BMC Gastroenterology

RESEARCH

Open Access

Concurrent nonalcoholic fatty liver disease may decrease liver fibrosis severity in patients with primary biliary cholangitis

Wenhui Ren[1†], Zilong Wang[2†], Xinyue Liu[3], Xin Liu[4], Danli Ma[2], Qian Jin[2], Jian Wang[2], Jiajun Feng[5], Huiying Rao[2], Xiaoxiao Wang[2*] and Rui Huang[2*]

Abstract

Background The purpose of this study was to evaluate how nonalcoholic fatty liver disease (NAFLD) impacts the progression and prognosis of primary biliary cholangitis (PBC).

Methods This retrospective study enrolled patients diagnosed with PBC. NAFLD patients were identified according to the 2023 American Association for the Study of Liver Diseases guidelines. The primary outcome measured the percentage of patients achieving a complete biochemical response as defined by the Paris criteria, while secondary outcomes included non-invasive fibrosis scoring systems and a transplantation-free survival risk model. Statistical analyses employed independent samples Student's t-test or Mann-Whitney U test for continuous variables and Pearson's chi-square or Fisher's exact test for categorical variables, with significance set at a two-tailed P-value of less than 0.05.

Results Among 363 patients diagnosed with PBC, 87 (24.0%) were also diagnosed with NAFLD. Biochemical response rates did not differ significantly between patients with only PBC and those with concurrent PBC and NAFLD ($P>0.05$). However, after one year of ursodesoxycholic acid (UDCA) treatment, significant differences were observed in aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis 4 (FIB-4) score between PBC patients with and without NAFLD (APRI: 0.35 vs. 0.47, $P=0.02$; FIB-4 score: 1.95 vs. 2.53, $P=0.01$). The GLOBE score revealed that patients with both PBC and NAFLD had higher 5-, 10-, and 15-year liver transplant-free survival rates compared to those with only PBC (81.9%, 58.3%, and 38.0% respectively, all $P<0.05$).

Conclusions Patients with concurrent PBC and NAFLD do not significantly impact the biochemical response to UDCA but may improve the degree of liver fibrosis and long-term prognosis.

Keywords Primary biliary cholangitis, Nonalcoholic fatty liver disease, Biochemical response, Progressive liver fibrosis, Long-term prognosis

†Wenhui Ren and Zilong Wang contributed equally to this work and shared first authorship.

*Correspondence:
Xiaoxiao Wang
wangxx0635@163.com
Rui Huang
strangehead@163.com

Full list of author information is available at the end of the article

Introduction

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune cholestatic liver disease characterized by the immune-mediated destruction of the small hepatic bile ducts. Recent advancements in understanding this disease, coupled with improvements in laboratory techniques, have led to an increase in its reported prevalence, with estimates ranging from 2.7 to 39.2 per 100,000 individuals between 2004 and 2014 [1]. PBC has a multifaceted etiology, involving genetic, immunological, and bile pathway interactions, and is distinguished by its clinical heterogeneity in manifestations, disease progression, and treatment responses [2, 3]. Often presenting insidiously, PBC typically lacks specific symptoms, which can delay diagnosis and potentially lead to end-stage liver disease [4, 5].

Nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic metabolic liver disease linked to insulin resistance, obesity, and genetic factors. Over the past four decades, its widespread prevalence has necessitated investigations into its prognostic and clinical implications, particularly when coexisting with other liver diseases [6]. Studies indicate that hepatitis B virus (HBV) infection in conjunction with NAFLD may lead to higher rates of HBsAg seroclearance and seroconversion, and less severe liver fibrosis [7, 8]. At the same time, some studies have proposed contrasting findings, indicating that CHB patients with MASLD exhibit more severe liver fibrosis, with a twofold increased risk of significant fibrosis [9]. These discrepancies may stem from variations in study populations (NAFLD vs. MASLD) and potential selection biases.

However, there is paucity of clinical data on how NAFLD impacts the progression and prognosis of PBC.

Previous research has shown that 57% of PBC patients (28 out of 49) exhibited histological or imaging-based evidence of hepatic steatosis [10], yet the specific prevalence of PBC coexisting with NAFLD is increasing, albeit unspecified. Recent studies suggest that PBC patients exhibit the lowest degree of hepatic steatosis compared to those with other chronic liver diseases [11]. The disease progression and prognosis in PBC patients with NAFLD are complex, with some studies suggesting no adverse effects on PBC activity, severity, or progression due to concurrent NAFLD [12]. Conversely, other researchers propose that PBC and NAFLD comorbidity may exacerbate liver disease burden and worsen prognosis [13]. The conflicting evidence introduces challenges in clinical decision-making, necessitating further investigation. Despite the growing prevalence of NAFLD among PBC patients, comprehensive information on how NAFLD influences PBC progression and prognosis remains scant. This retrospective study aims to assess the prevalence of NAFLD in PBC patients and explore its impact on biochemical responses, liver fibrosis, and mortality risk.

Materials and methods

Study design and population

This retrospective study was conducted by Peking University People's Hospital in Beijing, China, from January 2018 to August 2023. Inclusion criteria for participants encompassed individuals aged 18 years and above diagnosed with PBC or PBC/NAFLD, possessing detailed clinical and laboratory information as per medical records review. The diagnosis of PBC was established based on at least two of the following three criteria being present according to the 2018 American Association for the Study of Liver Diseases (AASLD) guidelines: (1) persistently elevated serum ALP levels of greater than six months duration, (2) a positive (≥1:80 titre) antimitochondrial antibody test and (3) liver histology in keeping with PBC [14]. The diagnosis of NAFLD was confirmed by the presence of hepatic steatosis on abdominal imaging, characterized by heightened echogenicity relative to the right kidney, reduced visualization of portal echoes, and hepatomegaly, in the absence of a readily identified alternative cause of steatosis (e.g., medications, starvation, monogenic disorders) in individuals who drink little or no alcohol (defined as <20 g/d for women and <30 g/d for men) according to the 2023 AASLD guidelines [15]. Participants were excluded from the study if they exhibited the following criteria: (1) incomplete clinical data; (2) presence of additional liver diseases, such as chronic hepatitis B and C infections, drug-induced liver disease, hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), IgG4 disease as well as alcohol-associated liver disease.; (3) less than one year of follow-up. Written informed consent was not deemed necessary for this study, as it had received approval from the Medical Ethics Committee of Peking University People's Hospital (No. 2022PHB231-001). The study protocol adhered to the ethical guidelines of the latest version of the Declaration of Helsinki (2024).

