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# Clinical Analysis of 75 Patients with Primary Biliary Cirrhosis

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## Abstract

**Background and aims:** Primary biliary cirrhosis is a chronic and slowly progressive cholestatic liver disease characterized by destruction of interlobular bile ducts, which if untreated, leads to fibrosis, cirrhosis and liver failure. It is more frequent among female patients and is usually diagnosed in the fifth decade of life. This study aims to determine the demographic, clinical, biochemical and serological characteristics and histological stage of patients with primary biliary cirrhosis.

**Methods:** Retrospective analysis of the adult patients diagnosed with primary biliary cirrhosis at our center from January 2005 to December 2013 was performed. Data collection included demographics, clinical features, biochemical and serological markers, and histological stage.

**Results:** 75 patients were diagnosed with primary biliary cirrhosis (mean age: 55 years, range: 19-83), of whom 92.0% were women. The most common symptoms at presentation were fatigue (40.0%), pruritus (40.0%), jaundice (28.0%) and dark urine (26.7%). 20.0% were asymptomatic at diagnosis. 48.0% of patients had cirrhosis at presentation. Positive antimitochondrial antibodies were found in 96% of cases. 34.8% of the patients were positive for antinuclear antibodies. Overlap syndromes were present in 10.6%. Liver biopsy was performed in 45.3% of the patients.

**Conclusions:** The clinical features of primary biliary cirrhosis were similar to those reported in the international literature but with a high percentage of symptomatic and cirrhotic patients at diagnosis.

**Keywords:** Primary biliary cirrhosis; Overlap syndromes; Clinical presentation; Laboratory features

**Abbreviations:** AIH: Autoimmune Hepatitis; ANA: Antinuclear Antibodies; ASMA: Anti-Smooth Muscle Antibodies; ALKM: Anti-Liver Kidney Microsomal Antibodies; pANCA: perinuclear Anti-Neutrophil Cytoplasmic Antibodies; AMA: Anti Mitochondrial Antibodies; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ-GT: Gamma-glutamyl transferase; ALP: Alkaline Phosphatase; PBC: Primary Biliary Cirrhosis; ULN: Upper Limit of Normal

## Introduction

Primary Biliary Cirrhosis (PBC) is a chronic cholestatic autoimmune liver disease characterized by the destruction of intrahepatic bile ducts and the presence of serum Anti-Mitochondrial Antibodies (AMA) [1]. The disease predominantly affects middle-aged women (with a gender distribution of female : male of about 10 : 1) [2]. The annual incidence rates range between 0.7 and 49 cases per million , while prevalence rates range between 6.7 and 402 cases per million [2]. Currently, the diagnosis of PBC is based on the presence of two out of three internationally accepted criteria: 1. Presence of Antimitochondrial Antibodies (AMA) (titer ≥ 1:40); 2. Elevation of alkaline phosphatase (ALP); 3. A compatible or diagnostic liver histology [1,3]. Half of the patients are asymptomatic at diagnosis. Fatigue and pruritus are the two symptoms of the early phase of the disease [2]. AMA is found in nearly 90-95% of patients with PBC. Positive Antinuclear Antibodies (ANA) are found in at least 1/3 of cases [1,3]. PBC and Autoimmune Hepatitis (AIH) may simultaneously coexist in some patients, designated as PBC/AIH overlap syndrome [1,3]. This study aimed to determine clinical characteristics of PBC.

