



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

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Background: Neutrophil-to-lymphocyte ratio (NLR) is one predictive factor for poor prognosis of patients with hepatocellular carcinoma (HCC). In response to contradictory data concerning the predictive ability of NLR, we performed a meta-analysis for the determination of its prognostic value in patients with HCC.

Methods: We systematically searched several databases including PubMed, EMBASE, Cochrane Library, Chinese National Knowledge Infrastructure and Wan Fang databases with the updated date of September 21, 2020. Inclusion criteria: RCT studies reporting the prognostic value of the serum levels of NLR in HCC patients receiving treatment were enrolled. Pooled estimates of odds ratio (OR) and diagnostic odds ratio (DOR) were used to assess the prognostic performance of NLR in HCC patients. Overall survival (OS) was the primary outcome and progression-free survival (PFS) was secondary outcomes. Data from studies reporting a hazard ratio and 95% confidence interval (CI) or a P value were pooled in a meta-analysis. Furthermore, risk of bias assessment of included studies is specified by Cochrane Risk Bias Assessment Tool.

Results: This analysis included 9 studies containing a total of 3,862 HCC patients. High baseline NLR was significantly correlated with poor prognosis or recurrence. The patient-based analysis of pooled estimates was as follows: sensitivity, 0.68 (95% CI: 0.58–0.77); specificity, 0.73 (95% CI: 0.61–0.82); DOR, 6.347 (95% CI: 5.450–7.391). 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 prognostic 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 effective prognostic factor for patients with HCC, especially for those from East Asian populations with high incidence. In the future, trials with larger sample sizes and more high-quality evidence are needed to further improve patient outcomes.

Keywords: Hepatocellular carcinoma (HCC); inflammation; neutrophil-to-lymphocyte ratio (NLR); prognostic value; prognosis

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Introduction

As the fifth most common malignancy worldwide, hepatocellular carcinoma (HCC) ranks 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). It is the second most common cancer in China and the third most common in Korea, and it is insidious and progresses rapidly (3,4). Currently, the overall survival (OS) of HCC is satisfactory due to recent improvements in clinical treatment (5). For instance, surgical resection of HCC is not only reliable and effective but also has a low associated mortality rate (6). Nevertheless, HCC prognosis remains poor. Death after curative resection is mainly attributed to tumor recurrence (7). The recurrence of HCC originates from either *de novo* tumors arising from the remnant liver or intrahepatic metastasis of the primary tumor (8). To date, the identified risk factors suggest that late recurrence primarily arises from continuous liver disease, whereas early recurrence is largely related to the characteristics of invasive tumors (8,9). Therefore, prognostic assessment of HCC is pivotal for improving the clinical outcomes of patient.

It is commonly known that HCC generally develops from chronic inflammation and cirrhosis (10). The inflammatory responses and immune status of HCC patients have an influence on survival and recurrence after treatment (11). Recently, accumulating evidence has shown that poorer prognosis is correlated with the presence of systemic inflammation in cancer patients (12-16). An elevated level of inflammation, including neutrophil to lymphocyte ratio (NLR), Glasgow Prognostic Score (GPS), C-reactive protein to albumin ratio and platelet to lymphocyte ratio (PLR), have been indicated to be associated with poor survival in HCC patients. Nevertheless, NLR might be more readily available and inexpensive objective compared with the other prognostic indexes that could be used in daily oncologic clinical practice. Moreover, neutrophil-to-lymphocyte ratio (NLR) has been reported as a dependable indicator to monitor and evaluate systemic inflammatory reactions (17). Furthermore, NLR can be repeatedly and easily measured using peripheral blood. Baseline NLR has been reported as a prognostic marker or a valuable factor in many kinds of cancers, including renal cancer (18) and HCC (19). Previous studies investigating its prognostic value in HCC patients undergoing specific treatments indicate that pretreatment NLRs are predictors of tumor recurrence and survival in HCC patients (20,21). However, the exact function of NLR

in HCC patients is controversial among studies as a result of many elements, such as variances in sample size, study designs, regional differences, and so on (22). Some studies report a strong correlation between higher NLR and poorer prognosis, while others do 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 which has high incidence of HCC (19). We thus conducted a meta-analysis to acquire a systematic and thorough understanding of 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 aimed to illuminate the prognostic value of NLR in HCC patients and determine whether the prognostic accuracy can be increased in a higher HCC-risk region. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-3237>).