Clinical and laboratory parameters

Demographic characteristics and clinical data, such as age, gender, liver cirrhosis and co-morbidities (e.g. hypertension, diabetes, and coronary heart disease), were documented in the electronic medical records system. Additionally, laboratory parameters including alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), albumin, urea, serum creatinine (Cr), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), Immunoglobulin A

(IgA), and Immunoglobulin M (IgM) were collected. Histories for alcohol intake were also obtained from the electronic medical record system.

Outcomes

The primary outcome was defined as the percentage of patients with a complete biochemical response following one year of ursodeoxycholic acid (UDCA) treatment using the PARIS I [16] (ALP ≤ 3 upper limit of normal (ULN), AST ≤ 2 ULN, and bilirubin ≤ 1 mg/dL after 1 year of UDCA) and PARIS II [17] (ALP and AST 1.5 ≤ upper limit of normal, with a normal bilirubin level after 1 year of UDCA) criteria. One of the secondary outcomes following one year of treatment with UDCA were the aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis 4 (FIB-4) Score. APRI is calculated by dividing the patient's AST level (adjusted for the upper limit of normal in the blood) by the patient's platelet count [18], with classifications for the absence of cirrhosis (< 1), inconclusive (1–2), and cirrhosis (≥ 2). The FIB-4 score, calculated as (Age × AST)/(Platelet count × ALT1/2), is commonly utilized for assessing the extent of fibrosis in individuals either suspected of or already diagnosed with hepatic fibrosis [19]. The resulting FIB-4 score is categorized into three groups: absence of cirrhosis (< 1.45), inconclusive (1.45–3.25), and cirrhosis (> 3.25) [20]. Furthermore, we utilized the GLOBE risk score model to predict the transplantation-free survival of patients diagnosed with PBC or PBC/NAFLD over a period of three to fifteen years as another of the secondary outcomes. The baseline survival curve at the mean GLOBE score S0(t) was: 0.9652, 0.9385, 0.8429, and 0.7361 at 3-, 5-, 10-, and 15-year follow-up, respectively. The survival S(t) for any given patients was then calculated by $S(t) = S0(t)^{\exp(\text{GLOBE score})}$ [21].

Statistical analysis

The statistical analysis was performed using SPSS 26.0 (Chicago, IL, USA). Continuous data with a normal distribution were reported as mean (standard deviation [SD]), while non-normally distributed variables were presented as median (interquartile range [IQR]). Independent samples Student's t test or Mann-Whitney U test were utilized to assess variations in the distribution of continuous variables. The frequencies of categorical variables were compared using either Pearson's chi-square or Fisher's exact test. Subgroup analysis was performed to investigate differences in biochemical response rate, APRI and FIB-4 score among patients with PBC and those with PBC/NAFLD. Multiple logistic regression analysis was applied to evaluate the relationship between NAFLD and liver fibrosis among individuals diagnosed with PBC when control for potential confounders (i.e., gender, age, the history of hypertension, diabetes, and coronary heart disease). Statistical significance was defined as a two-tailed P-value of less than 0.05.

Results

A total of 363 patients diagnosed with PBC were included in the analysis, of which 87 (24.0%) were found to also have NAFLD. The cohort had a mean age of 60.26 ± 10.98 years and was predominantly male ($n = 316$, 87.05%). 199 patients (54.82%) had a history of liver cirrhosis. The baseline clinical characteristics and laboratory parameters of patients with only PBC and those with both PBC and NAFLD are presented in Table 1. Statistical analysis revealed significant differences between disease status and a history of liver cirrhosis, hypertension, as well as levels of ALT, ALP, DB, Albumin, HDL, TG, and IgM (all $P<0.05$). The patients with PBC/NAFLD showed higher prevalence of hypertension ($P = 0.01$) but lower incidence of liver fibrosis ($P = 0.01$), along with significantly elevated levels of ALT, albumin, and TG compared to those with only PBC (all $P < 0.01$). Conversely, the only PBC group demonstrated higher levels of DB, HDL, and IgM (all $P < 0.01$), as well as increased APRI and FIB-4 scores, consistent with their greater degree of liver fibrosis. The study found that the biochemical response rate following one year of UDCA treatment was higher in patients with PBC/NAFLD compared to those with only PBC, although this did not reach statistical significance (Paris I criteria: 66.67% vs. 62.68%, $P = 0.50$; Paris I criteria: 60.92% vs. 57.61%, $P = 0.59$). Subgroup analysis, as presented in Table 2, did not reveal a significant difference between PBC patients with and without NAFLD.

There was a significant difference in APRI and FIB-4 scores following one year of UDCA treatment among PBC patients with and without NAFLD (APRI: 0.35 vs. 0.47, $P = 0.02$; FIB-4 score: 1.95 vs. 2.53, $P = 0.01$) (Fig. 1). Subgroup analysis results are presented in Table 3, indicating that the median FIB-4 score in PBC patients was higher than those with NAFLD in female individuals ($P = 0.01$) and those aged < 60 years ($P = 0.04$). Among individuals without a history of liver cirrhosis, both APRI and FIB-4 scores were observed to be higher in patients with PBC compared to those with PBC and NAFLD (all $P < 0.05$). Furthermore, the prevalence of liver fibrosis (as indicated by APRI > 1.5 or FIB-4 > 3.25) was more common in patients with only PBC than in those with PBC and NAFLD (FIB-4: 39.13% vs. 18.19%, $P = 0.04$; APRI: 13.77% vs. 2.27%, $P = 0.03$) (Fig. 2).

