ORIGINAL RESEARCH

Nonsteroidal anti-inflammatory drugs, especially aspirin, are linked to lower risk and better survival of hepatocellular carcinoma: a meta-analysis

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Objective: The roles of nonsteroidal anti-inflammatory drugs (NSAIDs) in the occurrence and prognosis of hepatocellular carcinoma (HCC) remain controversial. This analysis aimed to summarize the relationships between NSAIDs and HCC development.

Methods: Studies published prior to October 1, 2017, in the PubMed, Embase, Ovid, Web of Science, and Cochrane Library databases were systematically searched and analyzed.

Results: Eleven studies were included in this analysis. A meta-analysis of five studies revealed that aspirin use could significantly decrease the risk of HCC occurrence (hazards ratio [HR] = 0.64, 95% confidence interval [CI] = 0.45–0.91, $P = 0.014$). No significant difference was found for the use of NSAIDs (six studies) and non-aspirin NSAIDs (three studies) in HCC occurrence (HR = 0.74, 95%CI = 0.53–1.02, $P = 0.064$ and HR = 0.98, 95%CI = 0.87–1.12, $P = 0.81$, respectively). However, subgroup analysis of cohort studies demonstrated that NSAIDs significantly decreased the risk of HCC occurrence (HR = 0.58, 95%CI = 0.43–0.78, $P < 0.001$). HCC patients who received NSAIDs achieved better disease-free survival and overall survival compared with the non-NSAID users (HR = 0.79, 95%CI = 0.74–0.84, $P<0.001$ and HR = 0.60, 95%CI = 0.50–0.72, $P<0.001$, respectively). Additionally, a meta-analysis of two studies showed that aspirin treatment in HCC patients could significantly decrease the 2-year and 4-year mortalities (rate ratio [RR] = 0.50, 95%CI = 0.36–0.69, $P < 0.001$ and RR = 0.67, 95%CI = 0.45–0.998, $P = 0.049$, respectively). A meta-analysis of two studies showed that aspirin use was not associated with a higher risk of bleeding in HCC patients (HR = 0.71, 95%CI = 0.41–1.23, $P = 0.223$).

Conclusion: The use of NSAIDs, especially aspirin, is linked to a lower risk of HCC development and better survival in HCC populations. High-quality, well-designed trials should be conducted to reevaluate the relationships between NSAIDs and HCC.

Keywords: NSAID, hepatocellular carcinoma, aspirin, overall survival, recurrence

Introduction

It has been reported that worldwide 70%–90% of diagnosed primary liver cancers are hepatocellular carcinoma (HCC), which is the fastest growing cause of cancer-related death.[1–3] There has been a marked increase in HCC-related annual death rates in the past two decades.[2,4] The incidence and prevalence of HCC are increasing in Western countries, where HCC is now the leading cause of death in patients with liver cirrhosis. In addition, a recent study using the SEER registry projects has shown that the incidence of HCC will continue to rise until 2030;[1,5] that is, HCC imposes an enormous health burden worldwide.[3,6]

Nonsteroidal anti-inflammatory drug (NSAID) use, especially of aspirin, has been linked to reduced chronic inflammation and a risk of several cancers. The effects of

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aspirin and non-aspirin NSAIDs rely on several possible mechanisms, partly related to the inhibition of cyclooxygenase (COX) enzymes and prostaglandins, such as a decrease in angiogenesis and cancer cell proliferation, an increase in apoptosis, and a reduction in proinflammatory cytokine production.[7–9] Clinically, several studies have revealed that the long-term use of NSAIDs, including aspirin, is associated with a reduced risk of cancers and better survival.[10–13] However, for some cancers, no association was found.[14] Additionally, the effects of NSAIDs including aspirin were inconsistent in HCC. For example, Sitia et al[15] found that the effects of aspirin were present in hepatitis B virus-related carcinogenesis but not in chemical liver carcinogenesis. Sahasrabuddhe et al's study showed that the use of aspirin alone was associated with a 41% reduced risk of developing HCC, but the risk of developing HCC in non-aspirin NSAID users remained unchanged.[16]

The purpose of this study was to systematically review and analyze the published studies regarding the epidemiology and outcomes of HCC patients who received NSAIDs, via meta-analysis.

Materials and methods
Search strategy
We searched the PubMed, Ovid, Embase, Web of Science, and Cochrane Library databases for studies published prior to October 1, 2017. The following medical subject terms were used: "hepatocellular carcinoma", "liver cancer", "liver neoplasms", "hepatoma", "aspirin", "NSAIDs", and "nonsteroidal anti-inflammatory drug". Electronic searches were supplemented with manual searches of the reference lists of all retrieved review articles, primary studies, and abstracts from meetings to identify additional studies not found electronically. The literature was searched by two authors (YT and YL) independently.

Eligibility criteria
Two authors (YT and YL) independently selected the studies and discussed them with each other when inconsistencies were found. The articles that met the following criteria were included: (1) case–control, cohort studies or randomized controlled trials (RCTs), (2) subjects 18 years of age or older, and (3) availability of the hazard ratio (HR), rate ratio (RR), or odds ratio (OR) estimates, clinicopathological features or survival data of patients with HCC who received NSAIDs or aspirin. If the duration and sources of the recruited study populations overlapped by more than 30% in two or more studies by the same authors, we only included the most recent study or the study with the larger number of HCC patients.

Data extraction
Two researchers independently read the full texts and extracted the following information: publication data, study design, sample size, population, patients' ages, controlled variables, and follow-up period.

Methodological quality assessment
The Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of all cohort or case–control publications selected in the final analysis.[17] The scales allocated a maximum of nine stars for the quality of selection, comparability, exposure, and outcome of the study participants.[18] Two authors (YT and YL) independently assessed the study quality, and any inconsistency was discussed with the review team.

