Research Square

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Neutrophil-to-lymphocyte ratio predicts diagnosis and prognosis of patients with hepatocellular: A systematic review and meta-analysis

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Abstract

Background: Neutrophil-to-lymphocyte ratio (NLR) is one of the poor prognostic factors of Hepatocellular carcinoma (HCC) in patients. As contradictory data are seen concerning the predictive ability of NLR, a meta-analysis is performed for the determination of its prognostic value in patients with HCC in this study.

Methods: We systematically searched several databases including PubMed, EMBASE, and Cochrane Library with the updated date of January 21, 2020. Pooled estimates of odds ratio (OR) and diagnostic odds ratio (DOR) were used to assess the prognostic performance of NLR in HCC patients.

Results: Nine studies containing a total of 3,862 HCC patients were included. High baseline NLR was correlated with poor prognosis or recurrence significantly. The patient-based analysis of pooled estimates was as follows: sensitivity 0.68 [95% confidence interval (CI), 0.58-0.77], specificity 0.73 (95% CI, 0.61-0.82), and DOR 6.347 (95% CI, 5.450-7.391), respectively. The pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLHR) were 2.5 (95% CI, 1.8-3.6) and 0.43 (95% CI, 0.33-0.57). Furthermore, the area under the curve (AUC) of summary receiver operating characteristic (SROC) reflecting the diagnostic accuracy was 0.76 (95% CI, 0.72-0.80). Results obtained from subgroup meta-analyses and overall meta-analyses were accordingly consistent with each other.

Conclusions: Our findings suggested that NLR is an efficient prognostic factor for patients with HCC, especially for those from East Asian with high incidence. In the future, trails with larger sample sizes and more high-quality evidence are needed to further enhance the patient outcomes.

Background

As the fifth most common malignancy worldwide, hepatocellular carcinoma (HCC) ranks the third in mortality rate among cancers [1]. In the Asia-Pacific region, HCC is a major public health problem because of the relatively high incidence of viral hepatitis [2]. HCC is the second most common cancer in China and third in Korea, which is insidious and progresses rapidly [3, 4]. Currently, the overall survival of HCC is satisfying due to recent improvements in clinical treatment [5]. For instance, surgical resection of HCC is not only reliable and effective but also low in mortality rate [6]. Nevertheless, HCC prognosis remains poor. Still, death after curative resection is mainly attributed to high occurrence of tumor recurrence [7]. The recurrence of HCC originates from either *de novo* tumor arising from the remnant liver or intrahepatic metastasis of primary tumor [8]. To date, the identified risk factors indicate that late recurrence primarily arise from continuous liver disease whereas early recurrence is largely related to the characteristics of invasive tumor [8, 9]. Therefore, prognostic assessment of HCC is pivotal for improving the clinical outcomes of patients.

As known to all, HCC is generally developed from chronic inflammation and cirrhosis [10]. The inflammatory responses and immune status of HCC have an influence on the survival and recurrence after treatment [11]. Recently, more and more evidence has shown that poorer prognosis is correlated with the presence of systemic inflammation in cancer patients [12–16]. Meanwhile, neutrophil-to-lymphocyte ratio (NLR) has been reported as a dependable indicator to monitor and evaluate the systemic inflammatory reactions [17]. Furthermore, NLR can be repeatedly and easily obtained from peripheral blood. The baseline NLR has been reported to be a diagnostic marker or a valuable factor in many kinds of cancers, including renal cancer [18] and HCC [19].

Previous studies investigated its prognostic value in HCC patients experiencing specific treatments, and suggested that pretreatment NLRs are predictors of tumor recurrence and survival in patients with HCC [20, 21]. However, the exact function of NLR in HCC patients is conflicting among studies as a result of many elements, such as variances in sample size, study designs, regional differences, et cetera [22]. Some studies suggested that there is a strong correlation between higher NLR and poorer prognosis, while others did not [18, 23]. It was demonstrated that mutually contradictory data have arisen with regard to the predictive ability of NLR for HCC prognosis, especially in patients from East Asia with high incidence of HCC [19]. As a result, to carry out a meta-analysis has become a necessity so that we can acquire a systematically and thoroughly understanding relating the prognostic value of NLR in HCC patients.

To the best of our knowledge, few studies have systematically concentrated on the prognostic value of NLR in HCC patients, especially in those from a region with a high morbidity of this disease. In this study, we aim to illuminate the prognostic value of NLR in HCC patients and to find out whether the prognostic accuracy can be increased in a high-risk region of HCC.

