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Value of Renal Histology in Predicting Cardiorenal Outcomes in Heart Transplant–listed Patients

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Background. Cardiorenal syndrome (CRS) contributes significantly to morbidity and mortality in patients requiring mechanical circulatory support and transplantation. There are no validated markers to predict major adverse kidney events (MAKEs), for which simultaneous heart-kidney transplant (SHKT) could offer improved survival. We evaluate renal histology in predicting MAKEs in transplant-listed patients. **Methods.** We identified 18 patients with renal histology consistent with CRS from 655 consecutive heart transplant-listed patients between 2010 and 2019. Biopsies were analyzed for glomerular, tubular, interstitial, and arteriolar changes tallied to give a biopsy chronicity score. The primary outcome, MAKE, was a composite of death, need for renal replacement therapy (RRT), or estimated glomerular filtration rate decline >50%. These were evaluated at 2 time points: before and following the transplant. Secondary outcomes included the individual components of the composite outcomes and the need for short-term RRT following the transplant. **Results.** The mean age was 52.3 y, 22% were female. Five patients did not survive to transplant. One patient underwent successful SHKT. MAKE occurred in 8 of 18 before the transplant and in 8 of 13 following the transplant. Neither outcome was predicted by baseline biochemistry. The biopsy chronicity score was significantly higher in patients with MAKE before transplant (4.3 versus 1.7, $P = 0.024$) and numerically higher in patients requiring short-term RRT following transplant (3.2 versus 0.7, $P = 0.075$). Contrary to limited previous literature, interstitial fibrosis did not predict any outcome, whereas tubular atrophy and arteriosclerosis were associated with MAKE before transplant. **Conclusions.** A higher biopsy chronicity score was associated with adverse kidney endpoints, raising its potential utility over standard biochemistry in considering SHKT referral.

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INTRODUCTION

The prevalence of heart failure in developed countries is estimated between 1% and 2% of the adult population.[1] Renal dysfunction coexists in 60% to 65% of patients discharged following heart failure admission.[2] The complex interplay of concomitant cardiac and renal dysfunction is

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termed cardiorenal syndrome (CRS) and split into 5 categories, whereby type I CRS refers to acute heart failure precipitating acute kidney injury (AKI) and type II CRS refers to chronic heart failure causing chronic kidney disease (CKD). In addition to the direct hemodynamic consequence of impaired cardiac output and elevated venous pressures on renal perfusion, types I and II CRS are further exacerbated by multiple abnormal neurohumoral and inflammatory responses, resulting in a vicious cycle with potential to further progress the dual organ dysfunction.[3] CRS is overrepresented as a contributor to morbidity and mortality in patients requiring advanced heart failure therapies, such as durable mechanical circulatory support and heart transplantation, such that severe renal impairment remains a relative contraindication to these treatments.

Simultaneous heart and kidney transplant (SHKT) has been proposed as an option for these patients; however, there are no standardized eligibility criteria for dual organ transplantation referral, with critical supply issues necessitating more measured use. Markers of severity and indicators of reversibility of renal disease are essential to determining suitability for heart transplant alone (HTA) and SHKT. Renal histology may inform the severity of irreversible renal damage; however, there is an overall paucity of data on renal histology in CRS and its potential role in addressing these issues. We evaluate pretransplant renal histology in heart transplant–listed patients with CRS as a predictor of pretransplant and posttransplant renal outcomes.

MATERIALS AND METHODS

Consecutive patients listed for heart transplantation between January 2010 and December 2019 at a single transplant referral center were screened to identify those who underwent renal biopsy for study inclusion. Exclusion criteria included renal biopsy performed following a heart transplant, a biopsy of a transplanted kidney, or biopsy findings suggestive of a diagnosis other than CRS. The original biopsy specimens were retrieved, prepared, and stained with hematoxylin and eosin and special stains for analysis by a single pathologist (T.Y.), blinded to the original biopsy report. The findings of each specimen were reported according to glomerular, tubular, interstitial, and vascular compartments, as described below.

Glomerular Compartment

The total number of glomeruli, glomeruli with segmental sclerosis, and glomeruli with global sclerosis was recorded. The percentage of glomeruli affected by ischemic changes (ischemic glomeruli) was identified, defined as the presence of basement membrane thickening, capsular space dilatation, and/or wrinkling of capillary loops. These were then graded into minimal (≤10%), mild (11%–25%), moderate (26%–50%), or severe (>50%), adapted from the criteria proposed by Sethi et al to grade glomerulosclerosis, whereby ischemic-appearing glomeruli counted toward glomerulosclerosis.[4]

Tubular Compartment

Tubules were examined for the presence of tubular atrophy (TA) and graded into minimal (≤10%), mild (11%–25%), moderate (26%–50%), or severe (>50%), described by Sethi et al.[4]

TABLE 1.

