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Variceal Hemorrhage and Adverse Liver Outcomes in Patients with Cystic Fibrosis Cirrhosis

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Abstract

Objectives—Cirrhosis occurs in 5-10% of CF (cystic fibrosis) patients, often accompanied by portal hypertension. We analyzed three adverse liver outcomes, variceal bleeding (VB), liver transplant (LT), and liver death (LD), and risk factors for these in CF Foundation Patient Registry (CFFPR) subjects with reported cirrhosis.

Methods—We determined 10-year incidence rates for VB, LT, LD, and all-cause mortality (ACM), and examined risk factors using competing risk models and Cox-proportional hazard regression.

Results—From 2003-2012, 943 participants (41% female, mean age 18.1 years) had newly reported cirrhosis; 24.7% required insulin, 85% had prior pseudomonas. Seventy-three subjects had reported VB; 38 with first VB and new cirrhosis reported simultaneously and 35 with VB after cirrhosis report. 10-year cumulative VB, LT, and LD rates were 6.6% (95% Confidence Interval (CI): 4.0, 9.1%), 9.9% (95% CI: 6.6%, 13.2%), and 6.9% (95% CI: 4.0%, 9.8%), respectively, with an ACM of 39.2% (95% CI: 30.8, 36.6%). ACM was not increased in subjects with VB compared to those without (HR 1.10, 95% CI: 0.59, 2.08). CF related diabetes (CFRD (hazard

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ratio (HR): 3.141, 95% CI:1.56, 6.34) and VB (HR: 4.837, 95% CI: 2.33, 10.0) were associated with higher LT risk while only worse lung function was associated with increased LD in multivariate analysis. Death rate among subjects with VB was 24% with LT and 20.4% with native liver.

Conclusions—VB is an uncommon complication of CF cirrhosis and can herald the diagnosis, but does not affect ACM. Adverse liver outcomes and ACM are frequent by 10 years after cirrhosis report.

Keywords

Variceal bleeding; portal HTN; cirrhosis; liver; cystic fibrosis

Introduction

Cystic fibrosis-related liver disease (CFLD) has been hypothesized to result from absent or abnormal bicarbonate flow through the cystic fibrosis transmembrane regulator (CFTR), leading to increased viscosity of bile and ultimately bile stasis and obstruction.[1, 2] Even in the absence of cholestasis, the consequences of viscous bile can be intermittent intrahepatic ductal obstruction, inflammation, and subsequent fibrosis. While hepatic manifestations of cystic fibrosis (CF) are common and may include elevated serum transaminases, hepatic steatosis and imaging abnormalities, only 5-10% of CF patients progress to advanced liver disease with cirrhosis and portal hypertension.[3-5] When cirrhosis occurs, it presents early, almost uniformly before the second decade of life.[6-9] It has been estimated that more than half of patients with CF cirrhosis have esophageal varices.[3] Gastrointestinal bleeding from esophageal varices has been reported to occur often in CF patients with portal hypertension and frequently occurs in the context of preserved hepatic synthetic function.[4, 6, 10] Previous studies of the frequency and prevalence of variceal hemorrhage in CF cirrhosis with portal hypertension have primarily come from quaternary referral centers and have reported variceal bleeding (VB) rates of 40-50%.[6, 11] To our knowledge, there is no large population series to estimate the frequency of variceal hemorrhage in CF cirrhosis.

The CF Foundation Patient Registry (CFFPR) database prospectively collects demographic and encounter-based clinical data for approximately 85–90% of the United States (US) CF population.[12] It provides a rich tool for the analysis of CF complications, and since 2003, has captured enhanced liver-related data that can be systematically queried to investigate specific outcomes such as variceal hemorrhage in individuals with cirrhosis. As such, the goal of this study was to investigate the frequency and risk factors for variceal hemorrhage and adverse liver outcomes in children and adults with CF cirrhosis.

