

One-Year Outcomes of the Multi-Center Study to Transplant Hepatitis C-Infected kidneys (MYTHIC) Trial



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Introduction: Transplanting kidneys from hepatitis C virus (HCV) viremic donors into HCV-negative patients (HCV D-RNA-positive/R-negative) has evolved from experimental to “standard-of-care” at many centers. Nevertheless, most data derive from single centers and provide only short-term follow-up.

Methods: The Multicenter Study to Transplant Hepatitis C-Infected Kidneys (MYTHIC) study was a multicenter (7 sites) trial of HCV D-RNA-positive/R-negative kidney transplantation (KT) followed by 8 weeks of glecaprevir/pibrentasvir (G/P) initiated 2 to 5 days post-KT. Prespecified outcomes included probability of KT (vs. matched waitlist comparators) and 1-year safety outcomes, allograft function, and survival.

Results: Among 63 enrolled patients, 1-year cumulative incidence of KT was approximately 3.5-fold greater for the MYTHIC cohort versus 2055 matched United Network for Organ Sharing (UNOS) comparators who did not opt-in to receive a kidney from an HCV-viremic donor (68% vs. 19%, $P < 0.0001$). Of 30 HCV D-RNA-positive/R-negative KT recipients, all achieved HCV cure. None developed clinically significant liver disease or HCV-related kidney injury. Furthermore, 1-year survival was 93% and 1-year graft function was excellent (median creatinine 1.17; interquartile range [IQR]: 1.02–1.38 mg/dl). There were 4 cases of cytomegalovirus (CMV) disease among 10 CMV-negative patients transplanted with a kidney from an HCV-viremic/CMV-positive donor.

Conclusion: The 1-year findings from this multicenter trial suggest that opting-in for HCV-viremic KT offers can increase probability of KT with excellent 1-year outcomes. Trial Registration: NCT03781726

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KEYWORDS: cytomegalovirus infection; direct-acting antivirals; glecaprevir/pibrentasvir; hepatitis C virus; kidney transplantation; organ allocation

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The advent of direct-acting antivirals (DAAs) has transformed HCV into a curable infection. Owing to the opioid epidemic, the number of HCV-infected deceased donors has increased by an estimated 1000 additional annual donors.^{1,2} DAAs generated interest in transplanting HCV-viremic organs into HCV-negative patients followed by DAA treatment.^{2–9} Excellent HCV cure rates and good short-term allograft function among KT recipients from HCV-viremic donors into HCV-negative recipients (herein referred to as HCV D-RNA-positive/R-negative) have been reported.^{4,6,10–12} Nevertheless, determining clinical outcomes beyond HCV cure is an important next step for informed consent, and management of future transplant candidates offered this transplant option.²

Some studies involving HCV D-RNA-positive/R-negative KT recipients have reported high rates of complications, including polyomavirus (BK virus [BKV]) and CMV infection.^{10,13,14} Notably, CMV infection exists across a spectrum of severity, and determination of CMV disease requires expert adjudication. In addition, HCV has been associated with an increased risk for infrequent but potentially significant immune-related complications in KT recipients.¹⁵ Before the DAAs, KT recipients with HCV infection experienced elevated rates of acute transplant glomerulopathy and acute and chronic vascular rejection.^{15–17} Thus, there is a need for more detailed data on the risk of immunologic and infectious complications among HCV D-RNA-positive/R-negative KT recipients.

Here, we report the 1-year outcomes from the MYTHIC trial. Preliminary results for the 30 HCV D-RNA-positive/R-negative KT recipients were previously published and revealed safety and efficacy (100% cure) of an 8-week course of G/P initiated in the early post-transplant period.⁵ In this follow-up study, we aimed to evaluate the probability of receiving a KT between patients enrolled in MYTHIC versus matched comparators from UNOS, and we report the 1-year clinical outcomes among MYTHIC KT recipients, including allograft rejection and function, HCV antibody status, CMV, and BKV infections.

METHODS

Study Design and Participants

MYTHIC (NCT03781726) was an open-label clinical trial. The Institutional Review Boards at the 7 clinical sites approved the protocol. The sites conducted the MYTHIC protocol and followed the International Conference on Harmonization guidelines and the ethical principles that have their origin in the Declaration of Helsinki. Progress was monitored by an external data safety and monitoring board. Before obtaining consent,

all patients attended an informational session on HCV and KT. A study investigator answered questions and obtained written informed consent before commencing study-related procedures.