Subsequent analysis was conducted to examine the relationship between NAFLD and liver fibrosis in patients with PBC while controlling for other variables. The results of the multivariable analysis indicated that PBC patients with NAFLD had a significantly reduced risk of liver fibrosis compared to those without NAFLD (as measured by APRI: OR = 0.11 [95% CI: 0.01–0.93],

Table 1 Baseline characteristics between PBC patients with and without NAFLD

Characteristics	All patients (*n* = 363)	Only PBC (*n* = 276)	PBC & NAFLD (*n* = 87)	*P*-value
Age (years)	60.3 ± 11.0	60.8 ± 11.0	58.7 ± 10.7	0.12
< 60	172 (47.4)	125 (45.3)	47 (54.0)	0.16
≥ 60	191 (52.6)	151 (54.7)	40 (46.0)	
Gender (n,%)				
Male	47 (12.9)	35 (12.7)	12 (13.8)	0.93
Female	316 (87.1)	241 (87.3)	75 (86.2)	0.79
Co-morbidities (n, %)				
Hypertension	58 (16.0)	36 (13.0)	22 (25.3)	0.01
Diabetes	29 (8.0)	19 (6.9)	10 (11.5)	0.25
Coronary heart disease	20 (5.5)	15 (5.4)	5 (5.7)	0.91
Liver cirrhosis	199 (54.8)	162 (58.7)	37 (42.5)	0.01
APRI	0.43 (0.28, 0.87)	0.45 (0.29,1.03)	0.41 (0.25, 0.66)	< 0.01
FIB-4 Score	2.07 (1.30, 4.48)	2.12 (1.38, 4.84)	1.74 (1.15, 2.52)	< 0.01
Laboratory parameters				
ALT (U/L)	25.0 (17.0, 39.0)	23.5 (16.0, 38.0)	28.0 (20.0, 48.0)	< 0.01
AST (U/L)	31.0 (24.0, 46.0)	31.0 (24.0, 43.0)	33.0 (24.0, 50.0)	0.43
GGT (U/L)	61.0 (37.0, 121.0)	61.0 (36.0, 124.0)	59.0 (39.0, 104.0)	0.83
ALP (U/L)	119.0 (89.0, 164.0)	120.0 (90.0, 117.8)	109.0 (86.0, 144.0)	0.04
DB (μmol/L)	4.5 (3.3, 6.4)	4.7 (3.4, 7.2)	3.8 (3.1, 5.1)	< 0.01
TBIL (μmol/L)	14.6 (11.3, 19.0)	14.7 (11.4, 19.7)	13.8 (10.8, 18.3)	0.13
Albumin (G/L)	42.6 (39.4, 44.8)	42.1 (38.8, 44.3)	44.1 (42.4, 46.3)	< 0.01
Urea (mmol/L)	4.9 (4.0, 5.8)	4.8 (3.9,5.6)	5.0 (4.2, 5.8)	0.54
Cr (μmol/L)	61.0 (52.0, 69.0)	62.0 (52.0, 70.0)	58.0 (52.0, 69.0)	0.16
TC (mmol/L)	5.1 (4.4, 5.9)	5.1 (4.3, 5.9)	5.4 (4.7, 6.1)	0.14
LDL (mmol/L)	3.1 (2.5, 3.6)	3.0 (2.4, 3.6)	3.2 (2.6, 3.8)	0.06
HDL (mmol/L)	1.4 (1.1, 1.6)	1.4 (1.2, 1.7)	1.2 (1.1, 1.4)	< 0.01
TG (mmol/L)	1.3 (1.0, 1.9)	1.2 (0.9, 1.7)	1.7 (1.4, 2.2)	< 0.01
PLT (10^9/L)	190 (131, 255)	187 (116, 252)	219 (151, 277)	0.31
IgA*	2.7 (2.0, 3.6)	2.7 (2.0, 3.8)	2.8 (2.4, 3.3)	0.95
IgM*	2.1 (1.2, 3.7)	2.4 (1.4, 3.9)	1.3 (1.0, 2.0)	< 0.01

Categorical values are shown as n (%). Continuous variables are shown as mean ± SEs. Skewed data are presented as median (interquartile range, IQR)

PBC primary biliary cholangitis, *NAFLD* nonalcoholic fatty liver disease, *APRI* aspartate aminotransferase-to-platelet ratio index, *FIB-4* fibrosis 4 score, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transferase, *ALP* alkaline phosphatase, *DB* Direct bilirubin, *TBIL* total bilirubin, *Cr* creatinine, *TC* total cholesterol, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TG* triglyceride, *PLT*:platelet counts, *IgA* immunoglobulin A, *IgM* Immunoglobulin M

*Missing rate was 52.6%

P = 0.03; FIB-4: 0.31 [0.13–0.77], *P* = 0.04). Additionally, those who aged 60 years or old was identified as potential risk factors for liver fibrosis in PBC patients (3.10 [1.57–6.12], *P* < 0.01) (Table 4).

The GLOBE score identified the 3-, 5-, 10-, and 15-year liver transplant-free survival rates of patients with PBC and NAFLD were 89.4%, 81.9%, 58.3%, and 38.0% respectively, and significantly higher than those observed in patients with only PBC (all *P* < 0.05) (Fig. 3).

Discussion

This retrospective study investigated the prevalence of NAFLD in PBC patients and examined its association with biochemical response, liver fibrosis, and mortality risk. In this study, the prevalence of NAFLD in PBC patients was 24.0%, which aligns with the reported prevalence in the general population. Patients with both PBC and NAFLD did not exhibit differences in biochemical response after one year of UDCA treatment compared to those with only PBC. However, the combination of PBC with NAFLD seemed to protect against hepatic fibrosis. Moreover, the study found a decreased risk of death among PBC patients with NAFLD.

