

World Journal of *Transplantation*

World J Transplant 2022 August 18; 12(8): 211-280



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
Wongtanasarasasin 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

ABOUT COVER

Editorial Board Member of *World Journal of Transplantation*, Luis Cesar Bredt, FRCS (Hon), MD, PhD, Professor, Surgical Oncologist, Abdominal and Hepatobiliary Surgery, Renascença Hospital, Aracaju 49010-020, Sergipe, Brazil. lcbredt@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Transplantation* (WJT, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, etc.

INDEXING/ABSTRACTING

The WJT is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai; **Production Department Director:** Xu Guo; **Editorial Office Director:** Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Transplantation

ISSN

ISSN 2220-3230 (online)

LAUNCH DATE

December 24, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Maurizio Salvadori, Sami Akbulut, Vassilios Papalois, Atul C Mehta

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3230/editorialboard.htm>

PUBLICATION DATE

August 18, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Kidney disease in non-kidney solid organ transplantation

Kurtis J Swanson

Specialty type: Transplantation

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Grigoras A, Romania;
Kowalewski G, Poland; Ong LT,
Malaysia

Received: January 29, 2022

Peer-review started: January 29,
2022

First decision: March 25, 2022

Revised: April 7, 2022

Accepted: July 11, 2022

Article in press: July 11, 2022

Published online: August 18, 2022



Kurtis J Swanson, Division of Nephrology and Hypertension, University of Minnesota, Minneapolis, MN 55414, United States

Corresponding author: Kurtis J Swanson, MD, Assistant Professor, Division of Nephrology and Hypertension, University of Minnesota, 717 Delaware Street SE, Suite 353, MMC 1932, Minneapolis, MN 55414, United States. kjswanson88@gmail.com

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

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Swanson KJ. Kidney disease in non-kidney solid organ transplantation. *World J Transplant* 2022; 12(8): 231-249

URL: <https://www.wjgnet.com/2220-3230/full/v12/i8/231.htm>

DOI: <https://dx.doi.org/10.5500/wjt.v12.i8.231>

INTRODUCTION

Chronic kidney disease (CKD), most commonly defined as decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² 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 m². In one study of liver transplant recipients, approximately 57% had a GFR between 30-59 mL/min/1.73 m² [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 m², 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 m², *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 m² 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 iothexol 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 m². 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 m². 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 m² 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 NKSOT 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 NKSOT, 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 m² 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 m². Smail *et al*[18] also found that a pre-transplant eGFR < 60 mL/min/1.73 m² 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 m² ($P = 0.006$). 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 m² 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 m², 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 mL/min/1.73 m². 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 m² 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, <i>n</i>	Risk factors associated with kidney disease	Study conclusion
Kim <i>et al</i> [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 <i>et al</i> [18]	43	Pre-transplant eGFR < 60 mL/min/1.73 m 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% (<i>P</i> = 0.006); age, female sex, duration of diabetes pre-PTA (all <i>P</i> < 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 <i>et al</i> [19]	513	SCr > 1.5 mg/dL at transplant, age < 30	5 yr post-transplant ESKD rate of 13%
Odorico <i>et al</i> [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 <i>vs</i> 34% PAK patients (<i>P</i> = 0.035). PTA transplant was considered mildly renoprotective; this finding was not significant (HR = 0.29, 95%CI: 0.04-2.37, <i>P</i> = 0.182)
Chatzizacharias <i>et al</i> [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 <i>et al</i> [22]	28		Stable native kidney function comparing pre-transplant to post-transplant (0.95 ± 0.2 <i>vs</i> 0.96 ± 0.22, <i>P</i> > 0.05); limited follow up of 3 mo
Coppelli <i>et al</i> [17]	32		32 PTA recipients did not have significantly different creatinine pre- and post-transplant (0.95 ± 0.25 mg/dL <i>vs</i> 1.00 ± 0.19 mg/dL, <i>P</i> > 0.05); PTA lead to improvement in lipids, BP, and albuminuria
Genzini <i>et al</i> [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- <i>vs</i> post-transplantation = 57.3 ± 9 <i>vs</i> 34.8 ± 32 mL/min, <i>P</i> = 0.003); (group 2 CrCl pre- <i>vs</i> post-transplantation = 107.1 ± 25 <i>vs</i> 81.0 ± 23 mL/min, <i>P</i> = 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 <i>et al</i> [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 <i>vs</i> 55.6 post-transplantation (<i>P</i> < 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 m² [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 $10\% \pm 3\%$, 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 m² 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, <i>n</i>	Risk factors associated with kidney disease	Study conclusion
Ojo <i>et al</i> [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 <i>et al</i> [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%) <i>vs</i> 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 $10\% \pm 3\%$, 95%CI: 3%-15%
Herlenius <i>et al</i> [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 <i>vs</i> 52% not requiring RRT; 10%-20% incidence of CKD, 2%-8% rate of ESRD with a mortality rate between 25%-50%
Gonwa <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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% <i>vs</i> 26.8%, respectively ($P < 0.001$)
Kollman <i>et al</i> [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 $< 45 \text{ mL/min/1.73 m}^2$ 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 $< 30 \text{ mL/min/1.73 m}^2$ 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 $> 1 \text{ d}$ (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, <i>n</i>	Risk factors associated with kidney disease	Study conclusion
Ojo <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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 <i>et al</i> [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, <i>n</i>	Risk factors associated with kidney disease	Study conclusion
Ojo <i>et al</i> [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 <i>et al</i> [41]	296	AKI: Baseline GFR (OR = 0.98, 95%CI: 0.96-0.99, <i>P</i> = 0.012), pulmonary diagnosis other than COPD (OR = 6.80, 95%CI: 1.5-30.89, <i>P</i> = 0.013), mechanical ventilation > 1 d (OR = 6.16, 95%CI: 1.70-22.24, <i>P</i> = 0.006) and parenteral amphotericin B use (OR = 3.04, 95%CI: 1.03-8.98, <i>P</i> = 0.045)	AKI rate of 56% (<i>n</i> = 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% (<i>P</i> < 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, <i>P</i> = 0.0018) and AKI requiring RRT (HR = 6.77, 95%CI: 4.00-11.44, <i>P</i> < 0.0001) associated with mortality
Broekroelofs <i>et al</i> [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 <i>et al</i> [44]	425	Lower creatinine clearance (<i>P</i> = 0.03) and greater recipient height (<i>P</i> = 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 <i>et al</i> [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 <i>P</i> < 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, <i>P</i> < 0.001), and older age at transplant (RR = 1.02, 95%CI: 1.008-1.04), <i>P</i> = 0.004) were significant predictors of death
Ishani <i>et al</i> [9]	186	DBP than 90 mmHg (RR = 1.30, 95%CI: 1.05-1.60, <i>P</i> = 0.02), 1 mo post-transplant Cr (RR = 1.28, 95%CI: 1.02-1.70, <i>P</i> = 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, <i>P</i> = 0.0009)
Paradela de la Morena <i>et al</i> [46]	161	Older age (OR = 2.0; <i>P</i> < 0.001) and CMV infection (OR = 2.2; <i>P</i> = 0.045)	68.6% of the cohort developed CKD; CKD at 1 yr was associated with increased mortality compared to those without CKD (<i>P</i> = 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 m² 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 m² 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 m² (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 m² vs 114 mL/min/1.73 m², *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 \cdot 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, <i>n</i>	Risk factors associated with kidney disease	Study conclusion
Huard <i>et al</i> [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 <i>et al</i> [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% (<i>n</i> = 5). Two patients developed renal failure within the first year and required hemodialysis
Ueno <i>et al</i> [49]	24	Cumulative tacrolimus levels > 4500ng ng-day/mL associated with significantly decreased creatinine clearance at 2 yr (<i>P</i> = 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 , <i>P</i> < 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

