Prognostic value of the neutrophil-to-lymphocyte ratio in renal cell carcinoma: A systematic review and meta-analysis

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Abstract. The neutrophil-to-lymphocyte ratio (NLR) not only indicates the inflammatory response within the tumor microenvironment but may also correlate with tumor biological behavior (such as aggressiveness). The present study aimed to systematically review and conduct a meta-analysis on the impact of the NLR on the prognosis of patients with renal cell carcinoma (RCC). To this aim, a comprehensive search of multiple relevant databases, including PubMed, Embase and the Cochrane Library, was conducted to identify literature related to NLR and RCC prognosis. Following rigorous literature screening and quality assessment, a systematic quantitative analysis was ultimately performed on several studies that met the inclusion criteria. The results indicated a significant association between elevated NLR levels and poor prognosis in patients with RCC, suggesting that high NLR levels may serve as an independent predictor of unfavorable outcomes. Therefore, the present study provides important evidence for clinical decision-making, further demonstrating that NLR can serve as an independent prognostic indicator for patients with RCC, aiding healthcare professionals in making more precise judgments in patient management and treatment strategy formulation.

Introduction

According to the American Cancer Society, Renal cell carcinoma (RCC) is the most common malignant kidney tumor type in the United States, ranking sixth among cancer types in men and tenth in women, accounting for 5 and 3% of all tumor diagnoses, respectively; its incidence is on the rise (1,2). Despite advances in diagnostic and therapeutic techniques in recent years, a significant proportion of patients are still diagnosed with locally advanced disease and 17% of patients present with distant metastases at diagnosis, leading to a poor prognosis (3). Although radical or partial nephrectomy is the standard surgical treatment for patients with non-metastatic RCC, the prognosis for patients remains poor, especially for those with regional or distant advanced disease (2,4). In addition, immune checkpoint inhibitors (ICIs) and combination therapies have notably changed the treatment landscape of advanced renal cancer, but there are still some limitations in their application, such as heterogeneity in efficacy, immune-related adverse events and drug resistance (5). Therefore, identifying a reliable prognostic marker is crucial for individualized risk assessment and adjustment of treatment strategies. In previous years, increasing evidence has suggested that blood-based inflammatory markers, particularly the neutrophil-to-lymphocyte ratio (NLR), can predict the prognosis of patients with RCC (6-9).

The relationship between inflammatory responses and cancer has garnered significant attention in recent years (10,11). Due to their low cost and easy accessibility, hematological inflammatory markers, such as the NLR, have been widely tested (12). NLR, a simple and readily available inflammatory marker, is closely related to systemic inflammation (13), and has been widely used in prognostic studies of various cancer types, such as colorectal (14), prostate (15), uroepithelial (16), penile (17), lung (18) and breast (19) cancer. NLR is linked to poorer outcomes in multiple cancer types, including penile, colorectal, bladder, lung, breast, throat and ovarian cancer (17,20-25), and high NLR levels often predict poorer survival. Several meta-analyses have already explored the prognostic value of NLR in patients with RCC, with existing research indicating that a high NLR is associated with a poor prognosis (8,26). Despite this, most studies suffer from several problems, such as small sample sizes or single-center studies, or being limited to a single hospital or region, limiting their external validity and wide applicability. There are also inconsistent conclusions, with some studies finding a significant correlation between NLR and RCC prognosis (27,28), while others failed to reach a clear conclusion (29-31).

The present study included the most recent articles, thus ensuring the timeliness and reliability of the conclusions. The role of NLR in the prognosis of RCC, especially its predictive value for patient survival, recurrence and disease progression, was further clarified in the present study to provide a more up-to-date and accurate prognostic assessment.

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Materials and methods

Search strategy. Multiple databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com/) and Web of Science (http://webofscience.com) were searched for all relevant studies published from July 2021 to August 2024. The main terms used in the search strategy included the following: ('renal' or 'kidney') and ('carcinoma' or 'neoplasms' or 'cancer' or 'tumor') and ('NLR' or 'neutrophil-lymphocyte ratio' or 'neutrophil-to-lymphocyte ratio'). No language restrictions were applied in the literature search to ensure the comprehensiveness of the included studies. Some studies [such as Asif *et al* (32)] have multiple sets of data; therefore, in some analyses, certain studies are included >1 in the analysis.

Inclusion and exclusion criteria. Studies were selected based on the following inclusion criteria: i) Prospective or retrospective cohort studies that evaluated the relationship between NLR and overall survival (OS), recurrence-free survival (RFS), progression-free survival (PFS) and cancer-specific survival (CSS) in patients with RCC. The NLR values were taken before, during and after treatment. Most studies collected NLR within the first 30 days of treatment, while the study by Asif *et al* (32) included preoperative, perioperative and postoperative NLR; ii) the included patients had not received any treatment other than tumor-specific therapy prior to sample collection; and iii) studies that directly provided hazard ratios (HRs) with 95% confidence intervals (CIs) or had sufficient data to calculate these statistics. If study data were duplicated, only the data from the most recent study were used. The following exclusion criteria were applied: i) Studies that did not provide sufficient survival data for further analysis; ii) duplicate studies or publications; and iii) expert opinions, conference abstracts, editorials, case reports, letters, reviews or meta-analyses.

Date extraction. For each eligible study, two authors independently extracted the following items: Study characteristics (first author's name, recruitment region, publication year, study type and sample size), patient information (sex, age and ethnicity), pathological characteristics [TNM stage and histological subtype (33)], disease type (localized or metastatic), NLR cut-off values (number and/or percentage of patients with high vs. low NLR), clinical characteristics (treatment strategy, patient survival outcomes and follow-up duration), and OS, RFS, PFS and CSS outcomes. In cases of disagreement, consensus was reached through discussion with a third researcher.

Quality assessment. The quality of each included study was assessed using the Newcastle-Ottawa Scale (NOS), which comprises three factors: Selection, comparability and exposure (34). The highest possible NOS score is 9, with studies scoring ≥7, 4-6 and <4 being considered to have a low, medium and high risk of bias, respectively. Disputes regarding the quality assessment were resolved through discussion with a third reviewer.

