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Original Article

Characteristics and Inpatient Outcomes of Primary Biliary Cholangitis and Autoimmune Hepatitis Overlap Syndrome

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Abstract

Background and Aims: Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are hepatobiliary diseases of presumed immune-mediated origin that have been shown to overlap. The aim of this retrospective trial was to use national data to examine the characteristics and outcomes of patients hospitalized with overlapping PBC and AIH (PBC/AIH). ***Methods:*** The National Inpatient Sample was used to identify hospitalized adult patients with PBC, AIH, and PBC/AIH from 2010 to 2014 by International Classification of Diseases-Ninth Edition Revision codes; patients with hepatitis B virus and hepatitis C virus infection were excluded. Primary outcomes measures were in-hospital outcomes that included mortality, respiratory failure, septic shock, length of stay, and total hospital charges. Secondary outcomes were the clinical characteristics of PBC/AIH, including the comorbid extrahepatic autoimmune disease pattern and complications of cirrhosis. ***Results:*** A total of 3,478 patients with PBC/AIH were included in the study. PBC/AIH was associated with higher rates of Sjögren's syndrome ($p<0.001$; $p<0.001$), lower rates of Crohn's disease ($p<0.05$; $p<0.05$), and higher rates of cirrhosis-related complications when compared to PBC or AIH alone. There were similar rates of mortality between the PBC/AIH, PBC, and AIH groups. The PBC/AIH group had higher rates of septic shock when compared to the PBC group ($p<0.05$) and AIH group ($p<0.05$) after adjusting for possible confounders. ***Conclusions:*** PBC/AIH is associated with a lower rate of Crohn's disease, a higher rate of Sjögren's syndrome, higher rates of cirrhosis-related complications, and significantly increased risk of septic shock compared to PBC and AIH individually.

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Introduction

Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are diseases of presumed immune-mediated origin that affect the hepatobiliary system. They are distinct entities, though they share some similarities clinicopathologically.[1] Previous studies have suggested that variant forms of AIH develop in patients with PBC at diagnosis or during follow-up, and vice versa.[2–4] It has also been reported that patients with typical features of PBC or AIH can switch from one disease to another over time.[3] Moreover, some patients present with overlapping features of these two disorders within the spectrum of autoimmune liver diseases.[5] As a result of these observed clinical correlations, there has been an increased focus on the overlap of PBC and AIH.

Whether the coexistence of PBC and AIH are sequential, a concurrent occurrence of two independent autoimmune liver diseases (AILDs), or a primary AILD with one or more features of another AILD, is still under debate.[6] Nevertheless, it is important to recognize the coexisting disease pattern because it demonstrates unique clinical characteristics and outcomes that are different from either PBC or AIH. Previous studies have found that patients with both features of PBC and AIH developed cirrhosis more rapidly and had decreased responses to ursodeoxycholic acid and steroid therapy compared to AIH alone.[7] Compared to the PBC group, patients with PBC and AIH overlap have shown higher rates of mortality and orthotopic liver transplantation, with more cirrhosis-related complications, such as symptomatic portal hypertension, esophageal varices, gastrointestinal bleeding, and ascites.[8,9] Additionally, a large number of extrahepatic autoimmune diseases were found to be associated with AIH and PBC.[10]

Due to the relatively low prevalence of both PBC and AIH, systemic studies with sufficient numbers have been challenging. Indeed, the previous studies have been limited by small population sizes; thus, variable results have been ob-

Keywords: Primary biliary cholangitis; Autoimmune hepatitis; Extrahepatic autoimmune diseases; Cirrhosis-related complications; Septic shock; Hospital burden..

Abbreviations: AIH, autoimmune hepatitis; AILD, autoimmune liver disease; AITD, autoimmune thyroid disease; aOR, adjusted odds ratio; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; ICD-9 CM, International Classification of Diseases-Ninth Edition Revision, Clinical Modification; LOS, length of stay; NIS, Nationwide Inpatient Sample; PBC, primary biliary cholangitis; SJS, Sjögren's syndrome; Treg, regulatory T cell.

