Effect of Alcoholic Liver Disease and Hepatitis C Infection on Waiting List and Posttransplant Mortality and Transplant Survival Benefit

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Disease-specific analysis of liver transplant survival benefit, which encompasses both pre- and posttransplant events, has not been reported. Therefore, we evaluated the effect of alcoholic liver disease (ALD) and hepatitis C virus (HCV) infection on waiting list mortality, posttransplant mortality, and the survival benefit of deceased donor liver transplantation using United States data from the Scientific Registry of Transplant Recipients on 38,899 adults placed on the transplant waiting list between September 2001 and December 2006. Subjects were classified according to the presence/absence of HCV and ALD. Cox regression was used to estimate waiting list mortality and posttransplant mortality separately. Survival benefit was assessed using sequential stratification. Overall, the presence of HCV significantly increased waiting list mortality, with a covariate-adjusted hazard ratio (HR) for HCV-positive (HCV+) compared with HCV-negative (HCV−) HR = 1.19 ($P = 0.0001$). The impact of HCV+ was significantly more pronounced ($P = 0.001$) among ALD-positive (ALD+) patients (HR = 1.36; $P < 0.0001$), but was still significant among ALD-negative (ALD−) patients (HR = 1.11; $P = 0.02$). The contrast between ALD+ and ALD− waiting list mortality was significant only among HCV+ patients (HR = 1.14; $P = 0.006$). Posttransplant mortality was significantly increased among HCV+ (versus HCV−) patients (HR = 1.26; $P = 0.0009$), but not among ALD+ (versus ALD−) patients. Survival benefit of transplantation was significantly decreased among HCV+ compared with HCV− recipients with model for end-stage liver disease (MELD) scores 9-29, but was significantly increased at MELD ≥30. ALD did not influence the survival benefit of transplantation at any MELD score. *Conclusion:* Except in patients with very low or very high MELD scores, HCV status has a significant negative impact on the survival benefit of liver transplantation. In contrast, the presence of ALD does not influence liver transplant survival benefit. (HEPATOLOGY 2009; 50:400-406.)

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Cirrhosis secondary to chronic hepatitis C viral (HCV) infection and alcoholic liver disease (ALD) are the two most common indications for liver transplantation in the United States.[1] In the past 25 years, expert opinion on the role of diagnosis in determining the outcome after liver transplantation has evolved with greater understanding of disease processes, and longer intervals of observation of larger patient cohorts. For example, in the first reports, ALD was thought to be a poor indication.[2] Subsequently, several accounts of successful transplantation and clinical recovery of alcoholic

Abbreviations: ALD, alcoholic liver disease; CI, confidence interval; HCV, hepatitis C virus; MELD, model for end-stage liver disease; BMI, body mass index; HR, hazard ratio; UNOS, United Network for Organ Sharing.

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patients receiving liver transplantation challenged this assumption.[3-5] Most recently, retrospective single-center reviews have shown reduced survival emerging at longer-term follow-up of patients who resume heavy drinking.[6] In contrast, early reports of liver transplantation for HCV-associated cirrhosis, although limited by short-term follow-up, suggested that the clinical course of HCV in the allograft might be benign.[7,8] In 1999, Forman et al.,[9] using the United Network for Organ Sharing (UNOS) database between 1992 and 1998, showed that HCV-infected patients had worse patient and graft survival than those with chronic cholestatic diseases, a similar outcome to those transplanted for hepatitis B infection, autoimmune hepatitis, cryptogenic cirrhosis, and ALD, and better than that in patients undergoing transplantation for cancer. An analysis of the UNOS database from 1990 to 1996 by Roberts et al.[10] confirmed these results.

