Epidemiology of primary biliary cholangitis and its factors: An updated systematic review

Nan Wu

Peking University People's Hospital

Rui Jin

Peking University People's Hospital

Xiao-Xiao Wang

Peking University People's Hospital

Han-Ji Jiang

Peking University People's Hospital

Bi-Fen Luo

Peking University People's Hospital

Guang-Jun Song

Peking University People's Hospital

Bo Feng (✉ fengbo@pkuph.edu.cn)

Peking University People's Hospital <https://orcid.org/0000-0001-5084-6715>

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Abstract

Background To understand the latest data on the prevalence and incidence rates for primary biliary cholangitis (PBC) and its factors, we systematically reviewed recent studies on epidemiology of PBC.

Methods Case-finding and general population-based studies reporting prevalence and/or incidence rates for PBC were systematically identified by searching electronic databases combined with manual searching.

Results A total of 37,452 PBC patients from 22 studies based on cases and 6 based on general population were included, which covered over 112.62 million inhabitants and 107,490 individuals undergoing health check-ups. As for case-finding studies, global prevalence and incidence rates for PBC ranged from 2.6 to 58.2 per 100,000 inhabitants and 0.8 to 5.3 per 100,000 inhabitants/year during the past decade, in which the variable data are associated with gender, age, race and region. Of the individuals undergoing health check-ups, 1,034 were positive for type M2 antimitochondrial antibody (AMA-M2) and 150 were diagnosed as PBC, and prevalence rates of positive AMA-M2 and PBC ranged from 430.7 to 1,456.9 and 49.2 to 276.6 per 100,000 individuals. The prevalence ratios of male/female were 1:2.2 and 1:4.1 in individuals with positive AMA-M2 and in PBC patients.

Conclusions Global prevalence and incidence rates for PBC vary widely, which were significantly affected by gender, age, race and region. Studies based on general population showed a much higher prevalence of PBC and AMA-M2, and the association of gender with AMA-M2 may be far less than that with PBC in real world.

Backgrounds

Primary biliary cholangitis (PBC) is one of cholestatic liver diseases, which is induced by immune-mediated damage of biliary epithelial cells and characterized by destruction of small intrahepatic bile ducts with risk for progression to biliary fibrosis, even ultimately to cirrhosis, and hepatocellular cancer. The pathogenesis of PBC is still unclear. Most patients present asymptotically, and clinical symptoms are frequently fatigue, pruritis and arthralgia in some of PBC patients. A diagnosis of PBC can be made based on elevated alkaline phosphatase (ALP) and positive antimitochondrial antibody (AMA) at a titer $\geq$ 1:40. Histology is usually not necessary for diagnosis unless specific antibodies are absent, but it is useful for assessing the stage of disease and identifying coexistent liver diseases^[1].

The epidemiology of PBC has evolved since its first systematic description in the 1940s^[2], and assisted in our understanding of the disease itself and finding ways to prevent occurrence and progression of the disease. Earlier studies on the prevalence and incidence for PBC mainly focused on the differences in the epidemiological rates among various regions. Due to a lack of a uniform diagnostic guideline for PBC in the past, it was difficult to draw substantial and generalized conclusions on PBC prevalence over time and region^[3]. Boonstra, et al identified and systematically reviewed 24 epidemiological studies on PBC between 1972 and 2007, and summarized that the prevalence and incidence rates for PBC ranged from 1.91 to 40.2 per 100,000 inhabitants and 0.33 to 5.8 per 100,000 inhabitants/year^[4]. However, several studies showed that the prevalence and incidence rates for PBC have been increasing over time^[4–7]. As understanding and diagnosis of PBC have evolved in recent years, the previous studies may not reflect the current situation for PBC.

In the past decade, many new data have been accumulated on the prevalence and incidence for PBC around the world. This article will highlight recent data regarding the epidemiology of PBC and clarify those factors for distribution of the disease.

Methods

Search strategy

Studies were systematically searched from the electronic forms of the Medline, Embase and Cochrane databases, following by the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[8]. Manual searching was used to follow up references in identified studies and abstracts from international hepatology meetings. Eligible studies were identified from January 1st, 2008 to December 31st, 2018. The following strategy was used: ((primary billiary cirrhosis) or (primary billiary cholangitis) or (anti-mitochondrial antibodies) or (mitochondrial antibodies)) and ((epidemiology) or (prevalence) or (incidence) or (occurence)). Additionally, we searched the Chinese studies from Wanfang and CNKI electronic data using ((primary billiary cirrhosis) or (primary billiary cholangitis) or (anti-mitochondrial antibodies) or (mitochondrial antibodies)) and ((epidemiology) or (prevalence) or (incidence) or (screening)).

Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined by all authors. Studies were considered for inclusion if they met the following criteria: (i) English language or Chinese language; (ii) the reported incidence or prevalence of PBC or AMA in a population of defined size; (iii) published in peer-reviewed journals as full papers; (iv) published in international hepatology meetings as abstracts with original data. Studies were excluded if they: (i) published before 2008; (ii) only reported the frequency of PBC or AMA within a subgroup of patients with another condition; (iii) only reported the frequency of another medical condition amongst patients with PBC or positive AMA; (iv) were case reports or reviews. In the event of duplicate reports of the same study subjects, we included the most recent one.

Data extraction

Data were extracted independently by two investigators (WN and JR). Inconsistent data were discussed with the other authors when necessary. Consensus was achieved for all data inclusion before analysis. The following data were extracted: first author, publication year, study country or area, study period, number of patients with PBC or positive AMA, number of inhabitants, method of case-finding, method of case-ascertainment, prevalence per 100,000 inhabitants, incidence per 100,000 inhabitants per year, and those factors concerning to age, sex and race. Additional data were obtained through direct communication with the corresponding authors when necessary.

Quality assessment

Study quality was assessed and scored on the basis of (1) coverage of cases in the area, (2) definition of studied population, (3) case-finding method and (4) established diagnostic criteria. The quality was considered 'good' when the coverage of cases was high in defined population in the catchment area, and a good way to identify patients and well-established diagnostic criteria were used. Quality was considered 'moderate' when definition of study population and case-finding method were not described sufficiently and unrecognized diagnostic criteria were used with a reasonable chance to miss cases. It was considered 'poor' when the conditions were absent (Supplementary Table 1).

Results

Literature review

Electronic and manual searches identified a total of 1,724 English citations. After review of the titles and abstracts, 1,695 citations were excluded according to the eligibility and ineligibility criteria. The remaining 29 studies were selected for full article review. After careful examination of the full texts, five studies were excluded because of duplicate reports for the same subjects, reports unrelated to prevalence of PBC, and no data on prevalence or incidence for PBC. Twenty-four studies were thus included in this systematic review^[5–7,9–27,30], which comprises 22 studies based on cases and 2 based on general population (Figure 1). Among 327 studies published in Chinese (searched in Chinese database), 4 based on general population were selected and no papers based on cases were found^[28,29,31,32]. There was full concordance between the two independent reviewers with respect to the final inclusion and exclusion of the studies reviewed.

Characteristics of included studies based on cases

As shown in Table 1, among the 22 studies included in this review, 12 studies were from Europe, 4 from Asia, 5 from North-America and 1 from Oceania. Although all of them were published since 2008, the period of the studies spanned from 1980 to 2015. Studies varied in size from 10 to 8680 PBC patients which were 37,302 in total and covered over 112.62 million inhabitants. Median age at diagnosis ranged from 51 to 65, and the ratio of male/female from 1:2.3 to 1:18.8 which was 1:4.1 in total. Eight studies described the race distribution of patients. The cases were searched and found from hospital medical record system, population-based administrative database, commercial laboratories, and /or personal registry physicians among others. All of them were diagnosed on the basis of PBC guidelines in accordance with or similar to those made by American Association for the Study of Liver Diseases or European Association for the Study of the Liver^[33–35].

Global prevalence of PBC and its factors shown in cases-based studies

The included studies on prevalence of PBC showed significant variation in association with gender, age, region and race (Table 2). The lowest and highest prevalence rates of the disease were found in Brunei Darussalam and Crete, Greece, 2.6 and 58.2 per 100,000 age- and sex matched inhabitants, respectively^[6,10].

