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ORIGINAL RESEARCH ARTICLE

Burden of primary biliary cholangitis on the Italian National Health Service: retrospective analysis from an administrative database

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ABSTRACT

Introduction: Primary biliary cholangitis (PBC) is a rare, chronic, cholestatic, autoimmune, and disabling liver disease whose treatments are aimed at reducing its progression.
The aim was to describe patients with PBC, their healthcare resource utilization (HCRU) and costs on the Italian National Health Service (SSN).
Methods: From an Italian administrative healthcare database (~5.5 million inhabitants), called ReS Db, patients with PBC in 2021 (prevalent) were selected by specific codes and described by demographics, comorbidities, one-year HCRU, and health sector costs charged to the SSN. The 3-year treatment pattern was evaluated in a cohort of patients newly diagnosed in 2019 (incident).
Results: In 2021, 1375 patients with PBC were identified (prevalence: 28.2/100,000; females: 74.2%; mean age: 64 ± 15 years). During one-year follow-up of the prevalent cohort: 73.1% received ursodeoxycholic acid (UDCA); 3.0% obeticholic acid (OCA), and 3.4% off-label drugs; 19.9% were hospitalized, mainly for cirrhosis-related conditions; 61.2% were examined by a specialist. The annual mean cost was €4422/patient; drugs for PBC, concomitant drugs, and hospitalizations accounted for 12.1%, 31.7%, and 43.6% of total cost, respectively. Among the 40 incident patients, 38 (95%) received UDCA as first-line therapy.
Conclusion: The study described the real-world impact of PBC in Italy from the perspective of the SSN and highlighted the burden and therapeutic needs of patients treated with UDCA.

Keywords: Health care delivery, Healthcare cost, Primary biliary cholangitis, Public health

Introduction

Primary Biliary Cholangitis (PBC) is a chronic, rare, cholestatic, autoimmune liver disease influenced by genetic and environmental factors and characterized by progressive destruction of intrahepatic small bile ducts, leading to cholestasis, fibrosis, and, in the long term, cirrhosis and liver failure (1). Approximately 60-65% of patients are asymptomatic at diagnosis (2), and many develop symptoms over time, such as fatigue (13% after 1 year, 45% after 10 years) and pruritus (15% after 1 year, 46% after 10 years) (2) (1). PBC is associated with other comorbidities; most commonly with osteoporosis, hyperlipidemia, thyroid diseases, vitamin deficiencies, and Sjögren's syndrome (1,3).

Due to the complexity of underlying PBC etiology, the existing treatments cannot cure the disease, but can control liver biochemistry and symptoms to different extents (1). European and Italian guidelines recommend a stepwise approach with ursodeoxycholic acid (UDCA) being prescribed

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as first-line therapy (13-15mg/Kg/day); if there is only a partial or null response after 12 months, a second-line treatment should be prescribed; also, the recurrence of PBC following liver transplantation should be considered to change treatment (1,4). Until recently, obeticholic acid (OCA) has been the only second-line approved in combination with UDCA, in case of inadequate response, or as monotherapy, in case of intolerance to UDCA. OCA was marketed in Italy from 2017 until its withdrawal from the European market in July 2024 (5). Off-label drugs, such as fibric acid derivatives (e.g., bezafibrate and fenofibrate) and budesonide, are listed in European guidelines, and their case-by-case recommendations are included in the Italian position paper (1,4). Liver transplantation is indicated for advanced PBC; the percentage of patients transplanted has decreased over the last few decades due to the ever earlier recognition of PBC and prompt initiation of UDCA (1,6). Novel drugs are coming in the therapeutic armamentarium: two selective peroxisome proliferator-activated receptor agonists (i.e., elafibranor and seladelpar) have been recently approved by the European Medicines Agency, and authorized by the Italian Medicines Agency (AIFA) for treatment of PBC in adults as an add-on to UDCA, in case of inadequate response, or as monotherapy, in case of intolerance to UDCA (1,6-11).

A recent systematic review of studies in Europe reported prevalence rates ranging 10-58.2/100,000 population/year, with higher prevalence among the female population (3). This insufficient awareness of the disease contributes to the unmet needs and burden of disease, especially within the primary care settings from which patients are usually referred when suffering from bothersome symptoms such as fatigue and pruritus (1,3). The epidemiology of PBC is highly heterogeneous because of variable case-finding methods, diagnostic criteria, and studied populations (3). In Italy, the most recent prevalence rates come from a national study of primary care data (i.e., 27.9/100,000 in 2015) and from a study of administrative health data of the Lombardia region (i.e., 29.5/100,000 in 2010) (12,13). A further study, based exclusively on the hospital discharge database of the entire Italian population, estimated a lower prevalence rate (i.e. 3.39/100,000 in 2011-2015), presumably due to the inclusion of only hospitalized patients (14). More recent evidence highlights the heterogeneity of PBC epidemiology across regions and suggests an increasing prevalence over time, likely driven by improved disease recognition and diagnostic practices (15). Estimates of PBC prevalence need to be updated to give more information on PBC to healthcare providers and to increase their awareness of the disease to take into consideration when making a differential diagnosis of the symptoms reported by patients.

Overall, Italian data are consistent with broader European trends but underscore the need for population-based studies to better define the true epidemiological burden of PBC.

