The differences in the post-liver transplant outcomes of patients with autoimmune hepatitis who present with overlapping autoimmune liver diseases

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Abstract

Background

Patients with autoimmune hepatitis (AIH) may co-present with diagnostic features of primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Using a national transplant registry, the outcomes of patients with these presentations were compared.

Methods

The UNOS-STAR registry was used to select a study population of AIH liver transplant (LT) patients. Living and multi-organ transplant cases were excluded. Using the UNOS-registered diagnoses, the study population was subdivided into those with nonoverlapping AIH, those with AIH and PBC (AIH-PBC), and those with AIH and PSC (AIH-PSC). Specific endpoints included all-cause mortality, graft failure, and organ-system specific causes of death.

Results

There were 2048 entries included with 1927 having nonoverlapping AIH, 52 having PSC overlap, and 69 having PBC overlap. Patients with PBC overlap were more likely to have graft failure (aHR 3.53 95% CI 1.73–1.74), mortality secondary to general respiratory causes (aHR 3.55 95% CI 1.22–10.36), mortality secondary to acute respiratory distress syndrome (ARDS) (aHR 18.07 95% CI 3.331–98.74), and recurrent disease (aHR 9.65 95% CI 1.82–51.15). Case incidence rates reflected these findings, expressed in events per 1000 person-years (For the PBC overlap and nonoverlapping AIH cases, respectively. Graft failure: 28.87 events vs. 9.15 events, mortality secondary to general respiratory causes: 12.83 deaths vs. 3.87 deaths, ARDS: 6.42 deaths vs. 0.43 deaths, recurrent disease: 6.42 deaths vs. 1.18 deaths). No increased risks were found in the cohort with PSC overlap.

Conclusion

Patients with PBC diagnostic overlap may have greater risks for respiratory-induced mortality compared to nonoverlapping AIH. Further investigations are warranted to confirm these results.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by a loss of tolerance to hepatocyte-specific autoantigens (1). Expression of AIH can greatly range from being asymptomatic to manifesting as end-stage liver disease (2), with fulminant disease carrying a significant mortality risk (2). The phenotypic expression of AIH can vary depending on the underlying histological presentation (2). In particular, AIH has a proclivity to histologically overlap with PBC and PSC at a rate of 10–20% and 2–8% respectively (3), which may alter the rates of disease progression and affect the prognosis (4–6), with PSC-AIH generally conferring a higher morbidity and mortality risk (4).

In hepatology, the copresence of overlapping autoimmune conditions among AIH patients is thought to skew the prognostic outcomes; however, less is known about the implications of this diagnostic overlap on the post-liver transplant (LT) prognosis. This is despite the fact that certain cases of fulminant AIH and chronic AIH-related liver disease are at risk of liver failure (7), which may necessitate LT as a means of treating liver dysfunction and improving patient survival (8). However, as with non-transplant hepatology, there is a concern that differences in physiology among overlapping and nonoverlapping AIH may affect the post-LT prognosis via the means of increased disease recurrence or extra-hepatic complications following LT.

In this study, we stratify the national United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) transplant registry using the overlap indicators for AIH and PSC or AIH and PBC, in order to evaluate the prognostic effects of AIH-overlapping conditions on post-LT outcomes, specifically correlating the cumulative and adjusted risks for all-cause deaths and system-specific causes of death following LT.

Methods

Database

The UNOS-STAR database is a registry that contains transplant patient information. It describes both preoperative recipient and donor characteristics, as well as longitudinal follow-up. Data between 2005 and 2019 was queried in this analysis. UNOS-STAR is publicly available to biomedical researchers via data use agreements, and confidentiality is maintained as all contained data is de-identified. While UNOS is sponsored by the federal government, the contents of this paper were not influenced by any regulatory authorities. All findings and interpretations are solely the authors' viewpoints.

Study population and variables

A population of patients with AIH undergoing LT was selected from the UNOS STAR database. The study population was stratified according to whether the LT patient had a concomitant diagnosis of PBC or PSC. We selected 99,987 patients from the UNOS database who underwent LT from 2005 to 2019. Within these transplant recipients, we excluded those who were lost to follow-up (n = 3445) or retransplants (4310). Further exclusion criteria included removing those with prior liver transplantations (5437) or improbable biological values, such as creatinine < 0 (n = 5), along with those under the age of 18 (n = 6872). Additional non-applicable setups were excluded, including those with non-heart beating donors (n = 4427); those with a living donor (n = 3081);

those with a non-whole liver (n = 1012); those with multi-organ transplants (n = 6462); and those without diagnosis of AIH (n = 62,888) were excluded. Thus, the final cohort included 2048 patients with AIH: 1927 without overlap, 52 with PSC overlap, and 69 with PBC overlap.

Baseline characteristics of the study population were described. Variables included patient demographics, medications, relevant laboratory data, comorbidities, critical care and life-supporting assistive devices, and LT donor characteristics. The primary study endpoints were all-cause mortality and graft failure. Secondary mortality endpoints were the systems-specific causes of death, which included death due to general respiratory causes; this endpoint combined respiratory failure and acute respiratory distress syndrome (ARDS) as a composite endpoint.

