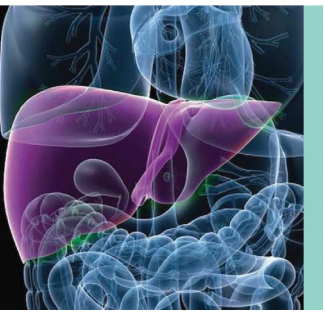

# Combined Heart and Liver Transplant: Indication, Patient Selection, and Allocation Policy

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## BACKGROUND

Combined heart and liver transplant (CHLT) is indicated for patients with some combination of heart and liver disease, or for patients with amyloid heart disease for whom a liver will stop its progression. Historically, concurrent hepatic failure was a contraindication to heart transplant, as was heart failure to liver transplant.[1] There are a few select centers across the United States that have successfully performed CHLT (Fig. 1).[1-4] The CHLT cohort is small, with only approximately 250 cases recorded in the United Network for Organ Sharing (UNOS) between 1988 and September 2018, but the number is rising slowly each year (Fig. 2). The current literature of CHLT outcomes is limited by small sample size and single-center experiences.[5,6]

## INDICATION FOR CHLT

There are three main cardiac and liver indications for CHLT[5] (Fig. 3):

1. Patients with primary heart disease who experience secondary cardiac cirrhosis caused by chronic hepatic venous outflow obstruction: This group includes patients with congenital heart defects that required Fontan procedure who ultimately experienced progressive

Abbreviations: A1AT, alpha-1-antitrypsin; CHLT, combined heart and liver transplant; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLA, human leukocyte antigen; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; UNOS, United Network for Organ Sharing.

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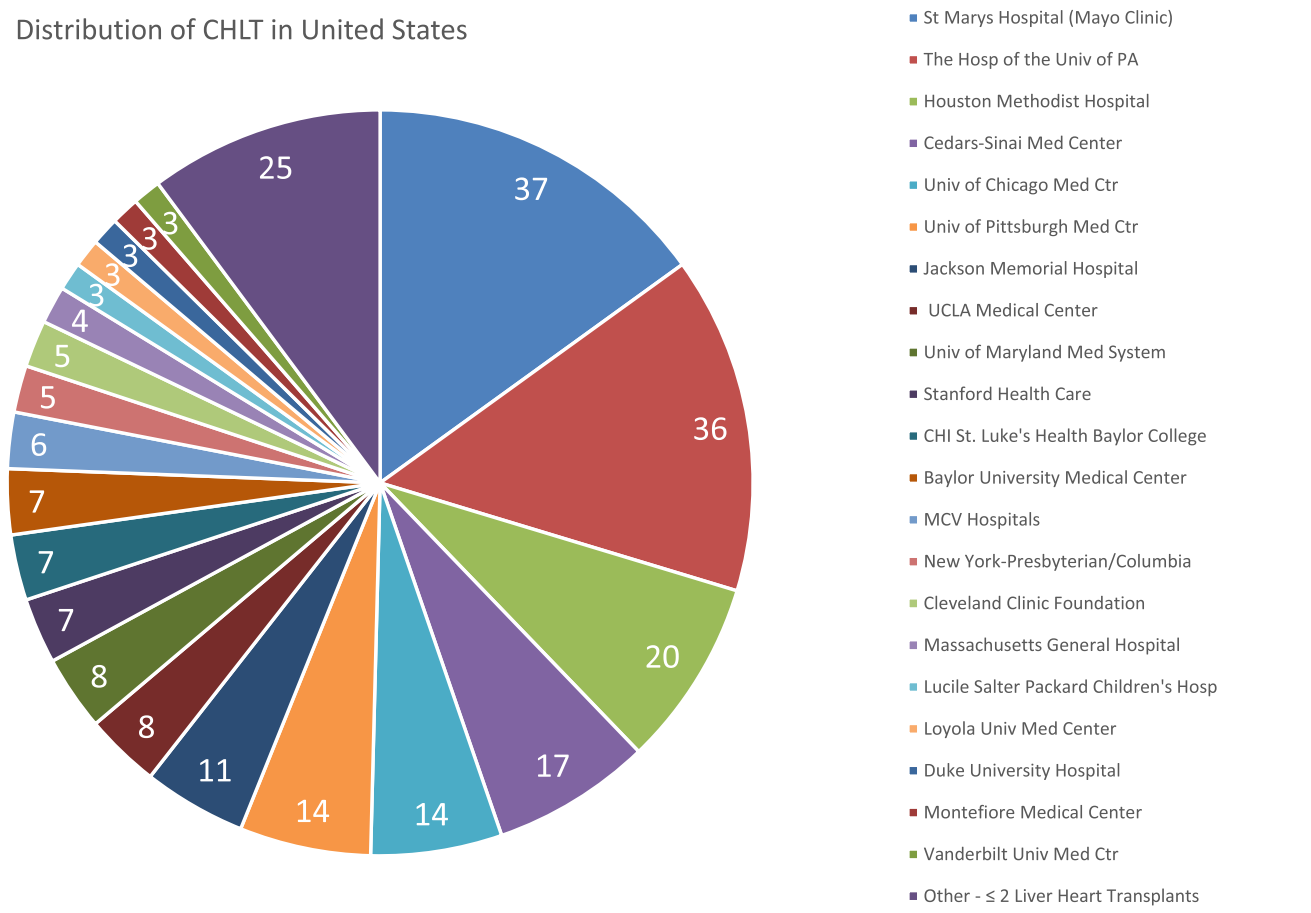


