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Statin use and risk of HCC in patients with MASLD and T2DM: an umbrella review and meta-analysis

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Abstract

Background The effect of statin use on hepatocellular carcinoma (HCC) in patients with metabolic dysfunction–associated steatotic liver disease (MASLD) or type two diabetes mellitus (T2DM) is still unclear. In this umbrella review, we aimed to assess the available evidence for the association of statin use and HCC risk in the target population.

Methods We carried out an umbrella review of previous systematic reviews/meta-analyses indexed in Cochrane, Embase, Scopus, and PubMed databases and published between Jan 1st, 2013, and Oct 22, 2024. We used random effects models to recalculate summary risk estimates for HCC incidence. Using A Measurement Tool to Assess methodological quality of systematic Review (AMSTAR2) tool, two independent reviewers evaluated each article for eligibility and methodologic quality and gathered data from the included studies.

Results Of the initially identified 1,038 systematic reviews/meta-analyses, three non-overlapping studies with medium/high quality were included for qualitative synthesis. Statin use in people with T2DM was reported in six studies belonging to two meta-analyses. The results showed that statins were associated with a decreased risk of HCC (RR: 0.16, 95% CI: [0.03, 0.98]). However, the association was nonsignificant in patients with MASLD comprising five studies from one meta-analysis (RR: 0.89, 95% CI: [0.56, 1.40]).

Conclusion Statin use is associated with a decreased incidence of HCC in people with T2DM. In patients with MASLD, the association is not significant. However, the effects of other variables including the stage of inflammation and/or liver fibrosis on the outcome need to be explored in future studies.

Keywords Statin, Hepatocellular carcinoma, Type 2 diabetes mellitus, Metabolic dysfunction–associated steatotic liver disease

Introduction

Hepatocellular carcinoma (HCC) is the fifth and the sixth most common cancer in men and women, worldwide, respectively [1, 2]. The rate of newly diagnosed HCC is approximately 0.5 million cases annually [3]. Subsequently, this malignancy is the second most frequent cause of cancer death [1].

Hepatitis B (HBV), and hepatitis C (HCV) viral infections, genetic factors, and lifestyle-associated risk factors including smoking, alcohol consumption, and obesity are considered common risk factors for HCC development [4]. While HBV is more prevalent in Asian and African countries; HCV is predominantly presented in Western Europe and North America. On the other hand, in central and eastern Europe, 30 to 40% of HCC cases occur in patients without common risk factors and are probably

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attributable to metabolism-associated diseases such as diabetes mellitus type 2 (T2DM), and metabolic dysfunction–associated steatotic liver disease (MASLD) previously known as nonalcoholic fatty liver disease (NAFLD) [5]. T2DM is one of the critical features of metabolic syndrome, and its association with several cancers, including HCC, has long been established. Furthermore, nonalcoholic fatty liver disease (MASLD), a spectrum of liver diseases including simple steatosis (MASLD) and nonalcoholic steatohepatitis (NASH), with or without fibrosis or cirrhosis, is most likely responsible for a large percentage of HCC cases [6]. In a study on 756 patients in Italy, Piscaglia et al. showed that the survival rate and prognosis of MASLD-HCC are lower and poorer than HCV-HCC without MASLD [7]. The prevalence of MASLD has grown worldwide, rising from 26% in studies conducted in 2005 or before, to 38% in research conducted in 2016 or later [8]. In addition, in patients with non-cirrhotic MASLD, the incidence of HCC ranges from 0.1 to 1.3 cases per 1,000 patient years [9]. Similarly, the prevalence of T2DM is growing and has reached 10.5% globally in 2021 according to the International Diabetes Federation report [10]. As a result, concerns over the increased risk of HCC have been raised by the high prevalence of these two metabolic-related diseases [11].