It is well known that women are susceptible to PBC. In present analysis, the mean proportion of female patients was 80.2% (69.8–100%) in total. The disease prevalence rates in women and men ranged from 8.3 to 64.4 per 100,000 inhabitants and 2.1 to 15.4 per 100,000 inhabitants, respectively. The impact of age on PBC prevalence was analyzed in six studies^[5,9,13,15,18,21]. Most of them demonstrated that prevalence of the disease increased along with age, and was significantly higher in patients aged ≥ 40 than those aged < 40 , with the highest prevalence rate occurring in patients aged 60–79 years. The impact of race on PBC prevalence was analyzed in five studies^[5,10,12,13,21]. The prevalence was 11.5 to 46.0, 30.8, and 2.3 to 5.6 per 100,000 inhabitants in White race, Black race (mainly African American), Yellow and Brown races (mainly Asian), respectively. It was noteworthy that the disease prevalence was 44.7 per 100,000 inhabitants in Asian American^[5]. Additionally, prevalence of 22.7 to 39.2, 11.1 to 58.2, and 2.6 to 25.5 (2.6 to 5.6 excepting Israel) per 100,000 inhabitants were reported in America, Europe, and Asia-Pacific regions, respectively (Figure 2).

Global incidence of PBC and its factors shown in cases-based studies

As shown in Table 2, data from different countries reported a wide difference in the disease frequency, ranging from an incidence of 0.8 to 5.3 per 100,000 inhabitants per year. The lowest and highest incidence rates were found in New Zealand and Italy, respectively^[12,19].

Part of studies analyzed the impact of gender, age, race and region on PBC incidence. There were year incidence rates of 1.4 to 11.3 per 100,000 inhabitants, and 0.04 to 2.3 per 100,000 inhabitants in women and men, respectively. Similarly to the impact of age on prevalence, incidence of the disease was significantly higher in patients aged ≥ 40 than those aged < 40 , with the highest incidence rate occurring during 60–79 years old. The impact of race on PBC

incidence was analyzed in only two studies, in which incidence rates were 8.2, 4.0, 4.4 and 1.4 per 100,000 inhabitants in Asian American, Black/African American, White race and native Israelis population, respectively^[5,13]. Additionally, annual incidence of 1.5 to 4.9, 1.0 to 5.3, and 0.8 to 2.0 (0.8 to 0.9 excepting Israel) per 100,000 inhabitants were reported in America, Europe, and Asia-Pacific region, respectively (Figure 2).

Epidemiology of positive AMA-M2 and PBC in general population-based studies

From the Medline, Embase and Cochrane databases, we found 2 studies based on general population, and from Chinese databases, we found 4 studies. All of the 6 studies were originated from Chinese individuals who undergoing health check-ups (Tables 3 and 4)^[27–32]. AMA-M2 was detected by ELISA or immunoblotting, and cases were ascertained on the basis of 2009 guidelines^[34,35]. The studies were performed after 2005 and varied in size from 6,658 to 36,459 individuals with 107,490 (female/male: 53,818/53,672) in total.

Out of 107,490 individuals, 1034 were positive for AMA-M2 and 150 were diagnosed as PBC, and total prevalence rates of positive AMA-M2 and PBC were 961.9 (ranging from 430.7 to 1,456.9) and 139.5 (49.2 to 276.6) per 100,000 individuals, respectively. When combining all of the six studies, prevalence rates of positive AMA-M2 were 609.5 (303.3 to 1,144.3) and 1315.4 (515.7 to 1,884.1) per 100,000 individuals in men and women, and the prevalence ratio of male/female were 1:2.2. Prevalence rates of PBC were 41.6 (23.5 to 53.5) and 171.1 (77.4 to 214.9) per 100,000 individuals in men and women, respectively, and the prevalence ratio of male/female were 1:4.1. Five study described the association of age and prevalence, and showed that prevalence rates of both positive AMA-M2 and PBC increased with age, and were significantly higher in individuals aged ≥ 40 than those < 40 , and the peaks occurred over 55 years old^[27,29–32].

Discussion

We systematically reviewed 22 studies based on cases and 6 based on general population, which originated from 17 countries or regions in America, Europe, and Asia-Pacific region. As for case-finding studies, global prevalence and incidence rates for PBC range from 2.6 to 58.2 per 100,000 inhabitants and 0.8 to 5.3 per 100,000 inhabitants/year during the past decade, respectively. The increase in PBC prevalence over time may result from increasing disease awareness, the improved diagnostic accuracy and digitalized patient registration with more complete data.

