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Original Article

The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: A systematic review and meta-analysis

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Abstract

Background: Anti-tuberculosis drug-induced liver injury (ATDILI) is a major safety concern in the treatment of tuberculosis (TB). The impact of chronic hepatitis C (CHC) infection on the risk of ATDILI is still controversial. We aimed to assess the influence of CHC infection on ATDILI through a systematic review and meta-analysis.

Methods: We systemically reviewed all English-language literature in the major medical databases with the subject search terms "anti-tuberculosis drug-induced liver injury" and "anti-tuberculosis drug-induced hepatotoxicity". We then performed a systematic review and meta-analysis of the papers relevant to hepatitis C in qualified publications.

Results: A total of 14 studies were eligible for analysis, which included 516 cases with ATDILI and 4301 controls without ATDILI. The pooled odds ratio (OR) of all studies for CHC infection to ATDILI was 3.21 (95% confidence interval (CI): 2.30−4.49). Subgroup analysis revealed that the CHC carriers had a higher risk of ATDILI than those without CHC both in Asians (OR = 2.96, 95% CI: 1.79−4.90) and Caucasians (OR = 4.07, 95% CI: 2.70−6.14), in those receiving standard four combination anti-TB therapy (OR = 2.94, 95% CI: 1.95−4.41) and isoniazid monotherapy (OR = 4.18, 95% CI: 2.36−7.40), in those with a strict definition of DILI (serum alanine aminotransferase [ALT] > 5 upper limit of normal value [ULN], OR = 2.59, 95% CI: 1.58−4.25) and a loose definition of DILI (ALT > 2 or 3 ULN, OR = 4.34, 95% CI: 2.96−6.37), and in prospective studies (OR = 4.16, 95% CI: 2.93−5.90) and case−control studies (OR = 2.43, 95% CI: 1.29−4.58).

Conclusion: This meta-analysis suggests that CHC infection may increase the risk of ATDILI. Regular liver tests are mandatory for CHC carriers under anti-TB therapy.

Keywords: Anti-tubercular agent; Anti-Tuberculosis drug-induced liver injury; Drug-induced liver injury; Hepatitis C; Meta-analysis; Tuberculosis

1. Introduction

Tuberculosis (TB) remains a major health problem worldwide. Drug-induced liver injury (DILI) is one of the most common adverse effects of anti-TB medication and is associated with the three major first-line drugs: isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA).[1−4] Anti-tuberculosis drug-induced liver injuries (ATDILIs) range from asymptomatic elevation of aminotransferase to clinical hepatitis, and they can be fatal.[1,2] The incidence of ATDILI

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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depends on the regimen used, the definition of DILI, and many other factors.[1−4]

Old age, female gender, human immunodeficiency virus (HIV) infection, abnormal baseline liver function tests, chronic alcohol drinking, chronic hepatitis B and C infections, and genetic factors have been proposed to be risk factors for ATDILI.[1−4] Our previous studies showed that genetic polymorphisms of some drug-metabolizing enzymes may be associated with ATDILI.[3,4] Furthermore, chronic hepatitis B infection has been reported to potentially increase the risk and severity of ATDILI, especially in Asians.[5] Similarly, some studies have suggested that chronic hepatitis C (CHC) infection may increase the incidence of ATDILI,[6−14] although other studies have not found an association between CHC infection and susceptibility to ATDILI.[15−19] The guidelines for anti-TB treatment in the USA, Taiwan and many other countries suggest screening for CHC infection status before starting treatment, and regular monitoring of liver biochemical tests in patients with CHC infection.[1,20] This recommendation is based on the belief that CHC infection can increase susceptibility to ATDILI. However, all of the relevant studies have a small sample size and variable results, and whether CHC infection can predispose to ATDILI is still unclear. Hence, we performed this systematic review and meta-analysis to assess the influence of CHC infection on the risk of ATDILI.