Statistical methods

Baseline characteristics were compared using mean-based and nominal-based statistics. These baseline variables were further analyzed through stratification by concurrent presence of either PBC or PSC overlap to control for confounding. Iterative models were created for the overlap set via sequence of Cox regression iterations, using the primary outcomes of interest as the regression endpoints. The regression models included the following models: model 1 – adjusted for age, BMI, ethnicity, and gender; model 2 – adjusted with additional inclusion of comorbidities of diabetes, hepatitis, alcoholic liver disease, and hepatocellular carcinoma; model 3 – additional inclusion of ascites or encephalopathy presence, laboratory data, and MELD score; model 4 - additional inclusion of LT donor demographic and donor laboratory information. Standard 95% two-tail confidence intervals with an alpha level of 0.05 were used to indicate statistical significance. For the all-cause mortality and graft failure endpoints, hazard-event analyses were conducted to determine the log-rank statistics, using the prespecified strata to evaluate the comparative outcomes.

Furthermore, additional supplementary analyses were conducted using the construction of subgroups as determined by AIH-overlap type: PBC and PSC. This included a competing risk regression analysis using overlap as a prognostic risk factor for all-cause mortality and graft failure, using Fine and Gray's proportional subdistribution hazards model (9). The results included a series of adjusted analysis models: model 1 - includes VOI (variable of interest) and demographics; model 2 - includes the addition of comorbidities, and liver disease etiologies; model 3 -includes the addition of hepatic variables, MELD score, and liver laboratory data; model 4 -includes the addition of donor demographics. These statistical interactions were evaluated from interaction plots created prior to regression analyses. Apart from exclusionary endpoints, variables were analyzed graphically to assess missing data patterns, and thus underwent random forest plot generation to reduce potential bias and improve the statistical power (10).

All statistical tests were conducted with RStudio version 1.2.5042 with R code version 3.6.3.

Results

Baseline characteristics

After excluding patients who did not meet the eligibility criteria, there were a total of 2048 patients who were included: 1927 had AIH without overlap, 52 had PSC overlap, and 69 with PBC overlap. The median time periods of follow-up for PSC overlap: 3.98 (25–75% IQR 1.20–8.01) years and PBC overlap: 4.27 (25–75% IQR 1.31–8.62) years. Table 1 denotes the baseline characteristics of the autoimmune-overlapping cohorts (PSC and PBC-overlap) compared to the nonoverlapping AIH cohort. Table 2 shows the Cox regression comparisons between the overlapping cohorts versus the nonoverlapping cohort using primary endpoints of all-cause mortality and graft failure. Table 3 shows the Cox regression comparisons for the etiology-specific causes of deaths observed among the overlapping cohorts versus the nonoverlapping cohort.

Table 1
Baseline characteristics stratified among AIH-overlapping (AIH-PSC and AIH-PBC) and nonoverlapping cohorts

Characteristics	Without Overlap Syndrome			Primary Sclerosing Cholangitis			P-value			Primary Biliary Cholangitis			P-value		
Number of Patients	**1927**			**52**						**69**					
Recipient Demographics															
Age, mean ± SD, y	49.50	± 13.80	year	46.10	± 13.60	year	0.06			53.10	± 11.60	year	0.05		*
Male sex, *n* (%)	540	(28.00)	%	29	(55.80)	%	< 0.001		***	10	(14.50)	%	0.02		*
Race, *n* (%)							0.01	†	*				0.02	†	*
White	1125	(58.40)	%	31	(59.60)	%				34	(49.30)	%			
Black	378	(19.60)	%	17	(32.70)	%				9	(13.00)	%			
Hispanic	342	(17.70)	%	2	(3.85)	%				19	(27.50)	%			
Asian	48	(2.49)	%	1	(1.92)	%				5	(7.25)	%			
Other	34	(1.76)	%	1	(1.92)	%				2	(2.90)	%			
BMI, mean ± SD, kg/m²	29.10	± 6.70	kg/m²	25.50	± 4.69	kg/m²	< 0.001		***	27.10	± 5.28	kg/m²	0.04		*
Comorbidities															
Hepatitis B, n (%)	14	(0.73)	%	0	(0.00)	%	1.00	†		0	(0.00)	%	1.00	†	
Hepatitis C, n (%)	80	(4.15)	%	2	(3.85)	%	1.00	†		1	(1.45)	%	0.53	†	
Alcoholic Liver Disease, n (%)	36	(1.87)	%	0	(0.00)	%	1.00	†		0	(0.00)	%	0.63	†	
Diabetes, n (%)	428	(22.20)	%	7	(13.50)	%	0.18			11	(15.90)	%	0.28		
Hepatic Variables															
Ascites, *n* (%)							0.08						0.59		
Absent	311	(16.10)	%	12	(23.10)	%				10	(14.50)	%			
Slight	977	(50.70)	%	30	(57.70)	%				32	(46.40)	%			
Moderate	639	(33.20)	%	10	(19.20)	%				27	(39.10)	%			
Encephalopathy, *n* (%)							0.002	†	**				0.74		
None	562	(29.20)	%	26	(50.00)	%				20	(29.00)	%			
1–2	1080	(56.00)	%	23	(44.20)	%				41	(59.40)	%			
3–4	285	(14.80)	%	3	(5.77)	%				8	(11.60)	%			
TIPS Procedure, n (%)	172	(8.93)	%	3	(5.77)	%	0.62	†		6	(8.70)	%	1.00		
MELD Scores, mean ± SD	25.30	± 9.53		24.70	± 9.68		0.54			25.10	± 7.99		0.90		
Immunosuppressants															
Mycophenolate Mofetil, *n* (%)	1588	(82.40)	%	41	(78.80)	%	0.63			57	(82.60)	%	1.00		
Cyclosporine, *n* (%)	72	(3.74)	%	1	(1.92)	%	1.00	†		3	(4.35)	%	0.74	†	
Tacrolimus, *n* (%)	1761	(91.40)	%	49	(94.20)	%	0.62	†		61	(88.40)	%	0.52		
Sirolimus, *n* (%)	25	(1.30)	%	0	(0.00)	%	1.00	†		2	(2.90)	%	0.24	†	
Steroids, *n* (%)	1783	(92.50)	%	49	(94.20)	%	1.00	†		61	(88.40)	%	0.30		
Laboratory Data															
Albumin (mg/dL)	2.92	± 0.73	mg/dL	2.74	± 0.64	mg/dL	0.12			2.90	± 0.84	mg/dL	0.64		
Creatinine (mg/dL)	1.37	± 0.97	mg/dL	1.36	± 1.23	mg/dL	0.28			1.41	± 0.96	mg/dL	0.88		