**FIG 1** Distribution of CHLT in UNOS 1988 to 2018.

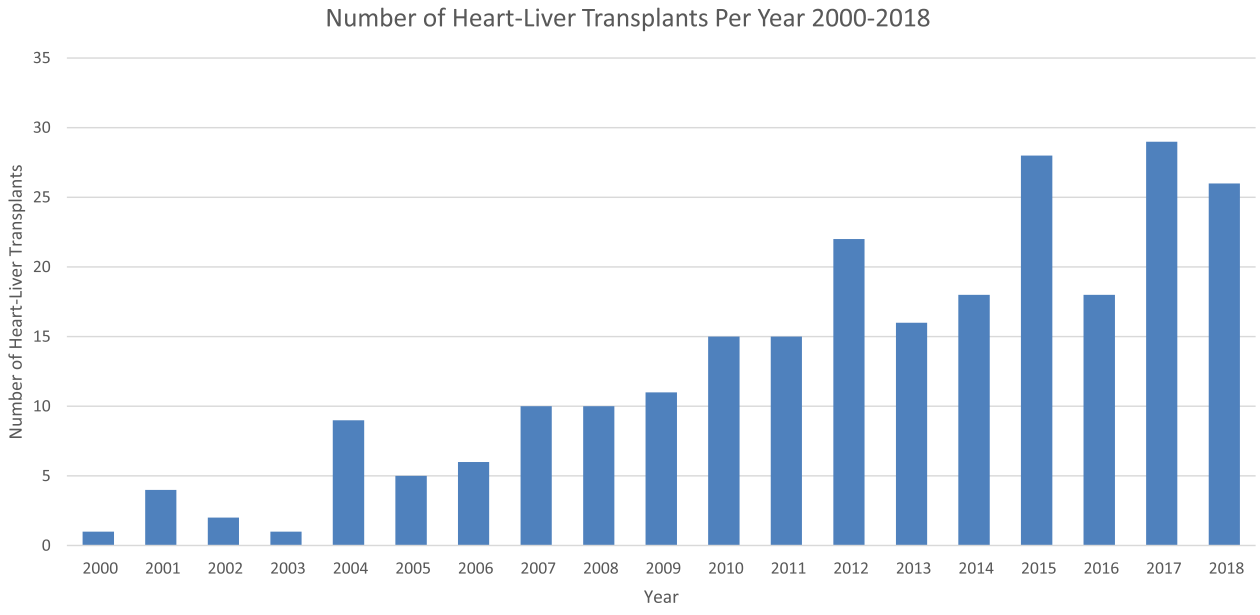


**FIG 2** Number of CHLTs annually.

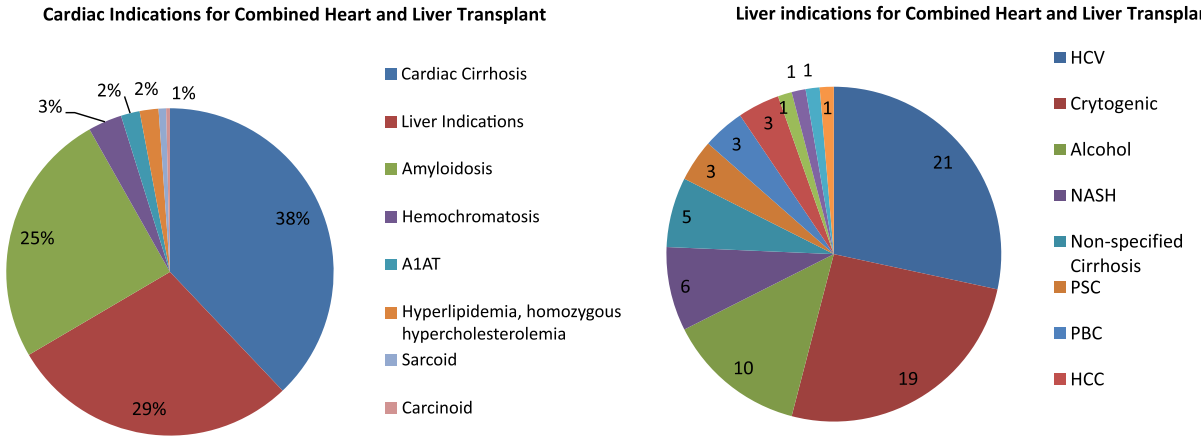


**FIG 3** Indications for CHLT.

hepatic fibrosis from their circulatory physiology. These patients are at increased risk for development of hepatocellular carcinoma (HCC) and require careful evaluation and surveillance.

2. Patients with a diagnosis of hereditary transthyretin amyloidosis leading to cardiomyopathy: Liver transplant is concurrently performed to remove the primary source of systemic transthyretin protein.
3. Patients with primary indication for liver transplant with concurrent heart disease.

The majority of our CHLT cohort at the University of Pennsylvania from 2010 to the present (33 patients) fell into the first category, with one-third of patients having congenital heart disease with Fontan physiology. The remainder of the cohort had other cardiomyopathies, including arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, nonischemic and ischemic cardiomyopathy, congenital constrictive and radiation-induced cardiomyopathy, and sarcoidosis.

## PATIENT SELECTION

Patient selection is important, and centers pursuing CHLT should have a detailed institutional protocol. It is critical that heart transplant candidates are screened for risk factors for liver fibrosis based on history, physical examination, laboratory values, and imaging studies. Patients at risk are carefully assessed by the hepatology/liver transplant team. Liver biopsies may be performed to assess the degree of fibrosis if cirrhosis is considered possible based on clinical findings. Transjugular biopsy is preferred because of concerns for bleeding from congested livers, especially with frequent use of anticoagulation in this patient population. In addition, hepatic venous pressure measurements can be obtained to provide additional assessment of hepatic reserve.

There are three potential pathways based on the comprehensive evaluation (Fig. 4). If the patient is deemed by hepatology to have minimal chronic liver disease and adequate hepatic reserve to tolerate heart transplant, they are "cleared" to undergo heart transplant alone. If the patient has evidence of advanced liver fibrosis histologically in combination with elevated hepatic venous pressure gradient and significant liver dysfunction (persistent abnormality in liver synthetic function, severe/refractory ascites), or evident cirrhosis on biopsy, they are considered for dual-organ transplant with CHLT from a single donor. Although this seems straightforward, it is not always so clear-cut, and sometimes questions remain. If liver status remains uncertain, our center has opted to perform intraoperative evaluation of the native liver at the very start of heart transplant with a mini-laparotomy to visualize the liver and determine the need for concurrent liver transplantation.