This retrospective observational cohort study was aimed at describing the prevalence of PBC and its burden on the Italian National Health Service (Servizio Sanitario Nazionale—SSN) in terms of healthcare resource utilization (HCRU) and health sector costs for PBC patients in Italy. The economic evaluation is presented as a cost description following the SSN viewpoint, in accordance with the classification proposed by Drummond et al. (16).

Methods

Data source

The administrative healthcare database of Fondazione Ricerca e Salute (ReS) collects and integrates the administrative healthcare data that Italian Local and Regional Health Authorities (HAs) provide to the Italian Ministry of Health annually for reimbursement purposes, in response to the universal coverage characteristic of the SSN. The ReS database includes data on approximately 5.5 million inhabitants per year from 2014 to 2022, representing around 9% of the Italian population. This population is uniformly distributed across Italy, and its age and gender distribution is consistent with ISTAT data, making it representative of the Italian population (17). More information about Fondazione ReS and its database is available in the online supplementary material (box 1).

Study design and populations

A retrospective longitudinal observational cohort analysis was conducted on the total population included in the ReS database from 1 January 2021 to 31 December 2021 (accrual year) and with continuous presence in the database back until 2014 (Fig. S1). Patients with PBC were identified by using specific codes of hospital diagnosis, disease waiver claim, or drug dispensation listed in Table S1. The cohort under investigation was defined as the "prevalent cohort", and the index date was defined as the first hospital admission with a diagnosis of cholangitis or activation of the disease exemption or drug dispensation, if recorded in 2021, or with 1 January 2021 if it was recorded in the previous period (2014-2020). In consideration of the potential misdiagnosis, patients with an active disease waiver claim code for care related to primary sclerosing cholangitis and to chronic hepatitis were excluded from the study (Table S1). The prevalent cohort was used to describe healthcare resource utilization and health sector costs. This cohort enables the annual cost incurred by the SSN for all patients with the condition to be calculated.

Moreover, commencing from the total population included in the ReS database from 1 January 2019 to 31 December 2019 and exhibiting uninterrupted presence in the database back until 2014, the cohort of patients who were newly diagnosed with PBC was identified through the codes listed in Table S2 and it was achieved by excluding those who already had evidence of the condition in the years preceding the year of interest (i.e. 2019). This cohort was designed as an "incident cohort" with the index date being defined as the earliest date related to one of the inclusion criteria in 2019. The incident cohort was followed up for 3 years (Fig. S2) and was used to describe the treatment pattern. This cohort enables the treatment trajectories of patients to be described from the first observed sign of the disease.

Demographics and comorbidities of the prevalent cohort

Sex and age were described on the index date. The prevalence of several comorbidities (those most common in the

general population, traceable through administrative data and PBC-related, listed in Table S3 where all codes and identification criteria were explicated) was identified during the entire look-back period (i.e., until 2014) (online supplementary material).

Healthcare resource utilization and health sector costs of the prevalent cohort

The prevalent cohort was analyzed throughout the first year of follow-up (i.e., 2022) to describe:

- the free filled prescriptions (i.e., those reimbursed by the SSN) of the following drugs, in terms of proportion of patients treated, mean DDD [defined daily dose (18)] per patient, and mean cost per patient treated (this cost was based on the actual quantity of medicines dispensed),
  - authorized and recommended drugs in European guidelines (4) for PBC (i.e., UDCA and OCA, Table S1);
  - off-label but recommended drugs in European guidelines (4) (i.e., bezafibrate – ATC code C10AB02, fenofibrate – ATC code C10AB05, and budesonide – A07EA06). Since fibric acid derivatives are authorized for treating dyslipidemia, the proportion of patients with dyslipidemia as a comorbidity during follow-up was also searched;
  - concomitant drugs, by pharmacological subgroup [ATC 3rd level code (18)];
- the admissions to inward hospitalizations (for one or more days), in terms of proportion of patients admitted and length of stay, by main diagnosis in the hospital discharge form (HDF);
- the admissions to the emergency department (ED), in terms of proportion of patients admitted, mean number of accesses, and proportion of patients moved to an inward hospitalization (for one or more days), by main diagnosis in the HDF;
- the local outpatient specialist care, in terms of proportion of patients examined and mean number of services performed, by grouping of specialist services;
- the cost charged to the SSN, in terms of mean per patient annual cost (€) and percentage distribution on the overall cost for pharmaceuticals (split into PBC-authorized and other drugs), hospitalizations, and local outpatient specialist care (Box S1).

The follow-up period started at the index date and stopped at the end of the observation period (i.e., 365 days after the index date), or earlier in case of loss to follow-up or death.

Health sector costs, referred to 2022, were obtained by summing up the cost of each item (i.e., each administrative data flow designed to track the actual cost incurred by the SSN) referring to any services or prescriptions received by the cohort during the follow-up period.

Treatment pattern within the incident cohort

The treatment pattern was analyzed for the incident cohort due to the availability of a longer follow-up period, such as three years, and according to a methodology reported in Box S2. The follow-up period started at the index date and stopped at the end of the observation period (i.e., 1095 days after the index date), or earlier in case of loss to follow-up or death.

