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Research article

Which is the best TACE agent for patients with different NLR hepatocellular carcinomas? A systematic review and network meta-analysis

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ABSTRACT

Background: Transarterial chemoembolization (TACE) is a common treatment for hepatocellular carcinoma (HCC), but the best therapeutic agent for TACE treatment has not been determined. The neutrophil/lymphocyte ratio (NLR) is a systemic immune system marker; however, the ability of the NLR to predict the prognosis of patients with HCC is unknown, and no studies have been conducted to determine the most appropriate TACE regimen for HCC patients with different NLRs.

Methods: The PubMed, Embase, Web of Science, and CNKI databases were searched through May 28, 2023. Comparisons of overall survival (OS) among cohort studies with different NLRs and different TACE treatment regimens were performed with a random effects model.

Findings: Thirty-five studies involving 9210 patients were included in this meta-analysis. The results showed that Group 3–4 (NLR<2.5) patients had a significantly longer OS than Group 1–2 (NLR 2.5–5.0). Among the patients, Group 1–3 (NLR 2.0–5.0) patients had the best survival after treatment with adriamycin (lnHR (95 % CI = 0.48 [0.31, 0.75] and lnHR (95 % CI = 0.41 [0.19, 0.91]). Among the Group 4 patients (NLR<2.0), the best outcome was obtained with platinum + adriamycin (lnHR (95 % CI = 0.59 [0.45, 0.78]), followed by adriamycin. A subgroup analysis of TACE combined with other treatments showed that adriamycin combined with sorafenib was the most effective and superior to the other treatment agents.

Interpretation: The NLR can be used to predict the prognosis of HCC patients treated with TACE; the higher the NLR is, the worse the prognosis. Adriamycin may be the best therapeutic agent for HCC patients treated with TACE.

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1. Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumour of the gastrointestinal tract that ranks fifth in global incidence and is one of the top three deadly cancers worldwide [1]. Additionally, HCC has become the worst prognostic cancer among all solid malignancies because of its difficult diagnosis, easy recurrence and poor prognosis [2]. Transarterial chemoembolization (TACE) has become the treatment of choice for nonsurgical resection of HCC [3]; this method involves placing a branch of the tumour-supplying artery via arterial cannulation, and chemotherapeutic agents are injected after performing an angiogram [4]. Many valuable studies have demonstrated that TACE significantly improves overall survival (OS) compared to nonaggressive treatment in HCC patients [5–8]. However, the most suitable agent for TACE treatment has not been determined, and there is no suitable biomarker to guide the choice of therapeutic agent for TACE of different grades to select the most suitable TACE agents for patients with different HCC stages.

Biomarker prediction for agent selection in TACE patients is a popular research topic [9]. Many studies have predicted the inflammatory cytokines TNF-α, IL-6, and NF-κB, but the predictive power of these cytokines has not been conclusive[[10]]; therefore, we propose the use of the inflammatory markers neutrophil-lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR) [11]. However, there is no consensus on whether the NLR can be used to predict the prognosis of HCC patients. Halazun et al. demonstrated the connection between the NLR and HCC incidence [12]. Wang C et al. demonstrated that the NLR was significantly associated with OS in patients treated with TACE for hepatocellular carcinoma [13], but some reports did not reach similar conclusions. A study by Li XM et al. reported no prognostic effect of the NLR [14]. Several studies have shown that the PLR can predict the prognosis of patients with myocardial infarction combined with diabetes mellitus, but its ability to predict cancer incidence has not yet been determined.

The primary objective of this meta-analysis was to confirm that the NLR and PLR are independent predictors of prognosis in HCC patients treated with TACE. The follow-up objective was to determine the optimal agents for TACE treatment in HCC patients with different NLRs to determine the most suitable agents. All of the above methods were used for accurate selection of agents for TACE and improvement of patient survival.

2. Methods

This study was designed and completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [15] and the Cochrane Handbook [16]. The protocol for this study was registered with PROSPERO, CRD42023441833 [17].

2.1. Search of databases

Two authors (Shuai Wang, Hefeng Geng) searched the PubMed, Embase, Cochrane Library, Web of Science, and CNKI databases for the period of establishment to July 2023. Duplicate literature, reports, letters and other noncompliant articles were manually excluded. The search terms used included “neutrophil/lymphocyte ratio”, “NLR”, “platelet/lymphocyte ratio”, “PLR”, “hepatocellular carcinoma”, “HCC”, “transarterial chemoembolization”, and “TACE”, with no language restriction (Supplementary Table 1).

2.2. Data collection and quality assessment

The inclusion criteria for patients were adult HCC patients treated with TACE, patients treated with TACE divided into conventional TACE (cTACE) and patients treated with drug-loaded microsphere TACE (DEB-TACE). Most of the TACE treatments involved in this article were conventional TACE treatments. A chemotherapeutic emulsion of iodized oil supplemented with granular embolic agent was used. The types of platinum agents used were carboplatin, oxaliplatin and cisplatin. The primary outcome metric was the relative risk of OS in patients with higher and lower NLRs, and the secondary outcome metric was OS in patients receiving different chemotherapy agents; the included studies were prospective cohort studies and retrospective cohort studies. Works such as animal studies, ongoing trials, letters, reviews, and abstracts were excluded, as were those for which data were unavailable and low-quality cohort studies (Newcastle–Ottawa Scale <5). Given that all the included studies were cohort studies, the Ottawa Newcastle Scale was used for critical appraisal. Study quality was assessed by the NOS scale and scored according to three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. Higher scores indicated higher quality of the literature (Supplemental Fig. 13).