All patients listed for CHLT must fulfill listing criteria for both heart and liver transplant programs. At our center, potential exclusion criteria for CHLT consideration are age older than 60 years, hepatitis C with positive viremia, diagnosis of AIDS, body mass index greater than 38 kg/m$^2$, severe chronic debilitation, and active malignancy. Although hepatitis C has traditionally been an exclusion criterion, it is no longer a contraindication in the modern era of hepatitis C virus (HCV) treatment. All candidates

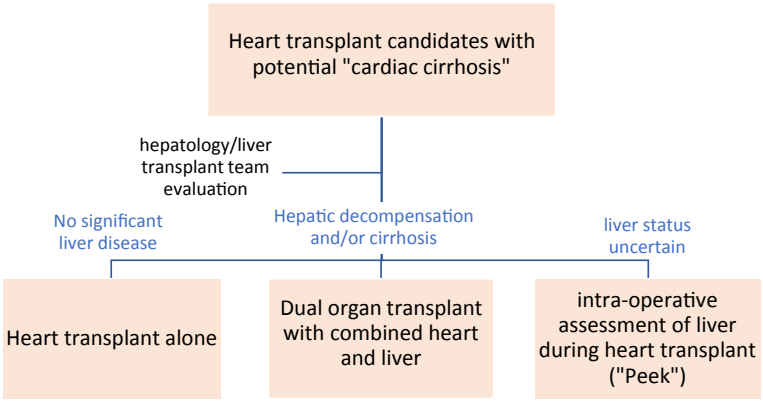


**FIG 4** Algorithm for evaluation and treatment.

are presented to both organ committees to determine candidacy, with one or more representative from each team present. If deemed a candidate, the patient will be listed for both the heart and liver teams with the appropriate allocation status/score for each organ.

## DONOR SELECTION AND OPERATIVE MANAGEMENT

To accommodate for candidates in need of multiorgan transplants, Organ Procurement and Transplantation Network (OPTN)/UNOS policy dictates that when the primary organ is a heart, lung, or liver, patients who receive an offer for one of these three primary organs usually receive the second, nonprimary organ from that donor, regardless of their wait-list priority for that second organ, if the donor is located with the same organ procurement organization (OPO) where the recipient candidate is registered.[7] The ability to pull a secondary organ from another OPO is dependent on local policy and practice. The CHLT candidates receive standard heart priority without additional priority for the combined heart-liver status. CHLT graft allocation is almost always based on the heart priority with liver following the heart. Theoretically, if the patient has primary liver disease with high Model for End-Stage Liver Disease (MELD) or MELD exception points, OPO policy can present the scenario of allocation driven by MELD with heart pulled by the liver. There is ongoing discussion regarding whether this allocation is appropriate or fair, and there are arguments that these patients should be given higher priority because of increased death on the wait list.[8] There have been concerns that combined allocation can negatively affect those on the wait list, but no current data support this claim.[9]

Donor/Recipient matching criteria such as age, size, and distance are decided by both teams and consistent for both organs. Because of the longer ischemic time needed for the liver, a graft of good quality is required, and thereby harder to obtain. When an appropriate donor is identified, both cardiac and liver teams make provisional acceptances after assessing the organs. Final acceptance is made after discussion between teams, and procurement timing is coordinated. Two recovery teams are dispatched for heart and liver procurements. Standard human leukocyte antigen (HLA) typing is completed at the time of heart transplant evaluation. If necessary, a virtual cross-match for recipient/donor compatibility is performed when a potential donor is being contemplated.

