A National Hospital-Based Study of Hospitalized Patients With Primary Biliary Cholangitis

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Epidemiological studies on primary biliary cholangitis (PBC) have been based primarily on tertiary referral case series. We aimed to estimate the incidence and prevalence and describe comorbidities in hospitalized patients with PBC in Italy using a national hospital-based data source. Data were extracted from the National Hospital Discharge Database, which includes all Italian individuals discharged from any hospital in the country. All adults diagnosed with biliary cirrhosis (International Classification of Diseases, Ninth Revision, Clinical Modification, 571.6) as the primary or secondary diagnosis from 2011 to 2015 were included. To determine whether a comorbidity was either more or less frequent in PBC patients compared with the general hospitalized Italian population, the standardized hospitalization ratio (SHR) was calculated. A total of 5,533 incident cases were identified from 2011 to 2015, 3,790 of whom were females (68.5%; female to male [F:M] ratio, 2.2:1). Prevalent cases were 9,664, of whom 7,209 were females (74.6%; F:M ratio, 2.9:1). The incident rate was 1.03 × 100,000 in males and 1.92 × 100,000 in females; prevalence was 1.89 × 100,000 in males and 4.75 × 100,000 in females. Extrahepatic autoimmune diseases, malignant neoplasms of liver and intrahepatic biliary ducts, and malignant neoplasms of gallbladder and extrahepatic bile ducts were found more frequently in PBC patients than in the general hospitalized population (SHR > 100), whereas cerebrovascular diseases and ischemic heart diseases were less frequent in PBC individuals (SHR < 100).

Conclusion: This national study provides a survey of comorbidities associated with PBC. Hospitalized patients with PBC are more likely to have extrahepatic autoimmune diseases, hepatocellular carcinoma, and biliary tract cancers and a low risk of cardiovascular events. (Hepatology Communications 2019;3:1250-1257).

Primary biliary cholangitis (PBC) is an immune-mediated disease affecting small bile ducts of the liver. Apart from rare variants, its course is generally slow but progressive, and it can evolve to cirrhosis, liver failure, and death. (1) PBC is a rare disease, (2) but incidence and prevalence show a great variability according to the different methods used and the geographical areas involved, with a median incidence of 1.55/100,000 and a median prevalence of 13.7/100,000. (3) Typical case-finding approaches include surveys, laboratory and histological databases, and transplant registries and are often affected by underdiagnosis rather than overdiagnosis. (4) Administrative registries offer an alternative approach with a number of possible advantages, (3) and several data are already available in PBC patients. (5-8)

Abbreviations: CI, confidence interval; F:M, female to male [ratio]; HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PBC, primary biliary cholangitis; SHR, Standardized Hospitalization Ratio; WHO, World Health Organization.

Received January 24, 2019; accepted June 18, 2019.

Supported by the Italian Ministry of Health in the role of auto-reactive hepatic natural killer cells in the pathogenesis of primary biliary cholangitis (PE-2016-02363915) and in the biocompatible nano-assemblies to increase the safety and the efficacy of steroid treatment against liver inflammation (GR-2018-12367794).

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In Italy, two recent studies described its epidemiology, but the features of more severe and hospitalized PBC patients are still unknown. Although PBC predominantly affects women, there is growing evidence of more male patients than expected. The proportion of males is largely variable, with a female to male (F:M) ratio of approximately 10:1, which is possibly an overestimation because it goes down to 2:1 when restricted to antimitochondrial antibody positivity in the general population and is close to 7:1 in the United Network for Organ Sharing liver transplant database. Lower F:M ratios have also been reported by recent studies based on administrative databases. The burden of comorbidities in terms of clinical and prognostic impact and costs for the health services is of key importance in medicine. Unfortunately, in PBC the real extent and number of comorbidities is largely unknown, with the few available data being related to the extrahepatic autoimmune comorbidities. The aim of our study was to estimate incidence and prevalence and describe comorbidities in hospitalized patients with PBC in Italy using a national hospital-based data source.

