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ORIGINAL ARTICLE

Impact of Inflammatory Bowel Disease Subtypes on the Post-liver Transplant Outcomes of Patients with Primary Sclerosing Cholangitis

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Abstract

Background and Aims Liver transplant patients with primary sclerosing cholangitis often present with concurrent inflammatory bowel disease. The effect of comorbid conditions on post-transplant prognosis was evaluated.

Methods The 2005–2019 United Network of Organ Sharing Standard Transplant Analysis and Research database was used to identify patients with primary sclerosing cholangitis. Patients were categorized as having Crohn's Disease, ulcerative colitis, unclassified inflammatory bowel disease, or no inflammatory bowel disease. Baseline characteristics were assessed between cohorts, and outcomes were examined using Cox regression. Outcomes included all-cause mortality, graft failure, infection-induced mortality, and organ system-delineated mortality. Supplementary analyses with unique exclusion and stratification criteria were also performed.

Results Among 2829 patients undergoing transplant, 1360 were considered to have ulcerative colitis, 372 were considered to have Crohn's Disease, and 69 were considered to have an unclassified form of inflammatory bowel disease. Primary sclerosing cholangitis patients with some form of inflammatory bowel disease had no increased risk for any outcomes. However, patients with ulcerative colitis had lower risks of general infectious (aHR 0.65 95%CI 0.44–0.95) and sepsis-induced (aHR 0.56 95%CI 0.35–0.91) mortality, whereas patients with Crohn's Disease had higher risks of sepsis-induced mortality (aHR 2.13 95%CI 1.22–3.70). Supplementary analyses showed effect modification by abdominal surgery history and era.

Conclusion The type of inflammatory bowel disease in liver transplant patients with primary sclerosing cholangitis was found to portend risk difference for infection-induced mortality, with ulcerative colitis found to be protective and Crohn's Disease predictive of increased mortality secondary to infectious etiologies. These associations warrant further investigation.

Keywords Liver transplant · Outcome assessment · Inflammatory bowel disease · Primary sclerosing cholangitis

Introduction

Patients with primary sclerosing cholangitis (PSC) suffer from autoimmune destruction of the hepatobiliary tracts, which culminates in ductal damage, ductopenia, lymphocytic infiltration of hepatobiliary tracts, parenchymal inflammation, and fibrosis [1]. There is currently no effective intervention in controlling the natural history of this condition, and it often results in cirrhosis and end-stage liver disease [2]. Liver transplant (LT) stands as the therapeutic intervention of choice to reverse liver failure [3]. However, LT is well known to have tremendous operative risk, and various recipient and donor risk factors alter the post-transplant prognosis [4–6]. Primary sclerosing cholangitis has a unique overlap with inflammatory bowel disease (IBD), classically associated with ulcerative colitis (UC), though Crohn's Disease

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(CD) is also seen [1, 7]. Inflammatory bowel disease, depending on phenotype severity, can likewise affect the post-transplant prognosis by increased luminal penetrance, intestinal and portal bacterial translocation, endotoxemia, and increased risk of sepsis and infections in the setting of peri and post-LT immunosuppression [7–9].

Previously, there had been concerns around initiating certain immunosuppressive regimens among PSC-IBD subtypes, given the potential risk of immunosuppression-induced IBD flare or colitis [10]. However, more recent studies suggest that this may not be true with certain agents, namely TNF-alpha inhibitors [10–12]. However, in a different perspective, the subacute to long-term prognosis of the post-LT course with respect to PSC recurrence, graft viability and survival, rejection, and system-specific causes of death have been seldomly evaluated. Further, there has been a paucity of literature evaluating the individual impact of PSC-UC and PSC-CD. Hence, a comprehensive examination of the prognostic relationships that exist between PSC-IBD subtypes and post-LT outcomes is needed to characterize the impact of IBD-subtypes on post-LT outcomes of PSC patients.

Methods

Database

The United Network for Organ Sharing (UNOS) Standard Transplant and Analysis Research (STAR) database was used for this cohort study. This database contains patient outcome and follow up information for transplant patients across the United States. For this study, data from 2005 to 2019 were queried. All patient data are deidentified, and confidentiality is established via data-use agreements and safety mechanisms. This initiative was also facilitated by the Health Resources and Services Administration Contract 234-2005-370011C; however, the contents of this study are not endorsed by any governmental body and solely represent author's viewpoints.

Study Population—Main and Supplementary Analyses

A total of 99,987 patients who received a liver transplant (LT) between 2005 and 2019 were identified. From this cohort, patients lost to follow up ($n=3445$) and patients who underwent retransplantation ($n=4310$) were excluded. Further exclusions include patients with impossible biological values (e.g., negative serum creatinine) ($n=5$), patients under 18 years of age ($n=6872$), patients with non-heart-beating organ donation ($n=4427$), patients with living donors ($n=3081$), patients with non-whole liver ($n=1012$), and patients with multiorgan transplant ($n=6462$). To focus on only patients with diagnosis of PSC, patients without the diagnosis of PSC were also excluded ($n=62{,}107$). This yields a final cohort of 2829 patients who received LT with the diagnosis of PSC with reported IBD data. This cohort was then stratified by whether they had CD, UC, or no IBD for analysis. Comparisons were conducted between the following cohorts: those with UC versus those without UC, those with CD versus those without CD, those with inflammatory bowel disease versus those without inflammatory disease, and those with UC versus those with CD.

Additional cohorts were generated to further describe the different relationships between IBD and outcomes of the transplanted PSC patient population. A supplementary study pool was produced according to the same procedure outlined above, and patients with hepatocellular carcinoma or cholangiocarcinoma were excluded. A second supplementary analysis stratified the main study population based on their abdominal surgical history. Again, using the main study population, a third analysis divided the time period into LT cases occurring before and after 2012. Similar to the main analysis, comparisons between UC-positive and UC-negative, CD-positive and CD-negative, IBD-positive ad IBD-negative, and UC and CD were conducted for each supplementary analysis. The results of these evaluations are included in Supplementary Tables 3–12 through 13.

Covariates and Study Endpoints

Covariates were chosen to better characterize patient overall health status and donor variables. These included recipient demographics, comorbidities, relevant hepatic laboratory markers, immunosuppressant medications, critical care and life-supporting assistive devices, and donor demographics and laboratory markers. The 'assistance' variable was a proxy for functional status based off the Karnofsky score, in which 1 represented scores between 80 and 100% (high functional status), 2 represented 50–70% (intermediate functional status), 3 represented 10–40% (low functional status), and 0 represented no data [13]. The primary outcomes of this study were all-cause mortality and graft failure, whereas secondary outcomes consisted of infectious-related mortality. The general infectious outcome was a composite of several pathogenic entities, including sepsis, viruses, spontaneous bacterial peritonitis, aspergillosis, pneumocystis pneumonia, and other opportunistic pathogens. These pathogenic entities were delineated for the main cohort only, provided that a sufficient number of deaths occurred for Cox regression to be conducted. Furthermore, mortality from cardiac, graft complications (including biliary, recurrent disease, rejection, and vascular dysfunction), gastrointestinal hemorrhage, respiratory, and renal causes were also sampled.

Statistical Analysis

To establish baseline characteristics for our cohort, a series of statistical tests were conducted. For nominal variables, Fisher's or Chi-squared tests were conducted. Student's t tests were used to evaluate parametric factors while Whitney-U tests were used to evaluate non-parametric factors.

Multivariable Cox regression analyses were conducted to evaluate the primary and secondary outcomes. For this, four successive models were generated, with each successive model incrementally adjusting for covariates as follows: Model 1—recipient demographics, Model 2—Model 1 covariates and recipient comorbidities, Model 3—Model 2 covariates and recipient liver status and laboratory markers, Model 4—Model 3 covariates and donor characteristics (donor age, gender, race, and BMI). For each iteration of the Cox regression model, an adjusted hazard ratio, 95% confidence interval, and p value were calculated. For each strata-outcome relationship, incidence rates were calculated and expressed in units of per 1000 person-years. Additionally, cumulative hazard analyses were run for our primary and secondary outcomes, and log-rank test was used to evaluate significance for these plots.

