American Journal of Transplantation 2006; 6: 140–149
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01161.x

Refractory Ascites After Liver Transplantation: An Analysis of 1058 Liver Transplant Patients at a Single Center

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A retrospective study of 1058 liver transplant recipients was performed to determine: (i) the incidence, etiology, timing, clinical features and treatment of refractory ascites (RA), (ii) risk factors for RA development, (iii) predictors of RA disappearance, (iv) predictors of survival following RA and (v) the impact of RA on patient survival. Sixty-two patients (5.9%) developed RA and its disappearance occurred in 27/62 cases. Patients having hepatitis C virus (HCV) had a significantly higher hazard rate of developing RA ($p < 0.00001$). No other baseline characteristic was associated with RA. Cox stepwise regression analysis of the hazard rate of RA disappearance found two significant factors: HCV recurrence as the reason for developing RA implied a poorer outcome ($p = 0.006$), whereas an unknown reason implied a favorable outcome ($p = 0.02$). In addition, survival following RA was significantly poorer among patients having bacterial peritonitis or HCV recurrence. Finally, the mortality rate was significantly (nearly 8.6 times) higher in patients following RA development while it was ongoing ($p < 0.00001$); however, if the RA disappeared, then the additional risk of death also disappeared. This study illustrates the importance of developing an optimal treatment strategy to (i) effectively treat RA if it develops and (ii) prevent hepatitis C recurrence.

Key words: Complication, hepatitis C, liver transplant, refractory ascites

Received 11 July 2005, revised 12 September 2005 and accepted for publication 26 September 2005

Introduction

Ascites is a common complication of advanced liver disease (1), and refractory ascites (RA) occurs when it cannot be satisfactorily treated by medical therapy. RA is known to carry a poor prognosis, with a 1 year transplant-free survival in advanced cirrhotic patients of 20–50% (2). Patients with RA usually have additional complications, including spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic hydrothorax (3–4). Large volume paracentesis (LVP), a transjugular intrahepatic portosystemic shunt (TIPS), peritoneovenous shunts and portocaval shunts have all been used (1–9) in treating patients with RA. Liver transplantation (LT) is the best therapeutic option for patients with end-stage liver disease and ascites, because the ascites usually disappears after LT. Ascites after LT has been reported, and its occurrence has been associated with hepatic vein outflow obstruction (10–12). The occurrence of RA following LT has been associated with stenosis of the inferior caval anastomosis, the piggyback technique, acute rejection, veno-occlusive disease, small-sized graft and a hypercoagulable state (10–23). However, because of its relative rarity of occurrence RA after LT has not yet been well studied. We therefore performed a retrospective study of 1058 consecutively treated adult liver transplant recipients at our center in order to more clearly determine: (i) the overall incidence, etiology, timing, clinical features and treatment of RA, (ii) risk factors for the occurrence of RA, (iii) predictors of the rate of disappearance of RA, (iv) predictors of survival following the occurrence of RA and (v) the impact that RA development has on patient survival. The results are provided in this report.

Materials and Methods

This is a retrospective review of 1174 consecutive cadaveric whole liver transplants performed in 1058 adult patients from November, 1993 to July, 2002 at the University of Miami/Jackson Memorial Medical Center. Patients who simultaneously received other organs (e.g. a kidney) in addition to the orthotopic liver transplant were not included in this study. Median follow-up among the ongoing survivors (as of the last follow-up date, October 31, 2004) was 75 months (range 27–131 months). Clinical data were obtained by retrospective review of medical records and computerized databases. Consistent with the definition established by the International Ascites Club (1), RA was defined as ascites that could not be satisfactorily treated by

medical therapy. In all cases at this center LVP was used to treat RA that did not respond to medical therapy.

Main indications for LT in our cohort included hepatitis C (44.8%), Laennec's (12.9%), cryptogenic (9.5%), etc. (distributions of baseline recipient and donor characteristics are displayed in Table 1). The liver grafts were procured using the standard organ procurement technique (24) and preserved with University of Wisconsin solution (25). Caval anastomoses were performed using the conventional technique (26) in 14.0% of the patients, our standard piggyback technique with 3 hepatic vein cuffs (27) in the majority of patients (75.1%) and other techniques including the modified piggyback technique with 1 hepatic vein or 2 hepatic vein cuffs (28), cavo-cavostomy (29–30) and cavoplasty (31) in the remaining 10.9% of the patients (Table 1). Hepatic arterial anastomoses were performed using the recipient hepatic artery (78.5%) or donor iliac arterial graft from the recipient aorta (21.5%). Biliary anastomoses were performed mainly as choledocho-choledochostomy (32.9%) or choledocho-jejunostomies (67.0%) with Roux-en-Y loops. Tacrolimus and steroids (methylprednisolone) were used as maintenance immunosuppression. Acute rejection episodes were treated with either steroids or OKT3, depending on the severity of the episode.

