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ORIGINAL ARTICLE

Cumulative risk of developing a new symptom in patients with primary biliary cholangitis and its impact on prognosis

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Key words
cholangitis, propensity score, quality of life, serum albumin.

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Abstract

Background and Aim: Symptoms of primary biliary cholangitis (PBC) frequently impair one's quality of life (QOL). Nonetheless, with improved treatment, the prognosis of PBC also improves. QOL plays an important role in patients with PBC. In this study, we aimed to reevaluate the transition of new symptom development in PBC and its predictive factors.

Methods: This retrospective multicenter study enrolled 382 patients with PBC for symptom analysis. The impact of a newly developed symptom on PBC prognosis was investigated by Kaplan–Meier analysis with propensity score matching and logistic progression analysis.

Results: The cumulative risk of developing a new symptom after 10 and 20 years of follow-up was 7.6 and 28.2%, and specifically that of pruritus, which was the most common symptom, was 6.7 and 23.3%, respectively. In Cox hazard risk analysis, serum Alb level (hazard ratio [HR], 1.097; 95% confidence interval [CI], 1.033–1.165; $P = 0.002$), the serum D-Bil level (HR, 6.262; 95% CI, 2.522–15.553, $P < 0.001$), and Paris II criteria (HR, 0.435; 95% CI, 0.183–1.036; $P = 0.037$) were significant independent predictors of a new symptom. Kaplan–Meier analysis showed that the overall survival and liver-related death were not significant between patients with and without a new symptom.

Conclusion: The cumulative risk of new symptom development is roughly 30% 20 years after diagnosis and could be predicted by factors including serum albumin levels, serum D-Bil level, and Paris II criteria.

Introduction

Primary biliary cholangitis (PBC) is a disease with slowly progressing cholestasis that will lead to cirrhosis and liver failure if left untreated. PBC was formerly called primary biliary cirrhosis because many patients were diagnosed as having cirrhosis due to the lack of specific symptoms indicating PBC. Recent advances in examination include the development of an antimitochondrial antibody, which is a sensitive serological hallmark of PBC, and

its treatment approach is ursodeoxycholic acid (UDCA) therapy. Although this disease mostly affects middle-aged females, the percentage of males is gradually increasing.[1]

A Japanese study reported that from 1980 to 1998, 69.9% of patients with PBC were asymptomatic during diagnosis, and the percentage of initially symptomatic patients who had a total