Statistical analysis. The primary endpoints of the present meta-analysis were OS, RFS, PFS and CSS for all patients with RCC. If the included studies directly reported survival analyses, HRs and 95% CIs were extracted to calculate the pooled HR; otherwise, these data were calculated and estimated from Kaplan-Meier survival curves using Engauge Digitizer software (version 4.1; https://engauge-digitizer.updatestar.com/en) (35,36). Cochran's Q test and the I^2 statistic were used to assess heterogeneity among the included studies (37). The present systematic review followed the Cochrane Handbook for Evaluation of Intervention Systems, and all analyses used only the random-effects model. Sensitivity analysis was conducted by omitting each study one-by-one to evaluate the stability of the results. Subgroup analysis was also performed to explore the potential sources of heterogeneity. Additionally, funnel plots and Egger's test were used to assess the risk of publication bias. Egger's test and the trim-and-fill method were conducted using Stata 12.0 software (StataCorp LP). Other statistical analyses were performed using Review Manager 5.3 software (Cochrane Collaboration). All P-values were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference.

Quality of evidence. The quality of evidence regarding the prognostic value of pre-treatment NLR for patients with RCC was evaluated using the Grading of Recommendations Assessment, Development and Evaluation system (38).

Results

Included literature. Based on the search strategy, 356 potentially relevant records were identified. After removing duplicates, the titles and abstracts of the remaining 288 records were reviewed. The full texts of 68 records that met the inclusion criteria were then assessed. Ultimately, 21 studies were included in the present meta-analysis (7,27-32,39-52). The study selection process is illustrated in a flow diagram presented in Fig. 1.

Study characteristics. A total of 4,459 patients with RCC were included in the present meta-analysis. Table I presents the main characteristics of the 21 included studies, which were published between 2021 and 2024. Among the 21 studies, 7 reported on localized/non-metastatic RCC, while 11 focused on metastatic RCC and 3 on mixed RCC. Additionally, of the 21 studies, 18 reported OS data, 6 reported RFS or PFS data and 6 reported CSS data. The histological types included clear cell RCC, papillary RCC, non-clear cell RCC and mixed types. The cut-off values for NLR ranged from 2.33 to 4.0. The HRs and 95% CIs for the 21 studies were derived from multivariate Cox regression analyses and Kaplan-Meier survival curves. The mean age of the patients ranged from 57 to 73 years and the mean follow-up period ranged from 15.3 to 93.5 months. The NOS scores were 7 or 8, indicating that the included studies were of a moderate to high quality (Table SI).

NLR and OS in RCC. In total, 18 studies involving 3,867 patients with RCC assessed the association between NLR and OS. The forest plot utilizing a random-effects model to investigate the association between NLR and OS demonstrated that in the overall population, a high NLR was significantly associated with a shorter OS time (HR, 2.00; 95%

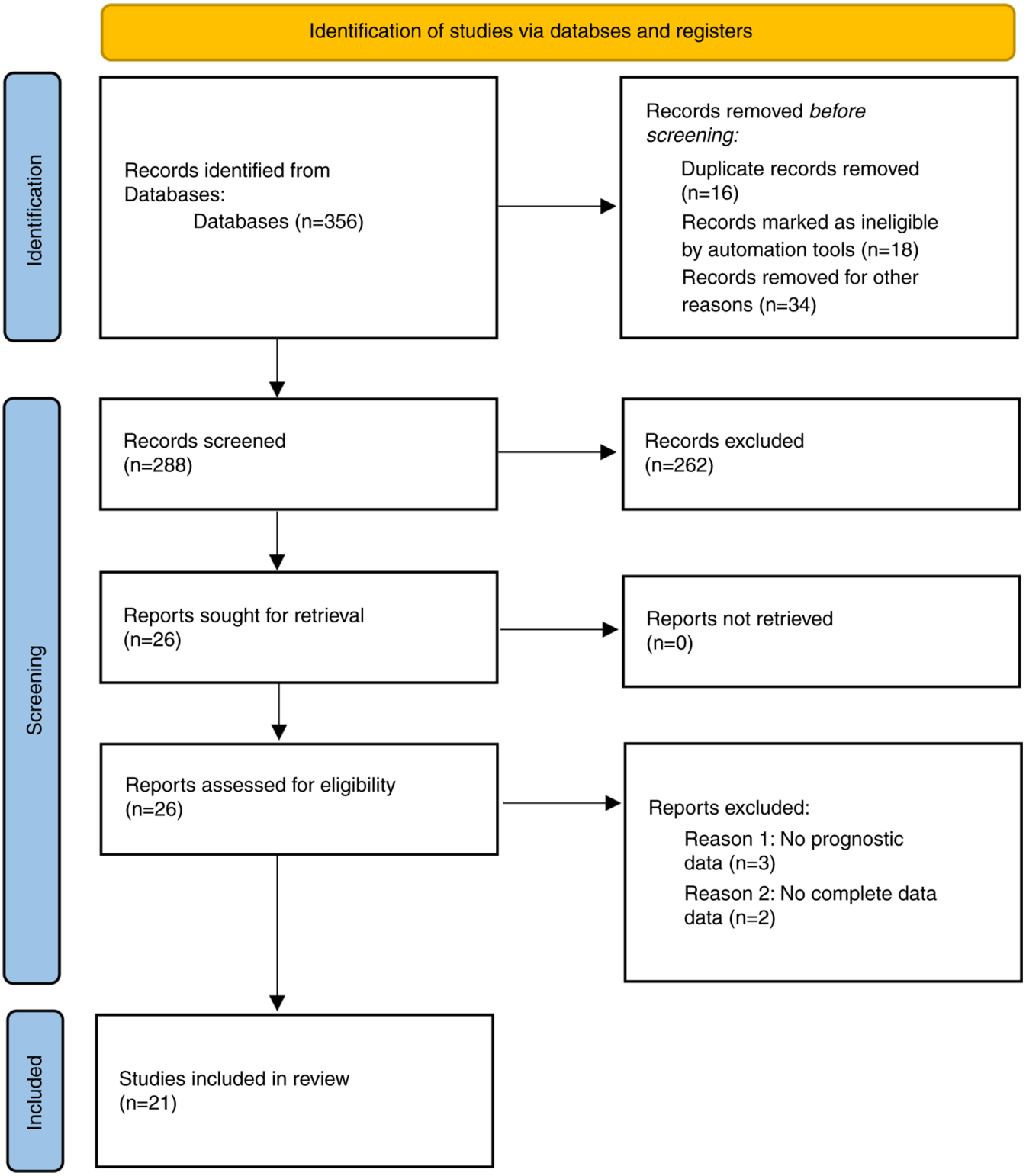

Figure 1. Flow chart of study selection process.