Our protocol for managing patients who develop ascites following orthotopic LT requires everyone to receive intensive diuretic therapy for at least one week (spironolactone and furosemide) along with a salt-restrictive diet. Lack of response or early recurrence of ascites which cannot be satisfactorily treated by medical therapy is defined as RA. LVP was used in treating each patient with RA. After each LVP was performed an intravenous infusion of albumin was administered (12.5 g/L of ascites removed). If clinically indicated, a determination of albumin or protein in the ascites fluid was made along with bacterial culture, cell count and cytology. In all patients with RA, Doppler ultrasound of the liver (DUSL) was performed to check the patency of the inferior vena cava, hepatic vein, portal vein and hepatic

Table 1: Distributions of baseline recipient and donor characteristics and results of the Cox stepwise regression analysis for the hazard rate of developing RA

Baseline chararcteristic	Observed N and median (range) if continuous, percentage if categorical	Univariable score test $p-value$	Cox model selection (y)	Cox model coefficient ±SE
Date of transplant	1058 4/1/1998 (11/1993–7/2002)	0.20		
Recipient age (years)	1058 51 (16–77)	0.61		
Donor age (years)	1057 39 (4–87)	0.13		
Male sex (recipient)	63.7% (674/1058)	0.88		
Recipient body weight (kg)	919 78.6 (29.5–159.1)	0.14		
Primary disease				
Cryptogenic	9.5% (101/1058)	0.67		
Hepatitis B	7.9% (84/1058)	0.93		
Hepatitis C	44.8% (474/1058)	< 0.00001	(y)	1.22 ± 0.28
Laennec's	12.9% (136/1058)	0.15		
Primary sclerosing cholangitis	5.1% (54/1058)	0.85		
Fulminant	4.6% (49/1058)	0.08		
Primary biliary cirrhosis	4.4% (47/1058)	0.06		
Autoimmune hepatitis	4.2% (44/1058)	0.11		
Other	6.5% (69/1058)	0.04		
Cold ischemia time (min)	994 463 (120–1350)	0.55		
Operating time (min)	931 600 (228–2174)	0.78		
PRBC (units)	1023 10 (0–120)	0.88		
VenaCava anastomosis				
Piggyback with 3 HV's	75.1% (795/1058)	0.73		
Piggyback varient	10.9% (115/1058)	0.99		
Conventional	14.0% (148/1058)	0.65		
Biliary anastomosis				
Choledocho-choledochostomy	32.9% (347/1056)			
Hepatico-jejunostomy	67.0% (708/1056)	0.59		
External	0.1% (1/1056)			
Artery				
Recipient hepatic artery	78.5% (831/1058)	0.75		
Arterial graft from aorta	21.5% (227/1058)			
Portal vein thrombosis	11.0% (116/1058)	0.94		
Veno-venous bypass	26.9% (285/1058)	0.26		
Replaced donor hepatic artery	22.0% (233/1058)*	0.16		
Pre-Tx serum Cr (mg/dL)	1055 0.9 (0.2–9.6)	0.19**		
Pre-Tx UNOS status:				
1	9.7% (93/960)	0.31		
2	53.3% (512/960)			
3	37.0% (355/960)	0.03		

*Numbers with left replaced, right replaced and both replaced were 93, 91 and 49, respectively.
Abbreviations: PRBC, packed red blood cells; HV's, hepatic vein cuffs.
**Due to the skewness of the serum Cr (creatinine) distribution, its p-value was based on the use of log-transformed values.

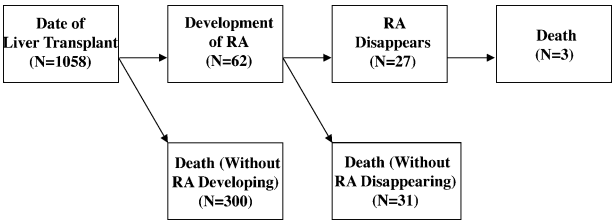

Figure 1: Clinical outcomes with respect to the development and disappearance of refractory ascites (RA) and death following orthotopic liver transplantation.

artery, and further diagnostic angiographic examinations were performed in most cases. Computed tomographic scanning, hemodynamic studies, coagulation studies and liver biopsies were also performed if clinically indicated. Rejection treatment, antibiotic therapy, radiological intervention, TIPS, Le Veen shunt, reanastomosis of the caval anastomoses and retransplantation were performed depending on the etiology and treatability of the RA.

Clinical outcomes with respect to the development of RA, disappearance of RA, and death following orthotopic LT are shown in Figure 1. Of the 1058 patients in this study, 62 (5.9 %) were observed to develop RA. Disappearance of the RA was observed in 27 of these 62 cases. The following numbers of patient deaths were observed: 300 without the development of RA, 31 following RA without its disappearance and 3 following RA and its disappearance.

A most important set of prognostic factors was determined using a Cox model (32–33) stepwise regression approach for each of the following outcome variables: (i) the hazard rate of developing RA, (ii) the hazard rate of RA disappearance following its development and (iii) the hazard rate of death following the development of RA. The first hazard rate (i.e. the hazard rate of developing RA) was modeled as time (in months) following transplantation, and the latter two hazard rates were modeled as time (in months) following the development of RA. In each of these analyses the score chi-squared test criterion was used, and any failures not due to the cause of interest (i.e. death when modeling either the hazard rate of developing RA or the hazard rate of RA disappearance) were treated as censored observations. Categorizations of continuous variables were considered in the prognostic factor analyses along with log transformations of highly skewed variables. In order to avoid the possibility of obtaining spurious results, only variables with univariable p-values of 0.05 or less were considered for entry into the Cox models. Subgroup differences for a particular hazard rate were also tested by the logrank test, and graphical display of these subgroup differences were shown using Kaplan-Meier curves. Tests of association were performed using *t*-tests and Pearson (uncorrected) chi-squared tests.

