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Prognostic value of neutrophil-to-lymphocyte ratio in patients with hepatocellular carcinoma receiving curative therapies: a systematic review and meta-analysis

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Abstract

Background Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide. The prognostic significance of the neutrophil-to-lymphocyte ratio (NLR) in HCC patients has been extensively studied; however, the prognostic value of NLR in HCC patients undergoing curative treatment remains unclear.

Objective This systematic review and meta-analysis aimed to comprehensively evaluate the precise significance of preoperative and postoperative NLR in predicting the prognosis of HCC patients receiving curative treatment.

Methods We conducted a comprehensive search of the PubMed, Cochrane Library, Embase, and Web of Science databases from inception to August 2024. Studies that included univariate and multivariate analyses evaluating the association between NLR and survival outcomes in HCC patients undergoing resection, transplantation, or ablation were included. The prognostic value of NLR in HCC patients receiving curative treatment was analyzed by calculating pooled hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Results A total of 43 studies involving 9,952 patients were included. Meta-analysis revealed that higher NLR was significantly associated with worse overall survival (OS) (HR = 1.55, 95% CI = 1.39–1.75, $P < 0.001$), recurrence-free survival (RFS) (HR = 1.77, 95% CI = 1.49–2.10, $P < 0.001$), and disease-free survival (DFS) (HR = 1.42, 95% CI = 1.25–1.63, $P < 0.001$) in HCC patients undergoing curative treatment. Subgroup analysis demonstrated a significant association between NLR and poor OS, independent of geographic region, type of survival analysis, preoperative or postoperative measurement, treatment modality, or NLR cutoff value. Publication bias and sensitivity analyses confirmed the robustness of these findings.

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Conclusion Elevated NLR is significantly associated with poorer OS, RFS, and DFS in HCC patients receiving curative treatment. Future research should focus on validating the optimal NLR threshold and exploring its predictive ability in different clinical settings.

Keywords Hepatocellular carcinoma, Neutrophil-to-lymphocyte ratio, Survival, Systematic review, Meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and poses a significant global health challenge, with an increasing incidence. It is typically induced by chronic viral infections (hepatitis B and C), non-alcoholic steatohepatitis, excessive alcohol consumption, and other factors that may lead to chronic liver inflammation and cirrhosis. The mortality rate of HCC continues to rise worldwide, particularly in Western countries [1]. Common treatment modalities for HCC include liver resection, liver transplantation, ablation, transarterial chemoembolization (TACE), radiotherapy, targeted therapy, and immunotherapy [2]. Curative treatment options primarily consist of liver resection, liver transplantation, and ablation; however, even after curative treatment, the prognosis for HCC patients remains poor. Studies have shown that up to 70% of HCC patients experience disease recurrence within five years following resection or local ablation, with a recurrence rate of 30–50% within three years [3].Thus, identifying reliable prognostic markers to assess survival and recurrence risk is crucial.

The neutrophil-to-lymphocyte ratio (NLR), a hematologic indicator reflecting systemic inflammatory response, has been extensively studied and shown in some research to predict the prognosis of HCC patients. In recent years, studies by Linda Wong et al. [4].have demonstrated that both preoperative and postoperative NLR are associated with the prognosis of HCC patients undergoing liver resection. Numerous studies have validated the importance of NLR as a prognostic factor, with substantial evidence indicating that preoperative and postoperative NLR are related to the prognosis of HCC patients who undergo liver resection. However, the optimal NLR cutoff value remains controversial [5]. This controversy may arise from various factors, including differences in study design, sample size, patient heterogeneity, and the timing of NLR measurement. Despite numerous studies investigating the prognostic significance of NLR in HCC, results remain inconsistent, possibly due to variability in treatment modalities, study designs, and patient characteristics. This study aims to systematically analyze the pooled data from multiple studies to clarify the role of NLR in predicting survival outcomes in HCC patients receiving radical treatments such as surgery, transplantation, or ablation.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Assessment of Multiple Systematic Reviews (AMSTAR) methodology [6]. Since only aggregate data were analyzed, patient informed consent and ethical approval from an ethics committee were not required. The meta-analysis has been registered with the PROSPERO registry (Registration ID: CRD42024578088).

Literature search

A comprehensive search was performed by two independent researchers (PJX and FW) in the PubMed, Web of Science, Cochrane Library, and Embase electronic databases from inception to August 22, 2024. In addition to the electronic database search, we also manually searched reference lists and relevant conference abstracts to ensure a comprehensive inclusion of studies. Furthermore, we did not include gray literature, as we aimed to focus on peer-reviewed studies published in major medical journals, which are generally considered more reliable.Only studies published in English were included. A search strategy combining subject terms and free-text terms was employed, such as "Hepatocellular Carcinoma," "Neutrophils," "Lymphocytes," and their related terms. Additionally, manual searches of relevant articles and reference lists were conducted to identify and include all eligible studies.

Selection criteria

The inclusion criteria were: (1) patients diagnosed with HCC based on histopathology or clinical criteria; (2) HCC patients who underwent liver resection, liver transplantation, or ablation; (3) NLR assessed pre- or post-treatment with a defined cutoff value; (4) studies reporting at least one outcome of interest; (5) univariate or multivariate analysis data on prognosis; (6) study designs including randomized controlled trials, cohort studies, or retrospective studies.

The exclusion criteria were: (1) HCC patients who did not undergo liver resection, liver transplantation, or ablation; (2) non-human studies or studies not published in English; (3) reviews, meta-analyses, letters, or reports; (4) lack of NLR data pre- or post-treatment; (5) studies based on overlapping cohorts from the same center.

The primary endpoints of interest in our study were the prognostic value of NLR in HCC, including overall

survival (OS), recurrence-free survival (RFS), and disease-free survival (DFS).

Data extraction

All data from each study were extracted and assessed by two independent researchers (PJX and FW) using predefined forms, including baseline characteristics and outcomes. Key information collected included: (1) general details such as the first author, publication year, demographic data, study type, NLR cutoff values, and treatment modalities; (2) long-term outcome data based on univariate or multivariate analyses for OS, RFS, or DFS.

Quality assessment

The quality of observational studies (both prospective and retrospective) was assessed using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions, Version I) [7]. Each outcome was individually evaluated across the seven domains of the ROBINS-I tool: confounding bias, selection bias, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of reported results. Each domain was rated as low, moderate, serious, or critical risk of bias, or as no information.

Statistical analysis

The prognostic role of the neutrophil-to-lymphocyte ratio (NLR) in patients with HCC undergoing curative treatment was evaluated by calculating combined hazard ratios (HRs) and 95% confidence intervals (CIs). Potential heterogeneity was assessed using Cochran's Q test and the I^2 statistic. A fixed-effects model was employed only if the p-value of the Q test was greater than 0.10 and I^2 was less than 50%. Otherwise, a random-effects model was applied to account for significant heterogeneity. Subgroup analyses were performed to explore the prognostic significance of NLR across various stratified populations. Sensitivity analysis was conducted using the "leave-one-out" method, which involved sequentially excluding each study to assess the impact of individual studies on the overall results.Funnel plots and Egger's test were used to evaluate the risk of publication bias, with a p-value less than 0.05 indicating significant bias [8].

Results

The flowchart of the literature search is presented in Fig. 1. Our initial search identified 4,081 articles. After removing 1,093 duplicates, 2,988 articles remained. Upon reviewing the titles and abstracts, 2,458 articles were excluded for being unrelated to the study topic, 189 articles were excluded for being non-human studies, and 48 articles were excluded for not being in English. We further excluded reviews, meta-analyses, letters, and reports, resulting in 129 articles. After a full-text review of these 129 articles, we excluded studies lacking NLR data before or after treatment and studies based on overlapping cohorts from the same center, ultimately including 43 studies with a total of 9,952 patients.

The 43 included studies were all retrospective in nature and demonstrated good geographical representation: 24 studies from China [9–32], 8 from Japan [33–40], 2 from Singapore [41, 42], 3 from the United States [43–45], 2 from South Korea [46, 47], 1 from Brazil [48]、1 from Serbia [49]and 2 from Taiwan [50, 51]. In studies examining the relationship with OS, NLR cutoff values ranged from 1.08 to 6 (median, 2.8), with 4 studies using a cutoff of 5. In studies investigating the relationship with RFS, NLR cutoff values ranged from 1.2 to 5 (median, 2.81), with 4 studies using a cutoff of 5. In studies exploring the relationship with DFS, NLR cutoff values ranged from 1.55 to 6 (median, 2.47), with 2 studies using a cutoff of 5, 2 studies using a cutoff of 2.81, and 2 studies using a cutoff of 2.

