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The global prevalence of co-occurrence of Sjögren syndrome and Hepatitis C virus infection: A systematic review and meta-analysis

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ABSTRACT

Sjögren syndrome (SS) is one of the lesser-known autoimmune diseases, with its mechanisms and pathogenesis not yet fully understood. However, recent studies indicate that infectious diseases, such as Hepatitis C virus (HCV) infection, may serve as risk factors for the development of SS. Accordingly, this study aimed to estimate the global co-occurrence rate of chronic HCV infection and SS. In this systematic review and meta-analysis, a comprehensive search for relevant studies was conducted in PubMed, Scopus, ISI Web of Science, and Google Scholar databases up to June 2024. Data from eligible studies were meticulously extracted and statistically analyzed using Comprehensive Meta-Analysis Software. The pooled prevalence of co-occurrence of HCV and SS was calculated using incidence rates with 95 % confidence intervals (CIs), and the association of chronic HCV infection with the development of SS was assessed via odds ratios (ORs) with 95 % *CIs*. Analysis of the articles retrieved from the databases showed 24 studies were considered eligible. The pooled estimate for the co-occurrence of HCV and SS was approximately 16.6 % (95 % CI: 8.8–28.9). Moreover, the results indicated that chronic HCV infection significantly increased the risk of developing SS (OR: 2.76; 95 % CI: 1.35–5.63). This study's findings revealed that HCV infection may play a role in the pathogenesis of and susceptibility to SS. Therefore, chronic HCV infection may trigger the onset of SS. However, further studies are required to confirm these results.

1. Introduction

Sjögren syndrome/Sicca syndrome (SS) is an autoimmune disease characterized by symptoms such as persistent dryness of the mouth and eyes and lymphocytic infiltrates in the exocrine glands (Voulgarelis and Tzioufas, 2010). According to the literature, the female-to-male ratio of this disease has been reported between 1:8 and 1:14 (Beydon et al., 2024; Qin et al., 2015). The exact etiology of SS has not yet been determined; however, combination studies suggest that genetic and environmental factors may contribute to susceptibility to SS. Viruses, particularly the hepatitis C virus (HCV), are among the most important exogenous risk factors crucial for triggering the onset of SS (Sherman and Sherman, 2015). HCV is a single-stranded RNA virus that belongs to the Flavivirus family (Houghton, 2009). HCV infection can manifest with hepatic and extrahepatic complications, such as cryoglobulinemia, arthritis, porphyria cutanea tarda, diabetes mellitus, and depression (Cacoub et al., 2016; Kuna et al., 2019).

The relationship between HCV and SS was first noted by Haddad et al. in 1992, who found that the frequency of lymphocytic sialadenitis in individuals infected with HCV was significantly higher than in the control group. This study introduced HCV infection as a potential candidate for the development of SS (Haddad et al., 1992). Dinescu et al. reported two women diagnosed with HCV-induced SS a few years later (Dinescu et al., 2017). In this regard, subsequent studies postulated that

Abbreviation: SS, Sjögren syndrome; HCV, Hepatitis C virus; Cis, 95 % confidence intervals; ORs, odds ratios; JBI, Joanna Briggs Institute; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

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SS commonly occurs in individuals with chronic HCV infection (Vitali, 2011). The literature suggests that some extrahepatic manifestations of HCV infection share clinical characteristics with SS (Liu and Chu, 2021). Numerous studies have confirmed the relationship between HCV infection and the occurrence of SS (Castro Ferreiro et al., 2002; Henderson et al., 2001). However, there are also studies presenting contradictory results (Barrier et al., 1993; King et al., 1994). Investigating this relationship offers two major advantages: 1) HCV infection and its related extrahepatic complications can impose a significant economic burden on healthcare systems (Keikha and al., 2020), and 2) evaluating the consequences of HCV infection can highlight the importance of monitoring and eradicating this virus (Calvaruso and Craxì, 2020; Lledó et al., 2019).

