Effects of Statins on the Hepatic Decompensation, Mortality, Complications and Drug Safety in Liver Cirrhosis: A Systematic Review and Meta-Analysis

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Abstract: Background and Aim: Evidence indicates statins seem to improve outcomes in cirrhotic patients. Systematic review and meta-analysis are performed to evaluate the effect and safety of statins in the setting of cirrhosis. Methods: We searched PubMed, EMBASE, and the Cochrane Library from inception through January 2018 to identify comparative studies evaluating the role of statins in cirrhosis. Pooled risk estimates with 95% confidence intervals were calculated using a random effects model. Results: Eight studies (4 retrospective cohort studies and 4 randomized controlled trials) involving 3,966 cirrhotic patients were included. Statin use was associated with 56% lower risk of progression to decompensated cirrhosis (RR, 0.44; 95% CI, 0.36–0.54) and 47% lower risk of mortality (RR, 0.53; 95% CI, 0.47–0.61). Subgroup analyses showed that these results were generally consistent regardless of study design, etiology of cirrhosis, stage of cirrhosis, follow-up time, method of identifying cirrhosis. For initial variceal bleeding, pooled RR was 0.48 (0.35–0.67). For ascites, pooled RR was 0.66 (0.45–0.99). For portal hypertension, using statins could increase the HVPG response rate, pooled RR was 2.61(1.03–6.62). For hepatocellular carcinoma, pooled RR was 0.47(0.36–0.63). For any adverse event and serious adverse events, using statins was almost equivalent to nonusers, pooled RR was 1.06 (0.50-2.25) and 0.77 (0.31–1.95). Conclusions: Statin use may be associated with reduced risk of hepatic decompensation and mortality in cirrhosis with well tolerated. Additionally, statin use appears to decrease portal hypertension and reduce the risk of initial variceal bleeding, ascites and hepatocellular carcinoma. Further RCTs will be required to confirm our findings.

Keywords: Statin, Liver Cirrhosis, Decompensation, Mortality, Meta-analysis

1. Introduction

Cirrhosis results from any chronic liver disease, which is the fifth leading cause of adult deaths and the eighth in economic cost among the major illnesses [1].According to the differences in prognosis, cirrhosis may be generally categorized as either compensated or decompensated. This classification mainly depends on the presence or absence of clinically evident decompensating events including variceal hemorrhage, ascites, and encephalopathy. Median survival in the compensated stage exceeds 12 years, while it is less than 2 years in patients who develop decompensation [2, 3]. Besides, other complications (spontaneous bacterial peritonitis, heporenal syndrome, portal vein thrombosis, hepatocarcinoma) may increase the risk of mortality and liver transplantation. Portal hypertension, determined by the hepatic venous pressure gradient (HVPG), is the initial and primary consequence of cirrhosis and results in the majority of its complications [4]. Non-selective β blocker (NSBB) is the mainstay of the pharmacological approach to the prophylaxis...
of hepatic decompensation, but its uses may be limited by potentially severe cardiovascular adverse events. Clinical trials assessing new drugs for primary and secondary prophylaxis are necessary [5].

Lipid-lowering agents such as statins (3-hydroxy-3-methylglutaryl-coenzyme) are widely used in reducing the risk of cardiovascular diseases. Interestingly, statins therapy has also been associated with reduced risk of death in a great variety of conditions such as pneumonia, chronic renal failure and cancers [6-10]. Many preclinical studies from rodent models of cirrhosis have showed a potential benefit of statins on liver fibrosis, endothelial dysfunction and portal hypertension in cirrhosis [11, 12]. In addition, several observational studies have also provided favorable evidence for hepatic decompensation and survival [13, 14]. However, statins undergo first-pass hepatic metabolism and may be associated with abnormal elevation in liver enzymes [15]. Because of decreased hepatic clearance, there have been concerns that patients with chronic liver disease may be at higher risk for statin-induced side effects [16]. Noteworthily, several studies have shown that statins are well tolerated in patients with abnormal liver enzymes, chronic liver disease, and liver cirrhosis [17-19].

Based on current evidence, guidelines from different organizations recommended to evaluate the effect of statins on compensated or decompensated cirrhosis [5, 20, 21]. We conducted a systematic review and meta-analysis to comprehensively evaluate the effects of statins on hepatic decompensation, mortality, complications, liver transplantation and adverse drug reaction.

