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META-ANALYSIS

Statins decrease the risk of hepatocellular carcinoma in metabolic dysfunction-associated steatotic liver disease: A systematic review and meta-analysis

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Abstract

BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease with a significant risk of developing hepatocellular carcinoma (HCC). Recent clinical evidence indicates the potential benefits of statins in cancer chemoprevention and therapeutics. However, it is still unclear if these drugs can lower the specific risk of HCC among patients with MASLD.

AIM
To investigate the impact of statin use on the risk of HCC development in patients with MASLD.

METHODS
A systematic review and meta-analysis of all the studies was performed that measured the effect of statin use on HCC occurrence in patients with MASLD. The difference in HCC risk between statin users and non-users was calculated among MASLD patients. We also evaluated the risk difference between lipophilic versus hydrophilic statins and the effect of cumulative dose on HCC risk reduction.

RESULTS
A total of four studies consisting of 291684 patients were included. MASLD patients on statin therapy had a 60% lower pooled risk of developing HCC compared to the non-statin group [relative risk (RR) = 0.40, 95%CI: 0.31-0.53, I^2 = 16.5%]. Patients taking lipophilic statins had a reduced risk of HCC (RR = 0.42, 95%CI: 0.28-0.64), whereas those on hydrophilic statins had not shown the risk reduction (RR = 0.57, 95%CI: 0.27-1.20). The higher (> 600) cumulative defined daily doses (cDDD) had a 70% reduced risk of HCC (RR = 0.30, 95%CI: 0.21-0.43). There was a 29% (RR = 0.71, 95%CI: 0.55-0.91) and 43% (RR = 0.57, 95%CI: 0.40-0.82) decreased risk in patients receiving 300-599 cDDD and 30-299 cDDD, respectively.

CONCLUSION
Statin use lowers the risk of HCC in patients with MASLD. The higher cDDD and lipophilicity of statins correlate with the HCC risk reduction.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Hepatocellular carcinoma; Statins; Lipophilic statin; Hydrophilic statin; Meta-analysis

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Core Tip: Current clinical evidence regarding the effect of statins on lowering the risk of hepatocellular carcinoma (HCC) among patients with metabolic dysfunction-associated steatotic liver disease (MASLD) is inconclusive. We performed a systematic review and meta-analysis of all the studies that evaluated the impact of statins on HCC occurrence in MASLD patients. The pooled data from four studies involving 291684 patients was included in the final analysis. Our findings show that statin use reduces the risk of HCC among patients with MASLD. The use of higher cumulative defined daily doses and lipophilic statins results in a significant reduction in HCC risk.

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide[1-3]. A recent meta-analysis revealed the global prevalence of MASLD has increased from 25.3% (1990–2006) to 38.2% (2016–2019)[4]. Studies have shown that patients with MASLD have an increased incidence of hepatocellular carcinoma (HCC)[5-9]. A systematic review showed that the HCC incidence in MASLD patients with and without cirrhosis at 10 years was up to 15% and 2.7%, respectively[10]. It is critical to understand that MASLD not only increases HCC risk but also liver cancer-related mortality[11]. A nationwide study from the United States found that HCC patients with alcoholic liver disease and MASLD as causes had significantly higher mortality rates than those with viral etiologies[12]. Furthermore, MASLD-associated HCC (MASLD-HCC) has a lower survival rate compared to hepatitis C virus-related HCC[13-15]. MASLD has also been linked to a lower reception of HCC surveillance, decreasing the detection of cancer in its early stages[16]. A Swedish multigenerational cohort study also revealed that first-degree relatives of MASLD patients had significantly increased hazards of HCC, major adverse hepatic outcomes, and liver-associated mortality[17]. The growing evidence of this troubling association has led to the curation of prevention strategies aimed at reducing HCC occurrence among MASLD patients[18-21]. While several modifiable risk factors are identified for MASLD-HCC, interest has also increased in the potential cancer chemopreventive role of certain widely used drugs[22].

