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DOI: 10.17235/reed.2021.8174/2021
Link: PubMed (Epub ahead of print)

Please cite this article as:
Olveira-Martín Antonio, Yebra-Carmona Jorge, Amaral-González Carla, Tejedor Marta, Eirás Pablo, Hernández-Pérez María, Suárez-Cabredo Carolina, Spigarelli-de Rábago Isabel, Suárez-Ferrer Cristina, Morales-Arráez Dalia, Chico Inmaculada, Díaz-Flores Felicitas , Rodríguez Raquel, Llorente Silvia, Molina-Pérez Esther, Hernández-Guerra de Aguilar Manuel Nicolás. Retrieval and treatment of patients with primary biliary cholangitis who are lost in the health system. Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.8174/2021.

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OR 8174

# Retrieval and treatment of patients with primary biliary cholangitis who are lost in the health system

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Received: 24/06/2020

Accepted: 04/08/2021

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*Abbreviations: PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid; AMA: antimitochondrial antibody; ALP: alkaline phosphatase.*

*Financial support: Intercept Pharmaceuticals contributed to the translation of this manuscript into English.*

*Acknowledgments: we are grateful to Intercept Pharmaceuticals for their financial support for the manuscript translation into English.*

*Conflicts of interest: Antonio Olveira: grant, personal fees, and nonfinancial support from Intercept Pharmaceuticals. Jorge Yebra: grant, nonfinancial support from Intercept Pharmaceuticals. Manuel Nicolás Hernández-Guerra de Aguilar and Esther Molina: personal fees and nonfinancial support from Intercept Pharmaceuticals. Carla Amaral, Marta Tejedor, Pablo Eirás, María Hernández-Pérez, Carolina Suárez-Cabredo, Isabel Spigarelli, Cristina Suárez-Ferrer, Dalia Morales-Arráez, Inmaculada Chico, Felicitas Díaz-Flores, Raquel Rodríguez, and Silvia Llorente: nothing to disclose.*

**ABSTRACT**

**Introduction**: hepatitis C patients loss to follow-up in the health care system has been shown to have negative consequences. This study aimed to investigate this issue as regards primary biliary cholangitis.

**Methods**: the databases (immunology, biochemistry, clinical reports, drug dispensation, appointments) of 4 reference hospitals in Spain (serving a population of 1,450,000 inhabitants) were analyzed. The diagnosis of primary biliary cholangitis was based on an antimitochondrial antibody titer ≥ 1:80, chronically elevated alkaline phosphatase, and the absence of other liver disease. Patients were classified as lost in the absence of reports indicating a diagnosis, specific medical follow-up, and/or treatment with bile salts.

**Results**: a total of 1372 patients with antimitochondrial antibody titers ≥ 1:80 were included between January 2010 and June 2019. A total of 697 (50.8 %) were classified

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as having primary biliary cholangitis, and 100 patients (14.3 %; 95 % CI: 11.8-17.2) were identified as lost. Of these, 30 were contacted and retrieved. The median age was 70 years, 93 % were female, median alkaline phosphatase was 185 IU/L, 10 % had pruritus, and 27 % had a transient elastography value > 9.5 kPa. The disease was confirmed and ursodeoxycholic acid was started in all 30 patients. Death was liver-related in 6 of the 100 patients classified as lost.

**Conclusion**: up to 14.3 % of patients (1 out of 7) with a definitive diagnosis of primary biliary cholangitis remain undiagnosed, thus preventing monitoring and treatment. More than a quarter are at risk of advanced liver disease and its complications. Patients lost in the system must be identified and retrieved, and searching hospital databases is a suitable approach to meet this goal.