CI, 1.50-2.65; P<0.00001; Fig. 2A). To explore whether individual studies influenced the heterogeneity and conclusions, a sensitivity analysis was conducted by sequentially excluding each study. After excluding the study by Wang *et al* (45), the heterogeneity among the RCC studies decreased (I^2=41%, P<0.00001; Fig. 2D). Overall, the sensitivity analysis results did not alter the above conclusions, confirming the robustness of the findings.

When evaluating the relationship between NLR and OS in non-metastatic RCC, 4 studies that included 1,761 patients were examined. In 11 studies involving 1,426 patients with metastatic RCC, a similar relationship between NLR and OS was observed. The meta-analysis showed that a high NLR was significantly associated with poorer OS in both patients with non-metastatic (HR, 2.98; 95% CI, 2.13-4.18; P<0.00001; I^2=0%; Fig. 3C) and metastatic RCC (HR, 1.67;

Table I. Characteristics of the studies included in the meta-analysis.

First author, year	Country	Sample size, n	Histology type	Metastatic state	Mean age, years	Treatment	Cut-off value, determination method	Outcome	Mean follow-up, months	NOS score	(Refs.)
Allenet *et al*, 2022	France	786	non-hereditary RCC	Non-metastatic	N/A	Surgery	2.70, based on previous study	OS, RFS	48.0	8	(27)
Parosanu *et al*, 2023	Romania	38	ccRCC	Metastatic	62.8	Targeted therapy and/or surgery	3.00, ROC curve	OS	15.3	8	(39)
Korkmaz *et al*, 2023	Turkiye	110	RCC	Metastatic	65.0	Surgery	2.33, ROC curve	OS, PFS	N/A	7	(28)
Parosanu *et al*, 2023	Romania	74	RCC	Metastatic	62.5	Surgery + immunotherapy	3.00, ROC curve	OS, CSS	15.3	7	(40)
Nagamoto *et al*, 2023	Japan	55	RCC	Mixed	66.0	Immunotherapy	2.90, ROC curve	OS, CSS	44.2	8	(41)
Asif *et al*, 2023	UK	203	Small renal cell cancer	Non-metastatic	73.0	Surgery	2.82, ROC curve	OS, CSS, RFS, MFS OS,	93.5	8	(32)
Ni *et al*, 2022	China	425	RCC	Mixed	65.0	Surgery or conservative treatment	2.90, ROC curve	CSS	32.7	8	(42)
Chaker *et al*, 2022	Tunis	202	RCC	Non-metastatic	59.5	Immunotherapy	3.20, ROC curve	RFS, MFS	39.8	8	(43)
Tucker *et al*, 2021	USA	110	ccRCC	Metastatic	61.0	Surgery	3.42, ROC curve	PFS, OS	N/A	8	(29)
Wang *et al*, 2023	China	198	RCC	Metastatic	57.0	Surgery or surgery + drugs[a]	3.11, ROC curve	OS	N/A	7	(44)
Shang *et al*, 2021	China	203	non-ccRCC	Non-metastatic	61.0	Image-guided cryoablation or radiofrequency ablation	4.00, data on follow-up and blood counts	CSS	46.0	8	(7)
Wang *et al*, 2023	China	210	RCC	Metastatic	59.0	Immunotherapy	2.85, ROC curve	OS, PFS	N/A	8	(45)
Young *et al*, 2024	UK	132	ccRCC	Metastatic	63.0	Targeted drug therapy	3.00, univariate analysis in ORR and DCR	OS	N/A	8	(31)
Khan *et al*, 2022	USA	158	RCC	Metastatic	61.3	Surgery + Immunotherapy	3.50, based on previous study	OS	N/A	8	(46)
Cheng *et al*, 2023	China	444	ccRCC	Non-metastatic	58.0	Immunotherapy	3.40, ROC curve	RFS, CSS, OS	70.0	8	(47)
Zhang *et al*, 2023	China	328	RCC	Non-metastatic	57.0	Surgery	2.52, ROC curve	OS	64.0	7	(48)
Cordeiro *et al*, 2022	Brazil	187	ccRCC	Non-metastatic	63.4	Immunotherapy	4.00, ROC curve	RFS	48.7	8	(30)
Anpalakhan *et al*, 2023	UK	200	RCC	Mixed	69.7	Surgery	3.40, ROC curve	OS	N/A	7	(49)
Rebuzzi *et al*, 2022	Turkiye	306	RCC	Metastatic	70.0	Surgery	3.20, ROC curve	OS, PFS	N/A	8	(50)
Aslan *et al*, 2022	Italy	52	RCC	Metastatic	65.0	Immunotherapy	3.40, median value of NLR	OS, PFS	N/A	8	(51)

Table I. Continued.

First author, year	Country	Sample size, n	Histology type	Metastatic state	Mean age, years	Treatment	Cut-off value, determination method	Outcome	Mean follow-up, months	NOS score	(Refs.)
Ueda *et al*, 2022	Japan	38	RCC	Metastatic	68.0	Surgery or surgery + drugs[a]	3.00, based on previous study	OS, PFS	N/A	8	(52)

[a]These studies did not delineate between the treatment modalities; therefore, data from these studies were not included in the 'surgery only' analyses. NLR, neutrophil-to-lymphocyte ratio; RCC, renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; ROC, receiver operating characteristic; ORR, objective response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; CSS, cancer-specific survival; MFS, metastasis-free survival; N/A, not applicable.

95% CI, 1.11-2.50; P=0.001; I^2=79%; Fig. 3A). Notably, heterogeneity remained significant in the metastatic RCC population (I^2=79%, P=0.001; Fig. 3A). The results indicated that the studies by Wang *et al* (45), Tucker *et al* (29) and Aslan *et al* (51) (Fig. 3A) influenced the heterogeneity. Therefore, a sensitivity analysis was performed in patients with metastatic RCC. The results showed that excluding any single study, except for the study by Wang *et al* (45), did not significantly affect the heterogeneity. However, after removing the study by Wang *et al* (45), there was a significant effect on heterogeneity (Fig. 3E).

