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Meeting report

Summary of a consensus conference on heart-liver transplantation

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ABSTRACT

Patients with severe heart disease may have coexisting liver disease from various causes. The incidence of combined heart-liver transplant (CHLT) is increasing as more patients with congenital heart disease survive to adulthood and develop advanced heart failure with associated liver disease from chronic right-sided heart or Fontan failure. However, the criteria for CHLT have not been established. To address this unmet need, a virtual consensus conference was organized on June 10, 2022, endorsed by the American Society of

Abbreviations: CAV, cardiac allograft vasculopathy; CHD, congenital heart disease; CHLT, combined heart-liver transplant; DCD, donation after circulatory death; FALD, Fontan-associated liver disease; HCC, hepatocellular carcinoma; HF, heart failure.

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134. Park S, Guo K, Heilman RL, et al. Combining blood gene expression and cellfree DNA to diagnose subclinical rejection in kidney transplant recipients. *Clin J Am Soc Nephrol*. 2021;16(10):1539–1551.
135. Schütz E, Fischer A, Beck J, et al. Graft-derived cell-free DNA, a noninvasive early rejection and graft damage marker in liver transplantation: A prospective, observational, multicenter cohort study. *PLOS Med*. 2017;14(4):e1002286.
136. Stites E, Kumar D, Olaitan O, et al. High levels of dd-cfDNA identify patients with TCMR 1A and borderline allograft rejection at elevated risk of graft injury. *Am J Transplant*. 2020;20(9):2491–2498.
137. Oellerich M, Sherwood K, Keown P, et al. Liquid biopsies: donor-derived cell-free DNA for the detection of kidney allograft injury. *Nat Rev Nephrol*. 2021;17(9):591–603.
138. Ventura-Aguiar P, Ramirez-Bajo MJ, Rovira J, et al. Donor-derived cell-free DNA shows high sensitivity for the diagnosis of pancreas graft rejection in simultaneous pancreas-kidney transplantation. *Transplantation*. 2022;106(8):1690–1697.
139. Williams MD, Fei M, Schadde E, Hollinger EF, Chan EY, Olaitan O. Early experience using donor-derived cell-free DNA for surveillance of rejection following simultaneous pancreas and kidney transplantation. *Transplant Direct*. 2022;8(5):e1321.
140. Yoo A, Riedel A, Qian I, et al. An initial analysis of the baseline levels of dd-cfDNA after pancreas transplantation: a prospective study from high-volume centers in the United States. *Transplant Direct*. 2023;9(4):e1459.
141. Roufosse C, Drachenberg C, Renaudin K, et al. Molecular assessment of antibody-mediated rejection in human pancreas allograft biopsies. *Clin Transplant*. 2020;34(11):e14065.
142. Chellappa S, Kushekhar K, Hagness M, Horneland R, Taskén K, Aandahl EM. The Presence of activated T cell Subsets prior to Transplantation Is Associated with Increased Rejection Risk in Pancreas Transplant Recipients. *J Immunol*. 2021;207(10):2501–2511.
143. Rovira J, Ramirez-Bajo MJ, Bañón-Maneus E, et al. Immune profiling of peripheral blood mononuclear cells at pancreas acute rejection episodes in kidney-pancreas transplant recipients. *Transpl Int*. 2022;35:10639.
144. Zemmour H, Planer D, Magenheim J, et al. Non-invasive detection of human cardiomyocyte death using methylation patterns of circulating DNA. *Nat Commun*. 2018;9(1):1443.
145. Korutla L, Rickels MR, Hu RW, et al. Noninvasive diagnosis of recurrent autoimmune type 1 diabetes after islet cell transplantation. *Am J Transplant*. 2019;19(6):1852–1858.

Transplantation. The conference represented a collaborative effort by experts in cardiothoracic and liver transplantation from across the United States to assess interdisciplinary criteria for liver transplantation in the CHLT candidate, surgical considerations of CHLT, current allocation system that generally results in the liver following the heart for CHLT, and optimal post-CHLT management. The conference served as a forum to unify criteria between the different specialties and to forge a pathway for patients who may need dual organ transplantation. Due to the continuing shortage of available donor organs, ethical issues related to multiorgan transplantation were also debated. The findings and consensus statements are presented.

1. Introduction

Patients with severe heart disease may have coexisting liver disease from various causes. Patients with advanced heart failure (HF) and chronic liver disease who undergo heart transplants alone have reduced survival compared to those without liver disease.[1] Combined heart-liver transplant (CHLT) is increasingly offered as an option for such patients (Fig. 1).[2,3] In recent years, approximately 40 to 50 CHLT surgeries have been performed annually in 25 centers in the United States. However, the decision of when liver transplantation is warranted in a patient with advanced HF and compensated chronic liver disease is challenged by difficulties in differentiating those patients with moderate hepatic fibrosis (which may be reversible) from those with advanced fibrosis and/or cirrhosis who could benefit from this intervention. This can be particularly challenging given the overlap in clinical symptoms in advanced cardiac and liver disease and the lack of rigorous data for CHLT.

With this in mind, a virtual consensus conference on CHLT was organized on June 10, 2022, and included 59 US multidisciplinary experts in cardiothoracic transplantation, liver transplantation, and medical ethics. These key leaders were selected based on heart-liver publications, experience, and symposia presentations. For real-world experience, several participants were invited based on their large program volume in transplantation. The objectives were to develop guidance for the interdisciplinary criteria for liver transplantation in the potential CHLT candidate, to evaluate the current allocation system that generally results in the liver following the heart for the CHLT recipient, and to develop standardized care recommendations for the collaborative management of CHLT recipients. Of note, approaches to chronic disease management of patients in need of CHLT, such as considerations for hepatocellular carcinoma (HCC) screening, were not addressed as being outside the scope of this discussion and will be a subject for future meetings. Participants were divided into 3 breakout discussion groups, all of which considered 7 critical questions that arose from 4 premeeting conference calls (see supplemental material for organization of the conference). Findings and consensus recommendations generated from a review of the existing literature in premeeting conference calls, robust discussion of key questions at the virtual consensus meeting, and expert opinion are outlined below. This manuscript was endorsed by the American Society of Transplantation.