The literature search, data collection, and study quality assessment were performed independently by two authors. We collected information about the studies (published authors, year, journal, sample size), patient characteristics (age, sex, liver function class, concomitant disease), NLR thresholds, PLR thresholds, risk ratios (HRs) for OS, TACE chemotherapy regimens, and other treatment measures [18]. We produced funnel plots to explore publication bias for network meta-analysis outcomes. In cases of disagreement, a third investigator discussed the case to reach a consensus. The articles were evaluated for grade, and the majority of the articles had a low evidence rating.

2.3. Statistical analysis

The analysis software used in the article was Stata MP (version 17), and the image processing software used was Photoshop. The extracted data were subjected to ordinary meta-analysis and network meta-analysis, and forest plots, funnel plots, network plots, ranked lists and ranked graphs were obtained. The survival outcome indicators were evaluated using the lnHR and 95 % confidence

interval (CI) [19]. Ordinary meta-analysis was used to determine the importance of the model by the I^2 value, and I^2>50 %. Heterogeneity was considered to exist, and a random-effects model was used; $I^2 \leq 50$ % was used as the fixed-effects model. If heterogeneity existed, sensitivity analysis or subgroup analysis was used to determine the source of heterogeneity. The node splitting method was used to evaluate whether the results of direct and indirect comparisons were inconsistent, and $P > 0.05$ was considered good consistency. Network meta-analysis was used to rank the pharmacological interventions in the study. The efficacy of each agent was judged by the surface under the cumulative ranking (SUCRA) curve. We calculated the ranking probability and SUCRA value and plotted the cumulative ranking probability and correlation graph to visually compare the advantages and disadvantages of various chemotherapy drugs. The higher the SUCRA score is, the better the efficacy [20].

First, we compared OS in patients with different NLRs and PPRs to determine the associations between the NLR and between the PLR and OS. Second, we compared the OS of HCC patients treated with TACE and different chemotherapeutic agents at different NLRs to determine the optimal treatment regimen. We also performed a subgroup analysis of HCC patients treated with TACE in combination with other therapies to explore the optimal TACE regimen for HCC patients with different NLRs.

3. Results

3.1. Characteristics of the included studies

A total of 182 articles were retrieved in the first search; 44 duplicates were excluded, 52 articles had inconsistent titles and

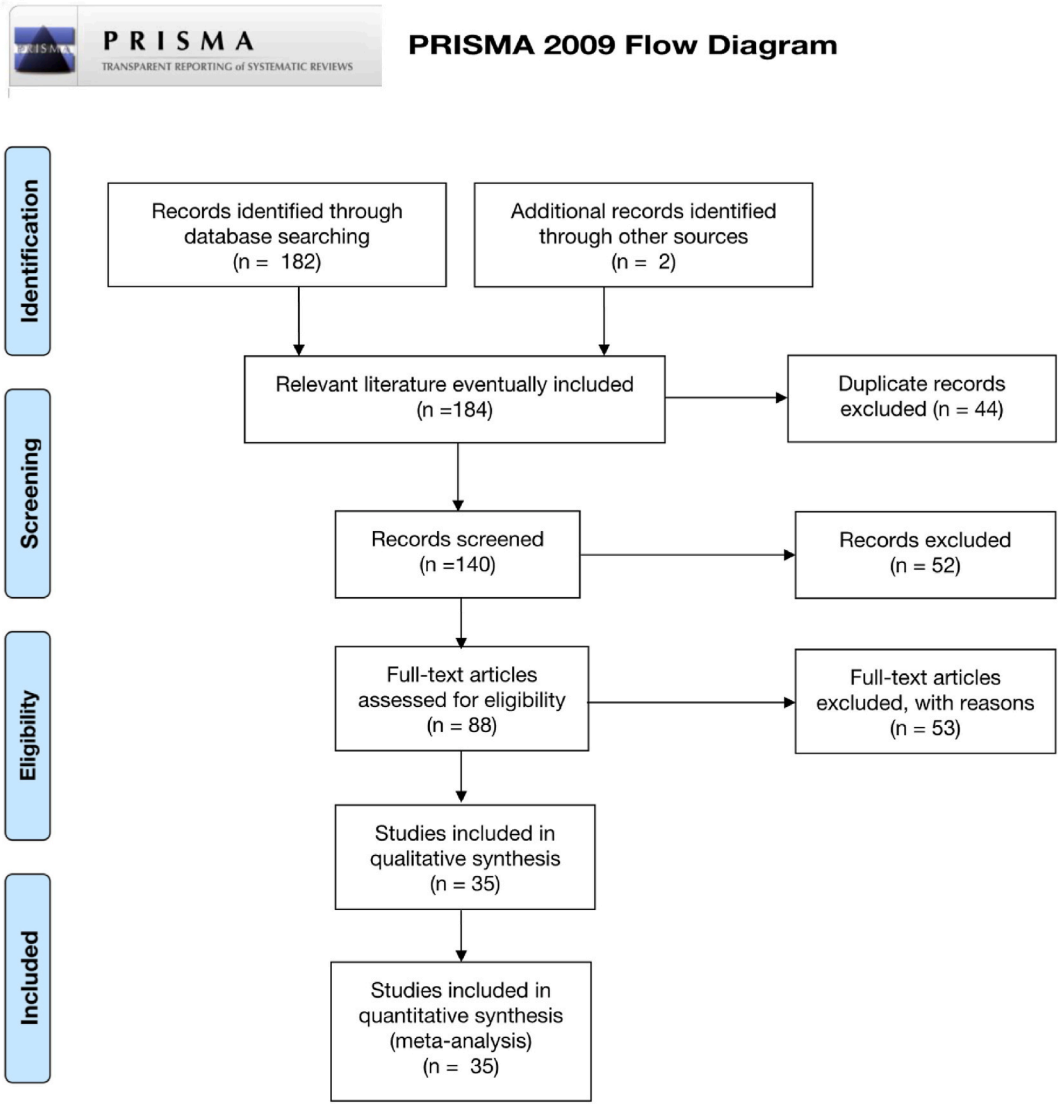

Fig. 1. PRISMA 2020 diagram of database search and study inclusion.

abstracts, and 53 articles were excluded after the full texts were read, resulting in the inclusion of 35 articles involving 9210 patients receiving TACE therapy for HCC. (Fig. 1).