The etiology and pathogenesis of PBC remains unclear, although it is well established that individual susceptibility is closely related to combinative reaction of genetic and environmental factors. Here, we focused on the impact of gender, age, race and region on epidemiology of PBC. Similarly to other reports, PBC mainly affects women, and the mean proportion of female patients is 80.2% in the review. The disease prevalence and year incidence rates range from 8.3 to 64.4, and 1.4 to 11.3 per 100,000 inhabitants in females, which are higher than those in male. The prevalence and incidence of PBC increase along with age, were significantly higher in patients aged ≥ 40 than those < 40 , and the peaks occurred in patients aged 60–79 years. It seems that they are higher in White and Black races than in Yellow and Brown races. There are widely variable data in different continents, different countries, and even different regions within the same country.

All of the 22 studies were based on searching for PBC cases in various databases, and they were subject to obvious shortcomings which may significantly influence the resulting prevalence and incidence rates. First, most of PBC patients are asymptomatic, and do not initially see a doctor unless they suffer a sense of discomfort or have abnormal liver function in physical examination. Even so, the diagnosis of PBC relies on the experienced physicians to a considerable extent. Second, all authors searched for PBC cases as possible as they could, however, the completeness of cases-finding and the extent of covering the local population remained doubtful in most of the studies (Supplementary Table 1). Third, the diagnostic criteria of PBC are well known as follows: biochemical evidence of cholestasis with elevation of alkaline phosphatase activity, presence of AMA and compatible liver histology. Implementation of the criteria was not consistent in different studies. As far as cholestatic liver function tests were concerned, except for elevated ALP analyzed in most of studies, there were other criteria for example cholestatic disorder of at least 6 month duration^[6,12,13,15], and/or a 1.5-fold or more increase in ALP^[13,21], or ALP > 120 U/L or 150 U/L^[5,17]. AMA positivity was defined by a titer $> 1:20$ or M2 antibody > 25.0 U in one study^[17].

The limitations discussed above decrease the number of PBC cases that are properly diagnosed or otherwise detected, thus reducing both prevalence and incidence rates^[36]. As the standard criteria have been well-established and are universally applied in clinical practice^[34,35], the risk of overdiagnosing PBC is negligible. Screening in general population has the potential to identify the largest number of AMA-positive subjects and PBC patients, with the minor discrepancy resulted from the above limitations. Therefore, we searched the epidemiological studies which were based on general population and published since 2008. Unfortunately, only six studies from China were found, which covered 107,490 individuals who underwent health check-ups (female/male: 53,818/53,672). The median prevalence rates of positive AMA-M2 and PBC were 961.9 (ranging from 430.7 to 1,456.9) and 139.5 (49.2 to 276.6) per 100,000 individuals, respectively, with similar trend with age to that in the studies based on cases. The total prevalence ratios of male/female were 1:2.2 and 1:4.1 in individuals with positive AMA-M2 and PBC. The present analysis demonstrated much higher prevalence of PBC in general population-based studies than case-finding studies, especially for middle-old age women. Due to the lowest prevalence for PBC in the Yellow race population including Chinese, the prevalence may be higher for the White and Black races in general population. On the other hand, individuals with positive AMA-M2 are much more than those with PBC, and earlier studies with small number of subjects also showed a high AMA prevalence of ranging from 588.2 to 1020.4 per 100,000 individuals^[37–40]. However, the total prevalence ratio of male/female was much less in individuals with positive AMA-M2 than in those with PBC, which suggested that AMA-M2 positive rate may be high in men in real world.

Despite correcting the discrepancy resulted from the case-finding studies, there were some limitations in the studies based on general population. Since all of the studies were originated from China, they cannot reflect global epidemiology for positive AMA and PBC in real world. Second, AMA and PBC-specific antinuclear antibodies were not detected in most of the six studies, which led to a loss of a small percentage of PBC patients with negative AMA. Third, these studies followed the diagnostic criteria of PBC, however, liver biopsy was not performed for individuals with positive AMA-M2 and normal ALP level. In spite of these limitations, several conclusions can be drawn from careful consideration of the available data.

Conclusions

we systematically reviewed global epidemiology of PBC by searching for the studies published for the recent eleven years. Case-finding studies showed widely variable data of global prevalence and incidence rates for PBC which were significantly affected by gender, age, race and region. Simultaneously, increasing trend in prevalence and relative steady incidence were observed comparing with earlier studies. Those studies based on general population showed a much higher prevalence of PBC than the case-finding studies, and a much higher frequency of AMA than that of PBC. These results suggest that there may be high prevalence rates of positive AMA and PBC in real world. Additionally, the association of gender with AMA positivity is far less than that with PBC.

