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Authors
Ragni, MV
DeVera, ME
Roland, ME
et al.

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Liver Transplant Outcomes in HIV(+) Hemophilic Men

Margaret V. Ragni, MD, MPH[1], **Michael E. DeVera, MD**[1], **Michelle E. Roland, MD**[2], **Michael Wong, MD**[3], **Valentina Stosor, MD**[4], **Kenneth E. Sherman, MD, PhD**[5], **David Hardy, MD**[6], **Emily Blumberg, MD**[7], **John Fung, MD, PhD**[8], **Burc Barin, MS**[9], **Donald Stablein, PhD**[9], and **Peter G. Stock, MD, PhD**[2]

[1]Departments of Medicine and Surgery, University of Pittsburgh, Pittsburgh, PA

[2]Departments of Medicine and Surgery, University of California, San Francisco CA

[3]Department of Medicine, Beth Israel Deaconess, Harvard University, Boston MA

[4]Department of Medicine, Northwestern University, Chicago IL

[5]Department of Medicine, University of Cincinnati, Cincinnati OH

[6]Department of Medicine, Cedars Sinai Medical Center, Los Angeles CA

[7]Department of Medicine, University of Pennsylvania, Philadelphia PA

[8]Department of Surgery, Cleveland Clinic Foundation, Cleveland OH

[9]Emmes Corporation, Rockville MD

Summary

Background—Hepatitis C virus infection is the major cause of end-stage liver disease and the major indication for transplantation (OLTX), including among HIV-HCV co-infected individuals. The age of HCV acquisition differs between hemophilic and non-hemophilic candidates, which may affect liver disease outcomes.

Objectives—The purpose of the study was to compare rates of pre- and post-OLTX mortality between co-infected hemophilic and non-hemophilic subjects without hepatocellular cancer participating in the Solid Organ Transplantation in HIV Study (HIV-TR).

Methods—Clinical variables included age, gender, race, liver disease etiology, BMI, antiretroviral therapy, MELD score, CD4+ cell count, HIV RNA PCR, and HCV RNA PCR. Time to transplant, rejection, and death were determined.

Results—Of 104 HIV-HCV positive subjects enrolled, 34 (32.7%) underwent liver transplantation, including 7 of 15 (46.7%) hemophilic and 27 of 89 (30.3%) non-hemophilic candidates. Although hemophilic subjects were younger, median 41 vs. 47 years, p=0.01, they

Reprint Requests: Margaret V. Ragni, MD, MPH, Professor of Medicine Division Hematology and Oncology, University of Pittsburgh Director, Hemophilia Center of Western Pennsylvania 3636 Boulevard of the Allies, Pittsburgh, PA 15213-4306 Phone: 412-209-7288; Fax: 412-209-7281 ragni@dom.pitt.edu.

Authorship Contributions MVR, MED, MER, and PGS designed the research project. MVR, MED, MER, MW, VS, KES, DH, EB, JF, BB, DS, and PS collected data and evaluated the results. MVR, BB, and DS analyzed the data. BB performed the statistical analysis and prepared the figures. MVR formulated the conclusions and wrote the paper.

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were more likely than non-hemophilic subjects to die pre-OLTX, 5 (33.3%) vs. 13 (14.6%), p=0.03, and reached MELD=25 marginally faster, 0.01 vs. 0.7 years, p=0.06. The groups did not differ in baseline BMI, CD4, detectable HIV RNA, detectable HCV RNA, time to post-OLTX death (p=0.64), graft loss (p=0.80), or treated rejection (p=0.77). The rate of rejection was 14% vs. 36% at 1-year and 36% vs. 43% at 3-year, hemophilic vs. non-hemophilic subjects, respectively, and post-OLTX survival, 71% vs. 66% at 1-year and 38% vs. 53% at 3-year.

Conclusions—Despite similar transplant outcomes, pre-transplant mortality is higher among co-infected hemophilic than non-hemophilic candidates.

