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SYSTEMATIC REVIEW

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Prevalence of primary sclerosing cholangitis (PSC) in Iranian adult patients with inflammatory bowel disease (IBD) or liver disorders: systematic review and meta-analysis

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ABSTRACT

Aim: To evaluate the prevalence of primary sclerosing cholangitis (PSC) among Iranian adult patients with inflammatory bowel disease (IBD) or liver disorders.

Background: PSC is a rare and chronic liver disease characterized by inflammation, fibrosis, and intra- and/or extrahepatic bile duct structure.

Methods: A systematic review and meta-analysis was conducted. The Web of Science, Scopus, Pubmed, Embase, Google Scholar, and local databases, including the IranDoc, IranMedex, SID, and MagIran databases, were searched for studies published before 6th February 2023 for the prevalence of PSC among Iranian adults.

Results: In total, 22 articles involving 19,747 Iranian participants were included in this meta-analysis. The overall pooled prevalence of PSC was 8% (95% CI: 5%–12%). Additionally, the prevalence of PSC stratified by gender was calculated based on four studies (n = 1402). The pooled prevalence of PSC was estimated to be 20% (95% CI: 11–31%) in males and 12% (95% CI: 3–38%) in females. The pooled prevalence of PSC was 6% (95% CI: 4–9%) in patients with IBD and 14% (95% CI: 8–23%) in patients with liver transplantation (LT).

Conclusion: The pooled prevalence of PSC was 8% in Iranian adults, and the prevalence was greater in males than in females.

Keywords: Primary sclerosing cholangitis, Iran, Prevalence, Systematic review, Meta-analysis.

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Introduction

Primary sclerosing cholangitis (PSC) is a rare and chronic liver disease characterized by inflammation, fibrosis, and intra- and/or extrahepatic bile duct structure (1). PCS is a progressive disorder that increases the risk of cholangiocarcinoma, colorectal cancer, and liver failure (2, 3). Although many PSC patients are asymptomatic, fatigue and pruritus are common symptoms (4, 5).

There is a close association between PSC and inflammatory bowel disease (IBD), while 70-80% of IBD patients have PSC (6). The most common form of IBD in PSC patients is ulcerative colitis (UC), and the least common form is Crohn's disease (CD) (7). In contrast, PSC has been reported in 8% and 3.5% of patients with UC and CD, respectively (8, 9). The histopathological and endoscopic features of IBD differ between patients with IBD-PSC and those with IBD alone (10). However, genetic and environmental factors are likely to contribute to the incidence and progression of PSC as an autoimmune disease, but the exact etiology of PSC is unknown. Although Ursodeoxycholic acid (UDCA) has been widely used in treating PSC, there is no established treatment for PSC patients in the guidelines (11).

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The incidence and prevalence of PSC in North America and North Europe are higher than in Asia (11). The incidence rate of PSC was reported to be 0.60 per 100,000 person-years (PY) (95% CI 0.37–0.88 per 100,000 PY) worldwide and 0.62–0.53 per 100,000 PY in Europe and North America (12). To our knowledge, no previous systematic review study has estimated the prevalence of PSC in the Iranian population. We aimed to systematically review the literature on the prevalence of PSC among Iranian adult patients with IBD or liver disorders.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines in the present study.

Search strategy and study selection

We searched the medical literature, including the Web of Science, Scopus, Pubmed, Embase, Google Scholar, and local databases, including IranDoc, IranMedex, SID, and MagIran, from inception to 6th February 2023 to identify case-control or cross-sectional studies with data regarding the prevalence of primary sclerosis cholangitis (PSC) in adult patients.

With the assistance of a librarian, we used combinations of MeSH terms and keywords related to "cholangitis, sclerosing," or "primary sclerosing cholangitis," and "prevalence," and "Iran" (supplementary Table 1). There were no language restrictions. All related studies were identified and transferred to information management software (EndNote), and duplicates were removed. Two authors (Z.N. and E.T.) independently screened the remaining articles. Any disagreements were resolved by a third author (B. H) using a modified Delphi system. To find the eligible studies, the initial screening was conducted by reading the article's title and abstract, and the secondary screening was subsequently conducted by reading the article's full text. In the subsequent step, the references of the initially identified articles were manually reviewed to identify possible missed articles from previous steps.

Inclusion and exclusion criteria

The inclusion criterion was original articles reporting the prevalence of PSC among the Iranian population. The exclusion criteria were as follows: 1) published by abstract only; 2) a case report, review, meta-analysis article or letter; 3) a cohort study with incomplete data or lack of information regarding the prevalence of PSC; 4) an article on the prevalence of PSC among children or adolescents; 5) an animal model or ex vivo sample; and 6) an article with low methodological quality.