The clinical and histological coexistence of NAFLD and PBC has recently been reported, potentially reflecting the global rise in NAFLD prevalence, which now approaches 30% [12]. Research has indicated that dyslipidemia in PBC patients may be due to the body's protective response, mitigating the detergent effect of bile acids on blood corpuscles and vascular endothelial cell membranes [22]. Additionally, bile acids are closely associated with lipid metabolism, and cholestasis in PBC patients can disrupt this process, leading to excessive liver fat accumulation [23]. Therefore, PBC patients are at high risk of steatosis. Hindi et al. observed NAFLD in over 50% of PBC patients in a small retrospective study [10]. In our study, 24% of PBC patients had NAFLD, which is lower than previous reports, potentially due to the patient group being older and, therefore, probably sicker than other cohorts reported in the literature.

The current study evaluated the impact of NAFLD on the biochemical response after one year of UDCA treatment in PBC patients according to the Paris I and II criteria. Consistent with previous studies, our study indicates that concurrent NAFLD does not affect PBC activity [12]. We conducted further subgroup analysis, exploring three relevant factors that also revealed no significant differences. According to the Paris I and II criteria, ALP, AST, and TBIL are established prognostic indicators for PBC [16, 17]. However, in NAFLD patients, ALT and AST are the primary abnormal biochemical markers suggesting chronic liver damage, while TBIL and ALP remain stable [15]. Huang's review on incomplete responses to UDCA also indicated that NAFLD does not significantly

Table 2 Subgroup analysis of biochemical response rate after one year of UDCA treatment among patients with PBC alone and those with PBC/NAFLD ($n=363$)

Subgroup		Paris I treatment response rate (*n*,%)		*P*-value	Paris II treatment response rate (*n*,%)		*P*-value
		Poor	Better		Poor	Better	
Gender							
Female	PBC	93 (38.6)	148 (61.4)	0.21	106 (44.0)	135 (56.0)	0.30
	PBC & NAFLD	23 (30.7)	53 (69.3)		28 (37.3)	47 (62.7)	
Male	PBC	10 (28.6)	25 (71.4)	0.29	11 (31.4)	24 (68.6)	0.31
	PBC & NAFLD	6 (50.0)	6 (50.0)		6 (50.0)	6 (50.0)	
Age (years)							
< 50	PBC	41 (32.8)	84 (67.2)	0.91	51 (40.8)	74 (59.2)	0.42
	PBC & NAFLD	15 (31.9)	32 (68.1)		16 (34.0)	31 (66.0)	
≥ 50	PBC	62 (41.1)	89 (58.9)	0.50	66 (43.7)	85 (56.3)	0.88
	PBC & NAFLD	14 (35.0)	26 (65.0)		18 (45.0)	22 (55.0)	
History of liver cirrhosis							
Yes	PBC	25 (21.9)	89 (78.1)	0.57	33 (28.9)	81 (71.1)	0.70
	PBC & NAFLD	13 (26.0)	37 (74.0)		16 (32.0)	34 (68.0)	
No	PBC	78 (48.1)	84 (51.9)	0.59	84 (51.9)	78 (48.1)	0.73
	PBC & NAFLD	16 (47.2)	21 (56.8)		18 (48.6)	21 (51.4)	

Categorical values are shown as n (%)

PBC primary biliary cholangitis, *NAFLD* nonalcoholic fatty liver disease

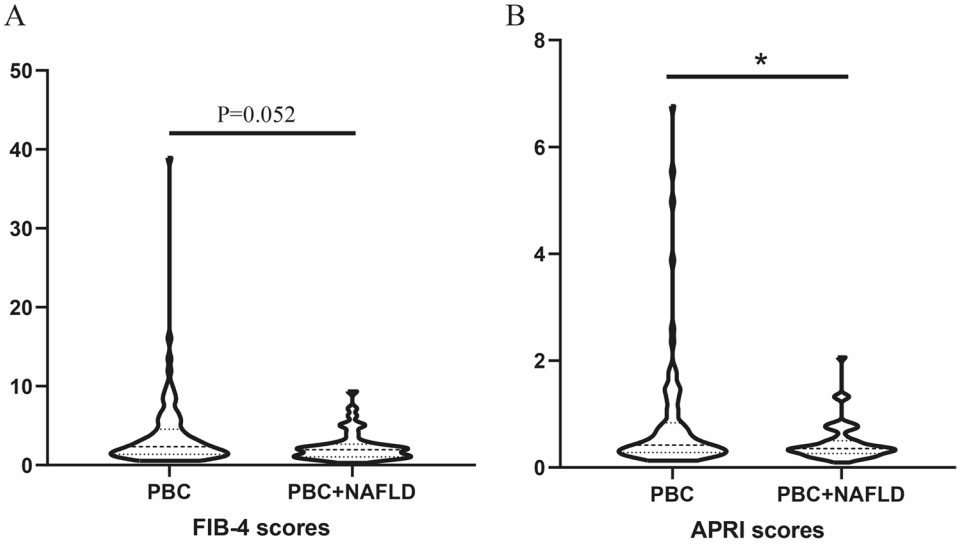

Fig. 1 The degree of liver fibrosis of PBC patients with and without NAFLD. **A** The FIB-4 scores of PBC patients with and without NAFLD. **B** The APRI scores of PBC patients with and without NAFLD. PBC: primary biliary cholangitis. NAFLD: nonalcoholic fatty liver disease. FIB-4: fibrosis 4 score. APRI: aspartate aminotransferase-to-platelet ratio index

affect PBC treatment outcomes [2]. In a previous study, liver samples of PBC patients with differing responses to UDCA were analyzed for underlying mechanisms, revealing that the poor responses of UDCA may be related to T cell activation and apoptosis causing ongoing bile-duct damage [24]. Various studies have shown that hepatocytes are the primary target for NAFLD, but not bile duct cells due to lipid accumulation [25]. Thus, while PBC and NAFLD together cause additional liver damage, they likely do not fully overlap with bile duct injuries, which may explain why NAFLD does not influence UDCA response in PBC.