2. Methods

2.1. Identification and retrieval of studies

We conducted a literature search for English-language articles assessing the link between CHC infection and ATDILI published up to September 2016 in PubMed, Medline, Embase and the Cochrane Database of Systemic Reviews using the medical subject heading search terms “anti-tuberculosis drug-induced liver injury” and “anti-tuberculosis drug-induced hepatotoxicity”. Articles were selected for full text review based on the title and abstract. In addition, we manually searched the reference lists of the retrieved articles to increase the yield of potentially relevant articles. Only the papers relevant to hepatitis C were selected for systematic review and meta-analysis. Two researchers independently examined all papers and assessed their eligibility for this study. Discordant opinions were resolved by consensus with the other co-authors.

2.2. Inclusion and exclusion criteria

We included both prospective studies and retrospective case−control studies into the meta-analysis. The included studies had to fulfill the following selection criteria: (1) patients receiving standard anti-TB treatment including INH for active TB, or INH single drug prevention therapy for latent TB; (2) having data on patients with or without ATDILI, and with or without CHC infection; (3) serum anti-hepatitis C virus (HCV) antibody tested in all patients and controls; (4) studies with a clear definition of ATDILI, in which how many times of the upper normal limit of serum alanine aminotransferase (ALT) and/or serum total bilirubin were specified as DILI; (5) ATDILI was defined as at least more than two times the upper limit of normal value (ULN) of serum ALT or aspartate aminotransferase (AST); and (6) published as a full-length article. The exclusion criteria were: (1) studies with fewer than five patients with CHC infection; (2) repeated use of the same patient/control groups in the second paper; and (3) incomplete data on the number of cases, controls and percentage of positive anti-HCV. Studies included in the analysis were reviewed for the following characteristics: authors and year of publication; ethnicity; prospective or retrospective case−control study; anti-TB regimen; and definition of ATDILI.

2.3. Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the incidence of ATDILI and CHC infection were calculated. Heterogeneity was assessed by between-study variance using I^2 statistics with a cutoff value of $\geq$50%, or the x^2 test for Cochran Q statistics with $p < 0.10$. If significant heterogeneity was found, a random effects model was selected to analyze the pooled data and subgroup analysis was performed. Funnel plots were used to assess publication bias. All statistical analyses were performed using Review Manager version 5.3.5 (RevMan for Windows, 2015; The Cochrane Collaboration, Oxford, UK).

3. Results

A total of 421 citations were retrieved on the initial major database search, from which 14 studies were determined to be eligible for meta-analysis (Fig. 1). The baseline characteristics of the included studies are listed in Table 1. Of the patients who underwent anti-TB treatment, 516 cases with DILI and 4301 controls were enrolled into this analysis. Eight studies focused on Asians, four studies were derived from studies on Caucasian patients, and only one study focused on African American patients (Table 1). Nine of the 14 studies were prospective studies, and the other five were retrospective case−control studies. Ten of the studies focused on patients with active TB receiving ongoing standard treatment with four-drug combination therapy, and the other four studies enrolled patients with latent TB undergoing isoniazid single-drug prophylactic treatment. Seven studies adopted the strict definition of DILI as serum ALT more than five times the ULN, while the other seven studies used a loose definition of DILI (ALT or AST > 2 or 3 ULN).

The pooled OR of all studies for CHC infection to ATDILI was 3.21 (95% CI: 2.30−4.49, Fig. 2). Mild heterogeneity was noted among the studies (I^2 = 37%, p = 0.08). However, no significant publication bias was detected in funnel plot analysis (Fig. 3). Further subgroup analysis revealed that the CHC carriers had a higher risk of ATDILI than those without CHC both in Asians (OR = 2.96, 95% CI: 1.79−4.90) and Caucasians (OR = 4.07, 95% CI: 2.70−6.14, Fig. 4), in those