This network meta-analysis included 35 studies [13,14,21–54], all of which were cohort studies. Among them, 28 were from China, 4 were from Korea [32,40,45,47], 1 was from the United States [31], and 1 was from Italy [38]. Thirty-four articles included the NLR and OS outcome indicators, and 10 articles included the PLR and OS outcome indicators. We collected basic characteristics from the included studies (Table 1). The literature was published from 2014 to 2022, with a sample size of 47–931. The NLR ranged from 1.57 to 5.0, and patients were categorized into four groups for subsequent analysis. Group 1: NLR3.5–5.0; Group 2: NLR2.5–3.5; Group 3: NLR2.0–2.5; Group 4: NLR<2.0. The PLRs ranged from 92 to 137 and were categorized into two groups for subsequent analysis. Group PLR <100.0; Group PLR >100.0. All cohort studies were of moderate to high quality (NOS >5). The articles were analysed for publication bias (Supplementary Table 2), and all the included studies had complete data and high-quality literature and were available for our analysis (Supplemental Fig. 1, Supplemental Fig. 2). We performed subgroup analyses of the different agents used for TACE treatment, and the results of the ES (95 % CI) and heterogeneity tests are summarized in Table 2.

3.2. The predictive power of the NLR for TACE treatment in patients with HCC

A total of 34 articles reported data on the association between the NLR and OS, with significant heterogeneity between studies (I^2 = 91.3 %, P = 0.000) according to a random effects model combining effect sizes (lnHRs) (95 % CI = 0.50 [0.45, 0.76]) (**Supplemental** Figure 3). To explore the connection between NLR and patient OS, we combined effect sizes for data from Groups 1 and 2 (NLR2.5–5.0) (lnHR (95 % CI = 0.91 [0.35, 1.46]) and combined effect sizes for data from Groups 3 and 4 (lnHR (95 % CI = 0.64 [0.42, 0.87]). Patients with a higher NLR had significantly worse OS than patients with a lower NLR did (Supplemental Fig. 4). To explore the sources of heterogeneity, we analysed the different NLRs in the groups. Group 1 (I^2 = 92.3 %, P = 0.000), combined effect size (lnHR (95 % CI = 0.74 [0.26, 1.21]), Group 2 (I^2 = 69.8 %, P = 0.000), combined effect size (lnHR (95 % CI = 0.38 [0.20, 0.56]), Group 3 (I^2 = 78.3 %, P = 0.000), combined effect size (lnHR (95 % CI = 0.65 [0.45, 0.85]), Group 4 (I^2 = 85.6 %, P = 0.000), and combined effect size (lnHR (95 % CI = 0.54 [0.19, 0.88]). Analysis of the NLR groups suggested that the NLR threshold may be a source of heterogeneity (**Supplemental** Figure 5) and confirmed that the higher the NLR was, the shorter the survival time was.

Table 1
Characteristics of the included studies.

Author	Year	National	Sample Size	Age	Men	NLR value	PLR value	TACE treatment protocol	NOS score
Huang ZL	2011	China	145	49 ± 42.22	134	3.3		ADM + Platin	7
Xu X	2014	China	178	54.3 ± 11.3	149	1.85		ADM + Platin	6
Zhang J	2014	China	138	56.8 ± 12.5	99	5.0		ADM + Platin	6
Fan W	2015	China	132	49 ± 38.52	87	3.1	137	ADM + Platin	6
Yang XG	2015	China	546	52 ± 13.25	453	3.02		ADM + Platin	7
Zhou D	2016	China	293	50 ± 22.22	151	2.6		ADM + Platin	5
Tian XC	2016	China	122	56 ± 12.75	107	2.61	96.13	ADM+5-FU	8
Wang WJ	2016	China	427	54.4 ± 12. 3	346	2.5		ADM	7
Liu C	2017	China	760	56.5 ± 51.85	643	2.2		ADM+5-FU	6
Liu C2	2017	China	793	56 ± 51.85	665	2.2		ADM+5-FU	6
Rebonato IT	2017	Italy	49	75 ± 9.75	39	2.03		ADM	8
Sun WH	2018	China	95	54.1 ± 13.2	84	2.51	96.84	ADM + Platin	5
He C	2019	China	216	53	200	1.77	94.62	ADM + Platin	7
Shen Y	2019	China	172	57 ± 6.667	143	2.21	98.87	ADM	7
Chon YE	2019	Korea	921	68.2 ± 10.7	700	5.0		ADM + Platin	7
Cruz JC	2019	US	190	65.2 ± 8.889	146	3.5		ADM	8
Chen LL	2019	China	120	55.9 ± 8.6	92	1.77		ADM	5
Liu HJ	2019	China	235	18–80	208	2.35		–	5
Hong YM	2020	Korea	73	–	56	1.6		ADM	7
Liu J	2020	China	180	54.3 ± 9.3	155	3.94		ADM	6
Sun S	2020	China	47	40 ± 10.37	44	3.09		ADM	7
Wang H	2020	China	181	53 ± 38.52	164	2.5		ADM	7
Wang C	2020	China	380	54.3 ± 12.3	311	2.4		ADM	6
Long J	2020	China	48	57.0 ± 11.2	36	3.5	100	ADM+5-FU	8
Zhang L	2021	China	314	55.0 ± 13.75	270	2.42	100	ADM + Platin	8
Liu Y	2021	China	128	56.96 ± 11.44	112	1.57	92	ADM + Platin	7
Chu HH	2021	Korea	931	59.4 ± 9.8	810	3.0		Platin	6
Wang FQ	2021	China	87	50.5 ± 9.7	79	2.95		ADM	6
Xu SH	2021	China	117	56.5 ± 12.8	98	3.22		ADM	5
Yang XG	2022	China	161	60 ± 42.96	146	2.95	115.75	ADM + Platin	5
Cho E J	2022	Korea	605	57 ± 21.48	498	1.7		ADM	7
Han Z	2022	China	171	–	144	2.195		5-FU + Platin	6
Li X	2022	China	114	53 ± 13.75	102	2.165	96.42	ADM	6
Zheng X	2022	China	95	54.8 ± 9.09	74	2.22		ADM	6