Baseline variables that were considered for their prognostic value included: date of transplant, age, sex, primary disease and body weight (kg) of the recipient, donor age, cold ischemia time, total operating time, number of units of packed red blood cells, fresh frozen plasma and platelets transfused at surgery, type of vena cava anastomosis, type of biliary anastomosis, use of an arterial graft (yes/no), presence of portal vein thrombosis (PVT) (yes/no), use of veno-venous bypass (yes/no), replacement of the donor hepatic artery (yes/no), pre-transplant serum creatinine level and pre-transplant UNOS status. Due to the retrospective nature of this study, accurate information as to the extent of pre-transplant ascites was not available. In addition, since most of these patients were transplanted prior to the implementation of the MELD score, the pre-transplant biochemical determinations total serum bilirubin, international normalized ratio and serum albumin were not considered. Variables determined at the time of development of RA that were considered for their prognostic value included: the reason for developing RA, time from transplant (in months) to the development of RA and the serum creatinine level.

Finally, the impact of the development of RA on the patient's subsequent risk of death was determined. Here, the outcome variable of interest was the hazard rate of death as a function of time (in months) following transplantation, and in order to avoid what is known as length-time bias (i.e. mistakenly assigning RA status at baseline), the development of RA was modeled as an indicator time dependent covariate in Cox's model (32–35), that is, $z1\{t\} = 1$ if RA has developed by time t, 0 otherwise. In this model the hazard rate of death at t months post-transplant was compared between patients that have vs. have not developed RA by time t. A second Cox regression model was fitted using two time dependent covariates, one representing the effect of RA development without its disappearance (i.e. $z2\{t\} = 1$ if RA developed but has not disappeared by time t, 0 otherwise) and the other representing the lasting effect of RA following its disappearance (i.e. $z3\{t\} = 1$ if RA has developed and disappeared by time t, 0 otherwise). In this latter model, it was of interest to determine how the increased risk of death following RA development changed once the RA had disappeared (i.e. comparison of the $z2\{t\}$ and $z3\{t\}$ effects). Finally, nonparametric representation of the effects of these time dependent covariates on the cumulative hazard was displayed using a generalization of Nelson-Aalen's cumulative hazard estimator (36–40). The advantage in using nonparametric estimates of the cumulative hazard is that (i) the shape of the hazard rate and comparisons among group-specific rates are directly assessed from the slopes of the cumulative hazard curves and (ii) the Cox model results are visually portrayed by these nonparametric estimates.

Results

Results of the Cox stepwise regression analysis for the hazard rate of developing RA are shown in Table 1. One factor was selected containing independent prognostic value, specifically, patients having hepatitis C virus (HCV) as their primary disease had a significantly higher hazard rate of developing RA ($p < 0.00001$). Once this factor was selected into the Cox model, no other variables contained additional prognostic information ($p > 0.05$). None of the other baseline demographic and biochemical characteristics (date of transplant, recipient age, sex and body weight, donor age and pre-transplant serum creatinine level) were associated with this outcome variable; nor were any of the surgery-related variables including cold ischemia time, operating time and number of units of packed red blood cells transfused during surgery (same for the number of transfused units of fresh frozen plasma and platelets; results not shown). Although patients with UNOS Status 3 had a significantly higher hazard rate of developing RA ($p = 0.03$), these patients were more likely to have hepatitis C as their primary disease ($p = 0.008$). Graphical portrayal of the HCV effect is shown by the Kaplan-Meier freedom from developing RA curves in Figure 2. Although HCV as the primary disease comprised 44.8% of the entire cohort, 72.6% (45/62) of the patients who developed RA had HCV as the primary disease. The observed percentage of patients who developed RA was 9.5% (45/474) among those

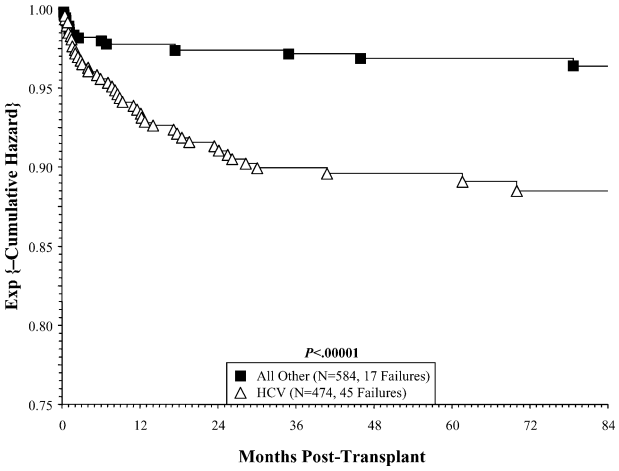

Figure 2: Kaplan-Meier freedom from development of RA curves by primary disease status: hepatitis C virus (HCV) infection versus all other subgroups combined ($p < 0.00001$).

with HCV as their primary disease in comparison with only 2.9% (17/584) for all other patients. On further review it also became clear that among those who developed RA, the median time to developing RA was actually distinctly longer among the 45 patients with HCV (8.2 months) in comparison with the 17 other patients (1.1 months).