Statistical analysis
Stata software version 14.0 (Stata Corporation, College Station, TX, USA) was used for data analysis. The effect measures of interest were the HR, RR, and the corresponding 95% confidence intervals (CIs). RRs were directly considered as HR. Odds ratios (ORs) were transformed into RRs according to the formula $RR = OR/[(1-P0)+(P0 \times OR)]$, where P0 stands for HCC incidence in the nonexposed group.[19] Heterogeneity across studies was assessed using the Cochran Q test. Higgins I^2 statistics were used to determine the degree of between-study heterogeneity.[20] Publication bias was examined by Begg's funnel plots and Egger's regression tests.[21] Sensitivity analyses were conducted to investigate the robustness of our results and to assess whether any of the included studies had a considerable influence on the results. A fixed-effects model was initially used for our meta-analyses. Since sensitivity analysis could not determine the source of heterogeneity, a random-effects model was subsequently used to accommodate the anticipated heterogeneity across studies. If a direct report of patient survival was not available,[22] an estimated value was derived indirectly from the Kaplan–Meier curves using Engauge Digitizer software (http://markummitchell.github.io/engauge-digitizer). A descriptive analysis was performed when the quantitative data could not be pooled. All statistical tests were two-tailed, and differences with $P < 0.05$ were considered statistically significant.

Results
Study and patient characteristics
As shown in Figure 1, 2265 records were identified through database searches. Overall, 228 full-text articles were assessed for eligibility after removing duplicates and
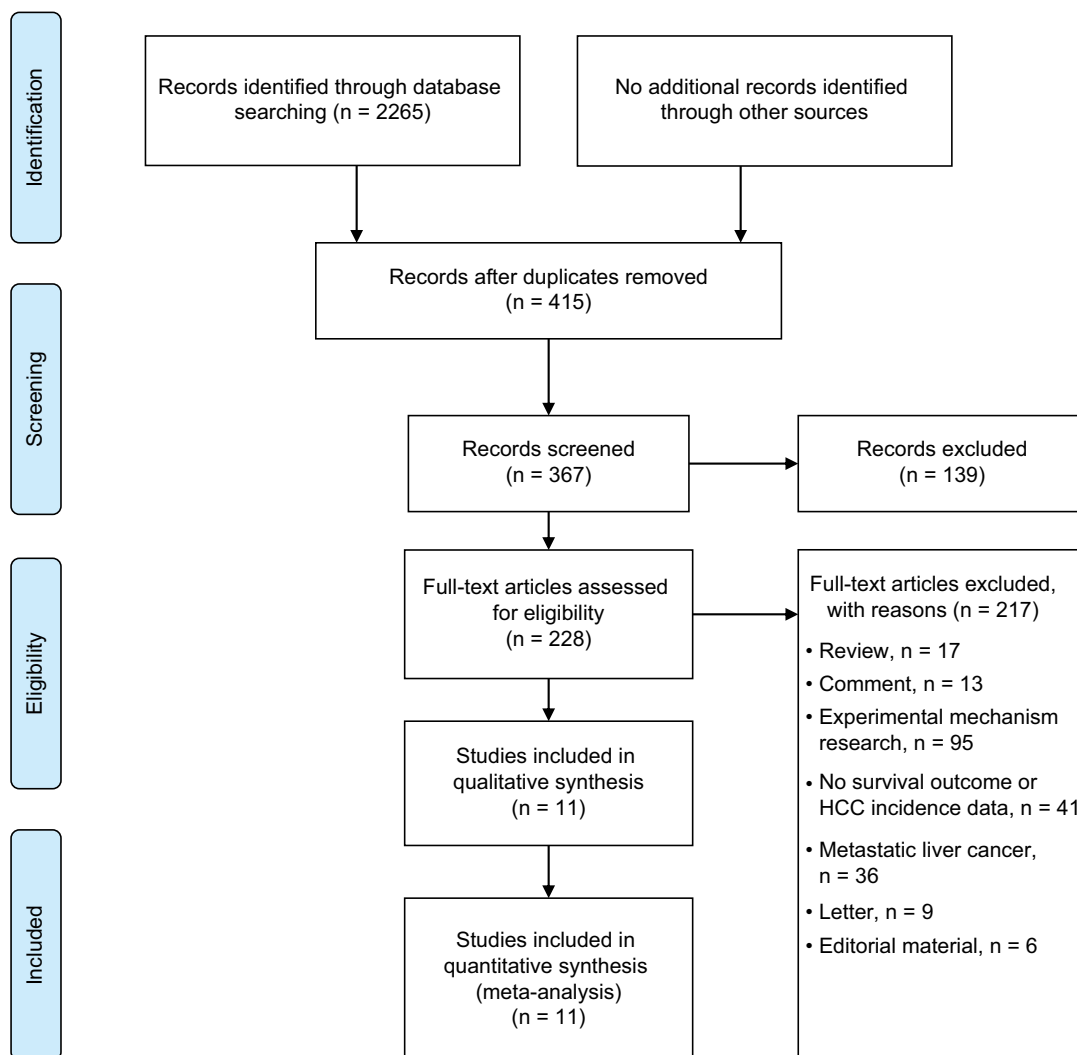
Figure 1 Study selection process

screening records. Eleven studies[16,22–31] were included in our analysis. Six studies[16,23–27] reported the epidemiology data of NSAID use related to HCC occurrence, and five[22,28–31] presented survival data. The baseline characteristics of the included studies are summarized in Tables 1 and 2.

Quality assessment of included studies

The NOS quality assessment scale was used to examine potential bias risks of case control studies and cohort studies. The detailed NOS items and scores of each study are presented in Table 3. Cohort studies by Sahasrabuddhe et al[16] and Wu et al[30] did not present adjusted variables in exposed and non-exposed individuals, leading to a one-star score for comparability. We did not conduct a methodological quality assessment for the study reported in the abstract.[25] The study by Takami et al[29] was randomized and non-blinded with no

patients lost to follow-up, which we considered to have a low risk of selection bias, attrition bias, and reporting bias.

NSAIDs and HCC risk

Heterogeneity was found when evaluating the association between NSAID use and HCC risk ($I^2 = 78.1\%$, $P < 0.001$, Figure 2A). We performed a publication bias analysis and sensitivity analysis of these six studies.[16,23–27] No publication bias was found by Begg's and Egger's tests ($P = 0.764$ and $P = 0.475$, respectively, Figure 2B and 2C). When each named study was omitted, no large influence was found in our sensitivity analysis (Figure 2D). Thus, a meta-analysis of six studies[16,23–27] with the random-effect model demonstrated that patients who received NSAIDs had a similar risk of HCC occurrence compared with those without NSAIDs (HR = 0.74, 95%CI = 0.53–1.02, $P = 0.064$, Figure 2A).

