RESEARCH ARTICLE

Statin use in cirrhotic patients with infectious diseases: A population-based study

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Abstract

Background

Recent studies have shown benefits of statins in patients with liver cirrhosis. However, it is still unknown if statins have a beneficial effect on the mortality of cirrhotic patients with bacterial infections.

Methods

The Taiwan National Health Insurance Database was searched, and 816 cirrhotic patients receiving statins with bacterial infections hospitalized between January 1, 2010 and December 31, 2013 were included in the study. A one-to-four propensity score matching was performed to select a comparison group based on age, sex, and comorbid disorders.

Results

The overall 30-day mortalities in statin and non-statin group were 5.3% and 9.8%, respectively (P = 0.001). After Cox regression modeling adjusting for age, sex, and comorbid disorders, the hazard ratio (HR) of statin use on 30-day mortality was 0.52 (95% confidence interval [CI]: 0.38–0.72, P<0.001). In subgroup analysis, the 30-day mortality effect of statin use was more pronounced in patients with pneumonia (HR = 0.34; 95% CI: 0.19–0.59; P<0.001) and bacteremia (HR = 0.55; 95% CI: 0.35–0.85; P = 0.008). Atorvastatin (HR = 0.59; 95% CI: 0.37–0.93) and rosuvastatin (HR = 0.59; 95% CI: 0.36–0.98) were associated with a decreased 30-day mortality risk compared to patients not taking statins.

Conclusions

Statin use decreases the 30-day mortality of cirrhotic patients with bacteremia and pneumonia.
Introduction

Bacterial infections are the major cause of hospitalization for patients with liver cirrhosis [1]. The mortality of patients with cirrhosis and bacterial infections is increased about four-fold during hospitalization [2]. In addition, bacterial infections can trigger or aggravate cirrhosis-related complications such as hepatic encephalopathy, ascites, or variceal bleeding [1–6], all of which may further increase the mortality of cirrhotic patients.

Statins are usually for the treatment of dyslipidemia or various cardiovascular diseases. However, other possible benefits of statins have been evaluated. Statin use could cause the liver damage occasionally. The potentially liver toxicity of statins have led to increasing concern by physicians. Although recent studies have shown beneficial effect of statins in cirrhotic patients [7–13], the effect of statins on bacterial infections in different population is unclear [14–16]. As such, examining the effect of statins on the mortality of cirrhotic patients with bacterial infections is an important area of research. Thus, the purpose of this study was to use the Taiwan National Health Insurance Database to examine the outcomes of hospitalized cirrhotic patients receiving statins with bacterial infections. Propensity score matching was performed to select a comparison group based on their age, sex, and comorbid disorders, socioeconomic status, or etiology of liver cirrhosis. In the subgroup analysis, we also calculate the hazard ratios of risk factors of statins for 30-day mortalities among cirrhotic patients with different bacterial infections, such as pneumonia, spontaneous bacterial peritonitis, urinary tract infection, or bacteremia. In this study, different statins were also evaluated for the 30-day mortalities in cirrhotic patients, compared to non-statin users.

Materials and methods

Database and ethical statement

The National Health Insurance Administration (NHIA) in Taiwan instituted a National Health Insurance program that covers more than 99% of the Taiwan population. In this program, all the enrolled medical institutions must provide medical records to the NHIA for medical payments. The medical records were established as a database, the Taiwan National Health Insurance Research Database (NHIRD). This database includes International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, medical procedures, hospitalization days, drugs, and other pertinent information of patients in Taiwan who have been hospitalized.

We used a dataset from the NHIRD to perform this study (application and agreement number 104359). This study was approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital (IRB B10403026). Because all of the data in the NHIRD is de-identified, the review board waived the requirement of informed patient consent.

Study sample

The database was searched for patients discharged between January 1, 2010 and December 31, 2013 with a primary or accessory diagnosis of cirrhosis (ICD-9-CM code 571.5 or 571.2). These ICD-9 codes have been used in past studies to identify patients with cirrhosis in Taiwan [17, 18]. This group of patients was then searched for those with bacterial infections.

