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

Valerio Manno,[1*] Alessio Gerussi,[2*] Marco Carbone,[2] Giada Minelli,[1] Domenica Taruscio,[3] Susanna Conti,[1**] and Pietro Invernizzi [2**]

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).

**These authors contributed equally to this work.*

***These authors contributed equally to this work.*

In Italy, two recent studies described its epidemiology,[6,7] 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,[1,9] which is possibly an overestimation because it goes down to 2:1 when restricted to antimitochondrial antibody positivity in the general population[3,10] and is close to 7:1 in the United Network for Organ Sharing liver transplant database.[11] Lower F:M ratios have also been reported by recent studies based on administrative databases.[5,6,8] The burden of comorbidities in terms of clinical and prognostic impact and costs for the health services is of key importance in medicine.[12-14] 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.[15] 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

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep4.1407

Potential conflict of interest: Dr. Invernizzi advises and received grants from Intercept. He received grants from Gilead.

ARTICLE INFORMATION:

From the [1]Service of Statistics, National Institute of Health, Rome, Italy; [2]Division of Gastroenterology and Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; [3]National Center for Rare Diseases, National Institute of Health, Rome, Italy.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Pietro Invernizzi, M.D., Ph.D.
Division of Gastroenterology and Center for Autoimmune Liver Diseases
Department of Medicine and Surgery
University of Milano-Bicocca
Via Cadore 48
20900 Monza (MB), Italy
E-mail: pietro.invernizzi@unimib.it
Tel.: +39 039 233 2187

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

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)	
2452 (Chronic lymphocytic thyroiditis)	Autoimmune diseases
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)	
70901 (Vitiligo)	
7100 (Systemic lupus erythematosus)	
7101 (Systemic sclerosis)	
7102 (Sicca syndrome)	
7103 (Dermatomyositis)	
7104 (Polymyositis)	
7140 (Rheumatoid arthritis)	
7141 (Felty'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)	

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 2. ABSOLUTE NUMBERS OF INCIDENT CASES OF PBC FROM 2011 TO 2015, STRATIFIED BY AGE AND GENDER, AND RATE RATIOS FOR AGE CATEGORY

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

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

*(×100,000).
†Reference.

TABLE 4. INCIDENCE AND PREVALENCE RATES (×100,000) STANDARDIZED TO WHO STANDARD POPULATION, YEAR, AND GENDER

	Incidence			Prevalence		
	DSR (95% CI)	DSR (95% CI)	DSR (95% CI)	DSR (95% CI)	DSR (95% CI)	DSR (95% CI)
Year	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.

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.[17] The more advanced stage of the disease probably accounts for the observed reduced rate of response to ursodeoxycholic acid[17] and consequently the higher hazard of liver-related complications and need for in-hospital assessment and treatment.[18,19] However, other factors may also explain this finding. We used a methodological

TABLE 5. ABSOLUTE NUMBER AND SHR OF COMORBIDITIES STRATIFIED BY GENDER

	Males		Females	
Disease Category	n	SHR (95% CI)	n	SHR (95% CI)
Infectious diseases	416	298 (270-328)	541	197 (181-215)
Neoplasms	593	120 (110-130)	823	71 (67-76)
Malignant neoplasms of liver and intrahepatic bile ducts	214	691 (601-709)	193	1,362 (1,177-1,569)
Malignant neoplasms of gallbladder and extrahepatic bile ducts	49	591 (437-781)	62	743 (570-953)
Endocrine diseases	713	151 (140-163)	1,393	133 (126-140)
Diseases of the nervous system	278	76 (67-86)	515	61 (56-67)
Ischemic heart diseases	290	87 (78-98)	233	66 (58-75)
Cerebrovascular diseases	204	79 (69-91)	312	66 (59-74)
Diseases of respiratory system	504	109 (99-119)	674	94 (87-102)
Gastrointestinal and liver diseases	1,394	213 (202-225)	2,266	407 (391-425)
Diseases of the genitourinary system	485	146 (134-160)	763	154 (143-165)
Autoimmune diseases	158	299 (257-349)	531	326 (299-355)

Abbreviation: SHR, Standardized Hospitalization Ratio.

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.[20] 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[8] or the Physician Claims Database and the Ambulatory Care Classification System Database in Alberta, Canada.[5] 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.[21,22] 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,[15,23] 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.[24] Our data confirm the well-established association of PBC with other autoimmune diseases, such as autoimmune thyroiditis, Sjögren's syndrome, and rheumatoid arthritis.[25] Among nonautoimmune comorbidities, we found a strikingly high incidence of hepatocellular and biliary neoplasms in PBC subjects. 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.[26] To our knowledge, there are scanty data on the incidence and prevalence of cholangiocarcinoma and gallbladder carcinoma in patients with PBC.[27,28]

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.[29] 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.[25] The major component of hyperlipidemia in PBC is lipoprotein-X, which has been found to have antiatherogenic properties.[30] Assuming that hospitalized patients with PBC are more likely to be affected by cirrhosis, we should remember that data about cardiovascular risk

in cirrhosis are still conflicting.[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.[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.