Biopsy chronicity score—sum of ischemic glomeruli, tubular atrophy, interstitial fibrosis, and binary arteriosclerosis

	Score
Ischemic glomeruli	
Minimal (≤10%)	0
Mild (11%–25%)	1
Moderate (26%–50%)	2
Severe (>50%)	3
Tubular atrophy	
Minimal (≤10%)	0
Mild (11%–25%)	1
Moderate (26%–50%)	2
Severe (>50%)	3
Interstitial fibrosis	
Minimal (≤10%)	0
Mild (11%–25%)	1
Moderate (26%–50%)	2
Severe (>50%)	3
Binary arteriosclerosis	
Minimal (intima/media <1)	0
Significant (intima/media >1)	1

Interstitial Compartment

The interstitium was examined for the presence of interstitial fibrosis (IF) and graded into minimal (≤10%), mild (11%–25%), moderate (26%–50%), or severe (>50%), as described by Sethi et al.[4] Presence of interstitial inflammation in nonscarred areas and areas of TA/IF were recorded.

Vascular Compartment

Arteries and arterioles present within specimens were examined for fibrous thickening and/or hyalinosis of the intima. Arteriosclerosis (AS) was graded into 3 categories based upon the ratio of intimal and medial layer thickness: none, intima/medial thickness <1, or intima/medial thickness >1, as described by Srivastava et al.[5] This was subsequently contracted into a binary score (binary arteriosclerosis: intima/medial thickness <1 or intima/medial thickness >1) to maintain consistency with the analysis conducted in the 2 original papers.[4,6]

Biopsy Chronicity Score

A chronicity score was calculated from the grading of ischemic glomeruli, TA, and IF and the binary arteriosclerosis grade, as described by Sethi et al, shown in Table 1.[4]

Demographic Data and Assessment of Renal Function

Baseline demographics, including age, gender, heart failure etiology, comorbidities, and heart failure therapy at the time of biopsy, were collected. Data regarding renal function, including serum creatinine (sCr) and urine albumin:creatinine ratio, were collected at the time of biopsy, before implantation with the ventricular assist device (VAD), before cardiac transplantation, before death, and at the latest available results. Additionally, the highest stable sCr, defined as 2 readings separated by at least 3 mo, was recorded between these time points. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula using sCr at all time points.[7] The 4-variable Kidney Failure Risk Equation (KFRE) score[8] was calculated at the time of biopsy.

The outcome of interest was major adverse kidney events (MAKEs), defined as a composite of all-cause mortality, need for

renal replacement therapy (RRT), or eGFR decline ≥50%. RRT was specifically defined as the requirement for RRT for at least 3 mo, or alternatively, death while on RRT. Evaluation of MAKE was undertaken at 2 discrete time points. The first time point was "before transplantation," defined by the period between renal biopsy and the first event to occur: implantation with a VAD, heart transplant, or death. The second time point was "following transplantation," defined by the period between the heart transplant and the most recent results available. Individual components of the composite outcome were also assessed for the 2 time points. The requirement for short-term RRT (<3 mo duration) immediately after heart transplant was evaluated as a separate outcome.

Descriptive statistics were summarized as mean ± SD or median with interquartile range for continuous variables and counts with percentages for categorical data. For reporting of continuous variables, *t* tests were used for normally distributed data and Kruskal-Wallis tests for nonnormally distributed data, with Bonferroni correction used for pairwise analyses. Univariate odds ratio (OR) with Fisher's exact test was reported for categorical data. Spearman correlation coefficients were used to determine the associations between continuous variables and biopsy chronicity score. All statistical tests were 2-sided, and *P* values <0.05 were considered significant. Statistical analyses were conducted using R Studio, version 1.4. The study protocol was approved by the Hospital Human Research Ethics Committee.

RESULTS

A total of 655 patients were listed or worked up for heart transplantation over the study period, of whom 408 were successfully transplanted. Of the remaining patients, 177 were deemed unsuitable (108 died, 33 were too sick, 36 fell outside transplantation criteria), 47 were too well, 12 declined, and 10 were either treated elsewhere or remained actively listed.

