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ORIGINAL ARTICLE

# Epidemiology and clinical course of primary biliary cholangitis in the Asia–Pacific region: a systematic review and meta-analysis

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## Abstract

**Aims** Epidemiological studies on primary biliary cholangitis (PBC) show heterogeneity. The aim of the present study was to synthesize the prevalence, incidence and clinical course of PBC in the Asia–Pacific region.

**Methods** PubMed, Medline, Cochrane library and EMBASE were searched for epidemiology and clinical course of PBC published up to July, 2019. Meta-analysis was conducted on the epidemiology and clinical course (decompensation, hepatocellular carcinoma and death/liver transplantation) of PBC patients. Random-effect model and fixed-effect model were used to evaluate the pooled prevalence, incidence, mortality/liver transplantation and their 95% confidence intervals as appropriate. Subgroup analysis was performed by stratification with gender, pre- and post-UDCA era, sub-region and publication year. Meta-regression was used to examine the heterogeneity.

**Results** Out of 3460 studies, 18 studies from 7 countries/regions were finally included. The overall prevalence of PBC was 118.75 cases per million (95% CI 49.96–187.55) in the Asia–Pacific region, with the high, medium and low prevalence being in Japan and China (191.18 cases per million), New Zealand (99.16 cases per million) and South Korea and Australia (39.09 cases per million), respectively. The incidence of PBC was 8.55 cases per million per year (95% CI 8.05–9.06). The 5-year accumulative incidence of decompensation, HCC and death/liver transplantation in PBC patients was 6.95% (95% CI 2.07–11.83%), 1.54% (95% CI 0.9–2.19%) and 4.02% (95% CI 2.49–5.54%), respectively.

**Conclusion** In the Asia–Pacific region, the prevalence and incidence of PBC are higher than once expected. PBC tends to be diagnosed at older age and has a relatively low incidence of HCC in this region.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s12072-019-09984-x) contains supplementary material, which is available to authorized users.

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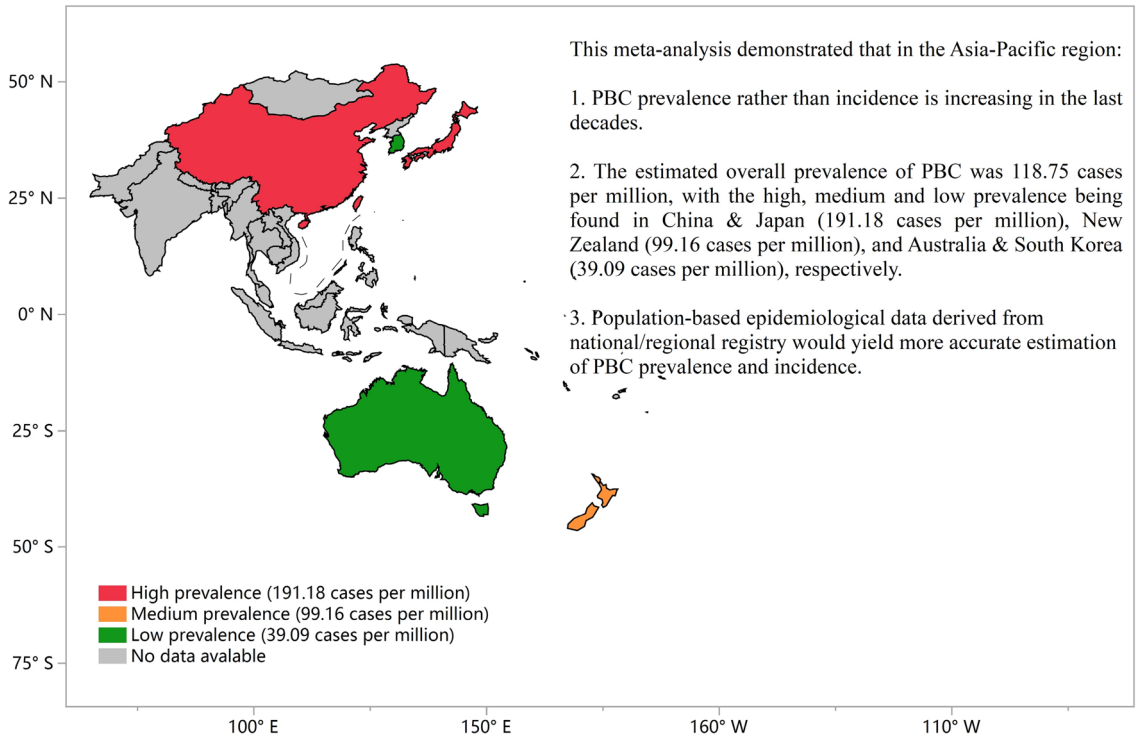
**Graphic abstract**




**Keywords** Primary biliary cholangitis · Prevalence · Epidemiology · Meta-analysis

## Introduction

Primary biliary cholangitis (PBC, previously referred as primary biliary cirrhosis) is a rare cholestatic liver disease with progressive non-purulent destruction of the small intrahepatic bile ducts [1–3]. This disease predominantly affects women with a female to male ratio of 10:1 [4]. Typically, untreated PBC is progressive and may eventually lead to cirrhosis, HCC, liver transplantation or even death.

The global prevalence and incidence of PBC vary widely with geographic region [5–8]. In Europe and North America, the prevalence is approximately 283–465 per million in general population, with an incidence of approximately 0.9–30.3 per million per year [9–11]. However, in the Asia–Pacific region, the prevalence, incidence and clinical course of PBC have not been well defined [12–15], although it has been increasingly diagnosed and treated in recent years [16–18].

Therefore, we conducted this systematic review and meta-analysis to summarize the epidemiology and clinical course of PBC in the Asia–Pacific region.

## Materials and methods

We conducted this systematic review and meta-analysis according to a predetermined protocol and in accordance with the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19].