The ROBINS-I tool evaluates every study in seven domains, as presented in the Table 1. There was no article of low quality.

Among the 43 studies, 7,919 patients underwent liver resection, 1,291 patients underwent liver transplantation, and 742 patients underwent radiofrequency ablation. The Newcastle-Ottawa Scale (NOS) scores of the included studies ranged from 6 to 9, indicating high quality [52]. The basic characteristics of the included studies are summarized in Table 2.

Impact of NLR on OS

Thirty-six studies involving 7,453 patients evaluated the association between NLR and OS. Significant heterogeneity was observed among the studies (I^2 = 75.6%, $P < 0.001$), and a random-effects model was used for analysis. The pooled analysis demonstrated that elevated NLR was significantly associated with poorer OS (HR = 1.55, 95% CI = 1.39–1.75, I^2 = 75.6%, $P < 0.001$) (Fig. 2).

Impact of NLR on RFS

Twenty-one studies involving 4,050 patients assessed the association between NLR and RFS. Significant heterogeneity was observed (I^2 = 72.2%, $P < 0.001$), and a random-effects model was used. The pooled analysis indicated that elevated NLR was significantly associated with poorer RFS (HR = 1.77, 95% CI = 1.49–2.10, I^2 = 72.2%, $P < 0.001$) (Fig. 3).

Impact of NLR on DFS

Sixteen studies involving 4,746 patients evaluated the association between NLR and DFS. Significant heterogeneity was detected (I^2 = 82.1%, $P < 0.001$), and a random-effects model was applied. The pooled analysis showed

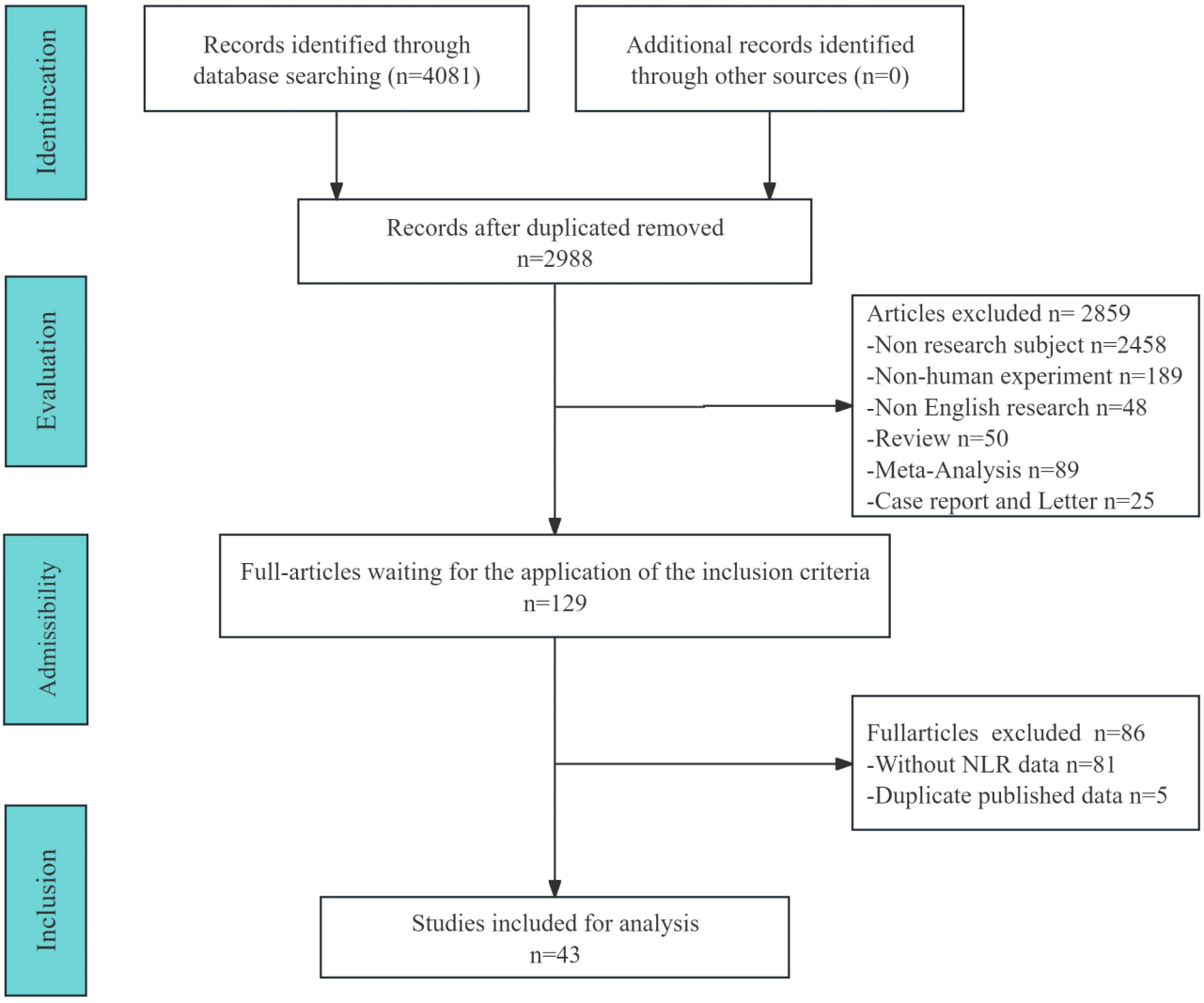

Fig. 1 Flow chart depicting the selection of studies

that elevated NLR was significantly associated with poorer DFS (HR = 1.42, 95% CI = 1.25–1.63, I^2 = 82.1%, $P < 0.001$) (Fig. 4).

Subgroup analyses

Subgroups of the prognostic value of NLR for OS in patients with HCC

Subgroup analyses were performed based on geographic region, type of survival analysis, pre- and post-treatment status, treatment modality, and NLR cutoff value. The analyses demonstrated that NLR remained significantly associated with poor OS, irrespective of geographic region, type of survival analysis, pre- and post-treatment status, treatment modality, or NLR cutoff value (Table 3).

Notably, subgroup analysis stratified by treatment modality revealed significant heterogeneity(I^2=74.7%, I^2=81.1%). While elevated NLR remained significantly associated with poorer OS across all therapeutic approaches, the effect size varied between resection (HR = 1.55), transplantation (HR = 1.95), and ablation (HR = 1.75) subgroups. This variation in magnitude may reflect distinct pathophysiological impacts of each intervention on systemic inflammation. Importantly, the limited number of studies investigating transplantation ($n = 5$ studies) and ablation ($n = 3$ studies) constrains statistical power, potentially obscuring genuine heterogeneity in treatment-specific associations.

Subgroups of the prognostic value of NLR for RFS in patients with HCC

Subgroup analyses were also conducted for RFS based on geographic region, type of survival analysis, pre- and post-treatment status, treatment modality, and NLR cutoff value. NLR remained significantly associated with poor RFS, regardless of these factors.

