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Original Article

The effect of statins on the risk of anti-tuberculosis drug-induced liver injury among patients with active tuberculosis: A cohort study

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Abstract *Background:* Tuberculosis (TB) remains prevalent worldwide, and anti-TB drugs are associated with drug-induced liver injury (DILI). Statins have pleiotropic effects which may decrease inflammation and achieve immunomodulation. However, few studies have investigated the pleiotropic effects of statins on the risk of DILI. The purpose of this study was to investigate whether statins prevent anti-tuberculosis DILI among active TB patients on standard anti-TB drug therapy.
Methods: We conducted a hospital-based retrospective cohort study using claims data from the Integrated Medical Database of National Taiwan University Hospital (NTUH-iMD). Patients with a positive TB culture were included. The use of statins was defined as a daily equivalent dose >0.5 mg of pitavastatin. Deterioration in liver function was evaluated according to elevated liver enzyme levels. The primary and secondary endpoints were the DILI and the severe DILI. The prognostic value of statins was evaluated by Kaplan—Meier analysis, and Cox proportional hazards models.

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Results: A total of 1312 patients with a diagnosis of TB and receiving anti-TB treatment were included. During the study period, 193 patients had the DILI and 140 patients had the severe DILI. Kaplan—Meier analysis showed a significant difference between the usual statin users and controls in the DILI. In multivariable Cox proportional hazards analysis, statins showed a protective effect against the primary and secondary endpoints. In addition, the protective effect of statins showed a dose—response relationship against the DILI.
Conclusion: Statin treatment had a protective effect against the risk of anti-TB DILI with a positive dose—response relationship.

Introduction

Tuberculosis (TB) remains prevalent worldwide, affecting an estimated 10.6 million people in 2022, and is now the second leading cause of death from a single infectious pathogen after covid-19.[1] The anti-TB standard treatment is a 6-month course,[2] and compliance is crucial for therapeutic success. However, adverse effects of anti-TB treatment often negatively affect compliance and outcomes. Among them, anti-TB drug-induced liver injury (DILI) is one of the most serious, causing substantial mortality, ranging from 3%—22%.[3,4]

The first-line anti-TB agents including isoniazid, rifampicin and pyrazinamide are potentially hepatotoxic and can cause DILI. The reported incidence of anti-TB DILI ranges from 2% to 28%.[2] Although the exact mechanism of anti-TB DILI is unknown, toxic metabolites are thought to play a crucial role.[2,5] Risk factors for anti-TB DILI include age, female sex, slow acetylator status, and pre-existing liver disease.[6] Treatment for DILI mostly focuses on only supportive care.[7] Few studies have investigated the use of antioxidants in preventing anti-TB DILI, and only early detection is recommended in contemporary guidelines.[8—10]

Statins are increasingly being prescribed to prevent cardiovascular disease.[11,12] However, concerns have been raised over the use of statins in TB patients, because idiosyncratic liver injury has been reported in about 1.9%—5.5% of statin users.[13] In contrast, other studies have shown the effectiveness of statins in patients with liver disease due to their pleiotropic properties.[14] A recent review by Eslami et al. concluded that statins may improve serum aminotransferase levels, ultrasound findings, and liver-related morbidity or mortality,[15] and a meta-analysis by Vahedian-Azimi et al. showed a significant reduction in mortality in statin users with chronic viral hepatitis.[16] Although the adjunctive role of statins in TB treatment has been discussed,[17] no studies have investigated the benefit or risk of DILI in TB patients receiving statin treatment. Therefore, we conducted this study to evaluate the effect of statins on anti-TB-related DILI.

Methods

Study design and study population

We conducted this hospital-based retrospective cohort study using claims data from the Integrated Medical Database of National Taiwan University Hospital (NTUH-iMD). This study was approved by the Research Ethics Committee of NTUH and complied with the Declaration of Helsinki (approval number: 201510009RINB). The need for written informed consent was waived due to retrospective study design. Patients with a diagnosis of TB and who underwent anti-TB treatment were retrospectively enrolled, and the protective effect of statins against DILI was evaluated.

Patients diagnosed with TB should meet the all three of the following criteria: (1) at least one positive culture result for *Mycobacterium tuberculosis* from the respiratory specimen, body fluid or soft tissue. (2) at least one hospitalization diagnosis or two outpatient or emergency department diagnosis for TB. (3) Use of anti-TB drugs (Supplementary file A). The exclusion criteria were (1) interval between the diagnosis of TB and last follow-up date in the NTUH-iMD $<$60 days, due to potential treatment received at another hospital and not enough observation duration in the present cohort, (2) underlying malignancy or diagnosis of malignancy during follow-up period, due to competition of morbidity and mortality and (3) patients with human immunodeficiency virus infection, due to elevated risk of infection other than TB and hepatotoxicity associated with antiretroviral therapy.