### Search strategy

PubMed, Medline, Cochrane library and EMBASE databases were searched for studies published in English language up to July, 2019. The search strategy was developed by the senior authors (expert hepatologists and methodologists). Search terms included prevalence, incidence and epidemiology in conjunction with primary biliary cirrhosis (cholangitis). The reference lists of original articles and reviews relevant to PBC were also hand searched. References were managed with EndNote software version X6.

The specific search strings in PubMed were as follows:

#1. Primary biliary cirrhosis (title/abstract)
#2. Primary biliary cholangitis (title/abstract)
#3. Epidemiology (title/abstract)

#4. Incidence (title/abstract)
#5. Prevalence (title/abstract)
#6. #1 or #2
#7. #3 or #4 or #5
#8. #6 and #7,
#9. Limit #8 to humans and English

### Inclusion and exclusion criteria

Two independent authors screened the titles and abstracts of all searched articles to identify original studies on the epidemiology and clinical course of PBC.

Articles were included if they met the following criteria: (1) the study was an original research; (2) the study was a cross-sectional or cohort study conducted in adults ≥ 18 years; (3) the study reported a prevalence or incidence of PBC or raw data that allowed the calculation of the estimates, and (4) the study was conducted in the Asia–Pacific region.

Exclusion criteria for the meta-analysis were as follows: (1) the study was a review article or an abstract; (2) the study did not specifically describe patients with PBC; (3) the study did not exclude other causes of liver disease such as viral hepatitis B and C, and (4) the study was conducted in patients with other pre-existing disease (e.g., HIV co-infected).

The full texts of the identified articles were reviewed by the two authors (NZ and WJD). Disagreements on the inclusion of articles were resolved by consensus or involvement of an expert hepatologist (JDJ).

### Quality assessment

Two authors (NZ and WJD) independently appraised each article for quality assessment with previously described criteria [20, 21] (Supplementary Table 2). Based on these criteria, the quality of each article was graded as low, medium or high. The disagreement was settled by joint review with an experienced methodologist (YYK).

### Data extraction

Two investigators (NZ and WJD) completed data extraction in duplicate. When multiple reports from the same study population were identified, only the most comprehensive one was used. If discrepancy aroused on the inclusion or exclusion of a paper, it was referred to a senior methodologist (YYK) for resolution. The following fields were extracted from each study: publication year, number of population screened, number of PBC cases, methods of diagnosis, mean age of screened population, sex ratio of PBC cases, prevalence and incidence of PBC, and incidence of liver-related events (decompensation, HCC and death/liver transplantation) of PBC. Decompensation events included ascites, variceal bleeding and hepatic encephalopathy.

### Statistical analysis

Meta-analysis was performed to estimate the prevalence, incidence and incidence of liver-related events associated with PBC in the Asia–Pacific region, sub-region (Oceania and East Asia) or specific country. In the case of the original rate or standard error of an individual study was not explicitly stated, it was calculated if the appropriate raw data were available.

The $I^2$ index was calculated to assess the between-study heterogeneity and Cochrane $Q$ test was used to determine statistical significance. An $I^2$ value > 50% or a Chi square $p$ value < 0.05 was considered as substantial heterogeneity. Pooled rates with 95% confidence intervals (95% CIs) were calculated using random-effect model if heterogeneity existed; otherwise the fixed-effect model was used.

In addition, meta-regression was performed by median age of PBC patients, publication year, sub-region of the publication, source of population, female/male ratio, case ascertainment method and publication quality to determine factors for the between-study heterogeneity. Variables with a $p < 0.20$ were included in the model; however, only those with a $p < 0.05$ were considered significant in the final model. Then subgroup analyses on PBC prevalence were performed by stratification with gender, the year of UDCA introduction (pre- and post-UDCA era), sub-region of the publication, and publication year.

Sensitivity analysis was conducted to estimate the influence of each study on the pooled results. Funnel plot and the Egger test were used to assess the presence of any publication biases. All analyses were performed with Stata Software (version 13.0, Stata Corp, College Station, TX, USA).

## Results

### Characteristics of included studies

The search strategy yielded a total of 3460 abstracts, with 828 from Medline, 1303 from EMBASE, 1229 from PubMed and 100 from Cochrane Library. After screening of all abstracts, 23 articles met the criteria for full-text review. Hand searching contributed 2 additional articles (Fig. 1).

After full-text review, 18 studies were finally included, with 9 articles reporting prevalence, 3 articles reporting incidence and 10 articles reporting liver-related events of PBC. These studies were conducted in 7 countries (2 in Australia, 1 in New Zealand, 1 in Singapore, 1 in India, 1 in South