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tained, without firm conclusions. To date, there have not been large nationally representative studies to elucidate the characteristics and outcomes of PBC and AIH overlap syndrome.

In this nationwide study, we aimed to examine the characteristics (including demographics, comorbidities, related interventions) and inpatient outcomes [including length of stay (LOS), total hospital charges, in-hospital mortality, respiratory failure, and septic shock] for patients admitted with concomitant PBC and AIH (i.e. PBC/AIH). Specifically, we investigated the comorbid extrahepatic autoimmune disease pattern and complications of cirrhosis in this patient population.

Methods

Data source

Data were obtained from the Nationwide Inpatient Sample (NIS) database, which is the largest all-payer inpatient care database in the USA. It is designed to approximate a 20% sample of the USA community hospitals. Yearly sampling weights are applied to generate national estimates.[11] This database has been used previously to provide estimate burdens of AIH[12] and PBC[13] hospitalizations in the USA. The data includes demographics (age, sex, race/ethnicity), hospital information (bed size, type), insurance, discharge disposition, total hospital charges, and LOS. Diagnoses and procedures were identified by International Classification of Diseases-Ninth Edition Revision, Clinical Modification (ICD-9 CM) codes.

Study design and inclusion criteria

This study was a retrospective cohort study of adult (18–90 years-old) patients hospitalized with discharge diagnoses of both PBC (ICD-9 CM code: 571.6) and AIH (ICD-9 CM code: 571.42) across the USA, from 2010 to 2014. Two control groups from the same time period were selected. One control group was all PBC patients without diagnosis of AIH (the PBC group), while the other control group was all AIH patients without diagnosis of PBC (the AIH group). All three groups excluded patients with the diagnoses of hepatitis B virus infection or hepatitis C virus infection. Demographic and clinical characteristics were collected (Table 1).

The Elixhauser Comorbidity Index,[14] which measures 29 common medical conditions and assigns different weights to compile a score, was used to analyze the severity of comorbidities. Other comorbid conditions included were hypercholesterolemia, vitamin D deficiency, osteoporosis, obesity, cirrhosis-related complications, hepatocellular carcinoma, inflammatory bowel disease (ulcerative colitis and Crohn's disease), lymphoma, non-dialysis dependent chronic kidney disease, end-stage renal disease and autoimmune diseases, including Sjögren's syndrome (SJS), systemic sclerosis (SS), rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease (AITD), psoriasis and celiac disease. Hepatobiliary procedures or interventions such as liver transplantation and endoscopic retrograde cholangiopancreatography (commonly referred to as ERCP) were also included. ICD-9-CM codes are provided in the Supplementary Table 1.

Primary outcomes measures were in-hospital outcomes that included mortality, respiratory failure, septic shock, LOS, and total hospital charges. Secondary outcomes were the clinical characteristics of PBC/AIH, including the comorbid extrahepatic autoimmune disease pattern and complications of cirrhosis.

Statistical analysis

SAS survey procedures (SAS 9.4; SAS Institute Inc, Cary, NC, USA) were used for all statistical analyses. The national estimates were calculated after accounting for the sample design elements (clusters, strata, and trend weights) provided by the NIS. Continuous variables were reported as weighted means±standard errors, and categorical variables were reported as weighted numbers (*n*) and percentages (%). The standard errors of weighted means were estimated by using the Taylor linearization method that incorporates the sample design. Rao-Scott modified chi-square test was used to test the difference of distribution for categorical variables, while weighted Student's *t*-test was used to analyze the normally distributed continuous variables. Variables that are not normally-distributed were tested by Wilcoxon rank-sum tests. A multivariate logistic regression was used to estimate the odds ratio of in-hospital mortality, respiratory failure, and septic shock after adjusting for patient demographics, hospital bed size, hospital location/teaching status, insurance type, median household income, Elixhauser Comorbidity Index score, and other comorbidities that showed statistically significant difference in comparisons between groups. In addition, a multivariate linear regression was used to estimate the average change in LOS and hospital charges after adjusting for the same covariates mentioned above.