Abbreviations

PBC, primary biliary cholangitis; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; AMA-M2, type M2 antimitochondrial antibody; ASINPI, Asian American, American Indian, Pacific Islander; AA, African American.

Declarations

Ethics approval and consent to participate

Ethical approval for this project was granted by the Institutional Review Board (IRB) of Peking University People's Hospital.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wu N contributed to design, data acquisition, statistical analysis and drafted the manuscript; Jin R contributed to data acquisition and statistical analysis; Wang XX and Jiang HJ participated in study design and data analysis; Luo BF and Song GJ participated in study planning and statistical analysis; Feng B contributed to funding, design, statistical analysis and drafted the manuscript; and all authors reviewed and approved the final manuscript.

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Tables

TABLE 1 Characteristics of included studies based on cases

Authors and publication year	Country	Study period	No. of patients	Population (million)	Age (range)	Sex (M/F)	Race	Case-finding methods	Case-ascertainment ^ε
Myers <i>et al</i> ^[9] , 2009	Canada	1994-2004	137	1.1	53 (44-64)	22/115	-	Population-based administrative data and ICD	I + II + III
Chong <i>et al</i> ^[10] , 2010	Brunei Darussalam	2007	10	0.39	51 (27-83)	0/10	Malays: 6; Chinese: 1; Indigenous: 1; Others: 1	Hepatology clinics register, department of pathology register and central pharmacy database	I + II + III + V
Baldursdottir <i>et al</i> ^[11] , 2012	Iceland	1991-2010	168	0.32	62 (13-92)	30/138	-	Laboratory database at the National University Hospital of Iceland (NUH)	I + II + III
Ngu <i>et al</i> ^[12] , 2012	New Zealand	1980-2008	71	0.49	60 (34-87)	6/65	94% were Caucasian. One Maori and one Asian	Public and private, outpatient clinics, hospital discharge summaries, and laboratory and pathology reports	I + II + III
Delgado <i>et al</i> ^[13] , 2012	Israel	1990-2010	138	1.08	55(47-60)	7/131	Ashkenazim:69; Sephardic Jews:54; Arab origin:15	Public and private, outpatient clinics, hospital discharge summaries, laboratory and pathology reports, and personal registry physicians	I + II + III
McNally <i>et al</i> ^[14] , 2014	England	1987-2003	982	2.05	65 (F/M: 65/64)	95/887	-	Personal registry physicians,	I + II + III

								hospital admission data and laboratory data, and National Statistics listings of deaths	
Boonstra <i>et al</i> ^[15] , 2014	Netherlands	2000-2008	992	5.86	57/61 (F/M)	121/871	-	Nationwide network and comprehensive registry, nationwide hospital billing system, laboratory database and personal registry of physicians	I + II + III
Koulentaki <i>et al</i> ^[16] , 2014	Greece	1990-2010	245	0.6	58 (24-87)	30/215	-	Medical record database at the liver outpatient clinics of hospitals	I + II + III
Kim <i>et al</i> ^[17] , 2015	USA	2010-2013	6107	-	adults	-	-	Electronic data from a large commercial laboratory	I + II + III
Kim <i>et al</i> ^[18] , 2016	South Korea	2009-2013	2824	38.42	57.4	393/2431	-	Nationwide Health Insurance Review and Assessment Service claims data and Rare Intractable Disease registration data on PBC	IV
Lleo <i>et al</i> ^[19] , 2016A	Italy	2000-2009	2970	9.74	61.7 (61.5-62.7)	897/2073	-	Administrative database of the inpatient population	IV
Lleo <i>et al</i> ^[19] , 2016B	Denmark	2000-2009	722	5.53	60.7	138/584	-	Danish	IV