Liver biopsy remains the gold standard method for evaluating the liver fibrosis stage. Unfortunately, we were unable to perform biopsies due to a lack of samples; hence, alternative noninvasive liver fibrosis assessment methods were utilized. Specifically, we employed FIB-4 and APRI concurrently, yielding relatively consistent results. Although various studies have demonstrated that hepatic steatosis decelerates liver fibrosis progression in other liver diseases such as HBV, its effect on fibrosis progression in PBC patients remains unclear (8).

Our analyses revealed a significant difference in APRI and FIB-4 scores after one year of UDCA treatment

Table 3 Subgroup analysis of APRI and FIB 4 score after one year of UDCA treatment among patients with PBC alone and those with PBC/NAFLD ($n = 182$)

Subgroup		APRI	*P*-value	FIB-4 score	*P*-value
Gender					
Female	PBC	0.5 (0.3, 1.0)	0.06	2.6 (1.4, 5.0)	0.06
	PBC & NAFLD	0.4 (0.3, 0.5)		2.1 (1.3, 2.7)	
Male	PBC	0.4 (0.3, 0.6)	0.06	2.4 (1.7, 3.1)	0.01*
	PBC & NAFLD	0.3 (0.2, 0.3)		1.0 (0.7, 1.2)	
Age (years)					
< 60	PBC	0.4 (0.3, 1.0)	0.08	1.5 (1.0, 3.4)	0.04*
	PBC & NAFLD	0.3 (0.3, 0.4)		1.2 (0.9, 2.0)	
≥ 60	PBC	0.5 (0.3, 0.9)	0.23	3.2 (2.2, 6.2)	0.17
	PBC & NAFLD	0.4 (0.3, 0.7)		2.3 (1.9, 4.6)	
History of liver cirrhosis					
Yes	PBC	0.6 (0.3, 1.3)	0.02*	3.4 (1.9, 6.2)	<0.01*
	PBC & NAFLD	0.4 (0.3, 0.7)		2.2 (1.2, 2.7)	
No	PBC	0.3 (0.2, 0.5)	0.93	1.4 (1.1, 2.1)	0.70
	PBC & NAFLD	0.3 (0.2, 0.4)		1.6 (1.1, 2.2)	

Continuous data are expressed as median (interquartile range, IQR)

PBC primary biliary cholangitis, *NAFLD* nonalcoholic fatty liver disease, *APRI* aspartate aminotransferase-to-platelet ratio index, *FIB-4* fibrosis 4 score

among PBC patients with and without NAFLD. PBC patients exhibited more significant liver fibrosis than those with PBC/NAFLD; however, conflicting conclusions have arisen from another study, indicating that concomitant NAFLD exacerbates liver fibrosis based on a small cohort study of 49 PBC patients. The inconsistency in results may be partly attributable to the small sample size and demographic differences. Notably, the findings primarily focused on NASH rather than simple steatosis, highlighting an important distinction between outcomes in PBC/NAFLD and PBC/NASH cases (9). In another retrospective study, 168 PBC patients and 68 PBC/NAFLD patients were enrolled. The researchers similarly used APRI and FIB-4 to estimate liver fibrosis. Although no statistically significant changes were observed, the authors noted a notable proportion of only PBC patients transitioning to higher FIB-4 and APRI scores compared to those with PBC/NAFLD (11). In other chronic liver diseases, some studies have reported that the combination of hepatitis B and NAFLD may reduce the degree of fibrosis by influencing HBV DNA levels [26]. However, there is a paucity of research on the mechanism by which PBC combined with NAFLD affects fibrosis. According to some reports in the literature, the possible reason is that there are differences in inflammatory cells and cytokine profiles between only PBC and PBC/NAFLD, liver Treg cells in PBC patients are decreased, and the recruitment of liver Treg cells in MAFLD is increased, which can restore immunity, and Treg tends to balance in PBC with liver fatty changes [27, 28]. Besides, insulin resistance and FXR receptor are involved in the process of bile acid metabolism, which may play a role in improving fibrosis, but the specific mechanism is not very clear and still needs further research in the future [29]. This

