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The SHELTER Trial of Transplanting Hepatitis C Virus–Infected Lungs Into Uninfected Recipients

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Background. SHELTER is a trial of transplanting lungs from deceased donors with hepatitis C virus (HCV) infection into HCV-negative candidates (sponsor: Merck; NCT03724149). Few trials have reported outcomes using thoracic organs from HCV-RNA+ donors and none have reported quality of life (QOL). **Methods.** This study is a single-arm trial of 10 lung transplants at a single center. Patients were included who were between 18 and 67 y of age and waitlisted for lung-only transplant. Patients were excluded who had evidence of liver disease. Primary outcome was HCV cure (sustained virologic response 12 wk after completing antiviral therapy). Recipients longitudinally reported QOL using the validated RAND-36 instrument. We also applied advanced methods to match HCV-RNA+ lung recipients to HCV-negative lung recipients in a 1:3 ratio at the same center. **Results.** Between November 2018 and November 2020, 18 patients were consented and opted-in for HCV-RNA+ lung offers in the allocation system. After a median of 37 d (interquartile range [IQR], 6–373) from opt-in, 10 participants received double lung transplants. The median recipient age was 57 y (IQR, 44–67), and 7 recipients (70%) had chronic obstructive pulmonary disease. The median lung allocation score at transplant was 34.3 (IQR, 32.7–86.9). Posttransplant, 5 recipients developed primary graft dysfunction grade 3 on day 2 or 3, although none required extracorporeal membrane oxygenation. Nine patients received elbasvir/grazoprevir, whereas 1 patient received sofosbuvir/velpatasvir. All 10 patients were cured of HCV and survived to 1 y (versus 83% 1-y survival among matched comparators). No serious adverse events were found to be related to HCV or treatment. RAND-36 scores showed substantial improvement in physical QOL and some improvement in mental QOL. We also examined forced expiratory volume in 1 s—the most important lung function parameter after transplantation. We detected no clinically important differences in forced expiratory volume in 1 s between the HCV-RNA+ lung recipients versus matched comparators. **Conclusions.** SHELTER adds important evidence regarding the safety of transplanting HCV-RNA+ lungs into uninfected recipients and suggests QOL benefits.

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Many patients on the waiting list with end-stage lung disease die or suffer health deterioration because of a lack of good-quality allografts. Among adults waitlisted for lung transplant in the year 2020, the mortality rate was 16.1 deaths per 100 waitlist years, an increase observed over prior years.[1] Many deceased donors have hepatitis C virus (HCV) infection acquired from injection drug abuse. Most thoracic organs from HCV-RNA$^+$ potential donors were discarded before the approval of all-oral direct-acting antiviral (DAA) therapy for HCV at the end of 2014.[2] The advent of DAAs enabled single-arm trials of transplanting HCV-RNA$^+$ donor organs into uninfected recipients, with most initial trials focused on abdominal organ transplant.[3-6] Although a number of registry-based and single-center observational studies have been published about transplanting HCV-RNA$^+$ donor lungs, only 3 registered trials involving 2 transplant centers reported results of this practice.[7-12] Clinical trials typically have the advantages of transparency related to defined protocols and oversight, as well as detailed prospective reporting of serious adverse events (SAEs) and other outcomes.

Woolley et al conducted the DONATE-HCV trial, in which 36 patients underwent lung transplant and 8 underwent heart transplant at a single center and then received a 1-mo course of DAA therapy. All DONATE-HCV lung recipients were cured of HCV and experienced 100% patient survival and graft survival with a median follow-up of 284 d. Compared with recipients of HCV-negative lungs, the DONATE-HCV recipients had lower lung allocation scores (LAS) and a higher odds of acute cellular rejection, although the difference in rejection rates was not statistically significant. No SAEs were adjudicated as related to HCV.[9]

The other 2 trials were conducted at the University of Toronto. Cypel et al conducted a trial with 22 recipients of lungs from HCV-RNA$^+$ donors. Eleven of the 22 lungs underwent ex vivo lung perfusion with ultraviolet C perfusate irradiation to reduce HCV levels in the allograft. Twenty recipients had detectable HCV and received a 12-wk course of oral sofosbuvir 400 mg plus velpatasvir 100 mg, starting >2 wk after transplant and eventually achieved HCV cure. However, 2 recipients experienced HCV recurrence and 1 had evidence of fibrosing cholestatic hepatitis.[7] Feld et al subsequently conducted a trial of 13 HCV-RNA$^+$ lung transplant recipients, all of whom received a 1-wk course of DAAs starting pretransplant in addition to ezetimibe, which inhibits HCV viral entry. Donor lungs were also treated with ex vivo lung perfusion plus irradiation. All recipients were cured of HCV. Two recipients died in the first 6 mo from sepsis and subarachnoid hemorrhage, respectively, but no SAEs were considered related to HCV.[8]