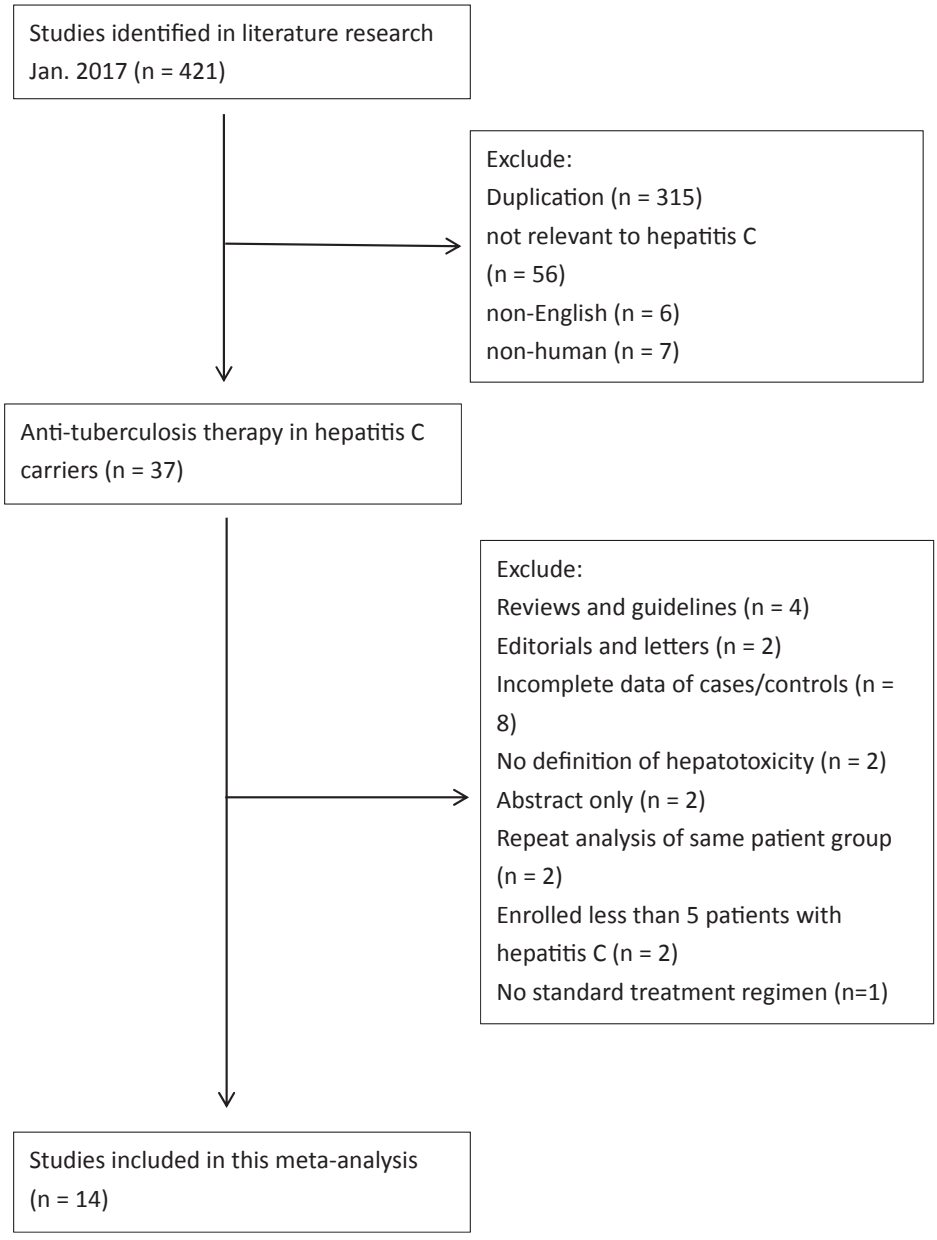

Fig. 1. Flow chart of the selection of eligible studies.

receiving standard four-drug combination anti-TB treatment (OR = 2.94, 95% CI: 1.95–4.41) and isoniazid single-drug prevention therapy (OR = 4.18, 95% CI: 2.36–7.40, Fig. 5), in those with a strict definition of DILI (OR = 2.59, 95% CI: 1.58–4.25) and a loose definition of DILI (OR = 4.34, 95% CI: 2.96–6.37, Fig. 6), and in prospective studies (OR = 4.16, 95% CI: 2.93–5.90) and case–control studies (OR = 2.43, 95% CI: 1.29–4.58, Fig. 7).

4. Discussion

Patients with chronic liver disease are more susceptible to ATDILI, however the impact of CHC infection on ATDILI is still under debate. The results of the present meta-analysis highlight that patients with CHC infection have a higher risk of ATDILI, regardless of the ethnicity, treatment regimen, and definition of DILI.

