Clinical Gastroenterology and Hepatology 2019;17:739–747

Cost Effectiveness of Transplanting HCV-Infected Livers Into Uninfected Recipients With Preemptive Antiviral Therapy

Emily D. Bethea,[*,‡,§,a] Sumeyye Samur,[*,‡,a] Fasiha Kanwal,[‖,¶] Turgay Ayer,[#] Chin Hur,[*,‡,§] Mark S. Roberts,[**,‡‡] Norah Terrault,[§§] Raymond T. Chung,[‡,§] and Jagpreet Chhatwal[*,‡,§]

*Institute for Technology Assessment, Massachusetts General Hospital, Boston, Massachusetts; §Liver Center and Gastrointestinal Division, Massachusetts General Hospital, Boston, Massachusetts; ‡Harvard Medical School, Boston, Massachusetts; ‖Department of Medicine, Gastroenterology and Hepatology, Baylor College of Medicine, Houston, Texas; ¶Houston Veterans Affairs Health Services Research and Development Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; #Department of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta, Georgia; **Department of Health Policy and Management, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania; ‡‡University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; §§University of California San Francisco Medical Center, Gastroenterology and Hepatology Division, San Francisco, California

BACKGROUND & AIMS: Guidelines do not recommend transplanting hepatitis C virus (HCV)-infected livers into HCV-uninfected recipients. Direct-acting antivirals (DAAs) can be used to treat donor-derived HCV infection. However, the added cost of DAA therapy is a barrier. We evaluated the cost effectiveness of transplanting HCV-positive livers into HCV-negative patients with preemptive DAA therapy.

METHODS: A previously validated Markov-based mathematical model was adapted to simulate a virtual trial of HCV-negative patients on the liver transplant waitlist. The model compared long-term clinical and economic outcomes in patients willing to accept only HCV-negative livers vs those willing to accept any liver (HCV negative or HCV positive). Recipients of HCV-positive livers received 12 weeks of preemptive DAA therapy. The model incorporated data from the United Network for Organ Sharing and published sources.

RESULTS: For patients with a model for end-stage liver disease (MELD) score ≥ 22, accepting any liver vs waiting for only HCV-negative livers was cost effective, with incremental cost-effectiveness ratios ranging from \$56,100 to \$91,700/quality-adjusted life-year. For patients with a MELD score of 28 (the median MELD score of patients undergoing transplantation in the United States), accepting any liver was cost effective at an incremental cost-effectiveness ratio of \$62,600/quality-adjusted life year. In patients with low MELD scores, which may not accurately reflect disease severity, accepting any liver was cost effective, irrespective of MELD score.

CONCLUSIONS: Using a Markov-based mathematical model, we found transplanting HCV-positive livers into HCV-negative patients with preemptive DAA therapy to be a cost-effective strategy that could improve health outcomes.

Keywords: ICER; QALY; Viremic Donor; Prevention; Simulation Modeling.

Over the past decade there has been a steady increase in the number of patients with end-stage liver disease in need of transplantation. With limited liver donor availability, we have not seen a parallel increase in the number of annual liver transplants performed.[1] As this shortage of transplant viable organs persists, it is of paramount importance that all transplantable organs are identified and allocated to those most in need. Hepatitis C virus (HCV)-infected donor organs are a potentially underutilized resource. This is becoming increasingly recognized as persons who inject drugs emerge as the fastest-growing donor category, and HCV-positive organs begin to compromise a larger portion of the donor organ supply.[2] With the advent of highly effective direct-acting antivirals (DAAs), the

[a]Authors share co-first authorship.

Abbreviations used in this paper: DAA, direct-acting antiviral; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; LT, liver transplant; MELD, model for end-stage liver disease; NAT, nucleic acid testing; QoL, quality of life; QALY, quality-adjusted life-year; SIM-LT, simulation of liver transplant candidate; SVR, sustained virologic response; UNOS, United Network for Organ Sharing.

Most current article

1542-3565/\$36.00
https://doi.org/10.1016/j.cgh.2018.08.042

number of patients in need of liver transplantation as the result of HCV-related liver disease is expected to decrease, while an increasing number of HCV-uninfected patients remain on the waitlist.[3,4]

Current guidelines do not recommend the use of HCV-positive donor livers for transplantation into HCV-negative recipients. This is because viremic donor livers carry a universal risk of HCV transmission, and if liver allograft HCV infection develops and cannot be treated successfully, there is a higher risk of complications, including potential graft failure.[5,6] Given this concern, HCV-positive donor livers historically have been reserved for HCV-infected waitlist patients. However, although HCV treatment in the interferon era was poorly tolerated and associated with complications that led to worse post-transplant outcomes, this is not the case with new HCV treatment regimens. If allograft HCV infection can be cured successfully with DAA therapy, then it may be time to revisit HCV-positive organ allocation policies.

Emerging data have shown excellent DAA efficacy in treating donor-derived HCV infection in lung, kidney, and liver transplant (LT) recipients.[7–9] A recent modeling study also highlighted the clinical importance of this approach, showing the potential benefits seen at various model for end-stage liver disease (MELD) scores when patients on the LT waitlist become open to accepting HCV-positive livers.[10] Despite the currently limited data, it is postulated that DAAs will continue to show successful post-transplant HCV cure.[11]

Although there is clear clinical rationale and physician consensus to support strategies aimed at increasing the static donor organ pool, the added cost of DAA therapy remains a logistical barrier. The current environment restricts reimbursement for treatment of donor-derived HCV infection, allowing payers to deny coverage and place the burden of DAA cost on individual patients. Although accepting HCV-positive organs could reduce a patient's time to transplant and waitlist-associated mortality, it also could increase post-LT complications associated with HCV allograft infection. The trade-offs of such a strategy have not been studied. However, such information can prove critical in helping inform policy level decisions surrounding HCV-positive organ use. To evaluate these trade-offs, we conducted a model-based analysis, providing some of the first cost-effectiveness data on the use of preemptive DAA therapy in HCV-negative waitlist patients receiving HCV-infected donor livers.

What You Need to Know

Background

There is a continued increase in the number of donor organs that are positive for hepatitis C virus (HCV) infection. HCV-infected livers have not been offered routinely to uninfected patients on the liver transplant waitlist. Approval and cost of direct-acting antiviral therapy are barriers.

Findings

Providing HCV-negative patients on the liver transplant waitlist the option of accepting an HCV-positive liver, with a plan for preemptive direct-acting antiviral therapy, is a cost-effective strategy that can improve health outcomes.

Implications for patient care

HCV-positive livers should be considered for transplantation into HCV-uninfected patients on the waitlist.

Methods

Model Overview

We adapted a previously validated Markov-based mathematical model, Simulation of Liver Transplant (SIM-LT), to conduct our cost-effectiveness analysis (Figure 1).[10,12,13] SIM-LT simulated a virtual trial of HCV-negative patients on the LT waiting list to compare long-term clinical and economic outcomes in patients willing to accept only HCV-negative livers vs those willing to accept any liver (ie, HCV-negative or HCV-positive). The model incorporated data from the United Network for Organ Sharing (UNOS) and has been validated with reported values from the Organ Procurement and Transplantation Network.[10,12] SIM-LT was developed from the health care payer's perspective with a lifetime horizon.

Baseline Population

We created a hypothetical cohort of HCV-negative decompensated cirrhotic patients (without hepatocellular carcinoma) who were active on the LT waiting list. At baseline, the mean age of patients in the model was 50 years, and MELD scores ranged between 12 and 40.

Simulation of Liver Transplant Waiting List

We simulated the lifetime course of decompensated cirrhotic patients waiting for LT. Patients' MELD scores naturally could change on the waiting list. To estimate the natural disease course and MELD score fluctuations, we used a previously published study based on UNOS data to estimate weekly changes in MELD score.[10,12,13] We aggregated data in paired groups of consecutive MELD scores as follows: 12 to 13, …, 38 to 39, and 40. We also estimated waitlist mortality by MELD score from the same data source (Supplementary Table 1). Although patients were on the waiting list, they could undergo LT, die from background mortality, or die from liver-related mortality based on their MELD scores.