In the year 2021, United Network for Organ Sharing (UNOS) registry data reveal that only 28 of 70 lung transplant centers in the United States performed a lung transplant from an HCV-RNA$^+$ donor into an uninfected recipient. Wider utilization of HCV-RNA$^+$ donor organs would help alleviate the need for transplantable organs. However, in addition to limited data about biological outcomes from trials, no trials have measured quality of life (QOL) among recipients of HCV-RNA$^+$ donor lungs. It is unknown whether transplant candidates considering HCV-RNA$^+$ donor lungs have concerns about worse QOL because of adverse physical effects of HCV infection or from anxiety about being cured.[13-15] The primary aim of the SHELTER trial was to determine safety and effectiveness of transplanting lungs from HCV-RNA$^+$ donors into HCV-negative patients. We also collected prospective data on QOL using the validated RAND-36 instrument.

MATERIALS AND METHODS

This study was a single-arm clinical trial (Open-Labeled Trial Of DAA Treatment of Hepatitis C-Negative Patients Who Receive Lung Transplants from Hepatitis C-Positive Donors: SHELTER) conducted at the Hospital of the University of Pennsylvania from November 2018 to November 2021 and approved by the University of Pennsylvania Institutional Review Board (IRB; #829397; CT.gov: NCT03724149). We convened an external data safety and monitoring board that reviewed study outcomes including adverse events. This investigator-initiated protocol was funded by Merck Sharpe and Dohme. Study conduct was consistent with the Declaration of Helsinki, the Declaration of Istanbul, and the International Society for Heart and Lung Transplantation statement on transplant ethics. **Methods S1 and S3** (**SDC,** http://links.lww.com/TXD/A540) provide the IRB-approved changes during the trial and study protocol.

Outcomes

The primary outcomes were HCV cure (ie, sustained virologic response at week 12), and SAEs attributable to HCV infection or HCV therapy in the first year after transplant. Secondary outcomes included longitudinal QOL measured using the RAND-36 instrument.[16] In post hoc analyses, we matched SHELTER lung recipients with similar comparators at the same center who received lungs from HCV-negative donors, and we compared waiting time to transplant, length of stay, posttransplant survival, and longitudinal trends in and in pulmonary function tests (PFTs). Criteria for selecting matched comparators are described ahead.

Participant Criteria

The criteria were designed to identify patients at low risk for hepatic complications from HCV and those who can tolerate the antiviral medications in the postoperative period. Patients were included who (1) had no evident contraindication to lung transplantation other than the underlying lung disorder, (2) had agreement from the primary clinical lung transplant team that participation was appropriate, (3) had a LAS of ≤55, (4) were able to provide informed consent, and (5) were aged between 18 and 65 y at enrollment (the age criterion was extended to 67 y during the study).

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A hepatologist confirmed the absence of chronic liver disease after history, physical, and serological evaluation. Each participant underwent transient elastography to rule out significant fibrosis (≥F2). For patients with cystic fibrosis, this cutoff was 11 kPa because the cutoff for advanced fibrosis in patients with cholestatic liver disease is higher than other conditions, whereas for all other patients, the cutoff was 8 kPa.

Patients were excluded who had hepatocellular carcinoma; were human immunodeficiency virus positive, HCV-RNA$^+$, and hepatitis B surface antigen and/or DNA positive; had allergy or intolerance to tacrolimus; had esophageal dysmotility and inability to safely swallow pills posttransplant; were retransplant candidates; had extracorporeal membrane oxygenation or mechanical ventilation as a bridge to lung transplant; were listed for multiorgan transplant; and/or had chronic kidney disease with an estimated glomerular filtration rate of <50 mL/min/1.73 m^2. **Table S1** (**SDC,** http://links.lww.com/TXD/A540) lists the full criteria for trial participation, including relative contraindications considered on a case-by-case basis.

Informed Consent

The processes of informed consent included at least 3 components. Firstly, one of the principal investigators (J.M.D. or M.M.C.) contacted the potential participant and offered a general description of HCV, its complications, and the goals of the trial. Secondly, the patient received education with an IRB-approved set of slides about HCV infection and its treatment (**Methods S4, SDC,** http://links.lww.com/TXD/A540). Lastly, the participant completed the processes of informed consent. The presentation and consent specified that the initial HCV therapy would be provided at no cost to the patient. If the initial treatment did not cure HCV, the participant would receive a second antiviral regimen at no cost. However, if any HCV-RNA$^+$ lung recipient needed >2 antiviral treatments, that recipient would have to pay through insurance or personal funds.

For eligible participants, their status in the OPTN portal was modified so that they could receive offers of HCV-RNA$^+$ lung allografts.