A total of 30 patients underwent HCV D-RNA-positive/R-negative KT and began 8 weeks of oral G/P between days 2 and 5 post-KT. The remaining patients either received a KT from an HCV antibody-positive/RNA-negative donor, received a transplant per usual care, or remained on the waitlist. HCV D-RNA-positive/R-negative KT recipients occurred between April 2019 and October 2019. HCV antibody-positive/RNA-negative donor transplants occurred between September 2019 and January 2020. All patients were followed for 1 year after consent or 1 year after KT; the last follow-up visit took place in January 2021. [Supplementary Methods S1](#) reveal the full inclusion/exclusion criteria.⁵ We included patients aged 21 to 65 years who were on dialysis or had an estimated glomerular filtration rate <15 ml/min per 1.73 m². We excluded patients with positive test results for HIV, hepatitis B virus, or known liver disease. All candidates were assessed for liver fibrosis and excluded when liver stiffness >8 kPa by Fibroscan. Donors had a kidney donor profile index (KDPI) at allocation ≤85%.

All MYTHIC KT recipients received induction and maintenance immunosuppression and antiviral prophylaxis following that center's standard-of-care. [Supplementary Table S1](#) reveals the study visit schedule.

Trial Outcomes

The primary outcome was HCV cure, defined as undetectable plasma HCV RNA 12 weeks after completion of G/P (sustained virologic response at 12 weeks).⁵ The primary analyses for this 1-year study were a comparison of the probability of transplant for the 63 participants who were enrolled in the MYTHIC trial versus matched comparators and 1-year post-KT outcomes of the 30 HCV D-RNA-positive/R-negative transplants, including severe adverse events, liver function, BKV and CMV viremia and clinical disease, allograft rejection, allograft function (estimated glomerular filtration rate and proteinuria), HCV RNA level 24 weeks after G/P completion, HCV antibody status, and survival.

Screening for BKV and testing for CMV followed each site's standard-of-care ([Supplementary Tables S2 and S3](#)). All BKV and CMV blood levels obtained in the 12 months post-KT were recorded. An investigator with expertise in transplant infectious disease (EAB) reviewed primary data for every patient with detectable CMV viremia (plasma or tissue) and adjudicated

each case as having no, probable, or definite CMV disease using standard definitions.^{18–20}

Restriction, Matching, and Statistical Analysis for the Outcome of Time to Transplantation

We compared 1-year probability of any KT between patients enrolled in MYTHIC ($n = 63$ focal patients) and matched waitlisted comparators from the deidentified UNOS registry. In this analysis, we included all the 63 MYTHIC patients who were eligible for KT offers from HCV-viremic donors regardless of whether or not they underwent transplant to evaluate the increased probability of transplant associated with “opting-in” for a HCV-viremic KT. For the comparators, we developed inclusion/exclusion criteria to identify transplant candidates who did not opt-in for HCV-viremic kidney offers but otherwise resembled the criteria for enrollment in MYTHIC. Next, we matched MYTHIC patients to UNOS comparators using characteristics that plausibly affect waitlist mortality and probability of receiving a KT (blood group, waiting time, and center aggressiveness with respect to transplanting deceased donor kidneys). We restricted the population of potential comparators based on the following: waitlisting ages 21 to 65 years from January 1, 2010 to December 31, 2019; transplant naive; panel-reactive antibodies $<80\%$; no history of cancer; and did not consent to KT from an HCV-viremic donor at waitlisting. After applying these criteria, we time-matched each MYTHIC focal patient to UNOS comparators who were (as of follow-up time from waitlisting equal to the index MYTHIC patient’s follow-up time at consent) alive; active on the waitlist; equal with respect to race, diabetes status, blood group, obesity (body mass index >35 kg/m²), dialysis status at waitlisting (on vs. off); were within 2 years of age; were (at waitlisting) within 1 year of the focal patient’s time on dialysis; were listed at a center within the same quintile of standardized transplant ratio (Supplementary Methods S2); and not willing to consider offers from HCV-viremic donors.

In the interests of flexibility, we allowed a variable number of matches per MYTHIC patient. Because the matched sets were of unequal size, we weighted each UNOS comparator by the inverse of the number of matches in the respective set.²¹ The purpose of the weighting was to align the UNOS comparator covariate distribution with that of MYTHIC across matched sets, analogous to 1:1 matching.²²

The event of interest was deceased donor KT, with death as a competing risk. For each of the MYTHIC and UNOS cohorts, we computed 1-year nonparametric cumulative incidence curves based on the weight function in gray.²³ The difference in 1-year cumulative incidence of KT between MYTHIC versus matched

UNOS comparators was tested using a basic Z-statistic (i.e., numerator = difference in 1-year cumulative incidence; denominator = SE of the numerator). A robust (sandwich) variance was used for the SE of the UNOS comparators to account for correlation within matched set.