Table 2
Summary table of treatment subgroups.

Subgroups (study , n)	ES (95 % CI)	I^2 (P)
Group2 NLR2.5–3.5	0.37 (0.26, 0.47)	75.9 % (0.002)
Platinum (7, 2303)	0.79 (0.66, 0.92)	
Adriamycin (4, 742)	0.45 (0.26, 0.65)	
Group3 NLR2.0–2.5	0.66 (0.58, 0.73)	75.1 % (0.129)
Adriamycin (5,810)	0.63 (0.53, 0.73)	
Fluorouracil (3, 1724)	0.75 (0.62,0.88)	
Group4 NLR<2.0	0.11 (0.07, 0.14)	85.6 % (<0.001)
Platinum (3, 522)	0.61 (0.39, 0.82)	
Adriamycin (3, 798)	0.09 (0.06, 0.13)	

3.3. Optimal TACE regimen for Group 1 (NLR 3.5–5.0) patients

Group 1 included 6 articles for network analysis [23,31,32,41,42,53]. Supplemental Fig. 6Ashows the network diagram for different TACE regimens in Group 1 patients in the 6 control groups. An inconsistency test was performed to determine whether the direct and indirect comparisons were consistent, and the results showed no inconsistency (P = 0.7399); therefore, the consistency model was used. According to the league diagram (Fig. 2A, Supplemental Fig. 9A), Group 1 patients had the best results for adriamycin (SUCRA = 80.5) (lnHR (95 % CI = 0.48 [0.31, 0.75]), followed by platinum (SUCRA = 76.4) and finally 5-fluorouracil (SUCRA = 53.7). In conclusion, Group 1 had the best prognosis after treatment with adriamycin.

3.4. Optimal TACE regimen for Group 2 (NLR 2.5–3.5) patients

Group 2 included 12 articles for network analysis [21,24–26,34,45,50–52,55–57]. Supplemental Fig. 6B shows a network diagram of different TACE regimens for Group 2 patients in the 8 control groups. An inconsistency test was performed to determine whether the direct and indirect comparisons were consistent, and the results showed no inconsistency (P = 0.6336); therefore, the consistency model was used. According to the league table (Fig. 2B, Supplemental Fig. 9B), Group 2 patients were better treated with adriamycin than with platinum combined with adriamycin (SUCRA = 87.1) (lnHR (95 % CI = 0.41 [0.19, 0.91]), followed by platinum (SUCRA = 68.8) or 5-fluorouracil combined with adriamycin (SUCRA = 68.2). In conclusion, Group 2 also had the best prognosis after treatment with adriamycin.

3.5. Optimal TACE regimen for Group 3 (NLR 2.0–2.5) patients

Group 3 included a total of 10 articles reporting OS [13,14,28,29,38,43,48,49,54,58]. Fig. 3A shows a network diagram of different TACE regimens for Group 3 patients in which 8 control groups were included. An inconsistency test was performed to determine whether the direct and indirect comparisons were consistent, and the results showed no inconsistency (P = 0.3081); therefore, the consistency model was used. According to the league table (Supplemental Fig. 7, Supplemental Fig. 9C), Group 3 patients had the best response to adriamycin (SUCRA = 78.0), followed by 5-fluorouracil combined with adriamycin (SUCRA = 65.0), 5-fluorouracil combined with platinum (SUCRA = 59.0), and platinum combined with adriamycin (SUCRA = 58.5). In conclusion, for patients whose NLR was 3, the best survival prognosis was obtained with adriamycin combined with TACE.

A subgroup analysis of TACE combined with other treatments was performed, and Fig. 3B shows a network diagram of TACE

