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AHA SCIENTIFIC STATEMENT

Dual-Organ Transplantation: Indications, Evaluation, and Outcomes for Heart-Kidney and Heart-Liver Transplantation: A Scientific Statement From the American Heart Association

Endorsed by the International Society for Heart and Lung Transplantation

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ABSTRACT: Although heart transplantation is the preferred therapy for appropriate patients with advanced heart failure, the presence of concomitant renal or hepatic dysfunction can pose a barrier to isolated heart transplantation. Because donor organ supply limits the availability of organ transplantation, appropriate allocation of this scarce resource is essential; thus, clear guidance for simultaneous heart-kidney transplantation and simultaneous heart-liver transplantation is urgently required. The purposes of this scientific statement are (1) to describe the impact of pretransplantation renal and hepatic dysfunction on posttransplantation outcomes; (2) to discuss the assessment of pretransplantation renal and hepatic dysfunction; (3) to provide an approach to patient selection for simultaneous heart-kidney transplantation and simultaneous heart-liver transplantation and posttransplantation management; and (4) to explore the ethics of multiorgan transplantation.

Key Words: AHA Scientific Statements ■ heart transplantation ■ kidney transplantation ■ liver transplantation

Over the past 5 decades, heart transplantation (HT) has become an important therapy for appropriate patients with advanced heart failure (HF), with a 1-year survival of almost 90% and a conditional half-life of 13 years.[1] However, the presence of comorbidities, including concomitant renal or hepatic dysfunction, can pose a barrier to isolated HT.[1–4] Because donor organ supply limits the availability of organ transplantation, appropriate allocation of this scarce resource is essential. Clear guidelines for simultaneous heart-kidney transplantation (SHKT) and simultaneous heart-liver transplantation (SHLT) are required.

The approach to HT candidates with renal and hepatic dysfunction entails multidisciplinary collaboration among cardiologists, nephrologists, hepatologists, and transplantation surgeons, as reflected by the composition of this writing group. This collaboration will involve joint discussions by relevant transplant selection committees and at the time of listing, changes in clinical status, and organ offers.

The purposes of this scientific statement are (1) to describe the impact of pretransplantation renal and hepatic dysfunction on post-HT outcomes; (2) to discuss the assessment of pre-HT renal and hepatic dysfunction; (3) to provide an approach to patient selection for SHKT and SHLT and posttransplantation management; and (4) to explore the ethics of multiorgan transplantation (MOT) and the rationale of the safety net approach to dual-organ transplantation.

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HEART-KIDNEY TRANSPLANTATION

Chronic Kidney Disease in HF

Chronic kidney disease (CKD) is defined as a persistently reduced estimated glomerular filtration rate (eGFR) <60 mL·min^{-1}·1.73 m^{-2} or at least 1 marker of kidney damage (eg, microalbuminuria) for a minimum of 3 months. In patients with HF across the spectrum of left ventricular ejection fraction, 40% to 60% have an eGFR <60 mL·min^{-1}·1.73 m^{-2}.[5,6] HF and CKD have complex bidirectional interactions that can lead to acute or chronic worsening of one another.[7,8] HF can negatively affect kidney function through hemodynamic mechanisms (decreased kidney perfusion from impaired cardiac output, chronic renal venous congestion) and neurohormonal activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, leading to renal vasoconstriction, endothelial dysfunction, tubular injury, and fibrosis.[9] Kidney dysfunction can also adversely affect cardiac function through acid-base and metabolic disorders, electrolyte imbalances, inappropriate fluid retention, and stimulation of circulating factors that adversely affect cardiac function such as fibroblast growth factor 23.[10] As a result of these interactions, kidney function often worsens as patients develop advanced HF.[11]

The presence of CKD portends worse outcomes in patients with HF.[6,11–13] In the Swedish Heart Failure Registry, CKD was associated with a 49% increased risk of death in patients with HF with reduced ejection fraction <40%.[6] In patients hospitalized with HF, in-hospital mortality increased as eGFR declined.[12] Use of some guideline-directed medical therapies in patients with HF, particularly sodium-glucose cotransporter-2 inhibitors,[14] can slow or prevent a decline in kidney function over time,[15] although data for patients with advanced HF and CKD are currently lacking.[16]

Posttransplantation Kidney Disease

Posttransplantation Acute Kidney Injury

Acute kidney injury (AKI), defined as an increase in serum creatinine by ≥0.3 mg/dL within a 48-hour time interval, an increase in serum creatinine to ≥1.5 times baseline value within a 7-day time period, or urine volume <0.5 mL·kg^{-1}·h^{-1} for 6 hours, occurs in 40% to 70% of HT recipients. Risk factors for AKI include preexisting comorbidities, right-sided HF, major bleeding, and the use of calcineurin inhibitors (CNIs). AKI is associated with subsequent CKD and increased mortality.[17–19] The largest study to date of post-HT AKI included HT recipients in the United Network Organ Sharing (UNOS) registry between 2009 and 2020. In an investigation of >28 000 patients, 12% required dialysis immediately after HT, with the incidence increasing from 7.9% in 2009 to 13.9% in 2020. Longer ischemic time, serum creatinine at transplantation >1.2 mg/dL, prior cardiac surgery, support with mechanical ventilation or extracorporeal membrane oxygenation, and history of congenital heart disease or restrictive/hypertrophic cardiomyopathy were predictors of AKI requiring dialysis. Whether the new allocation system, with increased use of temporary mechanical circulatory support as a bridge to HT,[20] will result in a higher incidence of post-HT AKI has not been evaluated. HT recipients on dialysis immediately after transplantation had a 7-fold increased risk of 30-day and 1-year mortality and an increased risk of rejection by 1 year.[3]