In addition to traditional curative techniques such as surgery, liver transplantation, and chemotherapy, several lines of research have focused on lowering the chance of developing HCC through several preventive variables [12]. The HBV vaccine and antiviral medications for HBV and HCV are the most well-established protective factors. Furthermore, aspirin and certain T2DM drugs (such as pioglitazone and metformin) were shown to protect against HCC development.

[13–15]. As the most widely used lipid-lowering medications, statins have also been shown to have anti-inflammatory, antiproliferative, proapoptotic, antiangiogenic, immunomodulatory, and anti-infective properties that inhibit the growth and metastasis of cancer [16–20]. A cytostatic effect, which prolongs the survival of cancerous patients, is detected by statins [21]. Nonetheless, there are some concerns about the potential hepatotoxicity of statins. Statins modulate cholesterol synthesis in liver, and there is some evidence that statin use can elevate liver enzymes level [22]. The current guidelines continue to recommend underutilization of statin in patients with MASLD owing to concerns regarding hepatotoxicity [23].

Clinical research on the incidence of cancer linked to statin use has produced contradictory findings. While some recent observational, RCTs, and meta-analysis studies have shown that statins may be associated with a reduced risk of HCC [20, 24–31], others have shown their neutral effect on HCC incidence [32, 33]. Statin treatment improves clinical outcomes and might lower the HCC occurrence in cirrhotic patients [34] and patients with HBV or HCV infections [26, 35–43]. The benefits of statins on chronic hepatitis C are defined by their effects on the related metabolic disorders, progression (reduction of HCV viral load), and improvement of therapeutic response by interferon-α plus ribavirin [44, 45].

To better investigate the protective role of statin against HCC development in patients with T2DM and MASLD, this umbrella review was designed on the existing systematic reviews and meta-analyses that investigated the association between statin use and the risk of HCC.

Subjects and methods

Search strategy

A systematic literature search was carried out using the Cochrane, Embase, Scopus, and PubMed databases between January 1, 2013, and October 22, 2024. Two study investigators (N.H. and S.J.) independently reviewed all relevant articles on the effect of statin use on the risk of HCC. Keywords used in the search included "Statin*", "Atorvastatin", "Lovastatin", "Fluvastatin", "Rosuvastatin", "Pravastatin", "Simvastatin", "Pitavastatin", "Hydroxymethylglutaryl CoA Reductase Inhibitors", "HMG-CoA Reductase Inhibitor (HMG-CoA Reductase Inhibitors)", "(HMG-CoA)", "Hydroxymethylglutaryl CoA Reductase Inhibitors", "HMG-CoA Reductase Inhibitor" AND "Cancer (cancerous growth)", "Carcinoma", "Tumor(tumour)", "Neoplasm(neoplasia, neoplas*)", "Malignancy (malignant growth)", "Lymphoma", "Melanom", "Lymphoma", "Sarcoma", "neurofibroma", "teratoma", "fibroadenoma, oncolog*" AND "Meta-analysis", "Systematic review", "Systematic Literature review", "Systematic scoping review", "Systematic narrative review", "Systematic qualitative review", "Systematic evidence review", "Systematic quantitative review", "Systematic meta review", "Systematic critical review", "Systematic mixed studies", "Systematic mapping review", "Systematic cochrane review", "Systematic search and review", "Systematic integrative review".

Our target population for measuring the effect of statins on the risk of HCC was patients with two metabolic diseases namely; T2DM and MASLD. Studies on patients with HBV or HCV were excluded from this umbrella review.

Two authors (N.H, S.J) independently reviewed the titles and abstracts of studies found in the search to exclude studies that did not address the research question of interest.

The remainder of the full text of the article, including references, was examined to determine whether they contained relevant information. In case of insufficient

data, an attempt was made to contact the authors of the respective studies to obtain additional information.

AMSTAR2 quality assessment

Critical appraisal of the systematic reviews was performed by two reviewers) N.H., S.J.(using AMSTAR2 [46] (A Measurement Tool to Assess Systematic Reviews) tool to independently assess the methodological quality of each systematic review included in the sample. Each of the sixteen questions in the AMSTAR2 tool was answered "yes", "no", or "partial yes", and discrepancies between reviewers for individual AMSTAR2 items were resolved via consensus or third-party adjudication.

