, it is well established that AKI, especially when severe, is a risk factor for incident and progressive chronic kidney disease (CKD) and eventually leading to progressive nephron loss and end-stage renal disease (ESRD)[3,4].

Kidney transplantation has been considered a preferred treatment for patients with ESRD and offers a better quality of life than dialysis[5,6]. While a previous study showed that showed that living donation of kidney is safe in a large cohort, nephrectomy is a major procedure which is associated with potential risks for the donor, including increased cardio-vascular risks and progression to ESRD in the long-term [7]. After donation of the kidney, it has been well known that all patients have hemodynamic changes associated with AKI and have compensated kidney function with the contralateral kidney after donation[6,8-12]. The degree of contralateral kidney function has been reported to be around 60%-70 % on average in previous studies[13,14], however, the degree of compensatory kidney function varies in each donor. In this review, we have discussed the topics related to the clinical factors of compensation and the mechanism of recovery after kidney donation.

CLINICAL FACTORS

Many variables are involved in the clinical settings for kidney recovery after kidney donation (Table 1, Figure 1). Age is one of the significant factors which affects the extent of recovery. Younger age is associated with favorable outcomes in many studies[6,8,15-19] and this is supported by the facts that aging is associated with underlying abnormalities and structural changes such as nephrosclerosis and nephron hypertrophy[16]. The rate of glomerular density has an inverse correlation with aging[20]. The number of nephrons decreases with aging and affects the function of the kidney[20]. Denic *et al*[21] investigated the risk factors associated with kidney abnormalities, and they demonstrated that mild hypertension and aging are associated with underlying abnormalities. They showed the changes of the volumes of kidney, cortex and medulla in living kidney donors[22].

Hypertension is also one of the significant factors which affect the extent of recovery in kidney function[6]. It is known that prevalence of hypertension increases with age. Hypertension was previously regarded as contraindication for living kidney donation, however, living donor donation was reported to be safe if hypertension is under controlled with medication[22]. On understanding of kidney aging, kidney function in people with advanced age have less reserve when they tend to develop CKD and have also higher risk of AKI[23]. As people get old, the prevalence of hypertension also increases, and glomerular hypertrophy has been identified as an integral feature of hypertensive nephropathy and seems to precede rather than to compensate for glomerulosclerosis[24].

Gender is another significant factor for kidney compensation and prognosis. Male gender is associated with poor prognosis in kidney donation[6,8,15], however, this is controversial since many studies showed that gender did not reach to conclusion as one of the independent factors[17,25,26]. This might be more related to the fact that male gender has a higher rate of smoking, which is one of the factors affecting the kidney function and is associated with hypertension.

Metabolic syndrome has been defined by the National Cholesterol Education Program Adult Treatment Panel III if three or more of the following five criteria are met: Waist circumference over 40 inches (men) or 35 inches (women); blood pressure over 130/85 mmHg; fasting triglyceride level over 150 mg/dL; fasting high-density lipoprotein cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women); fasting blood sugar over 100 mg/dL[27]. Metabolic syndrome has been shown to have a negative impact on remnant kidney function after nephrectomy since metabolic syndrome is associated with a high incidence of hypertension, obesity, hyperglycemia, and hyperuricemia[17,28,29].

The impact of serum uric acid level has been an emerging topic on the residual kidney function in living kidney donors. The total 4650 living-donor cohort study showed that donors with post-donation gout had higher risk of developing AKI and progression to CKD[30]. Other living-donor studies from Turkey and Korea also suggested that preoperative hyperuricemia are associated with impaired postoperative renal function at 6 and 12 mo[31-33]. It was also reported that preoperative hyperuricemia was strongly associated with suboptimal renal compensatory function or recovery at one year after renal donation[34]. Furthermore, hyperuricemia had 1.76-fold higher adjusted risk of adverse events

Table 1 Clinical factors associated with kidney recovery in living donors

Ref.	Significant factors		
Ohashi *et al*[17]	Age	Presence of metabolic syndrome	Chronic histological changes
Ibrahim *et al*[8]	Age	Sex	BMI
Rook *et al*[11]	Age	BMI	
Denic *et al*[21]	Age	HTN	
Shiraishi *et al*[15]	Age	Sex	BMI
	HTN		
Nishida *et al*[34]	Hyperuricemia	Chronic histological changes	
Yakoubi *et al*[25]	Age	BSA adjusted RKV	Preoperative eGFR
Shinoda *et al*[26]	BMI	RKV/BSA	
Okumura *et al*[6]	Age	Sex	History of HTN
	RKV/Wt		
Zabor *et al*[18]	Age	Sex	History of HTN
Lee *et al*[19]	Age	Sex	History of HTN
	BMI	History of DM	Preoperative eGFR
	RKV		
Vaz *et al*[42]	Age	Sex	

BMI: Body mass index; HTN: Hypertension; BSA: Body surface area; RKV: Remnant kidney volume; eGFR: Estimated glomerular filtration rate; CrCl: Creatinine clearance; mGFR: Measured glomerular filtration rate; Wt: Weight; DM: Diabetes.

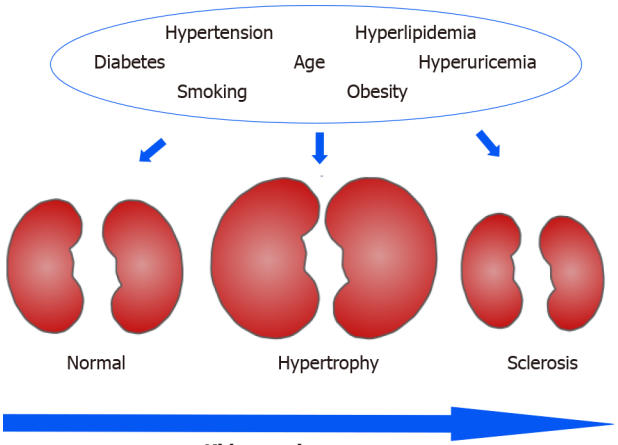

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Figure 1 Clinical factors associated with kidney compensation.

within 5 years after donation, such as cardiovascular events, initiation of dialysis, and *de novo* prescriptions for hypertension, hyperuricemia, diabetes, and dyslipidemia as well as lower estimated glomerular filtration rate (eGFR)[35].

The size of kidney is one of the important factors affecting the donor/recipient outcomes in kidney transplantation[36,37]. Since larger size of the kidney is associated with better renal function, it is recommended to choose the smaller kidney for donation to fulfil the principle of leaving the "better" kidney in donor if there is a more than 10% volume difference between kidneys in donor. The reasons to select suboptimal side of kidneys in donation, were cysts or tumors (46.5%), arterial abnormalities (22.7%), inferior size or function (19.8%), and anatomic abnormalities (11.0%), and those kidneys showed worse long-term overall graft survival regardless of the reasons[38].

Remnant kidney volume (RKV) in living donor is one of the important factors to determine the kidney recovery after donor nephrectomy[6,19]. Shinoda *et al*[26] showed the ratio of RKV to body

surface area (BSA) ratio has an independent factor to predict renal function or compensation after kidney donation. Yakoubi *et al*[25] also showed BSA adjusted with RKV was an independent predictor of kidney recovery after donation. With respect to recipient outcomes, the ratio of donated kidney volume to body weight (Wt) has been suggested as an important factor related to allograft function[39].

The ratio of RKV to Wt (RKV/Wt) was reported to be one of the significant associated factors in eGFR at 1 year after kidney donation[6]. Although it has been thought that a lower RKV/Wt can cause hyperfiltration and subsequent proteinuria[40], Song *et al*[41] suggested that a ratio of RKV/Wt less than 2.0 mL/kg did not affect the eGFR in donors but was associated with more severe proteinuria at 1 year after donor nephrectomy. There was no significant difference in the RKV/Wt ratio in the study [41], but they suggested the "deterioration" of kidney function since the donors were associated with presence of proteinuria at 1 year after donation. Thus, a lower RKV/Wt ratio might be associated with hyperfiltration and subsequently decrease "renal reserve".

Laterality of the donated kidney is another factor to evaluate when considering donor and recipient outcomes in kidney transplantation. Vaz *et al*[42] studied the outcomes of hand assisted laparoscopic donor nephrectomy (HALDN) of the left and the right kidney among 739 donors. This study concluded that, although most transplant centers and surgeons prefer performing left nephrectomies because of having a longer vein, right HALDN nephrectomy is a safe procedure with similar outcomes to left HALDN. Gunseren *et al*[43] compared right and left side laparoscopic donor nephrectomy outcomes and found that they had similar intraoperative outcomes. These authors noted, however, that dissection of lymphatic structures during left laparoscopic donor nephrectomy may cause chylous drainage and prolong hospitalization time compared to right-sided nephrectomy. Zeuschner *et al*[44] evaluated left and right pure laparoscopic donor nephrectomies and found a higher rate of complications for recipients of right grafts, but long-term function and graft survival were equivalent.

PATHOLOGICAL CHANGES OF NEPHRECTOMY

After the nephrectomy, the compensation of contralateral kidney function has been well known. Immediately after nephrectomy, an approximately 40% increase in renal plasma flow and glomerular filtration rate is measured in the remaining kidney[9,45]. This leads to developing glomerular hypertension and increased single-nephron filtration with compensatory glomerulomegaly. The glomerulomegaly from hyperfiltration also occurs in response to nephron loss. In addition to glomerulomegaly, hyperfiltration leads to tubular hypertrophy and hyperplasia. Prolonged hyperfiltration and glomerular hypertension causes glomerular sclerosis and decreased glomerular density (Figure 2).

Once glomerular size reaches a certain threshold, glomerularsclerosis, hypertension, proteinuria, and renal failure may develop[46]. This pathological process was associated with kidney function, blood pressure and metabolic conditions: Metabolic syndrome, hypertension, hyperglycemia and hyperuricemia[17,20,34,47,48]. However, these histological changes might not always be seen in donors since donors were in a relatively good state of health and the unaffected nephrons would respond with compensation[48]. Studies showed that donors who had hyperuricemia, had chronic histological changes such as intestinal fibrosis, tubular atrophy and arterial hyalinosis in the donated kidney[34]. Intestinal fibrosis and tubular atrophy have significant impacts on long term graft function[49]. It is thought that arteriosclerosis has a significant relationship with intestinal fibrosis and tubular atrophy since the chronic ischemic condition caused by arteriosclerosis induces histological changes such as intestinal fibrosis, tubular atrophy and glomerular sclerosis[50].

Rule *et al*[20] showed that increased GFR, body mass index and uric acid level and a family history of end stage renal disease were independent predictors of decreased glomerular density. The size of individual nephrons can reflect important elements of metabolic regulation. After living kidney donation, donors can develop glomerular hypertension and increased single-nephron filtration with compensatory glomerulomegaly[51-53]. Polichnowski *et al*[54] showed that contralateral nephrectomy is associated with kidney recovery from ischemic kidney injury and prevent tissue atrophy with capillary repair and tubule redifferentiation. This result supports that remnant kidney is not vulnerable but sustainable after kidney donation. However, we emphasize that the best strategy for AKI is prevention. It is rare to perform living donation in the setting of AKI, however, in deceased donors, Cima *et al*[55] reported that kidney transplant could be performed from donors with AKI depending on the histological grading score with glomerulosclerosis, tubular atrophy, intestinal fibrosis, vascular damage and acute tubular necrosis[55,56].

MOLECULAR CHANGES OF NEPHRECTOMY

At present, the specific mechanism after nephrectomy remain unclear. However, several hypotheses have been proposed and it has shown that endothelial injury and recovery have an important role in the pathogenesis of kidney injury[57]. As discussed above, renal blood flow and GFR significantly increased after nephrectomy. This has been a critical role of upstream factors responsible to recruit dormant

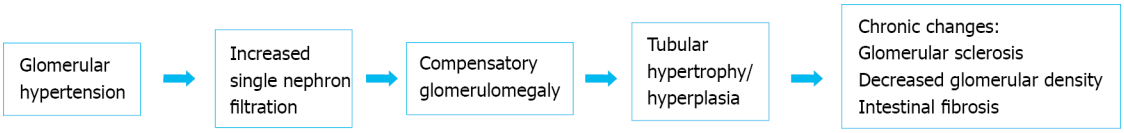

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Figure 2 Changes in kidney after nephrectomy.

nephrons and subsequently to improve in GFR. As renal blood flow increases and renal glomerular filtrate rate increases, it would lead to increase oxygen consumption and cause tissue hypoxia. It induces hypoxia-inducible factor 1 alpha and induces vascular endothelial growth factor. Hypoxia also induces phosphatase and tension homolog in tubules which causes tubule redifferentiation and repair [54].

In another way, renal tubular epithelial cells, which are surviving from ischemic injury, undergo differentiation[58]. These surviving epithelial cells express vimentin (an intermediate filament protein, which is found in undifferentiated mesenchymal cells but not in differentiated kidney cells), and proliferating cells nuclear antigen (a marker of mitogenesis), in contrast, damaged cells do not express either vimentin or proliferating cell nuclear antigen[59]. The molecular drivers in the process of intrinsic repair remain indeterminate, but the transcription factor Sox9 has been shown to be a critical part of the cellular repairing pathway in surviving renal tubular epithelial cells[60].

Oliver *et al*[60] reported that there are renal specific stem cells, which have been identified in the renal tubules as well as the papilla, however, the contribution of these cells still remains under investigation. Many recent studies have looked into the progenitor cell or bone marrow derived mesenchymal stem cells in renal repair[61]. The mesenchymal stem cell, which are derived from renal specific or bone marrow, may accelerate the process of repairing the injured tubules by direct proliferation or through paracrine effects. In transplant kidney, some studies suggest that the recipient derived cells may repopulate injured tubule[62,63], however, mesenchymal stem cells may predominantly play a role in their beneficial effects *via* paracrine mechanisms[64]. The mesenchymal stem cells may release microvesicles to communicate between cells and protect renal injury in addition to releasing cytokines [65].

CONCLUSION

We have performed living donor kidney transplant safely, however, a large cohort study showed that being a donor increased cardiovascular risk and progression to ESRD in the long term[7]. Since the degree of recovery from AKI affects the prognosis of kidney function[66], we believe that it is important to identify the risk of patients without compensation of kidney function of the contralateral kidney to predict the long term risk.

FOOTNOTES

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MINIREVIEWS

Kidney disease in non-kidney solid organ transplantation

Kurtis J Swanson

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Abstract

Kidney disease after non-kidney solid organ transplantation (NKSOT) is a common post-transplant complication associated with deleterious outcomes. Kidney disease, both acute kidney injury and chronic kidney disease (CKD) alike, emanates from multifactorial, summative pre-, peri- and post-transplant events. Several factors leading to kidney disease are shared amongst solid organ transplantation in addition to distinct mechanisms unique to individual transplant types. The aim of this review is to summarize the current literature describing kidney disease in NKSOT. We conducted a narrative review of pertinent studies on the subject, limiting our search to full text studies in the English language. Kidney disease after NKSOT is prevalent, particularly in intestinal and lung transplantation. Management strategies in the peri-operative and post-transplant periods including proteinuria management, calcineurin-inhibitor minimization/sparing approaches, and nephrology referral can counteract CKD progression and/or aid in subsequent kidney after solid organ transplantation. Kidney disease after NKSOT is an important consideration in organ allocation practices, ethics of transplantation. Kidney disease after SOT is an incipient condition demanding further inquiry. While some truths have been revealed about this chronic disease, as we have aimed to describe in this review, continued multidisciplinary efforts are needed more than ever to combat this threat to patient and allograft survival.

Key Words: Acute kidney injury; Chronic kidney disease; Solid organ transplant; Native kidneys; Calcineurin inhibitor toxicity; Renal replacement therapy; Kidney after solid organ transplant

Core Tip: Kidney disease in the non-kidney solid organ transplant population occurs at significantly higher rate than the general population. Pre-transplant morbidity as well as peri-/post-transplant events contribute to this prevalence. Management strategies throughout the journey of non-renal solid organ transplantation are being studied, including transplantation after native kidney failure to help offset the morbidity/mortality of chronic kidney disease and maximize the benefit of non-kidney solid organ transplantation.

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INTRODUCTION

Chronic kidney disease (CKD), most commonly defined as decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 or markers of kidney damage persistent at least 90 d per Kidney Disease Improving Global Outcomes (KDIGO) criteria, is a frequently observed post-transplant complication for non-kidney solid organ transplantation (NKSOT) recipients and is associated with adverse outcomes[1-3]. While quantifying the prevalence of CKD in any population is daunting, several studies have noted an incidence of CKD in NKSOT ranging between 6%-21%[2,3]. Notably, this is derived *via* CKD definition as GFR < 30 mL/min/1.73 m^2. In one study of liver transplant recipients, approximately 57% had a GFR between 30-59 mL/min/1.73 m^2[2,3]. This is compared to the estimated CKD rate of 15% in the general population[1].

Intuitively, end-organ disease compelling transplantation often leads to impaired kidney function, stemming from recurrent acute kidney injury (AKI) and subsequent CKD. Furthermore, the post-transplant milieu portends CKD through injurious transient and persistent insults, leading to the well described disproportionately high burden of kidney disease in SOT recipients[2-4]. The goal of this review is to condense the current literature in this field to: (1) Illustrate the scope of the problem; (2) Examine mechanisms leading to CKD in this population; and (3) Identify potentially modifiable risk factors and discuss management/treatment of CKD after NKSOT. In the following sections, we will discuss common factors driving AKI and CKD and then describe kidney disease after NKSOT in the following distinct contexts: Pancreas, liver, heart, lung, and intestinal transplantation.

KEY DEFINITIONS

AKI

While several definitions exist, we will use those endorsed by the KDIGO work group whereby AKI is defined as at least a 0.3 mg/dL increase in creatinine within 48 h or at least 1.5-1.9 times baseline increase in creatinine within 1 wk or decrease in urine output of at least 0.5 mL/kg/h for at least 6 h[1].

CKD

As in AKI, KDIGO has defined CKD, which is identified by markers of kidney damage, estimated GFR (eGFR) < 60 mL/min/1.73 m^2, and degree of albuminuria given the well described relationship between proteinuric kidney disease and CKD progression[1]. Unless otherwise stated, we will use these criteria to define CKD.

SCOPE OF CKD AFTER NKSOT

How common is CKD after NKSOT? This is an important question many have sought to answer given the well documented deleterious impact CKD has on cardiovascular and survival outcomes[2]. As described by Bloom *et al*[3] in their landmark review, historically varied CKD definitions as well as the reliance of estimating equations based on serum creatinine (SCr), of which their distinct strengths/weaknesses/limitations has made the assessment of CKD prevalence enigmatic at best. An oft-cited key study by Ojo *et al*[2] notes the following rates of 5-year post-transplant CKD: 21.3% among intestinal transplant (IT) recipients, 18.1% among liver transplant recipients, 15.8% among lung transplant recipients, 10.9% among heart transplant recipients, and 6.9% among heart-lung transplant recipients. Whereas this study offers a reference point, they utilized a stringent definition of CKD [GFR < 30 mL/min per 1.73 m^2, *via* four variable Modification of Diet in Renal Disease Study (MDRD)

equation]. While such conservative criteria lead to underestimation of CKD prevalence (as most patients with CKD fall in the eGFR 30-60 mL/min/1.73 m^2 range), shared patient characteristics of low muscle mass/malnutrition accentuate the already flawed estimating creatinine-based equations. Moreover, the paucity of proteinuria measurements performed clinically and/or analyzed in studies is a major contributor to the underestimation of CKD in NKSOT recipients.

Several studies have helped improve our understanding of CKD prevalence in NKSOT recipients which will be highlighted below. In their recent study, Shaffi *et al*[5] compared 26 eGFR equations in NKSOT recipients [*n* = 3622, including recipients of kidney (53%), liver (35%), and other or multiple organs (12%)] to measured GFR (mGFR) either *via* urinary iothalamate clearance or plasma iohexol clearance. They found that the proportion of absolute percent error < 30% (P_{30}) and mean absolute error for the CKD Epidemiology Collaboration equation (CKD-EPI) and the MDRD Study equations were 78.9% [99.6%, 95% confidence interval (CI): 76.9%-80.8%] for both and 10.6 (99.6%, 95%CI: 10.1-11.1) *vs* 11.0 (99.6%, 95%CI: 10.5-11.5) mL/min/1.73 m^2. Compared to the other 24 estimating eGFR equations the authors examined, the CKD-EPI and MDRD equations were significantly more accurate ($P < 0.001$). In their study examining 1135 pancreas transplant alone (PTA) recipients in Scientific Registry of Transplant Recipients (SRTR), Kim *et al*[6] observed that about 25% of the cohort had an eGFR below 61.3 mL/min/1.73 m^2. Gonwa *et al*[7] *via* prospective study serially measuring iothalamate clearance in 1447 liver transplant recipients observed the following: At 3 mo, 1 year, and 5 years post-transplant, the mean mGFR was 59.5 ± 27.1 mL/min, 62.7 ± 27.8 mL/min, and 55.3 ± 26.1 mL/min. Interestingly, the mean mGFR at the time of initial evaluation was 90.7 ± 40.5 mL/min. In their analysis of risk factors for CKD after heart transplantation, Hamour *et al*[8] observed that CKD post-heart transplant is common, noting probabilities of eGFR < 45 mL/min/1.73 m^2 were the following: 45% at year 1, 71% at year 5 and 83% at year 10. In their review which included 186 lung transplant recipients, Ishani *et al*[9] showed that CKD was commonly observed at 1 year post transplant and progressed henceforth: From a mean pre-transplant SCr of 0.88 ± 0.19 mg/dL to 1.22 ± 0.82 mg/dL at one month 1.67 ± 0.88 mg/dL at 12 mo and to 1.98 ± 1.1 mg/dL at three years post-transplant. Kidney disease after NSKOT appears to be common, progressive and is likely substantially underestimated due to patient factors as well as understated albuminuria.

MECHANISMS LEADING TO CKD IN NON-KIDNEY SOT

Across NSKOT, both shared and organ-specific factors give rise to CKD onset and progression. Comorbidities directly related to primary end-organ failure *e.g.*, diabetes mellitus, liver failure, heart failure, lung failure in addition to common baseline demographic characteristics (advancing age, female gender, diabetes mellitus, hypertension, hepatitis C virus infection, drug-induced nephrotoxicity) as well as transplant specific factors, namely perioperative AKI, as well as calcineurin inhibitor (CNI) use, all contribute to the development of CKD[2-4].

