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Original Article

Risk factors for viral hepatitis in pulmonary tuberculosis patients undergoing treatment: A systematic review and meta-analysis

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Abstract

Liver injury in tuberculosis patients, associated with noncompliance with treatment, is further exacerbated by viral hepatitis, which not only directly harms the liver but also increases susceptibility to drug-induced liver injury. The aim of this study was to analyze the associated risk factors for viral hepatitis in tuberculosis patients. This systematic review and meta-analysis adhere to the PRISMA 2020 statement, and the protocol has been registered with PROSPERO (CRD42023477241). Screening and selection of articles were carried out according to predetermined inclusion and exclusion criteria, utilizing four databases: Embase, Medline, Scopus, and ProQuest. Baseline characteristics and patient-related risk factors from each included study were extracted, followed by a meta-analysis of factors that potentially had significance, with the heterogeneities also being analyzed. Of the 21 included studies out of 6,415 identified records, 12 potential risk factors for hepatitis B and 15 for hepatitis C were subjected to meta-analysis. Some key risk factors included for hepatitis B and C were HIV infection (OR: 3.42; 95%CI: 2.19–5.34 and OR: 6.99; 95%CI: 5.09–9.61, respectively), smoking (OR: 1.55; 95%CI: 1.19–2.02 and OR: 3.06; 95%CI: 1.63–5.75, respectively) and alcohol consumption (OR: 2.38; 95%CI: 1.06–5.37 and OR: 4.32; 95%CI: 2.76–6.78, respectively). Furthermore, meta-analysis indicated that other significant risk factors for hepatitis B and/or C include injecting and non-injecting drug use, multiple sexual partners, tattooing, ear-nose piercing, blood transfusion, dental interventions, homelessness, incarceration, living with prisoners, sexually transmitted diseases, and diabetes mellitus. In conclusion, patients with tuberculosis who have risk factors such as smoking, HIV, or alcohol consumption should be screened for hepatitis B and C to prevent liver injury.

Keywords: Hepatitis B, hepatitis C, liver injury, risk factor, tuberculosis

Introduction

Tuberculosis cases remain persistently high and continue to be a significant infectious disease that contributes to global mortality [1]. According to the Global Tuberculosis Report 2023, approximately 10.6 million individuals worldwide were diagnosed with tuberculosis in 2022, with an estimated incidence of 133 new cases per 100,000 population [1]. A major concern raised in patients undergoing anti-tuberculous treatment is liver injury, as this is the most important adverse event leading to a lack of adherence to treatment and, consequently, treatment failure, which could potentially elevate the risk of developing drug resistance [2]. Current first-line drugs

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for tuberculosis, including isoniazid, rifampin, and pyrazinamide, are associated with hepatotoxicity, with the occurrence ranging from 3% to 28% [3].

Viral hepatitis co-infection with tuberculosis leads to a higher risk of drug-induced liver injury in individuals undergoing antituberculosis treatment, a phenomenon commonly observed in clinical practice [4-7]. A meta-analysis estimated the prevalence of hepatitis B co-infection with tuberculosis to be 7.1%, although this prevalence varies by region, ranging from 2.2% to 11.4% [8]. In contrast, the prevalence of hepatitis C co-infection among tuberculosis patients is approximately 7%, with global rates ranging from 7% to 11% [9]. Viral hepatitis infection accelerates liver cell injury, resulting in liver damage and increasing susceptibility to drug-induced liver injury [3,10]. Furthermore, viral hepatitis co-infection with tuberculosis is associated with severe forms of the disease, necessitating a higher frequency of retreatment and resulting in poorer treatment outcomes and increased mortality [11]. The aim of this study was to analyze the associated risk factors of viral hepatitis in tuberculosis patients. This study employs a systematic approach to synthesize data from previous studies, comprehensively identifying and analyzing the associated risk factors to provide a clearer understanding of these factors. By identifying viral hepatitis in this population, greater awareness of the risk of hepatic disorders or drug-induced liver injury in individuals with tuberculosis is expected, enabling the implementation of additional interventions.

Methods

Protocol registration

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. The protocol has been registered with PROSPERO under protocol number CRD42023477241.

Search strategy

The literature search for this systematic review was conducted on November 8, 2023, by two independent reviewers (SRA and HLA), with disagreements resolved through discussion with a third reviewer. Literature was obtained from four electronic journal databases: Embase, Medline, Scopus, and ProQuest, using the specific keywords (tuberculosis infection, risk factor, and hepatitis; with synonyms for each term according to MeSH terms) listed in **Underlying data**. Manual searches were additionally performed to ensure the inclusion of all studies relevant to the topic of this systematic review. All identified articles were entered into EndNote X9 software (Clarivate Analytics, Philadelphia, United States), where duplicates were removed. The screening process began with the review of titles and abstracts by two independent reviewers (SRA and HLA), with the third (AFI) involved in cases of discrepancy. Reports that cleared this stage proceeded to full-text retrieval for evaluation of eligibility. Studies meeting the eligibility criteria, including those found through manual searches, were incorporated into the systematic review and meta-analysis.

Study quality assessment

The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies [13], with a modified version of the scale applied to cross-sectional studies [14]. Studies scoring 7 or higher were categorized as high quality, those scoring between 5 and 6 as moderate quality, and those scoring 4 or lower as low quality. If any RCT studies were included, the assessment would have been conducted using the revised Cochrane risk-of-bias tool for randomized trials (ROB 2) [15]. The quality assessment of the studies was conducted independently by two reviewers (SRA and HLA), with two additional reviewers (AFI and MID) acting as a mediator in cases of discrepancy.

Eligibility criteria

Screening and selection of articles were conducted by applying specific inclusion and exclusion criteria. The included study designs comprised observational studies, including cohort, case-control, and cross-sectional studies, as well as randomized controlled trials. Participants in the included studies were individuals with tuberculosis who had viral hepatitis. Indicators assessed

included various patient-related risk factors for viral hepatitis among tuberculosis patients, such as biological factors (age, sex, HIV, diabetes mellitus, and chronic kidney disease), behavioral factors (history of smoking, drug use, alcohol, sexual activities, tattooing, piercing), social factors (homelessness, living with prisoner, and incarceration), and procedural factor (blood transfusion, dental intervention). Certain risk factors were excluded, such as those observed in post-mortem patients and after TB treatment completion, as they do not reflect the patient's risk prior to the outcome of anti-TB treatment. Additionally, specific demographics (regions and races) were excluded, considering that these risk factors provide limited importance in this review, which aims to assess the outcome for the general global population. Clinical presentations that primarily reflect the effects of the outcome rather than the risk factors and laboratory findings unrelated to the disease were also excluded. Narrative reviews, case reports, case series, and letters to the editor were excluded.

Data extraction

Data from the included studies were extracted into result tables, including author and year, country, study design, sample size, mean (SD) or median (range) age of participants, diagnostic criteria for TB, and diagnostic criteria for hepatitis B or hepatitis C. All biological and social patient-related risk factors for hepatitis that met the eligibility criteria were compiled into a separate table, incorporating the odds ratio, confidence interval, and *p*-value.

Statistical analysis

Review Manager (RevMan) 5.4 software (Cochrane Collaboration, Oxford, England) was employed for statistical analysis. The meta-analysis results were visualized in a forest plot, displaying the overall odds ratio (OR), 95% confidence interval (CI), and heterogeneity. A random effects model was used for the meta-analysis with heterogeneous data, while a fixed effects model was used for homogeneous data. The distribution of heterogeneous data was determined based on the Q test and I^2 statistics. If the I^2 value was greater than 50% or the *p*-value was less than 0.05, heterogeneity between studies was assumed; otherwise, the data were considered homogeneous. The degree of heterogeneity was estimated based on I^2 (0% to 40%: might not be heterogeneous, 30% to 60%: moderate heterogeneity, 50% to 90%: substantial heterogeneity, and 75% to 100%: considerable heterogeneity) [16].

Results

Literature search results and selection

A total of 6414 studies were identified (**Figure 1**). After duplicates were removed, 3037 articles remained for screening, with 76 proceeding to full-text retrieval. Eligibility criteria were applied during full-text assessment, leading to the exclusion of 56 studies due to irrelevant outcomes, and 20 studies were included in the final analysis. An additional study was identified through manual searching, resulting in a total of 21 studies for inclusion. The results of the critical appraisal identified 10 high-quality studies, 10 medium-quality studies, and 1 low-quality study.

