Original Article

Non-Genetic Risk Factors for First-Line Anti-Tuberculosis Drug-Induced Liver Injury in Active Pulmonary Tuberculosis Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Tuberculosis is still one of the leading causes of poor health and death worldwide. Drug-induced liver injury (DILI) is an important and serious side effect of anti-tuberculosis treatment and can cause non-adherence of patients to the treatment. To reduce the possibility of patients developing DILI, the risk factors must be identified.

Methods: This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Inclusion and exclusion criteria were used to screen and filter the articles that were obtained from literature searching performed through several journal databases. The extracted data were analyzed qualitatively and quantitatively. The quality of each study was also assessed using the modified Newcastle Ottawa Scale (NOS). The protocol for this systematic review has been registered with PROSPERO CRD42022384892.

Results: The results showed that, of the 13 studies analyzed qualitatively, 11 studies with a total of 4,920 patients were selected for quantitative analysis. The factors analyzed and the results were female gender (OR=1.10; 95% CI=0.72-1.67; *P*=0.65), age over 40 years (OR=1.60; 95% CI=1.04-2.46; *P*=0.03), body mass index less than 18.5 kg/m^2 (OR=0.96; 95% CI=0.52-1.79; *P*=0.9), active smoking (OR=0.71; 95% CI=0.34-1.49; *P*=0.36), frequent alcohol intake (OR=1.44; 95% CI=0.61-3.42; *P*=0.41), hepatitis B (OR=3.42; 95% CI=1.72-6.79; *P*<0.001]), and hepatitis C (OR=12.87; 95% CI=6.67-24.86; *P*<0.00001]).

Conclusion: In conclusion, the evidence from this review suggests that older age, hepatitis B, and hepatitis C are significant risk factors thought to increase the incidence of DILI in active pulmonary tuberculosis patients taking first-line anti-tuberculosis regimens.

Keywords: drug-induced liver injury, first-line anti-tuberculosis, pulmonary, risk factors, tuberculosis

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INTRODUCTION

Tuberculosis remains a leading cause of poor health outcomes and death from an infectious disease agent.[1,2] It was estimated that new cases of tuberculosis in 2020 reached 5.8 million and 1.6 million people died from the disease.[1,3] Indonesia is the second country with the most tuberculosis cases, with incidents in 2021 estimated at around 354 per 100,000 population.[4] The standard anti-tuberculosis regimen includes rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin.[5,6] Although these regimens have proven effective, various side effects can be caused by these drug regimens.[6,7] One of the quite serious side effects is drug-induced liver injury. Globally, the incidence of drug-induced liver injury (DILI) on anti-tuberculosis treatment ranges from 2% to 28% for various DILI criteria.[5,8,9]

Drug-induced liver injury in anti-tuberculosis treatment is an important and serious side effect of tuberculosis treatment.[10] This side effect can arise directly from metabolites, ingredients, or reactions to the immunological response due to the consumption of anti-tuberculosis drugs.[5,11] Patients with DILI may experience complaints such as nausea, vomiting, fatigue, malaise, jaundice, pruritus, and abdominal pain.[12] It can cause non-adherence to treatment in tuberculosis patients, so that it will increase the

possibility of treatment failure, which can lead to an increased incidence of drug resistance.[5,13,14] This causes the need for attention to the use of anti-tuberculosis drugs.[2,15]

To prevent or minimize the possibility of someone getting DILI due to tuberculosis treatment, timely and accurate early detection of DILI is important.[16,17] The risk factors present in the patient must be identified so that special attention is given to this population.[5,18] This study presents a systematic review and meta-analysis of non-genetic risk factors for DILI in active pulmonary tuberculosis patients receiving first-line anti-tuberculosis treatment

METHODS

This systematic review was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[19] The protocol for this systematic review was registered in PROSPERO (CRD42022384892).

Inclusion and exclusion criteria were used to screen and filter the articles that were obtained. The included study designs were observational studies such as cohort, case-control and cross-sectional, as well as randomized controlled trials. Only full-text articles in English or Indonesian were included. Participants in included studies were patients with active pulmonary tuberculosis who were taking first-line tuberculosis drugs such as rifampicin, isoniazid, pyrazinamide, ethambutol, and/or streptomycin, with drug-induced liver injury as the study outcome. The risk factors assessed must be non-genetic risk factors.