Diverse ethnicity may influence the susceptibility to DILI. However, in this meta-analysis, nine of the 14 studies involved Asian patients, four studies focused on Caucasians, while only one focused on African Americans. The association between CHC infection and ATDILI still existed in the subgroup analysis of Asian and Caucasian populations (Fig. 4). However, the study on African Americans did not show a statistical difference in isoniazid-related liver injury between CHC carriers and non-carriers. Therefore, further studies are needed to define the actual association between CHC infection and ATDILI in Black populations.

Since the three first-line anti-TB drugs, INH, RMP and PZA, have the potential to induce liver injury, it is reasonable

Table 1
Main characteristics of included studies in the order of publication year (n = 14).

First author, year	Publication country	Race	Study design	Sample size (case/control)	Anti-TB regimens	Main diagnostic criteria of DILI
Ungo, 1998[6]	USA	Caucasian	prospective	22/106	4 combination	ALT > 3 ULN
Sadaphal, 2001[15]	USA	Black	prospective	32/114	isoniazid	ALT > 3 ULN
Fernandez-Villar, 2003[16]	Spain	Caucasian	prospective	20/395	isoniazid	ALT > 5 ULN
Kwon, 2007[7]	Korea	Asian	Prospective	11/140	4 combination	ALT > 3 ULN
Sun, 2009[17]	Taiwan	Asian	prospective	42/219	4 combination	ALT > 5 ULN
Chien, 2010[8]	Taiwan	Asian	case–control	25/270	4 combination	ALT > 5 ULN
Wang, 2011[9]	Taiwan	Asian	prospective	68/292	4 combination	ALT > 5 ULN
Chan, 2012[10]	Taiwan	Asian	prospective	15/168	isoniazid	ALT > 3 ULN
Shu, 2013[18]	Taiwan	Asian	case–control	96/501	4 combination	ALT > 5 ULN
Lomtadze, 2013[11]	USA	Caucasian	prospective	54/234	4 combination	ALT > 2 ULN
Liu, 2014[19]	Taiwan	Asian	case–control	38/425	4 combination	ALT > 5 ULN
Mo, 2014[12]	China	Asian	prospective	6/940	4 combination	ALT > 3 ULN
Bliven-Sizemore, 2015[14]	USA	Caucasian	case–control	49/243	isoniazid	AST > 3ULN
Kim, 2016[13]	Korea	Asian	case–control	38/254	4 combination	ALT > 5 ULN

TB = tuberculosis; DILI = drug-induced liver injury; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal value.

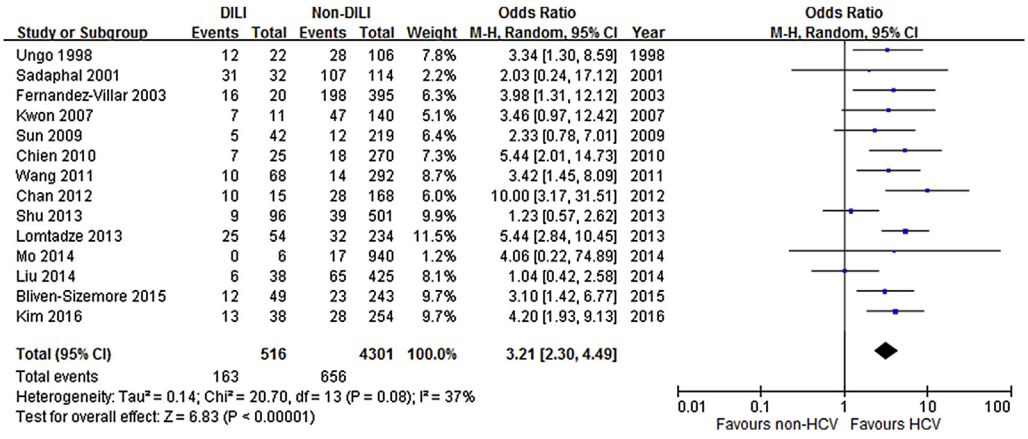

Fig. 2. Forest plot of association between chronic hepatitis C (CHC) infection and the risk of anti-tuberculosis drug-induce liver injury (ATDILI) in all eligible 14 studies. Events denote patients with CHC infection. CI = confidence interval; DILI = drug-induced liver injury; HCV = hepatitis C virus; M–H = Mantel-Haenszel.

to assume that isoniazid mono-therapy would be less toxic than a combination anti-TB regimen. In this meta-analysis, ten of the 14 studies focused on patients with active TB receiving ongoing standard treatment with four drugs, while four studies enrolled patients with latent TB under isoniazid monotherapy, and we found associations between CHC infection and ATDILI in both of these groups. This may be because isoniazid is the most incriminated drug capable of inducing liver injury among the anti-TB drugs.

