Annals of Hepatology 30 (2025) 101933

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Brief report

Identifying patients with undiagnosed primary biliary cholangitis using a clinical management process

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ARTICLE INFO

Article History:
Received 7 March 2025
Accepted 19 April 2025
Available online 1 June 2025

Keywords:
Primary biliary cholangitis
Undiagnosed patients
Clinical management process

ABSTRACT

Introduction and Objectives: Early diagnosis of primary biliary cholangitis (PBC) is fundamental, as treatment with ursodeoxycholic acid (UDCA) prevents its progression. The aim of our study is to investigate undiagnosed patients in our region and to treat retrieved patients.
Patients and Methods: Analysis of databases (immunology, biochemistry and other data from their medical records) was performed between January 2019 and December 2021. PBC was diagnosed if anti-mitochondrial antibodies were positive (>1:80) and alkaline phosphatase (AP) was chronically elevated in the absence of other liver disease. Identified patients were contacted.
Results: A total of 306 patients were identified and 221 had previously been diagnosed with PBC and were undergoing treatment.
Fifty-one patients did not meet the current criteria for diagnosis and treatment at their last blood test. Six patients had died by the time the study started. Finally, we found 28 patients with a probable diagnosis of PBC who could benefit from treatment (9.6%).
We contacted all 28 patients and 16 (57.14%) of them agreed to come to our hospital for diagnosis confirmation, ultrasound and fibroscan. All of them were women, aged between 46 and 74 years (mean 61.18, SD 9.19). Laboratory analysis showed a mean AP of 144.25 (SD 71.03) and mean GGPT of 115.62 (SD 98.42). Mean bilirubin was 0.55 (SD 0.22). Fibroscan showed a mean value of 6.05 kPa. UDCA was initiated in 14 patients; two patients refused treatment.
Conclusions: The use of hospital databases enabled us to diagnose and treat 16 (57.14%) of the 28 detected patients.

1. Introduction

Primary biliary cholangitis (PBC) is an autoimmune disease characterised by damage to the epithelial cells of the intrahepatic bile duct that causes cholestasis and can lead to liver cirrhosis [1,2].

Ursodeoxycholic acid (UDCA), the first line treatment used for this disease, results in biochemical and histological improvement, with beneficial results in terms of the need for liver transplantation and mortality. Therefore, early diagnosis and treatment of this disease is of vital importance [1–4]. As it is a rare disease, suspicion of PBC is low, and there is a risk of undiagnosis of patients during care.

Early diagnosis of PBC is essential, as treatment with ursodeoxycholic acid (UDCA) prevents progression to liver cirrhosis and improves survival [1,2].

The problem of undiagnosed patients is not unique to our institution or to our healthcare system and has been studied in other populations. Similar situations have been described in our speciality for both hepatitis B and C virus infections [3].

A recent multicentre study published in Spain revealed that 14.3% of patients with PBC are lost in the health care system [3]. This has been studied in other countries, with similar results [5–10].

The aim of our study is to investigate this outcome in our region and to treat retrieved patients appropriately.

2. Patients and Methods

Analysis and crossing of databases (immunology, biochemistry and other data from patients' medical records) was performed

Abbreviation: PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; AMA, antimitochondrial antibodies; AP, alkaline phosphatase

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https://doi.org/10.1016/j.aohep.2025.101933

between January 2019 and December 2021, from a referral hospital covering 700.000 patients.

PBC was diagnosed if antimitochondrial antibodies (AMA) were positive- (>1:80)- and with a chronically elevated alkaline phosphatase (AP) in absence of other liver disease. Identified patients were contacted. Once disease was confirmed, treatment with UDCA was offered and initiated if the patient desired.

2.1. Inclusion criteria

Patients ≥ 18 years with elevated AP and positive AMA (>1:80) are included, with exclusion of other liver diseases.

2.2. Exclusion criteria

Patients not meeting the inclusion criteria.

2.3. Statistics

All statistical analyses were performed with STATA 16.1, 1985-2019 StataCorp LLC software.

Frequencies were used for categorical variables while means were used for quantitative variables.

2.4. Ethical statement

The observational study was approved (12-12-2023) by the Comité Ético de Investigación Clínica del Área Sanitaria de Gipuzkoa. Informed consent was obtained from all the patients that participated in the study.

3. Results

A total of 306 patients (14 deceased patients before the start of the study) were identified from database crossing (Fig. 1) and 221 were diagnosed with PBC or overlap syndrome and were on treatment (8 were deceased). Therefore, there were 85 possibly undiagnosed patients (Fig. 2) at the time of statistical analysis (August 2024): 51 patients did not meet current diagnostic and treatment criteria at their last blood test and 6 patients were deceased. Finally, we found 28 patients with a probable diagnosis of PBC who could benefit from treatment (9.6%).