Deceased Donor Criteria

The original study criteria required that donors have a detectable HCV-RNA and genotype 1 or 4. However, given the availability of pangenotypic HCV therapies, we subsequently modified the donor criteria to allow a donor with HCV infection of any genotype. Additional donor criteria included donor age ≤55 y, Pao_2/FiO_2 ≥300 on FiO_2 = 100% and positive end-expiratory pressure = 5, cigarette use history ≤20 pack-years, no evidence of cirrhosis, and no prior treatment of HCV with DAA-based therapy. Donor exclusion criteria included donation after circulatory death and human immunodeficiency virus positivity. **Table S2** (**SDC,** http://links.lww.com/TXD/A540) lists the full donor criteria.

Overview of Center Protocols for Posttransplant Immunosuppression and Other Care

The clinical transplant team guided the selection of oral Immunosuppression. All 10 SHELTER recipients received basiliximab as induction and the center's usual oral regimen of tacrolimus, mycophenolate mofetil, and prednisone (ie, identical to what is typically used for recipients of organs from HCV-negative donors). The center protocol involves posttransplant surveillance allograft biopsies at approximately 6 wk, 12 wk, 6 mo, and at 12 mo, as well as when clinically indicated. PFTs are obtained weekly for the first 2 mo and at each clinic visit thereafter. Additionally, recipients undergo screening for anti-HLA donor-specific antibody 1 to 2 wk after transplantation and every 3 mo or earlier in the event of allograft dysfunction.

Posttransplant Protocol for HCV Treatment

Methods S2 (**SDC,** http://links.lww.com/TXD/A540) provides details about HCV genotyping and viral quantification. We tested recipients for HCV-RNA viral load by day 3 posttransplantation. We started a 12-wk course of DAA therapy when HCV-RNA was first detected. Throughout the trial, recipients of lungs from donors with HCV genotype 1 or 4 infection were treated with elbasvir and grazoprevir (Zepatier). Among recipients infected by HCV genotype 1a, we analyzed specimens for baseline nonstructural protein 5A resistance-associated substitutions. When these substitutions were present, the protocol called for extending elbasvir and grazoprevir therapy to 16 wk and adding oral ribavirin, if the patient could safely tolerate the drug.[17]

After the trial protocol was amended to allow organs from donors with HCV nongenotype 1 or 4, we treated recipients of those organs with sofosbuvir/velpatasvir (Epclusa), starting therapy after viral genotyping and the patient's insurance approved the therapy.

We subsequently measured quantitative HCV PCR at weeks 1, 2, 4, 8, and 12 (when antiviral therapy was completed) and then at weeks 4, 8, and 12 after therapy was completed.[18-23]

Matched Comparators for Analyses of Survival and Other Outcomes

As shown in **Figure S1** (**SDC,** http://links.lww.com/TXD/A540), we identified highly similar recipients who received double lung transplants from HCV-RNA-negative donors at the Hospital of the University of Pennsylvania between April 1, 2016, to January 1, 2021, and matched them in a 3:1 ratio to SHELTER recipients of HCV-RNA$^+$ donor lungs. One of the 30 comparators underwent lung transplant twice during the period and twice acted as a comparator. We applied iterative steps for our matching algorithm.[24] We calculated the propensity score for lung transplant recipients in the 2 groups on the following covariates: recipient age at transplant, body mass index, sex, race, cause of lung disease, LAS at transplant, and donor age. We then computed a Mahalanobis distance matrix on important continuous covariates including recipient age, donor age, LAS, and body mass index. To ensure that the algorithm prioritized donor age, we applied penalties to reduce the mathematical distance between the matched pairs. To ensure optimal balance, we performed exact matching on cause of lung disease and fine matching on race and sex. We used a standardized difference threshold of <0.1 to assess covariate balance (**Table S3, SDC,** http://links.lww.com/TXD/A540).[25,26] Matching was completed using the R statistical software (version 4.0.3), and R package "designmatch."[27] We used Gurobi as the optimizer, and the balance was assessed using the "cobalt" package.[28]

Statistical Analysis

Statistical analyses were descriptive. Continuous variables were reported as means or medians as appropriate. Categorical variables were reported as frequencies.