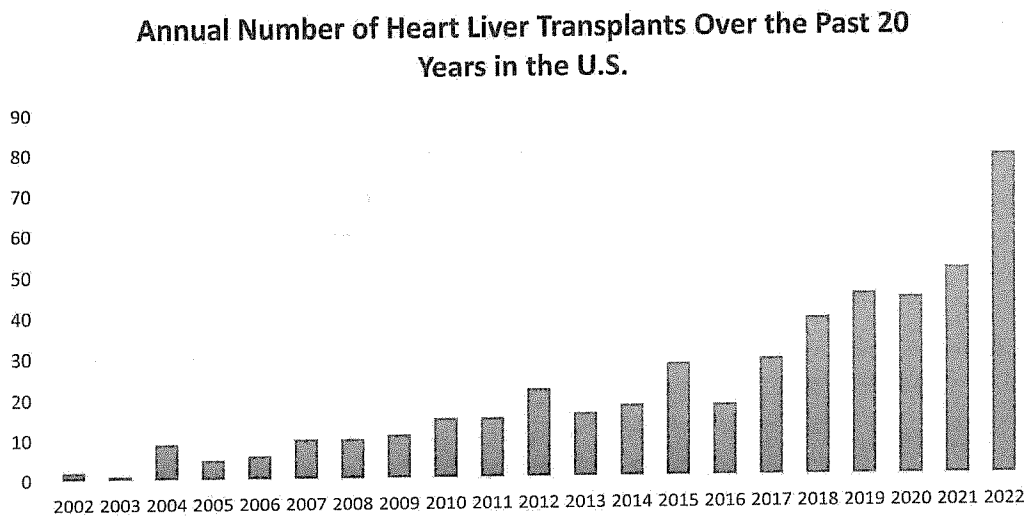

Figure 1. Annual number of heart-liver transplants over the past 20 years in the US.[2,3]

2. Findings

2.1. Question 1. What are the indications and the standard liver-related workup of the CHLT patient?

2.1.1. Background

The most common indications for liver transplant in CHLT include noncongenital heart disease with noncardiac cirrhosis (eg, hepatitis C virus, alcohol-associated cirrhosis), congenital heart disease (CHD) with congestive hepatopathy and variant transthyretin cardiac amyloidosis (though less common in the current era due to the advent of effective disease-directed therapies) (Table 1).[4] Liver disease in patients with CHD is discussed under Question 4.

CHLT continues to be a rare procedure in the US, representing <1% of all liver transplants being performed each year. Similarly, relatively few specialized centers perform this complex procedure, and thus decision-making surrounding evaluation and candidacy is highly center-specific.[4] In regard to liver indication and evaluation for CHLT, a National US Survey on CHLT assessment was recently reported which provided current community viewpoints on CHLT.[5] Selected results are noted in Table 2.

Table 2
Select results from the National US Survey on CHLT assessment. There were 40 respondents (of 48 centers) with a response rate of 83%, the majority hepatologists (72%) in university-based practice (84%).

Indications for CHLT	Percentages of respondents
Elevated hepatic venous pressure gradient	62%
Evidence of portosystemic collaterals	68%
Use in highly sensitized patient	15%
Use of METAVIR score for staging of fibrosis	36%
Bridging fibrosis	39%
CHLT evaluation	
Mandated upper endoscopy	65%
Cross-sectional imaging to assess varices	95%
Routine calculation of varices, ascites, splenomegaly, thrombocytopenia (VAST) score	18%

CHLT, combined heart-liver transplant

2.1.2. Breakout group discussion

All heart transplant candidates should undergo liver-related assessment, with those patients who are found to have abnormal findings referred to transplant hepatology for further testing (Fig. 2). An example protocol has been suggested (Fig. 3).[6] Dedicated liver imaging should be performed for heart transplant candidates with presence or prior history of liver disease or greater than 10 years of cardiac disease. If the liver appears potentially cirrhotic (nodular) on imaging, then liver transplant evaluation should be pursued. In this situation, participants agreed that a liver biopsy should be performed when technically feasible and acceptably safe.

A liver biopsy may not be required if there are stigmata of portal hypertension (eg, varices, ascites). In the presence of ascites, it is important to perform diagnostic paracentesis to determine the cause of ascites (hepatic or cardiac). Isolated hepatic venous pressure gradient should not be used to rule in or rule out portal hypertension especially in patients with Fontan-associated liver disease (FALD) as it may not be reliable. If cross-sectional imaging reveals portosystemic collaterals, upper endoscopy should be performed for variceal screening and the need for primary prophylaxis. In lower-risk patients (those with compensated HF), a normal elastography result (consistent with a liver biopsy of F0/F1) can be used to exclude advanced liver disease.

2.1.3. Consensus statements

#1. Liver transplant evaluation should be performed in heart transplant candidates if there is concern for coexisting liver disease based on clinical/laboratory findings or if the liver appears nodular on imaging.

#2. In patients being considered for CHLT, a liver biopsy is highly encouraged when technically feasible and acceptably safe. However, if stigmata of portal hypertension are present, including hepatic ascites and portosystemic collaterals, liver biopsy may not be required.

#3. If cross-sectional imaging reveals portosystemic collaterals, an upper endoscopy should be performed for variceal screening and the need for primary prophylaxis.

Table 1
Indications for combined heart-liver transplant.

I. Familial amyloidosis	II. Noncongenital heart disease with noncardiac cirrhosis	III. Congenital heart disease and congestive hepatopathy
Liver transplant is curative (in certain types)	Should follow the same rules as for other combined organs • Presence of cirrhosis or • Presence of portal hypertension with hepatic ascites and portosystemic collaterals	• Presence of cirrhosis or • Presence of portal hypertension with hepatic ascites and portosystemic collaterals • Hepatic venous pressure gradient measurements may not be reliable as can have intrahepatic AVMs • Liver masses are hard to characterize as LIRADS criteria do not apply

AVMs, arteriovenous malformation; LIRADS, Liver Reporting and Data System.