Posttransplantation CKD

CKD is commonly observed in HT recipients. In an analysis of the SRTR (Scientific Registry of Transplant Recipients) from 1990 to 2000, stage 4 or greater CKD (as defined as eGFR <30 mL·min^{-1}·1.73 m^{-2} and including the need for long-term dialysis)[21] was observed in 1.9% of HT recipients at 1 year and 10.9% at 5 years after transplantation.[2] Although definitions differ, the 2019 International Society of Heart and Lung Transplantation registry report demonstrates similar risk factors for CKD.[1] More severe kidney disease, specifically the need for dialysis, is less common after HT, observed in 1.5% of patients at 1 year, 2.9% at 5 years, and 6.0% at 10 years after HT.[1] In both the SRTR[2] and International Society of Heart and Lung Transplantation[1] registry, risk factors for the development of posttransplantation CKD include older age, worse pretransplantation eGFR, postoperative AKI, pretransplantation hypertension or diabetes, early infection or rejection, reoperation before discharge after HT, restrictive versus nonischemic cardiomyopathy, and use of cyclosporine over tacrolimus.[1]

CKD not only is common but also affects post-HT survival. In the SRTR analysis from 1990 to 2000, the development of post-HT stage 4 CKD was associated with a 4.5-fold increased risk of death.[2] In the 2019 International Society of Heart and Lung Transplantation registry report, creatinine ≥2.5 mg/dL was associated with an almost 50% increase in death at 5 and 10 years.[1]

Although worse renal function before and after HT portends worse outcomes after HT, data demonstrating improved survival with SHKT versus HT when pretransplantation glomerular filtration rate (GFR) is below a specific threshold are limited.[22–25] A UNOS registry analysis of >26 000 recipients who underwent transplantation from 2000 to 2010 determined that transplantation recipients derived increased survival for SHKT versus HT if they had eGFR <37 mL·min^{-1}·1.73 m^{-2}.[23] However, these findings should be interpreted with caution for several reasons. First, the threshold eGFR for the SHKT group was not uniform, so it is not clear that the observed improvement in survival in SHKT versus HT was attributable solely to the kidney transplantation (KT). Second, the absolute difference in median posttransplantation survival

was surprisingly small: 7.7 years for the SHKT cohort versus 7.1 years for the HT cohort. Third, only HT recipients stable in the immediate postoperative setting went on to receive SHKT,[26] and this selection may have accounted for much of the immediate difference in posttransplantation mortality between HT and SHKT recipients.

Evaluation of CKD in the HT Candidate

A key concern in SHKT eligibility is whether, and by how much, an individual will benefit more from an SHKT compared with alternatives such as isolated HT or kidney-after-heart transplantation (KAHT). In SRTR data, SHKT was associated with increased survival in dialysis-dependent patients (median survival SHKT, 12.6 versus HT, 7.1 years; $P<0.0001$) but not with non–dialysis-dependent patients (median survival SHKT, 12.5 versus HT, 12.3, $P=0.24$).[26]

Evaluation for CKD before transplantation offers prognostic information on kidney function after HT but cannot fully predict the trajectory of kidney function after HT because it is also dependent on donor characteristics and the perioperative and posttransplantation course. Moreover, prognosis is distinct from causation: Pretransplantation CKD may predict worse kidney function and lower survival after HT, but whether these disadvantages are mitigated by an SHKT is not established.

The goal of the pretransplantation evaluation of kidney function is to differentiate CKD that will not improve after HT from AKI or CKD that may reverse with the hemodynamic optimization afforded by HT. This evaluation should take into account (1) historical trends in kidney function during the months to years before cardiac decompensation; (2) current trends in kidney function when the patient is hemodynamically optimized, ideally over a few weeks' duration; (3) comorbidities (eg, diabetes, lupus) known to be associated with irreversible kidney damage; and (4) other findings such as the presence of proteinuria.[27]

In cases of urgent HT evaluation when a comprehensive assessment and prolonged hemodynamic optimization are not feasible, in the absence of documented preexisting kidney disease, the observed kidney dysfunction is likely acute and reversible if HT can be performed in a timely fashion with minimal complications. Table 1 summarizes the biomarkers and other modalities that have been investigated or proposed in this setting.

HT candidates should have 2 independent measurements for GFR at least 2 weeks apart using serum creatinine measurements and race-free equations for eGFR; Chronic Kidney Disease Epidemiology Collaboration refit without the race variable is recommended by the American Society of Transplantation[28] with significant implications for assessment of renal function in Black transplantation candidates.[44,45] The confirmatory GFR measurement should be a measured GFR.[30]

The results of ancillary testing may be used to assess for the presence, severity, and chronicity of intrinsic renal disease, including the presence of cortical scarring on renal ultrasound or proteinuria. A kidney biopsy is rarely required. Another challenge is marked changes in kidney function in an HT candidate while on the waiting list. In situations in which there is inadequate time to assess for AKI recovery, both heart and kidney specialists should weigh all factors (ie, perceived kidney reserve and recovery potential, risk or presence of CKD) in order to decide SHKT versus HT candidacy.

Proposed Algorithm for Heart-Kidney Transplantation Consideration

There is growing consensus on SHKT eligibility criteria. The 2016 International Society of Heart and Lung Transplantation listing criteria for HT propose irreversible renal insufficiency with a GFR <30 mL·min^{-1}·1.73 m^{-2} as a relative contraindication to HT.[46] However, ethical dilemmas for balancing donor stewardship and SHKT patient outcomes led to a 2019 consensus conference to establish national standards for SHKT.[27] Consensus recommendations from this conference included the following:

1. Patients with established GFR <30 mL·min^{-1}·1.73 m^{-2} may be considered for SHKT.
2. Patients with established GFR of 30 to 44 mL·min^{-1}·1.73 m^{-2} and firm evidence of CKD such as small kidney size or persistent proteinuria >0.5 g/d in the presence of stable hemodynamics may qualify for SHKT on an individual basis.
3. Patients with established GFR of 45 to 59 mL·min^{-1}·1.73 m^{-2} may not be appropriate for SHKT.