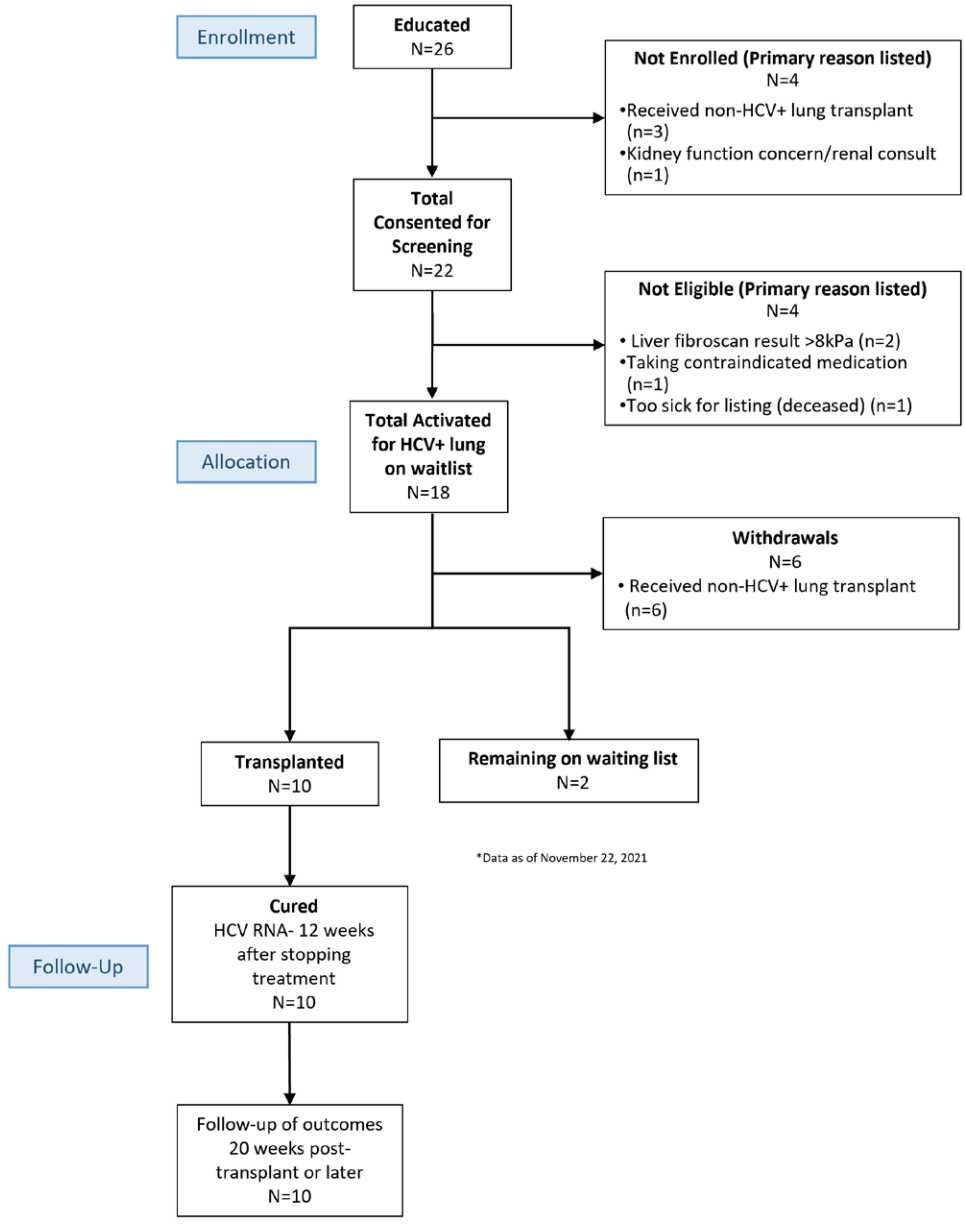

FIGURE 1. Flowchart. HCV, hepatitis C virus.

RESULTS

As displayed in **Figure 1**, 26 patients received formal education about the SHELTER trial, among whom 22 consented for screening and 18 were determined eligible. Ten patients received double lung transplants from HCV-RNA$^+$ donors, whereas 6 received HCV-RNA-negative donor lung transplants and 2 remained on the waiting list.

For the 10 recipients of HCV-RNA$^+$ lung transplants, we collected data for 1 y posttransplantation. As shown in **Table 1**, the median recipient age at transplant was 57 y (interquartile range [IQR], 44–67) and 50% were male. The cause of lung disease was chronic obstructive pulmonary disease for 7 recipients and interstitial lung disease for 3 recipients. The median LAS at listing was 33.1 and at transplant was 34.3 (IQR, 32.7–86.9). The median time from activation in the UNOS allocation system for HCV-RNA$^+$ organ offers to transplantation with HCV-RNA$^+$ donor lungs was 37 d (range, 6–373). **Table 2** shows that the median donor age was 38 y.

Five recipients of HCV-RNA$^+$ lung transplants had primary graft dysfunction grade 3 on day 2 or 3 posttransplant, although none required extracorporeal membrane oxygenation posttransplant.

Nine of the 10 recipients were infected with HCV genotype 1a and received elbasvir and grazoprevir. Among these 9 recipients, 7 were treated for 12 wk. Two were treated for 16 wk because of the results of nonstructural protein 5A testing, but we did not give ribavirin because of concerns about toxicity. The 10th recipient was infected with genotype 3 and received sofosbuvir/velpatasvir. **Figure 2** shows longitudinal trends in HCV viral loads. All 10 patients were cured of HCV, defined as sustained virologic response at week 12. See **Results S1 and S2** (**SDC,** http://links.lww.com/TXD/A540) for additional results.