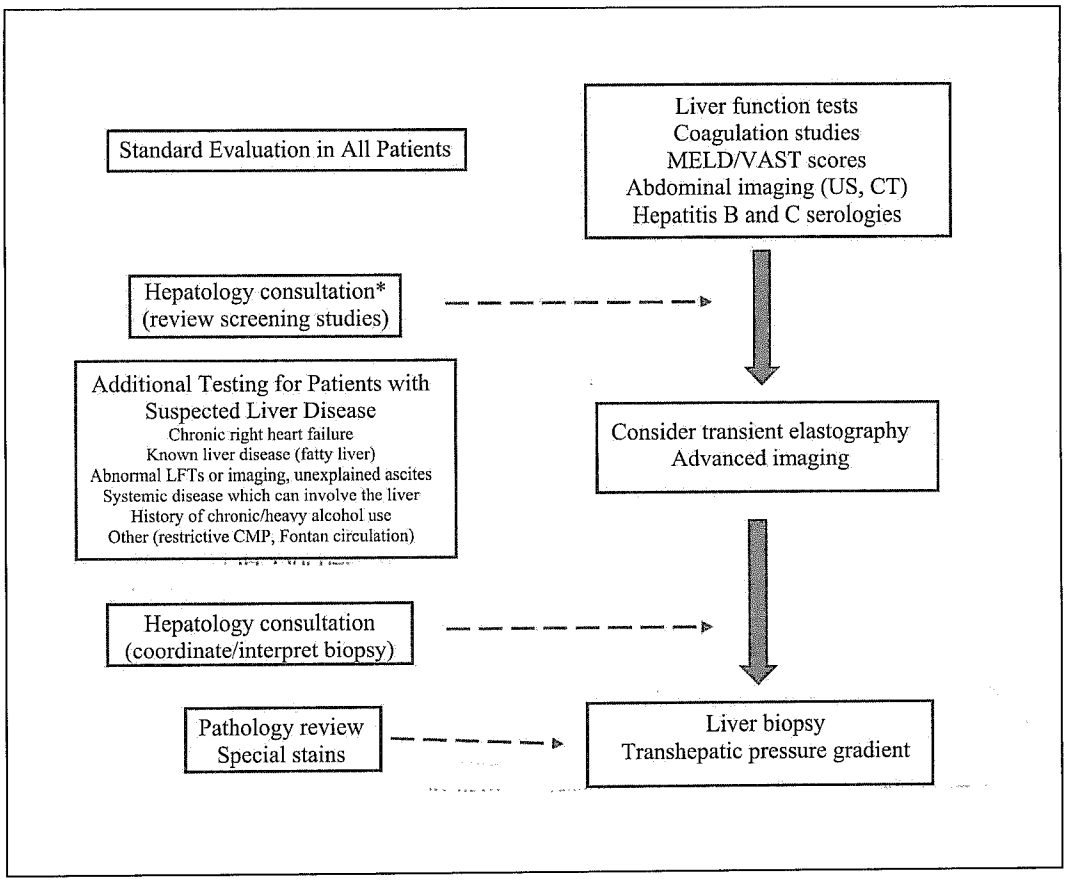

Figure 3. Proposed algorithm for evaluation of liver disease in potential heart transplant candidates. *An early hepatology consultation may result in a clear recommendation for liver biopsy (eg, in a patient with a history or imaging suggestive of cirrhosis, but no prior tissue diagnosis), thereby obviating the need for additional testing. CMP, cardiomyopathy; CT, computed tomography; HCV, hepatitis C virus; LFTs, liver function tests; MELD, model for end-stage liver disease; US, ultrasound. Modified from Givertz.[6]

#6. Biopsy-proven stage 3 fibrosis (F3 disease) without clinical evidence for portal hypertension may not require CHLT.

2.3. Question 3. The ethics of dual organ transplantation: Is CHLT organ allocation fair?

2.3.1. Background

Many of the ethical concerns of multiorgan transplantation have been previously addressed.[12] Nonetheless, potential ethical issues involved in CHLT remain a challenge in terms of both utility and equity, including the following scenarios. For every CHLT performed, 1 heart and 1 liver candidate may die due to lack of an organ. Organs used for multiorgan transplants tend to be of higher quality than those used for single-organ transplants due to younger donor age and better liver function.[13] "Permissive" CHLT listing criteria can deprive more single-organ candidates of these better organs. Regional review boards may apply exception criteria unevenly, affecting equity. Implications of listing (and pulling second organs) are primarily based on the degree of illness of the first organ. In this setting, the lack of standardized

Table 3
Consideration for liver transplant in the combined heart-liver transplant candidate with F3 on liver biopsy.

CHLT for F3	Heart only for F3
• **Heterogenicity on biopsy**	• **Rates of F3 regression in other disease?**
○ If F3, F4 is likely nearby	○ NASH post bariatric surgery, HCV post treatment
• **Sensitization**	○ 70% of F3 regressed, 14% remained F3[10]
○ Considering superior heart outcomes, an F3 liver for CHLT may be considered for highly sensitized patients	• **Little evidence exists on hepatic decompensation in noncirrhotic patients**
	○ Consider "benefit-based allocation"[11]
	○ Heart transplant saves 169 715 life years
	○ Liver transplant saves 65 296 life years