Characteristics of included studies

A total of 21 studies were included in the present study, covering the period from 2005 to 2023. The study locations were geographically diverse, with four studies conducted in Sudan and Ethiopia representing Africa [5,17-19], eight studies in Brazil and the USA representing the Americas [20-26], seven studies in India, Pakistan, Iraq, and Taiwan representing Asia [10,27-31], and two studies in Georgia and Denmark representing Europe [32,33]. The total sample size from all studies was 20,236 participants, with an overall mean age of 40.7±16.1 years. The hepatitis viruses analyzed included hepatitis B, hepatitis C, or both. All studies evaluated patient-related risk factors for different forms of hepatitis, although variations existed in the population characteristics and specific risk factors assessed. Risk factors that were discussed across multiple studies were subjected to meta-analysis to assess their significance. Detailed characteristics of the included studies are presented in **Table 1**.

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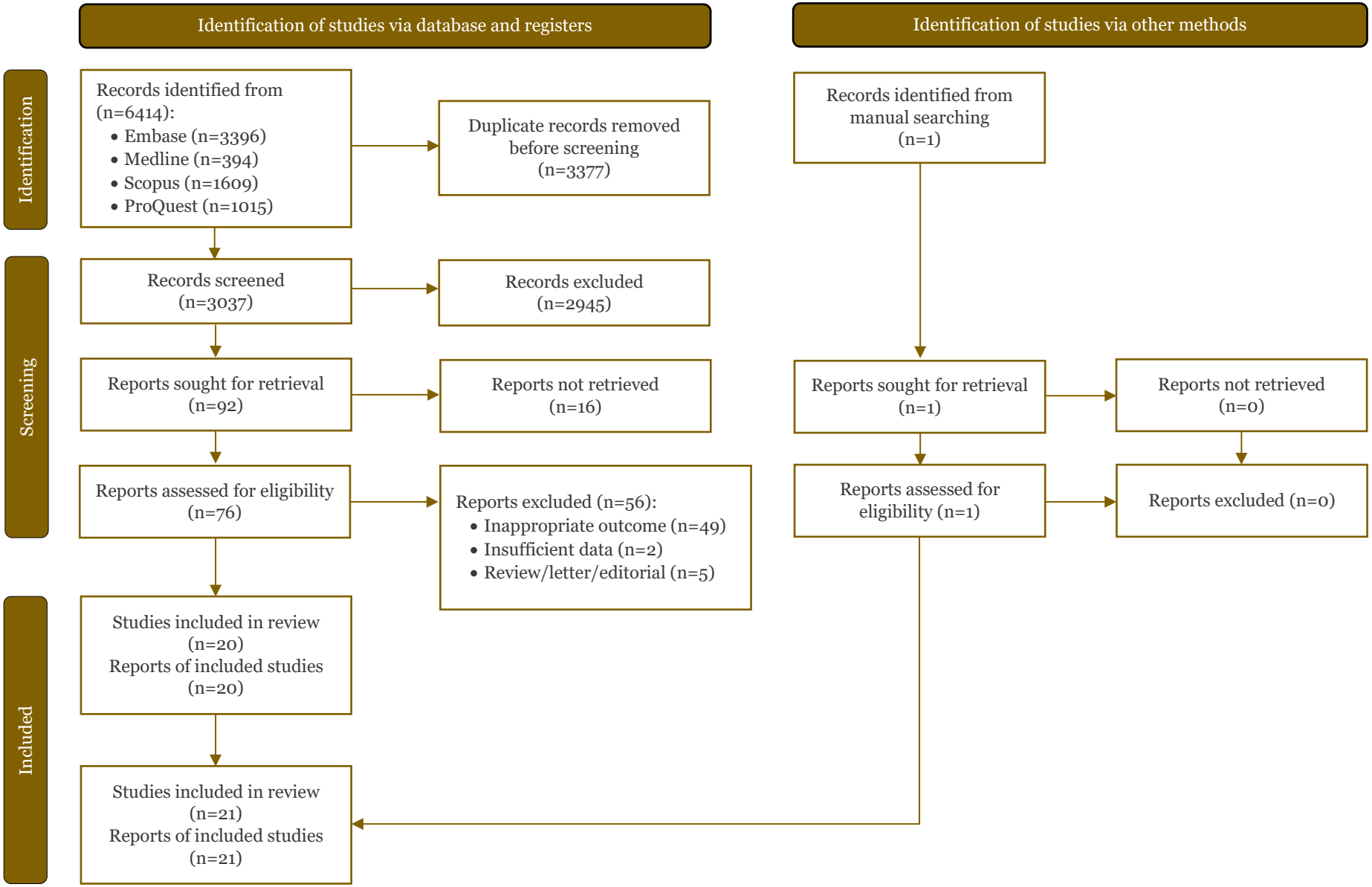

Figure 1. PRISMA flowchart showing study selection processes.

Table 1. Characteristics of the included studies

Author, year	Country	Study design	Sample size (n)	Age (mean±SD or median (min-max))	Criteria for tuberculosis patients	Criteria for hepatitis B	Criteria for hepatitis C
Abdallah *et al.*, 2015 [17]	Sudan	Cross-sectional	98	35.7±13.9	AFB sputum or radiological finding (+)	HBsAg (+)	N/A
Aires *et al.*, 2012 [20]	Brazil	Cross-sectional	402	44.1±15.6	Diagnosed as TB clinically	HBsAg or anti-HBc (+)	N/A
Blal *et al.*, 2005 [21]	Brazil	Cross-sectional	209	39.7±11.6	AFB smear or culture (+)	HepB serological marker (+)	N/A
Bushnell *et al.*, 2015 [22]	United States of America	Case control	9512	N/A	Diagnosed as TB in the medical records	HBsAg, HBeAg, or nucleic acid (+)	ELISA antibody test, RIBA, or nucleic acid test (+)
Campo *et al.*, 2014 [23]	United States of America	Case control	1421	48 (43–53)	Diagnosed as TB in the medical records	N/A	Diagnosed as hepatitis C in the medical records
Costi *et al.*, 2017 [24]	Brazil	Cross-sectional	138	38.0±12.9	Diagnosed based on clinical evaluation, chest radiograph, sputum smear microscopy, and culture	N/A	Anti-HCV or HCV RNA (+)
Feleke *et al.*, 2020 [5]	Ethiopia	Prospective cohort	3537	34.5±15.6	Diagnosed as TB and underwent DOTS	HepB serological marker (+)	HepC serological marker (+)
Gedefie *et al.*, 2023 [18]	Northeast Ethiopia	Cross-sectional	229	34.1±13.0	Diagnosed as TB and underwent DOTS	HBsAg (+) in blood	Anti-HCV (+)
Getie *et al.*, 2021 [19]	Northwest Ethiopia	Cross-sectional	145	31.6±11.9	Diagnosed based on AFB microscopy or Xpert MTB/RIF test	HBsAg (+) in blood	Anti-HCV (+)
Hussain *et al.*, 2015 [28]	North India	Cross-sectional	1215	N/A	Diagnosed as TB and underwent DOTS	HBV antibodies (+) in blood	N/A
Jørgensena *et al.*, 2021 [32]	Denmark	Retrospective cohort	110	Positive HBV serology: 53±24 Negative HBV serology 47±27	Diagnosed based on clinical criteria, radiological findings and/or culture, PCR test and microscopy results from relevant material	HBsAg, HBsAb, HBcAb/anti-HBc (+) in blood. If positive for HBsAg and/or HBcAb, the patient was tested for HBeAg and HBV-DNA	HCV-Ab/anti-HCV (+) in blood. If positive for HCV-Ab, HCV-RNA was tested.
Khan *et al.*, 2021 [11]	Pakistan	Case control	178	N/A	Diagnosed as TB and underwent DOTS	HBsAg, total anti-HBC, IgM anti-HBC, anti-HBS, and HBV DNA	N/A
Kim *et al.*, 2016 [10]	South Korea	Case control	379	Control (59.3±17.3), Case (HBV 50.0±15.1; HCV 59.9±14.9; HBV+HCV 54.3±9.5)	Diagnosed as TB and underwent treatment	HBsAg (+)	Positive for HCV antibody
Lomtadze N *et al.*, 2013 [25]	USA	Prospective cohort	326	37 (21–92)	Sputum smear with AFB or culture positive for M. tuberculosis	N/A	Positive HCV antibody test

