Incidence of acute rejection and patient survival in combined heart–liver transplantation

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Abstract
Combined heart–liver transplantation (CHLT) is indicated for patients with concomitant end-stage heart and liver disease or patients with amyloid heart disease where liver transplantation mitigates progression. Limited data suggest that the liver allograft provides immunoprotection for heart and kidney allografts in combined transplantation from the same donor. We hypothesized that CHLT reduces the incidence of acute cellular rejection (ACR) and the development of de novo donor-specific antibodies (DSAs) compared with heart-alone transplantation (HA). We conducted a retrospective analysis of 32 CHLT and 280 HA recipients in a single-center experience. The primary outcome was incidence of ACR based on protocol and for-cause myocardial biopsy. Rejection was graded by the International Society of Heart and Lung Transplantation guidelines with Grade 2R and higher considered significant. Secondary outcomes included the development of new DSAs, cardiac function, and patient and cardiac graft survival rates. Of CHLT patients, 9.7% had ACR compared with 45.3% of HA patients (p < 0.01). Mean pretransplant calculated panel reactive antibody (cPRA) levels were similar between groups (CHLT 9.4% vs. HA 9.5%; p = 0.97). Among patients who underwent testing, 26.9% of the CHLT and 16.7% of HA developed DSA (p = 0.19). Despite the difference in ACR, patient and cardiac graft survival rates were similar at 5 years (CHLT 82.1% vs. HA 80.9% [p = 0.73]; CHLT 82.1% vs. HA 80.9% [p = 0.73]). CHLT reduced the incidence of ACR in the cardiac allograft, suggesting that the liver offers immunoprotection against cellular mechanisms of rejection without significant impacts on patient and cardiac graft survival rates. CHLT did not reduce the incidence of de novo DSA, possibly portending similar long-term survival among cardiac allografts in CHLT and HA.

Abbreviations: ACR, acute cellular rejection; CHLT, combined heart–liver transplantation; cPRA, calculated panel reactive antibody; DSA, donor-specific antibody; HA, heart-alone transplantation; HLA, human leukocyte antigen; HSC, hepatic stellate cell; IQR, interquartile range; LSEC, liver sinusoidal endothelial cell; MELD, Model for End-Stage Liver Disease; MFI, mean fluorescence intensity; PD1, programmed death 1; SD, standard deviation; VAD, ventricular assistive device.

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INTRODUCTION

Combined heart–liver transplantation (CHLT) is indicated for patients with heart and liver failure or those with amyloid heart disease from hereditary transthyretin amyloidosis for whom a liver transplant will mitigate its progression.\(^1\) Historically, concurrent hepatic failure has been a contraindication to heart transplantation as was heart failure to liver transplant. However, select centers are performing CHLT with success.\(^3\)–\(^6\) The national CHLT cohort is small, with approximately 250 cases reported to the United Network for Organ Sharing between January 1988 and September 2018. The current literature on CHLT outcomes is limited by small sample sizes and single-center experiences.

The liver has long been perceived as an immunomodulatory organ. Numerous reports suggest that the liver is more tolerant to human leukocyte antigen (HLA) mismatch and alloimmune injury, including alloantibody-mediated injury, than other solid organs.\(^7\) To what degree the higher immunosuppression levels found in the portal system compared with peripheral blood or the regenerative capacity of the liver account for these findings is unclear.\(^8\) Several lines of evidence suggest that immunoprotective benefits of the liver allograft exist when both organs are transplanted from the same donor.\(^9,10\) Furthermore, a recent publication indicates that the immunoprotection provided by the liver allograft may extend to the cardiac allograft in CHLT.\(^11\) In this study, we assessed the immunologic outcomes in a cohort of CHLT patients. We hypothesized that CHLT would reduce the incidence of acute cellular rejection (ACR) and the development of de novo donor specific antibodies (DSAs) compared with heart-alone transplantation (HA).