Data extraction

The following variables were extracted from the included papers: author, year, participant characteristics (sample size, sex, age range, or mean age), method utilized for the diagnosis of PSC, prevalence of PSC, and 95% confidence intervals (95% CIs) (Table 1). Only the papers without missing data were included in the analysis.

Quality assessment

The quality of the included studies was independently assessed by 2 authors (Z.N. and E.T.) using the Newcastle–Ottawa quality assessment scale (NOS), which ranges from low quality (1-3) to moderate quality (4-6) and high quality (7-9). Three factors compose the scoring system: selection (a maximum of five stars), comparability (a maximum of two stars), and results (a maximum of three stars).

Data synthesis and statistical analysis

A meta-analysis of PSC incidence was conducted according to 22 included studies with 19,747 individuals. The prevalence of PSC as the primary outcome was reported as pooled proportions and 95% confidence intervals (CIs). In addition, subgroup analysis was carried out based on sex, type of disease, and province. Due to methodologic variations and sample diversity across studies (high heterogeneity), random effects linear mixed models (REMLs) were used to extract the pooled estimate.

Heterogeneity was assessed using the I-squared (I2) statistic, and a P value >50% for I2 indicated substantial heterogeneity; a corresponding P value <0.05 was also considered to indicate statistical significance. The risk of publication bias was evaluated by visual inspection of funnel plots and the Egger test. All the statistical analyses were performed with the R Project for Statistical Computing (version R-4.3.2), and the significance level was considered P=0.05.

Results

Characteristics of the included studies

After searching multiple databases, 264 papers were identified; 201 studies were screened by title and abstract