Author, year	Country	Study design	Sample size (n)	Age (mean±SD or median (min-max))	Criteria for tuberculosis patients	Criteria for hepatitis B	Criteria for hepatitis C
Memon *et al.*, 2021 [29]	Pakistan	Cross-sectional	589	N/A	Diagnosed based on AFB microscopy or Xpert MTB/RIF test	HBsAg (+) in blood	Anti-HCV (+)
Merza *et al.*, 2016 [30]	Iraq	Cross-sectional	214	40.3±20.3	Sputum smear with AFB or culture positive for M. tuberculosis	HBsAg	Anti-HCV
Rehman *et al.*, 2020 [31]	Pakistan	Cross-sectional	400	34.6±17.2	Sputum smear with AFB or culture positive for M. tuberculosis	N/A	Anti-HCV
Reis *et al.*, 2011 [26]	Brazil	Cross-sectional	402	44 (3–86)	Diagnosed as TB clinically and currently under treatment	-	anti-HCV (+) and HCV RNA (+)
Richards *et al.*, 2006 [33]	Georgia	Case control	272	35 (18–74)	Diagnosed as TB and underwent treatment	-	ELISA, RIBA and HCV PCR tests
Trigo *et al.*, 2016 [34]	Brazil	Prospective cohort	100	43.4±10.3	Sputum smear with AFB or culture positive for M. tuberculosis	HBsAg (-) with anti-HBc (+)	-
Wang *et al.*, 2011 [7]	Taiwan	Prospective cohort	360	57.6±19.6	Culture-confirmed pulmonary TB	serological tests for HBV, HBV viral load	serological tests for HCV, HCV viral load

AFB: acid-fast bacteria; Anti-HBc: hepatitis B core Antibody; Anti-HCV: hepatitis C virus antibody; DNA: deoxyribonucleic acid; DOTS: directly observed treatment, short-course; ELISA: enzyme-linked immunosorbent assay; HBeAg: hepatitis B e-antigen; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; N/A: not available; PCR: polymerase chain reaction; RIBA: recombinant immunoblot assay; RNA: ribonucleic acid; TB: tuberculosis.

Patient-related risk factors for hepatitis B and hepatitis C identified from the literature are presented in **Underlying data**. Several potential risk factors identified in more than one study were considered significant contributors to viral hepatitis and were further analyzed through meta-analysis.

For hepatitis B, factors included sex, age, HIV, smoking, injecting drug use, non-injecting drug use, multiple sexual partners, alcohol consumption, tattooing, ear-nose piercing, history of blood transfusion, and history of dental intervention. The factors analyzed for hepatitis C were similar, with additional factors such as low education, history of homelessness, history of incarceration, living with a prisoner, sexually transmitted infections, and diabetes mellitus.

Human-immunodeficiency virus (HIV)

Six studies were included in the analysis for hepatitis B, and eight studies for hepatitis C. HIV was found to significantly increase the risk of acquiring hepatitis B, with an OR of 3.42 (95%CI: 2.18–5.34; p<0.00001) and high heterogeneity across studies (I^2=77%; τ^2=0.16; χ^2=22.13; p-heterogeneity of 0.0005) (**Figure 2**). Similarly, the presence of HIV markedly elevated the risk of hepatitis C, with an OR of 6.99 (95%CI: 5.09–9.61; p=0.02) and moderate heterogeneity (I^2=58%; τ^2=0.08; χ^2=16.82; p-heterogeneity of 0.02).

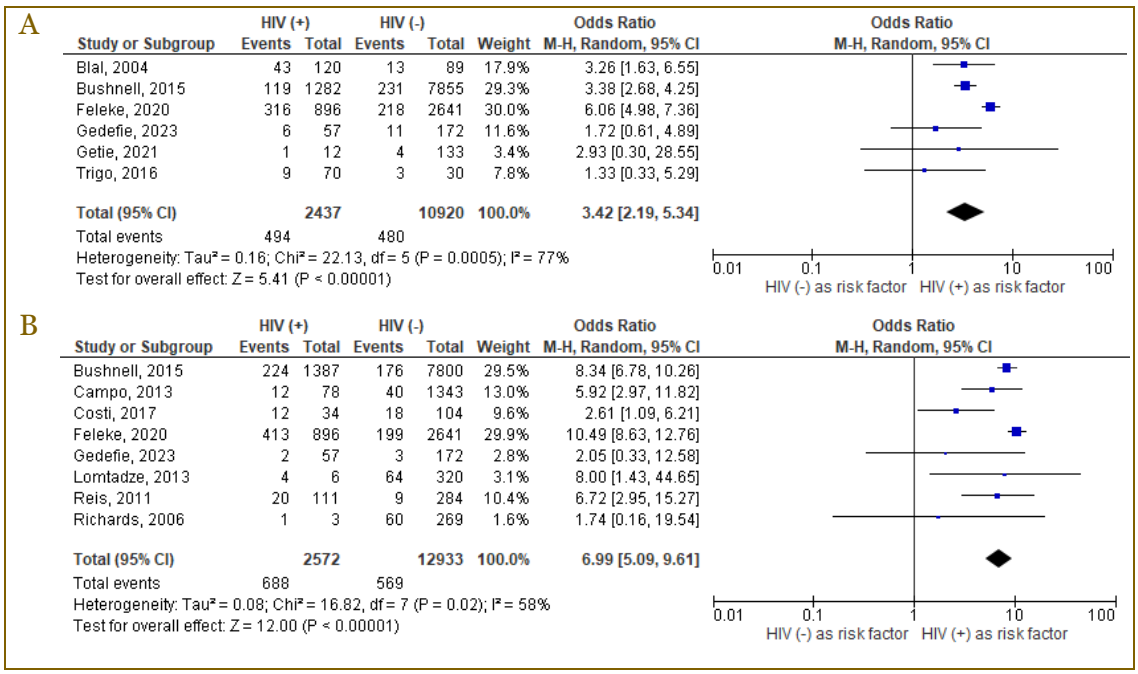

Figure 2. HIV as a risk factor for hepatitis B (A) and hepatitis C (B).

Injecting drug use (IDU)

Five studies were included in the analysis for hepatitis B, and similarly, five studies for hepatitis C. The history of injecting drug use was associated with an increased risk of hepatitis B (OR: 2.06; 95%CI: 1.38–3.08; p=0.0004), with low heterogeneity across the studies (I^2=0%; χ^2=2.28; p-heterogeneity of 0.68) as presented in **Figure 3**. For hepatitis C, the cumulative OR for injecting drug use was 14.09 (95%CI: 4.09–48.59; p<0.00001), with substantial heterogeneity (I^2=96%; τ^2=1.87; χ^2=89.21; p-heterogeneity of 0.00001).

Non-injecting drug use (NIDU)

Three studies were included in the analysis for hepatitis B, as presented in **Figure 4**. A history of non-injecting drug use has also been identified as a significant risk factor for hepatitis B virus infection, with a total OR of 14.09 (95%CI: 4.09–48.59; p<0.00001), with low heterogeneity across the studies (I^2=29%; χ^2=2.83; p-heterogeneity of 0.24).

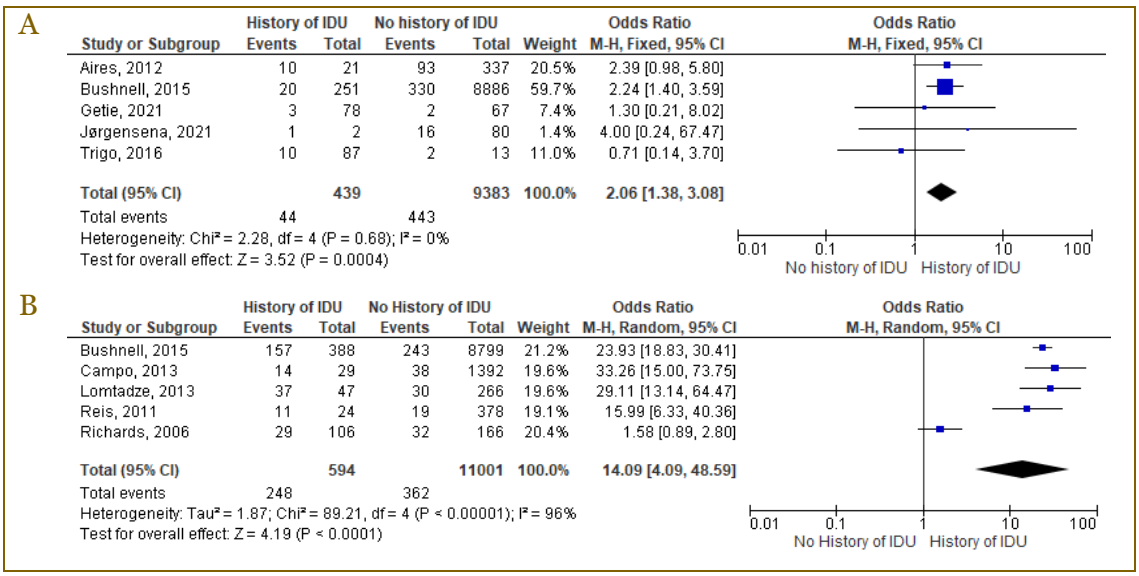

Figure 3. Injecting drug use as a risk factor for hepatitis B (A) and hepatitis C (B).

