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Review Article

Risk of Hepatitis C Virus Infection in Tuberculosis Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Tuberculosis (TB) and infection of Hepatitis C virus (HCV) have appeared as major public health problems. The present systematic review and meta-analysis aimed at determining the relationship between TB and the risk of HCV infection.

Methods: Google Scholar, Embase, Medline, Pubmed, web of sciences (ISI), and Scopus were searched until March 2022. The pooled ORs of HCV in patients with TB were calculated utilizing the random-effect model with a 95% confidence interval (CI). $\mathbf{I^2}$ test was utilized for evaluating the heterogeneity. To check publication bias Egger and Beggs' tests were used.

Results: From among 1500 articles from 2006 to 2020, 13 studies were examined and analyzed based on the inclusion/exclusion criteria. The overall risk of HCV infection in patients with TB was (OR: 1.34, 95% CI: 1.10-1.63, *P*=0.001). According to the type of the countries subgroup analysis, the risk of HCV infection in patients with TB in developing countries was (OR: 1.95, 95% CI: 1.00-3.80), which was higher than the risk in developed countries (OR: 1.47, 95% CI: 1.42-1.52). In addition, the risk of hepatitis C infection in men compared to women (OR: 1.84, 95% CI: 1.75-1.94, *P*=0.001) and in age groups over 65 yr compared to other age groups (OR: 1.46, 95% CI: 0.98-2.16) was significantly higher.

Conclusion: The results of this study emphasized the importance of screening HCV in patients with TB. Being aware of the presence or absence of HCV in these patients can contribute to their effective treatment.

Keywords: Hepatitis C virus; Systematic review; Meta-analysis; Tuberculosis

Introduction

Tuberculosis is the most common cause of death due to single-agent infectious diseases and is one of the major public health challenges in the world **(**1**)**. The worldwide incidence of this disease in 2020 was 132 per 100,000 people (2). The highest prevalence of the disease is in Southeast Asia (45%), followed by Africa (25%), the western Pacific (7%), and the United States and Europe

(3%)(3).HCV infection is considered a known cause of liver diseases such as cirrhosis, hepatocellular carcinoma, and chronic hepatitis(4). Another major health problem is getting this infection (5), the prevalence of which is between 2.5% and 3% worldwide and in the range of 3.4%-4.6% among patients with Tuberculosis (6-8).

Few studies have been conducted worldwide regarding the risk of HCV in tuberculosis patients and the effect of this infection on these patients, so there is little evidence on this subject (5). One of the important side effects of tuberculosis treatment is hepatotoxicity, which causes disruption of the treatment process and can lead to discontinuation of the patient's treatment (9). Hepatotoxicity is a side effect of first-line Directly Observed Treatment, Short-course (DOTS) drugs including Rifampin (RMP), Pyrazinamide (PZA), and Isoniazid (INH))(10, 11). Chronic liver disease during anti-tuberculosis treatment increases the risk of hepatotoxicity three to five times more often than in patients with TB who do not have a viral infection. Similarly, a fourteen-time increased risk of anti-tuberculosis hepatotoxicity has been reported in co-infection with HIV and HCV (4). AIDS is a set of clinical signs and symptoms that are directly related to immune system disorders caused by HIV infection. Opportunistic infections are considered to be the main causes of disability and death in patients with the final stages of HIV infection. Factors that rarely cause disease in people with normal immunity cause severe infections in people with AIDS(12) .

HCV infection increases hepatotoxicity due to anti-tuberculosis drugs and increases mortality up to 5% (6). Therefore, before the start of treatment TB patients should be tested for HCV and also monitored more closely (9). Patient characteristics that pose a greater risk for treating liver injury are not well understood. Older age, alcohol consumption, HIV, hepatitis B, and hepatitis C infection increase the hepatotoxicity risk.

Both HCV and TB infections are considered common infectious diseases. The relationship between HCV and TB infections has never been comprehensively investigated, even though these two infections have similar epidemiological risk factors (13-15) and also HCV infection has often been observed in TB patients (15).

Knowledge about the global impact of HCV among TB patients is not well documented and there is no data collected indicating the risk of HCV in TB patients. To address this issue, to assess the relationship between TB disease and HCV risk, a systematic review study and meta-analysis were conducted.