The relationship between HCV infection and Sjögren syndrome remains incompletely understood, with existing studies showing conflicting results and limited by small sample sizes. This knowledge gap underscores the critical need for a comprehensive, large-scale synthesis of available evidence. Our systematic review and meta-analysis address this imperative by: (1) providing the first robust pooled estimate of SS prevalence among HCV-infected populations worldwide, and (2) quantitatively evaluating the potential etiological association between chronic HCV infection and SS development. By aggregating data from diverse studies through rigorous meta-analytic methods, this work offers unprecedented statistical power to resolve current uncertainties and establish evidence-based conclusions about this clinically important relationship.

2. Materials and methods

2.1. Search strategy

We systematically searched PubMed, Scopus, Web of Science, and

Table 1
Characteristics of included studies.

First author	Year of publication	Country	Study design	Sample size		Age, gender			SS criteria	Diagnostic method	JBI	Ref
				Case number	Population	Age	Male	Female				
Portales	1997	Spain	Cross-sectional	4	56	45	32	24	Clinical examination	PCR	6	(Romero Portales et al., 1997)
Buskila	1998	Israel	Cross-sectional	7	90	57	48	42	Rheumatic assessment	ELISA	7	(Buskila et al., 1998)
Cacoub	1999	France	Cross-sectional	178	1614	47	872	742	Clinical questionnaire	ELISA	6	(Cacoub et al., 1999)
Rivera	1999	Spain	Cross-sectional	30	142	54	50	92	Lab evaluation	PCR	6	(Rivera et al., 1999)
Perniola	1999	Italy	Retrospective cohort	73	88	24	54	34	Clinical examination	ELISA-PCR	7	(Perniola et al., 1999)
Loustaud	2001	France	Prospective cohort	24	45	50	23	22	Clinical examination	ELISA-PCR	7	(Loustaud-Ratti et al., 2001)
Barrett	2001	Ireland	Prospective cohort	79	147	NA	NA	NA	European criteria	PCR	7	(Barrett et al., 2001)
El-Serag	2002	USA	Cross-sectional	31	34,204	48	33,576	628	Clinical examination	ELISA	8	(El-Serag et al., 2002)
Poynard	2002	France	Prospective cohort	181	1614	47	872	742	Clinical questionnaire	ELISA	8	(Poynard et al., 2002)
D'Amico	2002	Italy	Cross-sectional	69	150	57	59	91	European criteria	ELISA	6	(D'Amico et al., 2002)
Siagris	2002	Greece	Retrospective cohort	93	173	53	93	80	European criteria	ELISA	7	(Siagris et al., 2002)
Nagao	2003	Japan	Cross-sectional	81	110	48	59	51	European-Japanese criteria	PCR	6	(Nagao et al., 2003)
Kozanoglu	2003	Turkey	Cross-sectional	95	190	46	69	121	Rheumatic assessment	ELISA-PCR	7	(Kozanoglu et al., 2003)
Casals	2005	Spain	Retrospective cohort	180	360	NA	NA	NA	American-European criteria	ELISA-PCR	6	(Ramos-Casals et al., 2005)
Lu	2007	China	Cross-sectional	65	84	NA	NA	NA	Lab evaluative	RT-PCR	6	(Lu et al., 2007)
Potthoff	2009	Germany	Prospective cohort	73	247	50	27	46	American-European criteria	PCR	7	(Potthoff et al., 2009)
Michaluk	2010	Poland	Retrospective cohort	9	340	42	207	133	Clinical examination	PCR	8	(Zarebska-Michaluk et al., 2010)
Mohammed	2010	Egypt	Cross-sectional	27	306	NA	NA	NA	Clinical examination	ELISA	7	(Mohammed et al., 2010)
Cheng	2014	China	Cross-sectional	9	297	55	151	146	Clinical examination	ELISA-PCR	7	(Cheng et al., 2014)
Cacopardo	2014	Italy	Cross-sectional	12	310	47.5	200	110	European criteria	PCR	7	(Cacopardo et al., 2014)
Zeron	2015	Spain	Retrospective cohort	105	783	62.9	17	88	European criteria	ELISA	8	(Brito-Zerón et al., 2015)
Yeh	2016	Taiwan	Cross-sectional	397	9629	NA	1250	8379	European criteria	ELISA	7	(Yeh et al., 2016)
Hela	2019	Tunisia	Retrospective cohort	17	204	45.6	2	15	NA	PCR	7	(Gharbi et al., 2019)
Tung	2022	Taiwan	Retrospective cohort	177	17,166	51.3	3569	2800	European criteria	ELISA-PCR	8	(Tung et al., 2022)

Google Scholar through June 2024 using a combination of MeSH terms and free-text keywords including "hepatitis C virus" OR "HCV infection" (for HCV-related studies) AND "Sjögren syndrome" OR "Sicca syndrome" (for SS-related studies), with Boolean operators connecting search terms. Two independent investigators conducted the searches, supplemented by manual reference list screening of included articles and relevant reviews, plus consultation with field experts to identify additional studies, with any discrepancies resolved through consensus discussion involving a third researcher when needed.

