CKD in Recipients of Nonkidney Solid Organ Transplants

- ✓ Liver, heart, and lung transplantation have expanded over recent decades, resulting in a substantial number of patients with multiple comorbidities surviving longer with a successful nonkidney solid organ transplant(NKSOT).

- ✓ Many of these comorbidities have a direct impact on kidney function, creating a growing cohort of patients with chronic kidney disease (CKD).

Epidemiology

- ✓ CKD in NKSOT recipients as approaching and exceeding 25% at 10 years.

- ✓ The overall incidence of CKD was 16.5%, ranging from 6.9% in heart-lung transplants to as high as 21.3% in intestine transplants with a median follow-up of 36 months.

- ✓ After NKSOT, the incidence of kidney failure and subsequent kidney transplant eligibility is rising.

- ✓ In a registryanalysis of liver transplant recipients in 1995-2010, the incidence of kidney failure with replacement therapy within 5 years of transplant increased more than 2.5-fold to >55 per 1,000 patient-years.

Pathophysiology

- **Important risk factors include :**
  1. Preexisting CKD
  2. glomerulonephritis
  3. HBV and HCV infection
  4. comorbidities such as diabetes and hypertension.

- NKSOTtransplant candidates with a high illness acuity may experience repeated AKI, which also drives the development of CKD.

- ✓ Importantly, the organ allocation schema for liver transplant heavily favors candidates with kidney dysfunction, which leads to a higher prevalence of NKSOT recipients with CKD after liver transplant.

- ✓ Finally while perhaps not the sole or primary contributor to CKD, calcineurin inhibitor (CNI) use is often implicated in progressive CKD in NKSOT recipients.

Peritransplant AKI

- ✓ At the time of transplant surgery, AKI is common.
- ✓ occurs in up to 61% of liver, 60% of lung, and 30% of cardiac transplant recipients.
- ✓ Acute kidney injury is the result of operative and perioperative hypotension, bleeding, diuretics, and the institution of calcineurin inhibition (cyclosporine, tacrolimus)during the transplant hospitalization.

Trends in Transplant. 2009;
nefrologia2022;42(1):27–35

- Acute kidney injury, with or without the need for dialysis, is a strong risk factor for posttransplant CKD.[1]

- Although pretransplant AKI may be expected to be reversible, its contribution to future CKD in NKSOT recipients is exacerbated due to peri/posttransplant insults that include but are not limited to CNI use.[2]

1-Trendsin Transplant. 2009;
2-AJKD Vol 80 | Iss 1 | July 2022

Calcineurin Inhibitors

- ✓ CNIs are implicated in chronic vascular injury to native kidneys when used for treatment in solid organ transplant (SOT) recipients.

- ✓ Lesions associated with CNI use include:
  - focal hyalinosis of small renal arteries and arterioles
  - global or segmental glomerulosclerosis
  - tubular atrophy
  - striped interstitial fibrosis

Traditional Risk Factors

Global risk factors	Organ-specific risk factors		
	Heart	Liver	Lung
Age at transplantation Female gender Systemic hypertension Diabetes mellitus Drug-induced nephrotoxicity (non-immunomodulating drugs) Preoperative renal function Perioperative acute renal failure Calcineurin inhibitors	Systemic atherosclerosis Renal hypoperfusion due to congestive heart failure Cyanotic congenital cardiac disease	Secondary IgA nephropathy Hepatitis B- or C-associated glomerulonephritis Hepatorenal syndrome Oxalosis Repeat liver transplantation	Cystic fibrosis Pulmonary hypertension Focal segmental glomerulosclerosis secondary to chronic hypoxia

Trends in Transplantation 2009;3

Chronic Viral Infection

- ✓ Viral infections such as with HBV and HCV have historically been significant contributors to the risk of CKD in liver transplant in particular.

- ✓ Although BK virus reactivation is common in kidney transplant recipients, this has not manifested as a significant risk in NKSOT recipients

Kidney Pathology in SOT CKD

Biopsy-Diagnosed Kidney Disease in Patients After Transplantation of Other Organs and Tissues

	Liver (n = 41)	Lung (n = 30)	Heart (n = 20)
Histologic findings			
Acute tubular injury	49%	75%	70%
Interstitial fibrosis/tubular atrophy > 20%	51%	64%	35%
Arteriolar hyalinosis	13%	64%	35%
Benign nephrosclerosis	41%	54%	40%
Global glomerulosclerosis	18%	18%	30%
Nephrocalcinosis	13%	0	5%
Primary glomerular disease	26%[a]	0	15%[b]

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.

- ✓ SOT recipients are a unique subset of patients with CKD that often progresses to ESKD necessitating RRT.