Methods

The present Meta-analysis was reported according to Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (16).

Search strategy and selection criteria

A systematic search was performed to find cross-sectional, case-control, and cohort articles that investigated the relationship between TB and HCV risk. For this purpose, we searched Pubmed, Medline, Google Scholar, Scopus, Embase, and web of sciences (ISI) databases utilizing two sets of related Mesh and Non-Mesh terms: 1) "Tuberculosis OR "TB",2) "Hepatitis C virus" OR "HCV" to search titles, abstracts, or keywords until March 2021 with no limitation in respect of the language and time.

Inclusion criteria and data extraction

The inclusion criteria were a) original studies with observational design, b) study documented the occurrence, incidence, or prevalence of HCV in TB Patients. The studies (MA, NA, BC) were reviewed independently by three authors and then discussed with the fourth author (PA). Similarly, the reference list of related articles was manually reviewed to find other possible related articles that were not found in the electronic search.

The data such as authors, year of publication, study design, country, population, diagnostic method, OR, and Quality score were extracted by four independent researchers (MA, NA, BC, PA)

from included studies; The extracted data were compared and discrepancies between investigators were discussed for reaching a consensus and ensuring the accuracy of the data. If the text of the articles was not accessible, the responsible author was notified at least twice via email to send the full text of the article. Moreover, an email was sent to the publishers.

Exclusion criteria

The exclusion criteria were: 1) repeated reports; 2) case reports, editorials, review articles, and meta-analysis.

Quality Assessment

The quality assessment of each included study was based on a nine-star scoring system known as the Newcastle-Ottawa scale (NOS) (17). For non-randomized studies, representation of study groups, the comparability of case /controls, and the ascertainment of the outcome of interest /exposure on cases /control were assessed. ⩾7 points were defined as high quality, 6 points as medium quality, and ⩽5 points as low quality (18). Two investigators scored the method sections independently and the differences were resolved by agreement.

Statistical analysis

Meta-Analysis method using Comprehensive Meta-Analysis software (CMA; version 2.2.064) was conducted. The pooled ORs with 95% CI were obtained utilizing the random-effects model. In order to identify the heterogeneity of the results, the Cochran's Q test was used, then it was quantified by the $\mathbf{I^2}$ statistic. $\mathbf{I^2}$ statistic > 50% or Q statistics with $P<0.10$ were treated as a significant between-study heterogeneity. Moreover, the "tau-squared"(Tau ^{2} or $\mathbf{t^2}$) statistic was used to assess a between-study variance.

Subgroup analyses based on sex, country, and age were performed for finding the possible source of heterogeneity. In order to discover the relationship between the risk of HCV in TB patients and the year of study, a meta-regression analysis was conducted. A sensitivity analysis was conducted using the one-by-one exclusion of the studies from the meta-analysis. The publication bias was also evaluated using Beggs' funnel plots and asymmetry test (Egger and Beggs' test).

Ethics approval and Concent to participate

Because the data collection method was observation and there were no human participants in the current study, according to regulations obtaining informed consent is deemed unnecessary.

Results

Included studies

As described in Fig. 1, 1500 studies were obtained using electronic and hand searches of which, 800 studies remained after the exclusion of the duplicate references. We excluded 720 studies after screening title/abstract; therefore, 80 remaining studies should be checked carefully through reading the full texts. From among the remaining articles, 67 were excluded for the following reason: not having relevant data (n=19), being review article or letter to the editor (n=10), study being conducted in the general population (n=20), or the study wasn't reporting data regarding the risk of HCV among TB patients (n=18). Eventually,11 articles satisfied inclusion criteria for the quantitative meta-analysis and systematic review of the qualitative synthesis (Fig.1).