A proposed algorithm for evaluation for SHKT candidates based on these recommendations is described in Figure 1.

Heart-Kidney Transplantation

Patients who undergo SHKT may have improved survival, less rejection, and less cardiac allograft vasculopathy than patients undergoing HT alone.[1] Nonetheless, SHKT does not fully mitigate the risk of adverse renal disease after HT. Recipients of SHKT experience a higher rate of severe AKI after transplantation, with 26% to 37% of SHKT recipients needing dialysis in the early posttransplantation period compared with recipients of HT alone (7%–22%).[22,23,47] Furthermore, similar to patients undergoing HT, progressive renal dysfunction may still develop over time after SHKT.[48]

Surgical Considerations for Heart-Kidney Transplantation

As with isolated KT, anatomic planning for SHKT requires a thorough history and physical examination to guide additional preoperative imaging. In addition to vascular duplex ultrasound to determine vessel

Table 1. Assays for Evaluation of Kidney Function and Liver Function in HT Candidates

Tool	Parameter	Accuracy	Prognostic ability in HT setting	Comments/caveats
Evaluation of kidney function				
SCr and SCr-based race-free eGFR equation; CKD-EPI refit without the race variable[28,29]	eGFR	Only moderate correlation between SCr-based eGFR equations and measured GFR[30]	Higher SCr/lower eGFR is associated with a higher likelihood of CKD and ESKD after HT. Compared with HT recipients with GFR ≥90 mL·min^{-1}·1.73 m^{-2}, adjusted HR for mortality of 1.09 (95% CI, 1.02–1.26) for eGFR 45–59 mL·min^{-1}·1.73 m^{-2}; 1.22 (95% CI, 1.23–1.31) for eGFR 30–44 mL·min^{-1}·1.73 m^{-2}; and 1.55 (95% CI, 1.41–1.70) for eGFR <30 mL·min^{-1}·1.73 m^{-2}.[31] SHKT results in 30% reduction in mortality at eGFR <30 mL·min^{-1}·1.73 m^{-2}.[26]	Steady state must be observed to enable use of eGFR equations. SCr will be lower in conditions of sarcopenia or severely depressed GFR (plus tubular secretion element). As renal function declines, creatinine is secreted into urine and may lead to an overestimation of GFR.
CysC and CysC/SCr-based eGFR equations	eGFR	Only moderate correlation between CysC-based eGFR equations and measured GFR; no significant advantage over SCr[30]	Not investigated in HT setting	Steady state must be observed to enable use of eGFR equations.
24-h creatinine/urea clearance	eGFR	Better correlation with measured GFR compared with SCr-based equations[32]	Insufficient data in the HT setting	Requires 24-h urine collection Ideally done in steady state but can be done in non–steady-state conditions with at least 2 timed blood draws May be the most accurate assessment of eGFR
Kidney ultrasound	Parenchymal and structure abnormality; advanced CKD (shrunken size)	High interoperator and interreader variability	Not well studied in HT setting Normal cortical thickness is 7–10 mm; reduced cortical thickness may indicate progressive kidney disease or decreased eGFR.[33] Normal kidney volume range in men is 110–190 mL and in women is 90–150 mL. Kidney length of ≤8 cm correlates with kidney failure.	
Kidney biopsy	Kidney histology	Kidney histology is not well predicted by SCr.[34]	One report using histological criteria for SHKT eligibility (n=14) selected 8 patients for HT; all HTs were successful.[34]	Sampling variability Risk of bleeding, especially in the setting of antiplatelet and anticoagulant therapy
Evaluation of liver function				
Albumin	Synthetic function	NA	Hypoalbuminemia associated with increased risk of worsening HF, urgent cardiac transplantation, and death[35]	May be reduced because of malnutrition/cardiac cachexia and protein-losing enteropathy (ie, FALD)
AST/ALT	Cellular integrity	NA	Abnormal AST/ALT associated with congestion, elevated right-sided filling pressures, increased mortality[36]	
ALP, GGT	Obstruction/cholestasis	Less specific for hepatobiliary injury[37] Predictive value of GGT higher in NYHA class I–II HF (HR, 2.9) compared with class III–IV HF (HR, 1.2).[38]	In chronic HF, predictor of death or HT; in multivariate analysis, ALP and GGT and not transaminases independently predicted HT-free survival (GGT HR, 1.22; ALP HR, 1.52)[37] GGT and ALP have added prognostic value if considered concomitantly. Cutoff levels: GGT, 69 U/L in men and 36 U/L in women; ALP, 68 U/L in men and 111 U/L in women	ALP may be elevated in high bone turnover and non-HF causes of intrahepatic cholestasis. GGT may be elevated in patients with alcohol consumption. Both can be elevated from medication side effects.
Bilirubin, TB	Obstruction/hepatic synthetic functions	NA	TB predicts composite cardiovascular outcomes in chronic HF.[39] TB predicts death or HT in a study of 1032 patients (HR, 1.28).[37]	May be elevated in hemolysis or disorders of bilirubin conjugation
INR	Synthetic function	NA	Peak INR >2 is an independent predictor of mortality in patients with hypoxic hepatitis.[40,41]	May be elevated because of anticoagulation

(*Continued*)