Characteristics	Without Overlap Syndrome			Primary Sclerosing Cholangitis			P-value		Primary Biliary Cholangitis			P-value	
INR	2.25	± 1.08		2.02	± 0.90		0.07		2.04	± 0.87		0.11	
Total Bilirubin (mg/dL)	14.30	± 13.60	mg/dL	16.30	± 14.30	mg/dL	0.17		14.00	± 13.00	mg/dL	0.71	
Critical Care and Life Support													
Artificial liver devices, *n* (%)	1	(0.05)	%	0	(0.00)	%	1.00	†	0	(0.00)	%	1.00	†
Primary inotropic agent, *n* (%)							0.66	†				0.78	†
dobutamine, *n* (%)	40	(2.08)	%	3	(5.77)	%			3	(4.35)	%		
dopamine, *n* (%)	322	(16.70)	%	10	(19.20)	%			13	(18.80)	%		
epinephrine, *n* (%)	20	(1.04)	%	0	(0.00)	%			0	(0.00)	%		
levophed, *n* (%)	301	(15.60)	%	8	(15.40)	%			8	(11.60)	%		
neosynephrine, *n* (%)	301	(15.60)	%	8	(15.40)	%			12	(17.40)	%		
none, *n* (%)	896	(46.50)	%	22	(42.30)	%			32	(46.40)	%		
other, *n* (%)	47	(2.44)	%	1	(1.92)	%			1	(1.45)	%		
Secondary inotropic agent, *n* (%)							0.90	†				0.73	†
dobutamine, *n* (%)	13	(0.68)	%	0	(0.00)	%			1	(1.45)	%		
dopamine, *n* (%)	19	(0.99)	%	1	(1.92)	%			0	(0.00)	%		
epinephrine, *n* (%)	13	(0.68)	%	0	(0.00)	%			0	(0.00)	%		
levophed, *n* (%)	66	(3.43)	%	1	(1.92)	%			4	(5.80)	%		
neosynephrine, *n* (%)	95	(4.93)	%	2	(3.85)	%			3	(4.35)	%		
none, *n* (%)	1686	(87.50)	%	48	(92.30)	%			60	(87.00)	%		
other, *n* (%)	35	(1.82)	%	0	(0.00)	%			1	(1.45)	%		
Third inotropic agent, *n* (%)							1.00	†				0.64	†
dobutamine, *n* (%)	3	(0.16)	%	0	(0.00)	%			0	(0.00)	%		
dopamine, *n* (%)	4	(0.21)	%	0	(0.00)	%			0	(0.00)	%		
epinephrine, *n* (%)	5	(0.26)	%	0	(0.00)	%			0	(0.00)	%		
levophed, *n* (%)	6	(0.31)	%	0	(0.00)	%			1	(1.45)	%		
neosynephrine, *n* (%)	7	(0.36)	%	0	(0.00)	%			0	(0.00)	%		
none, *n* (%)	1888	(98.00)	%	52	(100.00)	%			68	(98.60)	%		
other, *n* (%)	14	(0.73)	%	0	(0.00)	%			0	(0.00)	%		
ICU admission, *n* (%)	406	(21.10)	%	8	(15.40)	%	0.41		10	(14.50)	%	0.24	
Ventilator Support, *n* (%)	141	(7.32)	%	1	(1.92)	%	0.18	†	4	(5.80)	%	0.81	†
Donor Demographics													
Donor Age, mean ± SD, y	41.20	± 17.20	years	40.50	± 18.80	years	0.71		37.90	± 17.10	years	0.12	
Donor Male sex, *n* (%)	1065	(55.30)	%	32	(61.50)	%	0.45		43	(62.30)	%	0.30	
Donor Race, n (%)							0.83	†				0.12	†
White	1233	(64.00)	%	37	(71.20)	%			43	(62.30)	%		
Black	332	(17.20)	%	8	(15.40)	%			8	(11.60)	%		
Hispanic	271	(14.10)	%	7	(13.50)	%			14	(20.30)	%		

Characteristics	Without Overlap Syndrome			Primary Sclerosing Cholangitis			P-value	Primary Biliary Cholangitis			P-value
Asian	46	(2.39)	%	0	(0.00)	%		4	(5.80)	%	
Other	45	(2.34)	%	0	(0.00)	%		0	(0.00)	%	
Donor BMI, mean ± SD, kg/m²	27.30	± 6.23	kg/m²	28.90	± 7.94	kg/m²	0.20	26.50	± 5.06	kg/m²	0.60
Donor Laboratory Data											
Donor Creatinine, mean ± SD, mg/dL	1.64	± 1.75	mg/dL	1.53	± 1.32	mg/dL	0.76	1.44	± 1.34	mg/dL	0.84
Donor Total Bilirubin, mean ± SD, mg/dL	0.93	± 0.80	mg/dL	0.75	± 0.45	mg/dL	0.25	0.94	± 0.82	mg/dL	0.92
* p < 0.05, ** p < 0.01, *** p < 0.001											
† Fisher's Test											