The perioperative setting is a crucial shared risk factor impacting kidney function both short and long term. Hypotension, hypoperfusion, fluid shifts, nephrotoxic agents, sepsis in the perioperative period all spur AKI[3,10]. In a fashion similar to pre-transplant organ dysfunction leading to kidney impairment, marginal allograft function begets renal decompensation and vice versa[3,10]. CNI use and its impact on renal function after NKSOT is a controversial topic. While CNI use is an oft-implicated cited reason for post SOT kidney disease, it does not tell the entire story[10]. In a recent study, Ojo *et al*[10] noted that CNI use constitutes the majority of histologic lesions observed on kidney biopsy, ranging from between 46%-60% of cases. Non-CNI related pathology, as illustrated in their description of orthotopic heart and liver transplant recipients in their cited figures, is also an important player and has been observed in 27%-40% of kidney biopsies. Importantly, histologic findings must be interpreted cautiously as these biopsies were subject to having multiple concurrent histologic patterns.

Kubal *et al*[11] expounded on this, conducting their own histologic study of 62 nonrenal SOT recipients with kidney biopsies, where they showed that only 35.5% (*n* = 22) of those biopsied had predominant features consistent with chronic CNI toxicity. Hypertensive nephropathy [43.5% (*n* = 27)], not without its own disputes, was the most common diagnosis. Nearly 20% (*n* = 12) of the cohort had biopsies showing alternative pathology including acute tubular necrosis (*n* = 5), mesangioproliferative glomerulonephritis (*n* = 2), diabetic nephropathy (*n* = 1), post infectious glomerulonephritis (*n* = 1), and membranous nephropathy (*n* = 1)[11].

In a recent review, Wiseman[12], as adapted from Schwarz *et al*[13], describes the clinical characteristics and histology of biopsy proven kidney disease after liver, lung and heart transplantation. Of note, primary glomerulonephritis was 26% in liver transplant recipients and acute tubular injury were the most commonly observed histologic patterns in lung and heart recipients. In addition to shared mechanisms leading to CKD, distinct factors inherent to the various subtypes of organ transplant exist. These have been suitably defined in the literature and will be discussed in the following sections[10]. Though SOT recipients may recover from these early post-transplant kidney perturbations, often AKI, irrespective of renal replacement therapy (RRT) need, in addition to a "pro-nephrotoxic" environment with ongoing insults (post-transplant diabetes, hypertension, hyperlipidemia, CNI use, transplant organ

dysfunction, cardiovascular disease, infection, malignancy) in addition to pre-existing kidney dysfunction contribute to progressive CKD[2,3,14,15].

KIDNEY DISEASE AFTER PANCREAS TRANSPLANTATION

PTA is a novel transplant option for non-uremic diabetic patients. Interestingly, there is evidence that PTA may be renoprotective *via* proteinuria reduction and reversal of diabetic kidney lesions[16,17]. Despite this, kidney disease often progresses for PTA recipients. The following studies detail some of the contributing factors leading to kidney disease.

Kim *et al*[6], in their study examining 1135 adult PTA recipients, showed that kidney function prior to transplantation is a strong predictor of end stage kidney disease (ESKD): PTA recipients with pre-transplant eGFR < 60 and 60-89.9 mL/min/1.73 m^2 were 7.74 (95%CI: 4.37-13.74) and 3.25 (95%CI: 1.77-5.97) times more likely to develop ESKD than patients with eGFR ≥ 90 mL/min/1.73 m^2. Smail *et al*[18] also found that a pre-transplant eGFR < 60mL/min/1.73 m^2 was associated with an end stage renal disease (ESRD) incidence at 1, 3, 5 years of 0%, 28.6% and 61.9% compared to those with an eGFR > 60 mL/min/1.73 m^2 (P = 0.006). Younger age, female sex, and duration of diabetes predicted the development of ESRD (all P < 0.05). However, there was no difference in patient survival based on pre-transplant eGFR (P = 0.73). Gruessner *et al*[19] examined 513 PTAs transplanted from 1966 to 2006. They observed a 5 year post-transplant ESKD rate of 13% and found that SCr > 1.5 mg/dL at time of transplant and age < 30 predicted kidney failure. Odorico *et al*[20] performed a retrospective analysis comparing PTA recipients (n = 27) and pancreas after kidney transplant (PSK) recipients (n = 61) to assess changes in kidney function. They observed that pre-transplant eGFR < 60 mL/min/1.73 m^2 was associated with CKD progression. Fascinatingly, 67% PTA patients showed an increase (> 10%) in their SCr from baseline *vs* 34% PAK patients (P = 0.035). PTA transplant was considered mildly protective in terms of progression of CKD, though this finding was not significant [hazard ratio (HR) = 0.29, 95%CI: 0.04-2.37, P = 0.182). Chatzizacharias *et al*[21] in their risk analysis of progression to kidney failure after pancreas transplant found that tacrolimus levels > 12 mg/dL at 6 mo post-transplant were associated with declining kidney function (HR = 14.3, 95%CI: 1.3-161, P = 0.03). Surprisingly, pre-transplant proteinuria (urine protein creatinine ratio > 100 mg/mmol) and low eGFR, which they defined as ≤ 45 and ≤ 40 mL/min/1.73 m^2, were not significantly associated with worsening CKD. Marchetti *et al*[22] in their inquiry of 28 PTA recipients observed stable native kidney function comparing pre-transplant to post-transplant (0.95 ± 0.2 *vs* 0.96 ± 0.22, P > 0.05). However, this follow up was only at 3 mo post-transplant. Coppelli *et al*[17] showed that at 1 year follow up, 32 PTA recipients did not have significantly different creatinine pre-and post-transplant (0.95 ± 0.25 mg/dL *vs* 1.00 ± 0.19 mg/dL, P > 0.05). They observed improvement in lipid levels, blood pressure as well as albuminuria. Genzini *et al*[23] in their single center retrospective review followed 45 PTA recipients. After stratifying by 24 h creatinine clearance (CrCl) post PTA [group 1 = CrCl ≤ 70 mL/min; (n = 20); group 2 = CrCl > 70; (n = 25)], they observed significant decreases in native kidney function at 1 year in both groups (group 1 CrCl pre- *vs* post-transplantation = 57.3 ± 9 *vs* 34.8 ± 32 mL/min, P = 0.003); (group 2 CrCl pre- *vs* post-transplantation = 107.1 ± 25 *vs* 81.0 ± 23 mL/min, P = 0.008). In group 1, 10/20 patients (50%) ended up with a CrCl < 30 mL/min, 5/20 (25%) initiated on hemodialysis, and 3/20 (15%) underwent kidney after pancreas transplantation. No patients in group 2 ended up with significantly decreased kidney function. Scalea *et al*[24] looked at PTA recipients over 14 years retrospectively and saw that 88% of patients had eGFR decrease with a mean decrement of 32.1 mg/min/1.73 m^2. Mean eGFR pre-transplantation was 88.9 *vs* 55.6 post-transplantation (P < 0.0001) with mean follow-up of 3.68 years. Donor demographics, immunosuppression, human leukocyte antigen mismatch were not significantly associated with progressive CKD in their analysis.

Studies on kidney function after PTA are limited in terms of sample size and duration of follow up. However, it would appear that the presence of pre-transplant CKD with eGFR < 60 mL/min/1.73 m^2 tends to associate with cumulative CKD. While more robust studies are needed to better characterize kidney function in this population, it would appear that pre-transplant native kidney function is an important predictor of progressive CKD for pancreas transplant recipients and ought to inform organ allocation practices as well as evaluation for kidney after pancreas transplantation. These results are summarized in Table 1.

KIDNEY DISEASE AFTER LIVER TRANSPLANTATION

Kidney disease is common for patients with liver failure, due to hemodynamic changes associated with portal hypertension as well as disease processes impacting both organs *e.g.*, viral hepatitis, hepatorenal syndrome, secondary immunoglobulin A nephropathy, oxalosis[2,3]. Although hepatitis C as a primary diagnosis of liver failure is declining, as described by the Organ Procurement Transplant Network/SRTR (OPTN/SRTR) 2019 annual data report, it still constitutes 12.6% of liver registrations [25]. In addition to its associations with glomerulonephritis, hepatitis C has been shown to increase the

Table 1 Kidney disease after pancreas transplant alone

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Kim *et al*[6]	1135	Pre-transplant eGFR < 60 mL/min/1.73 m^2. Pre-transplant eGFR 60-89.9 mL/min/1.73 m^2	PTA recipients with pre-transplant eGFR < 60 and 60-89.9 mL/min/1.73 m^2 were 7.74 (95%CI: 4.37-13.74) and 3.25 (95%CI: 1.77-5.97) times more likely to develop ESKD than patients with eGFR ≥ 90 mL/min/1.73 m^2
Smail *et al*[18]	43	Pre-transplant eGFR < 60mL/min/1.73m^2 was associated with a ESRD incidence at 1, 3, 5 yr of 0, 28.6% and 61.9% compared to those with an eGFR > 60 mL/min/1.73 m^2 1, 3, 5 yr incidence of 0.82, and 12.5% (P = 0.006); age, female sex, duration of diabetes pre-PTA (all P < 0.05)	The risk of progression to ESRD after PTA may be increased in patients with pretransplant eGFR below 60 mL/min/1.73 m^2, younger patients and in women
Gruessner *et al*[19]	513	SCr > 1.5 mg/dL at transplant, age < 30	5 yr post-transplant ESKD rate of 13%
Odorico *et al*[20]	27 PTA, 61 PAK	Pre-transplant eGFR < 60 mL/min/1.73 m^2	67% PTA patients showed an increase (> 10%) in their SCr from baseline *vs* 34% PAK patients (P = 0.035). PTA transplant was considered mildly renoprotective; this finding was not significant (HR = 0.29, 95%CI: 0.04-2.37, P = 0.182)
Chatzizacharias *et al*[21]	24	Tacrolimus levels > 12 mg/dL at 6 mo post-transplant	Tacrolimus levels, but not pre-transplant proteinuria or low eGFR < 45 mL/min/1.73 m^2 were associated with CKD progression
Marchetti *et al*[22]	28		Stable native kidney function comparing pre-transplant to post-transplant (0.95 ± 0.2 *vs* 0.96 ± 0.22, P > 0.05); limited follow up of 3 mo
Coppelli *et al*[17]	32		32 PTA recipients did not have significantly different creatinine pre- and post-transplant (0.95 ± 0.25 mg/dL *vs* 1.00 ± 0.19 mg/dL, P > 0.05); PTA lead to improvement in lipids, BP, and albuminuria
Genzini *et al*[23]	45; 20-group 1 CrCl ≤ 70 mL/min; 25-group 2 CrCl > 70 mL/min	CrCl < 70 mL/min	Kidney function at 1-yr: Group 1 CrCl pre- *vs* post-transplantation = 57.3 ± 9 *vs* 34.8 ± 32 mL/min, P = 0.003); (group 2 CrCl pre- *vs* post-transplantation = 107.1 ± 25 *vs* 81.0 ± 23 mL/min, P = 0.008). In group 1, 10/20 patients (50%) ended up with a CrCl < 30 mL/min, 5/20 (25%) initiated on hemodialysis, and 3/20 (15%) underwent kidney after pancreas transplantation. No patients in group 2 ended up with significantly decreased kidney function
Scalea *et al*[24]	123		88% of patients had eGFR decrease with a mean decrement of 32.1 mg/min/1.73 m^2. Mean eGFR pre-transplantation was 88.9 *vs* 55.6 post-transplantation (P < 0.0001) with mean follow-up of 3.68 yr. Donor demographics, immunosuppression, HLA mismatch were not significantly associated with progressive CKD in their analysis

PTA: Pancreas transplant alone; ESKD: End stage kidney disease; eGFR: Estimated glomerular filtration rate; ESRD: End stage renal disease; SCr: Serum creatinine; PAK: Pancreas after kidney transplant; HR: Hazard ratio; CI: Confidence interval; BP: Blood pressure; CrCl: Creatinine clearance; HLA: Human leukocyte antigen; CKD: Chronic kidney disease.

risk of developing diabetes mellitus[3]. As previously mentioned, CKD is often underreported in this group of NKSOT recipients due to liver failure mediated sarcopenia and malnutrition[26]. Here we will explore recent studies describing kidney function after liver transplantation. Ojo *et al*[2] utilizing SRTR data, observed that in 36849 liver transplant recipients at 1 year follow up, 8% had advanced CKD (CKD stage IV or V) and at 60 mo, 18.1% do. Key risk factors associated with chronic renal failure (CRF) after liver transplantation were pre-transplant GFR, particularly that of ≤ 29 mL/min/1.73 m^2 [relative risk (RR) = 3.78], post-operative renal failure (RR = 2.11), pre-transplant dialysis (RR = 1.45), hepatitis C (RR = 1.22), and pre-transplant diabetes mellitus (RR = 1.39).

Given the dilemmas associated with creatinine/eGFR interpretation in liver disease, several groups have attempted to evaluate kidney function after liver transplantation by serially following mGFR as summarized below. Cohen *et al*[27] looked at 353 liver transplant recipients with pre- and post-transplant mGFR *via* iothalamate clearance. Mean age at transplant was 50.3 years, with mean follow up of 6.8 years. 41% of their liver transplant recipients were transplanted due to cholestatic liver disease. Tacrolimus (51.7%) was the most common CNI used. At 3 years and 5 years in both the entire group (n = 353) and intensive follow-up group (n = 191), mean mGFR was > 50 mL/min/body surface area at 3 (56.5 and 56.4) and 5 years (56.6 and 53.9). Although mGFR at listing did not correlate well with 3 year mGFR in the intensive follow up group (correlation coefficient, r = 0.35). 1 year mGFR correlated relatively well with 3 year mGFR (r = 0.72). The authors reported a near doubling of transplant recipients with mGFR < 40 at 3 years posttransplant (39/191, 20.4%) *vs* pre-transplant (10/191, 10.5%). In the entire cohort of 353 orthotopic liver transplant (OLT) recipients, 15 patients (4.2%) developed

ESKD. Mean time to ESKD was 7.5 years after transplant (range = 2.5-11.3 years). In Kaplan-Meier analysis, the incidence of ESKD within 10 years was 10% ± 3%, 95%CI: 3%-15%.

In their study of 152 OLT recipients at least 5 years post-liver transplant, Herlenius *et al*[28] set out to describe the prevalence of CKD by linking early mGFR to late mGFR and to determine risk factors leading to CKD after liver transplant. At 5 years, 8 (5%) of the patients were on dialysis. GFR decreased by 36% at 5 years and 42% at 10 years. The authors observed that baseline mGFR had a weak correlation with 5-year mGFR (Pearson correlation coefficient, R^2 = 0.27). Stronger correlation was observed between 3 mo and 5 year mGFR [0.67 and R^2 = 0.46 (2-tailed P < 0.001) and 1 year and 5 year mGFR (0.72 and R^2 = 0.52 (2-tailed P < 0.001)]. They also conducted a multivariate logistic regression analysis on risk factors for developing advanced kidney disease (CKD IV, V) at 5 years post-liver transplant and found that only mGFR 3 mo post-liver transplant below 30 mL/min/1.73 m^2 was predictive (P = 0.03).

The following studies describe kidney disease after liver transplantation using eGFR: Wilkinson and Pham[29] reported the following rates in terms of incidence and mortality rate from AKI and CKD: 17%-95% rate of AKI with a mortality rate of 25%-74% in those on RRT *vs* 52% not requiring RRT; 10%-20% incidence of CKD, 2%-8% rate of ESRD with a mortality rate between 25%-50%. AKI risk factors included delayed graft function, poor liver allograft function, body mass index, use of cyclosporine-A and pre-transplant AKI. CKD risk factors included the following: AKI, need for hemodialysis, hepatorenal syndrome, CNI use, diabetes mellitus, hepatitis C, and age. Gonwa *et al*[30] inspected 834 liver transplant recipients which they stratified into 3 groups: Controls (n = 748), CRF [defined as sustained SCr > 2.5 mg/dL, (n = 41)], and ESRD (n = 45). They observed an incidence of "severe renal dysfunction", CRF + ESRD in 18.1% of OLT recipients after 13 years of follow up. In multivariate stepwise logistic regression analysis, increased creatinine by 1 mg/dL above the average of the group conferred the following risk for CRF or ESRD: Creatinine at 4 wk (odds ratio (OR) = 1.598, 95%CI: 1.076-2.372), creatinine at 3 mo (OR = 2.254, 95%CI: 1.262-4.025), and 1 year creatinine (OR = 2.582, 95%CI: 1.633-4.083). Survival was markedly decreased at year 13 in the ESRD group (28.2%) compared to the control group without significant kidney disease (54.6%). The authors also noted decreased survival after ESRD onset for those who did not receive a subsequent kidney transplant: 6 years after the onset of ESRD, patients receiving HD without a transplant had a survival of only 27% compared with 71.4% in the kidney transplant group (P = 0.04). O'Riordan *et al*[26], in their study of 230 OLT recipients, observed that at 5 years post-liver transplant, 71% had CKD with GFR < 60 mL/min. Pre-transplant factors associated with progression to ESRD included age, female gender, liver transplant from cytomegalovirus (CMV) positive donor to CMV positive recipient, and pre-liver transplant diabetes in univariate analysis (all P < 0.05). Though pre-OLT proteinuria was missing in 53% of patients, more than 40% of those with measurements had > 150 mg/L/d. Mean pre-transplant proteinuria = 0.21 ± 0.29 g/L (range = 0.00-2.09) and was significantly associated with CKD progression (OR = 5.36, 95%CI: 1.41-20.45, P = 0.01). In multivariate analysis for factors impacting CKD progression to stage 5 disease, pre-OLT total urinary protein (OR = 7.48, 95%CI: 1.04-53.97) and female gender (OR = 7.84, 95%CI: 2.04-30.08, P < 0.005) were the most predictive. In multivariate Cox regression analysis, GFR < 30 mL/min (HR = 3.05, 95%CI: 1.21-7.70, P = 0.02) was meaningfully associated with reduced patient survival. Similarly, survival was significantly decreased for those with GFR < 30 mL/min compared to those with GFR > 30 mL/min in Kaplan-Meier analysis (log rank P = 0.04). Wyatt and Arons[31] observed significant mortality in 358 liver transplant recipients who sustained AKI, irrespective of whether they required RRT or not: AKI without RRT [adjusted OR (aOR) = 8.69, 95%CI: 3.25-23.19, P < 0.0001]; AKI requiring RRT (aOR = 12.07, 95%CI: 3.90-37.32, P < 0.0001). Bahirwani *et al*[32] retrospectively reviewed 40 OLT recipients with CKD prior to transplant, which they defined as SCr ≥ 2 mg/dL for 90 d. Notable demographics included median eGFR of 24 mL/min (range 16-33), mean age of 56.5 years [interquartile range (IQR) = 52-60.5], 21 (53%) of the group had liver failure from hepatitis C, median Model of End Stage Liver Disease (MELD) of 26 (range = 22-31) and 19 (48%) of the recipients had pre-transplant diabetes. Interestingly, they observed the following median eGFR at 1, 2, and 3 years post-transplant 35 mL/min (IQR = 27-47), 34 mL/min (IQR = 20-51), and 37 mL/min (IQR = 22-55). 53% of recipients developed CKD stage 4 at 3 years. At a median follow up of 1.21 years post-transplant, 12 (30%) of recipients were on RRT. On univariate analysis, pre-transplant diabetes (HR = 4.23, 95%CI: 1.12-15.93, P = 0.03) and African American race (HR = 3.44, 95%CI: 1.04-11.35, P = 0.04) significantly predicted post-transplant RRT. This association was not significant on multivariate analysis. Interestingly, hypertension, hepatitis C, pre-transplant RRT, MELD score, pre transplant eGFR were not predictive of post-transplant RRT on univariate analysis (all P > 0.05). Cabezuelo *et al*[33] analyzed 184 OLTs for both early postoperative acute renal failure (> 50% increase in SCr within 1 wk of transplant) and late postoperative acute renal failure (similar increase in creatinine two to four weeks post-transplant). 12% of the cohort required RRT. Predictors of early acute renal failure were pre-transplant acute renal failure (OR = 10.2, P = 0.025), serum albumin (OR = 0.3, P = 0.001), duration of dopamine treatment (OR = 1.6, P = 0.001), and grade II-IV dysfunction of the liver graft (OR = 5.6, P = 0.002). Late postoperative risk factors were: Re-operation (OR = 3.1, P = 0.013) and bacterial infection (OR = 2.9, P = 0.017). Pham *et al*[34] in their review of AKI in NKSOT refer to a study whereby renal recovery after liver transplantation in recipients who were on dialysis at transplant was related to pre-transplant dialysis vintage: The percentage of renal function recovery for those who were on dialysis for ≤ 30 d 31-60 d, and 61-90 d were 71%, 56%, and 24%. They also note that in an analysis of the Canadian Organ Replacement

Register database by Al Riyami *et al*[35], despite a low incidence of ESRD (2.9%) in their cohort, the unadjusted mortality rate for those with AKI requiring dialysis compared to those who did not was 49.2% *vs* 26.8%, respectively ($P < 0.001$)[34,35].

A particularly interesting study by Kollmann *et al*[36] investigated whether donor type [donation after circulatory death (DCD) ($n = 57$) *vs* donation after brain death (DBD) ($n = 446$) or living donor liver transplantation (LDLT) ($n = 178$)] impacted AKI rates. They observed that perioperative AKI (defined as AKI within the first 7 postoperative days) was observed more often in the DCD group (61%; DBD, 40%; and LDLT, 44%; $P = 0.01$) and was associated with significantly higher peak aspartate aminotransferase levels ($P < 0.001$). DCD patients also had a significantly higher peak SCr ($P < 0.001$) and a trend toward higher rates of AKI stage 3 per Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease criteria (DCD, 33%; DBD, 21%; LDLT, 21%; $P = 0.11$). AKI recovery (DCD, 77%; DBD, 72%; LDLT, 78%; $P = 0.45$) and progression to CKD (DCD, 33%; DBD, 32%; LDLT, 32%; $P = 0.99$) were similar across groups. Patient survival was significantly lower in OLT recipients who received DCD or DBD organs and required perioperative RRT in multivariate analysis (HR = 7.90; 95%CI: 4.51-13.83; $P < 0.001$).