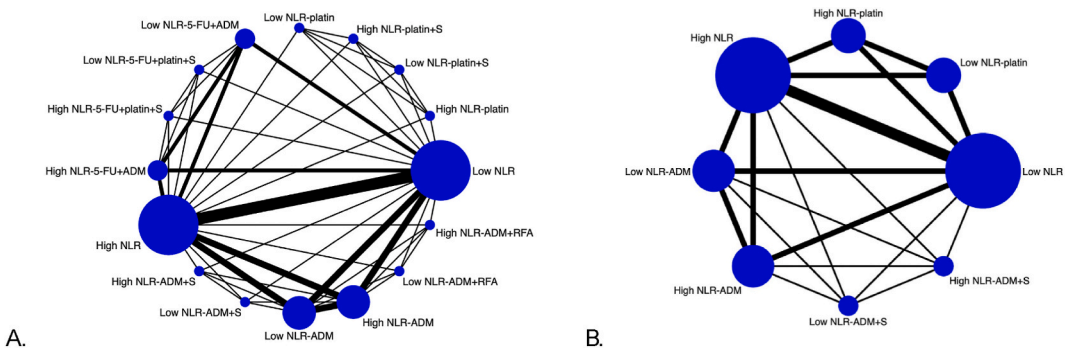

Fig. 2. Summary lnHRs and CIs from Group1(NLR 3.5–5.0) and Group2(NLR 2.5–3.5). A. Summary lnHRs and CIs from Group1. B. Summary lnHRs and CIs from Group2(NLR 2.5–3.5) According to SUCRA, Patients with HCC treated with TACE were ranked in order of OS improvement from left to right. In the lower left corner, the lnHR and 95 % CI of two comparisons of NMA are obtained through indirect comparison. The comparison between treatments should be read from left to right. Bold indicates statistically significant differences. NLR : Neutrophil/lymphocyte ratio, ADM: Adriamycin, Platin:Platinum, 5-FU: 5-Fluorouracil, S: Sorafenib.

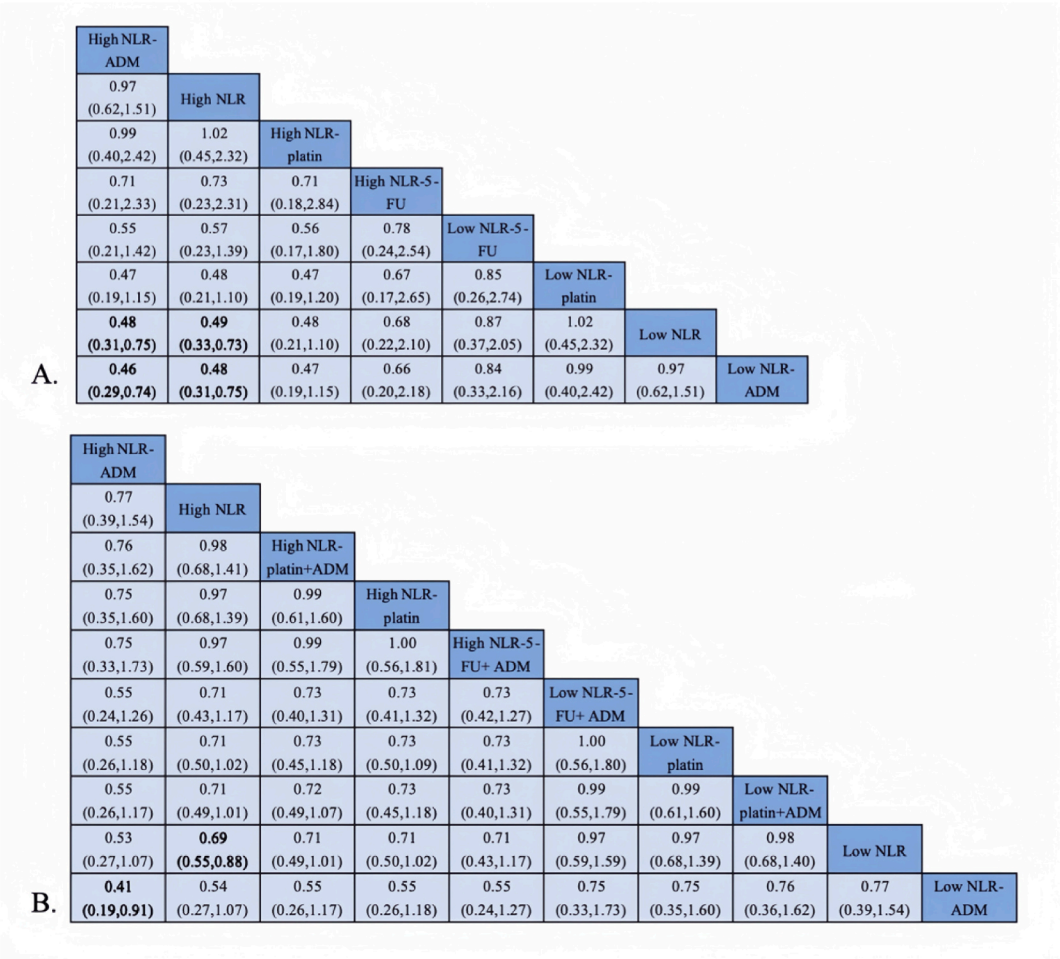

Fig. 3. Network of Group3 (NLR 2.0–2.5)for OS. A: Group3 network diagram, B: Group3 subgroup network diagram. The size of the nodes is proportional to the number of trial participants, and the thickness of the line connecting the nodes is proportional to the number of participants directly comparing the two treatments. NLR：Neutrophil/lymphocyte ratio, ADM：Adriamycin, Platin:Platinum, 5-FU: 5-Fluorouracil, S: Sorafenib, RFA: Radiofrequency ablation, Group3:NLR 2.0–2.5.

combined with other treatment options in Group 3 patients in the 14 control groups. An inconsistency test was performed to determine whether the direct and indirect comparisons were consistent, and the results showed no inconsistency (P = 0.8469); therefore, a consistency model was used. From the league table (Fig. 4, Supplemental Fig. 10A), it was found that adriamycin + Sorafenib was the most effective treatment (SUCRA = 87.0) (lnHR (95 % CI = 0.12 [0.02, 0.55]), followed by adriamycin (SUCRA = 85.0), 5-fluorouracil + adriamycin (SUCRA = 63.2), adriamycin + RFA (SUCRA = 60.7), 5-fluorouracil + adriamycin + platinum (SUCRA = 59.1), and platinum + adriamycin (SUCRA = 58.7). Therefore, patients in Group 3 treated with adriamycin combined with sorafenib had the best prognosis when combined with other treatments.