Table 2
Sequential Cox regression for the AIH-overlapping cohorts (AIH-PBC and AIH-PSC) compared to nonoverlapping AIH cohort using the primary endpoints

Primary Sclerosing Cholangitis Overlap											
(A) All-cause Mortality						**(B) Graft Failure**					
Incidence Rates per 1000 Person-Years						**Incidence Rates per 1000 Person-Years**					
With Primary Sclerosing Cholangitis		46.66	(24.34	-	80.08)	**With Primary Sclerosing Cholangitis**		19.44	(6.34	-	44.78)
Without Primary Sclerosing Cholangitis		47.46	(43.23	-	51.98)	**Without Primary Sclerosing Cholangitis**		9.15	(7.31	-	11.30)
Sequential Cox Regression Analysis						**Sequential Cox Regression Analysis**					
Model	**p-value**	**aHR**	**95% CI**			**Model**	**p-value**	**aHR**	**95% CI**		
1	0.86	1.06	(0.59	-	1.88)	1	0.16	1.94	(0.77	-	4.88)
2	0.89	1.04	(0.58	-	1.86)	2	0.17	1.92	(0.76	-	4.84)
3	0.74	1.10	(0.62	-	1.97)	3	0.14	2.01	(0.79	-	5.09)
†FM	0.75	1.10	(0.61	-	1.97)	†FM	0.14	2.04	(0.80	-	5.19)
Primary Biliary Cholangitis Overlap											
(A) All-cause Mortality						**(B) Graft Failure**					
Incidence Rates per 1000 Person-Years						**Incidence Rates per 1000 Person-Years**					
With Primary Biliary Cholangitis		73.77	(47.34	-	108.64)	**With Primary Biliary Cholangitis**		28.87	(13.28	-	54.09)
Without Primary Biliary Cholangitis		47.46	(43.23	-	51.98)	**Without Primary Biliary Cholangitis**		9.15	(7.31	-	11.30)
Sequential Cox Regression Analysis						**Sequential Cox Regression Analysis**					
Model	**p-value**	**aHR**	**95% CI**			**Model**	**p-value**	**aHR**	**95% CI**		
1	0.07	1.48	(0.97	-	2.26)	1	< 0.001 ***	3.39	(1.68	-	6.85)
2	0.06	1.49	(0.98	-	2.28)	2	< 0.001 ***	3.41	(1.68	-	6.91)
3	0.06	1.51	(0.99	-	2.31)	3	< 0.001 ***	3.53	(1.73	-	7.18)
†FM	0.07	1.49	(0.97	-	2.28)	†FM	< 0.001 ***	3.53	(1.73	-	7.24)
* 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 data; Model 4 includes Model 3 terms with the addition of donor demographics											

Table 3
Sequential Cox regression for the AIH-overlapping cohorts (AIH-PBC and AIH-PSC) compared to nonoverlapping AIH cohort using the etiology-specific causes of deaths

Primary Sclerosing Cholangitis Overlap												
(A) Death due to Graft Infection												
Incidence Rates per 1000 Person-Years												
With Primary Sclerosing Cholangitis			3.89	(0.10	-	21.47)						
Without Primary Sclerosing Cholangitis			0.32	(0.07	-	0.94)						
Sequential Cox Regression Analysis												
Model	**p-value**		**aHR**	**95% CI**								
1	0.04	*	13.32	(1.20	-	148.00)						
2	0.009	**	20.83	(2.17	-	200.33)						
3	0.003	**	31.72	(3.30	-	305.18)						
†FM	0.002	**	38.39	(3.98	-	370.49)						
Primary Biliary Cholangitis Overlap												
(B) Death due to General Respiratory Causes							**(C) Death due to Acute Respiratory Distress Syndrome**					
Incidence Rates per 1000 Person-Years							**Incidence Rates per 1000 Person-Years**					
With Primary Biliary Cholangitis			12.83	(3.51	-	32.52)	**With Primary Biliary Cholangitis**			6.42	(0.78	- 22.98)
Without Primary Biliary Cholangitis			3.87	(2.71	-	5.36)	**Without Primary Biliary Cholangitis**			0.43	(0.12	- 1.10)
Sequential Cox Regression Analysis							**Sequential Cox Regression Analysis**					
Model	**p-value**		**aHR**	**95% CI**			**Model**	**p-value**		**aHR**	**95% CI**	
1	0.04	*	2.91	(1.03	-	8.23)	1	0.003	**	13.85	(2.49	- 77.07)
2	0.03	*	3.19	(1.11	-	9.15)	2	< 0.001	***	23.57	(4.31	- 129.00)
3	0.03	*	3.34	(1.16	-	9.63)	3	< 0.001	***	19.26	(3.52	- 105.29)
†FM	0.02	*	3.55	(1.22	-	10.36)	†FM	< 0.001	***	18.07	(3.31	- 98.74)
(D) Death due to Recurrent Liver Disease												
Incidence Rates per 1000 Person-Years												
With Primary Biliary Cholangitis			6.42	(0.78	-	22.98)						
Without Primary Biliary Cholangitis			1.18	(0.59	-	2.12)						
Sequential Cox Regression Analysis												
Model	**p-value**		**aHR**	**95% CI**								
1	0.006	**	9.64	(1.93	-	48.22)						
2	0.005	**	10.15	(2.00	-	51.57)						
3	0.008	**	9.21	(1.79	-	47.26)						
†FM	0.008	**	9.65	(1.82	-	51.15)						