A total of 32 patients underwent renal biopsy for any reason. The median eGFR at the time of biopsy or transplant listing was significantly different in patients undergoing renal biopsy at 32.5 mL/min/1.73 m^2 compared with those who did not undergo biopsy (70 mL/min/1.73 m^2; $P < 0.001$). Of these patients, 18 had histology consistent with CRS, as shown in Figure 1. The reasons for excluded biopsies are shown in Figure 1. There was no significant difference in median listing eGFR between patients undergoing renal biopsy with and without CRS (32.5 and 33 mL/min/1.73 m^2, respectively).

All 18 biopsies were performed to confirm the diagnosis of CRS and exclude other native diseases; however, the degree of IF on 12 biopsies was additionally used to facilitate decisions about appropriateness for the SHKT listing based on physician discretion. A threshold of moderate IF by qualitative examination was historically used to recommend heart–kidney transplant listing. There were no complications arising from the original biopsy procedures. The diagnosis of CRS was confirmed through the absence of lesions consistent with other diseases on light and electron microscopy, such as diabetic nephrosclerotic lesions.

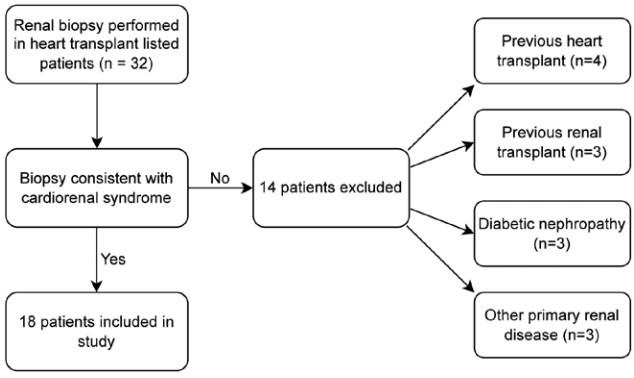

FIGURE 1. Flowchart of patient selection for inclusion/exclusion from study.

The baseline demographics of these patients are shown in Table 2. At biopsy, the mean age was 52.3 ± 16.2 y, with 22.2% being female. Half had ischemic etiology, and half were diabetic. Background medical therapy at the time of biopsy included beta-blockers in 72.2%, angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers in 22%, and loop diuretics in 88.9%. Three patients were on intravenous vasopressors or inotropes at the time of the biopsy. Overall survival to transplant, which is shown in Figure 2, was achieved in 13 patients, of whom 5 required VAD support. A further 2 VAD-supported patients did not survive to transplant, totaling 5 patients who did not survive to transplant.

Of the 13 patients who survived to cardiac transplant, 3 were listed for SHKT. This was successfully conducted in 1 patient. The second patient had a failed kidney transplant due to polymicrobial sepsis of the transplanted kidney, requiring a transplant nephrectomy. The third patient was too unstable at the time of the heart transplant, requiring veno-arterial extracorporeal membrane oxygenation and RRT support postoperatively, and died 3 d following heart transplant.

Biopsies were of good diagnostic quality, with a median of 11 glomeruli examined (interquartile range 7.25–17). The frequency of biopsy findings included within the chronicity score is shown in Figure 3, with a comprehensive summary of all biopsy findings detailed in **Table S1, SDC**, http://links.lww.com/TXD/A481. No patients had severe TA or IF, and only 2 patients had moderate TA. Otherwise, the severity of biopsy grades was spread across the remaining categories. The chronicity score was calculable in 17 of 18 patients, with 1 patient having insufficient arterioles present for grading. The overall mean chronicity score was 2.76 ± 2.41. The chronicity score correlated significantly with eGFR, sCr, and KFRE at the time of biopsy, as shown in Table 3.

MAKEs before transplant occurred in 8 of 18 and following transplant in 8 of 13 patients. Table 4 summarizes the baseline biochemistry and chronicity score as predictors of these composite outcomes. The baseline biochemistry, age at biopsy, and baseline KFRE score were not associated with MAKE before transplantation. Conversely, the chronicity score was significantly different between the 2 groups: 4.3 ± 2.3 for those with MAKE compared with 1.7 ± 1.9 for those without MAKE before transplant ($P = 0.024$). This was driven by pretransplant RRT, occurring in 6 patients, with a mean chronicity score of 4.5 in those requiring RRT compared with 1.8 in those who did not ($P = 0.023$). MAKE the following transplant was not predicted by any biochemical or biopsy parameter. Although not significantly predicted by any parameter, the chronicity score was numerically higher in patients requiring short-term RRT following transplant: 3.2 compared with 0.7 in those who did not ($P = 0.075$).