Due to the involvement of different study characteristics, subgroup analyses to explore the potential sources of heterogeneity in the metastatic RCC cohort were further performed after excluding the study by Wang *et al* (45) (Table II). In the subgroup analysis based on sample size, heterogeneity was higher in patients with clear cell RCC (HR, 1.63; 95% CI, 0.51-5.16; P=0.41; I^2=86%) and Caucasian patients (HR, 2.29; 95% CI, 1.09-4.81; P=0.03; I^2=76%). Therefore, the main sources of heterogeneity may be histological type (clear cell carcinoma) and ethnicity (Caucasian population), as these factors had the highest I^2 values, indicating the greatest variability in study results under these conditions.

When evaluating the relationship between NLR and OS in patients with RCC who underwent only surgical treatment, there were 7 relevant studies but the study by Asif *et al* (32) contained 3 datasets with different patient cohorts (preoperative, intraoperative and postoperative) and these datasets were therefore included in the analysis separately. Thus, 9 studies/cohorts involving 2,043 surgically treated patients were examined. In 5 studies involving 893 patients with non-surgically treated RCC, a similar relationship between NLR and OS was observed. The meta-analysis showed that a high NLR was significantly associated with poorer OS in both patients with surgically (HR, 1.99; 95% CI, 1.40-2.85; P=0.0001; I^2=62%; Fig. 4A) and non-surgically (HR, 2.07; 95% CI, 1.33-3.21; P=0.001; I^2=47%; Fig. 4C) treated RCC. Notably, heterogeneity remained significant in the surgically treated RCC population (Fig. 4A). Therefore, a sensitivity analysis was conducted for studies analyzing patients with surgically treated RCC. The results indicated that the study by Tucker *et al* (29) influenced the heterogeneity, and after excluding this study, the heterogeneity among the studies decreased (I^2=0%, P<0.00001; Fig. 4E). Overall, the sensitivity analysis results did not alter the aforementioned conclusions, confirming the robustness of the findings.

NLR and RFS/PFS in RCC. Due to the potential overlap in biological significance between RFS and PFS in specific clinical contexts (such as postoperative adjuvant therapy for solid tumors), and since some studies did not strictly distinguish between these endpoints, RFS and PFS were combined in this analysis. Additionally, merging the two endpoints improved statistical power and reduced bias from small sample sizes when individual analyses of RFS or PFS were infeasible. When examining the association between NLR and RFS/PFS, 11 studies involving 2,648 patients were selected. The forest plot of the meta-analysis showed that a high NLR was associated with poorer RFS/PFS in the overall population (HR, 1.70; 95% CI, 1.38-2.10; P<0.00001; I^2=18%; Fig. 2B).

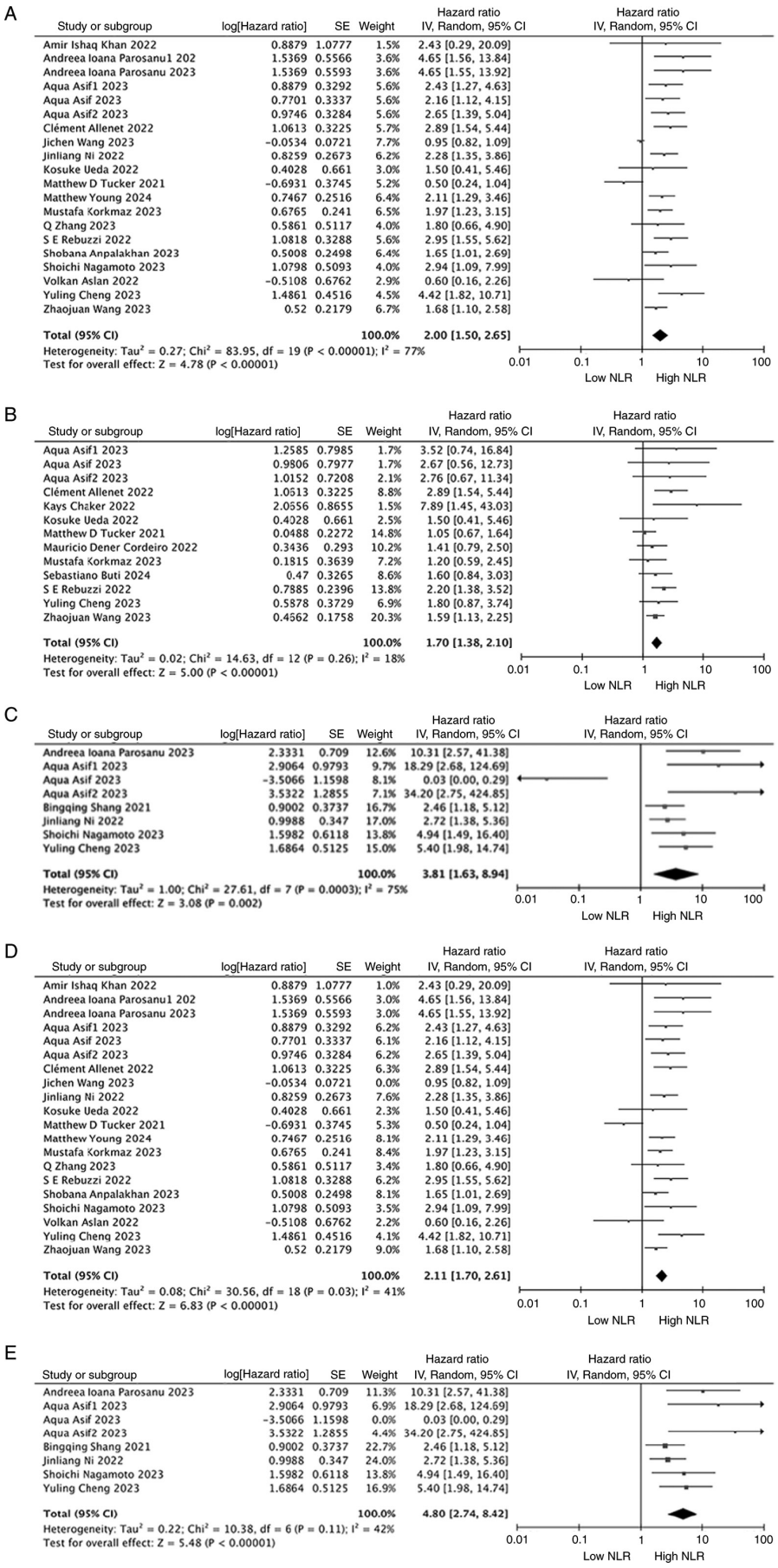

Figure 2. (A) Effect of the NLR on OS in RCC. (B) Effect of the NLR on recurrence-free survival/progression-free survival in RCC. (C) Effect of the NLR on CSS in RCC. (D) Effect of the NLR on OS in RCC after removing the study by Wang *et al* (44). (E) Effect of the NLR on CSS in RCC after removing the preoperative cohort in the study by Asif *et al* (32). NLR, neutrophil-to-lymphocyte ratio; RCC, renal cell carcinoma; OS, overall survival; CSS, cancer-specific survival; CI, confidence interval; SE, standard error.