Table 1 The basic characteristic of enrolled studies

Study	Country	Sample size	Study design	Study period	Gender (M/F)	Age (year) Median (range)	Treatment	Study center	Age (year) Median (range)	Survival outcomes	Cut- off value	NOS score
Utsumi, M.2024	Japan	151	Retrospective	2010–2022	122/29	71.0 ± 10.0	Hepatectomy	Single center	71.0 ± 10.0	OS, RFS	3.24	**8**
Yamamura, K. 2014	Japan	113	Retrospective	2003–2012	91/22	66 (35–80)	Hepatectomy	Single center	66 (35–80)	RFS	3	**7**
Ni, H. H.2022	China	105	Retrospective	2014–2017	85/12	< 45 years, 40 ≥ 45 years,57	Hepatectomy	Single center	< 45 years, 40 ≥ 45 years,57	OS	2.15	**7**
Chen, D.2024	China	222	Retrospective	2013–2019	184/38	> 65 years, 53 ≦65 years.169	Hepatectomy	Single center	> 65 years, 53 ≦65 years.169	OS, RFS	2.8	**7**
Cui, S.2023	China	218	Retrospective	2010–2020	197/21	53.9 ± 8.5	Liver Transplantation	Single center	53.9 ± 8.5	OS, DFS	OS: 4.1, DFS: 2.35	**7**
Qu, Z.2021	China	215	Retrospective	2010–2018	178/37	59.10 ± 10.49	Hepatectomy	Single center	59.10 ± 10.49	OS, RFS	3.29	**8**
Tsai, M. C.2023	Taiwan	104	Retrospective	2004–2018	84/20	54.2 ± 7.5	Liver Transplantation	Multicenter	54.2 ± 7.5	OS	4	**9**
Luo, H.2023	China	144	Retrospective	2013–2017	119/25	53.2 ± 10.1	Hepatectomy	Single center	53.2 ± 10.1	OS	2.6	**7**
Wu, W.2021	China	347	Retrospective	2014–2017	290/57	≥ 60 years, 95 < 60 years, 252	Hepatectomy	Single center	≥ 60 years, 95 < 60 years, 252	OS, DFS	OS:2.37, DFS:2.33	**7**
Ohira, M.2024	Japan	516	Retrospective	2010–2018	327/189	60 (13–75)	Liver Transplantation	Multicenter	60 (13–75)	RFS	5	**7**
Chen, Y.2021	China	515	Retrospective	2012–2017	420/95	≦65 years, 399 < 65 years,116	Radiofrequency Ablation	Multicenter	≦65 years, 399 < 65 years,116	DFS	1.55	**8**
Silva, J. P. M.2022	Brazil	161	Retrospective	2007–2018	108/ 53	62 ± 11	Hepatectomy	Single center	62 ± 11	OS, DFS	OS:1.715, DFS:2.475	**7**
Zhou, J.2022	China	91	Retrospective	2017–2018	81/10	< 45 years, 27 ≥ 45 years, 64	Hepatectomy	Single center	< 45 years, 27 ≥ 45 years, 64	OS, RFS	OS:4.191, RFS:2.271	**7**
Wang, J.2022	China	217	Retrospective	2017–2019	191/26	50.12 ± 12.7	Hepatectomy	Single center	50.12 ± 12.7	RFS	2.63	**7**
Halazun, K. J.2017	USA	339	Retrospective	2001–2012	271/68	57.8 ± 8.1	Liver Transplantation	Single center	57.8 ± 8.1	RFS	5	**7**
Cao, Y.2018	China	426	Retrospective	2001–2012	378/48	53 (45–61)	Hepatectomy	Single center	53 (45–61)	OS	1.62	**8**
Chu, M. O.2018	Taiwan	118	Retrospective	2013–2015	74/44	69.410.4	Radiofrequency Ablation	Single center	69.410.4	OS, RFS	2.5	**7**
Dan, J.2013	China	178	Retrospective	2005–2008	159/19	NLR increased 56.9 ± 12.57 NLR decreased 55.38 ± 11.82	Radiofrequency Ablation	Single center	NLR increased 56.9 ± 12.57 NLR decreased 55.38 ± 11.82	OS, RFS	1.9	**7**
Galun, D.2018	Serbia	109	Retrospective	2001–2012	65/44	66(18–82)	Radiofrequency Ablation	Single center	66(18–82)	OS	1.28	**7**
Harimoto, N.2016	Japan	190	Retrospective	1997–2015	107/83	< 59 years, 93 ≥ 59 years, 97	Liver Transplantation	Single center	< 59 years, 93 ≥ 59 years, 97	RFS, DFS	2.66	**7**
Hu, B.2013	China	256	Retrospective	2005–2006	227/29	64.1(32.0–86.0)	Hepatectomy	Single center	64.1(32.0–86.0)	OS	5	**8**
Hu, X. G.2016	Korea	213	Retrospective	2001–2011	166/47	53(20–79)	Hepatectomy	Single center	53(20–79)	OS, RFS	1.505	**7**

Table 1 (continued)

Study	Country	Sample size	Study design	Study period	Gender (M/F)	Age (year) Median (range)	Treatment	Study center	Age (year) Median (range)	Survival outcomes	Cut- off value	NOS score
Okamura, Y.2016	Japan	375	Retrospective	2002–2014	306/69	70(30–87)	Hepatectomy	Single center	70(30–87)	OS	2.8	**6**
Wang, Y.2019	China	889	Retrospective	2003–2015	791/98	50.4 (42.9–59.0)	Hepatectomy	Single center	50.4 (42.9–59.0)	OS, RFS	OS: 1.08, RFS: 1.91	**7**
Kong, W.2020	China	292	Retrospective	2009–2015	258/34	50(41.3–58.8)	Hepatectomy	Single center	50(41.3–58.8)	OS, DFS	2.47	**7**
Na, G. H.2014	Korea	224	Retrospective	2000–2011	184/40	51.9 ± 6.9	Liver Transplantation	Single center	51.9 ± 6.9	OS, DFS	6	**7**
Wang, D.2019	China	239	Retrospective	2012–2015	200/39	50.14 ± 11.98	Hepatectomy	Single center	50.14 ± 11.98	OS, RFS	2.92	**6**
Xiao, G. Q.2013	China	280	Retrospective	2000–2011	249/31	46.5(20.5–69.1)	Liver Transplantation	Single center	46.5(20.5–69.1)	DFS	4	**7**
Yang, H. J.2016	China	526	Retrospective	2004–2011	465/61	NLR < 2.81, 46.8 ± 10.9 NLR ≥ 2.81, 47.9 ± 11.5	Hepatectomy	Single center	NLR < 2.81, 46.8 ± 10.9 NLR ≥ 2.81, 47.9 ± 11.5	OS, DFS	2.81	**7**
Chan, A. W.2015	China	324	Retrospective	2001–2011	283/41	6.8 ± 10.9	Hepatectomy	Single center	6.8 ± 10.9	OS, DFS	5	**7**
Kabir, T.2019	Singapore	132	Retrospective	2010–2013	116/16	65.2 ± 10.2	Hepatectomy	Single center	65.2 ± 10.2	OS, RFS	2.7	**7**
Ismael, M. N.2019	USA	160	Retrospective	2001–2017	NLR < 5 96/26, NLR ≥ 5 29/9	NLR < 5 57 ± 8, NLR ≥ 5 58 ± 7	Liver Transplantation	Single center	NLR < 5 57 ± 8, NLR ≥ 5 58 ± 7	OS, RFS	5	**7**
Shimoda, M.2017	Japan	105	Retrospective	2000–2013	79/26	69.5	Hepatectomy	Single center	69.5	RFS	1.2	**6**
Yamamoto, M.2019	Japan	478	Retrospective	2009–2015	301/177	69 (63-77)	Hepatectomy	Single center	69 (63-77)	OS, DFS	2.2	**6**
Limaye, A. R.2013	USA	160	Retrospective	2000–2008	NLR < 5, 104 /28; NLR ≥ 5, 26/2	NLR < 5,55.5; NLR ≥ 5, 55.1	Liver Transplantation	Single center	NLR < 5,55.5; NLR ≥ 5, 55.1	OS, RFS	5	**7**
Ren, Y.2018	China	187	Retrospective	2012–2017	165/22	57(47–65)	Hepatectomy	Single center	57(47–65)	OS	2.8	**6**
Liao, W.2014	China	256	Retrospective	1999–2007	226/30	≤ 55 years, 176 > 55years, 80	Hepatectomy	Single center	≤ 55 years, 176 > 55years, 80	OS, DFS	2.31	**8**
Goh, B. K. P.2016	Singapore	166	Retrospective	2000–2013	142/22	66 (21–85)	Hepatectomy	Single center	66 (21–85)	OS, RFS	4	**8**
Yang, T.2016	China	1020	Retrospective	2004–2011	856/164	46 (15, 78)	Hepatectomy	Single center	46 (15, 78)	DFS	2.81	**6**
Ni, X. C.2015	China	367	Retrospective	2010–2012	308/59	< 55 years, 192; ≥ 55 years, 175	Hepatectomy	Single center	< 55 years, 192; ≥ 55 years, 175	OS, DFS	5	**6**
Lu, S. D.2016	China	963	Retrospective	2004–2011	830/133	≤ 60 ears, 828;> 60ears, 135	Hepatectomy	Single center	≤ 60 ears, 828;> 60ears, 135	OS, RFS	2.81	**7**
Okamura, Y.2015	Japan	256	Retrospective	2002–2012	205 /51	69.5 (30–86)	Hepatectomy	Single center	69.5 (30–86)	OS, RFS	2.81	**7**
Dai, T.2020	China	195	Retrospective	2005–2013	174 /21	51(42–59)	Hepatectomy	Single center	51(42–59)	OS, DFS	2	**6**