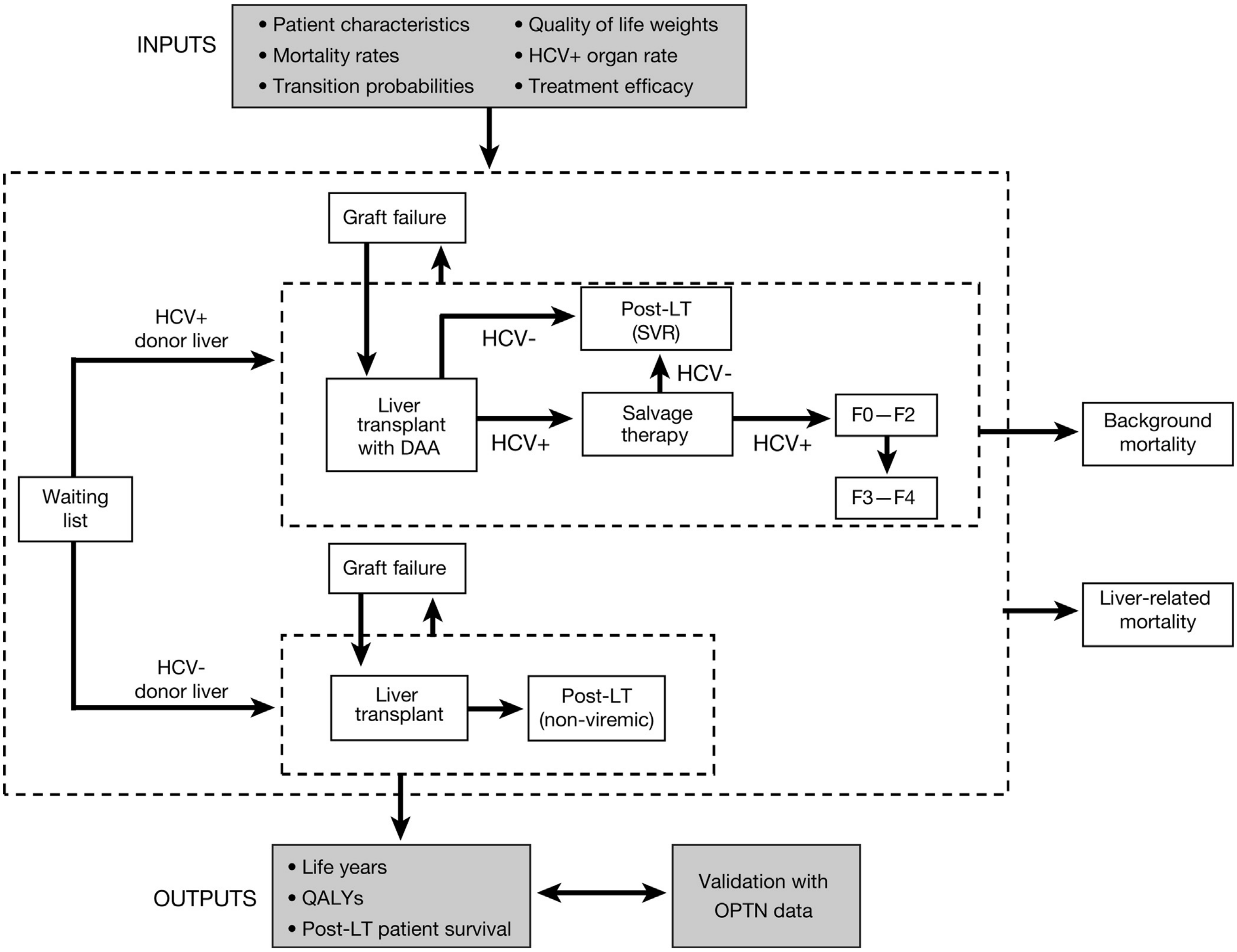


Figure 1. Model schematic for HCV-negative patients on the liver transplant waitlist. For each patient profile, the model simulated 2 scenarios, as follows: (1) accept any liver, and (2) accept only HCV-negative livers. OPTN, Organ Procurement Transplant Network.

Interventions

For each patient on the LT waiting list, we simulated 2 scenarios: first, accept only HCV-negative livers (ie, the current practice), and second, accept any liver (ie, HCV-negative or HCV-positive), followed by preemptive DAA treatment if an HCV-positive liver was accepted.

In both scenarios, the probability of receiving a liver transplant was based on MELD scores and geography (Supplementary Table 2, Supplementary Methods).[14] Patients could experience graft failure at any time after LT. If a patient had early acute graft failure they were listed as status 1A for retransplantation. We assigned the average probability of liver transplant and liver-related mortality to these patients, estimated from UNOS data.[12]

In the scenario of accepting only HCV-negative livers, patients moved to the post-LT (nonviremic) health state after successful HCV-negative liver transplant (Figure 1).

In the scenario of accepting any liver, if the incoming liver was HCV-negative, the patient moved to the post-LT (nonviremic) health state after transplant. If the incoming liver was HCV-positive, then preemptive antiviral treatment with DAAs was initiated. The status of the patient after LT was determined by their response to DAA therapy (ie, ongoing viremia or achievement of sustained virologic response [SVR]). If patients were treated successfully, they moved to the post-LT (SVR) state; otherwise, they were given salvage therapy. The SVR rate of the salvage therapy was assumed to be the same as with preemptive therapy. If patients failed salvage therapy, they followed the natural progression of disease and were assumed to have chronic HCV (Figure 1).

Preemptive therapy in our analysis was defined as antiviral treatment at the time of or shortly after liver transplantation (ie, administered within the days to weeks after transplant once allograft function stabilized). We incorporated DAA efficacy data from recent trials, including pangenotypic regimens, and used SVR rates seen with 12 weeks of therapy in post-LT patients (Supplementary Table 3).[15] We also accounted for the potential increased likelihood of fibrosing cholestatic hepatitis and graft failure in patients receiving HCV-positive livers (Supplementary Methods).

The likelihood of undergoing transplant in the scenario of accepting any liver was higher than the current practice of accepting only HCV-negative organs. We therefore increased the rate of receiving a liver by 5.9%[16] (ie, the proportion of HCV-positive organs among all liver donors in the United States). In the sensitivity analysis, we varied this rate from 2.9% to 26.7%, corresponding to the lowest and highest HCV-positive organ rates observed in UNOS regions.[17]

Costs

Patients in both strategies incurred costs that included the cost of waitlist patient care, the cost of transplantation, and the cost of post-LT patient management. In the scenario of accepting any liver, patients transplanted with an HCV-positive liver incurred the additional cost of DAA therapy. Previously published studies were used to determine the health-state costs in our model.[18,19] Because in practice the price of DAAs is lower than listed values, we applied a 23.1% discount on the wholesale acquisition cost of glecaprevir and pibrentasvir, $39,600,[20] in our base-case analysis, and further conducted a sensitivity analysis on a wide range of potential DAA prices ($10,000–$95,000). All costs were converted to 2017 US dollars (Supplementary Table 3).

Health-Related Quality of Life

For each health state in our model, we assigned health-related quality-of-life (QoL) weights, with 0 denoting death and 1 denoting perfect health. We derived EuroQol-5D instrument (ie, introduced by EuroQol Group of the researchers from five European countries,) values from a previous study and adjusted them to the US population norm with age and sex (Supplementary Table 4).[13]

To evaluate patients with MELD scores that may not accurately reflect disease severity (eg, a patient with a MELD score of 18 with refractory ascites and high associated morbidity), we conducted an additional analysis by decreasing a patient's QoL on the waiting list, using a QoL weight of 0.56.[21]

Model Outcomes

For each scenario, we estimated total costs and quality-adjusted life-years (QALYs) by MELD score, and the incremental cost-effectiveness ratio (ICER) of accepting any vs only HCV-negative livers. All future costs and QALYs were discounted at 3% per year. We projected outcomes for each UNOS region by adjusting the likelihood of LT and mortality on the waiting list using region-specific transplantation and death rates (Supplementary Table 5). In addition, we incorporated HCV-positive donor organ rates within each region (Supplementary Table 6) and adjusted the likelihood of transplant. Specific details are provided in the Supplementary Methods. A 1-way sensitivity analysis was performed to identify most sensitive model parameters. We also performed additional analyses to evaluate model outcomes under varying assumptions and scenarios, including incorporation of blood type and the Share 35 rule (ie, the UNOS policy that offers livers to both local and regional patients on the waitlist with a MELD score of 35 or higher).

Results

Cost-Effectiveness Analysis

The clinical and economic benefit of accepting any liver was dependent on the MELD scores at which patients were willing to accept an HCV-positive liver. For patients with a MELD score of 22 or higher, accepting any liver vs waiting for only HCV-negative livers was cost effective, with an ICER between $56,100 and $91,700 per additional QALY (Figure 2, Supplementary Table 7). For MELD scores of 18 to 20, even though a willingness to accept an HCV-positive liver was clinically beneficial, the ICER was greater than the commonly accepted willingness-to-pay threshold of $100,000/QALY. For perspective, at the current median MELD score at transplantation in the United States (ie, MELD score of 28), accepting any liver was deemed cost effective, with an ICER of $62,600 per additional QALY.