Author contributions: Swanson KJ contributed to the concept/design, article drafting, critical revision of article and approval of article.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United States

ORCID number: Kurtis J Swanson 0000-0001-5952-9054.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

REFERENCES

- 1 **Stevens PE**, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; **158**: 825-830 [PMID: [23732715](#) DOI: [10.7326/0003-4819-158-11-201306040-00007](#)]
- 2 **Ojo AO**, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; **349**: 931-940 [PMID: [12954741](#) DOI: [10.1056/NEJMoa021744](#)]
- 3 **Bloom RD**, Reese PP. Chronic kidney disease after nonrenal solid-organ transplantation. *J Am Soc Nephrol* 2007; **18**: 3031-3041 [PMID: [18039925](#) DOI: [10.1681/ASN.2007040394](#)]
- 4 **Clajus C**, Hanke N, Gottlieb J, Stadler M, Weismüller TJ, Strassburg CP, Bröcker V, Bara C, Lehner F, Drube J, Kielstein JT, Schwarz A, Gueler F, Haller H, Schiffer M. Renal comorbidity after solid organ and stem cell transplantation. *Am J Transplant* 2012; **12**: 1691-1699 [PMID: [22676355](#) DOI: [10.1111/j.1600-6143.2012.04047.x](#)]
- 5 **Shaffi K**, Uhlig K, Perrone RD, Ruthazer R, Rule A, Lieske JC, Navis G, Poggio ED, Inker LA, Levey AS. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. *Am J Kidney Dis* 2014; **63**: 1007-1018 [PMID: [24703720](#) DOI: [10.1053/j.ajkd.2014.01.436](#)]
- 6 **Kim SJ**, Smail N, Paraskevas S, Schiff J, Cantarovich M. Kidney function before pancreas transplant alone predicts subsequent risk of end-stage renal disease. *Transplantation* 2014; **97**: 675-680 [PMID: [24637866](#) DOI: [10.1097/01.TP.0000437556.87109.45](#)]