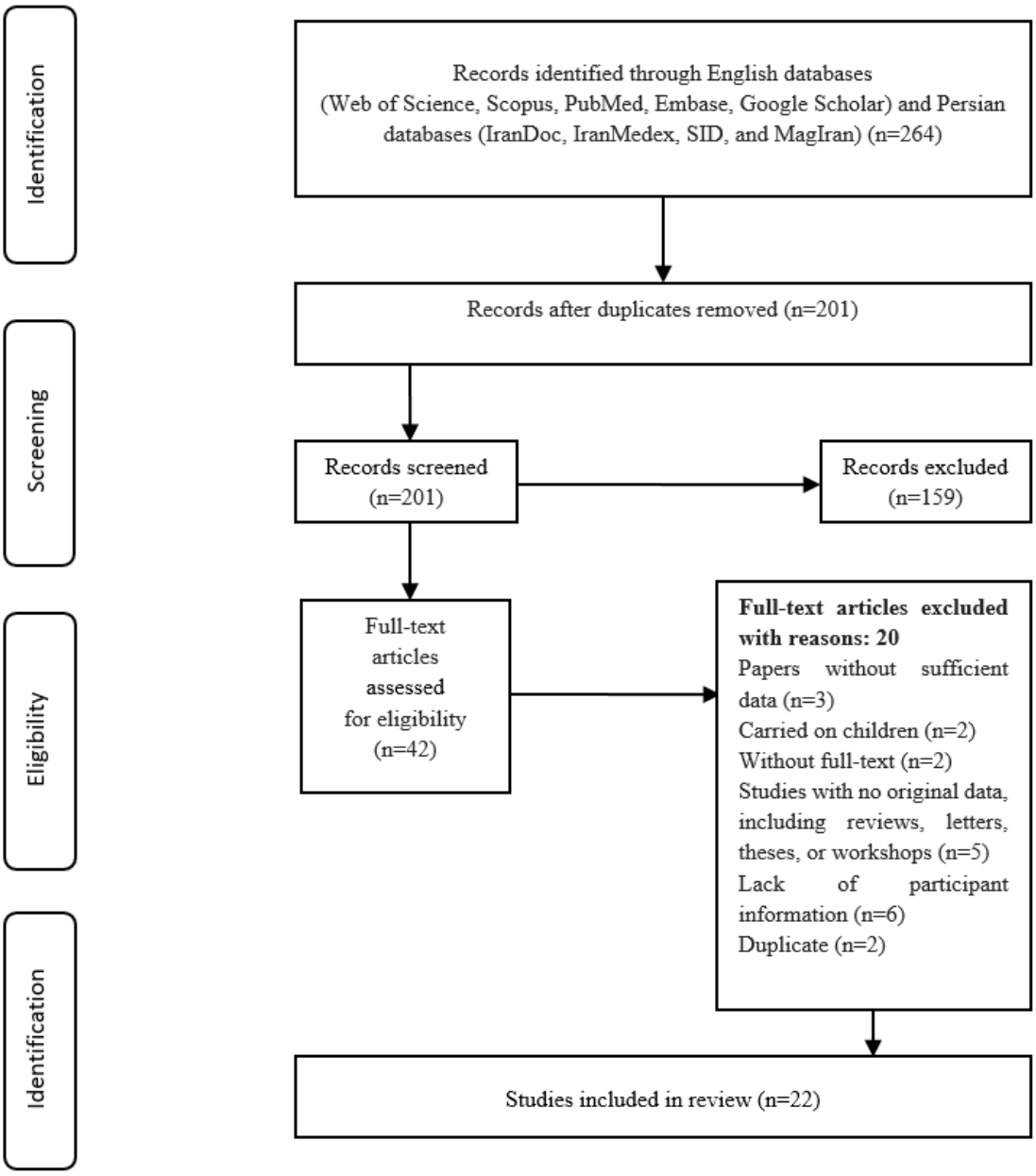

Figure 1. Flow chart of the literature selection process

after removing duplicates, and 159 papers were excluded based on the inclusion criteria. An eligibility assessment was conducted on 42 full-text articles, and 18 were excluded. The selection processes for the articles are shown in Figure 1. Finally, 22 articles were included in this systematic review. All the included studies were clinical-based studies published from 2009 to 2021 that included 19,747 participants from Iranian adults.

Overall prevalence of PSC

The final data source included 22 studies reporting the prevalence of PSC among Iranian adults. The characteristics of these studies are presented in Table 1. Of the included studies, 10 were conducted in Tehran Province, six were from Fars Province, two were from Isfahan Province, one was from Khorasan Province, one was from Northwest Iran, and one was from multiple centers, including centers in Isfahan, Kermanshah, Fars, and Tehran. The pooled prevalence of PSC in Iran was 8% (95% CI: 5%–12%) in 19,747 individuals based on 22 included studies, with significant heterogeneity among the studies (I2=98%, P<0.01) (Figure 2).

Table 1. Main characteristics of eligible studied reporting the prevalence of PSC in Iranian adults

Author (year)	Sitting	Province	Time duration	Number of participants	Target population	Age mean	Age SD/range	Gender (Male %)	Prevalence of PSC N (%)
Aghazadeh (2004)(31)	Gastrointestinal centers	Tehran	1992-2002	448	IBD (401UC+47CD)	31.9	11.8	44.63	16 (3.9%)
Saberifiroozi (2006)(32)	Nemazi Hospital	Fars	1994-2004	480	LT	39	13	63.12	147(30.6%)
Ganji (2006)(33)	Shariati Hospital	Tehran	2003-2004	7985	outpatient referrals to liver clinic	-	-	60	33 (0.4%)