Overlapping reviews

To avoid bias in the interpretation of results, the overlaps among included reviews in this umbrella review were assessed. First, systematic reviews and meta-analyses with both the same exposure and the same clinical conditions (Diabetes and/or MASLD) were grouped. Then, the following criteria were also considered: (1) for the systematic reviews/meta-analyses from the same authors, the last update was chosen; (2) the degree of overlap between overlapping reviews was evaluated. For this second step, a graphical citation matrix was constructed between the overlapping systematic reviews/meta-analyses (columns), and the included primary studies (rows). The corrected covered area (CCA) was estimated as a percentage:

$$CCA = \frac{N - r}{r \times c - r} \times 100$$

In the CCA formula '*N*'denotes total number of primary studies from all reviews, '*r*' shows the number of unique primary publication, and '*c*'represents the number of systematic reviews included in the study.

The overlapping is rated as: very high (CCA > 15%), high (CCA 11–15%), moderate (CCA 6–10%), and slight (CCA 0–5%) [47]. Both reviews were kept if the degree of overlap was slight or moderate. If the degree of overlap was high or very high, the systematic review/meta-analysis with the highest quality according to the AMSTAR2 was chosen. In the case of the same quality, the most recent one was included.

Data extraction

We extracted the following data from the included systematic reviews/meta-analyses: first author names', year of publication, number of studies included, gender, study type(case–control, cohort, randomized clinical trials, and …), type of statin, statin dosage, period of statin use, other treatment beside statin, whether the main goal of statin use was cancer or coronary microvascular disease(CMD), databases used, number of patients included, summary risk estimates(relative risk(RR), hazard ratio(HR), and odds ratio(OR) with their corresponding 95% interval, statistical heterogeneity(I2) and corresponding p-value, and quality assessment using JADAD or Newcastle–Ottawa (NOS) scales.

Statistical analysis

We re-calculated summary risk estimates (represented as RR) for HCC incidence in statin users vs. non-users with T2DM or MASLD. For statistical analysis, we combined the individual studies from the included meta-analyses and screened individual studies.

We used a random effect model for meta-analysis. By using the Metafor package in R 4.4.1 we calculated pooled risk ratio (RR) values and 95% CI for studies focused on patients with T2DM and MASLD as a pooled group and also exclusively for T2DM and MASLD. RR of more than 1 indicates that statin use would increase the risk of HCC in patients with diabetes mellitus and MASLD, and RR of less than 1 indicates that statin use can reduce the risk of HCC in these patients. I2 statistic and Cochran's Q statistic were applied to detect possible heterogeneity between studies. I2 reflects the proportion of the total variation across studies. An I2 value > 50% or P < 0.01 for the Q statistic was considered highly heterogenous.

Results

Literature selection

The specific literature screening process is shown in Fig. 1. In brief, 1038 studies were initially identified. After removing duplicates, 983 studies were obtained which were screened for unrelated studies, other type of cancers, adverse effects of statins, no abstract available, experiment design, not systematic review, full text unavailable, and books. Twenty-six studies on HCC were obtained from the screening step (Table 1).

Quality assessment of studies

Quality assessment of the obtained 26 studies results in 13 studies as moderate or high quality from which 4 studies published between 2020 and 2023 consisting of HCC patients with T2DM and/or MASLD, were finally selected (Table 1). Two studies were scored as moderate quality (Islam, et al., 2020, and Wang, et al., 2023), and two were scored as high quality (Zhang, et al., 2023).

Overlapping evaluation

Islam M, et al. 2020 and Li X, et al. 2020 had a high degree of overlap according to the CCA measure (22%). Since both of these studies had moderate quality and both were published in the same year, we selected Islam M et al. which included a larger number of studies (6 vs.

