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Prognostic value of neutrophil-to-lymphocyte ratio for the clinical outcomes of chronic kidney diseases: an update systematic review and meta-analysis

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Abstract

Background The correlation between the neutrophil-to-lymphocyte ratio (NLR) and clinical outcomes in patients with chronic kidney disease (CKD) remains inconsistent.

Methods PubMed, Embase, Web of Science, and the Cochrane Library were searched for relevant literature through March 8, 2025. All-cause mortality, major adverse cardiovascular events (MACE), cardiovascular death, and progression to end-stage renal disease (ESRD) or dialysis were evaluated. Odds ratios (OR) and 95% confidence intervals (CI) were used for effect estimation.

Results Thirty-six studies involving 26,074 patients were included. Meta-analysis indicated that high NLR was significantly associated with an increased risk of all-cause mortality (OR = 1.22, 95% CI: 1.15–1.29; $p < 0.00001$), MACE (OR = 1.42, 95% CI: 1.14–1.77; $p = 0.002$), cardiovascular mortality (OR = 1.21, 95% CI: 1.09–1.35; $p = 0.0004$), and ESRD (OR = 1.68, 95% CI: 1.17–2.43; $p = 0.005$). NLR levels were significantly higher in patients who died from all causes (SMD = 0.84, 95% CI: 0.58–1.11; $p < 0.00001$) and cardiovascular causes (SMD = 1.44, 95% CI: 0.77–2.11; $p < 0.0001$) compared to survivors. Sensitivity and subgroup analyses affirmed the robustness of the results. All indicators were rated as very low in the GRADE system.

Conclusion NLR is significantly associated with all-cause mortality, MACE, cardiovascular mortality, and adverse renal outcomes in CKD. The results are relatively stable, but due to high heterogeneity and publication bias, its clinical application should be approached with caution. Given the study's limitations, further large-scale prospective studies are required to confirm the association between NLR and CKD prognosis.

Clinical trial number Not applicable.

Keywords NLR, CKD, Prognostic value

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Introduction

Chronic kidney disease (CKD), which affects approximately 10% of the global population, is a progressive condition associated with increased morbidity and mortality, particularly due to cardiovascular events and end-stage renal disease (ESRD) [1]. Early identification of high-risk patients remains challenging, highlighting the need for accessible and cost-effective prognostic biomarkers [2].

Studies indicate that a microinflammatory state is prevalent in advanced CKD and is associated with complications such as anemia, vascular calcification, cardiovascular events, and all-cause mortality [3, 4]. Therefore, the management of chronic inflammation is essential in the care of patients with CKD.

The neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation and immune dysregulation, has emerged as a promising prognostic tool. Elevated NLR reflects a pro-inflammatory state associated with endothelial dysfunction and oxidative stress, key mechanisms driving CKD progression [5]. Observational studies indicate that increased NLR is linked to adverse CKD outcomes, including rapid renal decline, cardiovascular mortality, and initiation of dialysis [6]. However, these findings remain inconsistent, likely due to variations in study design, population heterogeneity (e.g., age, region, CKD stages), and limited sample sizes.

Previous meta-analyses, including those by Ao et al.'s [7] and Zhao et al. [8], identified NLR as a predictor of all-cause mortality (Ao: HR 1.93, 95% CI 1.87–2.00, Zhao: HR 1.45, 95% CI 1.20–1.75) and cardiovascular events (Ao: HR 1.45, 95% CI 1.18–1.79, Zhao: HR 1.52, 95% CI 1.33–1.72) in CKD. However, these studies had notable limitations: Ao et al. did not examine the association between NLR and ESRD or major adverse cardiovascular events (MACE), nor did they adequately adjust for confounders such as baseline eGFR or serum creatinine (Scr). Zhao et al. included a small sample size ($n = 1{,}442$) and did not report on ESRD outcomes. Moreover, neither study conducted stratified analyses, limiting the ability to identify sources of heterogeneity. More than 18 new cohort studies published since 2021 necessitate an updated synthesis of the evidence.

This meta-analysis updates the evidence base through 2025 and reassesses the prognostic value of NLR for all-cause mortality, MACE, and progression to ESRD or dialysis in CKD. Furthermore, subgroup analyses evaluate heterogeneity based on CKD stage, age, region, and NLR threshold. Our findings confirm that NLR is significantly associated with all-cause mortality, MACE, cardiovascular mortality, and adverse renal outcomes in CKD. Recent evidence supports the inclusion of NLR in standard CKD risk stratification protocols.

