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# The Implication of Inflammatory Bowel Disease on the Post-Liver Transplant Outcomes of Patients with Primary Sclerosing Cholangitis: Analysis of UNOS Registry

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## Background and Aims

In clinical hepatology, there is a concern that the presence of inflammatory bowel disease (IBD) in patients with primary sclerosing cholangitis (PSC) can affect disease presentation and prognosis via the mechanisms of increased intestinal permeability and bowel translocation. However, less is known about the effects of IBD on the post-liver transplant (LT) prognosis of patients with PSC.

## Methods

Between 2005 and 2019, the UNOS-STAR database was queried for PSC patients undergoing LT. Pediatric cases, those with multi-organ transplants, or those with living donors were excluded. Using the concurrent presence of either IBD subtype as primary exposure, the PSC recipient population was stratified into the following groups: with Crohn's disease (CD), with ulcerative colitis (UC), without CD, and without UC. All-cause mortality, graft failure (GF), and sepsis-related deaths were chosen as endpoints and evaluated via sequential Cox regression analysis (adjusted for MELD and covariates). For each comparison, cumulative hazard curves were drawn and log-rank p-values were derived.

## Results

There were 2760 cases total and median follow-up was 4 years. In comparing those with CD (n=372) to those without (n=2388), there were no significant differences in age (49.2 ± 13.3 vs 48.9 ± 13.4y p=0.72) and gender (males: 63.4% vs 68.4% p=0.06) between the groups. However, PSC recipients with CD had higher MELD scores (21.4 ± 8.93 vs. 22.7 ± 9.20 p=0.006). With respect to outcomes, there was no difference in the risks of all-cause deaths (adjusted HR (aHR)1.17 95%CI 0.91-1.50) and graft failure (aHR 1.32 95%CI 0.81-2.16). However, those with CD had a higher risk of sepsis-related deaths (aHR: 2.22 95%CI 1.26-3.88), which was reflected in the higher case-incidence rate (1000 person-years; 8.57 vs 4.42). In comparing UC (n=1360) to those without (n=1400), those with UC were younger (48.30y vs. 49.60y, p=0.005) and were more likely to be male (73.0% vs. 62.50%, p<0.001). However, there was no difference in the MELD scores (22.50 ± 9.26 vs. 22.50 ± 9.08 p=0.86). While there were no differences in the risk of all-cause mortality (aHR 0.94 95%CI 0.79-1.13) and GF (aHR 0.96 95%CI 0.66-1.39), the UC group had lower risks of sepsis-related deaths (aHR: 0.58 95%CI 0.35-0.94), which was also indicated by a lower case-incidence rate (1000 person-years; 3.63 vs 6.34). In the direct comparison of recipients with CD versus those with UC, recipients with UC had a lower risk of sepsis-related death (aHR 0.38 95%CI 0.20-0.73) and a lower case-incidence rate (1000 person-years; 3.63 vs. 8.57).

## Conclusion

The co-manifestation of UC in PSC patients resulted in a lower risk of sepsis-related deaths following LT. In contrast, those with CD had a higher risk. Further molecular and mechanistic studies are warranted to delineate the physiological basis for these findings.

## Univariate Analysis

| Characteristics | PSC with UC | PSC without UC | P-value |
|---|---|---|---|
| **Variable** | **n = 1360** | **n = 1400** | |
| **Recipient Demographics** | | | |
| Age, mean ± SD, y | 48.30 ± 13.40 | 49.60 ± 13.40 | 0.005 ** |
| Male sex, n (%) | 995 (73.20) | 875 (62.50) | < 0.001 *** |
| Race, n (%) | | | < 0.001 *** |
| White | 1102 (81.00) | 989 (70.60) | |
| Black | 183 (13.50) | 292 (20.90) | |
| Hispanic | 51 (3.75) | 65 (4.64) | |
| Asian | 17 (1.25) | 33 (2.36) | |
| Other | 7 (0.52) | 21 (1.50) | |
| BMI, mean ± SD, kg/m² | 25.20 ± 4.52 | 25.90 ± 5.08 | 0.007 ** |
| **Hepatic Variables** | | | |
| MELD Scores, mean ± SD | 22.50 ± 9.26 | 22.50 ± 9.08 | 0.86 |