## Patients and Methods

### Study population and data collections

We performed a retrospective analysis of all patients diagnosed and followed-up at our clinic with PBC from 2005 to 2013. The medical records of patients were reviewed using data at the time of first admission of each patient in our center. The following information was recorded: 1. Demographic characteristics, onset type of disease, symptoms at presentation, duration of symptoms or other evidence of liver disease, presence of concurrent autoimmune diseases. 2. Serologic and biochemical evaluation, including Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), gamma-glutamyl transferase (γ-GT), ALP, total protein, albumin, total and direct bilirubin, erythrocyte sedimentation rate, prothrombin time, platelet count, cholinesterase, total cholesterol. ANA, Anti-Smooth Muscle Antibodies (ASMA), anti-liver kidney microsomal antibodies (ALKM), perinuclear Anti-Neutrophil Cytoplasmic Antibodies (pANCA) and AMA were evaluated by indirect immunofluorescence using rodent liver, kidney, stomach tissues (Orgentec Diagnostika GmbH, Mainz, Germany). ANA detection was performed by IIF using HEp-2 cells. A titer of ≥ 1:80 for ANA and 1:20 for ASMA, ALKM, pANCA and AMA was considered to be positive. The immunofluorescence pattern of ANA was not available. 3. Abdominal ultrasound findings: liver size, spleen size and presence of ascites. 4. Findings at upper gastrointestinal endoscopy: presence of esophageal or gastric varices and/or portal hypertensive gastropathy. 5. Histological findings (if biopsy had been performed). The histological stage was classified according to Scheuer's

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classification [4]. Histological examination was performed by an independent pathologist.

The diagnosis of PBC was made if at least two of the following three criteria were fulfilled: 1. Elevated serum ALP (at least 1.5 times the ULN); 2. The presence of AMA in serum; 3. Histological findings consistent with PBC. Based on serum bilirubin and albumin values at diagnosis, the disease was classified as early (both bilirubin and albumin levels normal), moderately advanced (one parameter normal), and advanced (both parameters abnormal) [5]. Patients with PBC/AIH overlap syndrome were identified according to the criteria proposed by Chazouillères. These criteria require two of three features associated with AIH and two of three features associated with PBC [6]. The PBC criteria include 1. ALP levels at least 2x or γ-GT levels at least 5x upper limit of normal (ULN); 2. Positive AMA; 3. A liver biopsy showing florid bile duct lesion, and the AIH criteria comprise 1. ALT levels at least 5x ULN; 2. Immunoglobulin G levels at least 2x ULN or positive ASMA and 3. A liver biopsy with moderate or severe periportal or periseptal lymphocytic piecemeal necrosis.

### Statistical analysis

Descriptive statistical analysis was made. Categorical data are expressed as frequencies and percentages and continuous data as medians and ranges or mean ± SD. Statistical analysis was performed using IBM SPSS, version 21.0.

## Results

### Study population

A total of 75 patients with PBC, diagnosed and followed-up at our clinic from 2005 to 2013 were identified. All patients had been diagnosed with PBC according to accepted criteria. During the specified time period the number of annually diagnosed new cases has been stable (Figure 1).

The median age at diagnosis was 56 years (range, 19-83 years). 42.7% of patients were older than 60 years of age (Figure 2).

There was a female predominance (92.0%). Overlap syndromes were present in 8 (10.6%) patients (7 PBC with AIH and 1 PBC with primary sclerosing cholangitis). Patient's characteristics are described in Table 1.

### Clinical presentation

15 of 72 patients (20.8%) were asymptomatic at initial presentation (identified due to abnormal liver function tests). At diagnosis, 36 patients (48.0%) had cirrhosis and 15 (20.8%) had clinical decompensation (ascites, variceal hemorrhage or hepatic encephalopathy). According to Child-Pugh's classification, patients were grouped as follows: 13 (38.2%) in stage A, 10 (29.4%) in B and 11 (32.4%) in C.

The most common symptoms and signs at presentation were as follows: fatigue (40.0%), pruritus (40.0%), jaundice (28.0%), dark urine (26.7%), right upper side pain and discomfort (25.3%), abdominal distension (16.0%), weight loss (16.0%), loss of appetite (13.3%), nausea (10.7%), edema (9.3%), abdominal discomfort (8.0%), arthralgia (5.3%), upper GI bleeding (2.7%) and fever (1.3%) (Table 2).

There was a median delay of 6 months (range 0-243) from the first biochemical abnormalities or symptoms to the diagnosis of PBC. Patients were followed up for a median of 24 (0-185) months. The most common complications during the follow-up period are listed in Table 3.