Methods

Study population

Participant data for this study were collected from the CFFPR (Bethesda, Maryland). The data is entered electronically for all clinical encounters by designated staff at each CF Foundation-accredited Care Center. The data entry form contains a field for the clinician to select for cirrhosis and another to select for VB; when appropriate, cause of death may also

be specified with liver-related death as an option. As the CF registry does not distinguish cirrhosis from non-cirrhotic portal HTN, the term “cirrhosis” is used for the purpose of this study since both clinical entities can lead to the same adverse liver outcomes. Utilizing the CFFPR, we performed a cohort study to evaluate the incidence rate of and risk factors associated with variceal bleeding and adverse liver outcomes in CF subjects with reported cirrhosis. As variceal bleeding events were only captured after January 1, 2003 in the CFFPR, we limited our study population to individuals newly reported to have cirrhosis of their native liver from January 2003 to December 2012 (see Figure 1, consort diagram). IRB exemption of this study was obtained through the University of Michigan Institutional Review Board.

Outcomes and risk factors

We analyzed three time-to-event adverse liver outcomes: time from cirrhosis report to VB, liver transplant (LT), and liver-related death (LD). Secondarily, we also investigated time to all-cause mortality (ACM). Potential risk factors included demographics (race, age at time of cirrhosis diagnosis, gender), markers of CF disease severity (CF genotype, FEV1% predicted, FVC% predicted), *Pseudomonas aeruginosa* (PA) culture status, body mass index (BMI, kg/m2), and CF-related diabetes (CFRD). Severe genotype was defined as having both CFTR mutations in classes I-III; mild genotype was defined as one or more mutations in class IV-V.

Statistical analysis

Descriptive statistics were calculated for the total study population and compared between cirrhotic subjects who had VB reported on the same encounter when cirrhosis was first reported, those whose first VB was reported after the report of cirrhosis, and those with no reported VB during the study follow-up period. Continuous variables were compared using ANOVA test and Student's t test allowing for unequal variances and categorical variables with a Chi-square or Fisher's exact test when appropriate.

To estimate cumulative incidence of VB, liver transplant, and liver-related death, a competing risk model was used. For the analysis of VB, liver transplant and death were treated as competing events. For the analysis of liver-related death, other death and liver transplant were treated as competing events. For the analysis of liver transplant, ACM was treated as a competing event. Kaplan-Meier curves were used to estimate the incidence rate of total mortality in the study cohort over time. Cause-specific hazard competing risk models with time-varying covariates were used to study risk factors for all three adverse liver outcomes. Cox-proportional hazard regression models with time-varying covariates were used to study risk factors for all-cause mortality. To study cumulative incidence rate of VB from time of cirrhosis report, we focused on cirrhotic subjects who had no VB history at the time of diagnosis of cirrhosis, i.e., subjects who had VB at the time cirrhosis was reported were excluded. For analysis of liver transplant, liver death, or all-cause mortality, all identified patients with cirrhosis and follow-up were included. FEV1% predicted, ever positive for *Pseudomonas aeruginosa* (PA) in a respiratory tract culture, most recent PA status, BMI, and CFRD were included as time-varying covariates in the regression analyses for all outcomes. In the regression analysis for all-cause mortality, liver transplant and liver-

related death, one additional time-varying covariate, history of variceal hemorrhage, was also added. Since the exact date of liver transplantation is not captured in CFFPR (only the year of liver the transplantation is entered), we imputed the liver transplant date as July 1 in the reported year. Because frequent encounter data were available for this CF cohort of patients, last-value-carried-forward method was implemented for imputing time-varying covariates at the time of events. Both univariate and multivariate analysis results were presented.