Methods

Data sources and searches

A systematic search of several databases including PubMed, EMBASE and Cochrane Library was performed from inception to the updated date of January 21, 2020. The search terms were used as follows: ("liver cancer"[Mesh] OR "hepatoma"[Mesh] OR "hepatic carcinoma"[Mesh] OR "hepatocellular carcinoma"[Mesh]) and ("neutrophil to lymphocyte ratio", "neutrophil lymphocyte ratio" OR "neutrophil-to-lymphocyte ratio" OR "inflammatory markers"). Abstracts with complete result sections were included in this study. The bibliography of retrieved articles was manually checked for additional references. Only studies published in English were considered. This meta-analysis was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement issued in 2009 (Checklist file) [24, 25]. The present meta-analysis was also submitted to PROSPERO with the Registration number 156404.

Study Selection

All citations were reviewed one by one. Full texts of possibly involved articles were retrieved by titles or abstracts and eligible studies were determined through independent examinations by two investigators (Shan Lin and Shiping Hu). Disagreements on eligibility were settled by discussion with an arbitrator (Fenfang Wu). Studies that clearly met the following inclusion criteria were considered: (1) Participants were aged ≥ 18-year old for human studies; (2) Serum levels of NLR were measured prior to formal treatment; (3) Sample size was greater than 30; (4) RCTs were observational in nature; (5) Sufficient data of true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) were provided in order that the calculation of predictive ability of NLR as a predictor in HCC patients could be completed. Studies were eliminated if they met the following exclusion criteria: (1) Only animal or *in vitro* study was performed; (2) Information about diagnostic accuracy was lacked in control or experimental group; (3) Article type was review, commentary, poster, letter, supplementary issue, or editorial; (4) Duplicate data were contained or information was insufficient.

Data Extraction

Data from each trial were extracted by two reviewers (Shan Lin and Shiping Hu) independently. All discrepancies were discussed with and evaluated by a third investigator (Fenfang Wu) to resolve disagreement between the two reviewers until an agreement was reached. Prespecified data from each article included the request for documentation and recalculation of variables as follows: first author, year of publication, type of publication, study design, regions, sample size (male), enrollment period, median age (years), AUC (95% CI), baseline NLR cut-off, sensitivity and specificity. Enough figures of true-positive, false-positive, false-negative and true-negative could be used to calculate the prognostic value of NLR in HCC patients.

Quality Assessment

Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was adopted for quality assessment of the articles by two independent reviewers (Shan Lin and Shiping Hu) [26]. This tool consists of 4 domains: index test, patient selection, reference standard, and flow and timing. “Risk of bias” was evaluated for all 4 domains and “concerns regarding applicability” was assessed for the first 3 domains, with each item judged to be “yes,” “no,” or “unclear.”

The quality of eligible studies was evaluated by Newcastle-Ottawa Scale (NOS) Assessment [27]. On the basis of 3 parts including selection, comparability and exposure, the estimations of study quality were judged using a “star-rating system” with a maximum of 9 stars. The quality of each trail was defined as poor with 0–3 stars, fair with 4–6 stars, and good with 7–9 stars. Quality assessment of NOS was performed referring to the previous study with modifications [21].

Data Synthesis And Analysis

STATA version 12.0 (Stata Corp, College Station, TX) was used for all statistical analyses of TP, TN, FP and FN rates for each test in every study and assessment of sensitivity, specificity, PLR, NLHR and DOR for each eligible study. $P < 0.05$ for Q statistic and $I^2 > 50\%$ for I^2 statistic were considered to have statistically significant heterogeneity [28]. I^2 index was used to indicate the degree of heterogeneity among multiple studies with I^2 values of < 25%, 25–50% and > 50% respectively regarded as modest, moderate and substantial. A random-effects model was adopted when heterogeneity was substantial ($I^2 > 50\%$) [29]. Hardy-Weinberg equilibrium (HWE) in controls of each study was examined by Pearson’s χ^2 test with $P < 0.05$ considered statistically significant [30].

Summary receiver operator characteristic (SROC) curves and forest plots of pooled sensitivity and specificity were conducted to evaluate the predictive performance of NLR in HCC patients which was measured by calculating AUC as a summary index [31]. Moreover, subgroup analyses were performed on a regional or geographic basis. At last, possible publication biases were detected by Begg’s and Egger’s tests with $P < 0.05$ considered statistically significant [32, 33].

Results

Literature search

Initially, electronic search yielded 521 potentially relevant studies, of which 276 were left after removing duplicates in the databases. 52 were excluded because of obvious irrelevance based on titles or abstracts. The remaining 224 full-text manuscripts were assessed for eligibility, of which 167 were excluded as they failed to meet the requirements of data extraction, and further 48 were eliminated as they mismatched the eligibility criteria. Consequently, 9 articles were eligible and included. The above 9 studies included a total of 3,862 patients for meta-analysis of predictive value of NLR for HCC prognosis. The stepwise screening of included studies was shown in detail in Fig. 1.