- 7 **Gonwa TA**, Jennings L, Mai ML, Stark PC, Levey AS, Klintmalm GB. Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. *Liver Transpl* 2004; **10**: 301-309 [PMID: [14762871](#) DOI: [10.1002/Lt.20017](#)]
- 8 **Hamour IM**, Omar F, Lyster HS, Palmer A, Banner NR. Chronic kidney disease after heart transplantation. *Nephrol Dial Transplant* 2009; **24**: 1655-1662 [PMID: [19168463](#) DOI: [10.1093/ndt/gfn759](#)]
- 9 **Ishani A**, Erturk S, Hertz MI, Matas AJ, Savik K, Rosenberg ME. Predictors of renal function following lung or heart-lung transplantation. *Kidney Int* 2002; **61**: 2228-2234 [PMID: [12028464](#) DOI: [10.1046/j.1523-1755.2002.00361.x](#)]
- 10 **Ojo AO**. Renal disease in recipients of nonrenal solid organ transplantation. *Semin Nephrol* 2007; **27**: 498-507 [PMID: [17616280](#) DOI: [10.1016/j.semnephrol.2007.03.010](#)]
- 11 **Kubal C**, Cockwell P, Gunson B, Jesky M, Hanvesakul R, Dronavalli V, Bonser RS, Neil D. Chronic kidney disease after nonrenal solid organ transplantation: a histological assessment and utility of chronic allograft damage index scoring. *Transplantation* 2012; **93**: 406-411 [PMID: [22217532](#) DOI: [10.1097/TP.0b013e318240e984](#)]
- 12 **Wiseman AC**. CKD in Recipients of Nonkidney Solid Organ Transplants: A Review. *Am J Kidney Dis* 2022; **80**: 108-118 [PMID: [34979161](#) DOI: [10.1053/j.ajkd.2021.10.014](#)]
- 13 **Schwarz A**, Haller H, Schmitt R, Schiffer M, Koenecke C, Strassburg C, Lehner F, Gottlieb J, Bara C, Becker JU, Broecker V. Biopsy-diagnosed renal disease in patients after transplantation of other organs and tissues. *Am J Transplant* 2010; **10**: 2017-2025 [PMID: [20883535](#) DOI: [10.1111/j.1600-6143.2010.03224.x](#)]
- 14 **Boyle JM**, Moualla S, Arrigain S, Worley S, Bakri MH, Starling RC, Heyka R, Thakar CV. Risks and outcomes of acute kidney injury requiring dialysis after cardiac transplantation. *Am J Kidney Dis* 2006; **48**: 787-796 [PMID: [17059998](#) DOI: [10.1053/j.ajkd.2006.08.002](#)]
- 15 **Bloom RD**, Doyle AM. Kidney disease after heart and lung transplantation. *Am J Transplant* 2006; **6**: 671-679 [PMID: [16539623](#) DOI: [10.1111/j.1600-6143.2006.01248.x](#)]
- 16 **Fioretto P**, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 1998; **339**: 69-75 [PMID: [9654536](#) DOI: [10.1056/NEJM199807093390202](#)]
- 17 **Coppelli A**, Giannarelli R, Vistoli F, Del Prato S, Rizzo G, Mosca F, Boggi U, Marchetti P. The beneficial effects of pancreas transplant alone on diabetic nephropathy. *Diabetes Care* 2005; **28**: 1366-1370 [PMID: [15920053](#) DOI: [10.2337/diacare.28.6.1366](#)]
- 18 **Smail N**, Paraskevas S, Tan X, Metrakos P, Cantarovich M. Renal function in recipients of pancreas transplant alone. *Curr Opin Organ Transplant* 2012; **17**: 73-79 [PMID: [22186098](#) DOI: [10.1097/MOT.0b013e32834f0145](#)]
- 19 **Gruessner RW**, Sutherland DE, Kandaswamy R, Gruessner AC. Over 500 solitary pancreas transplants in nonuremic patients with brittle diabetes mellitus. *Transplantation* 2008; **85**: 42-47 [PMID: [18192910](#) DOI: [10.1097/01.tp.0000296820.46978.3f](#)]
- 20 **Odorico JS**, Voss B, Munoz Del Rio A, Levenson G, Becker YT, Pirsch JD, Hoffman RM, Sollinger HW. Kidney function after solitary pancreas transplantation. *Transplant Proc* 2008; **40**: 513-515 [PMID: [18374117](#) DOI: [10.1016/j.transproceed.2008.01.038](#)]