The notion that transplantation is always better than not undergoing transplantation was challenged by modeling studies of liver transplantation in patients with ALD by Poynard and colleagues,[11,12] which suggested that liver transplantation prolonged the lives of only those patients with severe liver failure. These studies, and the others cited above, all utilize the moment of transplantation as the starting point for observation. However, Merion et al.[13] and Schaubel et al.[14] have used the concept of survival benefit to encompass mortality during the continuum from first placement on the list, including all intervals after transplantation. Using model for end-stage liver disease (MELD) score as a marker of short-term mortality risk without transplantation, Merion et al.[13] showed that low MELD patients are at a greater mortality risk by undergoing transplantation than by remaining on the transplant waiting list. Using this analytical concept, they showed that patients at lower risk of death on the waiting list have no survival benefit from transplantation. Subsequently, Schaubel et al.[14] estimated survival benefit incorporating donor liver quality, and found that low-risk patients, in particular, are poorly served by receiving a high-risk allograft.

The impact of recipient diagnosis on liver transplantation survival benefit, which encompasses both pre- and posttransplant events, has received less attention. Because ALD and HCV infection are the most common underlying diagnoses in patients being considered for liver transplantation, we evaluated the effect of ALD and HCV infection on liver waiting list mortality, posttransplant mortality, and transplant survival benefit in a large national cohort.

Table 1. Prevalence of HCV and ALD in Study Cohort

	HCV−	HCV+	Total
ALD−	15,776 (40.6%)	12,322 (31.7%)	28,098 (72.2%)
ALD+	6,581 (16.9%)	4,220 (10.9%)	10,801 (27.8%)
Total	22,357 (57.5%)	16,542 (42.5%)	38,899 (100.0%)

Materials and Methods

This study used data from the Scientific Registry of Transplant Recipients supplemented by mortality information from the Social Security Death Master File. The study population consisted of all patients 18 years of age and older who were given an initial registration for deceased donor liver transplantation between between September 2001 and December 2006 (n = 38,899). HCV and ALD statuses were determined from diagnosis 1 and diagnosis 2 variables recorded on the waiting list candidate file. Indicators (0, 1) were set up for ALD and HCV, as well as the following: noncholestatic cirrhosis, cholestatic cirrhosis, acute hepatic necrosis, metabolic disease, and malignant neoplasm. Each patient could be given more than one diagnosis. Table 1 shows the prevalence of ALD and HCV in the cohort. Hazard ratios for each diagnosis indicator compared yes to no and were adjusted for all other covariates (including the other diagnosis indicators). Each subject was classified into one of four cells of an HCV × ALD 2 × 2 table, according to the presence/absence of HCV and ALD (see Table 1).

When assessing waiting list mortality, follow-up began at time of initial registration on the transplant waiting list. Patients were followed to the earliest of the following: liver transplantation, death, loss to follow-up, granting of exception score (to promote homogeneity in the study population; n = 2,337), living donor transplant (n = 951), or the end of the observation period (December 31, 2006—the most recent date for which reliable follow-up information was available at the time of the analysis). Status 1 candidates (n = 1,717) were also excluded. Cox regression was used to construct models of waiting list mortality. The model to evaluate diagnostic groups (ALD, HCV) used MELD scores at the time of registration. The model to compare the MELD effect by diagnostic groups used time-dependent MELD scores. All models were stratified by MELD and organ procurement organization and had the following covariates: diagnosis, age, sex, race, albumin, body mass index, diabetes, and medical condition classified as presence in the intensive care unit; hospitalized outside the intensive care unit; and not hospitalized.

To analyze posttransplantation mortality, a standard Cox regression model was used, with each patient's follow-up beginning at time of transplantation. Only pri-

Table 2. Influence of Diagnosis on Waiting List Mortality

Row	Patients	Comparison	HR	(95% CI)	*P* Value
1	All	ALD+ versus ALD−	1.03	(0.96-1.10)	0.47
2	HCV+	ALD+ versus ALD−	1.14	(1.04-1.25)	0.006
3	HCV−	ALD+ versus ALD−	0.93	(0.85-1.02)	0.12
4	All	HR: rows 2 versus 3	1.22	(1.08-1.38)	0.001
5	All	HCV+ versus HCV−	1.19	(1.09-1.30)	0.0001
6	ALD+	HCV+ versus HCV−	1.36	(1.21-1.53)	<0.0001
7	ALD−	HCV+ versus HCV−	1.11	(1.01-1.22)	0.02
8	All	HR: rows 6 versus 7	1.22	(1.08-1.38)	0.001

mary deceased-donor transplants were considered and adjustments were made for the same covariates used in the waiting list mortality model, plus pretransplant creatinine and donor risk index.[15]