Dehghani (2008)(34)	Liver Transplant Unit, Shiraz University of Medical Sciences	Fars	1994-2006	170	LT	31.4	13.3	63.5	18 (10.5%)
Darakhshan (2008)(35)	Gastrointestinal centers, Shahid Beheshti University of Medical Sciences	Tehran	1992-2007	803	IBD (671 UC) +109 CD+23IC)	33.10	18-80	43.81 in UC 64.22 in CD	37(5.51%) in UC 2 (1.83%) in CD
Vahedi (2009)(36)	Gastrointestinal centers	Tehran	2004-2007	500	207 CD+293 UC	33.8 in CD 37.1 in UC	12.9 in CD 13.7 in UC	47.3 in CD 41.29 in UC	6 (2.8%) in CD 28 (9.5%) in UC
Mirzaagha (2010)(37)	Shariati Hospital	Tehran	2003-2005	100	AILD	36.5	14-75	30	17 (17%)
Yazdanbod (2010)(38)	Gastroenterology clinic	Northwest of Iran	1998-2008	105	UC	33.5	13.1	41.9	2 (1.9%)
Alizadeh (2012)(39)	Talegani Hospital	Tehran	2004-2011	283	patients with cholangio carcinoma	59.7	14.4	63.6	16 (5.6%)
Jafarshad (2013)(40)	Imam Khomeini Hospital	Tehran	2011-2012	116	UC	36.34	8.67	49.1	24 (20.7%)
Khorashad (2015)(41)	Clinics of Ghaem and Emam Reza Hospitals	Khorasan	2011	447	IBD 384 UC +61 CD	38.6	13.3	39.37	
Fattahi (2017)(42)	Namazi Hospital	Fars	1993-2014	2766	LT	35	18-68	65.1	
MalekHosseini (2018)(30)	6 centers	Tehran, Mashhad, Kerman, Isfahan, Fars	1993-2016	3553	LT	32.4	18.3	61.57	
Baghaei (2018)(43)	Referral gastrointestinal diseases clinic	Isfahan	2016-2017	352	IBD (245 UC+ 80 CD)	53	13	51.4 in UC 46.2 in CD	
Jeddi (2019)(44)	Shiraz Liver Transplant Center	Fars	2017-2018	397	LT	44.3	12.8	64.5	
Toosi (2020)(45)	Tertiary referral center for chronic liver disease	Tehran	2013-2017	242	LT	40.18	14.2	59.5	
Lankarani (2021)(46)	Liver Transplant Center	Fars	2021	291	LT	47.73	12.9	67.7	
Lankarani (2021)(47)	Liver Transplant Center	Fars	2021	806	LT	44.7	13.2	66.6	