We used statin equivalent dose to more accurately compare the effect of different statins. We checked cut-off value by the receiver operating characteristic curve with Youden index. A daily equivalent dose $<$0.5 mg of pitavastatin (equivalent to $<$5 mg of atorvastatin) was defined as the control group. A daily equivalent dose $>$0.5 mg of pitavastatin was defined as usual statin use.[18]

Clinical demographics and outcome

Clinical data including age, sex, height, weight, underlying chronic hepatitis B and C, laboratory data including liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), total-bilirubin (T-Bil), serum creatinine, and negative conversion of sputum mycobacterial culture, comorbidities and medications including statins, acetylcysteine, anti-TB drugs and anti-hepatitis B (HBV) agents (Supplementary file A) were extracted from the NTUH-iMD. Comorbidities were defined according to the corresponding ICD-9 codes. The analysis also included the initial culture site of pulmonary or extrapulmonary TB.

We defined the DILI events according to any one of the following criteria: 1a) three times the upper limit of normal

(ULN; 3ULN) of AST/ALT, respectively, if the initial AST/ALT values were <31/41 units per liter (U/L); 2) a 2-fold elevation in AST/ALT if the initial values were ≥ 31/41 U/L; 3) a 2-fold elevation in T-Bil if the initial value was ≥ 1.2 mg/dL, or if the highest value was >3 mg/dL. The severe DILI was defined if reaching criterion 1b, namely five times the ULN (5ULN) of AST/ALT if the initial AST/ALT values were within normal range, or criteria 2 or 3 as above. Data were censored at the first occurrence of an outcome event or at the time of last follow-up. The primary study endpoint was the DILI (fulfilling criteria 1a, criteria 2 or criteria 3). The secondary endpoint was the severe DILI (fulfilling criteria 1b, criteria 2 or criteria 3).[10]

Statistical analysis

Descriptive analysis was performed according to use of statins. The Student's t-test, Wilcoxon rank sum test and Fisher's exact test were used to compare differences between the usual statin users and controls. Kaplan–Meier (KM) curves according to statin use were plotted, and log-rank test was used for comparisons.[19] A Cox proportional hazards model was used to investigate the impact of statins and other clinical or pharmaceutical variables on the DILI and the severe DILI during anti-TB treatment. Statistically significant variables in univariable analysis and clinically relevant variables were entered into the multivariable Cox regression model.[20] Dose response of statins was calculated by event rates with different doses of statins. P for trend was tested.[21]

Sensitivity analysis was done to confirm that changes in one variable did not affect the outcome. We further divided the control group into statin non-users and low-dose users (>0, <0.5 mg of daily pitavastatin). In addition, we changed the outcome definition to criteria 1a or 2, without considering bilirubin level; only 3ULN of AST or ALT, without considering baseline value of AST or ALT or bilirubin level; and Hy's law (3ULN of AST or ALT and 2-fold elevation of T-Bil)[22] (Table S4). Moreover, we excluded patients with hepatitis B and hepatitis C infection to evaluate the effect of statins on those without hepatitis B and C infection. A forest plot was generated to demonstrate the effect of statins with the use of various definitions of outcomes and clinical settings. A two-sided P-value <0.05 was considered to be statistically significant. Statistical analysis was performed with commercial software (SAS version 9.4, SAS Institute Inc., North Carolina, USA).

Results

We initially identified 3168 TB patients from 2008 to 2016, of whom we excluded 405 with a follow-up duration <60 days. We also excluded 1090 patients without positive TB cultures and 361 patients with malignancy (Fig. 1). Finally, we enrolled 1312 patients [497 women (37.9%) and 815 men; mean age: 60.2 ± 19.4 years] who were diagnosed with TB and received anti-TB treatment. Their detailed clinical characteristics are summarized in Table 1. The usual dose statin users were significantly older, more predominantly male, and had higher rates of congestive heart failure, diabetes mellitus and pulmonary TB than the controls. There were no significant differences in sputum culturing conversion rate within 60 days, other underlying disease, chronic hepatitis B or C, or the use of anti-HBV drugs or n-acetylcysteine (NAC) between the two groups. The median times to sputum culture conversion were 58 days (interquartile range (IQR): 64) in the usual statin users compared with 62 days (IQR 44) in the control group ($P = 0.47$).

During the TB treatment, 193 (14.7%) patients developed the DILI and 140 (10.7%) patients developed the severe DILI (Supplementary file B). The numbers of patients who developed the DILI and the severe DILI using different anti-TB regimens were showed in Table S1. The median time-to-events of the DILI and the severe DILI were 43 (IQR: 67) days and 41.5 (IQR: 67.5) days, respectively. A significant difference was found in peak ALT between the usual statin users and controls. The differences between initial and peak AST and ALT were both lower in the usual statin users than in the controls (Table S2).

Survival analysis

KM analysis was used to compare the time to the DILI and the severe DILI between the usual statin users and controls (Fig. 2). Fewer the DILI and the severe DILI events were noted in the usual statin users. The event rate in the usual statin user group was 4% (2/50) compared to 15.1% (191/1262) in the control group for the DILI; and 2% (1/50) in the usual statin user group compared to 11.0% (139/1262) in the control group for the severe DILI. The two KM curves showed significant differences in events between the usual statin user group and the control group, both in the DILI and the severe DILI (criteria 1 or 2 or 3) ($P = 0.020$ and 0.033, respectively).