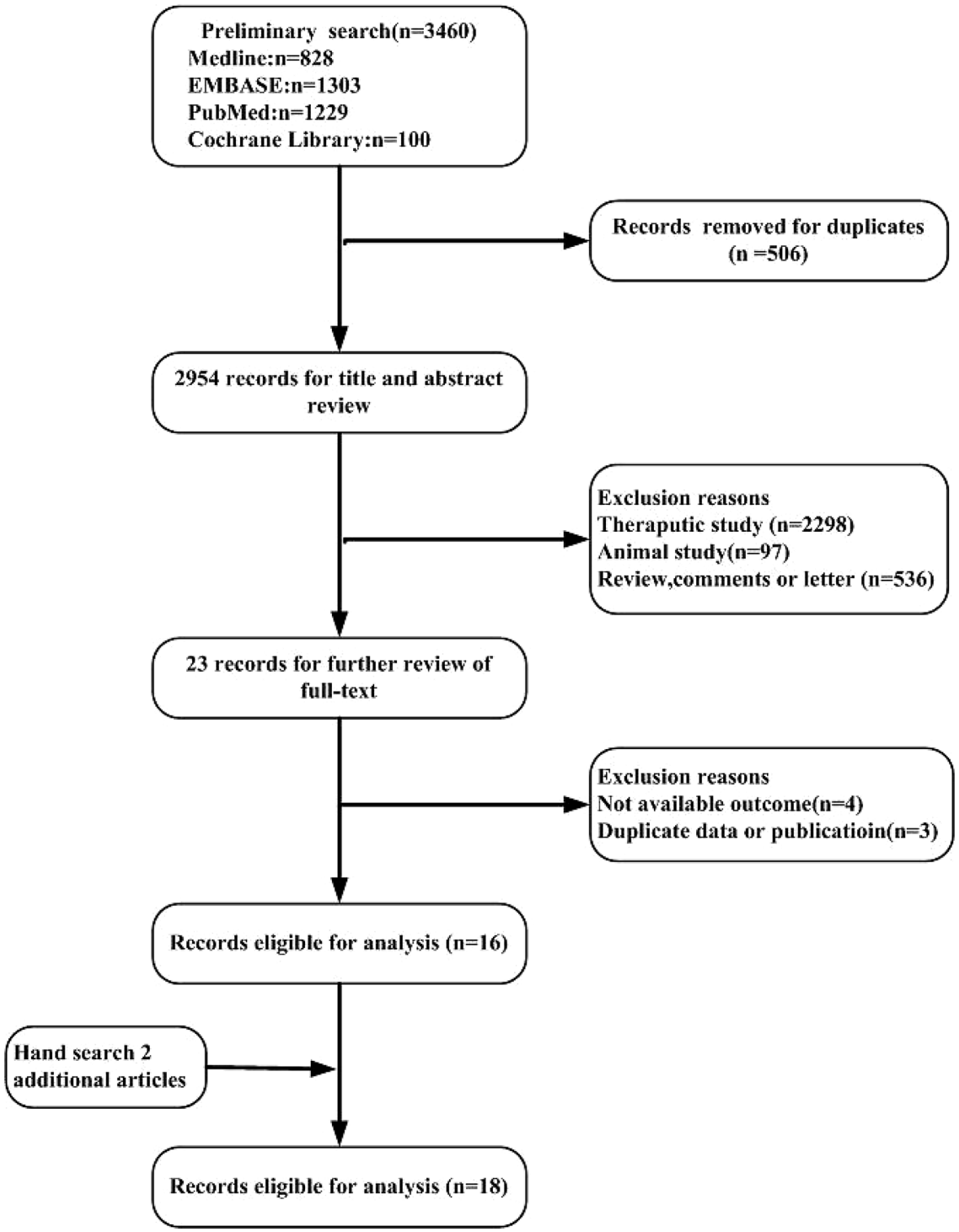



**Fig. 1** Flow chart for search and selection of the published articles

**Table 1** Characteristics of all the cited studies reporting PBC incidence and prevalence

| References | Country | Publication year | Diagnostic method[a] | Number of subjects | Study design | Study population | Age Mean ± SD or median (IQR) | Gender (female, %) |
|---|---|---|---|---|---|---|---|---|
| Watson [22] | Australia | 1995 | I/II/III | 4,390,000 | Cross-sectional | Population based | 57 (38–86) | 91.7 |
| Tsuji [23] | Japan | 1999 | I/II/III | 2,873,000 | Cross-sectional | Population based | 55.6 ± 12.0 | NA |
| Ohba [24] | Japan | 2001 | I/II/III | 17,899 | Cross-sectional | Hospital referred | 68 ± 8 | 95.0 |
| Sood [25] | Australia | 2004 | I/II/III | 4,880,000 | Cross-sectional | Population based | 61 ± 12 | 90.0 |
| Amaraprkar [26] | India | 2007 | I/II/III | NA | Cross-sectional | Hospital referred | 53.2 ± 6.9 | 100.0 |
| Fung [27] | Hong Kong SAR, China | 2007 | I/II/III | 6430 | Cross-sectional | Hospital referred | 66 (52-73) | 91.4 |
| Wong [28] | Singapore | 2008 | I/II/III | NA | Retrospective cohort | Hospital referred | 56.8 ± 1.8 | 94.0 |
| Azemoto [29] | Japan | 2010 | I/II/III | NA | Cross-sectional | Hospital referred | 65 (52–72) | NA |
| Liu [30] | China | 2010 | I/II | 8126 | Cross-sectional | Hospital based | 55 ± 15 | 48.0 |
| Ngu [31] | New Zealand | 2012 | I/II/III | 1,156,625 | Cohort | Hospital referred | 61 ± 1.5 | 92.0 |
| Harada [17] | Japan | 2013 | I/II | NA | Cross-sectional | Population based | 60.5 ± 11.2 | 87.4 |
| Zhang [33] | China | 2015 | I/II/III | NA | Retrospective cohort | Hospital referred | 65.7 ± 10.1 | 69.2 |
| Rong [32] | China | 2015 | I/II/III | 10,156 | Cohort | Hospital referred | 59.6 ± 10.9 | 87.3 |
| Kim [12] | South Korea | 2016 | I/II/III | 38,424,054 | Cross-sectional | Population based | 57.4 | 88.1 |
| Cheung [34] | Hong Kong SAR, China | 2017 | I/II/III | NA | Cross-sectional | Population based | 60.6 (51.8–72.6) | 79.0 |
| Fan [35] | China | 2017 | I/II/III | NA | Retrospective cohort | Hospital referred | 55.4 ± 12.1 | 85.9 |
| Chen [13] | China | 2018 | I/II/III | NA | Cohort | Hospital referred | 55 (48–63) | 86.1 |
| Tanaka [36] | Japan | 2019 | I/II/III | 127,000,000 | Cross-sectional | Population based | NA | 79.6 |

[a]Diagnostic method: I :cholestatic liver function tests (ALP elevation) II: presence of AMAs in serum; III: representative histological manifestations

*SD* standard deviation, *IQR* interquartile range

Korea, 5 in Japan and 7 in China). Among these studies, 12 were cross-sectional, 4 were retrospective cohort and 2 were prospective cohort studies (Tables 1, 2) [12, 13, 17, 22–36].