Statins are a common class of drugs used for primary and secondary prevention of cardiovascular diseases[23,24]. These drugs also inhibit the growth of tumor cells through varied pharmacological activities and regulation of the methyl-valerate pathway[25-28]. Consequently, statins are among the most studied chemopreventive agents, potentially reducing the risk of cancers of the breast, prostate, pancreas, and liver[29-33]. Despite initial safety concerns, subsequent

research has proven the safety and efficacy of these medications in patients with liver disease, especially MASLD[34-37]. With regard to their chemopreventive effects against HCC, previous studies have predominantly evaluated patient populations other than MASLD[38-42]. Therefore, the role of statin treatment in MASLD-HCC risk reduction has remained largely underinvestigated. A recent meta-analysis has reported that statin use decreases the HCC incidence among patients with MASLD[43]. However, the data on the clinical benefit of statins stratified by solubility status and doses is still incongruous. To our knowledge, this is the first meta-analysis to assess the variation in HCC risk in patients with MASLD between statin users and non-users. We also aim to calculate the risk difference between hydrophilic and lipophilic statins, as well as the effect of cumulative dose on HCC risk reduction.

MATERIALS AND METHODS

Data search and screening

The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement[44]. We performed a detailed search of electronic medical databases, including MEDLINE/PubMed, Web of Science, Embase, and Scopus, from January 1990 to June 2023. The following keywords were used in different combinations: (1) Hydroxymethylglutaryl-CoA reductase inhibitors OR HMG-CoA reductase inhibitors OR statins OR atorvastatin OR cerivastatin OR fluvastatin OR simvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin; (2) NAFLD OR nonalcoholic fatty liver disease OR NASH OR nonalcoholic steatohepatitis; and (3) HCC OR hepatocellular carcinoma OR liver cancer. Only articles in the English language were included. A manual bibliographic search of the included articles was also performed to find any missing studies. The search strategy in the current study is outlined (Figure 1).

Study selection and data extraction

Three researchers (Tarar ZI, Inayat F, and Gandhi M) independently searched for eligibility and screened abstracts, titles, and full manuscripts without the use of automation tools. Any disagreement was resolved through discussion with the senior author (Ali AH). Three reviewers (Tarar ZI, Inayat F, and Gandhi M) extracted data on an Excel sheet. The data on study design, year of publication, country of study, first authors, patient demographics, type and duration of statin use, study quality, and outcome measures were extracted. A fourth reviewer (Farooq U) reviewed the extracted data, and the final datasheet was drafted after a discussion between all four authors.

Eligibility criteria

The Population, Intervention, Control, and Outcome (PICO) framework was used to formulate the inclusion criteria as described in the Cochrane Collaboration Handbook[45,46]. The PICO characteristics for eligibility were: (1) Population: Patients older than 18 years with a history of MASLD; (2) Intervention: Use of statin therapy; (3) Comparison group: Statin non-users; and (4) Outcome: Risk of HCC development.

We excluded studies in which the underlying etiology of cirrhosis was a chronic liver disease other than MASLD, such as hereditary, alcohol-related, viral, and autoimmune causes.

Outcomes

The primary outcome of interest was the risk stratification for HCC among MASLD patients between statin users and non-users. We performed a subgroup analysis to examine the effect of lipophilic versus hydrophilic statins on HCC risk. We further analyzed the dose-dependent effect of statin on the risk of HCC development.

Statistical analysis

The random-effects model was used to calculate the pooled hazard ratios (HR) along with a 95%CI. Cochrane χ^2 and I^2 were applied to assess the heterogeneity and variance. Forest plots were used to present the results of the meta-analysis. The funnel plot and Egger's test for asymmetry were used to determine the publication bias. We utilized Comprehensive Meta-Analysis software version 3.0 (Biostat Inc., Englewood, NJ, United States) to conduct the analysis.

Quality assessment

We relied on the Methodological Index for Nonrandomized Studies (MINORS) criteria for assessing the quality of the included studies[47]. We scored comparative studies on 12 items of the MINORS criteria, and each item was scored from 0 to 2: (1) 0 if not reported; (2) 1 when reported but inadequate; and (3) 2 when reported and adequate. Therefore, a maximum ideal score of 24 could be obtained for comparative studies and 16 for non-comparative studies.

RESULTS

Literature search and study selection

A total of 1782 citations were found in the initial literature search; 1245 articles were removed as duplicates. We screened the remaining 537 reports and shortlisted 26 articles deemed relevant to our study question. These 26 articles were retrieved, and a comprehensive review was undertaken. Four studies were included in the final analysis[48-51]. The total