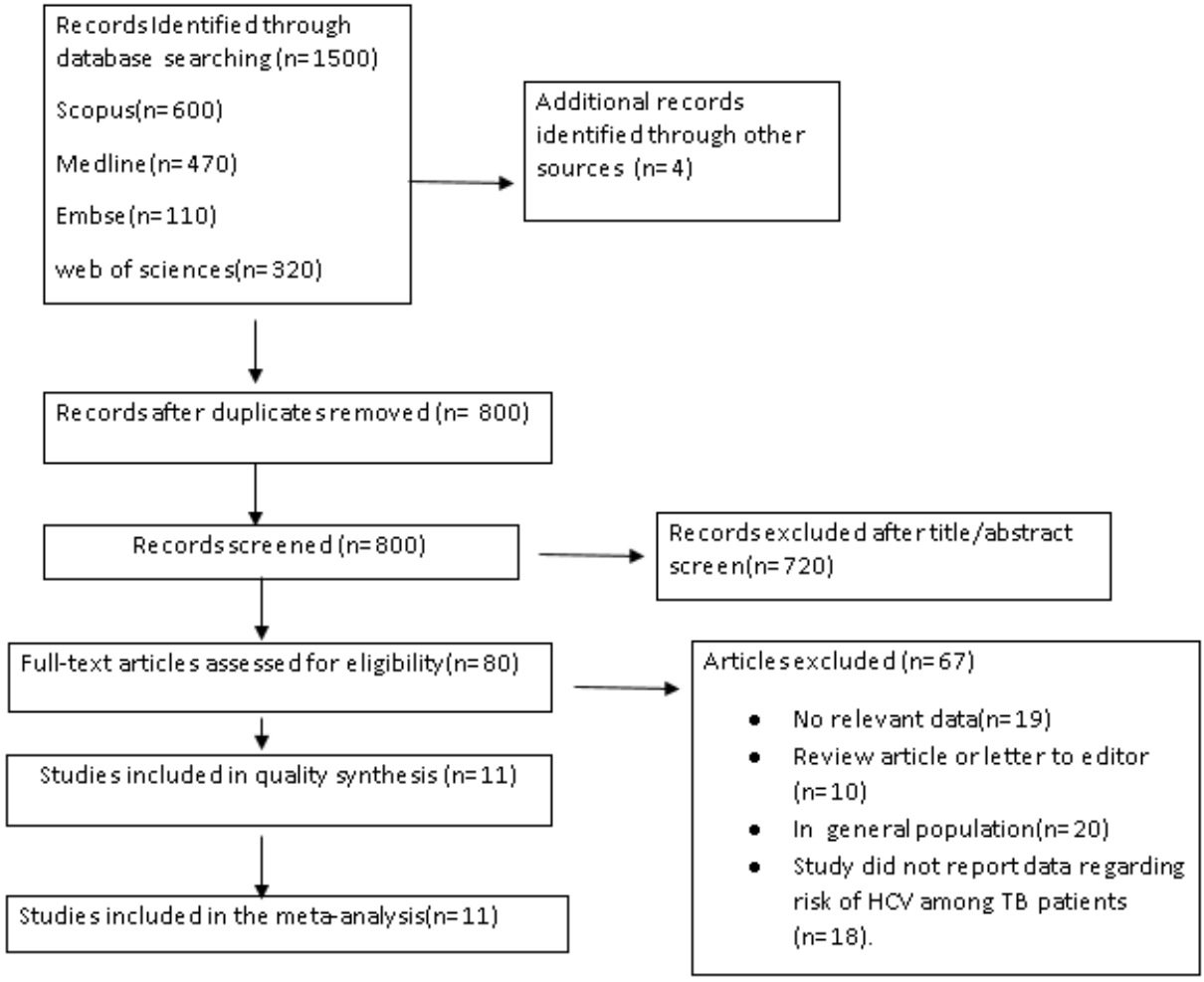

Fig.1: PRISMA Flow Diagram of the Study Selection Process

The characteristic of included studies is presented in Table 1. Thirteen remaining studies were cross-sectional, cohort, and case-control in design and were conducted from 2006 to May 2021. Overall, included studies summarized data from 33798 cases and 48282 control.

Fig. 2 indicates the forest plot of the effects of HCV in patients with TB. Based on the result of the random-effects meta-analysis, there was a statistically significant relationship in increasing the risk of hepatitis C among patients with tuberculosis (OR: 1.34, 95% CI: 1.10-1.63, *P*=0.001).