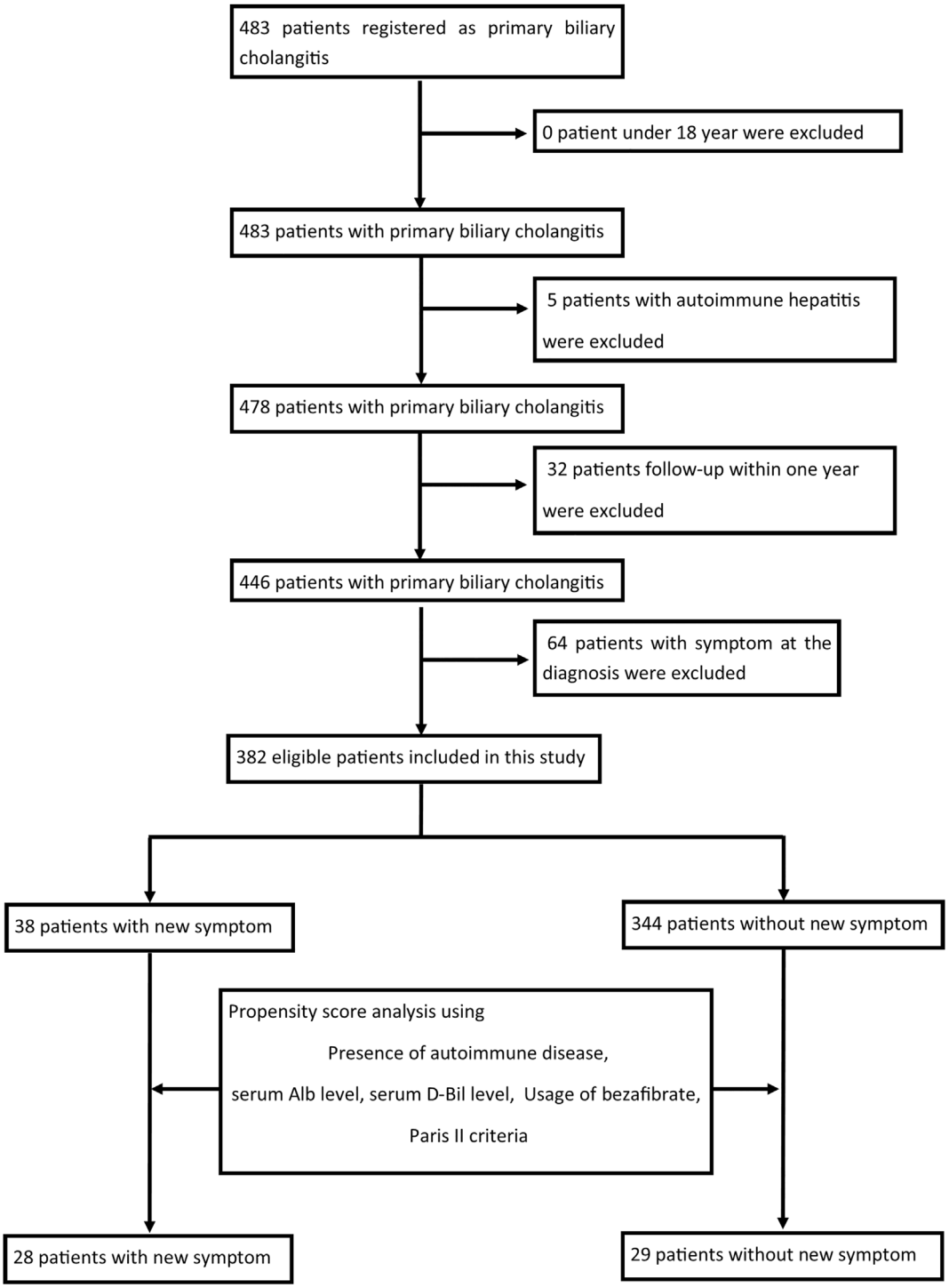


Figure 1 Strategy of this study. A total of 483 with primary biliary cholangitis were enrolled. After exclusion based on the study's criteria, 382 patients were analyzed, as reflected in Tables 1, 2, and 3 and Figure 2. These patients were reanalyzed (Fig. 3) by propensity score matching analysis using factors such as autoimmune disease occurrence, serum albumin level, serum direct bilirubin level, bezafibrate usage, and Paris II criteria, which showed significance in Table 3.

bilirubin (T-Bil) level of >3.0 mg/dL was 7.2%.[2] Previous studies showed that 61–90% of patients were asymptomatic at diagnosis and that 50–71% could develop a new symptom within 10 years of follow-up.[3,4] Among the symptoms of PBC, pruritus and fatigue are the most common, occurring in 20–70% of PBC cases.[4,5] Pruritus negatively affects one's mood, sleep quality, and social functioning.[5] Hence, the American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines recommend interventions for managing pruritus.[6,7] Given that PBC prognosis has improved due to the use of UDCA and bezafibrate, managing symptoms that can impair patient's quality of life (QOL) would be the next main target.

The disease in asymptomatic patients tends to progress considerably slower than that in symptomatic patients.[8,9] Hence, symptoms of patients with PBC may play an important role in not only QOL but also prognosis. However, a UK study showed that absolute survival is the same in all patients with PBC regardless of the symptoms.[4] These study differences may be explained by the fact that patients were diagnosed at an early stage and few patients have evidence of advanced disease at presentations.[10,11] However, no study has revealed the cumulative risk of developing a new symptom for a decade.

Therefore, the understanding of new symptom development in patients with PBC should be reexamined and measured. In this study, we aimed to assess the prevalence of newly developed symptoms in patients with PBC and the factors predicting it.

Methods

Subjects and serum samples. This retrospective multicenter analysis included all incident and prevalent alive cases of definite or probable PBC recorded between 1 January 1982, and 31 December 2014 in Niigata University Hospital and a related hospital. The original data in this study were the same as that previously reported by us.[1] The diagnosis of PBC was made based on the criteria established by the Intractable Hepato-Biliary Diseases Study Group of Japan.[12] We excluded patients aged <18 years; diagnosed with autoimmune hepatitis overlap syndrome, UDCA treatment before diagnosing PBC, and other liver diseases; manifesting initial symptom including pruritus, edema, jaundice, ascites, hepatic encephalopathy, or varices; and followed up within 12 months (Fig. 1). Fatigue was not surveyed in this study. Endoscopic examination to detect varices was performed every year.

All study participants had documented biochemical examination results including serum concentrations of total bilirubin (T-Bil), direct bilirubin (D-Bil), and albumin (Alb), prothrombin time, and serum activities of alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) when the time patients have diagnosed with PBC and after 12 months of treatment.

The presence of symptoms was determined by reviewing the medical records. Pruritus was determined by prescribing drugs including cholestyramine, nalfurafine hydrochloride, and antihistamines. Fatigue was excluded in this study because determining it from medical records was difficult. Liver-related death was defined as death associated with liver failure, hepatocellular carcinoma (HCC), and liver transplantation. All clinical records were examined to obtain records of death.