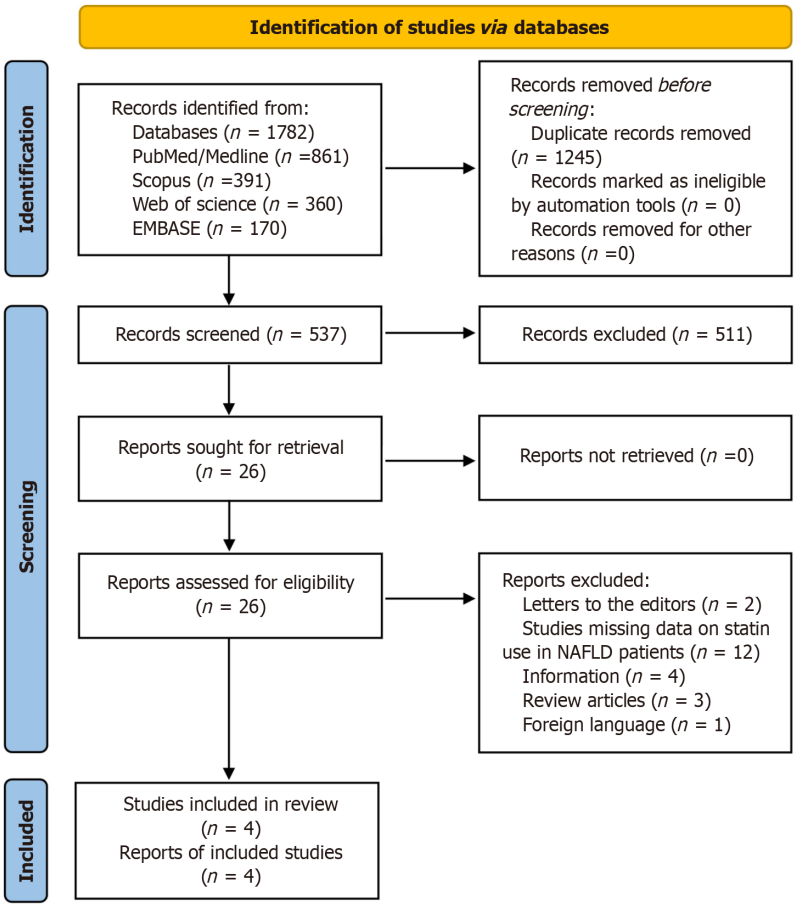

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram of the search strategy.

number of patients was 291684. Of these, 80246 were statin users, and 211438 were not under therapy with statins. The mean age of the study population was 57.0 ± 12.2 years. The gender distribution of included patients showed that 46.9% (136804) were male and 53.1% (154880) were female. Three studies were retrospective cohorts, and one was a case-control (Table 1)[48-51]. The three studies provided the outcome data in HR, whereas one study reported results as odds ratios (OR). We converted the OR results of this study to relative risk (RR) prior to its inclusion in the final analysis.

Outcomes

Patients with MASLD who were on statin therapy had a 60% less pooled risk of developing HCC compared to the non-statin group (RR = 0.40, 95%CI: 0.31-0.53, I^2 = 16.5%) (Figure 2A)[48-51]. We performed a subgroup analysis of lipophilic versus hydrophilic statins reported in two studies. Lipophilic statins were associated with a lower risk of HCC (RR = 0.42, 95%CI: 0.28-0.64). No statistically significant difference was noted among hydrophilic statin users (RR = 0.57, 95%CI: 0.27-1.20) (Figure 2B)[50,51].

Dose-dependent risk reduction

We analyzed the data based on the dose of statins and concluded that > 600 cumulative defined daily doses (cDDD) decrease the risk of HCC by 70% (RR = 0.30, 95%CI: 0.21-0.43). The administration of 300-599 cDDD and 30-299 cDDD of statins decreases the risk by 29% (RR = 0.71; 95%CI: 0.55-0.91) and 43% (RR = 0.57; 95%CI: 0.40-0.82), respectively (Figure 2C)[50,51].

Publication bias and quality assessment

A funnel plot and Egger's test were used to ascertain publication bias. There was no evidence of significant publication bias among the studies included in our final analysis (Figure 3). Using the Cochrane risk of bias tool, all studies were determined to have a low risk of bias.

Risk of bias assessment

Based on MINORS criteria for non-randomized studies, the quality of studies was classified as poor (score ≤ 5), fair (score 6-10), or high quality (score ≥ 11), as described previously[52]. All the studies were rated as high quality. The quality assessment of the studies is summarized in Supplementary Table 1.