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

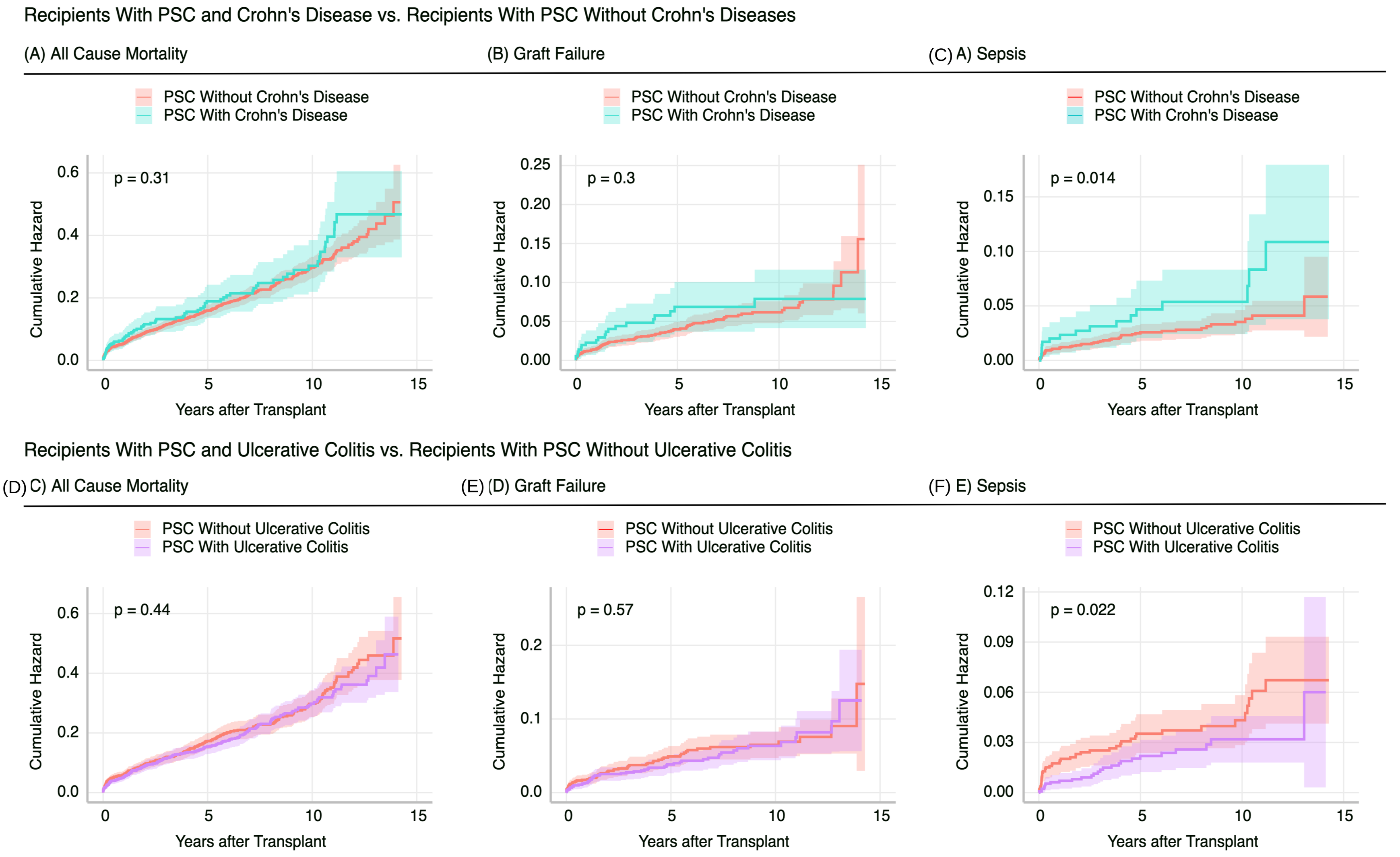
† Fisher's Test

| Characteristics | PSC with Crohn's Disease | PSC without Crohn's Disease | P-value |
|---|---|---|---|
| **Number of Patients** | **n = 372** | **n = 2388** | |
| **Recipient Demographics** | | | |
| Age, mean ± SD, y | 49.20 ± 13.30 | 48.90 ± 13.40 | 0.72 |
| Male sex, n (%) | 236 (63.40) | 1634 (68.40) | 0.06 |
| Race, n (%) | | | < 0.001 † *** |
| White | 315 (84.70) | 1776 (74.40) | |
| Black | 44 (11.80) | 431 (18.00) | |
| Hispanic | 4 (1.08) | 112 (4.69) | |
| Asian | 5 (1.34) | 45 (1.88) | |
| Other | 4 (1.08) | 24 (1.01) | |
| BMI, mean ± SD, kg/m² | 25.30 ± 4.74 | 25.60 ± 4.83 | 0.23 |
| **Hepatic Variables** | | | |
| MELD Scores, mean ± SD | 21.40 ± 8.93 | 22.70 ± 9.20 | 0.006 ** |