2. Methods

2.1. Literature Search

This systematic review and meta-analysis was performed in accordance with the guidelines of PRISMA (preferred reporting items of systematic reviews and meta-analyses) statement and MOOSE (meta-analysis of observational studies and epidemiology) [22, 23]. We searched PubMed, EMBASE, and the Cochrane Library from inception through 7 January 2018 by combining subject headings and keywords. Search terms included cirrhosis, cirrhotic, statins, Hydroxymethylglutaryl-CoA Reductase Inhibitors, HMG-coa reductase inhibitors, atorvastatin, Lipitor, simvastatin, Zocor, rosuvastatin, Crestor, cerivastatin, Lipobay, lovastatin, Mevacor, fluvastatin, Lescol, pravastatin, Pravachol, pitavastatin, Livalo (see Supplementary Material for PubMed search strategy). The literature search and screening were independently conducted by two systematic reviewers (L.Y. and Z.W.). After duplicate citations were removed, the title and abstract of studies were assessed for the initial screening, and the full text of potentially eligible articles were examined fatherly to determine whether they met inclusion criteria. In addition, bibliographies of included articles and review articles on the topic were manually searched for additional studies. Any disagreement between the reviewers was assessed by a third reviewer (J.W.) in accordance with inclusion criteria.

2.2. Inclusion Criteria

Randomized controlled trials (RCTs) or observational studies would be included if they met the following inclusion criteria:

1. conducted in adults with compensated or decompensated cirrhosis due to any cause.
2. evaluated and clearly defined exposure to statins.
3. reported association between statin exposure and hepatic decompensation (defined as the occurrence of hepatic encephalopathy, variceal hemorrhage and ascites), complications (portal hypertension, spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis, hepatocarcinoma), liver transplantation, mortality and adverse drug reaction. Effect of statins on portal hypertension was measured by hepatic venous pressure gradient (HVPG) response rate ratio of two groups. HVPG response was defined as either HVPG <12 mmHg or at least 20% decrease of HVPG from baseline after treatment.
4. provided a relevant risk estimate such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or related data for their calculations. We preferred to extract effect estimates using propensity score match (PSM) or adjusting for the most confounding factors. Conference abstracts were excluded as there may be differences between published and unpublished data [24]. If the same population was used in multiple publications, we only included data from the most recent all-inclusive studies.

2.3. Outcomes Assessed

Our primary outcome was the association between statin use and hepatic decompensation and mortality in cirrhosis. Secondary outcomes of interest were occurrence of variceal hemorrhage, ascites, hepatic encephalopathy, portal hypertension, hepatocarcinoma, liver transplantation and adverse drug reaction in cirrhosis. If at least two studies reported the same result, we would pool the result together for further analysis.

2.4. Data Extraction

Two reviewers (L.Y. and Z.W.) independently extracted data into a pre-established form. Extracted data included authors, year of publication, location, study design, type of statin, patient demographics, inclusion and exclusion criteria, etiology and stage of cirrhosis, interventions, follow up time, outcomes analyzed, method of outcome identification, risk estimates with 95% confidence interval (CI), and variables used for matching or adjustment. When data extraction was completed, data forms were compared and any disagreement between them was resolved by discussing with a third reviewer (J.W.).

2.5. Quality Assessment

Two reviewers (C.X. and L.C.) independently completed
the quality assessments. Any disagreement between them was resolved by discussing with the third reviewer (N.L.). The Newcastle–Ottawa scale was used for evaluating the quality of observational studies and the Cochrane risk of bias tool was used to evaluate risk of bias for RCTs. The Cochrane risk of bias tool is made up of five main aspects, selection bias is evaluated by methods of randomization and allocation concealment; performance and detection of bias are evaluated by checking for blinding of researchers or patients and outcome assessment; attrition and reporting bias are evaluated by incomplete and selective data reporting; The Newcastle–Ottawa scale assesses quality of observational studies from the three aspects including selection, comparability, and exposure/outcome.

2.6. Statistical Analyses

Using the DerSimonian and Laird random effects model and the inverse variance method, we pooled risk estimates and calculated an overall effect estimate with associated 95% confidence intervals (CI). Risk estimates (RR/HR) were considered equivalent. Heterogeneity among the studies was tested by calculating P value and the I² statistic. When I² >50% or P <0.1, we considered heterogeneity was substantial.

3. Results

3.1. Literature Search

The literature search identified 1,375 studies, of which 1,087 from Embase, 254 from PubMed and 34 from Cochrane. After excluding 201 duplicates, 1,174 titles and abstracts were reviewed. Further, we screened the remaining 100 studies, and excluded 1,074 obviously irrelevant papers. Among them, 92 studies were excluded based on the inclusion criteria. Thus, a total of 8 studies including 4 retrospective cohort studies and 4 RCTs were included in this systematic review and meta-analysis (Figure 1).