Table 1 Baseline characteristics of included studies

Ref.	Study design	Age (years)	Total patients (*n*)	Males/females	Statin users	Non-users	Cirrhosis	No cirrhosis	Follow-up (years)
Zou *et al*[51]	Cohort	52.1 ± 14.7	272430	126804/145626	73384	199046	34257	238173	727390 person-year
Pinyopornpanish *et al*[50]	Cohort	59 ± 10.4	1072	432/640	440	632	950	122	4326 person-year
German *et al*[49]	Case-control	64.3 ± 13.1	102	66/36	40	62	93	9	Not applicable
Lee *et al*[48]	Cohort	52.7 (41.6-64.4)	18080	9502/8578	6382	11698	0	18080	6.32 (3.04-10.10)

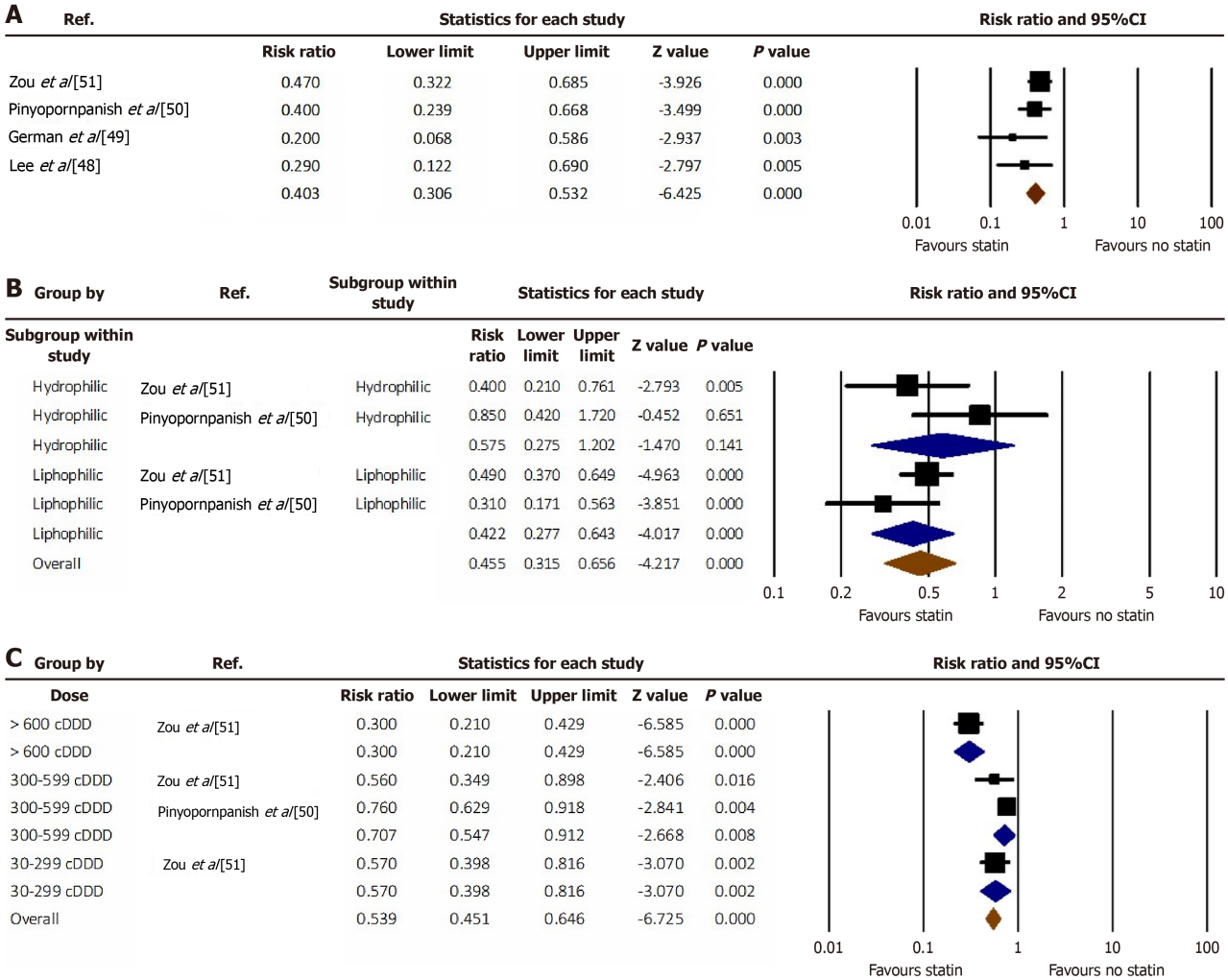

Figure 2 Forest plot. A: The risk difference of hepatocellular carcinoma among MASLD patients between statin users versus non-users; B: The risk difference of hepatocellular carcinoma among users of lipophilic versus hydrophilic statins; C: The dose-dependent risk reduction of hepatocellular carcinoma among statin users. cDDD: Cumulative defined daily doses.