Keywords

hemophilia; hepatitis C liver disease; HIV-HCV co-infection; liver transplantation

Introduction

Hepatitis C (HCV) is the major cause of chronic liver disease and the leading indication for liver transplantation. HIV infection accelerates HCV-related liver disease [1–3], in part, through an HIV-induced TGF-β1-dependent increase in HCV replication [4], leading to questions regarding the advisability of liver transplantation in co-infected individuals. Despite HCV recurrence in virtually all recipients [2, 5, 6], transplantation is considered safe and effective in co-infected candidates [6–11], if they have demonstrated previous response to combination antiretroviral therapy (cART) [7]. The latter slows HCV progression [12–14], in part through suppression of HIV RNA and HIV-induced fibrosis-promoting cytokines [15, 16]. Increasingly, co-infected individuals are developing end-stage liver disease (ESLD) and undergoing transplantation, up to 10% of whom have hemophilia [5, 7]. Indeed, among men with hemophilia, HCV-related ESLD is the leading cause of death [1]. A distinguishing feature of this group, in addition to phenotypic cure of hemophilia by liver transplantation, is their life-long HCV infection, as acquisition of HCV occurred with the first blood product [17], usually in the first year of life [1]. This is in contrast to HCV acquisition in non-hemophilic men, conservatively estimated to occur at age 15 years or later. As duration of HCV infection is a recognized risk factor for HCV progression [1], and, as at least one-fourth of co-infected hemophilic men have Metavir ≥ F3 fibrosis [18], we sought to determine whether transplant outcomes are poorer in co-infected hemophilic than non-hemophilic transplant candidates, within our larger study of OLTX in HIV-infected individuals.

Materials and Methods

Study Subjects

The HIV in Solid Organ Transplantation Multisite Study (HIV-TR) is a National Institute of Allergy and Infectious Diseases (NIAID)-funded prospective, observational trial that enrolled transplant candidates with HIV infection and end-stage liver disease (ESLD) from 21 U.S. university transplant centers between October 2003 and February 2010 (NCT00074386). This analysis includes transplant candidates from the eight centers that enrolled both hemophilic and non-hemophilic subjects. Inclusion criteria for the HIV-TR

study, previously described [7], include CD4+ cells > 100/μl, or > 200/μl if there was a prior opportunistic infection; and undetectable HIV-1 RNA, or predicted HIV suppression in those with hepatotoxicity or cART intolerance. Subjects with a history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis of > 1 month duration, primary CNS lymphoma, multidrug resistant fungal infections, or significant wasting were excluded from the study. Patients with hepatocellular carcinoma were excluded from this analysis since they are typically assigned a higher priority for liver transplantation regardless of MELD score. Outcomes included transplant, rejection, and mortality rates. As exact dates of HCV exposure were not known, we assumed HCV exposure occurred with initial clotting factor exposure during the first year of life among those with hemophilia [17], and with sexual or intravenous drug use exposure at 15 years of age or later, conservatively, among non-hemophilic subjects.

Data Collection

Clinical and laboratory data were collected on study subjects at screening, enrollment (time of placement on the transplant waiting list), and every three months until transplantation or death, and entered into an online data collection system at each of the participating sites. Clinical variables included age, gender, race, liver disease etiology, antiretroviral therapy (cART), body mass index (BMI), and cause of death, when appropriate. Laboratory tests included CD4+ cell count, HIV RNA PCR, HCV RNA PCR, and standard chemistry tests, including creatinine and bilirubin, for calculating MELD scores as follows: (MELD = [0.957 × Ln (creatinine mg/dl, maximum 4.0) + 0.378 × Ln (bilirubin mg/dl) + 1.120 Ln (INR) + 0.643] × 10.

Statistical Methods

Wilcoxon rank-sum test was performed for comparison of continuous variables, and Fisher's exact test was used for comparison of categorical variables. Log-rank test was used for comparison of time-to-event curves. Univariate and multivariate proportional hazards models were developed to examine predictors of pre-transplant mortality. Time-to-event analyses were performed on HIV-infected hemophilic and non-hemophilic transplant recipients who died (time to death), who developed graft loss (time to graft loss), or who developed organ rejection (time to rejection). Time-to-event analyses were also performed on HIV-infected hemophilic and nonhemophilic transplant candidates who died pre-transplant (time to death), who underwent transplantation (time to transplant), or who developed MELD score of 25, specifically, the time to MELD=25 from the day of study enrollment, satisfying transplant and study eligibility criteria. Among those undergoing liver transplantation, the 1-year and 3-year survival and 95% confidence intervals were calculated. Causes of pre- and post-transplant deaths were determined, comparing co-infected hemophilic and non-hemophilic candidates. The statistical analysis was carried out using SAS version 9.2, Cary NC.