Differing percentages of patients having pre-transplant renal insufficiency according to primary disease were found. Specifically, the percentage of patients having a pre-transplant serum creatinine $\geq$1.5 mg/dL was quite low in patients having primary biliary cirrhosis (2.1%, 1/47) and primary sclerosing cholangitis (3.7%, 2/54), slightly higher in patients having other (8.7%, 6/69), hepatitis B (9.5%, 8/84), autoimmune hepatitis (11.4%, 5/44), and HCV (11.9%, 56/472), and even higher in patients having Laennec's (19.3%, 26/135), cryptogenic (26.7%, 27/101) and fulminant (34.7%, 17/49) liver disease ($p < 0.00001$). The observed incidence of RA in the two subgroups having the least and in the three subgroups having the most renal insufficiency pre-transplant was 3.0% and 3.8%, respectively. Clearly, this lack of a difference supports the finding in Table 1 that pre-transplant renal insufficiency is not a strong predictor of the incidence rate of developing RA post-transplant.

Results of the Cox stepwise regression analysis for the hazard rate of RA disappearance following its development appear in Table 2. Two characteristics were selected into the Cox model containing independent prognostic value:

Table 2: Results of the Cox stepwise regression analysis for the hazard rate of RA disappearance following its development

Chararcteristic	Observed N and median (range) if continuous, % if categorical	Univariable score test p-value	Cox model selection (y) & score test p-value	Cox model coefficient ±SE
Reason for developing RA				
HCV recurrence	27.4% (17/62)	0.0004	(y) 0.006	−2.32 ± 1.04
Unknown	27.4% (17/62)	0.00007	(y) 0.02	0.90 ± 0.40
Other*	45.2% (28/62)	0.88		
Time to develop RA (months)	62 6.4 (0.2–78.6)	0.003**		
Time to develop RA ≥3 (months)	59.7% (37/62)	0.001		
Serum Cr (mg/dL) at RA	62 1.4 (0.5–5.6)	0.93**		
Date of transplant	62 11/1/1997 (3/1994–7/2002)	0.10		
Recipient age (years)	62 49 (28–71)	0.22		
Donor age (years)	62 43.5 (8–84)	0.18		
Male sex (recipient)	64.5% (40/62)	0.77		
Recipient body weight (kg)	54 82.7 (40.0–126.4)	0.90		
HCV as primary disease	72.6% (45/62)	0.02		
Cold ischemia time (min)	58 480 (203–900)	0.95		
Operating time (min)	53 580 (290–1140)	0.35		
PRBC (units)	60 10 (0–69)	0.99		
VC piggyback with 3 HV's	77.4% (48/62)	0.49		
Hepatico-jejunostomy	69.4% (43/62)	0.58		
Recipient hepatic artery	80.7% (50/62)	0.71		
Portal vein thrombosis	9.7% (6/62)	0.34		
Veno-venous bypass	21.0% (13/62)	0.03		
Replaced donor hepatic artery	14.5% (9/62)	0.84		
Pre-Tx UNOS status 3	51.8% (28/54)	0.76		

*The other reasons for developing RA include acute or chronic rejection (N = 10), bacterial peritonitis (N = 5), anastomotic stricture (N = 3), tumor (N = 3), hepatic artery thrombosis (N = 1), hepatitis B recurrence (N = 1), liver failure due to alcohol (N = 1), outflow problem (N = 1), portal vein thrombosis (N = 1), pulmonary hypertension (N = 1) and small transplanted liver (N = 1).

**Due to skewness of the time to developing RA and serum creatinine distributions, their p-values were based on using log transformed values. Abbreviations: PRBC, packed red blood cells; HV's, hepatic vein cuffs.

patients whose reason for developing RA was HCV recurrence had a significantly lower rate of RA disappearance ($p = 0.0004$ on univariable analysis and $p = 0.006$ in the Cox model) and patients with an unknown reason for developing RA had a significantly higher hazard rate of RA disappearance ($p = 0.00007$ on univariable analysis and $p = 0.02$ in the Cox model). Once these two factors were selected, no other variables contained additional prognostic value ($p > 0.05$). Three other factors were associated in univariable analysis with a significantly lower hazard rate of RA disappearance: time to develop RA $\geq$3 months ($p = 0.001$), HCV as primary disease ($p = 0.02$) and the use of a veno-venous bypass ($p = 0.03$). However, each of these factors was associated with the two variables already selected into the Cox model. Specifically, the percentage with a time to developing RA $\geq$3 months among patients whose reason for developing RA was HCV recurrence, unknown, and all other was 100% (17/17), 17.7% (3/17) and 60.7% (17/28), respectively ($p < 0.00001$). HCV recurrence as the reason for developing RA obviously occurred only in patients that had HCV as their primary disease, and having an unknown reason for developing RA was significantly less likely in patients that had a veno-venous bypass, 0% (0/13), in comparison with the others, 34.7% (17/49) ($p = 0.01$). Finally, the Kaplan-Meier freedom from RA disappearance curves in Figure 3 reflect the results of the Cox model in Table 2: the observed proportion of patients having RA that disappeared was only 1/17 among those with HCV recurrence as the reason for developing RA versus 14/17 among those with an unknown reason, and 12/28 for the others.