While a plethora of studies exist examining kidney function after liver transplantation exist, this appears to be representative of the body of work, including both studies using measured and eGFR to assess kidney function. As is the case of longitudinal studies, impaired kidney function definitions and immunosuppression eras have changed over time, rendering comparison difficult. Clearly AKI and CKD are adverse outcomes that lead to adverse outcomes including ESKD and patient mortality. While some risk factors are unmodifiable (age, sex, ethnicity), potentially modifiable risk factors, such as diabetes, hypoalbuminemia, proteinuria, and donor type were observed in these studies. Perhaps these modifiable risk factors can be diagnosed and managed as part of pre-transplant care to optimize before transplantation, especially in those with lower baseline kidney function. Moreover, these studies support the use of mGFR in select candidates and recipients both in the pre- and post-transplant contexts to better identify kidney disease. These studies are abbreviated in Table 2.

KIDNEY DISEASE AFTER HEART TRANSPLANTATION

With kidney and heart function intricately related, disease in one organ precipitates disease in the other; the same comorbidities (hyperlipidemia, hypertension, diabetes, metabolic syndrome, *etc*) lead to kidney and heart disease[2,10,37]. While heart failure can arise from kidney-sparing, acute conditions, *de novo* heart failure in CKD is a common occurrence, with rates cited between 17%-21%[38]. Estimating pre-heart transplant kidney disease can be challenging in waitlisted heart transplant candidates due to underestimated eGFR stemming from cardiac cachexia/poor nutrition. Moreover, thoracic transplantations (heart and lung) are complex, high-risk surgeries with high rates of AKI due to aortic cross-clamping, cardiopulmonary bypass, aggressive diuresis and fluid shifts[3]. The following studies describe kidney disease after heart transplantation: Ojo *et al*[2] described a perioperative acute renal failure rate of 20%-30% of heart transplant recipients with a 10.9% CKD IV/V rate at 60 mo post-transplant. In addition to shared mechanisms, they noted systemic atherosclerosis, renal hypoperfusion from cardiorenal disease as organ specific risk factors leading to kidney dysfunction[10].

In their retrospective cohort study of 233 orthotopic heart transplant (OHT) recipients, Cantarovich *et al*[39] observed that early renal dysfunction predicts poor long-term kidney function: A 30% decline in CrCl between 1 mo and 3 mo independently predicted the need for chronic dialysis ($P = 0.04$) and time to first CrCl < 30 mL/min at > 1 year after transplant ($P = 0.01$). Rubel *et al*[40] studied 370 OHT recipients with up to 10 year follow up looking for early GFR decline as well as ESKD. They found mean eGFR fell 24% at year one, 23% of patients developed a 50% reduction in GFR by year 3, and that 20% of the cohort developed ESRD at 10 years post-transplant. Significant predictors of post-transplant ESRD in Cox multivariate analysis included the following: GFR < 50 mL/min (HR = 3.69, $P = 0.024$); high mean cyclosporine trough in the first 6 mo (HR = 5.10, $P = 0.0059$); and presence of diabetes (HR = 3.53, $P = 0.021$). Lindelöw *et al*[37] investigated kidney outcomes in 151 of their OHT recipients with 9 year follow up. The average preoperative GFR (66 ± 17 mL/min per 1.73 m^2) declined to 52 ± 19 ($P < 0.0001$) at 1 year. From 2 years to 9 years after heart transplantation, overall kidney function remained fairly stable (all $P > 0.05$). There was no significant correlation between the preoperative GFR and postoperative renal function or survival. Recipient age predicted post heart transplant renal function. Boyle *et al*[14] set out to determine risks and consequences of post-heart transplant AKI in their study of 756 OHT recipients. They observed an AKI rate of 5.8% (44 of 756). Significant AKI risk factors were insulin dependent diabetes ($P = 0.019$) and prior cardiac surgery ($P = 0.014$). OHTs with AKI had higher preoperative SCr, lower preoperative GFR, lower preoperative albumin, lower preoperative hematocrit, increased cardiopulmonary bypass time, and increased blood transfusion needs compared to those without AKI (all $P < 0.01$). They observed a 50% (22/44) mortality rate in OHTs with AKI requiring dialysis compared to those who did not have AKI (1.4%, 10/712).

In their analysis of CKD risk factors after heart transplantation, Hamour *et al*[8] evaluated 352 OHT recipients. They found that the cumulative probability of eGFR < 45 mL/min/1.73 m^2 over time was the

Table 2 Kidney disease after liver

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Ojo *et al*[2]	36849	Pre-transplant GFR ≤ 29 mL/min/1.73 m^2 (RR = 3.78), post-operative renal failure (RR = 2.11), pre-transplant dialysis (RR = 1.45), hepatitis C (RR = 1.22), and pre-transplant diabetes mellitus (RR = 1.39)	8% with CKD IV/V at 1 yr; 18.1% at 5 yr. Pre-transplant GFR, particularly that of ≤ 29 mL/min/1.73 m^2, post-operative renal failure, pre-transplant dialysis, hepatitis C, and pre-transplant diabetes mellitus associated with CKD
Cohen *et al* [27]	353	1 yr mGFR correlated with 3 yr mGFR (r = 0.72)	At 3 and 5 yr in both the entire group (n = 353) and intensive follow-up group (n = 191), mean mGFR was > 50 mL/min/BSA at 3 (56.5 and 56.4) and 5 yr (56.6 and 53.9). Near doubling of transplant recipients with mGFR < 40 at 3 yr posttransplant (39/191, 20.4%) *vs* pre-transplant (10/191, 10.5%). 15 patients (4.2%) developed ESKD. Mean time to ESKD was 7.5 yr after transplant (range = 2.5-11.3 yr). The incidence of ESKD within 10 yr was 10% ± 3%, 95%CI: 3%-15%
Herlenius *et al*[28]	152	mGFR 3 mo post-liver transplant below 30 mL/min/1.73 m^2 predicted CKD IV, V (P = 0.03)	At 5 yr, 8 (5%) of the patients were on dialysis. GFR decreased by 36% at 5 yr and 42% at 10 yr. mGFR 3 mo post-liver transplant below 30 mL/min/1.73 m^2 predicted CKD IV, V (P = 0.03)
Wilkinson and Pham [29]		AKI risk factors: Delayed graft function, poor liver allograft function, BMI, use of cyclosporine-A and pre-transplant AKI; CKD risk factors: Acute kidney injury, need for hemodialysis, hepatorenal syndrome, calcineurin inhibitor use, diabetes mellitus, hepatitis C, and age	17%-95% rate of AKI with a mortality rate of 25%-74% in those on RRT *vs* 52% not requiring RRT; 10%-20% incidence of CKD, 2%-8% rate of ESRD with a mortality rate between 25%-50%
Gonwa *et al* [30]	834	Cr by 1 mg/dL above the average of the group conferred the following risk for CRF or ESRD: Cr at 4 wk (OR = 1.598, 95%CI: 1.076-2.372), Cr at 3 mo (OR = 2.254, 95%CI: 1.262-4.025), and 1 yr Cr (OR = 2.582, 95%CI: 1.633-4.083)	"severe renal dysfunction", CRF + ESRD in 18.1% of (OLTx) recipients after 13 yr of follow up; 6 yr after the onset of ESRD, patients receiving HD without a transplant had a survival of only 27% compared with 71.4% in the kidney transplant group (P = 0.04)
O'Riordan *et al*[26]	230	Univariate: Age, female gender, liver transplant from CMV positive donor to CMV positive recipient, and pre-liver transplant diabetes, pre-transplant proteinuria. Multivariate: Pre-OLT total urinary protein (OR = 7.48, 95%CI: 1.04-53.97) and female gender (OR = 7.84, 95%CI: 2.04-30.08, P < 0.005) were the most predictive	5 yr post-liver transplant, 71% had CKD; pre-OLT total urinary protein (OR = 7.48, 95%CI: 1.04-53.97) and female gender (OR = 7.84, 95%CI: 2.04-30.08, P < 0.005) were the most predictive of CKD progression. In multivariate Cox regression analysis, GFR < 30 mL/min (HR = 3.05, 95%CI: 1.21-7.70, P = 0.02) was associated with patient survival. Similarly, survival was significantly for those with GFR < 30 mL/min compared to those with GFR > 30 mL/min in Kaplan-Meier analysis (log rank P = 0.04)
Wyatt and Arons[31]	358		Mortality in 358 liver transplant recipients who sustained AKI, irrespective of whether they required RRT or not: AKI without RRT (aOR = 8.69, 95%CI: 3.25-23.19, P < 0.0001); AKI requiring RRT (aOR = 12.07, 95%CI: 3.90-37.32, P < 0.0001)
Bahirwani *et al*[32]	40	Univariate: Pre-transplant diabetes (HR = 4.23, 95%CI: 1.12-15.93, P = 0.03) and African American race (HR = 3.44, 95%CI: 1.04-11.35, P = 0.04). Multivariate: No significant predictors of CKD	53% of recipients developed CKD stage 4 at 3 yr. At a median follow up of 1.21 yr post-transplant, 12 (30%) of recipients were on RRT
Cabezuelo *et al*[33]	184	Early acute renal failure: Pretransplant acute renal failure (OR = 10.2, P = 0.025), serum albumin (OR = 0.3, P = 0.001), duration of dopamine treatment (OR = 1.6, P = 0.001), and grade II-IV dysfunction of the liver graft (OR = 5.6, P = 0.002). Late postoperative risk factors: Re-operation (OR = 3.1, P = 0.013) and bacterial infection (OR = 2.9, P = 0.017)	12% of the cohort required RRT
Pham *et al* [34]			The percentage of renal function recovery for those who were on dialysis for ≤ 30 d, 31-60 d, and 61-90 d were 71%, 56%, and 24%
Al Riyami *et al*[35]	4186		Despite a low incidence of ESRD (2.9%) in their cohort, the unadjusted mortality rate for those with AKI requiring dialysis compared to those who did not was 49.2% *vs* 26.8%, respectively (P < 0.001)
Kollman *et al*[36]	681; 57 DCD, 446 DBD; 178 LDLT	Perioperative AKI (defined as AKI within the first 7 postoperative days) was observed more often in the DCD group (61%; DBD, 40%; and LDLT, 44%; P = 0.01)	Perioperative AKI associated with DCDLT. No significant differences in stage 3 AKI per RIFLE, AKI recovery, and progression to CKD. Patient survival was significantly lower in OLTx recipients who received DCD or DBD organs and required perioperative RRT in multivariate analysis (HR = 7.90; 95%CI: 4.51-13.83; P < 0.001)

GFR: Glomerular filtration rate; RR: Relative risk; CKD: Chronic kidney disease; mGFR: Measured glomerular filtration rate; BSA: Body surface area; ESKD: End stage kidney disease; CI: Confidence interval; AKI: Acute kidney injury; BMI: Body mass index; RRT: Renal replacement therapy; ESRD: End stage renal disease; Cr: Creatinine; CRF: Chronic renal failure; CI: Confidence interval; OR: Odds ratio; OLTx: Orthotopic liver transplant; CMV:

Cytomegalovirus; HR: Hazard ratio; aOR: Adjusted odds ratio; DCD: Donation after circulatory death; DBD: Donation after brain death; LDLT: Living donor liver transplantation; DCDLT: Donation after circulatory death liver transplantation; RIFLE: Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease.

following: 45% at year 1, 71% at year 5 and 83% at year 10. In their multivariable logistic regression model for decrease in eGFR to < 45 mL/min/1.73 m^2 at 3 years, they found the following significant risk factors: Post-operative RRT for AKI, P < 0.001; pre-transplant diabetes (P = 0.005); increasing recipient age, (P < 0.001); female recipient (P = 0.029) and female donor (P = 0.04). Interestingly cyclosporine regimen was not significantly associated with CKD development progression. In their analysis of the Planning and Research Cooperative database, which included 141 OHTs, Wyatt and Arons[31] observed that postoperative AKI, especially that requiring RRT, was associated with increased mortality (aOR = 8.96, 95%CI: 1.75-45.80, P = 0.008).

As previously described, progressive CKD is common after heart transplantation. Similar to other NKSOT, perioperative/early AKI incites CKD and increased mortality. Modifiable risk factors exist in addition to those inherent to heart failure and subsequent transplantation. Though studies have mixed results, recipient age (as modified by selection/organ allocation), pre-transplant diabetes, as well as elevated CNI levels are potentially modifiable. Moreover, several of the risk factors described by Boyle *et al*[14] such as low pre-transplant albumin, lower preoperative hematocrit are perhaps biomarkers of frailty, malnutrition and may suggest a role for "pre-habilitation" to bolster nutrition, frailty, anemia preoperatively in hopes of abating AKI and future adverse renal and patient outcomes in heart transplantation. These studies are abridged in Table 3.

KIDNEY DISEASE AFTER LUNG TRANSPLANTATION

Lung transplantation shares many parallels with heart transplantation in terms of kidney disease. For one, end stage lung disease is a debilitating, profound state of illness rendering GFR estimations difficult due to the toll chronic lung disease exerts. As described previously, characteristics inherent to thoracic transplantation predispose lung transplant recipients to AKI[3]. Below are studies chronicling kidney disease after lung transplantation.

In their examination of SRTR, Ojo *et al*[2] observed a 2.9% incidence of CKD IV/V at 12 mo and 15.8% incidence of GFR < 30 mL/min/1.73 m^2 at 5 years post lung transplant. Rocha *et al*[41] examined 296 lung transplant recipients whereby they observed an overall AKI rate of 56% (n = 166). 8% of those with AKI required RRT (n = 23). AKI predictors included the following in multivariate analysis: Baseline GFR (OR = 0.98, 95%CI: 0.96-0.99, P = 0.012), pulmonary diagnosis other than chronic obstructive pulmonary disease (OR = 6.80, 95%CI: 1.5-30.89, P = 0.013), mechanical ventilation > 1 d (OR = 6.16, 95%CI: 1.70-22.24, P = 0.006) and parenteral amphotericin B use (OR = 3.04, 95%CI: 1.03-8.98, P = 0.045). Patient survival was significantly impacted both by AKI and AKI requiring RRT with one-year patient survival of 92.3%, 81.8% and 21.7% in the no AKI, AKI sans RRT and AKI requiring RRT subgroups, respectively (P < 0.0001). This relationship was observed at 5 (61%, 58% and 13%) and 10 years (59%, 55% and 13%) as well. Single lung transplant (HR = 1.78, 95%CI: 1.24-2.55, P = 0.0018) and AKI requiring RRT (HR = 6.77, 95%CI: 4.00-11.44, P < 0.0001) were independent variables associated with increased mortality in multivariate Cox proportional-hazards regression. In their prospective trial examining mGFRs in lung transplant recipients, Broekroelofs *et al*[42] identified an association between pulmonary diagnosis and GFR loss. A nearly 50% decrease in mGFR at 36 mo post transplantation (100 mL/min pre-transplant *vs* 51 mL/min at 36 mo post-transplant) was observed in lung transplant recipients. The highest median loss of GFR occurred in cystic fibrosis (CF) recipients (-10 mL/min/year, range -14 to -6 mL/min/year), compared to those who were transplanted for emphysema (-6 mL/min/year, range -27 to +12 mL/min/year) and pulmonary hypertension (-1 mL/min/year, range -6 to +7 mL/min/year). This is a relatively consistent finding as described in other studies with CF lung transplant recipients having more severe kidney complications than lung transplant recipients with lung failure from pulmonary hypertension[34,43].

Mason *et al*[44] retrospectively reviewed their 425 lung transplant recipients to describe dialysis after transplantation. In examining need for dialysis, they determined a prevalence 0.6%, 4%, 9%, 13%, 16% and 19%, at 30 d and 1, 3, 5, 7 and 9 years post-transplant. Significant risk factors associated with dialysis were the following: Lower creatinine clearance (P = 0.03) and greater recipient height (P = 0.0002). Notably, donor blood type O (P = 0.001) and head trauma as donor cause of death (P = 0.01) decreased risk for dialysis need. Mortality risk after ESRD was 100%, 17% and 3.1% per year at 3 mo, 1 year and 3 years, respectively. Median survival after starting dialysis was 5 mo. In their single center retrospective study, Canales *et al*[45] examined 186 lung transplant recipients (plus 33 heart-lung transplant recipients), looking for predictors of time to doubling SCr and ESKD. A major takeaway observed from their trial was the prevalence of CKD, particularly advanced CKD at 1 and 7 years compared to the NHANES III cohort. At 1 and 7 years, the prevalence of CKD IV (81 and 95 times) and

Table 3 Kidney disease after heart

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Ojo *et al*[2]	24024	Systemic atherosclerosis, renal hypoperfusion from cardiorenal disease	Perioperative acute renal failure rate of 20%-30% of heart transplant recipients with a 10.9% CKD IV/V rate at 60 mo post-transplant
Cantarovich *et al*[39]	233	30% in CrCl between 1 mo and 3 mo independently predicted the need for chronic dialysis (P = 0.04) and time to first CrCl < 30 mL/min at > 1 yr after transplant (P = 0.01)	Early renal dysfunction predicts poor long term kidney outcomes
Rubel *et al*[40]	370	Multivariate analysis: GFR < 50 mL/min (HR = 3.69, P = 0.024); high mean cyclosporine trough in the first 6 mo (HR = 5.10, P = 0.0059); and presence of diabetes (HR = 3.53, P = 0.021)	Mean eGFR fell 24% at year one, 23% of patients developed a 50% reduction in GFR by year 3, and that 20% of the cohort developed ESRD at 10 yr post-transplant
Lindelöw *et al*[37]	151	Age	The average preoperative GFR of 66 ± 17 mL/min per 1.73 m^2 declined to 52 ± 19 (P < 0.0001) at 1 yr. From 2 yr to 9 yr after heart transplantation, overall kidney function remained fairly stable (all P > 0.05)
Boyle *et al*[14]	756	Insulin dependent diabetes (P = 0.019) and prior cardiac surgery (P = 0.014)	AKI rate of 5.8% (44 of 756); they observed a 50% (22/44) mortality rate in OHTs with AKI requiring dialysis compared to those who did not have AKI (1.4%, 10/712)
Hamour *et al*[8]	352	Post-operative RRT for AKI, P < 0.001; pretransplant diabetes (P = 0.005); increasing recipient age, (P < 0.001); female recipient, (P = 0.029) and female donor (P = 0.04) associated for progression to eGFR < 45. CSA not associated	Cumulative probability of eGFR < 45 mL/min/1.73 m^2 over time was the following: 45% at year 1, 71% at year 5 and 83% at year 10
Wyatt and Arons[31]	141		Postoperative AKI, especially that requiring RRT, was associated with increased mortality (aOR = 8.96, 95%CI: 1.75-45.80, P = 0.008)

CKD: Chronic kidney disease; CrCl: Creatinine clearance; GFR: Glomerular filtration rate; HR: Hazard ratio; eGFR: Estimated glomerular filtration rate; ESRD: End stage renal disease; AKI: Acute kidney injury; OHT: Orthotopic heart transplant; RRT: Renal replacement therapy; CSA: Cyclosporine; CI: Confidence interval; aOR: Adjusted odds ratio.

V (10 and 20 times) were substantially higher in the lung, heart-lung transplant recipients than the general population as described by NHANES III. In their multivariate step model, older age, lower 1 mo GFR and CSA use in the first 6 mo were associated with faster doubling of SCr (all P < 0.05). AKI episodes (RR = 1.6, 95%CI: 1.2-2.0, P < 0.001), and older age at transplant (RR = 1.02, 95%CI: 1.008-1.04), P = 0.004) were significant predictors of death. Ishani *et al*[9] in their study of lung, heart-lung transplant recipients found that diastolic blood pressure greater than 90 mmHg (RR = 1.30, 95%CI: 1.05-1.60, P = 0.02), 1 mo post-transplant creatinine (RR = 1.28, 95%CI: 1.02-1.70, P =0.03) were associated with increased risk to time to doubling baseline SCr. Cause of lung failure, age at transplant, nor rejection were significantly associated. Tacrolimus use in the first 6 mo after transplant was associated with a decreased in the risk for doubling time of SCr (RR = 0.38, 95%CI: 0.19-0.79, P = 0.0009). Paradela de la Morena *et al*[46] retrospectively evaluated 161 lung transplant recipients at their center. They found that 68.6% of the cohort developed CKD. On multivariate analysis, older age (OR = 2.0; P < 0.001) and CMV infection (OR = 2.2; P = 0.045) were associated with CKD development. CKD at 1 year was associated with increased mortality compared to those without CKD (P = 0.001).

Kidney disease, both in terms of AKI and CKD, is common in lung transplant recipients. There appear to be certain risk factors associated with CKD development, namely lower pre- and early post-transplant creatinine, AKI, end stage lung disease from CF, and older recipient age. There appears to be a subset of lung transplant recipients at higher risk for progressive CKD. Early transplant nephrology referral may be of benefit for these patients. Despite CKD commonly manifesting post-lung transplant, modifiable/preventable risk factors including diastolic blood pressure and CMV infection are potential targets in terms of blood pressure optimization and prophylaxis strategies to mitigate CKD development. In summary, early multidisciplinary care and co-management from transplant pulmonology and nephrology is vital for appropriate patient selection and continued management of kidney disease in lung transplant recipients. These studies are summarized in Table 4.