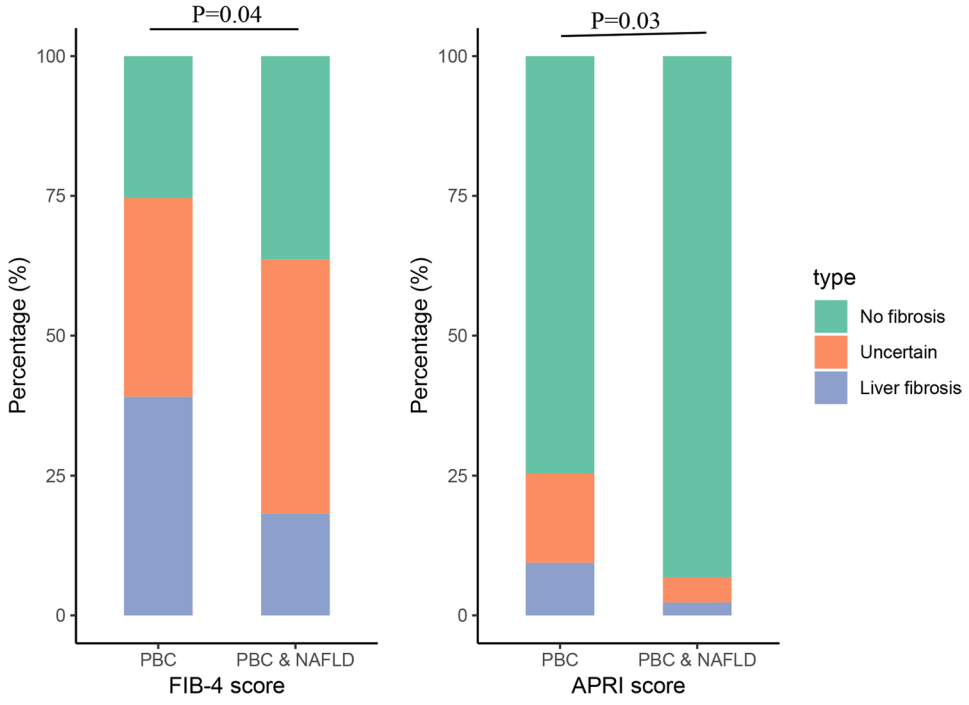

Fig. 2 Liver fibrosis stage classification in PBC and PBC with NAFLD patients using APRI and FIB-4 scores. **A** Classification of fibrosis stages by APRI in PBC and PBC/NAFLD patients. **B** Classification of fibrosis stages by FIB-4 in PBC and PBC/NAFLD patients. PBC: primary biliary cholangitis. NAFLD: nonalcoholic fatty liver disease. FIB-4: fibrosis 4 score. APRI: aspartate aminotransferase-to-platelet ratio index

Table 4 The effect of NAFLD on liver fibrosis in PBC patients when adjusting for the related factors ($n = 182$)

Characteristics	Liver fibrosis according to APRI			Liver fibrosis according to FIB 4 score		
	n,%	Adjusted OR [95% CI]	*P*-value	*n*,%	Adjusted OR [95% CI]	*P*-value
Gender						
Male	19(12.2)	Ref		57(36.5)	Ref	
Female	1(3.8)	0.29(0.04, 2.37)	0.25	5(19.2)	0.42(0.14, 1.24)	0.12
Age (years)						
< 60	12(14.1)	Ref		18(21.2)	Ref	
≥ 60	8(8.2)	0.43(0.15,1.17)	0.10	44(45.4)	3.10(1.57,6.12)	< 0.01
Hypertension	7(16.7)	2.55(0.77,8.42)	0.13	17(40.5)	1.39(0.59,3.28)	0.45
Diabetes	2(10.0)	0.51(0.08,3.29)	0.48	9(45.0)	1.80(0.60,5.38)	0.29
Coronary heart disease	3(25.0)	2.43(0.47,12.69)	0.30	6(50.0)	1.55(0.41,5.89)	0.52
Disease status						
PBC	19(13.8)	Ref		54(39.1)	Ref	
PBC & NAFLD	1(2.3)	0.11 (0.01,0.93)	0.04	8(18.2)	0.31 (0.13,0.77)	0.03

Categorical values are shown as n (%)

PBC primary biliary cholangitis, *NAFLD* nonalcoholic fatty liver disease, *APRI* aspartate aminotransferase-to-platelet ratio index, *FIB-4* fibrosis 4 score, *OR* odds ratio, *CI* confidence interval

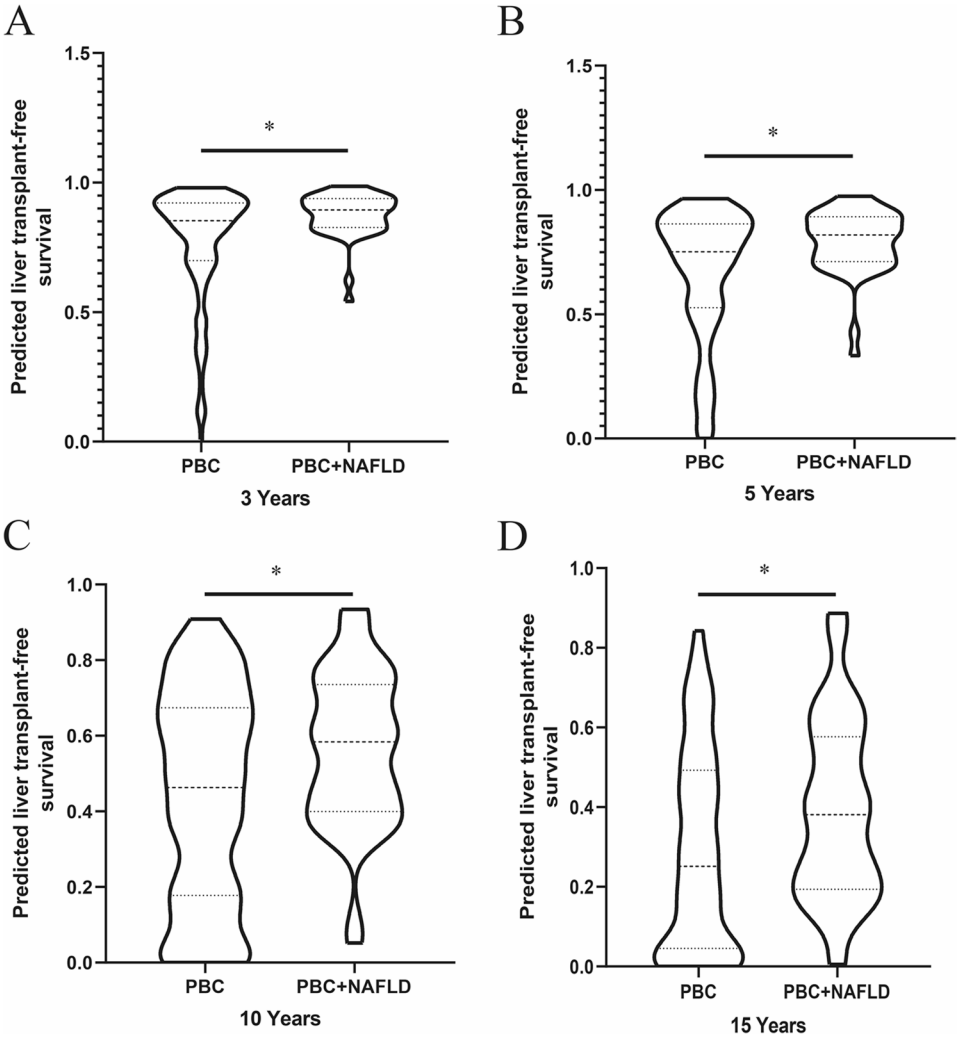

Fig. 3 The liver transplant-free survival rates of PBC patients with and without NAFLD according to the GLOBE score. **A** The 3-year liver transplant-free survival rates of PBC patients with and without NAFLD. **B** The 5-year liver transplant-free survival rates of PBC patients with and without NAFLD. **C** The 10-year liver transplant-free survival rates of PBC patients with and without NAFLD. **D** The 15-year liver transplant-free survival rates of PBC patients with and without NAFLD. PBC: primary biliary cholangitis. NAFLD: nonalcoholic fatty liver disease

underscores the need for further investigation using larger liver biopsy samples to validate current findings.