Studies were excluded if they were reviews, case reports, or case series studies. Studies that were conducted on patients with extrapulmonary tuberculosis and latent tuberculosis were also excluded. There were no restrictions on the publication year of included studies to ensure the quality of this systematic review.

A literature search was performed independently through several electronic journal databases, such as PubMed, EMBASE, EBSCO Medline, Scopus, and ProQuest on August 15, 2022.

Articles were independently reviewed according to the PRISMA flow diagram.[19] All articles obtained from the literature search were entered into the EndNote X9 software for duplicate removal. The screening process of the articles started with the title and abstract, then continued with full-text assessment. At each stage, all articles were validated based on the eligibility criteria that had been determined.

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, and a modified version for cross-sectional studies. A study was considered to be of high quality if the score was more than or equal to 7, moderate if the score was 5 to 6, and low if the score was less than or equal to 5.[20,21]

Data from the included articles were extracted into the result tables. The risk factors assessed were all risk factors for DILI studied in the articles, apart from genetic factors and laboratory test results (except for results indicating a disease). Each risk factor was also presented with an odds ratio (OR) and a value of *P*.

In addition, one of the serious side effects of anti-tuberculosis agents is drug-induced liver injury (DILI), which can cause non-adherence to treatment in tuberculosis patients and it will increase the possibility of treatment failure. To prevent the possibility of someone getting DILI due to tuberculosis treatment, the risk factors that exist in the patient must be identified. The incidence of active pulmonary tuberculosis who take first-line regimens remains high, while the available reviews have not focused on this specific population. In this review, we also focus on non-genetic risk factors.

Risk factors obtained from more than one study and potentially having a significant effect were then included in the quantitative analysis. The extracted data were entered into the RevMan software, and then a pooling meta-analysis was performed. The results were visualized in forest plots. From the forest plots, the overall odds ratio (OR) with a 95% confidence interval (CI) was obtained. Heterogeneity indexes were also shown for

the analysis of data distribution. Subgroup analysis was only performed if the number of studies included in an analysis of risk factors was sufficient and if high heterogeneity was found.

RESULTS

The results of a literature search and study selection are shown in Figure 1. From 5 journal databases, a total of 5055 articles were obtained. After duplicates were eliminated, 3562 articles entered the title and abstract screening stage.

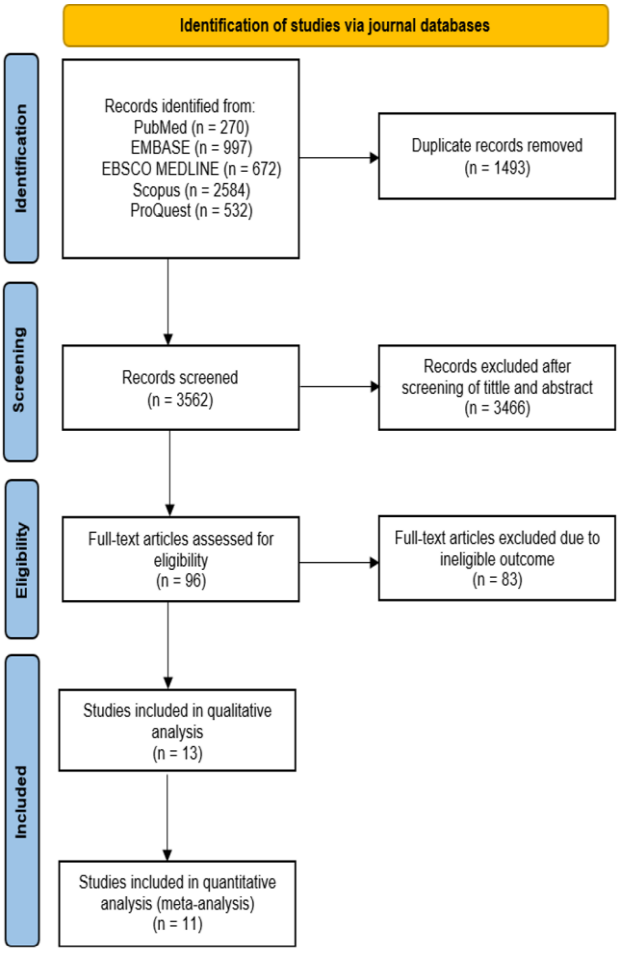

Figure 1. PRISMA flow diagram

From the screening, 3466 articles were irrelevant, so they were excluded. Then, as many as 96 full texts were assessed according to the eligibility criteria. As a result, thirteen articles met the inclusion criteria. After reviewing the risk factors discussed in each article, eleven studies with relevant risk factor data were included in the meta-analysis.