Materials and Methods

SOURCE OF DATA

Records from the National Hospital Discharge Database were used to identify patients with PBC. The National Hospital Discharge Database collects data of all patients discharged from any Italian hospital after an urgent or planned (diagnostic or interventional) admission. For each patient, demographic data (e.g., sex, date, place of birth) as well as the primary diagnosis and up to five secondary discharge diagnoses are recorded, and diagnoses are codified according to the World Health Organization (WHO) International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

CASE DEFINITION

For the purposes of this study, patients diagnosed with ICD-9-CM code 571.6, either reported as primary or secondary diagnosis in the discharge note, were considered as “PBC cases.” This code refers to the following pathologies: chronic nonsuppurative destructive cholangitis and cholangitic/cholestatic cirrhosis. Cases younger than 18 years of age were excluded from the analysis; the study period was 2011-2015. “Incident cases” were defined as patients diagnosed with PBC in their first hospital admission that occurred during the study period; a washout period (2001-2010) was used to avoid the inclusion of prevalent cases. “Prevalent cases” were considered all individuals diagnosed as PBC cases during the study period.

STATISTICAL ANALYSIS

Incidence and prevalence rates, age-standardized with the direct standardization method, having the
WHO Standard Population as reference, were calculated by gender, along with their 95% confidence intervals (CIs) based on Poisson distribution. Age and gender distributions of incident and prevalent cases and rates were described; the F:M ratio was calculated, and its distribution was described over the study period.

COMORBIDITIES

To determine the main comorbidities affecting PBC patients, we went through all discharge notes related to PBC cases. This search covered a time frame of 5 years before the first admission, having PBC as primary diagnosis. For each comorbidity, the standardized hospitalization ratio (SHR) as well as its 95% CI were calculated using the indirect standardization method considering the hospitalized Italian population as reference, stratified by gender. The SHR compares the number of patients hospitalized for specific diagnoses in the population of interest with the number of expected hospitalized patients with the same diagnosis. The average value of the population selected as reference is 100: SHR values less than 100 indicate a lower hospitalization rate, whereas values greater than 100 indicate a higher hospitalization rate due to a specific comorbidity. To be statistically significant, 95% CI for SHR should not contain 100. This tool allowed us to investigate whether the cohort of patients hospitalized for PBC had a greater risk of hospitalization due to the investigated specific comorbidities as compared with the whole Italian cohort of hospitalized patients. The ICD codes of comorbidities used in the study are given in Table 1.

Results

INCIDENCE, PREVALENCE, AND F:M RATIO

Median age did not differ according to gender (67 years for men and 65 years for women for incidence; 65 years for both genders for prevalence). Incidence and prevalence absolute numbers, crude rates stratified by gender and age, and the overall rate ratio for age category are reported in Table 2 and Table 3, respectively. During the study period, 5,533 incident cases of PBC were identified; 3,790 individuals were females (68.5%), with an F:M ratio for incident cases of 2.2:1. Prevalent cases were 9,664, of which 7,209 were females (74.6%), with an F:M ratio for prevalent cases of 2.9:1. Older patients (>70 years) showed the highest crude rates for incidence and prevalence, and the rate ratio for patients older than 70 were 8.57 (95% CI, 7.98-9.87) and 9.73 (95% CI, 8.94-10.59), respectively.

When the 5-year period of the study is considered overall, the incidence of PBC was 1.03 per 100,000 in males and 1.92 per 100,000 in females; the prevalence was 1.89 per 100,000 in males and 4.75 per 100,000 in females (Table 4). Data show a slight decrease of incidence and prevalence over the study period.

COMORBIDITIES

Results from the comorbidity analysis are provided in Table 5. For both genders, a significant excess of hospitalizations (SHR > 100) was found in PBC cases for the following disease categories: infectious diseases, malignant neoplasms of liver and intrahepatic bile ducts, malignant neoplasms of gallbladder and extrahepatic bile ducts, endocrine diseases, diseases of the digestive system, diseases of the genitourinary system, and autoimmune diseases. Neoplasms were significantly in excess only in male subjects. In contrast, diseases of the nervous system, ischemic heart diseases, and cerebrovascular diseases were less frequently present in PBC patients than in the general population (SHR < 100).

Discussion

This national hospital-based study of hospitalized patients with PBC in Italy provides an extensive survey of comorbidities associated with PBC. We reported incidence and prevalence of hospitalized PBC patients from 2011 to 2015 and showed that (1) PBC in Italy is a rare disease; (2) the F:M ratio is lower than expected; and (3) hospitalized patients with PBC have a high risk of cholangiocarcinoma, gallbladder cancer, and hepatocellular carcinoma (HCC) and a low risk of cerebrovascular and ischemic heart diseases, despite frequent dyslipidemia.