Results

Study population

Among 35,516 active CFFPR subjects from January 2003 to December 2012, 1290 (3.6%) were reported to have cirrhosis (Figure 1, consort diagram). Among these, 970 registry subjects with their native liver were newly reported to have cirrhosis during this period and were evaluated for subsequent VB. Excluding 27 subjects who had no further follow-up the remaining 943 cirrhosis subjects were included in the analysis (Figure 1). 41% of the study subjects were female, and 3.4% of these subjects had mild CFTR mutations (compared to 8.2% in the overall CF population). At the time of report of cirrhosis, the mean age of the study population was 18.1 (median=15.7, SD=11.6) years; 24.7% subjects were on chronic insulin and 84.6% subjects had history of PA-positive culture. Among the study cohort 169 (17.5%) patients died and 49 (5.2%) received a liver transplant. Repeated measures of severity of CF were available with a median of 60 BMI measurements, 40 FEV1% measurements, and 78 PA cultures per subject during the follow-up period. Excluding 38 subjects who had their first variceal hemorrhage recorded on the same day that cirrhosis was first recorded, 905 were included in the analyses for incident VB. Figure 1 shows the consort diagram and Suppl Table 1 shows the baseline characteristics of the study population. No baseline characteristics were found to be significantly different among the three groups: those without VB, those with VB and cirrhosis reported concurrently, and those with cirrhosis reported who subsequently had VB.

Variceal bleeding, liver transplant, and liver-related death over time

Variceal bleeding—Supplemental Figure 1 demonstrates age at first report of VB. The mean age at first VB was 18.8 years (median: 16.0, range 0.89 – 45.14). For two subjects, VB was recorded following liver transplant. Among the 71 subjects who had experienced VB with their native liver, there was a peak in adolescence, with VB being uncommon after 30 years of age. Among the 905 subjects included for the analysis of VB incidence, 35 had VB reported during a mean follow-up period of 3.6 years (range 0.003-10 years). The estimated 10-year cumulative VB rate was 6.6% (95% confidence interval (CI): 4.0, 9.1%) (Figure 2A).

Liver transplant (LT)—Of the 870 subjects with no reported VB, 34 (3.8%) underwent LT. In contrast, among the 73 subjects in whom a VB was reported, 15 (20.6 %) underwent LT. Of the 15 patients with VB who were transplanted, 8 received LT within one year of reporting a VB. The estimated 10-year cumulative LT rate was 9.9% (95% CI: 6.6%, 13.2%) (Figure 2B)

Liver-related death—The estimated 10-year cumulative liver-related death rate was 6.9% (95% CI: 4.0%, 9.8%) (Figure 2C)

Adverse liver outcomes—Overall, in 10 years, among the above 905 subjects who were followed and had not had a VB reported at the time when cirrhosis was reported, adverse liver outcomes (variceal hemorrhage, liver transplant, or death due to liver failure) were observed in 96 subjects. The estimated 10-year cumulative rate of any adverse liver-related outcomes was 20.4% (95% CI: 15.4, 25.5%).

All-cause mortality—Among the 943 cirrhosis subjects who were followed, the estimated 10-year cumulative total death rate among all patients with cirrhosis was 39.2% (95% CI: 30.8, 46.6%) (Figure 2D).

Risk factors for adverse liver outcomes (summarized in Table 1)

Variceal bleeding (VB)—In univariate analysis, among reported cirrhosis subjects with no prior VB at the time of initial cirrhosis report, only worse FEV1% predicted showed a tendency (p=0.070) for higher risk of VB (Supplemental Table 2A). In multivariate analysis, after adjusting all other risk factors, older age at cirrhosis report was the only risk factor associated with lower risk of VB; a one year increase in age was related to a 5% (95% CI: 0.3%, 10.5%) reduction in risk. FEV1%, severity of genotype, nutrition/BMI, and CFRD did not significantly affect the risk of VB.

Liver transplant (LT)—In the univariate model for LT, CFRD was associated with a 2.6-fold increase in risk (HR 2.590 for chronic insulin use vs no insulin use, 95% CI: 1.376, 4.875) and VB was associated with a 5-fold increase in risk (HR 5.121: 95%CI: 2.511-10.443). For both risk factors, hazard ratios were similar on multivariate analysis. In addition, older age was associated with decreased risk of liver transplant (HR 0.943; CI 0.899-0.989) (Supplemental Table 2B).

Liver-related death (LD)—Gender, age, FEV_1% predicted decrease, pseudomonas positivity, decreased BMI, CFRD, and VB were all associated with increased liver related mortality on univariate analysis. VB was associated with a 4-fold increase in risk (HR 4.11: 95%CI: 1.83 - 9.22). On multivariate analysis, only FEV_1% predicted decrease was associated with increased liver-related mortality (Supplemental Table 2C).