The Characteristics And Quality Of The Included Studies

All of the 9 included studies were written in English. For quality assessment of included study, baseline data of these studies were extracted and exhibited in Table 1. Regions of these 9 studies were all from East Asian with 7 from mainland China [34–40], 1 from Korea [41] and 1 from Taiwan [42]. All these studies were single-center trials published from 2012 to 2018. The 9 observational studies involved 3,862 HCC patients in total, of which 3,491 were from mainland China, 213 from Korea and 158 from Taiwan. The predictive performance of NLR for the prognosis of HCC patients was summarized in Table 2. The AUCs of the included studies ranged from 0.606 to 0.855 and the cut-off values from 1.505 to 2.979. Meanwhile, the sensitivity and specificity of the included studies were calculated or provided, with a range from 0.301 to 0.840 and 0.470 to 0.887 respectively.

Table 1
The main characteristics of the studies enrolled in the meta-analysis.

Author(Year)	Type of publication	Study design	Regions	Sample size (male)	Enrollment period	Median age (years)	NOS
Chen (2012)	Full-text	Retrospective	Taipei, Taiwan	158(95)	2003.07-2010.12	65.7 (31.8–82.8)	8
Du (2018)	Full-text	Retrospective	Xi'an, China	230(174)	2000.01-2012.12	44 (20–66)	7
Gao (2015)	Full-text	Retrospective	Beijing, China	825(690)	2008.10-2012.05	54.5 (25–75)	8
Hu (2016)	Full-text	Retrospective	Suwon, Korea	213(166)	2001.03-2011.12	53 (20–79)	8
Hu (2018)	Full-text	Retrospective	Beijing, China	545(442)	2013.07-2016.07	56.91	7
Li (2014)	Full-text	Retrospective	Beijing, China	506(420)	2005.04-2014.04	59.2 (28–85)	8
Liu (2016)	Full-text	Retrospective	Nanjing, China	223(189)	2004.07-2011.04	54 (21–82)	7
Liu (2017)	Full-text	Retrospective	Chengdu, China	760(643)	2007.01-2013.12	56.5 (19–89)	7
Tan (2018)	Full-text	Retrospective	Qingdao, China	402(299)	2008.09-2017.05	51.7(18–92)	8

Note: NR, no result.

Table 2
Predictive value of NLR to predict HCC in individual studies.

Study	AUC	95% CI	Cut-off value(ng/mL)	Sensitivity(%)	Specificity(%)	Number of patients			
						TP	FP	FN	TN
Chen (2012)	0.630	0.520–0.720	2.400	0.730	0.470	59	41	22	36
Du (2018)	0.625	0.527–0.732	2.270	0.639	0.653	57	49	32	92
Gao (2015)	0.811	NR	2.700	0.662	0.848	220	75	112	418
Hu (2016)	0.643	NR	1.505	0.775	0.486	83	54	24	52
Hu (2018)	0.738	0.699–0.774	2.979	0.539	0.858	199	25	170	151
Li (2014)	0.824	NR	2.140	0.780	0.690	143	100	40	223
Liu (2016)	0.606	NR	2.750	0.301	0.887	43	9	100	71
Liu (2017)	0.664	0.630–0.698	2.200	0.752	0.545	415	95	137	113
Tan (2018)	0.855	NR	2.200	0.840	0.860	210	21	40	131

Note: NR, no result.

Assessment Of Methodological Quality And Publication Bias

All studies were clearly defined by eligibility criteria and reasons for patient exclusion. The quality of each included study was assessed by QUADAS tool, and all of them had high QUADAS scores (≥ 10). Overall quality of included trials was moderate. The outcome of QUADAS-2 evaluation was provided in the ESM and shown in Fig. 2.

Subsequently, assessment of publication bias was conducted by funnel plot, which was shown in Fig. 3D, indicating that neither significant threshold effect nor significant asymmetry was observed. In other words, this meta-analysis had no obvious publication bias. Therefore, it seems unlikely that our findings would be greatly changed by unpublished studies.

Nlr For Predicting Prognosis In Patients With Hcc

There were 9 sets of data extracted from 9 eligible studies and presented in Table 2, including AUC, 95% CI, various optimal cut-off values of NLR, sensitivities, specificities, as well as TP/FP/FN/TN values. The

predictive value of NLR as a biomarker for prognosis of HCC patients was inspected in 9 studies with a total number of 3,862 subjects. The pooled data of these studies were summarized in Table 2. For summary of performance estimates, the pooled sensitivity of NLR was 0.68 (95% CI, 0.58–0.77) (Fig. 3A), specificity 0.73 (95% CI, 0.61–0.82) (Fig. 3B), PLR 2.5 (95% CI, 1.8–3.6) and NLHR 0.43 (95% CI, 0.33–0.57) respectively. The pooled DOR was 6.347 (95% CI, 5.450–7.391) using a random-effects model. The AUC of SROC for diagnostic accuracy summary was 0.76 (95% CI, 0.72–0.80) (Fig. 3C). To summarize, the predictive value of NLR for prognosis of HCC patients was shown in Fig. 4. It is concluded that high baseline NLR was prominently related to poor prognosis or recurrence