Table 1. Continued

Tool	Parameter	Accuracy	Prognostic ability in HT setting	Comments/caveats
Ultrasound, MRI, elastography	Parenchyma, size, obstruction	Extensive fibrosis can be seen in chronic or severe cases but inadequate for tissue characterization. Hepatic elastography integrated into hepatic imaging, including ultrasound, allows noninvasive assessment of hepatic fibrosis.	Liver stiffness assessed by transient elastography is associated with elevated right-sided filling pressures and worse outcomes in patients with HF.[42]	Not a substitute for liver biopsy when there is concern for cirrhosis
Biopsy	Liver histology	Gold standard for assessing hepatic cirrhosis Biopsy can distinguish cirrhosis from less advanced stages of fibrosis, outflow obstruction from elevated right atrial pressures, and forms of noncirrhotic portal hypertension.	A normal (≤5 mm Hg) gradient between hepatic wedge pressure and free hepatic vein pressure excludes significant portal hypertension.[43] Finding of cirrhosis on liver biopsy without sinusoidal hypertension may permit HT.	Prone to sampling error, heterogeneity of liver fibrosis, and procedural risks of biopsy

AKI indicates acute kidney injury; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CysC, cystatin C; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FALD, Fontan-associated liver disease; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; HF, heart failure; HR, hazard ratio; HT, heart transplantation; INR, international normalized ratio; MRI, magnetic resonance imaging; NA, not applicable; NYHA, New York Heart Association; SCr, serum creatinine; SHKT, simultaneous heart-kidney transplantation; and TB, total bilirubin.

patency, noncontrast computed tomography may be necessary to confirm suitable arterial targets for implantation of the kidney allograft.[49–52] One groin should be maintained free of vascular catheters, including temporary mechanical support devices, to ensure ease of allograft placement.

The major surgical consideration in SHKT is timing of the KT: immediate (a single operation) versus staged (KT performed after completion of HT). Immediately after HT, recipients may be hemodynamically unstable or require high-dose inotrope or vasopressor support, which increases surgical complexity and compromises

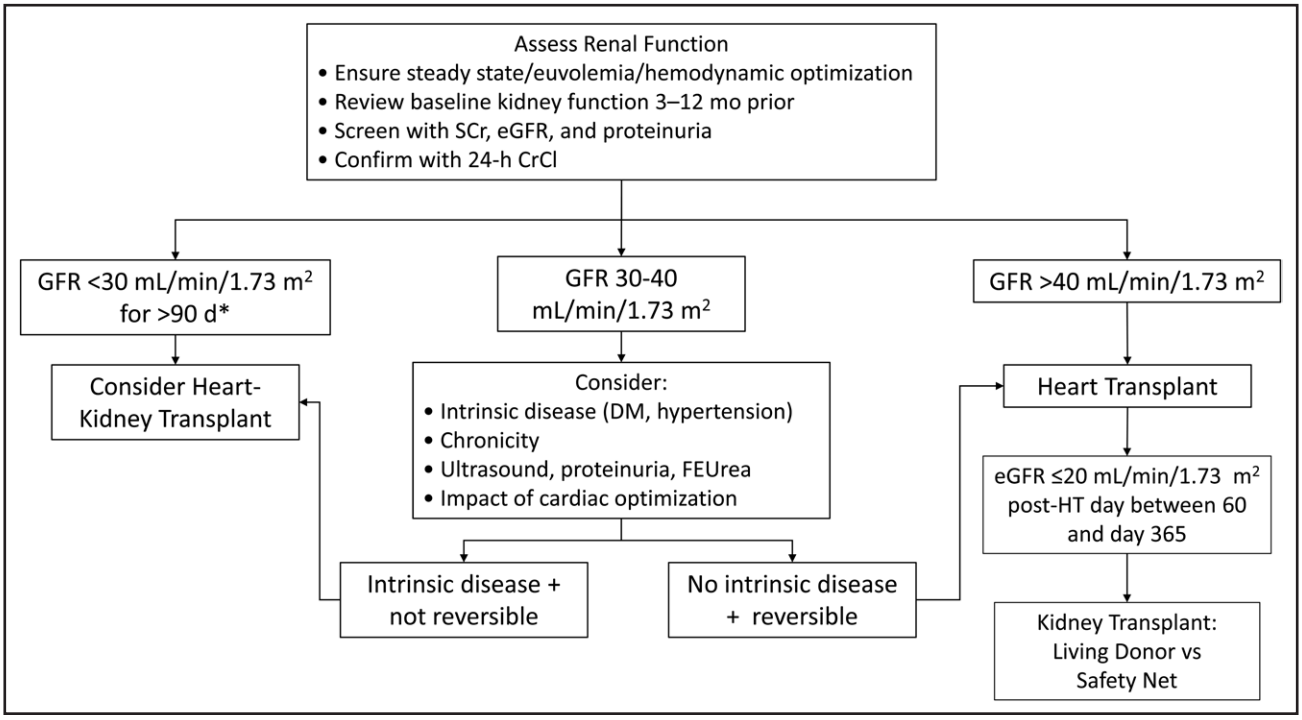

Figure 1. Proposed algorithm for heart-kidney transplantation consideration.
CrCl indicates creatinine clearance; DM, diabetes; eGFR, estimated glomerular filtration rate; FEUrea, fractional excretion urea; GFR, glomerular filtration rate; HT, heart transplantation; and SCr, serum creatinine. *For GFR <30 mL·min^{-1}·1.73 m^{-2} for <90 days, evaluation of intrinsic renal function with the above modalities may assist in determination of prognosis and likelihood of recovery with hemodynamic optimization.

kidney allograft function.[53,54] Reviewing the experience of liver-kidney transplantation shows that staged KT is associated with improved kidney function and increased graft and patient survival.[55] In a series of 30 SHKT recipients, the staged approach increased cold ischemic time for the kidney allograft with no impact on outcomes.[56] Given the benefits of hemodynamic optimization and stabilization with a staged approach, this may be considered the optimal approach for SHKT.