In patients with a poor quality of life, and low MELD scores that may not reflect disease severity accurately, accepting any liver was clinically beneficial (ie, QALYs were higher, irrespective of MELD score) (Figure 3). The ICER of accepting any liver for these patients ranged from $57,000 to $66,000, below the willingness-to-pay threshold of 100,000/QALY.

Cost-Effectiveness by United Network for Organ Sharing Regions

Results for each individual UNOS region, accounting for differences in HCV-positive donor organ rates as well as regional variations in transplant wait times and waitlist mortalities, showed that at MELD scores of 22 or 24 and higher, accepting any liver was a cost-effective strategy in all regions (Figure 4). In regions 1 to 9 and 11, accepting any liver was cost effective at the median MELD score at transplantation for each given region. In region 10, the median MELD score at transplant was 22, and accepting any liver became a cost-effective strategy at a MELD score of 24.

Sensitivity Analysis

In the accept-any-liver strategy, the highest clinical benefit was observed at a MELD score 28, and the

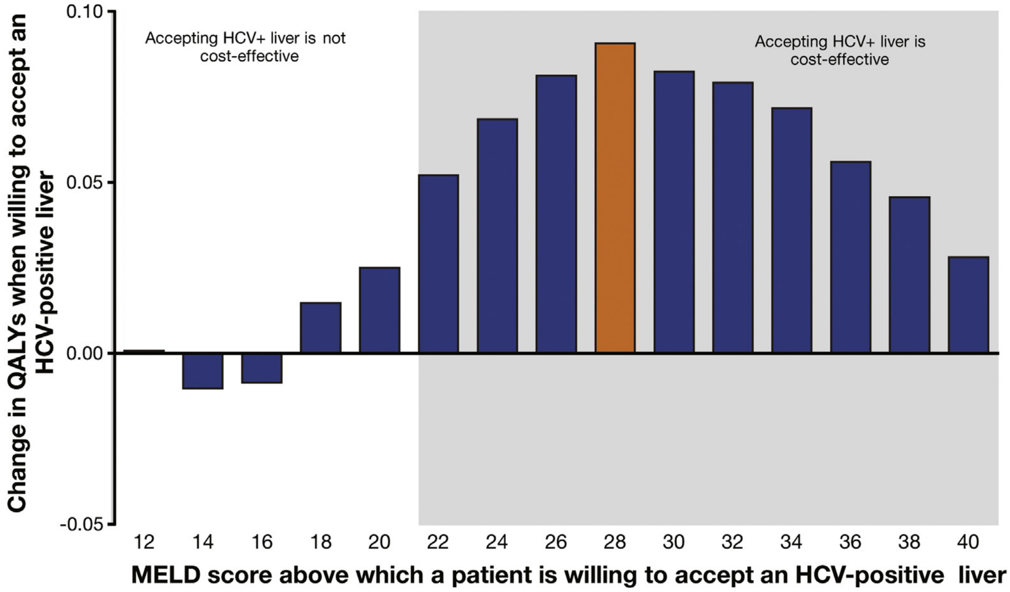


Figure 2. Change in QALYs for patients willing to accept any liver irrespective of HCV status. The shaded area shows where accepting any liver is cost effective. *Orange bar* shows the median MELD score at transplantation in the United States.

strategy was cost effective in patients with a MELD score of 22 or greater. A 1-way sensitivity analysis was performed and the 10 most sensitive model parameters are shown with tornado diagrams (Figure 5). At a MELD score of 28, the model parameters that most influenced the cost effectiveness of accepting any liver were the cost of LT and post-LT care. At a MELD score of 22, the cost of LT, cost of post-LT care, DAA price, and the QoL on the waiting list were sensitive model parameters that could impact cost-effectiveness results. Supplementary Tables 8 and 9 show all model parameters in decreasing order based on their impact on the ICER at MELD scores of 22 and 28.

The cost effectiveness of accepting any liver varied by blood type—for patients with blood types O and A, accepting any liver was cost effective when the MELD score was 22 or higher. It was cost effective for blood type B when the MELD score was 24 or higher, and for blood type AB when the MELD score was 28 or higher (Supplementary Figure 1). The regional Share 35 policy did not change model outcomes—accepting any liver remained cost effective in patients with a MELD score of 22 or greater (Supplementary Figure 2).

The cost of transplant can vary widely between transplant centers and the price of DAAs remains dynamic. We conducted a 2-way sensitivity analysis showing how the cost effectiveness of accepting any liver vs only HCV-negative livers would change with different combinations of DAA price and LT costs. Figure 6 shows these outcomes for MELD scores of 22, 28, and 34. Figure 6 uses the standard cost of LT used in cost-effectiveness analyses, which is different from the billed and reimbursement charges that hospitals and physicians receive for providing transplant care.

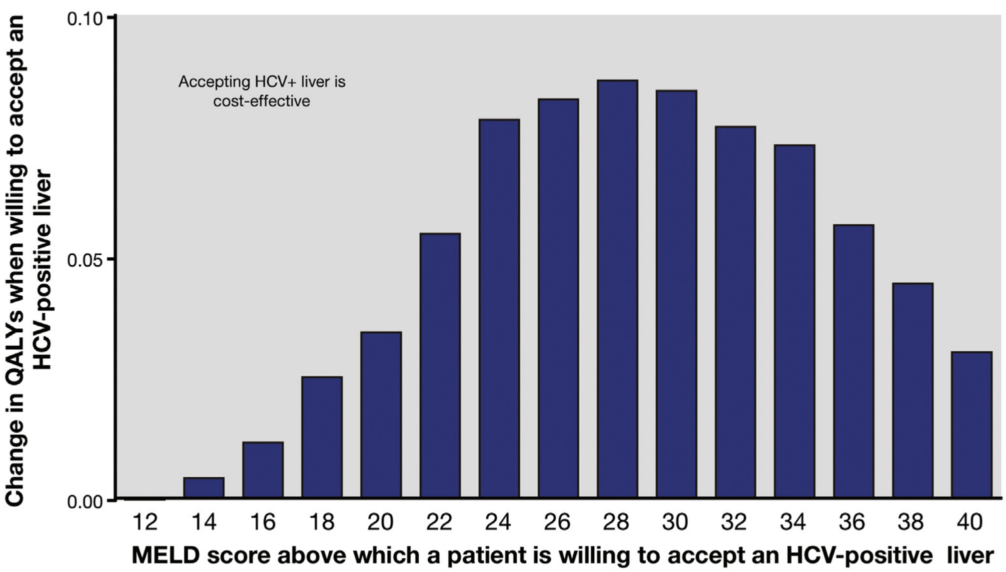


Figure 3. Change in QALYs for patients with a low QoL on the waitlist if they accept any liver vs accept only HCV-negative livers. It is cost effective to accept any liver in patients with a QoL of 0.56, by extension accepting any liver is always cost effective when QoL on the waitlist is 0.56 or less.