PATIENTS AND METHODS

Cohorts

This is a single-center retrospective analysis of 32 consecutive patients who received CHLT between 2008 and 2017 and 280 consecutive patients who underwent HA between 2013 and 2017. No pediatric patients were included in either cohort. HA recipients who received transplants from 2008 to 2012 were excluded because of incomplete immunologic and pathologic information. The electronic medical record was reviewed to collate recipient and donor characteristics and tissue typing data as well as patient and graft outcomes. The study was approved by the Institutional Review Board at the University of Pennsylvania.

All transplant recipients underwent pretransplant HLA testing and determination of calculated panel reactive antibody (cPRA). Anti-HLA antibodies were identified using the Luminex single-antigen bead panel according to the instructions provided by the manufacturer (One Lambda, A Thermo Fisher Scientific Brand). Allele specificities included more than 100 alleles covering HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPB1, and DPB1. Organ acceptance was based on a virtual cross-match, although a retrospective tissue cross-match using flow cytometry was also performed. In general, a mean fluorescence intensity (MFI) greater than 1000 to 3000 was listed as unacceptable for organ acceptance depending on the HLA locus. cPRAs were based on MFI values equal to or higher than 3000. Sensitized patients were avoided in HA but not in CHLT. In three cases of CHLT, desensitization was performed with a combination of rituximab, plasmapheresis, intravenous immunoglobulin, and thymoglobulin.\(^12\)

Patients were screened for the presence of de novo anti-HLA DSAs at 1, 3, 6, 12, 24, and 36 months after transplantation. Additional for-cause samples were included when available. De novo DSA was defined as either a newly detected donor-directed HLA antibody with MFI greater than 1000 or a pretransplant DSA less than 1000 MFI that had subsequently increased to greater than 1000 and was at least 50% greater compared with that of the pretransplant value. Antibody reactivity with bead panel patterns that appeared to be attributed to denatured epitopes were not reported as DSAs. In general, if the antibody reactivity was allele specific, high-resolution HLA typing of the donor was performed if donor material was available. Otherwise, the presence of DSA was not ruled out.

HA recipients received basiliximab and methylprednisolone as immunosuppression induction therapy, whereas CHLT recipients received methylprednisolone alone. Maintenance immunosuppression therapies were similar between the groups and consisted of tacrolimus, mycophenolate, and prednisone taper.

Following transplantation, surveillance myocardial biopsies were performed at Weeks 1, 2, 4, 6, 8, 10, and 12 and then monthly for the first year. Additional for-cause biopsies were included in the analysis when available. Cardiac cell-mediated rejection was graded according to International Society of Heart and Lung Transplantation guidelines.\(^13,14\) Cell-mediated rejection Grade 2R and above were defined as instances of cell-mediated rejection.

Instances of cell-mediated rejection graded 2R and greater were treated with high-dose corticosteroids. Grade 1R cell-mediated rejection was not treated. Plasmapheresis, intravenous immunoglobulin, and rituximab were used for antibody-mediated rejection.

Statistical analysis

The primary outcome of this study was the incidence of ACR diagnosed by myocardial biopsy. Secondary outcomes included the development of new DSAs, cardiac
function, and patient and cardiac graft survival rates. Categorical variables were analyzed using chi-square and Fisher’s exact tests. Continuous variables were compared by t-test or Wilcoxon rank sum test. Means were reported with standard deviations (SDs), whereas medians were reported with interquartile ranges (IQRs). Allograft survival was assessed using Kaplan–Meier survival curves, and comparisons were made using log-rank tests. All analyses were performed using SAS Version 9.4 (SAS Institute).