KIDNEY DISEASE AFTER INTESTINAL TRANSPLANTATION

Kidney disease after IT is understudied due to the rarity of IT. As described in OPTN/SRTR annual report, 104 ITs were performed in 2018[47]. We will highlight pertinent studies in the field of intestinal

Table 4 Kidney disease after lung

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Ojo *et al*[2]	7644		2.9% incidence of CKD IV/V at 12 mo and 15.8% incidence of GFR < 30 mL/min/1.73 m^2 at 5 yr post lung transplant
Rocha *et al*[41]	296	AKI: Baseline GFR (OR = 0.98, 95%CI: 0.96-0.99, *P* = 0.012), pulmonary diagnosis other than COPD (OR = 6.80, 95%CI: 1.5-30.89, *P* = 0.013), mechanical ventilation > 1 d (OR = 6.16, 95%CI: 1.70-22.24, *P* = 0.006) and parenteral amphotericin B use (OR = 3.04, 95%CI: 1.03-8.98, *P* = 0.045)	AKI rate of 56% (*n* = 166). Patient survival by AKI and AKI requiring RRT with one-year survival no AKI = 92.3%, AKI w/o RRT = 81.8% and AKI w/RRT 21.7% (*P* < 0.0001). At 5 (61%, 58% and 13%) and 10 yr (59%, 55% and 13%). Single lung transplant (HR = 1.78, 95%CI: 1.24-2.55, *P* = 0.0018) and AKI requiring RRT (HR = 6.77, 95%CI: 4.00-11.44, *P* < 0.0001) associated with mortality
Broekroelofs *et al*[42]	57	Highest median GFR in the CF recipients (-10 mL/min/year, range -14 to -6 mL/min/year), compared to those w/emphysema (-6 mL/min/year, range -27 to +12 mL/min/year) and pHTN (-1 mL/min/year, range -6 to +7 mL/min/year)	Nearly 50% decrease in mGFR at 36 mo post transplantation (100 mL/min pre-transplant *vs* 51 mL/min at 36 mo post-transplant)
Mason *et al*[44]	425	Lower creatinine clearance (*P* = 0.03) and greater recipient height (*P* = 0.0002)	HD prevalence = 0.6%, 4%, 9%, 13%, 16% and 19%, at 30 d and 1, 3, 5, 7 and 9 yr post-transplant. Mortality risk after ESRD was 100%, 17% and 3.1% per year at 3 mo, 1 yr and 3 yr, respectively. In other words, median survival after starting dialysis was 5 mo
Canales *et al*[45]	186	Older age, lower 1 mo GFR and CSA use in the first 6 mo were associated with faster doubling of serum creatinine (all *P* < 0.05)	At 1 and 7 yr, the prevalence of CKD IV (81 and 95 times) and V (10 and 20 times) were substantially higher in the lung, heart-lung transplant recipients than the general population as described by NHANES III; AKI episodes (RR = 1.6, 95%CI: 1.2-2.0, *P* < 0.001), and older age at transplant (RR = 1.02, 95%CI: 1.008-1.04), *P* = 0.004) were significant predictors of death
Ishani *et al*[9]	186	DBP than 90 mmHg (RR = 1.30, 95%CI: 1.05-1.60, *P* = 0.02), 1 mo post-transplant Cr (RR = 1.28, 95%CI: 1.02-1.70, *P* =0.03) were associated with increased risk to time to doubling baseline SCr	Cause of lung failure, age at transplant, nor rejection were significantly associated with doubling of Cr. Tacrolimus use in the first 6 mo after transplant was associated with a decreased in the risk for doubling time of SCr (RR = 0.38, 95%CI: 0.19-0.79, *P* = 0.0009)
Paradela de la Morena *et al*[46]	161	Older age (OR = 2.0; *P* < 0.001) and CMV infection (OR = 2.2; *P* = 0.045)	68.6% of the cohort developed CKD; CKD at 1 yr was associated with increased mortality compared to those without CKD (*P* = 0.001)

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; Cr: Creatinine; COPD: Chronic obstructive pulmonary disease; CI: Confidence interval; OR: Odds ratio; AKI: Acute kidney injury; RRT: Renal replacement therapy; HR: Hazard ratio; CF: Cystic fibrosis; pHTN: Portal hypertension; mGFR: Measured glomerular filtration rate; ESRD: End stage renal disease; CSA: Cyclosporine; AKI: Acute kidney injury; RR: Relative risk; CI: Confidence interval; DBP: Diastolic blood pressure; SCr: Serum creatinine; CMV: Cytomegalovirus.

transplantation discussing kidney disease. Huard *et al*[48] in their evaluation of SRTR data of 843 IT recipients, assessed incidence, risk factors, and impact on survival of severe CKD, which they defined as GFR < 30 mL/min/1.73 m^2 in IT recipients. They observed a cumulative incidence of severe CKD of 3.2%, 25.1%, and 54.1% 1, 5 and 10 years after IT, respectively. Female sex (HR = 1.34), older age (HR = 1.38/10 year increment), catheter-related sepsis (HR = 1.58), steroid maintenance immunosuppression (HR = 1.50), graft failure (HR = 1.76), acute cellular rejection (HR = 1.64), prolonged requirement for IV fluids (HR = 2.12) or total parenteral nutrition (HR = 1.94), and diabetes (HR = 1.54) were associated with severe CKD. Individuals with higher GFR at the time of IT (HR = 0.92 for each 10 mL/min/1.73 m^2 increment), and those receiving induction therapies (HR = 0.47) or tacrolimus (HR = 0.52) showed lower hazards of severe CKD. In adjusted analysis, severe CKD was associated with a significantly higher hazard of death (HR = 6.20). Herlenius *et al*[28] studied 10 patients after IT *via* serial measurements of GFR. They performed measurements at baseline, 3 mo post transplantation, and yearly thereafter. Median follow-up time for the cohort was 1.5 years (0.5-7.8 years). Tacrolimus was discontinued in four patients because of impaired renal function. These four patients were switched to sirolimus at 11, 18, 24, and 40 mo post transplantation. Median baseline GFR was 67 (22-114) mL/min/1.73 m^2 (22-114). In the adult patients, GFR 3 mo post transplantation had decreased to 50% of the baseline. At 1 year, median GFR in the adult patients was reduced by 72% (*n* = 5). Two patients developed renal failure within the first year and required hemodialysis. Notably, eGFR *via* MDRD formula consistently overestimated GFR by approximately 30% compared with the mGFR. Ueno *et al*[49] examined 24 adult IT recipients with at least 2 years survival in the tacrolimus-based era. They measured kidney function *via* 6 mo averages of SCr along with calculating creatinine clearance per the Cockcroft-Gault formula. Post-transplant mean CrCl was significantly lower at 2 years compared to baseline (49.6 mL/min/1.73 m^2 *vs* 114 mL/min/1.73 m^2, *P* < 0.0001). The authors also evaluated the role of tacrolimus by cumulative level, which they defined as the sum of weekly average tacrolimus levels (ng·day/mL). They found that

recipients with cumulative tacrolimus levels > 4500 ng ng·day/mL had significantly decreased CrCl at 2 years compared to those with cumulative tacrolimus levels less than 4500 ng ng·day/mL (P = 0.006).

Kidney disease after IT is understudied. Even so, there are key takeaways that can be derived from the data to date. In this moribund population, perhaps mGFR and/or cystatin C could be used adjunctively with typical estimating equations to better characterize kidney function and guide nephrology referral/management. One can surmise that a subset of patients *i.e.*, older, diabetic IT recipients, with persistent IV fluid needs could benefit from early transplant nephrology care. These results are described in Table 5.

DIAGNOSIS AND MANAGEMENT OF CKD POST NON-KIDNEY SOT

Uncertainty regarding kidney function is an overarching theme surrounding kidney disease in NKSOT. While mGFR would be the ideal, most accurate/precise test of function, it is impractical, expensive, and not widely available. As previously described, CKD-EPI and MDRD in some contexts appear to be acceptable eGFR equations that can aid in screening for and diagnosis of CKD. Bloom *et al*[3] endorse using MDRD, acknowledging that it is conservative *i.e.,* would be sensitive in that it has better capture of SOT recipients with permissible false-positivity. As with any test, patient selection is of utmost importance, in both a macro and micro sense *i.e.,* a test primarily based on clearance of a muscle waste product will be flawed in those with significant malnutrition, sarcopenia.

Nephrologists are aptly suited to manage kidney disease in NKSOT as the modifiable risk factors leading to progressive CKD are shared across SOT recipients and the general public alike. As is well described in Bloom *et al*'s seminal work, CKD management after NKSOT is founded on the same tenets of CKD management generally[3]. Fundamentally, CKD after NKSOT is CKD management + CNI considerations. In other words, the same diseases processes that effect native kidney function remain relevant after SOT. The literature/guidelines describing CKD management are well described and summarizing them is beyond the scope of this review[1,12,50]. The impact of therapies and management strategies for risk factors leading to CKD in NKSOT is understudied. In the following sections, we will highlight salient points on CKD management.

Proteinuria

Renin angiotensin aldosterone system (RAAS) blockade for proteinuria management in transplant recipients is extrapolated from the non-transplant CKD literature with limited direct evidence. Most research in this domain has occurred in kidney transplant. Knoll *et al*[51] attempted to answer this question in the context of kidney transplant with a randomized controlled trial. However, as is aptly put by Toto[52] in his comment from Nature Reviews Nephrology, this study did not "settle the controversy surrounding the use of RAAS blockade in the renal transplant population". Though proteinuria management in non-kidney SOT is understudied, RAAS blockade appears to be a reasonable approach not only for treating proteinuria, but also for those with significant risk factors for heart disease given their cardioprotective benefit[53,54].

CNI use/minimization strategies

With CNIs as possible potentiators of CKD, CNI-sparing/minimizing maintenance immunosuppression regimens have been proposed as a renoprotective management strategy. There is a large body of evidence examining CNI minimization in NKSOT, which we will discuss below. With the advent of tacrolimus and results of ELITE-SYMPHONY, tacrolimus has ousted cyclosporine CNI-wise, as tacrolimus appears to have a less nephrotoxic profile[55]. Mechanistically, this may be due to less renal vasoconstriction as has been demonstrated in both *in vivo* and *in vitro* studies[3,56,57]. Pancreas transplant wise, limited evidence exists supporting CNI minimization or sparing. While Kandula *et al*[58] compared tacrolimus-sirolimus based regimen to tacrolimus-mycophenolate immunosuppression in PTA recipients, mean tacrolimus levels were similar across groups at all time points.

In the context of liver transplantation, there is an expansive body of literature supporting the use of CNI-sparing or minimization therapy with sirolimus and mycophenolate[59-64]. For heart transplant recipients, CNI minimization/sparing has been shown as a viable immunosuppression approach. Cornu *et al*[65] in their systematic review and meta-analysis of eight studies on CNI minimization showed that creatinine clearance was preserved in individuals with impaired renal function, which they defined as eGFR < 60 mL/min, at 6 mo [+12.23 (+5.26, +18.82) mL·min^{-1}, P = 0.0003). Although longer term benefit was not shown in this study, CNI minimization strategies were not associated with increased rejection, mortality or adverse events compared to the standard CNI regimen approach (all P > 0.05). As is aptly described by Zuckermann *et al*[66], the use of induction in OHT recipients has "provided immunosuppressive cover" to allow for the following approaches: CNI minimization and delayed CNI introduction whilst kidney function is recovering post- heart transplantation[66-70].

In lung transplant recipients, evidence exists supporting the use of CNI sparing/minimization regimens. Högerle *et al*[71] in their recent review describe a following approaches including basiliximab induction, which showed favorable short term renal outcomes. They also noted CNI minimization

Table 5 Kidney disease after intestinal

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Huard *et al* [48]	843	Female sex (HR = 1.34), older age (HR = 1.38/10 yr increment), catheter-related sepsis (HR = 1.58), steroid maintenance immunosuppression (HR = 1.50), graft failure (HR = 1.76), ACR (HR = 1.64), prolonged requirement for IV fluids (HR = 2.12) or TPN (HR = 1.94), and diabetes (HR = 1.54)	Cumulative incidence of severe CKD of 3.2%, 25.1%, and 54.1% 1, 5 and 10 yr after intestinal transplant; in adjusted analysis, severe CKD was associated with a significantly higher hazard of death (HR = 6.20)
Herlenius *et al*[76]	10		In the adult patients, GFR 3 mo post transplantation had decreased to 50% of the baseline. At 1 yr, median GFR in the adult patients was reduced by 72% (n = 5). Two patients developed renal failure within the first year and required hemodialysis
Ueno *et al* [49]	24	Cumulative tacrolimus levels > 4500ng ng·day/mL associated with significantly decreased creatinine clearance at 2 yr (P = 0.006)	Post-transplant mean creatinine clearance was significantly lower at 2 yr compared to baseline (49.6 mL/min/1.73 m^2 *vs* 114 mL/min/1.73 m^2, P < 0.0001)

HR: Hazard ratio; ACR: Acute cellular rejection; TPN: Total parenteral nutrition; CKD: Chronic kidney disease; GFR: Glomerular filtration rate.

approaches with tacrolimus/mammalian target of rapamycin (mTOR) inhibitor combinations which showed improved renal function with comparable allograft/patient survival. Notably, mTOR use was associated with increased wound complications, proteinuria, hypertension, post-transplant diabetes and dyslipidemia. They also highlighted CNI minimization approaches with mTOR use instead of anti-metabolite immunosuppression. Strueber *et al*[72] examined 190 lung transplant recipients randomized to everolimus or mycophenolate mofetil 1 mo post-transplant. Though results limited due to lack of completion of the study protocol, rejection and infectious complications were lower in the everolimus group of whom 20%-28% of recipients were also on reduced CNI doses. In a 3-year multicenter randomized prospective study, Glanville *et al*[73] did not show significant differences in creatinine at 3 years comparing lung transplant recipients on mycophenolate sodium *vs* everolimus. While the authors stated that they utilized reduced 2-h post-dose CSA levels in the everolimus group and that "most levels measured were within pre-specified target ranges", granular data describing CNI levels in these cohorts is lacking. Further in support of CNI minimization/sparing is a study by Stephany *et al*[74], who observed improved GFR durable out to 18 mo for lung transplant recipients converted to sirolimus-based immunosuppression, with the greatest benefit incurred to lung transplant recipients without proteinuria.

In IT recipients, the benefit of CNI minimization/sparing strategies appears to be limited in terms of preserving renal function. Rutter *et al*[75] in their single center study demonstrated significant decline in renal function irrespective of tacrolimus exposure. Herlenius *et al*[76], in their study of 10 IT recipients, noted that 4 patients were switched from CNI to sirolimus based regimen. Of these, one developed renal failure leading to hemodialysis, one died due to hemorrhage with CKD IV at the time of death, and the other 2 had "stable GFR" at 2 and 3 years post conversion without developing rejection or intestinal allograft failure. Based on the initial successes of the BENEFIT and BENEFIT-EXT trials comparing belatacept to cyclosporine in kidney transplant recipients, belatacept in lieu of CNI or with CNI minimization has been proposed as a novel immunosuppression strategy for NKSOT[77,78]. There is mounting research describing CNI-minimizing or sparing approaches using belatacept in OHT recipients[79], lung transplant recipients[80], and PTA recipients[81,82]. More robust studies *e.g.*, randomized control trials with longer follow-up are needed to better understand outcomes related to belatacept in NKSOT as these early studies are limited in design (case-series, retrospective studies) and follow up.

An important caveat to belatacept use is that of liver transplantation. As demonstrated by Klintmalm *et al*[83] in their phase II trial and Schwarz *et al*[84], concerns exist regarding allograft function and safety with belatacept. Though results from a study conducted by LaMattina *et al*[85] were more favorable, these are limited due to small numbers as well as the patients being converted back to a CNI-based regimen. Thus, belatacept use in liver transplantation is at most controversial. Additional studies sufficiently powered are needed to determine efficacy and safety of belatacept in liver transplant recipients.

Approaches to minimize CNI use *via* induction/maintenance immunosuppression appear promising in terms of preserving renal function. While these often incur adverse effects related to specific therapies *e.g.*, mTOR inhibitors, in several instances, they have not lead to decreased allograft or patient survival. Appropriate, sufficient CNI minimizing immunosuppression tailored to preserve renal function while also staving off rejection is achievable *via* multidisciplinary collaboration and dialogue between transplant experts across nonrenal organ systems and transplant nephrology.

Hypoalbuminemia

Low serum albumin appears to impact kidney function in NKSOT recipients. As described in their review, Kim *et al*[86] note that hypoalbuminemia may indicate poor nutritional state, impact pharmacokinetics/pharmacodynamics, and/or represent an increased inflammatory state. As a relatively inexpensive, trackable biomarker, perhaps albumin and a goal albumin *e.g.*, greater than 3.0 g/dL could be a pre-transplant goal for the multi-disciplinary team including nutritionist/dieticians to help patients with pre-transplant CKD with high risk for progression.

Nephrology referral/management considerations

The integration of nephrology care into dedicated NKSOT care throughout various stages of pre-, peri-, and post-transplantation is critical for diagnosis and management of kidney disease. Wiseman[12], in his recent review, provides substantive recommendations on timing/appropriateness of nephrology referral, based on KDIGO guidelines, and management considerations across transplant timepoints in tabular form. As has been described throughout this study, SOT recipients are a unique subset of patients with CKD that often progresses to ESKD necessitating RRT. This has led to the growing demand for kidney transplantation (KT) after solid organ transplantation which will be discussed subsequently.

KIDNEY AFTER SOLID ORGAN TRANSPLANTATION

Kidney after NKSOT is an emerging RRT for the SOT community[87]. Though this is a relatively comorbid population, they have: (1) Overcome perioperative risks associated organ transplantation; and (2) Tolerated prior induction/maintenance immunosuppression. For patients deemed candidates, KT is a viable therapy for advanced kidney disease after solid organ transplantation. Cassuto *et al*[88], in their study examining the survival benefit of KT for kidney after heart (KAH), kidney after lung (KALu), and kidney after liver (KALi) in addition to repeat KT recipients. While they observed a survival benefit for kidney after SOT compared to the waitlist population as whole for prior heart, liver recipients, this was not the case for KALu recipients who had a 61% greater risk of death *vs* those on the waitlist for KT generally (HR = 1.61, 95%CI: 1.09-2.38, P = 0.017)[86]. El-Husseini *et al*[89] examined outcomes in their 15 year analysis of national data from the United Network of Organ Sharing (UNOS) database whereby they showed inferior median graft survival (7.8 years, 95%CI: 7.3-8.2) and patient survival (8.3 years, 95%CI: 7.9-8.3) compared to primary kidney (graft survival 10.7, 95%CI: 10.6-10.8; patient survival 12.2, 95%CI: 12.1-12.3) and repeat kidney (graft survival 10.5, 95%CI: 10.2-10.7; patient survival 13.2 years, 95%CI: 12.9-13.5) (P < 0.001). In subgroup analysis, the graft and patient median survival time and 1, 5, and 10 year survival rates for KALi, KAH, and KALu were comparable. After adjustment, KALu transplant was associated with increased risk of graft loss compared to primary KT (HR = 2.123, 95%CI: 1.516-2.974, P < 0.001) and increased risk of death (HR = 3.309, 95%CI: 2.395-4.572, P < 0.001) compared to the other kidney after SOT subgroups[87]. Lonze *et al*[90] looked at outcomes in KAH or KALu transplant recipients reported to UNOS and found that 5-year graft survival however was lower than for primary KT recipients (61% KAH *vs* 73.8% primary kidney, P < 0.001; 62.6% KALu *vs* 82.9% primary kidney, P < 0.001). Notably, death-censored graft survival (DCGS) was comparable to primary kidney transplant (84.9% KAH *vs* 88.2% primary kidney, P = 0.1; 87.6% KALu *vs* 91.8% primary kidney, P = 0.6). Moreover, renal transplantation incurred a survival benefit compared to dialysis after heart transplantation (HR = 0.57, 95%CI: 0.45-0.74, P < 0.001) and lung transplantation (HR = 0.46, 95%CI: 0.30-0.71, P < 0.001). Haugen *et al*[91] sought to answer if the survival benefit of kidney after non-kidney SOT extended to older recipients (≥ 65 years of age). In their analysis of the SRTR, they found that while DCGS was comparable to older kidney transplant recipients [adjusted HR (aHR) = 1.13, 95%CI: 0.93-1.37, P = 0.2], mortality was increased (aHR = 1.40, 95%CI: 1.28-1.54, P < 0.001). KT relative to no transplant lead to a survival benefit for NKSOT recipients (aHR = 0.47, 95%CI: 0.42-0.54, P < 0.001).

DISCUSSION

In this review, we abridged current literature describing kidney disease in NKSOT describing kidney disease in pancreas, heart, lung, liver, and IT recipients. We also discussed diagnosis, management and described the emerging RRT of kidney after NKSOT. Kidney disease after NKSOT is not one size fits all; although shared risk factors inherent to solid organ failure and the perioperative period exist, these are heterogeneous populations that experience AKI and CKD at varying degrees and rates. Chronic renal dysfunction after SOT is a nascent area of study due to prolonged survival after NKSOT being a relatively recent development in the field. More questions than answers persist on crucial management aspects: At what level of kidney impairment should we consider combined kidney-nonrenal SOT? What is the role of mGFR? Kidney biopsy? Cystatin C? Should the degree of kidney impairment influence maintenance immunosuppression *i.e.*, CNI use? What is the best way to manage proteinuria in this

population? Are their roles for novel biomarkers for predicting AKI recovery or CKD progression? Ought sodium-glucose cotransporter-2 inhibitors be used in this population?

The allocation dilemma weighs heavier in the broader context of the entire waitlist. Decisions regarding kidney after solid organ transplantation or even combined kidney-SOT with the knowledge that maximization of a limited resource, based on years of survival gained from KT, is not in this population presents serious ethical challenges in terms of justice, defying a utilitarian approach. Clinicians and researchers alike spanning multiple disciplines including physician-scientists, primary care providers, general nephrologists, transplant surgeons, non-kidney transplant specialists, as well as transplant nephrologists are tasked and capable of ushering in a new era of kidney disease prevention, diagnosis, management, preservation of kidney function, and when possible subsequent KT. With these efforts promoting robust, well-designed, multi-center prospective randomized controlled trials, hope exists towards deciphering the ever-present ambiguities surrounding kidney disease in non-renal organ transplantation and improving future patient, kidney, and allograft outcomes.

CONCLUSION

Kidney disease after SOT is an incipient condition demanding further inquiry. While some truths have been revealed about this chronic disease, as we have aimed to describe in this review, continued multidisciplinary efforts are needed more than ever to combat this threat to patient and allograft survival.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Emergency department visits and hospital admissions in kidney transplant recipients during the COVID-19 pandemic: A hospital-based study

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Abstract

BACKGROUND

Several studies have demonstrated that the coronavirus disease 2019 (COVID-19) has affected daily living and the healthcare system. No previous study has described the consequences of COVID-19 on emergency department (ED) visits and hospital admission among kidney transplant (KT) recipients.

AIM

To investigate the impact of the COVID-19 pandemic on ED visits and hospital admissions within 1 year in patients who underwent KT in Thailand.