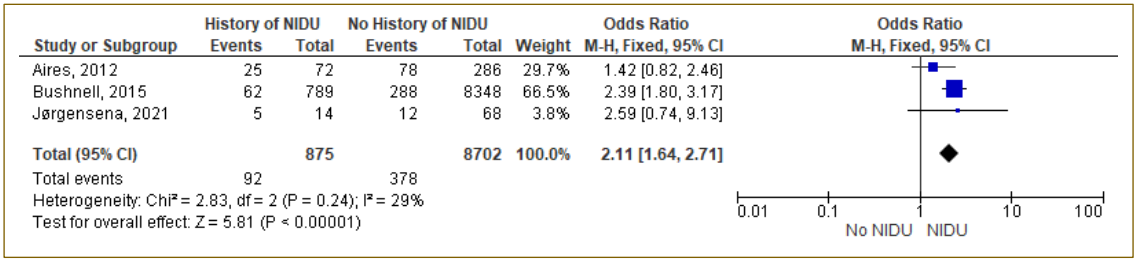

Figure 4. Non-injecting drug as a risk factor for hepatitis B.

Tattooing and ear-nose piercing

Three studies were included in the analysis for hepatitis B related to tattooing, and similarly, three studies for hepatitis C. Additionally, two studies were included in the analysis of ear-piercing as a risk factor for hepatitis C. The overall OR for tattooing associated with hepatitis B was 3.62 (95%CI: 1.09–11.95; p=0.03), while for hepatitis C, the OR was 5.49 (95%CI: 3.75–8.04; p<0.00001) as presented in **Figure 5**.

However, significant differences in heterogeneity were observed between the two: hepatitis B demonstrated high heterogeneity (I^2=70%; τ^2=0.73; χ^2=6.69; p-heterogeneity of 0.04), whereas hepatitis C showed low heterogeneity (I^2=0%; χ^2=1.20; p-heterogeneity of 0.55). Ear-piercing was significantly associated only with hepatitis C, with a total OR of 4.53 (95%CI: 1.89–10.88; p=0.0007) and low heterogeneity (I^2= 0%; χ^2=0.08; p-heterogeneity of 0.77).

Multiple sexual partners and sexually transmitted infection (STI)

Three studies analyzed multiple sexual partners as a risk factor for hepatitis B, and similarly, three studies analyzed sexually transmitted infections (STIs) as a risk factor for hepatitis B. Multiple sexual partners were identified as a risk factor for hepatitis B with an OR of 2.16 (95%CI: 1.49–3.34; p=0.0005) and low heterogeneity (I^2=0%; χ^2=1.86; p-heterogeneity of 0.39) as presented in **Figure 6**. Additionally, this analysis identified sexually transmitted infections as a risk factor for hepatitis C among patients with tuberculosis, with an OR of 3.78 (95%CI: 2.11–6.75; p<0.00001) and low heterogeneity (I^2=0%; χ^2=0.92; p-heterogeneity of 0.63).

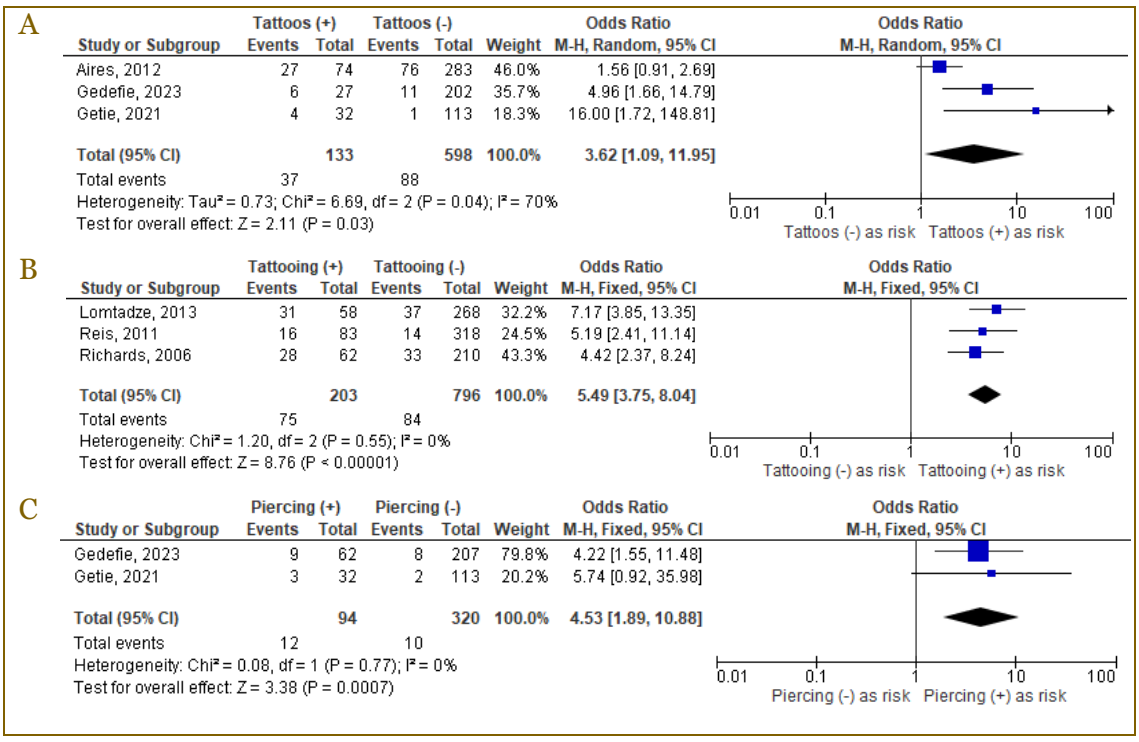

Figure 5. Tattooing as a risk factor for hepatitis B (A) and hepatitis C (B), and ear-nose piercing as a risk factor for hepatitis C (C).

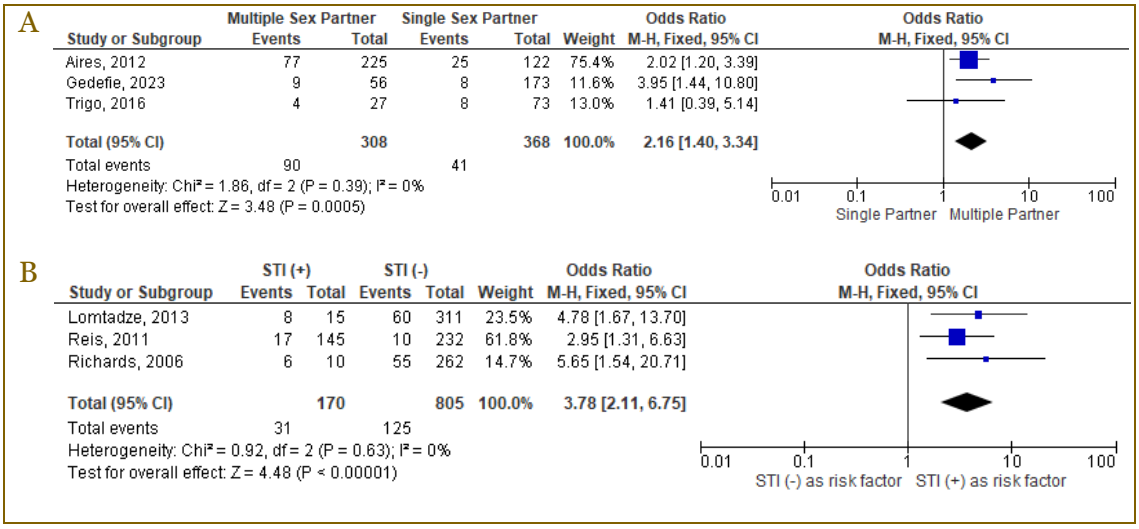

Figure 6. Multiple sexual partners as a risk factor for hepatitis B (A) and sexually transmitted infections as a risk factor for hepatitis C (B).

History of blood transfusion

Five studies were included in the analysis for hepatitis B, and similarly, five studies for hepatitis C. A history of blood transfusion has been identified as a risk factor for both hepatitis B and hepatitis C infections in patients with tuberculosis, with an OR of 1.66 (95%CI: 1.09–2.55; p=0.02) for hepatitis B and an OR of 2.30 (95%CI: 1.12–4.71; p=0.02) for hepatitis C as presented in **Figure 7**. The analysis demonstrated high heterogeneity among the studies for hepatitis B (I^2=0%; χ^2=3.92; p-heterogeneity of 0.42) and hepatitis C (I^2=51%; τ^2=0.30; χ^2=8.12; p-heterogeneity of 0.09).