Intraoperative management begins with the patient being prepped for both transplants. Once the heart and liver are accepted, the cardiac transplant begins with the median sternotomy before cross-clamp in the donor. It is at this time that the incision may extend to the abdomen to visualize the liver ("peek"). If it is determined that the liver should not be transplanted, there is time for reallocation of the liver to the backup recipient. The liver transplant proceeds after cardiac reperfusion and when the patient is relatively stable, reversed, and off cardiopulmonary bypass. At our center, an atrial cannula is left in place and used for venovenous bypass during the liver transplant, which provides significant stability. Usually, the liver transplant is quite straightforward. The patient is managed in the cardiac intensive care unit postoperatively by both teams.

## POSTOPERATIVE IMMUNOSUPPRESSION

Liver allografts have long been observed to be more "tolerant" to HLA mismatch and alloimmune injuries. In

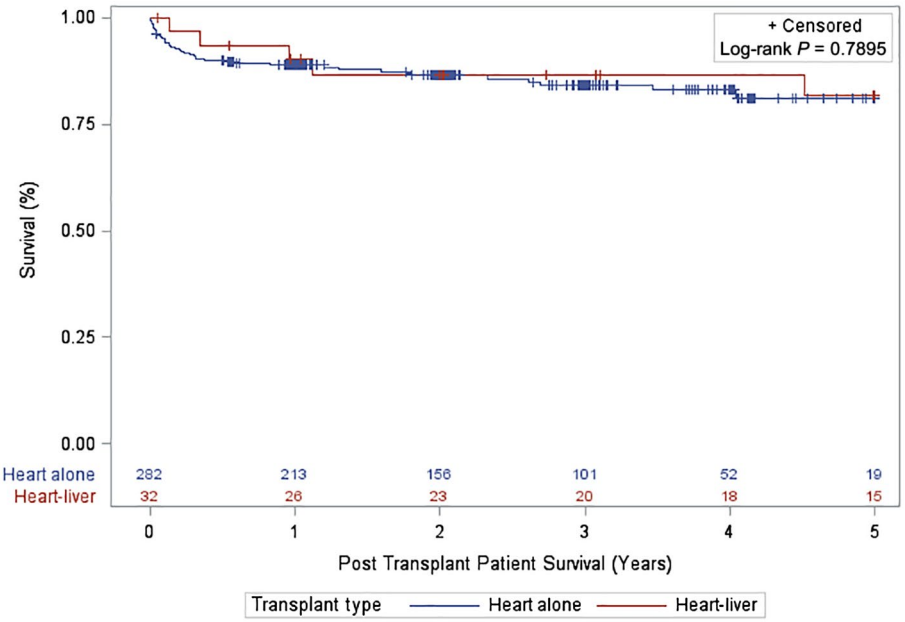


**FIG 5** Overall patient survival: CHLT versus heart alone.

addition, liver allografts demonstrate some degree of immune protection in combined organ transplants.[10-12] CHLT recipients usually do not receive induction therapy. They receive high-dose steroid at cardiac allograft reperfusion followed by taper. In addition, maintenance therapy with calcineurin inhibitor and mycophenolate mofetil is initiated postoperatively. Protocol endomyocardial biopsies are performed to surveil for cellular and antibody-mediated rejection. Routine posttransplant blood testing at predefined intervals is performed to screen for the development of donor-specific antibodies. In our patients, we have observed significantly fewer patients in the CHLT cohort experiencing cellular rejection of the cardiac allograft compared with heart transplant alone (unpublished data), suggesting immune-protective properties of the concomitant liver allograft.

## LONG-TERM OUTCOMES

Early results from the UNOS/OPTN database showed no difference in heart and liver graft survival compared with heart and liver transplants alone.[5] At our center, CHLT recipients have excellent short-term and long-term survival, comparable with those of heart transplant alone (Fig. 5).

## SUMMARY

CHLT is successful and increasing, with excellent survival for both cardiac and liver grafts. Outcomes are equivalent to single-organ transplants, and there are potential immunological benefits compared with heart transplant alone. Evaluation and decision to proceed for dual-organ transplant requires careful assessment by both organ teams at experienced centers to choose the appropriate recipients.

### CORRESPONDENCE

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