Clinical Management

Assessment of GFR

- ✓ the CKD-EPI creatinine equation, followed by the MDRD Study equation, may be considered the most appropriate estimates of GFR in NKSOT.

- ✓ The caveats that must be considered include the overestimation of GFR overall by these equations in the setting ofreduced muscle mass, which is common in NKSOT recipients.

General Principles:

- ✓ in the NKSOT population with kidney dysfunction, kidney biopsy is likely underused.

- ✓ As in the general population, a kidney biopsy should be considered under circumstances of:
  - ➢ rapid or unexplained decline in kidney function
  - ➢ active urine sediment
  - ➢ increasing or nephrotic-range proteinuria.

Relevant Recommendations From KDIGO in Solid Organ Transplant Recipients

For Hypertension and/or Albuminuria

- UAE <30 mg/d and BP >140/90: treat to ≤140/90 (grade 1B)
- UAE ≥30 mg/d and BP >130/80: treat to ≤130/80 (grade 2D)
- UAE ≥300 mg/d: use ACEI or ARB (grade 1B)
- DM and UAE 30-300 mg/d: use ACEI or ARB (grade 2D)

For CKD (eGFR < 60 mL/min)

- Dietary salt: Reduce intake to < 90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride). (Grade 1C)
- Acidosis: Bicarbonate supplementation can be given for patients with bicarbonate concentrations < 22 mmol/L. (Sodium bicarbonate is typically given in a daily dose of 0.5 to 1 mEq/kg daily; 1 tablet of sodium bicarbonate has 7.7 mEq, so typical dose is 1-2 tablets 3 times per day.) (Grade 2B)

Nephrology Referral (Grade 1B)

- AKI or abrupt sustained fall in GFR
- GFR <30 mL/min/1.73 m^2
- Consistent significant albuminuria (UACR ≥ 300 mg/g [≥30 mg/mmol] or albumin excretion rate ≥300 mg/d, equivalent to UPCR ≥ 500 mg/g [≥50 mg/mmol] or protein excretion rate ≥ 500 mg/d)
- Progression of CKD (drop in eGFR from baseline by 25% or a sustained decline in eGFR of >5 mL/min/1.73 m^2 per year)
- Urinary red cell casts or >20 RBCs per high-power field that is sustained and not readily explained
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
- Persistent abnormalities of serum potassium
- Recurrent or extensive nephrolithiasis
- Hereditary kidney disease

(SGLT2) inhibitors

- (SGLT2) inhibitors have been shown to slow CKD progression in both the diabetic and nondiabetic CKD populations33 but have not been studied extensively in the NKSOT population (or those with a kidney transplant);

- their effectiveness among NKSOT recipients might be reduced due to differences in infection risk and metabolic/hemodynamic concerns due to attendant CNI use.

Immunosuppression Modifications

CNI Withdrawal

- ✓ conversion from CNI to mTOR inhibitor (sirolimus) modest improvements in GFR .

- ✓ coupled with higher rejection rates and a high rate of mTOR inhibitor discontinuation specifically due to adverse events

CNI Minimization

- ✓ Minimizing CNI (rather than eliminating) may be safer and better tolerated but also has a more modest effect on kidney protection.

- ✓ MMF and CNI minimized more than 5 years from liver transplant, with stable or improved GFR and no increase in risk of rejection.

- ✓ conversion from MMF to everolimus with CNI dose reduction demonstrated no differences in kidney function with higher rates of side effects and acute cellular rejection .

- ✓ In a minority of patients mTOR inhibitors have been associated with progressive proteinuria and may synergize with CNI to exacerbate CNI nephrotoxic effects.

- ✓ mTOR inhibitors are discouraged from use for those patients with an estimated or measured GFR <40 mL/min/1.73m2 or proteinuria.

Belatacept Conversion

- ✓ The costimulation inhibitor belatacept is approved in kidney transplantation .
- ✓ It is currently not approved for use as a de novo immunosuppressive agent in liver, lung, or heart transplant recipients.
- ✓ **Belatacept carries a black box warning in liver transplant .**

- ✓ In summary, there are mixed data supporting CNI minimization or withdrawal with mTOR inhibitors during the first year after transplant to preserve GFR.

- ✓ After the first year after transplant, CNI minimization with **MMF** adjunctive therapy may improve GFR in the setting of mild CKD in liver transplant.