The baseline characteristics of included studies can be seen in Table 1. Study years ranged from 1996 to 2022. Most studies were conducted in Asia, including Pakistan, India, Iran, Malaysia, Singapore, Taiwan, and China. Two studies were from Europe (Portugal and Georgia). The most common study design was a cohort of 7 articles, followed by a case-control of 5 articles, and there was 1 article with a cross-sectional study design. Each study met the eligibility criteria for this systematic review, although there were slight differences in population characteristics, the regimen used, and the DILI criteria between each study.

Odds ratios, 95% CI, and a value of *P* for risk factors assessed in each study are shown in Table 2. From the factors analyzed, there were 7 factors widely discussed by studies and had the potential to significantly influence the incidence of DILI, while the qualitative analysis was not strong enough to conclude. They are gender, age, body mass index (BMI), active smoking, alcohol consumption, hepatitis B, and hepatitis C.

Table 2. Study Outcome: Risk Factors of DILI

Author, Year	Risk Factors	OR (95% CI)	*P*
Abbasi et al.[22], 2014	Male	1.03 (0.42–2.49)	>0.05
	Age >40 years	7.19 (2.75–18.79)	<0.05*
	BMI <18.5	0.73 (0.16–3.38)	>0.05
Baghaei et al.[23], 2010	Age >65 years	1.66 (1.08–2.53)	0.019*
	Male	0.77 (0.50–1.18)	>0.05
	Irian nationality	1.05 (0.61–1.81)	>0.05
	Unmarried	1.04 (0.60–1.79)	>0.05
	Active smoking	0.82 (0.50–1.34)	>0.05
	Opium	0.87 (0.50–1.51)	>0.05
	HIV	1.32 (0.57–3.06)	>0.05
	DM	0.89 (0.51–1.54)	>0.05
Cavaco et al.[24], 2022	Male	1.25 (0.72–2.18)	0.422
	Age ≥55 years	3.49 (2.02–6.07)	<0.001*
	Chronic diseases	1.75 (1.03–2.98)	0.039*
	Alcohol intake	0.48 (0.26–0.88)	0.018*
	Smoking habits	0.39 (0.22–0.72)	0.002*
	Other medication 3 drugs	2.53 (1.28–5.01)	0.008*
	Other hepatotoxic drugs	3.56 (1.98–6.42)	<0.001*
Chien et al.[25], 2010	Male	1.15 (0.48–2.77)	>0.05
	HBsAg (+)	1.54 (0.43–5.54)	>0.05
	Anti-HCV (+)	5.44 (2.01–4.73)	<0.01*
Fauzi et al.[26], 2004	High alcohol intake	2.33 (0.29–18.55)	>0.05
	HBsAg (+)	11.6 (1.15–116.4)	<0.05*
	HIV (+)	7.91 (0.74–84.37)	>0.05
	Severe CXR lesion	1.1 (0.26–4.52)	>0.05