Moreover, we investigated the effect of NAFLD on mortality risk among PBC patients. We assessed GLOBE scores due to the relatively few events (deaths) during the study period. Our analysis demonstrated that PBC coexisting with NAFLD reduced transplant-free survival rates, contrary to common expectations. PBC/NAFLD patients may exhibit a survival benefit, as evidenced by our prior analysis showing lower degrees of liver fibrosis compared to only PBC patients. In a study by Daniel et al., a retrospective observational study involving 68 PBC/NAFLD patients and 136 NAFLD alone patients found that PBC does not adversely affect the severity or course of NAFLD [30]. Furthermore, UDCA is the cornerstone of PBC treatment and may have beneficial effects on NAFLD patients. Literature suggests that UDCA could potentially prevent NAFLD progression due to its anti-apoptotic properties [31]. High-dose UDCA has also shown promise in improving aminotransferase levels, serum fibrosis markers, and selected metabolic parameters in NASH patients [32]. Additionally, lifestyle modifications may also positively impact prognosis in PBC/NAFLD patients.

Our data suggest that PBC patients with NAFLD may constitute a distinct clinical subgroup characterized by milder fibrotic progression and more favorable long-term outcomes. The underlying mechanisms remain unclear and warrant further investigation to optimize patient management. Nevertheless, the study has several limitations. First, as a retrospective single-center observational study with a relatively small sample size, potential selection bias may exist since we only included hospital-based patients with complete clinical records, potentially excluding those with milder disease who did not seek hospital care. Additionally, the retrospective design precludes establishing definitive temporal relationships between NAFLD development and fibrosis progression in PBC patients. Second, NAFLD diagnosis relied on ultrasound findings, which have lower sensitivity for mild steatosis compared to magnetic resonance imaging-proton density fat fraction (MRI-PDFF) or liver biopsy, and we lacked liver stiffness measurements to further characterize hepatic steatosis or fibrosis. Future prospective studies incorporating more sensitive imaging modalities and standardized clinical assessments are warranted to validate our findings. Third, liver fibrosis was assessed using APRI and FIB-4 scores without histological confirmation due to the absence of liver biopsy data. Finally, mortality risk was estimated using GLOBE score-derived equations rather than actual outcomes, which was necessary given the small number of deceased patients in our cohort.

Conclusions

In conclusion, patients with concurrent PBC and NAFLD do not impact the biochemical response but may improve the degree of liver fibrosis and long-term prognosis. Additional research is needed to elucidate this counter-intuitive finding.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04145-x.

Supplementary Material 1.

Acknowledgements
No applicable.

Authors' contributions
RH and XW supervised and conceived the project. WR, ZW, XL, DM, QJ, JW and JF designed and carried out most of the experiments. HR conducted experiment instruction. All authors reviewed the manuscript.

Funding
This research was funded by the National Natural Science Foundation of China (NSFC) (82300660 XW), Beijing Natural Science Foundation (7232195 XW), Peking University People's Hospital Scientific Research Development Funds (RDJ2022-21 RH, RDJP2022-60 XW) and Peking University Hepatology Institute Qi-Min Project (RH and XW).

Data availability
The dataset used and analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol adhered to the ethical guidelines of the latest version of the Declaration of Helsinki (2024), and was approved by the Medical Ethics Committee of Peking University People's Hospital (Approval No. 2022PHB231-001). The requirement of informed consent was waived by the Medical Ethics Committee of Peking University People's Hospital due to the retrospective nature of the study.

Consent for publication
No applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Clinical Epidemiology, Peking University People's Hospital, No.11 Xizhimen South Street, Beijing 100044, China
[2]Peking University Hepatology Institute, Peking University People's Hospital, No.11 Xizhimen South Street, Beijing 100044, China
[3]Department of Nephrology, Peking University People's Hospital, Peking University People's Hospital, Bei-jing 10044, China
[4]Department of Gastroenterology, Huaihe Hospital of Henan University, No.115 Ximen Avenue, Kaifeng 475000, China
[5]Department of Marketing, School of Business, Renmin University of China, No. 59 Zhongguancun Avenue, Beijing 100871, China

Received: 29 September 2024 / Accepted: 8 July 2025
Published online: 30 July 2025