Ethical information

Only de-identified patient demographics from the NIS database were used and there were no patients actively involved in this study. Therefore, Institutional Review Board approval was deemed unnecessary.

Results

Patient characteristics (Table 1)

In this study, a total of 56,369 patients were admitted with PBC, 82,747 with AIH, and 3,478 with PBC/AIH. Those with PBC/AIH, PBC, and AIH were predominantly women (89.3%, 84.3%, and 80.2%, respectively) with a Caucasian prevalence (58.2%, 71.2%, and 60%), as shown in Table 1. Compared to the PBC group, patients with PBC/AIH were younger in age (57.3 vs. 64.4 years, $p<0.001$) and more likely to be admitted to large (69.1% vs. 63.3%) and urban teaching (65.8% vs. 58.6%) hospitals. The PBC/AIH cohort was also associated with less hypercholesterolemia (2.3% vs. 3.8%, $p<0.05$), a lower rate of non-dialysis dependent chronic kidney disease (10.5% vs. 13.9%, $p<0.05$) and fewer comorbid Crohn's disease cases (0.4% vs. 0.9%, $p<0.05$). However, the PBC/AIH cohort was associated with significantly more SJS (7.2% vs. 3.1%, $p<0.001$) and systemic lupus erythematosus (5.7% vs. 2.2%, $p<0.05$). Compared with the AIH group, patients with PBC/AIH were demographically similar but were associated with higher rates of vitamin D deficiency (4.1% vs. 2%, $p<0.05$) and osteoporosis (11.4% vs. 7.4%, $p=0.002$), and a lower rate of obesity (10.2% vs. 13%, $p<0.05$). Fewer comorbid Crohn's disease (0.4% vs. 0.9%, $p<0.05$) cases and more SJS (7.2% vs. 2.4%, $p<0.001$) and systemic sclerosis (4.7% vs. 0.8%, $p=0.001$) cases were seen in the PBC/AIH group. Interestingly, the PBC/AIH group did not show significantly

Table 1. Comparison of selected variables in patients hospitalized with PBC, AIH, and concomitant PBC and AIH (PBC/AIH)