Author, Year	Risk Factors	OR (95% CI)	*P*
Khoharo et al.[27], 2010	Male	0.53 (0.32–0.85)	<0.01*
Lomtadze et al.[28], 2013	Anti-HCV (+)	5.44 (2.84–10.45)	<0.01*
	HBsAg (+)	3.31 (1.01–10.86)	<0.05*
	Male	2.77 (1.24–6.15)	<0.05*
	Age ≥40 years	0.74 (0.39–1.41)	>0.05
	Injection drug use	3.77 (1.82–7.77)	<0.01*
	History of incarceration	2.62 (1.09–6.28)	<0.05*
	Alcohol intake	1.22 (0.67–2.21)	>0.05
	Current smoker	1.92 (1.02–3.59)	<0.05*
	HIV (+)	1.45 (0.15–14.24)	>0.05
	Urban population	0.84 (0.35–2.06)	>0.05
	Tattoo	1.75 (0.82–3.68)	>0.05
	Internally displaced person	0.53 (0.12–2.37)	>0.05
	Sexually transmitted infection(s)	1.40 (0.37–5.27)	>0.05
Pande et al.[29], 1996	High alcohol intake	4.76 (2.25-10.05)	<0.001*
	Extensive disease	4.5 (1.88-10.93)	<0.001*
	Jaundice in past	1.08 (0.49-2.35)	>0.05
Saha, et al.[8], 2016	Chronic alcohol consumption	2.59 (0.88-7.66)	>0.05
	Hepatitis B infection	9.87 (0.60-163.09)	>0.05
	HIV infection	1.61 (0.56-4.62)	>0.05
	Existing chronic tuberculosis	0.45 (0.06-3.52)	>0.05
Tao, et al.[30], 2020	Non-O blood group	1.82 (1.18–2.82)	0.009*
Teleman, et al.[31], 2002	Male	0.60 (0.34-1.05)	>0.05
	Age >60 years	1.86 (1.08-3.20)	<0.05*
	Daily alcohol intake	1.27 (0.56-2.88)	>0.05
	Diabetes mellitus	0.91 (0.46-1.79)	>0.05
Wang, et al.[32], 2011	Severe CKD without hemodialysis	1.96 (0.51–7.62)	>0.05
	High initial HBV viral load	3.69 (1.52–8.98)	<0.05*
	High initial HCV viral load	2.67 (0.78–9.15)	>0.05
	Age >65 years	1.02 (0.58–1.8)	>0.05
	Male	0.43 (0.24–0.76)	<0.05*
	BMI <18.5	1.66 (0.81–3.41)	>0.05
	Current smoker	0.33 (0.12–0.96)	>0.05
	Cancer	0.73 (0.35–1.51)	>0.05
	Diabetes mellitus	0.55 (0.24–1.28)	>0.05
	Cavity on CXR	0.68 (0.36–1.27)	>0.05
	Extent on CXR unilateral	1.78 (1.00–3.14)	>0.05
	Miliary lesion on CXR	0.97 (0.32–2.94)	>0.05
	Acid-fast smear positive	1.11 (0.63–1.94)	>0.05
Zhong, et al.[7], 2021	Male	1.88 (1.37–2.60)	<0.001*
	Age >40 years	0.99 (0.71–1.36)	>0.05
	Low education	0.86 (0.61–1.21)	>0.05
	Low annual income	0.8 (0.5 – 1.3)	>0.05
	BMI <18.5	0.72 (0.49–1.04)	>0.05

Therefore, the factors continue to be analyzed quantitatively. The forest plot for significant risk factors can be seen in Figure 2–3, while the rest can be found in Figure 4. The studies were generally heterogeneous, except for the analysis of hepatitis B and hepatitis C as risk factors of DILI. For age risk factors, there were 2 forest plots analyzed, i.e. over 40 years and over 50 years.