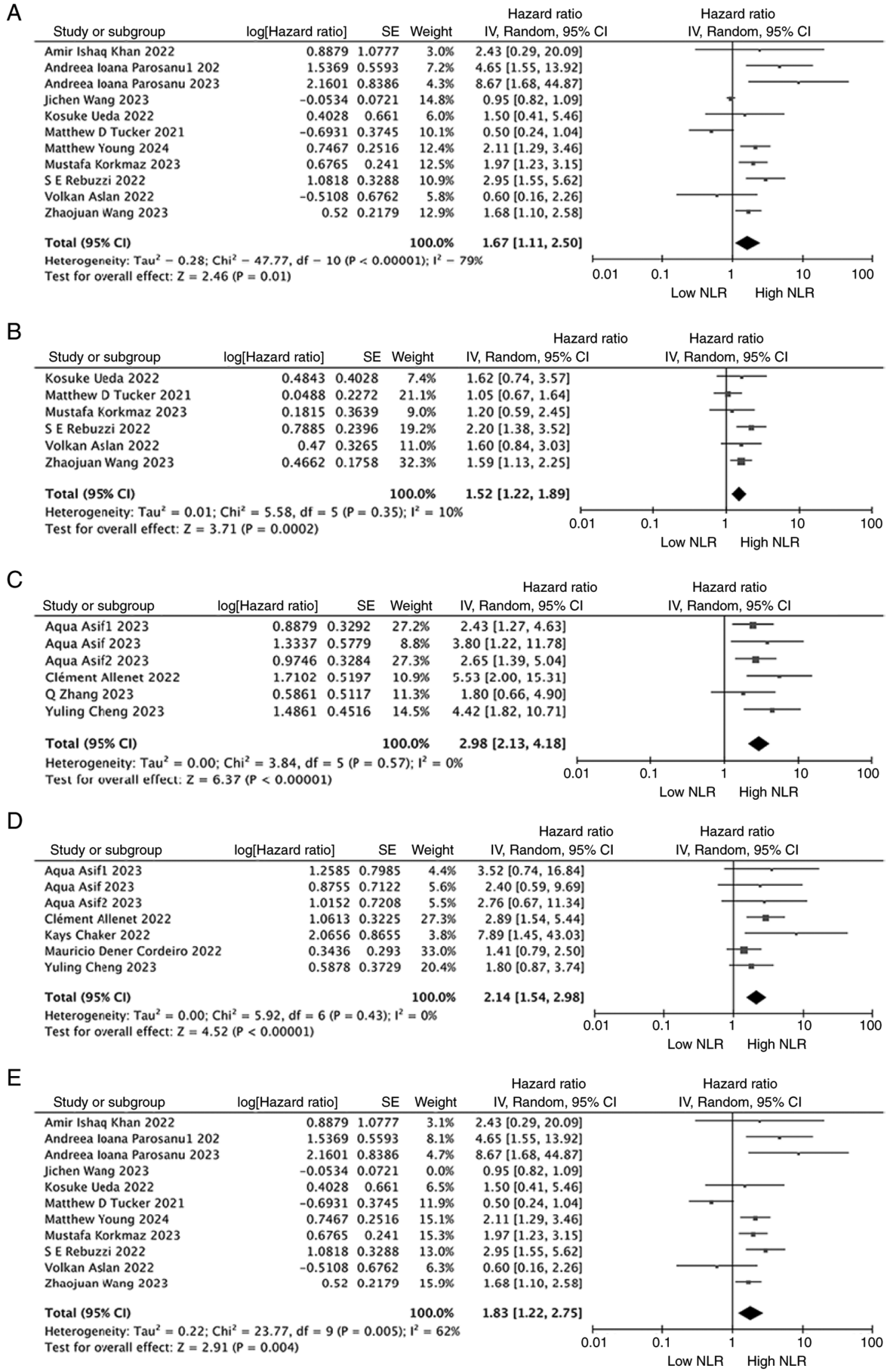

Figure 3. (A) Effect of the NLR on OS in metastatic RCC. (B) Effect of the NLR on PFS in metastatic RCC. (C) Effect of the NLR on OS in non-metastatic RCC. (D) Effect of the NLR on RFS in non-metastatic RCC. (E) Effect of the NLR on OS in metastatic RCC after removing the study by Wang *et al* (44). NLR, neutrophil-to-lymphocyte ratio; RCC, renal cell carcinoma; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CI, confidence interval; SE, standard error.

Table II. Subgroup analysis for overall survival in patients with metastatic renal cell carcinoma.

Subgroup[a]	No. of studies	No. of patients	HR (95% CI)	P-value	Heterogeneity	
					I^2, %	P-value
Overall	11	1426	1.67 (1.11-2.50)	0.01	79	<0.00001
Studies for subgroup analysis	10	1228	1.83 (1.22-2.75)	0.004	62	0.005
Ethnicity						
Caucasian	6	818	2.29 (1.09-4.81)	0.03	76	0.001
Asian	4	410	1.69 (1.25-2.28)	0.0006	0	0.43
Sample size						
≥200	2	516	2.11 (1.23-3.62)	0.007	51	0.15
<200	8	712	1.74 (0.98-3.06)	0.006	67	0.003
Histology type						
Clear cell carcinoma	3	280	1.63 (0.51-5.16)	0.41	86	0.0007
Others	7	948	1.95 (1.49-2.54)	<0.00001	29	0.21
Mean age, years						
≥65	4	506	2.00 (1.41-2.85)	0.0001	37	0.19
<65	6	722	1.96 (1.03-3.72)	0.04	73	0.002
Treatment						
Surgery or surgery + drugs	5	686	2.59 (1.83-3.66)	<0.00001	14	0.33
Drugs	5	542	1.20 (3.68-2.13)	0.53	68	0.01
NLR cut-off value						
≥2.75	8	1066	2.00 (1.21-3.31)	0.007	67	0.004
<2.75	2	162	1.29 (0.42-3.92)	0.66	63	0.1