3.6. Optimal TACE regimen for Group 4 (NLR <2.0) patients

Group 4 **included** 6 articles analysing OS outcome indicators [22,30,33,40,44,47]. Supplemental Fig. 6C shows a network diagram of different TACE regimens in Group 4 patients in the 4 control groups. An inconsistency test was performed to determine whether the direct and indirect comparisons were consistent, and the results showed no inconsistency (P = 0.3935); therefore, the consistency model was used. As shown in the league table (Supplemental Fig. 8, Supplemental Fig. 9D), adriamycin combined with platinum agent had synergistic efficacy on more Group 4 patients (SUCRA = 86.7) than did adriamycin alone (lnHR (95 % CI = 0.59 [0.45, 0.78]). In conclusion, Group 4 had the best prognosis among the groups.

Subgroup analysis was performed for TACE combined with other treatments. Supplemental Fig. 6D shows the network diagram for Group 4 patients treated with TACE combined with other treatment regimens; six control groups were included. An inconsistency test was performed to determine whether the direct and indirect comparisons were consistent, and the results showed no inconsistency (P = 0.1393); therefore, the consistency model was used. The league table (Fig. 5, Supplemental Fig. 10B) shows that adriamycin

High NLR-ADM+S															
0.75 (0.16,3.61)	High NLR-ADM														
0.57 (0.12,2.65)	0.75 (0.34,1.67)	High NLR													
0.41 (0.07,2.42)	0.55 (0.17,1.78)	0.73 (0.27,1.94)	High NLR-5-FU+ADM												
0.40 (0.05,3.26)	0.54 (0.11,2.55)	0.71 (0.15,3.31)	0.98 (0.17,5.75)	High NLR-ADM+RFA											
0.38 (0.04,3.21)	0.50 (0.09,2.70)	0.67 (0.14,3.14)	0.92 (0.18,4.59)	0.93 (0.11,7.89)	High NLR-5-FU+ platin+S										
0.37 (0.04,3.40)	0.50 (0.08,2.91)	0.66 (0.13,3.41)	0.91 (0.14,5.85)	0.93 (0.10,8.37)	0.99 (0.11,9.10)	High NLR-platin+S									
0.37 (0.04,3.40)	0.50 (0.08,2.91)	0.66 (0.13,3.41)	0.91 (0.14,5.85)	0.93 (0.10,8.37)	0.99 (0.11,9.10)	1.00 (0.16,6.43)	High NLR-platin								
0.23 (0.03,2.09)	0.30 (0.05,1.79)	0.41 (0.08,2.09)	0.56 (0.09,3.59)	0.57 (0.06,5.13)	0.61 (0.07,5.58)	0.61 (0.10,3.94)	0.61 (0.10,3.94)	Low NLR-platin+S							
0.23 (0.03,2.09)	0.30 (0.05,1.79)	0.41 (0.08,2.09)	0.56 (0.09,3.59)	0.57 (0.06,5.13)	0.61 (0.07,5.58)	0.61 (0.10,3.94)	0.61 (0.10,3.94)	1.00 (0.16,6.43)	Low NLR-platin						
0.23 (0.03,1.94)	0.30 (0.06,1.63)	0.40 (0.09,1.90)	0.55 (0.11,2.78)	0.56 (0.07,4.77)	0.61 (0.09,3.89)	0.61 (0.07,5.58)	0.61 (0.07,5.58)	0.99 (0.11,9.09)	0.99 (0.11,9.09)	Low NLR-5-FU+ platin+S					
0.21 (0.03,1.72)	0.28 (0.06,1.35)	0.38 (0.08,1.75)	0.52 (0.09,3.04)	0.53 (0.08,3.39)	0.57 (0.07,4.80)	0.57 (0.06,5.16)	0.57 (0.06,5.16)	0.93 (0.10,8.41)	0.93 (0.10,8.41)	0.94 (0.11,7.93)	Low NLR-ADM+RFA				
0.21 (0.04,1.23)	**0.28 (0.08,0.91)**	**0.37 (0.14,0.98)**	0.51 (0.17,1.49)	0.52 (0.09,3.02)	0.55 (0.11,2.78)	0.56 (0.09,3.59)	0.56 (0.09,3.59)	0.91 (0.14,5.85)	0.91 (0.14,5.85)	0.92 (0.18,4.59)	0.98 (0.17,5.72)	Low NLR-5-FU+ADM			
0.15 (0.03,0.71)	**0.20 (0.09,0.44)**	**0.27 (0.14,0.50)**	**0.37 (0.14,0.98)**	0.38 (0.08,1.74)	0.40 (0.09,1.90)	0.41 (0.08,2.09)	0.41 (0.08,2.09)	0.66 (0.13,3.41)	0.66 (0.13,3.41)	0.67 (0.14,3.14)	0.71 (0.15,3.29)	0.73 (0.27,1.94)	Low NLR		
0.12 (0.02,0.55)	**0.15 (0.07,0.35)**	**0.20 (0.09,0.45)**	**0.28 (0.09,0.91)**	0.28 (0.06,1.35)	0.31 (0.06,1.64)	0.31 (0.05,1.80)	0.31 (0.05,1.80)	0.50 (0.09,2.93)	0.50 (0.09,2.93)	0.51 (0.09,2.72)	0.54 (0.11,2.56)	0.55 (0.17,1.79)	0.76 (0.35,1.66)	Low NLR-ADM	
0.09 (0.01,0.56)	**0.12 (0.02,0.55)**	**0.15 (0.03,0.71)**	0.21 (0.04,1.24)	0.21 (0.03,1.72)	0.23 (0.03,1.95)	0.23 (0.03,2.10)	0.23 (0.03,2.10)	0.38 (0.04,3.42)	0.38 (0.04,3.42)	0.38 (0.05,3.22)	0.41 (0.05,3.26)	0.42 (0.07,2.43)	0.57 (0.12,2.65)	0.75 (0.16,3.58)	Low NLR-ADM+S