METHODS

We conducted a retrospective study at a university hospital in Thailand. We reviewed the hospital records of KT patients who visited the ED during the outbreak of COVID-19 (from January 2020 to December 2021). We used the previous 2 years as the control period in the analysis. We obtained baseline demographics and ED visit characteristics for each KT patient. The outcomes of interest were ED visits and ED visits leading to hospital admission within the 1st year following a KT. The rate of ED visits and ED visits leading to hospital admissions between the two periods were compared using the stratified Cox

proportional hazards model.

RESULTS

A total of 263 patients were included in this study: 112 during the COVID-19 period and 151 during the control period. There were 34 and 41 ED visits after KT in the COVID-19 and control periods, respectively. The rate of first ED visit at 1 year was not significantly different in the COVID-19 period, compared with the control period [hazard ratio (HR) = 1.02, 95% confidence interval (CI): 0.54-1.92; *P* = 0.96]. The hospital admission rate was similar between periods (HR = 0.92, 95%CI: 0.50-1.69; *P* = 0.78).

CONCLUSION

ED visits and hospital admissions within the 1st year in KT recipients were not affected by the COVID-19 pandemic. Despite these findings, we believe that communication between post-KT patients and healthcare providers is essential to highlight the importance of prompt ED visits for acute health conditions, particularly in post-KT patients.

Key Words: Emergency department visit; Hospital admission; Kidney transplant; COVID-19; Acute health conditions

Core Tip: Coronavirus disease 2019 (COVID-19) affects kidney transplant (KT) recipients in terms of hospital admission rates. This study showed that despite emergency department (ED) visits remaining unchanged during the COVID-19 pandemic, hospital admission rates increased. Although we could not establish the cause-effect relationship of these changes, we encourage healthcare providers to provide post-KT patients recommendations to visit ED promptly for acute health conditions.

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INTRODUCTION

In the United States, there were approximately 143 million total visits to an emergency department (ED) in 2018[1]. Over the last two decades, the rate of ED visits has increased, exceeding what could be accounted for by population growth[1]. Multiple factors, including extremes of age, women, public insurance, minority race/ethnicity, and country region, are associated with higher rates of ED visits in the general population[2]. Recently, there has been a significant increase in acute care delivery following hospitalization[3,4]. Acute care after hospital treatment is considered an indication of poor quality of care in some contexts, including kidney transplant (KT) patients[4,5]. Patients with end-stage renal disease (ESRD) account for 7.1% of total Medicare expenditures in the United States despite accounting for only 0.9% of Medicare treatments[6,7]. Patients with ESRD have visited the ED at a 6-fold higher rate than the general population; however, most previous studies excluded KT patients, who account for a growing proportion (around 22.8%) of prevalent ESRD patients[7]. The long-term advantages of KT are well documented and include improved survival and quality of life compared to dialysis[8,9]. On the other hand, the management of patients after KT is complex and resource-intensive, necessitating extensive care coordination, frequent laboratory monitoring, and ongoing patient engagement[9,10]. Furthermore, KT recipients frequently have multiple comorbidities, which complicates their care[11,12].

In recent years, coronavirus disease 2019 (COVID-19) has become the most critical disease and influenced human health across the globe[13]. This pandemic affects not only physical health but also mental health and well-being[14]. Transplant recipients, including KT patients, who are receiving immunosuppressive therapy are at the highest risk of severe illness, and as a result, are at a higher risk of an adverse outcome from COVID-19[15]. One of the unique aspects of the transplant recipient's life is that, in the post-operative phase, the patient should live in an isolated space, pay special attention to their living environment, and prefer a limited social life because of the immunosuppressive treatment involves immunosuppression in the patient[14]. A previous study demonstrated that the COVID-19 pandemic is associated with a significant reduction in average daily ED visits; however, the admission rates were increased[16]. This research investigated the effect of COVID-19 and the consequences on ED visits and admission rates among KT recipients within 1 year. In addition, this study assessed the

differences in the diagnoses of KT patients who visited an ED between COVID-19 and regular periods.

MATERIALS AND METHODS

Protocol

We conducted a single-center retrospective observational study at a university tertiary hospital between January 2018 and December 2021. The study protocol was approved by the institutional review board (IRB) of the Faculty of Medicine, Chiang Mai University (EXEMPTION-8745/65; Chiang Mai, Thailand). The IRB waived informed consent due to its retrospective design. Patient confidentiality was preserved by using anonymous health records. All methods employed in this study were performed following relevant guidelines and regulations.

Setting and study population

Maharaj Nakorn Chiang Mai Hospital (MNCMH) is a university hospital with 1500 beds, 151 intensive care units (ICUs) and sub-ICU beds, 28 operating rooms, and doctors from all subspecialties on duty. According to the Canadian Triage and Acuity Scale, the triage categorization is based on a five-level scale, ranging from blue (level 1, resuscitation) to white (level 5, non-urgency). Our ED provides a 24-h service with emergency physicians and skilled nurses. We categorized seven types of dispositions in the current study: ICU admission, general ward admission, observational unit admission, referral to another hospital, discharge, discharge against doctor's recommendation, and death.

We included all adult patients (age ≥ 18 years) who underwent KT at MNCMH between January 2017 and December 2020. Patients who died in the hospital after KT before hospital discharge were excluded. We collected data only from KT patients who visited the ED of MNCMH within 1 year after the date of transplantation (between January 2018 and December 2021). Extreme outliers and high-volume ED visitors (KT patients using the ED more than ten times per year) were excluded from the study population and were not included in the study analysis.

Data collection

Data were collected through the electronic medical records and chart review. To assess risk factors for ED visits and admissions following KT, age, sex, donor types, insurance, and Charlson comorbidity index were collected. Specifically, for KT recipients who visited the ED within 1 year after transplantation, we collected the following data: (1) Time to first and any ED visit since transplantation; (2) Triage level; (3) Total ED time; (4) Type of disposition; and (5) Invasive procedures during ED stay, which were intubation and cardiopulmonary resuscitation. The diagnosis for each ED visit is also collected using the International Classification of Diseases code.

Outcomes and data analysis

The primary outcome of interest was ED visits in the 1st year following KT. All recipients were followed until death or out of the study period. In-hospital deaths were retrieved from hospital medical records. Patients who did not visit ED at the end of the study period were considered censors. For patients with recurrent ED visits, the time to ED visit was defined as the time from the index date of transplantation to the date of the recurrent ED visit. The risk interval was, therefore, set as marginal since we assumed that the patients were at risk of any ED visit from the date of their transplantation.

Secondary outcomes included ED visits leading to hospital admissions following KT's 1st year. The number of ED visits and hospital admissions for any reason was calculated and compared between January 2018 and December 2019 and between January 2020 and December 2021. All responsible diagnoses from January 2018 to December 2019 were compared to all diagnoses from January 2020 to December 2021. We described continuous data using the mean ± SD for normally distributed variables. For skewed data, median and interquartile range were calculated. Categorical data were summarized using frequency and percentage. The independent *t*-test was used to compare continuous variables. For categorical variables, Fisher's exact probability test was performed. All tests were two-sided, with significance for all tests being determined as $P < 0.05$. All analyses were performed using STATA 16 (StataCorp, College Station, TX, United States).

For the primary analysis, the rate of ED visits within 1 year after KT was compared using the stratified Cox proportional hazards model. We presented two analytic approaches for each survival outcome, the rate of first ED visits and any ED visit after transplantation. For the rate of the first ED visit, we restricted the analysis to only the first ED visit, whereas all ED visits during the 1st year period were considered in the analysis of the rate of any ED visits. We employed the modeling method for recurrent events described by Kelly and Lim[17]. The risk interval was defined as the total time (marginal). We used a restricted risk set and assumed event-specific baseline hazards. To quantify the effect of the COVID-19 pandemic period on the control period, hazard ratios (HRs) were estimated from the stratified Cox's regression model. They were reported with 95% confidence intervals (CI) and *P* values. Kaplan-Meier curves were demonstrated, and a comparison of differences was made by the log-

rank test.

RESULTS

Patient characteristics

A total of 263 KT recipients were enrolled in this study, 112 in the COVID-19 period (underwent KT between January 2019 and December 2020) and 151 in the control period (underwent KT between January 2017 and December 2018). No recipient died during the follow-up period. Figure 1 illustrates the flow diagram of this study population. The mean ages were 45.5 ± 10.4 years and 43.7 ± 13.4 years for COVID-19 and control groups, respectively. Most of the participants received deceased donors. There were no significant differences in baseline demographics between the two periods (Table 1). Baseline demographics of KT patients who visited an ED during the study periods are summarized in Table 1.

ED visits

A total of 17.1% of KT recipients visited ED within 1 year after transplantation (15.3% in the COVID-19 period and 18.5% in the control period), accounting for 75 ED visits. The mean times to first ED visit since transplantations were 130.8 ± 106.2 and 120.6 ± 105.3 d for the COVID-19 and control periods, respectively. On the other hand, the rates of invasive procedures were similar among both periods. Table 2 summarizes the clinical variables of KT patients who presented to the ED within 1 year after transplantation. The rate of first ED visit at 1 year was not different in the COVID-19 period, compared with the control period when adjusting for confounding variables (HR = 1.02, 95%CI: 0.54-1.92; P = 0.96, Figure 2). Similarly, the rate of any ED visit in the following year was also not different between the two periods (HR = 1.24, 95%CI: 0.73-2.10; P = 0.43, Table 3). The five most responsible diagnoses are demonstrated in Table 4. Fever and abdominal pain were ranked first during the control period, while abdominal pain was the top diagnosis during COVID-19.

Hospital admissions

The admission rate in the COVID-19 period significantly decreased during the study period, compared with the control period (38.2% *vs* 65.9%; P = 0.02). In addition, the rate of any ED visit leading to hospital admission in the following year was also not different (HR = 0.92, 95%CI: 0.50-1.69; P = 0.78, Table 3).

DISCUSSION

In this retrospective study of KT patients, about one-sixth of KT recipients had at least 1 ED visit in the 1st year following transplantation. However, the rates of ED visits and hospital admissions were not affected by the impact of the COVID-19 pandemic. We also found that abdominal pain was responsible for most diagnoses across the COVID-19 and control periods. The impact of COVID-19 on ED visits and hospital admissions is demonstrated in several previous studies[15-17]. To the best of our knowledge, this is the first study investigating the effect of the COVID-19 pandemic on ED visits and admission rates among KT patients. KT recipients are usually advised to isolate themselves from the community because of the greater risk of being infected. Consequently, they might not visit the ED promptly. Our previous study showed that an average daily ED visit was significantly reduced during the COVID-19 pandemic, probably due to the fear of reaching COVID-19 in the hospital[15]. However, the present findings showed the difference. Despite the fear of contacting COVID-19, we found that ED visits by post-KT patients were not disturbed. A previous study demonstrated that KT recipients had a higher chance of a more severe course of COVID-19 infection than hemodialysis patients[18]; however, another finding showed that the severity and adverse outcomes were not different between KT recipients and those without for the COVID-19 infection[19].

Recently, telemedicine has become one of the most powerful strategies used to follow-up KT recipients[18,19]. Results from Yadav and Singh's study found that application of telemedicine in the transplant population enhances medication compliance, reduces hospitalization rates, and makes living donor evaluation convenient[19]. Telemedicine could be recommended as an alternative method, especially in the pandemic era, to avoid and reduce the rate of transmission in the hospital in KT population.

Although ED visits are not different between the two groups in our study, hospital admissions were higher for the COVID-19 group. This may reflect the natural consequence of inappropriate and untimely ED visits, resulting in a higher severity of diseases. We proposed that the reasons for these findings could be multifactorial. First, KT patients have a higher baseline chance of visiting ED than other patients. Previous studies have shown that acute care utilization in the following year after KT is relatively high[4,7,9]. In one retrospective study conducted in the United States, nearly half of KT

Table 1 Baseline demographics of kidney transplantation patients during the study period

Characteristics	COVID-19, *n* = 112	Control, *n* = 151	*P* value
Male sex, *n* (%)	70 (62.5)	93 (61.6)	0.92
Age at transplant, mean ± SD	45.5 ± 10.4	43.7 ± 13.4	0.23
Age at transplant, *n* (%)			0.20
< 40	35 (31.3)	55 (36.4)	
40-59	68 (6.7)	77 (51.0)	
≥ 60	9 (8.0)	19 (12.6)	
Donor type, *n* (%)			0.65
Living donor	41 (36.6)	59 (39.1)	
Deceased donor	71 (63.4)	92 (60.9)	
Insurance, *n* (%)			0.66
Universal coverage	24 (21.4)	56 (37.1)	
Social security scheme	33 (29.5)	40 (26.5)	
Government officer	55 (49.1)	55 (36.4)	
Charlson comorbidity index, mean ± SD	1.7 ± 1.5	1.8 ± 1.5	0.59

COVID-19: Coronavirus disease 2019.

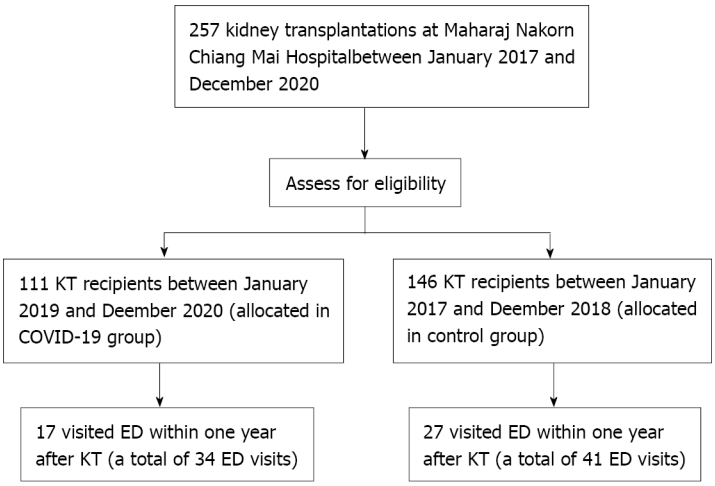

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Figure 1 Study flow. COVID-19: Coronavirus disease 2019; ED: Emergency department; KT: Kidney transplantation.

patients visited the ED within 1 year after KT[7]. Second, post-KT recipients are prescribed immunosuppressive agents. Usually, they are informed to seek medical evaluation even they have minor symptoms, such as low-grade fever or abdominal pain. Furthermore, fever and other unspecified symptoms could be one of the clinical features of COVID-19[20]. KT recipients might intend to visit ED as they considered themselves suspected of having this COVID-19 infection. Interestingly, our study found that hospital admissions were markedly increased in the COVID-19 group. Consistent with previous evidence, hospital admission during this disastrous period is likely higher than usual, mainly because of untimely and delayed ED visits[15].

Our findings regarding ED visits and admission rates during the COVID-19 pandemic may serve as a body of literature regarding the impact of COVID-19 in the various spectrum, including KT recipients. Not only the number of ED visits among post-KT patients were not less than the regular period, but also the admission rates were significantly high. Our data also suggest that clinicians and healthcare professionals should encourage KT recipients to visit EDs on time to reduce unfavorable outcomes.

Table 2 Clinical variables of kidney transplantation patients who presented to the emergency department within 1 year during the study period

Variables	COVID-19 (January 2020-December 2021), *n* = 34	Control (January 2018-December 2019), *n* = 41	*P* value
Time to first ED visit since transplantation in day, mean ± SD	130.8 ± 106.2	120.6 ± 105.3	0.88
Triage level, *n* (%)			0.71
Resuscitation	2 (5.9)	1 (2.4)	
Emergency	13 (38.2)	13 (31.7)	
Urgency	12 (35.3)	20 (48.8)	
Less urgency	5 (14.7)	6 (14.6)	
Non-urgency	2 (5.9)	1 (2.4)	
Total ED times in min, mean ± SD	275.8 ± 263.5	232.7 (120.6)	0.35
Total ED times in min, median (IQR)	210.5 (130-330)	222 (138-300)	0.35
Admission, *n* (%)	13 (38.2)	27 (65.9)	0.02
Type of disposition, *n* (%)			0.10
ICU admission	1 (2.9)	1 (2.4)	
General ward admission	12 (35.3)	25 (61.0)	
OU admission	0 (0)	1 (2.4)	
Referred	0 (0)	0 (0)	
Discharge	21 (61.8)	14 (34.2)	
Against advice	0 (0)	0 (0)	
Death at ED	0 (0)	0 (0)	
Intubation, *n* (%)	0 (0)	1 (2.4)	0.36
CPR, *n* (%)	0 (0)	0 (0)	N/A

COVID-19: Coronavirus disease 2019; CPR: Cardiopulmonary resuscitation; ED: Emergency department; ICU: Intensive care unit; IQR: Interquartile range; N/A: Not applicable; OU: Observational unit.

Table 3 Multivariable hazard ratios of emergency department visit and hospital admission by risk characteristics

Outcomes	Multivariable HR[1]	95%CI	*P* value
First ED visit	1.02	0.54-1.92	0.96
Any ED visit	1.24	0.73-2.10	0.43
ED visit leading to hospital admission	0.92	0.50-1.69	0.78

[1]Adjusted for sex, age, donor, insurance, Charlson comorbidity index.
CI: Confidence interval; ED: Emergency department; HR: Hazard ratio.

Limitations

This study had some limitations to be considered. This method could not account for underlying trends in hospital admission and ED attendance despite comparing two time periods. Differences in hospital admission patterns may be associated with the epidemic or the limits by chance. This problem might be solved with additional time series analysis or regression modeling over a longer time. We only conducted the investigation at a single university hospital. As a result, the design may be valid and generalizable to the situation with the same degree of care. Furthermore, some baseline data were not recorded, including causes of ESRD and hospital length of stay during index transplantation. Moreover, another perspective that this study did not address was the quality of life of post-KT patients who visited ED in the first following year. Further research should evaluate this aspect of the patients.

Table 4 Top five emergency department diagnoses recorded during the study period

No	ICD-10	Diagnoses	%
January 2018-December 2019			
1	R509	Fever, unspecified	12.8
2	R104	Other and unspecified abdominal pain	12.8
3	N185	Chronic kidney disease, stage 5	10.3
4	A099	Gastroenteritis and colitis of unspecified origin	10.3
5	A419	Septicemia, unspecified	10.3
January 2020-December 2021			
1	R104	Other and unspecified abdominal pain	23.7
2	N390	Urinary tract infection, site not specified	10.5
3	A419	Septicemia, unspecified	7.9
4	A099	Gastroenteritis and colitis of unspecified origin	5.3
5	R074	Chest pain, unspecified	5.3

ICD: International Classification of Diseases.

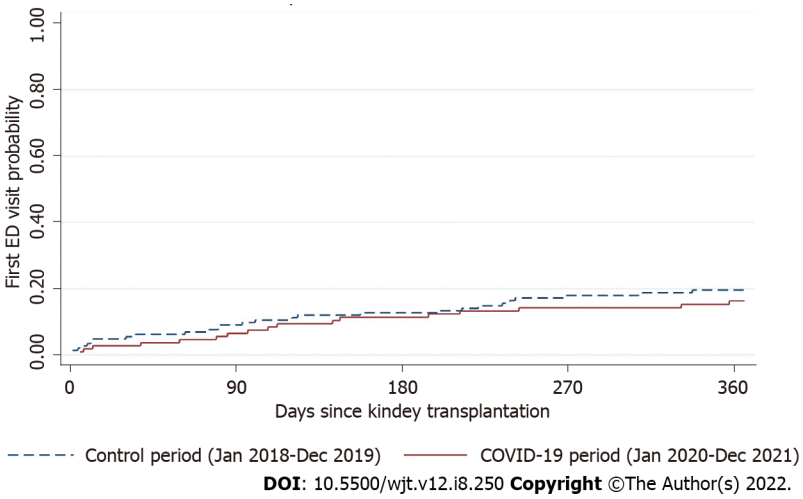

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Figure 2 Kaplan-Meier estimates of first emergency department visits in kidney transplantation patients who visited emergency department during coronavirus disease 2019 period (solid line) and control period (dot line). COVID-19: Coronavirus disease 2019; ED: Emergency department.

CONCLUSION

In conclusion, COVID-19 also affects KT recipients in terms of hospital admission rates. The present study points out that despite ED visits not being changed during the COVID-19 pandemic, hospital admission rates were increased. Although we could not determine the exact cause of this change, we believe that communication between post-KT patients and healthcare providers is necessary to emphasize the importance of timely ED visits for acute health conditions, especially in immunocompromised hosts like post-KT patients.

ARTICLE HIGHLIGHTS

Research background

Several investigations have shown that the coronavirus disease 2019 (COVID-19) has an impact on daily life and the healthcare system.

Research motivation

There has been no previous research on the effects of COVID-19 on emergency department (ED) visits and hospitalizations among kidney transplant (KT) patients. We conducted this study to explore the effects of COVID-19 on ED visits among post-KT recipients.

Research objectives

The aim of this study was to investigate the impact of the COVID-19 pandemic on the ED visits and hospital admissions within 1 year in patients who underwent KT in Thailand.

Research methods

We conducted a retrospective study. We reviewed hospital records of KT patients who visited ED during the outbreak of COVID-19. We used the previous 2 years as the control period in the analysis. We obtained baseline demographics and ED visit characteristics of each KT patient. The outcomes of interest were ED visits and ED visits leading to hospital admission within the 1st year following a KT.

Research results

We included a total of 263 patients: 112 during the COVID-19 period and 151 during the control period. There were 34 and 41 ED visits after KT in the COVID-19 and control periods, respectively. The rate of first ED visit at 1 year was not significantly different in the COVID-19 period, compared with the control period. The hospital admission rate was also similar between periods.

Research conclusions

The COVID-19 pandemic had no effect on KT recipients' ED visits or hospital admissions in the 1st year after transplantations.

Research perspectives

Despite these findings, we suggest that communication between post-KT patients and healthcare professionals is crucial in emphasizing the significance of timely ED visits for acute health issues, especially in post-KT patients.

FOOTNOTES

Author contributions: Wongtanasarasin W and Phinyo P designed the protocol, contributed to data collection, and data analyses; Wongtanasarasin W contributed to the formal analysis and wrote the first draft of the manuscript; and all authors read and critically reviewed the final version of the manuscript.

