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The Impact of Hepatitis C and Biliary Complications on Patient and Graft Survival Following Liver Transplantation

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Recurrent hepatitis C (HCV) and biliary complications (BC) are major causes of post liver transplant morbidity and mortality. The impact of these complications may be additive or synergistic. We performed a retrospective cohort study to analyze the effects of HCV and BC on all patients transplanted at two institutions over 6 years. BC was defined by imaging findings in the setting of abnormal liver function tests that required intervention. The primary outcomes were graft and patient survival over a mean 3.4 years. 709 patients (619 deceased, 90 living donor) were included, 337 with HCV and 372 without. BC was diagnosed more frequently in patients with HCV, 26% versus 18% ($p = 0.008$). One-year and overall patient and graft survival were significantly lower in patients with HCV, but BC impacted only 1-year graft survival. The combination of BC and HCV had no additional impact on survival or fibrosis rates on 1-year protocol biopsies. Multivariate analysis revealed HCV (HR 2.1) and HCC (HR 1.9) to be independent predictors of mortality. Since BC are diagnosed more frequently in HCV patients and only affect early graft loss, it is likely that recurrent HCV rather than BC accounts for the majority of adverse graft outcomes.

Key words: Biliary complication, liver transplant, recurrent hepatitis C virus

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Introduction

Hepatitis C virus (HCV) is a leading cause of end stage liver disease (ESLD) worldwide and the most common indication for orthotopic liver transplantation (OLT) in the United States and Europe (1). In contrast to most other leading indications for OLT, serologic and histologic recurrence of HCV after OLT is nearly universal, and death and allograft failure are more common in this population than in HCV negative recipients (2). The natural history of HCV disease is clearly accelerated in the posttransplant setting, leading to cirrhosis in 10–25% of patients within 5–10 years (3). Efforts to maximize long-term survival of patients with HCV following OLT have focused on eradication of the virus, but thus far, treatment of HCV with interferon-based regimens in the posttransplant setting has been disappointing. Uninhibited viral replication in the setting of immunosuppression, the high proportion of patients with genotype 1 or virus unresponsive to IFN-based therapies prior to OLT, and the serious side effects of IFN and RBV posttransplant render the treatment of recurrent HCV extremely difficult.

HCV recurrence is heterogeneous in its manifestations, however, and in the absence of reliably effective antiviral therapy, investigators have looked for modifiable risk factors for severe recurrence and poor clinical outcomes. To date, several potentially modifiable risk factors have been identified, including HCV viral load prior to transplantation (4). Biliary complications (BC) have more recently been added to the list of potentially modifiable variables that negatively impact posttransplant outcomes, and we hypothesized that BC might accelerate liver injury in the setting of HCV-related hepatic inflammation.

BC have been reported in 2–50% of post-OLT patients (5–26), the rate varying widely with the definition of biliary disease, the year of publication, the experience of the transplant center and the size of the patient cohort. The BC complications usually reported include bile leak, anastomotic strictures, nonanastomotic strictures and miscellaneous findings such as stones and sludge. Bile duct injury has been only inconsistently associated with diminished posttransplant outcomes, but adverse affects including attributable graft loss and patient mortality have certainly been reported (5,14,15,20,22,23,25). The histopathologic changes that occur as the result of chronic biliary obstruction have been well described in animal models and in humans in the nontransplant setting, including cholestasis, ductular proliferation, portal inflammation, fibrosis and ultimately secondary biliary cirrhosis. Once fibrosis occurs,

this cascade was thought to be irreversible until recent work in murine models and then humans demonstrated regression of fibrosis with relief of the obstruction (27–30).