Table 2 Assessment of bias for the included studies

No.	Study	Confounding	Bias in Classification of Interventions	Selection of Participants	Deviation from Intended Interventions	Missing Data	Measurement of Outcomes	Selective Reporting	Overall Risk of Bias
1	Utsumi et al. 2024	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Yamamura et al. 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
3	Ni et al. 2022	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Chen et al. 2024	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
5	Cui et al. 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Qu et al. 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
7	Tsai et al. 2023	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
8	Luo et al. 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
9	Wu et al. 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
10	Ohira et al. 2024	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
11	Chen et al. 2021	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
12	Silva et al. 2022	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
13	Zhou et al. 2022	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
14	Wang et al. 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
15	Halazun et al. 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
16	Cao et al. 2018	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
17	Chu et al. 2018	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
18	Dan et al. 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
19	Galun et al. 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
20	Harimoto et al. 2016	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
21	Hu et al. 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
22	Hu et al. 2016	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
23	Okamura et al. 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
24	Wang et al. 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
25	Kong et al. 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
26	Wang et al. 2019	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
27	Xiao et al. 2013	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk
28	Na et al. 2014	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
29	Yang et al. 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
30	Chan et al. 2015	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
31	Kabir et al. 2019	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
32	Ismael et al. 2019	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
33	Shimoda et al. 2017	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
34	Limaye et al. 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
35	Yamamoto et al. 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
36	Ren et al. 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
37	Liao et al. 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
38	Goh et al. 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
39	Yang et al. 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
40	Ni et al. 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
41	Lu et al. 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
42	Okamura et al. 2015	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk
43	Dai et al. 2020	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk

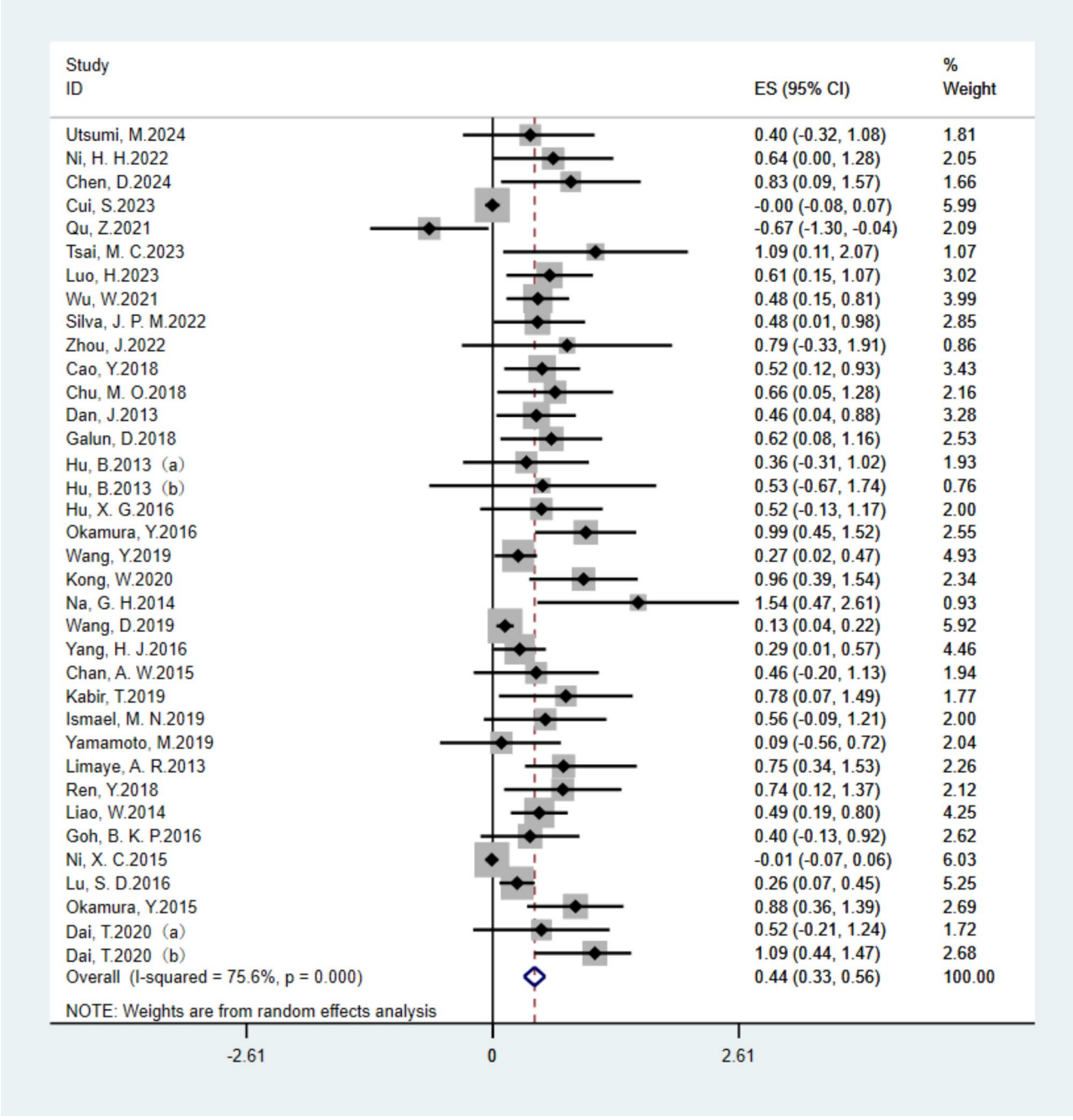

Fig. 2 Hazard ratio of overall survival based on multivariate analysis

However, in patients who underwent radiofrequency ablation (RFA), the higher NLR did not show a significant association with RFS (HR = 1.39, 95% CI = 0.87–2.23)(Table 4), which may be due to the small sample size in this subgroup, potentially limiting the statistical power to detect significance. Different treatment modalities, such as liver resection, liver transplantation, and ablation, may involve distinct immune responses, which could affect the prognostic value of NLR.

Subgroups of the prognostic value of NLR for DFS in patients with HCC

Subgroup analyses for DFS were also performed based on geographic region, type of survival analysis, pre- and post-treatment status, treatment modality, and NLR cutoff value. NLR remained significantly associated with poor DFS, regardless of the type of survival analysis, pre- and post-treatment status, or cutoff value. However, subgroup analyses based on geographic region and treatment modality showed that the prognostic value of