2.2. Inclusion and exclusion criteria

Studies were included if they were full-text English articles estimating either (1) the prevalence of SS in HCV-infected individuals (primary objective) or (2) the association between HCV and SS (secondary objective), using cross-sectional or cohort designs (case-control studies were excluded as they cannot assess prevalence) and employing standard diagnostic methods for both conditions; studies were excluded if they focused on non-SS diseases, were non-English publications, non-original research (e.g., reviews, case reports), involved HIV/HBV co-infection, used non-human models, or were duplicates.

2.3. Data extraction and quality assessment

The quality of eligible studies was assessed according to the Joanna Briggs Institute (JBI) checklist. The JBI checklist evaluates studies based on certain criteria such as sample size, research objectives, data collection processes, and statistical analysis methods. Studies were included if they achieved a score of at least six. The evaluation was conducted by two independent authors.

Data extracted from the eligible studies included the first author, publication year, study location, study design, population size, gender distribution, mean age, SS diagnostic criteria, HCV-related diagnostic techniques, and JBI score for each study (Table 1).

2.4. Statistical analysis

Data were pooled using Comprehensive Meta-Analysis Software (version 2.2) (Ali-Hassanzadeh et al., 2025). The prevalence of global co-occurrence of HCV and SS was expressed as a percentage with 95 % confidence intervals, and the potential relationship between HCV and SS was evaluated using odds ratios with 95 % confidence intervals. Heterogeneity among studies was assessed using the I^2 index and the Cochran Q-test. In cases of considerable heterogeneity, a random-effects model, specifically the DerSimonian and Laird method, was used to pool the data. Publication bias was also assessed using Egger's and Begg's regression p-value tests and funnel plots.

3. Result

3.1. Search strategy and study selection

Our initial database search identified 203 potential articles. After removing 47 duplicates, we screened 156 unique records. Through title/abstract screening, we excluded 98 studies (63 for irrelevant population/disease focus, 22 for non-original research, 8 for language restrictions, and 5 for animal/cell culture studies). Of the remaining 58 articles undergoing full-text review, we excluded 34 studies (12 for lacking outcome data, 9 for inappropriate study design, 7 for insufficient diagnostic criteria, 4 for HIV/HBV coinfection, and 2 for duplicate populations). Ultimately, 24 studies met all inclusion criteria and were included in our systematic review and meta-analysis (Fig. 1). The PRISMA flowchart in Fig. 1 details this selection process with complete exclusion rationale at each stage.

3.2. Characteristics of included studies

Table 1 summarizes the key information of the eligible studies. A total of 24 studies published from 1997 to 2022 evaluated the co-occurrence of SS and HCV infection. These studies were conducted in European and Asian countries, with one study in North America. The quality scores of the studies ranged from 6 to 8. In terms of study design, there were 13 cross-sectional studies, 7 retrospective cohort studies, and 4 prospective cohort studies. The analysis covered data from 68,349 individuals, with a mean patient age of 13 ± 48.9 years. Furthermore, 74.13 % of the patients were male, and the rest were female. Various diagnostic criteria were utilized in the analyzed studies, including clinical examinations, rheumatic assessments, clinical questionnaires, laboratory evaluations, as well as American-European and Japanese criteria to diagnose SS. In addition, serological and molecular methods