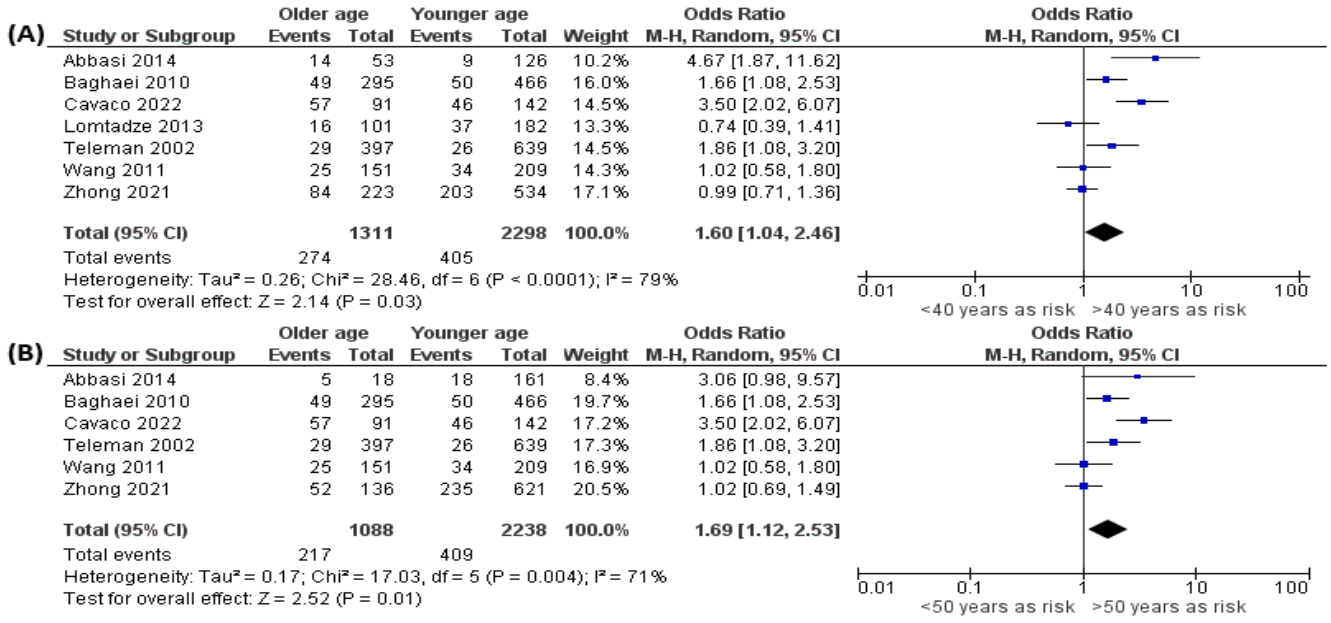

Figure 2. Forest plot of older age: more than 40 years old (A) and more than 50 years old (B) as a risk factor of DILI

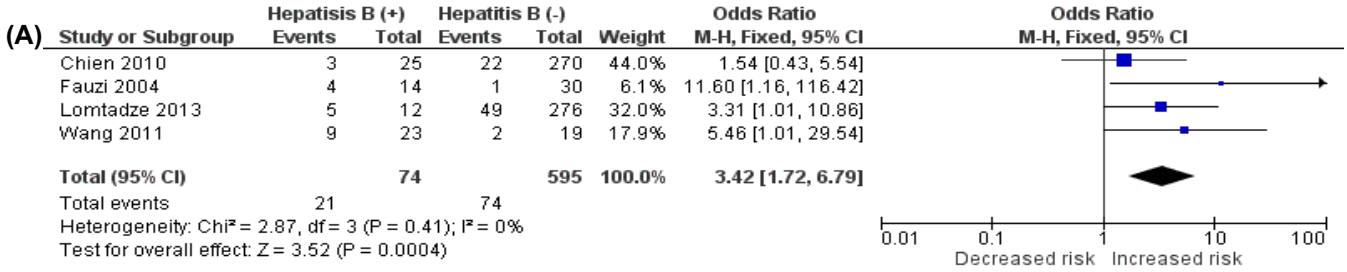

Figure 3. Forest plot of hepatitis: hepatitis B (A) and hepatitis C (B) as a risk factor of DILI

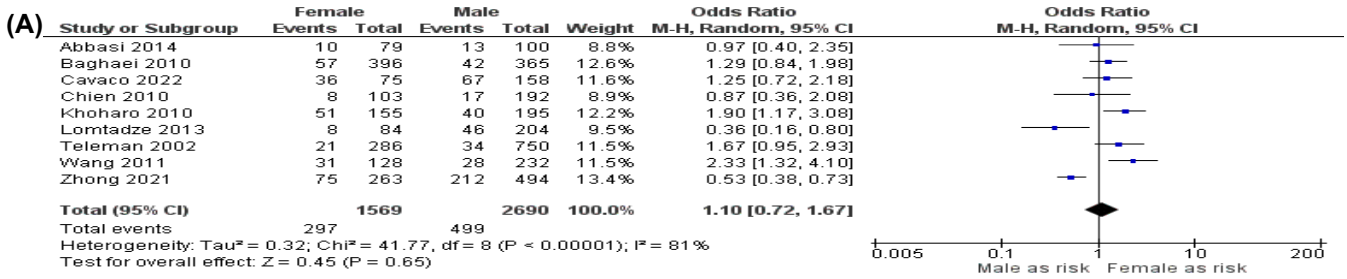

Figure 4. Forest plot of: gender (A), BMI <18.5 kg/m^2 (B), active smoking (C), and frequent alcohol intake (D) as a risk factor of DILI