![Figure 1. Flowchart of the literature search.](image-url)
regard to follow-up time, except for two RCTs [18, 27] with less than half a year, the others were more than one year. Four cohort studies [13, 14, 25, 26] matched or adjusted covariates such as age, gender, liver function, comorbidities or medications. All four cohort studies were of high quality with low risk in cases selection, comparability and outcome assessment. Two RCTs [27, 28] was of high quality with low risk of selection, detection, performance, attrition, and reporting biases. One RCT [18] with small sample size reported that the sum of withdrawals and losses to follow-up reached 29%, and the reasons of these missing data were imbalanced between the two groups. It was graded as low quality because the risk of attrition bias may be high. One RCT [29] being rated as low quality did not blind researchers or patients and provided safety data, so we thought this study may exist performance and reporting biases. Quality assessment of included studies is summarized in Table 2.

### 3.2. Study Characteristics and Quality Assessment

Characteristics of included studies are listed in Table 1. There were four retrospective cohort studies [13, 14, 25, 26] and four RCTs [18, 27-29] with a total of 3,966 cirrhotic patients (1,811 statin users and 2,155 nonusers). Sample sizes included compensated and decompensated cirrhosis. With regard to follow-up time, except for two RCTs [18, 27] with less than half a year, the others were more than one year. Four cohort studies [13, 14, 25, 26] matched or adjusted covariates such as age, gender, liver function, comorbidities or medications. All four cohort studies were of high quality with low risk in cases selection, comparability and outcome assessment. Two RCTs [27, 28] was of high quality with low risk of selection, detection, performance, attrition, and reporting biases. One RCT [18] with small sample size reported that the sum of withdrawals and losses to follow-up reached 29%, and the reasons of these missing data were imbalanced between the two groups. It was graded as low quality because the risk of attrition bias may be high. One RCT [29] being rated as low quality did not blind researchers or patients and provided safety data, so we thought this study may exist performance and reporting biases. Quality assessment of included studies is summarized in Table 2.

| Author; Year | Location | Design | Type of statin | Groups | N | Age(years) | Sex (%male) | Interventions(for RCTs) |
|--------------|----------|--------|----------------|--------|---|------------|-------------|------------------------|
| Kumar 2014  | USA      | Retrospective cohort | Simvastatin (49.4 %), atorvastatin(29.6 %), rosuvastatin, pravastatin, lovastatin and fluvastatin | Statins | 81 | 59.79±10.91 | 54.3 | NA |
| Mohanty 2016 | USA      | Retrospective cohort (Propensity Score Match) | Simvastatin (85%), lovastatin (10%), rosuvastatin, atorvastatin, pravastatin and fluvastatin | Statins | 685 | Median(IQR) 56 (52, 59) | 98.8 | NA |
| Chang 2017  | Taiwan   | Retrospective cohort (Propensity Score Match) | All types of statins | Nonusers | 675 | 56±11.2 | 72.9 | NA |
| Bang 2017   | Denmark  | Retrospective cohort (Propensity Score Match) | Simvastatin, atorvastatin, rosuvastatin, or combinations. | Statins | 248 | 57±9 | 61 | NA |
| Abraledes 2009 | Spain    | RCT    | Simvastatin | Statins | 28 | 58±10 | 60.7 | Simvastatin 40mg qd placebo |
| Pollo-Flores 2015 | Brazil  | RCT    | Simvastatin | Statins | 14 | Median(IQR) 56.5 (8.7) | 57 | Simvastatin 40mg qd+propranolol placebo+propranolol |
| Abraledes 2016 | Spain    | RCT    | Simvastatin | Statins | 69 | 57.42±11.31 | 65.2 | Simvastatin 40mg qd+EVL+NSBB placebo+EVLP+NSBB atorvastatin 20 mg qd+propranolol propranolol |
| Bishnu 2017 | India    | RCT    | Atorvastatin | Statins | 11 | 44±12.73 | 81.8 | Age, gender and Child–Pugh class, MELD score, diabetes, coronary artery disease, NASH and hepatocellular carcinoma, albumin, beta-blocker use, Age, FIB-4 index score, serum albumin, MELD score, Child–Pugh class |