Materials and methods

Literature search

This analysis was conducted in accordance with PRISMA 2020 guidelines [9] and registered with PROSPERO (CRD420251019397). XYJ and CYT independently developed the search strategy, selecting terms and keywords to query PubMed, Embase, Web of Science, and the Cochrane Library up to March 8, 2025. The search terms included: "Renal Insufficiency, Chronic", "Chronic Renal Insufficiencies", "Chronic Kidney Insufficiency", "Chronic Kidney Insufficiencies", "Chronic Renal Insufficiency", "Chronic Kidney Diseases", "Chronic Kidney Diseases", "Chronic Kidney Disease", "Chronic Renal Diseases", "Chronic Renal Disease", "CKD", "ratio", "Lymphocytes", "Lymphoid Cells", "Lymphoid Cell", "Neutrophils", "Lymphocyte", "Lymphoid Cells", "Lymphoid Cell", "Neutrophils", "Polymorphonuclear Neutrophils", "Neutrophil", "Polymorphonuclear Neutrophils", "Polymorphonuclear Neutrophil", "Polymorphonuclear Leukocyte", "Polymorphonuclear Leukocytes", "LE Cells", "LE Cell", "Neutrophil Band Cells", "Neutrophil Band Cell". Table S1 presents the details of literature searching.

Study selection

Inclusion criteria: (1) CKD patients; (2) Studies evaluating the prognostic effect of NLR on CKD, with outcomes including all-cause mortality, MACE, cardiovascular mortality, or composite renal outcomes (progression to ESRD or dialysis initiation); (3) Studies providing data on odds ratios (OR), risk ratios (RR), hazard ratios (HR), and 95% confidence intervals (CI), or reporting continuous variables as mean ± standard deviation (M ± SD) or median ± interquartile range (Median ± IQR), which could be directly extracted or calculated from available data; (4) Patient groups with high and low NLR defined based on a specified cut-off value; (5) Fully published studies; (6) Study design limited to cohort or case-control.

Exclusion criteria: (1) Reviews, comments, conference abstracts, case reports, and letters; (2) Patients without CKD; (3) Studies lacking data to calculate OR, RR, HR, or 95% CI; (4) Studies without survival data, MACE, or composite renal outcomes; (5) Duplicate or overlapping data. XYJ and CYT independently reviewed titles and abstracts and downloaded full texts for confirmation. Disagreements were resolved through discussion.

Data extraction

XYJ and CYT performed data extraction independently, with disagreements resolved through consensus. The first author, publication year, country, study type, sample size, patient age, study duration, detection timing, cut-off value, follow-up duration, and OR/RR/HR (95% CIs) or M ± SD / Median ± IQR for outcomes such as all-cause mortality, MACE, cardiovascular mortality, and

composite renal outcomes were extracted. Median ± IQR values were converted to M ± SD, and RR/HR (95% CIs) were converted to OR (95% CIs). For studies with unavailable extractable data, we contacted corresponding authors to obtain the original data.

Quality assessment

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS), which evaluates selection, comparability, and outcomes, with a maximum score of nine points [10]. Scores 7–9 indicated high quality, while scores 4–6 indicated moderate quality [11].

Statistical analysis

Pooled ORs with 95% CIs and standardized SMDs were used to evaluate the prognostic value of NLR in CKD. Heterogeneity was evaluated using Cochran's Q and I^2 [12], with $I^2 > 50\%$ or $p < 0.1$ indicating substantial heterogeneity. A random-effects model was applied for all analyses. Sensitivity and subgroup analyses were conducted to assess result stability and explore sources of heterogeneity, aiming to minimize confounding. Funnel plots and Egger's test were used to evaluate publication bias, with $p < 0.05$ considered statistically significant. All analyses were conducted using STATA 15.0 and Review Manager 5.4 software. Additionally, in accordance with the GRADE approach, the certainty of evidence for each outcome was rated as "high", "moderate", "low", or "very low" [13].