Should the KT not be possible after the initial HT, a proper allocation mechanism is needed to ensure that the kidney can be reallocated to a backup candidate in a timely fashion.[57] This would be required if the HT recipient remained unstable and the ischemic time of the KT would potentially be >24 hours.

Kidney-After-Heart Transplantation

KAHT may be an alternative to SHKT in patients with pretransplantation kidney dysfunction or unanticipated severe posttransplantation AKI. Patients who undergo KAHT commonly undergo transplantation before initiation of dialysis and often undergo living-donor transplantation; there have been no reports of immunological consequence from the use of organs from different donors.

In 1 single-center study, end-stage renal disease (ESRD) developed in 51 of 268 HT recipients (19%) over a 76-month follow-up period; of this group, 39 patients underwent KAHT during the follow-up period. This group had survival comparable to that of patients with HT without ESRD and improved survival compared with patients with HT with ESRD (17.5 years versus 17.1 years versus 7.3 years, respectively).[58] In another single-center study of 614 HT recipients, 121 (19.7%) developed ESRD during a median follow-up of 8.6 years, of whom 19 received KAHT. KAHT was associated with the best median survival compared with patients with HT on dialysis or patients with HT with non–dialysis-dependent ESRD (6.4 years versus 2.2 years versus 0.3 years, respectively).[59]

In a UNOS registry analyses of 456 KAHTs from 1995 to 2008[60] and 813 KAHTs from 2000 to 2015,[61] comparable kidney allograft survival[60] and patient survival[61] were demonstrated compared with SHKT. Potential benefits of KAHT over SHKT include increasing the deceased kidney donor pool. However, extended wait times for KT may increase morbidity and mortality; patients undergoing KAHT are highly selected in that they had to survive HT to receive the KT. A safety net policy could provide an approach that maximizes both beneficence and utility, the implications of which are discussed later.[27,62,63]

Immunosuppression for Heart-Kidney Transplantation

Specific considerations for immunosuppression in SHKT are based on the nephrotoxicity of the CNIs and extend to the choice of induction therapy and maintenance immunosuppression. Practices may vary by center, but the HT team will generally guide choice and target trough levels of immunosuppression.

The goal of induction therapy is to provide intense immunosuppression when the risk of allograft rejection is highest and to allow delayed initiation of nephrotoxic CNIs. Agents used for induction therapy include polyclonal anti-thymocyte antibodies to human thymocytes (anti-thymocyte globulin or rabbit thymoglobulin). These agents may reduce the risk of early rejection at the cost of more infections.[64,65] Anti–interleukin-2 receptor antagonists, for example, basiliximab, are also used.[66] No studies have conclusively demonstrated benefit or harm of induction immunosuppression in HT recipients. In SHKT recipients in particular, an analysis of 623 SHKT recipients in the Organ Procurement and Transplantation Network registry from 2000 to 2015 indicated that 37% received no induction, 33% received rabbit thymoglobulin, and 33% received an interleukin-2 receptor antagonist.[67] Those patients in a sensitized subgroup who received rabbit thymoglobulin had an 81% reduction in posttransplantation mortality, but there was no difference in outcomes among nonsensitized patients. However, this was an observational analysis; thus, causation cannot be inferred.

Compared with cyclosporine, tacrolimus-based immunosuppression is associated with decreased risk of acute rejection,[68,69] less nephrotoxicity, less hypertension, and more diabetes.[70,71] Mycophenolate mofetil has replaced azathioprine as the preferred antimetabolite agent given a reduction in both mortality and the incidence of treated rejection at 1 year.[72] Proliferation signal inhibitors (PSIs) or mammalian target of rapamycin inhibitors (sirolimus and everolimus) reduce the incidence of acute rejection and prevent the development of cardiac allograft vasculopathy.[73–76] However, PSIs are not initiated de novo after HT because of an increased risk of sternal wound dehiscence[74] and exacerbation of the nephrotoxic effects of CNIs.

However, when used in place of the CNI within 3 to 6 months of transplantation, PSIs may prevent progression of renal dysfunction in both HT[77,78] and KT recipients.[79] In HT recipients in the SCHEDULE trial[77] (Scandinavian Heart Transplant Everolimus De Novo Study With Early Calcineurin Inhibitor [CNI] Avoidance) and MANDELA trial[78] (A Study Investigating the Renal Tolerability, Efficacy, and Safety of a CNI-Free Versus a Standard Regimen in De Novo Heart Transplant [HTx] Recipients), when the CNI was withdrawn 3 to 6 months after transplantation with conversion to PSI in addition to mycophenolate mofetil, patients had improved renal function by 1 year; however, more frequent episodes of biopsy-proven rejection were observed. This concern has limited the widespread implementation of CNI-free regimens, which are generally tailored to those patients who are >1

year after transplantation with significant renal dysfunction and lower risk for rejection. In addition, specifically in SHKT, there is concern for PSI-related proteinuria and increased mortality in KT recipients on PSIs.[80]

Another potential option to minimize CNI nephrotoxicity in SHKT is the use of belatacept, a selective T-cell costimulation blocker. Although not approved by the US Food and Drug Administration for use in HT recipients, belatacept may in the future be an effective alternative immunosuppressive to mitigate CNI-related nephrotoxicity in HT and SHKT recipients.[81]

Some investigations have demonstrated that corticosteroid withdrawal is associated with increased risk of rejection in KT recipients.[82] Whether corticosteroid withdrawal is possible in SHKT is not established. Practices may be center specific, although generally corticosteroid maintenance is preferred.