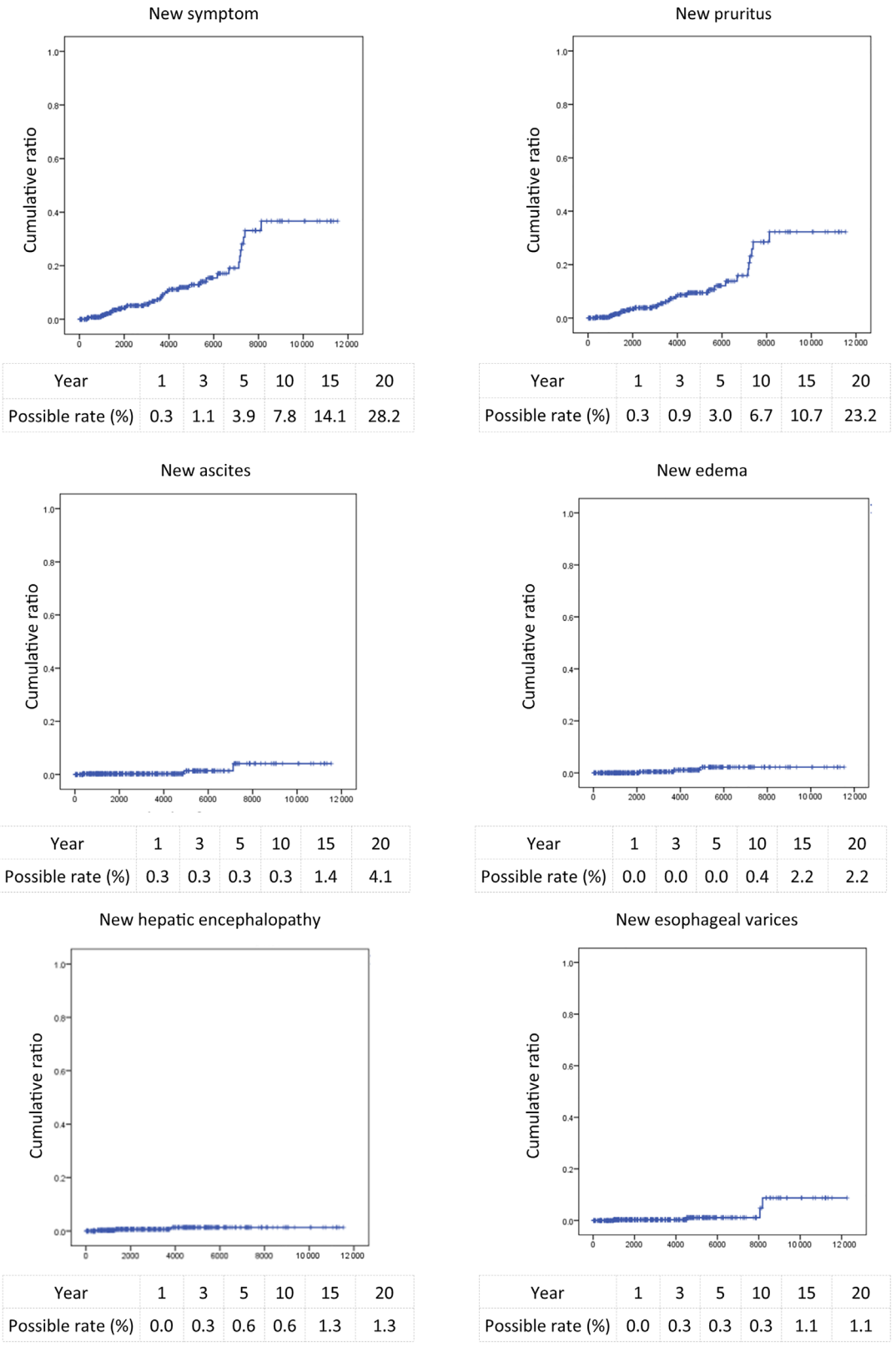
Calculations. The fibrosis-4 (FIB-4) and AST-to-platelet ratio indexes (APRI) were calculated according to previous reports.[13,14]

Generally, Paris II criteria are defined by the decrease in ALP level ≤1.5 times the normal limits, AST level ≤1.5 times the normal limit, or bilirubin level <1 mg/dL after 1 year of treatment.[15] Rotterdam criteria are calculated by the decrease in bilirubin level ≤normal limit and/or albumin level <normal limits after 1 year of treatment.[16] Rochester criteria are estimated by the decrease in ALP level ≤2 times the normal limit or Mayo score ≤4.5 after 6 months of treatment.[17] Barcelona criteria are

Table 1 The characteristics of primary biliary cholangitis patients

Parameter	$n = 382$
Age at the diagnosis (year)	59 ± 0.6
Sex (male/female)	58/324
Family history of PBC (*n*/%)	3/0.8
Presence of other autoimmune disease (*n*/%)	104/27.2
Presence of HCC (*n*/%)	2/0.5
Histology (*n*/%)	187/48.9
CNSDC (*n*/%)	117/66.9
Scheuer I, II/III, IV	146/10
Treatment	
UDCA (0/300–600 mg/over 600 mg)	55/82/245
Bezafibrate (*n*/%)	11/2.9
PSL (*n*/%)	24/6.3
Lab data	
Plt ($\times 10^4$/μL)	22.2 ± 0.4
PT %	98 ± 1.2
TP (g/dL)	7.6 ± 0.0
Alb (g/dL)	4.3 ± 0.1
AST (U/L)	39 ± 4.0
ALT (U/L)	37 ± 5.3
LDH (U/L)	214 ± 5.6
ALP (U/L)	428 ± 22.2
γ-GTP (U/L)	143 ± 16.1
T-Bil (mg/dL)	0.6 ± 0.0
D-Bil (mg/dL)	0.1 ± 0.0
BUN (mg/dL)	14.0 ± 0.2
Cre (mg/dL)	0.6 ± 0.0
IgM (mg/dL)	289 ± 14.8
Fib-4 index	1.75 ± 0.14
APRI	0.60 ± 0.13
AAR	1.04 ± 0.02
Biochemical response	
Barcelona criteria (*n*/%)	325/85.1
Paris I criteria (*n*/%)	336/87.9
Paris II criteria (*n*/%)	309/80.9
Rotterdam criteria (*n*/%)	341/89.3
Toronto criteria (*n*/%)	344/90.1
Ehime criteria (*n*/%)	339/88.7
Rochester criteria (*n*/%)	224/58.6

γ-GTP, gamma-glutamyl transpeptidase; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNSDC, chronic non-suppurative destructive cholangitis; D-Bil, direct bilirubin; HCC, hepatocellular carcinoma; IgM, immunoglobulin M; LDH, lactate dehydrogenase; Plt, platelet count; PSL, prednisolone; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; T-Bil, total bilirubin; UDCA, ursodeoxycholic acid.