In univariable analysis (Tables 2 and 3), the active diagnosis of chronic hepatitis B or chronic hepatitis C were the most relevant risk factors for the DILI and the severe DILI, with hazard ratios (HRs) of 1.68 (95% confidence interval (CI): 1.14–2.49, $P = 0.009$) and 2.56 (1.39–4.70, $P = 0.003$) for the DILI, and 1.95 (1.27–3.01, $P = 0.002$) and 3.55 (1.92–6.58, $P < 0.0001$) for the severe DILI. No statistically significant difference was noted in the DILI or the severe DILI between patients with pulmonary TB and those with extrapulmonary TB. The univariable HRs of statin use for the DILI and the severe DILI were 0.22 (0.06–0.90, $P = 0.035$) and 0.16 (0.02–1.12, $P = 0.065$), respectively.

Variables showing significance (p value < 0.10) for the DILI were selected for multivariable analysis. In addition, sex, bronchiectasis, congestive heart failure, diabetes mellitus, end-stage renal disease, and acetylcysteine were selected into multivariable analysis due to their possible relationship with the DILI. In multivariable analysis, chronic hepatitis B and chronic hepatitis C were still the most important risk factors. The usual statin users had significantly lower adjusted HRs for the DILI (0.22 [0.06–0.90], $P = 0.035$) and the severe DILI (0.15 [0.02–1.10], $P = 0.062$). In addition, age had a significantly higher adjusted HR for the severe DILI (1.01 [1.00–1.02], $P = 0.029$), and a borderline higher HR for the DILI (1.01 [1.00–1.02], $P = 0.09$).

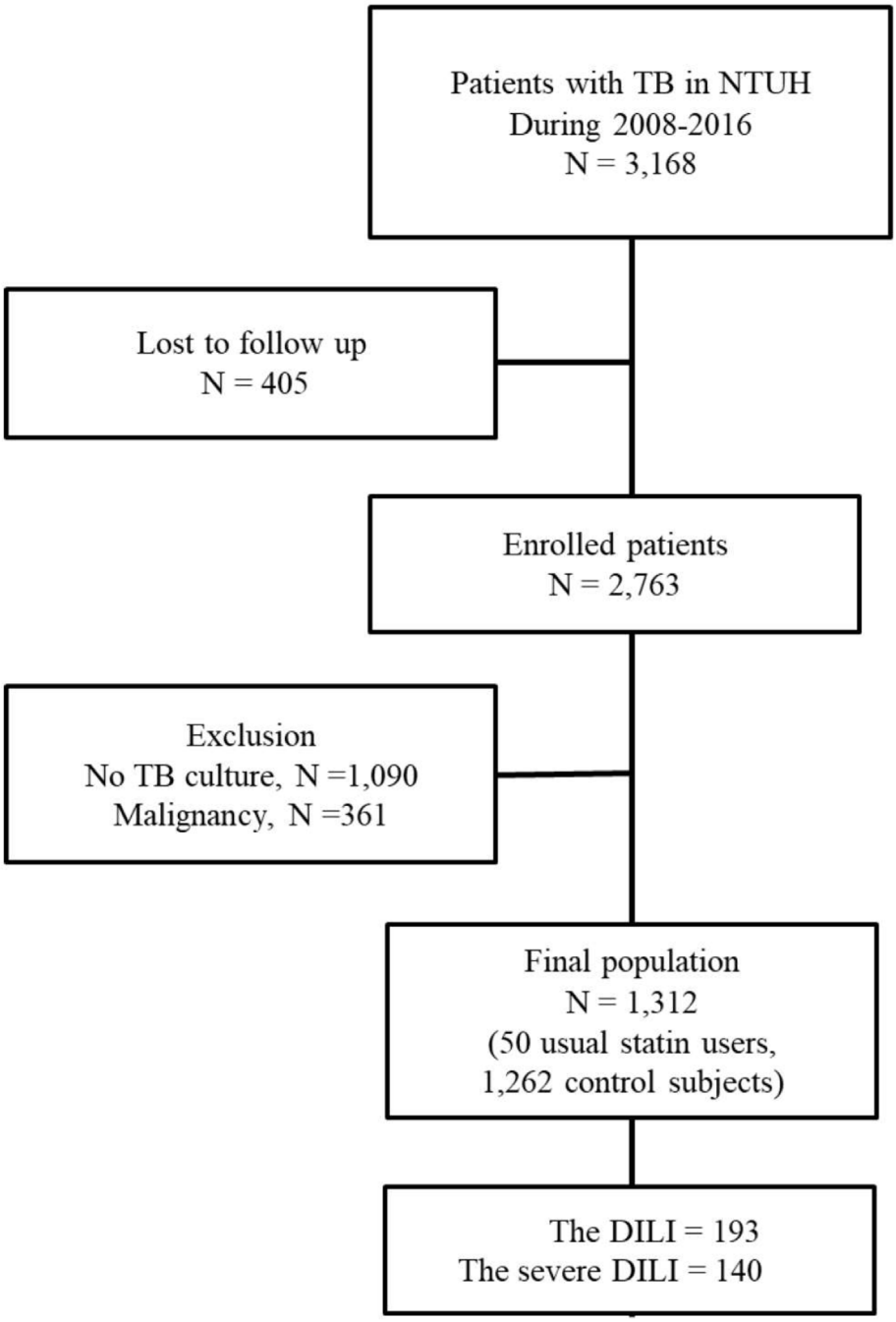

Figure 1. The study flowchart.