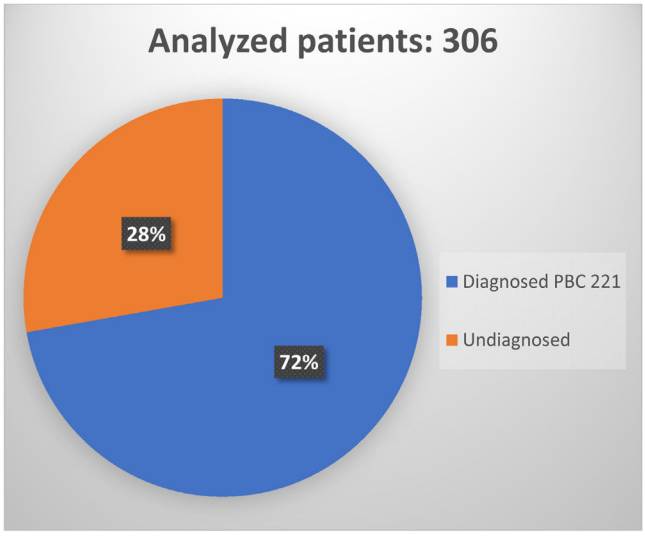

Fig. 1. Analyzed patients: diagnosed and undiagnosed PBC patients.

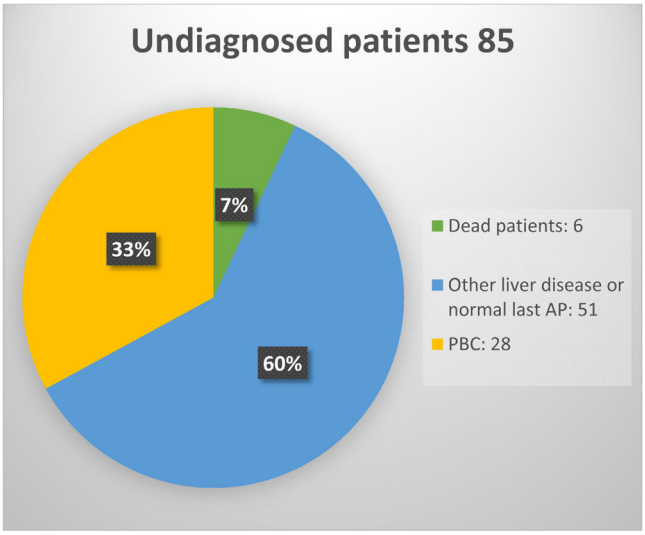

Fig. 2. Undiagnosed PBC patients.

We contacted all 28 patients and 16 (57.14%) of them agreed to come to our hepatology clinic laboratory, ultrasound and fibroscan studies and diagnosis. All of them were women (100%), aged between 46 and 74 years (mean 61.18, SD 9.19). The laboratory results revealed a mean AP (N:35-104U/L) of 144.25 (SD 71.03), a mean ALT (N:0-33U/L) of 28.12 (SD 19.10), a mean AST (N:0-31U/L) of 27.75 (SD 14.95) and a mean GGPT (N:6-42U/L) of 115.62 (SD 98.42). Mean bilirubin (N:0.0-1.1) was 0.55 (SD 0.22). All AMA were positive. IgM levels were elevated in 9 patients. Other laboratory data included: mean glucose (N:70-110 mg/dL) 102.43 (SD 11.41), mean triglycerides (N<150 mg/dL) 120.12 (SD 39.96), mean cholesterol (N<200 mg/dL) 207.5 (SD 29.95) and mean HDL cholesterol (N>50 mg/dL) 57.75 (SD 15.23).

The mean value of the body mass index of the studied patients was 27.77 (SD 3.33). Eight patients had arterial hypertension. Five patients met the criteria for metabolic syndrome.

No patient reported fatigue or pruritus. Extrahepatic manifestations of PBC were present in 7 patients (2 psoriasis, 3 rheumatoid arthritis, 2 Sjögren's syndrome). There were no cases of thyroid disease or systemic sclerosis.

Fibroscan results showed a mean value of 6.05 kPa (CAP 240.4). Ultrasound was performed in all patients and was normal in 11 and showed increased echogenicity in 5.

Treatment with UDCA was initiated in 14 patients. We explained the disease, the benefits of treatment and that UDCA is a safe drug, but 2 of them refused to start treatment.

The medical specialties that were following patients with undiagnosed PBC were as follows: general practitioners 8 patients; rheumatology 2 patients; ambulatory digestive services 4 patients; internal medicine 1 patient; dermatology 1 patient.

4. Discussion

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease with an autoimmune etiopathogenesis [1]. If not treated appropriately and early, it can eventually lead to biliary cirrhosis, which is why, until recently, the disease was known as primary biliary cirrhosis [2].