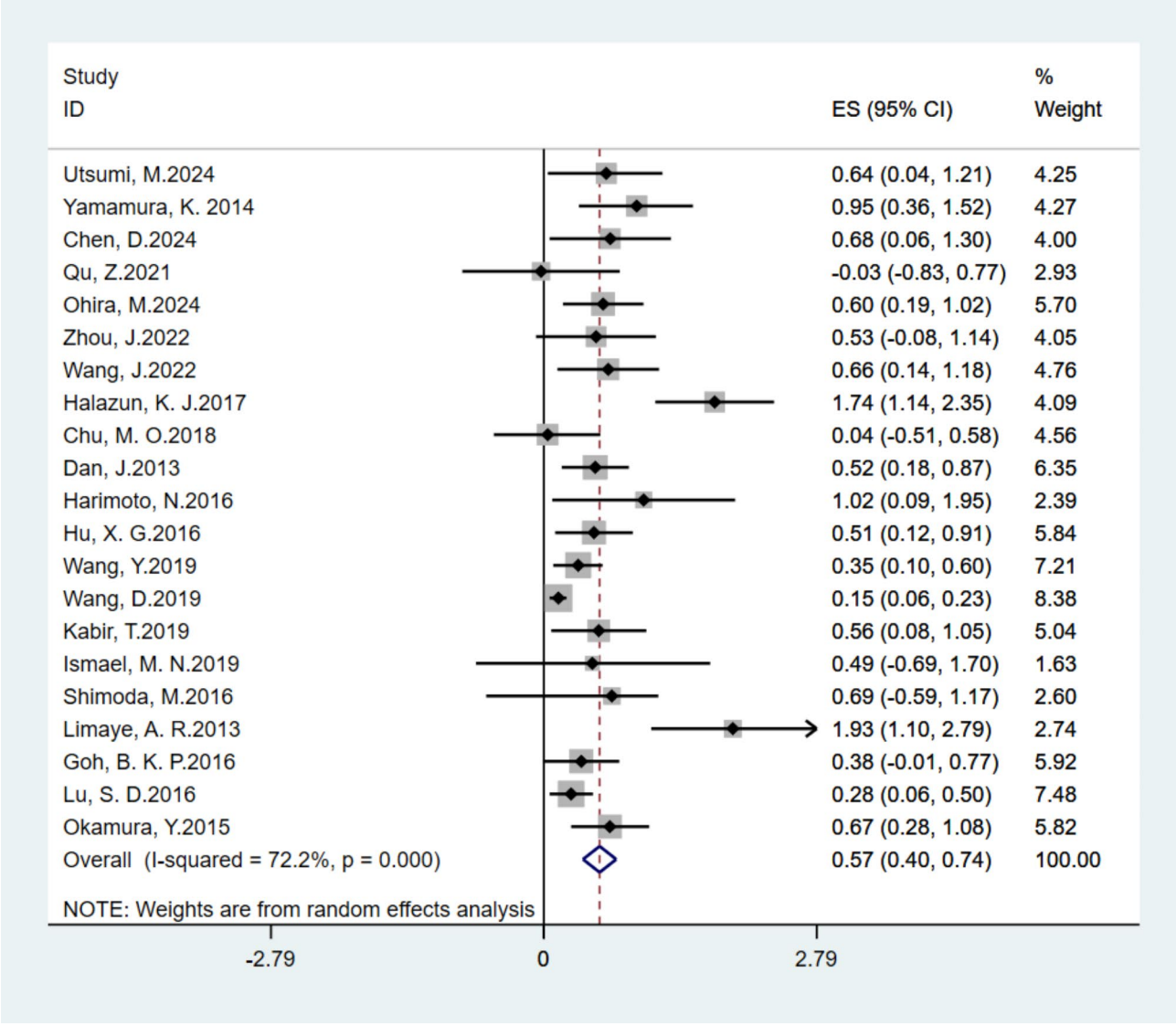

Fig. 3 Hazard ratio of recurrence-free survival based on multivariate analysis

NLR for DFS was not statistically significant in Western countries (HR = 1.28, 95% CI = 0.92–1.79) or in patients who underwent liver transplantation (HR = 1.67, 95% CI = 0.98–2.83). In contrast, the prognostic significance remained for patients in Eastern countries (HR = 1.43, 95% CI = 1.25–1.65) and those who underwent ablation therapy (HR = 1.58, 95% CI = 1.05–2.36) (Table 5).

Sensitivity analysis and publication bias test

Sensitivity analysis was conducted to test the stability of the meta-analysis results. The combined HRs and corresponding 95% CIs for OS, RFS, and DFS remained largely unchanged, indicating the robustness of the findings (Fig. 5A and B, and 5C).

Furthermore, funnel plots and Egger's test were used to assess potential publication bias. The results indicated significant publication bias ($P < 0.001$). The funnel plots for OS (Fig. 6A), RFS (Fig. 6B), and DFS (Fig. 6C) showed asymmetry, suggesting the presence of publication bias. However, after performing the trim-and-fill method, the pooled effect sizes and 95% CIs for all three indicators (OS, RFS, and DFS) did not change markedly, demonstrating the robustness of the meta-analysis results.

Discussion

This study systematically reviewed and analyzed the prognostic value of preoperative and postoperative neutrophil-to-lymphocyte ratio (NLR) in patients with hepatocellular carcinoma (HCC) undergoing curative treatment, including overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS). Our

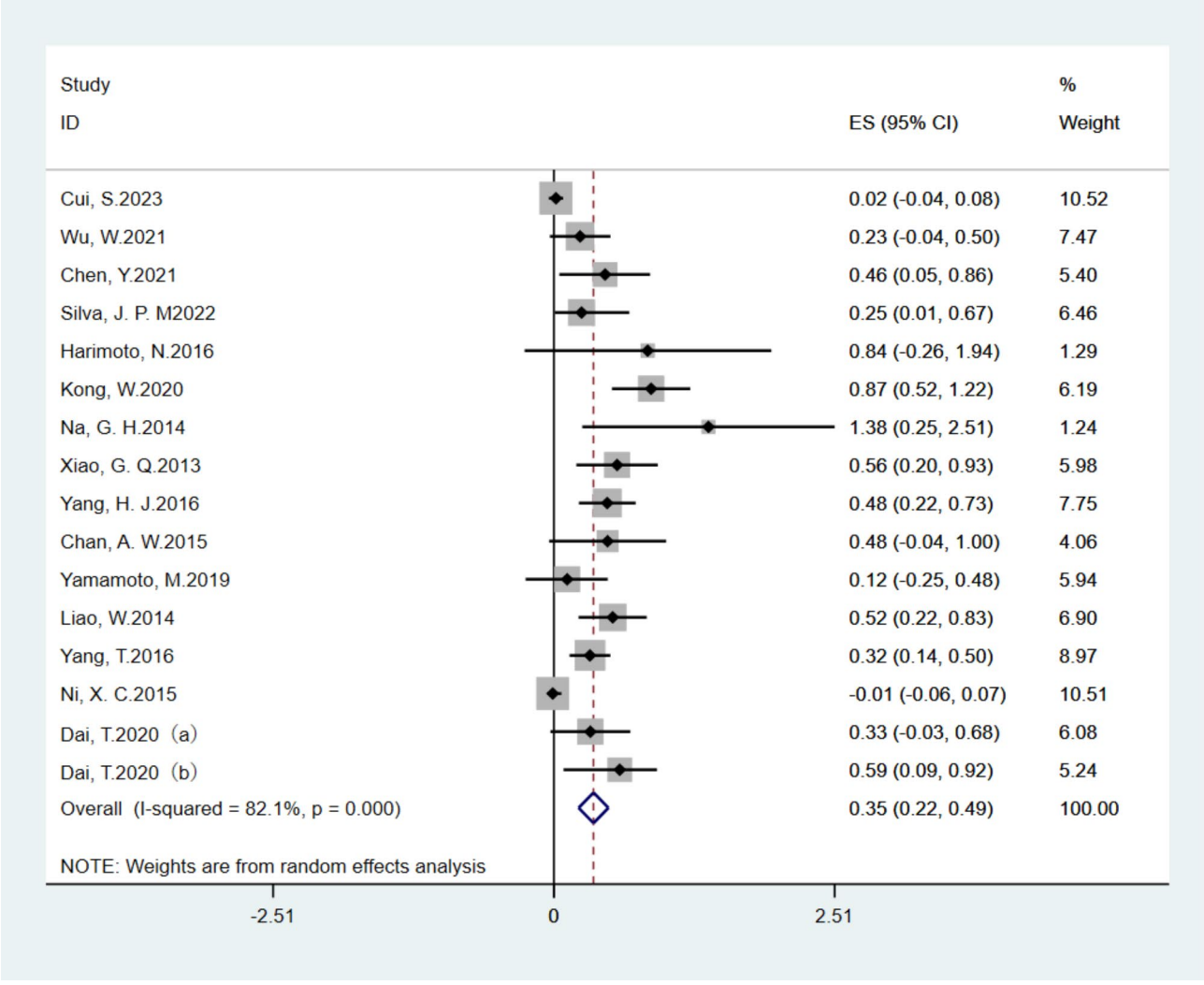

Fig. 4 Hazard ratio of disease-free survival based on multivariate analysis

Table 3 Subgroups of the prognostic value of NLR for OS in patients with HCC

Subgroups		Included studies	Patient	HR	95%CI	I^2	*P*-value
Countries	Eastern	33	7023	1.55	1.38–1.73	76.60%	< 0.01
	Western	3	430	1.73	1.26–2.36	0.00%	0.923
Univariate/ Multivariate	Univariate	15	2171	1.80	1.39–2.34	73.40%	< 0.01
	Multivariate	22	5422	1.46	1.28–1.68	78.90%	< 0.01
Treatment timing	Preoperative	31	6240	1.49	1.34–1.68	74.70%	< 0.01
	postoperative	6	1048	1.86	1.45–2.39	25.90%	0.240
Treatment methods	Hepatectomy	28	6464	1.55	1.36–1.77	74.70%	< 0.01
	Liver Transplantation	5	762	1.95	1.08–3.53	81.10%	< 0.01
	Radiofreguency Ablation	3	227	1.75	1.3–2.34	0.00%	0.836
Cut-off value	≦2.8	19	3760	1.72	1.54–1.92	4.00%	0.408
	> 2.8	17	3693	1.27	1.12–1.45	72.00%	< 0.01

findings indicate that higher NLR is significantly associated with poorer OS, DFS, and RFS. Elevated NLR levels are correlated with worse prognosis in HCC patients, particularly for long-term survival prediction after treatments like surgical resection or liver transplantation, where NLR has proven to be a strong independent prognostic factor [53].