Variable	PBC/AIH (*n*=3,478)	PBC (*n*=56,369)	*p*-value[a]	AIH (*n*=82,747)	*p*-value[b]
Age	57.3±0.6	64.4±0.2	<0.001	57.0±0.2	0.657
ECI score	11.2±0.5	11.6±0.1	0.333	10.7±0.1	0.206
Female	3,105 (89.3)	47,515 (84.3)	<0.001	66,318 (80.2)	<0.001
Caucasian	2,024 (58.2)	40,127 (71.2)	<0.001	49,616 (60.0)	<0.001
Large hospital bed	2,393 (69.1)	35,459 (63.3)	<0.05	53,479 (64.9)	0.076
Urban teaching hospital	2,280 (65.8)	32,854 (58.6)	<0.05	50,931 (61.8)	0.202
Hypercholesterolemia	79 (2.3)	2,116 (3.8)	<0.05	2,381 (2.9)	0.313
Vitamin D deficiency	144 (4.1)	1,688 (3.0)	0.157	1,677 (2.0)	<0.05
Osteoporosis	398 (11.4)	6,209 (11.0)	0.741	6,096 (7.4)	<0.05
Obesity	355 (10.2)	4,998 (8.9)	0.264	10,786 (13.0)	<0.05
Crohn's disease	13 (0.4)	499 (0.9)	<0.05	718 (0.9)	<0.05
Lymphoma	44 (1.3)	683 (1.2)	0.945	836 (1.0)	0.763
Non-dialysis dependent chronic kidney disease	366 (10.5)	7,836 (13.9)	<0.05	8,907 (10.8)	0.854
End-stage renal disease	46 (1.3)	813 (1.4)	0.781	819 (1.0)	0.466
Sjögren's syndrome	251 (7.2)	1,756 (3.1)	<0.001	1,957 (2.4)	<0.001
Systemic sclerosis	162 (4.7)	1,541 (2.7)	0.112	623 (0.8)	<0.05
Systemic lupus erythematosus	199 (5.7)	1,250 (2.2)	<0.05	4,775 (5.8)	0.961
Rheumatoid arthritis	119 (3.4)	2,153 (3.8)	0.590	3,522 (4.3)	0.244
Autoimmune thyroid disease	15 (0.4)	193 (0.3)	0.716	478 (0.6)	0.591
Psoriasis	44 (1.3)	742 (1.3)	0.918	886 (1.1)	0.714
Celiac disease	45 (1.3)	392 (0.7)	0.160	618 (0.7)	0.198
Ascites	720 (20.7)	8,327 (14.8)	<0.001	11,260 (13.6)	<0.001
Hepatic encephalopathy	185 (5.3)	2,072 (3.7)	0.073	2,920 (3.5)	<0.05
Variceal bleeding	56 (1.6)	648 (1.2)	0.379	577 (0.7)	0.080
Portal hypertension	682 (19.6)	8,696 (15.4)	<0.05	10,362 (12.5)	<0.001
Hepatorenal syndrome	80 (2.3)	803 (1.4)	0.124	912 (1.1)	<0.05
Spontaneous bacterial peritonitis	45 (1.3)	380 (0.7)	0.194	539 (0.7)	0.175
Respiratory failure	105 (3.0)	1,942 (3.4)	0.529	2,425 (2.9)	0.881
Septic shock	126 (3.6)	1,019 (1.8)	<0.05	1,406 (1.7)	<0.05
Mortality	110 (3.2)	2,301 (4.1)	0.190	3,122 (3.8)	0.380
LOS in days	5.9±0.2	5.8±0.1	0.628	5.8±0.1	0.628
Total hospital charges in dollars	61,539.8±3,977.3	54,295.5±1,565.4	0.075	51,638.1±1,215.1	<0.05

Values are reported as weighted means±standard errors and weighted numbers (%).
[a]*p*-value, comparison between PBC/AIH and PBC.
[b]*p*-value, comparison between PBC/AIH and AIH.
Abbreviation: ECI, elixhauser comorbidity index.

Table 2. Multivariate analysis for cirrhosis-related complications in patients hospitalized with primary biliary cholangitis (PBC), autoimmune hepatitis (AIH) and concomitant PBC and AIH (PBC/AIH)

Cirrhosis-related complications	Unadjusted OR or coefficient (95% CI)	*p*-value	aOR or coefficient* (95% CI)	*p*-value
Ascites[a]	0.6 (0.55, 0.66)	<0.001	0.58 (0.48, 0.71)	<0.001
Hepatic encephalopathy[a]	0.65 (0.56, 0.76)	<0.001	0.71 (0.5, 1.02)	0.063
Variceal bleeding[a]	0.43 (0.32, 0.56)	<0.001	0.47 (0.25, 0.88)	<0.05
Portal hypertension[a]	0.59 (0.54, 0.64)	<0.001	0.57 (0.47, 0.7)	<0.001
Hepatorenal syndrome[a]	0.47 (0.38, 0.6)	<0.001	0.49 (0.29, 0.84)	0.009
Spontaneous bacterial peritonitis[a]	0.5 (0.37, 0.67)	<0.001	0.55 (0.27, 1.11)	0.093
Ascites[b]	0.66 (0.61, 0.72)	<0.001	0.69 (0.56, 0.84)	<0.001
Hepatic encephalopathy[b]	0.68 (0.58, 0.8)	<0.001	0.79 (0.55, 1.13)	0.195
Variceal bleeding[b]	0.71 (0.54, 0.93)	<0.05	0.84 (0.45, 1.57)	0.582
Portal hypertension[b]	0.75 (0.69, 0.82)	<0.001	0.85 (0.69, 1.04)	0.105
Hepatorenal syndrome[b]	0.62 (0.49, 0.78)	<0.001	0.69 (0.41, 1.19)	0.184
Spontaneous bacterial peritonitis[b]	0.51 (0.38, 0.7)	<0.001	0.63 (0.31, 1.3)	0.215

[a]PBC/AIH as reference, results for the AIH group.