According to the subgroups analysis by age groups, the risk of hepatitis C infection among TB patients in the age group over 65 yr (OR: 1.46, 95% CI: 0.98-2.16,) was higher than that in the age group under 65 yr (*P*=0.04). Subgroup analysis by country showed that the risk of hepatitis C in patients with tuberculosis in developing countries (OR: 1.95, 95% CI: 1.00-3.80) was higher compared to developed countries (OR: 1.47, 95% CI: 1.42-1.52) (*P*=0.03). Moreover, the risk of this disease in men with tuberculosis was significantly 1.84 times higher than that in women (OR: 1.84, 95% CI: 1.75-1.94, *P*=0.001) (Fig. 3).

Table 1: Characteristics of the Studies Concerning the risk of HCV in TB Patients

Author	*Year of publication*	*Study Design*	*Country, populatin*	*Diagnostic meth-od (Tuberculosis*	*Diagnostic method (Hepatitis C viral*	*OR*	*Quality score*
Kim et al(19).	2016	Case-control	Korea, n= 128	Pulmonary tuber-culosis confirmed by WHO and national guideline	HCV antibodies,HCV RNA,aminotransferase (AST), alanine ami-notransferase(ALT)	0.36(0.22-0.60)	9
Chein et al(20).	2010	Case-control	Taiwan, n= 376	National Tuber-culosis Surveil-lance System	Baseline serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), HCV (anti-HCV) antibodies	3.42(1.56-7.45)	7
Torres et al(12).	2008	Case-control	Spain, n=2012	Microbiological and/or clinical	Spain County Hepatitis C Surveillance Program	6.90(2.81-16/96)	6
Campo et al(21).	2015	Case-control	King, n=1510	National Tuber-culosis Surveil-lance System	Public Health – Seattle & King County Hepatitis C Surveillance Program	1.40(0.95-2.07)	8
Richards et al(22).	2006	Case-control	Georgia, n=272	Microbiological and/or clinical	Baseline serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), HCV (anti-HCV) antibodies	1.34(1.10-1.63)	8
Feleke et al(5).	2020	Cohort	Ethiopia, n=3537	Notification data-base of active TB case	aseptic technique and Enzyme-linked immune Sorbent assay (ELIZA) test	1.47(1.26-1.73)	9
Ping et al(15).	2015	Cohort	Taiwan, n=59728	Taiwan National Health Insurance Research Data-base (NHIRD)	International Classifica-tion of Disease, 9th Revi-sion, Clinical Modifica-tion (ICD-9) code	1/51(1.45-1.56)	9
Khalili et al.(23).	2009	Cohort	Iran, n=102	National Tuber-culosis Surveil-lance System	HCV antibodies,HCV RNA,aminotransferase (AST), alanine ami-notransferase (ALT)	2.94(1.61-5.35)	5
Aung et al(24).	2018	Cohort	Georgia, n=454	National Tuber-culosis Program (NTP)	Baseline serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), HCV (anti-HCV) antibodies	1.31(1.01-1.71)	6
Yilin et al(25).	2014	Cohort	Taiwan, n=12547	National Health Insurance (NHI)	International Classifica-tion of Disease, 9th Revi-sion, Clinical Modification (ICD-9-CM) diagnostic criteria	1.02(0.81-1.27)	9
Uehara et al(11).	2016	Cross-sectiona	Brazil, n=621	National Tuber-culosis Surveil-lance System	International Classifica-tion of Disease, 9th Revi-sion, Clinical Modifica-tion (ICD-9) code	0.81(0.43-1.53)	5