### Associated autoimmune diseases

9 (12.0%) were diagnosed with concurrent extrahepatic autoimmune diseases. Among the 9 patients, autoimmune thyroiditis was the most common disorder - 5 patients. Rheumatoid arthritis was present in 3 patients, Grave's disease in 1 and ulcerative colitis in 1 and vitilligo in 1.

### Biochemical and serological characteristics of PBC

51 (68.0%) patients had dominant cholestatic pattern [ALT or AST / ALP ratio<1 (both xULN)] and 24 (32.0%) patients had dominant cytolytic pattern [ALT or AST / ALP ratio>1 (both xULN)]. AMA, ANA, ASMA, ALKM and pANCA were positive in 96.0%, 44.8%, 24.6%, 11.6% and 6.7% of patients respectively at some point during the course of their disease. Further serological and biochemical data are shown in Table 4.

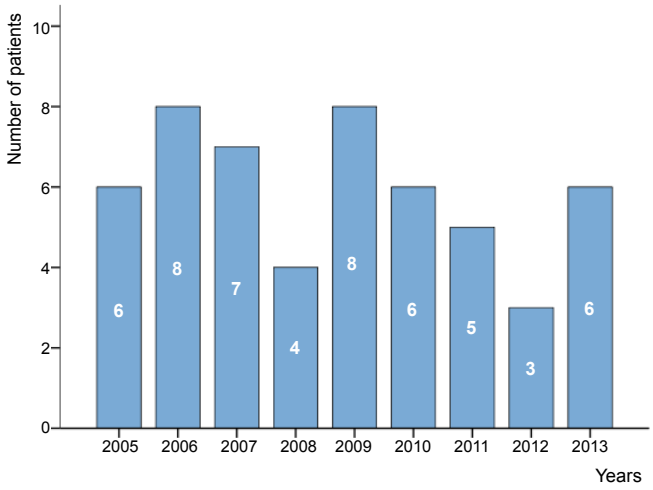


**Figure 1:** Distribution of annual number of newly diagnosed PBC cases, 2005-2013.

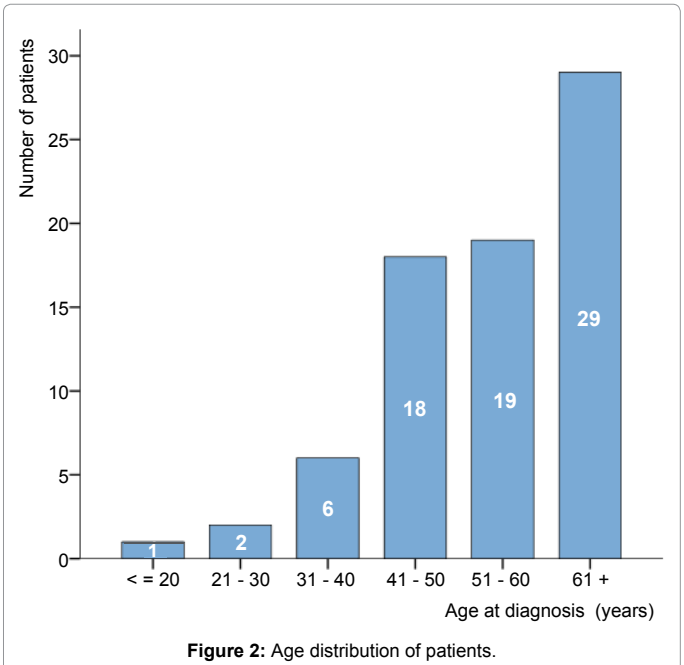


**Figure 2:** Age distribution of patients.

| Characteristics | Result |
|---|---|
| Age at diagnosis (y)<br>Age < 60, n (%)<br>Age ≥ 60, n (%) | 56.0 (19.0 – 83.0)<br>43 (57.3)<br>32 (42.7) |
| Gender<br>Male, n (%)<br>Female, n (%)<br>M : F ratio | <br>6 (8.0)<br>69 (92.0)<br>1 : 11.5 |
| Body Mass Index (kg/m$^2$), mean ± SD | 24.7 (19.0 - 36.4) |
| Mean observation period (months) | 24.0 (0-185) |
| Asymptomatic \ Symptomatic * | 18 (24) \ 57 (76) |
| Prognostic class, n (%)<br>Early PBC<br>Moderately advanced PBC<br>Advanced PBC<br>Not available | <br>16 (21.3)<br>26 (34.7)<br>23 (30.7)<br>10 (13.3) |
| Cirrhosis at presentation, n (%) | 36 (48.0) |
| Clinical decompensation at presentation, n (%)** | 15/72 (20.8) |
| Child-Pugh score<br>A, n (%)<br>B, n (%)<br>C, n (%)<br>Not available, n (%) | <br>13 (36.1)<br>10 (27.8)<br>11 (30.5)<br>2 |
| Oesophageal varices (EV), n (%)***<br>I-II<br>III-IV | 21/35 (60.0)<br>13 (61.9)<br>6 (19.3) |
| Histological stage at diagnosis<br>Early I-II, n (%)<br>Advanced III-IV, n (%) | <br>10/23 (43.5)<br>13/23 (56.5) |
| Splenomegaly, n (%) | 33 (44.0) |
| Hepatomegaly, n (%) | 40 (53.3) |
| Associated autoimmune diseases, n (%) | 9 (12.0) |
| Time to diagnosis, months | 6.0 (0-243) |
