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REVIEW

Aspirin in Patients with Viral Hepatitis: Systematic Review and Meta-Analysis of Observational Studies

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Abstract

Background Hepatocellular carcinoma (HCC) is a disease demonstrating increasing morbidity and mortality, especially in patients with chronic viral hepatitis. Studies have shown that aspirin can reduce the incidence of liver cancer; however, the degree of benefit in patients with viral hepatitis is unclear. This study focused on the association between aspirin use and HCC risk in patients with chronic viral hepatitis.

Methods A systematic search of the PubMed, Embase, Web of Science, and Cochrane Library databases was performed from the earliest available date to December 16, 2023. The primary outcome was HCC incidence, and the secondary outcome was gastrointestinal bleeding. The results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Meta-analyses were performed by using random or fixed-effects models based on the heterogeneity assessed via the I^2 statistic.

Results A total of 13 articles (303,414 participants and 14,423 HCC patients) were included in the analysis. The incidence of HCC in aspirin users was lower than that in non-aspirin users (HR 0.75; 95% CI, 0.68–0.83; $P < 0.001$; $I^2 = 90.0\%$). Subgroup analysis further showed that this effect may be more obvious in HCV patients, non-cirrhotic patients, patients with statins, and long-term aspirin users, but it may have the risk of gastrointestinal bleeding (HR 1.13; 95% CI, 1.07–1.20; $P = 0.906$; $I^2 = 0.0\%$).

Conclusions Our meta-analysis shows that in patients with chronic viral hepatitis, aspirin use is associated with a significantly reduced risk of liver cancer, but attention should be paid to the possible risk of gastrointestinal bleeding, and this conclusion needs further validation in the future.

Keywords Aspirin · Risk of hepatocellular carcinoma · Systematic review—meta-analysis · Observational studies

Introduction

Hepatocellular carcinoma is one of the most common malignant tumors throughout the world, ranking fourth among the causes of tumor death and possessing a high degree of malignancy, strong invasiveness and metastasis, poor prognosis, and a serious threat to the health of the population [1]. Risk factors include hepatitis B virus, hepatitis C virus, alcohol-related cirrhosis, fatty liver disease, diabetes, and various dietary exposures [2]. Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the two most common types of liver cancer. Due to the large population of chronic hepatitis patients in China, a considerable number of patients with liver cancer have developed, which directly threatens the lives and health of the population. Although the current comprehensive treatment methods (including surgery, intervention, and immunotherapy) have greatly reduced the mortality rate [3], due to economic costs and other reasons, it is currently necessary to find more effective measures to reduce the incidence of liver cancer in patients with chronic hepatitis from the source.

The benefits of aspirin in the prevention of colorectal cancer have been confirmed [4–6]. Recently, published articles have shown that aspirin may reduce the incidence rate of liver cancer [7–10], and the study by Simon et al. [11] showed that aspirin can reduce the incidence of liver cancer by 31%. Moreover, previous meta-analyses on this topic have included only a small subset of published studies based on study subjects, and differences in sample size may

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lead to inappropriate judgments of efficacy. Furthermore, a meta-analysis that solely focuses on studies of aspirin's effect on liver cancer incidence in patients with chronic viral hepatitis has yet to be conducted. Therefore, the purpose of this study was to investigate the effect of aspirin use on the incidence of hepatocellular carcinoma in patients with chronic hepatitis.

Methods

Search Strategy

Meta-analyses were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) list based on the Meta-analysis Guidelines for Observational Epidemiological Studies and the protocol for this study [12, 13] (ID: CRD42022350387). We conducted a systematic literature search of PubMed, Embase, Cochrane Library, and Web of Science databases (up to December 16, 2023) by using a combination of MeSH/Emtree and title/abstract keywords. The keywords were "Acetylsalicylic acid," "Aspirin," "Hepatocellular Carcinoma," "Liver cancer," "Hepatic cellular cancer," and "HCC." Supplementary material S1 shows the detailed search strategy, and Fig. 1 provides the complete search strategy. The titles and abstracts of all of the identified studies were screened by two junior researchers, and articles not related to the research question were excluded from the analysis. Subsequently, all of the remaining articles were fully reviewed according to the selection criteria. References were also reviewed to identify other relevant studies. Any differences were resolved via consultation between the two senior researchers.

Inclusion and Exclusion Criteria

The following inclusion criteria were adopted in this study: (1) observational studies based on cohort design, (2) patients with chronic viral hepatitis with ages > 18 years and without coagulation disorders, (3) aspirin exposure at any dose and duration, and (4) studies reporting hazard ratios and 95% confidence intervals (CIs) for HCC incidence. The exclusion criteria were as follows: (1) study subjects including non-hepatitis patients; (2) literature related to the combined use of statins and aspirin, splenectomy, hepatectomy, and alcoholic cirrhosis; and (3) review articles, case reports, and basic related studies.

Data Extraction

Two junior researchers independently collected data via preestablished forms. Differences were resolved through