* 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 data; Model 4 includes Model 3 terms with the addition of donor demographics

When compared with patients with AIH without overlap, patients with PSC overlap were more likely to be categorized as White, Black, or other race (White 59.6 vs 58.4; Black 32.7 vs 19.6; Hispanic 3.85 vs 17.7; Asian 1.92 vs 2.49; other 1.92 vs 1.76%, p = 0.01), whereas patients with PBC overlap were more likely to be categorized as Hispanic, Asian, or other race (White 49.3 vs 58.4; Black 13.0 vs 19.6; Hispanic 27.5 vs 17.7; Asian 7.25 vs 2.49; other 2.90 vs 1.76% p = 0.02). There was a difference in gender distribution between the PSC and PBC overlap groups. Those with PSC overlap were more likely to be male (55.8 vs 28.0%, p < 0.001), where patients with PBC overlap were more likely to be female (85.5 vs 72.0% p = 0.02). Furthermore, there was a lower BMI among both those with PSC overlap (25.5 vs 29.1 kg/m^2, p < 0.001) and PBC overlap (27.1 vs 29.1 kg/m^2 p = 0.04). Additionally, PBC overlap patients tended to be older (53.1 vs 49.5 years, p < 0.05).

Clinical outcomes

When comparing the primary outcomes of PSC-overlapping cohorts, there was no difference in all-cause mortality in the Final Model (FM) (aHR 1.10 95% CI 0.61–1.97) and graft failure (aHR 2.04, 95% CI 0.80–5.19). While there was no difference in the risk of all-cause mortality of patients with PBC-overlap (aHR 1.49 95% CI 0.97–2.28), they had higher risk graft failure (aHR 3.53, 95% CI 1.73–7.24), which was reflected in the case-incidence rates (28.9 vs 9.15 per 1000 person-years). Furthermore, upon evaluating secondary outcomes, those with PSC-overlap had higher risk of death due to graft infection (aHR 38.4 95% CI 3.98–370.5; case-incidence rate: 3.89 vs 0.32 per 1000 person-years); whereas those with PBC-overlap had higher risk of death due to general respiratory causes (aHR 3.55, 95% CI 1.22–10.4; case-incidence rate: 12.8 vs 3.87 per 1000 person-years), higher risk of death due to ARDS (aHR 18.07, 95% CI 3.31–98.7; case-incidence rate: 6.42 vs 0.43 per 1000 person-years), and recurrent disease, (aHR 9.65, 95% CI 1.82–51.15; case-incidence rate: 6.42 vs 1.18 1000 person-years).

In review of the competing risk regression outputs (indicated in the Supplementary Table 1), those with PSC-overlap had a nonsignificant difference in the risk of all-cause mortality (aHR 0.77, 95% CI 0.37–1.60) and in the risk of graft failure (aHR 2.08, 95% CI 0.81–5.34). For those with PBC-overlap, while there was no statistical difference in all-cause mortality (aHR 1.03, 95% CI 0.61–1.76), there was over three times the risk of graft failure (aHR 3.50, 95% CI 1.74–7.02).

Discussion

In our study, the findings showed that compared to nonoverlapping AIH, those with AIH- PBC were at a higher risk of graft failure in the multivariate Cox models. Furthermore, upon evaluating the systems-specific causes of death, AIH-PSC were noted to have higher risks of graft infection-related deaths, whereas AIH-PBC were at a higher risk of death due to respiratory causes, ARDS, and recurrent liver disease. In general, the physiologic and the prognostic effects of AIH-overlap on AIH patients who undergo LT have been seldomly investigated, albeit a few single-center studies showed similar observations of non-difference in survival between the overlapping and non-overlapping AIH patients and a greater likelihood of disease recurrence among overlapping AIH patients (12, 13). However, both studies are lowly powered and hence were limited in their comparative abilities. When examining the pre-LT features of AIH-overlap, the prognosis is altered due to the copresence of PBC or PSC, with AIH-overlap patients featuring higher risk of morbidity and mortality (4–6, 14). The culprit for these differences in outcomes may be related to the substandard response to steroid therapy demonstrated by patients with AIH-overlap, whereby the induction of steroid therapy is often not sufficiently effective to control the disease flare prior to LT (15). For example, a number of studies showed that a combined therapy targeting both the PBC and AIH was more effective in attaining remission than monotherapy with steroids (15, 16). These types of differences presume that the post-LT prognosis may be altered by similar mechanisms of overlap affecting the host systems and the graft during and following LT.