The individual biopsy components and their risk for both composite and individual outcomes are shown in **Table S1, SDC**, http://links.lww.com/TXD/A481 and **Table S2, SDC**, http://links.lww.com/TXD/A481. Mild TA was associated

TABLE 2.

Baseline demographics expressed as mean ± SD, median (IQR), and count (%)

	Overall (n = 18)
Age	52.3 y [21.4–69.2]
Female gender	4 [22.2]
Etiology	
Ischemic	9 [50]
Nonischemic	9 [50]
Comorbidities	
Diabetes	9 [50]
Hypertension	5 [27.8]
Atrial fibrillation	8 [27.8]
Baseline medical therapy (at biopsy)	
Beta-blocker	13 [72.2]
ACE-inhibitor	3 [16.7]
ARB	1 [5.6]
MRA	12 [66.7]
Loop diuretic	16 [88.9]
Digoxin	4 [22.2]
Vasopressor/inotrope	3 [16.7]
Support at time of bridge to transplant VAD (n = 7)	
Vasopressor/inotrope	2 [28.6]
Intra-aortic balloon pump	2 [28.6]
VA-ECMO prior implant	0 [0]
VPa-ECMO following implant	1 [14.3]
Biventricular VAD configuration	1 [14.3]
Support at time of heart transplant (n = 13)	
Vasopressor/inotrope	1 [7.7]
Intra-aortic balloon pump	1 [7.7]
VA-ECMO prior transplant	0 [0]
LVAD support	5 [38.5]
Biventricular VAD support	0 [0]

Values expressed as mean ± SD, median [IQR], and counts (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; VAD, ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VPa-ECMO, veno-pulmonary artery extracorporeal membrane oxygenation.

with an increased risk of MAKE before transplant (OR 16.2, $P < 0.001$). Significant AS (intima/medial thickness >1) was present in all patients with MAKE prior to transplant ($P \leq 0.001$).

DISCUSSION

CRS is a poor prognostic factor in patients listed for a heart transplant. In this study, we showed that a higher biopsy chronicity score was associated with adverse kidney events before transplantation, driven predominantly by the need for RRT. We showed a good correlation with biochemical measures of renal function, despite these not being significant predictors for adverse kidney events. Finally, we report the degree of TA and arteriolar changes as predictors of adverse kidney events before transplantation. Although we did not find any predictors of MAKE following heart transplant, the chronicity score was numerically higher in those requiring short-term RRT.

There is a well-established interaction between progressive renal dysfunction and mortality in patients undergoing HTA. Stages IV and V CKD with eGFR <30 mL/min/1.73 m^2 are associated with posttransplant 1-y mortality in an excess of 20%.[9] The proportion of patients on pretransplant dialysis has significantly increased from 3.0% between the years 1992 and 2000, compared with 4.6% between 2010 and 2018, despite an awareness that pretransplant dialysis utilization is associated with almost 20% lower survival at 1 y following HTA compared with nondialysis patients.[9] This reflects a higher proportion of patients being transplanted with pretransplant AKI, with the expectation that this would improve following transplantation.

Listing for SHKT has been adopted as a potential solution to this issue. According to Organ Procurement and Transplantation/United Network for Organ Sharing (OPTN/UNOS) data, although there was a 61% increase in the number of heart transplants in the United States from 2199 in the year 2000 to 3552 in 2019, there was a 650% increase in SHKT over this same time period from 29 to 219.[10] Reassuringly, no significant survival difference has been seen between the 2, with a median survival of 11.3 y for HTA and 12.4 y for SHKT ($P = 0.053$).[10] Unfortunately, there are no guidelines for SHKT referral.

Pretransplant dialysis requirement is the most commonly listed indication for SHKT referral. According to OPTN/UNOS data, pretransplant dialysis dependence was 2.8% in those referred for HTA compared with 53.2% in SHKT patients. In these patients, the median survival following SHKT was significantly higher at 12.4 y than their HTA counterparts at 9.9 y.[10] In nondialysis-dependent patients, there is a graduated benefit from SHKT over HTA according to baseline eGFR, with the greatest effect at lower eGFR; however, even in patients with eGFR between 45 and 59 (CKD stage IIIa), the hazard ratio for survival following SHKT compared with HTA was 1.2. Posttransplant dialysis requirement remains a strong predictor for mortality, with a median survival time of 11.9 y compared with 2.7 y in SKHT and HTA recipients, respectively,[10] which is a finding supported by previous registry data.[11,12]