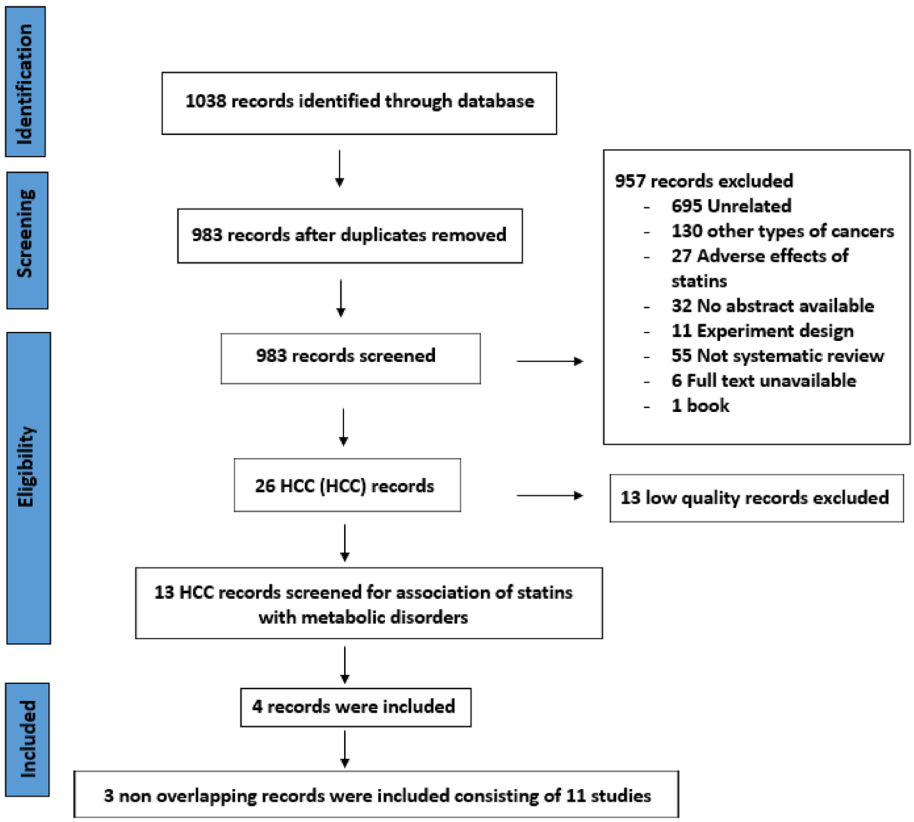

Fig. 1 Prisma flow diagram for study selection

5) and a larger number of patients (86,827 vs. 11,260) and removed Li X,et al.

Characteristics of included systematic reviews and meta-analyses

Table 2 summarizes the basic characteristics of the included reviews. All three included papers were meta-analyses. Except for the Zhang et al., 2023 study, which primarily examined the function of statins in lowering the risk of HCC incidence in individuals with MASLD, the other two studies only included a subset of under-studied patients with T2DM. The included patients in the three studies ranged from 86,827 to 684,363.

Statins use and risk of HCC in patients with T2DM and MASLD

In total, 11 individual studies from 3 systematic reviews were selected for statistical analysis. Six out of eleven studies focused on the association of T2DM with HCC and five studies explored this link in patients with MASLD.

The meta-analysis of the merged results of T2DM and MASLD showed that statin users are less likely to develop liver cancer than non-users (RR: 0.33, 95% CI:[0.11, 0.98], I^2: 99.59%, $P < 0.0001$). The results of statin users with T2DM showed that statin use in DM patients (RR: 0.16, 95% CI:[0.03, 0.98], I2: 99.52%, $P < 0.0001$) plays a preventive role in HCC.