## Methods for identification of primary biliary cholangitis/cirrhosis used in the original studies

In 17 studies, the diagnosis of PBC patients was based on the combination of the following criteria: (1) clinical presentation; (2) elevation of alkaline phosphatase of liver origin for at least 6 months; (3) presence of antimitochondrial antibodies (> 1:40) in serum or histological features of florid bile duct lesions.

In the remaining one study, PBC patients were identified from a medical record database using the International Classification of Disease, 10th revision (ICD-10).

The mean age at diagnosis of PBC was 60.23 years (95% CI 58.62–61.83) (Supplementary Fig. 1).

## PBC prevalence

The pooled overall prevalence of PBC was estimated to be 118.75 cases per million (95% CI 49.96–187.55) in the

**Table 2** Characteristics of the cited studies reporting clinical course of PBC

| References | Country | Publication year | Study period | Number of PBC |
|---|---|---|---|---|
| Ohba [24] | Japan | 2001 | 1997–1998 | 11 |
| Sood [25] | Australia | 2004 | 2002 | 249 |
| Amaraprkar [26] | India | 2007 | 1997–2003 | 10 |
| Ngu [31] | New Zealand | 2012 | 1980–2006 | 71 |
| Harada [17] | Japan | 2013 | 1980–2009 | 2946 |
| Zhang [33] | China | 2015 | 2001–2013 | 1255 |
| Rong [32] | China | 2015 | 1994–2014 | 1865 |
| Kim [12] | South Korea | 2016 | 2009–2013 | 2824 |
| Cheung [34] | Hong Kong | 2017 | 2000–2015 | 1016 |
| Fan [35] | China | 2017 | 2001–2016 | 769 |
| Chen [13] | China | 2018 | 2000–2017 | 732 |

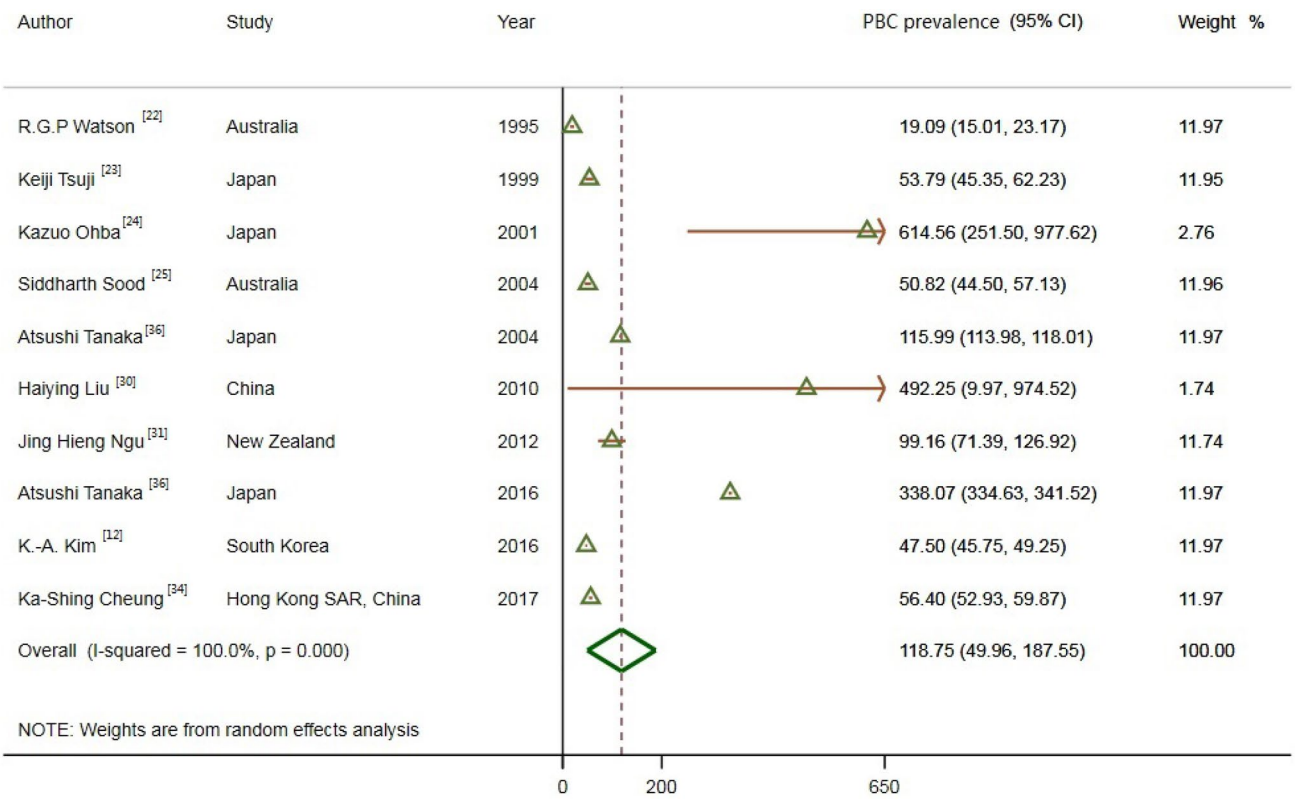



**Fig. 2** The estimated PBC prevalence in the Asia–Pacific region (cases per million)

Asia–Pacific region (Fig. 2), with 103.67 cases per million (95% CI 42.17-165.17) for females and 18.70 cases per million (95% CI 4.94–32.45) for males (Supplementary Fig. 2). The pooled PBC prevalence of pre-UDCA era and post-UDCA era were 36.24 cases per million (95% CI 2.23–70.24) and 146.47 cases per million (95% CI 64.13–228.80), respectively (Supplementary Fig. 3). The pooled prevalence in this decade (2009–2019) was 158.52 cases per million (95% CI 14.02–303.02) (Supplementary Fig. 4).