It should be noted that while the serum creatinine level at the time of RA development ($N = 62$) was not associated with the subsequent rate of RA disappearance (Table 2), the geometric mean creatinine level increased significantly

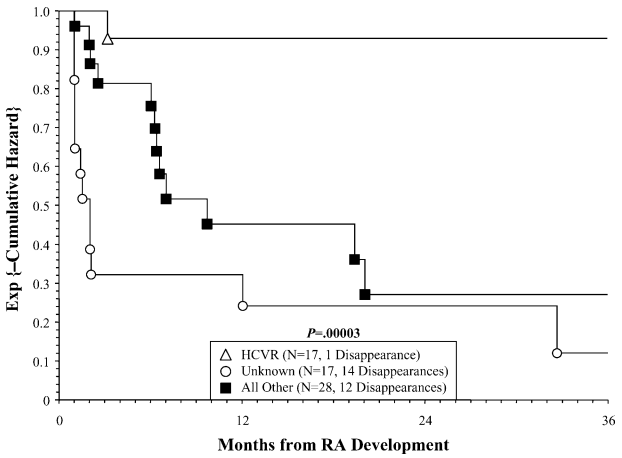

Figure 3: Kaplan-Meier freedom from disappearance of RA curves by reason for developing it: hepatitis C virus recurrence (HCVR), unknown, and all other ($p = 0.00003$).

in these patients between the time of transplantation and RA development: 1.04 ($SE = 1.04$) at transplantation versus 1.55 ($SE = 1.06$) at RA development ($p < 0.00001$). The percentage of these patients having a serum creatinine level $\geq$1.5 mg/dL was only 16.1% (10/62) at pre-transplant versus 50.0% (31/62) at the time of RA development ($p = 0.0002$, by McNemar's test). A significant increase in the serum creatinine level between the time of transplantation and RA development was observed for each 'reason for developing RA' subgroup. However, the percentage of patients having a serum creatinine level $\geq$1.5 mg/dL at the time of RA development was actually lower among those whose reason for developing RA was HCV recurrence in comparison with the other patients: 23.5% (4/17) versus 60.0% (27/45) ($p = 0.01$). This finding apparently suggests that the contribution of renal insufficiency to RA development may actually be less among those whose reason for developing RA is HCV recurrence.

In this study, 32 patients (51.6%) who developed RA underwent angiography. Four patients had stenosis of the caval anastomoses. Two of these patients had the piggyback technique performed for the caval anastomosis, and two underwent other techniques. Three were treated with balloon dilatation and one with reanastomosis. All are doing well.

With respect to death following the development of RA, there were five patients that had bacterial peritonitis as the reason for developing RA; each of them died within 4 months following RA development. Excluding this small high risk group, the Cox stepwise regression analysis found only one factor that contained significant prognostic value for the hazard rate of death following RA development: HCV recurrence as the reason for developing RA ($p = 0.004$). Its Cox model coefficient $\pm$SE was 1.07 ± 0.39. Once this unfavorable factor was selected, no other variables contained additional prognostic value ($p > 0.1$). These results are depicted by the Kaplan-Meier survival following RA development curves in Figure 4, which show that the estimated probabilities of surviving 2 years following RA development for patients who developed RA because of bacterial peritonitis, HCV recurrence, and all other reasons were 0.0%, 35.3% and 70.0%, respectively. The fact that RA disappearance did not occur in 21 of the 22 patients having bacterial peritonitis or HCV recurrence as the reason for developing RA appears to indicate the importance of RA disappearance in achieving a more favorable survival outcome.

In terms of overall patient survival, Figure 1 shows that a total of 334 deaths were observed in this cohort of 1058 patients. A Kaplan-Meier survival curve for the whole cohort yielded actuarial survival probabilities at 1, 3 and 5 years of 0.84 ± 0.01, 0.76 ± 0.01 and 0.70 ± 0.01, respectively (figure not shown). There were 203 patients still alive at 8 years post-transplant, and the Kaplan-Meier survival estimate at that time was 0.65 ± 0.02.

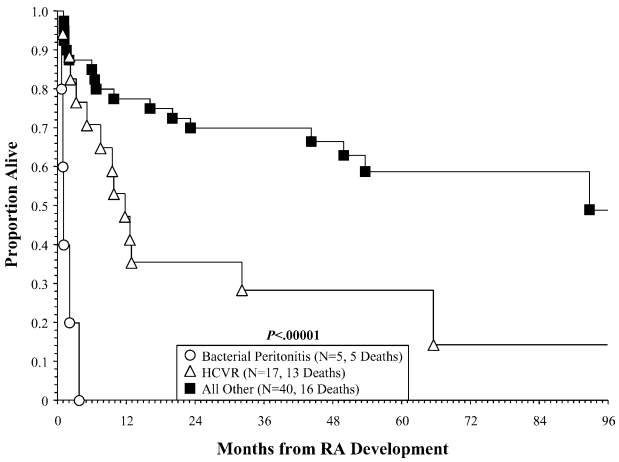

Figure 4: Kaplan-Meier survival following development of RA curves by reason for developing it: bacterial peritonitis, hepatitis C virus recurrence (HCVR) and all other ($p < 0.00001$).