Results

Study characteristics

A total of 1,324 studies were retrieved from the initial database search, with 479 excluded due to duplication. After reviewing titles and abstracts, 777 studies were further excluded. Ten studies were excluded due to unavailable full texts. Fifty-eight studies were assessed, and 22 were excluded for insufficient data on the primary outcome. Ultimately, 36 studies [5, 14–48], involving 26,074 patients, were included in this meta-analysis (Fig. 1).

Four continents (America, Asia, Europe, and Oceania) were represented among the 36 studies. Three studies [25, 27, 48] each comprised two cohort groups, and one study [14] included three, yielding a total of 41 research groups: 40 cohort studies and 1 case-control study. English-language literature published from the inception of the databases through March 8, 2025, was included. Eligible studies utilized NLR and included two analysis groups: death vs. survival, occurrence vs. non-occurrence, or high vs. low NLR. Of these, 29 assessed NLR's prognostic value for all-cause mortality, 10 for MACE, 7 for cardiovascular mortality, and 7 for ESRD outcomes.

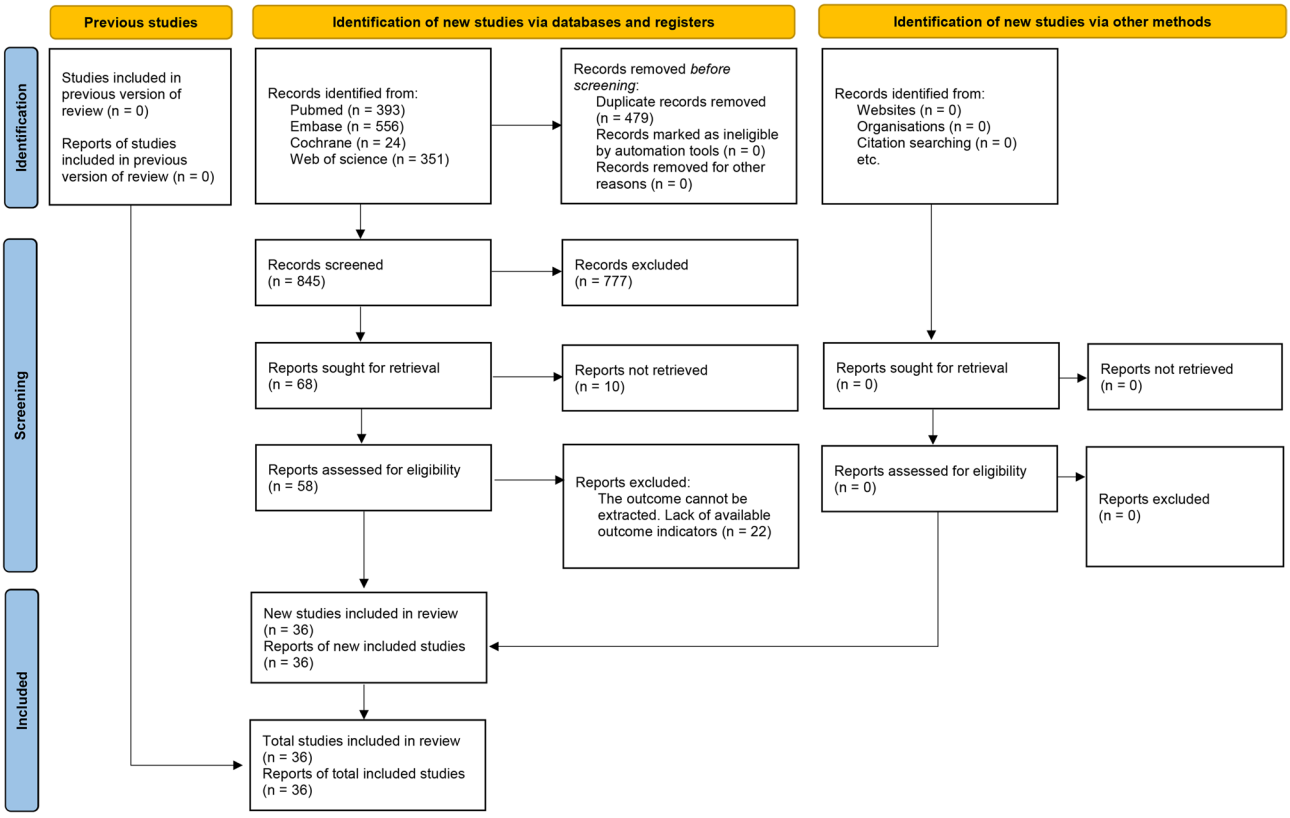

Fig. 1 Flow chart of literature screening

An overview of the included studies' characteristics is presented in Table 1.