| Overlap syndrome, n (%) | 8 (10.6) |

Data are presented as number and frequency for categorical data, or as median and interquartile range for continuous data.
*Disease-related symptoms include pruritus, jaundice, bleeding varices, severe general fatigue, and ascites
**In three patient information regarding the mode of presentation was not available
***Two patients did not have their varices classified

**Table 1:** Baseline characteristics of patients (N=75).

| Symptoms | n (%) |
|---|---|
| Symptoms and signs at presentation | |
| Fatigue | 30 (40.0) |
| Pruritus | 30 (40.0) |
| Jaundice | 21 (28.0) |
| Dark urine | 20 (26.7) |
| Right upper side pain and discomfort | 19 (25.3) |
| Abdominal distension | 12 (16.0) |
| Weight loss | 12 (16.0) |
| Loss of appetite | 10 (13.3) |
| Nausea | 8 (10.7) |
| Edema | 7 (9.3) |
| Abdominal discomfort | 6 (8.0) |
| Arthralgia | 4 (5.3) |
| Upper GI bleeding | 2 (2.7) |
| Fever | 1 (1.3) |
| Asymptomatic | 15 (20.8) |

**Table 2:** Clinical symptoms and signs at presentation.

## Ultrasound

Abdominal ultrasound examination was performed in all patients. Splenomegaly was found in 33 patients (44.0%), hepatomegaly in 40 patients (53.3%) and ascites in 12 (16.0%).

## Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed before the start of treatment in 35 patients (46.7%) – esophageal varices were observed in 21 (60.0%) of them and 11/27 (40.7%) had portal hypertensive gastropathy. 5 patients had grade I EV, 8 had grade II EV, 4 had grade 3 EV and 2 had grade IV EV.

## Histological findings

Of the patient cohort 34 (45.3%) had a liver biopsy at the time of the PBC diagnosis. The remaining 41 PBC patients did not undergo percutaneous liver biopsy because of advanced age (≥ 70, N=3), clinically overt cirrhosis (N=36), hepatic echinococcal cysts (N=1) or because they refused the procedure (N=1). In 11 cases the specimens were not available for review. Among 23 patients whose biopsies were available for review 10 (43.5%) were at stages I-II while 13 (56.5%) were at stages III-IV. Liver histology showed interface hepatitis in 5 patients with PBC and 5 patients with PBC/AIH overlap syndrome.