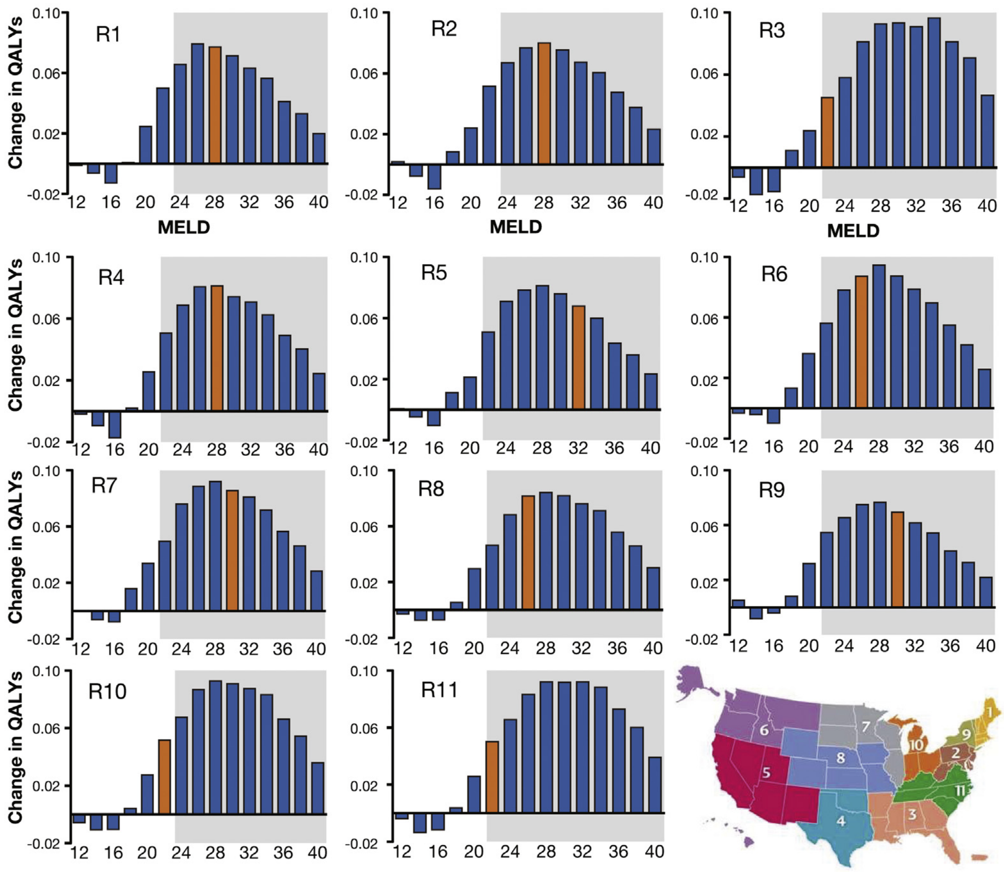


Figure 4. Change in QALYs for patients willing to accept any liver irrespective of HCV status in 11 UNOS regions. *Grey shaded area* shows MELD scores at which accepting any liver is cost effective. *Orange bars* show the median MELD score at transplantation within a given region. The map shows the 11 UNOS regions.

A threshold analysis on the efficacy of preemptive DAA treatment showed that our model outcome (ie, accepting any liver) is cost effective when SVR rates remain greater than 75% (Supplementary Figure 3).

Discussion

DAAs have provided us the opportunity to better utilize HCV-positive donor organs. We now can consider previously discarded HCV-positive livers for active use, expand the historically static liver donor pool, and allocate these viable organs in a manner that maximizes our ability to perform life-saving transplants. Although there are clear potential benefits to accepting HCV-positive organs, concerns surrounding the additional risks, including cost associated with preemptive DAA therapy, could impede clinical implementation. We conducted a model-based analysis to evaluate these trade-offs, and provide publicly available data on the economic impact of this proposed course of action. Our results show that for the median MELD at transplant in the United States, it is not only clinically beneficial but also cost effective for HCV-negative waitlist patients to accept HCV-positive donor livers. As the MELD score increases, it becomes increasingly cost effective to use this strategy, provided DAA efficacy in this setting remains robust.

The increasing cost of health care management has raised concerns regarding the affordability and budget impact of costly treatments. Given that out-of-pocket DAA expense is prohibitively high for the vast majority of patients, payer coverage in this setting will be critical.[22] The cost-effectiveness data provided here can be used to inform policy and support DAA coverage for this new use of therapy, emphasizing that although this strategy will result in an increase in initial spending, it is an advantageous investment that can improve long-term health outcomes.

We recognize that larger studies providing definitive clinical data on DAA efficacy in donor-derived HCV infection are required before the preemptive use of DAAs is accepted as the standard of care and incorporated into transplant guidelines. Encouragingly, smaller studies already are showing promising results, and it is strongly postulated that DAAs will continue to show excellent efficacy for this indication.[23] Furthermore, our threshold analysis showed that preemptive treatment with DAAs remains cost effective until the SVR rate decreases to less than 75%, which is highly unlikely.

Liver transplant waitlist priority is determined based on MELD score, a surrogate for mortality; quality of life is not factored in to national waitlist ranking. This factor impacts model generalizability because our base-case results represent the average waitlist patient without case-specific quality-of-life adjustments. We acknowledge that

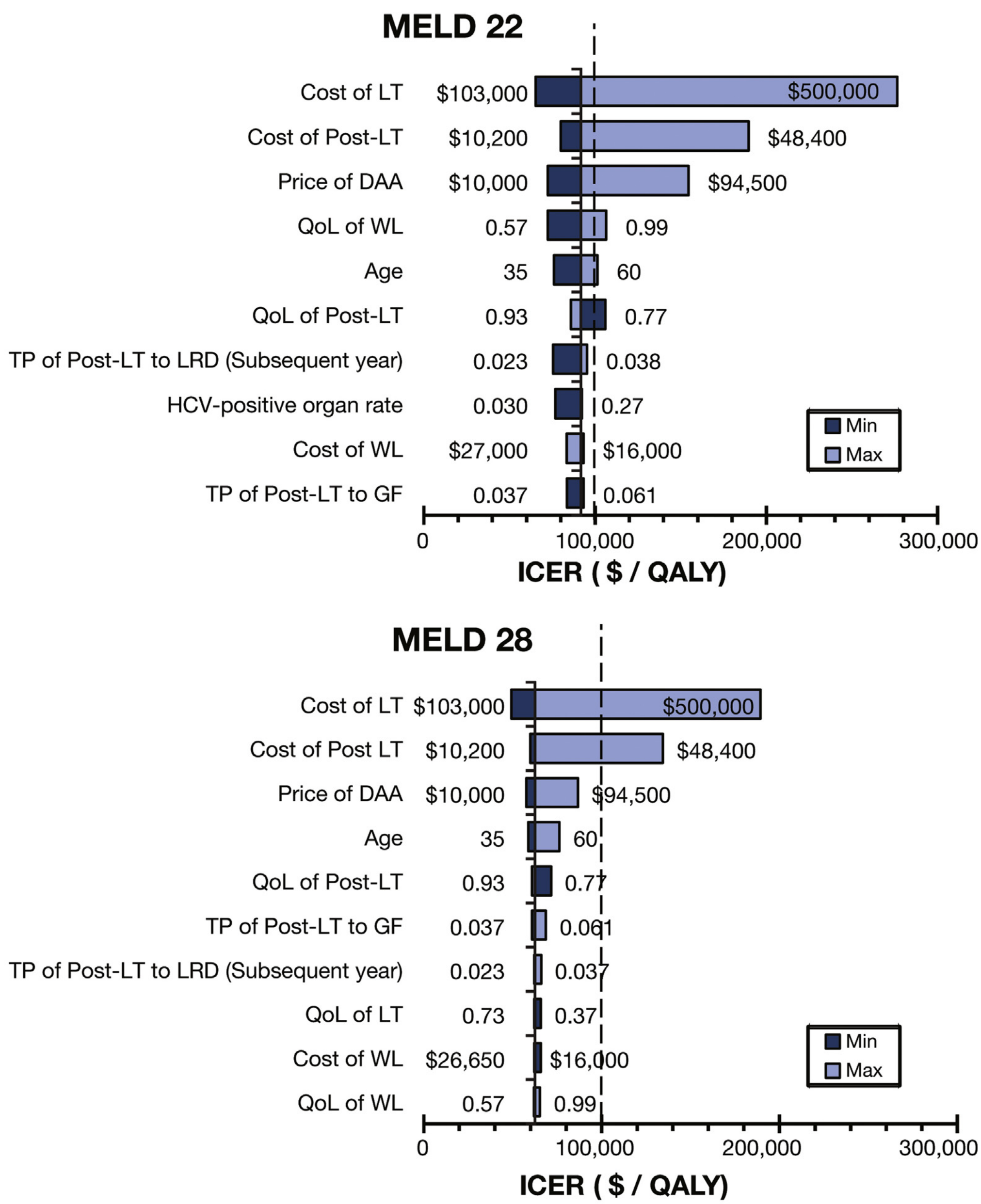


Figure 5. Tornado diagrams showing 10 most sensitive model parameters for MELD scores of 22 and 28. *Dashed line* shows commonly accepted willingness-to-pay threshold. GF, graft failure; LRD, liver-related death; Max, maximum; Min, minimum; WL, waiting list, TP, transition probability.

some of the patients who may benefit most from accepting HCV-positive livers are those with lower MELD scores that do not accurately reflect disease severity (eg, patients with refractory complications of portal hypertension, or recurrent cholangitis, who experience significant morbidity and higher mortality at lower MELD scores than the more general LT waitlist population). Although our primary results suggest accepting an HCV-positive organ is a cost-effective strategy starting at an approximate MELD score of 22, a separate analysis showed how a reduced QoL can make accepting an HCV-positive organ a uniformly cost-effective strategy, irrespective of MELD score. Of note, costs that are accruing for low QoL patients while on the waitlist—hospitalizations, antibiotic courses, large-volume paracentesis procedures—were not factored into the model for this select group of patients, but if incorporated would only further increase the cost effectiveness of accepting HCV-positive organs at lower MELD scores. This highlights the primary take-away from our analysis, which is not a specific MELD threshold at which a patient or provider should consider accepting an HCV-positive organ, but that movement toward routine utilization of HCV-positive livers is a clinically beneficial and cost-effective strategy.