It remains unknown whether biliary obstruction affects recurrent HCV disease in the transplant setting, and many clinicians feel that HCV and BC may have a synergistic affect on poor patient outcomes. This clinical observation may have a physiologic basis as in animal models, liver regeneration may be significantly altered or impaired in the setting of cholestasis (31–35). Katz and colleagues (12) recently published their experience in humans post-OLT with 54 HCV infected patients, 12 of whom developed BC. They found BC to be a statistically significant predictor of severe recurrence, but not of mortality or graft failure. This study, however, was in a small group of patients, and did not include patients without HCV for comparison. Due to the small sample size, they did not have the power to assess the potential synergism between HCV and BC that many clinicians believe negatively affects their patients in the posttransplant setting. We therefore aimed to determine whether the presence of BC impacts posttransplant outcomes in patients with and without HCV infection, and hypothesized that BC and HCV would be synergistic in their negative effects on posttransplant patient and graft survival.

Methods

Patients and definitions

All patients 18 years of age and older who underwent OLT between January 1999 and February 2005 at New York-Presbyterian Hospital in the United States and at the University of Padova in Italy were retrospectively assessed. Only patients who were retransplanted within 1 month or had HIV coinfection were excluded. Data including patient age, indication for and date of transplantation, HCV status, all posttransplant biliary and liver imaging, and retransplantation and vital status were obtained through chart, computer and data base review. This study was approved by the Columbia University institutional review board as minimal risk with waiver of consent.

HCV infection as the etiology of the patient's ESLD was defined as a positive HCV viral load at any time prior to transplantation. When BC were suspected due to abnormal liver function tests, patients generally underwent ultrasound or magnetic resonance cholangiopancreatography, followed by confirmatory endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiogram (PTC) with intervention when necessary. BC was defined for this study as evidence of biliary tract disease seen on ERCP or PTC and that required intervention. It was grouped into bile leaks, anastomotic strictures, nonanastomotic strictures and biliary stones or sludge. The interventions performed included percutaneous biliary or biloma drain placement, endoscopic stenting or sphincterotomy and/or surgical exploration as the clinical team deemed appropriate. Extended criteria donation (ECD) organs were defined as living donor (LDLT), donation after cardiac death, donor age over 65, significant graft steatosis, prolonged cold ischemia time, high-risk behavior in the donor and HCV or hepatitis B core antibody positivity. HCC was defined by UNOS data base information at listing or the presence of HCC on explant histology.

Transplantation and immunosuppression

Standard methods were used for biliary reconstruction. Duct-to-duct choledochocholedochostomy is preferred at both centers and was performed in 96% of cases. Patients with technical contraindications (e.g. significant duct mismatch, partial graft with multiple ducts) or those with underlying primary sclerosing cholangitis received a choledochojejunostomy with a Roux-en-Y reconstruction. Intraoperative biliary stents were not routinely placed.

Standard HCV immunosuppression was utilized, including a calcineurin inhibitor (tacrolimus or cyclosporine), a tapering dose of corticosteroids and in some cases a lymphocyte antiproliferative agent (mycophenolate mofetil or azathioprine). All acute cellular rejection episodes were biopsy proven and treated with maximization of baseline immunosuppression, calcineurin inhibitor conversion or limited use of bolus steroids. At both centers, clinical protocols reserve bolus steroids for Banff greater than 5 or rejection that does not respond to modulation of baseline immunosuppression.

Outcomes and statistics

The primary outcomes evaluated were overall and 1-year graft and patient survival. In addition, secondary outcomes included the incidence of diagnosed BC and the rates of rejection, defined as a Banff score of greater than or equal to 5, in patients with and without HCV. To further assess a potential interaction between HCV and BC, for HCV positive patients only, the 12 ($\pm$ 3) month liver biopsies were evaluated for fibrosis stage when available. Patients who died or were retransplanted before 1 year are excluded from this analysis. HCV negative patients did not routinely undergo protocol liver biopsies and are, therefore, not included in this secondary analysis. In addition, the causes of death for all HCV positive patients who expired during the study period were assessed to determine whether increased HCV progression led to higher death rates in HCV positive patients with BC.