## Discussion

Our study of all patients with PBC confirms some of the previous findings on PBC, including the average incidence around the age of 50-60 years, the female predominance (92% female) and the frequency of overlap syndromes (10.6%) [2,3,7,8]. We here report a rare case of PBC/PSC overlap syndrome - 39-year old man with cholestatic biochemical profile. The patient had positive AMA. Liver biopsy revealed bile duct

| Complications | n (%) |
|---|---|
| Coagulant function abnormality | 24 (32.0) |
| Esophageal varices | 30 (40.0) |
| Hypoalbuminemia | 26 (34.7) |
| Hypersplenism | 27 (36.0) |
| Ascites | 23 (30.7) |
| Variceal bleeding | 9 (12.0) |
| Hepatic encephalopathy | 8 (10.7) |
| Spontaneous bacterial peritonitis | 5 (6.7) |
| Cholangiocellular carcinoma | 1 (1.3) |
| Death | 25 (33.3) |

**Table 3:** Complications of chronic liver disease in the PBC cohort (n=75).

| Parameter | Result |
|---|---|
| Biochemical and hematological values<br>AST (IU/L )<br>ALT (IU/L )<br>γ-GTP (IU/L )<br>Alkaline phosphatase (IU/L )<br>Total bilirubin (μmol/l)<br>Direct bilirubin (μmol/l)<br>Total protein (g/l)<br>Albumin (g/L)<br>Erythrocyte sedimentation rate (mm/hr)<br>Platelet count (×10$^9$)<br>Prothrombin time (%)<br>Creatinine (μmol/l)<br>Total cholesterol (mmol/l)<br>Cholinesterase | <br>66 (16-358)<br>46 (11-704)<br>217(26-1440)<br>429 (52-5075)<br>25 (6-366)<br>20 (3-203)<br>73 (32-107)<br>34 (15-51)<br>50 (2-140)<br>188 (29-543)<br>86 (29-543)<br>68 (48-641)<br>5.8 (1.5-15.8)<br>5600 (777-17756) |
| Autoantibody profile<br>ANA positive, n (%)<br>SMA (≥1:40), n (%)<br>LKM positive, n (%)<br>pANCA, n (%)<br>AMA positive, n (%) | <br>24/69 (34.8)<br>17/69 (24.6)<br>5/43 (11.6)<br>2/30 (6.7)<br>72/75 (96.0) |

Data are presented as number and frequency for categorical data, or as median and interquartile range for continuous data

**Table 4:** Serological, biochemical and histological findings in patients with PBC.

proliferation, periductal fibrosis and loss of bile ducts. Endoscopic retrograde cholangiopancreatography demonstrated multiple bile duct strictures and irregularities. Few cases of overlapping between PBC/PSC have been described [9-11]. Auto-antibody profiles were also similar to those reported in the international literature except for a higher prevalence of anti-LKM-1 antibodies. We consider a possible misinterpretation of AMA as LKM [1-3,12]. In this study, 57 (76%) PBC patients presented symptoms (pruritus, jaundice, bleeding varices, severe general fatigue, and ascites) at diagnosis. According to previous studies 12.5-61% of patients were asymptomatic at diagnosis [7,13-18]. Comparison between these studies is difficult due to varying definitions of the symptoms of PBC (and hence asymptomatic PBC). Pruritus (40.0%), fatigue (40.0%) and jaundice (28.0%) were most common among the various manifesting symptoms. It was consistent with the studies in the other countries [8,16-18]. 12% were diagnosed with concurrent extrahepatic autoimmune diseases, which are much lower than reported in previous studies (24-61%) [16-19]. In the current cohort 21% had early PBC, 34% had moderately advanced PBC and 30% had advanced PBC which is different by that reported by Kuiper et al. in which the majority of patients (60%) had early PBC [5]. 48.0% had established cirrhosis already at PBC diagnosis. In our study 20.8% had decompensated liver cirrhosis at diagnosis, which is higher than that reported by Kim Ka et al. [14].

In summary, the clinical features of patients with PBC are consistent with those described in the literature with high percentage cirrhotic patients at diagnosis indicating that the disease has gone unrecognized for a considerable period of time prior to diagnosis.

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