RESULTS

Patient characteristics

A total of 32 CHLTs were performed between 2008 and 2017, and 280 HAs were performed between 2013 and 2017. The median age was significantly different between CHLT and HA recipients (42.5 years [IQR, 34.0–52.0 years] vs. 55.0 years [IQR, 46.0–62.0 years]; \( p < 0.01 \); Table 1). The sex and race of the cohorts were not significantly different, with the majority of each cohort being male and White. Pretransplant median body mass index was significantly lower in CHLT patients (25.0 kg/m\(^2\) [IQR, 21.6–29.1] vs. 27.6 kg/m\(^2\) [IQR, 24.1–31.6]; \( p = 0.01 \)). Of patients on the waiting list for CHLT, 76.6% received transplants, 21.1% improved and no longer required transplantation, 14.9% were removed from the waiting list as a result of clinical deterioration, and 6.4% passed away while awaiting transplant. For HA, 83.4% received transplants, 4.6% improved and no longer required transplantation, 3.5% were removed from the waiting list as a result of clinical deterioration, and 4.3% passed away while awaiting transplant.

The two groups had different indications for heart transplantation. In the CHLT cohort, the most common diagnosis was congenital heart disease with prior Fontan procedures (34.4%). The other common indications were arrhythmogenic right ventricular cardiomyopathy (18.8%) and hypertrophic cardiomyopathy (15.6%). In the HA cohort, the most common diagnosis was idiopathic cardiomyopathy (38.9%) followed by ischemic (24.6%) and familial cardiomyopathy (13.9%). The pretransplant ejection fraction was significantly higher in CHLT patients (27.5% vs. 15.0%, \( p < 0.01 \)). A smaller proportion of the CHLT recipients had ventricular assistive devices (VADs) inserted prior to heart transplantation (CHLT 6.3% vs. HA 30.7%, \( p < 0.01 \)).

Pretransplant serum creatinine values were similar (CHLT 1.3 mg/dl [IQR, 1.1–1.5 mg/dl] vs. HA 1.2 mg/dl [IQR, 1.0–1.5 mg/dl]; \( p = 0.34 \)). CHLT patients had a median Model for End-Stage Liver Disease (MELD) score of 16 (IQR, 11–20) and median bilirubin of 1.0 mg/dl (IQR, 0.8–1.8 mg/dl).

Characteristics of CHLT and HA donors, including age, sex, cause of death, ejection fraction, and creatinine, are described in Table 2.

Cell-mediated rejection

Surveillance biopsies were performed in 96.9% of CHLT patients and 95.3% of HA patients. The median number of biopsies performed in the first year was significantly higher in HA patients than in CHLT patients (15 [IQR, 13–16] vs. 13 [IQR, 11–15]; \( p < 0.01 \)). Average tacrolimus levels at the time of all available myocardial biopsies were not significantly different between CHLT and HA patients (9.6 \( \mu \)g/L ± 2.5 vs. 10.3 \( \mu \)g/L ± 1.7; \( p = 0.14 \)). The incidence of biopsy-proven cardiac allograft rejection among CHLT and HA recipients across the study duration was 9.7% and 45.3% respectively, \( (p < 0.01) \). Of 121 instances of ACR in HA recipients, 97.5% were graded as 2R, whereas 2.5% were graded as 3R. All instances of ACR in CHLT recipients were graded as 2R. Median time from transplantation to first recorded episode of ACR was 172 days (IQR, 115–1054 days) for CHLT and 73 days (IQR, 16–152 days) for HA \( (p = 0.07) \). Among CHLT patients, 66.7% of the first rejection episodes occurred within the first year of transplant, whereas among HA patients, 94.2% of the first rejections occurred within the first year. Of the three patients in the CHLT cohort who experienced cardiac allograft rejection, only one had concomitant liver rejection. None of the CHLT patients with cardiac rejection experienced grossly elevated liver function tests the day of or several days prior to the surveillance myocardial biopsy indicating cardiac rejection. The highest reported liver function tests at the time of heart biopsy were alanine aminotransferase, 46 U/L; aspartate aminotransferase, 39 U/L; and total bilirubin, 0.4 mg/dl. The CHLT patients who had cardiac rejection did not develop DSA.