There are several issues surrounding dual organ listing. Of primary importance is the critical shortage of donor organs, and dual organ transplantation lends to the ethical dilemma of diverting donor kidneys away from isolated kidney transplant candidates. The 2019 Organ Procurement and Transplantation/Scientific Registry of Transplant Recipients (OPTN/SRTR) reported median waitlist times of 5.1 mo for heart transplant,[13] whereas the median waitlist time for kidney transplants has not been calculable for over a decade because 50% of waitlisted candidates have not undergone transplant since 2008.[14] Second, it is difficult to determine the degree of renal dysfunction related to AKI or hemodynamic compromise that may improve following heart transplant compared with more chronic irreversible damage that is more likely to progress. Furthermore, there are no validated markers to predict this trajectory, nor adverse outcomes such as end-stage renal disease, need for long-term RRT, or mortality. Previous studies indicate a significant difference in pretransplant eGFR between these outcomes; however, the described values still fall well within the spectrum of values listed for heart transplant patients. The median CKD-EPI eGFR was 55.3 mL/min/1.73 m^2 for HTA patients progressing to end-stage renal disease or requiring renal transplant compared with 67.7 mL/min/1.73 m^2 for patients who did not.[15] Historically, various authors have quoted different eGFR cutoffs for SHKT referral ranging from 30 to 40 mL/min/1.73 m^2.[10] A heart/kidney workgroup consensus endorsed by the American Society of Transplantation has suggested SHKT referral in patients with established eGFR <30 mL/min/1.73 m^2 and evaluation of eligibility by a transplant nephrologist for those with eGFR between 30 and 44 mL/min/1.73 m^2, factoring in evidence of

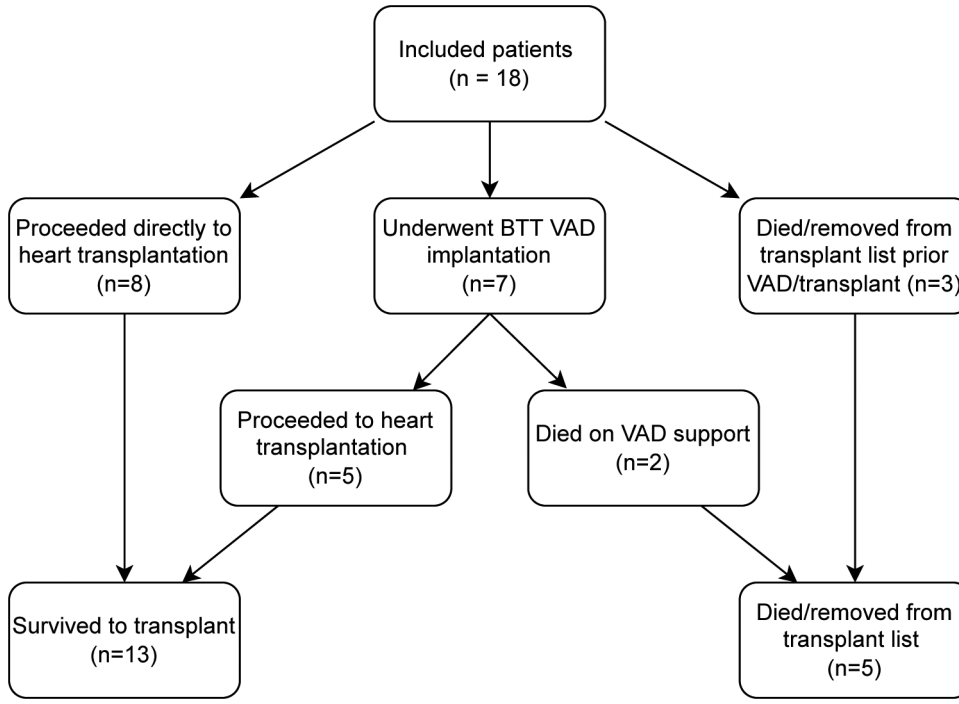

FIGURE 2. Flowchart of advanced heart failure therapies (transplant, VAD support) for included patients. VAD, ventricular assist device.