To evaluate for competing risks of all-cause mortality and graft failure, a modified version of Fine and Gray's cumulative incidence functionality was used to create a proportional subdistribution hazard model [14]. Using a similar regression model as described above, a Competing-risks regression model was produced. Random forest iterations were used to offset missingness and therefore enhance statistical power [15].

All statistical tests were conducted utilizing RStudio version 1.2.5042, using R code version 3.6.3.

Results

Main Analysis: Baseline Characteristics

A total of 1360 individuals were identified as having UC compared to 1469 individuals without this diagnosis. Patients with UC were younger (48.3 vs. 49.4 years, $p=0.01$), more likely to be male (73.2 vs. 63.2%, $p<0.001$), and had lower BMIs (25.2 vs. 25.8 kg/m^2, $p=0.02$). The racial make-up of the UC-positive group was also significantly different than that of the UC-negative group ($p<0.001$). Diabetes and alcoholic liver disease were significantly more prevalent in the non-UC group (diabetes: 13.00 vs. 9.49%, $p=0.004$; alcoholic liver disease: 1.29 vs. 0.37%, $p=0.01$). Tacrolimus-containing regimens were used more often in the UC-diagnosed group (95.5 vs. 93.1%, $p=0.007$).

Meanwhile, there were 372 cases considered to have CD, which were evaluated against 2457 cases without this diagnosis. A higher proportion of white patients was observed in the CD-positive cohort (84.70 vs. 74.60%), among other ethnic differences ($p<0.001$). Diabetes was again more prominent in the non-CD group (11.80 vs. 8.06%, $p=0.04$). Cases diagnosed with CD had a higher proportion of patients without ascites (35.5 vs. 31.7%, $p=0.04$) and lower MELD scores (21.4 vs. 22.7, $p=0.005$). Total bilirubin was also lower in the CD group (12.1 mg/dL vs. 13.9 mg/dL, $p=0.001$), as well as assistance levels ($p=0.04$).

When compared based on IBD presence (1801 patients with IBD versus 1028 without), those with IBD were again younger (48.4 vs. 49.7 years, $p=0.005$), more likely to be male (71.3 vs. 62.2%, $p<0.001$), and had lower BMIs (25.2 vs. 26.1 kg/m^2, $p<0.001$). The IBD-positive and -negative cohorts also had different racial distribution ($p<0.001$). Comorbidities were significantly different between groups—IBD-negative patients were more likely to present with simultaneous hepatitis C virus (4.96 vs. 3.22%, $p=0.03$), alcoholic liver disease (1.85 vs. 0.28%, $p<0.001$), and diabetes (15.30 vs. 9.05%, $p<0.001$). Again, the IBD-positive group exhibited lower rates of ascites ($p=0.03$) and hepatic encephalopathy ($p=0.03$). There was a significantly higher proportion of male donors in the IBD-positive group (59.6 vs. 54.6%, $p=0.01$) (see Fig. 1).

CD and PSC-UC patients were then compared, and significant differences were found among the cohorts' racial profile ($p=0.04$) and sex profile (73.2% males in PSC-UC vs. 63.4% males in PSC-CD, $p<0.001$). MELD scores were higher in the PSC-UC group (22.5 vs. 21.4, $p=0.02$). The PSC-UC group was more likely to use tacrolimus (95.5 vs. 91.9%, $p=0.009$) and have a higher total bilirubin (13.9 vs. 12.1 mg/dL, 0.002). This data and additional analyses are summarized in Tables 1, 2, 3, 4.

Main Analysis: Clinical Outcomes

The results of the sequential Cox regression analysis showed no statistical differences in the primary outcomes of all-cause mortality and graft failure between patients for any of the comparison (UC-positive vs. UC-negative, CD-positive vs. CD-negative, IBD-positive vs. IBD-negative, and UC-positive vs. CD-positive). Tables 5, 6, 7 through 8 show these results in tabular format, along with case-incidence rates. Cumulative hazards for all-cause mortality and graft failure were graphed in Fig. 2, and the adjusted hazard ratios (aHRs) from the aforementioned Cox regressions are shown in Supplementary Figs. 1–7 through 8, consisting of the Cox model covariates. When considering infectious-related mortality, those with PSC-UC had lower rates of mortality from general infectious causes (aHR 0.65 95% CI 0.44–0.95, $p=0.03$, case-incidence rates: 5.86 deaths vs. 9.29 deaths per 1000 person-years) and sepsis (aHR

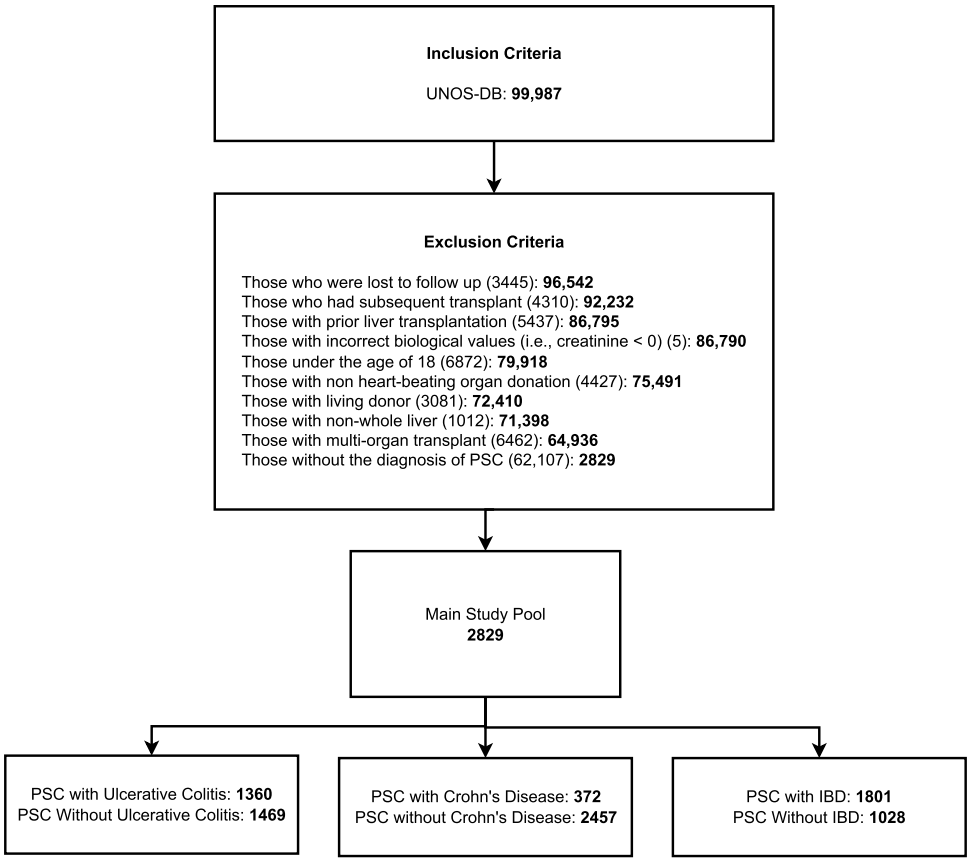

Fig. 1 This figure shows the patient selection process of this study

0.56 95% CI 0.35–0.91, $p = 0.02$, case-incidence rates: 3.63 deaths vs. 6.67 deaths per 1000 person-years). In contrast to PSC-UC, PSC-CD was found to increase the risk of death for sepsis (aHR 2.13 95% CI 1.22–3.70, $p = 0.008$, case-incidence rates: 8.57 deaths vs. 4.68 deaths). No differences in risk were found for general infectious causes of death, although case-incidence rates were elevated in PSC-CD (10.09 deaths per 1000 person-years) versus 7.25 deaths per 1000 person-years of the CD-negative group. Comparing the PSC-UC and PSC-CD cohorts, general infectious death risk was relatively reduced in PSC-UC patients (aHR 0.58 95% CI 0.33–1.00, $p = 0.05$, case-incidence rates: 10.09 deaths vs. 5.86 deaths per 1000 person-years), as well as sepsis-induced death risk (aHR 0.38 95% CI 0.20–0.73, $p = 0.003$, case-incidence rates: 8.57 deaths vs. 3.63 deaths per 1000 person-years). When combining IBD subtypes, no differences in risk for infectious death were detected between IBD-positive and IBD-negative cases. These regression models are included in Tables 9, 10, 11 through 12. Cumulative hazard curves for infection-related death are shown in Fig. 3, and several curves showed early divergence and significant cumulative risk differences.