### Table 1. Characteristics of included studies.

| Author; Year | Inclusion criteria | Etiology of cirrhosis | Stage of cirrhosis | Follow-up time | Outcomes analyzed | Method of outcome identification | Adjusted for         |
|--------------|--------------------|-----------------------|--------------------|----------------|-------------------|-------------------------------|----------------------|
| Kumar 2014   | Patients with biopsy-proven cirrhosis, patients on statin therapy at time of biopsy and for at least 3 months after biopsy confirmation of cirrhosis | HBV, HCV, alcohol, NASH, autoimmune hepatitis, cardiac cirrhosis, others | Compensated and decompensated cirrhosis | 36/30 months | Decompensation of cirrhosis, variceal bleeding, ascites, HE, mortality | Biopsy-proven cirrhosis patients having variceal bleeding, intractable ascites, hepatic encephalopathy, clinical jaundice ICD-9 coding for bleeding varices, ascites, SBP, HE | Age, gender and Child–Pugh class, MELD score, diabetes, coronary artery disease, NASH and hepatocellular carcinoma, albumin, beta-blocker use |
| Mohanty 2016 | HCV positive defined by ICD-9 codes compensated cirrhosis | HCV | Compensated cirrhosis | 2.3/1.7 years | Decompensation of cirrhosis, variceal bleeding, ascites, | Age, gender and Child–Pugh class, MELD score, diabetes, coronary artery disease, NASH and hepatocellular carcinoma, albumin, beta-blocker use | Age, FIB-4 index score, serum albumin, MELD score, Child–Pugh class |
| Author; Year | Inclusion criteria | Etiology of cirrhosis | Stage of cirrhosis | Follow-up time | Outcomes analyzed | Method of outcome identification | Adjusted for |
|-------------|--------------------|-----------------------|--------------------|---------------|-------------------|---------------------------------|-------------|
| Chang 2017  | ICD-9 codes for cirrhosis | HBV, HCV, alcohol     | Compensated cirrhosis | 5.5/5.4 years | Decompensation of cirrhosis, variceal bleeding, HE, HCC, liver transplantation, mortality | ICD-9 coding for ascites, SBP, hepatorenal syndrome, HE, variceal bleeding | Turcotte–Pugh scores |
| Bang 2017   | ICD-10 codes for alcoholic cirrhosis | Alcohol               | Compensated cirrhosis | 5.3/5.2 years | Decompensation of cirrhosis, mortality | ICD-10 codes and SKS (Danish Hospitals Classification System) codes for ascites, paracentesis, oesophageal varices with bleeding, initiation of spironolactone or furosemide, or banding of varices | age, year of cohort entry, sex, socioeconomic status, Charlson index score, use of diuretics or nonselective beta-blockers, smoking, alcohol intoxication, healthy adherer profile, and indication of statins (stroke, ischaemic heart disease, and hypertension) |
| Abraldes 2009 | Age between 18 and 75 years, positive diagnosis of cirrhosis, and severe portal hypertension defined as HVPG of 12 mmHg or greater | Alcohol, HCV, HBV, others | Compensated and decompensated cirrhosis | 30 days | HVPG response rate, safety | HVPG measured by hepatic vein catheterization studies, safety data were evaluated by laboratory tests and directed questionnaire | NA |
| Pollo-Flores 2015 | Age 18–75 years, diagnosis of cirrhosis with portal hypertension detected by an abdominal ultrasound with colour Doppler and an upper digestive endoscopy showing gastroesophageal varices, Both procedures were performed within the previous six months. The lowest HVPG value was 5 mmHg | HCV, HBV, alcohol, autoimmune | Compensated and decompensated cirrhosis | 3 months | HVPG response rate, safety | HVPG measured by hepatic vein catheterization studies, safety data were evaluated by laboratory tests and symptoms. | NA |
| Abraldes 2016 | Age between 18 and 80 years, previous diagnosis of liver cirrhosis, Index variceal bleeding within the previous 5-10 days, plan to start standard treatment for the prevention of variceal rebleeding, absence of pregnancy and commitment to use adequate contraception | Alcohol, HCV, HBV, primary biliary cirrhosis, NASH, others | Decompensated cirrhosis | 371/382 days | Mortality, safety, variceal rebleeding, ascites, SBP | Hospital follow-up evaluation | NA |
| Bishnu 2017 | Age: 18–60 years, cirrhosis (diagnosed clinically, radiologically, or histopathologically), portal hypertension (history of variceal bleed, ascites), | HBV, alcohol, NASH, wilson’s disease, cryptogenic | Compensated and decompensated cirrhosis | 1 year | HVPG response rate, variceal bleeding, HE, SBP, mortality | Outpatient visits or hospital follow-up evaluation | NA |
3.3. Meta-analyses

3.3.1. Hepatic Decompensation

Four cohort studies [13, 14, 25, 26] evaluated the association between statin use and development of hepatic decompensation in compensated cirrhosis. There were 1,689 statin users and 2,018 nonusers. Pooled RR with 95% CI was 0.44 (0.36–0.54), Cochran Q test P = 0.19, I² = 37% (Figure 2). Significant correlations still existed based on subgroup analyses for etiology of cirrhosis, follow-up time and method of identifying cirrhosis (Table 3).

3.3.2. Mortality

Four cohort studies [13, 14, 25, 26] and two RCTs [28, 29] evaluated the effect of statins on mortality. There were 1,769 statin users and 2,108 nonusers. Pooled RR with 95% CI was 0.53 (0.47–0.61), Cochran Q test P = 0.88, I² = 0% (Figure 3). There was no difference in the effect on mortality derived from different study design types ($X^2 = 0.53$ and $P = 0.47$). Pooled RR based on four cohort studies was 0.54 (0.47–0.61), Cochran Q test P = 0.75, I² = 0%, and the RR from the RCT was 0.38 (0.16–0.94). In addition, subgroup analyses also showed significant differences based on etiology of cirrhosis, stage of cirrhosis, follow-up time, method of identifying cirrhosis and high-quality study (Table 3). One RCT [29] being rated as low quality only included 23 patients and found no statistical difference.