HEART-LIVER TRANSPLANTATION

The liver is frequently affected by both acute and chronic HF. Acute HF can lead to liver injury through ischemia, congestion, or both.[83] In chronic HF, ischemia and congestion also contribute to chronic liver disease, often related to right ventricular failure, advanced biventricular failure, severe tricuspid regurgitation, restrictive/constrictive cardiomyopathy, and congenital heart disease, particularly in single-ventricle physiology palliated with a Fontan operation (Fontan-associated liver disease [FALD]).[84] The prevalence of abnormal liver function tests in patients with chronic HF, regardless of left ventricular ejection fraction, ranges from ≈15% to 50%.[38,39] Advanced liver disease and cirrhosis are considered to be contraindications to isolated HT[46]; patients with cirrhosis who undergo isolated HT have short-term mortality as high as 50%.[4] The prevalence of FALD depends on time from Fontan. Within the first decade, 35% of patients have bridging fibrosis,[85] although evidence of fibrosis is universally present by a decade after Fontan,[86,87] with severe fibrosis in 68% in 1 study.[88]

Evaluation of Liver Function in HT Candidates

Liver Enzymes and Liver Function Tests

Hepatic function includes hepatic protein synthesis (albumin, vitamin K–dependent coagulation factors), bilirubin disposition, and energy metabolism. Although abnormalities in these measures of hepatic function are associated with worse prognosis in patients with HF,[84] 2 caveats bear mention. First, it is necessary to distinguish hyperbilirubinemia due to liver disease from that due to disorders that affect bilirubin conjugation. Second, although serum albumin levels may be depressed as a result of inadequate hepatic synthetic function, in patients with FALD, albumin levels may also be depressed because of protein-losing enteropathy.

Nonetheless, in both acute and chronic HF, abnormal liver-related laboratory testing (including albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, gamma-glutamyl transpeptidase, and international normalized ratio) is associated with a worse overall prognosis in registries, clinical trials, and single-center observational studies.[84] Progression of liver disease in patients with FALD is also associated with worse outcomes but may improve with surgical correction as a result of improvement in congestion.[89]

Model for End Stage Liver Disease Scores

Although isolated liver-related laboratory testing can offer prognostic value in HF, the results of this testing are most useful when aggregated into equations developed for the prediction of medically relevant outcomes. The Model for End Stage Liver Disease (MELD) score, introduced for the assessment of 90-day mortality after portosystemic shunt placement,[90] was the major determinant of liver transplant organ allocation (Table 1). The MELD-Na score, which predicts wait-list mortality more accurately than MELD score alone,[91] is currently used for liver transplant allocation.

A modification of the MELD score (MELD-XI) that excludes international normalized ratio offers prognostic information in HT candidates. In a UNOS registry analysis, a MELD-XI score ≥14.1 was associated with increased post-HT mortality, infections, stroke, dialysis, rejection, and prolonged hospitalization.[92] In the Pediatric Heart Transplant Society Database, a MELD-XI score ≥11.5 was independently associated with mortality in patients with Fontan physiology undergoing HT.[93]

Hepatic Imaging

Hepatic imaging is an indispensable component of liver assessment in HT candidates. Liver ultrasound, abdominal computed tomography, and liver magnetic resonance imaging are the most common imaging techniques and can identify focal lesions, biliary abnormalities, abdominal ascites, and disturbance of portal and hepatic vein flow (Table 1). However, imaging is less useful for tissue characterization; thus, the diagnosis of cirrhosis in HT candidates should never rest on imaging findings alone because imaging can neither accurately characterize the degree of hepatic fibrosis nor distinguish cirrhosis from nodular regenerative hyperplasia[94] or noncirrhotic portal hypertension.[95]

Hepatic elastography, integrated into ultrasound, magnetic resonance imaging, and machines exclusively dedicated for transient elastography, allows noninvasive assessment of hepatic fibrosis. Although elastography has been studied as a method to stage the severity of FALD and cardiac function,[96–98] these techniques are unable to distinguish among hepatic outflow obstruction, hepatic congestion, and hepatic fibrosis and are not established to assess hepatic function in HT candidates.[99]

Liver Biopsy

The testing discussed previously may offer complementary information to guide the decision to proceed with liver biopsy, but these modalities are not a substitute for liver biopsy to assess HT candidacy. Liver biopsy remains the only accurate and reliable method of assessing hepatic histology in the process of assessing HT candidacy,[100] but it is also prone to sampling error due to heterogeneity of liver fibrosis, which may warrant repeat biopsy in discussion with hepatologists if the clinical suspicion is high.[101] Biopsy can distinguish cirrhosis from less advanced stages of fibrosis and identify forms of noncirrhotic portal hypertension. Transvenous liver biopsy is preferred because it allows assessment of wedged and free hepatic vein pressure measurements. A normal (≤5 mm Hg) gradient between hepatic wedge pressure and free hepatic vein pressure excludes significant portal hypertension, providing important information on the presence of chronic liver disease, which may affect HT candidacy.[43]

Although liver biopsies are the gold standard, they do not perfectly predict liver function after HT. In 1 study, there was no association between the presence of fibrosis and post-HT outcomes: 3 patients who died of postoperative liver failure had only stage 2 or 3 liver fibrosis.[102] On the other hand, even a finding of cirrhosis on liver biopsy without sinusoidal hypertension may permit HT.[103] In fact, a liver risk score incorporating fibrosis on liver biopsy with MELD-XI score improved the prognostication of this risk score: Those patients with an elevated MELD-XI score and liver fibrosis had increased 1-year post-HT mortality, longer ventilation times, more severe bleeding, and increased acute graft dysfunction, although this risk score has not been validated.[104]

Proposed Algorithm for Heart-Liver Transplantation Consideration

There are no current consensus criteria for SHLT.[105] The evaluation of patients with advanced HF being considered for transplantation with concomitant liver disease focuses on whether the liver disease may reverse with optimization of cardiac function or is advanced enough to affect perioperative risk or require dual-organ transplantation.