**Keywords**: Primary biliary cholangitis. Lost in the system. Lost to follow-up. Linkage to care.



## INTRODUCTION

Renewed interest in primary biliary cholangitis (PBC) (1,2) is evidenced by an increase in research in recent years to improve our knowledge of the natural history of the disease, its complications, and the outcome of the only treatment that has been available for decades, namely ursodeoxycholic acid (UDCA). UDCA leads to biochemical and histological improvements in most patients, with resulting benefits in terms of need for liver transplantation and mortality (1-4). Therefore, it has been and continues to be almost universally administered for the treatment of PBC. Recent developments in treatment provide a better prognosis for patients with an inadequate response to first-line therapy with UDCA. Obeticholic acid leads to significant decreases in alkaline phosphatase, bilirubin, and transaminases (5), as well as to stabilization or regression of liver fibrosis in 71 % of cases (6). This agent has also been approved as a second-line treatment (1,2). Bezafibrate leads to a marked decrease in liver biochemistry values and notable improvement in pruritus (7,8), and has been proposed as an off-label

second-line treatment (1,2). The combination of both drugs was recently shown to have cumulative effects and to be safe (3). Furthermore, the longer the time lag between the diagnosis of PBC and initiation of treatment, the lower the probability of response (9).

Therefore, it is very important to ensure that patients with PBC are identified so that they may have access to follow-up and appropriate treatments, thus modifying progression to cirrhosis and its associated complications. However, this objective clashes with the very low prevalence and incidence of PBC, with usual values of 1.9-40.2/100,000 inhabitants and 0.3-5.8/100,000/year, respectively (1). In Spain, prevalence is estimated at 19.5/100,000 inhabitants, and incidence at 1.7/100,000/year (10). These figures indicate that PBC is a rare disease and thus, usually unsuspected by physicians, with the risk that patients may be lost at any point during linkage to care. A similar loss has been reported in several countries for other liver diseases, such as hepatitis B (11-13) and especially, hepatitis C (12-18). Therefore, based on the data collected from 4 Spanish hospitals (Hospital Universitario La Paz, Madrid; Hospital Universitario de Canarias, Santa Cruz de Tenerife; Hospital Universitario de Santiago, Santiago de Compostela; Hospital Universitario de Valdemoro, Valdemoro), this study aimed to identify patients with PBC who were lost in the system, and to provide them with access to appropriate care. To our knowledge, this is the first such initiative in the setting of PBC.

**METHODS**

The 4 hospitals taking part in the study serve a population of 1,450,000 inhabitants within the public health network, and are reference institutions for primary and specialized care in their covered areas. They are also the reference centers for liver disease in their covered areas, and perform all the necessary chemistry, microbiology, and immunology testing. The results are computerized and can be accessed via the intranet at each center. The system also provides access to all episodes of care received by individual patients, all medical reports (all specialties), and all current and previous drug prescriptions.

**Design of the study**

First, immunology laboratories provided all the required results for antimitochondrial antibody (AMA) titers ≥ 1:80 between January 2010 and June 2019. These results were cross-referenced with alkaline phosphatase values (ALP). Registries were searched for evidence related to other possible liver diseases, including laboratory testing results, medical reports, treatment with UDCA, and episodes of care by any specialty. Patients with AMA ≥ 1:80, ALP above the upper limit of normal on at least 2 separate occasions, and absence of other liver diseases were considered to have PBC (1,2). The results were reviewed individually and patients were classified as baseline PBC (diagnosed and treated from diagnosis), baseline PBC lost in the system (no diagnosis, follow-up or treatment of the disease), PBC developed and detected (baseline normal ALP increased over time, with detection and treatment), and PBC developed and lost in the system (normal baseline ALP increased over time, with no detection or treatment). The department requesting the AMA test was analyzed (Gastroenterology, Internal Medicine, Rheumatology, other). All of the patients who were considered lost and rescuable were contacted by telephone or by mail in order to inform them that they might have the disease, and to invite them to attend the Hepatology Outpatient Clinic. A full history was taken during the first visit, and a full physical examination and complete laboratory testing were performed to confirm PBC and rule out other causes of liver disease. Abdominal ultrasound and transient elastography procedures were also performed, with a value of > 9.5 kPa considered to indicate a poorer prognosis (1). A reasonable effort was made (at least 3 calls) in the case of patients who could not be contacted initially. Patients were asked about the reason for not continuing follow-up of their disease, which was classed as 2 options: patient decision or not being aware of the disease. Lost patients with a confirmed diagnosis of PBC after this evaluation were treated in line with daily clinical practice.