![Figure 2. Forest plot to evaluate role of statins in hepatic decompensation in compensated cirrhosis.](image-url)
Figure 3. Forest plot to evaluate role of statins in mortality in cirrhotic patients.

### Table 3. Subgroup analysis of association between statins use and decompensation or mortality for each variable.

| Variable                            | No. of Trials | Pooled RR (95% CI) | I²(%) | P Value* |
|-------------------------------------|---------------|--------------------|------|----------|
| **Subgroup analysis of association between statins use and hepatic decompensation for each variable** |               |                    |      |          |
| Etiology of cirrhosis               |               |                    |      |          |
| Virus-related                       | 2             | 0.49 (0.38–0.63)   | 0    | 0.50     |
| Alcohol-related                     | 2             | 0.50 (0.27–0.92)   | 82   | 0.02     |
| Mixed                               | 1             | 0.58 (0.34–0.98)   | -    | -        |
| Follow-up time                      |               |                    |      |          |
| >5years                             | 2             | 0.38 (0.32–0.46)   | 0    | 0.79     |
| <5years                             | 2             | 0.56 (0.42–0.74)   | 0    | 0.87     |
| Method of identifying cirrhosis     |               |                    |      |          |
| Biopsy or prospective confirmation  | 1             | 0.58 (0.34–0.98)   | -    | -        |
| ICD codes                           | 3             | 0.42 (0.34–0.53)   | 41   | 0.18     |
| **Subgroup analysis of association between statins use and mortality for each variable** |               |                    |      |          |
| Study design                        |               |                    |      |          |
| Cohort study                        | 4             | 0.54 (0.47–0.61)   | 0    | 0.75     |
| RCT                                 | 2             | 0.38 (0.16–0.94)   | 0    | 0.97     |
| Etiology of cirrhosis               |               |                    |      |          |
| Virus-related                       | 2             | 0.58 (0.39–0.85)   | 52   | 0.12     |
| Alcohol-related                     | 2             | 0.59 (0.48–0.73)   | 0    | 0.35     |
| Mixed                               | 3             | 0.50 (0.33–0.75)   | 0    | 0.82     |
| Stage of cirrhosis                  |               |                    |      |          |
| Compensated                         | 3             | 0.54 (0.47–0.62)   | 0    | 0.55     |
| Decompensated                       | 1             | 0.39 (0.15–0.99)   | -    | -        |
| Mixed                               | 2             | 0.53 (0.33–0.84)   | 0    | 0.81     |
| Follow-up time                      |               |                    |      |          |
| >5years                             | 2             | 0.53 (0.43–0.64)   | 12   | 0.29     |
| <5years                             | 4             | 0.54 (0.45–0.65)   | 0    | 0.9      |
| Method of identifying cirrhosis     |               |                    |      |          |
| Biopsy or prospective confirmation  | 3             | 0.54 (0.47–0.62)   | 0    | 0.55     |
| ICD codes                           | 3             | 0.50 (0.33–0.75)   | 0    | 0.82     |
| Study quality                       |               |                    |      |          |
| high quality                        | 5             | 0.53 (0.47–0.61)   | 0    | 0.79     |
| Low/moderate quality                | 1             | 0.36 (0.02–8.04)   | -    | -        |

*P value for heterogeneity between subgroups.

### 3.3.3. Complications

(1) Variceal bleeding

Three cohort studies [14, 25, 26] and two RCTs [28, 29] reported outcomes on the association between statin use and risk of variceal bleeding. 1,521 statin users and 1,612 nonusers were included. The results of the meta-analysis showed that pooled RR with 95% CI was 0.77 (0.42–1.39), Cochran Q test \( P = 0.01 \), \( I^2 = 69\% \) (Figure 4). Noticeably, the direction of effect from one study [26] was contrary to other studies. On sensitivity analysis with exclusion of the study, the adjusted RR was 0.55 (0.41–0.74), Cochran Q test \( P = 0.37 \), \( I^2 = 5\% \). Two
cohort studies[14,25] with 2,720 patients (1,360 statin users and 1,360 nonusers) evaluated the association between statin use and initial variceal bleeding in compensated cirrhosis, sensitivity analysis focusing on the two studies showed a pooled RR of 0.48 (0.35–0.67), Cochran Q test P =0.50, I² =0%.