Table 1 Characteristics of studies with HCC occurrence risk data

Studies	Study design	Country	NSAIDs	NSAID duration	RR (95%CI)	Controlled variables	Hepatitis virus infection
Coogan et al (2000)[23]	Case–control	USA	Salicylates, indoles, propionic acids, fenamates, and/or oxicams	At least 4 days/week for at least 3 months, at least 1 year before admission	Regular use initiated >1 year; 0.9 (0.3–2.9); Nonregular use; 1.6 (0.8–3.1)	Age, sex	NA
Lee et al (2017)[24]	Cohort, retrospective	Korea	Aspirin	38.5 months (IQR, 10.4–68.7 months)	0.26 (0.09–0.74)	Cirrhosis	HBV
Oh et al (2017)[25]	Retrospective	Korea	Aspirin	NA	0.27 (0.09–0.76) in propensity score-matched pairs; 0.27 (0.10–0.74) in time-varying Cox proportional analyses	Time-varying Cox proportional hazards model; propensity score-matching	NA
Petrick et al (2015)[26]	Cohort, prospective	USA	Aspirin, ibuprofen	NA	0.68 (0.57–0.81)	NA	42 (26.6%) were anti-HCV positive and five (3.2%) were HBsAg positive in HCC cases; 10 (2.5%) were anti-HCV positive and three (0.8%) were HBsAg positive in controls
Sahasrabuddhe et al (2012)[16]	Cohort, prospective	USA	Aspirin, ibuprofen, naproxen, ketoprofen, piroxicam, sulindac, indomethacin, nambumetone	NA	0.59 (0.45–0.77) for aspirin use; 1.08 (0.84-1.39) for non-aspirin NSAID use	NA	NA
Yang et al (2016)[27]	Nested case–control	UK	Aspirin, COX-2 inhibitors, propionic acid derivatives, fenamic acid derivatives, acetic acid derivatives, and enolic acid derivatives	Two or more NSAID prescriptions	1.11 (0.86-1.44) for aspirin use; 1.05 (0.88-1.24) for NSAIDs	Age, sex, general practice, and number of years in the CPRD prior to the case's index date	HBV and/or HCV infection, 170 (14.2%) in HCC cases and 23 (0.5%) in controls

Abbreviations: CPRD, Clinical Practice Research Datalink; NSAID, nonsteroidal anti-inflammatory drug; COX-2, cyclooxygenase-2; NA, not available; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

No large influence was detected in NSAID use and HCC occurrence and, thus, we conducted further subgroup analysis based on NOS scores and study design (Figure 3). As shown in Figure 3A, no heterogeneity was found in studies with lower NOS scores ($I^2 = 55.1\%$, $P = 0.136$, Figure 3A), while heterogeneity was still detected in studies with high NOS scores ($I^2 = 80.2\%$, $P < 0.001$, Figure 3A). Additionally, no significant associations were found between NSAIDs and the risk of HCC occurrence in both the groups with lower and higher NOS scores (HR = 0.48, 95%CI = 0.22–1.04,

$P = 0.064$ and HR = 0.84, 95%CI = 0.58–1.24, $P = 0.386$, respectively, Figure 3A). Interestingly, when we performed subgroup analysis based on study design, no heterogeneity was found in either subgroup ($I^2 = 48.1\%$, $P = 0.123$ and $I^2 = 0.0\%$, $P = 0.475$, respectively, Figure 3B). Meta-analysis revealed that NSAID use could significantly decrease the HCC occurrence risk in four cohort studies[16,24–26] (HR = 0.58, 95%CI = 0.43–0.78, $P < 0.001$, Figure 3B), while no association between NSAIDs and HCC risk was found in case–control studies[23,27] (HR = 1.07, 95%CI = 0.91–1.26,

Table 2 Baseline characteristics of studies with HCC survival outcomes

Studies	Study design	Country/ area	HCC cases, n	NSAIDs	NSAID duration	Aspirin administration	Treatment regimen	Hepatitis virus infection	Controlled variables	Follow-up
Lee et al (2016)[22]	Cohort	Taiwan	9461	Aspirin	≥90 days	100 mg/day	Liver resection	HBV	Propensity score-matching	≥90 days
Li et al (2016)[28]	Case–control, retrospective	China	120	Aspirin	≥90 days	100 mg/day	TACE	HBV, n = 110; HCV, n = 5	Age, sex, date of HCC diagnosis, Child-Pugh score	12.0 (1.0–48.0) months
Takami et al (2016)[29]	RCT	Japan	232	Meloxicam	NA	None	Hepatic resection and/or microwave ablation	HBV, n = 24; HCV, n = 152	Age, sex, etiology	NA
Wu et al (2012)[30]	Cohort	Taiwan	4569	NA	At least 1 day per month on average	NA	Liver resection	HBV	NA	≥90 days
Yeh et al (2015)[31]	Cohort, retrospective	Taiwan	15,574	Conventional NSAIDs, aspirin, and COX-2 inhibitors	NA	NA	Liver resection	HBV, n = 8002; HCV, n = 4575	Age, sex, extent of liver resection, comorbidities and drug usage	1.8 (0.8–3.9) years

Abbreviations: HBV, hepatitis B virus; TACE, transarterial chemoembolization; NA, not available; RCT, randomized controlled trial.

$P = 0.402$, Figure 3B). Therefore, we assumed that the study design contributed to heterogeneity, and well-designed trials should be considered to evaluate the relationships between NSAIDs and HCC risk.

Five studies[16,24–27] reported aspirin use and risk of HCC occurrence. Heterogeneity was found ($I^2 = 80.2\%$, $P < 0.001$, Figure 4A); no publication bias was found by Begg's and Egger's tests ($P = 0.086$ and $P = 0.403$, respectively, Figure 4B and 4C); and no large influence was found after each named study was omitted by sensitivity analysis (Figure 4D). Accordingly, a meta-analysis of five studies with a random-effects model[16,24–27] with data on aspirin use and HCC risk revealed that aspirin use could significantly decrease the risk of HCC occurrence (HR = 0.64, 95%CI = 0.45–0.91, $P = 0.014$; Figure 4A). In two studies reported by Yang et al[27] and Oh et al,[25] the dose and daily frequency of aspirin were not available. However, in the studies of Sahasrabuddhe et al[16] and Petrick et al,[26] patients with any frequency of aspirin use were included. In the study by Lee et al,[24] 100 mg aspirin was used daily.