**Ethical issues**

The project was assessed and approved by the Ethics Committee of La Paz University Hospital (Madrid, Spain). A specific approval was requested to contact patients, taking into account the restrictive data protection laws in force in Spain (Law 3/2018 of 5

December 2018) and the European Union (Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016). This legislation enables access to patient data in order to prevent a risk of serious danger for a patient's health, provided that there is a sufficient reason and professional secrecy is maintained. The Ethics Committee considered that the protocol fulfilled the bioethical principles of autonomy, beneficence, nonmaleficence, and justice, and that contact was ethically desirable, thus exempting the study from informed consent.

**RESULTS**

During the study period, 1372 patients were identified (86 % female) with AMA ≥ 1:80. Of these, 697 (50.8 %) were classified as having PBC: 579 (83.1 %) were diagnosed and treated from the outset, 18 (2.6 %) had increased ALP during follow-up after being detected and treated, 91 (13.1 %) were identified as lost in the system at baseline, and 9 (1.3 %) had increased ALP during follow-up without being detected. Therefore, a total of 100 patients (14.3 %; 95 % CI: 11.8-17.2) were detected as having PBC and being lost in the system. ALP remained permanently normal in 675 patients (49.2 %) over a mean follow-up of 2.96 ± 2.41 years and 3.8 % (27/702; 95 % CI: 2.5-5.5) developed PBC during this period. No statistically significant differences were found between patients who developed PBC over time and those who did not with respect to age, sex, AMA titer, or baseline ALP (data not shown).

The departments requesting AMA testing in the 697 patients with PBC were Gastroenterology (368 [52.8 %]), Internal Medicine (143 [20.5 %]), Rheumatology (51 [7.3 %]), and other (135 [19.4 %]). The percentage of PBC patients lost (both at baseline and with increased ALP during follow-up) in each department was 6 %, 14 %, 31.4 %, and 31.1 %, respectively ($p < 0.001$ for a lower proportion of patients lost in Gastroenterology compared with the other departments [chi-squared]).

Of the 100 patients lost in the system, 31 had died, 2 refused care, and 37 could not be contacted due to a lack of data or lack of response. Of the 31 patients who died, 6 died of liver disease, that is, without an etiological diagnosis of PBC. Thirty patients agreed to be treated at the hepatology clinic. The reason for the lack of follow-up in all of these patients was unawareness of the disease. PBC was confirmed in all 30 patients,

who are now receiving treatment with UDCA. Table 1 and figure 1 show their main clinical, laboratory, and elastography data.

**DISCUSSION**

Despite an increased interest in PBC in recent years, our data show that 1 in every 7 affected patients is unaware of the disease and does not receive appropriate medical attention, including treatment. To our knowledge, this is the first study aimed at detecting and rescuing patients with PBC lost to follow-up.

The percentage of patients who were rescued (30 %) seems satisfactory and comparable to that reported in other studies of the same nature in the setting of hepatitis C (14). First, the diagnosis is straightforward and was confirmed in all patients, thanks to the high sensitivity and specificity of AMA, which make this antibody a very reliable marker (2). Second, all patients started treatment with an effective therapy, namely UDCA, with which there is broad clinical experience (19), and that has been shown to improve both liver biochemistry and the natural history of the disease (1-4). In addition, there are no severe adverse effects (20), and failures can be managed with alternative therapies (1,2). Therefore, patients clearly benefited from our initiative. In fact, 27 % of the rescued patients had transient elastography values higher than 9.5 kPa, which is associated with a greater risk of liver decompensation, transplantation, or death (1). Furthermore, 6 % of the lost patients had died of a liver-related cause without having been diagnosed with PBC. While these patients had a primary liver disease (mainly alcoholism and fatty liver), we do not know how the patient's undiagnosed PBC affected the course of their disease or how this could have been modified had the patient been diagnosed and treated earlier. Therefore, in order to prevent disease progression, lost patients must be detected and rescued. To do so, they must be identified using a combined laboratory testing approach (AMA and ALP), which is an effective and easily applied strategy.