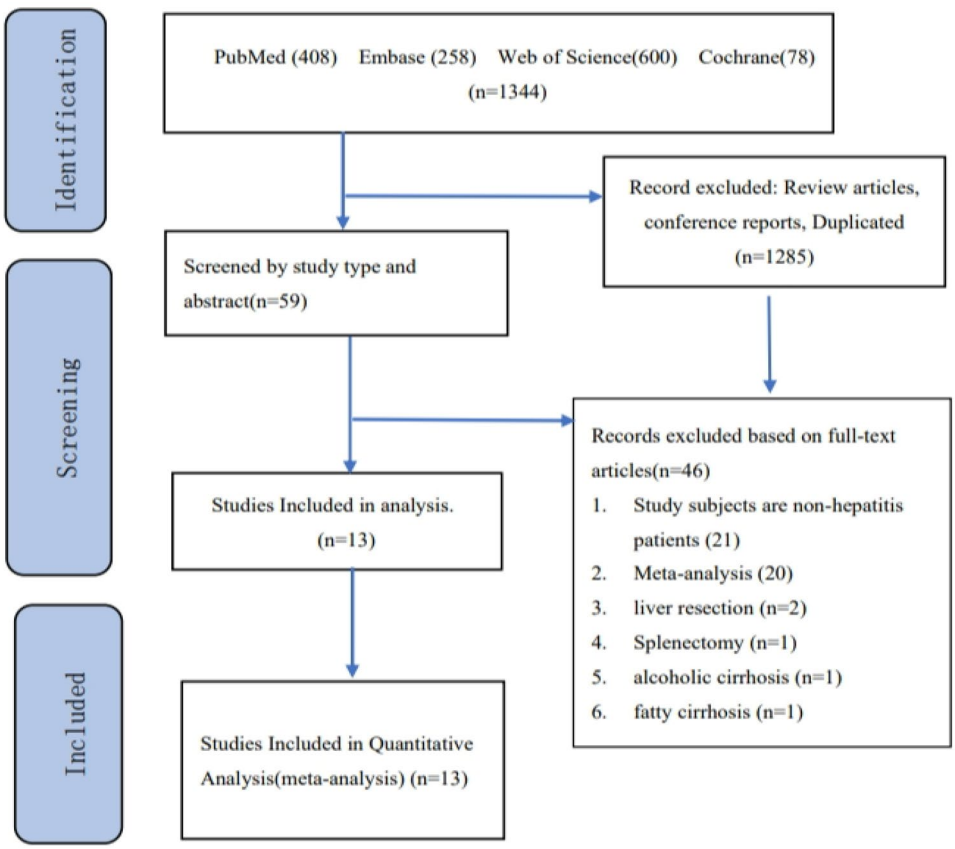


Fig. 1 Flow diagram of search strategy and study selection

discussion. The collected information mainly included author, publication year, country or region, age, number of liver cancer incidences, number of aspirin users, total number of people, follow-up time, type of hepatitis, reasons for taking aspirin, study design, aspirin dose, aspirin use time, liver cancer incidence, and hazard ratio (HR) and 95% confidence interval (CI) of gastrointestinal bleeding.

Assessment of Study Quality

The quality of the eligible studies was assessed by using the Newcastle–Ottawa-Quality Assessment Scale [14]. Studies were assessed by using three categories: selection of study groups (0–4 points), comparability (0–2 points), and exposure (0–3 points). A total score of ≤ 3 was considered to be low quality, scores between 4 and 6 were considered to be moderate quality, and scores ≥ 7 were considered to be high quality. These scores were only used to facilitate the interpretation of the meta-analysis results but were not used as a criterion for inclusion or exclusion of the studies.

Data Analysis

The main purpose of this meta-analysis was to examine the relationship between aspirin use and the incidence of HCC in patients with chronic viral hepatitis. We used Cochran's Q test and I^2 statistic to calculate heterogeneity among the studies. All of the P values were two-tailed, and $P < 0.05$ was considered to be statistically significant for all of the analyses (except for tests of heterogeneity and publication bias). If $I^2 > 50\%$ indicated significant heterogeneity between different studies, we chose a random effects model to calculate pooled HRs and 95% CIs. We also performed subgroup analyses of different types of hepatitis and the presence of cirrhosis. The stability of the outcomes was assessed by using a sensitivity analysis via sequential omission of each of the studies, which was conducted by altering the pooling model (fixed-effects model or random-effects model). In addition, Begg funnel plots and Egger linear regression were used to assess potential publication bias for the primary outcome of the included studies. All of the statistical analyses were performed by using STATA 17.0.

Results

Search Results

A total of 1344 related articles were retrieved by subject headings and subtopic headings in major databases, and a total of 13 articles with approximately 417,133 participants were finally included through further screening and evaluation [7, 9–11, 15–23].

Study Characteristics

The characteristics of the included studies are shown in Table 1. A total of 13 related articles with approximately 417,133 participants and 25,225 cases of incident HCC were included. Of the thirteen studies, 7 studies were conducted in patients with chronic hepatitis B [9, 10, 15, 19–22], and 2 studies were mainly conducted in patients with chronic hepatitis C [7, 23]. Additionally, four studies involved mixed patients with hepatitis B and C [11, 15, 17, 18]. In addition, we noted that most subjects took long courses of low-dose aspirin.

Quality Assessment Results

We assessed the quality of individual studies based on Newcastle–Ottawa quality assessment scores, and of the 13 cohort studies, 11 were rated as high quality and 2 as moderate quality. One study had a NOS score of 9, 8 had a NOS score of 8, 2 had a NOS score of 7, and 2 had a NOS score of 6, with a full score of 9. In short, the quality of the selected studies was relatively high, with NOS scores mainly ranging from 7 to 9. High-quality studies account for a larger proportion, which is conducive to reducing bias and improving the credibility of the results. The quality of the studies included in this study is high, which makes the meta-analysis results more credible.

Primary and Secondary Outcomes

Figure 2A shows the effect of taking aspirin on the incidence of liver cancer in patients with chronic viral liver disease. Thirteen observational studies were included, including 417,133 participants and 25,225 HCC patients. There was heterogeneity observed among the studies ($I^2 = 90.0\%$); therefore, a random effects model was used. The comprehensive results showed that aspirin could significantly reduce the incidence of liver cancer in patients with chronic hepatitis (HR 0.75; 95% CI 0.68–0.83; $P < 0.001$; $I^2 = 90.0\%$).

Figure 2B shows the effect of aspirin use on gastrointestinal bleeding in patients with chronic viral hepatitis. A total of 7 observational studies including 170,095 participants and 8961 HCC patients were included. There was no heterogeneity observed among the studies ($I^2 = 0.0\%$); therefore, a fixed-effects model was used. The combined results showed that aspirin had no significant effect on gastrointestinal bleeding in patients with chronic viral hepatitis (HR 1.13; 95% CI 1.07–1.20; $P = 0.906$; $I^2 = 0.0\%$).