The pooled sub-regional prevalence of PBC was 52.71 cases per million (95% CI 22.91–82.52) in Oceania (including Australia and New Zealand) and 156.22 cases per million (95% CI 65.68–246.76) in East Asia (including China, South Korea and Japan) (Supplementary Fig. 5). At country level, the highest and lowest prevalence of PBC was reported from Japan (221.01 cases per million, 95% CI 62.09–379.94) and Australia (34.98 cases per million, 95% CI 3.73–66.24), respectively (Supplementary Figs. 6, 7). The second highest prevalence of PBC was in China (204.87 cases per million,

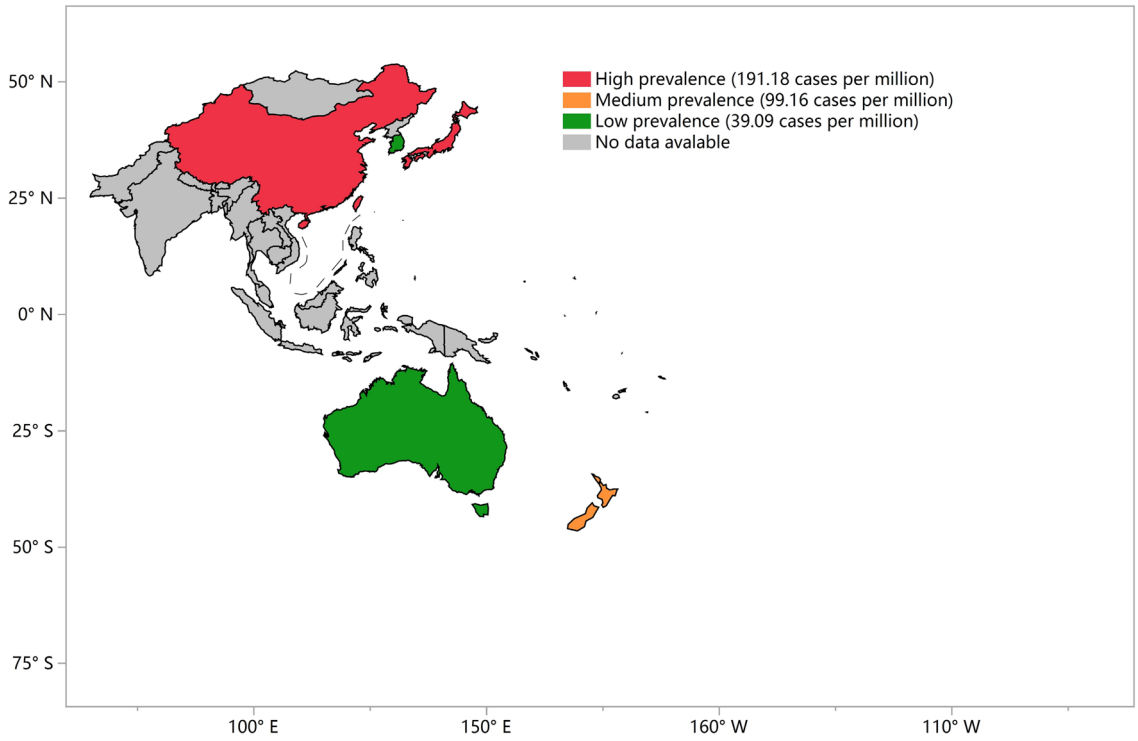



**Fig. 3** PBC prevalence in the Asia–Pacific region, with the high, medium and low prevalence being found in China and Japan (191.18 cases per million), New Zealand (99.16 cases per million), and Australia and South Korea (39.09 cases per million), respectively

95% CI − 199.99 to 609.74) (Supplementary Fig. 8). Based on these data, we divided the PBC prevalence into three categories: high in Japan and China (191.18 cases per million, 95% CI 73.61–308.76), medium in New Zealand (99.16 cases per million, 95% CI 71.39–126.92), and low in South Korea and Australia (39.09 cases per million, 95% CI 19.53–58.65) (Fig. 3; Supplementary Fig. 9).

## PBC incidence

Meta-analysis on incidence of PBC was performed on all 3 studies reporting PBC incidence (each from New Zealand, South Korea and Hong Kong SAR, China). The pooled overall PBC incidence was estimated to be 8.55 cases per million per year (95% CI 8.05–9.06). The highest and lowest incidences of PBC was reported from South Korea (8.57 cases per million per year, 95% CI 8.05–9.09) and New Zealand (8.09 cases per million per year, 95% CI 0.16–16.03), respectively (Fig. 4).

## Incidence of decompensation and HCC among PBC patients

The pooled 5-year incidence of decompensation among PBC patients was 6.95% (95% CI 2.07–11.83%) (Fig. 5). Specifically, the pooled 5-year incidence for ascites, variceal bleeding and hepatic encephalopathy was estimated to be 5.58% (95% CI 0.55–10.60%), 3.02% (95% CI 1.63–4.41%) and 1.31% (95% CI 0.24–2.37%), respectively (Supplementary Fig. 10).

The pooled overall 5-year and 10-year incidence for HCC associated with PBC was estimated to be 1.54% (95% CI 0.9–2.19%) and 4.51% (95% CI 2.01–7.01%), respectively (Fig. 6). The 10-year cumulative incidence of HCC in female PBC patients was significantly lower than that in male PBC patients [2.73% (95% CI 2.01–3.46%) vs 8.60% (95% CI 5.12–12.08%), $p < 0.001$] (Supplementary Fig. 11). Furthermore, the 5-year HCC incidence was highest in China (1.62%, 95% CI 0.60–2.64%) (Supplementary Fig. 12) and lowest (1.38%, 95% CI 0.95–1.81%) in South Korea

## Death/liver transplantation of PBC patients

The overall 5-year liver-related fatality (death/liver transplantation) was estimated to be 4.02% (95% CI 2.49–5.54%) among PBC patients. The highest fatality was found in Singapore (8.82%, 95% CI − 0.71 to 18.36%) and the lowest fatality was found in China (3.59%, 95% CI 1.26–5.92%) (Fig. 7; Supplementary Fig. 13).