- 21 **Chatzizacharias NA**, Vaidya A, Sinha S, Sharples E, Smith R, Jones G, Brockmann J, Friend PJ. Risk analysis for deterioration of renal function after pancreas alone transplant. *Clin Transplant* 2012; **26**: 387-392 [PMID: [21980989](#) DOI: [10.1111/j.1399-0012.2011.01534.x](#)]
- 22 **Marchetti P**, Boggi U, Coppelli A, Giannarelli R, Vistoli F, Aragona M, Del Prato S, Mosca F. Pancreas transplant alone. *Transplant Proc* 2004; **36**: 569-570 [PMID: [15110596](#) DOI: [10.1016/j.transproceed.2004.02.032](#)]
- 23 **Genzini T**, Marchini GS, Chang AJ, Antunes I, Hayashi A, Abensur H, Kataoka L, Crescentini F, Romão JE Jr, Rangel EB, Perosa M. Influence of pancreas transplantation alone on native renal function. *Transplant Proc* 2006; **38**: 1939-1940 [PMID: [16908329](#) DOI: [10.1016/j.transproceed.2006.06.083](#)]
- 24 **Scalea JR**, Butler CC, Munivenkatappa RB, Nogueira JM, Campos L, Haririan A, Barth RN, Philosophe B, Bartlett ST, Cooper M. Pancreas transplant alone as an independent risk factor for the development of renal failure: a retrospective study. *Transplantation* 2008; **86**: 1789-1794 [PMID: [19104423](#) DOI: [10.1097/TP.0b013e3181913fbf](#)]
- 25 **Kwong AJ**, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Foutz J, Booker SE, Cafarella M, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2019 Annual Data Report: Liver. *Am J Transplant* 2021; **21** Suppl 2: 208-315 [PMID: [33595192](#) DOI: [10.1111/ajt.16494](#)]
- 26 **O'Riordan A**, Wong V, McCormick PA, Hegarty JE, Watson AJ. Chronic kidney disease post-liver transplantation. *Nephrol Dial Transplant* 2006; **21**: 2630-2636 [PMID: [16735393](#) DOI: [10.1093/ndt/gfl247](#)]
- 27 **Cohen AJ**, Stegall MD, Rosen CB, Wiesner RH, Leung N, Kremers WK, Zein NN. Chronic renal dysfunction late after liver transplantation. *Liver Transpl* 2002; **8**: 916-921 [PMID: [12360433](#) DOI: [10.1053/jlts.2002.35668](#)]
- 28 **Herlenius G**, Fistouris J, Olsson M, Felldin M, Bäckman L, Friman S. Early renal function post-liver transplantation is predictive of progressive chronic kidney disease. *Scand J Gastroenterol* 2008; **43**: 344-349 [PMID: [18938662](#) DOI: [10.1080/00365520701679264](#)]
- 29 **Wilkinson A**, Pham PT. Kidney dysfunction in the recipients of liver transplants. *Liver Transpl* 2005; **S47-S51** [PMID: [16237714](#) DOI: [10.1002/lt.20618](#)]
- 30 **Gonwa TA**, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, Klintmalm GB. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLT) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation* 2001; **72**: 1934-1939 [PMID: [11773892](#) DOI: [10.1097/00007890-200112270-00012](#)]
- 31 **Wyatt CM**, Arons RR. The burden of acute renal failure in nonrenal solid organ transplantation. *Transplantation* 2004; **78**: 1351-1355 [PMID: [15548974](#) DOI: [10.1097/01.tp.0000140848.05002.b8](#)]
- 32 **Bahirwani R**, Forde KA, Mu Y, Lin F, Reese P, Goldberg D, Abt P, Reddy KR, Levine M. End-stage renal disease after liver transplantation in patients with pre-transplant chronic kidney disease. *Clin Transplant* 2014; **28**: 205-210 [PMID: [24382253](#) DOI: [10.1111/ctr.12298](#)]
- 33 **Cabezuelo JB**, Ramírez P, Ríos A, Acosta F, Torres D, Sansano T, Pons JA, Bru M, Montoya M, Bueno FS, Robles R, Parrilla P. Risk factors of acute renal failure after liver transplantation. *Kidney Int* 2006; **69**: 1073-1080 [PMID: [16528257](#) DOI: [10.1038/sj.ki.5000216](#)]