Subgroup Analysis

Subgroup analysis further demonstrated that aspirin use is linked to a lower incidence of HCC in patients with factors including HCV (HR 0.69; 95% CI 0.55–0.87; $P < 0.001$; $I^2 = 83.2\%$; Fig. 3A), noncirrhotic (HR 0.73; 95% CI

Table 1 Baseline characteristics of the studies included in the meta-analysis

Study	Region	Study design	HCC cases	Aspirin group	Total number	Average age	Follow-up (years)	Type of hepatitis	Definition of aspirin user	Aspirin dose	Reason for aspirin	Primary outcome (HR, 95% CI)	Secondary outcome (HR, 95% CI)
Liao et al. 2020 [7]	Taiwan	RC	278	1911	3822	64	10	HCV	Any use	NA	Treated with aspirin	0.56 (0.43–0.72)	NA
Hui et al. 2021 [10]	Hongkong	RC	1557	1744	35,111	53	3.3 no users, 2.8 users	HBV	At least 90 days	NA	Cardio-vascular preven-tion	0.41 (0.18–0.91)	1.11 (0.87–1.42)
Jang et al. 2022 [20]	South Korea	RC	2697	19,003	38,006	54.5	6.7	HBV	More than 90 consecutive days	Low-dose aspirin (≤ 160 mg)	Prevention of cardio-vascular events	0.85 (0.78–0.92)	1.09 (0.99–1.21)
Simon et al. 2020 [11]	Sweden	RCC	1612	14,205	50,275	NR	7.9	HBV/HCV	75 or 160 mg/day, ≥ 90 days	Low-dose aspirin (≤ 160 mg)	Cardio-vascular preven-tion	0.69 (0.62–0.76)	1.18 (0.89–1.29)
Lee et al. 2020 [23]	Taiwan	RC	436	1255	2453	63.2	5	HCV	Use > 180 days	Took 100 mg or less	Preventing cardio-vascular diseases	0.78 (0.64–0.95)	1.12 (0.89–1.40)
Lee et al. 2019 [22]	Taiwan	RC	697	2123	10,615	58.8	5	HBV	Regular use ≥ 90 days	≤ 100 mg/d	Antiplatelet therapy for cardio-vascular diseases	0.71 (0.58–0.86)	1.13 (0.93–1.37)
Yun et al. 2022 [9]	South Korea	RC	7083	9837	161,673	51.8	7.5	HBV	Taking aspirin for > 3 years	NA	Cardio-vascular preven-tion	0.84 (0.76–0.94)	NA
Lee et al. 2017 [21]	South Korea	RC	63	343	1459	NR	4.75	HBV	100 mg/day, ≥ 1 month	Aspirin 100 mg/day	Preventing cardio-vascular diseases	0.26 (0.09, 0.74)	1.11 (0.48–2.54)
Choi et al. 2021 [19]	South Korea	RCC	6539	7718	32,695	53.5	10	HBV	At least 90 days	NA	Preventing cardio-vascular diseases	0.98 (0.97–1.00)	NA

Table 1 (continued)

Study	Region	Study design	HCC cases	Aspirin group	Total number	Average age	Follow-up (years)	Type of hepatitis	Definition of aspirin user	Aspirin dose	Reason for aspirin	Primary outcome (HR, 95% CI)	Secondary outcome (HR, 95% CI)
Ho et al. 2018 [18]	China	RC	1055	6924	15,597	57.4	4.3	HBV/HCV	35.2 months	Low-dose aspirin	Aspirin used for anti-platelet therapy	HBV 0.82 (0.67–1.01), HCV 1.02 (0.84–1.24)	NA
Lee et al. 2023 [16]	South Korea	RC	1583	13,104	26,208	43	7.4	HBV	At least 90 days	NA	Aspirin used for anti-platelet therapy	Lower metabolic risk group 0.93 (0.84–1.03)	Lower metabolic risk group 1.22 (1.08–1.39)
Lee et al. 2023 [16]	South Korea	RC	316	2984	5968	43	7.4	HBV	At least 90 days	NA	Aspirin used for anti-platelet therapy	Higher metabolic risk group 0.72 (0.57–0.91)	Higher metabolic risk group 1.02 (0.79–1.32)
Hwang et al. 2018 [17]	South Korea	RC	773	NA	31,528	50.0	6.4	HBV/HCV	Regular aspirin prescription records (> 30 days) within 5 years before the index date	Regular aspirin prescription records	Aspirin used for anti-platelet therapy	0.65 (0.53–0.80)	NA
Lee et al. 2023 [15]	South Korea	RC	536	607	1723	61.2	5	HBV/HCV	At least 84 days	75–100 mg/day	Aspirin used for anti-platelet therapy	HBV 0.60 (0.41–0.87), HCV 0.45 (0.32–0.63)	NA

RC retrospective cohort, *RCC* retrospective case−control, *HCC* hepatocellular carcinoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HR* hazard ratio, *CI* confidence interval, *NA* not available