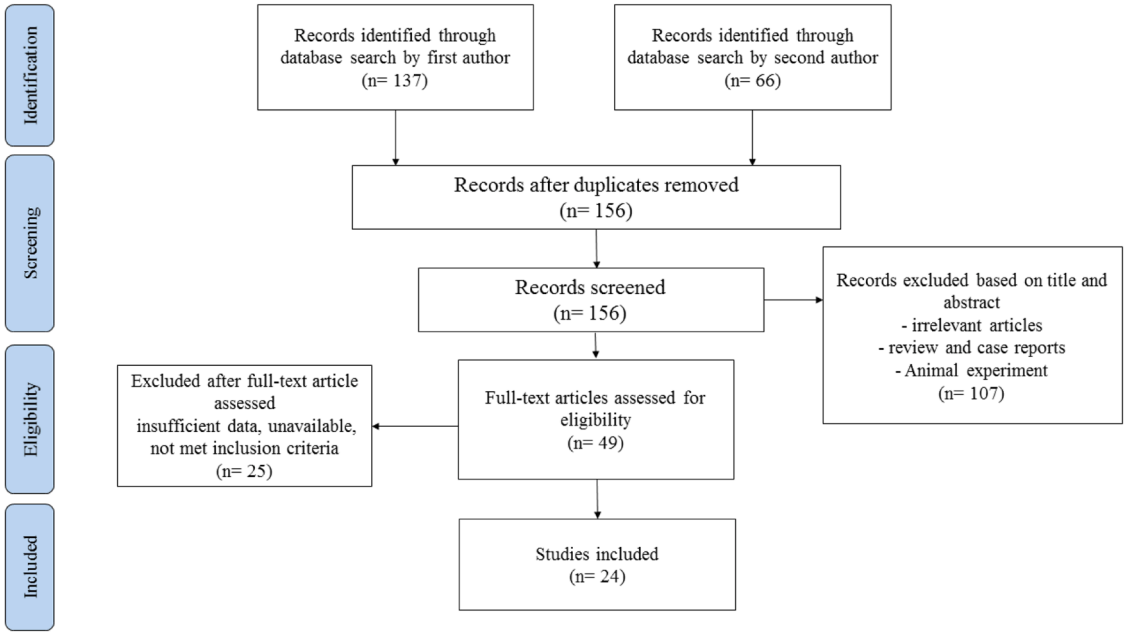

Fig. 1. Flowchart of the study selection process.

were used to diagnose HCV infection.

3.3. Main results

In the present analysis, data from 24 eligible studies were examined to calculate the prevalence of co-occurrence of HCV infection and SS. The pooled prevalence of SS among individuals with HCV infection was estimated at 16.6 % (95 % CI: 8.8–28.9; I^2: 99.4; p-value: 0.001; Egger's p-value: 0.031; Begg's p-value: 0.020) (Fig. 2).

The analysis of the data from the eligible studies showed chronic HCV infection significantly increased the risk of SS (OR: 2.76; 95 % CI: 1.35–5.63; p-value: 0.005; I^2: 79.2; p-value: 0.153; Egger's p-value: 0.8; Begg's p-value: 0.5). Therefore, the pooled prevalence of HCV/SS co-occurrence was estimated at 16.6 % (95 % CI: 8.8–28.9), and it was proved that chronic HCV infection increased the risk of SS by about 2.7-fold (Fig. 3).

The presence of publication bias was evaluated using the symmetric funnel plot as well as Egger's and Begg's p-value tests. Regarding the prevalence of SS/HCV co-occurrence, the results of Egger's and Begg's p-value tests were significant, and asymmetry was evident in the funnel plot. However, no significant asymmetry was observed in overall estimates in the analysis of the relationship between chronic HCV infection and SS (Fig. 4).

3.4. Subset analyses

To facilitate comparison, all supplementary overall estimates were summarized in Table 2. In the European population, the prevalence of HCV/SS was higher than in Asian countries. Additionally, subgroup analysis based on geographical distribution indicated that chronic HCV infection significantly increased the risk of SS in the European population. Subgroup analysis based on the study design revealed that chronic HCV infection significantly increased the risk of SS in both prospective and retrospective cohort studies. Considering that cohort studies are the most reliable to show the relationship between exposure and outcome over time, the results of the cohort study analysis suggested that chronic HCV infection can be regarded as an important exogenous risk factor for the development of SS (Table 2).

Moreover, subgroup analysis based on the diagnostic methods of SS and HCV infection indicated that the overall summary OR in studies that used the European diagnostic criteria and molecular techniques to identify SS and HCV infection, respectively, were higher than in studies using other methods.