Institutional review board statement: The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (EXEMPTION-8745/65).

Informed consent statement: The Institutional Review Board of the Faculty of Medicine, Chiang Mai University waived informed consent due to its retrospective design.

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ORIGINAL ARTICLE

Retrospective Study

Trends and outcomes of liver transplantation among older recipients in the United States

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Abstract

BACKGROUND

The average age of recipients and donors of liver transplantation (LT) is increasing. Although there has been a change in the indications for LT over the years, data regarding the trends and outcomes of LT in the older population is limited.

AIM

To assess the clinical characteristics, age-related trends, and outcomes of LT among the older population in the United States.

METHODS

We analyzed data from the United Network for Organ Sharing database between 1987-2019. The sample was split into younger group (18-64 years old) and older group (≥ 65 years old).

RESULTS

Between 1987-2019, 155758 LT were performed in the United States. During this period there was a rise in median age of the recipients and percentage of LT recipients who were older than 65 years increased ($P < 0.05$) with the highest incidence of LT among older population seen in 2019 (1920, 23%). Common primary etiologies of liver disease leading to LT in older patients when compared to the younger group, were non-alcoholic steatohepatitis (16.4% *vs* 5.9%), hepatocellular carcinoma (14.9% *vs* 6.9%), acute liver failure (2.5% *vs* 5.2%), hepatitis C cirrhosis (HCV) (19.2 % *vs* 25.6%) and acute alcoholic hepatitis (0.13% *vs* 0.35%). In older recipient group female sex and Asian race were higher, while model for end-stage liver disease (MELD) score and rates of preoperative mechanical

ventilation were lower ($P < 0.01$). Median age of donor, female sex, body mass index (BMI), donor HCV positive status, and donor risk index (DRI) were significantly higher in older group ($P < 0.01$). In univariable analysis, there was no difference in post-transplant length of hospitalization, one-year, three-year and five-year graft survivals between the two groups. In multivariable Cox-Hazard regression analysis, older group had an increased risk of graft failure during the five-year post-transplant period (hazard ratio: 1.27, $P < 0.001$). Other risk factors for graft failure among recipients were male sex, African American race, re-transplantation, presence of diabetes, mechanical ventilation at the time of LT, higher MELD score, presence of portal vein thrombosis, HCV positive status, and higher DRI.

CONCLUSION
While there is a higher risk of graft failure in older recipient population, age alone should not be a contraindication for LT. Careful selection of donors and recipients along with optimal management of risk factors during the postoperative period are necessary to maximize the transplant outcomes in this population.

Key Words: Liver transplant; Elderly; Outcomes; Hepatocellular carcinoma; Nonalcohol steatohepatitis

Core Tip: Liver transplantation (LT) among older patients is becoming more acceptable in the United States. The overall outcomes of LT for patients ≥ 65 years are comparable to younger recipients. While there is a higher risk of graft failure in older recipient population, age alone should not be a contraindication for LT. Careful selection of donors and recipients along with optimal management of risk factors during the postoperative period are necessary to maximize the transplant outcomes in this population.

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INTRODUCTION

Liver disease is one of the most frequent causes of death in the United States[1,2]. Liver transplantation (LT) is the most effective life-saving treatment for patients with end-stage liver disease and liver failure. Over the past few decades, the number of LT in the United States has increased and outcomes of these transplants have significantly improved[3,4]. According to the United Network for Organ Sharing (UNOS) database, in 1987 there were 1713 LT performed in the United States. Since then, there has been a more than five-fold increase in the number of LTs, with 8906 cases performed in 2020. As the general population becomes older, the average ages of LT recipients and donors have increased as well[5]. Over the past three decades, the characteristic of donors and recipients of LT for end-stage liver disease has changed considerably[3,6-8]. Our goal was to assess trends in the etiology of underlying liver disease, and outcomes of LT among older population in the United States.

MATERIALS AND METHODS

Patients and selection criteria

We evaluated all patients 18 years or older who underwent LT in the United States from January 1, 1987 to December 31, 2019 in the UNOS database. Patients without a documented primary diagnosis were excluded from the analyses. This study was approved by our Institutional Review Board.

Patient characteristics and outcome variables

All data were collected from the UNOS registry. Demographic information, such as listing diagnosis, age, gender and race, along with time on waiting list prior to transplant were included in the analyses. Additional variables, such as model for end-stage liver disease (MELD) score at listing on the waitlist and at the time of transplant, body mass index (BMI), pre-transplant diabetes mellitus (DM), hepatitis C

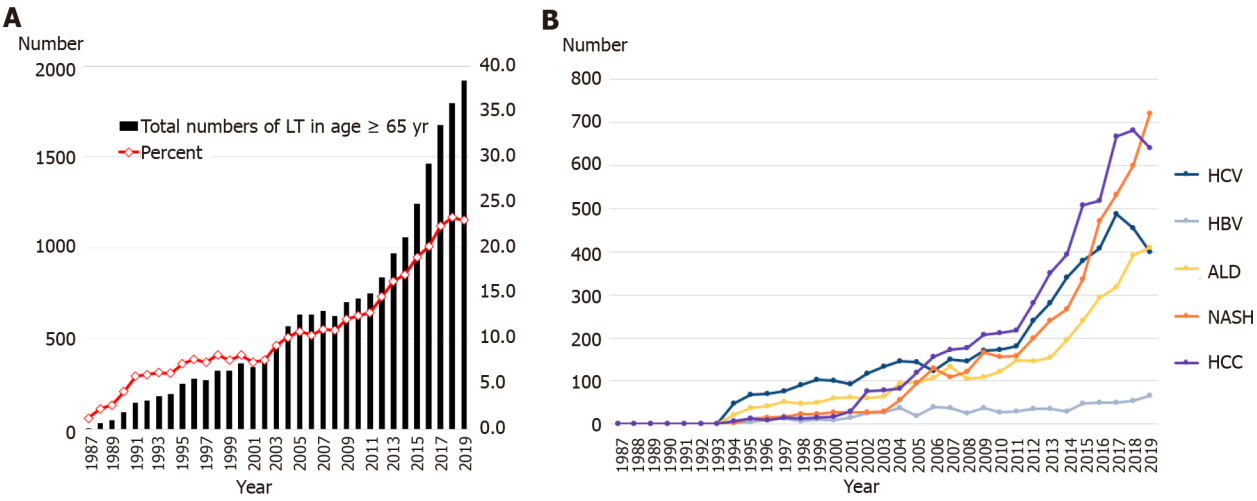

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Figure 1 Trend of liver transplant and indications for liver transplant in older group (age ≥ 65 years). A: Trend of liver transplant in older group (age ≥ 65 years); B: Trend of indications for liver transplant in older group (age ≥ 65 years). LT: Liver transplantation; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ALD: Alcohol related liver disease; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma.

virus (HCV) status, dialysis prior to transplant, previous abdominal surgery, spontaneous bacterial peritonitis, trans-jugular intrahepatic portosystemic shunt, portal vein thrombosis, mechanical ventilation status and donor risk index (DRI)[9], were included as well. The study groups were defined as older (≥ 65 years old) and younger (18-64 years old).

Statistics

Statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, United States). Non-parametric analyses were used to compare continuous variables (Mann-Whitney *U* test) and categorical variables (Chi-square test or Fisher's exact test). The overall survival and graft survival were calculated from the date of transplant to the date of the event using the Kaplan-Meier method. Survival curves were compared by using the log-rank test. Cox-Hazard regression analyses were applied to assess the association between multiple covariate factors and survival rates between two groups. Results were presented as hazard ratios and reported with 95% confidence intervals with *P* values. $P < 0.01$ was taken as statistically significant.

RESULTS

Recipient characteristics

Of the 155758 individuals who received a LT during the study period, 20000 were in older group (≥ 65 years old) and 135758 patients were in younger group (18-64 years old). The trends of LT in older patients are shown in Figure 1A. The overall number and percentage of LT in older group increased over the years, and the percentage of older recipients became > 20% after 2016. The trends of indications for LT in the older population is shown in Figure 1B. HCV cirrhosis was the most common indication for LT from 1994 to 2005. The number of patients requiring LT due to hepatocellular carcinoma (HCC) and non-alcoholic steatohepatitis (NASH) also gradually increased during the study period. HCC became the most common indication for LT in older group from 2006 to 2018. In 2019, NASH became the most common indication for LT in older group.

Table 1 presents the characteristics of recipients who underwent LT during the study period. The median age of recipients was 52 years in the younger group and 67 years in the older group. Recipients in older group were more likely to be female, White, and Asian compared to those in younger group ($P < 0.001$). Recipients in younger group were more likely to be HCV positive and have portal vein thrombosis, while recipients in older group were more likely to have pre-transplant DM. For primary etiology of liver disease, younger group was more likely to have alcohol-related liver disease (ALD), HCV cirrhosis and acute liver failure, while older group was more likely to have NASH and HCC. Additionally, the younger group was more likely to be on mechanical ventilation at the time of LT and have a prior history of LT.

Donor characteristics

The median donor age was higher in the older group (43 years *vs* 38 years, $P < 0.001$) (Table 2). The donors of older recipients were more likely to be female, have a higher BMI, and have a higher DRI.

Table 1 Baseline characteristics of the study population comparing age young group (age 18-64) *vs* older group (age ≥ 65 years)

	Young group, age 18-64 (*n* = 135758)	Older group, age ≥ 65 (*n* = 20000)	*P* value
Age (IQR)	52 (45-58)	67 (66-69)	< 0.001
Female, *n* (%)	47934 (35.3)	7612 (38.1)	< 0.001
Race, %			< 0.001
White	73.5	75.5	
Black	8.9	6.0	
Hispanic/Latino	12.5	12.1	
Asian	3.8	5.4	
Others	1.3	0.9	
BMI (IQR)	27.4 (24.0-31.7)	27.7 (24.5-31.5)	0.571
HCV, %	44876 (33.1)	5236 (26.2)	< 0.001
Diabetes, *n* (%)	226584 (22.3)	6784 (35.7)	< 0.001
L[1]-MELD	18 (12-26)	15 (10-22)	< 0.001
R[2]-MELD	21 (14-30)	18 (12-26)	< 0.001
Primary disease, %			
Alcohol cirrhosis	22.3	15.3	< 0.001
HCV cirrhosis	25.2	19.0	< 0.001
NASH	5.9	16.4	< 0.001
HCC	6.9	14.9	< 0.001
Acute liver failure	5.2	2.5	< 0.001
Acute alcoholic hepatitis	0.35	0.13	< 0.001
Previous surgery, *n* (%)	48407 (35.7)	8899 (44.5)	< 0.001
SBP, *n* (%)	9147 (6.7)	1084 (5.4)	< 0.001
TIPSS, *n* (%)	7231 (5.3)	1187 (5.9)	0.001
Portal vein thrombosis, *n* (%)	4875 (3.6)	1162 (5.8)	< 0.001
Mechanical ventilation, *n* (%)	10464 (7.6)	888 (4.3)	< 0.001
Dialysis, *n* (%)	14284 (10.5)	2059 (10.3)	0.167
Wait days, d (IQR)	82 (16-263)	118 (27-310)	< 0.001
Re-transplant, *n* (%)	10125 (7.5)	727 (3.6)	< 0.001

[1]Listing.
[2]Most recent.
IQR: Interquartile; BMI: Body mass index; HCV: Hepatitis C virus; NASH: Non-alcohol steatohepatitis; HCC: Hepatocellular carcinoma; SBP: Spontaneous bacterial peritonitis; TIPSS: Trans-jugular intrahepatic portosystemic shunt; MELD: Model for end-stage liver disease.

Outcomes

Kaplan-Meier survival analysis showed no significant differences in the 1, 3, and 5-year graft survival between the two groups, but overall survival was lower in the older group (Table 2). Multivariable Cox-Hazard regression analyses were performed to identify the factors associated with five-year graft failure (Table 3). Factors associated with five-year graft failure were recipient age ≥ 65 years, pre-LT DM, re-LT, male gender, African American race, ventilation at the time of LT, high MELD score (per 10), recipient portal vein thrombosis at time of LT, recipient HCV positive status, and high DRI. Transplants performed during the latter part of the study had a protective effect on five-year graft survival. In a subgroup analysis of older recipients, male gender, pre-LT DM, previous LT, ventilation at the time of LT, higher MELD score (per 10), portal vein thrombosis, HCV positive status, and higher DRI were associated with worse five-year graft survival (Table 4 and Figure 2).

Table 2 Donor characteristics and post-transplant outcomes

	Young, age 18-64 (*n* = 135758)	Older, age ≥ 65 (*n* = 20000)	*P* value
Donor age (IQR)	38 (24-52)	43 (28-56)	< 0.001
Donor female, *n* (%)	53967 (39.8)	8434 (42.2)	< 0.001
Donor race, %			< 0.001
White	70.3	68.2	
Black	14.6	15.5	
Hispanic/Latino	11.6	12.4	
Asian	2.1	2.4	
Others	1.4	1.6	
Donor BMI (IQR)	25.6 (22.5-29.5)	26.2 (23.0-30.3)	< 0.001
Donor HCV, *n* (%)	4912 (3.6)	907 (4.5)	< 0.001
Cold ischemia time, h (IQR)	6.9 (5.0-9.0)	6.1 (4.8-8.0)	< 0.001
Donor risk index (IQR)	1.53 (1.35-1.81)	1.61 (1.38-1.94)	< 0.001
Outcomes			
LOS, d (IQR)	11 (7-20)	10 (7-19)	0.261
Graft survival rate, (%)			
1 yr	84.0	84.1	0.416
3 yr	77.0	77.1	0.206
5 yr	72.6	72.9	0.010
Overall survival rate			
1 yr	88.6	86.5	< 0.001
3 yr	82.5	79.5	< 0.001
5 yr	78.3	75.1	< 0.001

IQR: Interquartile range; BMI: Body mass index; LOS: Post-transplant length of hospital stay; HCV: Hepatitis C virus.

DISCUSSION

This study utilized the UNOS database to analyze the trends and outcomes of LT in older patients. The results show an overall increase in total number of LT in older population over time, as well as significant changes in the trends of the primary etiology of LT. In older recipients, univariable analysis showed comparable graft survival, while multivariable analysis showed a lower graft and overall survival. But, these inferior results in older population may otherwise be considered acceptable.

The improvements in surgical techniques and perioperative care have allowed for a gradual increase LT for older recipients[4,5]. The presence of chronic liver diseases like HCV, NASH, and associated HCC in the older patients may have led to an increase in end-stage liver disease, requiring LT[10]. The recent improvements in HCV treatment has likely played a significant role in the change in primary indication for LT. Overall, the most current common indication for LT is ALD across all ages, however, our study shows that NASH and HCC are the leading causes of LT, with no increase in ALD in the older population. Durand *et al*[4] have shown that in LT, older recipients have a lower chance of liver allograft rejection. Additionally, they reported that patients with non-autoimmune conditions, such as NASH and alcoholic cirrhosis, do not require higher maintenance immunosuppression compared to other LT recipients[4]. Historically a subset of patients with positive HCV serostatus had a recurrence of HCV after LT[11]. HCV recurrence post-LT and subsequent chronic HCV infection would lead to drastic consequences, as chronic inflammation, fibrosis, and ultimately graft failure[12]. However, with the development of Direct-Acting Antivirals (DAA), there has been a major shift in the primary etiology of LT with the overall decrease in need of LT for chronic HCV infection[6]. Our analyses further showed that recipient HCV status was one of the risk factors for graft failure. This was likely before the availability of DAA, which has now become the therapy of choice for effectively curing HCV infection [13]. The recent studies show that DAA achieves high sustained virologic response in LT recipients and the elimination of HCV will prevent chronic inflammation, thereby avoiding the risk of compromising

Table 3 Multivariable cox regression for five-year graft survival

Variables	*B* (SE)	Hazard ratio (95%CI)	*P* value
Year of transplant	-0.04 (0.002)	0.958 (0.955-0.961)	< 0.001
Age ≥ 65	0.24 (0.02)	1.27 (1.22-1.32)	< 0.001
Male	0.10 (0.02)	1.11 (1.08-1.14)	< 0.001
BMI (per10)	-0.05 (0.01)	0.95 (0.93-0.98)	0.001
Race			0.001
Caucasian	Ref	1.0 (Ref)	
African American	0.23 (0.02)	1.26 (1.21-1.31)	< 0.001
Hispanic	-0.11 (0.02)	0.90 (0.86-0.94)	< 0.001
Asian	-0.21 (0.04)	0.81 (0.75-0.87)	< 0.001
Pre-LT diabetes	0.20 (0.02)	1.22 (1.18-1.26)	< 0.001
Ventilation	0.51 (0.03)	1.67 (1.59-1.76)	< 0.001
Pre-LT dialysis	0.20 (0.02)	1.23 (1.17-1.28)	< 0.001
Retransplant	0.44 (0.03)	1.55 (1.47-1.63)	< 0.001
PVT	0.21 (0.03)	1.23 (1.16-1.31)	< 0.001
R[1]-MELD (per 10)	0.04 (0.01)	1.05 (1.03-1.06)	< 0.001
HCV recipient	0.28 (0.01)	1.33 (1.29-1.36)	< 0.001
Donor race			< 0.001
Caucasian	Ref	1.0 (Ref)	
African American	0.06 (0.02)	1.06 (1.02-1.10)	0.001
Hispanic	0.10 (0.02)	1.11 (1.06-1.16)	< 0.001
Asian	0.19 (0.04)	1.21 (1.11-1.31)	< 0.001
Donor risk index	0.34 (0.03)	1.41 (1.34-1.48)	< 0.001
Cold ischemia time	0.014(0.002)	1.014 (1.010-1.019)	< 0.001

[1]Most recent.

BMI: Body mass index; LT: Liver transplantation; PVT: Portal vein thrombosis; CI: Confidence interval; HCV: Hepatitis C virus; MELD: Model for end-stage liver disease.

the graft[14,15].

As in our study, pre-transplant DM has previously been shown to be associated with worse outcomes in LT[16]. Diabetes is a metabolic disease and is associated with increased morbidity after LT[17,18]. The prevalence of NASH in patients with type 2 diabetes is more than 2-fold higher compared to the general population[19]. Poorly controlled diabetes is also strongly associated with NASH and accelerates the progression of liver disease. NASH and diabetes also increase cardiovascular risks[20]. These cumulative risk factors should be carefully evaluated for the post-transplant management of older patients.

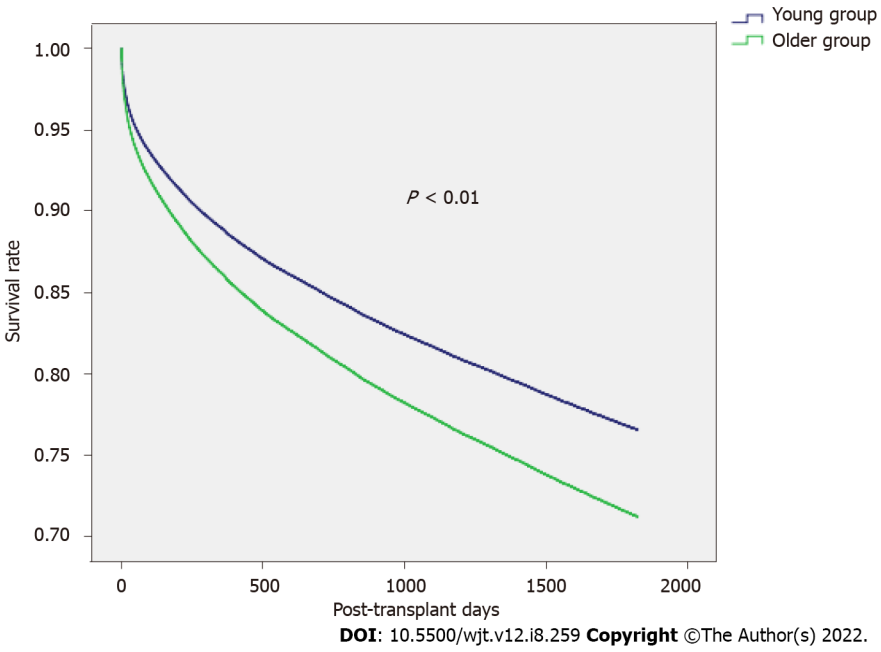
In patients with cirrhosis, the requirement of mechanical ventilation at time of transplant is associated with an increased risk of post-operative mortality[21]. In our study, older patients were less likely to be intubated at the time of transplant, this would be related to cautious recipient selection. The patients' requirements for dialysis and comorbidities of kidney dysfunction also had a significant impact on the outcomes of LT[22], which is further correlated with a higher MELD score. In our study, older patients had a lower MELD score and need for dialysis at the time of transplant, which might reflect the individual transplant center selection criteria for older recipients.

There were several limitations to this study. First, primary diagnosis at the time of listing for LT was used, but this diagnosis may not be accurate. If an alternative diagnosis is found post-transplant, these changes may not be recorded in the UNOS database. Secondly, we have evaluated only the patients who received LT, which means that older patients with comorbidities and/or severe clinical conditions who were not considered to be a candidate for LT, added to the selection bias in this study. Finally, long-term data regarding the graft and overall survival among older recipients is limited.

Table 4 Multivariable cox regression for five-year graft survival in older group

Variables	*B* (SE)	Hazard ratio (95%CI)	*P* value
Year of transplant	-0.05 (0.004)	0.954 (0.947-0.961)	< 0.001
Male	0.19 (0.04)	1.21 (1.12-1.30)	< 0.001
Re-transplant	0.41 (0.08)	1.50 (1.28-1.76)	< 0.001
Pre-LT diabetes	0.17 (0.04)	1.18 (1.10-1.27)	< 0.001
Ventilation	0.42 (0.08)	1.52 (1.30-1.76)	< 0.001
Portal vein thrombosis	0.18 (0.07)	1.20 (1.05-1.36)	0.006
MELD (per 10)	0.13 (0.02)	1.14 (1.10-1.18)	< 0.001
HCV Recipient	0.21 (0.04)	1.23 (1.15-1.33)	< 0.001
Donor age (per 10)	0.03 (0.01)	1.03 (1.002-1.054)	0.032
Donor risk index	0.25 (0.06)	1.29 (1.15-1.44)	< 0.001
Cold ischemia time	0.017 (0.006)	1.02 (1.01-1.03)	0.003

LT: Liver transplantation; MELD: Model for end-stage liver disease; HCV: Hepatitis C virus; CI: Confidence interval.