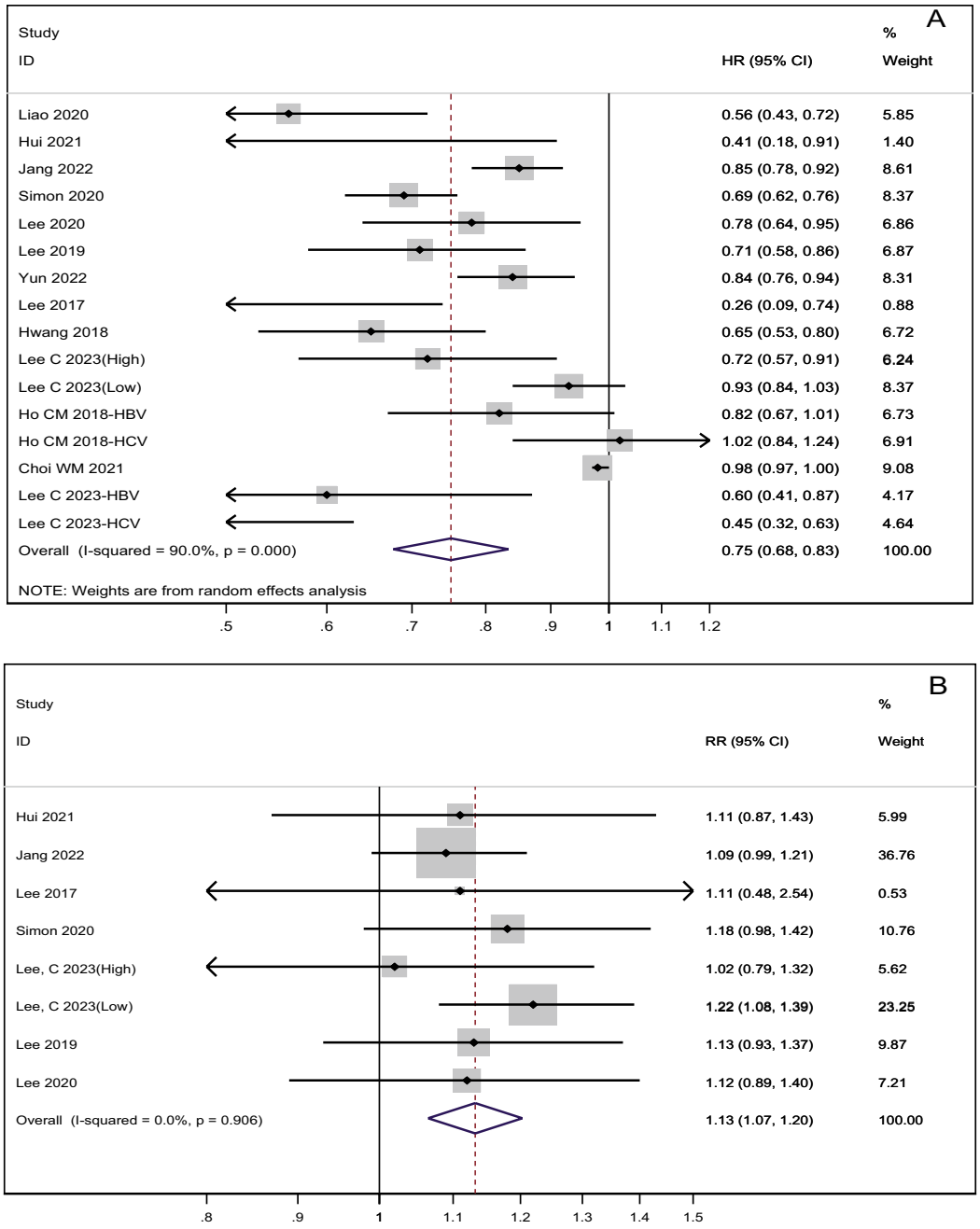


Fig. 2 **A** Forest plot of aspirin use and risk of HCC development in 13 observational studies (including 417,133 participants) and overall relative risk with their respective weights. The pooled results of the included studies showed that subjects taking aspirin had a significantly lower risk of HCC (HR 0.75; 95% CI 0.68–0.83). **B** Meta-analysis of overall pooled HR with 95% CIs across studies for secondary outcome. Forest plots showing the association between aspirin use and the risk of gastrointestinal bleeding in patients with viral hepatitis, according to a fixed-effects model

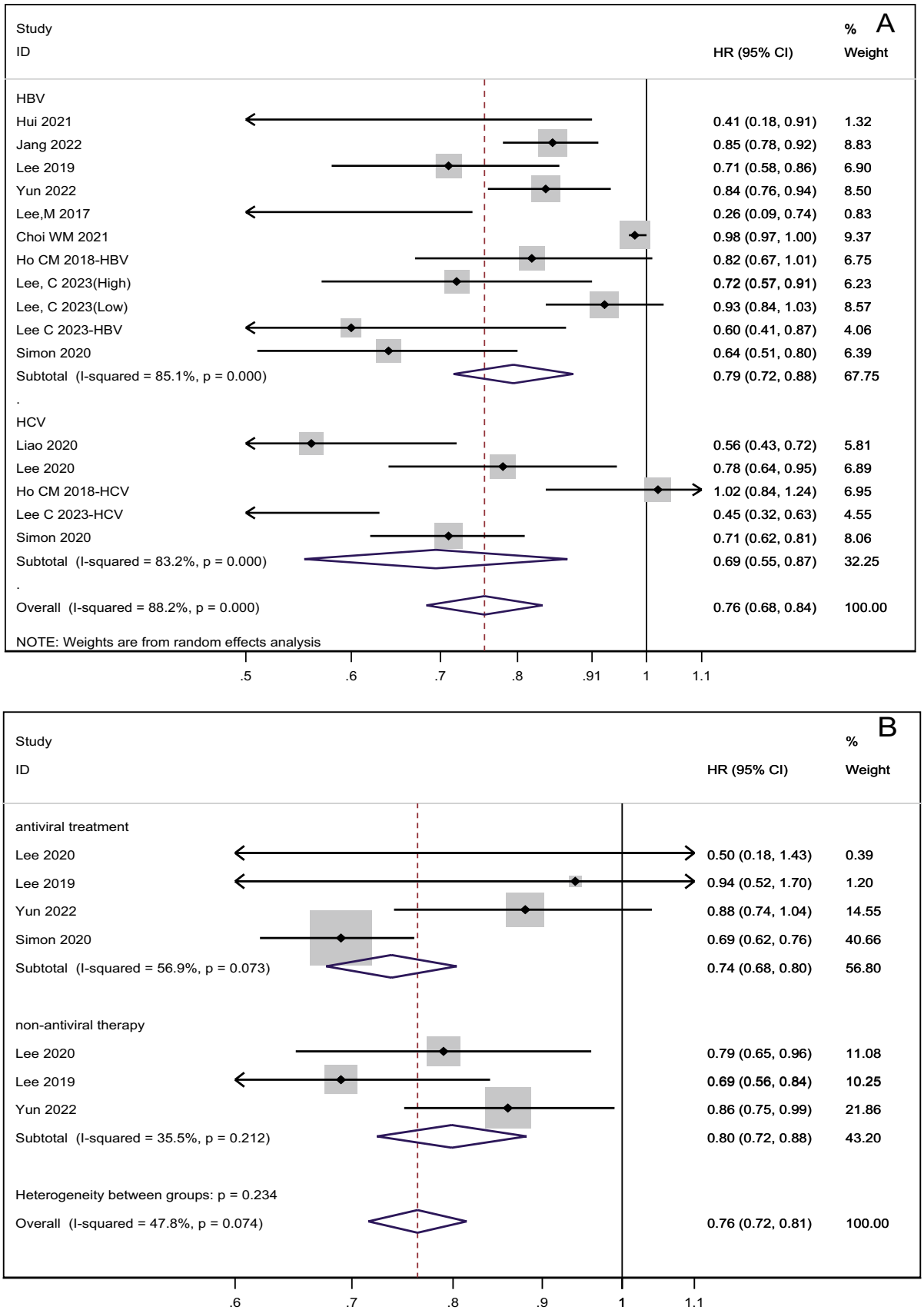


Fig. 3 **A** Subgroup analysis stratified by hepatitis type. **B** Subgroup analysis according to antiviral treatment