2016B		2009						National Patient Registry Laboratory database, a questionnaire for physicians	
Dahlqvist <i>et al</i> ^[20] , 2017	France	2006-2007	491	-	-	-	-		-
Gatselis <i>et al</i> ^[6] , 2017	Greece	2000-2015	482	0.75	56.3 ± 13.7	65/417	Caucasian: 439; Immigrants: 43	Medical record database at the Department of Medicine of University Hospital the Clinical Data Analysis and Reporting System and the Clinical Management System of Hong Kong Marshfield Epidemiologic Study Area (MESA) database using ICD-9 system code data	I + II + III
Cheung <i>et al</i> ^[21] , 2017	China	2000-2015	1016	7.3	60.6 (51.8-72.6)	214/802	Chinese		I + II + III
Kanth <i>et al</i> ^[22] , 2017	USA	1992-2011	79	-	58 (27-93)	4/75	Caucasian race: 78; Non-white: 1	Swedish inpatient, outpatient, and day clinic registries using ICD-9 and ICD-10	I + II + III + V
Wahlin <i>et al</i> ^[7] , 2017	Sweden	1987-2014	5411	-	-	1115/4296	-	Health Improvement Network database of pseudonymised UK family practice records	IV
Webb <i>et al</i> ^[23] , 2017	England	1998-2015	1403	-	63 (53-72)	-	-	Electronic health record-	-
Lu <i>et al</i> ^[5] , 2018	USA	2003-2014	3488	7.7	No data on	638/2850	ASINPI: 252;		I + II + IV

					median age ^b		Black/AA: 286; White: 2227; Unknown: 723	based data from geographically- diverse health systems	
Beretta- Piccoli <i>et al</i> ^[24] , 2018	Switzerland	2000- 2015	474	2.8	53 (45- 63)	73/401	White 443; Asian 10; Hispanic 8; Black 1	Local databases in all university hospitals and in two large secondary centers, and personal registry of physicians	-
Yoshida <i>et al</i> ^[25] , 2018	Canada	2013- 2015	8680	27.29	0 - ≥80	1863/6817	-	National hospital administrative records from the Canadian Institute for Health Information	IV
Marzioni <i>et al</i> ^[26] , 2018	Italy	2014- 2015	412	1.2	>14	82/330	-	Databases of 900 General Practitioners using ICD-9	IV
Summary			37,302	Over 112.62		5793/23,508			

^a Case-ascertainment criteria: I, positive AMA and/or AMA-M2; II, elevated serum ALP; III, histological features of PBC; IV, ICD-10 (K74.3) and/or ICD-9 (571.6); V, excluding other cholestatic causes.

^b No data on median age but age distribution of patients was shown.

M/F, male/female; ICD, International Classification of Diseases; PBC, primary biliary cholangitis; ASINPI, Asian American, American Indian, Pacific Islander; AA, African American.

TABLE 2 Prevalence and incidence of primary biliary cholangitis in cases-based studies^a

Authors and publication year	Prevalence (95% CI)	Prevalence on age	Prevalence on sex (M/F ^b)	Prevalence on race	Incidence (95% CI)	Incidence on age	Incidence on sex	Incidence on race
Myers <i>et al</i> ^[9] , 2009	22.7	Age range: total (M/F: 5.5/38.3) 20-39: 3.8 (1.7/5.8); 40-59: 24.7 (4.3/43.7); 60-79: 57.3 (16.7/95.2); ≥80: 13.7 (0/26.4)	-	-	3.0	Age range: total (M/F: 1.0/4.8) 20-39: 0.8 (0.2/1.4); 40-59: 3.6 (1.2/5.9); 60-79: 6.3 (2.6/9.7); ≥80: 2.2 (0/4.3)	-	-
Chong <i>et al</i> ^[10] , 2010	2.6	-	Female: 5.5	Malays: 2.3; Chinese: 4.1; Indigenous: 4.3	0-1.0	-	-	-
Baldursdottir <i>et al</i> ^[11] , 2012	38.3	-	12.5/64.4	-	3.4 (2.4-4.3)	≥40 Female: 12.3	-	-
Ngu <i>et al</i> ^[12] , 2012	9.9 (7.1-12.7)	-	2.1/ 17.5	Caucasian: 11.5; Maori: 2.5; Asian: 3.4	0.8 (0.1-1.6)	-	-	-
Delgado <i>et al</i> ^[13] , 2012	25.5	≥ 40: 21	3/33	native Israelis population: 21.1; immigrants: 31.0	2.0	45-54: 3.0 (Female)	0.04/3.0	native Israelis population: 1.4; immigrants: 2.9
McNally <i>et al</i> ^[14] , 2014	-	-	-	-	4.5 (4.1-4.9)	Age range: total (M/F: 0.9/7.7) 40-59: 3.2 (0.5 /5.9); 60-74: 6.6 (1.9/10.8); ≥75: 5.8 (0.9/8.9)	-	-
Boonstra <i>et al</i> ^[15] , 2014	13.2	70-79: 42.3 (peak prevalence)	2.5/22.5	-	1.1	Age range: total (M/F: 0.3/1.9) 20-29: 0/0.2; 30-39: 0.1/0.7; 40-49: 0.1/1.6; 50-59: 0.4/3.2; 60-69: 0.8/3.7; 70-79: 1.1/4.2;	-	-