- 34 **Pham PT**, Slavov C, Pham PC. Acute kidney injury after liver, heart, and lung transplants: dialysis modality, predictors of renal function recovery, and impact on survival. *Adv Chronic Kidney Dis* 2009; **16**: 256-267 [PMID: [19576556](#) DOI: [10.1053/j.ackd.2009.04.002](#)]
- 35 **Al Riyami D**, Alam A, Badovinac K, Ivis F, Trpeski L, Cantarovich M. Decreased survival in liver transplant patients requiring chronic dialysis: a Canadian experience. *Transplantation* 2008; **85**: 1277-1280 [PMID: [18475183](#) DOI: [10.1097/TP.0b013e31816c4e6b](#)]
- 36 **Kollmann D**, Neong SF, Rosales R, Hansen BE, Sapisochin G, McCluskey S, Bhat M, Cattral MS, Lilly L, McGilvray ID, Ghanekar A, Grant DR, Selzner M, Wong FSH, Selzner N. Renal Dysfunction After Liver Transplantation: Effect of Donor Type. *Liver Transpl* 2020; **26**: 799-810 [PMID: [32189415](#) DOI: [10.1002/lt.25755](#)]
- 37 **Lindelöw B**, Bergh CH, Herlitz H, Waagstein F. Predictors and evolution of renal function during 9 years following heart transplantation. *J Am Soc Nephrol* 2000; **11**: 951-957 [PMID: [10770975](#) DOI: [10.1681/ASN.V115951](#)]
- 38 **House AA**, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, Kasiske BL, Deswal A, deFilippi CR, Cleland JGF, Anker SD, Herzog CA, Cheung M, Wheeler DC, Winkelmayer WC, McCullough PA; Conference Participants. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; **95**: 1304-1317 [PMID: [31053387](#) DOI: [10.1016/j.kint.2019.02.022](#)]
- 39 **Cantarovich M**, Hirsh A, Alam A, Giannetti N, Cecere R, Carroll P, Edwards ME. The clinical impact of an early decline in kidney function in patients following heart transplantation. *Am J Transplant* 2009; **9**: 348-354 [PMID: [19120080](#) DOI: [10.1111/j.1600-6143.2008.02490.x](#)]
- 40 **Rubel JR**, Milford EL, McKay DB, Jarcho JA. Renal insufficiency and end-stage renal disease in the heart transplant population. *J Heart Lung Transplant* 2004; **23**: 289-300 [PMID: [15019638](#) DOI: [10.1016/S1053-2498\(03\)00191-8](#)]
- 41 **Rocha PN**, Rocha AT, Palmer SM, Davis RD, Smith SR. Acute renal failure after lung transplantation: incidence, predictors and impact on perioperative morbidity and mortality. *Am J Transplant* 2005; **5**: 1469-1476 [PMID: [15888056](#) DOI: [10.1111/j.1600-6143.2005.00867.x](#)]
- 42 **Broekroelofs J**, Navis GJ, Stegeman CA, van der Bij W, de Boer WJ, de Zeeuw D, de Jong PE. Long-term renal outcome after lung transplantation is predicted by the 1-month postoperative renal function loss. *Transplantation* 2000; **69**: 1624-1628 [PMID: [10836372](#) DOI: [10.1097/00007890-200004270-00017](#)]
- 43 **Navis G**, Broekroelofs J, Mannes GP, van der Bij W, de Boer WJ, Tegzees AM, de Jong PE. Renal hemodynamics after lung transplantation. A prospective study. *Transplantation* 1996; **61**: 1600-1605 [PMID: [8669104](#) DOI: [10.1097/00007890-199606150-00009](#)]
- 44 **Mason DP**, Solovera-Rozas M, Feng J, Rajeswaran J, Thuita L, Murthy SC, Budev MM, Mehta AC, Haug M 3rd, McNeill AM, Pettersson GB, Blackstone EH. Dialysis after lung transplantation: prevalence, risk factors and outcome. *J Heart Lung Transplant* 2007; **26**: 1155-1162 [PMID: [18022082](#) DOI: [10.1016/j.healun.2007.08.006](#)]
- 45 **Canales M**, Youssef P, Spong R, Ishani A, Savik K, Hertz M, Ibrahim HN. Predictors of chronic kidney disease in long-term survivors of lung and heart-lung transplantation. *Am J Transplant* 2006; **6**: 2157-2163 [PMID: [16827787](#) DOI: [10.1111/j.1600-6143.2006.01458.x](#)]
- 46 **Paradela de la Morena M**, De La Torre Bravos M, Prado RF, Roel MD, Salcedo JA, Costa EF, Rivas DG, Maté JM. Chronic kidney disease after lung transplantation: incidence, risk factors, and treatment. *Transplant Proc* 2010; **42**: 3217-3219 [PMID: [20970657](#) DOI: [10.1016/j.transproceed.2010.05.064](#)]
- 47 **Smith JM**, Weaver T, Skeans MA, Horslen SP, Miller E, Noreen SM, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Intestine. *Am J Transplant* 2020; **20** Suppl s1: 300-339 [PMID: [31898410](#) DOI: [10.1111/ajt.15675](#)]
- 48 **Huard G**, Iyer K, Moon J, Doucette JT, Nair V, Schiano TD. The high incidence of severe chronic kidney disease after intestinal transplantation and its impact on patient and graft survival. *Clin Transplant* 2017; **31** [PMID: [28241392](#) DOI: [10.1111/ctr.12942](#)]
- 49 **Ueno T**, Kato T, Gaynor J, Velasco M, Selvaggi G, Nishida S, Moon J, Levi D, Madariaga J, Tzakis A. Renal dysfunction following adult intestinal transplant under tacrolimus-based immunosuppression. *Transplant Proc* 2006; **38**: 1762-1764 [PMID: [16908274](#) DOI: [10.1016/j.transproceed.2006.05.066](#)]
- 50 **Kasiske BL**, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, Green MD, Jha V, Josephson MA, Kiberd BA, Kreis HA, McDonald RA, Newmann JM, Obrador GT, Vincenti FG, Cheung M, Earley A, Raman G, Abariga S, Wagner M, Balk EM; Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int* 2010; **77**: 299-311 [PMID: [19847156](#) DOI: [10.1038/ki.2009.377](#)]
- 51 **Knoll GA**, Fergusson D, Chassé M, Hebert P, Wells G, Tibbles LA, Treleaven D, Holland D, White C, Muirhead N, Cantarovich M, Paquet M, Kiberd B, Gourishankar S, Shapiro J, Prasad R, Cole E, Pilmore H, Cronin V, Hogan D, Ramsay T, Gill J. Ramipril vs placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol* 2016; **4**: 318-326 [PMID: [26608067](#) DOI: [10.1016/S2213-8587\(15\)00368-X](#)]
- 52 **Toto RD**. Transplantation: The role of RAAS blockade in kidney transplantation. *Nat Rev Nephrol* 2016; **12**: 129-131 [PMID: [26656455](#) DOI: [10.1038/nrneph.2015.201](#)]
- 53 **Heinze G**, Mitterbauer C, Regele H, Kramar R, Winkelmayer WC, Curhan GC, Oberbauer R. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol* 2006; **17**: 889-899 [PMID: [16481415](#) DOI: [10.1681/ASN.2005090955](#)]
- 54 **Ponticelli C**, Cucchiari D. Renin-angiotensin system inhibitors in kidney transplantation: a benefit-risk assessment. *J Nephrol* 2017; **30**: 155-157 [PMID: [28211033](#) DOI: [10.1007/s40620-017-0378-x](#)]
- 55 **Ekberg H**, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gürkan A, Margreiter R, Hugo C, Grinyó JM, Frei U, Vanrenterghem Y, Daloze P, Halloran PF; ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; **357**: 2562-2575 [PMID: [18094377](#) DOI: [10.1056/NEJMoa067411](#)]
- 56 **Nankivell BJ**, Chapman JR, Bonovas G, Gruenewald SM. Oral cyclosporine but not tacrolimus reduces renal transplant blood flow. *Transplantation* 2004; **77**: 1457-1459 [PMID: [15167607](#) DOI: [10.1097/01.tp.0000121196.71904.e0](#)]
- 57 **Epstein A**, Beall A, Wynn J, Mulloy L, Brophy CM. Cyclosporine, but not FK506, selectively induces renal and coronary artery smooth muscle contraction. *Surgery* 1998; **123**: 456-460 [PMID: [9551073](#)]