The bacterial infections included were bacteremia (ICD-9-CM code 038, 020.2, 790.7, or 112.81), cellulitis (ICD-9-CM code 681 or 682), pneumonia (ICD-9-CM code 481–487, without 484), biliary tract infection (BTI) (ICD-9-CM code 576.1, 575.0, 574.00, 574.01, 574.30, 574.31, 574.60, 574.61, 574.80, 574.81), necrotizing fasciitis (NF) (ICD-9-CM code 728.86), empyema (ICD-9-CM code 510), brain abscess (ICD-9-CM code 324), urinary tract infection
(UTI) (ICD-9-CM code 590.1, 595.0, 595.9 or 599.0), septic arthritis (SA) (ICD-9-CM code 711), perianal abscess (ICD-9-CM code 566), liver abscess (ICD-9-CM code 572.0), bacterial meningitis (ICD-9-CM code 320), and spontaneous bacterial peritonitis (SBP) (ICD-9-CM codes 567.2, 567.8, or 567.9. Patients with other diagnostic coding for secondary peritonitis, such as appendicitis, ischemic bowel disease, peritoneal dialysis catheter-related peritonitis, hollow organ or biliary tract perforation, or those having an additional procedure code for abdominal surgery were excluded from the study [18]. If a patient had multiple hospitalizations for an infection during the study period, only the first episode was included in the analysis. Of these patients, those taking statins including atovastatin, rosuvastatin, fluvastatin, simvastatin, pravastatin, lovastatin, and pitavastatin were considered the statin group. One-to-four propensity score matching was used to select a non-statin group according to age, sex, socioeconomic stat (SES), and comorbid disorders including the etiology of liver cirrhosis (alcoholism (ICD-9-CM codes 291, 303, 305.00–305.03, 571.0–571.3), chronic hepatitis B, or chronic hepatitis C), hepatocellular carcinoma (ICD-9-CM code 155.0), diabetes mellitus (DM) (ICD-9-CM code 250, or receiving insulin or oral hypoglycemic agents), renal function impairment (ICD-9-CM code 584, 585, 586, 572.4, or other procedure codes relate to renal failure), liver reserve, and steroid use. The individuals were classified into three groups: low SES, medium SES, and high SES. In this study, low SES was defined as monthly income lower than New Taiwan Dollar (NTD $ 20000) (about US$ 556). Medium SES was defined as monthly income between NTD $20001–40000 (about US$ 556–1111). High SES was defined as monthly income more than NTD $ 40001 (about US$ 1111). In this study, the liver reserve was defined the presence of number of cirrhotic-related complications (variceal bleeding, hepatic encephalopathy, or ascites) during hospitalization.

**Statistical analyses**

The SPSS statistical package version 22.0 for Windows was used to analyze the data. The chi square test was used to compare categorical variables, and Student’s t test was used to compare continuous variables. The proportional hazards Cox regression model was used to evaluate the comorbid factors, with reporting of hazard ratios (HRs) and 95% confidence intervals (CIs). The significance level was set at 0.05.

**Results**

After review of the database and application of the inclusion and exclusion criteria 816 patients with cirrhosis with bacterial infections receiving statins (statin group) were included in the study. After 1:4 propensity score matching, 3,264 cirrhotic patients with infections who were no receiving statins were included as the non-statin group. Table 1 shows the demographic characteristics of the statin and non-statin groups. The overall 30-day mortalities for the statin group and non-statin group were 5.3% and 9.8%, respectively (P < 0.001). After Cox regression modeling adjusting for age, sex, and other comorbid disorders, the HR for 30-day mortality of the statin group was 0.52 (95% CI, 0.38–072, P < 0.001) as compared to the non-statin group. Other statistically significant prognostic factors are summarized in Table 2. Age, etiology of liver cirrhosis, liver reserve, RFI, and steroid and statin usage were associated with significant differences in 30-day overall mortality.