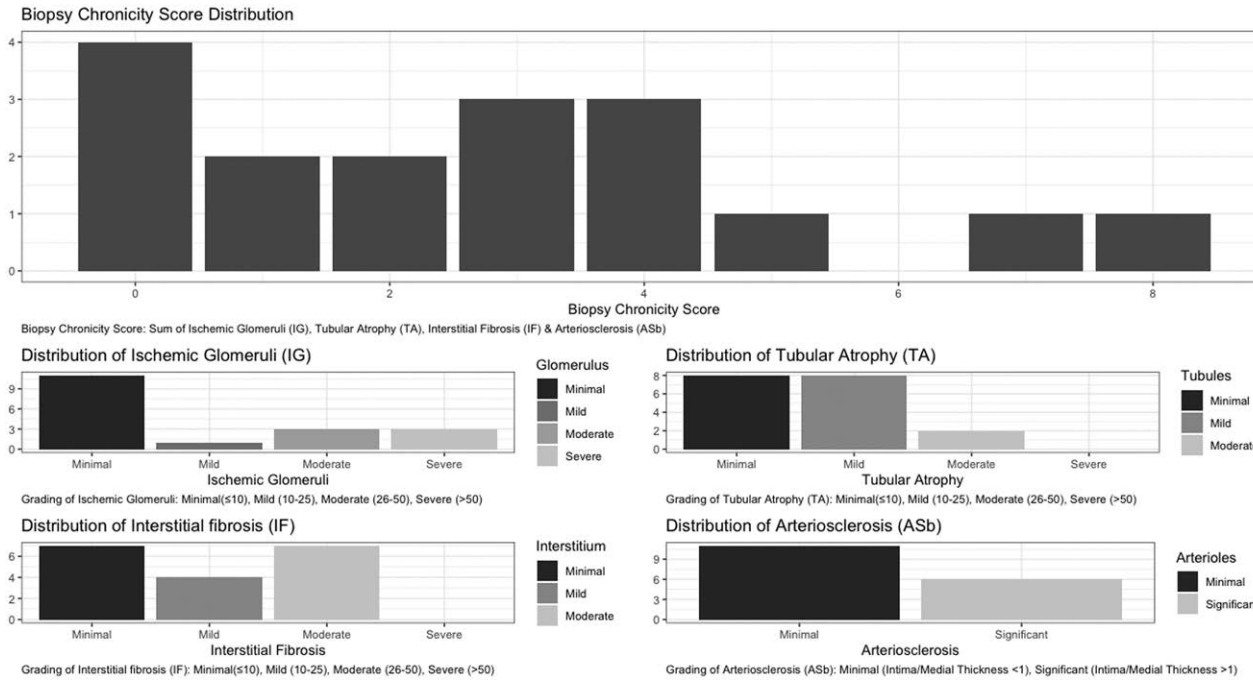

FIGURE 3. Distribution of renal biopsy findings and biopsy chronicity score.

chronicity, such as small renal size and presence of significant proteinuria.[16]

Renal histology may help inform this referral process; however, this has not been extensively described in this setting. Golestaneh et al described semiquantitative grading of IF and TA (IFTA) in 14 transplant-listed candidates, noting the majority of candidates proceeding to transplant had only minimal disease, with remaining candidates either dying or being managed with a VAD.[17] Labban et al described a prospective approach to HTA versus SHKT listing based on the degree of IFTA and concomitant glomerular disease.[18] Of the 30 patients studied, 8 proceeded to HTA and 5 to SHKT. No patients recommended for HTA with this system required postoperative RRT, although 1 underwent a subsequent renal transplant for worsening renal function. They found no correlation between the degree of IFTA and baseline eGFR, proposing that an eGFR-based approach in their small cohort may have resulted in 4 patients not being referred for SHKT despite moderate or greater disease, and conversely, 4 patients may have been unnecessarily referred for SHKT with only mild changes on biopsy.

TABLE 3.

Correlation between age, baseline biochemistry, and biopsy severity score

	Age at biopsy	Creatinine at biopsy	eGFR at biopsy	Urine albumin:creatinine ratio at biopsy	Kidney Failure Risk Equation score at biopsy	Biopsy chronicity score
Age at biopsy		**0.502***	**−0.488***	0.115	0.390	0.311
Creatinine at biopsy	**0.502***		**−0.984*****	0.330	**0.951*****	**0.600***
eGFR at biopsy	**−0.488***	**−0.984*****		−0.336	**−0.955*****	**−0.537***
Urine albumin:creatinine ratio at biopsy	0.115	0.330	−0.336		0.549	0.184
Kidney Failure Risk Equation score at biopsy	0.390	**0.951*****	**−0.955*****	0.549		**0.717****
Biopsy chronicity score	0.311	**0.600***	**−0.537***	0.184	**0.717****	

Computed correlation used the Spearman method with pairwise deletion.
Significant correlations are bolded.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
eGFR, estimated glomerular filtration rate.