Methods

Data sources and searches

A systematic search of several databases including PubMed, EMBASE, and the Cochrane Library in English, Chinese National Knowledge Infrastructure (<http://www.cnki.net/>) and Wan Fang databases in Chinese (<http://www.wanfangdata.com.cn>) was performed from inception to September 21, 2020. The search terms used were 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. This meta-analysis was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement issued (Checklist file) (24,25). The present meta-analysis was also submitted to PROSPERO (The International Prospective Register of Systematic Reviews; no. 156404).

Study selection

All citations were reviewed in turn. Full texts of potentially

relevant articles were retrieved by titles or abstracts, and eligible studies were determined through independent examinations by 2 investigators (Shan Lin and Shiping Hu). Disagreements on eligibility were settled through discussion with an arbitrator (Fenfang Wu). Studies that clearly met the following inclusion criteria were considered: (I) participants were aged ≥ 18 years old for human studies; (II) serum levels of NLR were measured prior to formal treatment; (III) sample size was greater than 30; (IV) randomized controlled trials (RCTs) were observational in nature; (V) sufficient data of true-positives (TP), false-positives (FP), false-negatives (FN), and true-negatives (TN) for calculating the predictive ability of NLR in HCC patients were provided. Studies were eliminated if they met the following exclusion criteria: (I) only animal or *in vitro* study was performed; (II) information about prognostic accuracy was lacking in a control or experimental group; (III) article type was a review, commentary, poster, letter, supplementary issue, or editorial; (IV) duplicate data were present or information was insufficient.

Data extraction

Data from each trial were extracted by 2 reviewers (Shan Lin and Shiping Hu) independently. All discrepancies or disagreements between reviewers were discussed with and evaluated by a third investigator (Fenfang Wu) 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), area under the curve (AUC) [95% confidence interval (CI)], baseline NLR cut-off, sensitivity, and specificity.

Quality assessment

Cochrane Risk of Bias Assessment Tool was adopted for quality assessment of the articles by 2 independent reviewers (Shan Lin and Shiping Hu) (26). This tool consists of 6 domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selection outcome reporting, and other resources of bias. "Risk of bias" was evaluated for all 6 domains and "concerns regarding applicability" was assessed with each item judged to be "yes", "no", or "unclear".

The quality of eligible studies was evaluated by

Newcastle-Ottawa Scale (NOS) (27). On the basis of 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 trial 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 according to a previous study with some modifications (21).

Statistical analysis

Stata version 12.0 (StataCorp, College Station, TX, USA) software was used for all statistical analyses of TP, TN, FP, and FN rates for each test in each study and in the assessment of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLHR), and diagnostic odd ratio (DOR) for each eligible study. A P value < 0.05 for Q statistic and an I^2 value $> 50\%$ for I^2 statistic were considered to indicate statistically significant heterogeneity (28). The I^2 index was used to indicate the degree of heterogeneity among multiple studies with I^2 values of $< 25\%$, $25\text{--}50\%$ 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 a P value < 0.05 was 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 a P value < 0.05 considered statistically significant (32,33).

Results

Literature search

Initially, the electronic search yielded 521 potentially relevant studies, of which 276 were excluded after removing duplicates in the databases. A total of 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 a further 48 were

eliminated as they did not match 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 is shown in

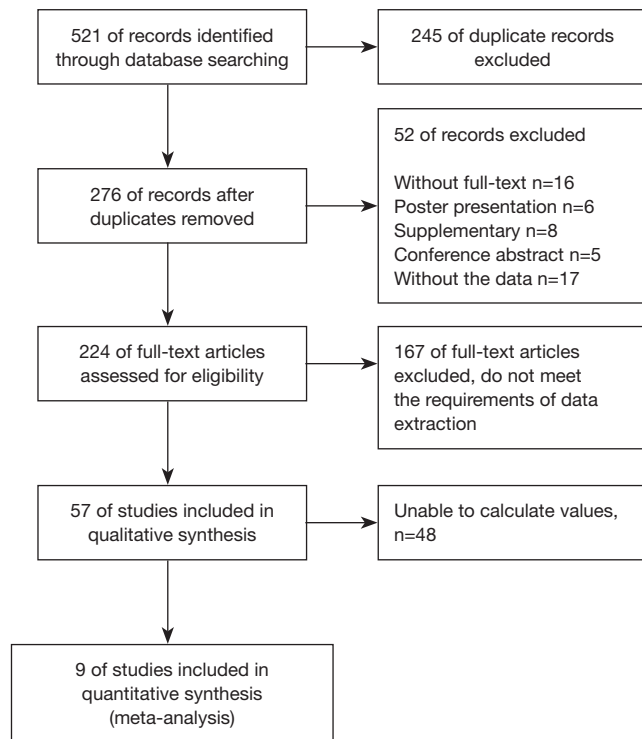


Figure 1 The selection process of the studies included in the meta-analysis.

detail in *Figure 1*.