REFERENCES

1) Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. Lancet 2015;386:1565-1575.
2) Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. Hepatology 2009;50:291-308.
3) Podda M, Selmi C, Lleo A, Moroni L, Invernizzi P. The limitations and hidden gems of the epidemiology of primary biliary cirrhosis. J Autoimmun 2013;46:81-87.
4) Guillemin F. Describing the epidemiology of rheumatic diseases: methodological aspects. Curr Opin Rheumatol 2012;24:187-192.
5) Myers RP, Shaheen A, Fong A, Burak KW, Wan A, Swain MG, et al. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. Hepatology 2009;50:1884-1892.
6) Lleo A, Jepsen P, Morenghi E, Carbone M, Moroni L, Battezzati PM, et al. Evolving trends in female to male incidence and male mortality of primary biliary cholangitis. Sci Rep 2016;6:1-8.
7) Marzioni M, Bassanelli C, Ripellino C, Urbinati D, Alvaro D. Epidemiology of primary biliary cholangitis in Italy: evidence from a real-world database. Dig Liver Dis 2019;51:724-729.
8) Zöller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet 2012;379:244-249.
9) Triger DR. Primary biliary cirrhosis: an epidemiological study. Br Med J 1980;281:772-775.
10) Mattalia A. Characterization of antimitochondrial antibodies in healthy adults. Hepatology 1998;27:656-661.
11) Harms MH, Janssen QP, Adam R, Duvoux C, Mirza D, Hidalgo E, et al. Trends in liver transplantation for primary biliary cholangitis in Europe over the past three decades. Aliment Pharmacol Ther 2019;49:285-295.
12) Volk ML, Hernandez JC, Lok AS, Marrero JA. Modified Charlson Comorbidity Index for predicting survival after liver transplantation. Liver Transpl 2007;13:1515-1520.
13) Ampuero J, Jimeno C, Quiles R, Rosales JM, Palomo N, Cordero P, et al. Impact of comorbidities on patient outcomes after interferon-free therapy-induced viral eradication in hepatitis. J Hepatol 2018;68:940-948.
14) Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis 1970;23:455-468.
15) Floreani A, Franceschet I, Cazzagon N, Spinazzè A, Buja A, Furlan P, et al. Extrahepatic autoimmune conditions associated with primary biliary cirrhosis. Clin Rev Allergy Immunol 2015;48:192-197.
16) Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol 2012;56:1181-1188.
17) **Carbone M**, **Mells GF**, Pells G, Dawwas MF, Newton JL, Heneghan MA, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology 2013;144:560-569.
18) Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, et al. The UK-PBC risk scores: derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology 2016;63:930-950.
19) Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen H, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology 2015;149:1804-1812.e4.
20) Frank L. Epidemiology. The epidemiologist's dream: Denmark. Science 2003;301:163.
21) Baldursdottir TR, Bergmann OM, Jonasson JG, Ludviksson BR, Axelsson TA, Björnsson ES. The epidemiology and natural history of primary biliary cirrhosis. Eur J Gastroenterol Hepatol 2012;24:824-830.
22) Örnolfsson KT, Olafsson S, Bergmann OM, Gershwin ME, Björnsson ES. Using the Icelandic genealogical database to define the familial risk of primary biliary cholangitis. Hepatology 2018;68:166-171.

23) 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;145:167-172.
24) Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology 2005;42:1194-1202.
25) Allocca M, Crosignani A, Gritti A, Ghilardi G, Gobatti D, Caruso D, et al. Hypercholesterolaemia is not associated with early atherosclerotic lesions in primary biliary cirrhosis. Gut 2006;55: 1795-1800.
26) Trivedi PJ, Lammers WJ, Van Buuren HR, Parés A, Floreani A, Janssen H, et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. Gut 2016;65:321-329.
27) Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1221-1228.
28) Akisawa N, Maeda T, Tsuda K, Nishimori I, Morita M, Iwasaki S, et al. Case report: primary biliary cirrhosis associated with cholangiocarcinoma. Dig Dis Sci 1998;43:2138-2142.
29) Longo M, Crosignani A, Battezzati PM, Squarcia Giussani C, Invernizzi P, Zuin M, et al. Hyperlipidaemic state and cardiovascular risk in primary biliary cirrhosis. Gut 2002;51:285-289.
30) Chang PY, Lu SC, Su TC, Chou SF, Huang WH, Morrisett JD, et al. Lipoprotein-X reduces LDL atherogenicity in primary biliary cirrhosis by preventing LDL oxidation. J Lipid Res 2004;45:2116-2122.
31) Sørensen HT, Thulstrup AM, Mellemkjar L, Jepsen P, Christensen E, Olsen JH, et al. Long-term survival and cause-specific mortality in patients with cirrhosis of the liver. J Clin Epidemiol 2003;56:88-93.
32) Van Dam GM, Gips CH. Primary biliary cirrhosis in the Netherlands: an analysis of associated diseases, cardiovascular risk, and malignancies on the basis of mortality figures. Scand J Gastroenterol 1997;32:77-83.
33) Crippin JS, Lindor KD, Jorgensen R, Kottke BA, Harrison JM, Murtaugh PA, et al. Hypercholesterolemia and atherosclerosis in primary biliary cirrhosis: what is the risk? Hepatology 1992;15:858-862.

Author names in bold designate shared co-first authorship.