Three studies[16,26,27] reported data on non-aspirin NSAID use and HCC risk. The non-aspirin NSAIDs in these three studies included ibuprofen,[26] COX-2 inhibitors (rofecoxib, celecoxib, and etoricoxib), propionic acid derivatives (ibuprofen, naproxen, ketoprofen, and tiaprofenic acid), fenamic acid derivatives (mefenamic acid), acetic acid derivatives (diclofenac, indomethacin, etodolac, and nabumetone), and enolic acid derivatives (piroxicam and meloxicam).[27] Since no heterogeneity was found between these three studies ($I^2 = 0.0\%$, $P = 0.952$, Figure 5A), sensitivity analysis was not conducted. Meta-analysis with a fixed-effect model showed that no significant difference was found for the use of non-aspirin NSAIDs in HCC occurrence (RR = 0.98, 95%CI = 0.87–1.12, $P = 0.81$; Figure 5A). Additionally, no publication bias was detected by Begg's and Egger's tests ($P = 0.548$ and $P = 0.425$, respectively, Figure 5B and 5C).

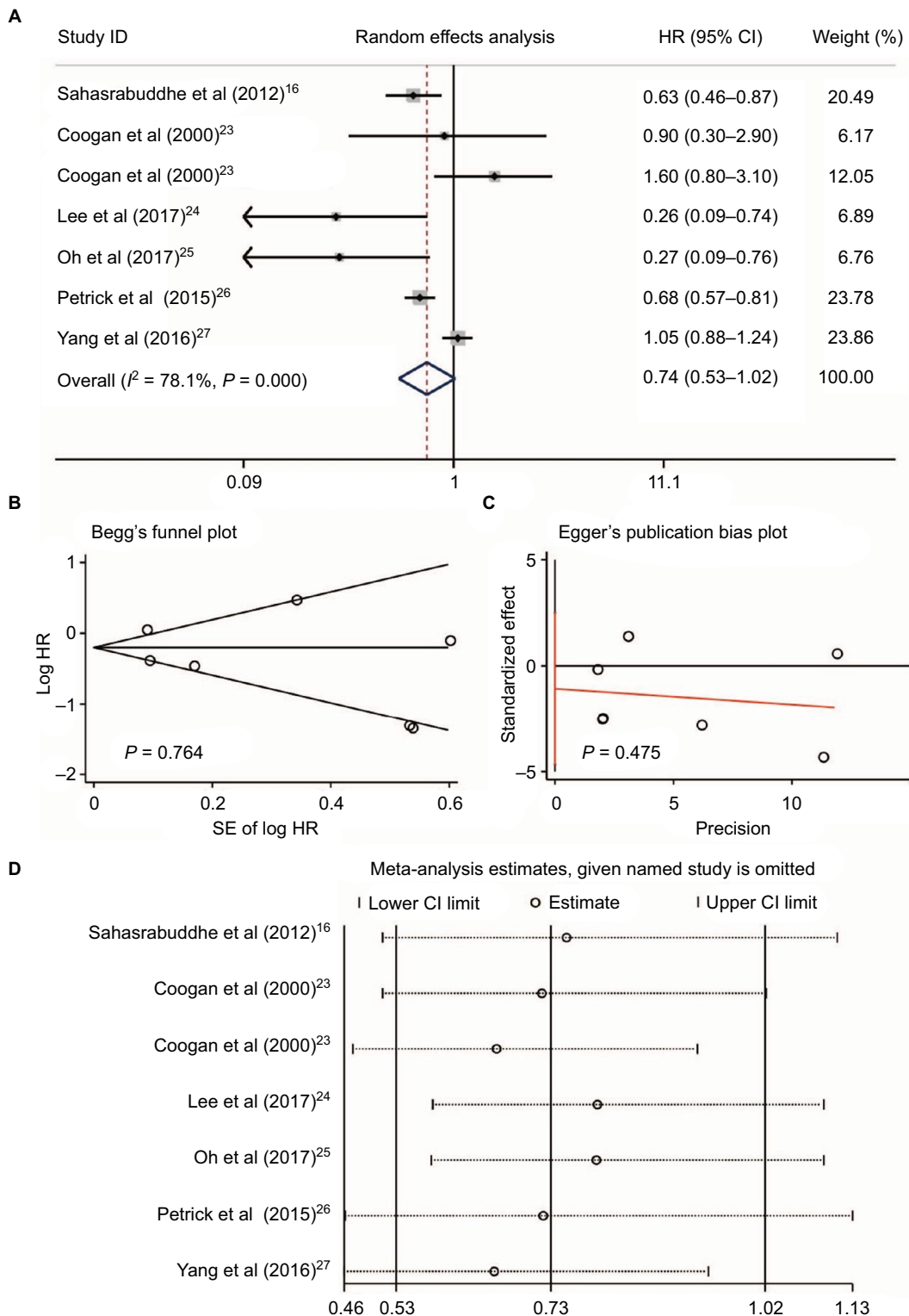## NSAIDs and HCC survival

No heterogeneity was found when evaluating disease-free survival (DFS) and overall survival (OS) of HCC patients who received NSAIDs ($I^2 = 0.0\%$, $P = 0.399$ and $I^2 = 0.0\%$, $P = 0.982$, respectively, Figure 6). Three studies[22,30,31] reported the DFS risk of HCC patients treated with NSAIDs. Two studies[22,28] presented OS data. Meta-analysis with a fixed-effect

Table 3 NOS quality assessment of included studies (case control studies and cohort studies)

Case–control studies		Coogan et al (2000)[23]	Yang et al (2016)[27]	Li et al (2016)[28]
Selection	Is the case definition adequate?	*	*	*
	Representativeness of the cases	*	*	*
	Selection of controls	*	*	*
	Definition of controls	*	*	*
Comparability	Comparability of cases and controls on the basis of the design or analysis	**	**	**
Exposure	Ascertainment of exposure	*	*	*
	Same method of ascertainment for cases and controls	*	*	*
	Non-response rate			
NOS scores		8	8	8

Cohort studies		Sahasrabuddhe et al (2012)[16]	Lee et al (2017)[24]	Petrick et al (2015)[26]	Lee et al (2016)[22]	Wu et al (2012)[30]	Yeh et al (2015)[31]
Selection	Representativeness of the exposed cohort	*					
	Selection of the non-exposed cohort	*	*	*	*	*	*
	Ascertainment of exposure	*	*	*	*	*	*
	Demonstration that outcome of interest was not present at start of study	*	*	*	*	*	
Comparability	Comparability of cohorts on the basis of the design or analysis	*	**	**	**	*	**
Exposure	Assessment of outcome	*	*	*	*	*	*
	Was follow-up long enough for outcomes to occur	*	*	*	*	*	*
	Adequacy of follow-up of cohorts	*	*	*	*	*	*
NOS scores		7	8	8	8	7	8

Notes: A study can be awarded a maximum of one asterisk (*) for each numbered item within the Selection and Exposure categories. A maximum of two asterisks (**) can be given for Comparability.
Abbreviation: NOS, Newcastle–Ottawa scale.