[a]Subgroups were predefined based on established criteria from a previous study (26), including ethnicity (Caucasian/Asian), sample size (≥200/<200), histology (clear cell/others), age (≥65/<65 years), treatment (surgery ± drugs/drugs), and NLR cut-off (≥2.75/<2.75). NLR, neutrophil-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Upon further assessment of the relationship between NLR and PFS in patients with metastatic RCC, a meta-analysis based on 6 studies involving 826 patients indicated that a high NLR was significantly associated with poorer PFS (HR, 1.52; 95% CI, 1.22-1.89; P=0.0002; I^2=10%; Fig. 3B). Regarding the relationship between NLR and RFS in patients with non-metastatic RCC, 5 studies involving 1,822 patients were examined. The forest plot showed that a high NLR was significantly associated with poorer RFS (HR, 2.14; 95% CI, 1.54-2.98; P<0.00001; I^2=0%; Fig. 3D).

When the relationship between NLR and RFS/PFS in patients with RCC who underwent only surgical treatment was examined, 5 studies involving 1,515 patients were included. The forest plot showed that a high NLR was significantly associated with poorer RFS/PFS (HR, 1.83; 95% CI, 1.25-2.69; P=0.002; I^2=44%; Fig. 4B). For the relationship between NLR and RFS/PFS in patients with RCC who did not undergo surgery, based on 5 studies involving 1,095 patients, the forest plot showed that a high NLR was significantly associated with poorer RFS/PFS (HR, 1.64; 95% CI, 1.28-2.10; P<0.0001; I^2=0%; Fig. 4D).

NLR and CSS in RCC. In total, 6 studies involving 1,404 patients reported data on the association between NLR and CSS. The forest plot of the meta-analysis indicated that a high NLR was significantly associated with poorer CSS (HR, 3.81; 95% CI, 1.63-8.94; P=0.002; I^2=75%; Fig. 2C). Of these 6 included studies, 3 studies involved non-metastatic RCC, 1 study involved metastatic RCC and 2 studies involved mixed type. Therefore, the association between NLR and CSS in patients with non-metastatic and metastatic RCC was not further investigated separately.

Additionally, a sensitivity analysis was conducted to explore whether any single study influenced heterogeneity and the overall conclusion. After excluding the preoperative cohort in the study by Asif *et al* (32), the heterogeneity among the non-metastatic RCC studies notably changed (I^2=42%, P<0.0001; Fig. 2E). However, the recalculated HR did not alter the aforementioned conclusions, confirming the robustness of the results.

OS and RFS/PFS in patients treated with ICIs. The prognostic value of NLR in patients with RCC who were treated exclusively with ICIs was also examined. In examining the relationship between NLR and OS in patients with RCC treated with ICIs only, 4 studies involving 761 patients were included. The results of the meta-analysis showed that high NLR was associated with poorer OS (HR, 2.05; 95% CI, 1.05-3.99; P=0.04; I^2=60%; Fig. 5A). In examining the relationship between NLR and RFS/PFS in patients with RCC