Dose—response and sensitivity analysis

With regards to the occurrence of the DILI with different doses of statins, dose—response effects were evaluated according to the daily statin equivalent dose. The patients were divided into five groups according to daily dose equivalent of pitavastatin (0—0.25, 0.25—0.5, 0.5—0.75, 0.75—1 and >1 mg). The DILI rates were 0.12, 0.27, 0.29, 0 and 0, respectively, showing a trend of fewer events of the DILI with increasing daily statin dose (p for trend: 0.036, Figure S1).

With regards to the occurrence of the DILI in the usual dose vs low dose vs non-statin users, although we defined a daily equivalent dose <0.5 mg of pitavastatin as the control group, the protective effect in this group was not clear. KM analysis showed the low-dose statins had similar effect for the DILI with the statin non-users (Fig. 3). The HRs (0.23 [0.05—1.22], $P = 0.09$ for the DILI; and 0.15 [0.02—1.32], $P = 0.09$ for the severe DILI) were borderline significantly lower for the usual statin users compared with the low-dose statin users. The KM curves of the low-dose and non-user groups nearly overlapped ($P = 0.89$ for the DILI and $P = 0.95$ for the severe DILI).

After adjusting the definition of an event to criteria 1a or 2, without considering bilirubin level, the KM analysis

Table 1 Demographic characteristics of tuberculosis patients by if statin use.

N = 1312	Total n	Statin (+) (n = 50)	Control (n = 1262)	*P* value
Age	60.2 ± 19.4	67.4 ± 12.7	59.9 ± 19.6	<0.001
Sex (male)	815 (62.1%)	40 (80.0%)	775 (61.4%)	0.008
Sputum conversion within 60 days	602 (45.9%)	26 (52.0%)	576 (45.6%)	0.38
COPD	106 (8.1%)	5 (10.0%)	101 (8.0%)	0.59
Bronchiectasis	45 (3.4%)	1 (2.0%)	44 (3.5%)	1.00
CHF	53 (4.0%)	7 (14.0%)	46 (3.7%)	0.003
DM	242 (18.5%)	27 (54.0%)	215 (17.0%)	<0.001
ESRD	58 (4.4%)	2 (4.0%)	56 (4.4%)	1.00
Chronic hepatitis B	128 (9.8%)	2 (4.0%)	126 (10.0%)	0.22
Chronic hepatitis C	36 (2.7%)	0 (0.0%)	36 (2.9%)	0.40
NAC	256 (19.5%)	13 (26.0%)	243 (19.3%)	0.24
Anti-HBV drug	27 (2.1%)	1 (2.0%)	26 (2.1%)	1.00
Pulmonary TB	1046 (79.7%)	46 (92%)	1000 (79.2%)	0.003

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end stage renal disease; NAC: n-acetylcysteine.

showed that the usual statin users had significantly fewer events ($P = 0.010$, Figure S2 (A)). For the definition of an event as highest AST/ALT levels achieving 3ULN (not considering initial levels), there was a significant difference between the two KM curves ($P = 0.014$, Figure S2 (B)). After adjusting the definition of an event according to Hy's law,[22] due to the strict criteria, events only occurred in the control group. KM analysis of events showed no significant difference between the two groups ($P = 0.33$, Figure S2 (C)). After excluding patients with hepatitis B and hepatitis C infection, the KM analysis of the DILI showed the usual statin users had significantly fewer events of the DILI ($P = 0.041$, Figure S2 (D)).

The adjusted HRs of statin use with various definitions of events and study populations are shown in Table S3. All adjusted HRs showed at least borderline significance ($p < 0.1$), with the exception of Hy's law. This lack of significance with Hy's law could be due to the strict criteria resulting in a low number of events within our study population. A forest plot of the HRs of different endpoints, populations and statin usage cutoff values are shown in Fig. 4. Although, some HRs were not significant, these results showed the consistency of the protective effect of statins against anti-TB DILI regardless of the definition of DILI, hepatitis B and hepatitis C infection, or dose of statins. Details of results are summarized in Table S4.

Discussion

The present study showed that the statin users had significantly fewer events of the DILI during anti-TB treatment in time-to-event analysis. The use of >0.5 mg of pitavastatin equivalent dose of statins per day had a significant independent protective effect against the DILI. In addition, a positive dose—response effect between the use of statins and the DILI was noted. The other independent risk factors for the DILI during anti-TB treatment were age and chronic hepatitis B and C infection.