For univariate analysis, chi-squared and Student's *t*-test were used as appropriate. Multivariate analysis was performed using logistic regression, Cox proportional hazards and Kaplan–Meier curves. The variables included in this analysis were HCV positivity, BC, BC in the setting of HCV (an interaction term), receipt of an LDLT graft, receipt of an ECD graft, at least one episode of rejection and the presence of HCC prior to transplantation. Additional analyses were done dividing BC into strictures and leaks among patients with different graft types (LDLT and DDLT) and HCV status. A p-value of less than 0.05 was considered statistically significant.

Results

Seven hundred and nine patients were included, 337 with HCV and 372 without (Table 1). Six hundred and nineteen patients underwent deceased donor transplantation (DDLT), and 90 LDLT. Mean age was 51 years (range 18–75) and mean posttransplant follow-up time was 178.8 weeks (range 0.4–397.9), or almost three and a half years. HCV positive patients had a significantly higher mean age and rate of HCC prior to transplantation, and were more likely to be transplanted at site 1(Table 1).

One hundred and seventy-three BC were diagnosed in 154 patients (22% of the entire cohort). Of these 173 BC, 133 were strictures (109 anastomotic and 24 nonanastomotic or diffuse), 31 bile leaks and 9 stones or sludge (Table 2). BC were diagnosed in 88 (26%) of the 337 patients with HCV and 66 (18%) of the 372 without HCV ($p = 0.008$, Table 2).

Table 1: Patient characteristics

	Overall n = 709	HCV + n = 337	HCV − n = 372	p-Value
Mean age in yrs (range)	51 (18–75)	48 (21–75)	54 (18–73)	<0.01
Site 1 (%)	348 (49)	182 (54)	166 (45)	0.01
Site 2 (%)	361 (51)	155 (46)	206 (55)	0.01
ECD	293 (41)	143 (43)	150 (40)	0.59
LDLT	90 (13)	47 (14)	43 (12)	0.37
HCC	172 (24)	109 (32)	63 (17)	<0.01

Abbreviations: DDLT = deceased donor liver transplant; LDLT = living donor liver transplant; ECD = extended criteria donation; HCC = hepatocellular carcinoma.

When BC type was further dissected, patients with and without HCV had similar numbers of leaks and stones, but differed significantly in the number of strictures (23% in HCV positive and 15% in HCV negative, p = 0.016, Table 2).

Twenty-nine (32%) of the 90 patients who received LDLT grafts had BC, as compared to 125 (20%) of the 619 DDLT (p = 0.013, see Table 2). Unlike in the HCV group, there was no difference in rate of strictures between LDLT and DDLT, but there was a significant difference in number of bile leaks encountered (11% in LDLT and 3% in DDLT, p = 0.003). Acute rejection with Banff score greater than or equal to 5 occurred in 122 (17%) of the 709 total patients (57 with HCV and 65 without, p = 0.92).

One-year patient and graft survival were 90% and 89%, respectively (Table 3). In univariate analysis, 1-year graft survival was significantly lower in patients with HCV than those without HCV (p = 0.009), as well as in patients with BC versus those without BC (p = 0.04) (Table 3). Although 1-year graft survival was the lowest in patients with both HCV and BC (p < 0.004), in multivariate analysis with logistic regression, the interaction term for this group was not independently predictive of worsened outcomes than HCV alone (p = 0.21). One-year patient survival was significantly lower in patients with HCV (0.028) but there was no impact of BC on survival (p = 0.41).

Overall survival was examined with Kaplan–Meier survival curves (Figure 1). In this model, significant differences in survival experiences were found between patients with HCV only or HCV and BC as compared to patients with neither complication (p-values 0.001 and < 0.001, respectively). There was not a significant difference in survival between patients with BC only and no complications (p = 0.61). In addition, the combination of HCV and BC did not confer a significant decrease in survival when compared to HCV alone (p = 0.19), but did decrease survival when compared to BC alone (p = 0.009). Kaplan–Meier survival curves were also done for HCV and HCC (Figure 2). Patients with HCV, HCC or both had significantly different survival experiences from patients with neither HCV nor HCC (p values for each < 0.001), but there was no significant difference between these three groups.