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

† Fisher's Test

## Prognostic Curves for Clinical Endpoints




## Cox Iterations for Primary Outcomes

| PSC with Crohn's Disease vs PSC without Crohn's Disease | | | | PSC with UC vs PSC without UC | | | |
|---|---|---|---|---|---|---|---|
| **(A) All-cause Mortality** | | | | | | | |
| **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 UC** | | 32.25 | (28.28 - 36.61) |
| **PSC without Crohn's Disease** | | 32.98 | (29.91 - 36.27) | **PSC without UC** | | 34.88 | (30.78 - 39.37) |
| **Sequential Cox Regressions** | | | | **Sequential Cox Regressions** | | | |
| **Model** | **p-value** | **aHR** | **95% CI** | **Model** | **p-value** | **aHR** | **95% CI** |
| 1 | 0.35 | 1.13 | (0.88 - 1.44) | 1 | 0.41 | 0.93 | (0.77 - 1.11) |
| 2 | 0.25 | 1.16 | (0.90 - 1.49) | 2 | 0.45 | 0.93 | (0.78 - 1.12) |
| 3 | 0.24 | 1.16 | (0.90 - 1.50) | 3 | 0.47 | 0.93 | (0.78 - 1.12) |
| †FM | 0.23 | 1.17 | (0.91 - 1.50) | †FM | 0.54 | 0.94 | (0.79 - 1.13) |
| **(B) Graft Failure** | | | | | | | |
| **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 UC** | | 7.82 | (5.91 - 10.14) |
| **PSC without Crohn's Disease** | | 7.96 | (6.48 - 9.69) | **PSC without UC** | | 8.69 | (6.68 - 11.10) |
| **Sequential Cox Regressions** | | | | **Sequential Cox Regressions** | | | |
| **Model** | **p-value** | **aHR** | **95% CI** | **Model** | **p-value** | **aHR** | **95% CI** |
| 1 | 0.23 | 1.34 | (0.83 - 2.18) | 1 | 0.61 | 0.91 | (0.63 - 1.31) |
| 2 | 0.23 | 1.34 | (0.83 - 2.19) | 2 | 0.68 | 0.92 | (0.64 - 1.34) |
| 3 | 0.24 | 1.34 | (0.82 - 2.19) | 3 | 0.69 | 0.93 | (0.64 - 1.34) |
| †FM | 0.27 | 1.32 | (0.81 - 2.16) | †FM | 0.83 | 0.96 | (0.66 - 1.39) |

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

† FM indicates Final Model

Footnote: *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

## Cox Iterations for Specific Causes of Death

**PSC with Crohn's Disease vs PSC without Crohn's Disease Donors**

| (A) Death due to Sepsis | | | |
|---|---|---|---|
| **Incidence Rates per 1000 Person-Years** | | | |
| **PSC with Crohn's Disease** | | 8.57 | (5.00 - 13.69) |
| **PSC without Crohn's Disease** | | 4.42 | (3.33 - 5.75) |
| **Sequential Cox Regressions** | | | |
| **Model** | **p-value** | **aHR** | **95% CI** |
| 1 | 0.02 * | 1.95 | (1.12 - 3.37) |
| 2 | 0.01 * | 2.05 | (1.18 - 3.56) |
| 3 | 0.008 ** | 2.13 | (1.22 - 3.71) |
| †FM | 0.005 ** | 2.22 | (1.26 - 3.88) |

**PSC with UC vs PSC without UC Donors**

| (B) Death due to Sepsis | | | | (C) Death due to General Infectious Causes | | | |
|---|---|---|---|---|---|---|---|
| **Incidence Rates per 1000 Person-Years** | | | | **Incidence Rates per 1000 Person-Years** | | | |
| **Hispanic Donors** | | 3.63 | (2.37 - 5.31) | **Hispanic Donors** | | 5.86 | (4.23 - 7.92) |
| **White Donors** | | 6.34 | (4.65 - 8.45) | **White Donors** | | 8.96 | (6.92 - 11.41) |
| **Sequential Cox Regressions** | | | | **Sequential Cox Regressions** | | | |
| **Model** | **p-value** | **aHR** | **95% CI** | **Model** | **p-value** | **aHR** | **95% CI** |
| 1 | 0.03 * | 0.57 | (0.35 - 0.94) | 1 | 0.04 * | 0.66 | (0.44 - 0.97) |
| 2 | 0.03 * | 0.58 | (0.36 - 0.95) | 2 | 0.05 * | 0.67 | (0.45 - 1.00) |
| 3 | 0.03 * | 0.57 | (0.35 - 0.93) | 3 | 0.05 * | 0.67 | (0.45 - 0.99) |
| †FM | 0.03 * | 0.58 | (0.35 - 0.94) | †FM | 0.05 * | 0.67 | (0.45 - 0.99) |

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

† FM indicates Final Model

Footnote: *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

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