There was a second CHLT patient who experienced liver rejection without cardiac rejection. Neither of the patients with liver rejection developed de novo DSAs. Liver rejection occurred 1024 and 2215 days after transplant.

Donor-specific anti-HLA antibody

The mean pretransplant cPRA was similar between CHLT and HA patients, 9.4% and 9.5%, respectively \( (p = 0.97) \). Posttransplant DSA testing was performed in 89.6% of HA and 81.3% of CHLT patients. The total number of DSA screenings was not significantly different between HA and CHLT recipients (3 [IQR, 2–5] vs. 3 [IQR, 2–4]; \( p = 0.45 \)). The total number of patients who developed de novo DSAs was not significantly different between the two groups (CHLT, 26.9%...
HA, 16.7%; \( p = 0.19 \); Table 3). Of those who developed DSAs, 42.9% of CHLT and 73.8% of HA patients developed DSAs within 1 year.

Among the 42 HA patients who developed de novo DSAs, 24 (57.1%) patients had at least one antibody to Class I, 30 (71.4%) had at least one antibody to Class II, and 12 (28.6%) had both Class I and II formations. Class I antibody specificity included HLA-A \( (n = 12 \) patients, 28.6%), HLA-B \( (n = 14, 33.3%) \), and HLA-C \( (n = 6, 14.3%) \). Class II included HLA-DQ \( (n = 22, 52.4%) \), HLA-DR \( (n = 14, 33.3%) \), and HLA-DP \( (n = 2, 4.8%) \). Median MFIs of the first observations of each DSA class formed in HA and CHLT recipients are reported in Table 3. Median time from transplantation to the first observation of Class I DSAs was 44 days (IQR, 9–342 days) and for Class II DSAs was 202 days (IQR, 10–664 days). A total of 32 patients (76.2%) developed DSAs not detected on pretransplant screening.

Among the 7 CHLT recipients who developed de novo DSAs, all were Class II. A total of 6 (85.7%) patients developed antibodies to HLA-DQ, and 3 (42.9%) patients developed antibodies to HLA-DR. No formation of antibody to HLA-DP was observed. The median time after transplantation to the first observed DSAs was 1483 days (IQR, 29–2191 days). A total of 5 patients (71.4%) developed de novo DSAs not detected on pretransplant screening.

Among the 121 HA recipients who had ACR, 17 (14.0%) patients developed Class I DSAs and 22 (18.2%) patients developed Class II DSAs. None of the 3 CHLT patients with ACR had DSA formation.

**Cardiac function and survival**

Median left ventricular ejection function was examined at 1 year (CHLT, 62.5% [IQR, 57.5%–65.0%];
TABLE 2 Donor characteristics

<table>
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<tr>
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<th>HA, N = 280</th>
<th>CHLT, N = 32</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Age, years, median (IQR)</td>
<td>37.0 (28.0–48.5)</td>
<td>27.5 (21.5–41.5)</td>
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<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>167 (59.6)</td>
<td>26 (81.3)</td>
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<tr>
<td>Female</td>
<td>113 (40.4)</td>
<td>6 (18.8)</td>
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<tr>
<td>Race/ethnicity, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>White</td>
<td>209 (74.6)</td>
<td>26 (81.3)</td>
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<tr>
<td>Black</td>
<td>45 (16.1)</td>
<td>3 (9.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24 (8.6)</td>
<td>2 (6.3)</td>
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<tr>
<td>Other</td>
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<td>1 (3.1)</td>
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<tr>
<td>Cause of death, n (%)</td>
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<td>&lt;0.01</td>
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<tr>
<td>Anoxia</td>
<td>133 (47.5)</td>
<td>17 (53.1)</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>76 (27.1)</td>
<td>1 (3.1)</td>
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<tr>
<td>Head trauma</td>
<td>69 (24.6)</td>
<td>13 (40.6)</td>
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<tr>
<td>Other</td>
<td>2 (0.7)</td>
<td>1 (3.1)</td>
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<tr>
<td>Body mass index, median (IQR)</td>
<td>27.1 (24.3–31.4)</td>
<td>25.1 (22.0–26.8)</td>
<td>&lt;0.01</td>
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<tr>
<td>Ejection fraction, %, median (IQR)</td>
<td>60.0 (55.0–65.0)</td>
<td>60.0 (55.0–65.0)</td>
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<tr>
<td>Creatinine, mg/dl, median (IQR)</td>
<td>1.0 (0.8–1.5)</td>
<td>1.0 (0.8–1.3)</td>
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<td>International normalized ratio, mean ± SD</td>
<td>1.3 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>0.07</td>
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<tr>
<td>Bilirubin, mg/dl, median (IQR)</td>
<td>0.7 (0.5–1.1)</td>
<td>0.8 (0.5–1.5)</td>
<td>0.11</td>
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</tbody>
</table>