Figure 3 shows longitudinal RAND-36 scores (higher scores are better). The RAND-36 responses showed substantial improvement in physical QOL and some improvement in

TABLE 1.

Demographic and clinical characteristics of 10 recipients in the SHELTER trial

Characteristic	
Age at consent, y, median (range)	57 (44–67)
Age at transplant, y, median (range)	57 (45–67)
Male sex, n (%)	5 (50)
White race, n (%)	10 (100)
Cause of lung disease, n (%)	
Interstitial lung disease	3 (30)
COPD/alpha-1-antitrypsin deficiency	7 (70)
Blood type, n (%)	
A	2 (20)
O	8 (80)
LAS at listing, median (range)	33.1 (32.7–85.0)
LAS at transplant, median (range)	34.3 (32.7–86.9)
Panel-reactive antibodies at listing, median (range)	0.0 (0–42)
Days from activation for lung offers from HCV-infected lung donors to transplantation, median (range)	37 (6–373)
Days from initial waitlisting to transplantation, median (range)	315 (7–791)
Antibody induction therapy with basiliximab,[a] n (%)	10 (10)
Days from transplant to starting HCV therapy, mean (range)	3.9 (2–7)
HCV genotype and DAA treatment (%)	
Genotype 1a; treated with elbasvir/grazoprevir	9 (90)
Genotype 3; treated with sofosbuvir/velpatasvir	1 (10)

[a]All 10 received the center's usual regimen of tacrolimus, mycophenolate mofetil, and prednisone.
COPD, chronic obstructive pulmonary disease; DAA, direct-acting antiviral; HCV, hepatitis C virus.

TABLE 2.

Deceased donor and allograft characteristics in the SHELTER trial

Characteristic	
Age, y, median (range)	38 (28-58)
Male gender, n (%)	5 (50)
White race, n (%)	9 (90)
Blood group, n (%)	
O	8 (80)
A	2 (20)
Cause of death, n (%)	
Anoxia	5 (50)
Stroke/ICH	3 (30)
Head trauma	2 (20)
Drug intoxication as cause of death, n (%)	5 (50)
Double lung transplant allograft, n (%)	10 (100)

ICH, intracerebral haemorrhage.

mental QOL from pretransplant to 1 y posttransplant. The median Physical Component Summary was 27 (range, 19.5–35.5) pretransplant and 40.5 (range, 22.1–51.1) posttransplant, whereas the median Mental Component Summary was 48 (range, 37–66) pretransplant and 53 (range, 30.7–61.5) posttransplant.

Outcomes for SHELTER Recipients Versus Matched Comparators

The median total days on the waiting list for SHELTER recipients was 315 (IQR, 245–377) versus 152 (IQR, 53–286) for the comparator group of 30 recipients of HCV-negative donor lung transplants. The median posttransplant length of stay was 33 d (IQR, 23–50) for SHELTER participants versus 23 d (IQR, 18–38) for the comparator group. One-year survival was 100% among SHELTER recipients versus 83% among comparators.

Figure 4 shows only rare episodes of clinically meaningful liver enzyme elevations in either group. **Figure 5** displays trends in forced expiratory volume in 1 s (FEV_1), forced vital capacity, and FEV_1/forced vital capacity pretransplant and at 12 mo. Focusing on FEV_1, considered the most important parameter of lung function after transplant, we found no clinically important differences in function between the 2 groups. Two comparator patients (7%) and 1 SHELTER recipient (10%) had biopsy-proven acute cellular rejection ≥grade A2. The **Supplemental Digital Content** (**SDC**, http://links.lww.com/TXD/A540) has details about the SHELTER recipient's rejection episode.

Adverse events

Table S4 (**SDC**, http://links.lww.com/TXD/A540) lists SAEs. No SAEs were adjudicated as related to HCV or treatment. The SAEs included 1 recipient who developed severe acute kidney injury, requiring dialysis intermittently for 2 mo posttransplant. His 12-mo estimated glomerular filtration rate was 29 mL/min/1.73 m^2.

DISCUSSION

The SHELTER trial adds to a growing body of evidence that lung transplant recipients with donor-derived HCV infection will experience very high cure rates and good clinical outcomes. The careful adjudication of adverse events for SHELTER recipients determined all as unrelated to HCV or antiviral therapy—a result that supports the safety of using these organs. We used high-quality multivariable matching to demonstrate that survival, organ rejection, liver inflammation, and pulmonary function were fairly similar between SHELTER recipients and comparator recipients of HCV-negative lungs.