Table 1. Characteristics of Included Studies

Author, Year	Location	Study Design	Final Participants	Age*	Criteria for Tuberculosis Patients	Used Regimens	Criteria of DILI
Abbasi et al., 2014	Pakistan	Cross-sectional	179 patients	36.51 (9.5)	Diagnosis of pulmonary tuberculosis, which was confirmed by AFB in sputum, age >20 years old	R, H, Z	Elevation of serum ALT >150 U/L
Baghaei et al.[23], 2010	Iran	Case control	761 patients	52.44 (21.43)	Diagnosis of pulmonary tuberculosis, which was confirmed by positive sputum or culture	2RHZE/4RH	Diagnosis was based on clinical symptoms and signs of hepatitis
Cavaco et al.[24], 2022	Portugal	Case control	233 patients	49.6 (18.1)	Diagnosis of pulmonary tuberculosis, age >16 years old, no contraindication for the treatment, normal baseline laboratory test, negative serology for hepatitis and HIV	2RHZE/4RH	Elevation of serum ALT >2x the upper limit of normal
Chien et al.[25], 2010	Taiwan	Retrospective Cohort	295 patients	66 (19)	Diagnosis of newly active pulmonary tuberculosis, AST/ALT <40 IU/L, total bilirubin <2 mg/dL, without excess alcohol ingestion within 2 months before the treatment	2RHZE/4RHE	Elevation of serum AST and/or ALT ≥3x the upper limit of normal with symptoms or elevation of serum AST and/or ALT ≥5x upper limit of normal without symptoms
Fauzi et al.[26], 2004	Malaysia	Case control	44 patients	Cases: 47 (14.1); Controls: 41.9 (13.5)	Diagnosis of pulmonary tuberculosis	2SHRZE/4RH2, 2SHRZ/4SRH2, 2HRZE/4RH2, 2HRZ/4RH2	Clinical features of icteric hepatitis, elevation of serum AST and/or ALT >5x upper limit of normal, serum total bilirubin >34.2 µmol/L, absence of acute hepatitis infection
Khoharo et al.[27], 2010	Pakistan	Prospective cohort	350 patients	34.62 (8.3)	Diagnosis of active pulmonary tuberculosis	R, H, Z	Presence of jaundice, elevation of serum AST and/or ALT ≥5x upper limit of normal levels, or elevation of serum total bilirubin >1.5 mg/dL
Lomtadze et al.[28], 2013	Georgia	Prospective cohort	326 patients	37 (21-92)	Diagnosis of newly active pulmonary tuberculosis (received <2 weeks of the regimens), age ≥18 years old	2RHZE/4RH	Elevation of serum ALT >1.25x the upper limit of normal
Pande et al.[29], 1996	India	Case control	492 patients	Cases: 39 (16.2); Controls: 31.6 (14.5)	Diagnosis of pulmonary tuberculosis	2RHE/7RH, 2RHZE/4RH, 2SHRZ/4RH, 2RHZ/4RH	Elevation of serum AST and/or ALT >150 U/L on three consecutive occasions or >250 U/L on one occasion, clinical features of icteric hepatitis, serum total bilirubin >34.2 µmol, and absence of hepatitis infection serology
Saha, et al.[8], 2016	India	Cohort retrospective	253 patients	All ages (N/A)	Diagnosis of pulmonary tuberculosis, which was confirmed by a positive smear and came for regular follow-up	R, H, Z	Elevation of serum AST and/or ALT ≥5x the upper limit of normal, serum total bilirubin > 1.47 mg/dL, or elevation of AST or ALT above pre-treatment levels with symptoms of nausea, vomiting, anorexia, and jaundice
Tao, et al.[30], 2020	China	Case-control	730 patients	Case: 49.80 (17.50); Control: 50.51 (17.84)	Diagnosis of new tuberculosis	R, H, Z, E, S	Elevation of serum ALT ≥3 upper limit of normal and R ≥5; ALP ≥2 upper limit of normal and R ≤2; ALT ≥3 upper limit of normal ALP ≥2 upper limit of normal and 2<R< 5. *R = (actual ALT/ALT ULN)/(actual ALP/ALP ULN)
Teleman, et al.[31], 2002	Singapore	Cohort retrospective	1036 patients	61 (16-82)	Diagnosis of active tuberculosis	R, H, Z, E, S	Elevation of serum AST and/or ALT >3x upper limit of normal, or serum bilirubin > upper limit of normal and elevation of AST and/or ALT >2x upper limit of normal
Wang, et al.[32], 2011	China	Cohort prospective	564 patients	57.6 (19.6)	Diagnosis of pulmonary tuberculosis, which was confirmed by positive sputum smear, CT scan, and clinical symptoms; ≥18 years old	2RHZE/4RH	Elevation of serum AST and/or ALT >3x upper limit of normal with symptoms or elevation of serum AST and/or ALT >5x upper limit of normal without symptoms
Zhong, et al.[7], 2021	China	Cohort retrospective	757 patients	All ages	Diagnosis of pulmonary tuberculosis	2RHZE/4RH	Elevation of serum ALT > 40 U/L