A

Study ID	Random effects analysis	HR (95% CI)	Weight (%)
Sahasrabuddhe et al (2012)[16]		0.63 (0.46–0.87)	20.49
Coogan et al (2000)[23]		0.90 (0.30–2.90)	6.17
Coogan et al (2000)[23]		1.60 (0.80–3.10)	12.05
Lee et al (2017)[24]		0.26 (0.09–0.74)	6.89
Oh et al (2017)[25]		0.27 (0.09–0.76)	6.76
Petrick et al (2015)[26]		0.68 (0.57–0.81)	23.78
Yang et al (2016)[27]		1.05 (0.88–1.24)	23.86
Overall (I^2 = 78.1%, P = 0.000)		0.74 (0.53–1.02)	100.00

0.09   1   11.1

B

Begg's funnel plot

P = 0.764

Log HR / SE of log HR

C

Egger's publication bias plot

P = 0.475

Standardized effect / Precision

D

Meta-analysis estimates, given named study is omitted

I Lower CI limit   o Estimate   I Upper CI limit

Sahasrabuddhe et al (2012)[16]

Coogan et al (2000)[23]

Coogan et al (2000)[23]

Lee et al (2017)[24]

Oh et al (2017)[25]

Petrick et al (2015)[26]

Yang et al (2016)[27]

0.46   0.53   0.73   1.02   1.13

Figure 2 NSAIDs, including aspirin use and HCC risk. The use of NSAIDs, including aspirin and HCC risk (**A**); publication bias of included studies by Begg's (**B**) and Egger's tests (**C**); and sensitivity analysis of included studies (**D**).
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; HCC, hepatocellular carcinoma.

A

B
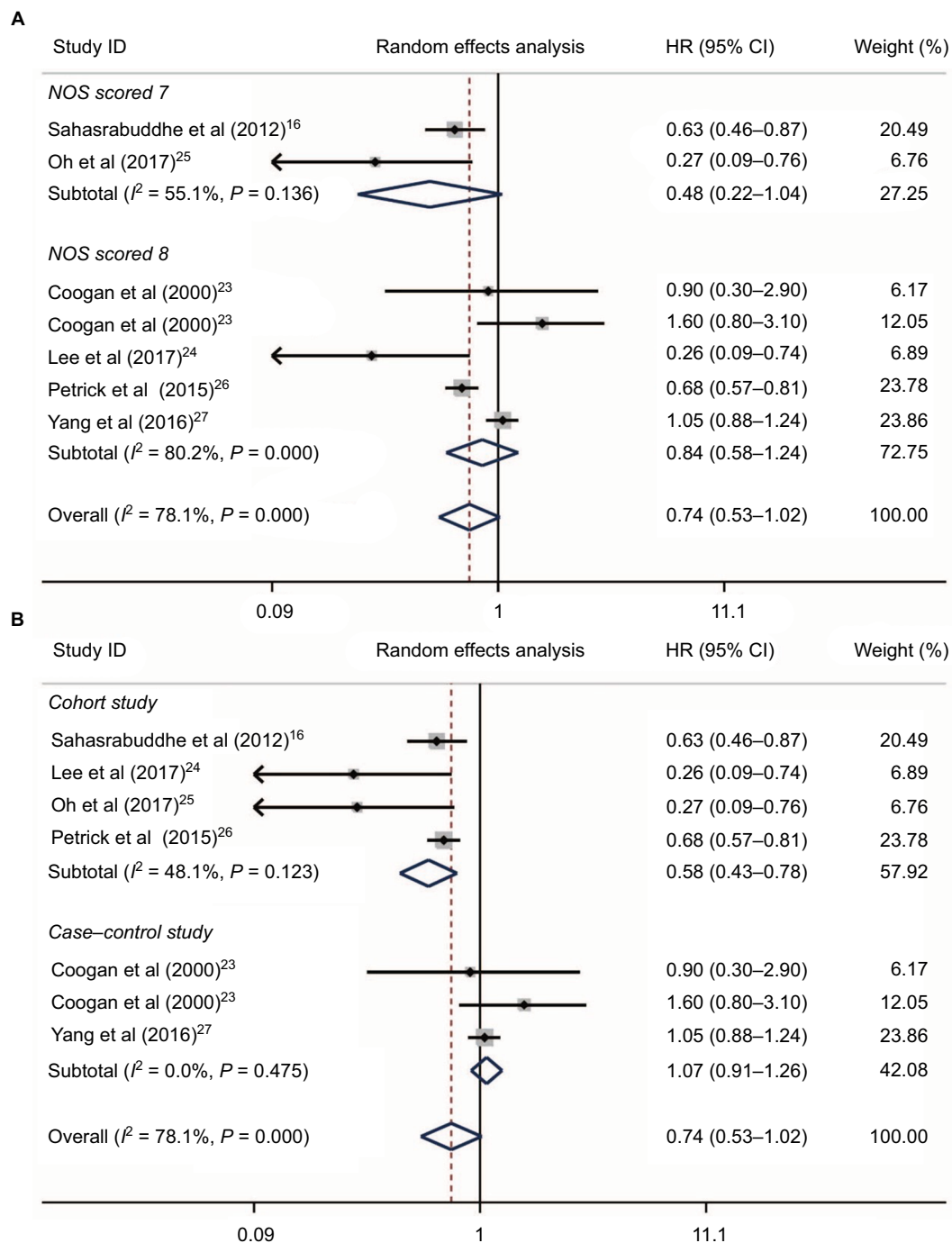
Figure 3 Subgroup analysis of links between NSAIDs and HCC risk based on NOS scores (**A**) and study design (**B**).
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; HCC, hepatocellular carcinoma.

model showed that HCC patients who received NSAIDs achieved better DFS and OS compared with non-NSAID users (HR = 0.79, 95%CI = 0.74–0.84, $P<0.001$ and HR = 0.60, 95%CI = 0.50–0.72, $P<0.001$, respectively, Figure 6A and 6B).