Statistical analyses

Statistical analyses were carried out using descriptive techniques appropriate for observational healthcare-database research. Categorical variables were summarized as proportions, while quantitative measures were reported through central tendency and variability indicators. All data extractions and consistency checks were performed using Oracle SQL Developer (Italian version 18.1.0.095; California, United States). Aggregation of healthcare resource utilization, cost variables, and graphical outputs was performed using Microsoft Excel Office 365 (Microsoft Company, Washington, United States). Final statistical computations were generated in RStudio (version 2022.07.2; Boston, MA).

Ethical considerations

Data were anonymized at the source and analyzed in aggregated form according to the European Regulations 2014/536 (19) and 2016/679 (20), to which the Regional/Local HAs, owners of the data, have agreed. Informed consent was waived according to the specific Italian Privacy Authority's provision (21). Ethical approval was waived according to the European Regulation 2014/536 (19), and it is not expected by the most recent national legislation on observational studies (22), which requires the Ethics Committee's positive opinion only for prospective observational studies, and does not refer to retrospective ones.

Results

Demographics and comorbidities

From the ReS database, patients affected by PBC in 2021 were 1375 (prevalence: 28.2/100,000 inhabitants)—Figure 1. Female patients were 74.2% (Table 1).

Prevalence of PBC increased with age until a peak in the eighth decade. Mean age was 64 ± 15 years. At least two comorbidities, of those investigated and listed in Table S3, were found in 61.0% of patients, with high frequencies of arterial hypertension (62.2%), dyslipidemia (27.3%), and thyroid diseases (22.8%) (Table 1). Autoimmune diseases (i.e., diseases of connective tissue, Inflammatory bowel disease, and rheumatoid arthritis) were found in 13.3% of patients.

Healthcare resource utilization and health sector costs

During the first year of follow-up, 73.9% of prevalent patients received at least one drug recommended for PBC: 73.1% UDCA, 3.0% OCA, 3.4% fenofibrate, budesonide, and bezafibrate, which are off-label drugs for PBC and used mainly for the concomitant presence of dyslipidemia (Table 2). The mean annual cost per treated patient, referred to 2022, of drugs recommended for PBC was € 723. UDCA was dispensed to 1005 patients, receiving a mean of 292.4 DDD and generating a mean cost per patient of € 258. OCA was dispensed to 41 patients, consuming a mean of 142.0 DDD and generating

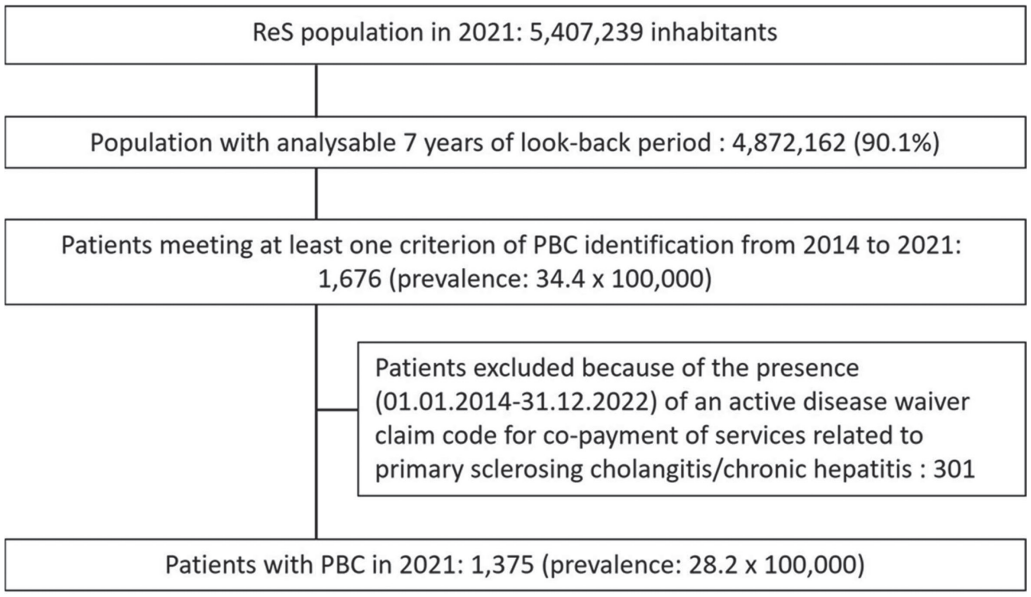

FIGURE 1 - The flowchart describes the steps to the identification of patients with PBC in 2021 (prevalent cohort), starting from the overall population in the database of Fondazione ReS (Ricerca e Salute) for 2021.

a mean cost per patient of € 11,411. Budesonide was used in 19 subjects, whereas fibrates were used in 29 patients; of these who were receiving fibric acid derivatives, 72.4% had dyslipidemia (identified by using codes listed in Table S3 in the supplementary material) as a comorbidity during the follow-up. Concomitant drugs were dispensed to 96.4% of patients. The mean annual cost of concomitant drugs was € 1453 per treated patient (Table 3). Grouping these drugs according to the ATC 3rd level code showed that: "Drugs for peptic ulcer/gastro-esophageal reflux disease" were the most dispensed (56.9% of patients), followed by "Vitamin A and D, included combinations of the two" (43.8%), "Antithrombotic agents" (31.9%), "Non-steroidal antiinflammatory drugs" (30.4%) and "Beta blocking agents" (30.0%). Systemic corticosteroids, penicillins, and lipid-modifying agents were each dispensed to a quarter of the cohort (Table 3).