Abbreviations: AILD: autoimmune liver disease, CD: Crohn's disease, CI: confidence interval, IC: indeterminate colitis, LT: liver transplant, PSC: primary sclerosing cholangitis, UC: (39) ulcerative colitis

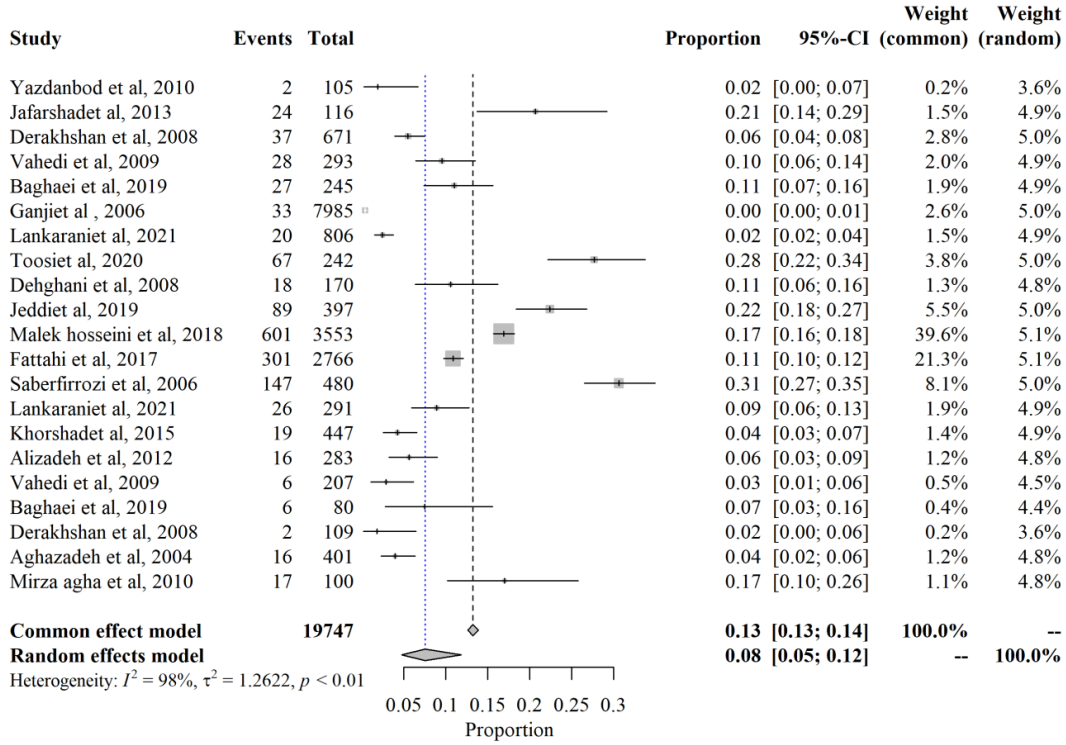

Figure 2. Forest plot of the pooled prevalence of PSC among Iranian adults

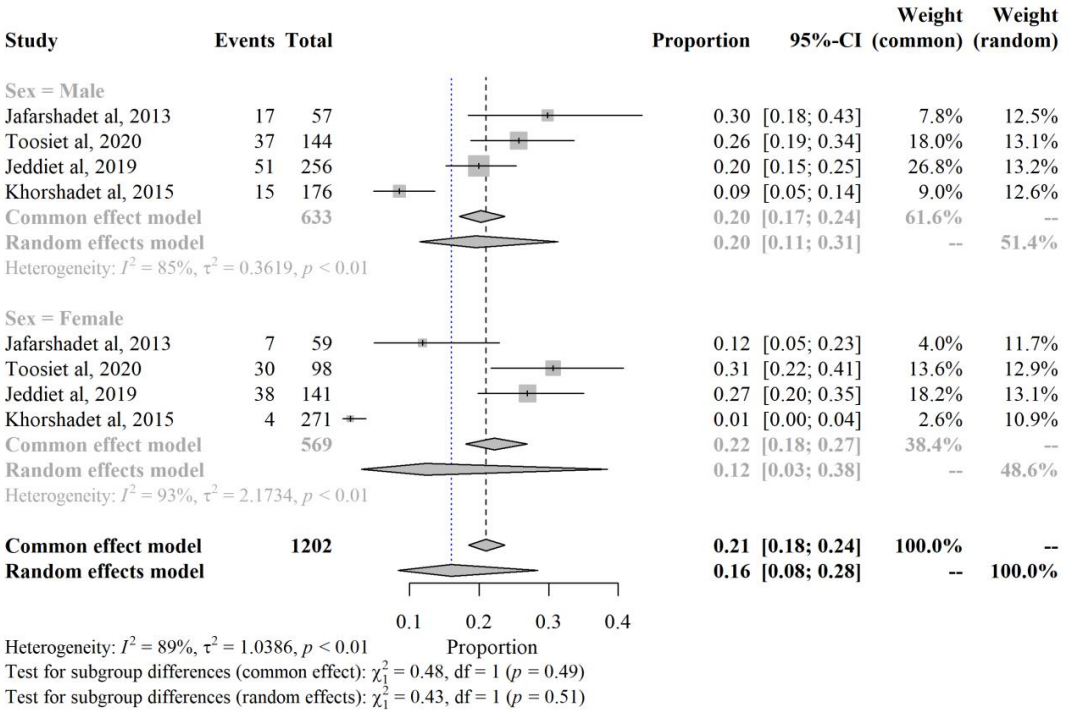

Figure 3. Forest plot of the pooled prevalence of PSC among Iranian adults by gender

Subgroup analysis

Subgroup analyses were performed based on sex, the coexistence of PSC with IBD or LT, and region. Based on four studies, the pooled prevalence of PSC in males was estimated to be 20% (95% CI: 11–31%). For females, the pooled prevalence was 12% (95% CI: 3–