Study quality

Thirty-two studies received scores of 7 to 8 on the NOS scale, indicating high quality, while four studies scored 6 [16, 21, 29, 38], classifying them as medium quality (Table S2, Table S3).

Meta-analysis results

NLR and all-cause mortality rate

Twenty-nine research groups comprising 20,157 participants analyzed both binary and continuous variables. Twenty-three research groups [5, 16, 19–22, 24–28, 30, 32, 34, 36, 37, 40, 43–45, 47] analyzing binary variables were included, and a forest plot (Fig. 2A) was generated for the meta-analysis. Due to substantial heterogeneity (I^2 = 70%, $p < 0.00001$), a random-effects model was employed (Fig. 2A). The results demonstrated a significant association between elevated NLR and increased all-cause mortality (OR = 1.22, 95% CI: 1.15–1.29; $p < 0.00001$, Fig. 2A).

In the continuous variable analysis, 10 research groups [18, 22, 28, 31–33, 35, 38, 40, 41] comprising 10,281 participants, were included, and a forest plot (Fig. 2B) was generated. Given the significant heterogeneity (I^2 = 93%, $p < 0.00001$), a random-effects model was employed. The analysis found significantly higher NLR levels in deceased patients compared to survivors (SMD = 0.84, 95% CI: 0.58–1.11; $p < 0.00001$; Fig. 2B).

NLR and MACE incidence

We anal*yzed the association* between NLR and MACE in 10 research groups [14, 17, 23, 26, 39, 47, 48], comprising 4,737 participants. A binary analysis and forest plot (Fig. 2C) were used for the meta-analysis. Due to significant heterogeneity (I^2 = 74%, $p < 0.0001$), a random-effects model was applied. The results demonstrated that higher NLR was linked to an increased risk of MACE (OR = 1.42, 95% CI: 1.14–1.77; $p = 0.002$; Fig. 2C).

NLR and cardiovascular mortality rate

We investigated the relationship between NLR and cardiovascular mortality in six study groups [28, 30, 34, 44, 48], involving 5,575 participants, using both binary and continuous analyses. A forest plot (Fig. 2D) was generated for binary outcomes across the six research groups. Due to significant heterogeneity (I^2 = 75%, $p = 0.001$), a random-effects model was applied (Fig. 2D). The results demonstrated that higher NLR was significantly linked to an increased cardiovascular mortality risk (OR = 1.21, 95% CI: 1.09–1.35; $p = 0.0004$, Fig. 2D).

We analyzed continuous variables in two study groups [28, 31] comprising 315 participants and generated a forest plot (Fig. 2E) for meta-analysis. Due to significant heterogeneity (I^2 = 77%, $p = 0.04$), a random-effects model was applied (Fig. 2E). The results showed that NLR levels were significantly higher in patients who died from cardiovascular causes compared to those who survived (SMD = 1.44, 95% CI: 0.77–2.11; $p < 0.0001$; Fig. 2E).

NLR and ESRD outcomes

We investigated the association between NLR and ESRD incidence in seven research groups [15, 25, 29, 42, 46, 47] involving 3,521 participants, analyzing both binary and continuous variables. Forest plots summarizing the meta-analysis results are shown in Fig. 2F. Due to significant heterogeneity (I^2 = 72%, $p = 0.001$), a random-effects model was applied (Fig. 2F). The results revealed that higher NLR was associated with increased ESRD risk (OR = 1.68, 95% CI: 1.17–2.43; $p = 0.005$, Fig. 2F).

Subgroup analysis

We conducted subgroup analyses of all-cause mortality, MACE incidence, and ESRD outcomes according to age, region, NLR cut-off values, creatinine levels, and study design (Table 2). Age and NLR cut-offs were stratified by their medians, while creatinine levels were classified following the 1992 CRF staging criteria from the Chinese Society of Nephrology [49].

Subgroup analysis of all-cause mortality rate

We conducted a subgroup analysis of all-cause mortality based on age, region, NLR cut-off value, and creatinine levels. NLR remained a significant predictor across subgroups of age, region, NLR cut-off value. In the subgroup with an NLR cut-off value < 3, I^2 decreased from 70 to 34%, indicating that the cut-off value contributed to heterogeneity in effect size.