Multivariate analysis with Cox proportional hazards were also performed (Table 4). The final model of overall patient survival included HCV, BC, HCV plus BC, HCC, rejection and living donation. HCV (HR 2.1) and HCC (HR 1.9) were the only variables found to be significant predictors of increased mortality when controlled for all other variables. BC alone and the interaction term for patients with BC in combination with HCV did not independently significantly predict overall patient mortality. When the biliary complications were divided into groups, and the model was run including only patients with strictures rather than total BC, there were no significant changes in hazard ratios for each variable (data not shown). The other subgroups of biliary complications were too small to analyze separately.

Two hundred and twenty-four HCV positive patients (66% of all HCV patients, 75% of the HCV patients alive without retransplantation at 1 year), had 1-year protocol liver

Table 2: Biliary complications (BC) by HCV status and donor type. Patients with HCV had significantly more BC overall, with the greatest difference between the two groups in number of strictures. Patients with LDLT grafts had significantly more BC than patients with DDLT grafts, with the greatest difference between the two groups in number of bile leaks

	No. pts with BC	No. BC total*	Leak	All strictures	Anastomotic stricture	Nonanastomotic diffuse	Stones sludge
Overall (%) n = 709	154 (22)	173	31 (4)	133 (19)	109 (15)	24 (3)	9 (1)
HCV+ (%) n = 337	88 (26)	92	13 (4)	76 (23)	59 (18)	17 (5)	3 (1)
HCV− (%) n = 372	66 (18)	81	18 (5)	57 (15)	50 (13)	7 (2)	6 (2)
p-value	0.008		0.584	0.016	0.145	0.022	0.321
LDLT (%) n = 90	29 (32)	30	10 (11)	20 (22)	17 (19)	3 (3)	0 (0)
DDLT (%) n = 619	125 (20)	143	21 (3)	113 (18)	92 (15)	21 (3)	9 (1)
p-value	0.013		0.003	0.386	0.348	1.000	0.612

*19 patients had two types of BC in the study period.

Table 3: One-year graft survival was significantly lower in patients with BC (p = 0.04), HCV infection (p = 0.009) or both HCV and BC (p = 0.004). One-year patient survival was significantly lower in HCV infection (p = 0.03) and HCV plus BC (p = 0.04) but not BC alone (p = 0.41)

	% 1-year graft survival			% 1-year patient survival		
	BC +	BC −	Total	BC +	BC −	Total
HCV +	80	88	85	84	89	88
HCV −	91	92	92	94	92	93
Total	85	90	89	89	91	90

biopsies available for review (Table 5). There was no significant difference in incidence of advanced fibrosis, defined as stage ≥3 (13% and 9%, respectively, p = 0.46). There was also no statistically significant difference in the incidence of stage ≥2 fibrosis (data not shown). Sepsis was the most common cause of death in HCV positive patients overall, followed by recurrent HCV and recurrent HCC (Table 5). The majority of the HCV patients who died due to sepsis (18 of the 28 patients) died within the first year without a 1-year protocol liver biopsy. Of the nine patients who did have biopsies, only one had at least stage 3 fibrosis. There were no significant differences in the frequency of each cause of death between patients with HCV and BC as compared to patients with HCV alone.

Discussion

HCV is a leading cause of ESLD worldwide and recurrent HCV is virtually universal. Patients transplanted for HCV-related cirrhosis have diminished outcomes when compared to patients without HCV infection, largely due to HCV reinfection of the graft. The impact that recurrent HCV has on graft function is unpredictable and as post-OLT antiviral treatment has proven difficult, investigators have focused on other modifiable risk factors for severe recurrence. Although there are now reports that BC may be associated with graft loss and death (5,14,15,20,22,23,25) as well as evidence in the nontransplant setting that hepatic fibrosis due to chronic biliary obstruction is somewhat reversible, (27–29) the interaction between HCV and BC has not been fully described.