The characteristics and quality of the included studies

All of the 9 included studies were written in English. For quality assessment of included studies, baseline data were extracted and are exhibited in *Table 1*. All of these 9 studies were all from East Asian regions, 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 is summarized in *Table 2*. The AUCs of the included studies ranged from 0.606 to 0.855, and the cut-off values ranged from 1.505 to 2.979. Meanwhile, the sensitivity and specificity of the included studies were calculated or provided, and ranged from 0.301 to 0.840 and from 0.470 to 0.887, respectively.

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 Cochrane Risk of Bias Assessment Tool, and all of them had high Cochrane scores (≥ 10). Overall quality of included trials was moderate. The outcome of Cochrane evaluation was shown in *Figure 2*.

Subsequently, assessment of publication bias was conducted by funnel plot, as shown in *Figure 3A*, indicating that neither

Table 1 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 [2019]	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

NR, no result; NOS, Newcastle-Ottawa Scale.

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 [2019]	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

NR, no result; NLR, neutrophil to lymphocyte ratio; HCC, hepatocellular carcinoma; AUC, area under the curve; CI, confidence interval; TP, true-positive; FP, false-positive; FN, false-negative; TN, true-negative.

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 (Table 2), including AUC, 95% CI: various optimal cut-off values of NLR, sensitivities, and specificities, as well as TP, FP, FN, and TN values. The predictive value of NLR as a biomarker for prognosis of HCC patients was inspected in 9 studies in a total number of 3,862 participants. The pooled data of these studies are summarized in Table 2. In the performance estimates of NLR, the pooled sensitivity was 0.68 (95% CI: 0.58–0.77) (Figure 3B), specificity was 0.73 (95% CI: 0.61–0.82) (Figure 3C), PLR was 2.5 (95% CI: 1.8–3.6), and NLHR was 0.43 (95% CI: 0.33–0.57). The pooled DOR was 6.347 (95% CI: 5.450–7.391) according to the random effects model. The AUC of SROC for prognostic accuracy summary was 0.76 (95% CI: 0.72–0.80; Figure 3D). A summary of the predictive value of NLR for the prognosis of HCC patients is shown in Figure 4. We concluded that high baseline NLR was prominently related to poor prognosis or recurrence.

Subgroup analysis

Subgroup analysis was performed and is 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), indicating a better prognostic value of NLR in HCC patients from mainland China than in those from Korea and Taiwan. For subgroup geographic analysis, NLR showed a much higher prognostic value in northern regions than in southern regions (DOR, 8; AUC, 0.80 *vs.* DOR, 3; AUC, 0.69). Interestingly, it was quite obvious that the prognostic value of NLR varies significantly across the North-South geographic boundary of East Asia.

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 (Figure 5). Furthermore, meta-regression and subgroup analysis were performed to identify other possible explanations of heterogeneity. Geography (North: $I^2=88.8\%$, $P\leq 0.001$ or South: $I^2=0$, $P=0.532$) may be mainly responsible, while the region (mainland China: $I^2=90.1\%$, $P\leq 0.001$, Korea or Taiwan) may not be a source of heterogeneity for the predictive value of NLR.