In the creatinine staging subgroup, I^2 decreased to 0% during the renal function compensated stage (2.1-5.0 mg/dl), indicating that renal function contributed to heterogeneity. Additionally, in the renal failure stage (5.1-7.9 mg/dl: $p = 0.08$), NLR's predictive value was not significant, whereas it was significant in early CKD (< 1.6 mg/dl: $p = 0.02$, 2.1-5.0 mg/dl: $p = 0.002$). Thus, NLR predicts all-cause mortality more accurately and consistently in early CKD.

Subgroup analysis of MACE incidence

We analyzed MACE incidence according to age, region, NLR cut-off values, and study design. When the NLR cut-off was ≥ 3, its predictive value for MACE was not significant ($p > 0.05$), whereas it was significant in other subgroups ($p < 0.05$). Heterogeneity did not substantially decrease.

In the study design subgroup, only one case-control study was included, which showed no significant

Table 1 Basic characteristics of the included literature

Author	Year	Region	Study design	Study period	Sample size	Gender		Age (mean/median)	eGFR (mean/median)	SCR (mean/median)	NLR cut-off	Quality score	Timing of blood test
						Male	Female						
Abe(a) [14]	2015	Japan	Cohort	2007–2013	86	58	28	57.6	NA	10.2	2.78	8	At the beginning of a dialysis session in HD patients and at outpatient clinic in PD patients within 1 month of the dialysis initiation day.
Abe(b) [14]	2015	Japan	Cohort	2007–2013	86	58	28	57.6	NA	10.2	3.67	8	At the beginning of a dialysis session in HD patients and at outpatient clinic in PD patients within 1 month of the dialysis initiation day.
Abe(c) [14]	2015	Japan	Cohort	2007–2013	86	58	28	57.6	NA	10.2	4.66	8	At the beginning of a dialysis session in HD patients and at outpatient clinic in PD patients within 1 month of the dialysis initiation day
Altunoren [15]	2019	Turkey	Cohort	2017–2022	740	440	300	62.8	40.5	1.79	2.76	7	Visit to the outpatient clinic
Branco [16]	2022	Portugal	Cohort	2020.3-2020.8	130	78	52	73.9	42.5	1.7	NA	6	NA
Chen [17]	2020	China	Cohort	2014–2017	70	41	29	49.83	2.71	787.72	2.23	8	NA
Chen [18]	2024	USA	Cohort	1999–2019	6880	3390	3490	67.03	50.62	NA	NA	7	NA
Fu [19]	2024	USA	Cohort	2005–2018	4444	2121	2323	60.64	72.56	1.12	NA	7	NA
Ge [20]	2024	China	Cohort	2012–2021	176	105	71	54.1	8.5	540.3	4.3	8	NA
Ginanja [21]	2023	Indonesia	Cohort	2018.1-2018.6	117	91	26	57.79	68.57	1.1	4.8	6	The first examination is at the time of admission and the next examination is at the time the patient is discharged from the hospital.
Hendra [22]	2021	Europe	Cohort	2020.3-2020.5	148	84	64	64.13	NA	NA	NA	7	NA
Immanuel [23]	2021	Indonesia	Case-Control	2018.1-2018.10	59	46	13	59.46	NA	NA	3.62	7	Within a maximum 3 days after hospital
Kim(a) [25]	2023	Korea	Cohort	2011–2020	141	86	55	56.47	49.4	1.76	0.88	7	NA
Kim(b) [25]	2023	Korea	Cohort	2011–2020	141	86	55	56.47	49.4	1.76	1.98	7	NA
Kim [24]	2025	Korea	Cohort	2016–2020	448	246	202	79.7	NA	NA	NA	7	At the beginning of the HD session from patients requiring HD.