Human Subjects Research

All subjects provided signed informed consent in accordance with the Declaration of Helsinki. The protocol and informed consent documents were approved by the Institutional Review Board (IRB) of each institution.

Results

Of 104 HIV-HCV enrolled candidates, nearly one-third, 34 (32.7%), underwent liver transplantation, including 7 of 15 (46.7%) with hemophilia and 27 of 89 (30.3%) without hemophilia. At baseline, as compared with non-hemophilic transplant candidates, those with hemophilia were younger (p=0.01) and male only (p=0.02). When the analyses were re-run, using male-only controls, results were similar (data not shown). The two groups did not differ in BMI (p=0.43), CD4+ count (p=0.48), proportion with detectable HIV RNA (p=0.70), or detectable HCV RNA (p=0.36), Table 1. There were also no differences in socio-economic characteristics between groups. The median duration of HCV infection among hemophilic subjects, based on exposure in the first year of life [17], was 40 years [IQR: 33–47], while the median duration of HCV infection among non-hemophilic subjects, based on a conservative assumption of exposure since 15 years of age, was 32 years [IQR: 29–37], p=0.001.

Comparing hemophilic with non-hemophilic transplant recipients, there was no difference in the median time to transplantation, 0.15 years vs. 0.03 years, respectively (p=0.15). There was also no difference in the proportion of recipients who died after transplantation, 4 of 7 (57.1%) in hemophilic subjects vs. 14 of 27 (51.8%) in non-hemophilic subjects, (Table 2), nor in the median time to post-transplant death, 1.29 years vs. 0.75 years, respectively, p = 0.64 (Figure 1A). The causes of post-transplant deaths were not statistically different between groups, with sepsis accounting for one-half of the hemophilic and one-fourth of the non-hemophilic deaths, Table 2.

The 1-year and 3-year post-transplant survival rates in hemophilic recipients, 71% (95% CI: 26–92%) and 38% (95%CI:6–72%), were similar to rates in non-hemophilic candidates, 66% (95%CI:44–80%) and 53% (95%CI:32–70%), respectively. The median time to graft loss was also not different between hemophilic and non-hemophilic transplant recipients, 1.29 years vs. 0.73 years, p = 0.80 (Figure 1B). The 1-year and 3-year cumulative rates of treated rejection in hemophilic transplant recipients were 14% (95%CI:2–67%) and 36% (95%CI:10–85%), while those in non-hemophilic transplant recipients were 36% (95%CI: 21–59%) and 43% (95%CI:25–66%), respectively. The median time to treated rejection also was not statistically different between hemophilic and non-hemophilic transplant recipients, 0.75 years vs. 0.02 years, p = 0.77 (Figure 1C).

Among transplant candidates who did not undergo transplantation, including 8 of 15 (53.3%) hemophilic and 62 of 89 (69.7%) non-hemophilic candidates, Table 2, significantly fewer hemophilic candidates remain alive, 3 (37.5%) vs. 49 (79.0%), p=0.03 (Fig 2A). The hemophilic group was more likely than their non-hemophilic counterparts to die before receiving a transplant, 5 of 15 (33.3%) vs. 13 of 89 (14.6%), and more quickly, with a median time to death of 0.07 years in those with hemophilia vs. 0.42 years in non-hemophilic subjects, p = 0.03, (Figure 2A). The causes of pre-transplant deaths were similar between groups, and included sepsis and multi-organ failure (Table 2).

The median time to transplant, as measured by time on the transplant waiting list, was marginally longer in hemophilic as compared with non-hemophilic candidates, 0.15 years

vs. 0.03 years, p=0.15 (Figure 2B). The median time to MELD=25, as measured in time on the transplant waiting list with MELD < 25, was marginally shorter in hemophilic subjects, 0.01 years vs. 0.7 years, p=0.06 (Figure 2C).