The particularly low prevalence reported is likely due to methodological issues; looking only at
hospitalizations from 2011 to 2015 to derive data on prevalence probably caused an underestimation because PBC patients diagnosed before 2011 and not hospitalized during the time frame 2011-2015 were missed and not included as prevalent cases. On the contrary, incidence is similar to previous studies\(^6,16\); indeed, to avoid inclusion of prevalent cases, the time frame used to derive incidence also included the years from 2001 to 2010, and this could have led to more precise estimates.

The F:M ratio in Italian PBC patients is lower than that reported in historical cohorts. Because our data are based on hospitalized cases, one might speculate that our finding is due to the inclusion

### Table 1. WHO International Classification of Diseases, Ninth Revision, Clinical Modification, Codes for Comorbidities

| ICD-9-CM Code | Disease Category |
|---------------|-----------------|
| 001-139       | Infectious diseases |
| 140-239       | Neoplasms |
| 155           | Malignant neoplasms of liver and intrahepatic bile ducts |
| 156           | Malignant neoplasms of gallbladder and extrahepatic bile ducts |
| 240-279       | Endocrine diseases |
| 320-389       | Diseases of the nervous system |
| 410-414       | Ischemic heart diseases |
| 430-438       | Cerebrovascular diseases |
| 460-519       | Diseases of respiratory system |
| 520.0-571.5; 571.8-579.9 | Gastrointestinal and liver diseases |
| 580-599       | Diseases of the genitourinary system |
| 135 (Sarcoidosis) | Autoimmune diseases |
| 2452 (Chronic lymphocytic thyroiditis) | |
| 2554 (Corticoadrenal insufficiency) | |
| 2810 (Pernicious anemia) | |
| 2830 (Autoimmune hemolytic anemias) | |
| 340 (Multiple sclerosis) | |
| 3580 (Myasthenia gravis) | |
| 555.XX (Regional enteritis) | |
| 556.XX (Ulcerative enterocolitis) | |
| 566 (Abscess of anal and rectal regions) | |
| 5790 (Celiac disease) | |
| 694.XX (Bullous dermatoses) | |
| 696.XX (Psoriasis and similar disorders) | |
| 697.XX (Lichen) | |
| 6996 (Psoriasis and similar disorders) | |
| 70901 (Vitiligo) | |
| 7100 (Systemic lupus erythematosus) | |
| 7101 (Systemic sclerosis) | |
| 7102 (Sicca syndrome) | |
| 7103 (Dermatomyositis) | |
| 7104 (Polymyositis) | |
| 7140 (Rheumatoid arthritis) | |
| 7141 (Feltly's syndrome) | |
| 7142 (Other rheumatoid arthritis with visceral or systemic involvement) | |
| 71430 (Polyarticular juvenile rheumatoid arthritis, chronic or unspecified) | |
| 71432 (Pauciarticular juvenile rheumatoid arthritis) | |
| 71433 (Monoarticular juvenile rheumatoid arthritis) | |
| 720.XX (Ankylosing spondylitis and other inflammatory spondylopathies) | |
of more males at the advanced stage. Indeed, males diagnosed with PBC experience worse outcomes than females, and this is probably due to a diagnostic delay in male subjects. The more advanced stage of the disease probably accounts for the observed reduced rate of response to ursodeoxycholic acid and consequently the higher hazard of liver-related complications and need for in-hospital assessment and treatment. However, other factors may also explain this finding. We used a methodological approach to account for these differences.

### Table 2. Absolute Numbers of Incident Cases of PBC from 2011 to 2015, Stratified by Age and Gender, and Rate Ratios for Age Category

| Age   | Male    | Crude Rate | Female  | Crude Rate | Total  | Crude Rate | Rate Ratio for Age Category (95% CI) |
|-------|---------|------------|---------|------------|--------|------------|-----------------------------------|
| 18-39 | n=169   | 0.43       | n=232   | 0.6        | n=401  | 0.51       | 1†                                |
| 40-69 | n=883   | 1.45       | n=2,099 | 3.28       | n=2,982| 2.39       | 4.61 (4.19-5.17)                   |
| 70+   | n=691   | 3.57       | n=1,459 | 5.23       | n=2,150| 4.55       | 8.57 (7.98-9.87)                   |
| Total | n=1,743 | 1.45       | n=3,790 | 2.9        | n=5,533| 2.21       |                                   |

*(×100,000).
†Reference.