Year	1	3	5	10	15	20
Possible rate (%)	0.3	1.1	3.9	7.8	14.1	28.2

Year	1	3	5	10	15	20
Possible rate (%)	0.3	0.9	3.0	6.7	10.7	23.2

Year	1	3	5	10	15	20
Possible rate (%)	0.3	0.3	0.3	0.3	1.4	4.1

Year	1	3	5	10	15	20
Possible rate (%)	0.0	0.0	0.0	0.4	2.2	2.2

Year	1	3	5	10	15	20
Possible rate (%)	0.0	0.3	0.6	0.6	1.3	1.3

Year	1	3	5	10	15	20
Possible rate (%)	0.0	0.3	0.3	0.3	1.1	1.1

Figure 2 Kaplan–Meier analysis of the cumulative ratio for newly developed symptoms. Kaplan–Meier analysis showed the individual cumulative ratios of newly developed symptoms including pruritus, jaundice, ascites, edema, encephalopathy, and varices.

Table 2 The difference of background between patients with/without new symptom

Parameter	With new symptom ($n = 38$)	Without new symptom ($n = 344$)	P value
Age at the diagnosis (year)	56 ± 1.6	59 ± 0.6	0.081
Sex (male/female)	6/32	52/292	0.816
Presence of other autoimmune disease (*n*/%)	17/44.7	87/25.3	0.011
Presence of HCC (*n*/%)	0/–	2/0.6	1.000
Histology (*n*/%)	25/65.8	162/47.1	0.222
CNSDC (*n*/%)	18/72.0	99/61.1	0.624
Scheuer I, II/III, IV	14/2	86/8	0.608
Treatment			
UDCA (0/300–600 mg/over 600 mg)	2/7/29	30/76/239	0.628
Bezafibrate (yes/no)	6/32	18/326	0.020
PSL (yes/no)	1/37	7/337	0.559
Lab data			
Plt ($\times 10^4/\mu L$)	23.3 ± 1.4	22.9 ± 0.4	0.796
PT %	105 ± 5.8	98 ± 1.2	0.251
TP (g/dL)	7.7 ± 0.1	7.6 ± 0.0	0.425
Alb (g/dL)	5.3 ± 0.9	4.2 ± 0.0	0.244
AST (U/L)	63 ± 12.7	58 ± 4.3	0.699
ALT (U/L)	68 ± 15.7	63 ± 5.6	0.759
LDH (U/L)	307 ± 21.9	255 ± 5.7	0.026
ALP (U/L)	521 ± 63.9	554 ± 23.6	0.631
γ-GTP (U/L)	273 ± 77.9	228 ± 15.9	0.575
T-Bil (mg/dL)	0.7 ± 0.1	0.7 ± 0.0	0.571
D-Bil (mg/dL)	0.2 ± 0.0	0.1 ± 0.0	0.031
BUN (mg/dL)	15 ± 0.5	15 ± 0.2	0.751
Cre (mg/dL)	0.65 ± 0.02	0.65 ± 0.01	0.781
IgM (mg/dL)	358 ± 34.9	342 ± 16.0	0.682
Fib-4 index	2.25 ± 0.35	2.26 ± 0.15	0.970
APRI	0.99 ± 0.18	1.06 ± 0.14	0.784
AAR	1.11 ± 0.07	1.11 ± 0.02	0.979
Biochemical response			
Barcelona criteria (*n*/%)	28/73.4	297/86.3	0.055
Paris I criteria (*n*/%)	32/84.2	304/488.4	0.442
Paris II criteria (*n*/%)	28/73.4	281/81.7	0.278
Rotterdam criteria (*n*/%)	35/92.1	306/88.9	0.784
Toronto criteria (*n*/%)	37/97.4	307/89.2	0.154
Ehime criteria (*n*/%)	28/73.4	311/90.4	0.006
Rochester criteria (*n*/%)	24/63.2	200/58.1	0.605

γ-GTP, gamma-glutamyl transpeptidase; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNSDC, chronic non-suppurative destructive cholangitis; D-Bil, direct bilirubin; HCC, hepatocellular carcinoma; IgM, immunoglobulin M; LDH, lactate dehydrogenase; Plt, platelet count; PSL, prednisolone; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; T-Bil, total bilirubin; UDCA, ursodeoxycholic acid.

calculated by the decrease in ALP level >40% from baseline or a normal lever after 1 year of treatment.[18] Additionally, Ehime criteria are calculated by the decrease in γ-GTP level ≤70% from baseline or a normal level after 12 months of treatment, which were originally 6 months but modified in this study.[19] Meanwhile, Toronto criteria were excluded because it needed data that should be collected 24 months after treatment.[20]

Statistical analysis. Data are expressed as median ± standard error of the mean (SEM) for quantitative data and as numbers for qualitative data. All statistical data were analyzed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Significant differences were determined by one of the following tests: *t*-test with Mann–Whitney *U* test, Wilcoxon's signed-rank test, and χ^2 test, as appropriate. The accumulation ratio of symptoms, overall survival, and liver-related death were estimated using the Kaplan–Meier method. Symptoms included pruritus, jaundice, edema, ascites, hepatic encephalopathy, and varices. The study's primary outcome was the cumulative risk of developing a new symptom during the follow-up periods. The secondary outcome was the significant predictors of the newly developed symptom in patients, determined using multivariate Cox proportional hazard models and calculated hazard ratio (HR) with 95% confidence interval (CI). The third outcome was the overall survival and liver-related death between patients with newly developed symptoms and those without symptoms after propensity score matching determined by logistic regression analysis. In addition, $P < 0.05$ was considered statistically significant.