Elevated NLR reflects an enhanced systemic inflammatory response and an immunosuppressive state, potentially promoting tumor progression and recurrence. The

Table 4 Subgroups of the prognostic value of NLR for RFS in patients with HCC

Subgroups		Included studies	Patient	HR	95%CI	I^2	*P*-value
Countries	Eastern	18	3391	1.57	1.38–1.79	52.10%	< 0.01
	Western	3	659	4.57	2.27–9.21	50.90%	0.130
Univariate/ Multivariate	Univariate	7	827	1.75	1.27–2.41	57.70%	0.028
	Multivariate	14	3223	1.79	1.45–2.18	75.40%	< 0.01
Treatment timing	Preoperative	16	3459	1.70	1.42–2.05	72.60%	< 0.01
	postoperative	5	591	2.08	1.32–3.29	63.50%	< 0.01
Treatment methods	Hepatectomy	14	3083	1.55	1.34–1.79	52.90%	0.010
	Liver Transplantation	5	849	3.25	1.73–6.05	72.50%	< 0.01
	Radiofreguency Ablation	2	296	1.39	0.87–2.23	54.50%	0.139
Cut-off value	≦2.81	10	1288	1.60	1.39–1.84	0.00%	0.731
	> 2.81	11	2762	1.92	1.45–2.53	83.10%	< 0.01

Table 5 Subgroups of the prognostic value of NLR for DFS in patients with HCC

Subgroups		Included studies	Patient	HR	95%CI	I^2	*P*-value
Countries	Eastern	15	4585	1.43	1.25–1.65	83.10%	< 0.01
	Western	1	161	1.28	0.92–1.79	-	-
Univariate/ Multivariate	Univariate	7	1319	1.43	1.11–1.88	84.40%	< 0.01
	Multivariate	9	3427	1.48	1.19–1.82	81.70%	< 0.01
Treatment timing	Preoperative	11	2797	1.40	1.21–1.63	82.40%	< 0.01
	postoperative	5	1949	1.45	1.22–1.72	26.90%	0.250
Treatment methods	Hepatectomy	11	3599	1.43	1.2–1.73	83.70%	< 0.01
	Liver Transplantation	4	1264	1.67	0.98–2.83	81.10%	< 0.01
	Radiofreguency Ablation	1	515	1.58	1.05–2.36	-	-
Cut-off value	≦2.47	8	2301	1.45	1.15–1.84	83.70%	< 0.01
	> 2.47	8	2445	1.46	1.15–1.86	82.80%	< 0.01

underlying mechanisms may involve immune microenvironment imbalance, release of pro-inflammatory factors, and polarization of tumor-associated macrophages (TAMs).

In HCC, NLR reflects an imbalance in the tumor immune microenvironment, typically characterized by an increase in neutrophils and a decrease in lymphocytes. This immune dysregulation not only leads to impaired anti-tumor immune surveillance but also promotes the release of pro-inflammatory cytokines, further driving the tumor microenvironment toward an immunosuppressive state.

Interplay Between Immune Microenvironment Imbalance and Pro-Inflammatory Cytokine Release. Studies have shown that a high NLR is often associated with an increased presence of regulatory T cells (Tregs), which suppress the function of CD8 + cytotoxic T cells, making HCC cells more adept at evading immune surveillance [54]. With the enhanced immunosuppressive state, neutrophils within the tumor microenvironment release substantial amounts of pro-inflammatory cytokines, such as IL-6, TNF-α, and TGF-β, which further accelerate HCC cell proliferation and metastasis.Moreover, these pro-inflammatory cytokines induce the polarization of tumor-associated macrophages (TAMs) toward an M2 phenotype, thereby creating a tumor-promoting microenvironment that facilitates cancer progression.

Positive Feedback Loop Between Pro-Inflammatory Cytokine Release and TAMs Polarization.Pro-inflammatory cytokines (such as IL-6 and TNF-α) not only directly stimulate tumor cell growth but also promote the differentiation of monocytes into M2-type TAMs within the hepatic microenvironment. Notably, M2-polarized TAMs have been well-documented for their immunosuppressive effects.M2-type TAMs secrete TGF-β and IL-10, which further suppress T-cell activity and promote tumor angiogenesis, thereby enhancing HCC invasion and metastasis [55]. Additionally, TAMs contribute to the maintenance of the cancer stem cell phenotype, which increases HCC resistance to therapy and heightens the risk of recurrence.

Reciprocal Enhancement Among Immune Imbalance, Pro-Inflammatory Cytokine Release, and TAMs Polarization.The dysregulated immune microenvironment leads to an increase in NLR, which in turn exacerbates the release of pro-inflammatory cytokines. These cytokines further drive the polarization of TAMs into an M2 phenotype, forming a vicious cycle that continuously enhances HCC immune evasion.Clinical studies have observed that HCC patients with high NLR often exhibit elevated levels of Tregs