CHLT, combined heart-liver transplant

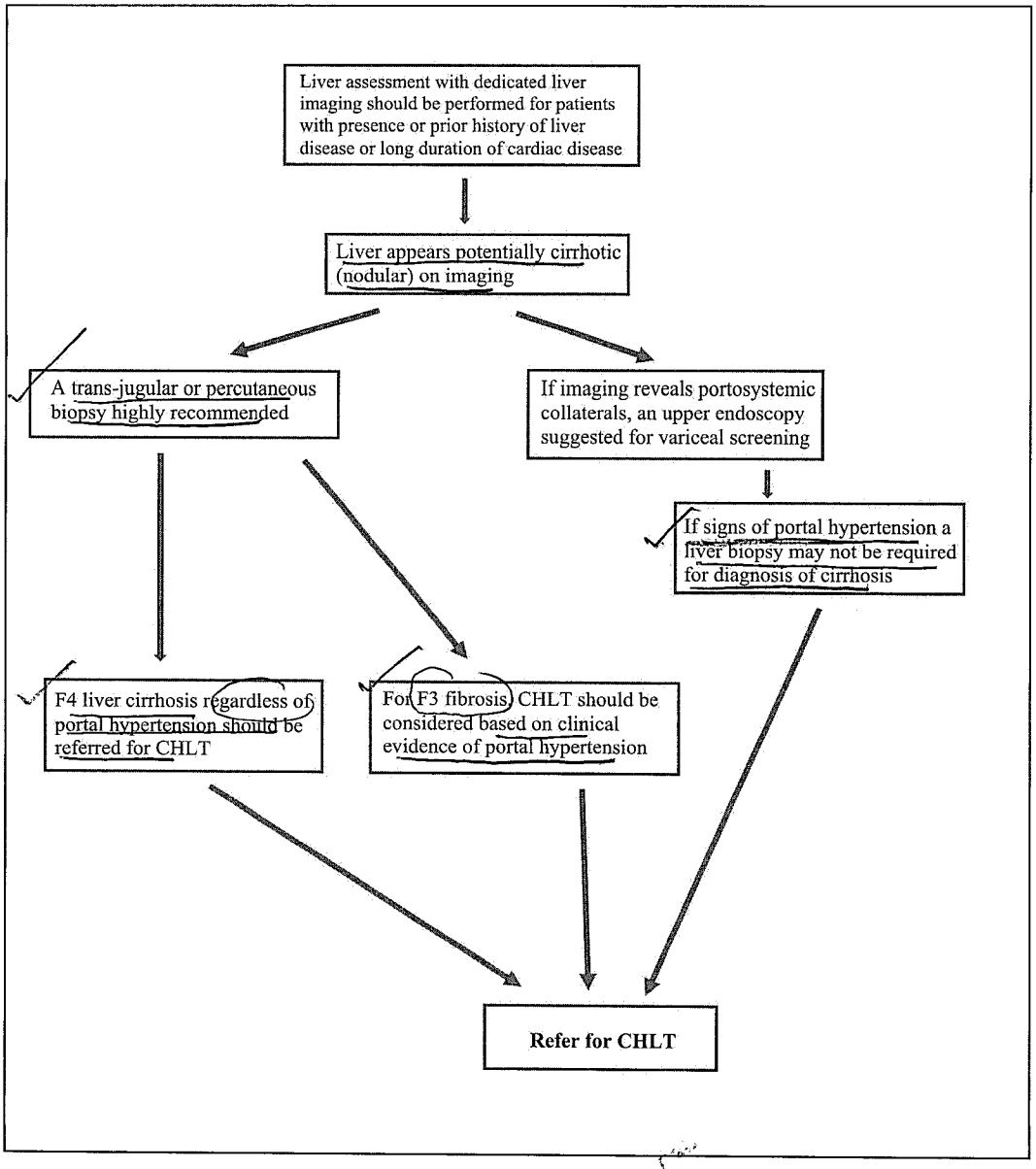

Figure 2. Workflow for liver-related assessment in noncongenital combined heart-liver transplant (CHLT).

2.2. Question 2. What criteria are necessary to proceed with CHLT?

2.2.1. Background and breakout group discussion

Biopsy-proven cirrhosis, regardless of the presence of portal hypertension, is generally considered an indication for CHLT. Biopsy-proven stage 3 fibrosis (F3) and/or clinical evidence of portal hypertension should be a consideration for CHLT. In patients with F3 fibrosis, consideration for CHLT may also depend on the recipient's age, the chronicity of right-sided heart or Fontan failure, and the presence of stigmata of portal hypertension. In patients with biopsy-proven F3 fibrosis, F4 fibrosis (cirrhosis) is likely imminent due to the natural history of congestive hepatopathy or understaging due to sampling error.[7] On the other hand, patients with F3 fibrosis may also have regression of fibrosis as has been observed in patients with nonalcoholic steatohepatitis post bariatric surgery and in those with hepatitis C virus post curative antiviral treatment.[8,9] Anecdotally, in rare circumstances patients with F3 fibrosis who are highly sensitized have been considered for CHLT due to reported superior heart outcomes, where the donor liver is known to absorb circulating antibodies (Table 3).[10,11] Regarding contraindications, although some programs reported an upper age limit for CHLT of 60 to 65 years, there should be caution in setting an age limit given the growing US population over 65 years and acceptable outcomes in transplantation in older adults. Considering a physiological age rather than chronological age for older patients being evaluated for CHLT may be reasonable.

2.2.2. Consensus statements

#4. Biopsy-proven cirrhosis regardless of portal hypertension is an indication for CHLT.

#5. Biopsy-proven fibrosis of any stage with clinical evidence of portal hypertension (hepatic ascites and portosystemic collaterals) should be a consideration for CHLT.

Table 4
Second Organ for Heart or Lung PTRs (OPTN Policy 5.10.E).

Step 1	Step 2	Step 3
If the OPO is offering the following organ:	And a PTR is also registered for one of the following organs:	The OPO must offer the second organ if the PTR is registered at a transplant hospital at or within 500 nautical miles of the donor hospital and meets the following criteria:
Heart	Liver or Kidney	Heart Adult Status 1, 2, 3 or any active pediatric status

OPO, Organ Procurement Organization; OPTN, Organ Procurement and Transplantation Network; PTR, potential transplant recipient.

criteria in listing for dual organs undermines equity. However, accountability for outcomes in multiorgan transplantation can help preserve equity and utility.