Patient characteristics are summarized with median and IQR or number (%). We used the 4-variable Modification of Diet in Renal Disease equation to calculate estimated glomerular filtration rate at 12 months.^{24,25} All analyses were carried out using SAS (version 9.4; SAS Institute; Cary, NC).

RESULTS

A total of 76 patients underwent screening; 12 were excluded and 1 was not enrolled owing to study closure. Of the 63 enrolled patients, 30 received HCV D-RNA-positive/R-negative KT, 4 received a KT from an HCV antibody-positive/HCV RNA-negative donor, and 8 received a standard-of-care KT. Among the other 21 patients who consented, 4 were ineligible for study participation and the 17 others remained on the waiting list until the end of follow-up (Supplementary Figure S1).

After restricting based on inclusion/exclusion criteria, there were 202,144 potential comparators in the UNOS database. Table 1 provides the descriptive

Table 1. Demographic and clinical characteristics of patients waitlisted for kidney transplantation who were enrolled in the MYTHIC trial vs. matched comparators

Patient characteristics	Before matching		After matching		Standardized difference [†]
	MYTHIC (n = 63)	UNOS (n = 202,144)	MYTHIC (n = 58)	UNOS (n = 2055)	
Age (mean)	52.2	49.4	52.5	52.5	0.007
% Female	38.1	37.4	37.9	34.5	0.070
% Black	25.4	29.6	27.6	27.6	0
% Hispanic	4.8	20.1	3.4	3.4	0
% Asian	4.8	7.2	1.7	1.7	0
% Blood type A	38.1	32.7	39.7	39.7	0
% Blood type B	19.0	14.8	19.0	19.0	0
% Blood type AB	1.6	3.8	1.7	1.7	0
% Blood type O	41.3	48.7	39.7	39.7	0
% Diabetes	39.7	45.3	37.9	37.9	0
Height	171.1	170.5	171.5	172.0	-0.049
Weight	86.2	85.1	86.8	86.6	0.010
% (BMI > 35)	12.7	16.4	10.3	10.3	0
% Not on dialysis at WL	49.2	25.3	48.3	48.3	0
Yrs on dialysis (at WL)	0.73	1.19	0.61	0.55	0.058

BMI, body mass index; MYTHIC, Multicenter Study to Transplant Hepatitis C-Infected Kidneys; UNOS, United Network for Organ Sharing; WL, waitlist.

[†]Note that the standardized difference is the ratio of the difference in means divided by a pooled estimator of the SD.

statistics for the 63 patients consented for MYTHIC and for comparator waitlisted patients before and after matching (Supplementary Table S4 provides additional data on MYTHIC KT recipients and Supplementary Table S5 reveals donor characteristics including genotype). A sufficiently close match was found for 58 (of 63) MYTHIC patients, with a median of 12 (IQR: 4–46) matches ($n = 2055$ total UNOS comparators selected as matches). After matching, there were no important differences in patient characteristics between the 2 groups using the conventional standardized difference threshold of 0.1 (Table 1).²⁶

Figure 1 displays the cumulative incidence of KT in MYTHIC patients and comparators. The 1-year cumulative probability of any KT (death as a competing risk) was 68% (95% CI: 57%–81%) for the MYTHIC cohort and 19% (14%–27%) for the matched UNOS comparators ($P < 0.001$). The median time from consent to KT was 8.0 weeks (IQR: 2.1–14.6) for the MYTHIC patients compared with 25.4 (IQR: 11.9–38.9) for the matched UNOS comparators.

The median KDPI of the 42 MYTHIC patients undergoing transplant was 51% (IQR: 37%–65%): (i) 30 per protocol HCV-viremic donors: 53% (IQR: 41%–65%); (ii) 4 HCV antibody-positive/RNA-negative donors: 46% (36.5%–62%); (iii) 8 standard-of-care donors: 28% (15%–65%); versus (iv) KTs in UNOS comparator group by 1-year of follow-up: 55% (IQR: 35%–73%). There was no significant difference in the KDPI of the MYTHIC kidney recipients versus transplanted UNOS comparators; however, it is important to note that kidneys from

HCV RNA-positive and/or HCV antibody-positive organs had a substantially worse KDPI score (adding approximately 20–25 percentage points) compared with kidneys from otherwise identical HCV-negative donors.²⁷ HCV-viremic or HCV antibody-positive/RNA-negative donor kidneys transplanted into the MYTHIC recipients would have had a substantially better KDPI if the HCV variable “penalty” was removed. Supplementary Table S5 reveals that MYTHIC recipients of HCV-viremic or HCV antibody-positive/RNA-negative donor transplants received kidneys from younger donors than the comparator group. KDPI scores recalculated as if the donors were HCV-RNA-negative and HCV antibody-negative are found in Supplementary Table S5.