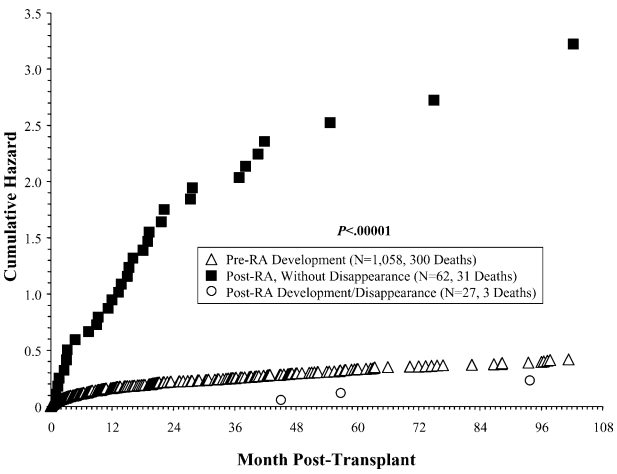

Figure 5: Nonparametric cumulative hazard plot of the mortality rate following orthotopic liver transplantation by three patient states: RA has not developed by time t (months post-transplant), RA has developed but not disappeared by time t, and RA has both developed and disappeared by time t ($p < 0.00001$).

Table 3: Cox model results to test the impact of (i) RA development and (ii) RA development prior to and following its disappearance on the hazard rate of death

	Model	Model coefficient	Wald test	
	covariate	±SE	Statistic	P-value
Cox model (i):	Z1{t}	1.39 ± 0.19	57.4	<0.00001
Cox model (ii)*:	Z2{t}	2.15 ± 0.19	129.1	<0.00001
	Z3{t}	−0.51 ± 0.58	0.7	0.38

Time dependent covariate definitions:
Z1{t} = 1 if the patient developed RA by time t months post-transplant, 0 otherwise.
Z2{t} = 1 if the patient developed RA without its disappearance by time t months post-transplant, 0 otherwise.
Z3{t} = 1 if the patient developed RA along with its disappearance by time t months post-transplant, 0 otherwise.
*The Cox model coefficients representing the effects of Z2{t} and Z3{t} were highly significantly different (likelihood ratio test statistic was 36.6, $p < 0.00001$).

Finally, it was of interest to assess the impact of RA development on patient survival. Cox model results of testing the impact of (i) RA development and (ii) RA development prior to and following its disappearance on the hazard rate of death are shown in Table 3. The first Cox model shows a highly significant unfavorable effect of RA development on patient survival (the effect of Z1{t}, $p < 0.00001$). However, a more accurate depiction is shown by the second Cox model in the table. Here, the unfavorable effect of RA development is shown to exist only as long as the RA does not disappear (the effect of Z2{t}, $p < 0.00001$); the Cox model coefficient and Wald test statistic for Z2{t} in the second model are much larger in comparison with those obtained for Z1{t} in the first model. In fact, the Cox model results indicate that the mortality rate following the RA development, while it is ongoing, is nearly 8.6 times greater (exponential function of the Cox model coefficient for Z2{t}) than the mortality rate among patients not having RA. In addition, not only was the effect of RA development without its disappearance (Z2{t}) highly significantly different from the longer-term effect of RA following its disappearance (Z3{t}) (P<.00001), but the Cox model coefficient for the effect of RA following its disappearance (Z3{t}) was not significantly different from zero ($p = 0.38$). This result indicates that the post-transplant mortality rate appears to be the same for patients whose RA has disappeared in comparison with those who did not or never will develop RA, that is, the significantly higher mortality rate that exists following the development of RA completely disappears once the RA itself disappears. These results remained the same if the baseline 'HCV as primary disease' variable was controlled in the model, and the significantly reduced mortality following RA disappearance was not affected by the time from RA development-to-its disappearance (results not shown). Lastly, graphical representation of the results of the second Cox model is shown by the cumulative hazard plot in Figure 5, where the mortality rate (slope of the curve) at a given time t months post-transplant is compared among patients in three distinct states: RA has not developed by time t (1st patient state, with 300 observed deaths), RA has developed but not disappeared by time t (2nd patient state, with 31 observed deaths), and RA has both developed and disappeared by time t (3rd patient state, with three observed deaths). The slopes of the curves in the figure indicate that (i) the mortality rate is much higher while the patient has ongoing RA and (ii) the mortality rate following RA disappearance is similar to the mortality rate that exists prior to its development.