There were limitations to our model predictions. First, outcomes data, including graft failure rates in donor HCV-positive to recipient HCV-negative liver transplant are limited; to obtain a value for model input, survival data were used as a proxy for graft failure.[24] Pretransplant and post-transplant risks, accounting for factors such as steatosis, which can impact allograph function, were included. By using a conservative approach, a likely overestimation of graft failure was incorporated with a high hazard ratio of 1.44, to maintain

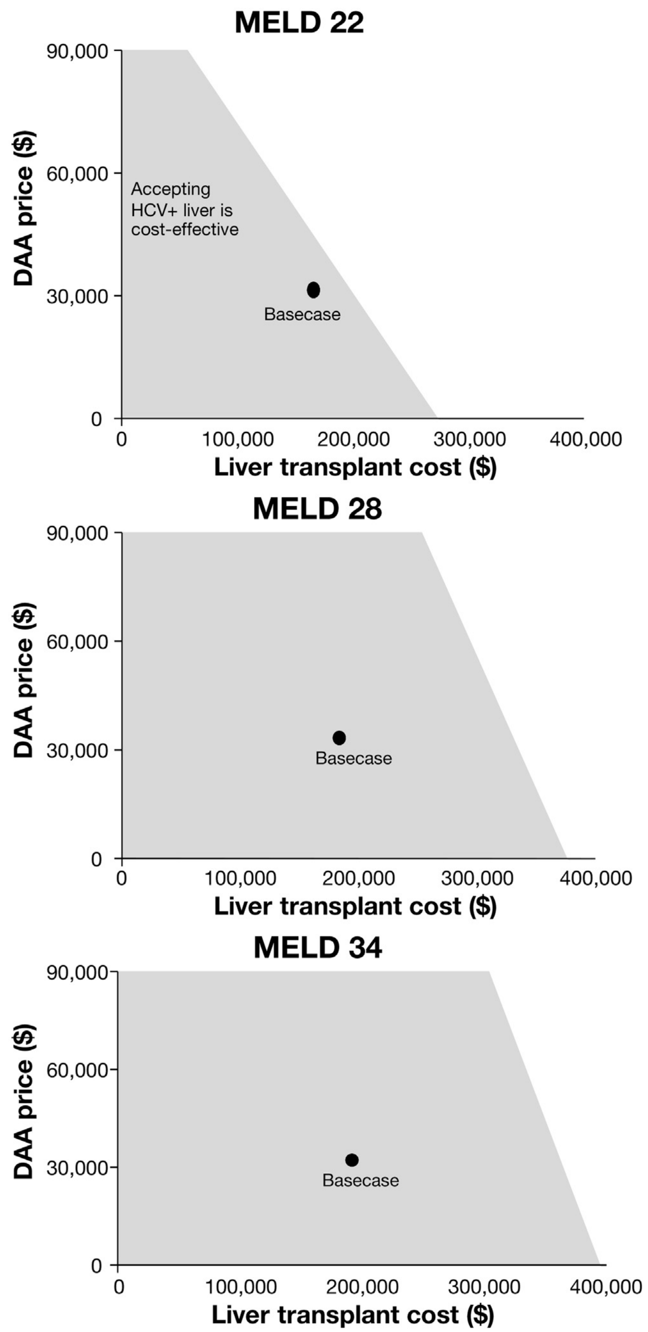


Figure 6. Two-way sensitivity analysis showing the relationship between the cost of LT and the DAA price below which accepting any liver is cost effective at a willingness-to-pay threshold of $100,000 per QALY.

model robustness and ensure the risks associated with receipt of an HCV-positive organ were not minimized. The model did not incorporate risks associated with accepting HCV-positive livers with advancing levels of fibrosis. Second, long-term data on transplant recipients who achieved SVR were extremely limited, and not incorporated in the model. Instead, we assumed that patient and graft survival would be similar to those of HCV-negative LT recipients. Third, our baseline population was HCV-uninfected patients awaiting transplant, we did not extend model outcomes to include HCV-positive waitlist populations. Fourth, HCV-positive region-specific donor organ rates represent both viremic and nonviremic livers; outcome analysis based on specific nucleic acid testing (NAT)-positive and NAT-negative rates were not performed. Fifth, providing donor organs to an increasing number of patients may have secondary effects on general waitlist mortality, this was not incorporated into the model given the lack of data. Sixth, donor age has an impact on long-term post-transplant survival, with recipients of younger donors experiencing better long-term outcomes.[25] Individual donor age was not factored into the current model, however, if incorporated it would further support the use of viremic organs. Our model did not include patients with hepatocellular carcinoma because these patients have a different natural disease history and require evaluation in a separate analysis.

Our current model evaluates preemptive DAA therapy, an approach that is likely to be uniformly agreed upon in NAT-positive donor organs showing a universal rate of HCV transmission. The timing of DAA initiation in nonviremic, NAT-negative, donor organs may present an additional challenge.[22] A recent study found the risk of HCV transmission from seropositive, nonviremic donors to be 16%, with the highest risk conferred by donors who died of a drug overdose.[26] As opposed to preemptive therapy, there are potential cost-saving benefits to a reactive approach to DAA initiation in nonviremic donors. However, until additional studies can further evaluate the clinical outcomes associated with these high-risk organs, administration of preemptive therapy irrespective of NAT status is likely to minimize patient harm.

In conclusion, we found that preemptive DAA therapy in donor HCV-positive to recipient HCV-negative liver transplant is a cost-effective strategy that can improve health outcomes.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.08.042.

References

1. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2015 annual data report: liver. Am J Transplant 2017;17(Suppl 1):174–251.
2. Levitsky J, Formica RN, Bloom RD, et al. The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation. Am J Transplant 2017;17:2790–2802.
3. Pais R, Barritt ASt, Calmus Y, et al. NAFLD and liver transplantation: current burden and expected challenges. J Hepatol 2016;65:1245–1257.
4. Kwong A, Kim WR, Mannalithara A, et al. Decreasing mortality and disease severity in hepatitis C patients awaiting liver

transplantation in the United States. Liver Transpl 2018;24:735–743.
5. Berenguer M. Treatment of hepatitis C after liver transplantation. Clin Liver Dis 2005;9:579–600, vi.
6. Berenguer M, Palau A, Aguilera V, et al. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant 2008;8:679–687.
7. Shah AP, Cameron A, Singh P, et al. Successful treatment of donor-derived hepatitis C viral infection in three transplant recipients from a donor at increased risk for bloodborne pathogens. Transpl Infect Dis 2017;19.
8. Khan B, Singer LG, Lilly LB, et al. successful lung transplantation from hepatitis C positive donor to seronegative recipient. Am J Transplant 2017;17:1129–1131.
9. Saberi B, Hamilton JP, Durand CM, et al. Utilization of hepatitis C virus RNA–positive donor liver for transplant to hepatitis C virus RNA–negative recipient. Liver Transplantation 2018;24:140–143.
10. Chhatwal J, Samur S, Bethea ED, et al. Transplanting HCV-positive livers into HCV-negative patients with preemptive antiviral treatment: a modeling study. Hepatology 2018;67:2085–2095.
11. Bowring MG, Kucirka LM, Massie AB, et al. Changes in utilization and discard of hepatitis C-infected donor livers in the recent era. Am J Transplant 2017;17:519–527.
12. Chhatwal J, Samur S, Kues B, et al. Optimal timing of hepatitis C treatment for patients on the liver transplant waiting list. Hepatology 2017;65:777–788.
13. Samur S, Kues B, Ayer T, et al. Cost effectiveness of pre–vs post–liver transplant hepatitis C treatment with direct-acting antivirals. Clin Gastroenterol Hepatol 2018;16:115–122. e10.
14. Massie AB, Caffo B, Gentry SE, et al. MELD exceptions and rates of waiting list outcomes. Am J Transplant 2011;11:2362–2371.
15. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. Available from: http://www.hcvguidelines.org. Accessed April 25, 2018.
16. Liver Kaplan-Meier Patient Survival Rates For Transplants Performed. Based on OPTN data as of January 27, 2018. Available from: http://optn.transplant.hrsa.gov.
17. Gonzalez SA, Trotter JF. The rise of the opioid epidemic and hepatitis C positive organs: a new era in liver transplantation. Hepatology 2018;67:1600–1608.
18. Saab S, Hunt DR, Stone MA, et al. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transpl 2010;16:748–759.
19. McAdam-Marx C, McGarry LJ, Hane CA, et al. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm 2011;17:531–546.
20. RedBook 2018. Accessed from IBM Micromedex (https://www.micromedexsolutions.com). Accessed: November 26, 2018.
21. Younossi ZM, Boparai N, McCormick M, et al. Assessment of utilities and health-related quality of life in patients with chronic liver disease. Am J Gastroenterol 2001;96:579.
22. Verna EC, Goldberg DS. Hepatitis C viremic donors for hepatitis C nonviremic liver transplant recipients: ready for prime time? Liver Transpl 2018;24:12–14.
23. Kling CE, Limaye AP, Landis CS, et al. Expanding access to transplantation with hepatitis C-positive donors: a new perspective on an old issue. Clin Transplant 2017;31.
24. Cholankeril G. The use of HCV positive donors in HCV negative liver transplant recipients. AASLD Liver Meeting 2016, Abstract ID: 1630.
25. Lue A, Solanas E, Baptista P, et al. How important is donor age in liver transplantation? World J Gastroenterol 2016;22:4966–4976.
26. Bari K, Luckett K, Kaiser T, et al. Hepatitis C transmission from seropositive, non-viremic donors to non-hepatitis C liver transplant recipients. Hepatology 2018;67:1673–1682.