To evaluate the effect of each kind of statin on the mortality of cirrhotic patients with bacterial infections, each of the individual statins were compared to the non-statin group. Because there were only a few patients receiving pravastatin, lovastatin, or pitavastatin, these were not included in the regression analysis. Results of the analysis are shown in Table 3. Oral atorvastatin and rosuvastatin were associated with a decreased 30-day mortality risk. The 30-day
Table 1. Demographic characteristics of the statin and non-statin groups.

|                      | Statin group (n = 816) | Non-statin group (n = 3264) | P value |
|----------------------|------------------------|-----------------------------|---------|
| Male                 | 467 (57.2)             | 1947 (59.7)                 | 0.208   |
| Age, y               | 66.28 ± 14.03          | 65.91 ± 14.78               | 0.526   |
| HCC                  | 53 (6.5)               | 195 (6.0)                   | 0.578   |
| Complication conditions |                        |                             |         |
| No complication      | 737 (90.3)             | 2957 (90.6)                 | 0.810   |
| 1 complication       | 71 (8.7)               | 274 (8.4)                   | 0.778   |
| 2 or 3 complications | 8 (1.0)                | 33 (1.0)                    | 0.937   |
| RFI                  | 116 (14.2)             | 455 (13.9)                  | 0.839   |
| DM                   | 551 (67.5)             | 2177 (66.7)                 | 0.653   |
| Etiology             |                        |                             |         |
| Alcoholism           | 69 (8.5)               | 284 (8.7)                   | 0.824   |
| HBV                  | 113 (13.8)             | 436 (13.4)                  | 0.714   |
| HCV                  | 99 (12.1)              | 369 (11.3)                  | 0.507   |
| Steroid              | 220 (27.0)             | 876 (26.8)                  | 0.944   |
| Socioeconomic status |                        |                             |         |
| Low                  | 289 (35.4)             | 1217 (37.3)                 | 0.322   |
| Medium               | 421 (51.6)             | 1652 (50.6)                 | 0.616   |
| High                 | 106 (13.0)             | 395 (12.1)                  | 0.489   |

Age presented as mean ± standard deviation; other data as number (percentage).

Abbreviations: HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; EVB, esophageal variceal bleeding; RFI, renal function impairment; DM, diabetes mellitus.

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Table 2. Adjusted hazard ratios of risk factor for 30-day mortality of cirrhotic patients with bacterial infections.

| Variable          | Hazard ratio | 95% Confidence Interval | P value |
|-------------------|--------------|-------------------------|---------|
| Male              | 1.18         | 0.94–1.48               | 0.155   |
| Age, y            | 1.01         | 1.00–1.02               | 0.018   |
| HCC               | 2.83         | 2.09–3.83               | <0.001  |
| Complication conditions |         |                         |         |
| No complication   |              |                         | <0.001  |
| 1 complication    | 2.68         | 2.05–3.50               | <0.001  |
| 2 or 3 complications | 3.80       | 2.07–6.98               | <0.001  |
| RFI               | 2.40         | 1.91–3.02               | <0.001  |
| DM                | 1.28         | 1.01–1.63               | 0.041   |
| Etiology of cirrhosis |            |                         |         |
| Alcoholism        | 1.39         | 0.98–1.98               | 0.067   |
| HBV               | 0.32         | 0.19–0.53               | <0.001  |
| HCV               | 0.16         | 0.08–0.35               | <0.001  |
| Steroid           | 2.55         | 2.06–3.15               | <0.001  |
| Socioeconomic status |          |                         |         |
| Low               |              |                         | 0.496   |
| Medium            | 1.07         | 0.86–1.34               | 0.539   |
| High              | 0.87         | 0.61–1.26               | 0.470   |
| Statin            | 0.52         | 0.38–0.72               | <0.001  |

Abbreviations: HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; EVB, esophageal variceal bleeding; RFI, renal function impairment; DM, diabetes mellitus.

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mortality risks of patients taking fluvastatin and simvastatin were not different compared to
the non-statin group. The cumulative survival plots for the individual statins are shown in
Fig 1.