In addition, prior studies have shown escalated rates of disease recurrence following LT among patients with autoimmune liver diseases (AIH, PBC, and PSC) (17–23), with recurrence rates of 16–43%, 10–50%, and about 20% respectively. The findings of a 6-fold increase in the rates of deaths due to disease recurrence suggests the concurrent presence of PBC as a comorbid diagnosis likely exacerbates the risk of recurrence, via mechanisms that are currently poorly defined. However, it is probable that the refractoriness of PBC-AIH overlap toward steroid therapy following LT may increase the recurrence risks (24–25). Furthermore, the histological changes may be pronounceably increased in the setting of simultaneous AIH- and PBC-related disease activity, which may escalate the risk of AIH-induced graft necroinflammation and disease recurrence (26). Similarly, PSC is thought to recur at an escalated rate (27, 28), resulting in biliary strictures and graft malfunction (27, 28). Furthermore, PSC are at a higher risk of steroid-resistant graft rejection (29, 30), which can debilitate the viability of the graft and result in graft failure. Combined, these features can exacerbate the rates of graft demise among AIH-PSC overlapping patients, as PSC and its phenotypic manifestations may exert these PSC-specific risks and curtail the survival of the graft. With steroid-resistant PSC, a stronger immunosuppressant regimen may be needed to achieve a therapeutic threshold; however, a downside of this would be the higher likelihood of infectious complications including graft infection observed among these patients. With disease recurrence, the stenotic trees in the biliary tract may serve as a nidus for infection in immunocompromised AIH-PSC patients. Furthermore, it is probable the coexisting bowel disease among AIH-PSC patients may serve as entry points for infectious pathogens. Currently, it is unclear why AIH-PBC patients experience higher rates of respiratory failure and ARDS-related deaths following LT. It can be presumed that while AIH-PBC patients necessitate higher immunosuppressant doses to maintain a rejection-free threshold, the AIH-PBC patients do not typically exhibit an infectious focus in the graft given the less frequent biliary involvement; hence, their manifestations of infective activity may include the commonly observed complications such as pneumonia and pneumonia-related ARDS, largely due to the immunocompromised state (31). Nonetheless, to identify the exact underlying causes, further studies are required.

Implications & limitations

Clinically, the post-LT care of AIH patients with PSC or PBC-overlap should be characterized by a general concern for the adverse outcomes observed in this study. For PSC-AIH patients, the graft function should be routinely monitored per the standard of care, but with greater clinical caution given the higher

likelihood of graft infection and failure. Symptoms of infection should warrant a comprehensive workup that not only include the localized infections of native organs, but also the infection of the graft. PBC-overlap patients should be warranted to undergo routine liver function checks during the immediate to subacute post-LT period to ensure the laboratory markers of PBC-disease activity is not rising (ie alkaline phosphatase).

In the future, high-powered studies that concern the effects of histological overlap between AIH and PBC or AIH and PSC should be conducted. Currently, given the limitations of the UNOS database, we used the registry diagnoses to indicate the clinical overlap of AIH and autoimmune liver conditions. While this method precludes the disease-specific histological features from defining the different subtypes of AIH within the overlap spectrum (either AIH-PSC or AIH-PBC), we ensured the clinical diagnoses of AIH-overlap were present prior to comparing the prognostic risks. Nonetheless, the clinical diagnoses cannot ascertain the histological characteristics and hence requires further studies for validation purposes.

Conclusion

The presence of AIH-overlap as presented by the concurrence of PBC or PSC can affect the post-liver transplant outcomes. For PBC-AIH overlap, there is a higher risk of death due to recurrent liver disease, respiratory causes, including ARDS; whereas for PSC-AIH overlap, there is a higher risk of deaths due to graft infection. While further studies are needed to elucidate the underlying features of pre-LT recipient histology that affect the post-LT outcomes, the current observations characterize the prognostic implications of the AIH-diagnostic overlap on post-LT mortality and graft failure risks.

Declarations

Conflict of Interest Statement:

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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Figures