The 19.9% of patients with PBC were admitted for an inpatient hospitalization, on average 1.6 times per year (min 1.0, max 2.0 times per year). The two most common primary diagnoses in the HDF were biliary cirrhosis and cirrhosis of the liver without mention of alcohol, both leading to a mean length of stay of 12 days and similar mean annual cost per inpatient (€ 9,784 and € 10,016, respectively). 18.6% of patients were admitted to the ED, on average, 1.7 times per year. Most users received a non-specific primary diagnosis of "general symptoms", while "chronic liver disease and cirrhosis" was recorded as the primary cause for access in 1.2% of cases, with more than half of these visits leading to hospitalization. Of these ED admissions, 37.0% were followed by inward hospitalization.

Local outpatient specialist care was required for 90.0% of patients and generated a mean annual cost of € 623/patient (Table 4). Laboratory tests (e.g., blood test or serum alkaline phosphatase—ALP) were the most frequent services, with a mean number of 48.2 performances per patient examined. Followed by specialist visit (61.2% of examined patients) and diagnostic imaging of the abdomen (39.5%). At least one musculoskeletal or thyroid region imaging test was performed on 13.7% or 6.1% of patients, respectively.

On average, the SSN has annually directly reimbursed € 4422/patient (Table 5). Pharmaceuticals and hospitalization-related costs accounted for about 43.8% and 43.6% of the total healthcare cost, respectively. Considering the drug cost, whereas "drugs used for PBC" accounted for 12.1% of the total cost, "other drugs" accounted for 31.7%.

Treatment pattern within the incident cohort

Among 40 patients newly diagnosed with PBC in 2019 and with at least 3 years of follow-up, 95% were treated with UDCA (Table S4). Most of them (82.5%) initiated UDCA within the first 3 months following the index date and were treated continuously (65.8%) over an average period ranging from 16.3 to 35.2 months. Eight patients interrupted and 4 discontinued the treatment with UDCA, on average at 4.9 and 2.3 months, respectively (Table S4). Early after the index date, one patient received the combination UDCA+bezafibrate continuously until the end of follow-up. Another patient received OCA monotherapy within the first month of follow-up and interrupted it before the end of follow-up. One patient receiving UDCA switched to OCA during the follow-up (Table S4).

Discussion

This retrospective observational study of a large Italian administrative healthcare database has been conducted to describe the burden of PBC patients in Italy in their real-world complexity. Real-world evidence from different types of real-world data sources has assessed patients with PBC in Italy both before and after the reimbursement of OCA (12,13,23,24).

TABLE 1 - Demographics and comorbidities of study patients with PBC in 2021 (prevalent cohort), at baseline (i.e., index date and look-back period)

Characteristics	Patients with PBC in 2021 (N = 1375)
Demographics	
Females [n; n/N%]	1021; 74.2
Mean age (SD)	64 (15)
Median age (Q1; Q3)	66 (54; 75)
Patient distribution by age group (years old) [n; n/N per 100,000]	
<40	78; 4.6
40-49	102; 15.3
50-59	278; 33.5
60-69	381; 55.4
70-79	344; 61.8
≥80	192; 43.6
Comorbidities* [n; n/N%]	
N = 0	191; 13.9
N = 1	345; 25.1
N = 2	324; 23.6
N ≥ 3	515; 37.4
Arterial hypertension	855; 62.2
Dyslipidaemia	375; 27.3
Thyroid diseases	313; 22.8
Diabetes	255; 18.5
Neoplasia (current/history)	234; 17.0
Chronic lung diseases	203; 14.8
Depression	165; 12.0
Osteoporosis	134; 9.7
Coronary artery disease	90; 6.5
Chronic kidney disease	80; 5.8
Heart failure	74; 5.4
Cerebrovascular diseases	69; 5.0
Cardiac arrhythmias	46; 3.3
Autoimmune diseases	183; 13.3
Diseases of connective tissue	91; 6.6
Inflammatory bowel disease	68; 4.9
Rheumatoid arthritis	38; 2.8

* The comorbidities analyzed are those listed in Table S3 in the supplementary material

TABLE 2 - Free-filled dispensations of drugs recommended for PBC to the prevalent cohort (N = 1375) during the first year of follow-up, by active substance

Active substance	Patients treated (n; n/N%)	Mean DDD/ patient treated	Mean cost / patient treated (€)
At least one dispensation of a drug recommended for PBC	1016; 73.9	-	723
Drugs authorized for PBC	1006; 73.2	297.9	722
Ursodeoxycholic acid	1005; 73.1	292.4	258
Obeticholic acid	41; 3.0	142.0	11,411
Drugs off-label	47; 3.4	151.3	167
Fenofibrate	21; 1.5	223.5	73
Budesonide	19; 1.4	78.9	314
Bezafibrate	8; 0.6	115.0	43

TABLE 3 - Free-filled dispensations of other drugs (first 15) to the prevalent cohort (n = 1375) during the first year of follow-up, by pharmacological subgroup