The definition of DILI may affect study outcomes, and there remains ongoing debate as to an adequate definition of DILI. According to the Council for International Organizations of Medical Sciences criteria, an ALT level of more than two times the ULN is regarded as DILI.[21] However, a mild increase in ALT may have no clinical significance. Therefore, an elevation of ALT level by more than five times the ULN, or more than three times the ULN with jaundice, is defined as significant DILI by the US DILI Network.[22,23] A higher threshold of ALT may select the patients who do have DILI and who require further management such as discontinuing or decreasing the dose of the incriminated drugs, close monitoring of liver function, and liver transplantation if necessary. In this analysis, we found that associations between CHC infection and ATDILI existed with both the strict and loose definitions of DILI (Fig. 6).

An elevation in liver enzymes during anti-TB treatment in CHC carriers may be due to activation of CHC or DILI. In general, the existence and titer of serum HCV RNA can represent the replication activity of HCV virus. However, most studies included in this meta-analysis only measured serum anti-HCV antibodies and did not provide data on HCV viral load. Ungo et al. suggested that positive serum HCV-RNA may be associated with ATDILI in a study from the US,[6] and Wang et al. found that a high initial HCV viral load had a tendency to increase the risk of DILI, but without statistical significance in a study conducted in Taiwan.[9] Another study conducted by Fernandez-Villar et al. in Spain demonstrated that the presence of HCV-RNA was significantly associated

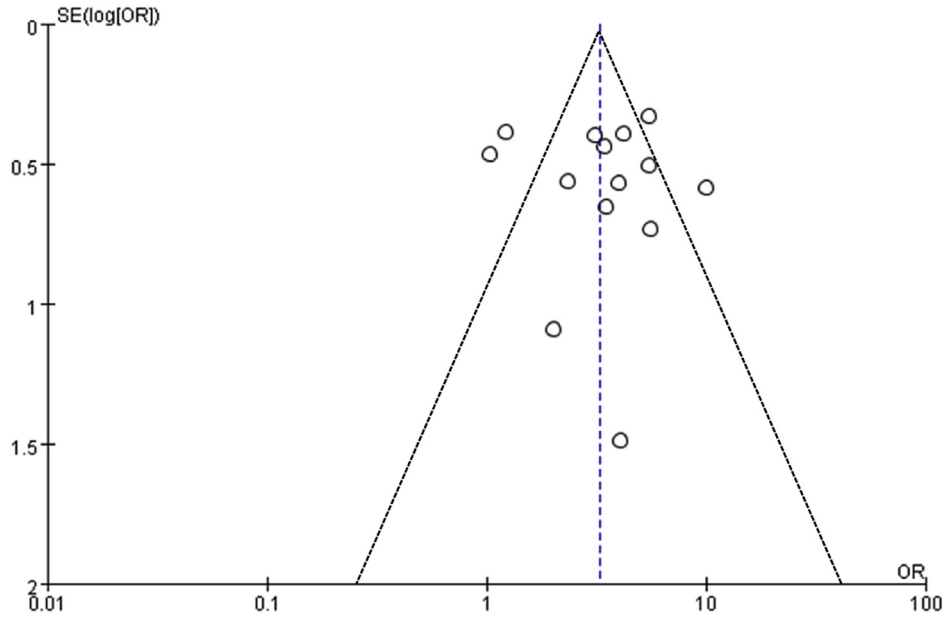

Fig. 3. Funnel plot for the assessment of publication bias.