We next stratified all patients based on four major infectious diseases in cirrhotic patients:
SBP, pneumonia, UTI, and bacteremia. There were 275 patients with pneumonia in the statin
group, and 948 in the non-statin group. Cox regression modeling adjusting for age, sex, SES,
and other comorbid disorders found that statins had a beneficial effect on 30-day mortality in
patients with pneumonia (HR = 0.34; 95% CI: 0.19–0.59, P < 0.001). There were 210 patients
with bacteremia in the statin group, and 1,024 in the non-statin group. Cox regression model-
ing showed that statins had a beneficial effect on 30-day mortality of patients with bacteremia
(HR = 0.55; 95% CI: 0.35–0.85; P = 0.008). No benefit of statins on 30-day mortality in patients
with SBP and UTI group was found. Regression analysis results are summarized in Table 4,
and cumulative survival plots for each type of infection are shown in Fig 2. The age of 30-day
mortalities for the statin group and non-statin group were calculated and the results were pro-
vided in Table 5. The stains significantly decrease the 30-day mortality in cirrhotic patients
more than 50 years old.

Table 3. Adjusted hazard ratios of different statins for 30-day mortalities of cirrhotic patients with bacterial
infections, compared to non-statin users.

| Statin     | Case/control | HR (95% CI) | P value |
|------------|--------------|-------------|---------|
| Statin     | 816/3264     | 0.52 (0.38–0.72) | <0.001 |
| Atorvastatin| 332/3264     | 0.59 (0.39–0.93) | 0.024   |
| Rosuvastatin| 286/3264     | 0.59 (0.36–0.98) | 0.040   |
| Fluvastatin| 87/3264      | 0.30 (0.07–1.20) | 0.088   |
| Simvastatin| 63/3264      | 0.19 (0.03–1.38) | 0.101   |

Abbreviations: HR, hazard ratio; CI, confidence interval.

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Fig 1. Kaplan–Meier survival analysis of 30-day mortally of cirrhotic patients with bacterial infections using
different kinds of statins, compared to non-statin users.

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Discussion

Statins are usually for the treatment of dyslipidemia, and are now also used for the prevention or treatment of various cardiovascular diseases. However, other possible benefits of statins have been the topic of current research. Although there is the potential of hepatotoxicity in statin users with chronic liver disease, the toxicity is usually mild and well tolerated. The safety of satins in patients with chronic liver disease has been shown in a prior study [19]. A number of current studies have shown beneficial effects of statins in cirrhotic patients [7–13]. However, the effect of statins in patients with cirrhosis and bacterial infections is unclear [14–16]. Statins have been shown to have anti-inflammatory effects, and are associated with reducing or preventing the risk of liver fibrosis progression in patients with chronic liver disease [20]. Statins

Table 4. Adjusted hazard ratios of risk factor of statins for 30-day mortalities of cirrhotic patients with different bacterial infections.

|                      | Case/control | HR (95% CI)   | P value |
|----------------------|--------------|---------------|---------|
| SBP (n = 123)        | 30/93        | 0.84 (0.29–2.49) | 0.757   |
| Pneumonia (n = 1223) | 275/948      | 0.34 (0.19–0.59) | <0.001  |
| UTI (n = 1262)       | 250/1012     | 0.89 (0.43–1.86) | 0.762   |
| Bacteremia (n = 1234)| 210/1024     | 0.55 (0.35–0.85) | 0.008   |

Abbreviations: SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection; HR, hazard ratio; CI, confidence interval

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Fig 2. Kaplan–Meier survival analysis of 30-day mortality of cirrhotic patients with different bacterial infections.

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have also been shown to decrease the hepatic venous pressure gradient and improve liver perfusion in patients with cirrhosis [21]. A prior study found that patients with cirrhosis taking statins experienced hospitalizations with infections at a rate 0.67 less than that of non-users [22]. However, the effect of statins on mortality of cirrhotic patients with bacterial infections is not clear.