Pharmacological subgroup	Patients treated (n; n/N%)	Mean DDD/ patient treated	Mean cost / patient treated (€)
At least one dispensation of concomitant drug	1326; 96.4	-	1453
Drugs for peptic ulcer/ gastro-esophageal reflux disease	782; 56.9	198	85
Vitamin A and D, incl. combination	602; 43.8	448	43
Antithrombotic agents	439; 31.9	234	208
Non-steroidal antiinflammatory drugs	418; 30.4	39	15
Beta-blocking agents	412; 30.0	115	43
Corticosteroids for systemic use, plain	355; 25.8	93	26
Beta-lactam antibacterials, penicillins	351; 25.5	13	16
Lipid modifying agents, plain	350; 25.5	228	116
High-ceiling diuretics	329; 23.9	173	17
Intestinal antiinfectives	234; 17.0	107	391
Thyroid preparations	233; 16.9	171	24
Quinolone antibacterials	231; 16.8	10	21
Aldosterone antagonists	192; 14.0	184	57
Opioids	188; 13.7	31	103
Angiotensin receptor blockers, plain	183; 13.3	343	80

TABLE 4 - Local outpatient specialist care (first 15 specialist service groups) performed during one year of follow-up to the prevalent cohort (n = 1375)

Specialist service group	Patients examined (n; n/N%)	Mean number of performances per patient examined	Mean cost per patient examined (€)
At least one performed a local outpatient specialist service	1,237; 90.0	53.5	623
Laboratory tests*	1,140; 82.9	48.2	209
Specialist visit	842; 61.2	3.5	67
Diagnostic imaging—abdomen	543; 39.5	1.6	119
Electrocardiogram	209; 15.2	1.4	25
Musculoskeletal imaging	188; 13.7	1.2	70
Diagnostic imaging—thorax	174; 12.7	1.4	76
Diagnostic imaging—breast	152; 11.1	1.7	60
Gastroenterology visit	143; 10.4	2.6	39
Diagnostic imaging—circulatory system	124; 9.0	1.3	70
Diagnostic imaging—heart	122; 8.9	1.2	76
Diagnostic imaging—spinal column	118; 8.6	1.6	97
Eye examination	109; 7.9	1.4	27
Diagnostic imaging—lower limb	88; 6.4	1.3	40
Diagnostic imaging—thyroid region	84; 6.1	1.1	32
Diagnostic imaging—head/neck	79; 5.7	1.2	103

* Include single laboratory tests, e.g., blood and leucocyte counts

Although OCA was withdrawn while our analyses were underway, the present study is still useful for healthcare planning to estimate the proportion of patients eligible for second-line therapy, especially thanks to the inclusion of populations frequently underrepresented or excluded from clinical trials (e.g., elderly, patients with cirrhosis and mixed phenotypes, like the variant PBC-autoimmune hepatitis (AIH)).

The prevalence of PBC found by this study (28.2/100,000) falls within the range reported by other European studies (10-58.2/100,000) (3,25). Particularly, our prevalence is very similar to the pooled point prevalence rates found in other Italian studies (i.e., 27.9/100,000 and 29.5/100,000), despite some differences in the methodologies and data sources used (12,13).

Consistent with literature, PBC is most identified among middle-aged and female patients, as also already seen in other autoimmune diseases (3,6,13,26).

More than half of the patients were affected by at least 2 comorbidities. Particularly, among the most common comorbidities in the general population, the highest rates have been found for cardio-metabolic diseases, such as arterial hypertension, dyslipidemia, and diabetes. Moreover, among the PBC-related comorbidities, the present study corroborates previous findings on the high prevalence of thyroid diseases, osteoporosis, and autoimmune diseases (1,12,26).

PBC is characterized by a long disease course and related symptoms, such as chronic pruritus and fatigue, which are disabling and can impact daily activities (1); however, these symptoms cannot be detected in administrative data (26). PBC and its related symptoms can reduce the quality of life of those affected, particularly younger patients, but to date, this represents an unmet clinical need. However, there are few studies describing the burden of PBC in terms of HCRU and costs incurred by national health systems, which would be useful for understanding the extent of this need (27-29).

TABLE 5 - Per patient mean health sector costs (referred to any services or prescriptions) charged to the Italian National Health Service during the first follow-up year for the healthcare of the prevalent cohort (N = 1375)

Administrative data flow and cost item	Per patient mean cost (€; % on total cost)
Pharmaceuticals	1936; 43.8
Drugs recommended for PBC	534; 12.1
Approved for PBC	528; 12.0
off-label for PBC	6; 0.1
Other drugs	1401; 31.7
Hospitalizations	1926; 43.6
at the index date	208; 4.7
inward hospitalizations (follow-up)	1656; 37.4
day hospitalizations (follow-up)	62; 1.4
Local outpatient specialist care	560; 12.7
Total cost	4422; 100.0

As already mentioned for the epidemiology, when HCRU and cost analyses come from different countries, estimates are likely to vary significantly depending on the local healthcare system, and direct comparisons cannot be made.

During the first year of follow-up in this study, a high percentage (73.9%) of patients with PBC (prevalent cohort) were treated with at least one drug recommended for PBC, in line with the findings of a study conducted on the Italian primary care database (88.4%) (12). However, the study found that 26% of the patients identified were not receiving any treatment for PBC; this finding could be due either to a genuine failure to administer the drugs recommended in the guidelines or to the misclassification of patients with this condition, and therefore constitutes a limitation of the study.