Additionally, we conducted a meta-analysis of the mortality rate of HCC patients who received aspirin treatment

in two studies.[22,28] Our results showed that aspirin treatment in HCC patients could significantly decrease the 2-year and 4-year mortalities (RR = 0.50, 95%CI = 0.36–0.69, $P < 0.001$ and RR = 0.67, 95%CI = 0.45–0.998, $P = 0.049$, respectively, Figure 7). Since only three studies[22,30,31] presented data on NSAID use and HCC survival and two studies[22,28] reported data on aspirin use and HCC survival, the relationships
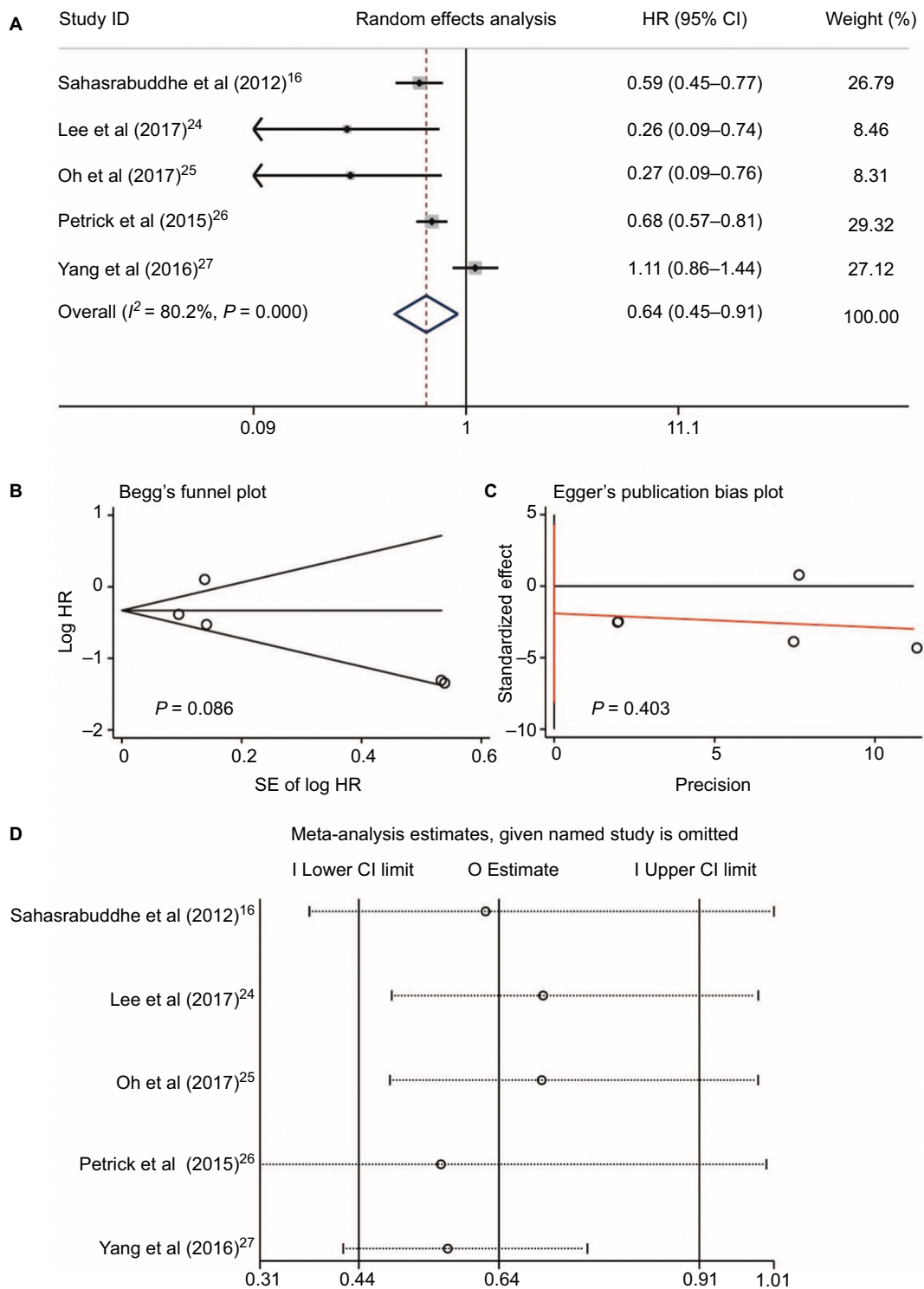
Figure 4 Aspirin use and HCC risk. Relationship between the use of aspirin and HCC risk (**A**); publication bias of included studies by Begg's (**B**) and Egger's tests (**C**); and sensitivity analysis of included studies (**D**).
Abbreviation: HCC, hepatocellular carcinoma.

A Study ID   Fixed effects analysis   HR (95% CI)   Weight (%)

Study ID	HR (95% CI)	Weight (%)
Sahasrabuddhe et al (2012)[16]	1.08 (0.84–1.39)	24.29
Petrick et al (2015)[26]	1.01 (0.72–1.42)	13.36
Yang et al (2016)[27] (COX-2 inhibition)	0.98 (0.55–1.72)	4.74
Yang et al (2016)[27] (PAD)	0.97 (0.76–1.24)	25.71
Yang et al (2016)[27] (FAD)	1.33 (0.52–3.39)	1.75
Yang et al (2016)[27] (AAD)	0.89 (0.70–1.14)	25.91
Yang et al (2016)[27] (EAD)	0.97 (0.53–1.77)	4.24
Overall ($I^2 = 0.0\%$, $P = 0.952$)	0.98 (0.87–1.12)	100.00

0.295   1   3.39

B Begg's funnel plot   **C** Egger's publication bias plot

Figure 5 Non-aspirin NSAIDs use and HCC risk. Relationship between the use of non-aspirin NSAIDs and HCC risk (**A**); publication bias of included studies by Begg's (**B**) and Egger's tests (**C**).
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; HCC, hepatocellular carcinoma; COX-2, cyclooxygenase-2; PAD, propionic acid derivatives; FAD, fenamic acid derivatives; AAD, acetic acid derivatives; EAD, enolic acid (oxicam) derivatives

between NSAID use and HCC clinical outcomes should be reevaluated by well-designed, large sample, multiple-centered RCTs in future.