In order to estimate transplant survival benefit (the mortality posttransplant relative to that on the transplant waiting list), we used sequential stratification, an analytic method that is an extension of Cox regression for evaluating time-dependent treatments (e.g., transplantation) in the presence of time-dependent patient variables.[16] In this analysis, each transplant recipient was matched to wait-listed patients who (at the time of the index patient's transplant) were at the same MELD score (i.e., share comparable clinical urgency), were from the same organ procurement organization, and had not been removed or deactivated. Patients in a given matched set were censored at transplant, but not if they were removed from the list for any other reason, or if their MELD score changed.

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Waiting List Mortality. As shown in Table 2, overall, the presence of ALD did not influence mortality on the waiting list (hazard ratio [HR] 1.03) Examining the issue in more detail, among HCV-positive (HCV+) subjects, the coincidence of ALD significantly contributed to mortality (HR 1.14, 95% confidence interval [CI] 1.04 -1.25; $P < 0.006$), whereas in HCV-negative (HCV−) patients, the presence of ALD had no effect (Table 2).

As also shown in Table 2, on average, the waiting list mortality of HCV infected patients was significantly greater than that in HCV- subjects (HR 1.19, $P = 0.0001$). The presence of HCV infection increased mortality in both ALD positive (ALD+) (HR 1.36, 95% CI 1.21-1.53; $P < 0.0001$) and ALD negative (ALD-) (HR 1.11, 95% CI 1.01-1.22; $P = 0.02$) subjects. Furthermore, as also indicated in Table 2 (rows 4 and 8), there was a significant interaction between HCV and ALD on waiting list mortality. Specifically, as indicated in row 4, the effect of ALD was significantly accentuated among HCV+ (compared with HCV−) patients, with the ratio of ALD+/ALD− HRs being 1.22 ($P = 0.001$). Correspondingly, the HCV effect on wait list mortality was significantly accentuated among ALD+ patients (row 8; $P = 0.001$).

In Table 3, we list the relative increase in waiting list mortality per one unit increase in MELD score, by ALD and HCV status. It can be seen that increasing MELD score was strongly associated with waiting list mortality in all four diagnostic categories. Moreover, it appears that MELD is a stronger predictor of waiting list mortality for ALD− compared to ALD+ patients (Table 3).

Posttransplant Mortality. The presence of ALD did not influence mortality after transplantation (HR 0.95), whereas posttransplant mortality was significantly greater in HCV-infected patients than in non-HCV subjects (HR 1.26, 95% CI 1.10-1.45; $P = 0.0009$) (see Table 4). Note that median posttransplant follow-up time was 1.76 years.

The coincidence of ALD did not significantly contribute to mortality in either HCV+ or HCV− subjects. In contrast, HCV infection increased posttransplant mortality in both ALD+ (HR 1.30, 95% CI 1.07-1.59; $P < 0.01$) and ALD− subjects (HR 1.25, 95% CI 1.08-1.45; $P = 0.004$), with the interaction between HCV and ALD on posttransplantation mortality being nonsignificant.

Transplant Survival Benefit. As shown in Fig. 1, selected patients with HCV alone or ALD alone demonstrated a survival benefit, which was significant in urgency strata defined by MELD scores ranging from 12 through

Table 3. Influence of MELD Score on Waiting List Mortality by Diagnosis

Diagnosis Group	Relative Increase in Waiting List Mortality per Unit Increase in MELD (95% CI)	*P* Value
ALD+, HCV+	17.4% (16.5-18.2)	<0.0001
ALD+, HCV−	17.9% (17.1-18.7)	<0.0001
ALD−, HCV+	19.7% (19.1-20.2)	<0.0001
ALD−, HCV−	19.2% (18.6-19.7)	<0.0001