Causes of death and risk factors for death

Almost two-thirds of deaths among these cirrhotic subjects were pulmonary related (Table 2 displays causes of death by VB history and LT status in subjects with cirrhosis). Among CF subjects who had VB reported, death was reported for 20.0% in those with and 24.1% in those without LT (given unknown actual date of LT and low count of LT, no survival analysis was carried out to compare effect of LT on risk of mortality). Among those who did not have VB reported, death was reported in 5.9% in the group who received LT and in 17.9% in the group without LT. Among reported cirrhosis subjects with their native liver who had not had VB, 20.0% (30/150) of deaths were due to liver disease/liver failure compared to 35.7%

(5/14) in the VB native liver group. Five of the 49 subjects who received LT died within a median of 2.5 years (range 0.28-8.4 years), but none were due to liver disease/liver failure.

Supplemental Table 2D shows the Cox proportional hazard regression model results for all-cause mortality (ACM). In univariate analysis, a 10% reduction of FEV1% was associated with a 78.6.0% increase in risk of ACM (HR for 10% increase in FEV1%: 0.56, 95% CI: 0.51, 0.61); low BMI and CFRD were strongly associated with increased mortality risk. On multivariate analysis, older age at first reported cirrhosis (HR: 1.032, 95% CI: 1.016, 1.049), and chronic insulin requirement (HR for chronic insulin use vs. normal glucose intolerance: 2.45, 95% CI: 1.57, 3.83) were all associated with higher risk of ACM in addition to lower FEV1%. Recent positive status of PA (but not lifetime history of positivity) was associated with lower risk (HR: 0.65, 95% CI: 0.45, 0.95) of all-cause mortality. Notably, history of VB did not increase risk of all-cause mortality in this cohort.

Discussion

This longitudinally captured registry based study demonstrates that variceal hemorrhage is not very common in CF cirrhosis, with less than 10% of patients experiencing variceal hemorrhage in the 10 years after the report of cirrhosis. This bleeding rate is substantially less than the 40 or 50% rate that has previously been reported in the literature among patients with CF cirrhosis.[3, 6, 11] Bleeding typically occurs in adolescence, with rare occurrence under 9 years or over 40 years of age, reaffirming the early onset of CF cirrhosis.[9] In our study, cirrhosis had not previously been reported in half of the patients with variceal bleeding until the sentinel bleeding event. The database does not contain reliable data on platelet count and provides no data on spleen size, so it is impossible to determine whether laboratory or physical findings might have suggested a diagnosis of cirrhosis or portal hypertension earlier. Earlier detection of advanced CF liver disease would have implications for immunizations (hepatitis A, B, pneumococcus), anticipatory guidance (avoiding NSAIDs, recognizing signs and symptoms of GI bleeding), and in prophylactic management in adults such as screening endoscopy, propranolol or variceal band ligation).[13-16]

Identification of risk factors for bleeding in CF patients with cirrhosis and portal hypertension would also be helpful in managing and counseling patients. In multivariate analysis, only younger age at report of cirrhosis was identified as a risk factor for variceal bleeding. Commonly identified complications of CF such as decreased pulmonary function, compromised nutritional status and CFRD were not found to be risk factors. It is unclear why younger age at reporting of cirrhosis is a risk factor for variceal bleeding. Earlier recognition of cirrhosis may be associated more aggressive and rapidly progressive form of CF liver disease. Considering overall mortality rate increases as patients become older, it is also possible that death due to lung failure played a role.