TABLE 4.

Biochemistry and chronicity score at the time of biopsy as a predictor of MAKE before and following transplant

	Overall	No MAKE before transplant (n = 10)	MAKE before transplant (n = 8)	*P*	No MAKE following transplant (n = 5)	MAKE following transplant (n = 8)	*P*
Age, y	57.8 (49.0–63.1)	59.8 (56.1–64.8)	53.0 (33.1–61.9)	0.27	60.9 (35.6–67.8)	56.2 (49.1–59.4)	0.62
Baseline eGFR, mL/min/1.73 m^2	33.4 ± 13.0	36.3 ± 10.6	29.9 ± 15.4	0.49	31.6 ± 15.0	33.5 ± 12.6	0.81
Baseline Cr, mg/dL	2.17 (1.64–2.66)	2.02 (1.64–2.36)	2.28 (2.02–3.80)	0.27	2.43 (1.73–2.74)	2.14 (1.84–2.34)	0.83
Baseline uACR, mg/g	63.7 (12.4–122.1)	51.3 (12.4–108.0)	4024.8 (15.0–19734.5)	0.72	141.6 (100.9–5054.9)	12.4 (11.5–103.5)	0.19
Baseline KFRE	−2.6 ± 2.0	−3.3 ± 1.3	−1.6 ± 2.6	0.16	−1.5 ± 1.3	−2.7 ± 2.6	0.41
Biopsy chronicity score	2.76 ± 2.41	1.70 ± 1.95	4.29 ± 2.29	0.02	3.0 ± 1.6	2.4 ± 2.6	0.64

Values expressed as mean ± SD and median (interquartile range).
eGFR, estimated glomerular filtration rate; MAKE, major adverse kidney event; KFRE, Kidney Failure Risk Equation; uACR, urine albumin:creatinine ratio.

The BANFF classification is well established for evaluating postrenal transplant histology; however, it is less relevant in the setting of CRS because of the emphasis on inflammatory markers of rejection. Quantitative scoring systems such as the one proposed by Sethi et al are gaining traction in predicting progression to CKD in nonrenal transplant cohorts.[4] Srivastava et al validated this scoring system in 676 patients undergoing a renal biopsy, showing that all biopsy components showed utility and, furthermore, that a chronicity score derived from tallying the glomerular, tubular, interstitial, and arteriolar grades showed a graded response for risk of kidney disease progression.[5]

Our chronicity score was adapted from the score validated by Srivastava, with the main difference being the use of glomerular ischemic changes as a more subtle marker of CRS rather than global glomerulosclerosis, which is a more generalized marker of advanced disease from any pathology, such as diabetes. It performed well despite small numbers. The chronicity score correlated with traditional markers such as eGFR; however, it outperformed them for the prediction of MAKE before transplantation. This was driven by the need for pretransplant RRT, which is known to be associated with higher posttransplant morbidity and mortality. Furthermore, although there were no predictors of MAKE following transplant, the chronicity score was numerically higher in those requiring short-term RRT following transplant, which is an established risk factor for early mortality following HTA. These findings raise the possibility of the use of a chronicity score to inform SHKT referral to improve outcomes in these patients.

In our study, IF was not a key indicator of any outcome. If we were to adopt the binary approach to IFTA severity described by Labban et al to our cohort, there would be almost equal numbers of patients with and without MAKE and its components at both time points. In our cohort, TA and AS were more useful in predicting MAKE before transplant. Similar findings were reported by Waiser et al, who evaluated renal allograft loss due to types I and II CRS.[19] They described significant tubular pathology, with epithelial cytoplasmic vacuolization and luminal dilatation with flattening of the epithelium and loss of brush border of the proximal tubules, as well as a hyaline arteriolar thickening in all biopsies.