Under the current policy (5.10.E), when an organ procurement organization is offering a heart, and a liver is also available from the same deceased donor, potential transplant recipients who meet certain criteria must be offered the second organ (Table 4). This allocation process for CHLT was not associated with a greater risk of liver waitlist mortality compared to patients from control match runs.[14]

In a previous study, CHLT candidates fared worse on the waitlist compared to heart or liver-alone transplant candidates, even after stratifying by the previous waitlist cardiac status (1A/1B/2) or model for end-stage liver disease score, suggesting that CHLT candidates are a distinct population for which CHLT is warranted.[15]

2.3.2. Breakout group discussion

In general, HF has a greater impact on waitlist mortality than liver disease, so it appears appropriate and ethical that in patients listed for CHLT, the heart takes precedence with a plan for the liver to accompany the heart. In the current allocation system, prioritization for CHLT is based on heart allocation status. In the rare case where the candidate has severe primary liver disease and concomitant heart dysfunction which precludes liver-only transplantation, the allocation system should not be agnostic to these patients.

2.3.3. Consensus statement

#7. For the majority of CHLT candidates, the current allocation system appears appropriate where prioritization for CHLT is based on heart allocation urgency status and the liver follows.

2.4. Question 4. What are unique concerns for CHD patients, particularly the Fontan population who require CHLT?

2.4.1. Background

The CHLT rate for adult CHD in the US has increased dramatically as more patients with CHD survive into adulthood. Many of these CHD patients have undergone the Fontan procedure with an estimated global population of 70 000 by 2025 which creates the potential for chronic congestive hepatopathy known as FALD warranting CHLT. Survival has been shown to be comparable between the CHD-heart transplant alone and CHD-CHLT groups.[16] Therefore, it is important that chronic CHD patients with disease of several years undergo liver assessment to exclude the need for CHLT.[17]

There are numerous considerations for Fontan patients undergoing heart transplants including anatomical complexity and surgical reconstruction (which may result in longer bypass, ischemic time, and prolonged bleeding). Fontan patients are generally not temporary or durable mechanical circulatory support candidates due to anatomical considerations and therefore may qualify for prioritization at status 1-3 only by seeking exceptions. CHD-specific conditions such as HCC, cyanosis, protein-losing enteropathy, plastic bronchitis, and unsuitability for inotropic support or mechanical circulatory support may be considered for exception status.[18]

Features of liver cirrhosis identified by computed tomography imaging may not be an absolute contraindication to heart transplant alone in the Fontan population.[19] In -one study, 41% of Fontan patients evaluated for heart transplant had cirrhosis suggested by imaging, however, 1-year mortality and post-transplant liver function were comparable between heart transplant alone and CHLT. In another study, Fontan patients with cirrhosis by imaging and portal hypertension appeared to have better survival and less cardiac rejection with CHLT as compared to those with heart transplants alone.[20]

2.4.2. Breakout group discussion

Liver biopsy may play a smaller role in the evaluation of FALD, owing to low interrater reliability among pathologists for qualitative interpretation of the degree of fibrosis in FALD. Information from imaging and biomarkers may be sufficient to determine need for CHLT. Although there is increased risk of complications with liver biopsy due to chronic high right-sided filling pressures, biopsy may be helpful in certain patients where there is ambiguity about the severity of liver disease. Workup of patients with FALD should be based on multiple assessment modalities to include staging of liver fibrosis (if biopsy is done), portal hypertension assessment, and HCC screening imaging. In the presence of liver masses, biopsy should be considered. From previous studies and experience of the conference participants, it is expected that most Fontan patients will have some degree of liver disease due to chronic congestive hepatopathy.[21] Due to a constraint of participants, the lack of broader inclusion of pediatric heart transplant medical

directors posed a limitation to this discussion. In addition, there is a need for more studies on the natural history of CHD patients with FALD and other liver diseases.

2.4.3. Consensus statement

#8. Adult patients with Fontan physiology may have more tendency toward CHLT due to chronically elevated central venous pressures that result in FALD. A liver biopsy plays a lesser role in the evaluation of FALD and information from imaging, biomarkers, and clinical presentation may be sufficient to determine need for CHLT in FALD.

2.5. Question 5. What are other considerations for CHLT, such as the surgical approach, donation after circulatory death (DCD) donors, or CHLT for highly sensitized patients?

2.5.1. Background

Care planning for CHLT candidates requires multidisciplinary collaboration between cardiac surgery and liver surgery, anesthesia, critical care, hepatology, cardiology, perfusion medicine, and nephrology. This includes development of intraoperative and peri-operative care plans, donor selection criteria, patient optimization/shunt embolization, intraoperative immunosuppression and antimicrobials, synchronization, and postoperative review of intraoperative course and workflow.

Surgical approaches of CHLT include heart-first approach, en bloc technique, or liver-first approach.[22] The heart-first approach is the most used and provides maximal technical flexibility and less procurement risk. It also allows rapid cardiac implantation and cardiac recovery prior to liver reperfusion. However, there are advantages to the other methods. The en bloc CHLT technique reduces surgery time and shortens liver cold ischemic time but increases the risk for phrenic nerve injury.[23,24] There is no clear indication for the liver-first approach except possibly in the highly sensitized patient. The liver-first approach may be applicable in experienced centers for highly sensitized patients where it has been demonstrated to provide a protective effect on the donor heart by absorption of circulating antibodies.[25] For all approaches, a comprehensive team approach is critical to optimize care for patients.

2.5.2. Breakout group discussion

DCD donor hearts should be avoided for now as it may place the liver allograft at risk due to a potentially higher risk of primary donor heart dysfunction. The role of DCD donation and normothermic regional perfusion during DCD procurement remains ethically controversial and both DCD and normothermic regional perfusion should be deferred for CHLT until more experience is obtained and the ethical issues have been adequately addressed.