Abbreviations: CHLT, combined heart–liver transplantation; HA, heart-alone transplantation; IQR, interquartile range; SD, standard deviation.

TABLE 3 Development of DSAs

<table>
<thead>
<tr>
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<th>HA, N = 251</th>
<th>CHLT, N = 26</th>
<th>p value</th>
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<tbody>
<tr>
<td>Presence of DSAs, n (%)</td>
<td>42 (16.7)</td>
<td>7 (26.9)</td>
<td>0.19</td>
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<tr>
<td>Class I DSA, n (%)</td>
<td>24 (9.6)</td>
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<tr>
<td>Class II DSA, n (%)</td>
<td>30 (12.0)</td>
<td>7 (26.9)</td>
<td>0.06</td>
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<tr>
<td>Days to DSA Class I, median (IQR)</td>
<td>44 (9–342)</td>
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<td></td>
</tr>
<tr>
<td>Days to DSA Class II, median (IQR)</td>
<td>202 (10–664)</td>
<td>1483 (29–2191)</td>
<td>0.12</td>
</tr>
<tr>
<td>Class I HLA-A MFI, median (IQR)</td>
<td>2475 (1650–2950)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I HLA-B MFI, median (IQR)</td>
<td>1800 (1600–2400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I HLA-C MFI, median (IQR)</td>
<td>2025 (1725–5500)</td>
<td></td>
<td></td>
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<tr>
<td>Class II HLA-DR MFI, median (IQR)</td>
<td>3075 (1000–5150)</td>
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<td></td>
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<tr>
<td>Class II HLA-DQ MFI, median (IQR)</td>
<td>3425 (1500–8950)</td>
<td>7360 (1600–14600)</td>
<td>0.67</td>
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<tr>
<td>Class II HLA-DR MFI, median (IQR)</td>
<td>3600 (1900–7500)</td>
<td>2250 (1200–2300)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Abbreviations: CHLT, combined heart–liver transplantation; DSA, donor-specific antibody; HA, heart-alone transplantation; HLA, human leukocyte antigen; IQR, interquartile range; MFI, mean fluorescence intensity.

HA, 65.0% [IQR, 60.0%–65.0%]; p = 0.23) and 3 years (CHLT, 65.0% [IQR, 60.0%–65.0%]; HA, 65.0% [IQR, 60.0%–65.0%]; p = 0.76) and was not found to be different between the two groups. Cardiac allograft survival was similar for CHLT and HA at 1 (93.8% vs. 89.0%; p = 0.39) and 5 years (82.1% vs. 80.9%; p = 0.73; Figure 1A). Patient survival was not significantly different between CHLT and HA at 1 (93.8% vs. 89.0%; p = 0.39) and 5 years (82.1% vs. 80.9%; p = 0.73; Figure 1B).