In regard to the definitions of DILI, we used non-standard DILI criteria for several reasons. First, DILI defined according to Hy's law is associated with very poor outcomes.[22] In real-world practice, discontinuing anti-TB medications is usually considered before liver function deteriorates to such an extent. Second, the patterns of DILI can include hepatocellular injury or cholestasis, and anti-TB medications can cause either one or both.[23] Third, the current definitions of DILI still lack clear consensus.[7,13,24,25] Therefore, our definition of the DILI is more flexible and encompasses different complex patterns of liver injury before reaching the severity of Hy's law and is in accordance with Taiwan Guidelines for TB Diagnosis & Treatment.[10] Due to concerns about the inconsistent results yielded by the various definitions of DILI, we performed sensitivity analysis regarding different DILI criteria, and the results showed the consistency of the protective effect of statins against anti-TB DILI.

Effect of statins against DILI

Due to conflicting data on the effect of statins on liver disease, a meta-analysis quantified the potential protective effect of statins on some liver-related health outcomes, but focused on patients with chronic viral hepatitis.[16] They found borderline non-significant reductions in AST and ALT in the patients treated with statins. In our study, there were significantly lower elevations of peak AST and ALT in the usual statin users than the control group. We showed that statin users had a significantly lower adjusted HR for the DILI. Dongiovanni et al. also found that use of statins was associated with protection against liver damage in non-alcoholic steatohepatitis.[26] Their study setting was very similar to ours, and even though the number of statin users was small, the protective effect was significant. In addition, a significant dose-dependent relationship was shown in our cohort study, and hepatitis was identified after a diagnosis of TB. Although this did not confirm the causal relationship between statins and liver protection, the time to event sequence was considered in this study. Statins exhibits pleiotropic properties, including antiproliferative, antimetastatic, proapoptotic, antiangiogenic, and immunomodulatory modes of action. Previous studies found that

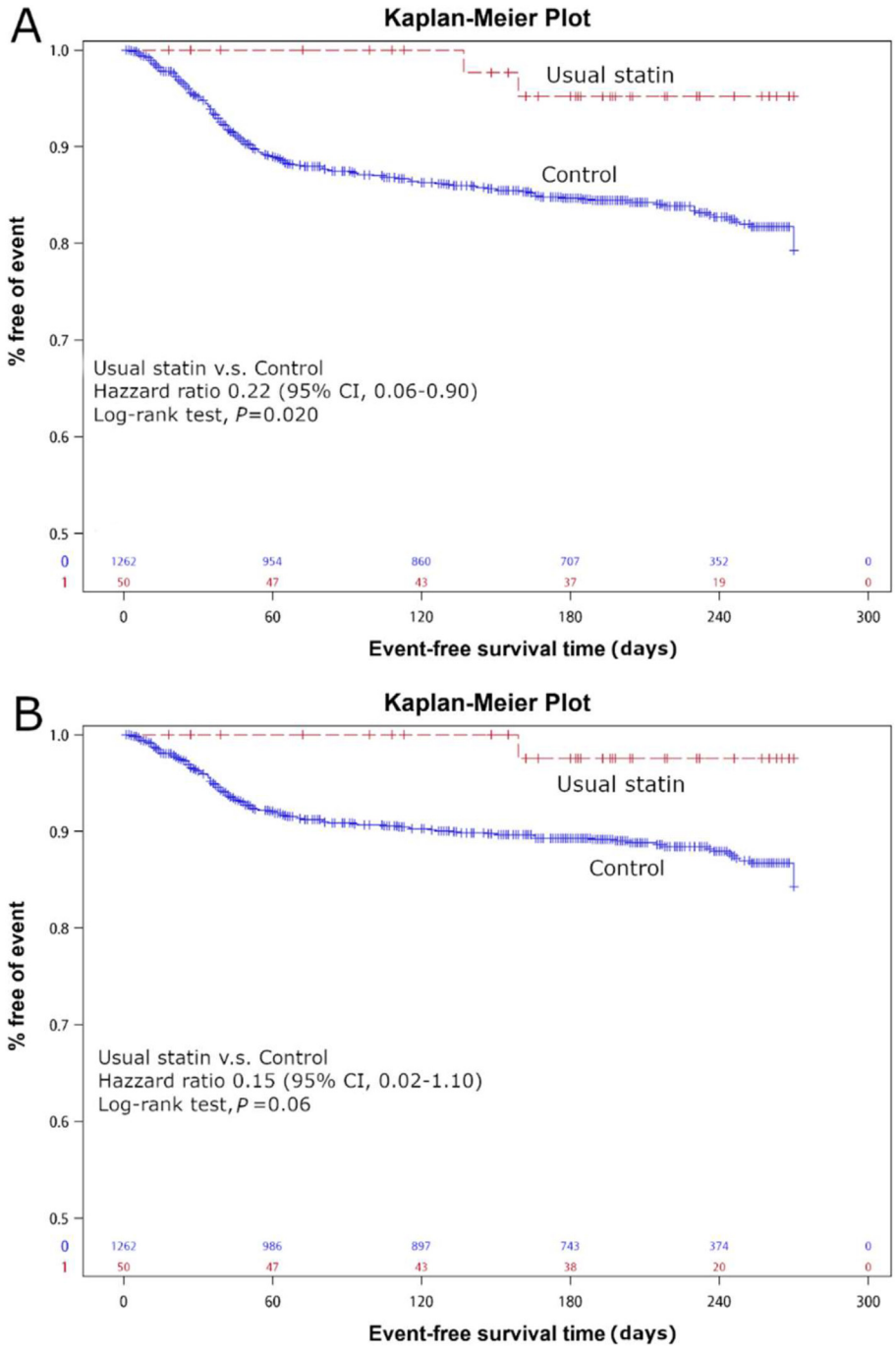

Figure 2. Kaplan—Meier (KM) curves of time to events in TB patients during anti-TB medication use by statin use or not, (A) event defined as the DILI, (B) event defined as the severe DILI.