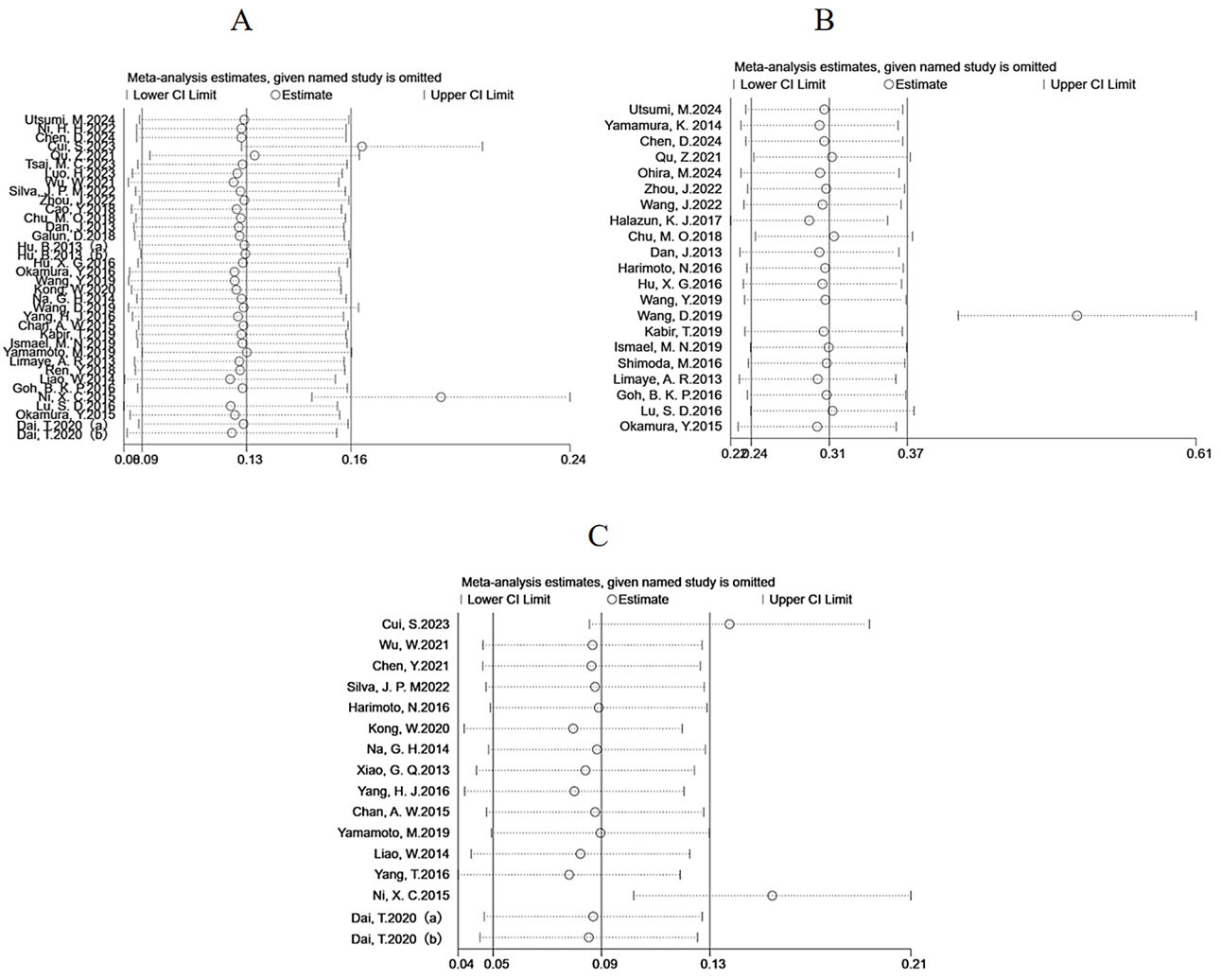

Fig. 5 Sensitivity analysis. (**A**) OS. (**B**) RFS. (**C**) RFS

and M2-type TAMs, further supporting the synergistic interactions among these components [56].Future research should focus on exploring the role of NLR across different immune microenvironment subtypes and investigate whether combining anti-inflammatory therapy or immunotherapy could disrupt the NLR–pro-inflammatory cytokine–TAM axis, thereby improving the survival outcomes of HCC patients.

Immune Microenvironment Imbalance: In HCC, a high neutrophil-to-lymphocyte ratio (NLR) indicates a greater number of neutrophils and fewer lymphocytes, leading to diminished immune surveillance. This imbalance facilitates tumor cells' evasion from immune recognition and promotes tumor development. Regulatory T cells (Tregs) play a crucial role in suppressing immune cells, further aiding tumor immune evasion [57]. High NLR is often associated with increased Tregs, suggesting weakened immune surveillance, making tumor cells more likely to escape immune detection and continue proliferating. Zhang et al. [58] reported that in HCC, high expression of PD-L1 + neutrophils and Tregs is significantly correlated with elevated NLR, thereby impairing anti-tumor immunity. Tregs are particularly important in suppressing the activity of effector T cells, significantly reducing the effectiveness of anti-tumor immune responses. Hong et al. [58] noted that Treg activity is positively correlated with NLR in HCC patients, indicating that elevated NLR exacerbates tumor immune evasion, ultimately leading to poorer survival outcomes.

Release of Pro-Inflammatory Factors: Studies have shown that in HCC, neutrophils can release various pro-inflammatory cytokines, such as IL-6 and TNF-α, which not only promote tumor growth and metastasis but also inhibit lymphocyte function, further weakening the anti-tumor immune response [59].

These cytokines not only directly influence tumor cells but also alter the immune characteristics of the tumor microenvironment, increasing the prevalence of immunosuppressive cells, such as TAMs, and creating an environment conducive to tumor growth(61).

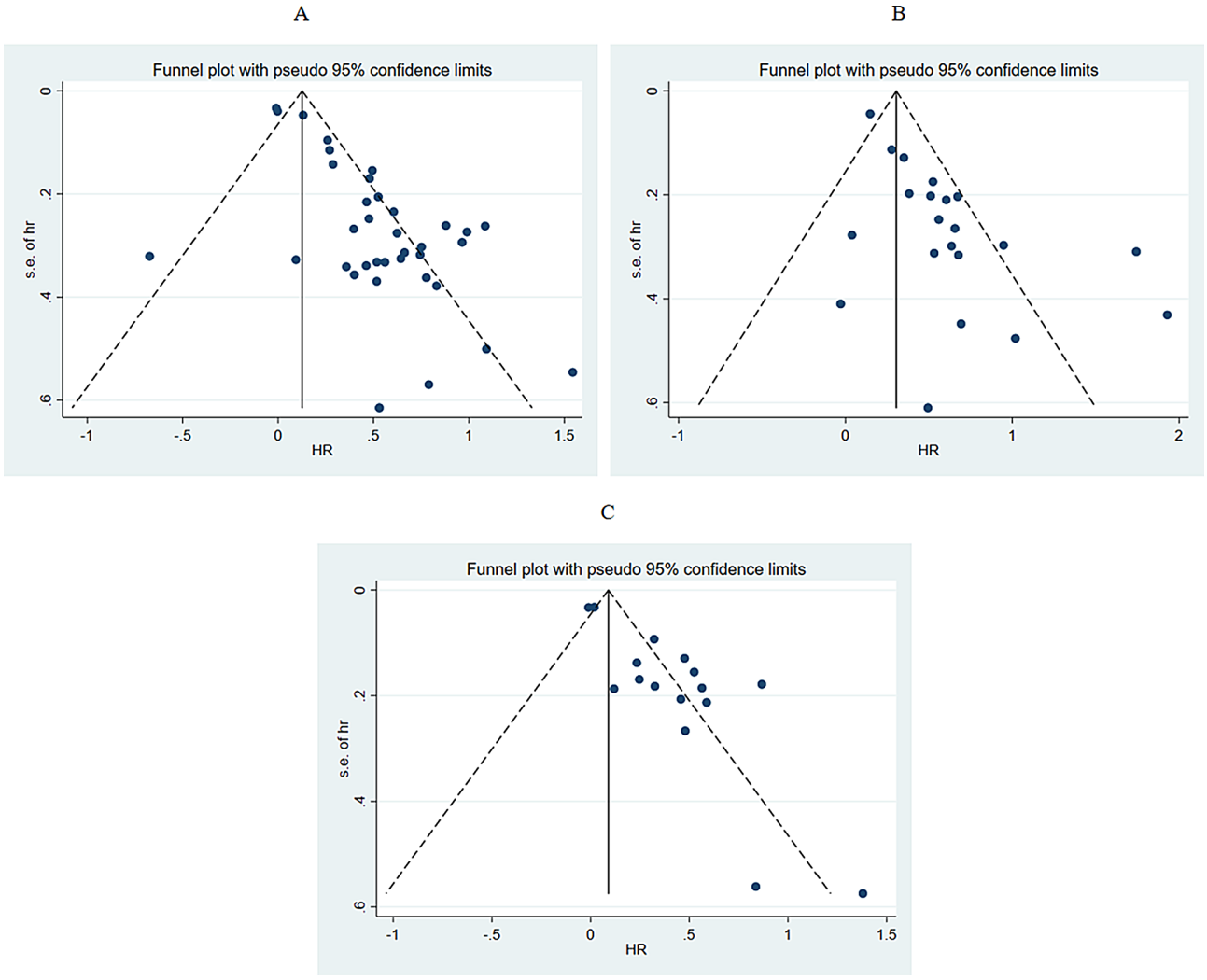

Fig. 6 Funnel plot. (**A**) OS; (**B**) RFS; (**C**) DFS

Tumor-Associated Macrophage (TAM) Polarization: In HCC, elevated NLR is associated with the M2 polarization of TAMs, which supports tumor growth and immune evasion [60].TA AMs promote tumor progression by releasing cytokines like TGF-β and IL-10 and by interacting with tumor cells through extracellular vesicles [61].M M2-polarized TAMs, in particular, create a pro-inflammatory microenvironment that enhances tumor cell invasiveness and migration [62], for example, by promoting epithelial-mesenchymal transition (EMT) via IL-8 and enhancing migration through the TLR4/STAT3 signaling pathway. These cells also promote HCC progression by expanding cancer stem cells and fostering tumor development [63]. In the tumor microenvironment, TAMs secrete various cytokines, such as TGF-β, IL-10, and PDGF, to promote tumor growth, angiogenesis, immune evasion, and cell proliferation through different mechanisms [64, 65].