DOI: 10.5500/wjt.v12.i8.259 **Copyright** ©The Author(s) 2022.

Figure 2 Comparison of graft survival in older group (age ≥ 65 years) *vs* young group (age 18-64).

CONCLUSION

The number of LT in older recipients has significantly increased over time along with the change in indication of LT. Older age alone should not be a contraindication for LT, however, careful evaluation processes and postoperative care are necessary to improve the transplant outcomes.

ARTICLE HIGHLIGHTS

Research background

The average age of liver transplant and the number of liver transplant in the older recipients is increasing.

Research motivation

We wanted to investigate the outcomes of expansion of criteria of liver transplantation (LT) with increasing inclusion of older recipients and donors. We also wanted to identify any potentially modifiable risk factors that may be associated lower with graft or patient survival.

Research objectives

We compared one, three- and five-year graft and patient survival between two groups of liver transplant recipients: Younger group (18-64 years old) and older group (≥ 65 years old) between the period of 1987-2019 in the United States.

Research methods

We analyzed data from the United Network for Organ Sharing database between 1987-2019. The sample was split into younger group (18-64 years old) and older group (≥ 65 years old).

Research results

The number of LT for older patients was highest in 2019 (1920). In the older group, the percentage of non-alcoholic steatohepatitis and hepatocellular carcinoma as the primary etiology for LT was higher than younger group compared to the older group (16.4 % *vs* 5.9%; 14.9% *vs* 6.9%). On univariable analysis, there was no difference in post-transplant length of hospitalization, one-year and five-year overall survivals between the two groups. On multivariable Cox-Hazard regression analysis for graft survival, older group (hazard ratio: 1.27, $P < 0.001$) had higher risk of graft failure which was associated with male gender, pre-transplant diabetes, previous history of LT, ventilation at the time of LT, high model for end-stage liver disease score, recipient portal vein thrombosis, hepatitis C virus positive status, and higher donor risk index.

Research conclusions

Older age alone should not be considered to be a contraindication for LT.

Research perspectives

Careful evaluation process and postoperative care are necessary to improve transplant outcomes.

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FOOTNOTES

Author contributions: Okumura K, Nishida S contributed to the study design, data analysis, data interpretation, and writing manuscript; Lee JS, Dhand A, Sogawa H, Veillette G, John D, Misawa R, Bodin R, Wolf DC, and Diflo T revised manuscript and critical revisions; and all authors approved the final version of the manuscript.

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SYSTEMATIC REVIEWS

Gastrointestinal manifestations, risk factors, and management in patients with post-transplant lymphoproliferative disorder: A systematic review

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Abstract

BACKGROUND
Patients with a history of solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT) are at an increased risk of developing post-transplant lymphoproliferative disorder (PTLD). The gastrointestinal (GI) tract is commonly affected as it has an abundance of B and T cells.

AIM
To determine typical GI-manifestations, risk factors for developing PTLD, and management.

METHODS
Major databases were searched until November 2021.

RESULTS
Non-case report studies that described GI manifestations of PTLD, risk factors for developing PTLD, and management of PTLD were included. Nine articles written within the last 20 years were included in the review. All articles found that patients with a history of SOT, regardless of transplanted organ, have a propensity to develop GI-PTLD.

CONCLUSION
GI tract manifestations may be nonspecific; therefore, consideration of risk factors is crucial for identifying GI-PTLD. Like other lymphoma variants, PTLD is very aggressive making early diagnosis key to prognosis. Initial treatment is reduction of immunosuppression which is effective in more than 50% of cases; however, additional therapy including rituximab, chemotherapy, and surgery may also be required.

Key Words: Post-transplant lymphoproliferative disorder; Gastrointestinal manifestations; Reduction of immunosuppression; Risk factors; Epstein-Barr virus

Core Tip: Patients with a history of solid-organ or hematopoietic stem cell transplantation are at an increased risk of developing post-transplant lymphoproliferative disorder (PTLD). The gastrointestinal (GI) tract is commonly affected as it has an abundance of B and T-cells. GI tract manifestations may be nonspecific; therefore, consideration of risk factors is crucial for identifying GI-PTLD. Like other lymphoma variants, PTLD is very aggressive making early diagnosis key to prognosis. Initial treatment is reduction of immunosuppression which is effective in more than 50% of cases; however, additional therapy including surgery and chemotherapy may also be required. We performed a systematic review of GI-PTLD to better describe GI manifestations, risk factors for disease, and management of GI-PTLD.

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INTRODUCTION

While primary and secondary lymphoid neoplasms only constitute 1%-4% of all gastrointestinal (GI) malignancies[1,2]; post-transplant lymphoproliferative disorder (PTLD) is one of the most common post-transplant malignancies within the GI tract. PTLD is a lymphoma variant which can manifest in patients having solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). Patients with a history of SOT are at increased risk of developing PTLD which may be more prone to develop in the GI tract. Review of the typical GI symptoms and timing of symptom development will be invaluable to the clinician caring for patients with a transplantation history, especially as this patient population continues to grow. Risk factors for developing PTLD are important to identify as PTLD can present in a myriad of ways and clinical suspicion greatly aids in timely evaluation and treatment for PTLD. We performed a review of the GI manifestations of PTLD. We described risk factors associated with the development of PTLD. Additionally, we reviewed the management of patients diagnosed with PTLD and associated complications.

MATERIALS AND METHODS

Protocol

This review has been in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA)[5].

Eligibility criteria, literature search, and search strategy

An expert librarian conducted a systematic literature search using a priori protocol to identify studies reporting on GI-PTLD manifestations, risk factors for the development of GI-PTLD, and management of GI-PTLD. The search strategies included "gastrointestinal manifestations", "risk factors", "management", "reduction of immunosuppression", "post-transplant", "lymphoproliferative disorder", "EBV", and "PTLD". The search was run in November 2021 across multiple databases, including Medline, and Scopus. The search was restricted to articles in English and identified searches were exported to a reference manager (EndNote). We cross-checked reference lists of identified sources for additional relevant studies. We also cited high-quality articles in *Reference Citation Analysis* (https://www.refere

ncecitationanalysis.com).

Study selection

This systematic review included studies that evaluated GI manifestations of PTLD. Studies were included irrespective of primary organ transplantation. Information was gathered from nine of the most relevant articles pertaining to GI-PTLD. Additional studies were incorporated to provide background on PTLD manifestations, risk factors, imaging, treatment, and outcomes. Studies reporting performance in pediatric age groups (< 18 years), conference abstracts, and non-English studies were excluded. Studies were restricted to full text. Two authors decided on the final selection (Reiche W, Tauseef A). Details presented in PRISMA flow diagram (Supplementary Figure 1).

RESULTS

PTLD can manifest as nodal or more commonly as extranodal disease occurring in solid organ tissue outside of lymph nodes[6]. The most involved extranodal sites are the GI tract (23%-30%), lungs (4%-23%), bone marrow (15%-17%), central nervous system (5%-15%), liver (5%-13%), and the allograft itself (15%-19%)[7-9] in Figure 1. The GI tract is one of the most affected organs due to the preponderance of B and T lymphocytes which are prone to develop malignant change[10]. Patients with GI-PTLD usually present with nonspecific constitutional symptoms including fatigue, fever, night sweats, lymphadenopathy, and weight loss[11,12]. Not uncommonly, patients may also have nausea, vomiting, abdominal pain, abdominal fullness, diarrhea or increased ostomy output, and occult or evident bleeding. PTLD may present as a small bowel obstruction, GI bleeding, gastric or intestinal perforation, or obstruction [13].

One study evaluating the location of PTLD found the stomach was one of the most common sites of involvement. Out of a total of 472 patients, 56 patients (11.9%) had gastric PTLD while 415 patients (88.1%) had PTLD in other locations[13] (Table 1). The small bowel is another common area of involvement, PTLD of the small bowel was diagnosed in 50% of patients having PTLD after small bowel transplantation (SBT)[14]. In patients requiring surgery for GI-PTLD complications, organ involvement varied: Small bowel (50%), proximal right colon (31.2%), and stomach, duodenum, and transverse colon (6.2%)[15].

SOT or HSCT are known risk factors for developing lymphoma or other lymphoproliferative disorders[11]. While studies have shown GI-PTLD can develop after most types of transplant, the incidence of PTLD after intestinal transplantation was determined to be higher than other types of SOT [16]. The mean time to PTLD varies and is dependent on host factors and transplant type. One study found the mean time for development of PTLD is 1 year for patients having HSCT, while the time to PTLD presentation may be up to 7 years after SOT[11,16-18]. The mean interval from transplantation to PTLD diagnosis after SBT was 2.7 years[14]. After liver transplantation, the average time from transplantation to diagnosis of PTLD was 7.2 years[15].

Induction and maintenance regimens are selected based on the risk of acute organ rejection associated with the transplant. T-cell depleting therapy (recombinant anti-thymocyte globulin), interleukin-2 receptor subunit alpha (IL2RA), or no immunosuppression may be used for induction therapy. For instance, for adult heart transplants, T-cell depleting therapy is most commonly used for induction; however half of transplant patients do not receive induction[19]. In lung transplants, induction therapy is used nearly 80% of the time and most commonly IL2RA are used[20,21]. For kidney transplants, induction therapy is provided 90% of the time and is usually T-cell depleting therapy[22,23]. Most commonly, induction is not used after liver transplant[24,25]. For pancreas transplant induction, T-cell depleting therapy is most commonly used (90%)[26]. Lastly, intestinal transplant induction is usually comprised of T-cell depleting agents (63.9%) or no induction (27.8%)[27]. Current trends in maintenance immunosuppression therapy for pancreas, heart, lung, kidney, liver, intestinal transplants are as follows: Pancreas transplants most often use tacrolimus, mycophenolate mofetil (MMF) and nearly 70% of patients are on corticosteroids[26]. Heart transplant maintenance therapy most often includes tacrolimus and MMF and corticosteroids are used nearly 50% of the time[19]. Lung transplants typically are treated with tacrolimus, MMF, and corticosteroids (80%)[21]. Kidney transplants are either treated with tacrolimus, MMF, and corticosteroids (54.1%) or tacrolimus and MMF (36.8%)[22,23]. Liver transplants are typically treated with tacrolimus, MMF, and steroids in 65% of patients[24,25]. Intestinal transplants are treated with tacrolimus (73%) and corticosteroids may be used (37.4%)[28].

Imaging findings of GI-PTLD are variable and can appear as wall thickening, dilatation, an eccentric or exophytic mass, luminal ulceration, short segment intussusception, and soft tissue nodules in the peritoneum (Figure 2)[12]. Solid organ involvement is usually in the form of infiltrating lesions appearing as a solitary or a multi-nodular mass[17]. Additional risk factors for developing GI-PTLD include induction immunosuppression, prolonged duration of immunosuppression, younger age, fewer human leukocyte antigen matches, use of anti-lymphocyte antibodies, prior splenectomy, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis C, and human herpesvirus 8 (HHV-8)[10,12,15,17,29,30] (Table 2). EBV is the most common risk factor for developing PTLD, risk is higher in recipients who

Table 1 Study details

Ref.	Localization of PTLD	Time from transplant to PTLD (yr)	Classification	
			Monomorphic	Polymorphic
Wozniak *et al*[17]	Small bowel: 9/19 Colorectal: 3/19 Liver: 2/19	7.4	9/19	10/19
Koo *et al*[14]	Small bowel: 11/12 Colorectal: 1/12	2.7	1/12	8/12
Khedmat *et al*[13]	Stomach + small bowel: 13/45 Stomach + pancreas: 3/45 Stomach + liver: 7/45 Stomach: 56/472	4.1	23/39	13/39
Khedmat *et al*[16]	Colorectal + liver: 10/73 Colorectal + small bowel: 22/73 Colorectal + stomach: 2/73 Colorectal: 81/563	4.1	36/57	18/57
Cruz Jr *et al*[15]	Colorectal: 6/17 Small bowel: 11/17	7.2	13/17	3/17
Ganne *et al*[18]	Small bowel: 1/8 Stomach: 1/8	4.8	0/2	2/2

PTLD: Post-transplant lymphoproliferative disorder.

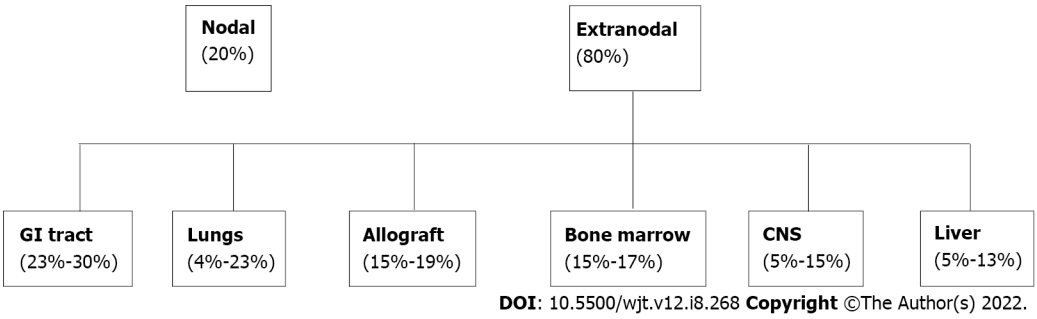

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Figure 1 Distribution of post-transplant lymphoproliferative disorder by organ involvement. GI: Gastrointestinal.

are initially seronegative but develop positivity after transplantation[15,31,32]. EBV can be transmitted *via* the graft; however, non-leukoreduced blood products also have the potential to transmit EBV[31]. EBV is present in 60%-70% of patients diagnosed with PTLD[30]. CMV can increase the likelihood of developing PTLD by seven times[33,34]. Hepatitis C and HHV-8 are also risk factors for developing PTLD especially when patients have EBV seropositivity[33]. If more than one risk factor is present, there appears to be cumulative risk[35].

According to the revised 2017 World Health Organization classification of tumors of hematopoietic and lymphoid tissues, PTLD is categorized into four major groups based on morphologic pattern: Non-destructive PTLD, monomorphic PTLD, polymorphic PTLD, and classic Hodgkin lymphoma PTLD. Apart from the polymorphic group, all other groups are further sub-categorized. Non-destructive PTLD are usually EBV-positive and are characterized by architectural preservation of the involved tissue without features suggestive of malignant lymphoma. The subcategories for non-destructive PTLD include plasmacytic hyperplasia, florid follicular hyperplasia, and infectious mononucleosis PTLD. Monomorphic or polymorphic PTLD may follow non-destructive PTLD lesions; however, most non-destructive PTLD have polyclonal B-cells. Polymorphic-PTLD are characterized by a heterogenous population that includes immunoblasts, plasma cells, and small to moderate sized lymphoid cells that

Table 2 Study details regarding gastrointestinal post-transplant lymphoproliferative disorder

Ref.	Noted findings regarding GI-PTLD
Plummer *et al*[11]	PTLD presentation is non-specific. Prognosis is variable dependent on burden of disease, age at the time of diagnosis, and morphological subtype
Small *et al*[7]	EBV infection is crucial in the pathophysiology of PTLD. EBV+ patients are more likely to respond to RIS. Chemotherapy can be utilized after RIS if RIS appears unsuccessful
Dako *et al*[12]	Imaging of PTLD involving GI tract is variable. Imaging of PTLD may appear as a large mass, luminal ulceration, intussusception, or soft tissue nodules
Wozniak *et al*[17]	Risk of acute cellular rejection increased when treatment for PTLD occurred. Notable risk factors for PTLD include chronic immunosuppression, viral infection, and increased time from transplantation
Koo *et al*[14]	Incidence rate of PTLD after small bowel transplantation was up to 50%
Khedmat *et al*[13]	Clinical presentation of PTLD is nonspecific. Early treatment with RIS, rituximab, chemotherapy, or surgical therapy, if indicated, can decrease mortality rates
Khedmat *et al*[16]	Patients with PTLD and colorectal symptoms were noted to have a higher risk of metastatic disease. Colorectal PTLD may occur more frequently and may be more aggressive in men compared to women. Multi-organ failure may be more common in men compared to women if there is colorectal PTLD
Cruz Jr *et al*[15]	Surgical intervention uncommonly required for PTLD. Most common surgical need is for intestinal obstruction
Ganne *et al*[18]	PTLD was found to respond to rituximab irrespective of EBV status. Patients with higher EBV titers usually benefited from combination RIS, rituximab, and CHOP therapy. EBV-specific donor cytotoxic lymphocyte infusions may be effective but may lead to graft rejection. GI bleeding may be a presenting feature of disease

PTLD: Post-transplant lymphoproliferative disorder; EBV: Epstein-Barr virus; RIS: Immunosuppression; GI: Gastrointestinal.

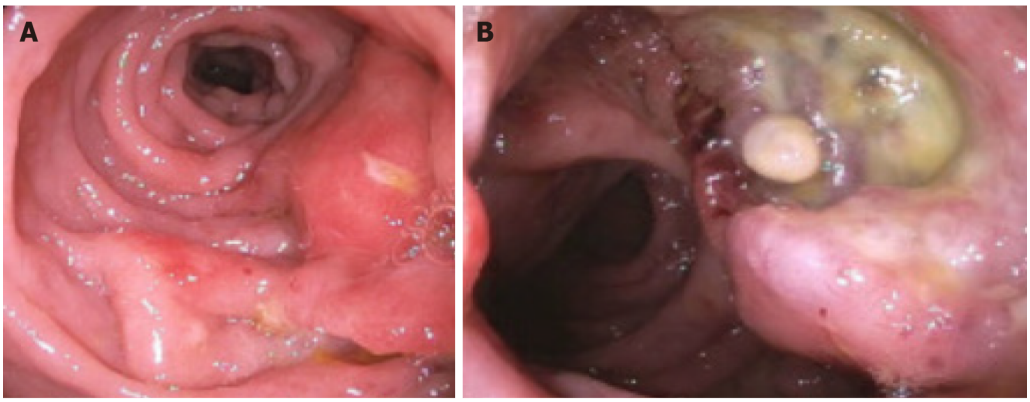

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Figure 2 Endoscopic appearance of post-transplant lymphoproliferative disorder. A: Nodular and ulcerated mucosa noted in the sigmoid colon; B: Ulcerated rectal mass.

efface the architecture of lymph nodes or may form destructive lesions but do not fulfill the criteria for lymphoma. Most cases of polymorphic-PTLD are EBV-positive. Monomorphic PTLD comprise 60%-80% of all PTLD and fulfill criteria for B-cell or T/natural killer-cell neoplasms (Figures 3-6). The least common form of PTLD are the classic Hodgkin lymphoma PTLD which are almost always EBV-positive [36].

Distinction is often made between early PTLD and late PTLD. The former more often associated with EBV positivity and graft involvement while less commonly associated with monomorphic morphology and less often presenting as extranodal disease[8]. Treatment has not been found to differ based on this categorization[29,37,38]. Studies comparing early *vs* late PTLD have not shown a significant difference in survival[39,40]. Determination of EBV status is a crucial first step after the diagnosis of GI-PTLD has been made. EBV-specific cytotoxic T-cell immunity or donor lymphocyte infusions have been used as second line therapies if reduction of immunosuppression (RIS) or rituximab is not working, patients with EBV may be more responsive to RIS than patients without EBV[7,18]. However, there is no approved treatment in the United States or Europe. Several studies have failed to show improvement with antivirals alone in instances when patients have EBV and PTLD[29,31,,40,,41,].

Once GI-PTLD diagnosis has been confirmed with endoscopic biopsy, patients can be managed with RIS, chemotherapy, and surgical intervention for complications[11]. The most important first step in

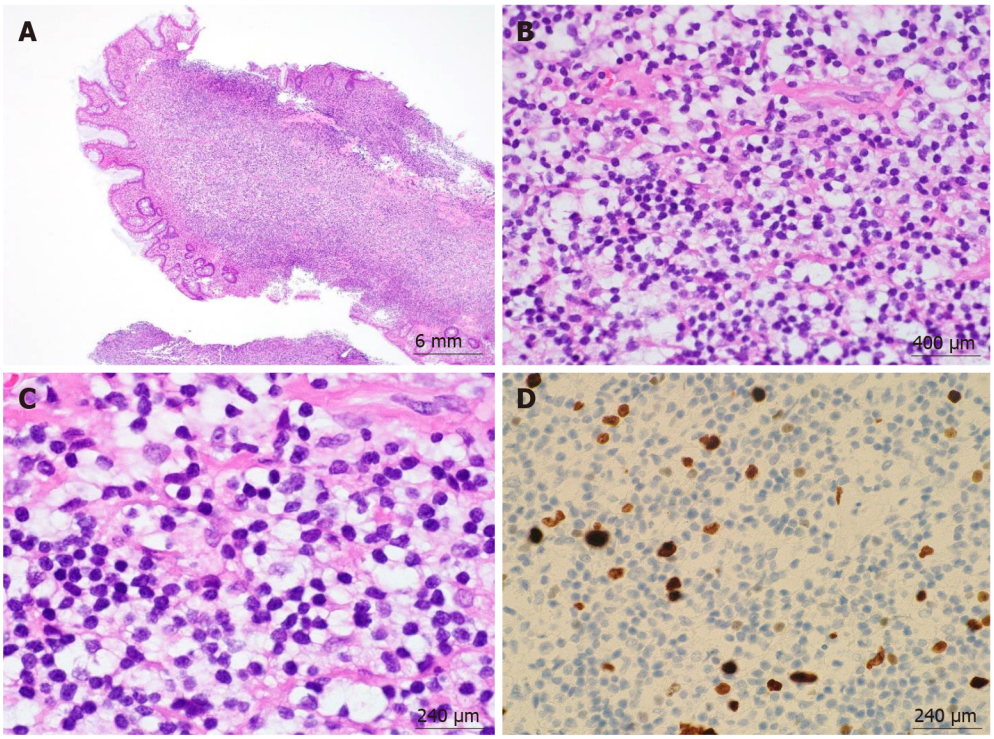

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Figure 3 Post-transplant lymphoproliferative disorder, monomorphic type (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue) arising in a sigmoid colon polyp. A: 4 ×/6 mm; B: 60 ×/400 μm; C: 100 ×/240 μm; D: 100 ×/240 μm. Hematoxylin & eosin stain showed a dense lymphoid infiltrate in the lamina propria composed of monotonous small-sized lymphoid cells with mature chromatin and abundant clear cytoplasm. Ki-67 showed low proliferation index.