UDCA was the most dispensed drug for PBC (73.1% of patients) with an average consumption of 292.4 DDD/patient, corresponding to about 10 months of therapy/patient. This treatment rate was as expected based on other real-world findings, and since UDCA is the sole first-line drug to have been approved by drug agencies and recommended by guidelines (1,4,12,28). Also, the focus on the 3-year treatment, considered as the study period, has shown that the majority of the incident cohort received UDCA, which is largely consistent with the recommendation that UDCA should be initiated at the time of diagnosis for all patients (1). The extant literature reports that up to 40% of patients with PBC demonstrate an inadequate response to UDCA and require further treatment, and 3-5% are intolerant to UDCA and require a change of therapy. The present study, among 40 incident subjects, observed 8 who interrupted and 4 who discontinued UDCA. However, it is not possible to trace the causes of this, as this information is not collected from health administrative data. (3,26). According to guidelines, the low or lack of response to UDCA can typically be predicted within 6-12 months of therapy, while the intolerance can be identified even earlier, and a second-line treatment should be initiated as early as possible to reduce the risk of disease progression and poor outcomes (1,26). In Italy, since 2017, the dispensation of OCA was authorized and reimbursed by the SSN in addition to UDCA following at least 12 months of continuous therapy with UDCA, alternatively as monotherapy in case of intolerance to UDCA administered for less than 3 months (30). From this study, the prevalence of OCA dispensations from hospital and community pharmacies was 3.0%. This extremely low value may be due to either low use of the drug, particularly in facilities not specialized for the treatment of PBC, or possible loss of dispensing information when the patient is hospitalized. Ultimately, in July 2024, OCA was withdrawn from the European market, based on the outcomes from the COBALT study (5,31). Alternatives to UDCA and/or OCA include off-label drugs, such as budesonide, fenofibrate, and bezafibrate. More than one drug can be added based on the characteristics of PBC patients; specifically, fibrates are candidates in addition to UDCA and/or OCA, despite not being licensed for PBC (6,26). In the Italian administrative pharmaceutical database, the diagnosis of PBC is not linked to the filled drug prescription; however, a specific search of dyslipidemia in prevalent patients who were receiving bezafibrate/fenofibrate during the one-year follow-up was conducted, and 72.4% of prevalent patients were found to be concomitantly affected by dyslipidemia. Budesonide, although generally discouraged due to potential side effects and a less favorable risk-benefit profile in patients with PBC without AIH, is another off-label medication used for short-term therapy in non-cirrhotic patients with signs of hepatic inflammation (32). Budesonide was dispensed to very few patients (19) and for a mean consumption of 78.9 DDD per patient, corresponding to less than 3 months of therapy, which could be the case of patients non-responding to UDCA or assessed for alternative aetiologies (e.g., AIH) and receiving immunosuppressive treatment in addition to UDCA (e.g., budesonide and systemic corticosteroids) (1).

Analysis of incident patients showed that almost all of them were treated with UDCA as initial therapy, in line with what was expected, while only 1 case started therapy with OCA.

During the follow-up period, most patients received at least one concomitant drug. Drugs for peptic ulcer/gastroesophageal reflux disease and vitamins (especially vitamin D) were the most dispensed, as found also in previous real-world Italian studies (12,28). Moreover, this study population was mainly composed of women of post-menopausal age, for whom calcium and vitamin D supplementation should be considered by default (1,26). Systemic corticosteroids were dispensed to a quarter of the cohort. This proportion could have included patients who did not respond to UDCA and were assessed for alternative aetiologies (e.g., AIH) or overlap syndrome PBC-AIH, therefore treated with immunosuppressive treatment, like systemic corticosteroids, in addition to UDCA (1). Another quarter of patients received lipid-modifying agents during the follow-up. Hyperlipidemia is primarily treated with lipid-modifying agents and is one of the most common comorbidities in patients with PBC (1,4,26). The 19.9% of patients were admitted for inpatient hospitalizations, mainly due to chronic liver disease and cirrhosis. A similar rate was described by a previous Italian study (28).

61.2% of patients were referred to a specialist, on average, 3.5 times during the follow-up year. It is evident that a considerable proportion of patients do not receive consultation from any medical specialist or are followed in private health care facilities whose data are not collected in the administrative databases analyzed.

Although some drugs for PBC, such as OCA, are expensive, the overall cost for patients was mainly borne by concomitant drugs. Also, the high per-patient mean annual cost for inward hospitalizations suggests that some patients require more intensive care, which could be related to worsening PBC, but we cannot confirm this with our data source. In any case, addressing the unmet therapeutic needs may prevent the progression of the disease and the subsequent requirement for hospitalizations to treat complications.

Strengths and limitations

The main strength of this study lies in the utilization of a large database, representative of the general population. The ReS database constitutes 9.1% of the Italian population in 2021, which is variably extended from north to south and

overlaps by age group (17). Another strength of the ReS database lies in the heterogeneity of the collected population. This is of particular interest for PBC because the ReS database allows the clinical practice of centers of different levels in the treatment of PBC, doctors with different knowledge of the disease, and patients of varying complexity to be studied. The results of this study, although derived from an unvalidated algorithm, can be valuable when combined with those from clinical studies. In fact, they can be used to monitor trends over time, identify unmet needs, and improve healthcare management, access to medicines, and treatment pathways. In this context, the proposed identification algorithm could be useful as a starting point for the construction of process indicators for PBC (12).