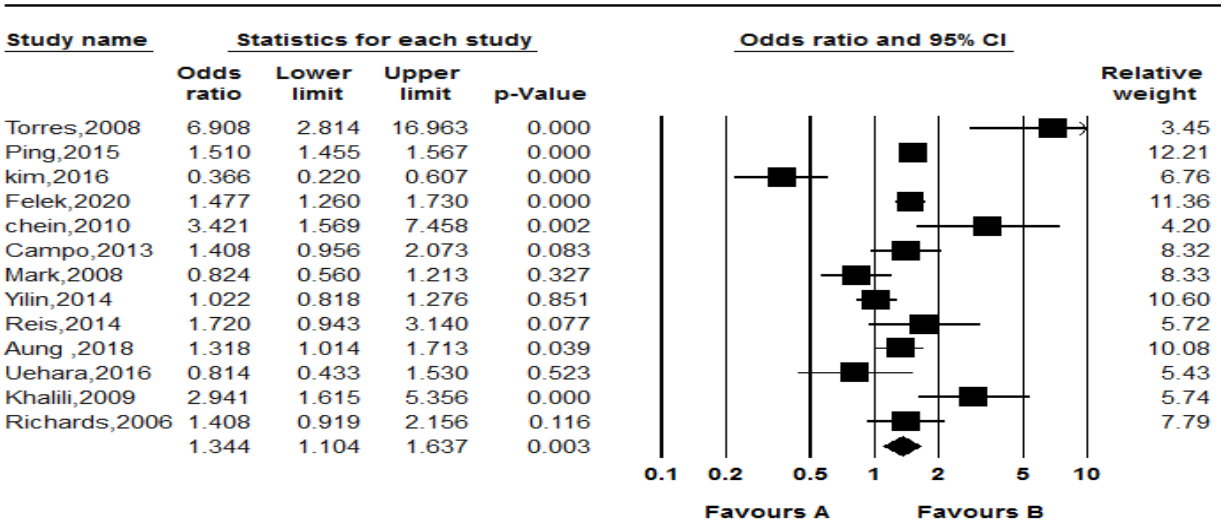

Fig. 2: Forest Plot of Odds Ratio Estimates of the Risk of HCV in TB Patients

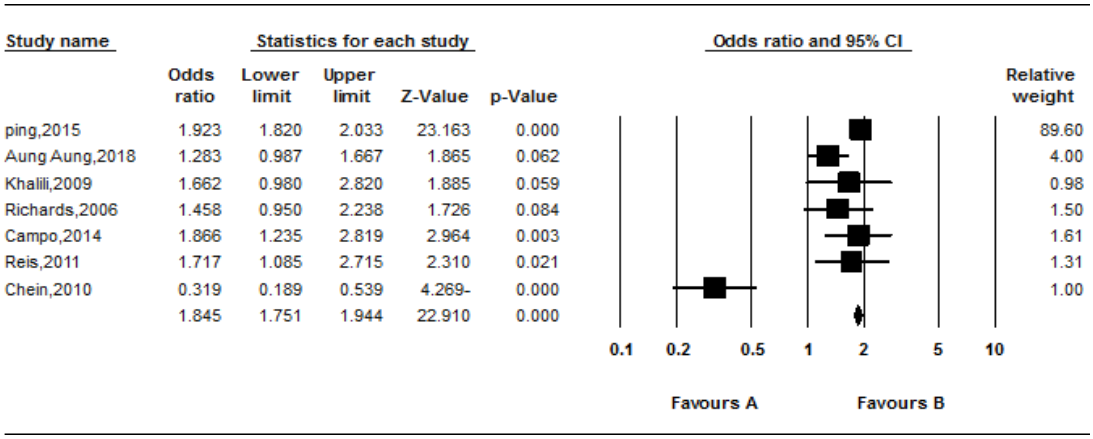

Fig. 3: Forest Plot of Odds Ratio Estimates of the Risk of HCV in TB Patients Based on Gender

Study quality was assessed based on the Newcastle-Ottawa Scale (NOS). Overall, n=2 were low quality, n=3 were medium quality, and n=8 were high- quality studies. However, after analysis based on quality assessment, no significant differences were observed between the results of high or medium quality studies and low or medium quality studies.

Sensitivity analysis, heterogeneity, and publication bias

Sensitivity analysis results showed no significant influence on the results. The Q test results indicated a significant heterogeneity among the studies (P<0.001). The $\mathbf{I^2}$ and tau-squared statistics were 84.02 and 0.28, respectively.

Although a slight asymmetry was in the Beggs' Funnel plot (Fig.4), no evidence of publication bias was indicated using Eggers (P=0.24) and Beggs' P=0.36) asymmetry test.