By univariate and multivariate analysis, CFRD and variceal bleeding were associated with an increased risk of liver transplantation. In contrast, while low BMI, CFRD, variceal bleeding and other factors were significant on univariate analysis, on multivariate analysis, only poor lung function (decreased FEV1%) was associated with increased risk of liver-

related mortality. Chronic antibiotic exposure in patients with pulmonary exacerbations due to CF-specific pathogens and an acidic, more permeable gastrointestinal tract may not only alter the intestinal microbiome but trigger an inflammatory cascade that leads to Kupffer cell mediated liver injury.[17] Chronic cough may also lead to increased intra-abdominal pressures affecting splanchnic flow. Compromised nutritional status with advanced lung disease might also impact tissue elasticity or healing, promoting variceal bleeding. Insulin resistance has been known to be associated with worse outcomes in other liver conditions such as fatty liver disease; similarly, CF-related diabetes (CFRD) may be a modifier of liver disease by interfering with healing and immune response to infections. CFRD and insulin resistance could conceivably be associated with another genetic modifier of the liver disease. [18, 19]

Our data demonstrate substantial overall mortality among reported CF cirrhosis patients, with 39.2% dying within 10 years of initial report and at a mean age of 18 years. By comparison, mortality per decade between ages 20 and 50 years was only 20%-30% in two modern era analyses of unselected CF subjects.[21, 22] Importantly and surprisingly, however, variceal hemorrhage was not associated with increased all-cause mortality, although it was associated with more liver-related mortality on univariate analysis only. Furthermore, two-thirds of deaths were attributed to lung disease in this cirrhotic population, highlighting the critical role of declining lung function in patients with CF cirrhosis.

Cirrhotic subjects who had experienced variceal hemorrhage were 5 times more likely to be transplanted and were transplanted quickly (more than half within a year of variceal bleeding). Gastrointestinal bleeding has often prompted consideration of liver transplant in CF, and our data confirms this.[23-26]. Further study is needed regarding indications and timing of liver transplantation in CF liver disease and the impact of variceal bleeding on decision-making.

This study represents an analysis of nearly 1000 North American children and adults with reported CF cirrhosis and provides important data regarding the incidence of variceal hemorrhage, adverse liver outcomes, and related risk factors. As with any registry-based studies, we encountered limitations secondary to incomplete, inadequate, or misclassified data. The registry forms did not differentiate between cirrhosis and non-cirrhotic portal hypertension, although the outcomes we studied pertain to both. This registry-based study is less vulnerable to ascertainment bias than single-center reports, which could partly explain the lower rate of variceal bleeding observed in this population. Due to limitations of the registry, we could not account for the impact of potential primary prophylaxis in some (likely adult) patients, which may have decreased the bleeding rate. Lastly, the number of subjects with reported variceal bleeding targeted in this analysis is small as patients with variceal bleeding who were reported to have cirrhosis on the same date of the bleeding event could not be included in the survival analysis for first variceal bleeding, hence may have led to further underestimation of the rate. (In Supplemental Figure 2 we provide cumulative incidence curves from birth rather than from cirrhosis diagnosis with an explanatory footnote.) In recent years, improvements have been made to the liver-related case report forms in the CF registry, which should serve to improve the quality of future liver-specific

data. This study underscores the importance of collecting prospective clinical data regarding liver disease in this vulnerable population.

This study yields several key messages. Variceal bleeding in CF liver disease is a much less common than previously thought, and often heralds the recognition of unsuspected cirrhosis. Except for younger age at cirrhosis diagnosis, there were no additional risk factors associated with increased risk of variceal bleeding. Notably, variceal hemorrhage does not impact all-cause mortality in CF patients but does coincide with other adverse liver outcomes, including liver transplantation. This differs significantly from the adult experience with cirrhosis where substantial mortality (up to 15%) is associated with variceal bleeding. [27] Ultimately, 10-year all-cause mortality is substantial in patients with CF cirrhosis at nearly 40%, though death is most commonly due to pulmonary complications. The role and timing of liver transplantation in CF cirrhosis complicated by variceal hemorrhage warrants data with higher fidelity before formal recommendations can be made. Prospective detailed studies of children and adults with early identification of CF cirrhosis are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