DISCUSSION

This meta-analysis has comprehensively assessed the impact of statin use on HCC risk in patients with MASLD. We included four observational studies. Our findings are summarized as follows: (1) Statin use reduces the risk of HCC in patients with MASLD; (2) Lipophilic statins are more potent in lowering the risk of HCC compared to hydrophilic statins; and (3) The risk reduction with cDDD of statin follows a U-shaped curve.

Liver cancer is a major contributor to the global cancer burden, and its incidence rate has increased in recent decades. According to the Global Cancer Statistics, HCC of the liver parenchyma is the sixth most frequently diagnosed cancer worldwide, with approximately 865269 new cases reported in 2022[53]. With a 5-year survival rate of only 18%, liver

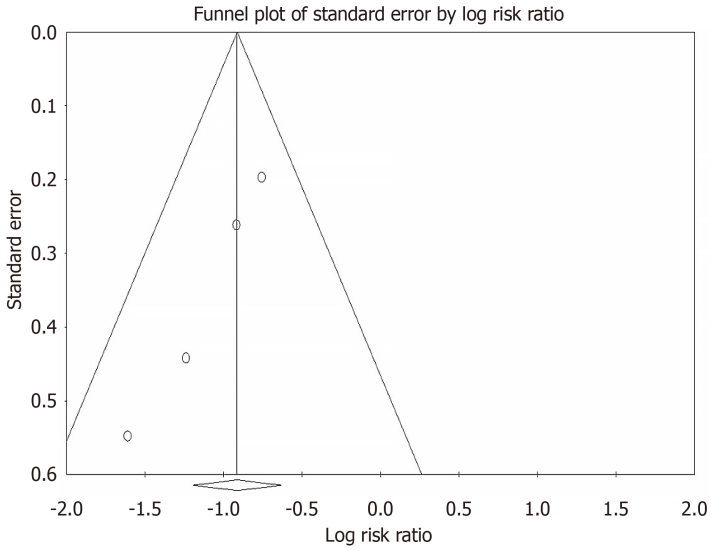

Figure 3 Funnel plot for publication bias.

cancer constitutes the third most common cause of cancer-related mortality worldwide, with over 757948 deaths in 2022 [53,54]. MASLD is the fastest-growing cause of HCC in several countries, including the United States, the United Kingdom, and France[55]. Global MASLD-HCC case numbers are projected to increase significantly due to the rapidly rising MASLD prevalence rates[56,57]. This warrants a concerted effort to reduce the incidence of HCC in MASLD by exploring the impact of lifestyle modification and chemoprevention[58,59]. Current clinical evidence indicates a growing interest in the chemopreventive role of statin therapy[60].

Our results show that statin therapy significantly reduces the risk of HCC in MASLD patients. Statin use has previously been linked to a lower risk of HCC in the general population[61]. These agents have also resulted in a similar clinical benefit in patient populations with diabetes and cirrhosis[62,63]. However, the data regarding chemopreventive effects of statins for MASLD-HCC has remained inconclusive. MASLD is closely associated with metabolic syndrome, which consists of diabetes mellitus, hypertension, dyslipidemia, and obesity. These conditions lead to systemic inflammation and raise the HCC risk, likely by activating oncogenic pathways[64]. Lipid accumulation in MASLD causes a number of cellular derangements, including lipotoxicity, endoplasmic reticulum stress, and the generation of reactive oxygen species leading to DNA damage resulting in oncogenesis[65,66]. The antineoplastic effect of statin occurs through both hydroxymethylglutaryl-CoA reductase-dependent and independent pathways. Clinical evidence shows that lipid-lowering agents other than statins have fewer anticancer effects[67]. Despite their established safety in MASLD, statins remain underused in this patient population[68-70]. Therefore, our meta-analysis highlights the importance of statin usage in patients with MASLD in the context of HCC prevention.