Discussion

This study illustrates the following points. Firstly, the incidence of RA after LT was 5.9% and disappearance of RA occurred in slightly fewer than half of the patients who developed it. Secondly, hepatitis C as the primary disease was the sole factor associated with a significantly higher incidence rate of RA developing after LT; a similar result was recently reported in another study (41). Thirdly, there was no association between the piggyback technique and the incidence rate of RA after LT. Fourthly, the most important predictors of (i) the rate of RA disappearance following its development, and (ii) the mortality rate following RA development were the reasons for RA development. Specifically, hepatitis C recurrence as the reason for developing RA was associated with a significantly lower rate of RA disappearance along with a significantly higher mortality rate following RA development. In addition, patients with an unknown reason for developing RA had a significantly higher rate of RA disappearance, whereas all of the patients with bacterial peritonitis as the reason for developing RA died shortly after its development. Most of the patients with an unknown reason for developing RA had an early development of RA (within 3 months post-transplant), whereas all of the patients whose reason for developing RA was hepatitis C recurrence had a late RA development. Lastly, the mortality rate was significantly higher in patients following RA development as long as it was ongoing; however, once the RA disappeared (if it did), the additional risk of death also disappeared.

Traditionally, outflow obstruction due to stenosis of the hepatic veins or upper caval anastomoses by the piggyback technique has been reported (10–12). This study confirmed that outflow obstruction of the caval anastomoses occurs. However, the results in Table 1 show no effect of type of vena cava anastomosis on the hazard rate of developing RA, and the data in Tables 1 and 2 shows a similar percentage that developed RA between those having piggyback with three hepatic vein cuffs versus the other patients, 6.0% versus 5.3%. Among the 14 patients who developed RA without having piggyback with three hepatic vein cuffs, 7 patients had conventional anastomosis (4.7%) and 7 patients had piggyback variant (6.1%), which includes the modified piggyback technique, cavocavostomy and cavoplasty. It is well known that caval anastomotic stenosis causes outflow obstruction and subsequently causes RA. Analysis of the complications of piggyback technique in a multi-center study from Europe showed outflow complications were significantly more frequent when venous reconstruction was performed using two suprahepatic veins than when the three veins were used (10). Cirera et al. (11) reported that after their technical modification to use all three hepatic veins for piggyback anastomosis (previously they had used only the left and medium hepatic veins), massive ascitic fluid loss in their patients had become anecdotal. Our standard method utilizes the piggyback technique with three hepatic vein cuffs (n = 795, 75%). In this study period we performed the modified piggyback technique (3.5%) with two hepatic vein cuffs (n = 36) or one hepatic vein cuff (n = 2) due to the size discrepancy between the donor and recipient cava (most of the donor livers were pediatric donors with a small cava). A slightly higher percentage in this group was observed to develop RA, 8% (3/38); however, for simplicity, this group was combined with the other piggyback variants in the data analysis. The other operative factors, including presence of PVT, presence of replaced hepatic artery, arterial reconstruction methods, biliary reconstruction methods, use of veno-venous bypass and operative time did not affect the incidence rate of RA after LT.

Our results demonstrate that a variety of causes of RA exist after LT. Etiologies of the 25 patients having early RA (developing within 3 months post-transplant) include an unknown cause (N = 14), bacterial peritonitis (N = 5), outflow obstruction of the caval anastomosis (N = 3), acute rejection (N = 2) and heart failure (N = 1). Etiologies of the 37 patients having late RA include recurrent hepatitis C (17 patients), chronic rejection (N = 7), an unknown cause (N = 3), tumor (N = 3), hepatic artery or PVT (N = 2), hepatitis B recurrence (N = 1), anastomotic stricture (N = 1), acute rejection (N = 1), liver failure due to alcohol (N = 1) and small transplanted liver (N = 1). Most of the patients with an unknown etiology resolved with LVP and had a good prognosis thereafter. Although we could not fully determine the etiology in these patients, it may have been due to surgical disruption of lymphatic ducts or patient condition with massive ascites before LT. The prognosis for the small group of patients whose reason for developing RA was bacterial peritonitis was poor, with all dying of sepsis. An increased risk of developing peritoneal infection has been reported in patients having massive ascites (5). Thus, since intra-abdominal sepsis (due to biliary leakage, infected hematoma or abscess) is known to cause endotoxemia and to worsen vasodilatation, its development must be investigated and treated properly.

Patients whose reason for developing RA was recurrent HCV disease did not respond to treatment and had a poor prognosis. Post-transplant liver biopsy results showed significant HCV-related morphologic changes in all of these 17 patients (100%). In addition, among 13 patients having sufficient material for an evaluation of fibrosis stage and grade, 10 patients had fibrosis stage of III or greater (77%), and 7 patients had hepatitis activity of moderate or greater (54%). The use of LeVeen shunt or TIPS in addition to LVP provided some relief to these patients from the RA; however, their ultimate clinical course was dismal. As shown in Figures 3 and 4, only 1 of the 17 patients (6%) whose reason for developing RA was HCV recurrence had complete disappearance of the RA, and 13 of the 17 patients (76%) developed end-stage liver failure due to HCV recurrence and died. Thus, while the overall probability of a patient with HCV developing RA is only approaching 10%,

more successful treatment strategies to prevent HCV recurrence need to be developed.