However, studies on statin use in MASLD showed an insignificant effect of statin in HCC prevention(RR: 0.89, 95% CI: [0.56, 1.4], I2: 92.45%, $P < 0.0001$). From five studies on statin use in HCC prevention in patients with MASLD, two studies (Lee and Pinyopornpanish-2) reported a negative effect of statin on HCC risk in patients with MASLD (Lee, ALT(Alanine aminotransferase) elevation, RR: 2.30, 95% CI:[1.02, 5.16], Lee, no ALT elevation, RR: 1.56, 95% CI:[0.58, 4.21], Pinyopornpanish-2, non-cirrhotic, RR: 1.54, 95% CI:[1.13, 2.09]), and cirrhotic RR: 0.85, 95% CI:[0.75, 0.96]) (Fig. 2.c). However, three studies showed the beneficial effect of statin use on HCC in patients with MASLD (Pinyopornpanish-1, RR: 0.49, 95% CI: [0.3, 0.79], German, RR: 0.35, 95% CI: [0.16, 0.78], Zou, RR: 0.67, 95% CI: [0.55, 0.81]).

Table 1 Critical appraisal of the selected systematic reviews/meta-analysis by AMSTAR2.Bolds are the non-overlapping selected studies

	Component of PICO	Apriori Design	selection of the study designs	literature search	Duplicate selection	Data extraction in duplicates	Justified exclusion studies	Adequate details for included studies	Risk of bias (RoB)	Funding reports	Appropriate methods	Impact of RoB on individual studies	Impact of RoB on individual studies where interpreting and discussing the results	Heterogeneity	Publication bias	Conflict of interest	AMSTAR2 Results
Zheng et al. (2017) [44]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Partial Yes	No	No	No	No	Yes	Yes	Yes	Critically low quality
Islam M, et al. (2020) [48]	**Yes**	**Partial Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Moderate quality**
Khajeh E, et al. (2022) [49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Critically low quality
Khazzale S, et al. (2022) [50]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low quality
Li X, et al. (2020) [51]	Yes	Partial Yes	Yes	Yes	N/A	Yes	Yes	Partial Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate quality
Li et al. (2021) [52]	Partial Yes	Yes	Yes	N/A	Yes	Yes	Partial Yes	Partial Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Moderate quality
Memel Z, et al. (2021) [13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	N/A	N/A	Yes	Yes	Yes	Low quality
Pradelli D, et al. (2013) [53]	Yes	No	Yes	No	Yes	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Critically low quality
Shi M, et al. (2014) [28]	Yes	Partial Yes	Yes	Yes	N/A	Yes	Yes	Partial Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate quality
Singh p.p., et al. (2013) [24]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low quality
Wang J et al. (2021) [54]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	N/A	No	No	No	No	No	Yes	Yes	Yes	Critically low quality
Wang et al. (2022) [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Low quality
Wong et al. (2021) [55]	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High Quality
Yi et al. (2017) [56]	Yes	Partial Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Moderate quality

Table 1 (continued)

	Component of PICO	Apriori Design	selection of the study designs	literature search	Duplicate selection	Data extraction in duplicates	Justified exclusion studies	Adequate details for included studies	Risk of bias (RoB)	Funding reports	Appropriate methods	Impact of RoB on individual studies	Impact of RoB on individual studies where interpreting and discussing the results	Heterogeneity	Publication bias	Conflict of interest	AMSTAR2 Results
Zhang et al. (2023) [57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Low quality
Zhong G, et al. (2016) [58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	N/A	Yes	Yes	Yes	Yes	Critically low quality
Zhou et al. (2016) [59]	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Partial Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate quality
Chang y, et al. (2020) [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High Quality
Fasiarusso A.et al. (2020) [30]	Yes	No	Yes	Yes	N/A	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low quality
Zeng R, et al. (2023) [15]	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate quality
Vahedian-Azimi A, et al. (2021) [61]	Yes	Yes	Yes	Yes	N/A	Yes	N/A	Yes	Yes	No	No	N/A	N/A	Yes	Yes	Yes	Critically low quality
Zhang J, et al. (2023) [57]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Partial Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**High quality**
Li Z, et al. (2022) [62]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate quality
Gu Y, et al. (2019) [34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Critically low quality
Wang S, et al. (2023) [63]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Partial Yes**	**Partial Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Moderate quality**
Zhang X, et al. (2023) [64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate quality