We noted that lipophilic statins were associated with a higher reduction in the risk of HCC among MASLD patients. The use of hydrophilic statins had no significant effect on HCC risk reduction. A Swedish prospective cohort study also reported an association between lipophilic statins and reduced 10-year HCC incidence and death among patients with viral hepatitis-related chronic liver disease[71]. In contrast, two meta-analyses reported that the beneficial effect of statins in lowering the risk of HCC was similar for both hydrophilic and lipophilic statins[72,73]. Pre-clinical studies revealed the effectiveness of lipophilic statins in preventing viral replication, potentiating antiviral therapy, and stimulating antitumor immunity compared to hydrophilic statins[74]. Kato *et al*[75] described reduced surface expressions of anion transporter proteins in hepatocytes during inflammation and carcinogenesis, preventing hydrophilic statins from penetrating the cells. Lipophilic statins readily diffuse across the cell membrane and induce potent antitumor effects through G0/G1 cell cycle arrest and suppression of the Ras/Raf/MEK/ERK pathway[75].

The higher doses of statin (cDDD > 600) correlated with a greater risk reduction of HCC in our analysis. The beneficial effects plummeted with the cDDD of 300-599 but increased again with the lower cDDD. Congruent to our findings, Tsan *et al*[76] found that a high dose duration of the statin product was associated with greater hepatoprotective effects in the hepatitis B cohort. Similarly, a meta-analysis showed increasing cDDD of statins resulted in HCC risk reduction in general as well as at-risk non-MASLD populations, confirming a dose-dependent effect[72]. A retrospective study from the United States based on 9135 chronic hepatitis C patients also substantiated a dose-dependent reduction in incident cirrhosis and HCC[77]. A nationwide, nested case-control study from the Republic of Korea found a dose-dependent risk reduction, with doses greater than 720 cDDD showing greater clinical effectiveness[78]. In a Taiwanese study, statin usage also dose-dependently reduced the incidence of HCC, decompensation, and death in cirrhosis patients[79]. On the other hand, a few studies have revealed that a higher dose of statin has no significant benefit over a lower dose in HCC prevention[80,81]. However, these studies had limitations such as a small sample size and inclusion of patients with several different types of cancer. Therefore, further population-based studies are warranted to determine the dose effect of statins on MASLD-HCC prevention.

Our meta-analysis has several strengths. We examined the use of statins specifically in patients with MASLD, avoiding the heterogeneity of patient populations with other high-risk liver conditions. We conducted a detailed literature search of all the major databases and a manual search of the bibliographies of the included studies. Furthermore, three investigators searched and screened the databases separately, and a fourth reviewer approved the final studies included in the analysis. Our meta-analysis consists of four studies, but the combined total number of patients was sufficiently large. Finally, we used a random-effects model to provide a more conservative pooled estimate. This meta-analysis is unique as it offers pooled evidence regarding HCC risk stratified by solubility status and doses of statins in patients with MASLD. Therefore, it may provide guidance for future clinical trial design that would form the basis for deriving an effective HCC prevention strategy in these patients. A recent literature review found that statins had the strongest clinical evidence currently available among all the chemopreventive agents for MASLD-HCC[82]. While the effect of statins requires further evaluation, an expert panel supports their regular use for HCC prevention in patients with MASLD[83].

Limitations

The small number of included studies constituted a major limitation. Moreover, the non-randomized, observational nature of the studies could result in bias due to flaws in study selection criteria, design, and the presence of confounding factors, including the concurrent use of other drugs, comorbidities, activity status, and genetic predisposition. It could potentially make it difficult to prove that statins alone were responsible for the protective effect against HCC in these patients. However, an updated meta-analysis has recently indicated that only statin use was significant for HCC chemoprevention in subgroup analyses accounting for concurrent drugs such as aspirin and metformin[84]. Large-scale randomized prospective trials are required to further evaluate the effects of statins on HCC prevention in the MASLD population.

CONCLUSION

This systematic review and meta-analysis evaluates the difference in HCC risk between MASLD patients on statin treatment and those who did not receive these medications. Based on the available data, our findings conclude that the use of statins lowers the risk of HCC in patients with MASLD. Lipophilic statins are found to be more potent in reducing the risk of HCC compared to hydrophilic statins. The reduction in risk with cDDD of statin follows a U-shaped curve. Further reliable research with a rigorous study design is required to confirm our results in the future.

FOOTNOTES

Author contributions: Tarar ZI, Farooq U, Inayat F, Basida SD, Ibrahim F, and Gandhi M concepted and designed the study, participated in the acquisition of data, interpretation of results, writing of the original draft, and critical revisions of the important intellectual content of the final manuscript; Nawaz G, Afzal A, Chaudhary AJ, Kamal F, and Ali AH contributed to the analysis and interpretation of results and drafting of the manuscript; Ghouri YA reviewed, revised, and improved the manuscript by suggesting pertinent modifications; all authors critically assessed, edited, and approved the final manuscript and are accountable for all aspects of the work.

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