Other organ system-based and infection subtype-related mortality outcomes were evaluated via Cox regression. No differences in risk were reported, apart from a decreased risk of death from renal causes in PSC-IBD patients (aHR 0.30 95% CI 0.12–0.76, $p = 0.01$, case-incidence rates: 0.84 deaths per 1000 person-years vs. 2.47 deaths per 1000 person-years). These analyses are presented in Supplementary Tables 1.1–1.3 through 4. Supplementary Table 2 includes Competing-risks regression models for the primary outcomes, conducted for each of the aforementioned comparisons. No analyses showed significant differences in risk.

Supplementary Analysis—Excluding Primary Liver Cancer

The main study population was refined by excluding patients with hepatocellular carcinoma or cholangiocarcinoma, and baseline characteristics and outcomes were again assessed. Similar results to those of the main cohort were observed—all-cause mortality and graft failure showed no differences in risk between cohorts. However when compared to UC-negative or CD-negative patients, PSC-UC patients experienced lower risk of mortality secondary to general infectious causes (aHR 0.61 95% CI 0.41–0.91, $p = 0.02$) and due to sepsis (aHR 0.52 95% CI 0.32–0.86, $p = 0.01$), and PSC-CD patients demonstrated a higher risk of mortality secondary to sepsis (aHR 2.09 95%CI 1.18–3.69, $p = 0.01$). Combining IBD subtypes led to these associations falling out of significance. Analyses

Table 1 Baseline characteristics of liver transplant recipients with primary sclerosing cholangitis stratified by ulcerative colitis

Variable	Comparison of PSC with ulcerative colitis vs PSC without ulcerative colitis				
	PSC without ulcerative colitis		PSC with ulcerative colitis		*p*-value
	n = 1469	51.93%	*n* = 1360	48.07%	
Recipient demographics					
Age (years)	49.40	± 13.40 years	48.30	± 13.40 years	0.01*
Gender, male (%)	928	63.20%	995	73.20%	< 0.001***
Race					< 0.001***
White (%)	1045	71.10%	1102	81.00%	
Black (%)	300	20.40%	183	13.50%	
Hispanic (%)	68	4.63%	51	3.75%	
Asian (%)	34	2.31%	17	1.25%	
Other (%)	22	1.50%	7	0.52%	
BMI (kg/m^2)	25.80	± 5.08 kg/m^2	25.20	± 4.52 kg/m^2	0.02*
Comorbidities					
Hepatitis B (%)	18	1.23%	19	1.40%	0.81
Hepatitis C (%)	67	4.56%	42	3.09%	0.05
Alcoholic liver disease (%)	19	1.29%	5	0.37%	0.01*
Diabetes (%)	191	13.00%	129	9.49%	0.004**
Assistance[b]					0.71
0 (%)	28	1.91%	34	2.50%	
1 (%)	375	25.50%	335	24.60%	
2 (%)	602	41.00%	558	41.00%	
3 (%)	464	31.60%	433	31.80%	
Hepatic Variables					
Ascites					0.54
Absent (%)	460	31.30%	450	33.10%	
Slight (%)	698	47.50%	638	46.90%	
Moderate (%)	311	21.20%	272	20.00%	
Encephalopathy					0.16
None (%)	731	49.80%	720	52.90%	
1–2 (%)	646	44.00%	570	41.90%	
3–4 (%)	92	6.26%	70	5.15%	
MELD score	22.50	± 9.05	22.50	± 9.26	0.99
Medications					
Mycophenolate mofetil (%)	1216	82.80%	1153	84.80%	0.16
Cyclosporine (%)	43	2.93%	36	2.65%	0.74
Tacrolimus (%)	1367	93.10%	1299	95.50%	0.007**
Sirolimus (%)	13	0.89%	13	0.96%	1.00
Steroids (%)	1370	93.30%	1282	94.30%	0.31
Laboratory markers					
Albumin (mg/dL)	2.94	± 0.73 mg/dL	2.95	± 0.73 mg/dL	0.80
Creatinine (mg/dL)	1.23	± 0.91 mg/dL	1.26	± 1.13 mg/dL	0.47
INR	1.88	± 1.37	1.86	± 1.33	0.22
Total bilirubin (mg/dL)	13.50	± 12.30 mg/dL	13.90	± 12.40 mg/dL	0.27
Life support variables					
Primary inotropic agent					0.86
Dobutamine (%)	29	1.97%	25	1.84%	
Dopamine (%)	250	17.00%	237	17.40%	
Epinephrine (%)	22	1.50%	19	1.40%	

Table 1 (continued)

Variable	Comparison of PSC with ulcerative colitis vs PSC without ulcerative colitis				
	PSC without ulcerative colitis		PSC with ulcerative colitis		*p*-value
	n = 1469	51.93%	*n* = 1360	48.07%	
Levophed (%)	247	16.80%	211	15.50%	
Neosynephrine (%)	218	14.80%	227	16.70%	
None (%)	667	45.40%	609	44.80%	
Other (%)	36	2.45%	32	2.35%	
Secondary inotropic agent					0.87
Dobutamine (%)	6	0.41%	9	0.66%	
Dopamine (%)	10	0.68%	13	0.96%	
Epinephrine (%)	8	0.55%	9	0.66%	
Levophed (%)	46	3.13%	49	3.60%	
Neosynephrine (%)	79	5.38%	72	5.29%	
None (%)	1297	88.30%	1190	87.50%	
Other (%)	23	1.57%	18	1.32%	
Tertiary inotropic agent					0.73[a]
Dobutamine (%)	1	0.07%	3	0.22%	
Dopamine (%)	1	0.07%	3	0.22%	
Epinephrine (%)	2	0.14%	1	0.07%	
Levophed (%)	8	0.55%	6	0.44%	
Neosynephrine (%)	8	0.55%	5	0.37%	
None (%)	1442	98.20%	1338	98.40%	
Other (%)	7	0.48%	4	0.29%	
ICU admission					0.65
ICU (%)	128	8.71%	111	8.16%	
No ICU (%)	1341	91.30%	1249	91.80%	
Ventilator support (%)	32	2.18%	29	2.13%	1.00
TIPS procedure (%)	81	5.51%	86	6.32%	0.40
Donor demographics					
Donor age (years)	42.10	± 17.60 years	41.80	± 16.80 years	0.87
Donor gender, male (%)	824	56.10%	811	59.60%	0.06
Donor race					0.78
White (%)	1017	69.20%	946	69.60%	
Black (%)	262	17.80%	223	16.40%	
Hispanic (%)	142	9.67%	144	10.60%	
Asian (%)	28	1.91%	25	1.84%	
Other (%)	20	1.36%	22	1.62%	
Donor BMI (kg/m^2)	27.50	± 6.69 kg/m^2	27.80	± 6.87 kg/m^2	0.30
Donor laboratory markers					
Donor Creatinine (mg/dL)	1.52	± 1.46 mg/dL	1.66	± 1.87 mg/dL	0.09
Donor Total Bilirubin (mg/dL)	0.88	± 0.69 mg/dL	0.88	± 0.80 mg/dL	0.95

[a]Fisher's Test

[b]Assistance, a variable that represents functional status as defined by the Karnofsky score

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 2 Baseline characteristics of liver transplant recipients with primary sclerosing cholangitis stratified by Crohn's disease