(2) Ascites
Two cohort studies and one RCT [25, 26, 28] evaluated outcomes on the association between statin use and risk of ascites. There were 835 statin users and 925 nonusers. Pooled RR with 95% CI was 0.66 (0.45–0.99), Cochran Q test P =0.19, I² =39% (Figure 4). Two cohort studies [25, 26] with 1,613 patients (766 statin users and 847 nonusers) reported the association between statin use and risk of the first occurrence of ascites, sensitivity analysis focusing on the two studies revealed a pooled RR of 0.56 (0.40–0.79).

(3) Hepatic encephalopathy
Three studies [14, 26, 29] reported outcomes on the association between statin use and risk of hepatic encephalopathy. 767 statin users and 849 nonusers were included. Pooled RR with 95% CI was 0.61 (0.37–1.02), Cochran Q test P =0.15, I² =48% (Figure 4). Two cohort studies [14, 26] with 1,593 patients (756 statin users and 837 nonusers) evaluated the association between statin use and risk of the first occurrence of hepatic encephalopathy, sensitivity analysis focusing on the two studies revealed a pooled RR of 0.64 (0.33–1.23).

(4) Spontaneous bacterial peritonitis
Three studies [25, 28, 29] reported outcomes on the association between statin use and risk of spontaneous bacterial peritonitis. There were 835 statin users and 925 nonusers. Pooled RR with 95% CI was 0.66 (0.24–1.80), Cochran Q test P =0.43, I² =0% (Figure 4). Sensitivity analysis focusing on the two RCTs showed a pooled RR of 0.21 (0.03–1.71).

(5) Hepatocellular carcinoma
Two cohort studies [14, 25] with 2,720 patients (1,360 statin users and 1,360 nonusers) evaluated the association between statin use and risk of hepatocellular carcinoma in decompensated cirrhosis. Pooled RR with 95% CI was 0.47 (0.36–0.63), Cochran Q test P =0.47, I² =0% (Figure 4).

Figure 4. Forest plot to evaluate role of statins in hepatic complications in cirrhotic patients.
Portal hypertension

Three RCTs [18, 27, 29] with 102 patients evaluated the association between statin use and HVPG response rate. HVPG response rate was 50.0% among 50 statin users and 17.3% among 52 nonusers. Pooled RR with 95% CI was 2.61 (1.03–6.62), Cochran Q test P = 0.17, I² = 44% (Supplementary Figure 1). Using statins may help to reduce portal pressure and increase the HVPG response rate. Of the three RCTs, two RCTs [18, 29] compared statins plus NSBB with NSBB alone, sensitivity analysis focusing on the two RCTs showed a pooled RR of 3.98 (0.31–50.95).

3.3.4. Liver Transplantation

Two cohort studies [14, 25] evaluated the association between statin use and risk of liver transplantation in decompensated cirrhosis. 1,360 statin users and 1,360 nonusers were included. Pooled RR with 95% CI was 0.46 (0.21–1.01), Cochran Q test P = 0.44, I² = 0% (Supplementary Figure 2).

3.3.5. Adverse Drug Reactions

Three RCTs [18, 27, 28] reported the results of adverse drug events. Adverse events reported in the three RCTs are summarized in Table A1. Any adverse event rate was 20.2% among 114 statin users and 18.8% among 128 nonusers. There was no significant difference between the two groups (Cochran Q test P = 0.20, I² = 38%; RR 1.06; 95% CI, 0.50–2.25) (Figure 5). In addition, the three RCTs also reported the results of serious adverse events, and no statistical difference was found (Cochran Q test P = 0.87, I² = 0%; RR 0.77; 95% CI, 0.31–1.95) (Figure 5).

4. Discussion

This is the first meta-analysis (only included cirrhosis) to comprehensively evaluate the role of statins in cirrhosis with regard to hepatic decompensation, mortality, complications of cirrhosis, liver transplantation and adverse drug reactions. In the present meta-analysis, we found that use of statins was associated with a significant 56% reduction in the risk of progression to decompensated cirrhosis and 47% lower risk of mortality. In addition, use of statins could not only help to reduce portal pressure and increase the HVPG response rate, but also reduce the risk of occurrence of initial variceal bleeding, ascites and hepatocellular carcinoma in cirrhosis. It was noteworthy that adverse drug events from statins were comparable to nonusers, and statins using in cirrhosis did not significantly increase the incidence of adverse events.

A meta-analysis by Kamal et al. [30] reported that statins may retard the progression of hepatic fibrosis, reduce the risk of hepatic decompensation or mortality in patients with chronic liver disease. However, the report by Kamal et al did not perform subgroup analysis for people with cirrhosis. Ma et al. [31] conducted a meta-analysis and evaluated the role of statins on risk of cirrhosis in chronic viral hepatitis, but they failed to perform subgroup analysis evaluating the correlation between statins and cirrhotic mortality. Although the meta-analysis by Kim et al. [32] performed a subgroup analysis for cirrhosis in the risk of decompensation and mortality, as the above two meta-analyses, they did not include recently updated two articles [13, 29]. This meta-analysis only included cirrhotic patients and our results were based on various subgroup analyses and more believable. In addition, the three meta-analyses did not evaluate the effect of statins on complications of cirrhosis, liver transplantation and adverse drug reactions.