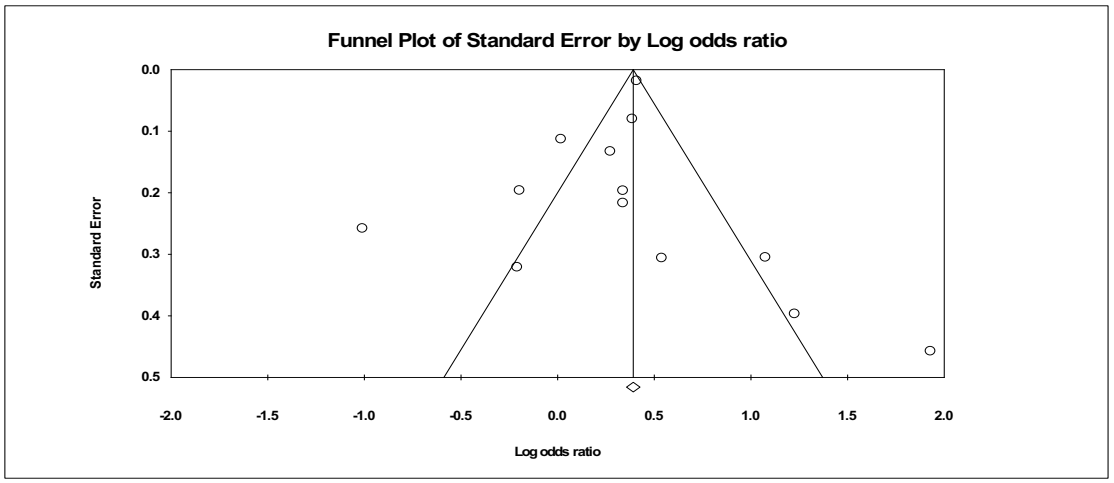

Fig. 4: Funnel Plot of Studies on the Risk of HCV in TB Patients

Univariable meta-regression analyses were performed to recognize possible variables associated with our results. The result of the meta-regression exploring the relationship between the risk of HCV in patients with TB and the year of study is indicated in Fig. 5. HCV risk in TB patients has a significant downward trend (B=-0.003, Tau ^{2}=0.09, *P*=0.001).

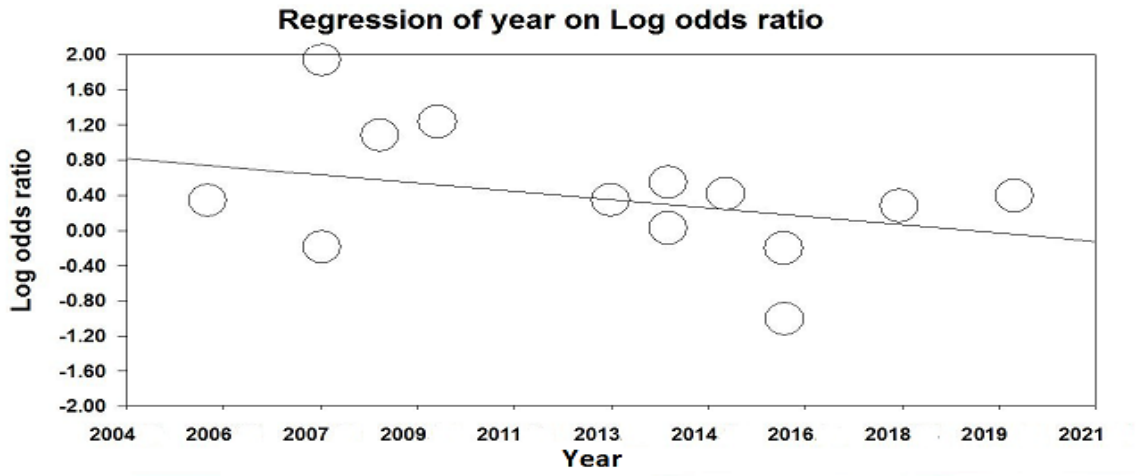

Fig. 5: Meta-regression of the relationship between the risk of HCV in TB Patients and the Year of Study

Discussion

In this meta-analysis study, Strong evidence of an increased risk of HCV among patients with TB was observed. And the risk of HCV in these patients was 1.34 times higher than that in the general population. In the analyses of the subgroups, the risk of HCV among patients with TB in developing countries was almost twice that of developed countries. Similarly, the risk of HCV among patients with tuberculosis in the age groups over 65 yr and men was significantly higher than that in people who did not have tuberculosis.