The quality assessment score is crucial for interpreting the results. In general, it is advisable to give more weight to studies with higher quality scores. Consequently, the subgroup analysis of high-quality studies (JBI score > 6) revealed that chronic HCV infection increased the susceptibility to SS by about 4.68-fold (Table 2).

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Portalles	0.071	0.027	0.175	4.943-	0.000
Buskila	0.078	0.038	0.154	6.283-	0.000
Cacoub	0.110	0.096	0.127	26.274-	0.000
Rivera	0.211	0.152	0.286	6.408-	0.000
Pemiola	0.830	0.736	0.895	5.582	0.000
Loustaud	0.533	0.389	0.672	0.447	0.655
Barrett	0.537	0.457	0.616	0.906	0.365
El-Serag	0.001	0.001	0.001	38.986-	0.000
Poynard	0.112	0.098	0.128	26.229-	0.000
D'Amico	0.460	0.382	0.540	0.979-	0.328
Siagris	0.538	0.463	0.611	0.987	0.323
Nagao	0.736	0.646	0.810	4.747	0.000
Kozanoglu	0.500	0.429	0.571	0.000	1.000
Casals	0.500	0.449	0.551	0.000	1.000
Lu	0.774	0.672	0.851	4.716	0.000
Potthoff	0.296	0.242	0.355	6.229-	0.000
Michaluk	0.026	0.014	0.050	10.671-	0.000
Mohammed	0.088	0.061	0.126	11.587-	0.000
Cheng	0.030	0.016	0.057	10.238-	0.000
Cacopardo	0.039	0.022	0.067	10.910-	0.000
Zeron	0.134	0.112	0.160	17.785-	0.000
Yeh	0.041	0.037	0.045	61.387-	0.000
hela	0.083	0.052	0.130	9.466-	0.000
Tung	0.010	0.009	0.012	60.408-	0.000
	0.166	0.088	0.289	4.416-	0.000

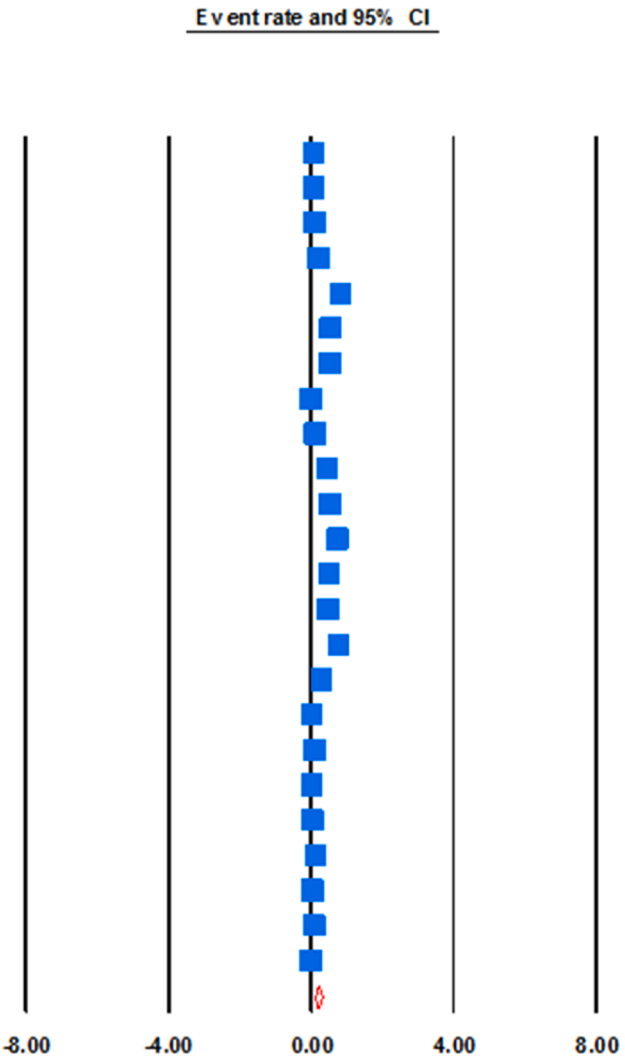

Fig. 2. Pooled prevalence of SS among patients with chronic HCV infection.