Similar to rates reported throughout the literature, we found BC in 22% of patients. BC was significantly associated with early (1-year) graft loss, likely due to the pathological changes, inflammation and fibrosis known to occur in the setting of BC. This effect was not great enough, however, to statistically significantly diminish patient survival at 1 year or at end of study follow-up in our large, multicenter cohort of patients. These findings are not inconsistent with other recent reports that show no decrease in patient and graft outcomes (25,36) or show a greater impact of BC upon severity of HCV recurrence (12) and graft survival (11) than overall patient mortality. Though HCV had a greater impact on 1-year patient and graft survival in patients with BC in our 2 × 2 analysis, implying an interaction between the two problems, this difference did not reach statistical significance and was not confirmed by an interaction term in multivariate analysis. HCV and HCC were found to be the only independent predictors of overall mortality in multivariate analysis, which is also consistent with previously published literature.

In addition, in the HCV positive patients, BC were not associated with a significant increase in the incidence of

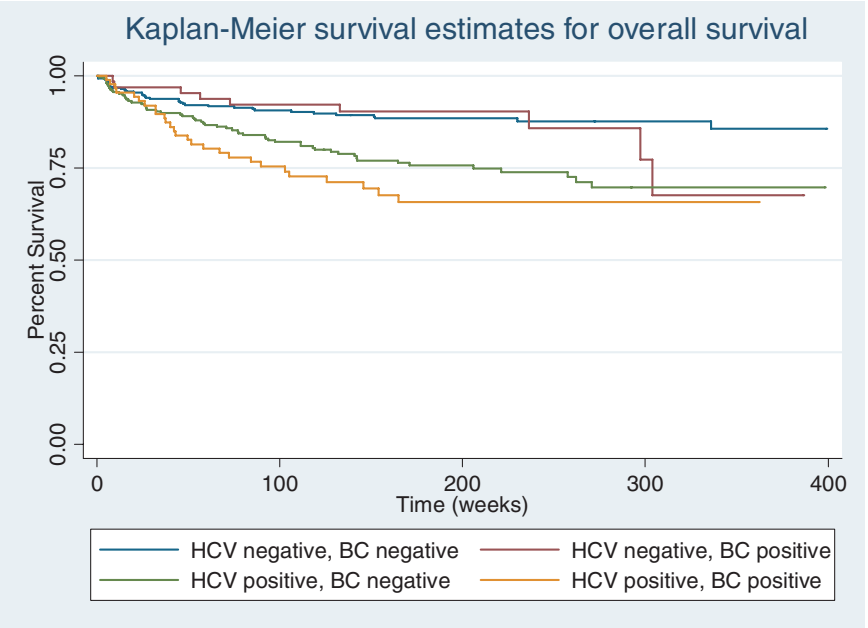

Figure 1: Kaplan–Meier survival analysis for patients with HCV, BC and both HCV and BC.

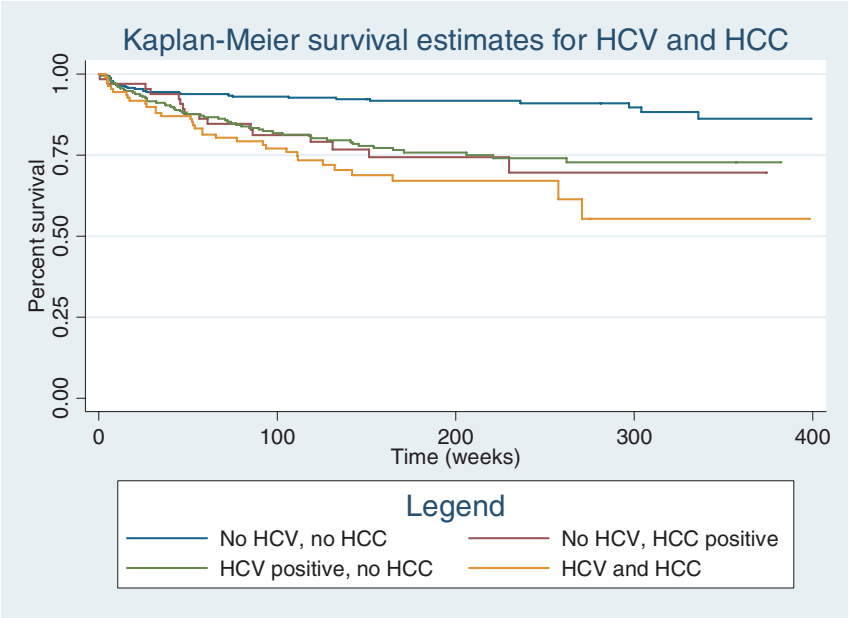

Figure 2: Kaplan–Meier survival analysis for patients with HCV, HCC and both HCV and HCC.