One-Year Outcomes Among MYTHIC Participants

Survival

The 1-year survival was 28 of 30 HCV donor-positive/recipient-negative patients (93%). As reported, 1 patient died of *Staphylococcus aureus* bacteremia and multiorgan failure 9 months post-transplant after developing CMV infection.⁵ A second patient died unexpectedly at home of presumed cardiac cause in the 12th month post-KT, during the COVID-19 pandemic. Both patients had achieved sustained virologic response at 12 weeks, and neither death was deemed related to study participation (both patients had normal liver function at last follow-up). At 1 year, all 28 surviving HCV D-RNA-positive/R-negative patients had well-functioning allografts.

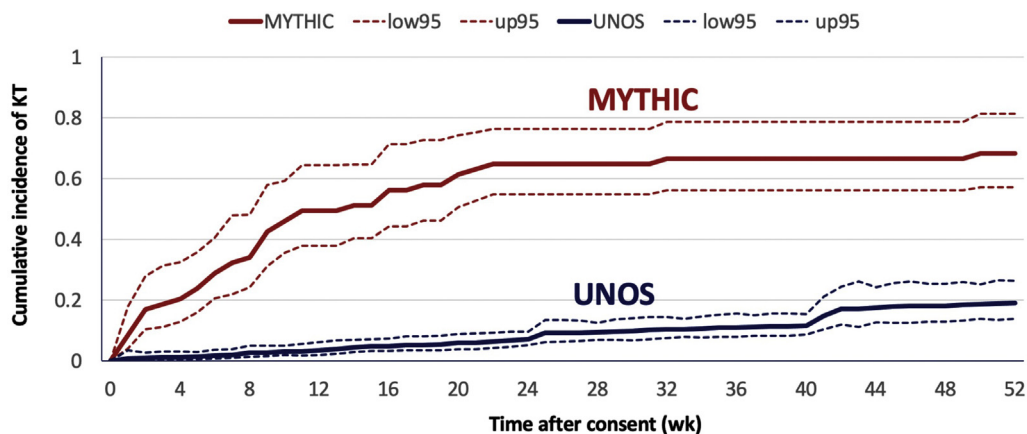


Figure 1. Cumulative incidence of KT among patients consented for MYTHIC and matched comparators. We time-matched each MYTHIC focal patient, individually, to UNOS comparators who were (as of follow-up time from waitlisting equal to the index MYTHIC patient’s follow-up time at consent) as follows: alive; active on the wait list; equal with respect to race, diabetes status, blood group, obesity (BMI >35 kg/m²), dialysis status at waitlisting (on vs. off); were within 2 years of age; were (at waitlisting) within 1 year of the focal patient’s time on dialysis; were listed at a center quintile based on standardized transplant ratio (intended to reflect the rate of deceased donor transplantation at that center vs. others); and not willing to consider offers from HCV-viremic donors. The time axis in Figure 1 is time since matching, with the time clock reset to 0 at the time of matching. To avoid immortal time bias, each matched UNOS comparator had follow-up time (since waitlisting) equal to that of their respective index MYTHIC patient; that is, as described in the Restriction, Matching, and Statistical Analysis for the Outcome of Time to Transplantation subsection of the Methods section. BMI, body mass index; HCV, hepatitis C virus; KT, kidney transplantation; MYTHIC, Multicenter Study to Transplant Hepatitis C-Infected Kidneys; UNOS, United Network for Organ Sharing.

The 4 recipients of HCV antibody-positive/RNA-negative donor transplants and the 8 recipients of standard-of-care KT were alive with functioning allografts at 1-year post-transplant. Among the enrolled patients remaining on the waitlist, 1-year survival was 100%.

Sustained Virologic Response After Transplantation

All 30 HCV D-RNA-positive/R-negative patients responded rapidly to G/P therapy, achieved HCV cure, and had undetectable HCV RNA when measured between 32 and 52 weeks post-transplant.

At baseline, 28 of 30 of the HCV D-RNA-positive/R-negative patients (93%) had negative HCV antibody levels pretransplant and 2 (7%) had detectable HCV antibodies. HCV antibody became detectable in the first 4 weeks post-transplant in 13 of 28 (46%) who were negative at baseline (Figure 2). At 1-year post-KT, 27 of 28 surviving HCV D-RNA-positive/R-negative patients underwent HCV antibody testing; only 2 of 25 (8%) who were negative at baseline had a detectable HCV antibody, whereas 1 had an indeterminate result.