- 58 **Kandula P**, Fridell J, Taber TE, Sharfuddin A, Yaqub MS, Phillips CL, Chen J, Mujtaba M. Impact of tacrolimus-sirolimus maintenance immunosuppression on proteinuria and kidney function in pancreas transplant alone recipients. *Transplantation* 2012; **94**: 940-946 [PMID: [23037007](#) DOI: [10.1097/TP.0b013e3182696a13](#)]
- 59 **Cotterell AH**, Fisher RA, King AL, Gehr TW, Dawson S, Sterling RK, Stravitz RT, Luketic VA, Sanyal AJ, Shiffman ML, Posner MP. Calcineurin inhibitor-induced chronic nephrotoxicity in liver transplant patients is reversible using rapamycin as the primary immunosuppressive agent. *Clin Transplant* 2002; **16** Suppl 7: 49-51 [PMID: [12372044](#) DOI: [10.1034/j.1399-0012.16.s7.7.x](#)]
- 60 **Nair S**, Eason J, Loss G. Sirolimus monotherapy in nephrotoxicity due to calcineurin inhibitors in liver transplant recipients. *Liver Transpl* 2003; **9**: 126-129 [PMID: [12548505](#) DOI: [10.1053/jlts.2003.50026](#)]
- 61 **Neff GW**, Montalbano M, Slapak-Green G, Meyer D, Berney T, Safdar K, Schiff ER, Tzakis AG. Sirolimus therapy in orthotopic liver transplant recipients with calcineurin inhibitor related chronic renal insufficiency. *Transplant Proc* 2003; **35**: 3029-3031 [PMID: [14697970](#) DOI: [10.1016/j.transproceed.2003.10.002](#)]
- 62 **Cantarovich M**, Tzimas GN, Barkun J, Deschênes M, Alpert E, Tchervenkov J. Efficacy of mycophenolate mofetil combined with very low-dose cyclosporine microemulsion in long-term liver-transplant patients with renal dysfunction. *Transplantation* 2003; **76**: 98-102 [PMID: [12865793](#) DOI: [10.1097/01.TP.0000054367.57978.4C](#)]
- 63 **Pfützmann R**, Klupp J, Langrehr JM, Uhl M, Neuhaus R, Settmacher U, Steinmüller T, Neuhaus P. Mycophenolatemofetil for immunosuppression after liver transplantation: a follow-up study of 191 patients. *Transplantation* 2003; **76**: 130-136 [PMID: [12865798](#) DOI: [10.1097/01.TP.0000071522.74885.48](#)]
- 64 **Hao JC**, Wang WT, Yan LN, Li B, Wen TF, Yang JY, Xu MQ, Zhao JC, Wei YG. Effect of low-dose tacrolimus with mycophenolate mofetil on renal function following liver transplantation. *World J Gastroenterol* 2014; **20**: 11356-11362 [PMID: [25170222](#) DOI: [10.3748/wjg.v20.i32.11356](#)]
- 65 **Cornu C**, Dufays C, Gaillard S, Gueyffier F, Redonnet M, Sebbag L, Roussoulières A, Gleissner CA, Groetzner J, Lehmkuhl HB, Potena L, Gullestad L, Cantarovich M, Boissonnat P. Impact of the reduction of calcineurin inhibitors on renal function in heart transplant patients: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2014; **78**: 24-32 [PMID: [24251918](#) DOI: [10.1111/bcp.12289](#)]
- 66 **Zuckermann A**, Schulz U, Deuse T, Ruhpawar A, Schmitto JD, Beiras-Fernandez A, Hirt S, Schweiger M, Kopp-Fernandes L, Barten MJ. Thymoglobulin induction in heart transplantation: patient selection and implications for maintenance immunosuppression. *Transpl Int* 2015; **28**: 259-269 [PMID: [25363471](#) DOI: [10.1111/tri.12480](#)]
- 67 **Delgado DH**, Miriuka SG, Cusimano RJ, Feindel C, Rao V, Ross HJ. Use of basiliximab and cyclosporine in heart transplant patients with pre-operative renal dysfunction. *J Heart Lung Transplant* 2005; **24**: 166-169 [PMID: [15701432](#) DOI: [10.1016/j.healun.2003.09.043](#)]
- 68 **Cantarovich M**, Giannetti N, Barkun J, Cecere R. Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. *Transplantation* 2004; **78**: 779-781 [PMID: [15371689](#) DOI: [10.1097/01.tp.0000130179.18176.3d](#)]