The differential prognostic value of NLR across treatment modalities may stem from distinct immune responses post-intervention. In liver transplantation, immunosuppressive regimens (e.g., calcineurin inhibitors) likely attenuate lymphocyte activity [66, 67], which may affect the prognostic value of NLR. Conversely, ablation induces localized necrosis, triggering acute inflammation that elevates neutrophils transiently [68], which may distort NLR's relationship with survival outcomes. Additionally, resection-associated ischemia-reperfusion injury could sustain systemic inflammation [69], reinforcing NLR's prognostic role in this subgroup. These pathophysiological distinctions underscore the need for modality-specific interpretation of NLR.

Our subgroup analyses revealed that treatment modality and geographic region significantly impact the prognostic value of NLR. The results for OS showed that the prognostic significance of NLR was not affected by geographic region, type of survival analysis, pre- and

post-treatment status, or NLR cutoff value. For RFS, NLR remained significantly associated with worse outcomes across these factors. However, in the subgroup of patients who underwent radiofrequency ablation, higher NLR was not significantly associated with poorer RFS, likely due to the limited sample size of only two studies involving 296 patients, which may reduce the reliability and representativeness of these results. On the other hand, subgroup analyses based on geographic region and treatment modality indicated that NLR did not have statistically significant predictive power for DFS in Western countries or among patients who underwent radiofrequency ablation. This could also be due to the small number of studies and limited sample sizes included.

Notably, we observed significant heterogeneity across pooled analyses, which persisted despite extensive subgroup analyses based on geographic region, treatment modality, and NLR cutoff values. Unfortunately, the lack of patient-level data limited our ability to explore other potential sources of heterogeneity. For instance, the measurement of NLR levels may be influenced by variations in laboratory testing methods, sample processing protocols, or equipment differences, which we were unable to account for in this meta-analysis. Similarly, we were unable to perform subgroup analyses based on patient-specific characteristics, such as liver disease etiology (e.g., viral hepatitis, alcohol-related liver disease, or non-alcoholic fatty liver disease) and the degree of liver dysfunction (e.g., Child-Pugh score or MELD score), which are known to impact prognosis in HCC patients.

Furthermore, heterogeneity in the pooled estimates for survival outcomes may have been exacerbated by differences in the confounders included in the multivariable models across studies. For example, some studies adjusted for tumor stage and treatment type, while others did not, potentially introducing bias. Despite this high heterogeneity, the consistent association between elevated NLR and poorer clinical outcomes across studies provides reassurance that the observed associations are likely valid.

Our subgroup analyses emphasize the importance of NLR in predicting OS, RFS, and DFS in HCC patients. NLR can serve as an effective biomarker to aid clinicians in better assessing patient prognosis. Future studies should further validate the utility of NLR in different clinical settings and explore its optimal cutoff value. The subgroup analyses also revealed geographic differences, with a more pronounced association between NLR and OS and RFS in Eastern countries, possibly due to genetic and environmental factors [5]. This finding implies that region-specific cutoff values and strategies may be necessary when using NLR as a prognostic marker. Additionally, the results suggest that different treatment modalities might require tailored NLR thresholds and strategies [70].

Although the neutrophil-to-lymphocyte ratio (NLR) is a well-established prognostic marker in hepatocellular carcinoma (HCC), several other inflammation-based indices have also been studied for their prognostic value. To further evaluate the clinical relevance of NLR, it is essential to compare it with other commonly used prognostic indicators, such as the platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and Glasgow prognostic score (GPS).

NLR vs. PLR (Platelet-to-Lymphocyte Ratio).The PLR is another systemic inflammatory marker that reflects the balance between platelet-mediated tumor growth and lymphocyte-driven immune response. A recent study by Ji et al. (2016) found that both NLR and PLR were significant prognostic factors for disease-free survival (DFS) and overall survival (OS) in HCC patients undergoing curative resection. However, the study indicated that NLR had a stronger predictive power compared to PLR for recurrence risk in post-surgical patients [71].

NLR vs. PNI (Prognostic Nutritional Index).The PNI, calculated using serum albumin and lymphocyte count, is an indicator of both nutritional status and immune function. Mei et al. (2021) compared NLR, PLR, and PNI in HCC patients receiving anti-PD-1 immunotherapy and found that PNI was more strongly associated with treatment response, whereas NLR had better prognostic significance for OS and DFS [72].

NLR vs. GPS (Glasgow Prognostic Score).The Glasgow Prognostic Score (GPS) is an inflammation-based score incorporating C-reactive protein (CRP) and albumin levels. Recent meta-analyses have demonstrated that GPS provides superior prognostic value compared to NLR in predicting long-term survival in HCC patients [73, 74].

However, NLR remains more widely used due to its simplicity and ease of measurement. A recent comprehensive review also highlighted that a combination of GPS and NLR may further improve prognostic accuracy [75].Among various inflammatory markers, NLR is one of the most robust predictors of HCC prognosis, particularly for patients undergoing surgery or immunotherapy. While GPS and PNI offer additional prognostic insights, they require more complex calculations and may not be as widely applicable as NLR in routine clinical practice. Further research is needed to determine whether a combination of these markers can improve prognostic accuracy in HCC.

Our study has several limitations. First, most included studies were conducted in East Asia, particularly China, which could lead to regional bias, and the generalizability of the findings to other populations needs further validation. Second, some treatment modalities, such as radiofrequency ablation, had limited sample

sizes, reducing the statistical power and representativeness of the results in subgroup analyses. Third, the retrospective nature of most included studies may introduce selection bias and unmeasured confounding factors. The optimal NLR cutoff value varied significantly across studies, likely due to differences in sample size, study design, patient heterogeneity, and the timing of NLR measurement. Fourth, although this study focused on the prognostic value of NLR levels in HCC patients undergoing curative therapies, the relationship between changes in NLR levels over time and survival outcomes remains an important area for investigation. Such an analysis would require individual patient-level data to longitudinally track NLR dynamics, which were not available in the included studies.Therefore, large-scale, multicenter prospective studies are needed to further validate the prognostic value of NLR. We recommend that future research prioritize the collection of patient-level data to allow for more detailed subgroup analysis and exploration of other sources of heterogeneity, which is also conducive to exploring the prognostic significance of NLR changes. In addition, to explore the potential of NLR combined with other biomarkers in order to improve the accuracy of prognosis assessment and and the implementation of personalized treatment for HCC patients.

Conclusion

This systematic review and meta-analysis provide robust evidence that an elevated neutrophil-to-lymphocyte ratio (NLR) is significantly associated with poorer overall survival (OS), recurrence-free survival (RFS), and disease-free survival (DFS) in hepatocellular carcinoma (HCC) patients undergoing curative treatment. Our findings, derived from a comprehensive analysis of 43 studies involving 9,952 patients, confirm that higher NLR levels are predictive of adverse clinical outcomes, irrespective of geographic region, treatment modality, preoperative or postoperative measurement, or survival analysis method. Subgroup analyses further validate the prognostic significance of NLR across various clinical settings, highlighting its potential as a valuable, non-invasive biomarker for individualized risk assessment in HCC management. However, the variability in NLR cutoff values across studies underscores the need for standardized thresholds to optimize its clinical utility. Despite the strong association between NLR and survival outcomes, heterogeneity among included studies and potential publication bias necessitate further research. Future large-scale, multicenter prospective studies should focus on establishing the optimal NLR threshold and exploring its predictive value in different therapeutic contexts. Additionally, investigating the interplay between NLR, systemic inflammation, and the tumor microenvironment may provide deeper insights into its mechanistic role in HCC progression.

In conclusion, our study underscores the clinical relevance of NLR as an independent prognostic marker in HCC patients receiving curative treatment. Integrating NLR into routine clinical practice may enhance prognostic accuracy and inform personalized treatment strategies in this high-risk population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13972-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Conceptualization, Resources, Project administration and Funding acquisition: J. P. and F. W.; Methodology: H. C. and Z. C.; Software and Formal analysis: F. W. and Z. C.; Validation: Z. C. and J. T.; Data Curation: H. C and J. P.; Writing-Original Draft: all authors; Writing - Review & Editing: all authors; Visualization: X. L., J. T.; Supervision: X. L., F. W.

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

Declarations

Competing interests
The authors declare no competing interests.

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