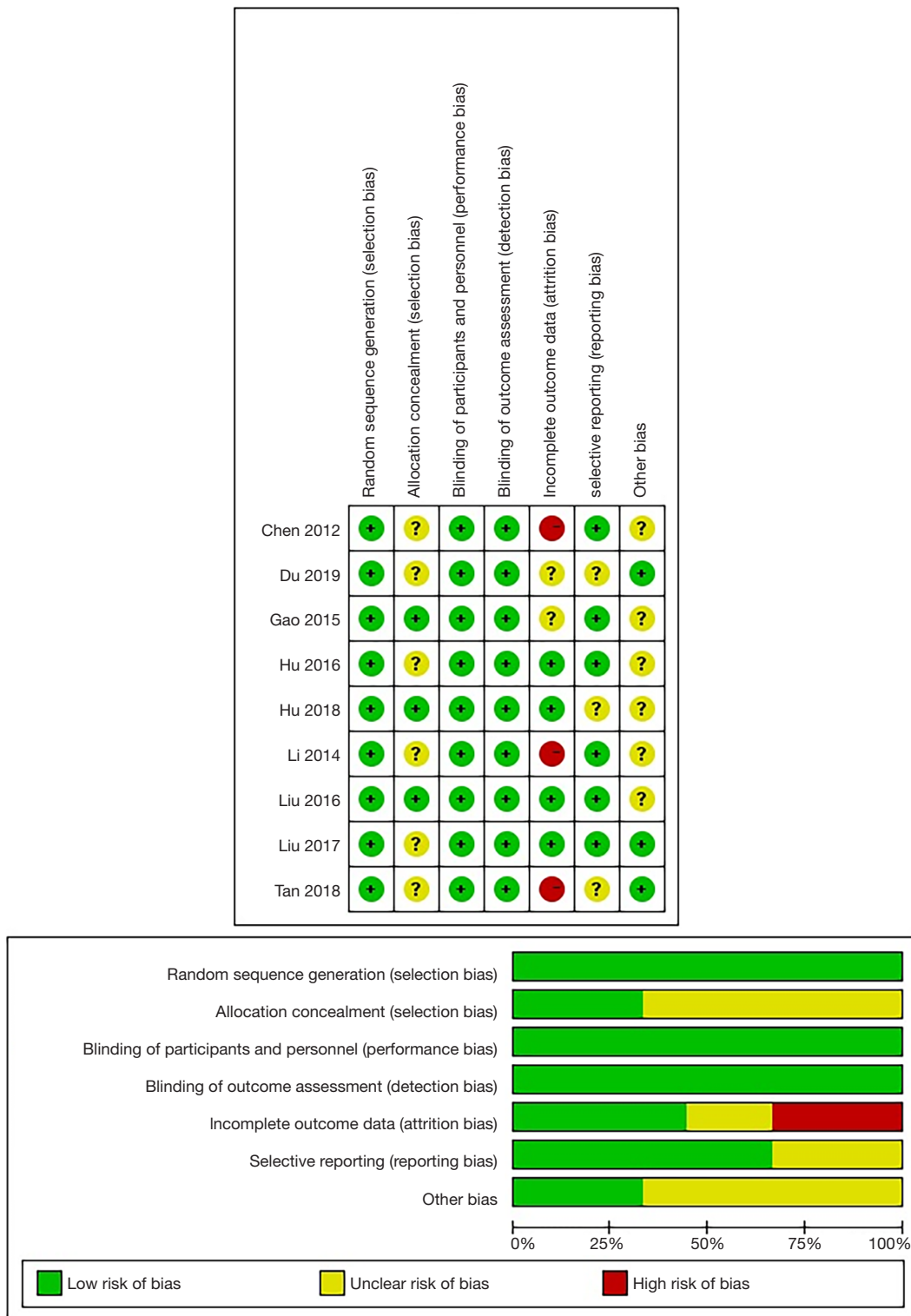


Figure 2 Quality assessment of included eligible studies using Cochrane Risk Bias Assessment Tool.