CF Cystic Fibrosis

VB	variceal bleeding
ALO	adverse liver outcomes
LT	liver transplant
LD	liver death
ACM	all-cause mortality
PA	pseudomonas aeruginosa
HR	hazard ratio
CI	confidence interval
FVC	forced vital capacity
CFRD	CF-related diabetes
CFLD	cystic fibrosis-related liver disease
CFTR	cystic fibrosis transmembrane regulator
CFFPR	CF Foundation Patient Registry
FEV	forced expiratory volume
BMI	body mass index
NSAID	non-steroidal anti-inflammatory drug

What is known

- Cirrhosis occurs in 5-10% of patients with Cystic Fibrosis (CF).
- Variceal bleeding is common in CF cirrhosis but synthetic function is usually preserved until late in the course

What is new

- The cumulative rate of variceal bleeding in this large population of CF patients after first report of cirrhosis was only 6.6% at 10 years, while liver transplant was 9.9%, liver death 6.9%, overall adverse liver outcomes 20%, and all-cause mortality 39%.
- CF-related diabetes and VB are significant risk factors for liver transplant in CF cirrhosis
- All-cause mortality was not impacted by variceal bleeding.

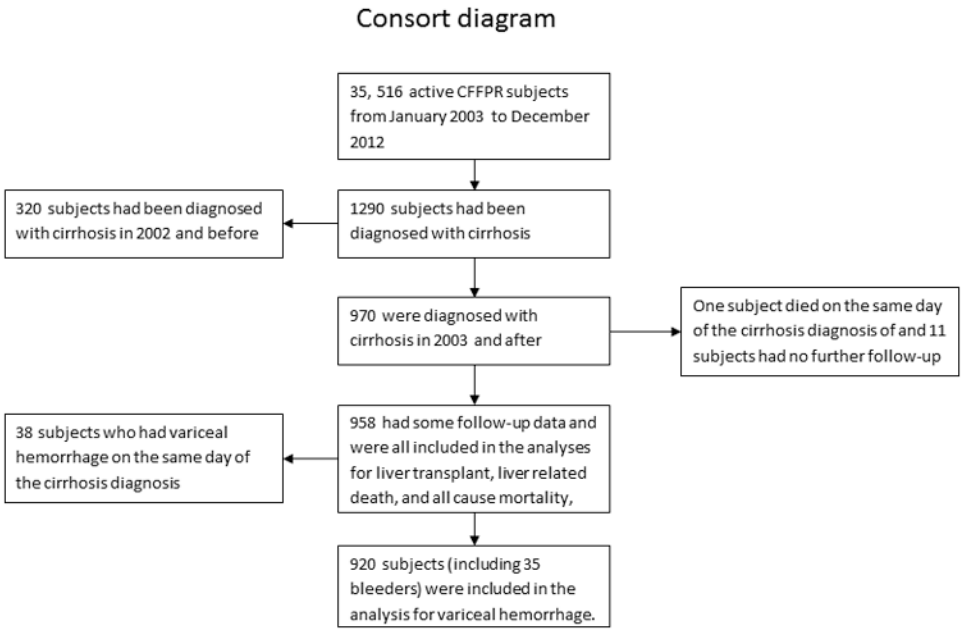

Figure 1.
Consort Diagram of Study Population

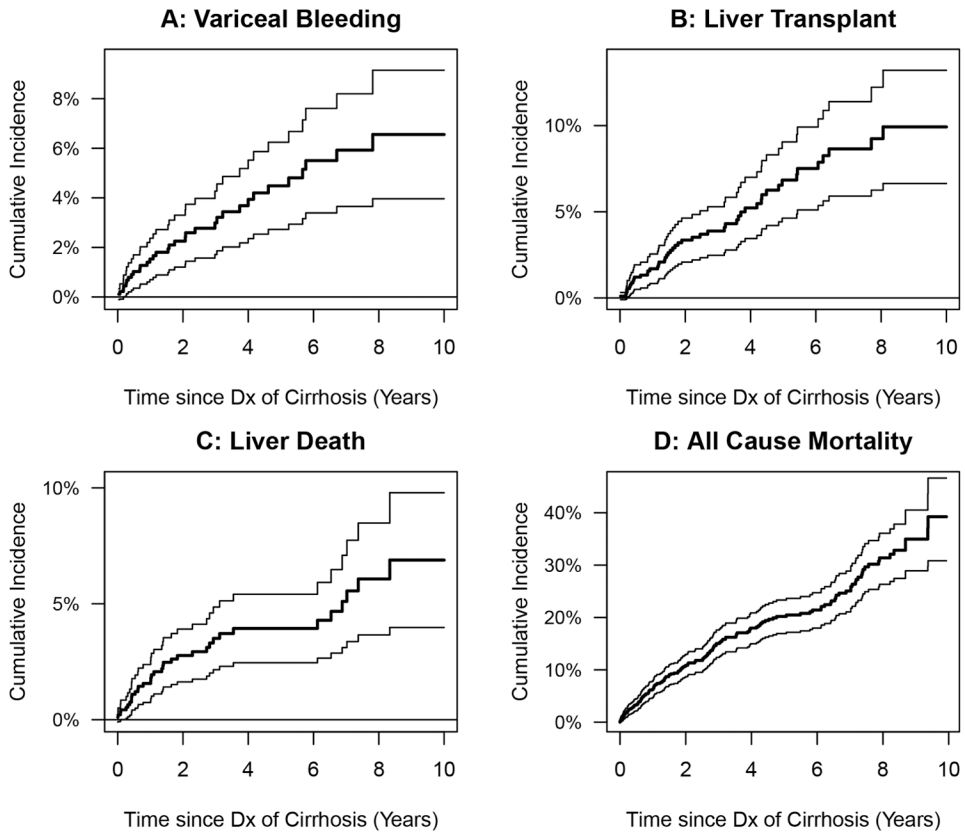

Figure 2.

Cumulative Incidence Curves for Variceal Bleeding (Among Patients Who Had No History of VB at the Time of Report of Cirrhosis) (A), Liver Transplant (B), Liver Related Death (C), and All-Cause Mortality (D)

Table 1