Table 4. Influence of Diagnosis on Posttransplant Mortality

Row	Patients	Comparison	HR	(95% CI)	*P* Value
1	all	ALD+ versus ALD−	0.95	(0.85–1.06)	0.35
2	HCV+	ALD+ versus ALD−	0.97	(0.83–1.13)	0.70
3	HCV−	ALD+ versus ALD−	0.93	(0.80–1.08)	0.34
4	all	HR: rows 2 versus 3	1.04	(0.85–1.27)	0.69
5	all	HCV+ versus HCV−	1.26	(1.10–1.45)	0.0009
6	ALD+	HCV+ versus HCV−	1.30	(1.07–1.59)	0.01
7	ALD-	HCV+ versus HCV−	1.25	(1.08–1.45)	0.004
8	all	HR: rows 6 versus 7	1.04	(0.85–1.27)	0.69

40 for ALD patients, and among MELD scores from 15 through 40 for HCV. In both HCV-alone and ALD-alone recipients, the survival benefit tended to increase with greater waiting list urgency. Note that Fig. 1 pertains to patients with one (and only one) of HCV or ALD.

The influence of diagnosis on survival benefit was estimated by calculating the multiplier of HR for survival benefit in both diagnostic categories. Recall that the survival benefit HR is the covariate-adjusted ratio of posttransplant to wait list mortality; the lower the HR, the stronger the survival benefit. The multipliers in Table 5 indicate how this HR is modified by HCV and ALD. An HR multiplier greater than 1 indicates that the presence (versus absence) of a diagnosis (be it HCV or ALD) increases the benefit HR and, hence, reduces the survival benefit derived from liver transplantation; the opposite is true if the HR multiplier is less than 1. As shown in Table 5, HCV+ patients experienced significantly less liver transplant survival benefit than HCV− recipients, at MELD scores in the 9-14 (33% reduction in survival benefit; $P = 0.03$) , and 15-29 strata (15% reduction; $P = 0.04$), whereas HCV patients with high MELD scores (30-40) experienced a significantly greater benefit (by 31%; $P = 0.0008$). In contrast, the presence of ALD when compared with nonalcoholic transplant recipients did not influence survival benefit ($P > 0.05$ for all MELD categories).

We performed various sensitivity analyses. Although MELD allocation did not commence until February 2002, the recording of MELD scores was mandatory from September 2001 onward. All patients included in the study are MELD-era patients, in the sense that mandated MELD scores are available for all. As a check, we refitted the models with pre-MELD (allocation) era as an adjustment covariate. The results were virtually identical to those reported (data not shown). This is not surprising, for two reasons. First, only 3,620 of 38,899 (i.e., only 9%) of the population was initially listed during the period of September 2001 through February 2002. Second, it is unlikely that patients listed during this period are systematically different than the remainder of the study popula-