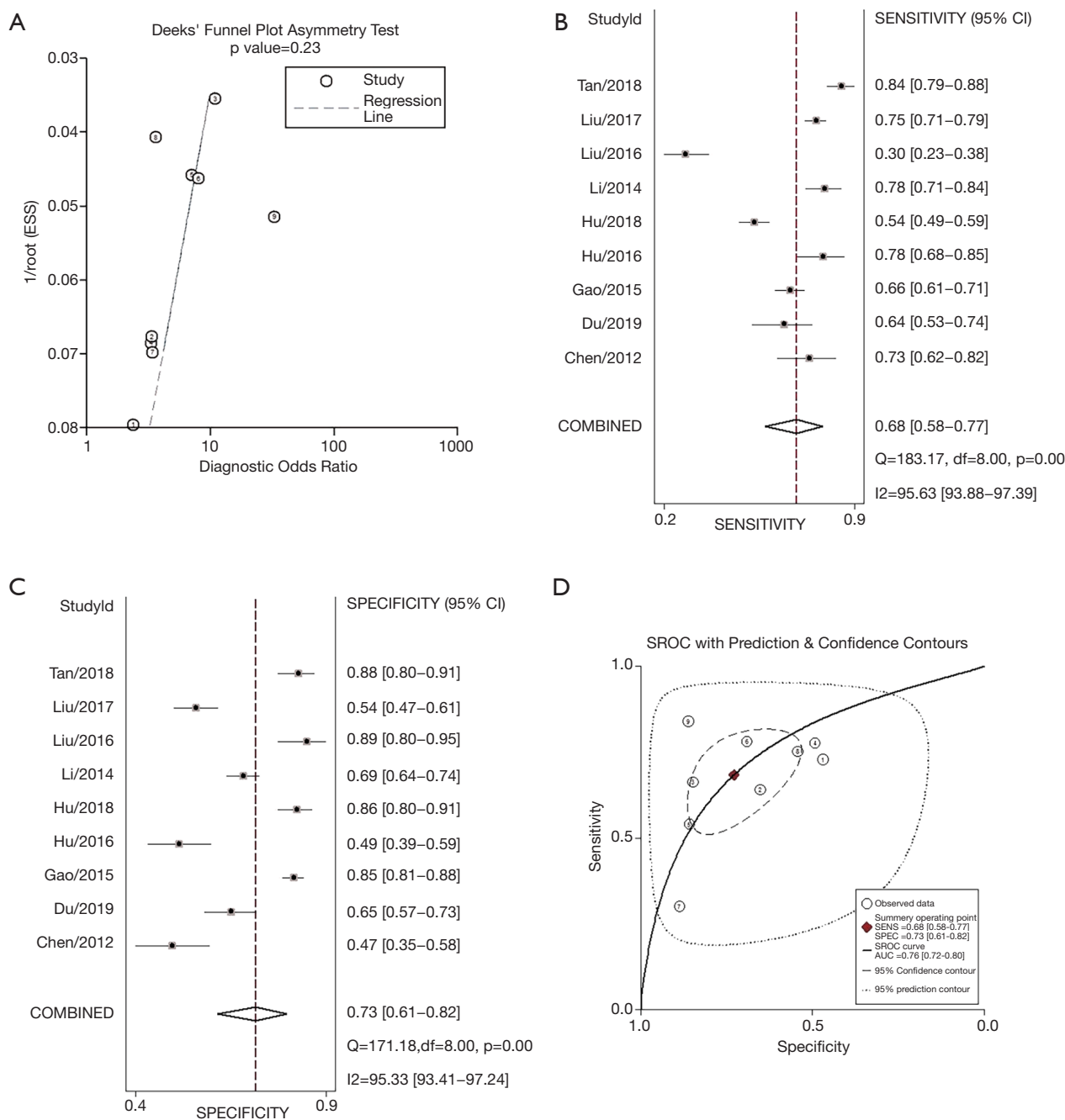


Figure 3 Forest plots of sensitivity, specificity, AUC, and Deeks funnel plot of NLR for predicting prognosis of HCC. (A) Funnel plot. (B) Sensitivity. (C) Specificity. (D) AUC. AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; HCC, hepatocellular carcinoma.

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 relationship between

increased NLR levels and clinical outcomes of HCC was comprehensively and systematically determined in HCC patients, especially in those from East Asia. We mainly investigated the association between high baseline NLR

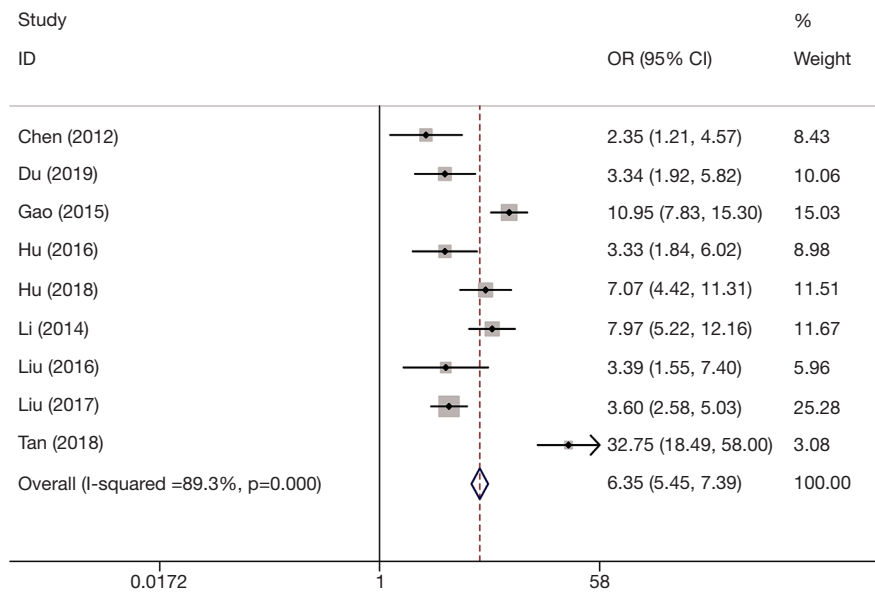


Figure 4 The forest plot for the predictive value of NLR for prognosis in patients with HCC. NLR, neutrophil-to-lymphocyte ratio; HCC, hepatocellular carcinoma.