Reprint requests
Address requests for reprints to: Jagpreet Chhatwal, PhD, Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimac Street, 10th Floor, Boston, Massachusetts 02114. e-mail: JagChhatwal@mgh.harvard.edu; fax: (617) 726-9414.

Conflicts of interest
These authors disclose the following: Raymond T. Chung has received grant support from Gilead, AbbVie, Merck, and Janssen; Fasiha Kanwal has received grant support from Merck and Gilead; Turgay Ayer has received grant support from Merck and Gilead; Norah Terrault has received grant support from Gilead, Merck, BMS, and AbbVie; Chin Hur consults for Novo Nordisk; and Jagpreet Chhatwal consults for and has received grants from Merck and Gilead. The remaining authors disclose no conflicts.

Funding
This study was supported in part by research scholar grant RSG-17-022-01-CPPB from the American Cancer Society; Health Resources and Services Administration contract 234-2005-37011C; National Institutes of Health grant DK078772; National Science Foundation award 1722665; and the Massachusetts General Hospital Research Scholars Program. Also supported in part by the Veterans Affairs Health Services Research and Development Service Center for Innovations in Quality, Effectiveness and Safety (CIN 13-413) and Public Health Service grant P30DK05633 (F.K.), and in part by the National Science Foundation award 1452999 (T.A.). The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the sponsors.

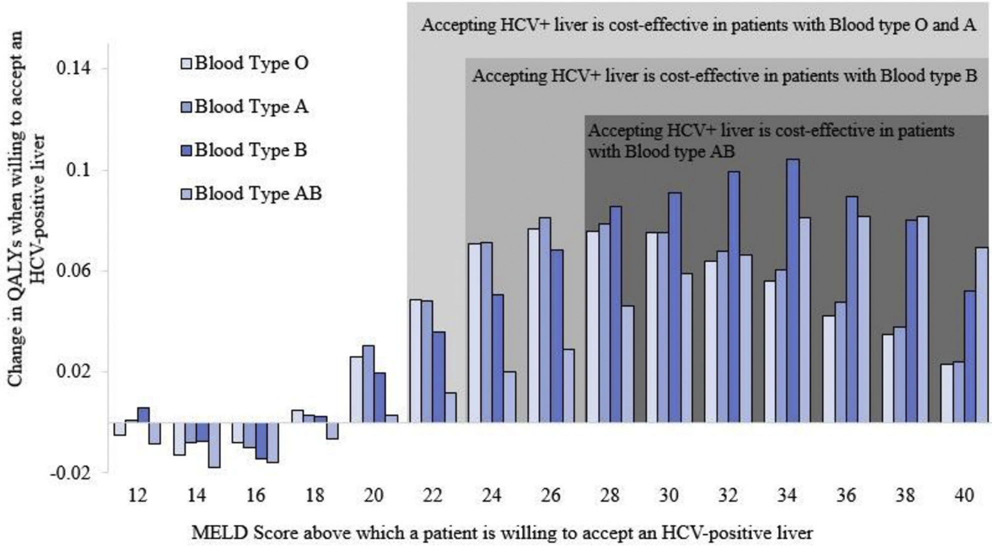
Supplementary Methods

Transplant Rate and Mortality by United Network for Organ Sharing Region

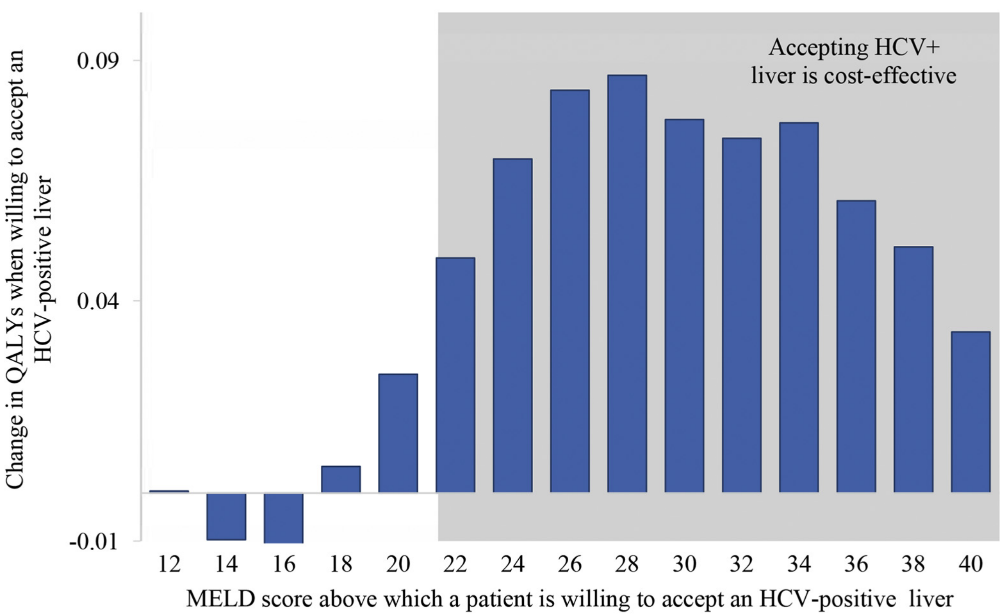
We used UNOS-reported transplantation and death rates for each region to adjust the probability of receiving an LT and the probability of death on the waiting list. Specifically, we estimated the ratio of the observed transplant rate of each region and the overall rate in the United States. Using the ratio, we estimated region-specific rates as follows: region-specific probability $= 1 - (1 - \text{national probability})^{\text{ratio}}$.