Subgroup Analysis

Subgroup analysis was performed and summarized in Table 3. On the basis of comparisons of DOR and AUC, NLR was variable to some extent regarding prognostic value in HCC patients. For subgroup regional analysis, the DOR and AUC of NLR in mainland China were significantly higher than those in Korea (DOR, 7; AUC, 0.79 vs DOR, 3; AUC, 0.64) and Taiwan (DOR, 7; AUC, 0.79 vs DOR, 2; AUC, 0.63), pointing a better prognostic value of NLR in HCC patients from mainland China than that from Korea and Taiwan. For subgroup geographic analysis, NLR showed a much higher prognostic value in North than that in South (DOR, 8; AUC, 0.80 vs DOR, 3; AUC, 0.69). Interestingly, it is not hard to find that the prognostic value of NLR varies significantly across the north-south geographic boundary.

Table 3
Subgroup analysis on the basis of different standards.

Studies	Number		Sensitivity	Specificity	PLR	NLHR	DOR	AUC
Regions	7	China	0.66(0.52–0.77)	0.78 (0.68–0.86)	3.0 (2.1–3.9)	0.43(0.31–0.61)	7 (4–12)	0.79(0.75–0.83)
	1	Korea	0.775	0.486	NR	NR	3 (2–6)	0.64
	1	Taiwan	0.730	0.470	NR	NR	2 (1–4)	0.63(0.52–0.72)
Geography	6	North	0.72(0.63–0.79)	0.76 (0.64–0.84)	2.9 (1.9–4.4)	0.37(0.28–0.50)	8 (4–14)	0.80(0.76–0.83)
	3	South	0.66 (0.45–0.82)	0.63 (0.40–0.80)	1.8 (1.3–2.4	0.54 (0.41–0.72)	3 (3–4)	0.69(0.65–0.73)

Note: NR, no result.

Analysis Of Publication Bias And Heterogeneity

Heterogeneity analysis and SROC were performed. There was no “shoulder arm” pattern seen in the SROC space, suggesting an absence of threshold effect. The publication bias, which was detected by Begg’s funnel plot and Egger’s test, was at a very low level of probability as shown in Fig. 5. Furthermore, meta-regression and subgroup analysis were accomplished for seeking other possible explanations of heterogeneity. The characteristics of geography (North: I^2 = 88.8%, $P \leq 0.001$ or South: I^2 = 0, P = 0.532) may harbor the main source, but the region (mainland China: I^2 = 90.1%, $P \leq 0.001$, Korea or Taiwan) maybe not a heterogeneity source of predictive value of NLR.

Discussion

As a conventional inflammatory marker, the prognostic function of NLR in HCC patients has been investigated in recent years. In this study, the exact connection between increased NLR levels and clinical outcomes of HCC was comprehensively and systematically determined in patients, especially in those from East Asia. We mainly investigated the association between high baseline NLR and prognosis of HCC. The pooled outcomes in these cohorts manifest that high baseline NLR was a remarkable predictor of poor prognosis of HCC patients, proposing that NLR is a valuable inflammatory biomarker with high sensitivity, specificity and DOR. In addition, subgroup analyses indicate that NLR worked better in HCC patients from mainland China than that from Korea and Taiwan. Moreover, high baseline NLR also significantly correlated with the prognostic value concerning geography, indicating NLR exhibits a better prognostic role in North than that in South.

Generally, high baseline NLR reflects a local and systemic inflammation, which forms a favorable microenvironment to promote tumor invasion and metastasis [43]. Previous studies reported that NLR not only reflects a tumor-friendly microenvironment but also the systemic immune status, which on one hand benefits tumor invasion and on the other restrains the host immune surveillance [44–46]. It is noteworthy that other laboratorial markers of systemic inflammatory response in addition to NLR also have been reported to play a prognostic role in patients with cancer, such as modified Glasgow prognostic score [47, 48], and notably C reactive protein (CRP) [49]. Besides, biological markers [50, 51] and gene polymorphisms [52] are also suggested to be used for prognosis in cancer patients. Nevertheless, NLR stands out with its low cost and broad practicality even in primary hospitals factoring in cost-effectiveness and accessibility [18]. The pooled results of our meta-analysis encourage a routine monitoring of NLR for poor prognosis and recurrence of HCC patients, regardless of tumor stage and geographic region.