The SHELTER trial is also the first study to reveal improvement in mental and physical QOL from pretransplant to 1 y posttransplant among recipients of HCV-RNA$^+$ donor lungs. Lung transplantation is expected to provide marked improvements in health-related QOL, with a prior study by Singer et al[29] demonstrating improvements in disability and health-relatedQOL regardless of the quality metric or survey used. Among patients awaiting lung transplantation, impaired physical function adversely impacts health-related QOL, although all aspects of QOL are adversely affected.[30,31] We showed that recipients of allografts that were historically considered high risk because of HCV infection still experienced the expected improvement in QOL, despite the need for additional monitoring and antiviral therapy. Taken together, this work suggests that lung transplant candidates often feel vulnerable from their illness, will commonly accept HCV-RNA$^+$ organs, and should expect improvement in QOL after transplant despite the fact that most patients endure SAEs.

Despite extensive efforts to increase the pool of deceased donor organs, many individuals with end-stage lung disease face long waiting times for transplant or die waiting.[32] Transplanting lungs from HCV-RNA$^+$ donors provides an important new option. Potential deceased donors with HCV infection are more likely to be male and usually younger than HCV-negative donors, which may make their organs feasible

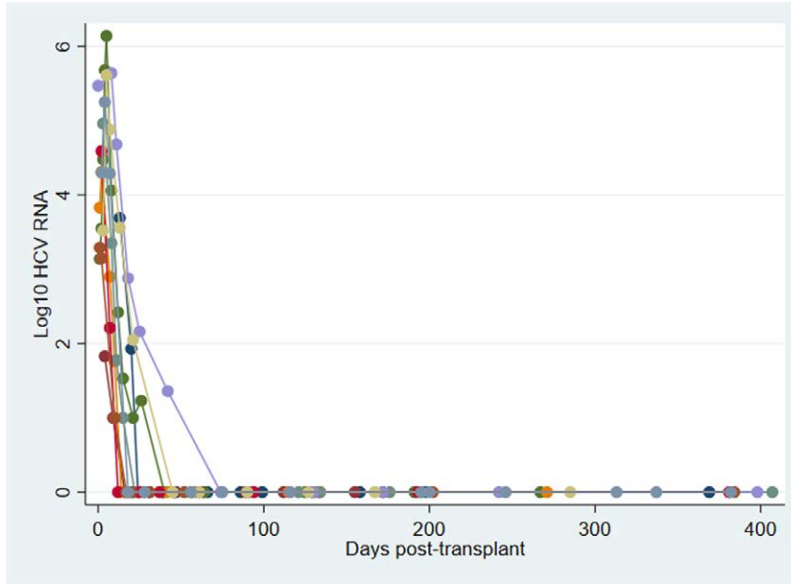

FIGURE 2. Recipient HCV viral load over time among 10 recipients of lung transplants from HCV-RNA+ donors. HCV, hepatitis C virus.

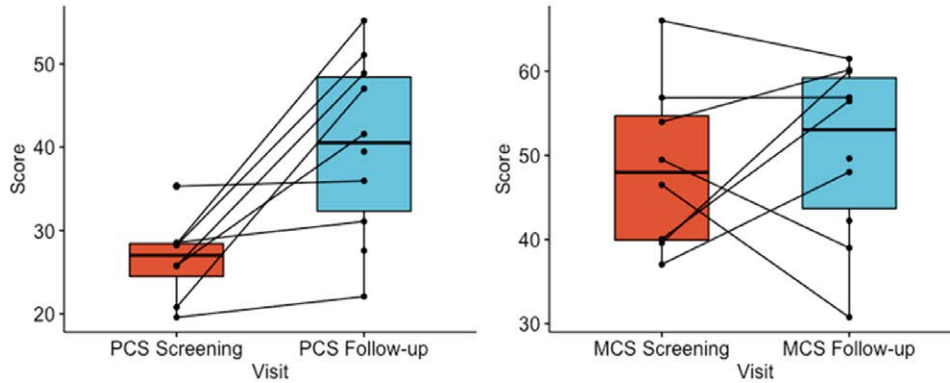

FIGURE 3. Physical and mental health QOL scores from pretransplant (N = 9)* and at 12 mo posttransplant using HCV-RNA+ donor lungs (N = 10), assessed with the RAND-36 instrument. *One participant was too ill to complete pretransplant survey. HCV, hepatitis C virus; MCS, Mental Component Score; PCS, Physical Component Score; QOL, quality of life.