Nevertheless, some limitations must be mentioned. An overestimation of 10-15% of the PBC prevalence could occur when using the ICD-9-CM code 571.6 because it includes all types of biliary cirrhosis (e.g., secondary cirrhosis), although PBC represents the majority (12,13). The exclusion of patients with chronic hepatitis and secondary sclerosing cholangitis should have mitigated this limitation. However, this may have influenced the results of the study, which must therefore be interpreted accordingly. Also, an underestimation could occur because PBC is mostly asymptomatic at diagnosis, especially in the early stages and in men; therefore, some patients could be undiagnosed or misdiagnosed (13). In addition, it cannot be completely ruled out that the criteria used to identify the study cohort avoided the misclassification of subjects with secondary sclerosing cholangitis, since this condition could be excluded only by using the specific exemption code but not the other codes shared with PBC. Moreover, a potential overlap between PBC and AIH at onset can occur (1). Another limitation of the study is the potential overestimation of certain comorbidities. This is because some of these conditions (e.g., hypertension and ulcerative colitis) are identified using medications that are not always specific to them as proxies. Furthermore, any clinical information (e.g., body mass index, smoking habits, and use of chemicals and outcomes from laboratory tests, like measures of ALP, GGT, and bilirubin levels), environmental factors, diagnoses of PBC-related symptoms (i.e., pruritus and fatigue) or results from any prognostic models of response to UDCA were not evaluable in the ReS administrative healthcare database.

Conclusions

This retrospective observational cohort study is, to our knowledge, the most recent real-world study describing the burden of disease of patients with PBC in Italy, from the SSN perspective. The available data has highlighted the significant unmet medical needs of patients with PBC, a matter that is particularly salient given the recent availability or the advent of new second-line therapeutic options. The novel drugs mean great expectations for patients with PBC, but it remains of utmost importance that the health policy promotes structured training for general and specialist practitioners to properly apply the international and national recommendations through a holistic approach. Concurrently, it is imperative for patients to be engaged and empowered in the recognition and management of their symptoms, in conjunction with their clinicians, to promptly establish the correct treatment and adhere to it.

Disclosures

Conflict of interest: GR, LD, NA, SC, CP, and NM are employees of Fondazione ReS and have no competing interests with any financial organization regarding the material discussed in the manuscript.
GM, VA, and VB are employees of Ipsen Italy who supported the study. VA reports having Ipsen Stock options.
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Data availability statement: The datasets analyzed during the current study are not publicly available and are not available from the corresponding author on reasonable request, because they are owned by the Italian Regional/Local Health Authorities, who have not authorized Fondazione ReS to make them available.

Authors' contributions: Conceptualization, GR, LD; data curation, LD; formal analysis, LD; funding acquisition, NM, CP; investigation, GR, LD, SC, NA, CP; methodology, LD, GR; project administration LD, CP; software, LD; supervision, PI, MC, AG, UVG, NM; validation, CP, NA, GM, VA, VB; writing—original draft, NA, SC, CP; writing—review and editing, NA, SC, CP, GM, VA, VB, PI, MC, AG, UVG. All authors have read and agreed to the published version of the manuscript.

References

1. Carbone M, Gerussi A, Cardinale V, et al.; AISF Expert Panel. Position paper of the Italian Association for the Study of the Liver (AISF): management and treatment of primary biliary cholangitis. Dig Liver Dis. 2024;56(9):1461-1474. CrossRef PubMed
2. Prince MI, Chetwynd A, Craig WL, et al. Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. *Gut*. 2004;53(6):865-870. CrossRef PubMed
3. Gazda J, Drazilova S, Janicko M, et al. The epidemiology of primary biliary cholangitis in European countries: a systematic review and meta-analysis. Canadian Journal of Gastroenterology & Hepatology. 2021 CrossRef
4. Hirschfield GM, Beuers U, Corpechot C, et al.; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol*. 2017;67(1):145-172. CrossRef PubMed