Table 3 Logistic regression analysis of predictors for newly developed symptom

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95 % CI)	*P* value
Age at the diagnosis (year)	1.001 (0.979–1.043)	0.513		
Sex (male/female)	0.578 (0.240–1.391)	0.221		
Presence of other autoimmune disease (*n*/%)	0.543 (0.286–1.032)	0.063		
Presence of histology	0.527 (0.2531–1.099)	0.088		
Scheuer I, II *versus* III, IV	1.236 (0.289–5.274)	0.775		
Presence of HCC	20.218 (0.000–22 836)	0.925		
Lab data				
Plt ($\times 10^4/\mu L$)	0.991 (0.953–1.031)	0.662		
PT %	0.993 (0.953–1.029)	0.710		
TP (g/dL)	1.136 (0.656–1.967)	0.650		
Alb (g/dL)	1.082 (1.019–1.150)	0.011	1.097 (1.033–1.165)	0.002
AST (U/L)	1.002 (0.998–1.005)	0.400		
ALT (U/L)	1.001 (0.998–1.004)	0.567		
LDH (U/L)	1.000 (0.998–1.003)	0.852		
ALP (U/L)	1.000 (0.999–1.001)	0.920		
γ-GTP (U/L)	1.001 (1.000–1.002)	0.082		
T-Bil (mg/dL)	2.226 (0.939–5.278)	0.069		
D-Bil (mg/dL)	18.776 (3.757–93.83)	<0.001	6.262 (2.522–15.55)	<0.001
BUN (mg/dL)	1.002 (0.951–1.099)	0.548		
Cre (mg/dL)	1.164 (0.146–9.315)	0.886		
IgM (mg/dL)	0.999 (0.998–1.001)	0.374		
Fib-4 index	1.307 (0.970–1.199)	0.161		
APRI	1.038 (0.911–1.183)	0.577		
AAR	1.024 (0.418–2.509)	0.958		
Treatment				
UDCA 0 mg *versus* 300–600 mg *versus* over 600 mg	1.819 (0.939–3.526)	0.076		
Bezafibrate	1.962 (0.471–8.169)	0.355		
PSL	0.309 (0.129–0.739)	0.008		
Biochemical response				
Barcelona criteria	1.122 (0.539–2.337)	0.758		
Paris I criteria	2.392 (0.971–5.389)	0.058		
Paris II criteria	0.434 (0.208–0.906)	0.026	0.435 (0.183–1.036)	0.037
Ehime criteria	1.691 (0.814–3.509)	0.159		
Rochester criteria	0.556 (0.280–1.107)	0.095		
Rotterdam criteria	0.628 (0.209–2.230)	0.527		
Toronto criteria	0.387 (0.053–2.835)	0.350		

γ-GTP, gamma-glutamyl transpeptidase; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; D-Bil, direct bilirubin; HCC, hepatocellular carcinoma; IgM, immunoglobulin M; LDH, lactate dehydrogenase; OR, odds ratio; Plt, platelet count; PSL, prednisolone; PT, prothrombin time; T-Bil, total bilirubin; UDCA, ursodeoxycholic acid.

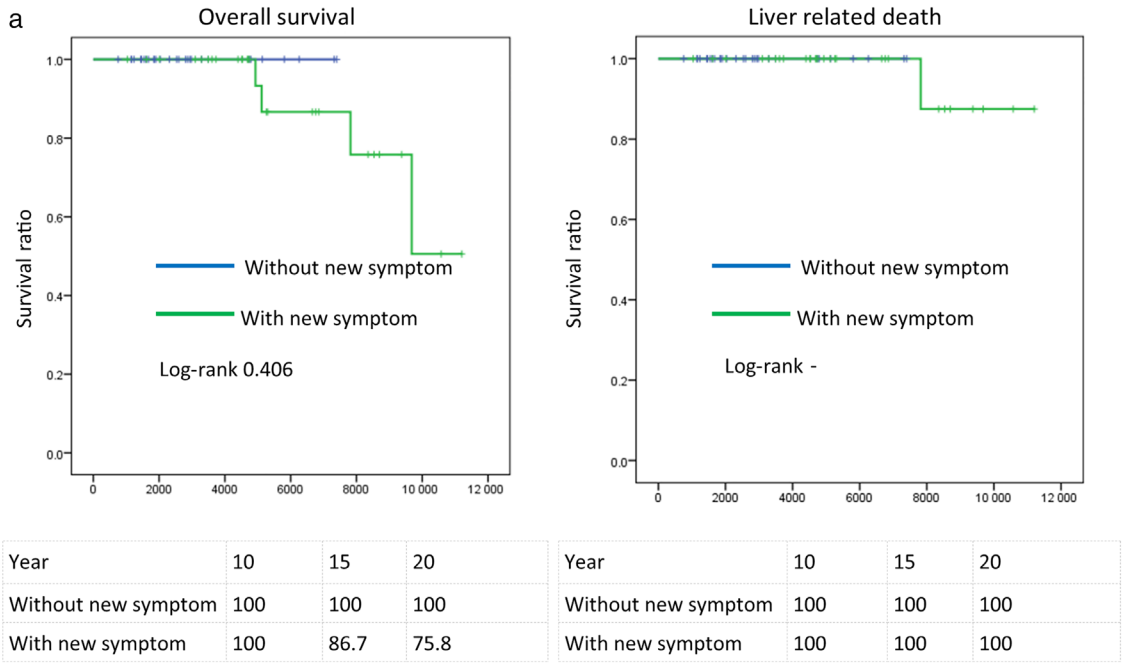
The Institutional Review Board of the University of Niigata reviewed and approved this study (approval No. 2021-0060). This work was conducted in accordance with the Declaration of Helsinki.