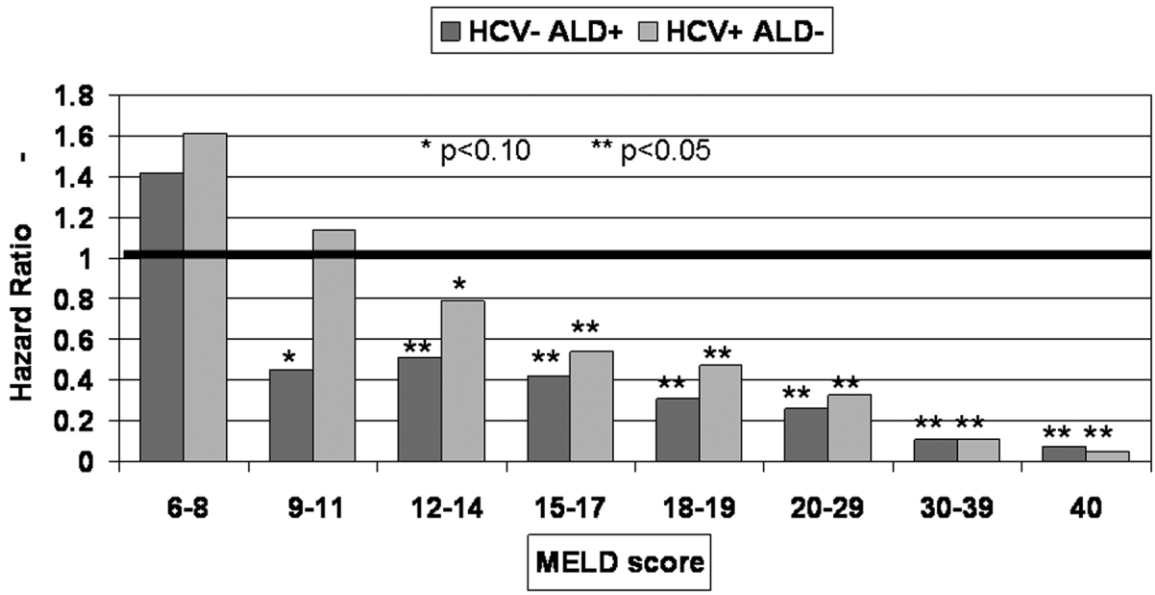

Fig. 1. Transplant survival benefit by diagnosis (HCV−/ALD+, HCV+/ALD−) and MELD score. *$P < 0.10$. **$P < 0.05$.

Table 5. Influence of HCV and ALD Transplant Survival Benefit by MELD Score

MELD	HCV Multiplier of HR for TX / WL	ALD Multiplier of HR for TX / WL
6-8	0.67 ($P = 0.24$)	0.94 ($P = 0.91$)
9-14	1.33 ($P = 0.03$)	0.96 ($P = 0.79$)
15-29	1.15 ($P = 0.04$)	0.97 ($P = 0.65$)
30-40	0.59 ($P = 0.0008$)	0.77 ($P = 0.12$)

tion with respect to diagnosis or mortality, after adjusting for MELD and the lengthy list of other adjustment covariates.

Subjects were not stratified according to the presence of hepatocellular carcinoma. There were 969 HCCs among the HCV+/ALD− cohort, 186 among the HCV−/ALD+ cohort, 137 among subjects with both HCV and ALD, and 904 among the subjects without either diagnosis. Results were virtually unchanged upon exclusion of HCC patients, which makes sense given that HCC is only a modest predictor of mortality (data not shown).

Discussion

Liver transplantation takes place within a continuum of care. In the early papers on liver transplantation, outcome tended to be assessed by measuring patient or graft survival from the time of transplantation. Such studies did not consider the interval before transplantation, perhaps because waiting times tended to be short. In recent years, many patients spent an extended time on the liver transplant waiting list. According to UNOS, the median waiting time before transplantation for liver transplant candidates in blood group O in 2003 to 2004 was 458 days (95% CI 414-508).[1] Unfortunately, patients may die while waiting. An analysis of U.S. adult liver transplant candidates added to the waiting list between February 2002 and June 2005 and followed up to November 2005 indicated that 15.3% (range, 0%-32.2%) died or were withdrawn from the list due to deterioration before receiving a liver transplant.[17] In 2007, 2,395 persons were removed from the liver transplant waiting list either because of death or because they were too sick to undergo transplantation.[1] Adopting a notion akin to the intent-to-treat principal used in randomized controlled clinical trials, the death of these patients can be judged as a failure of transplantation. At the same time, up to two-thirds of all recipients in the UNOS database were surviving at 5 years.[1] Therefore, it was appropriate to include events in the first 5 years after transplantation when considering the success of transplantation.

Survival benefit considers outcome of transplantation by starting the clock at the time of placement on the waiting list, and encompasses events in the pretransplant waiting list time interval, the peritransplant and posttransplant long-term follow-up.[13,14] Pretransplant mortality reflects severity of liver failure. Perioperative mortality is influenced by severity of candidate illness, but also by quality of the donor graft and by perioperative complications such as vascular injury. Late mortality is influenced by recurrent disease such as cancer or hepatitis, by new onset diseases, and worsening systemic disorders that are often exacerbated by medications. By adopting survival benefit as a measure of success in liver transplantation, Schaubel et al.[14] were able to show that a combination of recipient urgency and donor organ quality determined whether it was better for an individual patient to progress to transplantation with a donor graft, or whether waiting for the next allograft with a lesser risk profile was the better option.