In univariate proportional hazards models for pre-transplant mortality, including hemophilia status and baseline factors (Table 1), having hemophilia, HR=3.0, p=0.04, and higher baseline MELD score, HR=1.2, p<0.0001, were significantly associated with increased risk of pre-transplant death. In the multivariate model, higher baseline MELD score was significantly associated with increased risk of pre-transplant death, HR=1.2 (95%CI:1.1–1.3), p<0.0001, while being hemophilic was marginally associated with increased risk of pre-transplant death, HR=3.6 (95%CI:1.0–13.5), p=0.06. When the time-to-event and proportional hazards models analyses were rerun using a male-only control, results were unchanged (data not shown).

Discussion

This study confirms that HIV/HCV co-infected individuals with hemophilia experience poorer pre-transplant outcomes than co-infected individuals without hemophilia. Hemophilic candidates had significantly higher pre-transplant mortality rates than did co-infected non-hemophilic transplant candidates. Further, they reached MELD of 25 marginally faster, despite similar HIV viral load and CD4 counts, and spent marginally more time on the transplant waiting list. While it is not possible to establish the mechanism for these differences, it is useful to note differences between groups, specifically younger age at baseline and HCV acquisition via clotting factor infusion in hemophilic transplant candidates. Further, we also presume that the duration of HCV infection was longer in this group: conservatively we estimate 40 years in hemophilic subjects vs. 32 years on non-hemophilic subjects. Yet, whether the poorer pre-transplant outcomes among hemophilic subjects are attributable to any of these differences is not known. Further, while difference in rates of classification, listing, MELD grading, or transplantation criteria could exist between groups is not known, but is unsupported by current evidence. Whether end-stage liver disease progresses more rapidly in individuals with hemophilia is not known, although recent data from a large observational cohort study of co-infected hemophilic men suggest that the rates of fibrosis are similar to those in other co-infected groups [18]. It is also possible that individuals with hemophilia, because of their co-morbidity (bleeding), present to liver transplantation clinics later in the course of their ESLD, but this is not supported by the baseline data in this observational study. Further studies are needed to determine whether hemophilia status affects survival pre-transplantation, and whether MELD is a measure of 90-day mortality in co-infected hemophilic men vs. non-hemophilia men. In addition, if duration of HCV infection differs between groups, it might also be helpful to model ESLD progression by age of first HCV exposure.

On the basis of the findings of this study, careful consideration should be given to earlier, more aggressive monitoring of co-infected individuals, especially those with hemophilia awaiting liver transplantation. The MELD score, an established predictor of medical urgency for liver transplantation and ESLD survival [19], has been shown also in recent studies to be an independent marker of pre-transplant mortality in co-infected transplant candidates [20–

22]. Thus, more frequent determination of MELD scores and/or liver ultrasound in co-infected transplant candidates during the pre-transplant period, or in individuals with co-infection, even *before* signs or symptoms of ESLD, for example at the time of routine quarterly HIV labs [20], might afford more careful follow-up, earlier detection of ESLD progression, and provide evidence as to whether the rate of MELD score increase predicts pre-transplant mortality.

Further, if the effects of age of HCV exposure on ESLD progression can be quantitatively modeled, additional MELD points might be assigned based on duration of HCV infection or based on the trajectory of MELD increase, similar to the priority MELD system in use for hepatocellular carcinoma. The latter assigns additional MELD points based on tumor stage, thereby equalizing risk, and successfully alleviated the higher mortality experienced by such individuals [23]. Post-transplant outcomes in co-infected hemophilic transplant candidates, by contrast, appear to be similar to those in co-infected candidates without hemophilia, including rates of survival, graft survival, and rejection. These findings, while limited by small numbers, are consistent with the favorable published outcomes following transplantation in co-infected individuals [2, 7, 10, 24]. This suggests that if the factors associated with poor pre-transplant outcome in co-infected individuals with hemophilia can be identified, their outcomes may be comparable to non-hemophilic candidates.