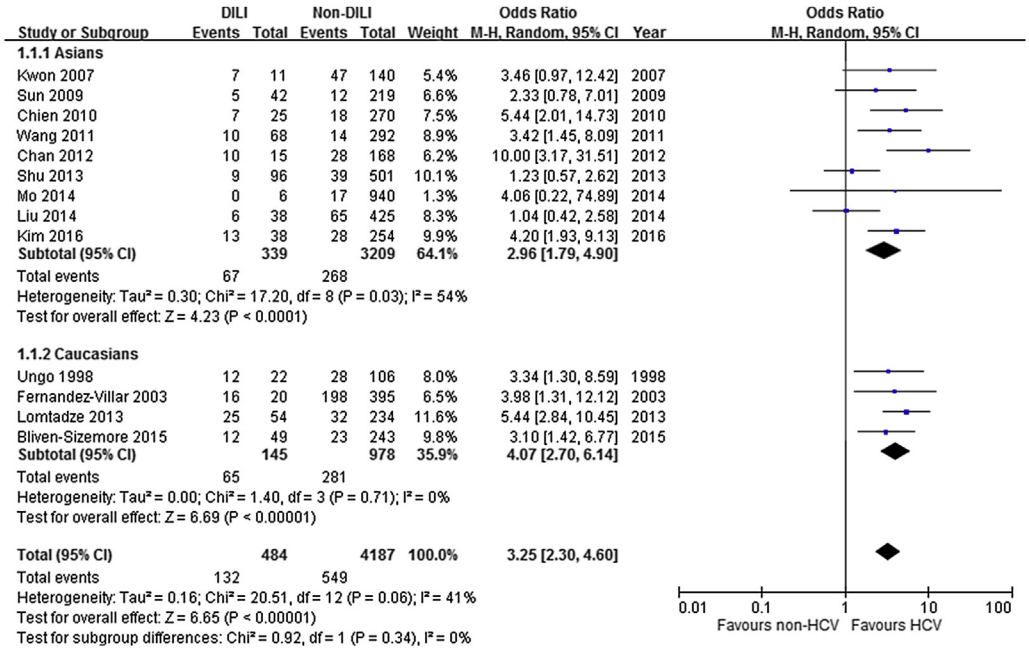

Fig. 4. Odds ratio of chronic hepatitis C (CHC) infection to anti-tuberculosis drug-induced liver injury (ATDILI) by the subgroup analysis of different ethnic populations. Events denote patients with CHC infection. CI = confidence interval; DILI = drug-induced liver injury; HCV = hepatitis C virus; M−H = Mantel-Haenszel.

with ATDILI in both univariate and multivariate analyses, while the presence of anti-HCV was only significant in the univariate analysis.[24] Mo et al. also supported the role of HCV-RNA in the predisposition to ATDILI in Chinese patients, and emphasized that HCV-RNA is a better indicator of ATDILI than anti-HCV in HCV carriers.[12] However, recent studies from Lomtadze et al.[11] and Kim et al.[13] did not find an association between detectable serum HCV-RNA and ATDILI. Therefore, the role of HCV-RNA in the susceptibility to ATDILI seems controversial, and further large-scale studies with different ethnic populations are needed to elucidate this association.

The reason why patients with CHC infection have a higher incidence of ATDILI remains to be clarified. However, several explanations have been proposed. First, reactivation of HCV with flare-ups of hepatitis may contribute to liver injury, which manifests as the presence and/or high serum HCV-RNA as in the aforementioned studies. Second, potential liver