Among the 4 patients who underwent HCV antibody-positive/RNA-negative transplantation, none had detectable HCV RNA at any point post-transplant. At 6 months, 1 had detectable HCV antibody, 2 had no HCV antibody, and the fourth did not undergo testing.

Key Safety Events

At 1 year, the 28 surviving HCV D-RNA-positive/R-negative patients had a median serum creatinine of 1.17 mg/dl (IQR: 1.02–1.38) and median estimated glomerular filtration rate of 60.0 ml/min per 1.73 m² (IQR: 51.4–80.8). Figure 3 reveals their longitudinal serum creatinine levels.

There were 3 previously reported cases of biopsy-confirmed acute rejection among the HCV D-RNA-positive/R-negative transplants.⁵ The median 12-month urine protein-to-creatinine ratio of HCV D-RNA-positive/R-negative patients was 0.14 (range: 0.03–0.64), with no cases of *de novo* glomerulonephritis.

There were rare mild abnormalities in liver biochemistry tests, but no grade 3 elevations (Supplementary Figure S2 reveals the stable trends in liver function tests). Of the alanine transaminase elevations >100, 2 occurred in the first week post-transplant whereas the other 2 occurred in the setting of CMV viremia (described subsequently). All surviving HCV D-RNA-positive/R-negative patients had normal biochemistry results at 1-year post-transplant. Treatment-related adverse events and severe adverse events during G/P therapy have been previously reported, with no severe adverse events deemed related to either HCV or G/P; updated severe adverse events for the entire 1-year study period are found in Supplementary Table S6.⁵

Patient	Pre-KT	Start of Rx	Week 4 of Rx	1-year Post-KT
1	Blue	Blue	Blue	Blue
2	Blue	Blue	Blue	Blue
3	Blue	Red	Yellow	Blue
4	Blue	Red	Red	Yellow
5	Blue	Blue	Blue	Blue
6	Blue	Red	Gray	Blue
7	Blue	Blue	Blue	Blue
8	Blue	Red	Blue	Blue
9	Blue	Gray	Blue	Blue
10	Blue	Red	Gray	Blue
11	Blue	Blue	Yellow	Black
12	Blue	Blue	Red	Blue
13	Blue	Red	Red	Blue
14	Blue	Gray	Red	Blue
15	Blue	Yellow	Blue	Blue
16	Blue	Red	Gray	Blue
17	Blue	Red	Blue	Blue
18	Blue	Red	Red	Blue
19	Blue	Red	Red	Red
20	Blue	Red	Red	Red
21	Blue	Gray	Blue	Blue
22	Blue	Blue	Blue	Gray
23	Blue	Blue	Blue	Blue
24	Blue	Blue	Blue	Blue
25	Red	Red	Red	Red
26	Blue	Gray	Yellow	Black
27	Blue	Blue	Blue	Blue
28	Blue	Blue	Blue	Blue
29	Red	Red	Red	Red
30	Blue	Blue	Blue	Blue

Figure 2. Hepatitis C antibody status for each HCV-aviremic recipient of a kidney transplant from an HCV-viremic donor, at 4 time points. Heatmap revealing the HCV antibody status of the 30 recipients of HCV-viremic transplants at the following 4 time points: baseline, start of glecaprevir/pibrentasvir treatment (postoperation day 3), week 4 of treatment (1 month after transplant), and 1 year after kidney transplant. Negative HCV antibody is shaded as blue; positive, red; indeterminate, yellow; missing, gray. The antibody status at 1 year was unknown for the 2 patients who died (black). HCV, hepatitis C virus; KT, kidney transplantation; Rx, treatment.

All 30 HCV D-RNA-positive/R-negative patients underwent polymerase chain reaction screening for BKV in the blood and/or urine, with a median of 7 tests (IQR: 4–11). There were 5 (17%) who had detectable BK virus in the blood at any point in the first year post-transplant, 4 of which were >1000 copies/ml and one >10,000 copies/ml. In 3 patients, immunosuppression was reduced owing to BK viremia. None were biopsied and all had a 12-month creatinine level ≤1.2 mg/dl.