We acknowledge several limitations of this study. First, although this study represents the largest liver transplantation experience in co-infected individuals with hemophilia to date, the numbers are small, with hemophilic subjects representing only 14% of the co-infected group. The small numbers limited post-transplant comparisons and fitting of multivariate proportional hazards models. Second, the severity classification of hemophilia in the subjects is not known, which may interfere with assumptions about date of first treatment (and first HCV exposure): despite this, the majority of hemophilia A patients and the majority with hepatitis C have severe hemophilia [1], and, thus, we assume for the majority of subjects our assumptions regarding factor initiation are correct [17]. Even in those with milder disease, with potential infusion at age 5, this is still significantly younger at age of exposure (and longer duration infection) than among those with sexual exposures, estimated conservatively to begin at age 15. Third, follow-up was limited: while post-transplant survival, graft survival, and rejection rates appear similar between groups, ongoing prospective follow-up will be necessary to evaluate long-term transplant outcomes. Fourth, the impact of antiretroviral and/or antiviral HCV therapy toxicity on pre-transplant outcomes was not assessed as part of this study, yet it is known that up to 24% of co-infected individuals change or discontinue antiretroviral therapy due to toxicity [25]. Fifth, access to and quality of medical care may have differed between groups, impacting liver disease outcomes. Gaps in hemophilia care do exist, despite a nationwide federally-funded comprehensive hemophilic care network, and fear of bleeding complications by providers and patients may delay HCV treatment, liver biopsy, and/or transplant evaluation [7, 18]. Medical care of co-infected illicit drug users may also vary considerably, especially when complicated by lack of insurance, economic support, and psychosocial services. By matching hemophilic and non-hemophilic subjects from the same centers, we hoped to reduce at least some, but not all, of these potential biases. Sixth, selection criteria for

enrollment on the HIV-TR study may be more stringent than those used in general practice, and referral bias, i.e. that some hepatology clinics refer patients earlier than others, may potentially explain our results. However, it should be noted that as not all transplant centers accept hemophilia patients, we included only those centers prepared to transplant both hemophilic and non-hemophilic subjects in this study. The findings of this study, therefore, may underestimate the potential impact of long duration HCV infection on transplant outcomes.

In summary, the findings of this study underscore the importance of increased provider monitoring of morbidity and early mortality in co-infected individuals with ESLD, and the need for early referral for transplant evaluation, and for close surveillance to reduce pre-transplant mortality and improve health outcomes [26, 27].

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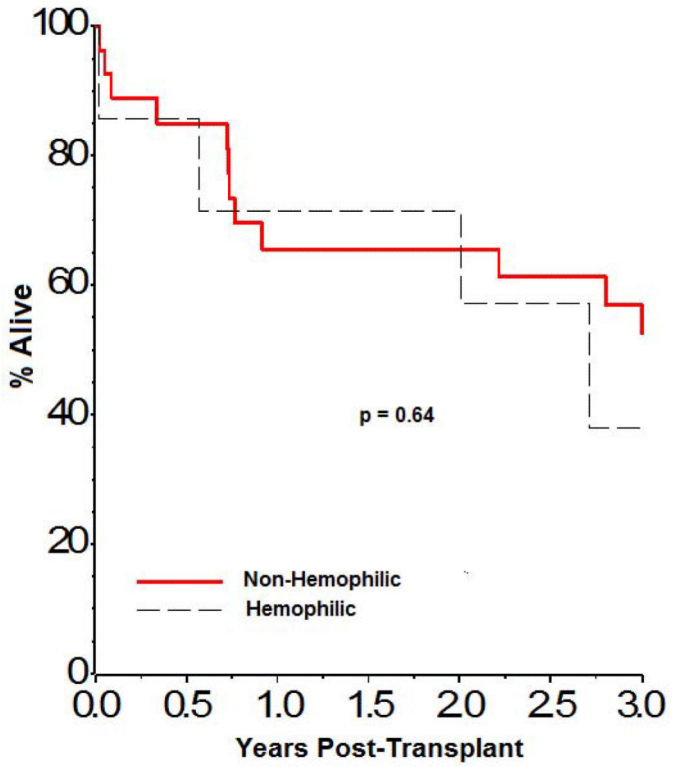
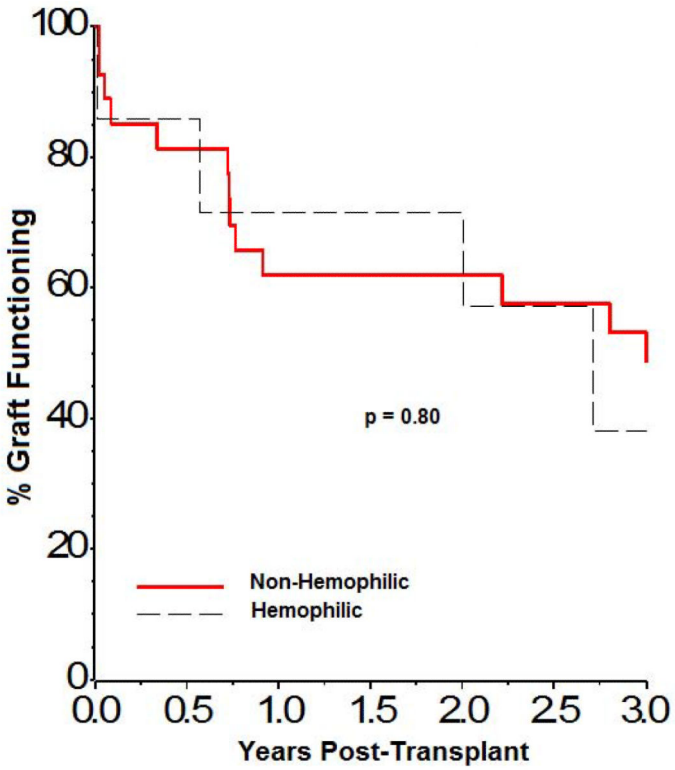