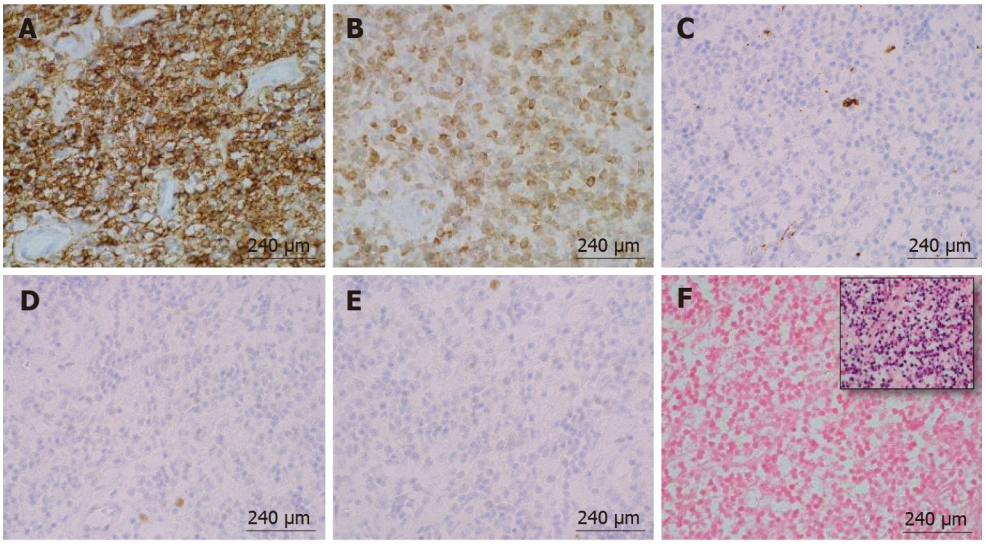

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Figure 4 Immunohistochemical and *in-situ* hybridization staining of post-transplant lymphoproliferative disorder, monomorphic type (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue) arising in a sigmoid colon polyp. A: CD20, 100 ×/240 μm; B: B-cell lymphoma (BCL)-2, 100 ×/240 μm; C: CD10, 100 ×/240 μm; D: BCL-6, 100 ×/240 μm; E: CD5, 100 ×/240 μm; F: EBER-ISH (inset: Positive control), 100 ×/240 μm. The monotonous small-size lymphocytes stained positive for CD20 and B-cell lymphoma-2 and were negative for the rest of the stains.

treatment is RIS[11,15]. Immunosuppressant therapy is usually decreased to 50% for calcineurin-inhibitors (cyclosporine, tacrolimus) and MMF or azathioprine, if also prescribed, are discontinued[42]. In the largest study to date evaluating the efficacy of standard RIS, response was nearly 45%. Rates of up to 80% have been reported[31]. More than 70% of the time, RIS will be efficacious regardless of PTLD subtype, EBV status, and early *vs* late disease. RIS may not be sufficient in monomorphic PTLD[43]. RIS may not work if the disease is bulky, the cancer stage is severe, if multi-organ dysfunction is present, if

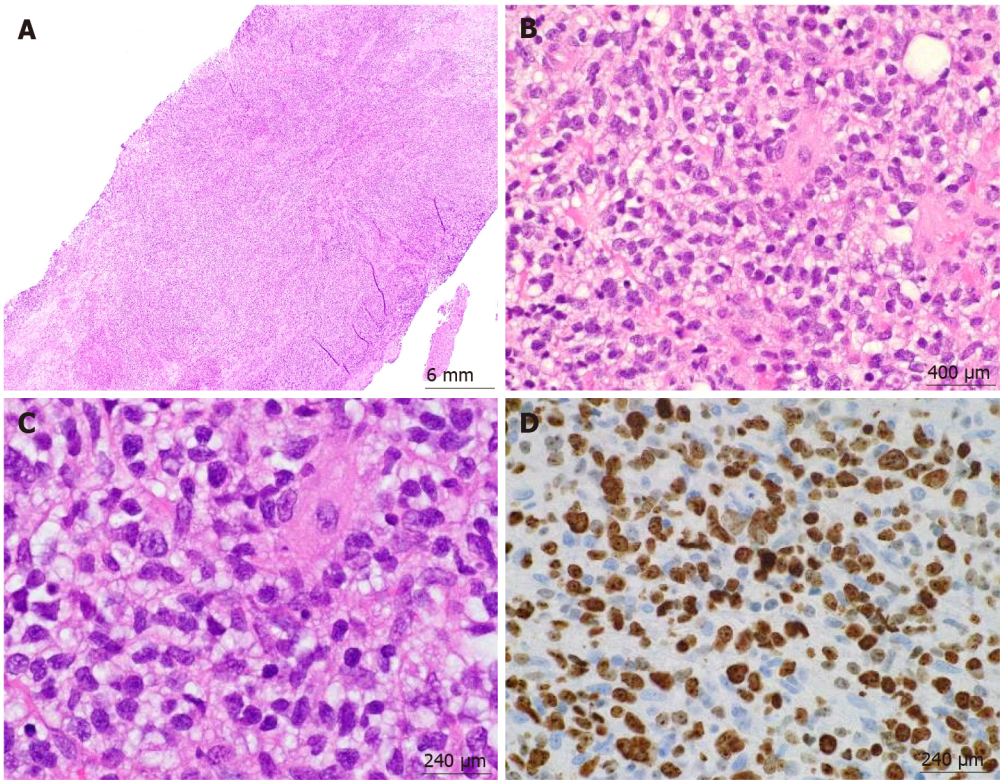

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Figure 5 Post-transplant lymphoproliferative disorder, monomorphic type (diffuse large B-cell lymphoma, non-germinal center type) arising from an ulcerated anal mass. A: 4 ×/6 mm; B: 60 ×/400 μm; C: 100 ×/240 μm; D: 100 ×/240 μm. Hematoxylin & eosin stain showed a diffuse lymphoid infiltrate composed of large pleomorphic cells with clear to eosinophilic cytoplasm, irregular nuclear contours, and prominent nucleoli in a background of fibroadipose tissue. Ki-67 showed high proliferation index.

quick treatment is needed, or for older adults[33,44]. Although beneficial as the first step in management, RIS can be associated with acute cellular rejection with the highest risk in the first year after transplantation[36].

If RIS is not sufficient, patients should be considered for antiviral therapy, rituximab, and chemotherapy[7]. Treatment is dependent on the PTLD subtype. Classical Hodgkin lymphoma PTLD is treated with standard adriamycin, bleomycin, vinblastine, and dacarbazine. Patients with PTLD diffuse large B-cell lymphoma type are treated according to the PTLD-1 trial with rituximab induction (weekly rituximab for four weeks) followed by stratification based on response. Patients in clinical remission may be treated with maintenance rituximab weekly for 4 wk. Patients with a suboptimal response may be treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (Figure 7)[45].

Rituximab has been found to be an effective therapy for PTLD. In one study including 8 patients with PTLD after SOT, complete resolution of PTLD was observed in 7 cases. Rituximab was administered at a dose of 375 mg/m^2 once a week for four consecutive weeks. Additionally, this study found patients with PTLD usually respond to anti-CD20 monoclonal antibodies irrespective of EBV status[18]. Radiotherapy has been found to have a favorable effect in stage 1 plasmacytoma-like PTLD; however, it is infrequently used for solitary PTLD. Radiotherapy is most often utilized in treatment for central nervous system PTLD[45].

Surgery should be considered in patients who develop GI complications including perforation, hemorrhage, and most commonly intestinal obstruction. Surgical resection is rarely considered in patients as PTLD tends to be multi-focal. A retrospective review of 5677 patients after isolated liver transplantation found only 16 patients developed post-transplantation GI complications associated with PTLD requiring surgical intervention. Overall mortality in this cohort was 69% and most patients died within the first year of explorative laparotomy. This same study found initial mortality higher in patients receiving surgery; however, long-term outcomes do not appear to be affected[15]. Prognosis is dependent on burden of disease, location of PTLD, morphological subtype, and other patient-related factors[11]. Once present, PTLD progression is aggressive; however, early appropriate treatment can decrease mortality rates. In one study comparing gastric PTLD and non-gastric PTLD, patients developing GI-PTLD had survival rates of 71% and 54% at one and five years, respectively[13].

Mortality rates in patients requiring surgery compared to rituximab and chemotherapy found no significant difference between treatment type. Mortality associated with surgical treatment was 16%, like that observed in patients who received rituximab. While mortality rates in patients treated with

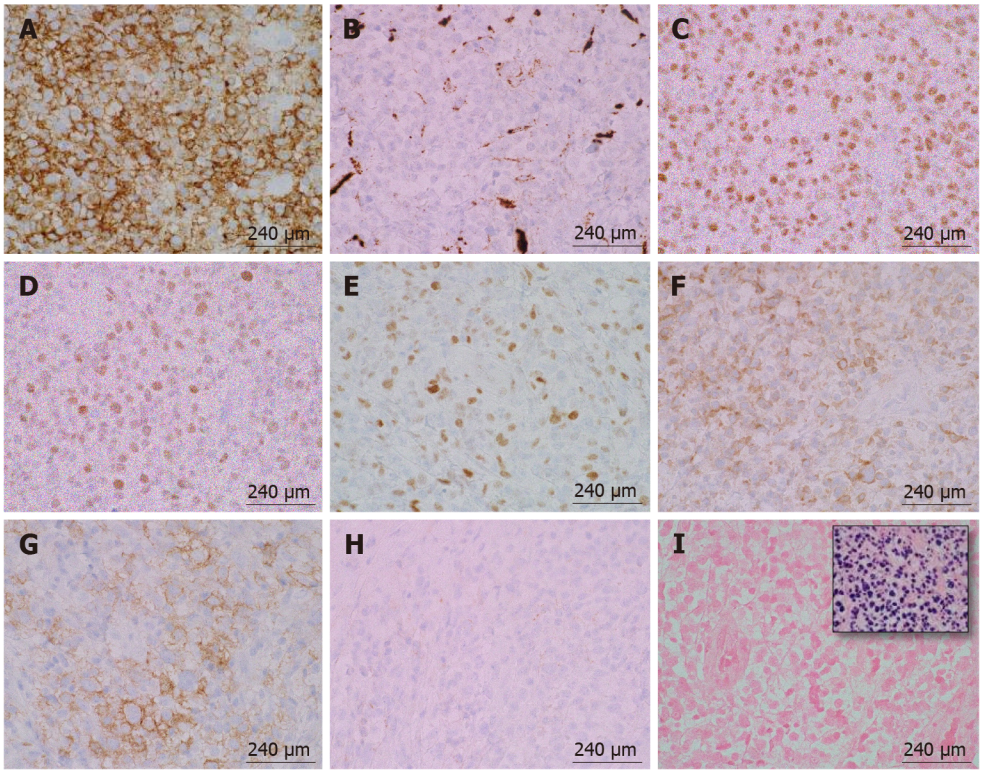

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Figure 6 Immunohistochemical and *in-situ* hybridization staining of post-transplant lymphoproliferative disorder, monomorphic type (diffuse large B-cell lymphoma, non-germinal center type) arising from an ulcerated anal mass. A: CD20, 100 ×/240 μm; B: CD10, 100 ×/240 μm; C: B-cell lymphoma (BCL)-6, 100 ×/240 μm; D: MUM-1, 100 ×/240 μm; E: c-MYC, 100 ×/240 μm; F: BCL-2, 100 ×/240 μm; G: CD30, 100 ×/240 μm; H: CD21, 100 ×/240 μm; I: EBER-ISH (inset: Positive control), 100 ×/240 μm. The large pleomorphic lymphocytes stained positive for CD20, B-cell lymphoma (BCL)-6, MUM-1, and BCL-2. These cells had a borderline staining for c-MYC (30%-40%), but FISH studies were negative for c-MYC rearrangements. CD30 was positive only in a subset of cells. EBER-ISH was negative.CD21 was negative and showed loss of follicular dendritic meshwork.

chemotherapy and radiotherapy with interferon alfa were 42.6% and 33%, respectively[13]. A favorable response to treatment has been noted in EBV-positive patients as they were more responsive to RIS compared to EBV-negative patients[29]. Similarly, a favorable outcome was also noted in patients who had localization to the stomach[13].

Conversely, colorectal involvement has been associated with a more severe disease presentation than PTLD involving non-colorectal sites. In one study, 75% of patients who developed colorectal symptoms had multi-organ involvement, significantly higher than the control group[16]. This same study found colorectal involvement was more likely in men. Male transplant patients developed colorectal PTLD more often than women 19.3% to 8.5%, respectively. Similarly, male transplant patients had a significantly shorter time from transplantation to diagnosis of the disease.

DISCUSSION

PTLD should be considered in patients with a history of SOT or HSCT as the large resident lymphocyte population in the GI tract has increased potential to develop malignancy. PTLD should be suspected to occur sooner after HSCT, within 1 year, and on average 4 to 5 years after SOT. However, there are multiple factors which appear to have a role in the time to development such as level of immunosuppression and presence of concomitant disease. Transplant type also appears to impact time to development as induction, maintenance, and the extent of inherent lymphoid tissue in the graft all contribute to the relative risk of developing PTLD. For instance, PTLD occurred sooner on average after small bowel transplant and later for liver transplant; in the studies reviewed, there was an approximate 4.5-year difference in time to onset of PTLD. Induction therapy, associated with increased risk of PTLD, is less frequently used after liver transplant while it is commonly used after intestinal transplants. The small bowel also has a greater supply of lymphoid tissue compared to the liver.

Diagnosis of PTLD can be problematic as the clinical spectrum and diagnostic testing are nonspecific. The illness script of PTLD is highly variable ranging from nonspecific abdominal symptoms to overt hemorrhage, perforation, or obstruction. The stomach and small intestine are the most frequently involved organs in the GI tract making clinical questioning and inquiry of symptoms which may

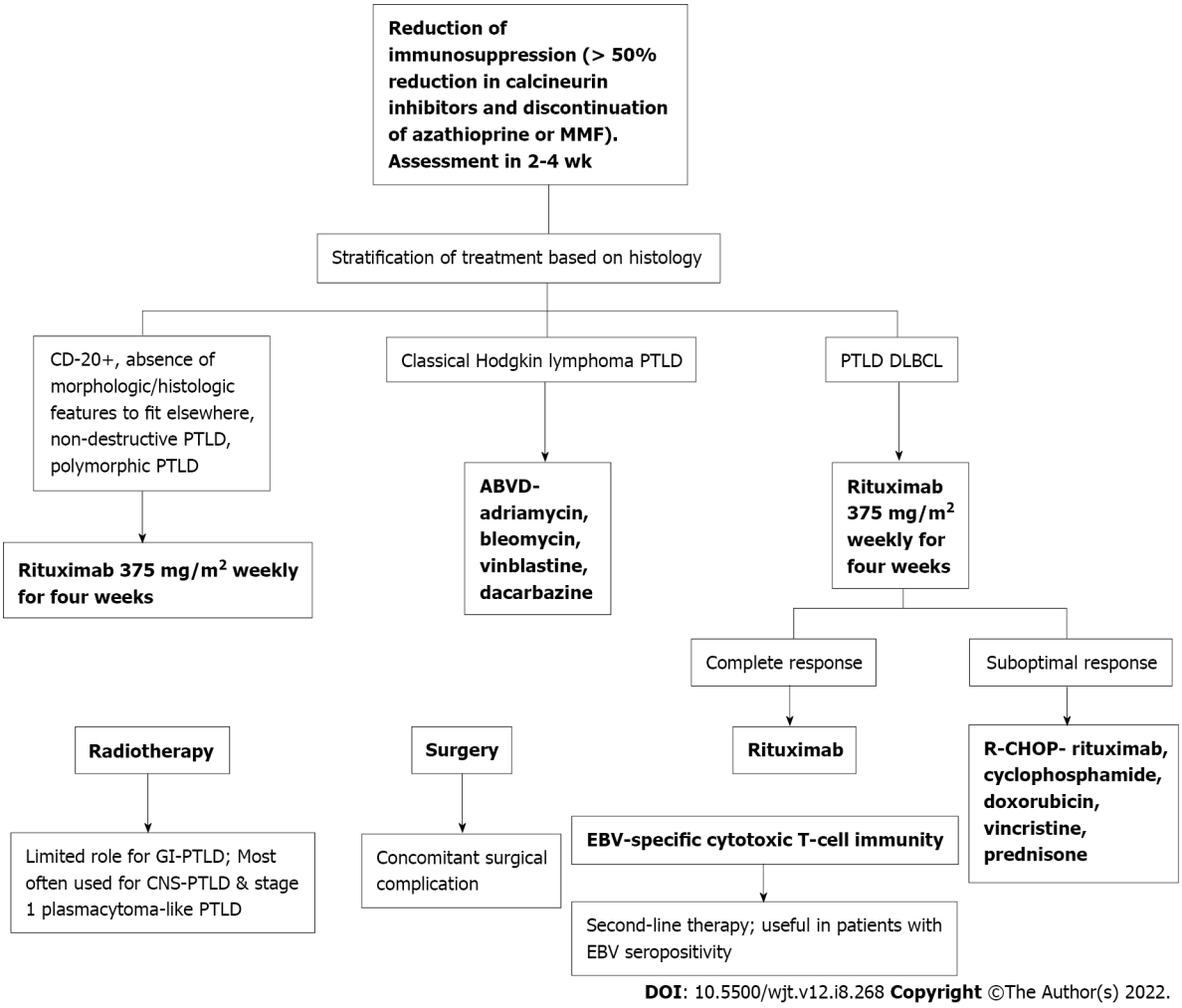

Figure 7 Workflow of the treatment for post-transplant lymphoproliferative disorder. PTLD: Post-transplant lymphoproliferative disorder; EBV: Epstein-Barr virus; GI: Gastrointestinal; MMF: Mycophenolate mofetil; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; DLBCL: Diffuse large B-cell lymphomas.

represent pathology in these organs important. Imaging findings of PTLD in the GI tract may range from focal intraluminal disease to perforation or metastatic disease. The various clinical presentations and wide-ranging imaging findings make it difficult to specifically identify PTLD by clinical presentation or imaging alone.

Consideration of PTLD should increase in patients with risk factors. Most importantly determination of EBV-status and risk factors for EBV infection need to be determined. EBV infection has been noted to increase the risk of PTLD by 6-76 times[46]. As mentioned previously, elucidation of details surrounding the transplant including transplant type, determination of RIS regimen including whether induction therapy was utilized are important. As transplantation continues to increase, so will the number of patients at risk for development of PTLD[14,19,22,23,25].

Like other lymphomas, PTLD is aggressive and mortality rates improve with early treatment. Prognosis and treatment are dependent on time of disease presentation, morphological subtype of PTLD, and concomitant systemic disease. The most important step in management is RIS; which is usually efficacious. Subsequently, rituximab and chemotherapy based on morphologic subtype have been found to be effective[18]. Differences in outcomes between surgery and treatment with rituximab are not well elucidated, nor is the role of endoscopy in management of PTLD. Broadly, treatment must consider both the risk of acute graft rejection and worsening lymphoproliferative disorder.

CONCLUSION

This study is a systematic review elucidating GI manifestations, associations, and management of GI-PTLD. Key points after review of the included studies are the presentation, imaging, and direct appearance of GI-PTLD is highly variable making clinical suspicion essential for timely diagnosis. Patients with nonspecific GI symptoms, and history of organ transplantation, should be evaluated for

GI-PTLD. Early detection is key for prognosis. Lastly, treatment is dependent on several factors and may include RIS, rituximab, chemotherapy, surgery, or a combination of these interventions. Initial treatment is intuitive and technically easy; however, RIS can be associated with acute graft rejections.

ARTICLE HIGHLIGHTS

Research background

Post-transplant lymphoproliferative disorder (PTLD) is one of the most common post-transplant malignancies within the gastrointestinal (GI) tract. PTLD is a lymphoma variant which can manifest in patients having solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT).

Research motivation

The current understanding of GI manifestations of PTLD including timing to development, risk factors for development, and treatment is limited by small sample size. Previous studies have noted a propensity for the GI tract to develop PTLD; therefore, more information regarding when it may develop, how it manifests, and treatments are needed especially as transplantation becomes more prevalent.

Research objectives

To identify the timing and clinical presentation of GI-PTLD, risk factors for its development, and treatment.

Research methods

We performed a systematic review after an extensive literature search.

Research results

The timing of GI-PTLD is variable but on average develops 4-5 years following SOT and may occur within 1 year after HSCT. Presentation may be insidious including nonspecific abdominal discomfort to fulminant hemorrhage, perforation, or obstruction. GI-PTLD is most likely to develop in the small intestine and stomach. Transplant type, level of induction and maintenance immunosuppression, Epstein-Barr virus-status among other risk factors increase the likelihood one may develop PTLD. PTLD is aggressive and mortality improves with early treatment which is dependent on extent of disease, and morphological subtype. The most important step of therapy is reduction of immunosuppression (RIS) which usually is effective.

Research conclusions

The presentation, imaging, and direct appearance of GI-PTLD is highly variable making clinical suspicion key for diagnosis. Early detection is key for prognosis; therefore, consideration of risk factors is essential. Treatment is dependent on several factors and may include RIS, rituximab, chemotherapy, surgery, or a combination of these interventions. Initial treatment is intuitive and technically easy; however, RIS can be associated with acute graft rejections.

Research perspectives

This study suggests ascertainment of risk factors is crucial for increasing clinical suspicion when assessing patients who may have GI-PTLD. The clinical and radiological presentation of GI-PTLD is highly variable; therefore, a high index of suspicion for GI-PTLD must be maintained so that early endoscopic diagnosis may allow for targeted treatment. Future prospective studies are needed to better elucidate incidence rates of GI-PTLD and the role of endoscopy in treatment.

FOOTNOTES

Author contributions: Reiche W, Tauseef A, and Sabri A involved in data acquisition; Reiche W drafted the article, final approval; Tauseef A contributed to the data acquisition; Sabri A involved in pathology figures, drafting the article; Mirza M, Cantu D, Silberstein P, Chandan S involved in critical revision, final approval.

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