In our subgroup analysis, a better prognostic value of prognosis was observed in HCC patients from mainland China (DOR, 7; AUC, 0.79) than that from both Korea (DOR, 3; AUC, 0.64) and Taiwan (DOR, 2; AUC, 0.63). This may be explained by the fact that HCC is the second common leading cancer in mainland China, indicating HCC is more severe here than the other two regions [53]. For subgroup geographic analysis, better prognostic performance of NLR as a predictor of prognosis was seen in HCC patients from the North (DOR, 8; AUC, 0.80) than that from the South (DOR, 3; AUC, 0.69). This may be related to the differences resting in dietary habits and lifestyles of people in the North and South, as well as the climatic environment [54]. It has been interestingly indicated that the incidence of HCC is influenced by the differences in habits between the North and the South, and people living in the South may have a relatively low risk of HCC.

Subsequently, meta-regression and interaction revisited subgroup analyses were adopted for decision of the causes for heterogeneity observed among included studies. Several stratified analyses concerning region or geography were performed for the investigation of the sources of heterogeneity. Moreover, the outcome of any single study as a main source of heterogeneity was ruled out by performing a “leave-one-out” sensitivity analysis. The pooled results indicate that the main source may lie in the characteristics of geography (North: I^2 = 88.8%, $P \leq 0.001$ or South: $I^2 = 0$, $P = 0.532$). However, the region (mainland China: $I^2 = 90.1\%$, $P \leq 0.001$, Korea or Taiwan) maybe not a heterogeneity source of predictive value of NLR. Consistently, differences in environmental factors, population characteristics, lifestyles and sample sizes have been most investigated to describe the reasons for heterogeneity in various studies [55]. Still and all, further verifications of the above conclusions need to be done by incorporating more studies that are in accordance with the inclusion criteria.

In addition, our study also has many limitations. Firstly, literature search was restricted within the openly published studies. In this situation, relevant studies that have not been openly published but also may meet the inclusion criteria of our meta-analysis are inevitably passed. Secondly, heterogeneity was observed in this study because of confounding factors, including the cut-off value of NLR and sample size. In spite of this, meta-regression and subgroup analyses have eliminated the capability of fully explaining the heterogeneity by both of the above-mentioned confounders. Thirdly, the correlation between elevated NLR and clinicopathological parameters of patients, including tumor stage and differentiation grade, was not analyzed because of insufficient data for analysis or lack of relevant information in some of the enrolled studies. Lastly, the association between high baseline NLR and poor prognosis of HCC was demonstrated in a majority of original studies, which may be explained by an easy-to-reach publication of positive results, ultimately leading to the difficulty in searching for more controversial studies.

Conclusion

The present meta-analysis shows a significant association between high baseline NLR and poor prognosis in HCC patients, especially in those from East Asian with high incidence of HCC. Therefore, NLR is an inflammatory factor for efficient evaluation of prognosis of HCC, which can be useful in determining individual treatment designs and stratifying patients. Even so, larger scale and more well-designed investigations are warranted for a better comprehension of the prognostic value of NLR in HCC patients.

Abbreviations

NLR, Neutrophil-to-lymphocyte ratio; HCC, Hepatocellular carcinoma; OR, odds ratio; DOR, diagnostic odds ratio; CI, confidence interval; AUC, area under the curve; OS, overall survival; TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; NOS, Newcastle–Ottawa Scale; PLR, positive likelihood ratio; NLHR, negative likelihood ratio; HWE, Hardy-Weinberg equilibrium; SROC, summary receiver operating characteristics.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed in this study are included in the included original studies.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization, SL, SPH and FFW; Data curation, SL and SPH; Formal analysis, SL and YR; Methodology, SL, SPH and YR; Software, SL and SPH; Supervision, FFW; Validation, all authors; Writing-original draft, SL and SPH; Writing-review and editing, all authors. All authors have read and approved the manuscript.