[b]PBC/AIH as reference, results for the PBC group.

*Adjusted for age, sex, race, primary insurance payer, hospital type, hospital bed size, income quartile, Elixhauser Comorbidity Index score, hypercholesterolemia, vitamin D deficiency, osteoporosis, obesity, Crohn's disease, Sjögren's syndrome, systemic sclerosis, systemic lupus erythematosus, autoimmune thyroid disease, and non-dialysis dependent chronic kidney disease.

different Elixhauser Comorbidity Index scores when compared to the PBC or AIH groups.

Liver-related comorbid conditions

This study's analysis revealed that PBC/AIH was associated with higher rates of ascites (20.7% vs. 14.8%, $p<0.001$) and portal hypertension (19.6% vs. 15.4%, $p<0.05$) compared to PBC. Similarly, compared to AIH, PBC/AIH cases were associated with higher rates of ascites (20.7% vs. 13.6%, $p<0.001$) and portal hypertension (19.6% vs. 12.5%, $p<0.001$), and associated with higher rates of hepatic encephalopathy (5.3% vs. 3.5%, $p<0.05$) and hepatorenal syndrome (2.3% vs. 1.1%, $p<0.05$). Furthermore, multivariate analysis (Table 2) demonstrated that PBC/AIH was associated with higher rates of ascites compared to PBC [adjusted odds ratio (aOR): 0.69, 95% confidence interval (CI): 0.56–0.84, $p<0.001$] or AIH (aOR: 0.58, 95% CI: 0.48–0.71, $p<0.001$). In addition, PBC/AIH was associated with higher rates of variceal bleeding (aOR: 0.47, 95% CI: 0.25–0.88, $p<0.05$), portal hypertension (aOR: 0.57, 95% CI: 0.47–0.7, $p<0.001$) and hepatorenal syndrome (aOR: 0.49, 95% CI: 0.29–0.84, $p<0.05$). Interestingly, when comparing the rates of hepatocellular carcinoma, liver transplantation, and interventions including diagnostic and therapeutic ERCP, there was no difference between PBC/AIH vs. PBC, or PBC vs. AIH.

In-hospital outcomes

For the measures of hospital stay outcomes, there was a similar rate of mortality (3.2% vs. 4.1%, $p=0.190$) and respiratory failure (3% vs. 3.4%, $p=0.529$) between the PBC/AIH and PBC groups. Moreover, there was no statistically significant difference in hospitalization burden found in terms of LOS (5.9±0.2 days vs. 5.8±0.1 days, $p=0.628$) or total hospital charges ($61539.8±3977.3 vs. $54295.5±1565.4, $p=0.075$). However, the PBC/AIH group had a significantly higher rate of septic shock (3.6% vs. 1.8%, $p<0.05$) than the PBC group. Additionally, compared to the AIH group, the PBC/AIH group was associated with a higher rate of septic shock (3.6% vs. 1.7%, $p<0.05$) and higher total hospital charges ($61539.8±3977.3 vs. $51638.1±1215.1, $p<0.05$). The rates of mortality (3.2% vs. 3.8%, $p=0.380$), respiratory failure (3% vs. 2.9%, $p=0.881$), and LOS (5.9±0.2 days vs. 5.8±0.1 days, $p=0.628$) were not markedly different between the PBC/AIH and AIH groups (Table 1). Patients with PBC (aOR: 0.54, 95% CI: 0.35–0.83, $p<0.05$) and AIH (aOR: 0.49, 95% CI: 0.32–0.75, $p=0.001$) retained the lower rates of septic shock compared to patients with PBC/AIH (Table 3) after adjusting for possible confounders.