### Table 3. Absolute Numbers of Prevalent Cases of PBC from 2011 to 2015, Stratified by Age and Gender, and Rate Ratios for Age Category

| Age   | Male    | Crude Rate | Female  | Crude Rate | Total  | Crude Rate | Rate Ratio for Age Category (95% CI) |
|-------|---------|------------|---------|------------|--------|------------|-----------------------------------|
| 18-39 | n=274   | 0.69       | n=351   | 0.91       | n=625  | 0.80       | 1†                                |
| 40-69 | n=1,252 | 2.05       | n=4,112 | 6.44       | n=5,364| 4.29       | 5.37 (4.95-5.84)                   |
| 70+   | n=929   | 4.80       | n=2,746 | 9.84       | n=3,675| 7.78       | 9.73 (8.94-10.59)                  |
| Total | n=2,455 | 2.05       | n=7,209 | 5.52       | n=9,664| 3.86       |                                   |

*(×100,000).
†Reference.

### Table 4. Incidence and Prevalence Rates (×100,000) Standardized to WHO Standard Population, Year, and Gender

| Year   | Incidence  | Prevalence  |
|--------|------------|-------------|
|        | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) |
|        | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) | DSR (95% CI) |
|        | Male | Female | Total | Male | Female | Total | Male | Female | Total | Male | Female | Total | Male | Female | Total |
| 2011   | 1.22 (1.08-1.40) | 2.17 (2.00-2.37) | 1.71 (1.60-1.84) | 2.20 (1.97-2.46) | 5.35 (5.02-5.70) | 3.85 (3.65-4.07) |
| 2012   | 1.14 (1.01-1.31) | 2.05 (1.88-2.25) | 1.61 (1.50-1.73) | 2.04 (1.80-2.30) | 5.41 (5.03-5.82) | 3.80 (3.57-4.05) |
| 2013   | 0.92 (0.80-1.07) | 1.99 (1.83-2.19) | 1.48 (1.38-1.59) | 1.87 (1.61-2.17) | 4.79 (4.49-5.11) | 3.40 (3.20-3.62) |
| 2014   | 0.92 (0.81-1.07) | 1.72 (1.57-1.90) | 1.34 (1.24-1.45) | 1.72 (1.52-1.94) | 4.13 (3.84-4.44) | 2.98 (2.80-3.17) |
| 2015   | 0.95 (0.82-1.11) | 1.68 (1.53-1.86) | 1.33 (1.23-1.44) | 1.65 (1.46-1.85) | 4.11 (3.83-4.40) | 2.94 (2.77-3.12) |
| 2011-2015 | 1.03 (0.97-1.09) | 1.92 (1.85-2.00) | 1.49 (1.44-1.54) | 1.89 (1.79-2.00) | 4.75 (4.6-4.9) | 3.39 (3.30-3.48) |

Abbreviation: DSR, direct standardized rate.
approach that overcomes selection biases typically encountered in most tertiary referral, retrospective case series that constitute most of the available epidemiological studies in PBC patients. In view of this, our data are in line with reports from registries based on general population registries, such as the Swedish National Population and Housing Census in Sweden or the Physician Claims Database and the Ambulatory Care Classification System Database in Alberta, Canada. Interestingly, a recent study using the Icelandic registry, which is a well-defined database encompassing all PBC cases diagnosed in Iceland from 1991 to 2015 identified through multiple case-finding strategies, recently showed an F:M ratio of 4.6:1. Evidence is accumulating to support the concept that males with PBC have been probably missed by historical cohorts.