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Figures

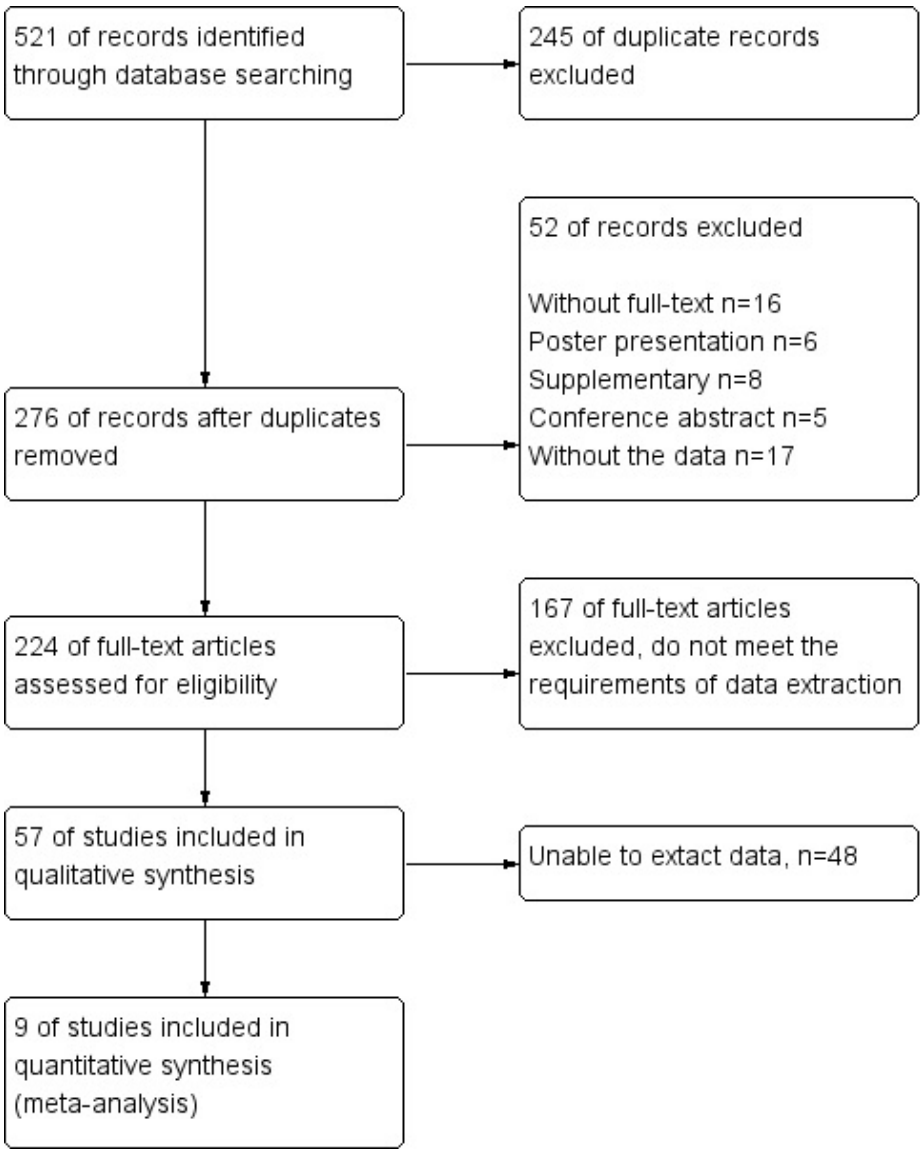

Figure 1

The selection process of the included studies in the meta-analysis.

Figure 2

Quality assessment of included eligible studies using QUADAS-2.