Performing CHLT solely for the purpose of sensitization (no F3/F4 on liver biopsy) may not be appropriate because of significant surgical risk, ethical issues (ie, the liver does not go to the patient who is highest on the list), and the current effective strategies for managing desensitization. In addition, domino liver transplant may not always be possible due to an abnormally functioning liver from chronic HF. For highly sensitized patients (F3/F4 on liver biopsy), performing liver transplant first prior to heart transplant in experienced centers is possible but is not broadly supported given increased donor heart ischemic time and potential perioperative complications.

2.5.3. Consensus statement

#9. The role of CHLT for the sole indication of antibody sensitization (no F3/F4 on liver biopsy) should be balanced with the risk of CHLT surgery at experienced centers, severity of illness of the recipient, and likelihood of transplant based on sensitization status, consideration of the "domino" use of the recipient's liver, evolving desensitization therapies and the ethics of this approach.

2.6. Question 6. What are recommendations for post-CHLT management?

2.6.1. Background

The first issue of post-CHLT care is whether induction therapy is warranted. There are two main goals for induction—to provide intense immunosuppression when the risk of allograft rejection is the highest and to allow delayed initiation of nephrotoxic immunosuppressive drugs in patients with compromised renal function (ie, antithymocyte globulin or IL-2 receptor monoclonal antibody, basiliximab). According to the United Network for Organ Sharing registry queried from January 2000 to June 2018, 135 of 260 CHLT recipients (52%) were administered induction therapy with no difference in survival with induction vs no induction.[26]

Surveillance protocols for acute rejection in both heart and liver transplant recipients vary across respective programs. Because CHLT recipients have a lower risk of acute rejection than heart-alone recipients, less intensive rejection surveillance may be feasible.[27]

Surveillance for chronic rejection (cardiac allograft vasculopathy [CAV]) in heart transplant recipients typically involves annual coronary angiography. However, CHLT recipients have a reported lower risk of CAV than recipients of heart transplants alone.[27] After the first-year coronary angiogram, less frequent CAV surveillance is utilized at some centers in the absence of risk factors for CAV development such as antibody sensitization. Noninvasive measures of surveillance for CAV are also currently being utilized.[28]

2.6.2. Breakout group discussion

Due to a lack of reliable data to guide routine use of induction therapy in all CHLT patients, individualized induction therapy should be used in CHLT recipients based on factors such as antibody sensitization, kidney function, infection risk, and bleeding risk. The immunologic protection of the liver allograft may lead to less intense induction treatment with IL-2 receptor monoclonal antibody as opposed to antithymocyte globulin administration. In low-risk patients, prednisone could be weaned off in the setting of CHLT given the immunologically privileged status of CHLT. However, pretransplant conditions may support ongoing steroid maintenance, such as autoimmune hepatitis and sarcoidosis. Proliferation signal inhibitors should be avoided early given the risk for early renal insufficiency (potentiating calcineurin inhibitor nephrotoxicity) and delayed wound healing as well as the box warning for increased risk

of hepatic artery thrombosis in the first 30 days posttransplant. Using proliferation signal inhibitors later after CHLT should be considered for renal sparing in liver transplant and possible benefits regarding HCC.[29] The immunosuppression protocols in CHLT recipients should involve multidisciplinary collaboration between heart transplant and liver transplant specialists balancing the risk of infection and rejection (antibody sensitization, demographic risk factors, mechanical circulatory support).

CHLT recipients should undergo per-protocol rejection surveillance with endomyocardial biopsies for heart transplant rejection and laboratory analysis for liver transplant rejection with frequency of surveillance dictated by clinical risk (including antibody sensitization). The role of noninvasive methods of rejection surveillance such as gene expression profiling and donor-derived cell-free DNA is uncertain given the lack of validation in heart-liver transplant recipients.

2.6.3. Consensus statements

#10. The following are recommendations for post-CHLT management:

1. Induction therapy should be used on an individualized basis in CHLT recipients based on factors including antibody sensitization, renal function, risk of infection, and risk of bleeding. Antithymocyte globulin or IL-2 receptor monoclonal antibodies are suggested induction therapies.
2. The immunosuppression protocols in CHLT recipients should involve multidisciplinary collaboration between heart transplant and liver transplant specialists balancing the risk of infection and rejection. In low-risk patients, prednisone can be weaned off in the setting of CHLT.
3. CHLT recipients should undergo per-protocol acute rejection surveillance with endomyocardial biopsies for heart transplant rejection and laboratory analysis for liver transplant rejection with frequency of surveillance dictated by clinical risk (including antibody sensitization). The role of noninvasive methods of rejection surveillance such as gene expression profiling and donor-derived cell-free DNA is uncertain given the lack of validation in CHLT recipients.
4. CHLT recipients have a lower risk of CAV. After the first-year angiogram, less frequent CAV surveillance may be warranted in the absence of risk factors for CAV development.

2.7. Question 7. What are the unmet needs and future considerations for CHLT?

2.7.1. Background and breakout group discussion

There are several unmet needs in CHLT. There should be consideration for a prospective national database of dual organ transplant candidates to better understand reasons for declining candidacy, waitlist outcomes, and posttransplant outcomes with more granular detail. The registry should include more refined coding of CHD (codes for FALD), pretransplant liver biopsy findings, perioperative complications, and better assessment of posttransplant complications including malignancy and liver failure. Additionally, in patients with CHD, understanding how older age, frailty, anatomical complexity, collateral blood vessels, comorbid conditions, and developmental and social issues may impact posttransplant outcomes is essential to decision-making. Risk adjustments for posttransplant outcomes are essential in CHD where patients may have worse early outcomes but better late outcomes and thus programs should not be disadvantaged based on the high early risk. As many CHD-CHLT patients are young adults, risk assessment of pregnancy seems necessary and access to pregnancy planning and care should be considered. Finally, there is a need for more education of patients and caregivers regarding the degree of liver and heart disease.

2.7.2. Consensus statements

#11. A prospective national database of CHLT candidates should be considered.