statins reduce the risk of hepatocellular carcinoma occurrence and chronic liver diseases through these pleiotropic effects.[14,27] The probable explanation for the potential hepatoprotective effect of statins was the ability to inhibit the prenylation of small guanosine triphosphate hydrolases, thereby reducing inflammation.[28] Another probable mechanism was that statins diminished the activation of hepatic stellate cells through the reduction of oxidative stress.[29]

New evidence has emerged regarding the safety and efficacy of statins in the treatment of TB. Cross et al. conducted a randomized, open-label, multicenter study and demonstrated that adjunctive rosuvastatin therapy was safe but did not significantly improve culture conversion rates.[30] In addition, Adewole et al. conducted a phase IIA trial to evaluate the effect of statins in treatment-naïve TB patients, and found that adding atorvastatin led to a significant fall in sputum colony forming units but no difference in early bactericidal activity. Moreover, combining atorvastatin did not result in any serious side effects.[31] In several pre-clinical models, statins plus anti-TB therapy improved outcomes and disease burden more than anti-TB medications alone.[32,33] Gu et al. reported that long-term

Table 2 Univariable and multivariable analyses of risk factors for the DILI in TB patients during anti-TB treatment using a Cox proportional-hazards model.

N = 1312	Univariable			Multivariable		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age	1.007	1–1.02	0.05	1.01	1.00–1.02	0.09
Sex (male)	1.17	0.87–1.57	0.31	0.96	0.71–1.31	0.82
COPD	1.48	0.94–2.32	0.09	1.40	0.86–2.26	0.17
Bronchiectasis	0.95	0.45–2.02	0.90	0.94	0.44–2.01	0.88
CHF	0.90	0.42–1.90	0.77	0.84	0.39–1.83	0.66
DM	1.05	0.73–1.50	0.80	1.05	0.73–1.53	0.79
ESRD	1.31	0.69–2.47	0.41	1.24	0.65–2.37	0.51
Chronic hepatitis B	1.68	1.14–2.49	0.009	1.58	1.03–2.43	0.038
Chronic hepatitis C	2.56	1.39–4.70	0.003	2.14	1.15–3.96	0.016
Statin	0.22	0.06–0.90	0.035	0.22	0.06–0.90	0.035
NAC	1.04	0.72–1.48	0.85	0.95	0.66–1.37	0.80
Anti-HBV drug	1.96	0.97–3.98	0.06	1.40	0.64–3.04	0.40
Pulmonary TB	1.22	0.84–1.76	0.30			

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end stage renal disease; NAC: n-acetylcysteine.

Table 3 Univariable and multivariable analyses of risk factors for the severe DILI in TB patients during anti-TB treatment using a Cox proportional-hazards model.

N = 1312	Univariable			Multivariable		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age	1.01	1.00–1.02	0.027	1.01	1.00–1.02	0.029
Sex (male)	1.38	0.96–1.97	0.08	0.84	0.58–1.23	0.37
COPD	1.11	0.61–2.00	0.74	0.95	0.51–1.77	0.88
Bronchiectasis	0.35	0.09–1.43	0.14	0.35	0.09–1.44	0.15
CHF	1.28	0.60–2.73	0.53	1.27	0.57–2.79	0.56
DM	1.10	0.72–1.66	0.66	0.99	0.65–1.52	0.97
ESRD	1.08	0.48–2.44	0.86	0.98	0.43–2.25	0.96
Chronic hepatitis B	1.95	1.27–3.01	0.002	1.73	1.07–2.79	0.026
Chronic hepatitis C	3.55	1.92–6.58	<0.0001	2.83	1.51–5.30	0.001
Statin	0.16	0.02–1.12	0.065	0.15	0.02–1.10	0.062
NAC	1.00	0.65–1.53	0.99	0.91	0.59–1.40	0.67
Anti-HBV drug	2.37	1.11–5.08	0.026	1.51	0.66–3.47	0.33
Pulmonary TB	0.99	0.66–1.48	0.94			

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end stage renal disease; NAC: n-acetylcysteine.

treatment with statins lowered the mortality rate in patients with chronic liver diseases in a meta-analysis.[34] Another meta-analysis by Ma et al. showed that statin use in patients with virus-related cirrhosis was associated with a significantly reduced risk of virus-related cirrhosis and decompensation.[35] To the best of our knowledge, no prior study has evaluated the effect of statins on anti-TB DILI.

In our study, the cut-off daily equivalent dose of statins was set as 0.5 mg of pitavastatin. The usual daily dose of pitavastatin in adults is 1–2 mg. The rationale for this lower cuff-off point was to ensure that the patients took a sufficient daily dose of statins during the TB treatment period. The cut off value was also checked by the receiver operating characteristic curve with Youden index.