Results

Study population. This study included 382 patients with PBC (Table 1). At diagnosis, the median age ± SEM was 59 ± 0.6 year, and most of them were female ($n = 324$, 84.8%). The median follow-up period was 3018 ± 134 days. HCC was detected in two patients during PBC diagnosis and in two other patients during follow-up. Almost half of the patients underwent liver biopsy for diagnosis. Furthermore, 66.9% of the patients were histologically diagnosed with chronic nonsuppurative destructive cholangitis, and only 10 (6.4%) of 156 patients were in the advanced stage (Scheuer stages III and IV). Regarding treatment, 85.6, 2.9, and 6.3% of the patients were treated with UDCA, bezafibrate, and prednisolone, respectively. Prednisolone was used for treating other existing autoimmune diseases. Serum AST and ALT levels were almost at the normal limit before starting treatment. Fibrosis markers including FIB-4 index, APRI, and alanine aminotransferase ratio (AAR) were mildly increased, especially AAR, but did not reach the liver cirrhosis level. Moreover, 80% of the patients achieved a biochemical response, except for Rochester criteria.

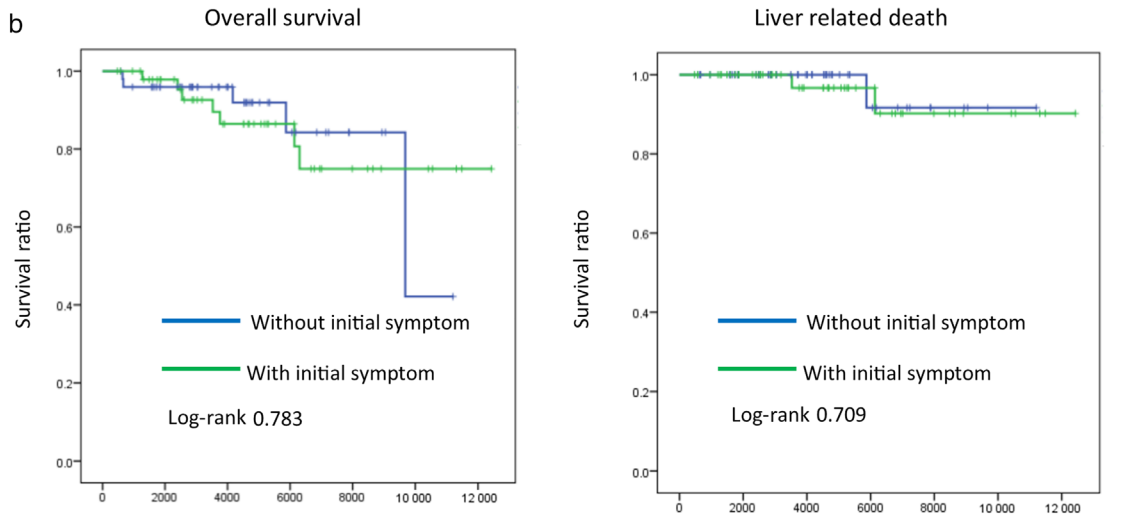
Accumulation ratio of newly developed symptoms The frequency of patients with PBC with newly

developed symptoms was analyzed by Kaplan–Meier analysis. The 1-, 3-, 5-, 10-, 15-, and 20-year probability rates of new symptom development were 0.3, 1.1, 3.9, 7.6, 14.1, and 28.2% (Fig. 2). Specifically, such rates were 0.3, 0.9, 3.0, 6.7, 10.7, and 23.2% for pruritus; 0.3, 0.3, 0.3, 0.3, 1.4, and 4.1% for ascites; 0.0, 0.0, 0.0, 0.4, 2.2, and 2.2% for edema; 0.0, 0.3, 0.6, 0.6, 1.3,



Year	10	15	20
Without new symptom	100	100	100
With new symptom	100	86.7	75.8

Year	10	15	20
Without new symptom	100	100	100
With new symptom	100	100	100



Year	10	15	20
Without initial symptom	95.9	91.9	84.3
With initial symptom	89.5	86.4	74.9

Year	10	15	20
Without initial symptom	100	100	91.7
With initial symptom	96.7	96.7	9.02

Figure 3 Kaplan–Meier analysis of survival ratio with or without new symptom. Propensity score matching analysis determined by logistic progression analysis showed no significance in both the overall survival and liver-related death between patients with and without a new symptom (a) and between patients with and without an initial symptom (b).

and 1.3% for hepatic encephalopathy, and 0.0, 0.3, 0.3, 0.3, 1.1, and 1.1% for esophageal varices. No patients developed jaundice during this period.

Therefore, pruritus was the most common new symptom. The data also suggested that only few patients who were asymptomatic during diagnosis would develop a new symptom.

We also compared the accumulation ratio of new symptoms in patients based on when they were diagnosed due to the prolonged study duration. We classified the patients into two groups: those who were diagnosed before and after 2000. Kaplan–Meier analysis showed no significance between the two groups (data not shown).