						>80: 0.9/2.4		
Koulentaki <i>et al</i> ^[16] , 2014	36.5	-	-	-	2.1 (0.4-3.6)	-	-	-
Kim <i>et al</i> ^[17] , 2015	-	-	-	-	1.5			
Kim <i>et al</i> ^[18] , 2016	4.8	20-29: 0.2; 30-39: 1.0; 40-49: 3.6; 50-59: 8.4; 60-69: 12.4; 70-79: 10.7; >80: 5.4	1.1/8.3	-	0.9	20-29: 0.05; 30-39: 0.3; 40-49: 0.6; 50-59: 1.6; 60-69: 2.0; 70-79: 1.8; >80: 1.1	0.3/1.4	-
Lleo <i>et al</i> ^[19] , 2016A	11.1 (10.9-11.3)	-	5.8/16.2	-	1.7 (1.4-1.9)	-	1.1/2.1	-
Lleo <i>et al</i> ^[19] , 2016B	11.5 (11.3-11.8)	-	3.4/19.0	-	1.1 (1.1-1.2)	-	0.5/1.8	-
Dahlqvist <i>et al</i> ^[20] , 2017	24.3	-	-	-	1.0	Age range: M/F 20-29: 0 /0.2; 30-39: 0.2/0.6; 40-49: 0.05/1.3; 50-59: 0.2/2.2; 60-69: 0.5/2.6; 70-79: 0.6 /2.7; 80-89: 0.8/1.8; 90-99: 0/1.3		-
Gatselis <i>et al</i> ^[6] , 2017	58.2	-	-	-	-	-	-	-
Cheung <i>et al</i> ^[21] , 2017	5.64	Age range: M/F 20-39: 0.9/7.5; 40-59: 2.4/14.8; 60-79: 8.9/50.9; ≥80: 10.9/35.3		5.6 (Chinese)	0.8	Age range: M/F 20-39: 0.1/0.1; 40-59: 0.3/1.7; 60-79: 1.1/3.4; ≥80: 1.6/3.2		0.8 (Chinese)
Kanth <i>et al</i> ^[22] , 2017	-	-	-	-	4.9	-	sporadic/11.3	-

Wahlin <i>et al</i> ^[7] , 2017	34.6	-	-	-	2.2±0.9	-	-	-
Webb <i>et al</i> ^[23] , 2017	-	-	7.6/61.7	-	2.3 (2.2-2.4)	-	-	-
Lu <i>et al</i> ^[5] , 2018	39.2	≤40: 5.4; 41-50: 21.6; 51-60: 46.6; 61-70: 86.2; ≥71: 88.8	15.4/57.8	ASINPI: 44.7; Black/AA: 30.8; White: 46.0	4.3	≤40: 0.8; 41-50: 3.1; 51-60: 6.1; 61-70: 9.9; ≥71: 6.7	2.3/6.0	ASINPI: 8.2; Black/AA: 4.0; White: 4.4
Beretta-Piccoli <i>et al</i> ^[24] , 2018	15-20	-	-	-	-	-	-	-
Yoshida <i>et al</i> ^[25] , 2018	31.8 (30.9-32.7)	-	-	-	-	-	-	-
Marzioni <i>et al</i> ^[26] , 2018	28	-	-	-	5.3	-	-	-

^a Per 100,000 inhabitants.

M/F, male/female; ASINPI, Asian American, American Indian, Pacific Islander; AA, African American.