Variable	Comparison of PSC with Crohn's disease vs PSC without Crohn's disease				
	PSC without Crohn's disease		PSC with Crohn's disease		*p*-value
	n = 2457	86.85%	*n* = 372	13.15%	
Recipient demographics					
Age (years)	48.80	± 13.40 years	49.20	± 13.30 years	0.64
Gender, male (%)	1687	68.70%	236	63.40%	0.05
Race					< 0.001[a,***]
White (%)	1832	74.60%	315	84.70%	
Black (%)	439	17.90%	44	11.80%	
Hispanic (%)	115	4.68%	4	1.08%	
Asian (%)	46	1.87%	5	1.34%	
Other (%)	25	1.02%	4	1.08%	
BMI (kg/m^2)	25.60	± 4.84 kg/m^2	25.30	± 4.74 kg/m^2	0.28
Comorbidities					
Hepatitis B (%)	33	1.34%	4	1.08%	0.81[a]
Hepatitis C (%)	95	3.87%	14	3.76%	1.00
Alcoholic liver disease (%)	24	0.98%	0	0.00%	0.06[a]
Diabetes (%)	290	11.80%	30	8.06%	0.04*
Assistance[b]					0.04*
0 (%)	56	2.28%	6	1.61%	
1 (%)	596	24.30%	114	30.60%	
2 (%)	1010	41.10%	150	40.30%	
3 (%)	795	32.40%	102	27.40%	
Hepatic Variables					
Ascites					0.04*
Absent (%)	778	31.70%	132	35.50%	
Slight (%)	1155	47.00%	181	48.70%	
Moderate (%)	524	21.30%	59	15.90%	
Encephalopathy					0.72
None (%)	1260	51.30%	191	51.30%	
1–2 (%)	1053	42.90%	163	43.80%	
3–4 (%)	144	5.86%	18	4.84%	
MELD score	22.70	± 9.17	21.40	± 8.93	0.005**
Medications					
Mycophenolate Mofetil (%)	2065	84.00%	304	81.70%	0.29
Cyclosporine (%)	67	2.73%	12	3.23%	0.71
Tacrolimus (%)	2324	94.60%	342	91.90%	0.05
Sirolimus (%)	23	0.94%	3	0.81%	1.00[a]
Steroids (%)	2309	94.00%	343	92.20%	0.23
Laboratory Markers					
Albumin (mg/dL)	2.94	± 0.73 mg/dL	2.99	± 0.74 mg/dL	0.24
Creatinine (mg/dL)	1.25	± 1.03 mg/dL	1.19	± 0.93 mg/dL	0.10
INR	1.87	± 1.22	1.84	± 2.00	0.11
Total bilirubin (mg/dL)	13.90	± 12.40 mg/dL	12.10	± 12.30 mg/dL	0.001**
Life support variables					
Primary inotropic agent					0.91[a]
Dobutamine (%)	46	1.87%	8	2.15%	
Dopamine (%)	419	17.10%	68	18.30%	
Epinephrine (%)	37	1.51%	4	1.08%	

Table 2 (continued)

Variable	Comparison of PSC with Crohn's disease vs PSC without Crohn's disease				
	PSC without Crohn's disease		PSC with Crohn's disease		*p*-value
	n = 2457	86.85%	*n* = 372	13.15%	
Levophed (%)	398	16.20%	60	16.10%	
Neosynephrine (%)	391	15.90%	54	14.50%	
None (%)	1104	44.90%	172	46.20%	
Other (%)	62	2.52%	6	1.61%	
Secondary inotropic agent					0.86[a]
Dobutamine (%)	13	0.53%	2	0.54%	
Dopamine (%)	18	0.73%	5	1.34%	
Epinephrine (%)	15	0.61%	2	0.54%	
Levophed (%)	85	3.46%	10	2.69%	
Neosynephrine (%)	131	5.33%	20	5.38%	
None (%)	2158	87.80%	329	88.40%	
Other (%)	37	1.51%	4	1.08%	
Tertiary inotropic agent					0.47[a]
Dobutamine (%)	4	0.16%	0	0.00%	
Dopamine (%)	4	0.16%	0	0.00 %	
Epinephrine (%)	2	0.08%	1	0.27%	
Levophed (%)	11	0.45%	3	0.81%	
Neosynephrine (%)	10	0.41%	3	0.81%	
None (%)	2416	98.30%	364	97.80%	
Other (%)	10	0.41%	1	0.27%	
ICU admission					0.68
ICU (%)	205	8.34%	34	9.14%	
No ICU (%)	2252	91.70%	338	90.90%	
Ventilator support (%)	56	2.28%	5	1.34%	0.33
TIPS procedure (%)	142	5.78%	25	6.72%	0.55
Donor demographics					
Donor age (years)	42.00	± 17.20 years	42.10	± 17.20 years	0.99
Donor gender, male (%)	1405	57.20%	230	61.80%	0.10
Donor race					0.27[a]
White (%)	1691	68.80%	272	73.10%	
Black (%)	423	17.20%	62	16.70%	
Hispanic (%)	254	10.30%	32	8.60%	
Asian (%)	50	2.04%	3	0.81%	
Other (%)	39	1.59%	3	0.81%	
Donor BMI (kg/m^2)	27.70	± 6.87 kg/m^2	27.10	± 6.10 kg/m^2	0.22
Donor laboratory markers					
Donor creatinine (mg/dL)	1.60	± 1.71 mg/dL	1.52	± 1.35 mg/dL	0.79
Donor Total bilirubin (mg/dL)	0.88	± 0.75 mg/dL	0.89	± 0.69 mg/dL	0.78

[a]Fisher's test

[b]Assistance, a variable that represents functional status as defined by the Karnofsky score

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3 Baseline characteristics of liver transplant recipients with primary sclerosing cholangitis stratified by inflammatory bowel disease

Variable	Comparison of PSC with inflammatory bowel disease vs PSC without inflammatory bowel disease				*p*-value
	PSC without inflammatory bowel disease		PSC with inflammatory bowel disease		
	$n=1028$	36.34%	$n=1801$	63.66%	
Recipient demographics					
Age (years)	49.70	± 13.50 years	48.40	± 13.30 years	0.005**
Gender, male (%)	639	62.20%	1284	71.30%	< 0.001***
Race					< 0.001***
White (%)	674	65.60%	1473	81.80%	
Black (%)	248	24.10%	235	13.00%	
Hispanic (%)	61	5.93%	58	3.22%	
Asian (%)	28	2.72%	23	1.28%	
Other (%)	17	1.65%	12	0.67%	
BMI (kg/m^2)	26.10	± 5.18 kg/m^2	25.20	± 4.58 kg/m^2	< 0.001***
Comorbidities					
Hepatitis B (%)	12	1.17%	25	1.39%	0.75
Hepatitis C (%)	51	4.96%	58	3.22%	0.03*
Alcoholic liver disease (%)	19	1.85%	5	0.28%	< 0.001***
Diabetes (%)	157	15.30%	163	9.05%	< 0.001***
Assistance[b]					0.24
0 (%)	20	1.95%	42	2.33%	
1 (%)	242	23.50%	468	26.00%	
2 (%)	419	40.80%	741	41.10%	
3 (%)	347	33.80%	550	30.50%	
Hepatic variables					
Ascites					0.03*
Absent (%)	307	29.90%	603	33.50%	
Slight (%)	485	47.20%	851	47.30%	
Moderate (%)	236	23.00%	347	19.30%	
Encephalopathy					0.03*
None (%)	500	48.60%	951	52.80%	
1–2 (%)	457	44.50%	759	42.10%	
3–4 (%)	71	6.91%	91	5.05%	
MELD score	22.80	± 9.11	22.40	± 9.17	0.11
Medications					
Mycophenolate Mofetil (%)	858	83.50%	1511	83.90%	0.80
Cyclosporine (%)	30	2.92%	49	2.72%	0.85
Tacrolimus (%)	960	93.40%	1706	94.70%	0.17
Sirolimus (%)	10	0.97%	16	0.89%	0.98
Steroids (%)	966	94.00%	1686	93.60%	0.77
Laboratory Markers					
Albumin (mg/dL)	2.93	± 0.73 mg/dL	2.95	± 0.73 mg/dL	0.54
Creatinine (mg/dL)	1.24	± 0.90 mg/dL	1.24	± 1.09 mg/dL	0.06
INR	1.87	± 1.00	1.87	± 1.52	0.05*
Total bilirubin (mg/dL)	13.90	± 12.40 mg/dL	13.50	± 12.30 mg/dL	0.40
Life support variables					
Primary inotropic agent					0.72
Dobutamine (%)	19	1.85%	35	1.94%	
Dopamine (%)	168	16.30%	319	17.70%	
Epinephrine (%)	18	1.75%	23	1.28%	

Table 3 (continued)