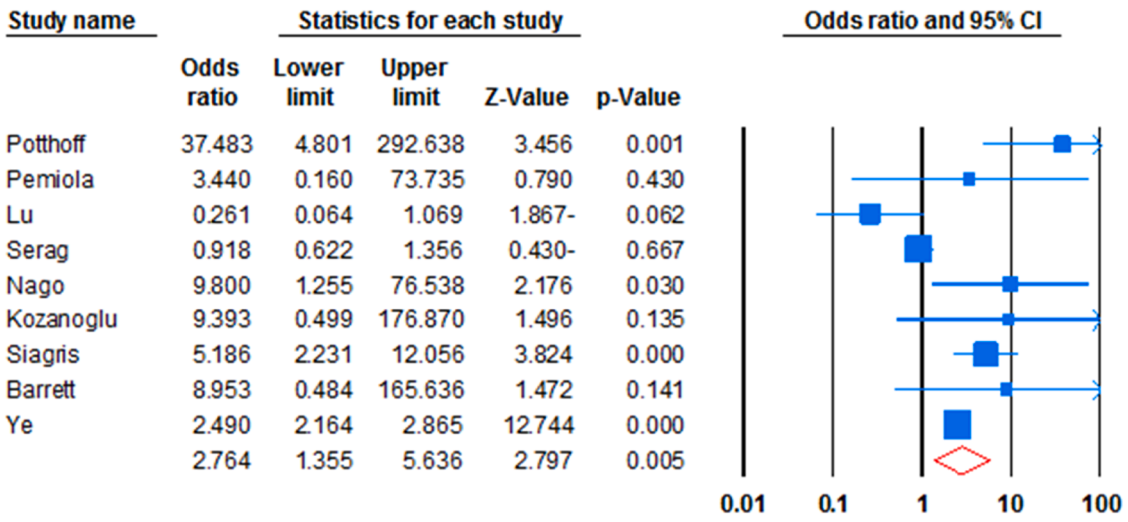

Fig. 3. Meta-analysis on the association between chronic HCV infection and SS.