TABLE 3 Characteristics of included studies based on general population

Authors and publication year	Province	Study period ^a	Population	Age (range)	Sex (M/F)
Liu <i>et al</i> ^[27] , 2010	Guangdong	200606-200609	8,126	44 (18-83)	4,248/3,878
Guo <i>et al</i> ^[28] , 2014	Hebei	201102-201210	20,970	4m-93y	10,550/10,420
Cai <i>et al</i> ^[29] , 2015	Jiaotong University, Shanghai	201203-201303	6,658	46.1 ± 12.7	3,845/2,813
Chen <i>et al</i> ^[30] , 2016	Xuhui District, Shanghai	201201-201406	19,012	≥ 18	8,310/10,702
Ye <i>et al</i> ^[31] , 2018	Guizhou	201404-201607	36,459	M: 42.5 ± 13.6 F: 42.5 ± 13.4	18,687/17,772
Qu <i>et al</i> ^[32] , 2018	Pudong, Shanghai	201701-201712	16,265	49 ± 22 (21-76)	8,178/8,087
Summary			107,490		53,818/53,672

^a Indicated as YYYYMM-YYYYMM. M/F, male/female.

TABLE 4 Prevalence of patients with positive AMA-M2 or primary biliary cholangitis in general population-based studies^a

Authors and publication year	No. of patients with positive AMA-M2 (M/F)	Prevalence of positive AMA-M2 (95% CI)	Prevalence of positive AMA-M2 on age	Prevalence of positive AMA-M2 on sex (M/F)	No. of patients with PBC (M/F)	Prevalence of PBC (95% CI)	Prevalence of PBC on age	Prevalence of PBC on sex (M/F)
Liu <i>et al</i> ^[27] , 2010	35 (15/20)	430.7 (300-580)	Age range: total (M/F: 353.1/515.7) 30-39: (200/100); 40-49: (300/450); 50-59: (250/350); ≥ 60: (220/1320)		4 (1/3)	49.2 (12.8-109.3)	>40 (Female): 155.8	23.5/77.4
Guo <i>et al</i> ^[28] , 2014	156 (32/124)	743.9	-	303.3/1190	58	276.6	-	-
Cai <i>et al</i> ^[29] , 2015	97 (44/53)	1456.9	Age range: total (M/F: 1144.3/1884.1) 16-45: 1155.2 (1145.5/1166.8); 46-55: 1469.8 (972.8/2159.2); 56-65: 1899.7 (1291.1/3017.2); 66-75: 2564.1 (1785.7/3809.5); > 75: 2061.9 (0/4347.8)		8 (1/7)	120.2	-	-
Chen <i>et al</i> ^[30] , 2016	133 (33/100)	699.6	Age range: total (M/F: 397.1/934.4) 18-49: 16.9 (0/41.5); 50-59: 1740.5 (714.3/2251.2); 60-69: 578.9 (161.2/856.2); 70-79: 1147.4 (942.8/1219.5); 80-89: 1187.9 (1077.6/1243.2); ≥90: 1574.8 (3225.8/621.1)		25 (2/23)	131.5	Age range: total (M/F: 24.1/214.9) 50-59: 316.5 (0/473.9); 60-69: 85.8 (0/142.7); 70-79: 174.6 (67.3/228.7); 80-89: 360.0 (107.8/486.5)	
Ye <i>et al</i> ^[31] , 2018	438 (135/303)	1201.3	≤ 40: 739.3; 41-60: 1363.5; ≥ 61: 2601.0	M: 722.4 F: 1704.9	39 (10/29)	107.0	≤ 40: 24.0; 41-60: 123.4; ≥ 61: 415.1	M: 53.5; F: 163.2
Qu <i>et al</i> ^[32] , 2018	175 (69/106)	1075.9	Age range: total (M/F: 843.7/1310.7) ≤ 30: 0/37.0;		16 (4/12)	98.4	Age range: total (M/F: 48.9/148.4) 31-45: 32.2/65.0;	

31-45: 901.2/1267.1;

46-60: 50.6/263.4;

46-60: 1567.2/2107.5

≥ 61: 530.5/1231.5

≥ 61: 2652.5/6403.9

Summary 1034 (328/706)

150

(18/74)

1. ^a Per 100,000 inhabitants.

AMA-M2, type M2 antimitochondrial antibody; M/F, male/female; CI, confidence interval; PBC, primary biliary cholangitis.

Figures

Figure 1

Flowchart of studies published in English for inclusion.

Figure 2

Prevalence and annual incidence rates for primary biliary cholangitis based on case-finding studies in various countries.

Supplementary Files

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