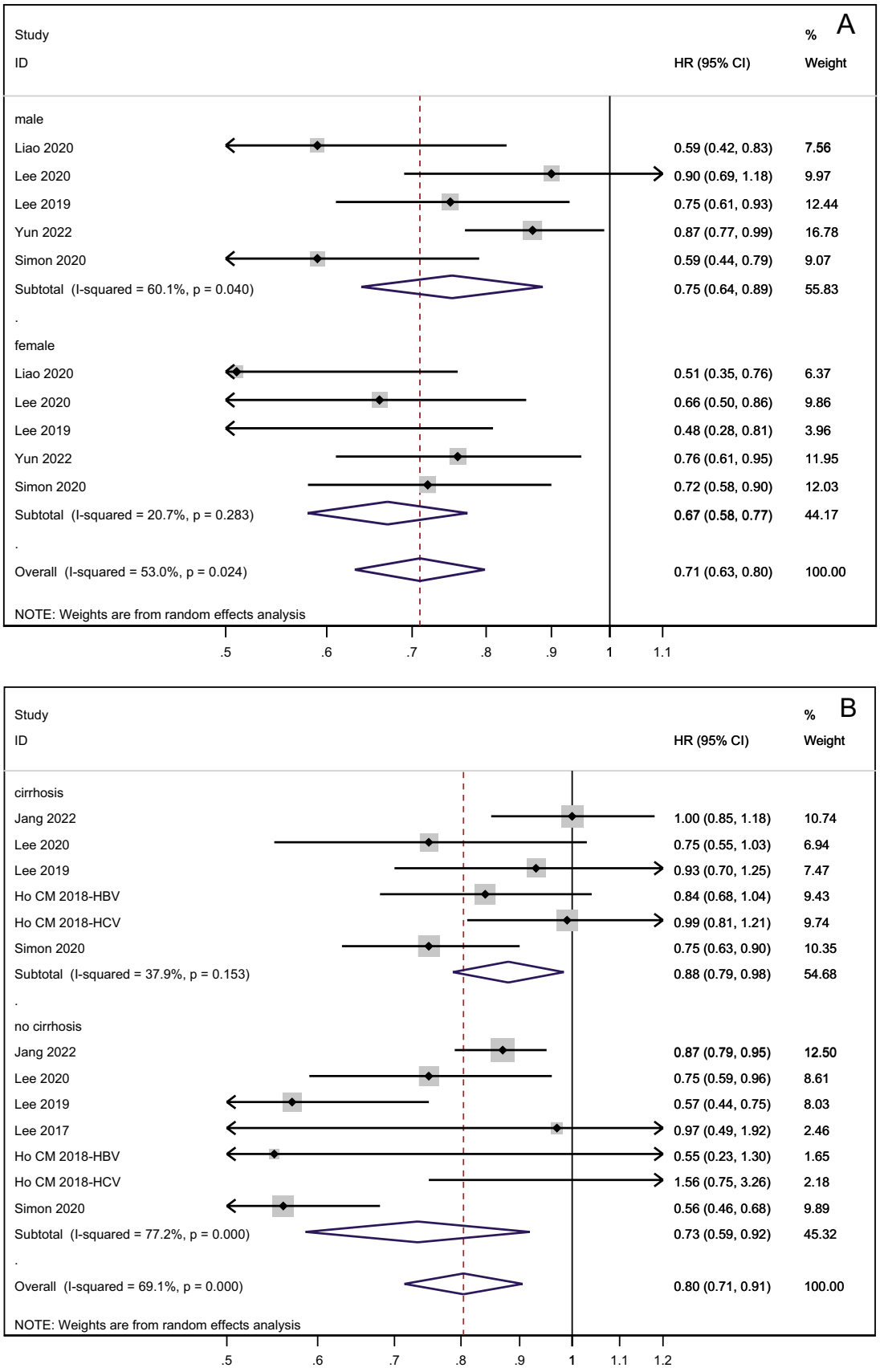
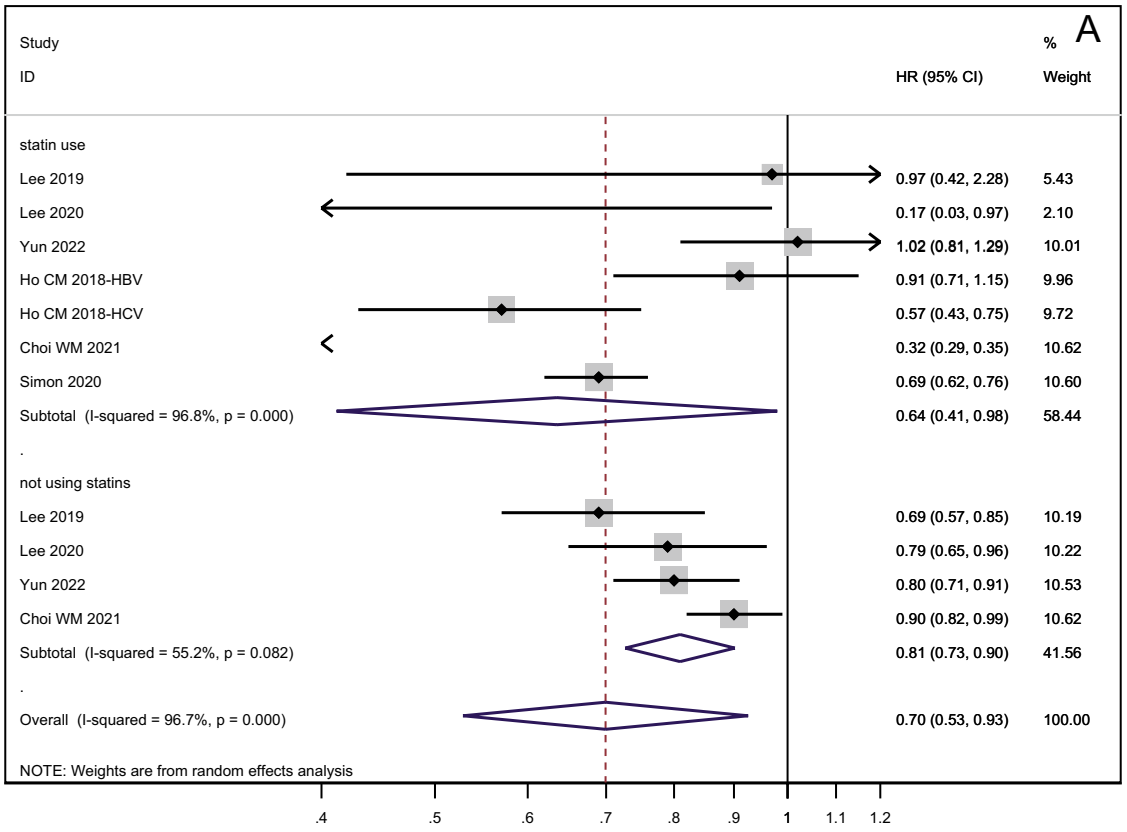