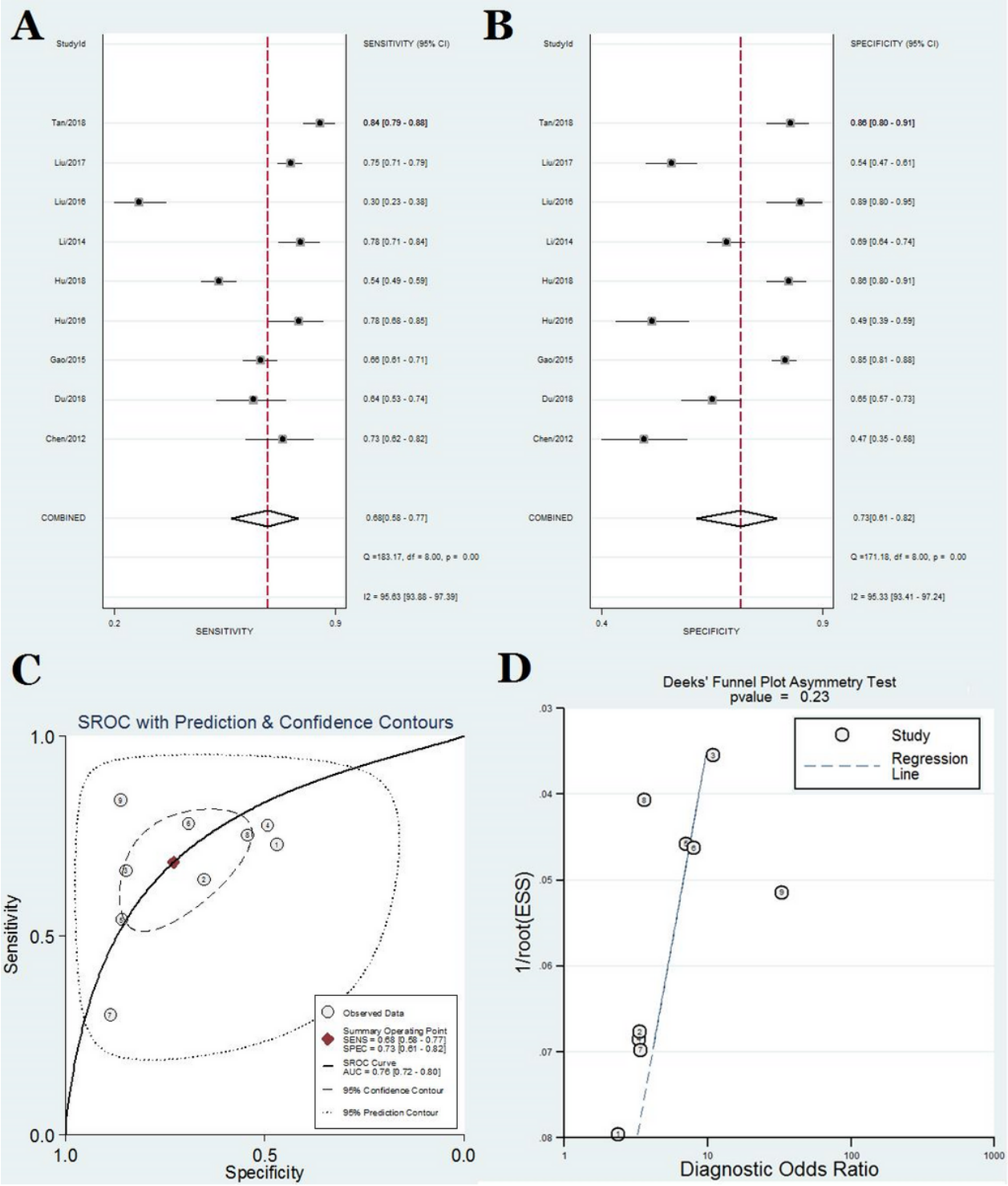

Figure 3

Forest plots of sensitivity, specificity, area under the curve (AUC) and deeks funnel plot of NLR for predicting prognosis of HCC. (A) Sensitivity; (B) Specificity; (C) AUC; (D) Funnel plot.