This meta-analysis provided evidence for a protective effect against hepatic decompensation in cirrhosis regardless of etiology of cirrhosis, follow-up time and method of identifying cirrhosis. Portal hypertension is the initial and main consequence of cirrhosis and is responsible for hepatic decompensation [20]. All three RCTs [18, 27, 29] being
included in the present meta-analysis found statins could significantly decrease the HVPG in patients who received NSBB or not. Because the data types were inconsistent, we could not pooled HVPG value directly. The results of this meta-analysis showed using statins could increase the HVPG response rate. Statistical significance was disappeared when compared statins plus NSBB with NSBB alone, this might be due to the small sample size.

Hepatic decompensation can be divided into three main categories: variceal bleeding, ascites and hepatic encephalopathy. For variceal bleeding, the pooled results of five studies showed use of statins was not significantly associated with lower risk of variceal bleeding and substantial heterogeneity was visible. Sensitivity analysis showed a study by Kumar et al. [26] might be the cause of heterogeneity. We tried to analyze the study from the perspectives of clinical features and methodologies. We found that this study only matched two groups by age, gender and Child–Pugh, but other studies adjusted many more potential factors using either randomization or propensity score match. Furthermore, low proportion of endoscopic proven varices and failure to grade the risk of varices could be confirmed in the table of baseline characteristics. These known or unknown factors may be responsible for higher risk of variceal bleeding in statin users. We conducted a separate sensitivity analysis focusing on patients with compensated cirrhosis, and statin use showed a significant reduction in the risk of initial variceal bleeding. One RCT [28] which included decompensated cirrhosis found that adding simvastatin to standard therapy didn’t significantly reduce the risk of rebleeding compared with standard therapy. Besides, we also found using statins was associated with lower risk of ascites and hepatic encephalopathy. However, statistical difference was not significant in hepatic encephalopathy, which might be attributed to fewer studies.

The present meta-analysis showed that statins had a beneficial effect on overall survival in cirrhosis, and the benefit was still existed in subgroup analysis based on study design, etiology of cirrhosis, stage of cirrhosis, follow-up time, method of identifying cirrhosis and high-quality study. However, we could not determine whether survival benefit come from less rates of hepatic decompensation or reduction in cardiovascular-related deaths. Of the four cohort studies evaluating the effect of statins on mortality, three studies [13, 14, 26] provided a multivariate HR for mortality after adjusting for cardiovascular diseases. A study by Mohanty et al. [25] performed a propensity-matched analysis in which patients with high cardiovascular risk factors were excluded, and merged results suggested that the survival benefit of statins might not be affected by cardiovascular diseases. Hepatic decompensation and hepatocellular carcinoma were established important predictors for death in cirrhosis [3, 33], and as the risk of decompensation and HCC were reduced in this meta-analysis, it seemed more likely that survival benefit was in fact due to a reduction in decompensation and HCC. This analysis also found that statins might reduce the risk of liver transplantation or spontaneous bacterial peritonitis, but there was no statistically significance, which might be limited to fewer studies.

Multiple mechanisms may be involved with effect of statins on decreasing the risk of decompensation or death among cirrhotic patients. Statins may improve the activity of endothelial nitric oxide synthase and increase bioavailability of nitric oxide in the liver, thereby resulting in decreased vascular resistance and intrahepatic vasodilatation [12, 34]. The above effects can not only help to reduce portal hypertension, but also improve liver function by increasing hepatic inflow. On the other hand, Statins also have anti-fibrotic and anti-inflammatory effects on cirrhotic liver. The anti-inflammatory effect may be achieved through a decreased production of inflammatory cytokines and leukocyte migration to the sub-endothelial space [35]. By up-regulating the expression of Kruppel-like factor-2 (KLF-2), statins exert anti-fibrotic effects due to inhibition of hepatic stellate cell activation [11].