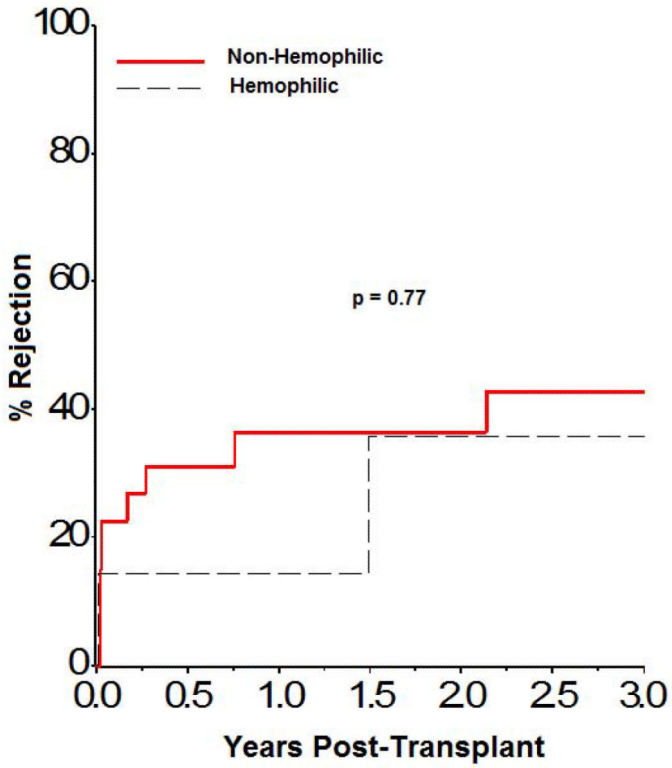
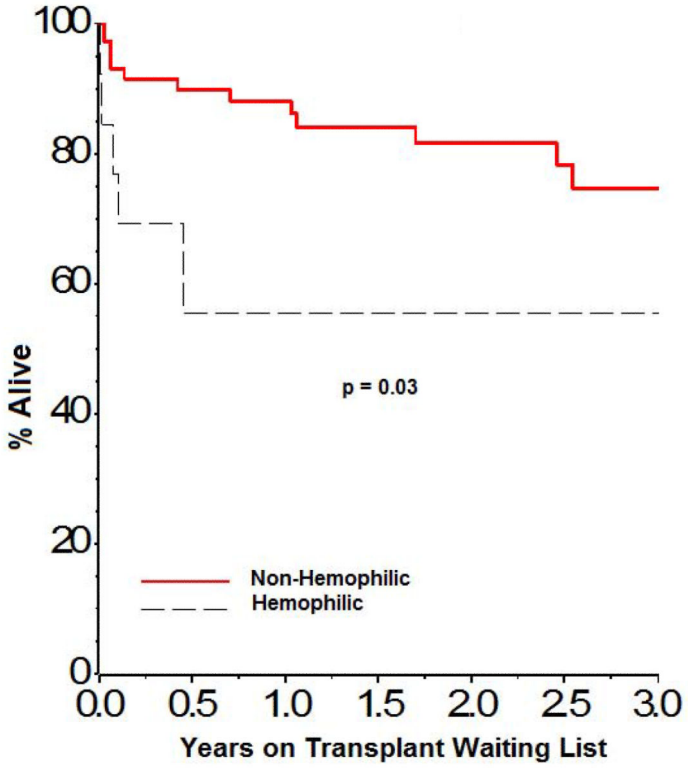
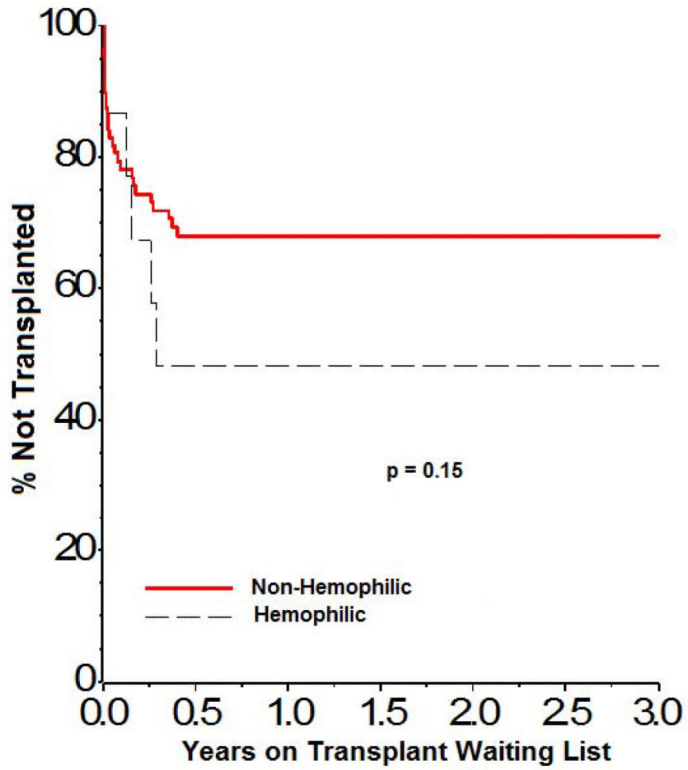