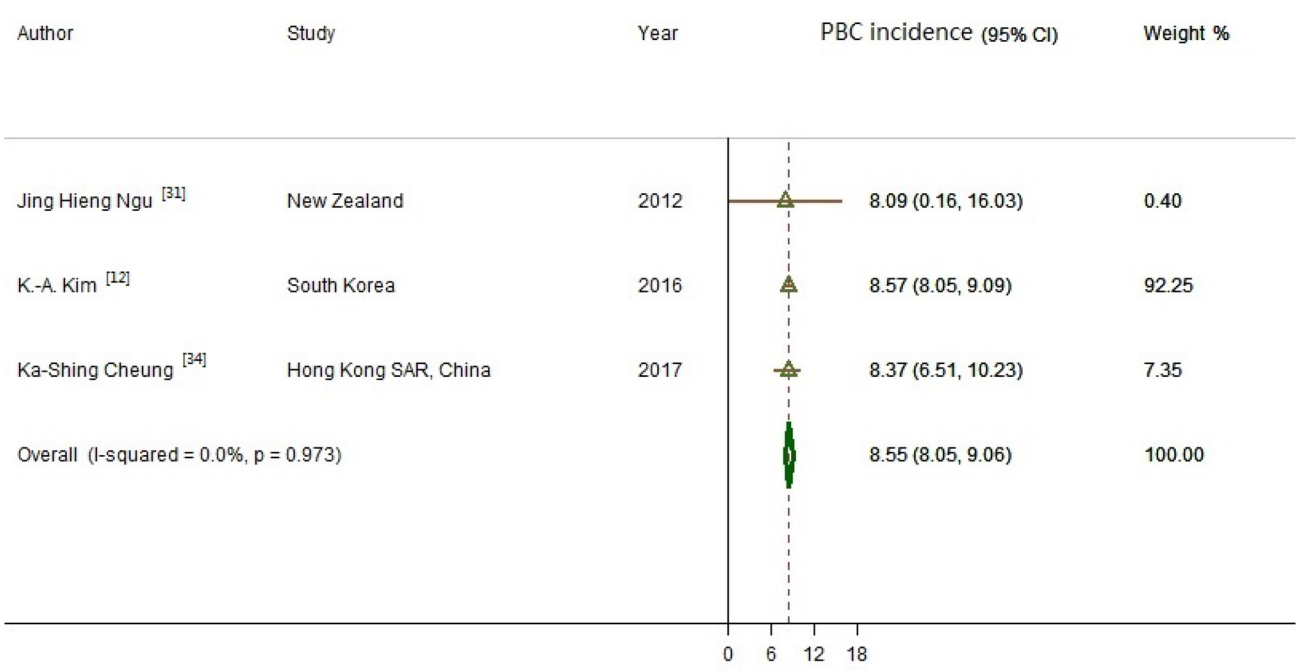



**Fig. 4** PBC incidence estimated in the Asia–Pacific region (cases per million per year)

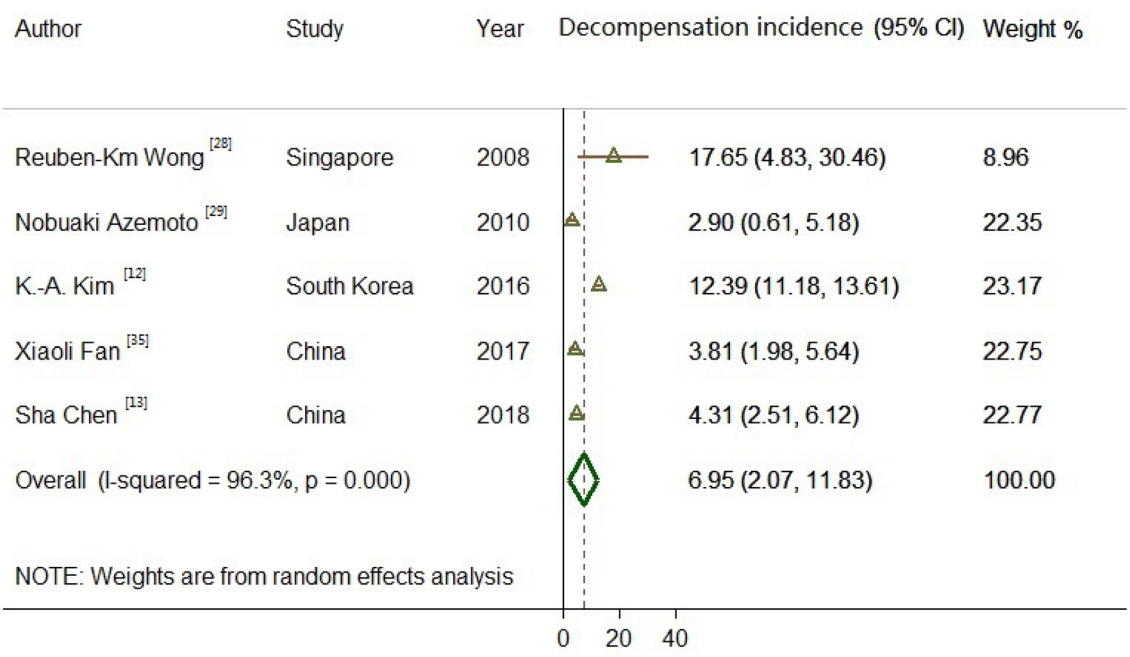



**Fig. 5** Decompensation incidence among PBC patients estimated in the Asia–Pacific region (%)

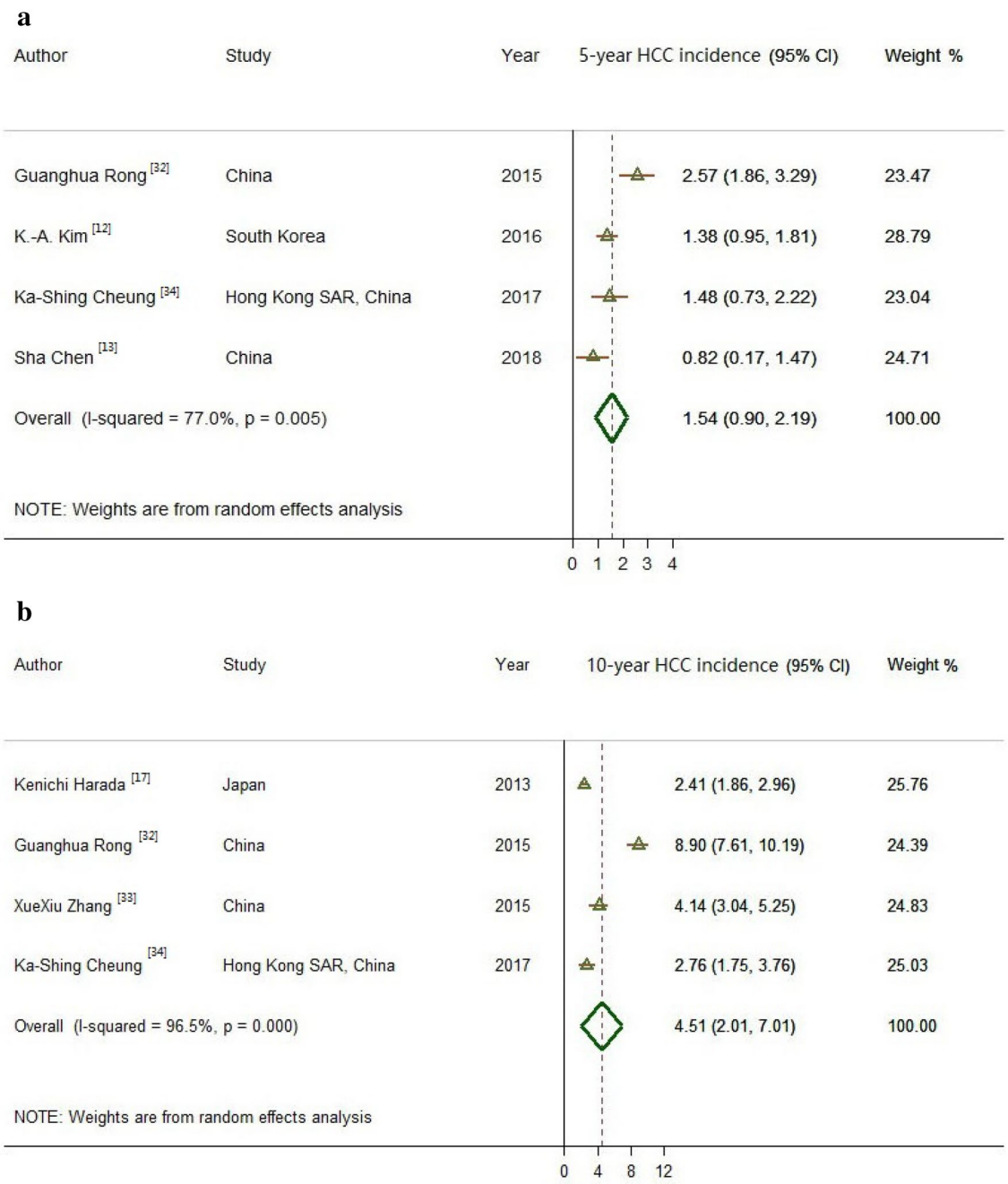



**Fig. 6** The 5-year (**a**) and 10-year (**b**) incidence for HCC associated with PBC patients estimated in the Asia–Pacific region (%)

## Study quality

Of all the studies, 6 were cohort and 12 were cross-sectional. According to the quality assessment criteria, 1 study (5.56%) was graded as high quality, 17 (94.44%) as medium quality (Supplementary Table 1). Meta-regression found no effect of study quality on the estimation of PBC prevalence ($p = 0.816$) (Supplementary Table 2).

## Study heterogeneity and publication bias

Meta-regression showed that year of publication ($p = 0.108$) marginally explained about 0.7% of the heterogeneity (Supplementary Table 2).

Subgroup analysis stratified by year of publication demonstrated that the pooled prevalence of PBC was increasing in the last 25 years: 36.24 cases per million (95% CI 2.23–70.24) in the period from 1995 to 2000, 98.95 cases