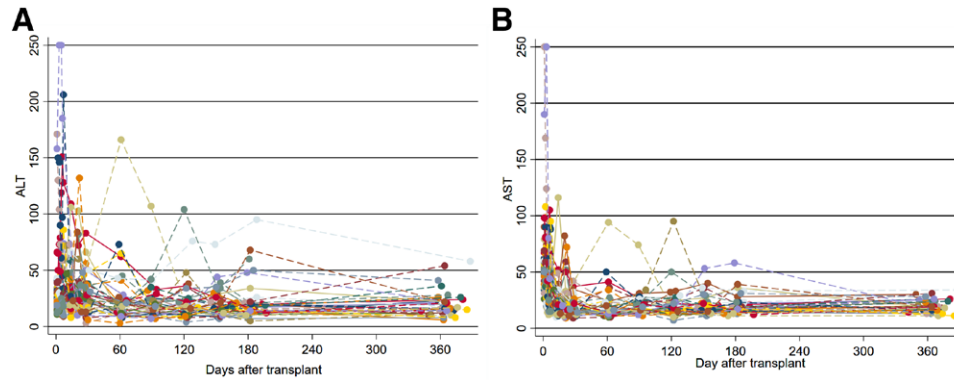

FIGURE 4. ALT (A) and AST (B) over time among 10 recipients of lung transplants from HCV-RNA+ donors versus matched comparator recipients of HCV-negative donor lungs. Ten SHELTER lung transplants were matched to 30 HCV-negative lung transplants. ALT and AST levels of >250 IU/L were replaced with 250 IU/L to facilitate data presentation. Solid lines represent SHELTER trial participants; dashed lines represent matched comparator recipients of HCV-negative lungs. ALT, alanine transaminase; AST, aspartate transaminase; HCV, hepatitis C virus.

for many waitlisted candidates. However, the allocation of HCV-RNA+ lungs to suitable candidates depends on the expertise of the center expertise and the willingness of clinicians and their patients to accept them. Cypel et al[33] reported on a series of 124 HCV-RNA+ lung transplants that the University of Toronto accepted after the organs were turned down by US centers, demonstrating that many US centers were highly selective about organs from donors with HCV. From a center perspective, the practice of transplanting HCV-RNA+ organs requires expertise from pharmacy, including anticipating drug