The current finding was similar to those of Aung et al. (OR: 1.31, 95% CI: 1.01-1.71)(24).A high prevalence of HCV co-infection and a low prevalence of HIV co-infection was observed for TB patients in a cross-sectional study (22). There was a significantly higher prevalence of TB disease in HCV-infected patients (OR: 1.43; 95% CI, 1.25–1.64)(26, 27).

HCV co-infection was an independent risk factor for hepatitis during antituberculosis treatment, even with performing normal baseline liver biochemical tests, and it was associated with more indolent recovery from hepatitis than non-infected patients. HBV co-infection was not associated with a higher rate of hepatitis, but it was relevant to delayed onset of hepatitis, higher ALT levels, and slower recovery from hepatitis (28, 29) .The mortality rate in patients with hepatitis episodes during anti-tuberculosis treatment was significantly higher. What is not fully understood is the mechanisms of drug-induced hepatitis during anti-tuberculosis treatment (20, 30). In the medical literature, the reported incidence of hepatotoxicity and its clinical types in patients receiving treatment with INH, RMP, and PZA varies considerably, ranging from 2.5% to 34.9% (31-33).

Drug-induced hepatotoxicity during TB treatment in patients with HBV infection has been investigated (34). In Korea, a more frequent trend was found toward transaminase elevation of the ULN in hepatitis B carriers for at least five times more than that in control subjects (8% vs. 2%, *P*= 0.05) (35) . In Hong Kong, compared to 4.7% of TB patients without HBV infection, 16% of patients with TB with HBsAg developed symptomatic hepatitis (34, 36). However, HBV carriers with TB who received INH, RMP, PZA, and EMB had a hepatotoxicity rate of 29%, which was similar to the 26% experienced by HBV-negative patients (37) . Concerning HCV infection, few studies have investigated the risk of drug-induced hepatotoxicity during the treatment of TB patients with HCV infection. An independent risk factor for the development of hepatotoxicity was being HCV-positive (almost 30% of HCV- infected individuals developed hepatotoxicity compared with 11% of non-HCV-infected individuals during standard short-course anti-tuberculosis regimens) (34, 38, 39) .Viral infections which are chronic liver diseases, can increase hepatotoxicity. In patients with TB, HCV infection can cause a significant change in the number of TCD4+ lymphocytes as well as an increase in liver enzymes. Health conditions in different countries play an important role in the spread of various diseases, including HCV and TB. Public health and health services have problems that can influence the risk of infectious diseases in these countries (40, 41) .In previous studies, there is little information about the differences between social, health, cultural, and economic fields. Therefore, these differences should be considered in future studies.

The results of metaregression, according to the year of the publication, show a decrease in HCV in patients with tuberculosis, which can be related to several factors. Over the past decades, better health conditions and faster access to health services around the world have improved TB prevention and control. Screening and education of high-risk groups (drug users, prisoners) and certain populations by the health system in different countries have also had a significant positive effect on the control and management of infectious diseases (42). HCV risk factors in patients with TB reported by selected studies are among the most well-known risk factors mentioned in various studies around the world (43, 44). Health decisions, policymakers, and primary health care providers must implement special programs for people at risk. By paying attention to these people the prevalence of this disorder can be reduced significantly. However, despite some strengths such as novelty and comprehensive search strategy, this study lacks information in the field of old texts including academic databases and research projects, which limits our study.

The results of this study highlight the importance of HCV screening in patients with TB. These patients have HCV can be very helpful. Steps should be taken by Health decision-makers and policymakers to educate and screen groups at risk for HCV and TB.

Conclusion

Strong evidence suggesting an increased risk of HCV in patients with tuberculosis was found. The results of the study show the importance of HCV screening in patients with tuberculosis.

Abbreviations

HCV: hepatitis C virus; TB: Tuberculosis; OR: Odds Ratio; INH: Isoniazid; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; NOS: Newcastle-Ottawa Scale; DOTS: Directly Observed Treatment, Short-course; RMP: Rifampin; PZA: Pyrazinamide.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of intrests

The authors declare that they have no competing interests.

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