Table 1 (continued)

Author	Year	Region	Study design	Study period	Sample size	Gender		Age (mean/median)	eGFR (mean/median)	SCR (mean/median)	NLR cut-off	Quality score	Timing of blood test
						Male	Female						
Lano [26]	2022	France	Cohort	2014–2016	183	106	77	65.5	NA	8.52	3.49	7	At the beginning of the midweek HD session.
Lau(a) [27]	2023	China	Cohort	2010–2020	225	129	96	59	2.9	NA	3.05	8	The first time-point was 2 months after initiation of dialysis). The second time-point was 1 year after enrollment.
Lau(b) [27]	2023	China	Cohort	2010–2020	225	129	96	59	2.9	NA	4.63	8	The first time-point was 2 months after initiation of dialysis. The second time-point was 1 year after enrollment.
Li [28]	2017	China	Cohort	2012–2016	268	146	122	48.7	NA	913.6	3.5	7	The fasting blood samples were taken before initiation of the midweek HD session at baseline
Li [29]	2022	China	Cohort	1997–2017	245	136	109	33	89.99	NA	2.41	6	Collected from the initial medical records at the renal biopsy.
Liu [30]	2016	China	Cohort	2006–2015	1778	1058	720	47.4	6.4	7.9	NA	7	NA
Lu [31]	2018	China	Cohort	2014–2016	86	37	49	54.6	NA	888.4	4.5	7	After a 10-h overnight fast prior to dialysis.
Luo [32]	2024	Israel	Cohort	2008–2019	2254	1529	725	76	NA	1.4	7.32	7	Only data from the initial admission were considered.
Milosevic [33]	2024	Serbia	Cohort	18 months	130	98	32	66	NA	882	NA	7	Before the HD (bHD) and after the HD (aHD) procedure.
Neuen [34]	2016	Australia	Cohort	2007–2012	170	102	68	54	NA	NA	3	7	3 months after the commencement of HD
Ouellet [35]	2016	USA	Cohort	2016–2022	130	67	63	45.7	NA	NA	2.486	8	After a minimum overnight fast of 8 h, prior to the midweek HD session
Ozgur [36]	2021	Turkey	Cohort	2015–2020	110	70	40	62.1	NA	NA	NA	7	NA
Sastrawan [37]	2020	Indonesia	Cohort	2018–2019	53	36	17	51	NA	NA	2.84	7	NA
Sato [5]	2017	Japan	Cohort	2009–2016	78	51	27	63.4	4.9	10.1	3.5	8	At the beginning of the first dialysis session
Shankar [38]	2021	South India	Cohort	2020.7-2020.10	90	60	30	47.2	NA	8.2	NA	6	NA
Solak [39]	2013	Japan	Cohort	39 months	225	107	118	50.36	26.86	NA	2.81	7	At admission

Table 1 (continued)

Author	Year	Region	Study design	Study period	Sample size	Gender		Age (mean/median)	eGFR (mean/median)	SCR (mean/median)	NLR cut-off	Quality score	Timing of blood test
						Male	Female						
Tatar [40]	2016	Turkey	Cohort	2008–2010	165	105	60	73.8	29.6	NA	NA	8	At least three measurements (basal, one year and last control outpatient clinic values
Valencia [41]	2024	Mexico	Cohort	2016–2022	130	66	64	45.7	NA	NA	2.486	8	After a minimum overnight fast of 8 h, prior to the midweek HD session.
Wang [42]	2021	China	Cohort	2009–2018	966	443	523	35	92.58	83.87	2.67	7	Collected at the time of renal biopsy and at the follow-up visit.
Wozi-wodzka [43]	2019	Poland	Cohort	5 years	84	50	34	61.5	10.5	445.9	3.9	8	NA
Xiang [44]	2018	China	Cohort	2009–2015	355	220	135	58	NA	1013.2	NA	7	At the start of each dialysis session after a 2-day interval.
Yaprak [45]	2016	Turkey	Cohort	24 months	80	32	48	56.8	NA	7.68	2.52	8	At the beginning of an HD session in the middle of the week.
Yoshi-tomi [46]	2019	Japan	Cohort	2009–2017	350	239	111	68	33.6	NA	1.87	7	Early in the morning after an overnight fast
Yuan [47]	2018	China	Cohort	2011–2017	938	544	394	52.8	57.22	NA	2.09	7	NA
Zeng(a) [48]	2020	China	Cohort	2010–2017	1502	852	650	51	NA	708.1	2.74	7	NA
Zeng(b) [48]	2020	China	Cohort	2010–2017	1502	852	650	51	NA	708.1	3.96	7	NA