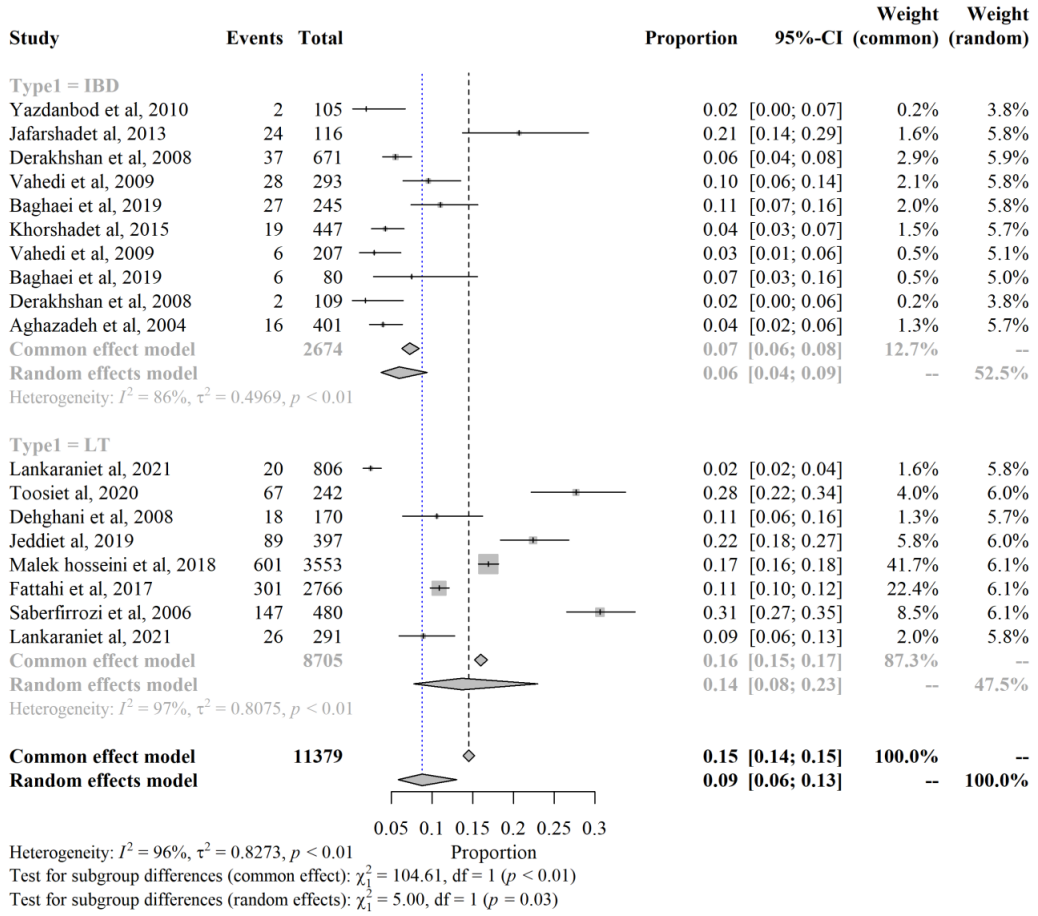

Figure 4. Forest plot of the pooled prevalence of PSC among Iranian adults with concurrent disease

38%) according to the same four studies. Significant heterogeneity was observed among the studies in both the male and female subgroups (I2=89%, P<0.01). However, the difference in the incidence of PSC between males and females was not statistically significant (P=0.51) (Figure 3).

Subgroup analysis of eight studies revealed that the pooled prevalence of PSC in patients with IBD was estimated to be 6% (95% CI: 4–9%) based on ten studies and 14% (95% CI: 8–23%) of LT recipients. Notably, significant heterogeneity was observed among the studies in both the IBD and LT patient subgroups (I2=96%, P<0.01) (Figure 4).

The pooled prevalence of PSC was estimated to be 6% (95% CI: 3–13%) in Tehran Province, 10% (95% CI: 7–14%) in Isfahan Province, and 12% (95% CI: 6–22%) in Fars Province. The results indicated a significantly greater prevalence of PSC in the Fars Province than in the Tehran and Isfahan Provinces (P=0.39). Notably, there was significant heterogeneity observed among the studies within the subgroups stratified by province (I2=98%, P<0.01) (Figure 5).

Assessment of publication bias

Egger's test (P=0.0970) did not suggest the presence of publication bias in the conducted studies. Additionally, the funnel plot analysis indicated no evidence of publication bias (Figure 6).

Discussion

The pooled prevalence of primary sclerosing cholangitis was estimated to be 8% in Iranian adult patients with IBD or liver disorders. To our knowledge, there is no previous systematic review reporting on the prevalence of PSC among Iranians. There are geographical differences in the global prevalence of PSC, with most studies conducted in North America, Europe, and Australia. It was demonstrated that northern