There are several limitations to the current study, most importantly, the small sample size and use of a retrospective cohort. As a result, important confounders such as comorbidities, the difference in heart failure therapy, the interaction of time to transplant, use of mechanical circulatory support, and posttransplant immunosuppression regimes could not be assessed. We focused on patients with CRS to address the question of reversibility of renal impairment following transplant as the key question driving decisions for single versus dual organ listing, thus excluding patients with other pathologies. To date, it is the largest cohort of biopsies consistent with CRS in a heart transplant population. Concomitant hypertensive, diabetic, amyloid, and native kidney disease are commonly present in heart transplant candidates and were not included in our study cohort. These pathologies have their own known trajectory, and decisions regarding dual organ listing need to be assessed on a case-by-case basis. The impact of the chronicity score and the individual biopsy components may have been underestimated because of our small sample size,

particularly given that outcomes such as the need for short-term RRT were overrepresented (10 of 13 patients). Furthermore, we were unable to evaluate the additional grading system implemented using the chronicity score in the Boston Kidney Biopsy Cohort, whereby various cutoffs for the chronicity score were used to further categorize patients into minimal, mild, moderate, or severe.[5] However, the heart transplant cohort is inherently sicker than the Boston Kidney Biopsy Cohort Study, in which this graded system was validated, and, furthermore, will be subjected to additional nephrotoxicity (surgical and immunosuppressive) through the peritransplant course; thus, it is likely a lower cutoff would need to be adopted in guiding single versus dual organ transplant listing. Future larger prospective studies could further test the utility of a biopsy chronicity score to evaluate pretransplant and postcardiorenal outcomes and determine optimal cutoffs to facilitate decision-making for HTA versus SHKT referral.

CONCLUSION

Decision-making and management of advanced heart failure patients with CRS are challenging due to the competing interests of poor outcomes following HTA in these patients, and limitations in transplant organ supply. Renal histology provides valuable insight into disease severity and potential for reversibility beyond what can be determined by eGFR alone.

REFERENCES

1. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. *Eur J Heart Fail.* 2020;22:1342–1356.
2. Patel RB, Fonarow GC, Greene SJ, et al. Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol.* 2021;78:330–343.
3. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e840–e878.
4. Sethi S, D'Agati VD, Nast CC, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. *Kidney Int.* 2017;91:787–789.
5. Srivastava A, Palsson R, Kaze AD, et al. The prognostic value of histopathologic lesions in native kidney biopsy specimens: results from the Boston Kidney Biopsy Cohort Study. *J Am Soc Nephrol.* 2018;29:2213–2224.
6. Srivastava A, Schmidt IM, Palsson R, et al. The associations of plasma biomarkers of inflammation with histopathologic lesions, kidney disease progression, and mortality-the Boston Kidney Biopsy Cohort Study. *Kidney Int Rep*. 2021;6:685–694.
7. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612.
8. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA.* 2011;305:1553–1559.
9. Khush KK, Hsich E, Potena L, et al.; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-eighth adult heart transplantation report—2021; focus on recipient characteristics. *J Heart Lung Transplant.* 2021;40:1035–1049.
10. Agarwal KA, Patel H, Agrawal N, et al. Cardiac outcomes in isolated heart and simultaneous kidney and heart transplants in the United States. *Kidney Int Rep.* 2021;6:2348–2357.
11. Kim D, Choi JO, Cho YH, et al. Impact of preoperative renal replacement therapy on the clinical outcome of heart transplant patients. *Sci Rep.* 2021;11:13398.
12. Shoji S, Kuno T, Kohsaka S, et al. Incidence and long-term outcome of heart transplantation patients who develop postoperative renal failure requiring dialysis. *J Heart Lung Transplant.* 2022;41:356–364.
13. Colvin M, Smith JM, Ahn Y, et al. OPTN/SRTR 2019 annual data report: heart. *Am J Transplant.* 2021;21:356–440.
14. Hart A, Lentine KL, Smith JM, et al. OPTN/SRTR 2019 annual data report: kidney. *Am J Transplant.* 2021;21(Suppl 2):21–137.
15. Habib PJ, Patel PC, Hodge D, et al. Pre-orthotopic heart transplant estimated glomerular filtration rate predicts post-transplant mortality and renal outcomes: an analysis of the UNOS database. *J Heart Lung Transplant.* 2016;35:1471–1479.
16. Kobashigawa J, Dadhania DM, Farr M, et al.; Consensus Conference Participants. Consensus conference on heart-kidney transplantation. *Am J Transplant.* 2021;21:2459–2467.
17. Golestaneh L, Deshpande PP, Parikh C, et al. Tubulointerstitial disease is a common finding in biopsy specimens of end-stage heart failure patients awaiting heart transplantation. *J Heart Lung Transplant.* 2014;33:446–448.
18. Labban B, Arora N, Restaino S, et al. The role of kidney biopsy in heart transplant candidates with kidney disease. *Transplantation.* 2010;89:887–893.
19. Waiser J, Knebel F, Rudolph B, et al. Renal allograft loss caused by cardiorenal syndrome: frequency and diagnosis. *Transplantation.* 2015;99:1208–1215.