Note: Mean (SD) or Median (Range)

DISCUSSION

Drug-induced liver injury is a known complication of using anti-tuberculosis drugs. In the use of anti-tuberculosis drugs, DILI occurs due to the presence of a metabolite, primary compound, or an immunological response that is toxic to the blood vessels of the liver, biliary epithelial cells, and hepatocytes. In most cases, the exact mechanism by which anti-tuberculosis drugs are used for DILI and the factors that influence it are still not fully understood. There have been several animal studies studying predictable DILI reactions in which the incidence of DILI is dose-dependent on the drug administered. Necrosis of liver tissues is found in zones far from the hepatic arterioles. Many free radicals are found in these areas, resulting from the high metabolism in these areas and the low detoxification capacity of antioxidant agents.[33–35]

In addition to predictable DILI reactions, there are unpredictable DILI reactions, where this reaction is the most common type of DILI reaction found in most cases. Most of these metabolic or hypersensitivity reactions occur unrelated to the size of the dose given, where these reactions can cause damage to liver cells and tissues or cholestasis.[36,37]

In idiosyncratic DILI, necrosis tends to be patchy and not confined to specific zones. Anti-tuberculosis drugs can be neoantigens or haptens if the drug is immunogenic, or its metabolites can move freely or bind covalently to liver proteins. The immune response that can arise can be in the form of cytotoxic antibodies, T cells, and sometimes eosinophilic hypersensitivity reactions can arise. Interleukins that can play a role in programmed cell death of hepatocytes are TNF-alpha, IFN-gamma, and interleukin (IL)-12, which have opposite effects to monocyte chemotactic proteins-1, IL-13, IL-4, and IL-10.[36,37]

Several genetic variations or variations in drug biotransformation pathways can result from detoxification processes or abnormal synthesis of hepatotoxic metabolites. This reaction can have a very variable latency period and can recover if there is re-exposure that occurs within a few days to a few weeks.[33,36,37]

In the included study, there were several risk factors that were most discussed, i.e., gender, age, BMI, smoking, alcohol consumption, and hepatitis B and C infection. Of these various risk factors, the factor that has the potential to increase the risk of DILI and is found to be significant in included studies is age over 40 years. Nonetheless, there are several studies showing that the relationship between DILI and age is not significant. Therefore, further quantitative studies are needed, which will be discussed in another section.

In addition, there are other risk factors that were found to be significant but were not widely discussed in some of the included studies. These risk factors include people with chronic diseases, consuming more than 3 drugs other than anti-TB drugs, consumption of hepatotoxic drugs, use of injecting drugs, a history of prison, and a blood type other than O. In the study of Cavaco et al, bivariate analysis showed that chronic disease increased the risk of DILI in patients on tuberculosis treatment, but the multivariate analysis showed that this result was not significant.[24]

In addition to these two factors, Cavaco et al also examined risk factors in the form of consumption of hepatotoxic drugs, where these risk factors increased the risk of DILI by 2.3 times.[24] Risk factors such as injecting drug use and a history of imprisonment were examined by Lomtadze et al.[28] In that study, it was also found that these two factors were not significant after multivariate analysis. The study of Tao et al examined the effect of blood group on the incidence of DILI. The study shows that patients with non-O blood group have a higher risk of developing DILI compared to people with blood group O. This could be due to complement-mediated destruction of erythrocytes through the Ii antigen system, especially in the case of patients taking rifampicin.[30]

Various studies have examined the relationship between age and the incidence of DILI with different age cut-offs. In a study conducted by Abbasi et al, Baghaei et al, Cavaco et al, and Teleman et al found a significant relationship between age >40 years and the incidence of DILI and

age above 50 years with OR values ranging from 1.66 to 4.67.[22–24,31] In contrast to the studies already mentioned, studies conducted by Lomtadze et al, Wang et al, and Zhong et al showed that there was no significant relationship between the incidence of DILI and age >40 years and 50 years.[7,28,32]

In this review, a quantitative analysis was performed for patients aged over 40 years and aged 50 years, with the results consistent that old age is associated with an increased risk of DILI in patients with OR=1.60 (95% CI=1.60–2.46) and OR=1.69 (95% CI=1.12–2.53), respectively. The mechanism of the relationship between age and the incidence of DILI is still not known with certainty.