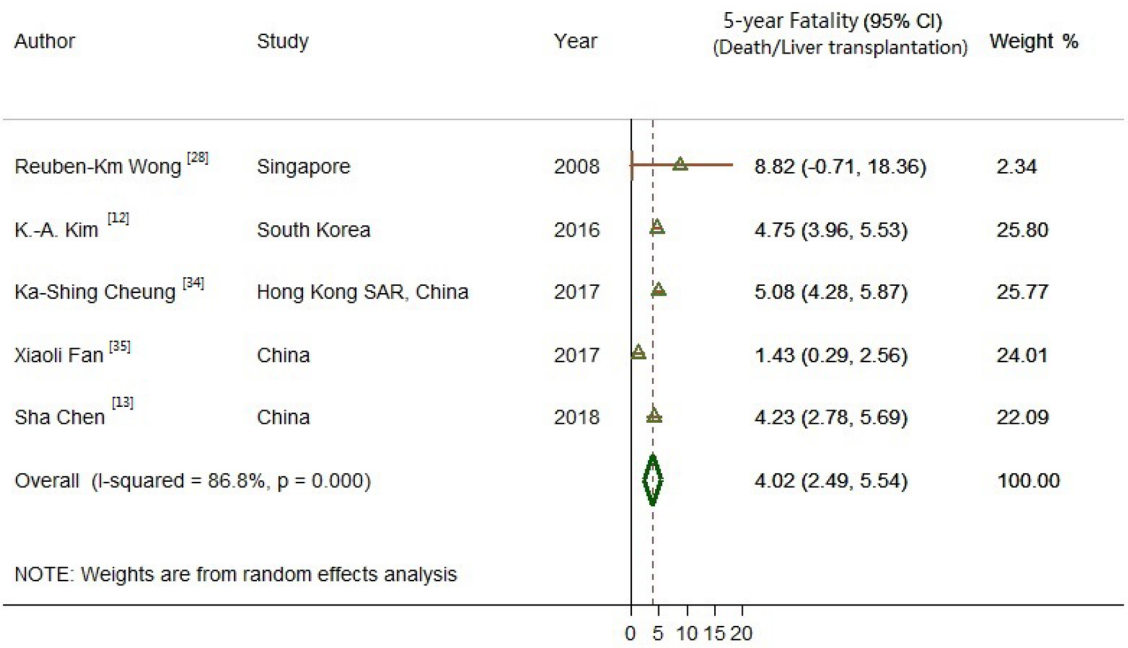



**Fig. 7** Fatality (death/liver transplantation) of PBC estimated in the Asia–Pacific region (%)

per million (95% CI 35.27–162.23) from 2001 and 2005, and 158.52 cases per million (95% CI 14.02–303.02) from 2010 to 2017 (Supplementary Fig. 14).

Sensitivity analysis showed one study conducted in South Korea (2016) contributed most to heterogeneity of the estimates of PBC prevalence (Supplementary Fig. 15, Supplementary Table 3). No publication bias was found using Egger's test ($p = 0.831$) and funnel plot (Supplementary Table 4, Supplementary Fig. 16).

## Discussion

In this meta-analysis, we estimated that the prevalence of PBC was 118.75 cases per million in the Asia–Pacific region, with the high, medium and low prevalence being found in Japan and China (191.18 cases per million), New Zealand (99.16 cases per million), and South Korea and Australia (39.09 cases per million), respectively. The estimated incidence of PBC was 8.55 cases per million per year. The 5-year accumulative incidence of decompensation, HCC and death/liver transplantation in PBC patients were 6.95%, 1.54% and 4.02%, respectively.

As a key finding, the PBC prevalence in Japan (221.01 cases per million) and China (204.87 cases per million) was close to that in Europe and the United States [9–11], although the overall prevalence of PBC in the Asia–Pacific region remained at a relatively low level. Of note, the highest PBC prevalence, which was even higher than that in Europe and the United States, was reported from a Japanese study which was conducted in 22,865 atomic bomb survivors who lived in Nagasaki [24]. This indicates that development of PBC may be influenced by environmental factors. The high PBC prevalence reported by the Chinese study conducted in people who came to a hospital for health checkup, which might not be the same as general population and overestimate the PBC prevalence [30]. Despite these considerations, our meta-analysis demonstrated that PBC is not as rare as it was expected in the Asia–Pacific region.

We also found that the prevalence and, to a lesser extent, the incidence, of PBC in the Asia–Pacific region had an increasing tendency [8, 11, 18]. For example, a study from Hong Kong SAR, China, reported the PBC prevalence increased from 31.1 cases per million in 2000 to 82.3 cases per million in 2015, with the annual incidence being increased from 6.7 cases per million per year to 8.1 cases per million per year [34]. Similarly, in two studies conducted in Victoria, Australia, the prevalence of PBC has also increased dramatically from 19.1 cases per million in 1991 to 51.0 cases per million in 2004 [22, 25]. The increase of annual incidence could be attributed to the increase in disease awareness, improvement in diagnostic techniques and utility of electronic medical records to generate data, in addition to the true increase in the incidence [34, 37]. Similarly, the increase in prevalence may attribute to the improved survival owing to the availability of

ursodeoxycholic acid (UDCA), in addition to the increase in PBC incidence [38].

Another finding of our study was that patients tend to be diagnosed with PBC at an older age (60.23 years) in Asian countries, compared with reported from western countries ($54.5 \pm 12$ years) [39]. As shown in a study from South Korea in 2016, the age group with the highest incidence of PBC cases was 60–69 years [12]. Similarly, in a study from Hong Kong SAR, China, PBC was commonly diagnosed between the ages of 60 and 79 years [34]. One of the reasons for this discrepancy may be due to the different awareness and availability of PBC diagnosis in the Asia–Pacific region, in addition to a true late onset of PBC in Asia–Pacific population.

In this meta-analysis, we found that the 5-year incidence of decompensation among PBC patients was similar to Europe and the United States. However, the 5-year incidence of PBC-related HCC was relatively lower than that reported in western countries [40–42], for unknown reasons. Not surprisingly, we also found that PBC-related HCC incidence was higher in male patients (with a male to female ratio of 3:15), which was in line with previous studies [41, 43].This finding suggests that male gender per se is a risk factor for HCC development, as demonstrated in liver disease of other etiology [44].

Our study also has several limitations. First, limited number of original studies could be included in this meta-analysis. Second, between-studies' heterogeneity existed in this study which cannot be explained by meta-regression or subgroup analysis. However, we still hope this study provides a useful summary of epidemiology and clinical course of PBC in the Asia–Pacific region.

In conclusion, this meta-analysis showed that the prevalence and incidence of PBC in the Asia–Pacific region are higher than once expected, with a faster increase in prevalence; PBC tends to be diagnosed at an older age and has a relatively low incidence of HCC in this region. Population-based epidemiological data derived from national/regional registry would yield more accurate estimation of PBC prevalence/incidence and clinical course in the Asia–Pacific region.

**Author contributions** NZ, JDJ and YYK designed the study and drafted the manuscript. NZ, WJD and SC extracted the data. NZ, WJD, HM and XJO assessed the quality of evidence. NA and SSW analyzed the data. YYK, HY and JDJ interpreted the results and finalized the manuscript. All the authors approved the final version of the paper.

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## Compliance with ethical standards

**Conflict of interest** Na Zeng, Weijia Duan, Sha Chen, Shanshan Wu, Hong Ma, Xiaojuan Ou, Hong You, Yuanyuan Kong and Jidong Jia declare no conflict of interests.

**Ethical approval** This article does not contain any study with human participants or animals performed by any of the authors.

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