Variable	Comparison of PSC with inflammatory bowel disease vs PSC without inflammatory bowel disease				*p*-value
	PSC without inflammatory bowel disease		PSC with inflammatory bowel disease		
	n = 1028	36.34%	*n* = 1801	63.66%	
Levophed (%)	176	17.10%	282	15.70%	
Neosynephrine (%)	152	14.80%	293	16.30%	
None (%)	470	45.70%	806	44.80%	
Other (%)	25	2.43%	43	2.39%	
Secondary inotropic agent					0.57[a]
Dobutamine (%)	4	0.39%	11	0.61%	
Dopamine (%)	5	0.49%	18	1.00%	
Epinephrine (%)	5	0.49%	12	0.67%	
Levophed (%)	35	3.40%	60	3.33%	
Neosynephrine (%)	53	5.16%	98	5.44%	
None (%)	907	88.20%	1580	87.70%	
Other (%)	19	1.85%	22	1.22%	
Tertiary inotropic agent					0.72[a]
Dobutamine (%)	1	0.10%	3	0.17%	
Dopamine (%)	0	0.00%	4	0.22%	
Epinephrine (%)	1	0.10%	2	0.11%	
Levophed (%)	5	0.49%	9	0.50%	
Neosynephrine (%)	4	0.39%	9	0.50%	
None (%)	1011	98.30%	1769	98.20%	
Other (%)	6	0.58%	5	0.28%	
ICU admission					0.61
ICU (%)	91	8.85%	148	8.22%	
No ICU (%)	937	91.10%	1653	91.80%	
Ventilator support (%)	24	2.33%	37	2.05%	0.72
TIPS procedure (%)	54	5.25%	113	6.27%	0.31
Donor demographics					
Donor age (years)	42.10	± 17.90 years	41.90	± 16.90 years	0.95
Donor gender, male (%)	561	54.60%	1074	59.60%	0.010**
Donor race					0.59
White (%)	698	67.90%	1265	70.20%	
Black (%)	190	18.50%	295	16.40%	
Hispanic (%)	103	10.00%	183	10.20%	
Asian (%)	22	2.14%	31	1.72%	
Other (%)	15	1.46%	27	1.50%	
Donor BMI (kg/m^2)	27.70	± 6.98 kg/m^2	27.60	± 6.66 kg/m^2	0.84
Donor laboratory markers					
Donor creatinine (mg/dL)	1.50	± 1.45 mg/dL	1.64	± 1.78 mg/dL	0.15
Donor total bilirubin (mg/dL)	0.87	± 0.69 mg/dL	0.88	± 0.78 mg/dL	0.99

[a]Fisher's test

[b]Assistance, a variable that represents functional status as defined by the Karnofsky score

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

comparing PSC-UC and PSC-CD patients saw those with UC experiencing lower rates of general infectious mortality (aHR 0.54 95% CI 0.31–0.95, $p = 0.03$) and sepsis mortality (aHR 0.37 95% CI 0.19–0.71, $p = 0.003$). Supplementary Tables 3, 4 through 5 show these findings, along with case-incidence rates.

Table 4 Baseline characteristics of liver transplant recipients with primary sclerosing cholangitis stratified by either ulcerative colitis or Crohn's disease

Variable	Comparison of PSC with ulcerative colitis vs PSC without ulcerative colitis				
	PSC without ulcerative colitis		PSC with ulcerative colitis		*p*-value
	n = 372	21.48 %	*n* = 1360	78.52%	
Recipient demographics					
Age (years)	49.20	± 13.30 years	48.30	± 13.40 years	0.22
Gender, male (%)	236	63.40 %	995	73.20%	< 0.001***
Race					0.04[a,*]
White (%)	315	84.70%	1102	81.00%	
Black (%)	44	11.80%	183	13.50%	
Hispanic (%)	4	1.08%	51	3.75%	
Asian (%)	5	1.34%	17	1.25%	
Other (%)	4	1.08%	7	0.52%	
BMI (kg/m^2)	25.30	± 4.74 kg/m^2	25.20	± 4.52 kg/m^2	0.91
Comorbidities					
Hepatitis B (%)	4	1.08%	19	1.40%	0.80[a]
Hepatitis C (%)	14	3.76%	42	3.09%	0.63
Alcoholic liver disease (%)	0	0.00%	5	0.37%	0.59[a]
Diabetes (%)	30	8.06%	129	9.49%	0.46
Assistance[b]					0.07
0 (%)	6	1.61%	34	2.50%	
1 (%)	114	30.60%	335	24.60%	
2 (%)	150	40.30%	558	41.00%	
3 (%)	102	27.40%	433	31.80%	
Hepatic variables					
Ascites					0.19
Absent (%)	132	35.50%	450	33.10%	
Slight (%)	181	48.70%	638	46.90%	
Moderate (%)	59	15.90%	272	20.00%	
Encephalopathy					0.80
None (%)	191	51.30%	720	52.90%	
1–2 (%)	163	43.80%	570	41.90%	
3–4 (%)	18	4.84%	70	5.15%	
MELD score	21.40	± 8.93	22.50	± 9.26	0.02*
Medications					
Mycophenolate mofetil (%)	304	81.70%	1153	84.80%	0.18
Cyclosporine (%)	12	3.23%	36	2.65%	0.67
Tacrolimus (%)	342	91.90%	1299	95.50%	0.009**
Sirolimus (%)	3	0.81%	13	0.96%	1.00[a]
Steroids (%)	343	92.20%	1282	94.30%	0.18
Laboratory markers					
Albumin (mg/dL)	2.99	± 0.74 mg/dL	2.95	± 0.73 mg/dL	0.38
Creatinine (mg/dL)	1.19	± 0.93 mmg/dL	1.26	± 1.13 mg/dL	0.26
INR	1.84	± 2.00	1.86	± 1.33	0.38
Total Bilirubin (mg/dL)	12.10	± 12.30 mg/dL	13.90	± 12.40 mg/dL	0.002**
Life support variables					
Primary inotropic agent					0.91[a]
Dobutamine (%)	8	2.15%	25	1.84%	
Dopamine (%)	68	18.30%	237	17.40%	
Epinephrine (%)	4	1.08%	19	1.40%	

Table 4 (continued)

Variable	Comparison of PSC with ulcerative colitis vs PSC without ulcerative colitis				
	PSC without ulcerative colitis		PSC with ulcerative colitis		*p*-value
	n = 372	21.48 %	*n* = 1360	78.52%	
Levophed (%)	60	16.10%	211	15.50%	
Neosynephrine (%)	54	14.50%	227	16.70%	
None (%)	172	46.20%	609	44.80%	
Other (%)	6	1.61%	32	2.35%	
Secondary inotropic agent					0.97[a]
Dobutamine (%)	2	0.54%	9	0.66%	
Dopamine (%)	5	1.34%	13	0.96%	
Epinephrine (%)	2	0.54%	9	0.66%	
Levophed (%)	10	2.69%	49	3.60%	
Neosynephrine (%)	20	5.38%	72	5.29%	
None (%)	329	88.40%	1190	87.50%	
Other (%)	4	1.08%	18	1.32%	
Tertiary inotropic agent					0.50[a]
Dobutamine (%)	0	0.00%	3	0.22%	
Dopamine (%)	0	0.00%	3	0.22%	
Epinephrine (%)	1	0.27%	1	0.07%	
Levophed (%)	3	0.81%	6	0.44%	
Neosynephrine (%)	3	0.81%	5	0.37%	
None (%)	364	97.80%	1338	98.40%	
Other (%)	1	0.27%	4	0.29%	
ICU admission					0.62
ICU (%)	34	9.14%	111	8.16%	
No ICU (%)	338	90.90%	1249	91.80%	
Ventilator support (%)	5	1.34%	29	2.13%	0.45
TIPS procedure (%)	25	6.72%	86	6.32%	0.87
Donor demographics					
Donor age (years)	42.10	± 17.20 years	41.80	± 16.80 years	0.97
Donor gender, male (%)	230	61.80%	811	59.60%	0.48
Donor race					0.33[a]
White (%)	272	73.10%	946	69.60%	
Black (%)	62	16.70%	223	16.40%	
Hispanic (%)	32	8.60%	144	10.60%	
Asian (%)	3	0.81%	25	1.84%	
Other (%)	3	0.81%	22	1.62%	
Donor BMI (kg/m^2)	27.10	± 6.10 kg/m^2	27.80	± 6.87 kg/m^2	0.17
Donor laboratory markers					
Donor Creatinine (mg/dL)	1.52	± 1.35 mg/dL	1.66	± 1.87 mg/dL	0.44
Donor total bilirubin (mg/dL)	0.89	± 0.69 mg/dL	0.88	± 0.80 mg/dL	0.80