Figure 1. Post-Transplant Outcomes in HIV-HCV Co-Infected Liver Transplant Recipients

The time to death (1A), graft loss (1B), and rejection (1C) in hemophilic (dashed line) and non-hemophilic transplant recipients (solid line).





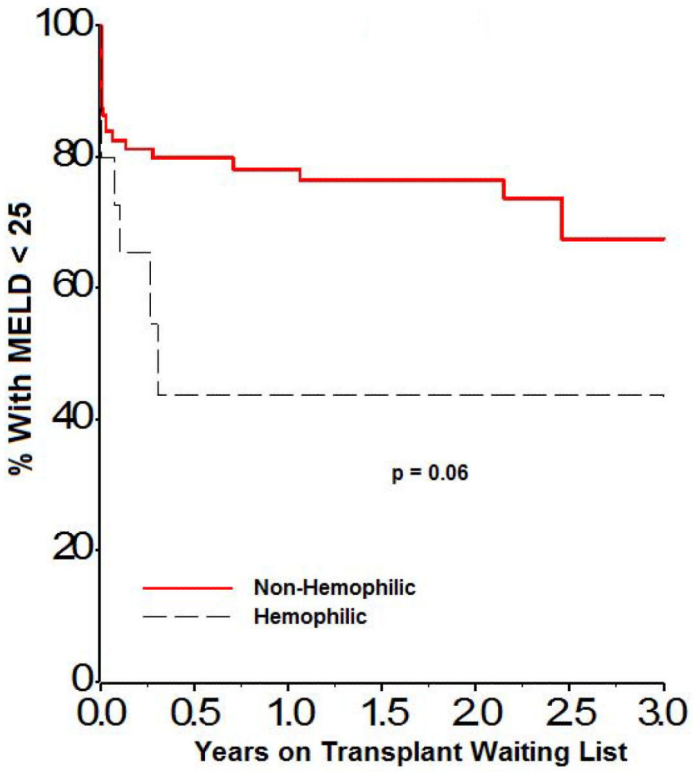


Figure 2. Pre-Transplant Outcomes in HIV-HCV Co-Infected Hemophilic Liver Transplant Candidates

The time to death (2A), transplantation (2B), and MELD=25 (2C) in hemophilic (dashed line) and in non-hemophilic liver transplant candidates (solid line).