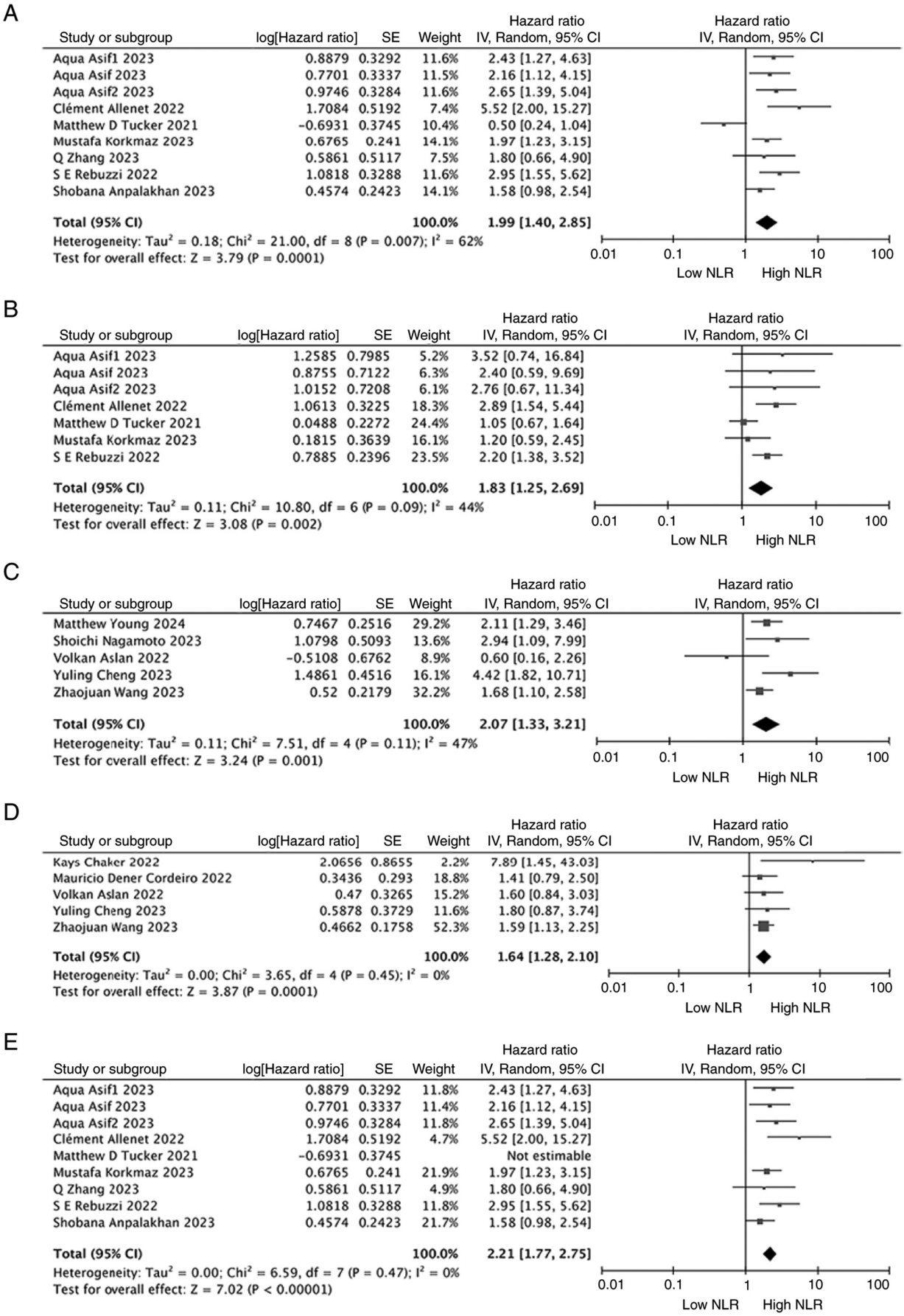

Figure 4. (A) Effect of the NLR on OS in RCC treated with surgery. (B) Effect of the NLR on RFS/PFS in RCC treated with surgery. (C) Effect of the NLR on OS in non-surgical RCC. (D) Effect of the NLR on RFS/PFS in non-surgical RCC. (E) Effect of the NLR on OS in RCC treated with surgery after removing the study by Tucker *et al* (29). NLR, neutrophil-to-lymphocyte ratio; RCC, renal cell carcinoma; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CI, confidence interval; SE, standard error.

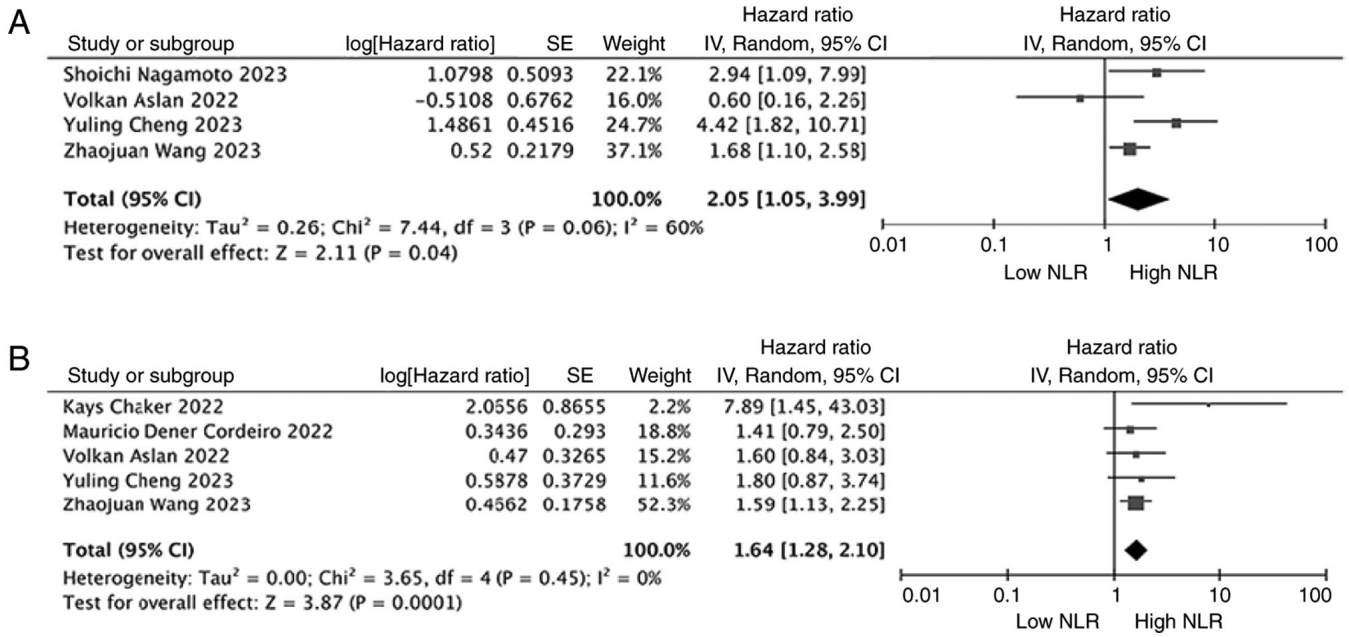

Figure 5. (A) Effect of the NLR on overall survival in ICI treatment. (B) Effect of the NLR on progression-free survival in ICI treatment. NLR, neutrophil-to-lymphocyte ratio; ICI, immune checkpoint inhibitor; CI, confidence interval; SE, standard error.

treated with ICIs only, 5 studies involving 1,095 patients were included. The results of the meta-analysis showed that high NLR was associated with poorer RFS/PFS (HR, 1.64; 95% CI, 1.28-2.10; P=0.001; I^2=0%; Fig. 5B).

Publication bias. The publication bias for OS, RFS/PFS and CSS was assessed without considering the staging of patients with RCC. For OS and CSS, the funnel plots were asymmetric (Fig. S1A and B). Egger's test also indicated the presence of publication bias (both P<0.001). Therefore, the trim-and-fill method was employed to test the asymmetry of the funnel plot by hypothesizing the existence of unpublished studies. The recalculated results demonstrated that a high NLR was significantly associated with OS and CSS, with statistical significance (P<0.05) after trimming and filling. Furthermore, the combined results before and after trimming had P<0.05, suggesting the stability of the results (Fig. S2A and B). For RFS/PFS, the funnel plot was relatively symmetric (Fig. S1C). Additionally, Egger's test showed no significant publication bias (P=0.667).

Discussion

Inflammatory factors in the human body have a crucial role in the occurrence, development and prognosis of tumors (53). The inflammatory response is a defense mechanism of the body against injury and infection, but chronic inflammation can induce abnormal cell proliferation, DNA damage and immune escape, thereby promoting the occurrence and development of tumors (53,54). Inflammatory factors in the tumor microenvironment, such as tumor necrosis factor-α, interleukins (such as IL-6 and IL-1β) and C-reactive protein (55-57), not only participate in the proliferation, invasion and metastasis of tumor cells but also affect the tumor's response to treatment. Therefore, the levels of inflammatory factors are often closely related to the prognosis of patients with cancer, with higher levels often indicating a poorer clinical prognosis (53,58). Investigating the mechanisms by which inflammatory factors affect tumors can help reveal the patterns of tumor occurrence and development, and provide new insights and targets for early diagnosis, personalized treatment and the prognosis assessment of tumors.