CMV viremia was detected in 10 HCV D-RNA-positive/R-negative patients, but only 5 had any episode of CMV >1000 IU/ml (all among CMV donor-positive/recipient-negative patients). The 10 CMV donor-positive/recipient-negative patients received 6 months of valganciclovir prophylaxis and CMV testing per each center's standard-of-care (Supplementary Table S3), with a median of 11

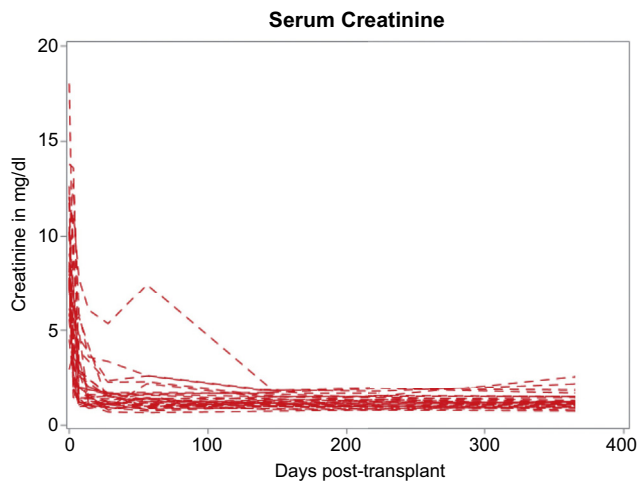


Figure 3. Post-transplant trends in serum creatinine in 30 HCV-negative recipients of HCV-viremic kidneys. HCV, hepatitis C virus.

(IQR: 3–18) measurements. Furthermore, 5 patients (50%) had a peak viral load >1000 IU/ml ≥6 months post-KT and after valganciclovir cessation, with 4 adjudicated to have probable or definite CMV disease (Figure 4).

DISCUSSION

In this prospective multicenter study, we confirm that HCV cure persists at 1-year post-transplant in recipients of HCV-viremic kidneys, with continued excellent kidney and liver function. This study provides important data revealing the benefit of opting-in for kidney offers from HCV-viremic donors by

comparing study participants with matched waitlist comparators to determine probability of transplantation. Furthermore, we performed detailed chart review and expert adjudication to better understand the risks of CMV disease in HCV D-RNA-positive/R-negative KT. Overall, the 1-year data from this multicenter trial extend the body of literature suggesting transplanting HCV-viremic donor kidneys into well-selected HCV-negative recipients is safe and associated with excellent outcomes. We report no adverse liver outcomes when DAAs were commenced within 2 to 5 days post-KT; in contrast to reports of fibrosing cholestatic HCV and clinically significant hepatitis with delayed initiation of DAAs (1 month or longer delays).^{10,28} In this study, liver biochemical indices were reassuring in patients prospectively followed to 1 year. Using advanced statistical matching methods, we revealed that MYTHIC participants who opted to receive kidney offers from HCV-viremic donors had a 3.5-fold higher cumulative probability of transplant within 1 year versus matched waitlist comparators. Nevertheless, these data must be taken in context: (i) increased national utilization of HCV-viremic donors will continue to attenuate the magnitude of this advantage; (ii) patients in this study were carefully selected, including exclusion of those with liver disease (e.g., pretransplant Fibroscan); and (iii) DAAs were administered within the first week of transplant, which may not be replicable in routine US clinical practice.²⁹

There have been concerns of a disproportionate risk of CMV infection since a 2019 publication from the