This comprehensive study regarding the comorbidities in PBC thoroughly describes the comorbidities of hospitalized patients with PBC in Italy. Previous studies have focused primarily on extrahepatic autoimmune comorbidities associated with PBC and data available on nonautoimmune comorbidities are usually scarce or come from single-center cohorts. A previous pilot study from United States, still the largest one investigating comorbidities on PBC, questioned participants about the presence of all types of concomitant diseases but adopted a case-finding strategy (tertiary centers) that probably partially biased the results. Our data confirm the well-established association of PBC with other autoimmune diseases, such as autoimmune thyroiditis, Sjögren's syndrome, and rheumatoid arthritis. Among nonautoimmune comorbidities, we found a strikingly high incidence of hepatocellular and biliary neoplasms in PBC patients. A higher incidence of HCC in PBC patients has already been reported to be associated with advanced disease stage, male gender, and nonresponse to ursodeoxycholic acid. To our knowledge, there are scanty data on the incidence and prevalence of cholangiocarcinoma and gallbladder carcinoma in patients with PBC.

The other significant finding is the low frequency of ischemic heart diseases and cerebrovascular diseases in PBC patients compared with the general population. Patients with PBC typically show various degrees of dyslipidemia, but historical studies investigating cardiovascular risk in PBC failed to show higher cardiovascular mortality rates. There is also evidence that hypercholesterolemia is not associated with surrogate measures of atherosclerosis, such as intima-media thickness and presence of stenosis on ultrasound of carotid arteries, in patients with PBC. The major component of hyperlipidemia in PBC is lipoprotein-X, which has been found to have antiatherogenic properties. Assuming that hospitalized patients with PBC are more likely to be affected by cirrhosis, we should remember that data about cardiovascular risk

| Disease Category                                | Males       | Females       |
|------------------------------------------------|-------------|---------------|
| Infectious diseases                            | 416         | 541           |
| Neoplasms                                      | 593         | 823           |
| Malignant neoplasms of liver and intrahepatic   | 214         | 193           |
| bile ducts                                     |             | 1,362         |
| Malignant neoplasms of gallbladder and          | 49          | 62            |
| extrahepatic bile ducts                        |             | 743           |
| Endocrine diseases                             |             |               |
| Diseases of the nervous system                  | 713         | 1,393         |
| Ischemic heart diseases                         | 278         | 515           |
| Cerebrovascular diseases                        | 290         | 233           |
| Diseases of respiratory system                  | 204         | 312           |
| Gastrointestinal and liver diseases             | 504         | 674           |
| Diseases of the genitourinary system            | 1,394       | 2,266         |
| Autoimmune diseases                            | 485         | 763           |

Abbreviation: SHR, Standardized Hospitalization Ratio.
in cirrhosis are still conflicting.\(^\text{30,31}\) Our finding of a lower rate of hospitalizations for cardiovascular diseases emphasizes that the excess in mortality experienced by PBC patients is likely not due to these diseases.\(^\text{25,32,33}\)

Our study has some limitations. Administrative databases do have the strength to represent an entire population, overcoming limitations of single hospital-based case-finding strategies, but could produce some degree of misclassification that may affect conclusions. As far as our study is concerned, the main weakness in the National Hospital Discharge Database is that the code used to identify PBC is not specific for this entity. We cannot exclude that some cases of other cholestatic disorders might have been included in the analysis as PBC cases. However, it is likely that this misclassification has been at least partly negligible (e.g., sclerosing cholangitis [primary or secondary] can also be identified by a different and more specific code in ICD-9-CM, such as 576.1 [sclerosing cholangitis]). Another possible concern derives from the use of a database aimed for hospitalized cases to study a slow-progressing disease like PBC, when most patients are now seen on an outpatient basis. Nevertheless, our study also included a proportion of patients who received care under a “day-hospital service,” a scheme created for planned investigations and not acute care; it turns out that “hospitalized patients” does not necessarily mean “acutely sick patients.” Furthermore, the code 576.1 could have been used for a secondary diagnosis, meaning that the main cause of admission might have not been related to PBC.

To conclude, this national hospital-based study of hospitalized PBC provides an extensive survey of comorbidities associated with PBC. Our hospital-derived data suggest that PBC is a rare cause of hospitalization in Italy. Hospitalized patients with PBC are more likely to have extrahepatic autoimmune diseases and HCC and a low risk of cardiovascular events, and our data suggest a high risk for biliary tract cancers. Future studies should be aimed to validate these findings and also evaluate the burden of comorbidities on health care systems.

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