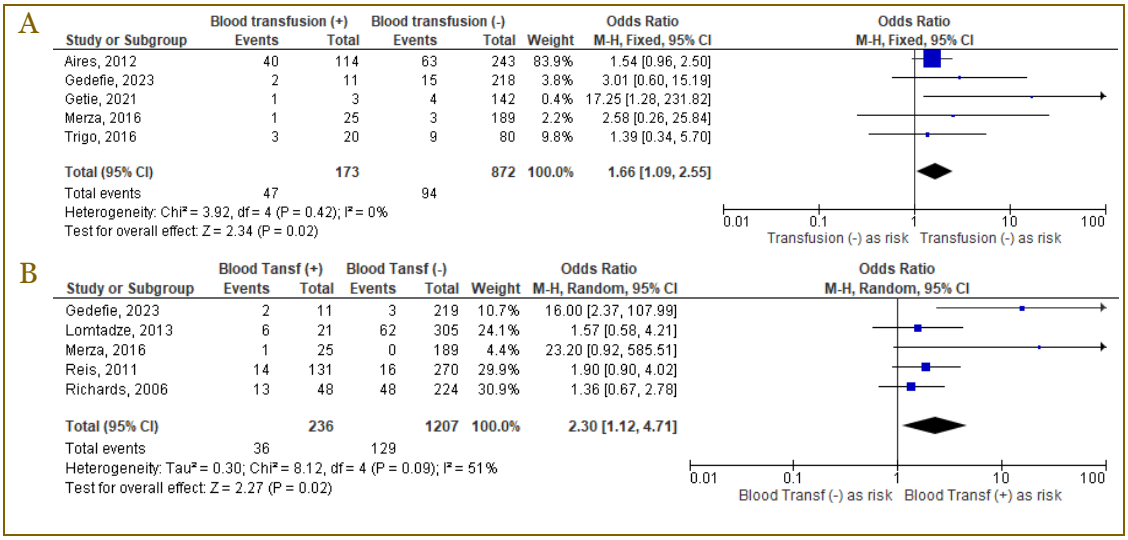

Figure 7. History of blood transfusion as a risk factor for hepatitis B (A) and hepatitis C (B).

History of dental intervention

Two studies were included in the analysis. A history of dental interventions has been identified as a risk factor for hepatitis C infection among patients with tuberculosis, with an OR of 15.50 (95%CI: 2.20–109.08; p=0.006), as presented in **Figure 8**. The analysis demonstrated low heterogeneity among the studies (I^2=0%; χ^2=0.28; p-heterogeneity of 0.60).

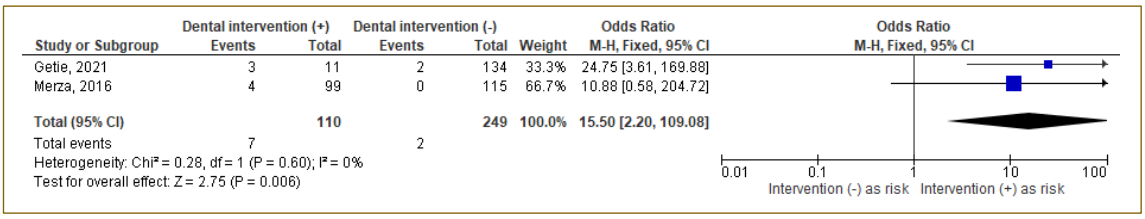

Figure 8. History of dental intervention as a risk factor for hepatitis C.

Alcohol

Eight studies were included in the analysis for hepatitis B, and similarly, eight studies for hepatitis C. Smoking and excessive alcohol consumption were identified as significant risk factors for hepatitis infection, with the OR for excessive alcohol consumption was 2.38 (95%CI: 1.06–5.37; p=0.04) for hepatitis B and 4.32 (95%CI: 2.76–6.78; p<0.0001) for hepatitis C as presented in **Figure 9**. The analysis demonstrated high heterogeneity among the studies for hepatitis B (I^2=89%; τ^2=1.05; χ^2=62.41; p-heterogeneity <0.00001) and hepatitis C (I^2=82%; τ^2=0.25; χ^2=38.36; p-heterogeneity <0.00001).

Smoking

Six studies were included in the analysis for hepatitis B, and four studies for hepatitis C. Smoking was identified as a significant risk factor, with an OR of 1.55 (95%CI: 1.19–2.02; p=0.001) for hepatitis B and 3.06 (95%CI: 1.63–5.75; p=0.0005) for hepatitis C as presented in **Figure 10**. The analysis demonstrated low heterogeneity among the studies for hepatitis B (I^2=36%; χ^2=7.86; p-heterogeneity of 0.16), moderate heterogeneity for hepatitis C (I^2=53%; τ^2=0.20; χ^2=6.44; p-heterogeneity of 0.09).

History of homelessness

Two studies were included in the analysis. A history of homelessness was identified as a significant risk factor for hepatitis C infection, with an OR of 11.40 (95%CI: 5.09–25.56; p<0.00001), as presented in **Figure 11**. The analysis indicated high heterogeneity among the studies (I^2=82%; τ^2=0.28; χ^2=5.76; p-heterogeneity of 0.02).

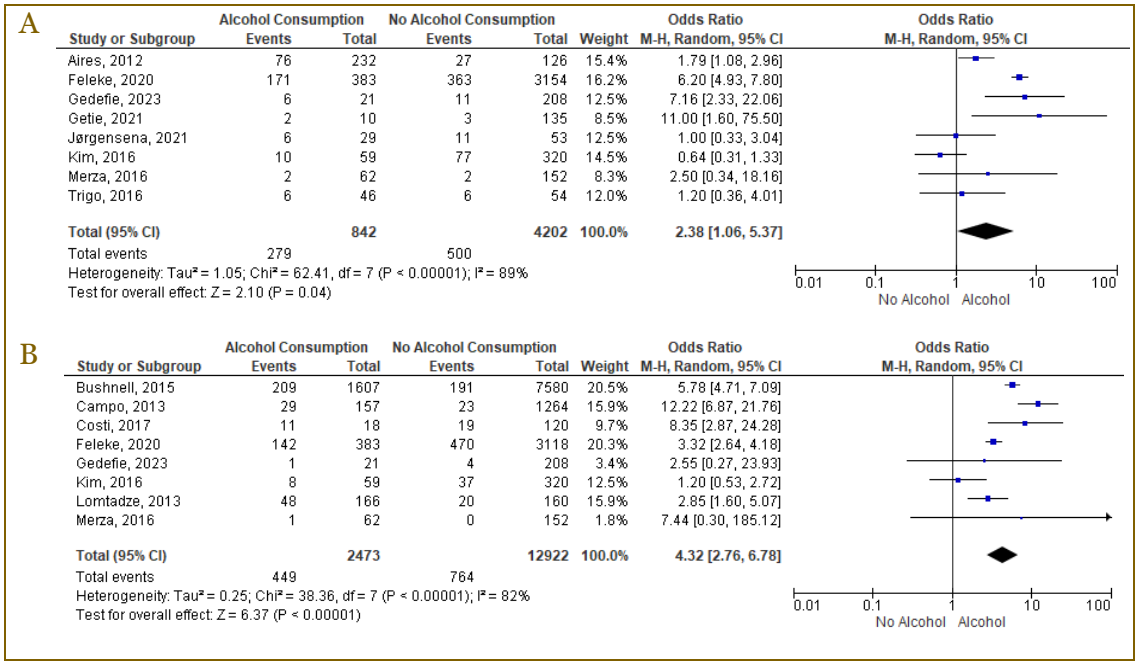

Figure 9. Alcohol consumption as a risk factor for hepatitis B (A) and hepatitis C (B).