References

1. Lu M, Zhou Y, Haller IV, Romanelli RJ, VanWormer JJ, Rodriguez CV, Anderson H, Boscarino JA, Schmidt MA, Daida YG, et al. Increasing prevalence of primary biliary cholangitis and reduced mortality with treatment. Clin Gastroenterol Hepatol. 2018;16(8):1342–e13501341.
2. Huang LX, Wang ZL, Jin R, Chen HS, Feng B. Incomplete response to ursodeoxycholic acid in primary biliary cholangitis: criteria, epidemiology, and possible mechanisms. Expert Rev Gastroenterol Hepatol. 2022;16(11–12):1065–78.
3. Jeong SH. Current epidemiology and clinical characteristics of autoimmune liver diseases in South Korea. Clin Mol Hepatol. 2018;24(1):10–9.
4. Shen ZX, Wu DD, Xia J, Wang XB, Zheng X, Huang Y, Li BL, Meng ZJ, Gao YH, Qian ZP, et al. Prevalence and clinical characteristics of autoimmune liver disease in hospitalized patients with cirrhosis and acute decompensation in China. World J Gastroenterol. 2022;28(31):4417–30.
5. Khanna A, Leighton J, Lee Wong L, Jones DE. Symptoms of PBC - Pathophysiology and management. Best Pract Res Clin Gastroenterol. 2018;34–35:41–7.
6. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77(4):1335–47.
7. Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liu CH, Liao SH, Hong CM, Lan TY, Yang HC, et al. Metabolic Dysfunction-Associated steatotic liver disease facilitates hepatitis B surface antigen seroclearance and seroconversion. Clin Gastroenterol Hepatol. 2024;22(3):581–e590586.
8. Yao R, Lu S, Xue R, Wang J, Qiu Y, Chen Y, Liu J, Zhu L, Zhan J, Jiang S, et al. NAFLD is associated with less severe liver fibrosis in chronic hepatitis B: a multi-center, retrospective study. Ann Hepatol. 2024;29(1): 101155.
9. Hong S, Hao Y, Sun L, Li P, Yang J, Zhang F, He L, Zhang J, Wei H. Prevalence and risk factors of significant fibrosis in chronic hepatitis B patients with concurrent metabolic dysfunction-associated steatotic liver disease. Ann Hepatol. 2024;30(2):101589.
10. Híndi M, Levy C, Couto CA, Bejarano P, Mendes F. Primary biliary cirrhosis is more severe in overweight patients. J Clin Gastroenterol. 2013;47(3):e28–32.
11. Zhang Y, Hu X, Chang J, Chen J, Han X, Zhang T, Shen J, Shang N, Han J, Wang H, et al. The liver steatosis severity and lipid characteristics in primary biliary cholangitis. BMC Gastroenterol. 2021;21(1):395.
12. Minuk GY, Iliant V, Zhou N, Kaita KD, Wong SG, Peretz D, Uhanova J. Concomitant nonalcoholic fatty liver disease does not alter the activity, severity or course of primary biliary cholangitis. Liver Int. 2018;38(6):1110–6.
13. Wong GL, Chan HL, Yu Z, Chan AW, Choi PC, Chim AM, Chan HY, Tse CH, Wong VW. Coincidental metabolic syndrome increases the risk of liver fibrosis progression in patients with chronic hepatitis B–a prospective cohort study with paired transient elastography examinations. Aliment Pharmacol Ther. 2014;39(8):883–93.
14. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American association for the study of liver diseases. Hepatology. 2019;69(1):394–419.
15. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77(5):1797–835.
16. Corpechot C, Abenavoli L, Rabahi N, Chrétien Y, Andréani T, Johanet C, Chazouillères O, Poupon R. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48(3):871–7.
17. Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol. 2011;55(6):1361–7.
18. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):518–26.
19. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, Torriani MSS, Dieterich FJ, Thomas DT. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25.
20. Liver EAftSot. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis– 2021 update. J Hepatol. 2021;75(3):659–89.
21. Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, Floreani A, Ponsioen CY, Mayo MJ, Invernizzi P, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology. 2015;149(7):1804–e18121804.
22. Reshetnyak VI, Maev IV. Features of lipid metabolism disorders in primary biliary cholangitis. Biomedicines. 2022. https://doi.org/10.3390/biomedicines10123046.
23. Jia W, Li Y, Cheung KCP, Zheng X. Bile acid signaling in the regulation of whole body metabolic and immunological homeostasis. Sci China Life Sci. 2023. https://doi.org/10.1007/s11427-023-2353-0.
24. Hardie C, Green K, Jopson L, Millar B, Innes B, Pagan S, Tiniakos D, Dyson J, Haniffa M, Bigley V, et al. Early molecular stratification of high-risk primary biliary cholangitis. EBioMedicine. 2016;14:65–73.
25. Wang H, Mehal W, Nagy LE, Rotman Y. Immunological mechanisms and therapeutic targets of fatty liver diseases. Cell Mol Immunol. 2021;18(1):73–91.
26. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis b. Hepatology. 2016;63(1):261–83.
27. Rong G, Zhou Y, Xiong Y, Zhou L, Geng H, Jiang T, Zhu Y, Lu H, Zhang S, Wang P, et al. Imbalance between T helper type 17 and T regulatory cells in patients with primary biliary cirrhosis: the serum cytokine profile and peripheral cell population. Clin Exp Immunol. 2009;156(2):217–25.
28. Savage TM, Fortson KT, de Los Santos-Alexis K, Oliveras-Alsina A, Rouanne M, Rae SS, Gamarra JR, Shayya H, Kornberg A, Cavero R, et al. Amphiregulin from regulatory T cells promotes liver fibrosis and insulin resistance in non-alcoholic steatohepatitis. Immunity. 2024;57(2):303–e318306.
29. Jia W, Li Y, Cheung KCP, Zheng X. Bile acid signaling in the regulation of whole body metabolic and immunological homeostasis. Sci China Life Sci. 2024;67(5):865–78.
30. Iluz-Freundlich D, Uhanova J, Van Grubert M, Minuk GY. The impact of primary biliary cholangitis on non-alcoholic fatty liver disease. Eur J Gastroenterol Hepatol. 2021;33(4):565–70.
31. Mueller M, Castro RE, Thorell A, Marschall HU, Auer N, Herac M, Rodrigues CMP, Trauner M. Ursodeoxycholic acid: effects on hepatic unfolded protein response, apoptosis and oxidative stress in morbidly obese patients. Liver Int. 2018;38(3):523–31.
32. Ratziu V, de Ledinghen V, Oberti F, Mathurin P, Wartelle-Bladou C, Renou C, Sogni P, Maynard M, Larrey D, Serfaty L, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol. 2011;54(5):1011–9.

Publisher's Note