Adverse events

Two studies[24,28] presented the hazard risk of bleeding in HCC patients who received aspirin treatment. No heterogeneity was found ($I^2 = 47.7\%$, $P = 0.167$, Figure 8). Meta-analysis showed that aspirin use was not associated with a higher risk of bleeding in HCC patients (HR = 0.71, 95%CI = 0.41–1.23, $P = 0.223$, Figure 8). Additionally, a study by Li et al[28] also found no differences of bleeding risk between the aspirin group (6/60, 10%) and non-aspirin group (7/60, 11.7%) in unresectable HCC. Another study by Yeh et al[31] evaluated the bleeding risk of HCC in patients who received NSAIDs after

curative liver resection. They found that the incidence of de novo upper gastrointestinal bleeding in NSAID users was significantly higher than that of nonusers (25.3% vs 18.7%; $P < 0.001$). Therefore, the bleeding risk of NSAIDs including aspirin in HCC patients still needs further evaluation.

Discussion

HCC is a type of inflammation-associated cancer;[32] an environment of chronic inflammation results in continuous rounds of cell injury, necrosis, and regeneration that leaves the liver prone to the development of activating mutations in oncogenes and the inactivating genetic and epigenetic suppression of tumor suppressor genes.[33–35] Currently, anti-inflammatory therapy is effective at preventing early neoplastic progression and malignant conversion.[35–37]

A   Disease-free survival
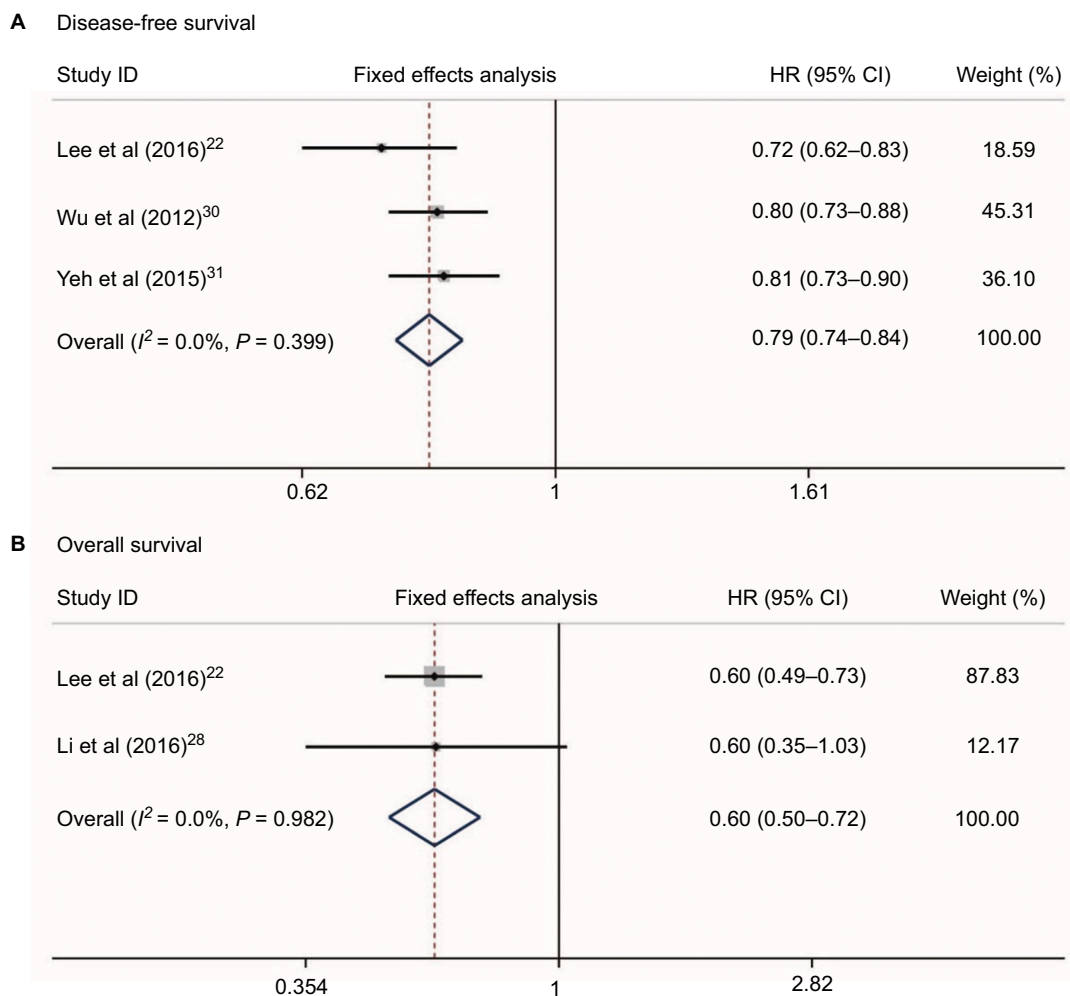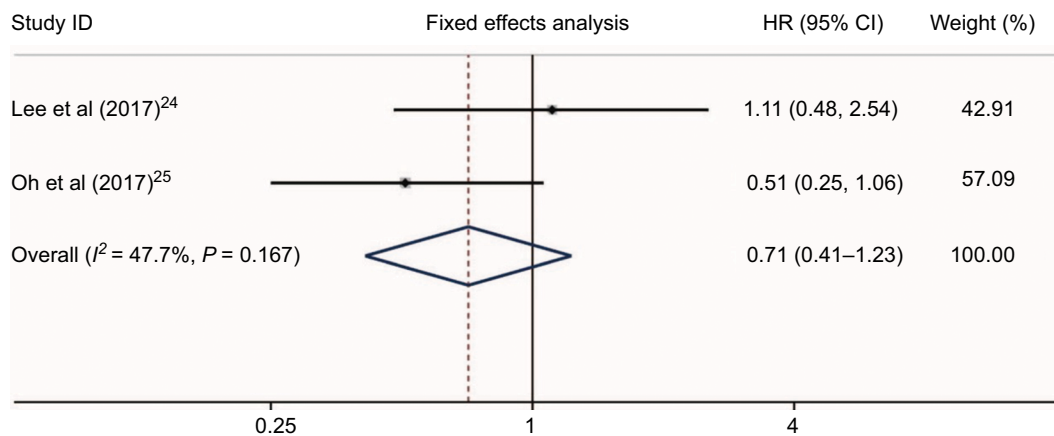

B   Overall survival

Figure 6 Relationship between NSAIDs use and disease-free survival (**A**) and overall survival (**B**) in HCC patients.
Abbreviation: HCC, hepatocellular carcinoma.