Table 2 Characteristics of the systematic reviews/meta-analysis included in the umbrella review

Study	Included studies	Years Searched	Study type(s)	Population	Chronic Systemic Disease	Conclusions
Islam M [48]	Goh MJ [41] Kim G [40] Tran KT [65] Tsan YT [35] McGlynn KA [66]	January 1, 1990, and September 1, 2019	case–control, Prospective cohort, retrospective cohort, nested cohort	6 studies(Goh et al., Kim et al., McGlynn et al., Lai et al., Tsan et al., with 86,827 patients	Type 2 diabetes	The rate of HCC reduction was also significant among patients with diabetes (RR: 0.44, 95% CI: 0.28–0.70)
Zhang J [57]	German MN [67] Lee TY [68] Pinyopornpanish K-1 [69] Pinyopornpanish K-2 [70] Zou B [71]	January 1, 2000 to February 27,2022	case–control, and cohort	5 studies (Lee et al., German et al., 2 studies by Pinyopornpanish et al., and Zou et al.) with 684,363 patients	MASLD	Statin use reduced the incidence of HCC in patients with MASLD (OR: 0.49; 95% CI, 0.33–0.73)
Wang S [63]	Tseng CH [72]	to July 1, 2022	retrospective or prospective cohort	1 study (Tseng et al.) with 66,237 patients	Type 2 diabetes	Statin use reduced the risk of HCC in patients with type 2 diabetes (HR:0.46, 95% CI, 0.39–0.54)

Discussion

Liver cancer is strongly linked to dyslipidemia and metabolic disruption [73]. This umbrella review sought to explore the data addressing the associations between statin use and the risk of HCC in patients with metabolic diseases such as T2DM and MASLD. To that purpose, we merged data from three medium/high-quality studies (1 MASLD and 2 T2DM), which included 153,064 T2DM patients and 648,363 MASLD patients. We discovered statistically significant favorable relationships between statin use and reduced risk of HCC in persons with T2DM. However, the findings in MASLD patients were not significant.

Despite the fact that the relationship between statin use and lowering the risk of several cancer types has already been extensively studied, we discovered only 24 articles on HCC, with only three nonoverlapping systematic reviews/meta-analyses of moderate or high quality investigating the role of statin use on HCC risk in patients with MASLD (Zhang et al., 2023) or T2DM (Islam et al., 2020, and Wang et al., 2022).

There was significant heterogeneity among the included studies in both T2DM and MASLD investigations (I2: 99.59% and 95.28%, respectively). Heterogeneity in systematic reviews/meta-analyses can be caused by differences in sample size, study design, medication information such as duration of exposure, dose, and type of statins (lipophilic vs hydrophilic), reported estimates, control selection, confounders, or follow-up duration. In addition to the previously mentioned sources of heterogeneity in meta-analyses, in this meta-analysis, the concomitant use of other medications with statins, such as aspirin, which is frequently administered along with statin, especially in older adults, may be the reason for the observed heterogeneity within studies [74, 75].

The meta-analysis included studies with follow-up times ranging from six months to over thirteen years, which may explain the observed heterogeneity in the impact of statins on cancer risk reduction among included studies. A longer duration of statin use (> 5 years) has recently been shown to significantly reduce the incidence of liver cancer (HR:0.26, 95% CI: [0.11–0.64]) [76].

The primary causes of neoplastic change in people with type 2 diabetes are endogenous or exogenous hyperinsulinemia, hyperglycemia, and/or chronic inflammation [77]. Moreover, it has long been indicated that T2DM is related to low plasma HDL cholesterol, and hypertriglyceridemia [78]. According to several studies, dyslipidemia may be associated with an increased risk of liver cancer [79]. Additionally, the rapid proliferation of cancer cells requires cholesterol for modulating various cancer signaling pathways [80]. These can partly explain the high prevalence of HCC in patients with T2DM.