In the present analysis, we found distinct differences in waiting list mortality, posttransplant mortality, and transplant survival benefit between patients infected with HCV and patients with ALD. HCV patients were at increased risk for waiting list mortality when compared with patients without HCV, and this effect was greater in subjects with both HCV and ALD. On the other hand, ALD patients had the same pretransplant mortality as non-ALD patients. This is itself interesting because in the original derivation of the MELD score, patients with alcoholic liver disease or primary biliary cirrhosis had a short-term survival benefit compared with patients with other forms of liver failure.[18] The present analysis failed to confirm this advantage in the alcoholic cohort. In contrast, the present data suggest that HCV infection per se affects mortality, as opposed to only leading to mortality through liver failure from cirrhosis or hepatoma. These data also suggest that successful treatment of HCV in the pretransplantation phase might reduce the need for transplantation.

Posttransplant mortality was greater in HCV+ subjects than HCV− recipients. In contrast, ALD did not influence posttransplant mortality. These data suggest that HCV infection is progressive and harmful to patient and graft survival, consistent with previous reports.[19] The absence of impact of ALD can be explained by the relative infrequency of posttransplantation alcoholism and the observation that it takes up to 10 years to see an adverse effect on graft survival in the subset of patients who return to heavy drinking.[20-22]

When contrasting wait list and posttransplantation survival, both ALD+ and HCV+ patients showed a survival benefit from liver transplantation. However, whereas ALD did not affect the survival benefit compared with non-ALD patients, the HCV+ cohort in the inter-

mediate urgency MELD scores had a lesser survival benefit than non-HCV subjects. Because survival benefit was enhanced when pretransplant mortality was greatest, whereas survival benefit was reduced with greater posttransplant mortality, the effect of these two elements in the HCV patients might be expected to cancel each other out. The fact that survival benefit was worse in the HCV+ cohort shows that the influence of posttransplant mortality outweighed the influence of pretransplant mortality in HCV+ patients in the mid-range MELD scores. The implication of this observation is that when considering strategies aimed at improving transplant benefit in HCV-infected persons, it will be necessary to address both pre- and posttransplant survival. One attractive option is pretransplant antiviral treatment, which reduces pretransplant deaths and also ameliorates posttransplant infection, thereby improving on transplant survival benefit. Everson et al.[23] demonstrated the potential of this approach in a proof of principal paper that used interferon-α and ribavirin, starting in low doses and gradually increasing the exposure to both agents. Unfortunately, toxicity and tolerability limit the efficacy of interferon-α and ribavirin in this population, and more effective, less toxic antiviral agents will be needed for a pretransplant antiviral strategy to fully impact transplant survival benefit.

Among patients with MELD $\geq$30 (i.e., those with the highest wait list mortality and greatest transplant benefit), our results indicate that the survival benefit for HCV-infected patients is significantly greater than that of similar non-HCV patients. However, we would not advocate an addition (upward adjustment) to the MELD score for HCV patients, absent a more comprehensive refocusing of the waiting list methodology, which would itself require a systematic consensus-driven review of waiting list priorities and goals of therapy. Similarly, we would not be in favor of imposing a subtraction to the MELD score for HVC+ patients with MELD 9-29, even though such patients were found to have significantly reduced survival benefit relative to similar HCV− patients.

Our study does have limitations. Due to the use of registry data, there are several potential sources of imprecision in our study, such as inconsistent classification of diagnosis by the recording transplant programs, or inconsistent application by the UNOS regional review boards of the rules to grant MELD exception scores. Given that such misclassification is likely to be independent of the patient's prognosis, such imprecision would tend to attenuate—as opposed to accentuate—the results we report.

Recent analyses suggest that serum sodium predicts wait list mortality.[24] Because serum sodium concentration was not a requested datum in the Scientific Registry of Transplant Recipients database before 2004, it was missing for more than half the records in the analysis. Notwithstanding this limitation, when we repeated the analysis adjusting for serum sodium (treating "missing" as a separate category), the results were virtually identical to those presented. Hence, it appears that the correlation of serum sodium with each of HCV and AC was insufficient to introduce bias into the results we report.

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