5. Agenzia Italiana del Farmaco. Ocaliva (acido obeticolico): raccomandazione per la revoca dell'autorizzazione all'immissione in commercio nell'Unione Europea a causa di un beneficio clinico non confermato. Nota Informativa Importante; 2024. Online (Accessed February 2026)
6. Trivella J, John BV, Levy C. Primary biliary cholangitis: epidemiology, prognosis, and treatment. *Hepatol Commun*. 2023;7(6):e0179. CrossRef PubMed
7. Giannini EG, Pasta A, Calabrese F, et al. Second-line treatment for patients with primary biliary cholangitis: a systematic review with network meta-analysis. *Liver Int*. 2025;45(1):e16222. CrossRef PubMed
8. Agenzia Italiana del Farmaco. Determina 30 aprile 2025. Classificazione, ai sensi dell'articolo 12, comma 5, della legge 8 novembre 2012, n. 189, del medicinale per uso umano, a base di seladelpar, «Lyvdelzi». (Determina n. 607/2025). (25A02778) (GU Serie Generale n.113 del 17-05-2025). 2025; Online (Accessed February 2026)
9. Hirschfield GM, Bowlus CL, Mayo MJ, et al.; RESPONSE Study Group. A phase 3 trial of Seladelpar in primary biliary cholangitis. N Engl J Med. 2024;390(9):783-794. CrossRef PubMed
10. Kowdley KV, Bowlus CL, Levy C, et al.; ELATIVE Study Investigators' Group; ELATIVE Study Investigators' Group. Efficacy and safety of Elafibranor in primary biliary cholangitis. N Engl J Med. 2024;390(9):795-805. CrossRef PubMed
11. European Medicines Agency. Iqirvo. Elafibranor. European Commission decision. 2024. Online (Accessed February 2026)
12. Marzioni M, Bassanelli C, Ripellino C, et al. Epidemiology of primary biliary cholangitis in Italy: evidence from a real-world database. Dig Liver Dis. 2019;51(5):724-729. CrossRef PubMed
13. Lleo A, Jepsen P, Morenghi E, et al. Evolving trends in female to male incidence and male mortality of primary biliary cholangitis. Sci Rep. 2016;6(1):25906. CrossRef PubMed
14. Manno V, Gerussi A, Carbone M, et al. A national hospital-based study of hospitalized patients with primary biliary cholangitis. Hepatol Commun. 2019;3(9):1250-1257. CrossRef PubMed
15. Colapietro F, Bertazzoni A, Lleo A. Contemporary epidemiology of primary biliary cholangitis. Clin Liver Dis. 2022;26(4):555-570. CrossRef PubMed
16. Drummond MFSM, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes, 4th ed. Place published: Oxford: Oxford University Press, 2015. ISBN: 9780199665884
17. ISTAT. Demo Istat. Bilancio demografico e popolazione. Online (Accessed February 2026)
18. Norwegian Institute of Public Health - WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. Online (Accessed February 2026)
19. European Parliament and Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 2014. Online (Accessed February 2026)
20. European Parliament and Council of the European Union. Regulation (EU) 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). 2016. Online (Accessed February 2026)
21. Garante per la protezione dei dati personali. Provvedimento recante le prescrizioni relative al trattamento di categorie particolari di dati, ai sensi dell'art. 21, comma 1 del d.lgs. 10 agosto 2018, n. 101. Online (Accessed February 2026)
22. Ministero della Salute. Decreto 30 novembre 2021. Misure volte a facilitare e sostenere la realizzazione degli studi clinici di medicinali senza scopo di lucro e degli studi osservazionali e a disciplinare la cessione di dati e risultati di sperimentazioni senza scopo di lucro a fini registrativi, ai sensi dell'art. 1, comma 1, lettera c), del decreto legislativo 14 maggio 2019, n. 52. (22A01189). Online (Accessed February 2026)
23. D'Amato D, De Vincentis A, Malinverno F, et al.; Italian PBC Registry and the Club Epatologi Ospedalieri (CLEO)/Associazione Italiana Gastroenterologi ed Endoscopisti Digestivi Ospedalieri (AIGO) PBC Study Group. Real-world experience with obeticholic acid in patients with primary biliary cholangitis. *JHEP Rep Innov Hepatol*. 2021;3(2):100248. CrossRef PubMed
24. Terracciani F, De Vincentis A, D'Amato D, et al. Long-term results from the Italian real-world experience on obeticholic acid treatment in primary biliary cholangitis: The RECAPITULATE study. Dig Liver Dis. 2023; 55(S44-S5). CrossRef
25. de Veer RC, van Hooff MCB, Werner E, et al.; Dutch PBC Study Group. Incidence and prevalence of primary biliary cholangitis in the Netherlands – a nationwide cohort study. JHEP Rep Innov Hepatol. 2024;6(8):101132. CrossRef PubMed
26. Invernizzi P, Floreani A, Carbone M, et al. Primary biliary cholangitis: advances in management and treatment of the disease. Dig Liver Dis. 2017;49(8):841-846. CrossRef PubMed
27. Rice S, Albani V, Minos D, et al.; UK-PBC Consortium. Effects of primary biliary cholangitis on quality of life and health care costs in the United Kingdom. Clin Gastroenterol Hepatol. 2021;19(4):768-776.e10. CrossRef PubMed
28. Gerussi A, Restelli U, Croce D, et al. Cost of illness of primary biliary cholangitis - a population-based study. Dig Liver Dis. 2021;53(9):1167-1170. CrossRef PubMed
29. Samur S, Klebanoff M, Banken R, et al. Long-term clinical impact and cost-effectiveness of obeticholic acid for the treatment of primary biliary cholangitis. Hepatology. 2017;65(3):920-928. CrossRef PubMed
30. Agenzia Italiana del Farmaco. Determina 26 luglio 2017. Classificazione del medicinale per uso umano «Ocaliva», ai sensi dell'art. 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 1392/2017). (17A05919) (GU Serie Generale n.196 del 23-08-2017). 2017; Online (Accessed February 2026)
31. Kowdley KV, Hirschfield GM, Coombs C, et al. COBALT: a confirmatory trial of obeticholic acid in primary biliary cholangitis with placebo and external controls. Am J Gastroenterol. 2025;120(2):390-400. CrossRef PubMed
32. Hirschfield GM, Beuers U, Kupcinskas L, et al. A placebo-controlled randomised trial of budesonide for PBC following an insufficient response to UDCA. J Hepatol. 2021;74(2): 321-329. CrossRef PubMed