Despite the large degree of heterogeneity among studies in individuals with T2DM, all studies found that statin treatment was related with lower HCC risk. The type of antihyperglycemic medicine is one of the primary explanations of the variability in statins'impact on cancer risk reduction. In a comprehensive study involving 1,847,051 hospitalized patients with T2DM, Kautzky-Willer et al. [81] found that concomitant use of statins and insulin-sparing glucose-lowering

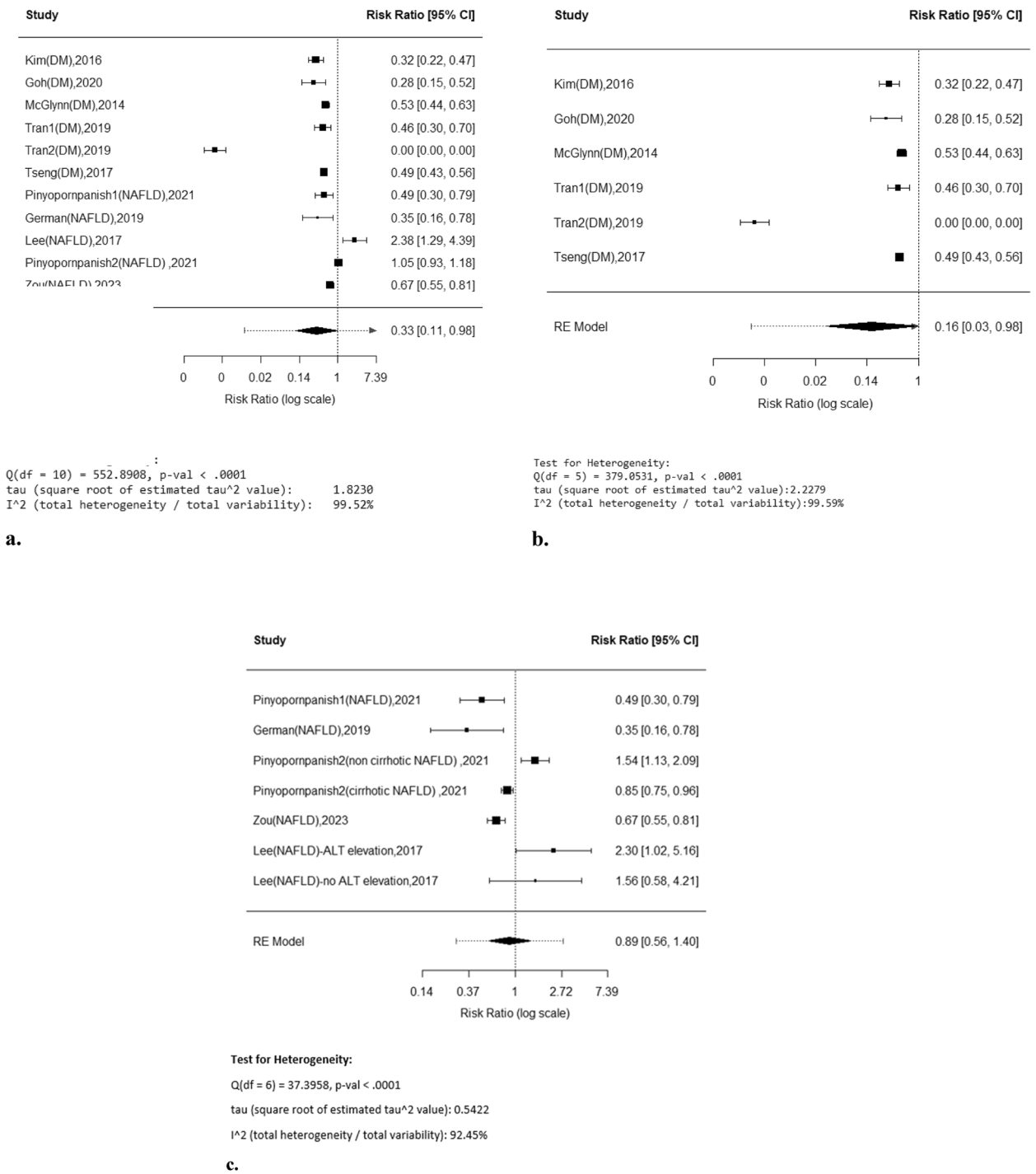

Fig. 2 Meta-analysis of the association between statin use and HCC risk in patients with a. T2DM or MASLD, b. T2DM, and c. MASLD studies

medications has an impact on HCC risk reduction in both genders (men: OR: 0.54, 95% CI: [0.47–0.61]; women: OR: 0.60, 95% CI: [0.51–0.71]). The results for insulin were comparable (men: OR: 0.70, 95% CI: [0.62–0.8]; women: OR: 0.77, 95% CI: [0.64–0.94]).

MASLD and T2DM are the major manifestations of metabolic syndrome that often coexist. The prevalence of T2DM in patients with MASLD is approximately 60% [82, 83]. The focus of included studies in this umbrella review were on T2DM or MASLD exclusively

and they had not explicitly mentioned what percentage of T2DM patients also had MASLD and vice versa.

We reviewed the characteristics of patients in the five MASLD studies to explore the rationale for heterogeneity and also the insignificant effect of statin treatment on HCC prevention. The demographic and clinical characteristics of statin users/nonusers have not been included in two studies that have claimed HCC is more frequent in statin users (Pinyopornpanish-2 and Lee).

In studies demonstrating statins'favorable benefits on lowering the risk of HCC, there were no significant differences in the mean age of statin users versus nonusers. ALT, along with other liver enzymes like aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT), is a marker of liver dysfunction. High ALT or AST levels are independent risk factors for the development of cirrhosis and HCC, according to several studies [84]. However, one study (Pinyopornpanish-1) found that statin users and non-users had comparable levels of ALT [85]. Furthermore, aspirin and metformin use was higher in statin