Fig. 4 **A** Subgroup analysis stratified according to sex. **B** Subgroup analysis stratified by cirrhosis



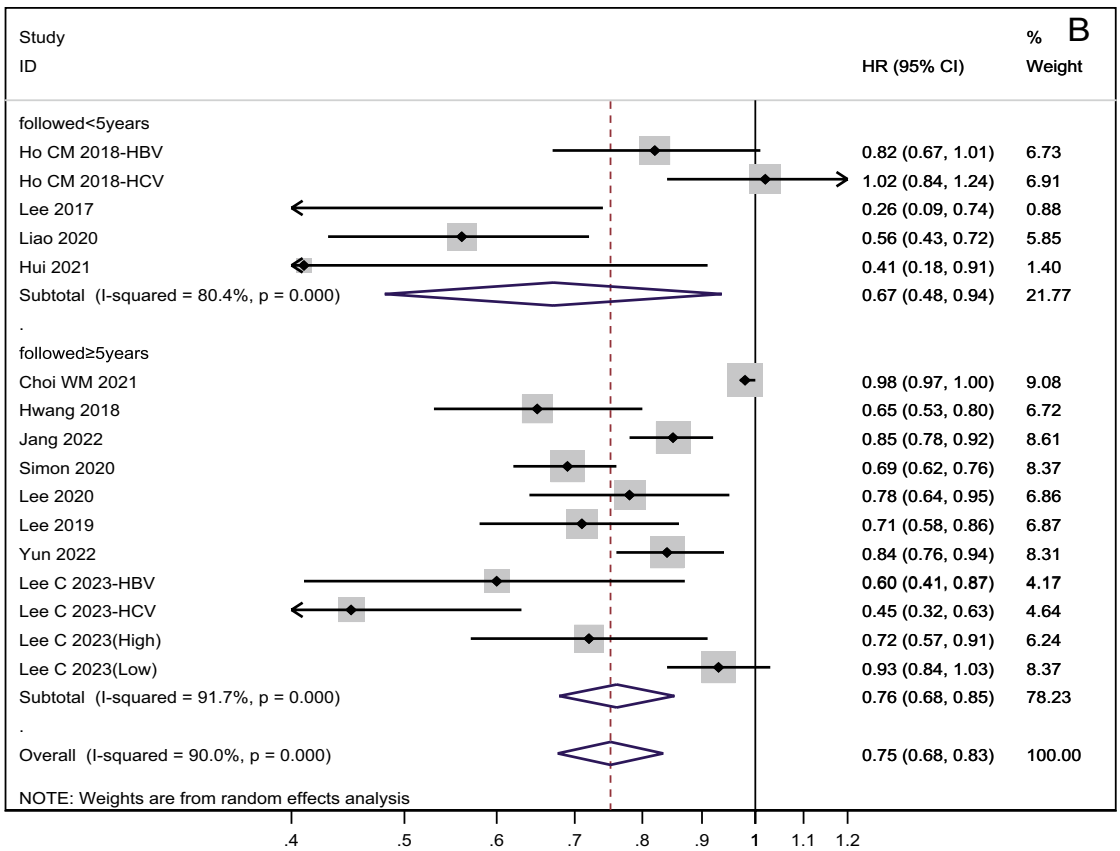


Fig. 5 **A** Subgroup analysis stratified by time of statin use. **B** Subgroup analysis stratified by follow-up time