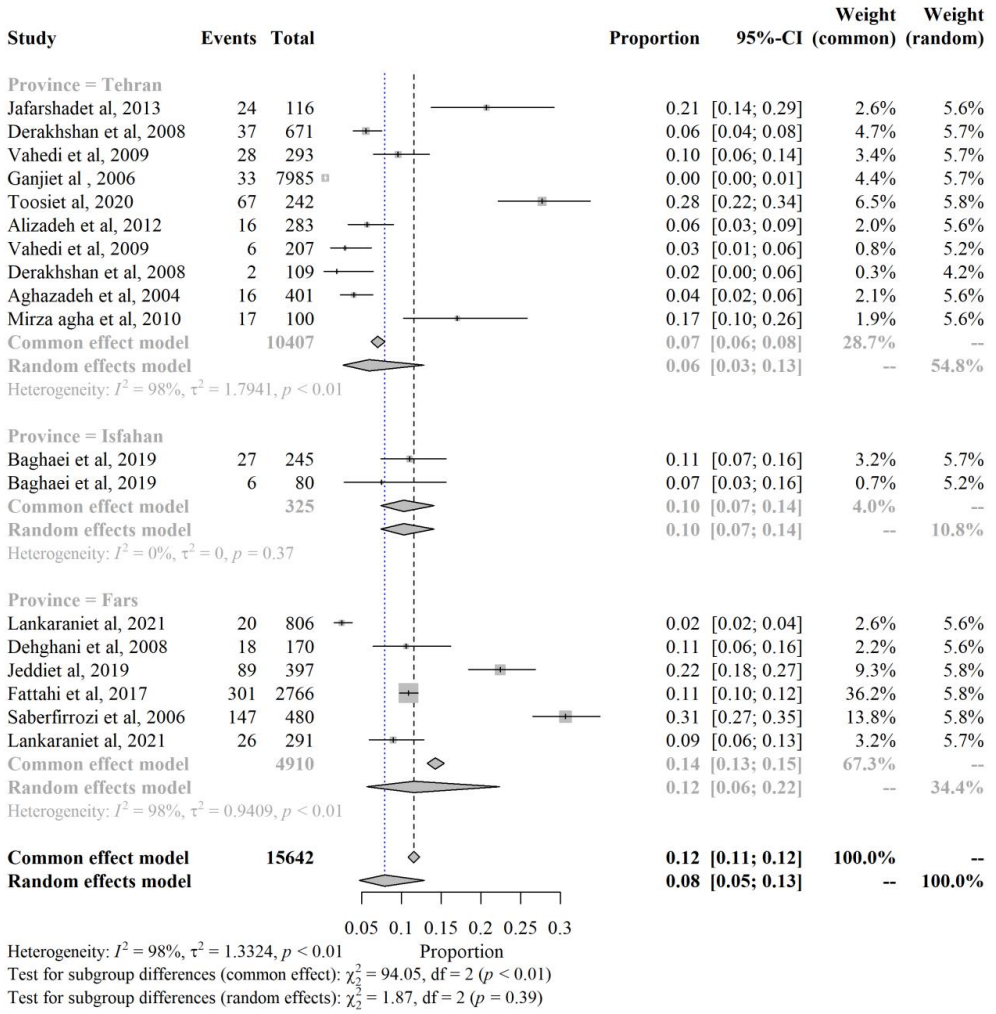

Figure 5. Forest plot of the pooled prevalence of PSC among Iranian adults by region

Europe (Finland, 1.58; Norway, 1.3 per 100,000 people) and North America (Minnesota, 1.47) have the highest reported incidences of PSC, while the lowest incidence was observed across the Mediterranean Basin (Italy, 0.1) (12). Furthermore, previous studies reported a wide range of prevalence of PSC, from 31.7 in Finland (13) and 23.99 in Minnesota (14) to 1.33 in Singapore (15) and 0.0 in Alaskan natives (16).

A previous systematic review estimated that the prevalence of PSC, a hepatic manifestation in IBD patients, was 1.67% (95% CI: 1.47–1.88%; I2: 99.10%) (17). The prevalence of PSC in patients with IBD ranged from 20.0% in Singapore (18) to 88.1% in Iceland (19). The prevalence of the concurrence of PSC with IBD was lower in cohorts from Asia (15, 20). A study of 12,216 patients with IBD at 5 tertiary care IBD centers in India reported a low prevalence of PSC (0.39%) (18).

The close association of PSC with IBD leads to PSC-IBD as a unique form of disease that is different from PSC without IBD and IBD without PSC (21). Patients with PSC-IBD have specific features and distinct treatments compared to those with IBD or PSC alone. According to a systematic review of population-based studies, the prevalence of UC reportedly ranged from 0% in Singapore (15) to 78.6% in Iceland (19), while the prevalence of CD ranged from 5.7% in the UK (22) to 34.7% in Canada (23) among PSC patients. Similarly, the results of a systematic review containing 776,700 patients reported that the pooled prevalence of PSC in patients with UC, CD, and unclassified IBD were 2.47%, 0.96%, and 5.01%, respectively (24). In our systematic review, the prevalence of PSC was 6% in patients with IBD and 14% in patients who were candidates or who received liver transplants among Iranian adults.