An important consideration is the depth of investigation necessary to determine the need for liver transplantation, namely when to pursue liver biopsy. Both acute and chronic elevations of right-sided heart pressures can result in symptoms of portal hypertension and hepatic synthetic dysfunction. FALD may require unique considerations based on the age of the patient; histological evidence of fibrosis in FALD is typically observed at least 10 years after Fontan.[106] A proposed algorithm for the evaluation of liver disease in the HT candidate is shown in Figure 2.

Heart-Liver Transplantation

The most common cardiac indication for SHLT is cardiac cirrhosis, often from congenital heart disease, particularly the failing Fontan with FALD.[106,107] Other cardiac indications for SHLT include metabolic disorders with cardiac complications that are curable with liver transplantation, including familial hypercholesterolemia[108] and variant transthyretin amyloidosis,[109] although the latter is less common with the advent of effective disease-modifying therapy.

From 1989 to 2021, the SRTR recorded 449 SHLTs. Both single-center studies and analyses of large databases have demonstrated favorable outcomes after SHLT.[110–113] In an SRTR analysis, survival of SHLT at 1, 3, and 5 years was 86.8%, 82.8%, and 81.3%, respectively.[111] In a UNOS registry analysis, survival after SHLT was comparable to that after HT alone.[114]

Surgical Considerations for Heart-Liver Transplantation

Various operative techniques for concomitant transplantation have been described, including as separate organs or en bloc.[115–122] Sequential heart-liver transplantation is the most common surgical approach to SHLT whereby the heart and liver are procured separate from one another. HT is performed on cardiopulmonary bypass, after which the recipient is weaned from cardiopulmonary bypass with the chest left open. Liver transplantation is then performed with veno-venous bypass or extracorporeal membrane oxygenation, in which case peripheral or central cannulation may be used. In en bloc SHLT, the heart and liver are procured with the connecting inferior vena cava remaining intact.[116,118,120] Both organs are implanted nearly simultaneously with the patient on cardiopulmonary bypass and are reperfused at the same time, decreasing hepatic ischemic time.

The benefits of sequential versus en bloc SHLT remain debated and center dependent, although the en bloc technique may be advantageous in certain scenarios such as in patients with FALD to allow protection from longer cold ischemic time for the liver and from metabolic and hemodynamic derangements for the heart.[123] However, the outcomes of both techniques appear comparable, with centers reporting 90% to 100% 1-year survival.[115,116,119,120]

Heart-after-liver transplantation is a unique approach that takes advantage of the immunoprotection of the donor liver. In 7 highly allosensitized heart-liver transplantation candidates with positive prospective flow crossmatches, performing heart-after-liver transplantation resulted in near elimination of donor-specific anti-HLA antibodies and prevention of adverse immunological outcomes, although there was no control group and 5 of the 7 patients also received intensive immunosuppression with eculizumab.[124] Given the shorter ischemic time of donor hearts (4 hours) compared with livers (24 hours) in this study, it is not clear whether this approach will easily translate to other centers, although the use of an ex vivo perfusion platform may make this approach feasible.

Immunosuppression in Heart-Liver Transplantation

Specific immunosuppressive considerations in SHLT recipients are related to lower risk of rejection of SHLT compared with HT recipients,[125] which may be related