[a]Fisher's test

[b]Assistance, a variable that represents functional status as defined by the Karnofsky score

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 5 Sequential cox regression using ulcerative colitis as a prognostic risk factor for all-cause mortality and graft failure

(A) All-cause mortality				(B) Graft failure			
Incidence rates per 1000 person-years				Incidence rates per 1000 person-years			
PSC with ulcerative colitis		32.25	(28.28–36.61)	PSC with ulcerative colitis		7.82	(5.91–10.14)
PSC without ulcerative colitis		34.81	(30.81–39.16)	PSC without ulcerative colitis		9.03	(7.03–11.41)
Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.44	0.93	(0.78–1.11)	1	0.48	0.88	(0.61–1.26)
2	0.41	0.93	(0.78–1.11)	2	0.51	0.89	(0.62–1.27)
3	0.44	0.93	(0.78–1.11)	3	0.51	0.89	(0.62–1.27)
[a]FM	0.53	0.94	(0.79–1.13)	[a]FM	0.67	0.93	(0.65–1.33)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 6 Sequential cox regression using Crohn's disease as a prognostic risk factor for all-cause mortality and graft failure

(A) All-cause mortality				(B) Graft failure			
Incidence rates per 1000 person-years				Incidence rates per 1000 person-years			
PSC with Crohn's disease		37.32	(29.42–46.63)	PSC with Crohn's disease		10.09	(6.17–15.54)
PSC without Crohn's disease		32.99	(29.97–36.23)	PSC without Crohn's disease		8.19	(6.70–9.90)
Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.34	1.13	(0.88–1.44)	1	0.28	1.30	(0.81–2.11)
2	0.28	1.15	(0.90–1.47)	2	0.26	1.32	(0.81–2.14)
3	0.25	1.16	(0.90–1.49)	3	0.26	1.32	(0.81–2.15)
[a]FM	0.24	1.16	(0.91–1.50)	[a]FM	0.29	1.30	(0.80–2.12)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Supplementary Analysis—Cases Between 2005–2012 and 2012–2019

The main study population was modified a second time to include cases before and after 2012. Outcomes of these cohorts demonstrated no risk differences for all-cause mortality and graft failure for LT occurring before 2012. However, when considering cases after 2012, PSC-UC cases had lower risk for graft failure (aHR 0.45 95% CI 0.22–0.91, $p = 0.03$), and PSC-CD cases had higher risk for both graft failure (aHR 2.84 95% CI 1.34–6.04, $p = 0.006$) and all-cause mortality in the final model only (aHR 1.58 95% CI 1.00–2.47, $p = 0.05$). Graft failure risk was also comparatively reduced in the PSC-UC group compared to the PSC-CD group (aHR 0.25 95% CI 0.10–0.60, $p = 0.002$). When isolating cases occurring from 2012 and earlier, infectious-driven mortality was not significantly increased or decreased for any of the final models, for any of the comparisons. The post-2012 era only saw a decreased risk of general infection mortality for PSC-UC patients compared to PSC-CD patients (aHR 0.28 95% CI 0.09–0.85, $p = 0.02$). These assessments in which the 2005–2019 time period is partitioned into 2 components are included in Supplementary Tables 6–8 through 9.

Table 7 Sequential cox regression using inflammatory bowel disease as a prognostic risk factor for all-cause mortality and graft failure

(A) All-cause mortality				(B) Graft failure			
Incidence rates per 1000 person-years				Incidence rates per 1000 person-years			
PSC with inflammatory bowel disease		33.35	(29.84–37.15)	PSC with inflammatory bowel disease		8.60	(6.85–10.66)
PSC without Inflammatory Bowel Disease		33.97	(29.24–39.22)	PSC without Inflammatory Bowel Disease		8.16	(5.91–10.98)
Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.95	0.99	(0.82–1.20)	1	0.59	1.11	(0.76–1.62)
2	0.94	1.01	(0.83–1.22)	2	0.52	1.13	(0.77–1.66)
3	0.90	1.01	(0.84–1.22)	3	0.52	1.13	(0.77–1.66)
[a]FM	0.79	1.03	(0.85–1.24)	[a]FM	0.43	1.17	(0.80–1.71)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 8 Sequential cox regression using inflammatory bowel disease as a prognostic risk factor for all-cause mortality and graft failure: ulcerative colitis vs Crohn's disease

(A) All-cause mortality				(B) Graft failure			
Incidence rates per 1000 person-years				Incidence rates per 1000 person-years			
PSC with ulcerative colitis		32.25	(28.28–36.61)	PSC with ulcerative colitis		7.82	(5.91–10.14)
PSC with Crohn's disease		37.32	(29.42–46.63)	PSC with Crohn's disease		10.09	(6.17–15.54)
Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.26	0.86	(0.66–1.12)	1	0.28	0.75	(0.45–1.26)
2	0.22	0.85	(0.65–1.10)	2	0.31	0.77	(0.46–1.29)
3	0.19	0.84	(0.64–1.09)	3	0.29	0.76	(0.45–1.27)
[a]FM	0.20	0.84	(0.64–1.10)	[a]FM	0.29	0.75	(0.45–1.27)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Supplementary Analysis—Cases Stratified by Abdominal Surgery History

A third inquiry of the main study population involved stratifying cases by having a positive or negative history of abdominal surgery. Cases that had a prior history of abdominal surgery experienced no differences in risk for all-cause mortality, graft failure, or infectious mortality subtypes. Considering the cohort of patients that did not have past abdominal surgery, no risk differences were identified for the primary outcomes. However, these PSC-CD cases did have increased risks for general infectious mortality (aHR 2.50 95% CI 1.20–5.23, $p = 0.01$) and sepsis (aHR 3.38 95% CI 1.49–7.63, $p = 0.003$). Similar associations persisted when comparing these PSC-CD patients to PSC-UC patients without prior abdominal surgery, with lower risks of general infectious mortality (aHR 0.32 95% CI 0.13–0.75, $p = 0.009$) and sepsis mortality (aHR 0.20 95% CI 0.07–0.57, $p = 0.002$) observed for the PSC-UC group. Data for these analyses (including