The safety of using statins in patients with cirrhosis is an important concern. Many studies have shown that use of statins was safe in in patients with liver disease [19, 36-38]. This meta-analysis showed using statins in cirrhosis did not increase adverse events or even serious adverse events compared with nonusers. Liver and muscle toxicity are two concerns for clinicians. A study by Abrraldes et al. [27] reported a patient (1/30) with 2.37-fold increase in AST level in simvastatin group, and another study by Abrraldes et al. [28] also found a patient (1/70) with a greater than 3-fold increase in liver transaminases. However, Pollo-Flores et al. [18] found no patients who received simvastatin showed an increase in aminotransferases levels, on the contrary, they found that the patients in the simvastatin group had a small improvement in Child–Pugh score. A moderate rise in serum aminotransferase levels has been reported in 1%–3% of cardiovascular patients after using statins [39], the hepatotoxicity of statins in cirrhotic patients does not seem to be higher than that among the cardiovascular patients and should not be a major concern. Observational studies suggested that myalgia could occur in up to 10% of persons prescribed statins, whereas rhabdomyolysis continued to be rare [40]. We summarized adverse events from three RCTs and found the incidence of muscle weakness and myalgias was 4.7% (2/43) in statin users and 6.0% (3/50) in nonusers. A study by Abrraldes et al. [28] included patients with compensated cirrhosis who recovered from variceal bleeding and reported two cases(2/70) of rhabdomyolisis in simvastatin users, the two patients had a deteriorated liver function at baseline(bilirubin over 5 mg/dl). This suggests that patients with severely deteriorated liver function may develop rhabdomyolysis, a close monitoring of muscle enzymes may be essential.

We conducted a comprehensive literature search and comprehensively evaluated the role of statins in cirrhosis with regard to hepatic decompensation, mortality, complications of cirrhosis, liver transplantation and adverse drug reactions. However, this review has some limitations. First, most of the important results come from cohort studies, although these studies were high-quality and adjusted for various confounders, it was not possible to eliminate the potential of residual confounding, such as indications of statin use,
responses to statins. Additionally, most studies failed to account for time between disease diagnosis and exposure ascertainment, which might lead to immortal time bias, thereby overestimating the beneficial effects of statins. Second, due to insufficient data, the effect of individual statins or the duration of statin treatment could not be assessed, which might be important factors affecting the outcomes. Third, ICD codes were used for diagnoses and outcomes identification in several studies, misclassification bias was possible although this bias might be equally distributed between study groups. Fourth, because of the small number of studies, detecting publication bias did not have much practical significance, but the potential bias might overestimate the true effect. Moreover, several secondary outcomes only included two or three studies, these findings need further confirmation.

5. Conclusion

In conclusion, statin use may be associated with reduced risk of hepatic decompensation and mortality in cirrhosis. Additionally, statin use appears to decrease portal hypertension and reduce the risk of initial variceal bleeding, ascites and hepatocellular carcinoma. More importantly, statins are well tolerated in cirrhotic patients, but we should pay attention to the occurrence of rhabdomyolysis, especially in patients with severely deteriorated liver function. Further RCTs with large sample size will be required to confirm our findings.

Author Contributions

Xinxing Tantai contributed the study concept and design, acquisition of data, analysis and interpretation of data and drafted the manuscript. Jinhai Wang and Na Liu contributed the study concept and design, interpretation of data, revision of the manuscript. Longbao Yang and Zhongcao Wei contributed literature search and screening and data extraction. Cailan Xiao and Lirong Chen contributed quality assessment. All authors approved the final draft of the article.
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| Study or Subgroup | Statin users Events | Nonusers Events | Total Events | Total Weight | Risk Ratio M-H Random 95% CI Year |
|-------------------|---------------------|----------------|--------------|--------------|----------------------------------|
| Abraldes (2009)   | 9                   | 28             | 37           | 33.3%        | 2.89 [0.88, 8.50] 2009           |
| Polito-Flores (2015) | 6                 | 11             | 17           | 9.5%         | 15.17 [0.05, 242.32] 2015        |
| Bhalkar (2017)    | 10                  | 11             | 21           | 56.9%        | 1.62 [1.00, 3.30] 2017           |
| Total (95% CI)    | 50                  | 52             | 102          | 100.0%       | 2.61 [1.03, 6.62]          |
| Total events      | 25                  | 9              | 34           |              |                                  |
| Heterogeneity: Tau² = 0.30, Chi² = 3.55, df = 2 (P = 0.17); I² = 44% |
| Test for overall effect: Z = 2.02 (P = 0.04) |

Figure A1. Forest plot to evaluate role of statins in HVPG response rate in cirrhotic patients.

| Study or Subgroup | Rate Ratio log[Rate Ratio] | SE | IV, Random 95% CI Year |
|-------------------|---------------------------|----|-----------------------|
| Mohanty (2016)    | -0.9853                   | 0.4799 | 71.6% | 0.37 [0.15, 0.66] 2016 |
| Chang (2017)      | -0.2553                   | 0.7615 | 28.4% | 0.75 [0.17, 3.34] 2017 |
| Total (95% CI)    |                           |     | 100.0% | 0.46 [0.21, 1.01]         |
| Heterogeneity: Tau² = 0.00, Chi² = 0.60, df = 1 (P = 0.44); I² = 0% |
| Test for overall effect: Z = 1.93 (P = 0.05) |

Figure A2. Forest plot to evaluate role of statins in liver transplantation in cirrhotic patients.

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