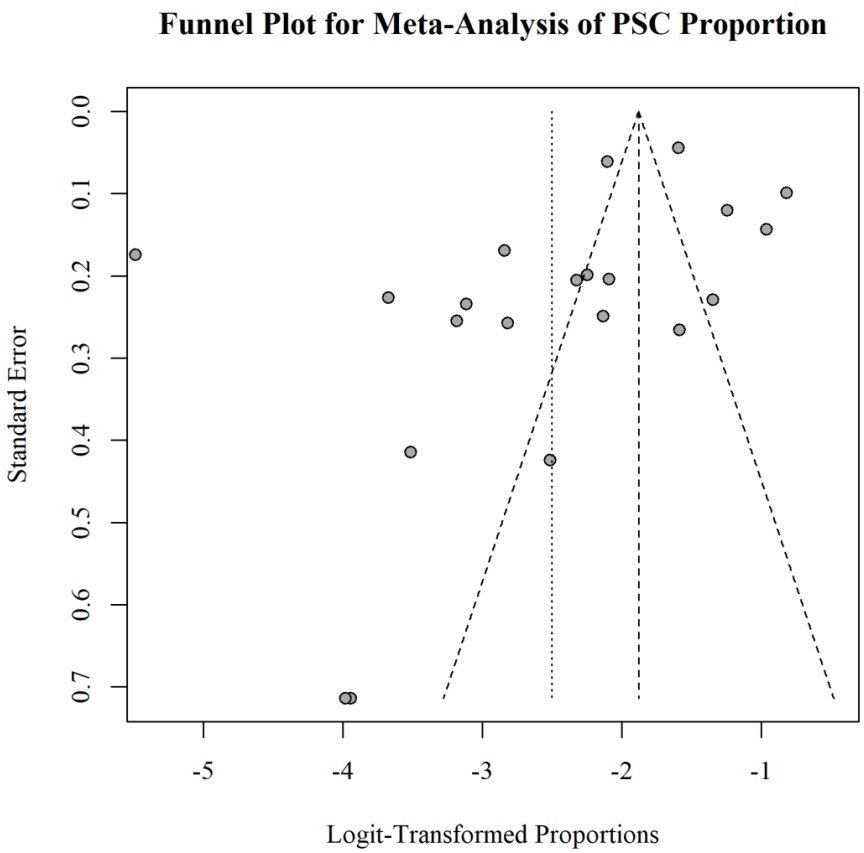

Figure 6. Funnel plot showing the risk of bias for PSC incidence and standard error in Iran

Furthermore, sex might significantly affect the prevalence of PSC. Regarding the sex distribution, in this study, 51.4% of the studied population were men, and 46.8% were women; these two groups were not significantly different. Studies related to sex differences in the prevalence of PSC are scarce and have produced controversial findings. A retrospective analysis of data from 37 centers in Europe, North America, and Australia (1980-2010) revealed that 65.5% of PSC patients were men (25). According to other studies, the prevalence of PSC in men was reported to be 51% in New Zealand (2016) (26), 71.4% in the U.S. (2017) (14), and 71.4% in Sweden (2005) (27). In contrast, data from the worldwide PSC Partners Patient Registry established in 2014 revealed that PSC is greater in women (52.5%) than in men (28).

Another study on the effect of PSC in patients with IBD by Trivedi et al., over 10 years showed that the female sex was associated with reduced risk liver transplantation or PSC-related death in PSC-IBD alone group vs the IBD alone group (HR, 0.74; P = .025) (29). To verify the relative independence of predictive phenotype features in the progression of liver disease in PSC patients, Weismüller et al., found that advancing age at diagnosis, having small duct disease, or CD at the time of PSC diagnosis, and also the protective effect of female sex have significant influences (25). It seems that other factors including the coexistence of IBD or other liver or autoimmune diseases with PSC, age, race, and age of patients in the diagnosis of PSC may influence the effect of sex in the incidence and progression of PSC and related outcomes.

In these data, we observed the highest prevalence of PSC in Fars province and then in Isfahan and Tehran provinces. As mentioned before, there is no registry system to record data for patients with PSC. Therefore, we have no data regarding the prevalence of PSC in the general population and all provinces of Iran. All of the included studies in this systemic review and meta-analysis were in hospital settings that may influence our findings about the prevalence of PSC in different provinces of Iran. It is notable that Abu-Ali Sina Hospital in Shiraz is the

main referral hospital for liver transplants in Iran and has the highest rate of successful liver transplants in Iran. This may explain the higher prevalence of PSC in Shiraz compared to other included provinces of Iran.

Along with geographical differences in genetic and environmental factors, one explanation for the various prevalence rates of PSC in Asia is that there are limited studies concerning the prevalence of PSC in Asian populations, including Iranians, compared to those on other continents. We found only one multicenter study reporting the prevalence of PSC in Iran, and all eligible studies in our systematic review were clinic-based. Therefore, there is a need for cohort or population-based studies to be implemented to determine the prevalence of PSC in the Iranian population.

One of the limitations of this study was the small number of studies reviewed. Most of the included studies were cross-sectional and clinic-based, and only one was conducted as a multicenter study 29). There is no registry system for recording the profiles of patients with PSC. All of the studies were conducted in Fars (Shiraz city), the main site of liver transplants in Iran; Tehran, the capital of Iran; and Isfahan, Khorasan, and Kerman. Therefore, we have no data about the prevalence of PSC in other provinces, and our results cannot be generalized to the general population in Iran. Another limitation of the study is that only four papers reported the prevalence of PSC based on gender. Additionally, this study is not registered in PROSPERO.

Conflict of interests

The authors declare no conflict of interest.

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