Supplementary References

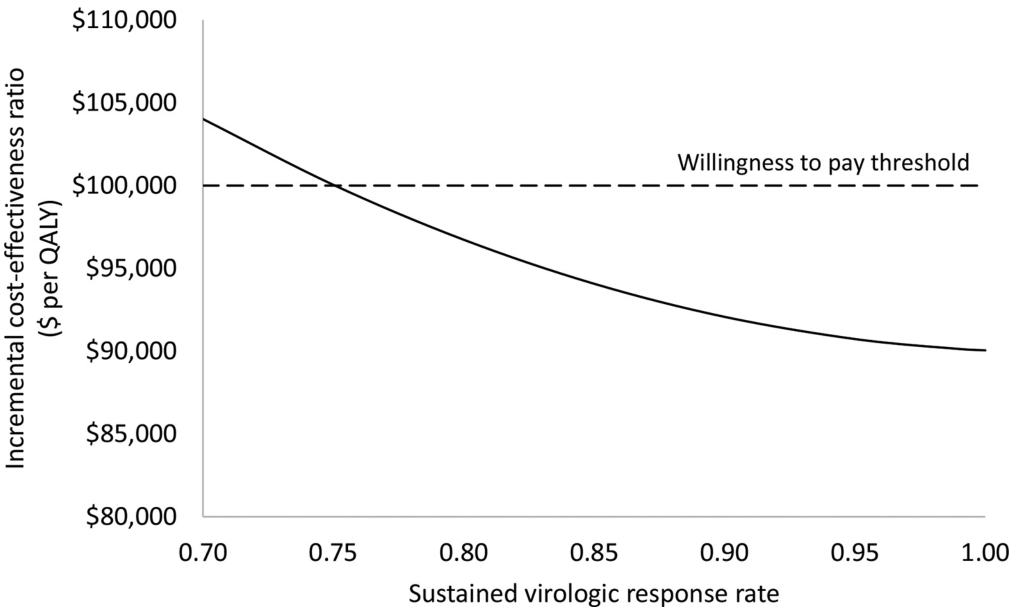
1. Alagoz O, Maillart LM, Schaefer AJ, et al. The optimal timing of living-donor liver transplantation. Manage Sci 2004; 50:1420–1430.
2. Massie AB, Caffo B, Gentry SE, et al. MELD exceptions and rates of waiting list outcomes. Am J Transplant 2011; 11:2362–2371.
3. Reau N, Kwo PY, Rhee S, et al. MAGELLAN-2: safety and efficacy of glecaprevir/pibrentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1-6 infection. J Hepatol 2017; 66:S90–S91.
4. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649–659.
5. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16:685–697.
6. Gane E, Manns M, McCaughan G, et al. Ledipasvir/sofosbuvir with ribavirin in patients with decompensated cirrhosis or liver transplantation and HCV infection: SOLAR-1 and -2 trials. AASLD Liver Meeting 2015, Abstract ID: 1049.
7. Levitsky J, Verna EC, O'Leary JG, et al. Perioperative ledipasvir–sofosbuvir for HCV in liver-transplant recipients. N Engl J Med 2016;375:2106–2108.
8. Liver Kaplan-Meier Patient Survival Rates For Transplants Performed OPTN data. Available from: http://optn.transplant.hrsa.gov. Accessed January 27, 2018.
9. Berenguer M, Prieto M, San Juan F, et al. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. Hepatology 2002; 36:202–210.
10. Berenguer M, Prieto M, Rayon JM, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology 2000;32:852–858.
11. Samuel D, Feray C. Recurrent hepatitis C after liver transplantation: clinical and therapeutical issues. J Viral Hepat 2000; 7:87–92.
12. Cholankeril G. The use of HCV positive donors in HCV negative liver transplant recipients. AASLD Liver Meeting, Abstract ID: 1630 2016.
13. Chong CA, Gulamhussein A, Heathcote EJ, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol 2003;98:630–638.
14. Chhatwal J, Kanwal F, Roberts MS, et al. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med 2015; 162:397–406.
15. Thompson Coon J, Rogers G, Hewson P, et al. Surveillance of cirrhosis for hepatocellular carcinoma: a cost-utility analysis. Br J Cancer 2008;98:1166–1175.
16. Chhatwal J, Ferrante SA, Brass C, et al. Cost-effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 Infection in the United States. Value Health 2013; 16:973–986.
17. RedBook Online 2014. Available from: http://www.redbook.com/redbook/online/. Accessed November 10, 2015.
18. McAdam-Marx C, McGarry LJ, Hane CA, et al. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm 2011;17:531–546.
19. Saab S, Hunt DR, Stone MA, et al. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transpl 2010;16:748–759.
20. Northup PG, Abecassis MM, Englesbe MJ, et al. Addition of adult-to-adult living donation to liver transplant programs improves survival but at an increased cost(-). Liver Transplant 2009;15:148–162.
21. Hanmer J, Lawrence WF, Anderson JP, et al. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making 2006;26:391–400.
22. Edwards EB, Harper AM, Hirose R, et al. The impact of broader regional sharing of livers: 2-year results of "Share 35." Liver Transplant 2016;22:399–409.



Supplementary Figure 1. Change in QALYs if patients accept any liver vs accepting only HCV-negative livers by different blood types. *Shaded areas* show the cost effectiveness of accepting any liver for each blood type. Accepting any liver is always cost effective in patients with a MELD score of 28 or higher (ie, regardless of the blood type).



Supplementary Figure 2. Change in QALYs if patients accept any liver vs accepting only HCV-negative livers when the Regional Share 35 policy is incorporated. Analysis of model outcomes to incorporate the Regional Share 35 policy involved increasing the transplant rates in patients with a MELD score of 35 or higher by 11.8% and decreasing the rates in patients with a MELD score less than 35.[22] Regional Share 35 did not have an impact on the cost-effectiveness results (ie, willing to accept any liver still was cost effective in patients with a MELD score ≥22).



Supplementary Figure 3. Cost effectiveness of accepting an HCV-positive liver based on the efficacy of preemptive treatment with DAAs. Accepting an HCV-positive liver is cost effective as long as the DAA SVR rate is at or above 75%.

Supplementary Table 1. Weekly Waitlist Mortality Based on MELD Score

MELD score	Weekly probability of liver-related death
6–7	0.000014
8–9	0.000697
10–11	0.000691
12–13	0.000022
14–15	0.000681
16–17	0.000235
18–19	0.003659
20–21	0.007021
22–23	0.009891
24–25	0.011323
26–27	0.047260
28–29	0.078599
30–31	0.159678
32–33	0.192294
34–35	0.211013
36–37	0.273120
38–39	0.344884
40	0.481372

Data are from Alagoz et al[1] and UNOS.

Supplementary Table 2. Weekly Likelihood of Liver Transplantation Based on MELD Score

MELD score	Weekly probability of liver transplant
<14	0
14–15	0.008161
16–17	0.012561
18–19	0.026286
20–21	0.036498
22–23	0.052484
24–25	0.066997
26–27	0.078408
28–29	0.082616
30–31	0.084809
32–33	0.087066
34–35	0.084809
36–37	0.068787
38–39	0.066997
40	0.052484

Data from Massie et al.[2]

Supplementary Table 3. List of Model Variables Used in SIM-LT, Base-Case Values, and Minimum and Maximum Values Considered in the Sensitivity Analysis Are Shown

Parameter	Base case	Minimum	Maximum	References
Baseline age, *y*	50	35	65	Assumption
SVR rate				
Preemptive therapy SVR rate	0.950	0.900	0.980	3–7
Salvage therapy SVR rate	0.950	0.900	0.980	Assumption
Transition probabilities (annual)				
LT to liver-related death (1st year of 1st LT)	0.082	0.061	0.102	8
LT to liver-related death (1st year of repeat LT)	0.190	0.142	0.237	8
LT to graft failure (1st year of 1st LT)	0.105	0.079	0.131	8
LT to graft failure (1st year of repeat LT)	0.214	0.160	0.267	8
Post-LT to liver-related death (1st year)[a]	0.074	0.056	0.093	8
Post-LT to liver-related death (subsequent year)[a]	0.030	0.023	0.038	8
Post-LT to graft failure[a]	0.049	0.037	0.062	9
F0–F2 to liver-related death (1st year of 1st LT)	0.082	0.061	0.102	8
F0–F2 to liver-related death (subsequent year of 1st LT)	0.046	0.035	0.058	8
F0–F2 to liver-related death (1st year of repeat LT)	0.190	0.142	0.238	8
F0–F2 to liver-related death (subsequent year of repeat LT)	0.053	0.040	0.067	8
F3–F4 to liver-related death (1st year of 1st LT)	0.082	0.061	0.102	8
F3–F4 to liver-related death (subsequent year of 1st LT)	0.046	0.035	0.058	8
F3–F4 to liver-related death (1st year of repeat LT)	0.190	0.142	0.237	8
F3–F4 to liver-related death (subsequent year of repeat LT)	0.053	0.040	0.066	8
F0–F2 to graft failure (1st year of 1st LT)	0.105	0.079	0.131	8
F0–F2 to graft failure (1st year of repeat LT)	0.214	0.160	0.267	8
F3–F4 to graft failure (1st year of 1st LT)	0.194	0.145	0.242	10
F3–F4 to graft failure (1st year of repeat LT)	0.214	0.192	0.237	8
F0–F2 to graft failure (subsequent year of 1st LT)	0.050	0.038	0.063	8
F0–F2 to graft failure (subsequent year of repeat LT)	0.059	0.044	0.073	8
F3–F4 to graft failure (subsequent year of 1st LT)	0.050	0.038	0.063	8
F3–F4 to graft failure (subsequent year of repeat LT)	0.059	0.044	0.073	8
Graft failure to liver-related death	0.652	0.489	0.815	UNOS data
Graft failure to repeat transplant	0.805	0.604	1.000	UNOS data
F0–F2 to F3–F4	0.200	0.150	0.250	11
HCV-positive organ rate	0.059	0.029	0.267	8
Hazard ratio for increased graft failure	1.44	1.08	1.80	12
Health-related QoL weights				
Transplant waiting list	0.800	0.570	0.990	13,14
LT	0.600	0.370	0.730	15
F0–F2	0.828	0.716	0.865	14,15
F3–F4	0.801	0.693	0.837	14,15
Post-LT	0.890	0.770	0.930	15
Virus-free post-LT	0.890	0.770	0.930	15
Graft failure	0.800	0.570	0.990	13,16
Costs, $				
12-week HCV treatment	30,450	10,000	94,500	17
Wait list (annual)	21,300	16,000	26,650	18
LT-1st year (annual)	184,400	103,000	500,000	19,20
Post-LT (annual)	13,600	10,200	48,400	20

[a]Post-LT probabilities correspond to those in post-LT (nonviremic) and post-LT (SVR) stages in the model.