DISCUSSION

In this single-center experience of CHLT, we examined the potential immunologic consequence of including the liver with the cardiac allograft when transplanted simultaneously. We observed that the incidence of biopsy-proven ACR in the cardiac allograft was significantly reduced in the CHLT cohort compared with HA and that there was a trend toward more remote occurrence of rejection relative to the date of transplant in the CHLT.
cohort. The difference in the incidence of rejection was not reflected in patient or graft survival rates. Nor was the difference in ACR reflected by the development of posttransplant de novo DSA, as it was similar between CHLT and HA.

The current report adds to the growing literature providing evidence of the liver’s unique role in offering immunoprotection to kidney and heart allografts transplanted from the same donor compared with allografts transplanted alone.[9–11,15–19] Prior studies analyzing national databases have demonstrated lower rates of rejection for allografts cotransplanted with donor-specific primary liver, kidney, and heart allografts than for allografts transplanted alone but are limited by an inability to discern the mechanisms for the decreased risk of rejection.[19] More granular data from the Mayo Clinic indicate that a lower incidence of rejection among CHLT may be attributed to a decreased incidence of T cell–mediated rejection, but not antibody-mediated rejection, compared with HA recipients.[11]

Development of rejection and de novo DSAs in heart transplant patients has been associated with decreased graft and patient survival rates.[20,21] Similar findings have

**FIGURE 1** (A) Cardiac allograft survival. Allograft survival for CHLT and HA patients at 1 year (93.8% vs. 89.0%; \( p = 0.39 \) using the log-rank test) and 5 years (82.1% vs. 80.9%; \( p = 0.73 \) using the log-rank test). (B) Patient survival. Patient survival for CHLT and HA patients at 1 year (93.8% vs. 89.0%; \( p = 0.39 \) using the log-rank test) and 5 years (82.1% vs. 80.9%; \( p = 0.73 \) using the log-rank test)
been observed in kidney transplant patients who formed de novo DSAs.\textsuperscript{[22–24]} Whether the combination of a liver with a heart will increase allograft survival remains unknown. In our series as well as that from the Mayo Clinic, overall graft survival was similar between CHLT and HA. Both our series as well as the Mayo Clinic series assessed left ventricular ejection fraction as a secondary outcome, and neither found a difference between CHLT and HA cohorts. Unlike the University of Pennsylvania, the Mayo Clinic performs a yearly coronary angiography to assess coronary vasculopathy, associated with chronic antibody-mediated rejection, which was notable for a reduction in the incidence and severity among CHLT compared with HA patients. Whether the reduction in vasculopathy will manifest as improved ejection fraction or cardiac allograft survival with a longer duration of follow-up remains to be determined.

The mechanism by which the transplanted liver protects a kidney or cardiac allograft remains unknown, but evidence points to several biologic processes. Clinically, it has been demonstrated in liver alone, CHLT, and combined liver and kidney transplantation that DSA levels drop rapidly in the majority of recipients, with many undetectable within months of transplant.\textsuperscript{[13,25–27]} The liver has extensive sinusoid endothelial surfaces that may facilitate absorption of circulating antibodies. Supporting this theory, animal models demonstrate an increase in an antibody-mediated pattern of injury as the size of the liver allograft decreases.\textsuperscript{[28]} The rapid clearance mechanism indicates the potential role of complement receptors. It is known that the complement receptor of the immunoglobulin superfamily is expressed on hepatic Kupffer cells and binds C3b and iC3b opsin to clear immune complexes.\textsuperscript{[29]} The liver also releases HLA Class I antigen that binds and inactivates corresponding antibodies that are further cleared by phagocytic Kupffer cells.\textsuperscript{[30–33]}