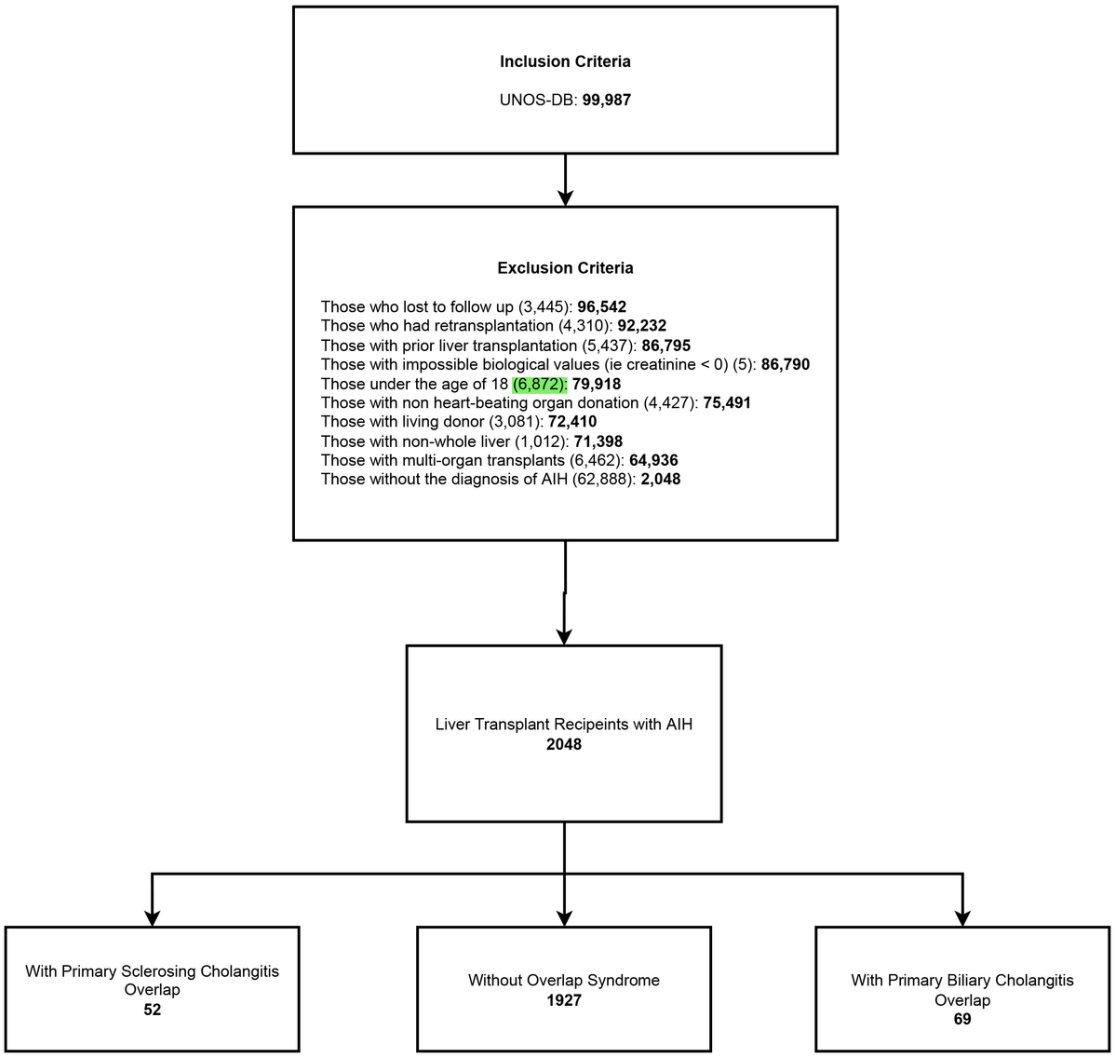

Figure 1

This figure represents the patient selection process of the study

Figure 2: Prognostic Differences in the Cumulative Hazards of All-Cause Mortality and Graft Failure

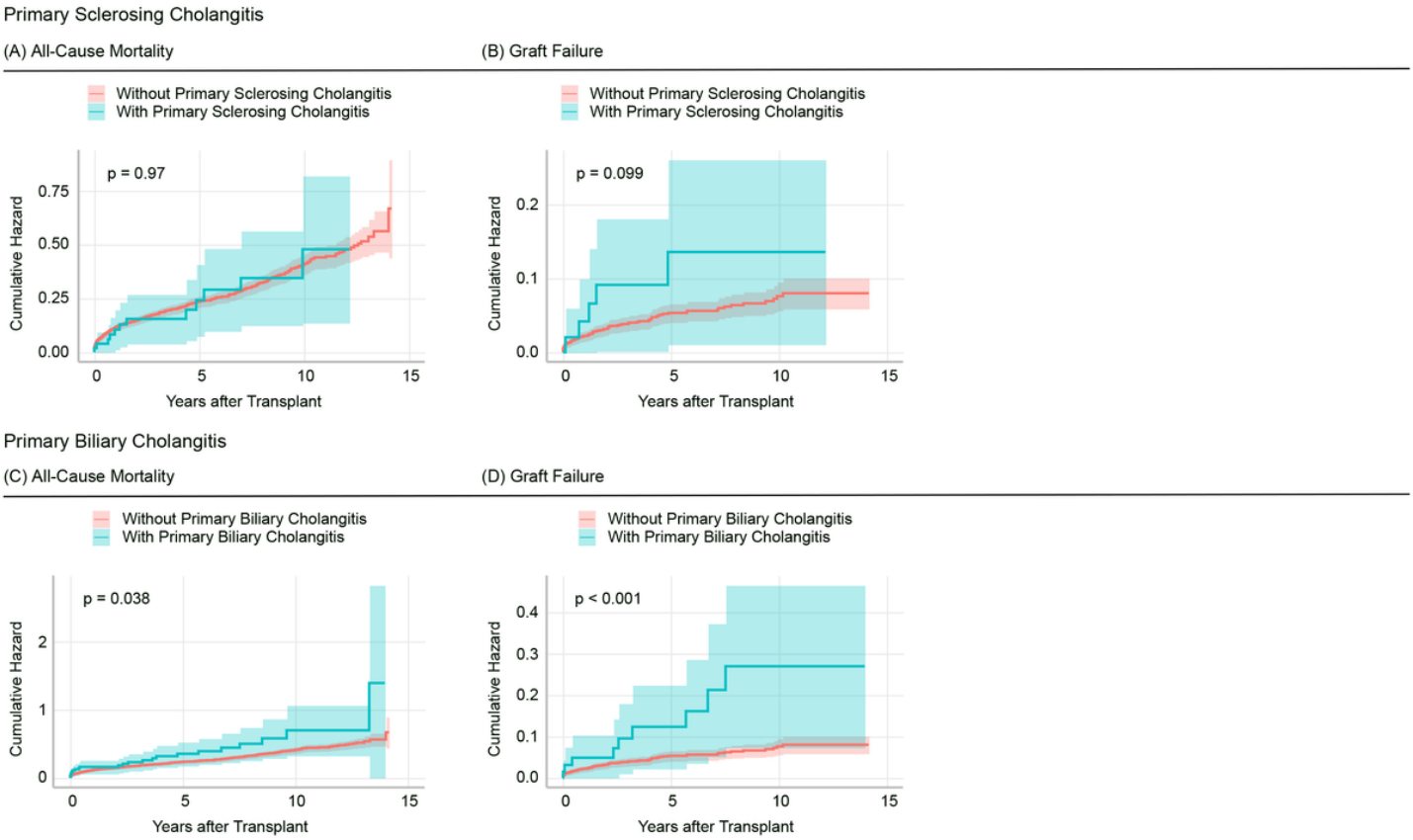

Figure 2 demonstrates all-cause mortality and graft failure. (A) and (B) represent the cumulative hazards for all-cause mortality and graft failure in liver transplant recipients with Primary Sclerosing Cholangitis (PSC) overlap. (C) and (D) represent the cumulative hazards for all-cause mortality and graft failure in liver transplant recipients with Primary Biliary Cholangitis (PBC) overlap. The p-value indicates the respective log-rank p-value for each curve.