Characteristics of patients with new symptoms. Patients with PBC developing new symptoms had a significantly high rate of autoimmune disease (44.7 *vs* 25.2%, $P = 0.011$) and bezafibrate usage (15.8 *vs* 0.3%, $P = 0.020$) but a low rate of Ehime criteria (73.7 *vs* 90.1%, $P = 0.006$) compared with those without new symptoms (Table 2). Regarding laboratory data obtained during diagnosis, patients with new symptoms had significantly higher serum levels of lactate dehydrogenase (306.9 ± 21.9 *vs* 254.5 ± 5.7, $P = 0.026$) and D-Bil (0.2 ± 0.0 *vs* 0.1 ± 0.0, $P = 0.031$), but the serum levels of ALP and γ-GTP, which could reflect cholestasis, were not significant. Thus, patients with PBC who would develop new symptoms may have characteristics of a genetically strong factor for PBC,

Table 4 The difference of background between patients with/without initial symptom

Parameter	With initial symptom ($n = 66$)	Without initial symptom ($n = 374$)	*P* value
Age at the diagnosis (year)	59 ± 1.6	59 ± 0.6	1.000
Sex (male/female)	7/59	55/319	0.447
Presence of other autoimmune disease (*n*/%)	27/39	102/271	0.029
Presence of HCC (*n*/%)	2/64	5/369	0.283
Presence of varices (*n*/%)	11/55	18/356	0.001
Histology (*n*/%)	43/18	187/148	0.035
CNSDC (*n*/%)	34/12	131/62	0.426
Scheuer I, II/III, IV	3/36	22/152	0.582
Treatment			
UDCA (0/300–600 mg/over 600 mg)	10/15/41	28/78/268	0.099
Bezafibrate (yes/no)	4/62	10/364	0.139
PSL (yes/no)	3/63	21/353	1.000
Lab data			
Plt ($\times 10^4/\mu L$)	19.3 ± 0.9	22.7 ± 0.4	0.001
PT %	88 ± 2.9	99 ± 1.3	0.002
TP (g/dL)	7.7 ± 0.1	7.7 ± 0.0	0.740
Alb (g/dL)	4.1 ± 0.1	4.3 ± 0.1	0.026
AST (U/L)	67 ± 9.8	55 ± 3.3	0.222
ALT (U/L)	74 ± 17.5	57 ± 4.1	0.350
LDH (U/L)	259 ± 11.6	262 ± 5.8	0.810
ALP (U/L)	668 ± 62.4	551 ± 22.7	0.083
γ-GTP (U/L)	273 ± 33.3	233 ± 16.6	0.284
T-Bil (mg/dL)	1.5 ± 0.4	0.7 ± 0.0	0.034
D-Bil (mg/dL)	0.7 ± 0.3	0.2 ± 0.0	0.056
BUN (mg/dL)	14 ± 0.6	15 ± 0.2	0.505
Cre (mg/dL)	0.64 ± 0.03	0.65 ± 0.01	0.661
IgM (mg/dL)	450 ± 38.1	344 ± 13.9	0.011
Fib-4 index	2.69 ± 0.40	2.44 ± 0.17	0.562
APRI	1.03 ± 0.11	0.96 ± 0.08	0.606
AAR	1.12 ± 0.07	1.14 ± 0.02	0.734
Biochemical response			
Barcelona criteria (*n*/%)	54/81.8	315/84.2	0.590
Paris I criteria (*n*/%)	54/81.8	326/81.2	0.246
Paris II criteria (*n*/%)	43/65.2	302/80.7	0.009
Rotterdam criteria (*n*/%)	53/80.3	332/88.8	0.068
Toronto criteria (*n*/%)	59/89.3	334/89.3	1.000
Ehime criteria (*n*/%)	56/84.8	332/88.8	0.407
Rochester criteria (*n*/%)	34/51.5	219/58.6	0.345

γ-GTP, gamma-glutamyl transpeptidase; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNSDC, chronic non-suppurative destructive cholangitis; D-Bil, direct bilirubin; HCC, hepatocellular carcinoma; IgM, immunoglobulin M; LDH, lactate dehydrogenase; Plt, platelet count; PSL, prednisolone; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; T-Bil, total bilirubin; UDCA, ursodeoxycholic acid.

need additional treatment such as bezafibrate, but have a low response against treatment.

Factors predicting the development of a new symptom in patients with PBC. The factors predicting new symptom development in patients with PBC were investigated by Cox hazard analysis (Table 3). Univariate analysis showed that serum Alb level (HR, 1.082; 95% CI, 1.019–1.150; $P = 0.011$), serum D-Bil level (HR, 18.776; 95% CI, 3.757–93.824; $P < 0.01$), prednisolone usage (HR, 0.309; 95% CI, 0.129–0.739; $P = 0.008$), and Paris II criteria (HR, 0.434; 95% CI, 0.208–0.906; $P = 0.026$) showed significance in predicting a new symptom. In the multivariate analysis, the serum Alb level (HR, 1.097; 95% CI, 1.033–1.165; $P = 0.002$), the serum D-Bil level (HR, 6.262; 95% CI, 2.522–15.553, $P < 0.001$), and Paris II criteria (HR, 0.435; 95% CI, 0.183–1.036; $P = 0.037$) were significant independent predictors of a new symptom. Kaplan–Meier analysis showed patients with PBC with high serum D-Bil levels (cut-off value was 0.14 with Youden index) and patients without Paris II criteria had significantly higher possibilities of a new symptom (log-rank test = 0.016, and 0.022, respectively) but patients with high Alb level (cut-off value was 4.19 with Youden index) had no significance (log-rank test = 0.054) (Figure S1, Supporting information).