The problem of patients being lost in the health system is not unique to our institution or to our health system, and has been investigated elsewhere. Within our specialty, similar situations have been reported in Canada, the Netherlands, the United Kingdom, and Saudi Arabia, both for hepatitis C virus and hepatitis B virus (11-17). The largest

study published to date was performed in Utrecht (the Netherlands) (14), where 14.1 % of 1913 HCV serology results were identified as being lost in the system. Our finding was almost identical, thus demonstrating how widespread the problem is. Health care professionals have always considered data protection legislation to constitute an insurmountable barrier for access to lost patients. Therefore, we have been reticent when searching for them, and the only initiatives undertaken have been somewhat limited. In the section of special categories, European regulations authorize the use of medical data in situations of interest for public health, and to guarantee quality levels in health care. Similarly, the evaluation by our ethics committee supported the search for, and contact with, these patients. Therefore, we believe that our study and others could be used as the basis for future initiatives in PBC and other liver diseases.

Given that results are inadequately evaluated, the problem can be mitigated by setting up prospective warning mechanisms. This process should not be complicated if based on an updated electronic clinical history (21). Furthermore, every attempt should be made to advance our knowledge of PBC. While these losses were significantly greater in specialties such as Internal Medicine and Rheumatology as they are more directly involved in PBC, patients are also lost in Gastroenterology. The successful rescue of these patients depends on direct access to a clinic specialized in liver diseases, where simplifying the cascade of care may increase the chances of successful rescue. Reaching patients will probably be facilitated by the fact that PBC is a rare disease and by telephone contact, which is much more dynamic.

Our study has some limitations. First, we examined a problem and a course of action in Spain that may differ in other countries. Nevertheless, data from other countries lead us to believe that, although the situation occurs in different settings, the incidence and the solutions applied are similar. Second, the retrospective design of the study prevents us from obtaining the reason for requesting AMA (e.g., increase in ALP, incidental finding in the study of rheumatic diseases), and this may have affected the probability of loss. Third, these initiatives are time-consuming and expensive, and require the participation of appropriately qualified staff. In our case, the whole process was carried out by medical staff. Given that our results were favorable, the process

might be managed by specialized nursing staff in the future (14). Finally, PBC AMA-negative patients would be missed by applying our search strategy. Adding antiSP100 and antiGP210 antibodies to the immunology database request would be of help (1,2).

In conclusion, a significant number of patients with PBC and confirmatory diagnostic data have not been evaluated, and are therefore lost in the health system. Since lost patients are not treated or followed up, they are at risk of advanced liver disease, including cirrhosis and its complications. Affected patients can be searched for, and rescued effectively, by analyzing previous laboratory results in the health system databases.

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Table 1. Main characteristics of the patients retrieved

| | n = 30 |
|---|---|
| Age [years], median (IQR) | 70 (60-80) |
| Female, n (%) | 28 (93) |
| Other autoimmune disease, n (%) | 14 (47) |
| Body mass index (kg/m$^2$), median (IQR) | 26.9 (26-29) |
| Pruritus, n (%) | 3 (10) |
| Asthenia, n (%) | 8 (27) |
| ALP (IU/L), median (IQR) | 185 (135-321) |
| GGT (IU/L), median (IQR) | 101 (70-204) |
| Total bilirubin (mg/dL), median (IQR) | 0.6 (0.4-0.9) |
| Elastography (kPa), median (IQR) | 7.1 (5.2-10) |
| Elastography > 9.5 kPa, n (%) | 8 (27) |

IQR: interquartile range; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase.

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Fig. 1. Elastography values of the patients.