Fig. 4. Summary lnHRs and CIs from Group3(NLR 2.0–2.5) subgroup. According to SUCRA, Patients with HCC treated with TACE were ranked in order of OS improvement from left to right. In the lower left corner, the lnHR and 95 % CI of two comparisons of NMA are obtained through indirect comparison. The comparison between treatments should be read from left to right. Bold indicates statistically significant differences. NLR：Neutrophil/lymphocyte ratio, ADM: Adriamycin, Platin:Platinum, 5-FU: 5-Fluorouracil, S: Sorafenib, RFA: Radiofrequency ablation, Group3: NLR 2.0–2.5.

High NLR-ADM+S							
0.95 (0.66,1.37)	High NLR-platin						
0.91 (0.66,1.26)	0.97 (0.78,1.19)	High NLR					
0.88 (0.63,1.23)	0.93 (0.71,1.22)	0.97 (0.78,1.19)	High NLR-ADM				
0.56 (0.40,0.78)	**0.59 (0.45,0.78)**	**0.61 (0.50,0.76)**	**0.64 (0.51,0.79)**	Low NLR-ADM			
0.54 (0.39,0.75)	**0.57 (0.47,0.71)**	**0.59 (0.51,0.69)**	**0.62 (0.50,0.76)**	0.97 (0.79,1.19)	Low NLR		
0.53 (0.36,0.76)	**0.55 (0.44,0.69)**	**0.57 (0.47,0.71)**	**0.59 (0.45,0.78)**	0.93 (0.71,1.22)	0.97 (0.79,1.19)	Low NLR-platin	
0.50 (0.34,0.73)	**0.53 (0.36,0.76)**	**0.54 (0.39,0.75)**	**0.56 (0.40,0.78)**	0.88 (0.64,1.23)	0.92 (0.66,1.26)	0.95 (0.66,1.36)	Low NLR-ADM+S

Fig. 5. Summary lnHRs and CIs from Group4 (NLR<2.0) **subgroup.** According to SUCRA, Patients with HCC treated with TACE were ranked in order of OS improvement from left to right. In the lower left corner, the lnHR and 95 % CI of two comparisons of NMA are obtained through indirect comparison. The comparison between treatments should be read from left to right. Bold indicates statistically significant differences. NLR：Neutrophil/lymphocyte ratio, ADM: Adriamycin, Platin:Platinum, 5-FU: 5-Fluorouracil, S: Sorafenib, Group4:NLR<2.0.

combined with sorafenib (SUCRA = 86.7) was more effective than was adriamycin combined with platinum (SUCRA = 81.4) alone (lnHR (95 % CI = 0.53 [0.40, 0.78]) or adriamycin (SUCRA = 70.4) alone (lnHR (95 % CI = 0.53 [0.36, 0.76]). Therefore, patients in Group 4 who were treated with adriamycin combined with sorafenib had the best prognosis.

3.7. Predictive power of the PLR for TACE treatment in patients with HCC

A total of 10 articles reported data on the association between PLR and OS, with significant heterogeneity between studies (I^2 =

76.8 %, P = 0.000) according to a random effects model combining effect sizes (lnHRs) (95 % CI = 0.52 [0.21, 0.82]) (**Supplemental** Figure 11). To explore the connection between PLR thresholds and patient OS, we divided the PLRs into two groups: PLR<100 and PLR>100. After combining effect sizes, Group PLR<100 (lnHR (95 % CI: 0.42 [−0.04, 0.87]) and Group PLR>100 (lnHR (95 % CI: 0.49 [0.09, 0.90]) were used. Patients with a higher PLR had shorter OS than patients with a lower PLR did (Supplemental Fig. 12).

4. Discussion

The results of our network meta-analysis first showed that an increase in the NLR is directly related to poor survival. Follow-up network analysis revealed that for HCC patients treated with TACE in Groups 1–3 (NLR 2.0–5.0), adriamycin was the most effective treatment option and was superior to other treatment options; for patients in Group 4 (NLR <2.0), adriamycin + platinum agent therapy was superior to adriamycin alone. When TACE was combined with other treatments, adriamycin + sorafenib was superior. Our results suggest that the NLR is a reliable prognostic indicator for patients with HCC treated with TACE and can guide clinical dosing. For Group 1–3 (NLR 2.0–5.0) patients, the prognosis was better with adriamycin treatment. A total of 35 articles containing 9210 patients were included in our meta-analysis, and the quality of the articles was good. Patients in Groups 3–4 had longer OS than patients in Groups 1–2 did, indicating that the higher the NLR is, the worse the prognosis. We also briefly explored the connection between PLR and OS in patients with HCC. The PLR may be an independent predictor of the prognosis in HCC patients.

The role of inflammatory factors in cancer development is currently under constant investigation, and several inflammatory markers have been shown to predict the prognosis of patients with different cancers. The NLR is a systemic immune marker that is associated with the level of inflammation in the body. Neutrophils can promote tumorigenesis, angiogenesis, and tumour cell movement, leading to tumour invasion and metastasis. Lymphocyte deficiency affects the antitumour response and is often associated with poorer prognosis in tumour patients. Patients with hepatocellular carcinoma are treated with TACE, but different chemotherapy regimens have different therapeutic effects. Therefore, we explored the ability of different NLRs to predict the best treatment regimen when TACE is used for treating HCC patients through a network meta-analysis to verify the ability of the NLR to predict the prognosis of TACE-treated HCC patients and to determine the accurate selection of agents for TACE and improvement of patient survival.