Figure 2

This figure represents the cumulative hazard curves for the primary outcomes of the study, stratified by the overlapping conditions (AIH-PSC and AIH-PBC)

Figure 3: Prognostic Differences in the Cumulative Hazards of Specific-Causes of Death

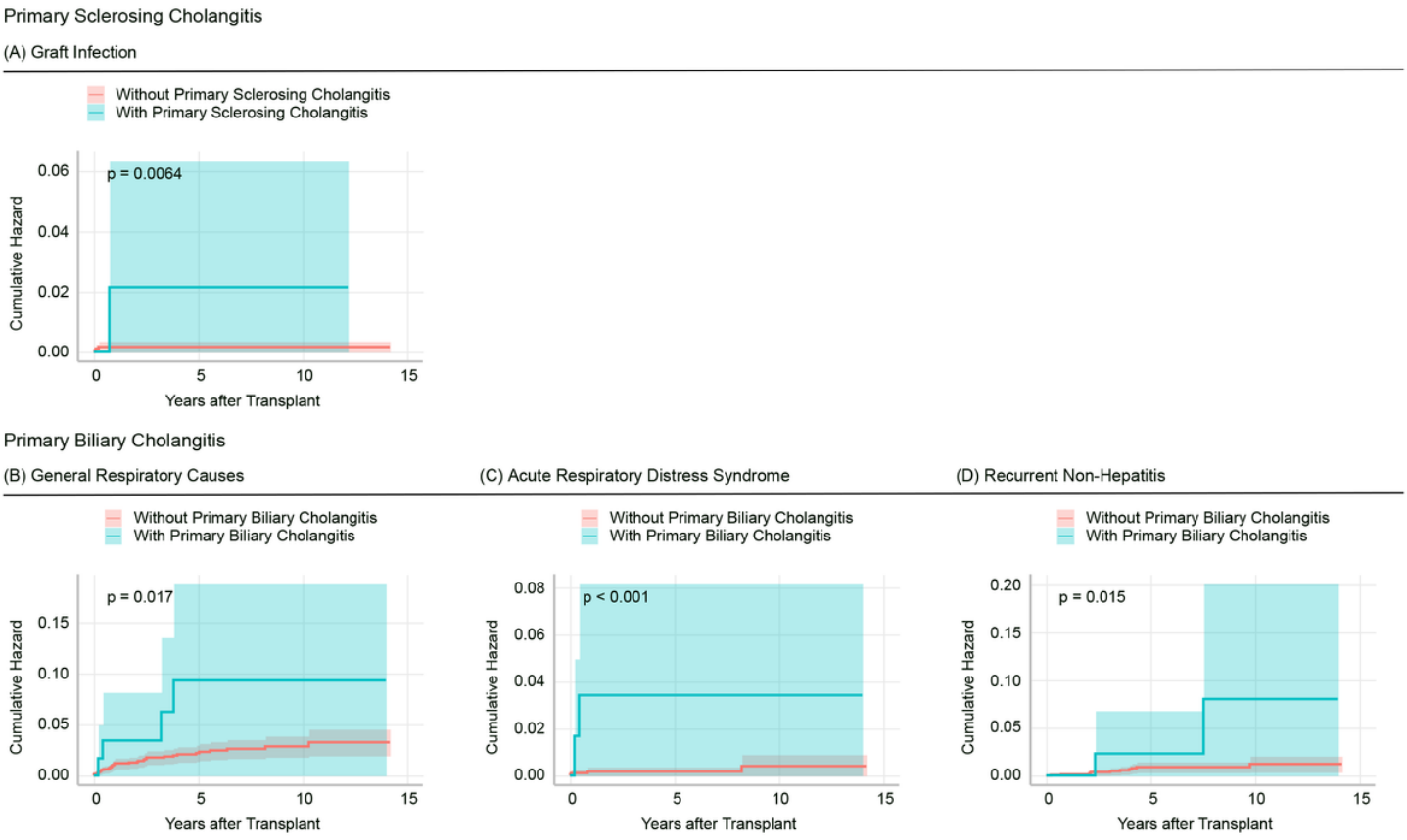

Figure 3 demonstrates specific causes of death. (A) represent the cumulative hazard for death due to graft infection in liver transplant recipients with Primary Sclerosing Cholangitis (PSC) overlap. (B), (C), and (D) represent the cumulative hazards for death due to general respiratory causes, acute respiratory distress syndrome, and recurrent non-hepatitis in liver transplant recipients with Primary Biliary Cholangitis (PBC) overlap. The p-value indicates the respective log-rank p-value for each curve.

Figure 3

This figure represents the cumulative hazard curves for the secondary outcomes of the study, stratified by the overlapping conditions (AIH-PSC and AIH-PBC)

Supplementary Files

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- SupplementaryFigure1.pdf
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