- 69 **Andreassen AK**, Andersson B, Gustafsson F, Eiskjaer H, Radegran G, Gude E, Jansson K, Solbu D, Sigurdardottir V, Arora S, Dellgren G, Gullestad L; SCHEDULE Investigators. Everolimus initiation and early calcineurin inhibitor withdrawal in heart transplant recipients: a randomized trial. *Am J Transplant* 2014; **14**: 1828-1838 [PMID: [25041227](#) DOI: [10.1111/ajt.12809](#)]
- 70 **Eisen HJ**, Kobashigawa J, Starling RC, Pauly DF, Kfoury A, Ross H, Wang SS, Cantin B, Van Bakel A, Ewald G, Hirt S, Lehmkuhl H, Keogh A, Rinaldi M, Potena L, Zuckermann A, Dong G, Cornu-Artis C, Lopez P. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. *Am J Transplant* 2013; **13**: 1203-1216 [PMID: [23433101](#) DOI: [10.1111/ajt.12181](#)]
- 71 **Högerle BA**, Kohli N, Habibi-Parker K, Lyster H, Reed A, Carby M, Zerrouh M, Weymann A, Simon AR, Sabashnikov A, Popov AF, Soresi S. Challenging immunosuppression treatment in lung transplant recipients with kidney failure. *Transpl Immunol* 2016; **35**: 18-22 [PMID: [26892232](#) DOI: [10.1016/j.trim.2016.02.002](#)]
- 72 **Strueber M**, Warnecke G, Fuge J, Simon AR, Zhang R, Welte T, Haverich A, Gottlieb J. Everolimus Versus Mycophenolate Mofetil De Novo After Lung Transplantation: A Prospective, Randomized, Open-Label Trial. *Am J Transplant* 2016; **16**: 3171-3180 [PMID: [27104933](#) DOI: [10.1111/ajt.13835](#)]
- 73 **Glanville AR**, Aboyoun C, Klepetko W, Reichenspurner H, Treede H, Verschuuren EA, Boehler A, Benden C, Hopkins P, Corris PA; European and Australian Investigators in Lung Transplantation. Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. *J Heart Lung Transplant* 2015; **34**: 16-25 [PMID: [25049068](#) DOI: [10.1016/j.healun.2014.06.001](#)]
- 74 **Stephany BR**, Boumitri M, Budev M, Alao B, Poggio ED. Absence of proteinuria predicts improvement in renal function after conversion to sirolimus-based immunosuppressive regimens in lung transplant survivors with chronic kidney disease. *J Heart Lung Transplant* 2009; **28**: 564-571 [PMID: [19481016](#) DOI: [10.1016/j.healun.2009.03.010](#)]
- 75 **Rutter CS**, Russell NK, Sharkey LM, Amin I, Butler AJ. Decline in renal function following intestinal transplant: is the die cast at 3 months? *Clin Transplant* 2021; **35**: e14249 [PMID: [33565629](#) DOI: [10.1111/ctr.14249](#)]
- 76 **Herlenius G**, Fägerlind M, Krantz M, Mölne J, Olausson M, Gäbel M, Friman V, Oltean M, Friman S. Chronic kidney disease--a common and serious complication after intestinal transplantation. *Transplantation* 2008; **86**: 108-113 [PMID: [18622286](#) DOI: [10.1097/TP.0b013e31817613f8](#)]
- 77 **Vincenti F**, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, Massari P, Mondragon-Ramirez GA, Agarwal M, Di Russo G, Lin CS, Garg P, Larsen CP. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant* 2010; **10**: 535-546 [PMID: [20415897](#) DOI: [10.1111/j.1600-6143.2009.03005.x](#)]
- 78 **Durrbach A**, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, Rial Mdel C, Florman S, Block A, Di Russo G, Xing J, Garg P, Grinyó J. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). *Am J Transplant* 2010; **10**: 547-557 [PMID: [20415898](#) DOI: [10.1111/j.1600-6143.2010.03016.x](#)]
- 79 **Launay M**, Guitard J, Dorent R, Prevot Y, Prion F, Beaumont L, Kably B, Lecuyer L, Billaud EM, Guillemain R.