From the standpoint of cell-mediated rejection, there are multiple viable mechanisms for encompassing hepatic immunity in the transplant setting.\textsuperscript{[34,35]} Programmed death 1 (PD1) is an inhibitory molecule expressed on recently activated T cells. Interaction of PD1 with its ligand (PD-L1) results in decreased function of T cell populations and may help create an immunoprotective environment.\textsuperscript{[34,35]} This interaction on liver sinusoidal endothelial cells (LSECs) results in poor T cell activation, whereas on hepatic stellate cells (HSCs) results in T cell apoptosis.\textsuperscript{[36,37]} In vitro studies have shown the ability of LSECs to inhibit T helper type 1 cells and T-helper 17 cells release of inflammatory signal molecules interferon \( \gamma \) and interleukin 17 as well as the ability of HSCs to promote immunosuppressive function of regulatory T cells.\textsuperscript{[38,39]} Suicidal emperiploesis, a nonapoptotic method resulting in the degradation of cytotoxic T-cell (CD8) T cells by hepatocyte lysosome and endosome structures, has been shown to clear 75% of alloantigen-specific CD8 T cells in the first 24 hours of antigen encounter in the liver.\textsuperscript{[40]}

The liver also receives a higher concentration of immunosuppression from the portal system than systemic blood from first-pass metabolism.\textsuperscript{[8]} The impact of this on intrahepatic innate and adaptive immune responses is unknown. However, these mechanisms would be expected to equally affect CHLT and HA patients, as HA patients still have functioning livers. Perhaps considered less frequently, the liver possesses an unmatched capacity to regenerate. As such, immune-mediated hepatocellular injuries may be less recognizable when compared with other organs such as the kidney.

Both CHLT and HA cohorts had similar cPRAs prior to transplant and did not have a significant difference in the percentage of patients who developed de novo DSA after transplantation. Unlike the HA cohort, we did not observe the development of Class I DSAs among CHLT, supporting the theory that Class I DSAs are preferentially cleared by the liver. This phenomenon has been previously reported in isolated liver transplants and combined liver and kidney transplants as well as CHLTs.\textsuperscript{[11,26,41]} As mentioned previously, Kupffer cell–facilitated clearance of HLA Class I antibodies plays a role, but evidence also suggest variable hepatic microvascular Class II expression, which provides fewer Class II DSA targets compared with constitutive kidney and heart microvascular expressions.\textsuperscript{[42]} This may also explain the preferential clearance of HLA Class I DSA by the liver.

The formation of DSA in our CHLT cohort is higher than previously reported among CHLT and liver-alone transplant recipients.\textsuperscript{[11,43–45]} Differences in immunosuppression induction and maintenance regimens between transplant centers as well as the definition of a DSA possibly explain these findings; however, this is a limited sample of patients. The CHLT cohort had no formation of DSA antibodies to Class I antigens and did not form antibodies to Class II DP antigens. Prior research has also demonstrated minimal formation of Class I DSAs in liver-alone transplant recipients.\textsuperscript{[43]} Our CHLT cohort had similar or decreased rates of liver rejection compared with previous CHLT studies and experienced less ACR of the liver than previously reported series of liver-alone transplant recipients.\textsuperscript{[4,6,46,47]} Although interesting, these data reflect relatively small series and in the future require larger prospective studies using similar diagnostic tools.

There are several limitations to our study. Aside from the fact that this is a retrospective analysis conducted from a single center with a relatively small sample size, the patients in the CHLT and HA groups had fundamental differences with respect to age and indications for transplant. We are also somewhat limited in the ability to categorize antibody mediated rejection; although our pathologists routinely look for histologic evidence of antibody mediated rejection on myocardial biopsies, they do
not routinely stain for complement component C4d unless there is clinical suspicion. In addition, not all patients completed posttransplant DSA screening.

In summary, the combined transplantation of a heart with a liver allograft from the same donor reduced the incidence of ACR compared with HA recipients despite lower induction and baseline immunosuppression in the CHLT group relative to the HA group. Although there was a reduction in rejection, we did not observe a reduction in the development of de novo DSA or a decrement in allograft survival. Longer term follow-up is required to determine the evolution of DSA and whether the inclusion of a liver allograft will lead to prolonged cardiac survival.

CONFLICT OF INTEREST
Malek Kamoun consults for Vertex and advises Omixon, Immucor, and Luminex.

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REFERENCES