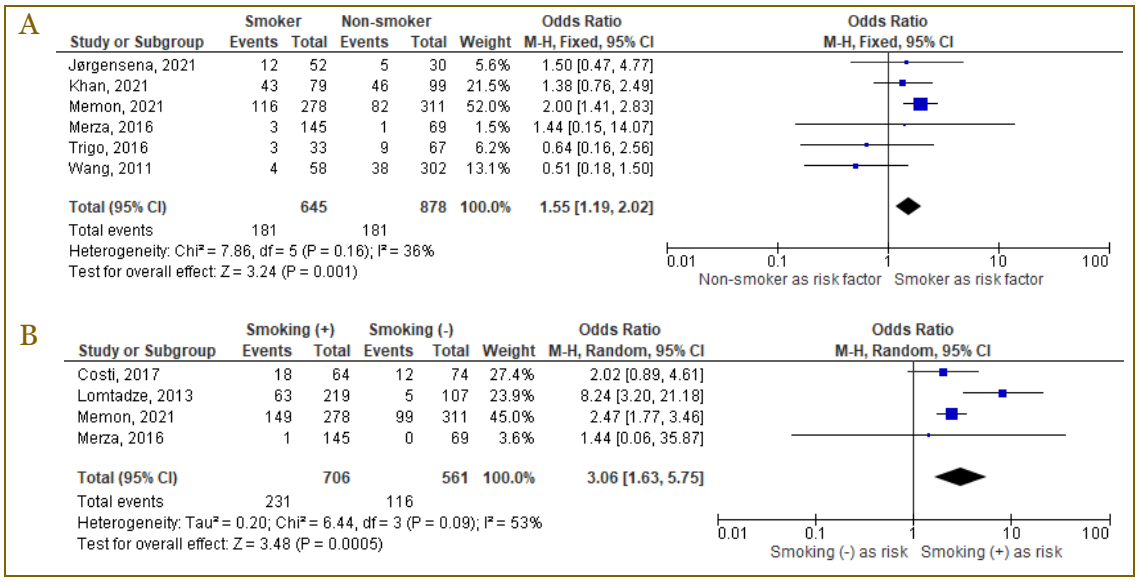

Figure 10. Smoking as a risk factor for hepatitis B (A) and hepatitis C (B).

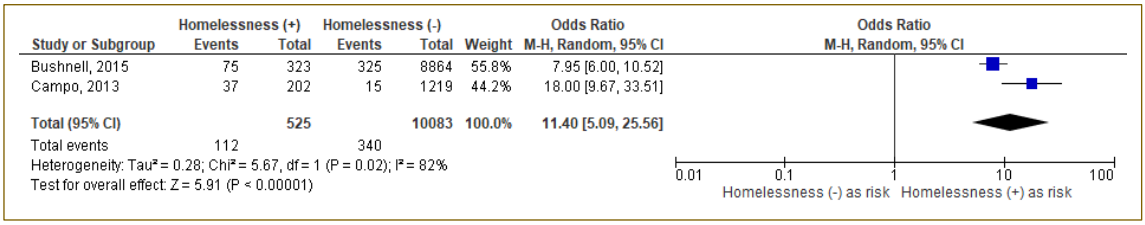

Figure 11. History of homelessness as a risk factor for hepatitis C.

History of incarceration and lived with prisoner

The present study includes five studies that identify a history of incarceration as a significant risk factor for hepatitis C infection (**Figure 12**), with an OR of 6.32 (95%CI: 3.84–10.41; p<0.00001) and moderate heterogeneity (I^2=59%; τ^2=0.18; χ^2=9.80; p-heterogeneity of 0.04).

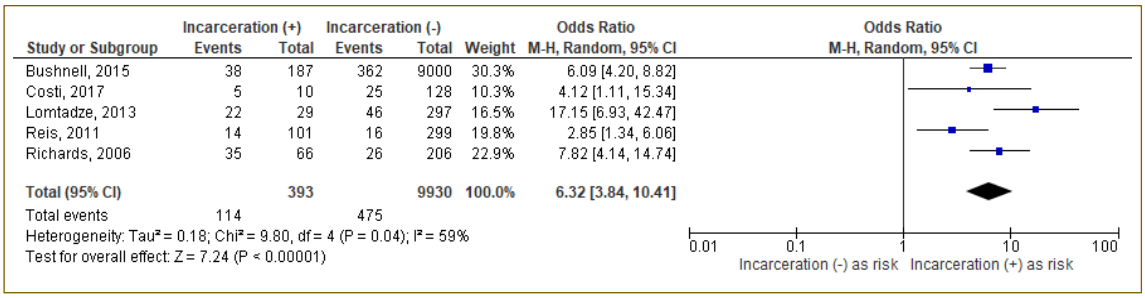

Figure 12. History of incarceration as a risk factor for hepatitis C.

Two studies were included in the analysis of living with a prisoner as a risk factor for hepatitis C, identifying it as a significant risk factor for hepatitis C infection (**Figure 13**), with an OR of 3.40 (95%CI: 2.19–5.28; p<0.00001) and low heterogeneity (I^2=0%; χ^2=0.23; p-heterogeneity of 0.63).

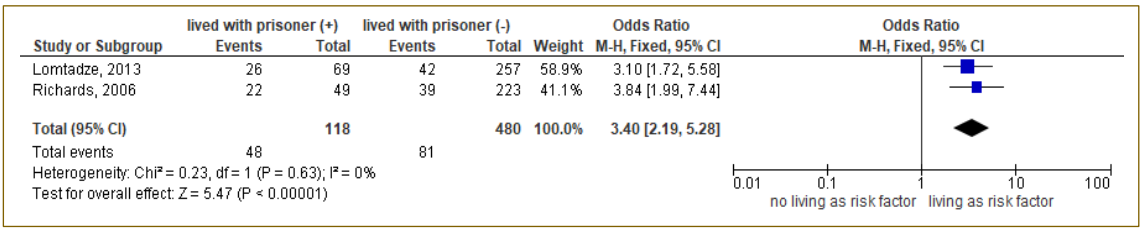

Figure 13. Lived with prisoners as a risk factor for hepatitis C.

Diabetes mellitus

Two studies identified diabetes mellitus as a significant risk factor for hepatitis C infection (**Figure 14**), with an OR of 2.54 (95%CI: 1.50–4.31; p=0.0005) and low heterogeneity (I^2=0%; χ^2=0.52; p-heterogeneity of 0.48).

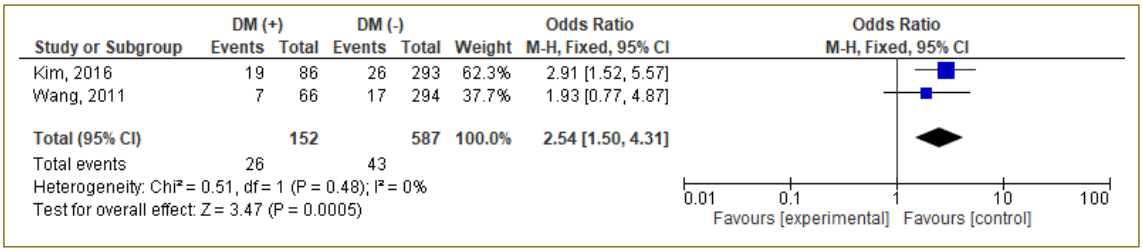

Figure 14. Diabetes mellitus as a risk factor for hepatitis C.

Age and gender

Although some studies report significant associations between sex, older age, and low education with viral hepatitis, the meta-analysis results in this review do not demonstrate a significant influence of these factors (**Figure 15**). The OR for male gender was 0.85 (95%CI: 0.41–1.77) for hepatitis B and 1.45 (95%CI: 0.66–3.23) for hepatitis C. For older age, the OR was 1.05 (95%CI: 0.90–1.23) for hepatitis B and 1.66 (95%CI: 1.01–2.74) for hepatitis C. Low education showed an OR of 1.10 (95%CI: 0.47–2.61) for hepatitis C.

Heterogeneity analysis

The results of the heterogeneity investigation are presented in **Table 2**. The displayed data are the results of subgroup analyses for each risk factor, particularly for those that exhibited high heterogeneity in data distribution in the meta-analysis. Most of this heterogeneity is believed to stem from differences between studies, such as sample size, diagnostic criteria, study quality, and study design. The results highlight the characteristics that most influence heterogeneity for each risk factor based on the subgroup analyses. The findings from this heterogeneity analysis enhance the value of this review by allowing for a more thorough and detailed assessment of the risk factors for viral hepatitis in tuberculosis patients.