- Belatacept-based immunosuppression: A calcineurin inhibitor-sparing regimen in heart transplant recipients. *Am J Transplant* 2020; **20**: 553-563 [PMID: [31452337](#) DOI: [10.1111/ajt.15584](#)]
- 80 **Timofte I**, Terrin M, Barr E, Sanchez P, Kim J, Reed R, Britt E, Ravichandran B, Rajagopal K, Griffith B, Pham S, Pierson RN 3rd, Iacono A. Belatacept for renal rescue in lung transplant patients. *Transpl Int* 2016; **29**: 453-463 [PMID: [26678245](#) DOI: [10.1111/tri.12731](#)]
 - 81 **Mujtaba MA**, Sharfuddin AA, Taber T, Chen J, Phillips CL, Goble M, Fridell JA. Conversion from tacrolimus to belatacept to prevent the progression of chronic kidney disease in pancreas transplantation: case report of two patients. *Am J Transplant* 2014; **14**: 2657-2661 [PMID: [25179306](#) DOI: [10.1111/ajt.12863](#)]
 - 82 **Perez CP**, Patel N, Mardis CR, Meadows HB, Taber DJ, Pilch NA. Belatacept in Solid Organ Transplant: Review of Current Literature Across Transplant Types. *Transplantation* 2018; **102**: 1440-1452 [PMID: [29787522](#) DOI: [10.1097/TP.0000000000002291](#)]
 - 83 **Klintmalm GB**, Feng S, Lake JR, Vargas HE, Wekerle T, Agnes S, Brown KA, Nashan B, Rostaing L, Meadows-Shropshire S, Agarwal M, Harler MB, Garcia-Valdecasas JC. Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomized study. *Am J Transplant* 2014; **14**: 1817-1827 [PMID: [25041339](#) DOI: [10.1111/ajt.12810](#)]
 - 84 **Schwarz C**, Rasoul-Rockenschaub S, Soliman T, Berlakovich GA, Steininger R, Mühlbacher F, Wekerle T. Belatacept treatment for two yr after liver transplantation is not associated with operational tolerance. *Clin Transplant* 2015; **29**: 85-89 [PMID: [25377272](#) DOI: [10.1111/ctr.12483](#)]
 - 85 **LaMattina JC**, Jason MP, Hanish SI, Ottmann SE, Klassen DK, Potosky D, Hutson WR, Barth RN. Safety of belatacept bridging immunosuppression in hepatitis C-positive liver transplant recipients with renal dysfunction. *Transplantation* 2014; **97**: 133-137 [PMID: [24342980](#) DOI: [10.1097/01.TP.0000438635.44461.2e](#)]
 - 86 **Kim S**, McClave SA, Martindale RG, Miller KR, Hurt RT. Hypoalbuminemia and Clinical Outcomes: What is the Mechanism behind the Relationship? *Am Surg* 2017; **83**: 1220-1227 [PMID: [29183523](#) DOI: [10.1177/000313481708301123](#)]
 - 87 **Chandrakantan A**, de Mattos AM, Naftel D, Crosswy A, Kirklin J, Curtis JJ. Increasing referral for renal transplant evaluation in recipients of nonrenal solid-organ transplants: a single-center experience. *Clin J Am Soc Nephrol* 2006; **1**: 832-836 [PMID: [17699294](#) DOI: [10.2215/CJN.01191005](#)]
 - 88 **Cassuto JR**, Reese PP, Sonnad S, Bloom RD, Levine MH, Olthoff KM, Shaked A, Naji A, Abt P. Wait list death and survival benefit of kidney transplantation among nonrenal transplant recipients. *Am J Transplant* 2010; **10**: 2502-2511 [PMID: [20977641](#) DOI: [10.1111/j.1600-6143.2010.03292.x](#)]
 - 89 **El-Husseini A**, Aghil A, Ramirez J, Sawaya B, Rajagopalan N, Baz M, Mei X, Davenport DL, Gedaly R. Outcome of kidney transplant in primary, repeat, and kidney-after-nonrenal solid-organ transplantation: 15-year analysis of recent UNOS database. *Clin Transplant* 2017; **31** [PMID: [28881060](#) DOI: [10.1111/ctr.13108](#)]
 - 90 **Lonze BE**, Warren DS, Stewart ZA, Dagher NN, Singer AL, Shah AS, Montgomery RA, Segev DL. Kidney transplantation in previous heart or lung recipients. *Am J Transplant* 2009; **9**: 578-585 [PMID: [19260837](#) DOI: [10.1111/j.1600-6143.2008.02540.x](#)]
 - 91 **Haugen CE**, Luo X, Holscher CM, Bowring MG, DiBrito SR, Garonzik-Wang J, McAdams-DeMarco M, Segev DL. Outcomes in Older Kidney Transplant Recipients After Prior Nonkidney Transplants. *Transplantation* 2019; **103**: 2383-2387 [PMID: [30747853](#) DOI: [10.1097/TP.0000000000002596](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