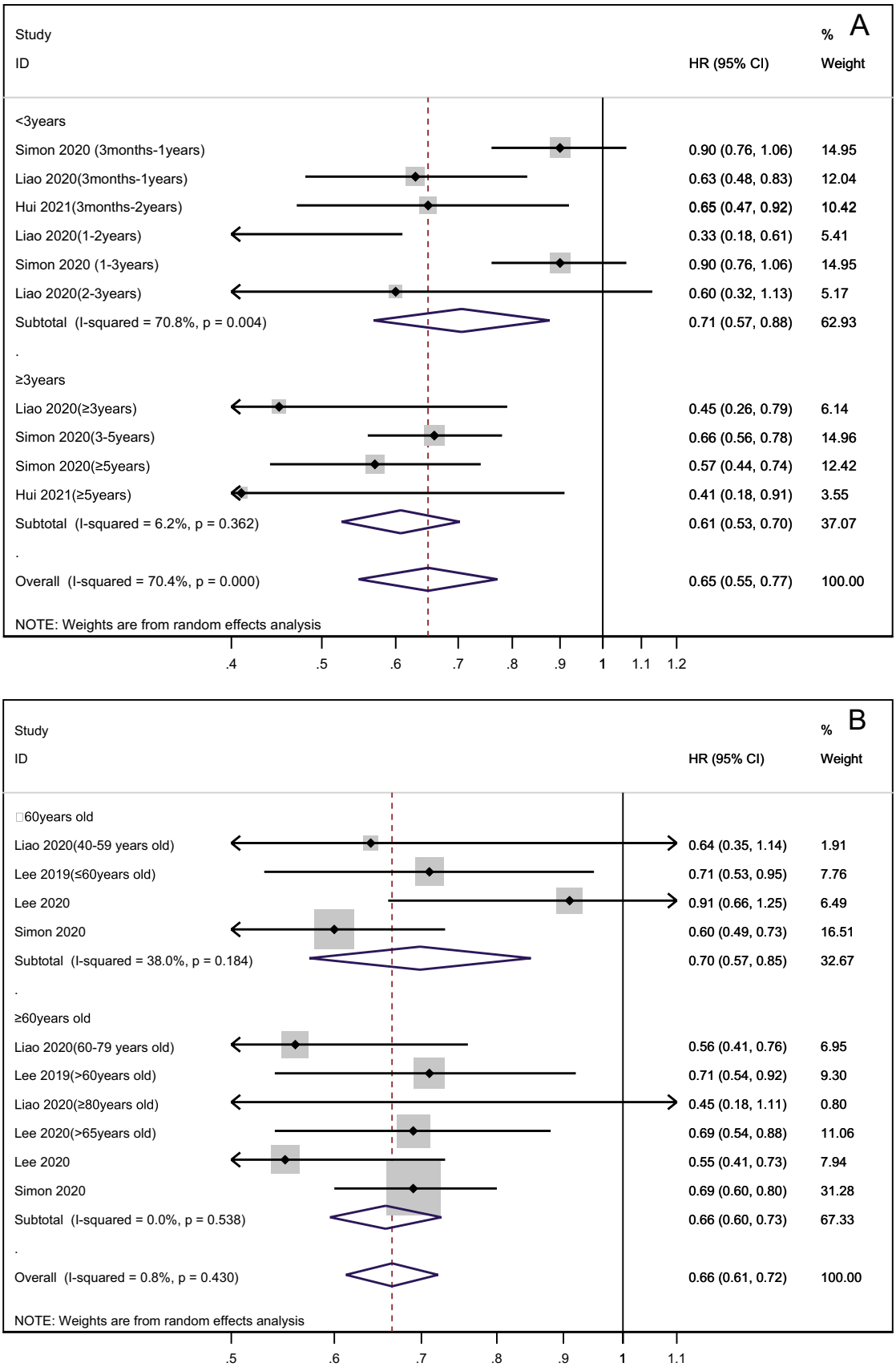


Fig. 6 **A** Subgroup analysis stratified by aspirin use. **B** Subgroup analysis stratified by age

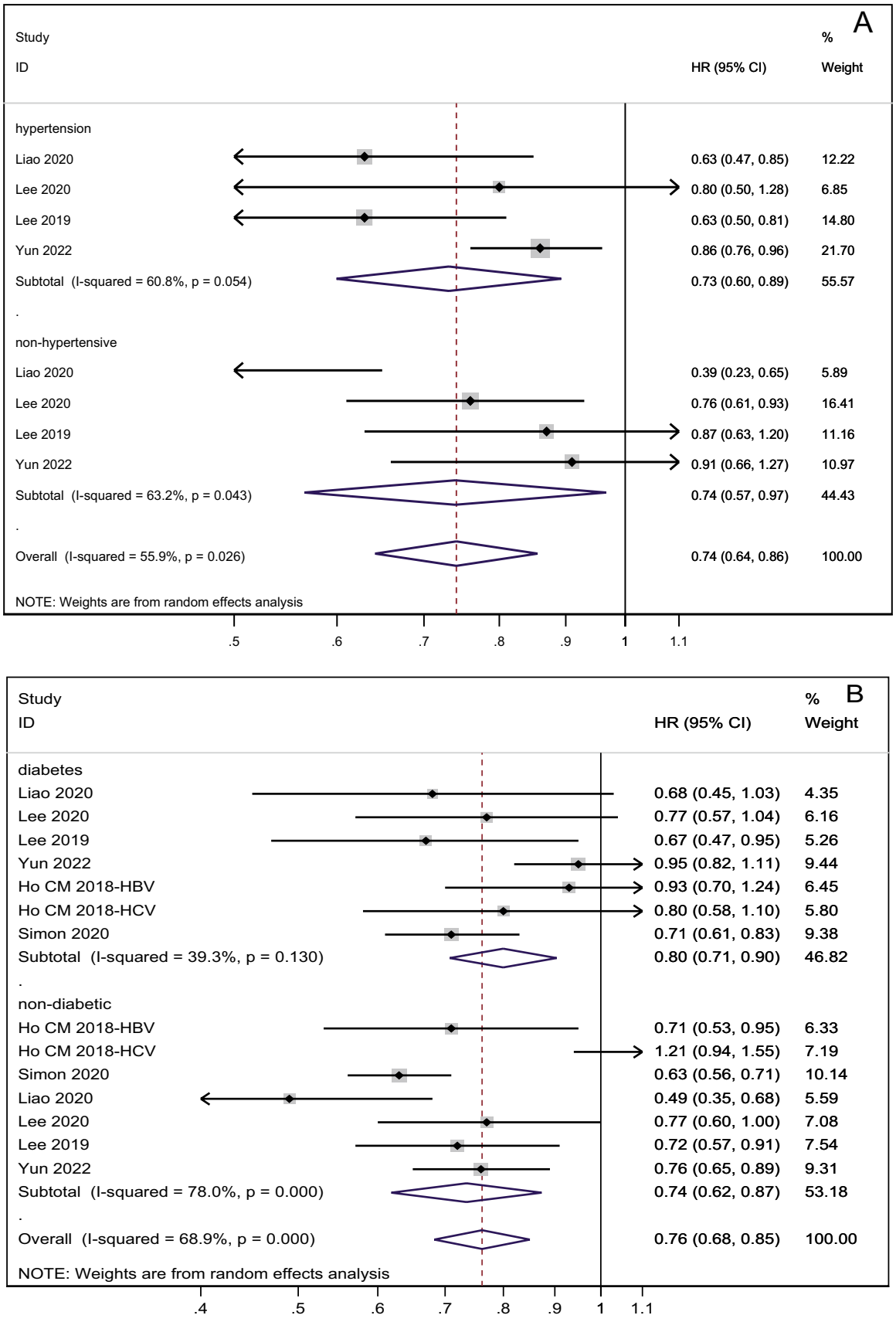


Fig. 7 **A** Subgroup analysis stratified by hypertension. **B** Subgroup analysis stratified by diabetes

0.59–0.92; $P < 0.001$; $I^2 = 77.2\%$; Fig. 4B), combined use of statins (HR 0.64; 95% CI 0.41–0.98; $P < 0.001$; $I^2 = 96.8\%$; Fig. 5A), and ≥ 3 years of aspirin use (HR 0.61; 95% CI 0.53–0.70; $P = 0.362$; $I^2 = 6.2\%$; Fig. 6A) Diabetes and hypertension (Fig. 7).

Sensitivity Analyses and Publication Bias

As the included studies were observational studies with a low risk of bias, we performed sensitivity analyses to assess the effect of any one study on the pooled HR and 95% CI by deleting each separate study at a time (Supplementary material). Sensitivity analyses did not demonstrate any significant differences between the calculated combined results beyond the 95% confidence limits (Supplementary material Fig. S1). Publication bias was detected using funnel plots, Begg's rank correlation test, and Egger's regression asymmetry test; however, the funnel plot showed significant asymmetry between studies (Supplementary Material Fig. S2), suggesting possible publication bias.