Outcomes of Subsequent Kidney Transplant in the NKSOT Population

- ✓ Kidney transplant conferred a survival benefit, with a greater than 50% reduction in mortality for prior lung, liver, and heart transplant recipients.
- ✓ the importance of timely referral of SOT recipients, including elderly patients, for kidney transplant.
- ✓ In August 2017, a new allocation system for simultaneous liver-kidney (SLK) transplantation was implemented

Eligibility Criteria for Simultaneous Liver-Kidney Transplantation

Per OPTN/UNOS criteria for eligibility for simultaneous liver-kidney transplant, candidates must meet at least 1 of the following conditions:

1. CKD with GFR <60 mL/min for >90 days with:
   a. Kidney failure treated by maintenance KRT, or
   b. GFR <30 mL/min at time of listing for kidney
2. Sustained AKI with:
   a. 6 Consecutive weeks of KRT, or
   b. GFR <25 mL/min for 6 consecutive weeks, or
   c. Combination of 2a and 2b for 6 consecutive weeks
3. Metabolic disease (hyperoxaluria, aHUS, familial non-neuropathic systemic amyloidosis, or methylmalonic aciduria)[a]

"Safety net" provision for kidney after liver transplant: Liver transplant recipients who continue to receive dialysis or who have GFR ≤20 mL/min in the period 2-12 months after liver transplant will receive priority for kidney allocation for kidneys with KDPI >20%.

Early Identification and Management of NKSOT Candidates and Recipients at Risk of CKD

Box 2. Future Research Needs in the Prevention and Management of CKD in NKSOT

Pre/Peritransplant

- Role of kidney biopsy in determining etiology/severity of pretransplant kidney injury and relationship to posttransplant kidney function
- Biomarkers to predict kidney recovery in AKI immediately after transplant
- Interventions to preserve kidney function intra/postoperatively
- Perioperative immunosuppression strategies to promote renal recovery

Posttransplant

- Role of SGLT2 inhibition in NKSOT recipients with CKD
- Appropriate blood pressure goal in NKSOT recipients
- Role of kidney biopsy in the management of CKD after NKSOT
- Immunosuppression strategies to slow progression of CKD
- Noninvasive biomarkers in predicting CKD progression in NKSOT

- ✓ Biomarkers of injury also should be further explored.
- ✓ urinary neutrophil gelatinase-associated lipocalin (NGAL) when measured at 24 hours after reperfusion has been shown to be independently associated with CKD at 5 years after liver transplant.

Involvement of the general nephrologist earlier in posttransplant management may be valuable because even mild CKD in the first year after liver transplant has been associated with increase in mortality.

Conclusion

- ✓ In NKSOT recipients, the etiology of CKD is often multifactorial.
- ✓ Judicious use of simultaneous kidney-SOT and management of perioperative AKI are important interventions for NKSOT patients at risk for advanced CKD.

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- ✓ Collaborative care between transplant clinicians and nephrology practitioners is likely to be valuable in the SOT patient population to attenuate kidney function decline, appropriately manage late-stage CKD, and reduce the increasing burden upon the kidney transplant waiting list.

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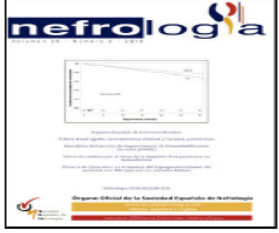

Original article

Acute kidney injury and chronic kidney disease after liver transplant: A retrospective observational study

- ✓ a good number of long-term liver transplant survivors developed CKD after transplant.
- ✓ Viral hepatitis had no role in the pathogenesis of CKD.
- ✓ management of post-transplant AKI may potentially improve patient survival and decrease post-transplant death risk.

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MINIREVIEWS

Kidney disease in non-kidney solid organ transplantation

Kurtis J Swanson

Hypoalbuminemia

- ✓ Low serum albumin appears to impact kidney function in NKSOT recipients.
- ✓ 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.

- **CNI use/minimization strategies:**
- 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.
- Mechanistically, this may be due to less renal vasoconstriction as has been demonstrated.

- **multidisciplinary efforts are needed more than ever to combat this threat to patient and allograft survival.**

Chronic Renal Failure after Transplantation of a Nonrenal Organ

Silas P. Norman and Akinlolu O. Ojo

Division of Nephrology, Department of Medicine, University of Michigan Medical School, Ann Arbor, Michigan, USA

- ✓ Acute kidney injury and CKD are common and increasingly important consequences of successful nonrenal organ transplantation.
- ✓ Liver transplant recipients appear to be at the highest risk of renal dysfunction.
- ✓ Early recognition of kidney impairment and referral for nephrology services may positively impact kidney outcomes.

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Chronic Renal Failure after Transplantation of a Nonrenal Organ

- the high mortality associated with ESRD was substantially mitigated by kidney transplantation among patients with nonrenal transplants.

- attention to preexisting renal diseases , pretransplantation renal function, and modifiable cardiovascular risk factors might reduce the longterm risk of chronic renal failure after the transplantation of nonrenal organs.


Thank you!