Discussion

This nationwide study examined the characteristics and inpatient outcomes of PBC/AIH compared to PBC or AIH alone. The major finding included that PBC/AIH was associated with a specific extrahepatic autoimmune disease pattern, with SJS being the most common extrahepatic autoimmune disease. PBC/AIH patients had significantly higher rates of cirrhosis-related complications. Furthermore, this study found that PBC/AIH was associated with a higher rate of septic shock compared to PBC and AIH, individually. This finding remained significant after adjusting for possible confounders, which suggests that PBC/AIH patients may present with an increased level of immunosuppression that increases the risk of dysregulated response leading to disseminated infection.

In regards to the higher rate of septic shock observed in the PBC/AIH cohort in this study, one possible explanation is the compromised immune system in PBC/AIH patients. It has been reported that PBC and AIH have a shared altered immune regulatory mechanism. Lohse *et al*.[15] described the concept of "spontaneous immunosuppression" in AIH, based upon observations in a murine model of experimental AIH as well as in patients. T cells obtained during remission markedly suppressed the liver-specific T cell responses by

Table 3. Multivariate analysis for outcomes in patients hospitalized with PBC, AIH, and concomitant PBC and AIH (PBC/AIH)

Outcomes	Unadjusted OR or coefficient (95% CI)	*p*-value	aOR or coefficient* (95% CI)	*p*-value
Mortality[a]	1.2 (0.99, 1.45)	0.07	1.19 (0.76, 1.86)	0.44
Respiratory failure [a]	0.97 (0.79, 1.18)	0.74	0.95 (0.61, 1.49)	0.83
Septic shock[a]	0.46 (0.38, 0.55)	<0.001	0.49 (0.32, 0.75)	<0.05
LOS in days[a]	−0.13 (−0.68, 0.41)	0.63	−0.1 (−0.63, 0.43)	0.71
Total hospital charges[a] in dollars	−9,901.76 (−17,517.55, −2,285.96)	<0.05	−8,557.16 (−16,148.88, −965.43)	<0.05
Mortality[b]	1.3 (1.07, 1.58)	<0.05	1.21 (0.78, 1.9)	0.40
Respiratory failure[b]	1.14 (0.94, 1.39)	0.19	1.1 (0.7, 1.74)	0.67
Septic shock[b]	0.49 (0.4, 0.59)	<0.001	0.54 (0.35, 0.83)	<0.05
LOS in days[b]	−0.13 (−0.68, 0.42)	0.64	−0.01 (−0.55, 0.53)	0.97
Total hospital charges[b] in dollars	−7,244.33 (−14,931.49, 442.84)	0.07	−3,376.62 (−11,056.4, 4,303.17)	0.39

[a]PBC/AIH as reference, results for the AIH group.
[b]PBC/AIH as reference, results for the PBC group.
*Adjusted for age, sex, race, primary insurance payer, hospital type, hospital bed size, income quartile, Elixhauser Comorbidity Index score, hypercholesterolemia, vitamin D deficiency, osteoporosis, obesity, Crohn's disease, Sjögren's syndrome, systemic sclerosis, systemic lupus erythematosus, autoimmune thyroid disease, and non-dialysis dependent chronic kidney disease, cirrhosis.