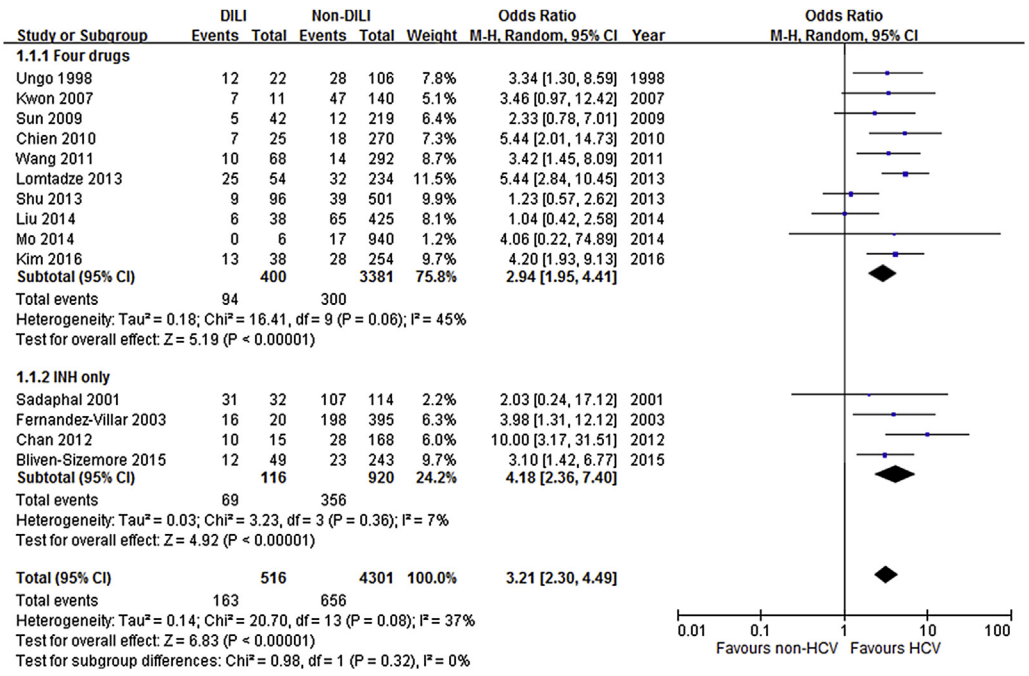

Fig. 5. Odds ratio of chronic hepatitis C (CHC) infection to anti-tuberculosis drug-induced liver injury (ATDILI) by the subgroup analysis of different treatment regimens. Events denote patients with CHC infection. CI = confidence interval; DILI = drug-induced liver injury; HCV = hepatitis C virus; M–H = Mantel-Haenszel.

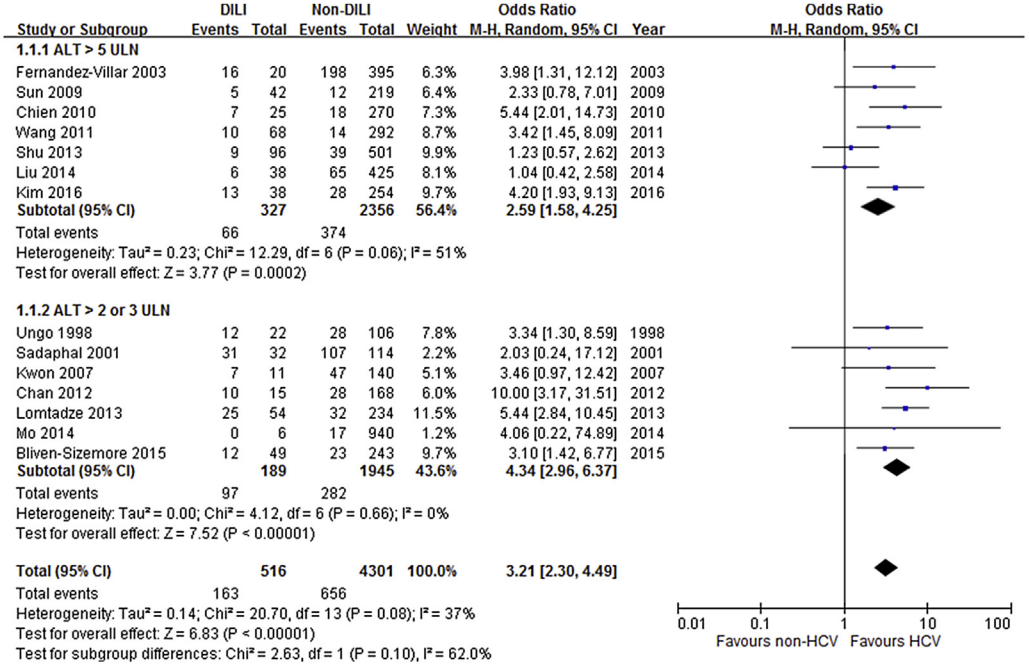

Fig. 6. Odds ratio of chronic hepatitis C (CHC) infection to anti-tuberculosis drug-induced liver injury (ATDILI) by the subgroup analysis of different definition of DILI. Events denote patients with CHC infection. CI = confidence interval; DILI = drug-induced liver injury; HCV = hepatitis C virus; M–H = Mantel-Haenszel.

dysfunction in HCV carriers may impair the disposition of anti-TB drugs, which may in turn result in the accumulation of more toxic metabolites. Third, HCV core protein may change lipid metabolism and induce steatosis,[25] which may interact with DILI to augment the liver injury. However, the true mechanism and interplay between HCV and ATDILI remains to be elucidated.