In our study with propensity score matching, we demonstrate that statins were associated with lower risk of mortality in patients with cirrhosis and bacterial infections as compared to patients who were not taking statins. This beneficial effect of statins has been shown in prior studies [11,22]. A prior meta-analysis showed that statin use was associated with a 42% reduction in the risk of developing cirrhosis in Eastern and Western countries [12]. Another meta-analysis showed that pooled HR for the progression of hepatic fibrosis for patients taking statins was 0.49 as compared to those not taking statins [23].

An important point about the current population-based study is that statins were being used to treat dyslipidemia and various cardiovascular diseases in the vast majority of patients. However, as pointed out in a prior study statin use cannot be recommended for use in all cirrhotic patients [11]. On the other hand, clinicians should understand that cirrhosis is not a contraindication to statins in patients with dyslipidemia or other cardiovascular diseases. In this study, the socioeconomic status is not the factor for 30-day mortality. In Taiwan, liver cirrhosis is considered as a catastrophic illness in our health insurance program. Almost the medical payment can be covered by the health insurance program. This is the reason why socioeconomic status is not the factor for short-term mortality in our study.

Our analysis of individual statins showed that atorvastatin and rosuvastatin were associated with a significantly decreases risk of 30-day mortality risk in cirrhotic patients with bacterial infections. However, these results were not found with other statins and this is presumably due to small numbers of patients taking other statins. We also evaluated the effect of statins in patients with different types of bacterial infections, and found that statins decreased the 30-day mortality of patients with pneumonia and bacteremia. Comparing to other bacterial infectious diseases in cirrhotic patients, UTIs are considered a less severe infection. In the current study, the 30-day mortality of patients with UTIs in the statin and non-statin group was only 3.6% and 4.0%, respectively. The finding of no difference between the statin and non-statin group may be due to the overall low mortality rate associated with UTIs. There was also no difference in mortality in patients with SBP, and this may be because there were only 30 patients with cirrhosis and SBP.

While this study demonstrated an important role of statins in cirrhotic patients with bacterial infection, there are several limitations that need to be considered regarding this population-based study. First, data of the Mayo Clinic model for end-stage liver disease (MELD) score and Child-Pugh score were not available. This is an essential disadvantage because no laboratory data such as bilirubin level, albumin level, or prothrombin time were available in the dataset. In this study, the stage of liver cirrhosis was defined the presence of number of

### Table 5. The age of 30-day mortalities for the statin group and non-statin group.

| Age, y (case numbers) | Statin /Non-statin (case numbers) | 30-day mortality (%) | P value |
|-----------------------|----------------------------------|----------------------|---------|
|                       | Statin group | Non-statin group | | |
| ≤ 40 (n = 156)        | 32/124       | 7.3               | 0.393 |
| 40–49 (n = 462)       | 79/383       | 7.3               | 0.122 |
| 50–59 (n = 795)       | 148/647      | 8.4               | 0.018 |
| 60–69 (n = 786)       | 176/610      | 9.2               | 0.024 |
| >70 (n = 1881)        | 381/1500     | 10                | 0.049 |

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cirrhosis-related complications (variceal bleeding, hepatic encephalopathy, or ascites) during hospitalization. The major cirrhosis-related complications were considered in the regression analyses for mortality risk. These clinical factors of liver cirrhosis have been considered important factors for staging liver cirrhosis [24,25]. Third, the reason for receiving statin could not be clarified in this study. People who use statins may be wealthier, so the socioeconomic status was considered in this study, even by propensity score matching or regression analysis. Lastly, the duration of exposure to statins was not known. We could not understand the duration of statin usage before or after hospitalizations from the dataset we applied.

In conclusion, this nationwide population-based study showed that statins can decrease the 30-day mortality of cirrhotic patients with bacteremia or pneumonia. Although we cannot recommend the routine use of statins in cirrhotic patients, statins should not be considered a contraindication in cirrhotic patients, even those with pneumonia or bacteremia.

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**Author Contributions**

- **Conceptualization**: Hsing-Feng Lee.
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- **Visualization**: Hsing-Feng Lee.
- **Writing – original draft**: Tsung-Hsing Hung.
- **Writing – review & editing**: Tsung-Hsing Hung, Hsing-Feng Lee.

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