T cells obtained during the active phase of the AIH. Thus, it is postulated that spontaneous remission and long-lasting remission after discontinuance of immunosuppressive therapy may result from spontaneous immunosuppression. In addition, more data have suggested that regulatory T cells (Tregs) are numerically impaired in AILDs, especially during its active phase.[16] Similarly, it was reported that the pathogenesis of PBC likely involves an imbalance in immune tolerance rather than an over-reactive immune system directed against a self-antigen,[17,18] which explains the extensive failure of immunosuppressants in treating PBC.[19] Hence, immunoregulatory failure and dysfunction of Tregs play a vital role in the initiation and pathogenesis of both PBC and AIH, leading to further altered immune regulation in PBC/AIH, which may contribute to the increased rate of septic shock. An alternative explanation for the higher rate of septic shock in patients with PBC/AIH could be attributed to the treatment method. We hypothesize that more aggressive immunosuppressive induction and maintenance therapy offered to patients with PBC/AIH based on the rapid progression of disease course and higher rates of complications may further compromise the ability to protect against infection. Taken together, underlying dysregulation of the immune system from concomitant AILDs and related immunosuppressive treatment may increase the risk of septic shock.

Despite having the highest rate of septic shock, PBC/AIH had similar in-hospital mortality rates and LOS compared to PBC and AIH individually after adjusting for confounding factors. Previous studies have shown worse long-term mortality rates and more liver-related deaths in the PBC/AIH overlap group.[8,20] A plausible explanation for the contrary finding in this study is that PBC/AIH concomitant disease is a chronic progressive disease, either by its pathophysiology or as a result of effective treatment, and is associated with less acute decompensation that would contribute to in-hospital mortality.

This analysis revealed that PBC/AIH patients were relatively young and more likely to be admitted to a large teaching hospital when compared to PBC patients. This finding reflects the complexity and severity of PBC/AIH. Not surprisingly, PBC/AIH was associated with more vitamin D deficiency and osteoporosis. These patients were also less likely to be obese when compared to AIH patients. These findings can be explained by steatorrhea and weight loss from malabsorption due to decreased biliary secretion of bile acids, which are commonly seen in advanced PBC.[21,22] Interestingly, this study found significantly less Crohn's disease in the PBC/AIH group compared to either PBC or AIH. However, there was no difference in the incidence of ulcerative colitis found between all three groups. Ulcerative colitis has been reported to share similar human leukocyte antigen haplotypes with PBC,[23] and the same atypical antineutrophil cytoplasmic antibodies with AIH.[24] However, the data available regarding the association between Crohn's disease and PBC or AIH are very limited. The authors of one Japanese study commented on genetic polymorphisms, suggesting that they may be related to PBC and Crohn's disease susceptibility. Three alleles involved in the interleukin-12 signaling pathway perform in opposite directions in these two diseases, indicating an opposite pathogenic pathway that leads to a different balance of immune responses.[25] Further investigation on how PBC and AIH interaction can affect the pathogenesis of Crohn's disease is needed.

The observation of concurrent extrahepatic autoimmune diseases has been reported frequently in patients with AILDs.[26,27] The "mosaic of autoimmunity" has been proposed to describe this condition.[28] In our study's hospitalized patient cohort, SJS was the most common extrahepatic autoimmune comorbidity of PBC/AIH. Consistently, two other studies documented SJS as the most common

systemic autoimmune disease in AILDs.[10,26] It is reported that both PBC and SJS are characterized by inflammation of target epithelial elements sharing a similar target antigen.[10,29] Similarly, an inflammatory process with CD3+ T cell predominant lymphocytic infiltration on histological examination has been found in both liver and labial salivary glands in AIH patients.[30] These findings support a close relationship between PBC/AIH and SJS. AITD was reported to have a high prevalence rate in AILDs. In one study that focused on the gastroenterology clinic population, AITD was found in 18.3% of patients.[10] Conversely, this study's inpatient population cohort did not show a significantly high number of patients with AITD. This result may be attributed to underestimation by lacking specific ICD-9 codes or missing documentation in hospitalized patients, given the relative chronic course of AITD.