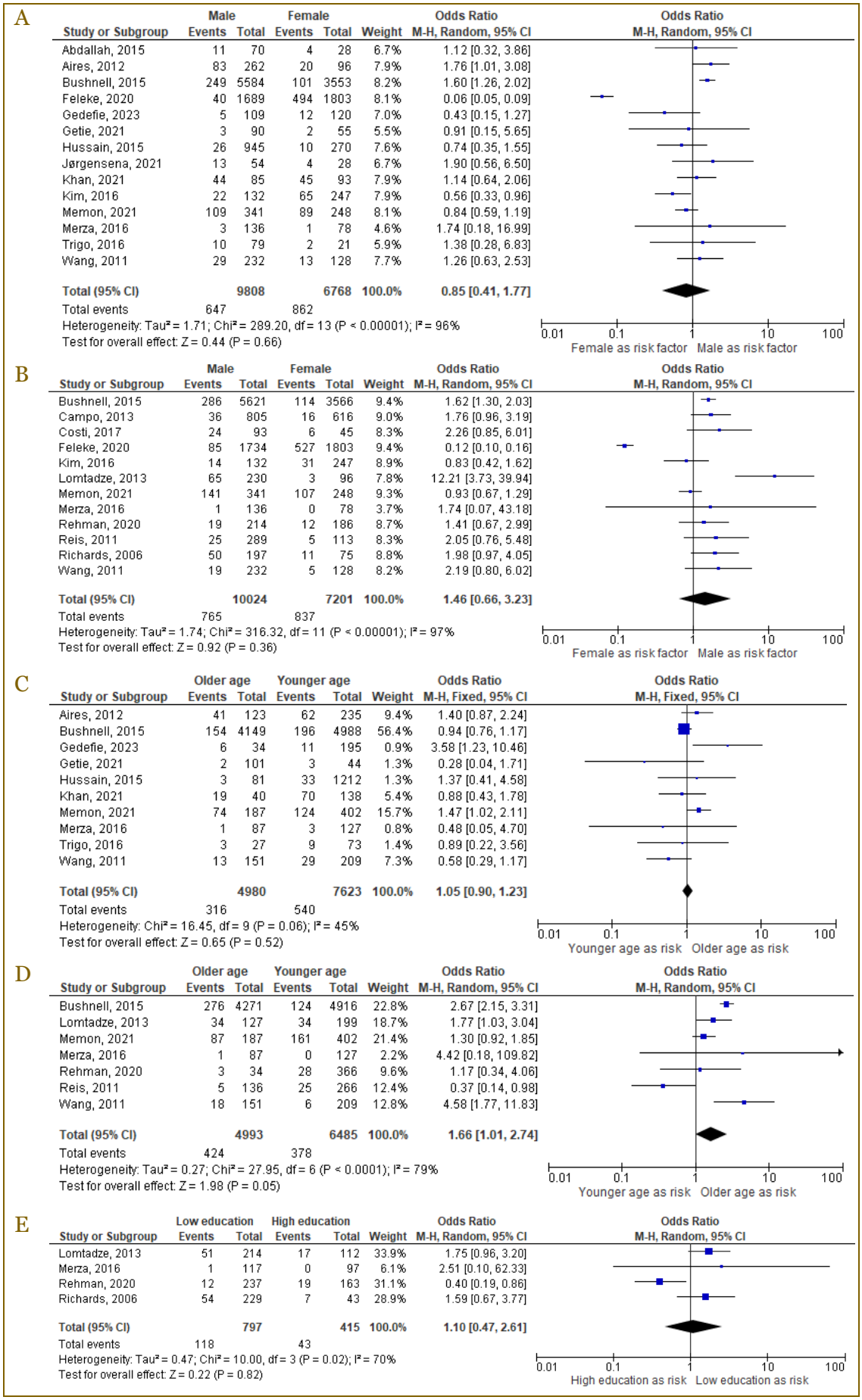

Figure 15. Male gender as a risk factor for hepatitis B (A) and C (B), older age as a risk factor for hepatitis B (C) and hepatitis C (D), and low education (E) as a risk factor for hepatitis C.

Table 2. Heterogeneity analysis

Analyzed risk factor	Hepatitis type	I^2	Heterogeneity classification	Studies (n)	Heterogeneity analysis
Sex (male)	Hepatitis B	96%	Considerable heterogeneity	14	Criteria for hepatitis B: • HBsAg: 0.53 (95%CI: 0.16–1.73); heterogeneity: τ^2=2.19; χ^2=138.67; df=6 (p<0.00001); I^2=96% • Anti-HBc: 0.74 (95%CI: 0.35–1.55) • Combination of hepatitis B diagnostic markers: 1.53 (95%CI: 1.27–1.86]; heterogeneity: τ^2=0.00; χ^2=1.73; df=5 (p=0.88); I^2=0%
Age (older)	Hepatitis B	45%	Moderate heterogeneity	10	Analyzed with the fixed effect model
HIV	Hepatitis B	77%	Substantial/considerable heterogeneity	6	Sample size: • 100–1000: 2.44 (95%CI: 1.45–4.10); heterogeneity: τ^2=0.00; χ^2=1.87; df=3 (p=0.60); I^2=0% • >1000: 4.54 (95%CI: 2.56–8.05); heterogeneity: τ^2=0.16; χ^2=14.53; df=1 (p=0.0001); I^2=93%
Smoking	Hepatitis B	36%	Homogenous/moderate heterogeneity	6	Analyzed with the fixed effect model
Injecting drug use	Hepatitis B	0%	Homogenous	5	Analyzed with the fixed effect model
Non-injecting drug use	Hepatitis B	29%	Homogenous	3	Analyzed with the fixed effect model
Multiple sexual partners	Hepatitis B	0%	Homogenous	3	Analyzed with the fixed effect model
Alcohol consumption	Hepatitis B	89%	Substantial/considerable heterogeneity	8	Criteria for hepatitis B: • HBsAg: 3.59 (95%CI: 1.08–11.97); heterogeneity: τ^2=1.48; χ^2=36.75; df=4 (p<0.00001); I^2=89% • Combination of hepatitis B diagnostic markers: 1.56 (95%CI: 1.01–2.39); heterogeneity: τ^2=0.00; χ^2=1.08; df=2 (p=0.58); I^2=0%
Tattooing	Hepatitis B	70%	Substantial heterogeneity	3	Criteria for hepatitis B: • HBsAg: 6.22 (95%CI: 2.33–16.59); heterogeneity: τ^2=0.00; χ^2=0.88; df=1 (p=0.35); I^2=0% • HBsAg + Anti-HBc: 1.56 (95%CI: 0.91–2.69)
Ear-nose piercing	Hepatitis B	0%	Homogenous	2	Analyzed with the fixed effect model
History of blood transfusion	Hepatitis B	0%	Homogenous	5	Analyzed with the fixed effect model
History of dental intervention	Hepatitis B	0%	Homogenous	2	Analyzed with the fixed effect model
Gender (male)	Hepatitis C	97%	Considerable heterogeneity	12	Study design: • Cross-sectional: 1.27 (95%CI: 0.86–1.87); heterogeneity: τ^2=0.05; χ^2=5.10; df=4 (p=0.28); I^2=22% • Case control: 1.53 (95%CI: 1.15–2.03); heterogeneity: τ^2=0.03; χ^2=4.15; df=3 (p=0.25); I^2=28% • Cohort: 1.01 (95%CI: 0.08–12.63); heterogeneity: τ^2=4.74; χ^2=56.22; df=2 (p<0.00001); I^2=96%
Age (older)	Hepatitis C	79%	Substantial/considerable heterogeneity	7	Criteria for hepatitis C: • anti-HCV: 1.43 (95%CI: 1.07–1.89); heterogeneity: τ^2=0.00; χ^2=1.46; df=3 (p=0.69); I^2=0% • anti-HCV and viral load: 1.72 (95%CI: 0.52–5.65); heterogeneity: τ^2=0.95; χ^2=16.56; df=2 (p=0.0003); I^2=88%
Low education	Hepatitis C	70%	Substantial heterogeneity	4	Study design: • Cross-sectional: 0.50 (95%CI: 0.16–1.62); heterogeneity: τ^2=0.26; χ^2=1.18; df=1 (p=0.28); I^2=15% • Case control: 1.59 (95%CI: 0.67–3.77) • Cohort: 1.75 (95%CI: 0.96–3.20)
HIV	Hepatitis C	58%	Moderate/substantial heterogeneity	8	Quality of study: • Low quality: 2.61 (95%CI: 1.09–6.21) • Moderate quality: 8.03 (95%CI: 6.60–9.77); heterogeneity: τ^2=0.00; χ^2=2.41; df=3 (p= 0.49); I^2=0% • High quality: 7.79 (95%CI: 4.18–14.54); heterogeneity: τ^2=0.16; χ^2=4.06; df=2 (p=0.13); I^2=51%