The prevalence of PBC in Spain is 20.2 per 100.000 inhabitants, according to a recent study [11], which estimated that there are at least 9.400 patients diagnosed with the disease. The estimated incidence was 2.2/100.000 of the total population [11]. As it is a rare liver disease, the suspicion of PBC is often low, so there is a risk of losing patients in the course of care [3].

The diagnosis of PBC is based on the determination of liver enzyme parameters suggestive of cholestasis (AP and GGPT) together with the presence of circulating AMA [1].

UDCA has been used for decades and has been able to achieve biochemical and histological improvements in many patients [2]. This has led to clear benefits in terms of the need for liver transplantation and mortality in these patients [1,2]. In patients in whom the target improvement is not achieved due to inadequate response to UDCA, which can be as high as 40% [4], there is the possibility of using obeticholic acid as second-line therapy, with improvements in AP, bilirubin and histology in recently published studies. Bezafibrate is also being used as a second-line off-label treatment and even triple therapy with UDCA, obeticholic acid and bezafibrate is sometimes used with encouraging results [4].

It is known that the later the diagnosis and initiation of treatment, the lower the likelihood of response, so an early diagnosis in these patients is of great importance [1,2].

Recently, the usefulness of actively searching for patients lost to the system in other pathologies, such as chronic hepatitis B and HCV [3], has been published.

A study was also carried out in PBC in 4 hospitals in Spain [3], three of them tertiary (La Paz, Madrid, HU Infanta Elena, Valdemoro, Madrid; HU Canarias, Santa Cruz de Tenerife; HU Santiago de Compostela). They reviewed immunology databases (AMA), biochemistry (AP), medication dispensing (UDCA) and medical appointments. They made the diagnosis of PBC based on AMA $\geq$ 80, chronic elevation of AP, and absence of other liver pathologies (see inclusion criteria). They found that 14.3% of patients (1 in 7) with a definitive diagnosis of PBC remained undiagnosed, thus lacking monitoring and treatment. This study was the first to focus on rescuing patients lost in the system with PBC.

In the study by Oliveira et al [3], of the 30 patients rescued from the system, 27% had fibroscan parameters indicating a worse prognosis (>9.5 kPa) [1]. Hence, the relevance of rescuing these patients in order to initiate the correct treatment and try to prevent disease progression.

In Portugal, Garrido et al [5] have retrieved 23 patients not known to the hepatology services. These patients had significantly higher stiffness compared to those followed by the hepatology services (14.3 kPa vs. 6.2 kPa) [5].

Recently, Donato et al [6], in Italy, investigated rare diseases that can be diagnosed in primary care by general practitioners, through a disease management procedure, without modifying routine clinical practice, identifying patients with undiagnosed PBC.

In the U.K., Hutchison et al [7] and Berry et al [8], and in Spain, Jofré Peralta et al [9] and Calero Gonzálvez et al [10], have published abstracts with identification of undiagnosed patients suffering PBC.

Our wish was to set up a study at the Hospital Universitario Donostia to recover the patients we have lost in the system who may suffer from PBC in order to offer them the possibility of diagnosis and treatment of their disease.

From 306 patients identified in the databases, we found 28 patients with a probable diagnosis of PBC who could benefit from treatment (9.6%).

We contacted all 28 patients and 16 (57.14%) of them agreed to come to our hospital for the study. All were women (100%), and Fibroscan results showed a mean value of 6.05 kPa (CAP 240.4), showing initial disease. Laboratory data were mean AP 144.25 and mean bilirubin 0.55. This was different from other studies, as they retrieved advanced disease cases more frequently [3,5]. Treatment with UDCA was initiated in 14 patients. Two patients refused treatment.

The origin of the undiagnosed patients was diverse, with the majority coming from primary care, but also from outpatient digestive consultations. In the latter cases, AP was usually normal and sometimes slightly elevated. The patients were asymptomatic, without fatigue or pruritus, and with slight AP elevations in the majority of the cases, which may explain the delay in diagnosis. Therefore, in the presence of mild elevations of AP, especially in women, further investigation should be considered if this is maintained over time.

5. Conclusions

In our region, up to 9.6% of patients with PBC go undetected, which hinders their follow-up and treatment. Efforts are needed to identify and locate these undiagnosed patients. The use of hospital databases is an appropriate tool and allowed us to diagnose and treat 16 (57.14%) of the 28 patients detected.

Author contributions

AC: Data Curation, Conceptualization, Writing-Review and Editing. MJSI: Data Curation, Conceptualization, Writing-Review; JS: Data Curation, Conceptualization and Review; BF: Data Curation, Conceptualization and Review; IG: Data Curation, Conceptualization and Review; AP: Data Curation, Conceptualization and Review; ST: Data Curation, Conceptualization and Review; LA: Data Curation, Conceptualization and Review, EZ: Data Curation, Conceptualization, Writing-Review and Editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interests

None.

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