Supplementary Table 4. Health-Related Quality-of-Life Utilities of the US Population

Age group	Male	Female
20–29	0.928	0.913
30–39	0.918	0.893
40–49	0.887	0.863
50–59	0.861	0.837
60–69	0.84	0.811
70–79	0.802	0.771
80–89	0.782	0.724

Data from Hanmer et al.[21]

Supplementary Table 6. HCV-Positive Organ Rate by UNOS Regions

UNOS region	HCV-positive organ rate
Region 1	0.129
Region 2	0.106
Region 3	0.055
Region 4	0.037
Region 5	0.040
Region 6	0.029
Region 7	0.028
Region 8	0.047
Region 9	0.051
Region 10	0.088
Region 11	0.057
National	0.059

NOTE. We incorporated the increased likelihood of graft failure in patients who received infected livers. We assumed these patients could experience a higher probability of graft failure within the first 3 months of LT. We specifically increased the probability of experiencing graft failure by a hazard ratio of 1.44 (range, 1.08–1.80)[12] with the following formula: adjusted graft failure probability $= 1 - (1 - \text{graft failure probability})^{\text{hazard ratio}}$.
Data are from UNOS.[8]

Supplementary Table 5. Transplantation and Death Ratios by UNOS Regions

Region	Transplantations, rate per 100 person-years	Ratio, region/US	Deaths, rate per 100 person-years	Ratio, region/US
1	30.5	0.709	19	1.061
2	34	0.791	18.4	1.028
3	110.2	2.563	20.1	1.123
4	29.8	0.693	15.9	0.888
5	28.7	0.667	16.9	0.944
6	50.5	1.174	21.3	1.190
7	47.8	1.112	19.2	1.073
8	37.9	0.881	16	0.894
9	26.4	0.614	17.2	0.961
10	68.8	1.600	20	1.117
11	76.9	1.788	18.9	1.056
US	43.0		17.9	

NOTE. We further accounted for the HCV-positive donor organ rates to adjust the transplant rate within the region. Specifically, we used the following formula: adjusted transplant probability $= 1 - (1 - \text{region-specific transplant probability})^{(1 + \text{HCV-positive organ rate})}$.

Supplementary Table 7. Cost Effectiveness of Accepting Any Liver Vs Accepting Only HCV-Negative Liver by MELD Score

	QALY		Cost		
MELD score	Accept only HCV-negative liver	Accept any liver	Accept only HCV-negative liver	Accept any liver	ICER
12	9.349	9.349	$323,675	$324,032	Dominated[a]
14	8.862	8.851	$326,490	$327,315	Dominated[a]
16	8.249	8.241	$338,081	$339,983	Dominated[a]
18	7.355	7.370	$328,309	$331,388	$209,440
20	6.769	6.794	$319,639	$323,313	$146,960
22	6.271	6.323	$303,147	$307,926	$91,732
24	5.714	5.783	$281,885	$287,162	$77,083
26	4.685	4.767	$232,742	$238,292	$68,307
28	3.769	3.859	$187,605	$193,277	$62,569
30	2.840	2.922	$141,629	$146,648	$60,905
32	2.248	2.328	$112,300	$116,952	$58,737
34	1.832	1.904	$91,544	$95,718	$58,217
36	1.307	1.363	$65,193	$68,468	$58,426
38	1.009	1.055	$50,365	$52,946	$56,536
40	0.617	0.645	$30,693	$32,269	$56,095

[a]Accept any liver strategy dominated (ie, it resulted in lower QALYs at higher costs compared with accepting HCV-negative livers only).

Supplementary Table 8. One-Way Sensitivity Analysis Showing Model Parameters in a Decreasing Order Based on Their Impact on ICER at a MELD Score of 22

Parameter	Change in ICER ($) when the parameter has its Minimum value	Maximum value
Base case	91,732	
Cost of LT	65,290	276,488
Cost of post-LT stages	80,069	165,591
Price of DAA	72,453	154,611
QoL of post-LT[a]	72,478	106,518
Waiting list mortality[b]	114,446	86,139
Age	76,092	101,386
QoL of LT	106,033	85,983
Post-LT to LRD (subsequent year)[a]	75,573	95,263
HCV-positive organ rate	76,797	92,398
Cost of WL	93,256	83,368
TP: post-LT to GF[a]	83,684	93,366
HR of graft failure	82,770	92,148
TP: GF to death	83,905	92,856
TP: GF to LT	85,906	93,695
QoL of F0–F2	92,108	84,497
TP: post-LT viremic to GF (1st year)[c]	85,014	91,731
Post-LT to LRD (1st year)[a]	86,435	92,957
Waiting list transplant probability[b]	91,312	97,445
SVR rate of salvage therapy	92,410	87,393
TP: post-LT viremic to LRD (subsequent year of repeat LT)[c]	91,771	87,630
TP: post-LT viremic to GF (subsequent year of repeat LT)[c]	91,822	88,412
TP: post-LT viremic to LRD (1st year of 1st LT)[c]	94,386	91,076
TP: F3–F4 to GF (1st year)	91,884	88,626
QoL of F3–F4	91,846	88,648
TP: F0–F2 to F3–F4	88,643	91,777
SVR rate of preemptive therapy	91,666	94,370
TP: post-LT viremic to LRD (subsequent year of 1st LT)[c]	91,896	89,209
TP: post-LT viremic to LRD (1st year of repeat LT)[c]	89,642	91,819
QoL of GF	91,811	89,796
TP: post-LT viremic to GF (subsequent year of 1st LT)[c]	92,476	90,716
TP: post-LT viremic to GF (1st year of repeat LT)[c]	91,815	90,344
QoL of WL	91,740	91,108

GF, graft failure; HR, hazard ratio; LRD, liver-related death; TP, transition probability.
[a]Post-LT corresponds to post-LT (nonviremic) and post-LT (SVR) stages in the model.
[b]Parameters with a value by each MELD score. Basically, we used ±25% change from baseline values.
[c]Post-LT viremic corresponded to stages including salvage therapy, F0–F2, and F3–F4 in the HCV-positive arm in the model.

Supplementary Table 9. One-Way Sensitivity Analysis Showing Model Parameters in a Decreasing Order Based on Their Impact on ICER at a MELD Score of 28

Parameter	Change in ICER ($) when the parameter has its Minimum value	Maximum value
Base case	62,569	
Cost of LT	49,204	189,356
Cost of post-LT stages	59,920	111,370
Price of DAA	57,667	86,666
Age	58,822	76,279
QoL of post-LT[a]	71,617	60,821
TP: post-LT to GF[a]	60,867	68,629
Post-LT to LRD (subsequent year)[a]	62,161	66,024
QoL of LT	65,846	62,094
Cost of WL	65,815	62,163
QoL of WL	62,014	65,365
HCV-positive organ rate	62,491	65,392
HR of graft failure	61,459	64,329
Waiting list mortality[b]	68,365	65,946
Post-LT to LRD (1st year)[a]	64,745	62,388
TP: F3–F4 to GF (1st year)	62,521	64,721
TP: post-LT viremic to GF (subsequent year of repeat LT)[c]	62,207	64,352
SVR rate of preemptive therapy	62,411	64,452
TP: post-LT viremic to LRD (1st year of repeat LT)[c]	64,385	62,413
TP: post-LT viremic to LRD (subsequent year of repeat LT)[c]	62,185	64,048
TP: post-LT viremic to GF (1st year of repeat LT)[c]	62,515	64,004
QoL of F3–F4	62,427	63,747
Waiting list transplant probability[b]	61,687	62,809
QoL of GF	62,507	63,599
TP: post-LT viremic to GF (1st year)[c]	62,985	62,135
QoL of F0–F2	62,060	62,707
TP: post-LT viremic to LRD (subsequent year of 1st LT)[c]	62,626	62,005
TP: post-LT viremic to GF (subsequent year of 1st LT)[c]	62,014	62,600
TP: F0–F2 to F3–F4	62,977	62,397
TP: post-LT viremic to LRD (1st year of 1st LT)[c]	62,416	62,878
TP: GF to death	62,539	62,936
TP: GF to LT	62,360	62,571
SVR rate of salvage therapy	62,571	62,491

GF, graft failure; HR, hazard ratio; LRD, liver-related death; TP, transition probability.
[a]Post-LT corresponds to post-LT (nonviremic) and post-LT (SVR) stages in the model.
[b]Parameters having a value by each MELD score. Basically, we used ±25% change from baseline values.
[c]Post-LT viremic correspond to stages including salvage therapy, F0–F2, and F3–F4 in HCV-positive arm in the model.