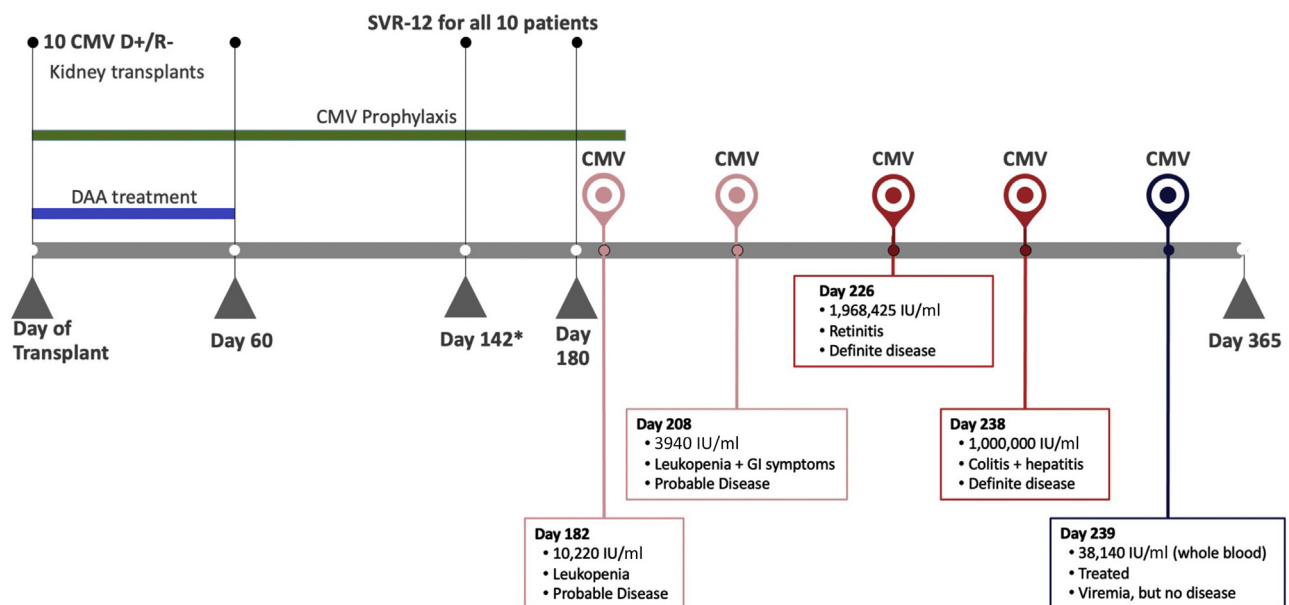


Figure 4. CMV outcomes among 10 CMV D+/R– recipients of HCV-viremic donor kidneys in MYTHIC. There were 5 cases of clinically significant CMV viremia >1000 IU/ml among CMV D+/R– recipients. The timeline of disease onset and symptoms experienced is illustrated. CMV, cytomegalovirus; D+/R–, donor-positive/recipient-negative; DAA, direct-acting antiviral; GI, gastrointestinal; SVR-12, sustained virologic response at 12 wk.

Methodist Healthcare/University of Tennessee that reported a 60% rate of CMV viremia in HCV D-RNA-positive/R-negative KT^s.¹⁰ That study focused only on CMV viremia, rather than CMV disease, the end point of CMV clinical trials.^{20,30} With respect to CMV outcomes, our study reported different results. First, only 5 patients (16.7%) had CMV viremia > 1000 IU/ml, all of which were in “high-risk” CMV donor/recipient mismatches (i.e., CMV donor-positive/recipient-negative). On the basis of adjudication by an infectious disease expert, only 2 of the 10 CMV donor-positive/recipient-negative patients (20%) had definite CMV disease, consistent with the 16% rate reported from the largest clinical trial of valganciclovir prophylaxis,³⁰ with 2 additional cases deemed “probable.” Of note, before, the CMV trials only reported “definite” CMV cases, and it is unknown how many “probable” cases occurred.³⁰ Therefore, our overall rate of CMV disease (definite or probable) may be similar or higher than that of the IMPACT study, albeit a smaller sample size.³⁰ Future studies will require a larger sample size with adjudication of CMV cases in matched comparators.

An additional insight provided from this study is that although *de novo* HCV antibody is found in a subset of HCV-negative recipients, persistence of antibody at 1-year post-transplant is uncommon. The early presence of HCV antibody has been found in the THINKER trial (confirmed to be IgG),³¹ but the loss of antibody over time in our study suggests that the source of antibody is more likely donor-transmitted IgG, rather than recipient plasma cells, which would be expected to lead to persistent HCV antibody production.

The carefully collected 1-year MYTHIC outcome data add to the growing literature regarding the safety and efficacy of HCV D-RNA-positive/R-negative KT^s. Nevertheless, it is important to note that we used stricter inclusion/exclusion criteria than standard waitlisting criteria. Furthermore, it is well known that 10% to 20% of KT candidates may have underlying viral hepatitis or liver disease associated with diabetes.³² Notably, a Fibroscan excluded 12% of eligible MYTHIC participants.³¹ Whether a Fibroscan is needed for all HCV-negative patients being evaluated for transplantation with a kidney from an HCV-viremic donor is unknown, especially when DAAs are administered early post-transplant; therefore, our results may only apply in patients without pre-existing liver disease. Although rare, there have been reports of fibrosing cholestatic HCV that occurred in the setting of delayed initiation of DAAs >30 days.^{10,28} Therefore, it could be argued that elimination of the risk of fibrosing cholestatic HCV requires early initiation of

DAAs. Nevertheless, to apply the MYTHIC protocol to general practice (i.e., treatment within 5 days post-transplant) would require a frameshift in HCV treatment in the setting of routine care, with either insurance preapproval pretransplant or hospitals/centers covering the costs of DAA therapy before insurance approval.^{31,33}

Our study has limitations, including the modest sample size of 30 patients. Second, there were no prospective uninfected comparators for post-transplant outcomes and complications, including CMV disease. Third, because absence of significant liver fibrosis was a screening criterion, we cannot address the safety of this approach in recipients with more advanced liver fibrosis. Fourth, protocol kidney biopsies were not uniformly obtained; therefore, we cannot exclude the possibility of transient mild glomerular injury in the setting of early HCV viremia. Nevertheless, the absence of any clinically significant proteinuria at 1-year with normal serum creatinine measurements in most patients is reassuring. Fifth, immunosuppression protocols varied by center, but we detected no center effect on any of our efficacy or safety outcomes. Sixth, our study mandated a KDPI of <85% and highly sensitized patients, and those with immune-mediated end-stage kidney disease were excluded. Therefore, it is unclear whether higher KDPI kidneys from HCV-viremic donors would be associated with similar outcomes. Finally, longer-term follow-up (2- to 5-year data) will be needed to determine whether exposure to donor HCV viremia through transplant is associated with late complications.