As stated in the Methods section, the extent of pre-transplant ascites was not available due to the retrospective nature of this study. Thus, it was not possible to determine whether the extent of pre-transplant ascites was associated with one or more of the following: pre-transplant renal insufficiency, having HCV as the primary disease, and the rate of developing RA. In addition, except for the information obtained on patients at the time of RA development, repeated measurements on all 1058 patients over time post-transplant to monitor the degree of renal insufficiency (with serum creatinine levels and any starting dates of hemodialysis) and repeated biopsy results to monitor the exact times-to-developing HCV recurrence (with genotype, stage, and grade information) were not readily available. Clearly, some of this information could be quite useful in making more accurate determinations of subsets of patients who are more likely to develop RA. However, our study did find that the pre-transplant serum creatinine level was not associated with the rate of developing RA. In addition, the serum creatinine level at RA development was not associated with the rate of RA disappearance. Lastly, while the serum creatinine levels were significantly higher in patients at the time of RA development, the observed significantly smaller percentage of elevated serum creatinine levels among patients whose reason for developing RA was HCV recurrence indicates that the contribution of renal insufficiency to RA development may actually be less among those whose RA is caused by HCV recurrence.

Diagnosis of the etiology of RA using DUSL is critical for determining the most appropriate course of treatment. Since DUSL has been shown to be highly sensitive and specific for determining vascular insults after LT (42–43), it should be performed to check the patency of the hepatic veins and caval anastomosis with the ultimate goal of correcting any detected outflow obstruction. Corroborating angiography and hemodynamic studies should be also performed if mechanical stenosis is suspected by DUSL. In our study, venogram results were available in 25 of 32 patients who developed RA and underwent angiography: 4/5 of the venogram positive patients had DUSL positive (80% sensitivity), and 18/20 of the venogram negative patients had DUSL negative (90% specificity). The detection of stenosis of TIPS by DUSL has also been reported to yield 93–100% sensitivity and 77–89% specificity (44–45), and the detection of tumor involvement in the hepatic vein by DUSL has been reported to yield 81% sensitivity and 97% specificity (46). Finally, ascites fluid should always be sent for bacterial analysis, culture and cytology. In addition, coagulation studies to detect such problems as anti-thrombin deficiency are required for the work-up of veno-occlusive disease (14), and a liver biopsy should also be performed when necessary for patients with suspected recurrent disease or rejection.

Successful treatment of RA depends, in part, on its etiology. Initially, all patients are treated with LVP. The prognosis in patients having mechanical obstruction is generally good as long as the outflow obstruction is treated without delay (usually with balloon dilatation or reanastomosis of the outflow tract). LeVeen shunt is one of the options used in treating RA (13); however, there is a risk of developing complications, including infection, thrombosis and heart failure, following its placement. Thus, heart function should be monitored carefully after the placement of a LeVeen shunt. TIPS should also be considered as a treatment option in controlling RA after LT; however, the use of TIPS is associated with an increased risk of infection as well as the development of liver failure (16–17,47–48). Consideration of a patient for TIPS after LT should therefore not be taken lightly. Renal function and bilirubin should be checked carefully prior to selecting a patient for TIPS. In patients having RA due to coagulation disturbances, the treatment should include fresh frozen plasma (14). Patients with RA and liver failure due to chronic rejection might be potential candidates for retransplantation (18); however, retransplantation in patients with recurrent HCV is controversial because of its high recurrence rate and poor prognosis.

From a statistical perspective, by utilizing the time-dependent covariate approach in analyzing the impact of RA development on patient survival, as we have done in this study, we have properly avoided what is known as length-time bias. Since each patient begins in a pre-RA development state immediately post-transplant, all patients therefore contribute patient-months of follow-up to the estimation of the 'pre-RA development' mortality rate. Once a patient develops RA, this patient immediately begins contributing survival experience to the 'post-RA development' state. The mortality rate at a given time t months post-transplant is therefore compared between patients that have versus have not developed RA by time t. By erroneously assigning RA status to all patients at baseline, an apparently common mistake in the organ transplant literature, the statistical analysis would not control for the fact that patients must live long enough in order to be able to develop RA. An overestimate of the pre-RA mortality rate and an underestimate of the post-RA mortality rate would therefore occur. The time dependent covariate approach, which was employed in this study, properly avoids this type of bias from occurring.

In conclusion, while the overall incidence of RA after LT was acceptably low at 5.9%, it was threefold higher in patients having HCV as their primary disease, 9.5%, versus only 2.9% among those having other primary diseases ($p < 0.00001$). Prognosis following development of RA was significantly influenced by the reason for RA development, with bacterial peritonitis and HCV recurrence indicating much poorer outcomes and unknown etiology indicating a more favorable outcome. Finally, while unresolved RA after LT clearly portends a significantly higher mortality rate in comparison with patients who have not developed

RA ($p < 0.00001$), the increased risk of death due to RA apparently disappears once the RA itself disappears. Clearly, early diagnosis and treatment of RA, depending in part on its etiology, are critical in order to prevent further morbidity and mortality.

Acknowledgment

The authors gratefully acknowledge Ms. Wynn Howard for her expertise in preparing the figures of this manuscript.

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