Table 5
Summary of the consensus conference statement on CHLT.

Summary of the consensus conference statement for CHLT
#1. Liver transplant evaluation should be performed in heart transplant candidates if there is concern for coexisting liver disease based on clinical/laboratory findings or if the liver appears nodular on imaging.
#2. In patients being considered for CHLT, a liver biopsy is highly encouraged when technically feasible and acceptably safe. However, if stigmata of portal hypertension are present, including hepatic ascites and portosystemic collaterals, a liver biopsy may not be required.
#3. If cross-sectional imaging reveals portosystemic collaterals, an upper endoscopy should be performed for variceal screening and the need for primary prophylaxis.
#4. Biopsy-proven cirrhosis regardless of portal hypertension is an indication for CHLT.
#5. Biopsy-proven fibrosis of any stage with clinical evidence of portal hypertension (hepatic ascites and portosystemic collaterals) should be a consideration for CHLT.
#6. Biopsy-proven stage 3 fibrosis (F3 disease) without clinical evidence for portal hypertension may not require CHLT.
#7. For the majority of CHLT candidates, the current allocation system appears appropriate where prioritization for CHLT is based on heart allocation urgency status and the liver follows.

(continued on next page)

Table 5 (*continued*)

Summary of the consensus conference statement for CHLT
#8. Adult patients with Fontan physiology may have more tendency toward CHLT due to chronically elevated central venous pressures that result in FALD. A liver biopsy plays a lesser role in the evaluation of FALD and information from imaging, biomarkers, and clinical presentation may be sufficient to determine the need for CHLT in FALD.
#9. The role of CHLT for the sole indication of antibody sensitization (no F3/F4 on liver biopsy) should be balanced with the risk of CHLT surgery at experienced centers, the severity of illness of the recipient, and the likelihood of transplant based on sensitization status, consideration of the "domino" use of the recipient's liver, evolving desensitization therapies and the ethics of this approach.
#10. The following are recommendations for post-CHLT management:
a. Induction therapy should be used on an individualized basis in CHLT recipients based on factors including antibody sensitization, renal function, risk of infection, and risk of bleeding. ATG or IL-2 receptor monoclonal antibodies are suggested induction therapies.
b. The immunosuppression protocols in CHLT recipients should involve multidisciplinary collaboration between heart transplant and liver transplant specialists balancing the risk of infection and rejection. In low-risk patients, prednisone can be weaned off in the setting of CHLT.
c. CHLT recipients should undergo per-protocol acute rejection surveillance with endomyocardial biopsies for heart transplant rejection and laboratory analysis for liver transplant rejection with frequency of surveillance dictated by clinical risk (including antibody sensitization). The role of noninvasive methods of rejection surveillance such as gene expression profiling and donor-derived cell-free DNA is uncertain given the lack of validation in CHLT recipients.
d. CHLT recipients have a lower risk of CAV. After the first-year angiogram, less frequent CAV surveillance may be warranted in the absence of risk factors for CAV development.
#11. A prospective national database of CHLT candidates should be considered.
#12. Risk adjustment for posttransplant outcomes in CHD patients undergoing CHLT should be determined to avoid disadvantages in regulatory monitoring (by United Network for Organ Sharing).
#13. Risk assessment of pregnancy in CHD-CHLT recipients is needed.

ATG, antithymocyte globulin; CAV, cardiac allograft vasculopathy; CHD, congenital heart disease; CHLT, combined heart-liver transplant; FALD, Fontan-associated liver disease.

#12. Risk adjustment for posttransplant outcomes in CHD patients undergoing CHLT should be determined to avoid disadvantages in regulatory monitoring (by United Network for Organ Sharing).

#13. Risk assessment of pregnancy in CHD-CHLT recipients is needed.

3. Summary

CHLT can improve survival and quality of life of patients with severe heart and liver disease. However, in the setting of organ scarcity, CHLT should be considered with respect to the individual patient's need for both organs and the effect of CHLT on liver-alone candidates' access to transplants. Furthermore, a multidisciplinary approach for CHLT is needed to optimize outcomes. However, there continue to exist controversies and uncertainties related to CHLT. Establishing a national database of CHLT candidates and outcomes is needed to provide more rigorous data on the trajectory of this patient population, especially for adult CHD patients. We hope the results of this consensus conference will provide a more standardized pathway for evaluating patients for CHLT and provide guidance for future research and policies to further refine CHLT criteria. The consensus conference statements from the CHLT workgroup are summarized in Table 5.

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Data availability statement

Due to nature of paper data is not available.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2023.12.002.

Appendix

Participants in the Consensus Conference on Heart-Liver Transplantation

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References

1. Khush KK, Hsich E, Potena L, et al. 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(10):1035–1049. https://doi.org/10.1016/j.healun.2021.07.015.
2. Alexopoulos SP, Wu WK, Ziogas IA, et al. Adult combined heart-liver transplantation: the United States experience. *Transpl Int.* 2022;35:10036.
3. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report – 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant.* 2019;38(10):1056–1066. https://doi.org/10.1016/j.healun.2019.08.004.
4. Zhao K, Mclean RC, Hoteit MA, Olthoff KM. Combined heart and liver transplant: indication, patient selection, and allocation policy. *Clin Liver Dis (Hoboken).* 2019;13(6):170–175. https://doi.org/10.1002/cld.812.
5. Shingina A, Chadha R, Lim N, et al. Combined heart liver transplantation survey in North America: evaluation and organ listing practices. *Liver Transpl.* 2023;29(6):591–597. https://doi.org/10.1097/LVT.0000000000000079.
6. Givertz MM. Assessing the liver to predict outcomes in heart transplantation. *J Heart Lung Transplant.* 2015;34(7):869–872. https://doi.org/10.1016/j.healun.2015.04.002.

7. Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JP. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. *Mod Pathol.* 2015;28(7):932–943. https://doi.org/10.1038/modpathol.2015.40.
8. Lassailly G, Caiazzo R, Ntandja-Wandji LC, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. *Gastroenterology.* 2020;159(4):1290–1301.e5. https://doi.org/10.1053/j.gastro.2020.06.006.
9. Rockey DC, Friedman SL. Fibrosis regression after eradication of hepatitis C virus: from bench to bedside. *Gastroenterology.* 2021;160(5):1502–1520. https://doi.org/10.1053/j.gastro.2020.09.065. e1.
10. Vaikunth SS, Higgins JP, Concepcion W, et al. Does liver biopsy accurately measure fibrosis in Fontan-associated liver disease? A comparison of liver biopsy pre-combined heart and liver transplant and liver explant post-transplant. *Clin Transplant.* 2020;34(12):e14120. https://doi.org/10.1111/ctr.14120.
11. Izzy M, Alexopoulos S, Shingina A. Combined heart-liver transplantation for congestive hepatopathy with bridging fibrosis: is it warranted? *JHEP Rep.* 2021;3(4):100292. https://doi.org/10.1016/j.jhepr.2021.100292.
12. OPTN Ethics Committee. Ethical Implications of Multi-organ Transplants. https://optn.transplant.hrsa.gov/media/2989/ethics_boardreport_201906.pdf; June 2019. Accessed March 29, 2022.
13. Shaw BI, Sudan DL, Boulware LE, McElroy LM. Striking a balance in simultaneous heart kidney transplant: optimizing outcomes for all wait-listed patients. *J Am Soc Nephrol.* 2020;31(8):1661–1664. https://doi.org/10.1681/ASN.2020030336.
14. Sulewski ME, Wolf JH, Hasz R, et al. Combined heart-liver transplantation; implications for liver-alone wait list mortality. *Transplantation.* 2014;98950(5):e45–e47. https://doi.org/10.1097/TP.0000000000000318. ivc.
15. Schaffer JM, Chiu P, Singh SK, Oyer PE, Reitz BA, Mallidi HR. Combined heart-liver transplantation in the MELD era: do waitlisted patients require exception status? *Am J Transplant.* 2014;14(3):647–659. https://doi.org/10.1111/ajt.12595.
16. Bryant III R, Rizwan R, Zafar F, et al. Contemporary outcomes of combined heart-liver transplant in patients with congenital heart disease. *Transplantation.* 2018;102(2):e67–e73. https://doi.org/10.1097/TP.0000000000001978.
17. Emamaullee J, Zaidi AN, Schiano T, et al. Fontan-associated liver disease: screening, management, and transplant considerations. *Circulation.* 2020;142(6):591–604. https://doi.org/10.1161/CIRCULATIONAHA.120.045597.
18. Reardon LC, Lin JP, VanArsdell GS, et al. Orthotopic heart and combined heart liver transplantation: the ultimate treatment option for failing Fontan physiology. *Curr Transplant Rep.* 2021;8(1):9–20. https://doi.org/10.1007/s40472-021-00315-4.
19. Simpson KE, Esmaeeli A, Khanna G, et al. Liver cirrhosis in Fontan patients does not affect 1-year post-heart transplant mortality or markers of liver function. *J Heart Lung Transplant.* 2014;33(2):170–177. https://doi.org/10.1016/j.healun.2013.10.033.
20. Sganga D, Hollander SA, Vaikunth S, et al. Comparison of combined heart–liver vs heart-only transplantation in pediatric and young adult Fontan recipients. *J Heart Lung Transplant.* 2021;40(4):298–306. https://doi.org/10.1016/j.healun.2020.12.008.
21. Goldberg DJ, Surrey LF, Glatz AC, et al. Hepatic fibrosis is universal following Fontan operation, and severity is associated with time from surgery: a liver biopsy and hemodynamic study. *J Am Heart Assoc.* 2017;6(5):e004809. https://doi.org/10.1161/JAHA.116.004809.
22. Ceulemans LJ, Strypstein S, Neyrinck A, et al. Combined liver-thoracic transplantation: single-center experience with introduction of the "Liver-first" principle. *Transpl Int.* 2016;29(6):715–726. https://doi.org/10.1111/tri.12781.
23. Vaikunth SS, Concepcion W, Daugherty T, et al. Short-term outcomes of en bloc combined heart and liver transplantation in the failing Fontan. *Clin Transplant.* 2019;33(6):e13540. https://doi.org/10.1111/ctr.13540.
24. Brozzi NA, Loebe M, Souki FG, et al. En-bloc simultaneous heart-liver transplantation in adult patients. *Ann Surg.* 2021;274(6):e1284–e1289. https://doi.org/10.1097/SLA.0000000000003721.
25. Daly RC, Rosenbaum AN, Dearani JA, et al. Heart-after-liver transplantation attenuates rejection of cardiac allografts in sensitized patients. *J Am Coll Cardiol.* 2021;77(10):1331–1340. https://doi.org/10.1016/j.jacc.2021.01.013.
26. Abdulameer H. Outcomes of induction immunosuppressive therapy in combined heart-liver transplantation. *J Heart Lung Transplant.* 2021;40(4):S134–S135. https://doi.org/10.1016/j.healun.2021.01.419.
27. Wong TW, Gandhi MJ, Daly RC, et al. Liver allograft provides immunoprotection for the cardiac allograft in combined heart-liver transplantation. *Am J Transplant.* 2016;16(12):3522–3531. https://doi.org/10.1111/ajt.13870.
28. Nikolova AP, Kobashigawa JA. Cardiac allograft vasculopathy: the enduring enemy of cardiac transplantation. *Transplantation.* 2019;103(7):1338–1348. https://doi.org/10.1097/TP.0000000000002704.
29. Cillo U, De Carlis L, Del Gaudio M, et al. Immunosuppressive regimens for adult liver transplant recipients in real-life practice: consensus recommendations from an Italian Working Group. *Hepatol Int.* 2020;14(6):930–943. https://doi.org/10.1007/s12072-020-10091-5.