This study revealed higher rates of cirrhosis-related complications, most notably in ascites in the PBC/AIH group compared with PBC or AIH alone. Moreover, the PBC/AIH group demonstrated higher rates of variceal bleeding, portal hypertension and hepatorenal syndrome when compared to the AIH group. These results are consistent with previous findings[7–9] in which clinically significant progression to cirrhosis-related complications were more likely to be seen in the PBC/AIH population. In AILDs such as PBC or AIH, liver fibrogenesis is a complex process, influenced by immune and inflammatory mechanisms. The activation of hepatic stellate cells is considered the most important event in the fibrogenesis of both PBC[31] and AIH.[32] Portal fibroblasts, located around portal tracts, have been reported to be of particular importance in PBC and differentiate from hepatic stellate cells in regards to their profibrogenic function.[33] The targets of the autoimmune response in AIH are hepatocytes, whereas the target in PBC is the biliary epithelial cells. In addition to the classic wound healing reaction from un-resolving inflammation and persistent liver injury, the proliferation of bile ducts and the direct or indirect contribution of bile acid to the fibrogenic process has been reported in PBC.[34,35] Furthermore, other mediators (such as CD4+ and CD8+ T cell response[36,37] and nitric oxide[38,39]) and other mechanisms (such as oxidant stress liver injury[40,41]) for the process of liver fibrogenesis have been shown to be shared by PBC and AIH. Considering the shared and disease-specific features between PBC and AIH fibrogenesis pathways, it can be hypothesized that an overlapping immune-mediated process accelerates the liver fibrogenesis in PBC/AIH overlap syndrome by targeting both hepatocytes and biliary epithelial cells, which may subsequently cause a higher prevalence of cirrhosis-related complications. Although the exact pathways of the overlapping immune-mediated process are unclear, this hypothesis is supported by several retrospective studies on the treatment of PBC/AIH, in which stable and decreased liver fibrosis states were observed in the patients with PBC/AIH who received combined immunosuppressive therapy.[5,42,43]

This study has several strengths and limitations. With nationwide samples, the NIS database provided the largest sample size to study two concomitant uncommon conditions, PBC and AIH. Therefore, our results are based on a high-power study and provide a national review of the disease. However, all diagnoses are dependent on the accuracy of ICD-9 codes, for which validation is routinely performed by the Agency for Healthcare Research and Quality, although coding errors may compromise the quality of the data. A recent study using the main diagnostic ICD-9-CM code (571.6) for PBC showed a good accuracy with most clinical and demographic parameters, comparable to the previously reported data.[13] There are other inherent limitations of this NIS study. For example, NIS provides inpatient data but none of the laboratory values, images, or pharmacological interventions are recorded. Therefore, information about outpatient follow-up, long-term outcomes or prognosis are not available, and additional information that may help better classify PBC/AIH overlap syndrome, such as liver function test results and histologic findings are not available. Also, a small proportion of patients who had readmissions were counted more than once, and this group of patients was non-identifiable. Therefore, the prevalence of disease might be overreported.

In conclusion, this national study used a large data set from the USA to examine the characteristics and in-hospital outcomes of PBC/AIH. Our results strengthened previous data showing high rates of cirrhosis-related complications, and also SJS as the most common extrahepatic autoimmune disease associated with AILDs in patients with PBC/AIH. The study identified that PBC/AIH is independently associated with a higher rate of septic shock compared to PBC and AIH individually. This result provokes clinicians to consider sepsis screening early in patients' presentations to the hospital and optimize the treatment of infections. Although previous studies reported worse liver-related mortality and long-term survival, this study did not observe worse in-patient mortality in PBC/AIH patients. These findings will inspire more work to be done in the future. Prospective studies at genetic and clinicopathological levels will assist in gaining a better understanding of the mechanism of the overlap between PBC and AIH, including the role of Treg cells and their interactions with immunosuppressive therapy. Ultimately, more progress in the field of immunomodulated therapy is expected.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (YJ, NP), acquisition of data (YJ, BX), analysis and interpretation of data (YJ, BX, BR), drafting of the manuscript (YJ, BX, BR, NP), critical revision of the manuscript for important intellectual content (YJ, BX, BR, NP), administrative, technical, or material support, study supervision (NP).

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