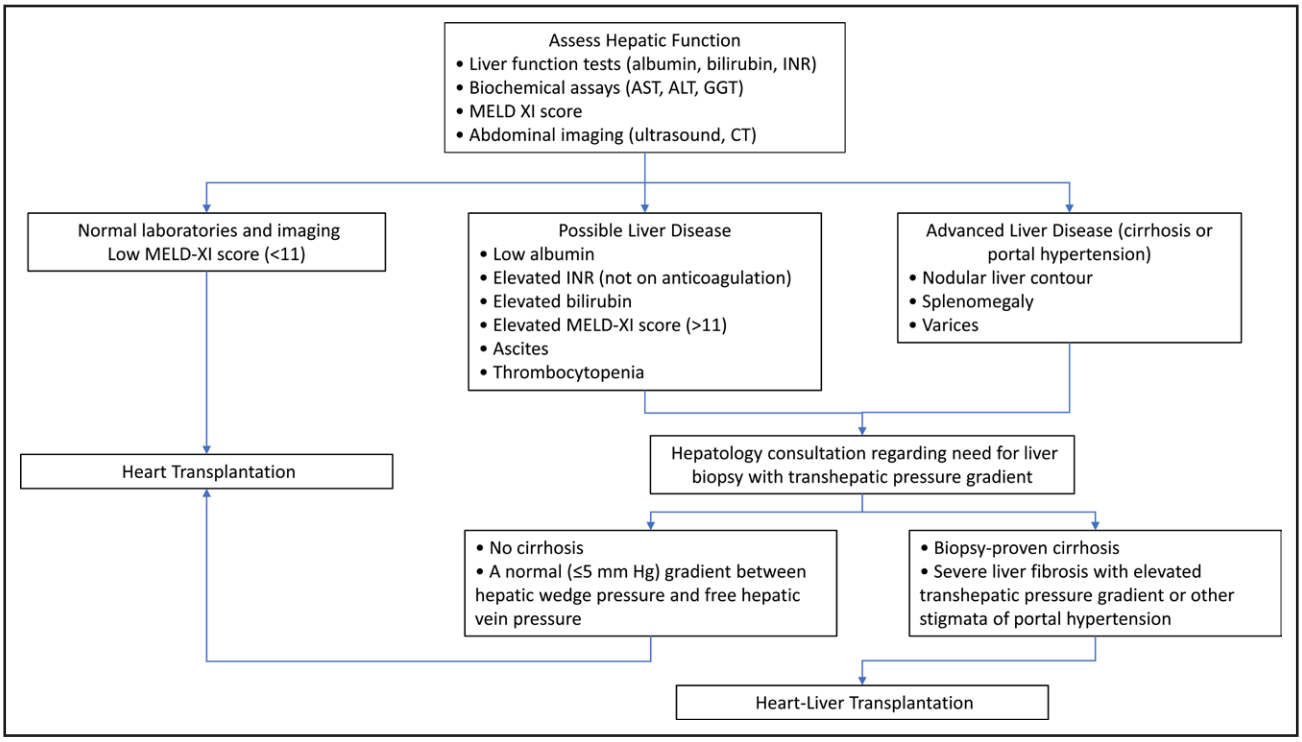

Figure 2. Proposed algorithm for heart-liver transplantation consideration emphasizing criteria for which there are either published supporting data or expert consensus on HT alone vs SHLT for a patient with suspected underlying liver disease.
For borderline cases of severe fibrosis or cirrhosis without stigmata of portal hypertension, multidisciplinary review and center-specific thresholds for risk will influence the case-by-case decision-making process. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; GGT, gamma-glutamyl transferase; HT, heart transplantation; INR, international normalized ratio; MELD-XI, Model for End-Stage Liver Disease excluding INR; and SHLT, simultaneous heart-liver transplantation.

to the presence of circulating soluble HLA antigens derived from the liver allograft, which serve as an "antigen sink" for circulating antibodies.[125,126] This is in contrast to SHKT, in which specific immunosuppression considerations focus on minimizing the nephrotoxicity of the CNIs with the use of induction immunosuppression and avoidance of the combination of CNIs and PSIs, which may result in increased nephrotoxicity.

There is no demonstrated benefit of induction immunosuppression in liver transplantation recipients.[127] Thus, given the immunoprotection of the liver in SHLT, induction immunosuppression may not be routinely indicated in the absence of renal dysfunction when a delay in CNI initiation is anticipated.[128] In contrast to SHKT, on the basis of the potential immunological protection by the liver in SHLT, aggressive steroid minimization or elimination may be possible in SHLT, although this is not established. Whether there is a lower risk of HT rejection with the use of CNI-free regimens in the SHLT population is also not established.

MOT Policies

MOT allocation policies, like those for SHKT and SHLT, can create inequities for patients awaiting MOT or those awaiting single-organ transplantation. These inequities may be greatest for KT candidates, for whom there is the largest gap between the number of candidates on the waiting list and the number of transplantations performed.[129,130] The Organ Procurement and Transplantation Network/UNOS Ethics Committee performed an analysis focusing on the ethical principles of equity and utility in the allocation of MOT to help guide future standardization and allocation policies for different organ combinations.[131] These concerns would be greater still for candidates considered for heart-liver-kidney transplantation.[132]

Safety Net Policies

A safety net policy was established for liver-kidney transplantation recipients in 2017. Since 2017, there has been a 16% decrease in simultaneous liver-kidney transplantations with an increase in kidney-after-liver transplantations,[133] suggesting better use of donor organs. A safety net approach also theoretically allows living kidney donation, which not only has superior outcomes compared with a deceased kidney donor but also increases the overall donor pool. However, the living kidney donation rate is low, with only 10 living kidney transplantations after liver transplantations between August 30, 2017, and December 31, 2019,[134] making the widespread feasibility of this option unclear.

Table 2. Knowledge Gaps in SHKT and SHLT

Unresolved issues	Potential solutions
Biomarkers to assess degree of kidney or liver disease and potential for recovery with improvement in cardiac function Impact of the use of pretransplantation mechanical circulatory support on the need for dual-organ transplant (particularly SHKT) Impact of pretransplantation kidney or liver disease on posttransplantation outcomes Optimal timing and surgical approach for SHKT and SHLT, including the impact of longer ischemic time and use of ex vivo perfusion platforms Optimal immunosuppression, including the need for induction therapy, role of corticosteroid weaning, and use of proliferation signal inhibitors	More research on the mechanisms of cardiorenal syndrome, congestive hepatopathy, and cardiac cirrhosis More complete registry data on pretransplantation kidney or liver function Detailed information on kidney and liver function, including serial creatinine measurements and results of liver biopsies Accurate coding of congenital heart disease Detailed outcome assessment of those declined for transplantation and wait-list and posttransplantation outcomes

SHKT indicates simultaneous heart-kidney transplantation; and SHLT, simultaneous heart-liver transplantation.

A proposed safety net policy for SHKT put forth in the 2019 consensus conference[27] and approved by the Organ Procurement and Transplantation Network is awaiting implementation.[135] In this policy, HT recipients would qualify for the safety net if they (1) were registered on the kidney waiting list before the 1-year anniversary of their HT and (2) were on long-term dialysis or with persistent GFR ≤20 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ between days 60 and 365 after transplantation.[135] Some critically ill HT recipients face a high rate of renal allograft dysfunction attributable to perioperative hemodynamic instability and may benefit from this option, assuming that a living donor is not available.

The possibility of a liver-after-heart transplantation safety net policy has not been explored because hepatic decompensation after HT may portend prohibitive medical and surgical risk of a rescue liver transplantation.

CONCLUSIONS

MOT is a solution to advanced HF with concomitant advanced renal or hepatic disease. However, a lack of consensus on the evaluation and candidacy of patients for MOT remains; unresolved issues are described in Table 2. This scientific statement summarizes the latest diagnostic and prognostic algorithms used to assess concomitant renal or hepatic disease in patients with advanced HF and proposed algorithms for assessment of SHKT and SHLT candidacy. Ultimately, in the setting of organ scarcity, SHKT and SHLT must balance the benefit to the individual with that of other candidates awaiting single-organ transplantation. Future efforts to standardize the assessment of renal and hepatic disease and the criteria for SHKT and SHLT and to assess outcomes of simultaneous versus delayed MOT will optimize the allocation of the scarce resource of donor organs.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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