Other significant parameters

We also found that age and chronic hepatitis B and C infection were other independent risk factors for the DILI. These findings are consistent with some previous studies. Lucena et al. reported that older age appeared to be a risk factor for DILI,[36] and Pedraza et al. reported that the incidence rate of DILI in patients >65 years was higher than expected.[37] In a two-year Icelandic study, the age-standardized incidence of DILI increased from 9 per 100,000 people in the group aged 15–29 years to 41 per 100,000 people in the group aged ≥80 years.[38] In a meta-analysis, Wang et al. found that chronic hepatitis B infection increased the risk of anti-TB DILI (odds ratio 2.18), which is similar to our result (HR 1.58).[39] In a retrospective

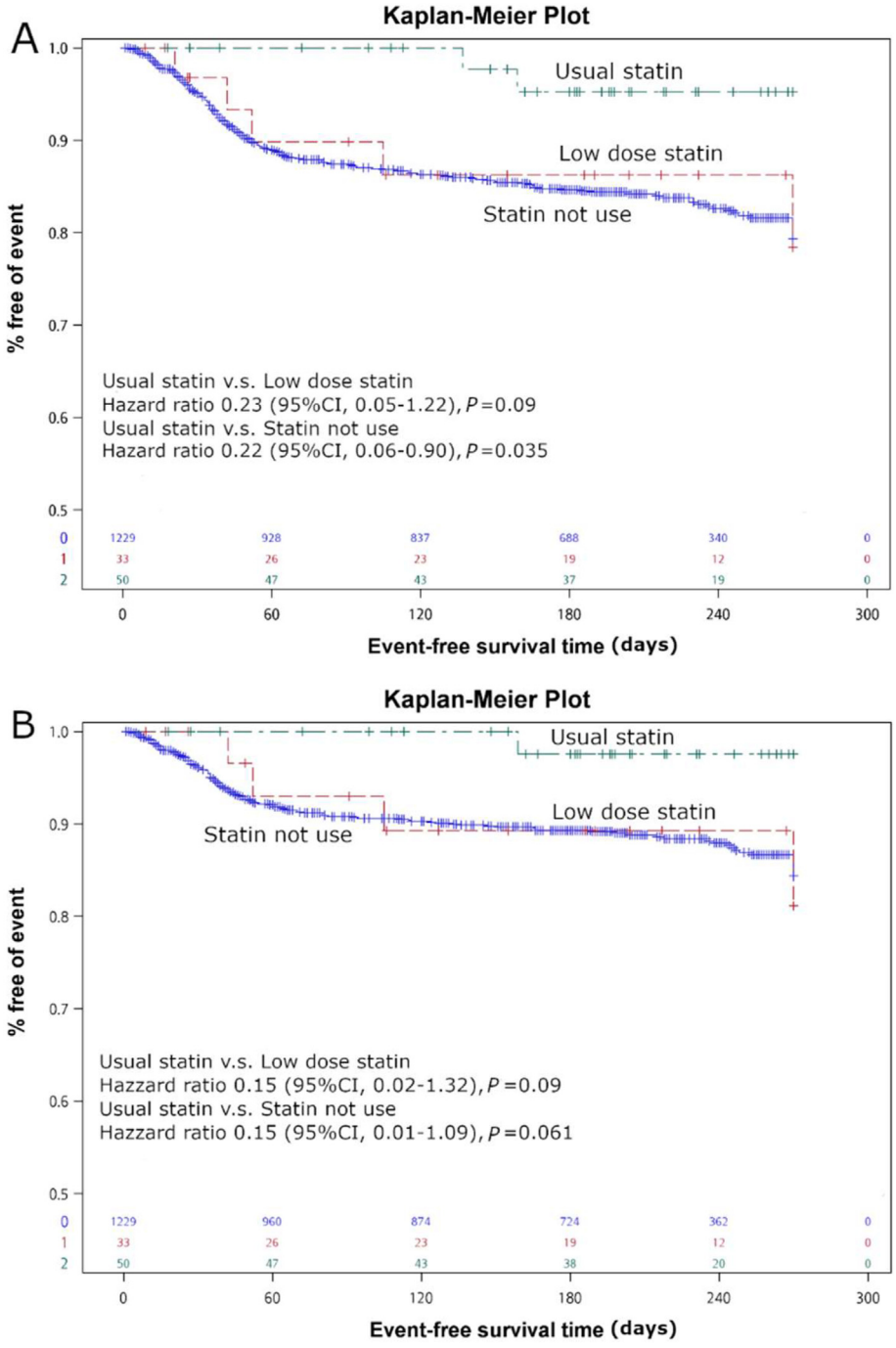

Figure 3. Kaplan—Meier (KM) curves of time to events in TB patients during anti-TB medication use by statin dose response, (A) event defined as the DILI, (B) event defined as the severe DILI.

study, Kim et al. reported that the incidence of anti-TB DILI was significantly higher in patients with hepatitis C virus infection.[40] NAC has been shown to prevent anti-TB DILI in animal studies,[5] and a few studies of NAC in TB patients have shown protective effects against hepatotoxicity.[41] However, a hepatoprotective effect was not shown in our study. A recent randomized controlled trial found that NAC did not shorten the time to DILI improvement, but reduced the length of hospital stay.[42] Further investigations are still needed to clarify the effect of NAC in anti-TB DILI. Prior studies assessing the risk of DILI in pulmonary and extrapulmonary tuberculosis were inconsistent.[43—45] In our study, we found no statistically significant difference in DILI between patients with pulmonary TB and those with extrapulmonary TB.