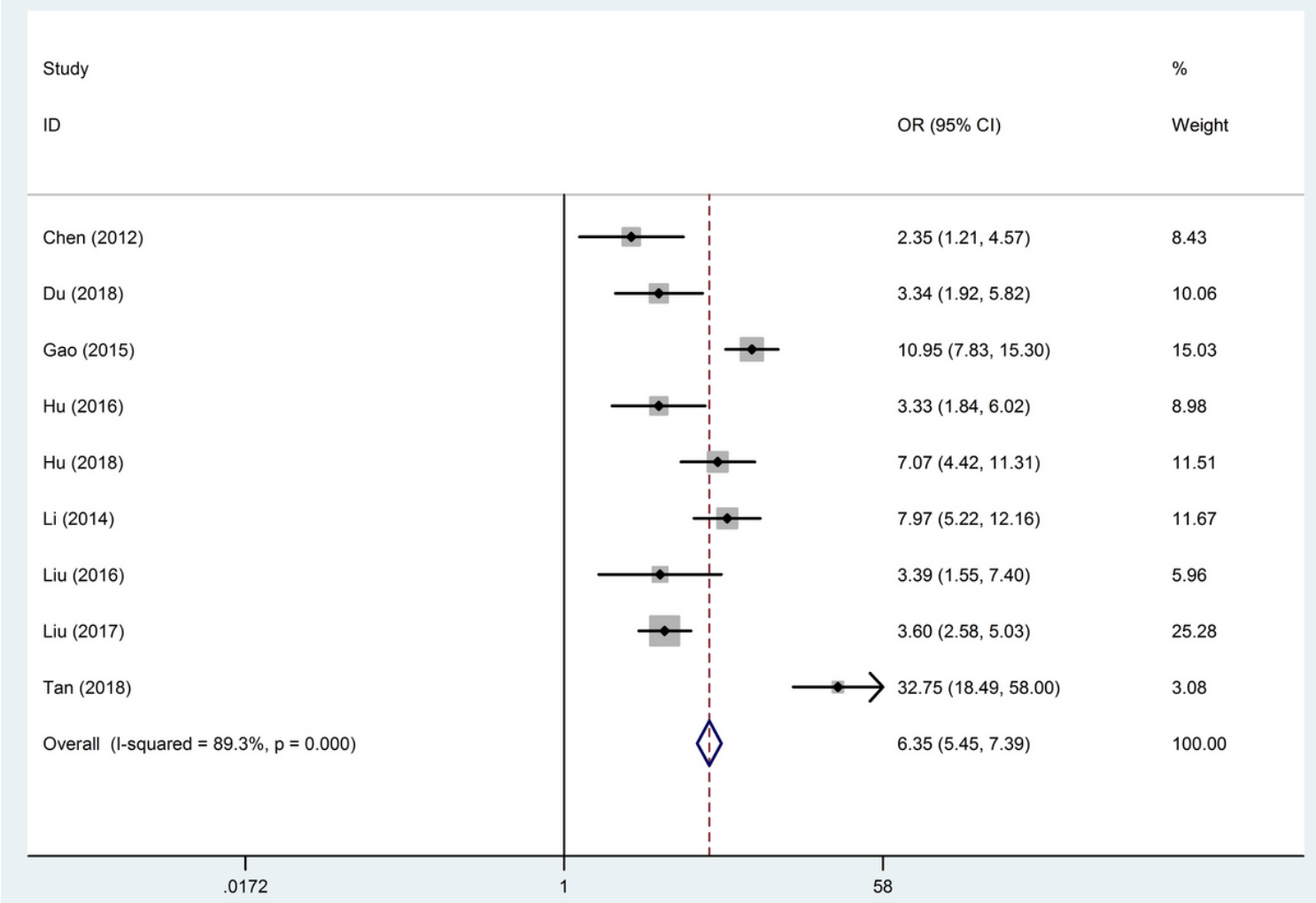

Figure 4

The forest plot for the predictive value of NLR for prognosis in patients with HCC.

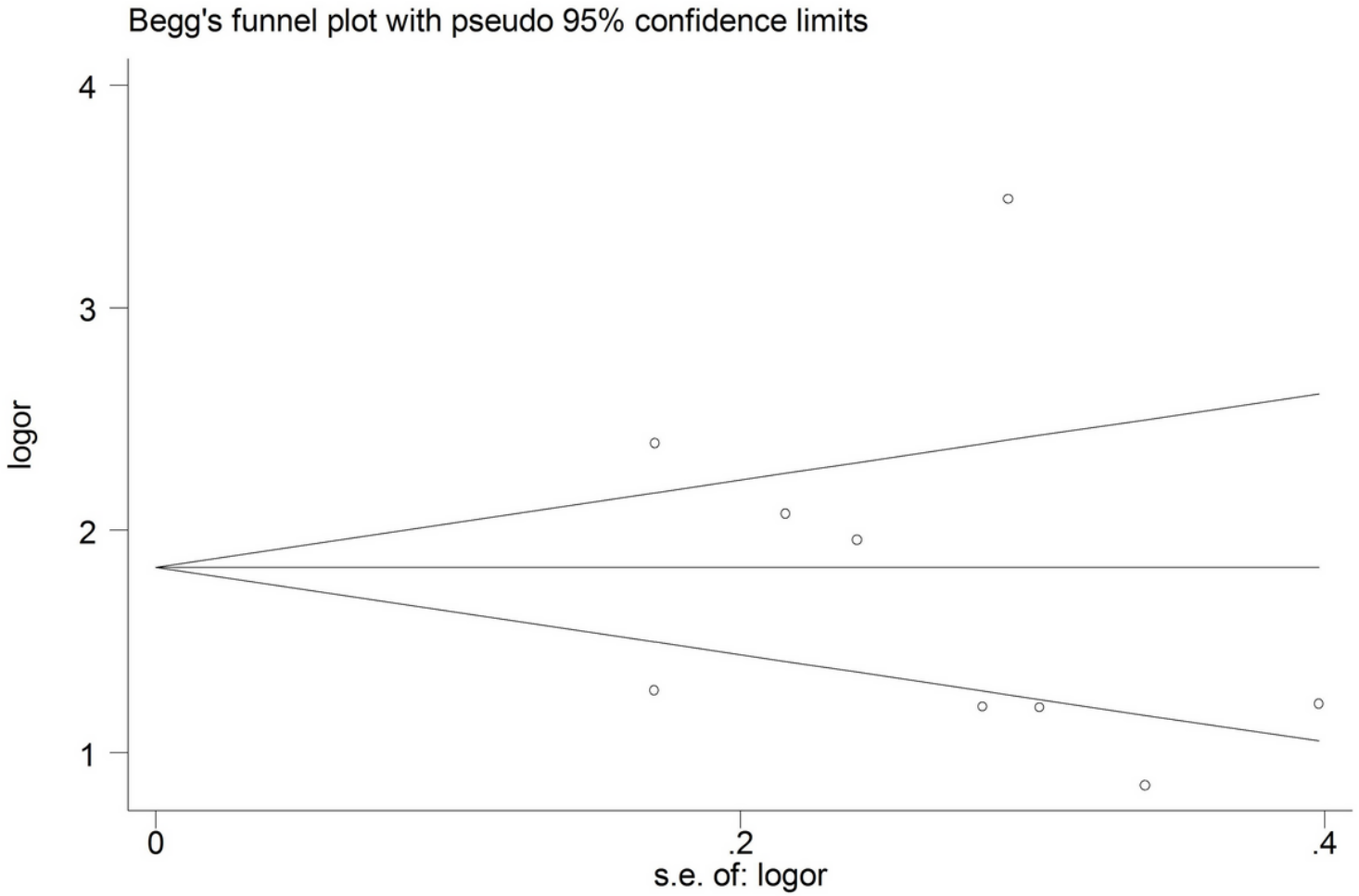

Figure 5

Begg’s funnel plot for testing the publication bias.

Supplementary Files

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- PRISMAchecklist.pdf