Discussion

Liver cancer-related treatment costs impose a considerable burden on global health, and its morbidity and mortality are still increasing [24]. Studies have shown that nonsteroidal anti-inflammatory drugs, such as aspirin, have a certain effect on the prevention and treatment of liver cancer [25, 26]. Our results showed that aspirin use was associated with a significant reduction in the risk of HCC in patients with chronic viral hepatitis, and these benefits did not appear to increase the risk of gastrointestinal bleeding.

The possible mechanism by which aspirin reduces the incidence of hepatocellular carcinoma.

More than 50% of HCC cases are attributable to chronic HBV infection [27]. Inflammatory damage, cell necrosis, and fibrosis caused by HBV infection are important causes of HCC. The possible mechanisms of HCC initiation include viral factors (such as insertional mutagenesis and inappropriate expression of viral gene products). Previous studies have shown that host factors associated with antiviral immune responses play an important role [28], which is characterized by the inability of dysfunctional virus-specific CD8 + T cells to clear HBV from the liver [29]. HBV continues to act on hepatocytes, thus leading to tissue damage; moreover, platelets exist at the site of inflammatory damage. Platelet depletion can reduce the accumulation of hepatovirus-specific CD8 + T cells to improve liver burden, thereby reducing the incidence of long-term HCC [30]. In this pathway, aspirin inhibits platelet activation by blocking the production of thromboxane TXA2 [31]. In addition, Zhang et al. [32] found that aspirin inhibited HCC cell growth by inducing the expression of other CREB/ATF1-responsive genes in an AMPK-dependent manner. Additionally, aspirin has been reported to inhibit the viral replication of flaviviruses, such as HCV [33, 34], and the anti-HCV effect of aspirin has been reported to be due to its inhibitory effect on COX-2 expression through the activation of MEK12/p38 MAPK [33]. Further studies have shown that aspirin has a greater early benefit in patients with hepatitis C and may prevent the risk of reinfection with HCV [35]. In our subgroup analysis, it was also shown that hepatitis C patients had a lower incidence of liver cancer than hepatitis B patients taking aspirin.

We have previously discussed in detail the specific mechanism by which aspirin reduces the incidence of liver cancer in patients with chronic viral hepatitis, which provides options for future prevention; however, we know that aspirin (as a first-line antiplatelet drug) is generally a preventative drug for people at risk of occlusive cardiovascular or cerebrovascular events. Another extremely important point is that for some high-risk groups, an important risk of prolonged or overdose aspirin involves gastrointestinal bleeding, especially in patients with chronic hepatitis, who often progress to cirrhosis due to chronic inflammation, which can lead to esophageal varices. Inappropriate aspirin use may lead to common complications such as gastrointestinal bleeding and even more severe intracranial hemorrhage, which directly threatens the patient's life; our results also show the associated risk of gastrointestinal bleeding, since this article mainly focuses on patients with chronic hepatitis, a considerable proportion of whom are patients with cirrhosis. Due to the progression of the disease, the decompensated stage of cirrhosis leads to gastroesophageal varices, even taking low-dose aspirin to prevent cardiovascular and cerebrovascular diseases may lead to increased risk of gastrointestinal bleeding.

The results of this paper suggest that aspirin use in patients with chronic hepatitis can reduce the incidence of liver cancer. However, further clinical trials are needed to confirm this recommendation. As a first-line nonsteroidal anti-inflammatory drug (NSAID), aspirin exerts powerful anti-inflammatory and antiplatelet effects, thereby reducing the process of liver fibrosis and the incidence of liver cancer [35, 36]. Clinical studies have shown that the incidence of liver cancer in patients taking aspirin is significantly lower than that in the non-aspirin group [37]. In contrast, some studies have shown that aspirin is ineffective in reducing the incidence of liver cancer [38]. The main purpose of taking aspirin in such patients is to prevent cardiovascular and cerebrovascular diseases, and they also take lipid-lowering drugs (such as atorvastatin) and hypoglycemic drugs (such as metformin). Whether these confounding factors interfere with the current results requires further research. Some

researchers believe that the combination of aspirin and lipid-lowering drugs or hypoglycemic drugs plays a possible role [38, 39], and previous studies have shown that the combination of simvastatin and the cyclooxygenase-2 inhibitor NS398 can inhibit excessive proliferation [40]. Our meta-analysis focused on patients with viral hepatitis and demonstrated that aspirin can significantly reduce the incidence of liver cancer without significantly increasing the risk of gastrointestinal bleeding. This provides the possibility of a choice for patients with viral hepatitis, especially early-stage patients; however, its efficacy and safety still need to be confirmed by further large-scale, clinical, randomized controlled trials.

This study had several advantages. First, this article is the first to conduct a systematic review and meta-analysis of the incidence of liver cancer after taking aspirin in patients with viral hepatitis (excluding ordinary patients). Second, this paper includes two recently published high-quality articles [15, 16], which greatly increases the sample size to minimize bias and ensure the relative reliability of the results. Third, this article discusses the specific mechanism of aspirin's effect on the incidence of liver cancer in patients with chronic hepatitis, as well as the subgroup analysis of HBV and HCV, to further explore the relevant mechanism of these effects. Fourth, the median follow-up time of the included studies was sufficient for a meaningful assessment of HCC incidence. Finally, the results presented in the NOS quality list show that the methods that were used in the original study are of high quality.

The paper also had several shortcomings. First, due to the fact that the studies that were included in the meta-analysis were observational, high-quality, large-scale RCTs must be performed to demonstrate the effectiveness of the protocol in a highly controlled setting. Second, a high degree of heterogeneity was observed in the overall effect of aspirin on HCC incidence; however, the NOS assessment indicated that the quality of the included articles was reliable, which suggests that the dose and timing of aspirin and the large sample size may be the source of the heterogeneity.

In conclusion, this systematic review and meta-analysis demonstrated that aspirin use significantly reduces the risk of HCC in patients with chronic viral hepatitis, but this requires attention to the risk of gastrointestinal bleeding. In addition, aspirin may benefit patients with HCV, those without cirrhosis, those taking concomitant statins, and those taking long-term treatment, and these findings may need further confirmation in the future.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12029-024-01027-5.

Author Contribution Wentao Bian and Wenkai Bian contributed to the conception and design of the work. Wentao Bian, Qingyu Li, and Yulian Li collected information and analyzed data used in the systematic review and meta-analysis. Wenkai Bian provided software and participated in the production of pictures. Wentao Bian and Wenkai Bian substantively revised it.

Data Availability The datasets related to the research results of this article are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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