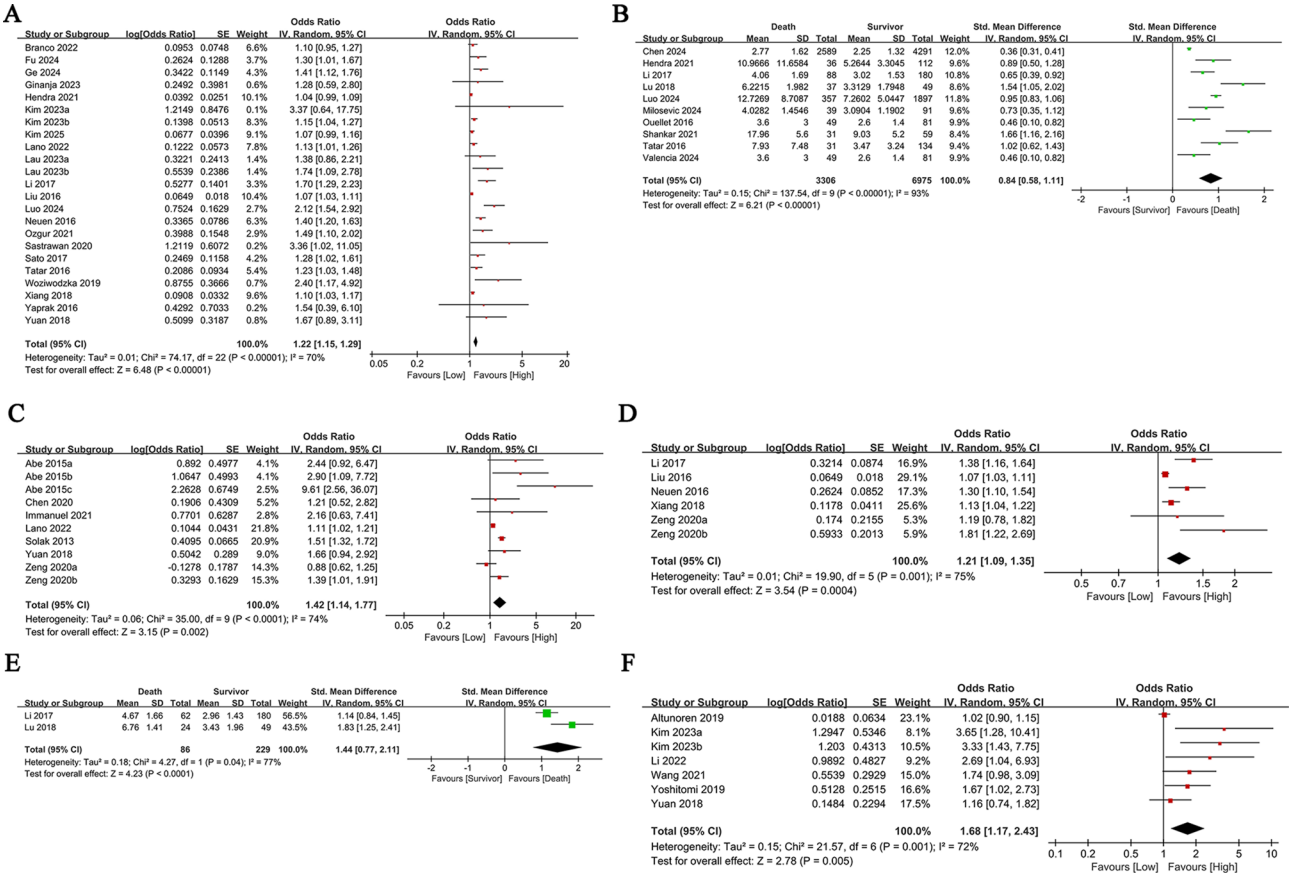

Fig. 2 Forest plot. (**A**) Dichotomous variables of all-cause mortality; (**B**) Continuous variables of all-cause mortality; (**C**) Dichotomous variables of MACE incidence; (**D**) Dichotomous variables of cardiovascular mortality; (**E**) Continuous variables of cardiovascular mortality; (**F**) Dichotomous variables of ESRD outcomes

predictive value of NLR ($p = 0.22$). Conversely, cohort studies demonstrated a significant predictive value for MACE ($p = 0.003$), with heterogeneity remaining largely unchanged.