longer term graft loss or significant (≥stage 2) or advanced (≥stage 3) fibrosis on 1-year posttransplant protocol biopsies. The rates of death due to recurrent HCV did not differ between patients with and without BC. Although sepsis was the most common cause of death in the HCV patients, 17% of patients died due to advanced recurrent HCV, likely accounting for the excess mortality in the HCV positive patients. The majority of the septic deaths occurred within the first year, and none were associated with advanced recurrent HCV.

One unexpected finding in our study was the significantly higher rate of BC in patients with HCV as compared to those patients without HCV. When we further probed our data and divided BC into types, this increased rate in HCV infected patients is clearly driven by the increased occurrence of treated strictures, as there is no difference in leaks and stones between the two groups. This association between HCV and BC was demonstrated previously by Fujikawa et al. with anastomotic strictures (9), but refuted by Guichelaar and colleagues in patients with nonanastomotic lesions (11) and by others looking at patients with all types of BC (8,24). There are several possible explanations for our finding. Some investigators have postulated that HCV infection may be a risk factor for BC (9,26), however, there is little evidence that HCV plays a causative role. In addition, BC may be underdiagnosed in HCV-negative patients as more minor changes in liver functions tests are not as aggressively investigated. Increased use of ECD grafts in HCV patients may also be responsible for increased rates of diffuse ischemic type strictures, although this was not the case in our cohort as there was no difference in use of ECD grafts in patients with and without HCV. Perhaps a more likely explanation is that BC are overdiagnosed in patients with HCV, and that cholestasis from recurrent disease, rather than or in addition to physiologically significant BC, is present in many of these patients. Strictures are more subject to radiographic interpretation than leaks that may explain the difference in stricture, but not leak rates in HCV positive patients. In the presence of jaundice, stenting of insignificant strictures may occur or pruning of the ducts seen in advanced liver disease may be labeled as diffuse structuring. The difficulty in differentiating these two processes is further compounded by the increasingly recognized entity of fibrosing cholestatic hepatitis C, a severe form of HCV infection with prominent cholestasis on liver biopsy and laboratory investigation. More definitive proof of BC is difficult in this setting, however, as when a posttransplant patient exhibits signs of graft dysfunction, many variables are changed simultaneously. Even in the nontransplant setting, predicting the pattern of liver function test recovery can be difficult (37–39). Further investigation should be done to verify the predominance of diffuse strictures in HCV positive patients and correlate this finding to ischemia times, hepatic artery function and ECD status.

Table 4: Overall patient survival in a Cox proportional hazards model found survival to be significantly diminished in patients with HCV infection and hepatocellular carcinoma (HCC), when controlling for all other variables. Biliary complications (BC) and BC plus HCV (an interaction term) did not independently impact overall survival

Predictor	HR	95% CI	p-Value
HCV	2.10	1.38–3.20	0.001
HCC	1.92	1.35–2.72	0.001
BC	1.23	0.59–2.57	0.58
BC and HCV	1.00	0.42–2.38	0.99
Rejection	1.15	0.75–1.77	0.52
LDLT	1.26	0.77–2.06	0.35

Table 5: One-year protocol biopsy results in HCV positive patients with biopsies available and causes of death for all expired HCV positive patients

	All HCV patients	HCV alone	HCV and BC	p-Value
Fibrosis	n = 224	n = 161	n = 63	
≥ Stage 3	23 (10%)	15 (9%)	8 (13%)	0.46
Cause of death	n = 86	n = 59	n = 27	
Recurrent HCV	15 (17%)	8 (14%)	7 (26%)	0.22
Recurrent HCC	15 (17%)	13 (22%)	2 (7%)	0.13
Sepsis	28 (33%)	19 (32%)	9 (33%)	0.82
Other	17 (20%)	11 (19%)	6 (22%)	0.77
Unknown	11 (13%)	8 (14%)	3 (11%)	1.00

We did not find a difference in ECD use or graft loss due to biliary tract disease in HCV positive and HCV negative patients and thus it seems unlikely that this will explain the differences in stricture rates seen.