Table 1

Clinical Characteristics of HIV-HCV Co-Infected Liver Transplant Candidates

		Hemophilic Subjects N=15	Non-Hemophilic Subjects N=89	p value
Baseline Characteristics				
Median Age:	Years [IQR]	41 [35–48]	47 [44–52]	p = 0.01
Gender:	No. Male	15 (100%)	64 (71.9%)	p = 0.02
Race:	No. Caucasian	14 (93.3%)	61 (68.5%)	p = 0.46
	No. Black	1 (6.7%)	17 (19.1%)	
	No. Other	0 (0%)	5 (5.6%)	
	No. Unknown	0 (0%)	6 (6.7%)	
HIV Risk:	No. MSM	0 (0%)	31 (34.8%)	p<.0001
	No. IVDU	0 (0%)	42 (47.2%)	
	No. Transfusion	15 (100%)	3 (3.4%)	
	No. Heterosexual/Multiple Partners	0 (0%)	8 (9.0%)	
	No. Unknown	0.0%)	5 (5.6%)	
Coverage:	Private insurance	7 (46.7%)	36 (40.5%)	p = 0.98
	Medicare	4 (26.7%)	23 (25.8%)	
	Medicaid	3 (20.0%)	18 (20.2%)	
	Self pay	0 (0%)	1 (1.1%)	
	Other	1 (6.7%)	11 (12.4%)	
Employment:	Full-time	4 (26.7%)	10 (11.2%)	p = 0.23
	Part-time	0 (0%)	6 (6.8%)	
	Not Employed	11 (73.3%)	73 (82.0%)	
Median BMI:	kg/m^2 [IQR]	24 [23–27]	25 [22–28]	p = 0.43
Median CD4:	No./μl [IQR]	313 [139–467]	281 [204–482]	p = 0.48
HIV RNA:	No. ≥48 copies/ml	3 (20.0%)	13 (14.6%)	p = 0.70
HCV RNA:	No. ≥50 copies/ml	15 (100%)	78 (87.6%)	p = 0.36
MELD Score:	[IQR]	20 [13–22]	14 [11–19]	p = 0.12

MSM is men who have sex with men; IVDU is intravenous drug users; MELD is model for endstage liver disease; IQR is interquartile range.

Table 2

Clinical Outcomes in HIV-HCV Co-Infected Liver Transplant Candidates

	Hemophilic Subjects N = 15	Non-Hemophilic Subjects N = 89
Transplant Recipients		
No. Candidates Transplanted	7 (46.7%)	27 (30.3%)
No. Candidates Expired Post-Transplant	4 (57.1%)	14 (51.8%)
Transplant Candidates		
No. Candidates Not Transplanted	8 (53.3%)	62 (69.7%)
No. Candidates Alive Pre-Transplant	3 (37.5%)	49 (79.0%)
No. Candidates Expired Pre-Transplant	5 (62.5%)	13 (21.0%)
Causes of Death		
Pre-Transplant Deaths		
Sepsis, infection	3 (60.0%)	2 (15.4%)
Multi-organ failure	1 (20.0%)	2 (15.4%)
ESLD/recurrent HCV	0 (0%)	4 (30.8%)
Other causes	0 (0%)	2 (15.4%)
Unknown	1 (20.0%)	3 (23.1%)
Post-Transplant Deaths		
Sepsis, infection	2 (50.0%)	4 (28.6%)
Multi-organ failure	0 (0%)	2 (14.3%)
ESLD/recurrent HCV	1 (25.0%)	3 (21.4%)
Other causes	1 (25.0%)	4 (28.6%)
Unknown	0 (0%)	1 (7.1%)