Significance of overall survival and liver-related death in patients with PBC developing a new symptom. The impact of a new symptom on PBC prognosis was assessed by Kaplan–Meier analysis after propensity score matching was determined by logistic regression analysis. In propensity score analysis, factors such as serum Alb level, serum D-Bil level, bezafibrate usage, and Paris II criteria, which showed significance in the abovementioned analysis, were included (Table 3). After matching, 28 patients had no new symptom, whereas 29 patients had a new symptom. Kaplan–Meier analysis showed that overall survival and liver-related death were both not significant between patients with and without a new symptom (Fig. 3a). We also analyzed the prognosis of 446 patients with and without initial symptoms using the same method. Likewise, propensity score analysis included serum Alb level, bezafibrate usage, and Paris II criteria (Table 4). Neither overall survival nor liver-related death showed significance between patients with and without initial symptoms (60 *vs* 60) (Fig. 3b).

Discussion

This study revealed the percentage of newly developed symptoms and each of the symptoms in patients with PBC in a long-term real-world setting. Factors such as serum Alb level, bezafibrate usage, and Paris II criteria could predict the development of a new symptom. In addition, having a new symptom had no significant impact on overall survival and liver-related death in these patients.

Furthermore, the probability of developing a new symptom in initially asymptomatic patients with PBC was 3.9% after 5 years and 28.2% after 20 years, and the most common symptom was pruritus, which reached 23.2% 20 years after PBC diagnosis. These results were considerably less than recent reports. A UK study showed that the rate of new symptom development in initially asymptomatic patients with PBC was 50% after 5 years and 95% after 20 years.[4] This difference may be attributed to the study design. The symptoms were determined by clinicians, resulting in a lower rate than the surveys from patients. Furthermore, fatigue, which was one of the most frequent symptoms in PBC patients, was excluded because the prevalence of that was difficult to determine from the medical record. These two factors may play an important role in making a difference in the results. In addition, the rate of liver fibrosis may also be attributed. In a previous report, histological liver cirrhosis was found in 16% of initially asymptomatic patients and 32% of initially symptomatic patients. Our study, however, showed that only 10 (6.4%) of 156 patients had an advanced stage (Scheuer stages III and IV). PBC is widely known, and unlike before, annual diagnostic examination for PBC has also been widely accepted in Japanese society for early detection and treatment, thereby making an important difference. This difference may also suggest that early diagnosis and treatment could prevent patients with PBC from developing a new symptom and maintain a good QOL.

As mentioned, this study also demonstrated that a new symptom could be predicted by serum Alb and D-Bil levels and Paris II criteria. The association of Paris II criteria could be attributed to less UDCA effectiveness and severe liver damage. Also, the high D-Bil level could reflect bile duct stagnation as a sign of advanced PBC. We consider that these factors can fairly predict a new symptom in patients suffering from PBC. A recent study also suggested that a new symptom can be predicted through laboratory examination before treatment.[21] However, the reason for how high serum Alb levels are related to the development of a new symptom in our study remains unknown. Thus, precise studies using questionnaires such as VAS and PBC-40 are required to confirm the importance of serum Alb levels. Based on these previous studies and our experience-based opinions as clinicians, we believe our results could be statistically false-positive due to the limitation of our studies, including the methods of symptoms determination.

Moreover, our study showed that patients with PBC developing new symptoms had no significant impact on overall survival and liver-related death compared with asymptomatic patients. Because the most common symptom in this study was pruritus, which may have had less influence on the prognosis, no significant difference between the two groups was observed. A recent review supported that pruritus is not associated with the degree of liver function, disease duration, or histologic severity.[5] Another study also supported our results, showing that survival in initially asymptomatic patients was not affected by the new symptom.[4] However, some studies reported that initially symptomatic patients had a poorer prognosis than initially asymptomatic patients.[8,9,22–24] The importance of a symptom on the prognosis might be different between before and after PBC diagnosis. The duration of how early to treat symptoms may be an important factor in patients' outcome. Additionally, the limitations of our study including the determination of symptoms, absence of fatigue, and the fact that a low rate of liver-related death might have comprised the difference between the results of our and previous studies. In the future, conducting a prospective multicenter study is necessary to investigate the true impact of a symptom.

Meanwhile, this study has some limitations. First, we could not calculate UDCA/kg because of the lack of weight data,

even though 85.6% of the patients were treated with UDCA and 64.2% of patients used over 600 mg/day, which may be sufficient for Japanese patients. Second, diagnosing newly developed symptoms fully depended on clinician's discretion in each facility; thus, the true prevalence rate might be higher than that in this study, considering that patients may be hesitant to discuss their symptoms with their physicians. We were supposed to use questionnaires such as VAS and PBC-40 to identify patient symptoms more precisely.

In conclusion, 30% of initially asymptomatic patients could develop a new symptom within two decades. The factors reflecting disease severity were serum Alb level, serum D-Bil level, and UDCA response, which were independent factors predicting the development of a new symptom. In addition, the prognosis (both overall survival and liver-related death) of PBC did not differ between patients with and without a new symptom. These findings may be helpful in future considerations of PBC treatment.

Patient consent statement. Patients had an opportunity to refuse joining this study by opting out.

Data availability statement. The datasets in this study are not available.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Kaplan–Meier analysis of new developed symptoms. Analysis showed patient with Paris II criteria had significantly lower rate of new developed symptoms.