Summary of Findings from Cause-Specific Competing Risk Regression Model

Outcome	Significant on Univariate Analysis (HR)	Significant on Multi-Variate Analysis (HR)
VB		Age at 1st Reported Cirrhosis (0.895)
LTP		Age at 1st Reported Cirrhosis (0.899)
	CFRD (2.590)	CFRD (3.141)
	VB (5.121)	VB (4.837)
LRM	Gender (2.271)	
	Age (1.044)	
	FEV1↑ (0.591)	FEV1↑ (0.674)
	PA ever (2.998)	
	BMI under (6.647)	
	CFRD (5.196)	
	VB (4.110)	
ACM	Age (1.055)	Age (1.032)
	FEV1↑ (HR 0.560)	FEV1↑ (0.623)
		Recent PA (0.649)
	BMI under (5.590)	
	CFRD (5.563)	CFRD (2.454)

Table 2

2A. Death (count, %) by Variceal Bleeding (VB)and Liver Transplant (LT) Status				
	No VB (N=870)		VB (N=73)	
	No LT N=836	LT N=34	No LT N=58	LT N=15
Total number of deaths (%)	150 (17.9%)	2 (5.9%)	14 (24.1%)	3 (20.0%)

2B. Cause of Death by Variceal Bleeding and Liver Transplant Status				
Primary cause of death (Count (%))	No VB or LT N=150	No VB, had LT N=2	Had VB, no LT N=14	Had VB hadLT N=3
Respiratory/cardiorespiratory	101 (67.3%)	0	8 (57.1%)	2 (66.7%)
Liver Disease/Liver Failure	30 (20.0%)	0	5 (35.7%)	0
Trauma	0	0	0	0
Suicide	0	1 (50%)	0	0
Transplant related: Other^	4 (2.7%)	1 (50%)	1 (7.1%)	1 (33.3%)
Other	9 (6.0%)	0	0	0
Unknown	6 (4.0%)	0	0	0

* Among the 15 who had variceal bleeding and transplant, two had transplant before the first reported variceal hemorrhage, one of whom died of respiratory/cardiorespiratory cause, the other was alive at the end of follow-up.

^ Lung transplant is included here