LDLT patients were also more likely to have BC than DDLT patients. When this group was looked at in greater detail, this difference is driven by an increased incidence of bile leaks in LDLT recipients. The high incidence of BC in this group is perhaps due to the greater technical difficulties of this operative procedure. BC are in fact known to be major causes of morbidity and mortality specifically in the LDLT population, and work is ongoing to minimize the risks of these complications (40–42).

The major limitation of our study is the lack of liver histology data from a central pathologist for the entire cohort. Although comparing the severity of liver injury in all groups would be ideal, this kind of comparison was not possible in this retrospective study given the lack of protocol biopsies in the HCV negative patients and relative lack of protocol biopsies beyond year 1 in the HCV positive patients. In those patients with HCV who did have 1-year protocol biopsies, BC did not significantly impact the incidence of significant or advanced fibrosis at 1 year. Additionally, though early histology is a good predictor for long-term outcomes, many other unmeasured factors such as antiviral treatment and minimizing rejection may alter this impact. Since BC should affect the short-term progression of HCV, long-term changes in fibrosis would be affected more by immunosuppression changes and the use of antiviral therapy in patients with progressive disease. Additionally, long-term graft loss did not differ in HCV patients with and without BC. By providing relatively long-term follow-up with graft loss and mortality, which are less subjective endpoints, we believe we would have captured any consequences of synergistic hepatic injury for the patient if it existed. Further follow-up with 3- and 5-year survival and fibrosis scores may more accurately reflect the true impact of HCV and BC as sequelae of these variables may increase over time.

Another weakness of our analysis may be our definition of BC as it includes all patients with imaging evidence of an abnormal bile duct in the setting of abnormal liver function tests who received an intervention, which may not be specific enough to ensure physiologically significant biliary obstruction. Accurate retrospective determination of the efficacy of such an intervention to prove the physiological significance of these findings, however, was not possible. In addition, we grouped all types of BC together in the main analysis, perhaps combining complications with different origins and different effects on patient and graft outcomes. Further analysis was performed, however, separating these groups without significant changes in our findings. Last, we would have liked to perform additional analysis looking at cause of death and graft failure for the entire cohort, but this was not possible to do accurately in this retrospective multicenter study. Cause of death was determined in those patients with HCV, and there were no significant differences between patients with and without BC, neither in terms of recurrent HCV, if BC accelerated progression of HCV, or sepsis if death was related to diffuse stricturing and recurrent biliary sepsis. The numbers in each category were small, however, and definitive conclusions may not be drawn from these data.

As it has been shown that the duration of biliary obstruction may be the most important risk factor for severe and sustained liver injury (28), when abnormal biliary anatomy is found in the setting of graft dysfunction, action should be taken to relieve a potential obstruction without delay. Our data add additional support, however, to the notion that recurrent HCV infection remains the most prominent risk factor for death and graft failure, and that BC are not synergistic with recurrent HCV in this effect. In addition, we found that BC (specifically strictures) is more likely to be diagnosed in patients with HCV, possibly signifying that we are overdiagnosing BC in patients who are cholestatic from recurrent HCV. Therefore, early and aggressive treatment of HCV may also be a part of the initial therapeutic paradigm in patients with HCV and elevated liver functions tests, even when the pattern is most consistent with cholestasis. Additional work to improve post-OLT antiviral treatment, slow the process of fibrosis, and better differentiate fibrosing cholestatic HCV from extrahepatic biliary obstruction is needed.

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