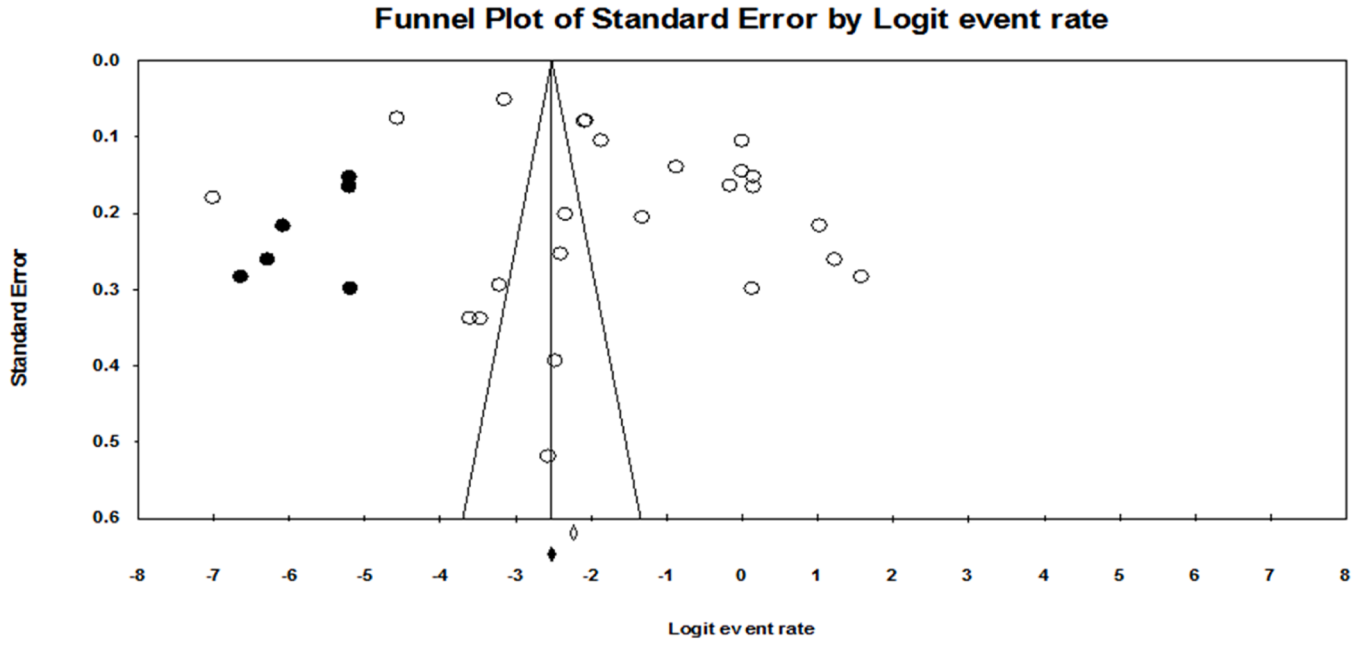

Fig. 4. Funnel plot with pseudo 95 % confidence limits of all 24 eligible studies in the overall meta-analysis.

4. Discussion

Sjögren syndrome is one of the least known systemic autoimmune diseases. Previous observational studies have consistently suggested that viral infections, particularly HCV infection, may serve as risk factors for SS. However, some studies have reported conflicting findings, indicating that the relationship between HCV infection and SS requires further clarification through comprehensive investigations. Accordingly, this study evaluated the overall co-occurrence of chronic HCV infection and SS using the data from the existing studies to systematically explore the relationship between HCV infection and SS through detailed statistical analysis.

According to the literature, HCV exhibits a high affinity and tropism for lacrimal and salivary epithelial cells (Arrieta et al., 2001). Recent studies have identified several mechanisms linking HCV infection to SS, including molecular mimicry between HCV and salivary glands, the accumulation of HCV particles in these glands, and direct infection. These factors can trigger immune complex reactions, potentially resulting in autoimmune reactions such as SS (Ramos-Casals et al., 2001). An animal model study demonstrated that transgenic mice expressing HCV envelope proteins E1 and E2, lacrimal glands, and salivary lesions resembling the pathological features of SS (Koike et al., 1997). In another hand, our findings are consistent with more recent investigations highlighting the complex relationship between viral infections and autoimmune phenomena. For instance, recent studies have emphasized the role of chronic viral infections, including HCV, in triggering Sjögren-like features through chronic antigenic stimulation and molecular mimicry (Goh and Kerkar, 2024; Maslinska and Kostyra-Grabczak, 2022). Moreover, updated meta-analyses suggest that anti-viral treatment may impact the course of HCV-associated autoimmune manifestations. This aligns with the notion that HCV may act as a trigger rather than a true etiologic agent for SS (Tomasiewicz et al., 2015; Cacciato et al., 2020). These insights support the idea that HCV-associated SS may represent a distinct clinical phenotype, requiring tailored diagnostic and therapeutic approaches.

The results of the present study showed that the global prevalence of

Table 2
Subset analyses of the association between SS and chronic HCV infection.

Items	% (95 % CI)	OR (95 % CI); p-value
Geographical area		
Asian countries	14.3 % (3.3–44.8)	1.70 (0.32–8.91); 0.5
European countries	22.6 % (21.4–23.9)	12.31 (2.7–56.04); 0.01
Study design		
Cross-sectional	18.9 % (8.3–37.5)	1.57 (0.66–3.76); 0.3
Cohort	22.9 (8.6–48.3)	12.72 (2.1–7.04); 0.01
Prospective cohort	33.7 % (13.7–61.8)	41.8 (4.5–385.82); 0.01
Retrospective cohort	20.0 % (3.3–64.5)	5. 03 (2.23–11.36); 0.01
SS Diagnostic criteria		
European criteria	22.3 % (8.0–48.5)	9.07 (2.54–32.45); 0.01
Other criteria	21.3 % (11.2–36.8)	0.96 (0.31–2.92); 0.9
HCV diagnostic test		
Molecular assay	25.0 % (8.4–54.6)	6.39 (0.6–58.9); 0.1
Serological assay	16.0 % (7.9–29.8)	2.36 (1.12–4.59); 0.02
Quality assessment score		
> 6	16.0 % (7.4–31.3)	4.68 (1.97–11.09); 0.01
≤ 6	37.1 % (17.2–62.5)	1.47 (0.04–51.33); 0.8