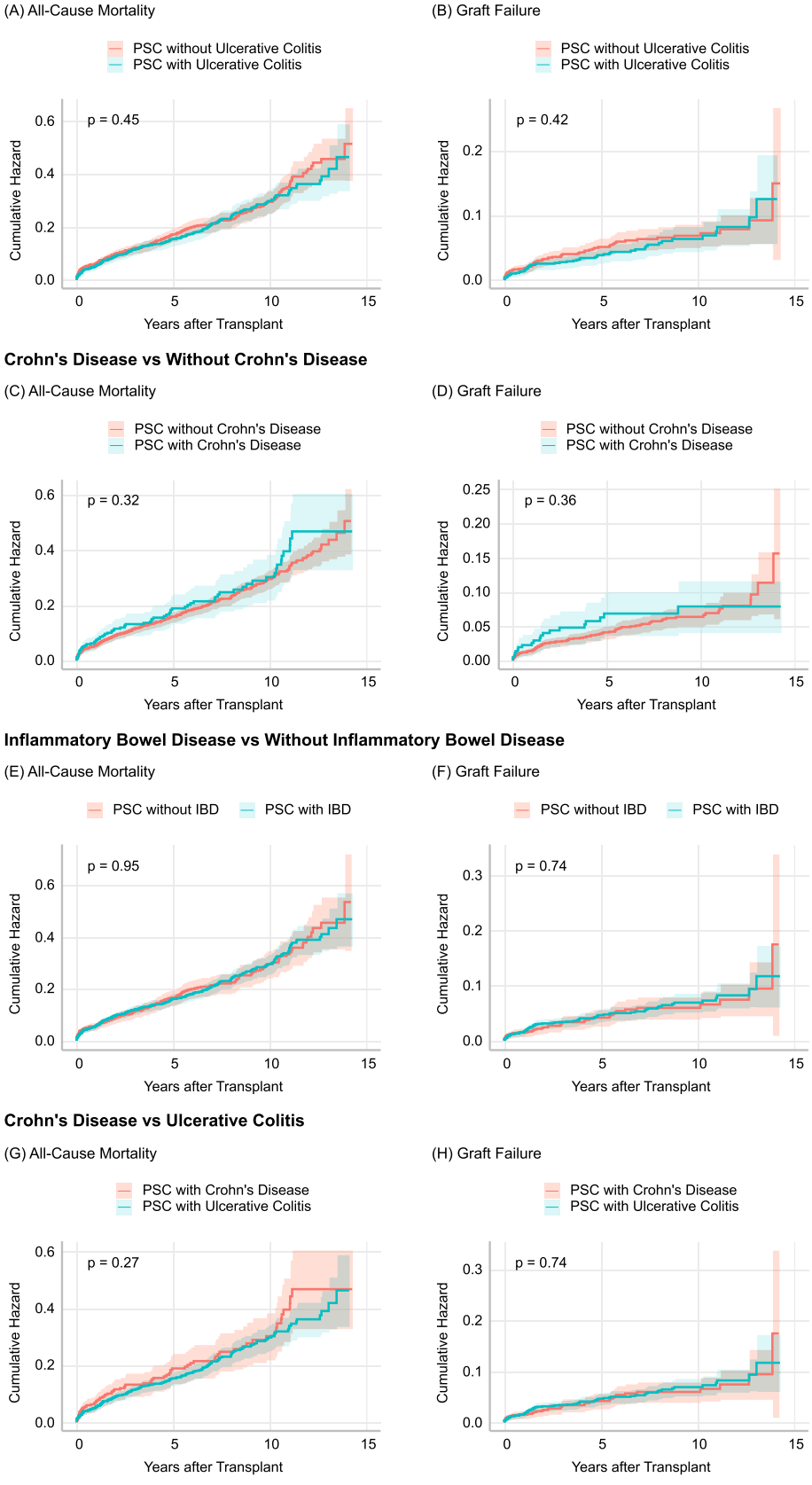

Fig. 2 This figure shows the prognostic differences in the cumulative hazards using all-cause mortality (Fig. 2a, c, e, g) and graft failure (Fig. 2b, d, f, h) as endpoints

Table 9 Sequential cox regression using ulcerative colitis as a prognostic risk factor for death due to general infectious causes and sepsis

(A) Death due to general infectious causes				(B) Death due to sepsis			
Incidence rates per 1000 person-years				Incidence rates per 1000 person-years			
PSC with ulcerative colitis		5.86	(4.23–7.92)	PSC with ulcerative colitis		3.63	(2.37–5.31)
PSC without ulcerative colitis		9.29	(7.26–11.70)	PSC without ulcerative colitis		6.67	(4.97–8.76)
Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.02*	0.64	(0.43–0.93)	1	0.01*	0.55	(0.34–0.89)
2	0.03*	0.64	(0.44–0.95)	2	0.02*	0.56	(0.35–0.90)
3	0.03*	0.64	(0.44–0.95)	3	0.02*	0.55	(0.34–0.89)
[a]FM	0.03*	0.65	(0.44–0.95)	[a]FM	0.02*	0.56	(0.35–0.91)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 10 Sequential cox regression using Crohn's disease as a prognostic risk factor for death due to general infectious causes and sepsis

(a) Death due to general infectious causes				(b) Death due to sepsis			
Incidence rates per 1000 person-years				Incidence rates per 1000 person-years			
PSC with Crohn's disease		10.09	(6.17–15.54)	PSC with Crohn's disease		8.57	(5.00–13.69)
PSC without Crohn's disease		7.25	(5.86–8.88)	PSC without Crohn's disease		4.68	(3.57–6.02)
Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.16	1.41	(0.87–2.30)	1	0.02*	1.89	(1.10–3.26)
2	0.15	1.43	(0.88–2.33)	2	0.01*	1.97	(1.14–3.39)
3	0.12	1.47	(0.90–2.39)	3	0.01*	2.05	(1.19–3.55)
[a]FM	0.12	1.48	(0.90–2.42)	[a]FM	0.008**	2.13	(1.22–3.70)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

case-incidence rates) are presented in Supplementary Tables 10–12 through 13.

Discussion

This is the first study to investigate the prognostic implication of IBD in post-LT outcomes, stratified by the IBD subtypes of CD versus UC. Prior literature has clearly delineated the clinical phenotype of PSC-IBD vs IBD alone, but the impact of PSC-IBD versus PSC alone is less understood 7. A retrospective review of a single center in London noted a significant risk associated with active IBD at the time of LT and future graft failure, most commonly due to recurrent PSC 16. They also found a higher numerical incidence of thrombotic events in the PSC-IBD cohort compared to the isolated PSC cohort, though a statistically significant association was not found 16. Recently, Irles-Depe et al. published a retrospective study on 4 LT centers in France regarding graft survival and complications post-LT in PSC-IBD vs PSC alone, finding no significant association with comorbid IBD 17. Our analysis of PSC-IBD vs PSC alone is concordant with the primary findings of their study. Our PSC-UC versus PSC-CD had no differences in primary outcomes in the overall analysis. We further stratified our study cohort by history of abdominal

Table 11 Sequential cox regression using inflammatory bowel disease as a prognostic risk factor for death due to general infectious causes and sepsis

(A) Death due to general infectious causes			(B) Death due to sepsis		
Incidence rates per 1000 person-years			Incidence rates per 1000 person-years		
PSC with inflammatory bowel disease	7.13	(5.54–9.03)	PSC with inflammatory bowel disease	5.03	(3.71–6.67)
PSC without inflammatory bowel disease	8.54	(6.24–11.41)	PSC without inflammatory bowel disease	5.50	(3.69–7.89)

Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.44	0.86	(0.58–1.26)	1	0.86	0.96	(0.60–1.54)
2	0.52	0.88	(0.60–1.30)	2	0.99	1.00	(0.62–1.61)
3	0.54	0.89	(0.60–1.31)	3	1.00	1.00	(0.62–1.61)
[a]FM	0.57	0.89	(0.60–1.32)	[a]FM	0.91	1.03	(0.64–1.65)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 12 Sequential cox regression using inflammatory bowel disease as a prognostic risk factor for death due to general infectious causes and sepsis: ulcerative colitis vs Crohn's disease

(A) Death due to general infectious causes			(B) Death due to sepsis		
Incidence rates per 1000 person-years			Incidence rates per 1000 person-years		
PSC with Ulcerative Colitis	5.86	(4.23–7.92)	PSC with Ulcerative Colitis	3.63	(2.37–5.31)
PSC with Crohn's Disease	10.09	(6.17–15.54)	PSC with Crohn's Disease	8.57	(5.00–13.69)

Sequential cox regression				Sequential cox regression			
Model	*p*-value	aHR	95% CI	Model	*p*-value	aHR	95% CI
1	0.06	0.59	(0.35–1.01)	1	0.007**	0.43	(0.23–0.80)
2	0.05*	0.58	(0.34–0.99)	2	0.005**	0.41	(0.22–0.77)
3	0.05*	0.58	(0.33–0.99)	3	0.004**	0.40	(0.21–0.75)
[a]FM	0.05*	0.58	(0.33–1.00)	[a]FM	0.003**	0.38	(0.20–0.73)

Model 1 includes VOI (variable of interest) and demographics; Model 2 includes Model 1 terms with the addition of comorbidities and liver disease etiologies; Model 3 includes Model 2 terms with the addition of hepatic variables, MELD score, and liver laboratory markers; Model 4 includes Model 3 terms with the addition of donor demographics

[a]FM indicates final model

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

surgery, to potentially account for higher severity of IBD activity, and found no difference in rates of all-cause mortality or graft failure.