In conclusion, the prospective multicenter MYTHIC trial revealed 100% HCV cure rates and excellent 1-year post-transplant kidney function in HCV D-RNA-positive/R-negative KT^s. As the practice of using HCV-viremic donor organs becomes more routine, these data should provide reassurance to patients, providers, and insurers. Although the implementation of this practice in future trials or center protocols may vary, we believe that appropriate patient education and informed consent, followed by assurances of early access to DAAs, will provide for excellent patient outcomes, preservation of patient safety, and increased access to transplantation.

DISCLOSURE

Some of the authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. CMD reports receiving grant support from AbbVie, GlaxoSmithKline, and ViiV and serving on a grant review committee for Gilead Sciences. ND reports being an investigator on clinical trials funded by

Merck and a consultant and a speaker for Merck. JL reports conducting research and serving as a speaker and a consultant for Novartis; serving as a consultant and stockholder for Transplant Genomics Inc.; and serving as a speaker for Gilead. JF reports having equity and serving as consultant for Transplant Genomics, Inc.; serving in the consulting and speaker's bureau for Novartis; serving in the speaker's bureau for Sanofi; and receiving grant support from Veloxis, AbbVie, Vitaeris, Hansa, Viela Biopharma, and Eurofins–Viracor. JJK is an employee of AbbVie and may hold AbbVie stocks. KES reports receiving research grants/contracts (paid to institution) from AbbVie, Bristol-Myers Squibb, Gilead, Inovio, Intercept, and Merck and serving on the advisory board/consulting for Inovio, UniQure, and Abbott Labs. DSMB reports receiving support from MedPace, Inovio, and Watermark. MES reports receiving grant support to Massachusetts General Hospital from Gilead Sciences, AbbVie, Merck & Co., and EMD Serono; participating in scientific advisory board meetings for Gilead and Traveer Therapeutics; and serving as a scientific consultant to Bioporto. PPR reports receiving investigator-initiated grants to the University of Pennsylvania from Merck and Gilead for trials involving HCV-viremic organs. RJF reports receiving grant support from Gilead and AbbVie and providing consulting to Sanofi. RRA reports receiving research grants from Bristol-Myers Squibb, Hookipa Biotech GMBH, and Novartis. RRA is an advisor and on the speakers bureau for Genzyme/Sanofi and Veloxis. RSB reports receiving grant support to Weill Cornell Medicine from Gilead Sciences, AbbVie, and Merck & Co., and having consulted personally for AbbVie, Gilead, and Merck & Co. RTC reports receiving research grant support to Massachusetts General Hospital from AbbVie, Gilead, Merck, Bristol-Myers Squibb, Janssen, Boehringer, and Roche. All the other authors declared no competing interests.

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00001C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. Some data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

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AUTHOR CONTRIBUTIONS

MES, DSG, RRA, CD, RJF, RSB, JF, ESW, KES, JL, JDL, JJK, RTC, and PPR designed the study. MES, DSG, RRA, CD, RJF, RSB, JF, ESW, KES, JLG, ND, ML, IAS, SS, JL, RTC, and PPR enrolled and followed the patients. EB adjudicated cases of CMV. DES, MES, DSG, MF, RL, RTC, and PPR analyzed the data. DES, MF, DSG, and PPR made the figures. PPR, MES, DSG, RJF, DES, RTC, and RF drafted the paper. All authors revised the paper and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Methods S1. Inclusion and exclusion criteria for the MYTHIC Trial.

Methods S2. Statistical methods to categorize centers by acceptance of deceased donor kidneys.

Table S1. Summary of the visit schedule.

Table S2. Policies for screening for BK virus at the 7 MYTHIC clinical sites table with one row for each center.

Table S3. Policies for CMV screening and prophylaxis at the 7 MYTHIC clinical sites table with one row for each center.

Table S4. Characteristics of MYTHIC patients who received kidney transplants by HCV NAT status.

Table S5. Characteristics of deceased donors who provided kidneys to MYTHIC participants and deceased donors who provided kidneys to waitlisted comparators who later received a transplant.

Table S6. Serious adverse events among 30 HCV-viremic deceased donor kidney recipients.

Figure S1. Patient flow.

Figure S2. Trends in liver function tests.

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