Current views on the ability of the NLR to predict the prognosis of patients with HCC are still controversial. Mouchli's study suggested that the NLR could be a reliable biomarker for predicting the prognosis of HCC patients [59]. A study by Cruz JC showed that a higher NLR is associated with higher rates of HCC tumour progression [31]. Minici. R confirmed the prognostic role of several inflammation-based scores in patients who underwent chemoembolization for hepatocellular carcinoma [60]. Chon YE showed that the NLR has better prognostic ability in HCC patients treated with TACE [32]. Chu HH's study confirmed that a higher NLR predicted a poorer prognosis for patients with intermediate-stage HCC receiving TACE [45]. The NLR is a risk factor for recurrence after TACE in HCC patients [61]. Young.S. showed that the NLR predicts PFS and OS in HCC patients receiving TACE and may be superior to other inflammation scores [62]. A recent meta-analysis published by LI D showed that a higher pretreatment SII was associated with lower survival in HCC patients treated with TACE [63]. Consistent with our findings, different NLRs in HCC patients treated with TACE predicted patient OS, and a higher NLR was associated with poorer prognosis. The SII is valuable for predicting the prognosis of HCC patients after TACE. However, no studies have determined the optimal treatment plan for HCC patients treated with TACE and with different NLRs. Our network meta-analysis showed that the best results were obtained with adriamycin in Group 1–3 HCC patients, followed by adriamycin combined with platinum-based therapy. Group 4 HCC patients were more likely to be treated with adriamycin + platinum-based agents than with adriamycin alone or platinum-based agents alone. The Chan KM study showed that patients with a higher NLR had significantly worse PFS and OS than did other patients. Patients with advanced HCC treated by TACE benefit from combination therapy with TKIs [64]. This finding is in agreement with our subgroup analysis, which showed the best results with adriamycin + sorafenib for HCC patients in Groups 3–4.

A clear connection between an elevated NLR and a worse prognosis in HCC patients has currently not been established. However, some hypotheses have proposed that neutrophils are the main source of circulating vascular endothelial growth factor (VEGF), which in turn promotes tumour angiogenesis and metastasis [65]. Decreased lymphocytes in the body reduce the immune effect against malignant tumours. Therefore, there is a connection between the NLR and HCC prognosis. The NLR is a simple and convenient biomarker that can help identify patients who have a significant survival advantage after TACE [66].

In the treatment of HCC with TACE, the injection of embolic agents leads to liver function damage, as well as different degrees of fever, gastrointestinal reactions, peripheral neuropathy and other adverse reactions, which in turn affects patient prognosis. TACE reduces the blood and oxygen supply to tumour cells by embolizing the hepatic arteries to inhibit the expansion of cancer cells, and it can directly deliver chemotherapeutic agents to tumour lesion sites to increase the concentration of the agent locally in the tumour. TACE can directly deliver chemical agents to the tumour site, thus increasing the local agent concentration in the tumour. Compared with intravenous chemotherapy, first-pass elimination of the liver can be avoided as much as possible, and the toxic effects of agents can be reduced. However, adverse reactions are still unavoidable. The reporting of adverse effects is unclear and must be refined in future studies.

To explore the prognosis of NLR-negative patients, we analysed real cases in a clinical review and concluded that the NLR can be used as a prognostic factor for hepatocellular carcinoma patients and that patients with a low NLR have a better prognosis. In combination with machine learning, the model parameters are adjusted to construct the optimal model for prediction.

There are still several limitations in our study. First, most of the included literature was from China, and the included studies were cohort studies and lacked randomized controlled trials, which led to the overall poor quality of the literature. However, we conducted a quality assessment, and all studies were eligible for inclusion. The included cohort studies were all retrospective studies, which have certain subjectivity and will introduce bias. The network meta section was added due to greater heterogeneity. The included literature

contained several Chinese-language papers with a low level of evidence. Second, the meta-analysis included less PLR-related data, resulting in a lack of persuasive evidence for the connection between the PLR and OS. In the future, it may be possible to confirm the PLR as an independent predictor of OS in HCC patients. Finally, the included studies had fewer descriptions of agent safety, and subsequent expansion of the search is needed to further explore adverse reaction-related events.

5. Conclusion

In conclusion, our network meta-analysis showed that the NLR and PLR were correlated with OS in HCC patients and that the higher the NLR was, the worse the prognosis was in HCC patients treated with TACE. Treatment with adriamycin was better for Group 1–3 (NLR 2.0–5.0) HCC patients, and treatment with adriamycin + platinum was better for Group 4 (NLR <2.0) HCC patients. When combined with other treatments, TACE was more effective when combined with adriamycin and sorafenib. It is recommended that HCC patients undergo NLR testing first and then select subsequent TACE medications based on the NLR.

Data sharing statement

All data generated or analysed during this study are included in the supplementary files.

Data availability statement

The data supporting the findings of this study are publicly available at Pubmed. Additional details on accessing the data can be found at https://pubmed.ncbi.nlm.nih.gov. Please note that due to privacy concerns, some portions of the data may be redacted or anonymized. Further information on data use restrictions can be obtained by contacting ws322577@163.com.

CRediT authorship contribution statement

Shuai Wang: Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Data curation. **Yizhen Li:** Methodology, Data curation, Resources. **Ziang Xu:** Data curation. **Kaisi Yang:** Software. **Ling Yang:** Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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