NSAIDs are potential agents for chemoprevention against liver cancer based on their anti-inflammatory properties. Previous experimental studies have revealed that NSAIDs may inhibit liver cancer cellular growth and induce cell apoptosis by modifying COX enzymatic pathways, which mediate inflammation.[38,39] Although many epidemiological studies demonstrated that treatment with NSAIDs reduces the incidence and mortality of certain malignancies, including HCC, no consistent conclusion was found.[23] In the studies included in our analysis, Sahasrabuddhe et al[16] and Petrick et al[26] conducted two large sample cohort studies and showed that NSAIDs were associated with an approximately 30%–40% reduced risk of developing HCC. Consistent results were also observed in patients who used aspirin. However, the risk of developing HCC remained unchanged in the users of non-aspirin NSAIDs.[16,26] The evidence presented in these two studies is not robust enough to recommend the use of

NSAIDs or aspirin in the prevention of HCC.[7] The case–control studies by Yang et al[27] and Coogan et al[23] showed that NSAIDs, including aspirin monotherapy and non-aspirin NSAIDs, were not associated with HCC occurrence. Oh et al's study[25] was reported as conference abstract and Lee et al's study[24] was performed in chronic hepatitis B patients on antiviral treatment, leading to the conclusion that the aspirin group showed a significantly lower risk of HCC.

This meta-analysis of cohort studies showed that NSAIDs could significantly decrease the risk of HCC occurrence. Our results showed that aspirin use could significantly reduce the risk of developing HCC. HCC patients who received NSAIDs or aspirin treatment achieved better survival compared with non-users. In vitro studies have shown that NSAIDs can potentiate apoptotic pathways by increasing death signal-associated receptors and decreasing proinflammatory signals.[40,41] Considering the anti-inflammatory mechanisms of

A 2-year mortality

Study	Fixed effects analysis	RR (95% CI)	Aspirin	Control	Weight (%)
Lee et al (2016)[22]		0.49 (0.32–0.75)	22/279	154/960	67.76
Li et al (2016)[28]		0.52 (0.32–0.82)	17/60	33/60	32.24
		0.50 (0.36–0.69)	39/339	187/1020	100.00

Overall (I^2 = 0.0%, P=0.880)

0.321　　　　　1　　　　　3.12

B 4-year mortality

Study	Random effects analysis	RR (95% CI)	Aspirin	Control	Weight (%)
Lee et al (2016)[22]		0.53(0.37–0.76)	31/188	158/528	44.96
Li et al (2016)[28]		0.80 (0.63–1.03)	97/60	46/60	55.04
		0.67 (0.45–0.998)	67/248	204/588	100.00

Overall (I^2 = 71.7%, P = 0.060)

0.375　　　　　1　　　　　2.67

Figure 7 Two-year (**A**) and 4-year mortalities (**B**) of HCC patients who received aspirin treatment.
Abbreviation: HCC, hepatocellular carcinoma.

NSAIDs, the anti-platelet effects of aspirin and our results, we cautiously drew the conclusion that NSAIDs, especially aspirin, might be a therapeutic strategy for HCC. However, as reviewed by Sahin et al,[42] the pattern of COX-2 expression in HCC is different from that of other cancers. A low expression of this critical enzyme is associated with poor differentiation, whereas higher expression levels of COX-2 have been observed in well-differentiated HCC samples.[43,44] Therefore, the exact roles of non-aspirin NSAIDs in HCC aggressiveness need to be studied further.

Previous research has demonstrated that platelets are key facilitators of this inflammation-mediated injury. The elevation of the circulating platelet count is frequently found in patients with cancer[45,46] and is associated with an increased risk of venous thromboembolism and poor prognosis.[46,47] Moreover, platelet depletion or the inhibition of platelet function has been shown to reduce or prevent cancer growth and distant metastasis in animal models.[15,48–50] Unlike other

NSAIDs, aspirin has an antiplatelet effect. In an animal study, aspirin prevented HCC formation and prolonged the survival of mice with a chronic immune-mediated inflammatory liver disease by attenuating platelet-mediated inflammation.[15] Platelets are involved in thrombosis, inflammatory responses, liver regeneration,[51,52] and the regulation of angiogenesis.[53,54] In several tumor cell lines, platelets affected the epithelial-mesenchymal transition, invasion, and metastasis.[55] Clinical studies have shown that high platelets are involved in the extrahepatic metastasis and recurrence of HCC.[56–58] Buergy et al[59] demonstrated that an elevated platelet level at the time of diagnosis was associated with a shorter survival in many solid tumors, including pancreatic adenocarcinoma, gastric cancer, and HCC. Nouso et al[60] recruited 157 HCC patients with Child-Pugh class C cirrhosis and found that a high platelet level was an independent predictor of poor OS. Considering previously published reports and our results, we assumed that aspirin could decrease HCC risk and improve

Figure 8 Bleeding risk of HCC patients who received aspirin treatment.
Abbreviation: HCC, hepatocellular carcinoma.

survival. Unfortunately, all the included studies that reported the survival data of NSAIDs were small sample, non-RCT studies. Further trials are needed in the future.

This meta-analysis has some limitations. First, most of the studies included in this analysis were not RCTs, leading to potential biases. Second, some studies included in this analysis did not report HCC risk factors, including hepatitis B virus/hepatitis C virus infection status. Third, the included studies that reported the survival outcomes of HCC patients who received NSAIDs had small sample sizes, and most of them included patients who received hepatic resection and might have had small HCC tumors and compensatory liver function, which poses a high risk of selection bias.

Conclusion

In summary, our results indicate that the use of NSAIDs, especially aspirin, could reduce HCC risk and improve survival in this population. Some NSAIDs have moderate selectivity for COX-1, others inhibit both COX isoforms including aspirin, indomethacin, naproxen and ibuprofen, other NSAIDs favor COX-2 inhibition, and the other ones including celecoxib, rofecoxib, lumiracoxib, valdecoxib and etoricoxib are highly selective for COX-2. Different types of NSAIDs and drug doses had different roles in the inhibition of COX-1 and COX-2.[61] Therefore, further studies to understand the impact of various doses and durations in the use of NSAIDs, especially aspirin intake, on the development and progression of HCC, are needed. The causal relationship between NSAIDs and HCC risk cannot be determined and further well-designed trials are required.

Disclosure

The authors report no conflicts of interest in this work.

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