Limitations

This study has several limitations. First, the number of TB patients who used statins in this cohort was small. The use

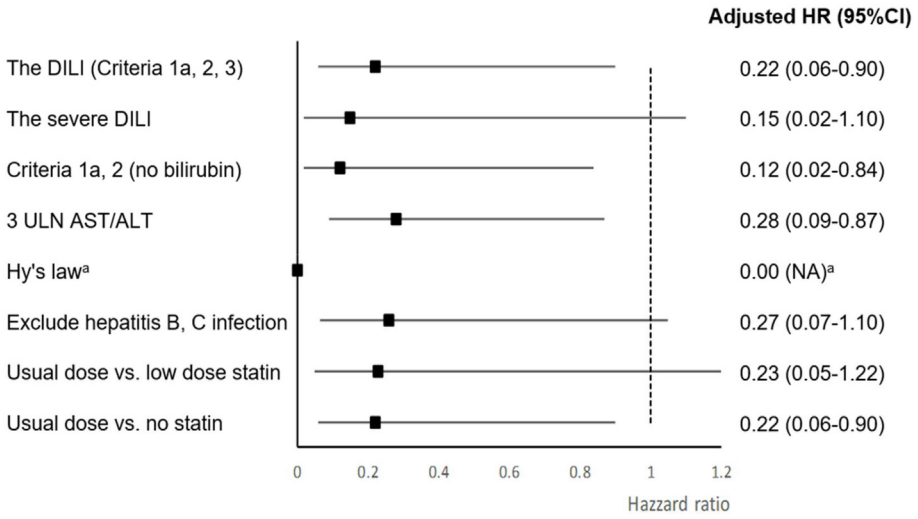

Figure 4. Forest plot of hazard ratios of different definitions of events, excluding hepatitis B and C infection and different doses of statins as sensitivity analysis.
[a] The 95% confidence interval (CI) could not be calculated due to no occurrence of event in the usual statin group.
AST: aspartate aminotransferase; ALT: alanine aminotransferase; DILI: drug-induced liver injury; ULN: upper limit of normal; vs.: versus

of statins seemed to be under-prescribed, but the power was 0.81 after correcting for our sample size and the HR. Second, the number of events was small. However, sensitivity analysis showed the same results, which made our conclusion more robust regarding exposure and events. Due to the retrospective design, we cannot infer any definite causal relationship between the use of statins and liver injury. However, Cox proportional hazards analysis took time-to-event into consideration rather than only comparing the differences in event rates. Third, the lower chronic hepatitis B and C infection rates and higher female ratio in usual statins group may be confounding factors. An imbalance between genders would likely lead the research results towards the null hypothesis. However, our results remained statistically significant. Fourth, the lack of chest computed tomography or other imaging information may turn more difficult to precisely monitor the effect of anti-TB therapy. Fifth, our database lack information regarding the time sequence of anti-TB drug use. Finally, this study was conducted in Taiwan, an area with a high prevalence of hepatitis virus infection. Further studies in other area and ethnicities are needed after validation.

Conclusion

In the present study, the DILI rate ranged from 10.7% to 14.7% according to our definition of the DILI. The independent risk factors included older age, hepatitis B or C virus infection, and low-dose or not receiving statin treatment. The use of >0.5 mg pitavastatin equivalent dose of statins per day was significantly associated with a lower risk of developing the DILI during anti-TB treatment. Further studies are required to validate the protective effects of statins on DILI in patients being treated for TB.

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CRediT authorship contribution statement

Chun-Kai Huang: Conceptualization, Methodology, Project administration, Software, Validation, Data curation, Formal analysis, Investigation, Visualization, Writing — original draft, Writing — review & editing. **Jei-Yie Huang:** Formal analysis, Funding acquisition, Software, Writing — review & editing. **Chin-Hao Chang:** Data curation, Investigation, Methodology, Software. **Shang-Jie Tsai:** Software, Data curation, Investigation, Methodology. **Chin-Chung Shu:** Conceptualization, Data curation, Methodology, Resources, Supervision, Validation, Visualization, Writing — original draft, Writing — review & editing. **Hao-Chien Wang:** Conceptualization, Resources, Supervision. **Kuo-Liong Chien** Conceptualization, Methodology, Supervision.

Declaration of competing interest

All authors declared no conflict of interests.

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CKH and CCS conceived and designed this study. JYH, CHC and SJT assisted the data analysis. CKH and CCS were responsible for writing the manuscript. HCW and KLC took part in manuscript review and revision. All authors contributed to the article and approved the submitted version.

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Appendix A. Supplementary data

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