When the primary analysis was partitioned by time period to account for potential era effect, we noted a significantly higher rate of graft failure in patients with PSC-CD after the year 2012. When considering recurrent PSC as a leading indication for graft failure, our findings are inconsistent with prior studies on IBD-PSC. In a massive retrospective study on data from 1980 to 2010, Weismuller et al. found PSC-CD to have a milder clinical course compared to PSC-UC 18. Inadequate control of IBD-related disease activity post-LT has been identified as a major risk factor for recurrence of PSC 19. We may potentially be observing a transition in immunosuppressive practices during this latter era that is

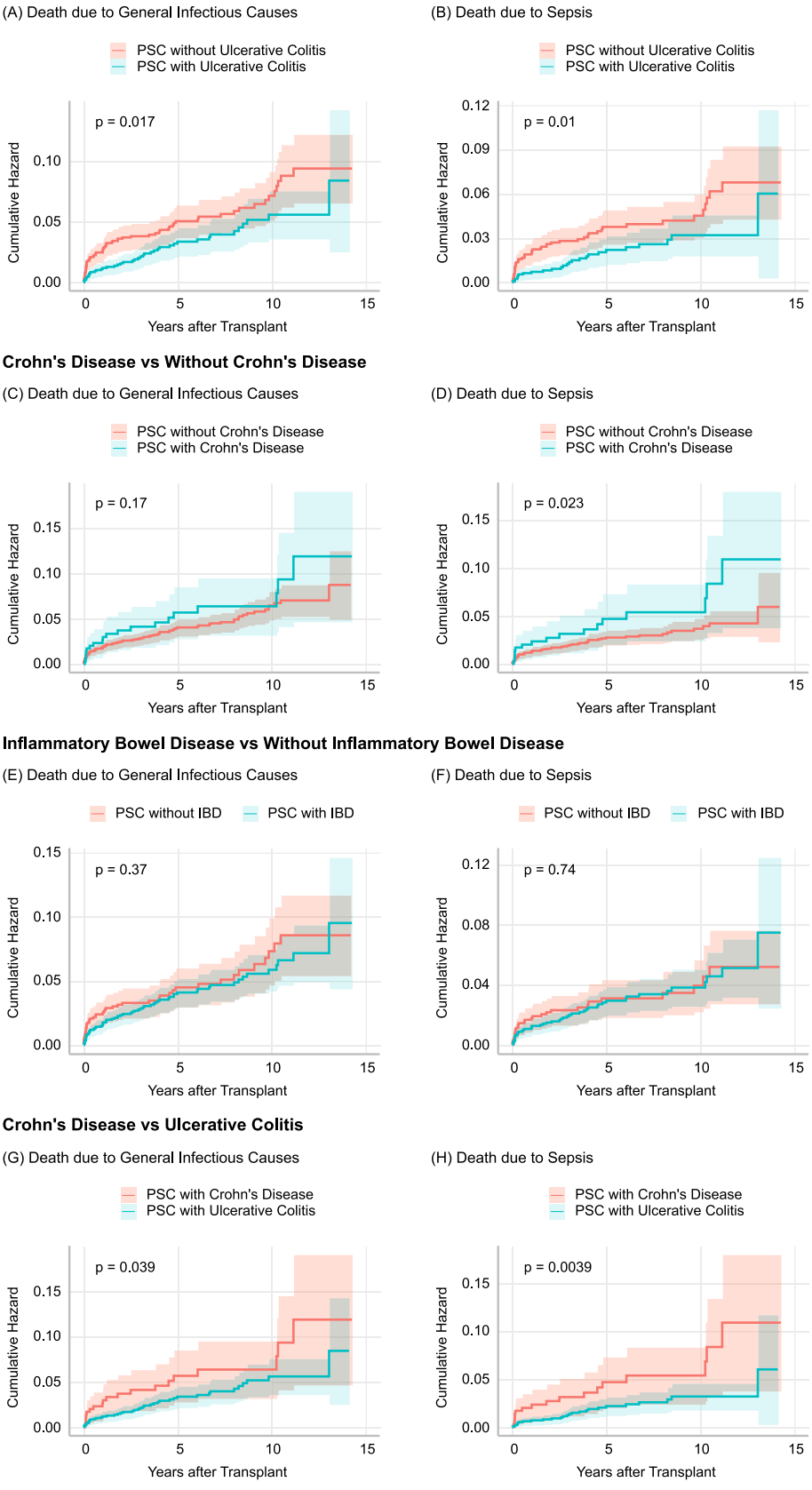

Fig. 3 This figure shows the prognostic differences in the cumulative hazards using general infectious mortality (Fig. 3a, c, e, g) and sepsis (Fig. 3b, d, f, h) as endpoints

contributing to increased risk of infection- and sepsis-related mortality in patients with PSC-CD.

When delineating the post-LT outcomes using the IBD subtypes, our results demonstrate that patients with PSC-CD have increased rates of post-LT infection-related mortality. The cumulative hazard curves show that the highest rates of these deaths among PSC-CD appear within the first few months. The rates begin to plateau around years 2–3. When looking to control for confounders of this relationship, the increased rates persisted even when excluding patients with primary liver cancer, such as hepatocellular carcinoma and cholangiocarcinoma. Interestingly, PSC-CD patients without a history of abdominal surgery would further have disproportionate rates of fatal infection. This may suggest that a history of surgical complications of CD did not contribute to this relationship. It may also suggest that surgical management, perhaps for an area of disease refractory to medical treatment, is protective against certain infectious complications. There is also contribution of an era effect to these findings, with no differences detected in the early cohort, though general infection-related mortality was significantly increased in PSC-CD after the year 2012. Consistent with the above discussion on graft failure, this may potentially be due to the evolution of immunosuppressive regimens.

In 2011, a Cochrane review was published on the adverse effects of biologics, including TNF-α inhibitors. This was not a study for IBD specifically, but adalimumab, golimumab, certolizumab, and infliximab were associated with risk of serious infection 20. In 2017, Westwerouen van Meeteren et al. published a meta-analysis investigating the safety of TNF-inhibitors in IBD post liver transplant, and found no significant difference in infection risk based on TNF-inhibitor exposure. However, the conclusions from this study are significantly limited by study size. In 2018, Kirchgesner et al. published a large retrospective cohort study in France assessing infection risk in IBD, stratified according to exposure to thiopurine monotherapy, anti-TNF monotherapy, both, or neither. They found significantly higher risk of serious infection with anti-TNF monotherapy exposure compared to thiopurine monotherapy or therapy with neither, and an even higher risk with the use of both agents compared to either monotherapy 21. Therefore, the increasing prevalence of biologic therapy for IBD is our leading explanation for the observed era effect on infection.

We were unable to assess what type of infection was most prevalent in PSC-CD, but are able to report no significant differences in respiratory, viral, or fungal infections when analyzing the whole cohort. The above-mentioned study by Irles-Depe noted an increased rate of CMV infections in PSC-IBD, though we did not find any association with PSC-CD specifically 17. A retrospective cohort study published in 2022 evaluating risk of serious infection with vedolizumab versus TNF inhibitors in IBD subtypes noted a higher risk in CD patients treated with vedolizumab22. This included a higher rate of gastrointestinal infections in CD, including *Clostridium difficile*, possibly reflecting a direct complication of inadequately controlled disease activity. As mentioned above, there is a significant risk of flare-up of IBD activity in patients post-LT. It is therefore plausible that a phenotypic difference in PSC-CD is accounting for difficulties in controlling disease activity post-LT, which may directly lead to gastrointestinal infection or any infection secondary to increased need for immunosuppression including corticosteroids.

Limitations

Our study is limited by both retrospective design and the data available in the UNOS database. We could not isolate any specific infectious etiology after 2012 to characterize our findings in the PSC-CD cohort. Our study was also limited in that we could not specify baseline IBD disease activity or site of involvement, such as ileal CD, due to lack of endoscopic or histologic markers. We also lacked data on IBD-related pharmacotherapy in the baseline population. This baseline data will be necessary for further investigation into the higher rates of graft failure in PSC-CD. A prospective study that details the severity and phenotype of IBD in patients with PSC who undergo LT will be helpful in categorizing IBD subtypes and specific IBD-related complications and their impact on post-LT prognosis.

Conclusion

To our knowledge, this is the largest study of post-LT outcomes in patients with PSC-IBD and it is the only study to examine these outcomes in patients with PSC-CD compared to PSC-UC. A broad implication of our study is that PSC-CD and PSC-UC represent distinct clinical entities with potential differences in their pathogenesis, phenotypes, and outcomes. It therefore may be important for future research to address these two entities independently, as opposed to PSC-IBD as a whole. Overall, we found no difference in primary outcomes between the PSC-CD and PSC-UC. However, we found PSC-CD patients to suffer from a higher rate of fatal infections post-LT, especially when analyzing the cohort strictly after the year 2012.

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Declarations

Conflict of interest The authors of this manuscript certify they share no affiliation or involvement with any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. None declared.

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