Analyzed risk factor	Hepatitis type	I^2	Heterogeneity classification	Studies (n)	Heterogeneity analysis
Smoking	Hepatitis C	53%	Moderate/substantial heterogeneity	4	Study design: • Cross-sectional: 2.39 (95%CI: 1.76–3.26); heterogeneity: τ^2=0.00; χ^2=0.29; df=2 (p=0.86); I^2=0% • Cohort: 8.24 (95%CI: 3.20–21.18)
Injecting drug use	Hepatitis C	96%	Considerable heterogeneity	5	Sample size: • 100–1000: 8.85 (95%CI: 1.24–62.92); heterogeneity: τ^2=2.85; χ^2=40.47; df=2 (p<0.00001); I^2=95% • >1000: 24.59 (95%CI: 19.55–30.93); heterogeneity: τ^2=0.00; χ^2=0.60; df=1 (p=0.44); I^2=0%
Alcohol consumption	Hepatitis C	82%	Substantial/considerable heterogeneity	8	Criteria for hepatitis C: • anti-HCV: 2.70 (95%CI: 1.84–3.98); heterogeneity: τ^2=0.06; χ^2=5.88; df=4 (p=0.21); I^2=32% • anti-HCV and viral load: 5.86 (95%CI: 4.79–7.16); heterogeneity: τ^2=0.00; χ^2=0.44; df=1 (p=0.51); I^2=0% • Medical record: 12.22 (95%CI: 6.87–21.76)
Tattooing	Hepatitis C	0%	Homogenous	3	Analyzed with the fixed effect model
History of blood transfusion	Hepatitis C	51%	Moderate/substantial heterogeneity	5	Criteria for hepatitis C: • anti-HCV: 6.10 (95%CI: 0.88–42.31); heterogeneity: τ^2=1.92; χ^2=6.30; df=2 (p=0.04); I^2=68% • anti-HCV and viral load: 1.59 (95%CI: 0.95–2.67); heterogeneity: τ^2=0.00; χ^2=0.40; df=1 (p=0.53); I^2=0%
History of homelessness	Hepatitis C	82%	Substantial/considerable heterogeneity	2	No subgroup analysis needed to be performed due to the inclusion of only two studies, which differed in sample size and criteria for hepatitis diagnosis
History of incarceration	Hepatitis C	59%	Moderate/substantial heterogeneity	5	Study design: • Cross-sectional: 3.12 (95%CI: 1.62–6.01); heterogeneity: τ^2=0.00; χ^2=0.23; df=1 (p=0.63); I^2=0% • Case control: 6.49 (95%CI: 4.71–8.94); heterogeneity: τ^2=0.00; χ^2=0.47; df=1 (p=0.49); I^2=0% • Cohort: 17.15 (95%CI: 6.93–42.47)
Lived with prisoner	Hepatitis C	0%	Homogenous	2	Analyzed with the fixed effect model
Sexually transmitted infection	Hepatitis C	0%	Homogenous	3	Analyzed with the fixed effect model
Diabetes mellitus	Hepatitis C	0%	Homogenous	2	Analyzed with the fixed effect model

Discussion

In this systematic review and meta-analysis, we identified several patient-related risk factors significantly associated with viral hepatitis in TB patients, derived from an analysis of 21 studies. These factors encompass a range of demographic, behavioral, and medical aspects, highlighting the multifaceted nature of viral hepatitis risks within this population. Notably, conditions such as HIV infection, smoking, and alcohol consumption were found to be significant risk factors. Additionally, behaviors including drug use, tattooing, ear-nose piercing, homelessness, incarceration and living with prisoners, multiple sexual partners, and specific medical interventions further complicate the risk landscape.

This study may serve as a foundation for healthcare providers to identify the risk factors associated with viral hepatitis that contribute to liver injury development in TB patients undergoing treatment [5,19]. By focusing on patients with high susceptibility to hepatitis, clinicians can implement baseline screenings for hepatitis B and C at the time of TB diagnosis and prior to initiating treatment [5,19]. This proactive approach aligns with findings from prior studies, reinforcing the need for early detection and intervention, especially in countries with high hepatitis burden [2,5,19].

HIV was found to significantly increase the risk of acquiring hepatitis B. Similarly, the presence of HIV markedly elevated the risk of hepatitis C. This may be related to the fact that HIV enhances the replication of hepatitis B and C viruses, increasing the risk of reactivation in asymptomatic and chronic hepatitis patients [35,36]. Other than HIV, diabetes mellitus is identified as a significant risk factor for hepatitis C infection. Immunosuppression and chronic inflammation in diabetes mellitus increase the risk of tuberculosis and hepatitis C co-infection, with poor metabolic control and additional risk factors further elevating the likelihood of hepatitis C in TB patients [10,18,37].

The shared use of syringes and needles among injecting drug users was associated with an increased risk of hepatitis B and hepatitis C as this facilitates direct blood contact, serving as a primary transmission route for hepatitis B and, particularly, hepatitis C [38,39]. This mechanism also correlates with a history of blood transfusion as a risk factor for hepatitis B and hepatitis C.

Not only injecting drug use but non-injecting drug use has also been identified as a significant risk factor for hepatitis B virus infection. Potential transmission route in non-injecting drug use involves percutaneous or mucosal exposure through drug-use paraphernalia, such as pipes or straws used for smoking, snorting, or sniffing, and a history of risky sexual behavior with individuals in the injecting drug use population or a history of blood transfusion [40,41]. Tattooing and ear-nose piercing are significant risk factors for hepatitis B and C transmission due to amateur artists' practices that may compromise sterility and the varying virucidal properties of various ink brands [42-44]. Notably, ear-piercing was significantly associated only with hepatitis C [44].

Multiple sexual partners were identified as a risk factor for hepatitis B. This mode of transmission is more prevalent among men who have sex with men (MSM). This is due to the increased trauma of anal intercourse, as well as in heterosexual relationships and individuals engaging in sexual activities with sex workers [45-47]. Additionally, this analysis identified STIs as a risk factor for hepatitis C among patients with tuberculosis. The presence of STIs in MSM, including HIV-1, herpes simplex virus type 2 (HSV-2), chlamydia, human papillomavirus (HPV), gonorrhea, and syphilis, impairs the function of dendritic cells in the entry points (anal mucosa, rectum, and sigmoid colon) to capture and retain infectious HCV, thereby elevating the risk of transmission [48,49].

A history of dental interventions has been identified as a risk factor for hepatitis C infection among patients with tuberculosis. The transmission of the Hepatitis C virus during dental interventions can occur directly through blood produced by ultrasonic scalers or other high-speed equipment, through saliva and nasopharyngeal secretions or indirectly via contaminated instruments, operative equipment, and the dental environment. This risk is especially heightened in patients with periodontal disease and poor oral hygiene, as the highest concentrations of Hepatitis B and C viruses are typically found in the gingival sulcus [50,51]. Excessive alcohol consumption poses a significant risk factor for hepatitis B and hepatitis C infection. Individuals with excessive alcohol consumption were more likely to engage in risky behaviors such as

unprotected sexual intercourse, which led to a higher risk of transmitting viral hepatitis [5,18]. Smoking was identified as a significant risk factor for both hepatitis B and hepatitis C. Smoking and hepatitis are linked by shared risk factors, particularly substance use disorders, which explains their frequent co-occurrence in affected populations [52].

A history of homelessness was identified as a significant risk factor for hepatitis C infection. High-risk behaviors, such as intravenous drug use and needle sharing, increase the likelihood of both tuberculosis and hepatitis C virus transmission among individuals experiencing homelessness [22,23,53]. History of incarceration is also a significant risk factor for hepatitis C infection. This increased risk is driven by substance use, tattooing, and unprotected sexual activity within correctional settings [25,33]. Similarly, living with a prisoner poses a risk for HCV due to shared high-risk behaviors and environments, highlighting the need for targeted interventions to break transmission cycles [25,33].

The strength of this review lies in its rigorous methodology, conducted in accordance with the PRISMA 2020 guidelines. A broad range of relevant studies was included, with appropriate selection criteria, resulting in 21 studies from various continents and countries. As a result, the findings from this systematic review and meta-analysis are likely generalizable, given that systematic reviews provide the highest level of evidence for clinical practice. This review identifies factors contributing to hepatitis in tuberculosis patients, supporting the development of targeted management strategies.

The limitations of this study include the observed heterogeneity in certain risk factors, which warrants caution when interpreting the results. Furthermore, the presence of several studies with medium to low quality may affect the overall strength of the evidence. To address these issues, this study recommends encouraging more high-quality cohort research in the future.

Conclusion

HIV, smoking, alcohol consumption, drug use, multiple sexual partners, tattooing, piercing, blood transfusions, dental interventions, homelessness, incarceration, living with prisoners, sexually transmitted infections, and diabetes mellitus are significantly associated with hepatitis B and C in tuberculosis patients. Monitoring and addressing these factors are essential to prevent liver injury and complications in tuberculosis treatment, such as non-compliance, bacterial resistance, and increased morbidity.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

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