NLR is a simple and reliable marker that can be used to predict immune responses to infectious and non-infectious stimuli and serves as a reliable indicator of cancer-associated inflammation, as well as a predictor of tumor survival and treatment outcomes (59,60). NLR has an important role in the prognosis of RCC. This may be due to the fact that NLR reflects the inflammatory response of the body, which serves a notable role in tumor progression and metastasis (8). The present study systematically evaluated the impact of NLR on the prognosis of patients with RCC through a systematic review and meta-analysis of 4,459 patients. The results showed that a high NLR was significantly associated with a poor OS, RFS/PFS and CSS in patients with RCC. Additionally, the results of the present study indicated that a high NLR was significantly associated with a poor OS and RFS/PFS in patients with RCC, regardless of the metastasis status or treatment type. In the meta-analysis of metastatic RCC, the association between NLR and OS demonstrated significant heterogeneity (I^2=79%). Despite sensitivity analyses, the heterogeneity remained high. To further investigate the source of heterogeneity, subgroup analyses based on the characteristics of the included studies were performed, which demonstrated the stability and reliability of the results. Overall, the results from the pooled data of the present systematic review and meta-analysis suggest that NLR may be used as a prognostic indicator for patients with RCC, aiding in clinical decision-making and the selection of individualized treatment strategies.

Neutrophils are a key component of the acute phase of inflammation and are associated with cancer development. Neutrophils can directly influence tumor cells, promoting cancer progression, and indirectly modify the tumor microenvironment to facilitate cancer metastasis (61). Moreover, neutrophils can release vascular endothelial growth factor, affecting tumor development (60,62). By contrast, lymphocytes have an important role in the antitumor immune response. Increased lymphocyte infiltration in the tumor region is associated with improved responsiveness to treatment and prognosis in patients with solid tumors (60). Additionally, lymphopenia (reduction in $CD4^+$ T cells) can impair lymphocyte-mediated antitumor responses (63). Therefore, NLR not only reflects the patient's inflammatory response but also represents a decrease in antitumor immunity, with elevated NLR often indicating lower survival rates and more aggressive disease in patients with cancer.

The results of the present study align with several others (26,64-68), indicating that patients with high NLR typically have poorer outcomes, which further underscores the potential clinical value of NLR. This similarity may be attributed to the use of the same inclusion criteria and measurement tools in all studies, as well as the comparable sample sizes, which likely led to the consistency of the findings. Moreover, these similar results provide a solid evidence base for future research, as NLR, a simple and easily obtainable inflammatory marker, has been repeatedly validated in various studies as being closely associated with patient prognosis. Looking ahead, multicenter prospective studies are needed to further confirm the applicability and feasibility of NLR in different populations. For patients with high NLR, future clinical research could explore interventions such as anti-inflammatory treatments or immune modulation therapies to reduce NLR levels, thereby improving prognosis.

Although NLR demonstrates considerable predictive value for prognosis in various cancer types [such as colorectal (14), prostate (15), uroepithelial (16), penile (17), lung (18) and breast (19) cancer], the use of this single marker has its limitations. These limitations include non-specificity (interference by infection or coexisting disease), variability in measurement time points and methods, lack of consistent thresholds and confounding effects of therapeutic interventions on inflammatory signals. Future studies should focus on the combined use of NLR with other inflammatory markers, molecular biomarkers and clinical pathological features (such as TNM staging and tumor markers) to build more accurate prognostic models. This integrated approach could provide essential insights for personalized treatment strategies. In the context of personalized therapy, NLR, as a marker of immune-inflammatory response, could assist in predicting the response of patients to immunotherapy or targeted therapies. Future research may investigate the relationship between NLR and treatment response, exploring whether treatment plans can be tailored based on NLR levels, thereby improving therapeutic efficacy and minimizing unnecessary side effects.

Despite the notable potential of NLR as a prognostic indicator in clinical practice, its translation into routine clinical use faces several challenges. Future studies need to address issues such as standardizing NLR measurement methods and managing the heterogeneity arising from factors such as ethnicity, age, sex and histological type. Additionally, staging may influence NLR levels through systemic inflammatory responses and immunosuppressive status, which is particularly relevant in patients with advanced disease. Subgroup analyses based on staging were not performed in the present study, primarily due to sample size limitations that could have affected the statistical power. The present study was designed to initially evaluate the overall prognostic value of NLR. However, future research will aim to expand the cohort and conduct more targeted analyses to validate the staging-specific effects. Furthermore, large-scale multicenter prospective studies will be essential to provide a stronger evidence foundation for the widespread application of NLR.

The present analysis has several limitations warranting consideration. Primarily, the reliance on non-randomized observational designs with limited participant numbers may restrict generalizability. Although random-effects models were applied to address variability, residual heterogeneity persisted in stratified assessments, potentially reflecting unmeasured covariates or population diversity. While sensitivity analyses mitigated detection bias, residual selection bias or unmeasured confounders may persist despite analytical controls. Regarding methodological validity, statistical adjustments using the trim-and-fill method indicated that the core findings remained consistent; however, undetected publication bias in smaller cohorts could still influence effect estimates. Additionally, the absence of standardized NLR thresholds remains a critical gap. Current practices often adopt optimal thresholds derived from receiver operating characteristic curves or extrapolate values from prior cohorts, introducing comparability challenges across datasets. Prospective validation through multicenter collaborations is imperative to establish NLR criteria consistent with clinical endpoints (such as progression-free intervals) while accounting for treatment-era effects and biomarker-temporal dynamics.

In conclusion, the results of the present meta-analysis suggest that elevated NLR is a potential biomarker for the prognostic evaluation of patients with RCC. Clinically, for the treatment of RCC, NLR could be considered in the routine assessment of patients to more accurately predict the prognosis of this disease.

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Availability of data and materials

All data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

KCL conceived the manuscript and performed data acquisition, data analysis and statistical analysis. XC assisted with

data acquisition, data analysis and manuscript preparation. XC reviewed the manuscript and polished the grammar. KCL and XC confirm the authenticity of all the raw data. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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