There are some limitations to this meta-analysis. First, we could not completely rule out the possibility of active HCV hepatitis, alcoholic liver disease and non-alcoholic fatty liver

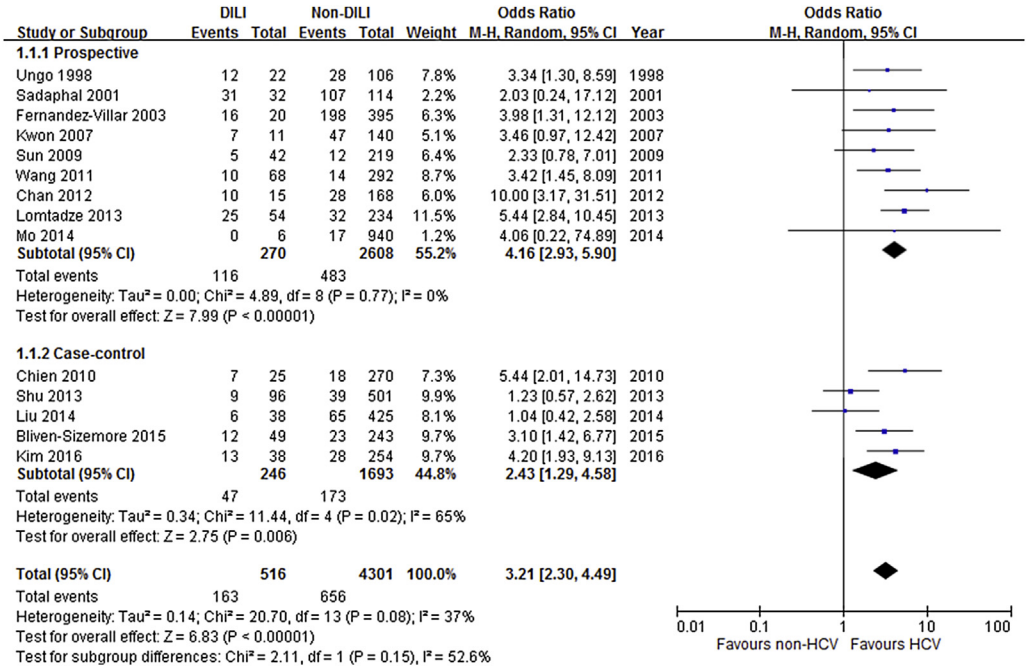

Fig. 7. Odds ratio of chronic hepatitis C (CHC) infection to anti-tuberculosis drug-induced liver injury (ATDILI) by the subgroup analysis of different study designs. Events denote patients with CHC infection. CI = confidence interval; DILI = drug-induced liver injury; HCV = hepatitis C virus; M–H = Mantel-Haenszel.

disease in the enrolled studies, although the strict diagnostic criteria of DILI may exclude some patients with alcoholic liver disease and non-alcoholic fatty liver disease. Second, we did not have data on the anti-viral treatment in the patients with HCV included in this study. Interferon-based treatment and new direct-acting antiviral agents used to treat HCV may influence HCV activity and alter the susceptibility to ATDILI. However, almost all of the papers included in this meta-analysis were published before the advent of direct-acting antiviral agents, therefore we assume that HCV infection was not eradicated in most of the patients. Third, patients with HIV infection were included in some of the studies in this meta-analysis, which may have affected the risk of ATDILI. However, only a few patients with HIV were enrolled, and the ATDILI status was not well demonstrated in most of the studies. Therefore, further analysis of the impact of HIV co-infection on ATDILI was difficult in this meta-analysis.

In conclusion, this meta-analysis re-emphasized that CHC infection may increase the risk of ATDILI in both Asians and Caucasians, and in both anti-TB combination therapy and isoniazid monotherapy. This study underscores the importance of closely monitoring liver tests in HCV carriers before and during anti-TB treatment.

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