HCV/SS co-occurrence was approximately 16.6 % (95 % CI: 8.8–28.9), and chronic HCV infection significantly increased the risk of SS (OR: 2.76; 95 % CI: 1.35–5.63; p-value: 0.005). However, it is important to acknowledge the considerable heterogeneity present in the pooled estimates. To reduce subgroup heterogeneity, analyses were conducted based on potential confounders, and sensitivity analyses were also performed based on the leave-one-out meta-analysis method. Nevertheless, neither approach significantly reduced the heterogeneity of the pooled estimates. Wang et al. (2014) conducted a meta-analysis of 10 studies and reported that HCV infection increased the risk of SS by about 3.3-fold (Wang et al., 2014). Furthermore, Younossi et al. (2016) analyzed 11 studies and showed that HCV significantly increased the risk of SS (Younossi et al., 2016). Similar to the results of the present study, both studies reported a high degree of heterogeneity. However, the present study included a larger sample size with data from 24 studies and performed several subgroup analyses.

The results of the subgroup analysis revealed that the frequency of co-occurrence of HCV and SS was higher in European countries compared to Asian populations. Variations between these populations may be attributed to environmental factors and the distribution of HCV among different geographical groups. Furthermore, the number of studies included from Asian populations was limited, suggesting that the results cannot be generalized to all populations. Thus, further epidemiological studies are required to explore this association in diverse geographical regions.

Cohort studies provide a more robust framework to estimate the associations between exposures and outcomes compared to cross-sectional studies. In the present study, both prospective and retrospective cohort studies showed that HCV infection increased the risk of SS. Some researchers believe that eradicating HCV could mitigate the risk of SS. However, Tung et al. (2022) showed that anti-HCV therapies cannot reduce the risk of SS (Tung et al., 2022). Therefore, further large-scale trials are warranted to evaluate the role of anti-HCV therapies in decreasing the risk of SS.

This systematic review and meta-analysis have some limitations that should be acknowledged. First, there was substantial heterogeneity among the included studies in terms of diagnostic criteria for both SS and Hepatitis C virus infection, as well as differences in geographic regions, sample sizes, and study designs. Second, due to limited data availability, subgroup analyses based on demographic variables such as age, sex, or disease duration could not be performed. Third, publication bias could not be fully ruled out, especially given the limited number of studies from certain regions. Lastly, some included studies may have misclassified HCV-associated sicca symptoms as primary SS due to overlapping clinical features, which might have influenced the pooled prevalence estimate. These factors should be considered when interpreting the findings.

This systematic review and meta-analysis demonstrate that the co-occurrence of SS and Hepatitis C virus (HCV) infection is a recognized clinical phenomenon with a notable global prevalence. While some cases may represent true overlap, others likely reflect HCV-induced sicca symptoms that mimic SS. These findings underscore the importance of careful differential diagnosis to avoid overdiagnosis and misclassification. Given the evolving landscape of antiviral therapies, further research is warranted to clarify the causal relationship between HCV infection and Sjögren-like manifestations, identify specific biomarkers that differentiate primary SS from HCV-associated SS, and evaluate the impact of HCV eradication on autoimmune features. Future large-scale prospective studies with standardized diagnostic criteria are essential to refine clinical approaches and inform treatment strategies.

5. Conclusion

The present study showed that chronic HCV infection is a reliable biomarker for predicting the development of SS. Moreover, the results of the subgroup analysis revealed a significant positive relationship between chronic HCV infection and SS in cohort studies and studies with high-quality scores. Nevertheless, the results should be interpreted with caution, and further studies are required to confirm the reliability of the findings.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have approved this manuscript for publication.

CRediT authorship contribution statement

Nasir Arefinia: Writing – original draft, Software, Conceptualization. **Hedyeh Askarpour:** Writing – original draft, Visualization, Methodology, Investigation. **Zohreh-Al-Sadat Ghoreshi:** Methodology, Investigation, Formal analysis, Conceptualization. **Habibeh Mashayekhi-Sardoo:** Writing – review & editing, Project administration, Investigation, Data curation, Conceptualization. **Mohammad Ali-Hassanzadeh:** Writing – review & editing, Visualization, Validation, Supervision, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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