Several studies have stated that this is related to decreased kidney function in older people, which causes a decrease in drug clearance, resulting in an increase in drug concentration in the liver, which causes increased toxicity in that organ.[34] At a younger age, the type of DILI that often appears is the hepatocellular type, while in older people, the type that often appears is the cholestatic type.[38] Research by Cavaco et al revealed that the aging process is associated with decreased organ volume, kidney function, blood flow, and liver function in carrying out metabolic, detoxification, and regeneration processes. This reduction in structure and function can, of course, also affect the pharmacokinetics of the drugs consumed.[24]

Hepatitis B and C are factors other than older age that significantly increase the risk of DILI based on the meta-analysis conducted. All studies examining hepatitis B and C used laboratory indicators of HBsAg and anti-HCV, respectively, except for the study of Wang et al, which used high HBV and HCV viral load as parameters, while the study of Saha et al did not elaborate on the laboratory indicators used to define hepatitis B and C.[8,32]

The results of the studies were continued in the meta-analysis, except for the study of Saha et al because the information from the studies was limited for the synthesis.[8] As a result, the data on the analysis of the two risk factors showed homogeneous data. The odds ratio of hepatitis B as a risk factor for DILI was 3.42 (95% CI=1.72–6.79) and the odds ratio of hepatitis C was 12.87 (95% CI=6.67–24.86), so that hepatitis C was considered a non-genetic factor that plays a major role in the incidence of DILI.[8,25,26,28,32]

As the name implies, hepatitis B and C are inflammation of the liver caused by the hepatitis B and C viruses.[39] The mechanism by which hepatitis B and C increase the risk of DILI is not known with certainty, but it is thought that the presence of an actively replicating hepatitis virus induces a pro-inflammatory environment, thereby affecting the detoxification process in the liver and increasing toxicity due to drugs.[32,40,41] Some studies suggest that a higher baseline viral load is associated with the development of more frequent DILI.[40,42] In addition to hepatitis C, the HCV core protein can affect lipid metabolism and cause hepatic steatosis, which leads to hepatocyte apoptosis and facilitates liver inflammation and fibrosis.[40]

Although some studies show significant results for gender, BMI, active smoking, and alcohol consumption as risk factors for DILI, the results of the meta-analysis in this review show that these factors are not significant in influencing DILI. The odds ratios were 1.10 (95% CI=0.72–1.67; *P*=0.65) for female gender, 0.96 (95% CI=0.52–1.79; *P*=0.9) for BMI less than 18.5 kg/m^2, 0.71 (95% CI=0.34–1.49; *P*=0.36) for active smoking, and 1.44 (95% CI=0.61–3.42; *P*=0.41) for frequent alcohol intake. However, all forest plots for these factors show high heterogeneity, so this has the potential to affect the results of this finding.

Further risk factor analysis may be needed when more homogeneous and more study data are available. In this group, conducting subgroup analysis is also challenging because there are relatively few studies investigating these risk factors. The limitation of this systematic review is that some risk factors cannot be advanced to the meta-analysis stage due to the lack of research discussing these risk factors.

CONCLUSION

This systematic review and meta-analysis includes studies addressing non-genetic risk factors

of DILI in patients with active pulmonary tuberculosis using first-line anti-tuberculosis regimens. As a result, it was found that older age, hepatitis B, and hepatitis C were significant risk factors for increased DILI risk. Patients with these risk factors should receive closer monitoring and early intervention if DILI symptoms appear. Educating patients, such as recognizing the symptoms of DILI and seeking medical attention immediately if they experience these symptoms. With that, unwanted complications in the form of DILI can be prevented, and problems of treatment failure and drug resistance can be avoided in the patients. It was also found that other risk factors, such as gender, BMI, active smoking, and alcohol consumption, were not significant in causing DILI. Still, the studies were generally heterogeneous, so that more homogeneous studies needed to be conducted for further analysis. Other possible factors like chronic disease, hepatotoxic drug use, injection drug use, incarceration history, and non-O blood type warrant further investigation.

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CONFLICT OF INTEREST

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

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