users than in nonusers, according to three studies showing the role of statins in lowering the incidence of HCC. The result of a 20-year cohort study on the association between aspirin use and cancer risk showed that long-term (≥ 5 or ≥ 10 years) aspirin use can reduce cancer incidence by 10% in several types of cancers including liver cancer [86]. Aspirin can decrease cancer by several mechanisms including inhibition of cancer signaling pathways through the inhibition of cyclooxygenase (COX) enzyme [87] and decreasing cancer-associated inflammation and cancer proliferation [88]. Similarly, the correlation between metformin use and decreased risk of liver cancer has been established [89].

Study limitations

The primary limitation of our investigation was the absence of comprehensive statin user/nonuser characteristics in two studies that reported a greater frequency of HCC among statin users with MASLD. This made it impossible for us to determine the actual impact of statins on the risk of HCC in MASLD patients. The availability of data regarding confounding variables such as ALT level, and concurrent use of statin and aspirin and glucose-lowering medications could also help us to find subgroups of patients for whom statin use might be protective against HCC development.

Conclusions

Statin use seems to have a protective effect on HCC risk among people with T2DM. However, it is still unclear if statin use might have beneficial effect on HCC risk in specific subgroups.

Abbreviations

HCC	Hepatocellular carcinoma
T2DM	Type 2 Diabetes
MASLD	Nonalcoholic fatty liver disease
HR	Hazard ratio
OR	ODDs ratio
RR	Risk ratio
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
HDL	High density lipoprotein

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Not applicable.

Authors' contributions

N.H. and ME. K. contributed to the study design. Z.E. conducted the literature search. N.H. and S.J. performed study selection, extracted the data and assessed the methodological quality, any disagreement was solved by LN, N.H. conducted the statistical analysis.N.H. and L.N. wrote the paper, ME.K. reviewed the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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