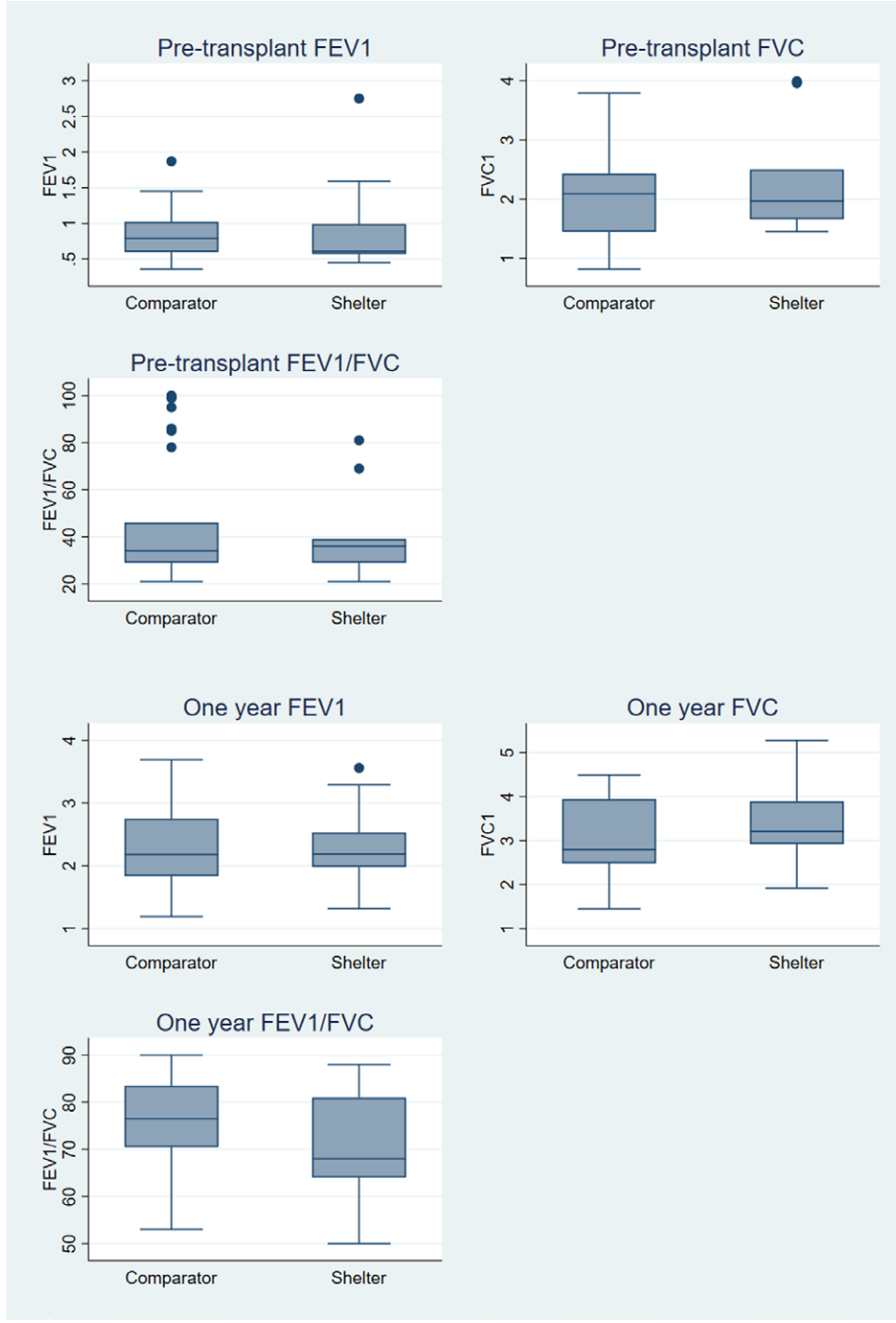

FIGURE 5. PFTs among 10 recipients of lung transplants from HCV-RNA^{+} donors versus comparator recipients of HCV-negative donor lung transplants. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCV, hepatitis C virus; PFT, pulmonary function test.

interactions and a plan for supporting patients through the process of drug approval. DAAs also pose particular management concerns for lung transplant recipients. Firstly, data on bioavailability with pill-crushing are limited, which was the reason our original exclusion criteria included esophageal dysmotility, which is common among candidates with connective tissue diseases, including systemic sclerosis and Sjogren's syndrome.[34] Secondly, drug interactions need careful consideration. A prominent example is that sofosbuvir/velpatasvir should not be used with amiodarone, which has a long half-life, such that teams should have a well-established plan for the management of postoperative arrhythmias. In contrast, contemporary antiviral regimens such as sofosbuvir/velpatasvir and glecaprevir/pibrentasvir have a number of advantages, such as the fact that they are pangenotypic, can be used in the setting of kidney failure, and appear capable of curing donor-derived HCV with a treatment duration of ≤1 mo, depending on when the antiviral is started.[8,9]

In post hoc analyses, we implemented matching tools to identify highly similar recipients of HCV-negative donor lungs. It is possible that the 100% survival rate among SHELTER participants was due to careful patient selection

or that recipients had closer management by the transplant team due to their trial participation. The lack of liver inflammation among SHELTER recipients is notable, consistent with other studies, and likely reflects the beneficial effects of treating HCV in the first few days, before the viral infection becomes fully established.[35] PFTs by 12 mo posttransplant did not show clinically meaningful differences in FEV_1 between recipients of HCV-RNA$^+$ donor lungs and comparator recipients of HCV-negative lung transplants. Rates of acute cellular rejection grade ≥A2 were low in both groups.

Study limitations include small size and implementation at a single, high-volume transplant program. We acknowledge that our post hoc comparisons of outcomes to matched recipients were not powered to test for clinically meaningful differences. We do not have QOL data on comparators. It is also possible that the SHELTER results may not be generalizable to smaller volume programs or that the supports of trial participation—which included periodic follow-up with a study coordinator and DAA provided immediately after transplant—were partially responsible for the positive outcomes. Nonetheless, the SHELTER results are concordant with results from observational studies at other centers and multicenter UNOS registry data.

We also acknowledge the need to educate candidates and implement informed consent related to HCV-RNA$^+$ lung transplants, which requires the investment of additional time by the center. As shown in the study slides (**Methods S4, SDC,** http://links.lww.com/TXD/A540), this education should cover a range of issues including side effects of antiviral medications, the risk of liver disease from HCV if the virus is not cured, and the need to maintain universal precautions in the household especially while the patient is viremic. In prior work, our group and others found that most patients have minimal accurate knowledge about HCV and require education before any meaningful discussion about the acceptance of HCV-RNA$^+$ organs can take place.[36] Although some patients may stigmatize HCV infection, others may simply be focused on the probability of cure or make an instinctive decision to accept HCV-RNA$^+$ donor organ transplants.[37,38] Humar et al collected free-text responses to examine attitudes and beliefs about lung transplant with HCV-RNA$^+$ lungs in a cohort of 67 waitlisted patients who opted-in for HCV-RNA$^+$ donor organ offers. Many patients cited a sense of "desperation" in deciding to consider HCV-RNA$^+$ donor transplants. Among the 21 patients who did eventually receive an HCV-RNA$^+$ donor lung transplant, 83% reported no adverse impacts on their health related to exposure to HCV.[39]

In summary, recipients of HCV-RNA$^+$ lung transplants in the SHELTER trial experienced 100% HCV cure, no SAEs related to HCV or antiviral therapy, and improvement in QOL. Recipients did not manifest evidence of liver inflammation from donor-derived HCV and had good pulmonary function. HCV-RNA$^+$ donor lungs are a valuable pathway to expand access to transplant at programs that are willing to address important issues related to informed consent and provide timely access to antiviral therapy.

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