Table 3 Subgroup analysis on the basis of different standards

Studies	Number	Region	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)

NR, no result; PLR, positive likelihood ratio; NLHR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve.

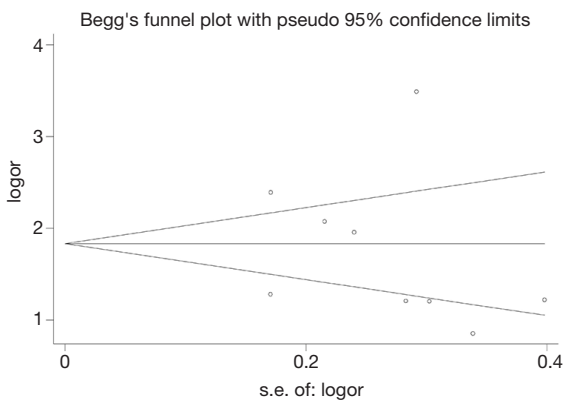


Figure 5 Begg's funnel plot for testing publication bias.

and HCC prognosis. The pooled outcomes in these cohorts indicated that high baseline NLR was a remarkable predictor of poor prognosis of HCC patients, indicating that NLR is a valuable inflammatory biomarker with high sensitivity, specificity, and DOR. In addition, subgroup analyses indicated that NLR worked better as a prognostic predictor in HCC patients from mainland China than in those from Korea and Taiwan. Moreover, high baseline NLR also significantly correlated with the prognostic value geographically, indicating that NLR exhibits a better prognostic role in the North than in the South of East Asia.

Generally, high baseline NLR reflects 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 systemic immune status, which both benefits tumor invasion and restrains host immune surveillance (44-46). It is worth noting that in addition to NLR, other laboratory markers of systemic inflammatory response have been reported to play a prognostic role in cancer patients, such as modified Glasgow prognostic score (47,48), and notably C reactive protein (CRP) (49). Furthermore, biological markers (50,51) and gene polymorphisms (52) have also been suggested as prognostic indicators in cancer patients. Nevertheless, NLR stands out with its low cost, broad practicality, and accessibility (18). The pooled results of our meta-analysis encourage 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 was observed in HCC patients from mainland China (DOR, 7; AUC, 0.79) than in those 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 most common cancer in mainland China, indicating that HCC is more severe in China than the other 2 regions (53). For subgroup geographic analysis, a better prognostic performance of NLR as a predictor of prognosis was seen in HCC patients from the North (DOR, 8; AUC, 0.80) than in those from the South (DOR, 3; AUC, 0.69). This may be related to differences in the dietary habits and lifestyles of people in the North versus the South, as well as climate differences (54). Interestingly, it has been indicated that the incidence of HCC is influenced by differences in habits between northern and the southern populations, and people living in the South may have a relatively low risk of HCC.

Subsequently, meta-regression and interaction revisited subgroup analyses were adopted to determine the causes of heterogeneity observed among the included studies. Several stratified analyses concerning region or geography were performed to investigate the sources of heterogeneity. Moreover, the outcome of any single study as a main source of heterogeneity was ruled out by performing leave-one-out sensitivity analysis. The pooled results indicated that the main source of heterogeneity stemmed from geographical characteristics (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) was not found to be a source of heterogeneity in the predictive value of NLR. It has been consistently found that differences in environmental factors,

population characteristics, lifestyle, and sample sizes are the main sources of heterogeneity (55). Further verification of the above conclusions needs to be achieved by incorporating more studies that conform to the inclusion criteria.

Several limitations in our study should also be mentioned. First, the literature search was restricted to open-access studies. However, relevant studies that were not readily available might also have met the inclusion criteria of our meta-analysis but were inevitably excluded. Second, 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 eliminated the need to fully explaining the heterogeneity by both of the above-mentioned confounders. Third, 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 easily accessible publication of positive results, ultimately leading difficulty in locating more controversial studies.

Conclusions

In conclusion, the present meta-analysis revealed a significant association between high baseline NLR and poor prognosis in HCC patients, especially in those from East Asian regions with high incidence of HCC. Therefore, NLR may be used as 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 to further elucidate the prognostic value of NLR in HCC patients.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-3237>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-3237>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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