Subgroup analysis of ESRD outcomes

We analyzed ESRD outcomes by age and region. In the aged < 55 group, heterogeneity decreased from 72 to 39%, indicating that age contributed to heterogeneity. NLR remained a significant predictor across all age groups. Regarding region, only one European study reported no statistically significant association between NLR and ESRD, while in Asian populations, NLR remained a significant predictor and heterogeneity decreased to 39%. These findings suggest that both age and region influence heterogeneity in ESRD outcomes.

Sensitivity analysis

A sensitivity analysis was performed to evaluate the stability of our results and the clinical significance of NLR. Sequentially excluding each study did not substantially alter the effect size, which remained stable throughout. This indicates that no individual study was found to significantly influence the findings for all-cause mortality (Fig. 3A and B), MACE incidence (Fig. 3C), cardiovascular mortality (Fig. 3D), or ESRD outcomes (Fig. 3E), demonstrating the reliability of our results.

Publication bias

Publication bias was evaluated using funnel plots and Egger's test. Funnel plots demonstrated asymmetry for all-cause mortality (Fig. 4A and B), cardiovascular mortality (Fig. 4C and D), and ESRD outcomes (Fig. 4E), indicating potential publication bias. In contrast, the funnel plot for MACE (Fig. 4F) appeared symmetrical, suggesting no bias. Egger's test confirmed the presence of bias for all-cause mortality ($p = 0.000$ and $p = 0.034$), cardiovascular mortality ($p = 0.019$), and ESRD ($p = 0.001$), as all p-values were below 0.05. For MACE, Egger's test did not reveal any notable publication bias ($p = 0.101$). Publication bias assessment was not conducted for subgroups with fewer than three studies.

Table 2 Pooled ORs in subgroup analyses

Subgroup	All-cause Mortality (Dichotomous Variables)				MACE (Dichotomous Variables)				ERSD (Dichotomous Variables)			
	Study group	OR [95%CI]	*P* value	I^2	Study group	OR [95%CI]	*P* value	I^2	Study group	OR [95%CI]	*P* value	I^2
Total	23	1.22 [1.15, 1.29]	<0.00001	70%	10	1.42 [1.14, 1.77]	0.002	74%	7	1.68 [1.17, 2.43]	0.005	72%
Age												
≥ 55y	6	1.19 [1.11, 1.27]	<0.00001	63%	5	2.44 [1.14, 5.23]	0.02	77%	4	1.86 [1.01, 3.42]	0.05	81%
<55y	17	1.41 [1.13, 1.75]	0.002	84%	5	1.32 [1.05, 1.65]	0.02	52%	3	1.55 [1.01, 2.37]	0.05	32%
Region												
Asia	14	1.25 [1.14, 1.36]	<0.00001	73%	9	1.56 [1.19, 2.04]	0.001	60%	6	1.87 [1.33, 2.64]	0.0003	39%
Europe	7	1.15 [1.04, 1.28]	0.005	58%	1	1.11 [1.02, 1.21]	0.02	NA	1	1.02 [0.90, 1.15]	0.77	NA
America	1	1.30 [1.01, 1.67]	0.04	NA	/	/	/	/	/	/	/	/
Oceania	1	1.40 [1.20, 1.63]	<0.0001	NA	/	/	/	/	/	/	/	/
NLR cut-off												
≥ 3	10	1.40 [1.20, 1.64]	<0.0001	82%	5	1.75 [1.12, 2.75]	0.01	76%	/	/	/	/
<3	5	1.48 [1.01, 2.18]	0.05	34%	5	1.35 [0.99, 1.84]	0.06	58%	7	1.68 [1.17, 2.43]	0.005	72%
Scr (μmol/L, mg/dl)												
<133, <1.6	3	1.57 [1.08, 2.30]	0.02	66%	/	/	/	/	4	1.91 [1.00, 3.65]	0.001	81%
133–177, 1.6-2.0	3	1.14 [1.05, 1.24]	0.002	0%	/	/	/	/	/	/	/	/
178–442, 2.1-5.0	NA	NA	NA	NA	/	/	/	/	/	/	/	/
443–707, 5.1–7.9	3	1.32 [0.97, 1.81]	0.08	81%	/	/	/	/	/	/	/	/
≥707, ≥ 8.0	4	1.21 [1.06, 1.38]	0.004	71%	10	1.42 [1.14, 1.77]	0.002	74%	/	/	/	/
Study design												
Cohort	/	/	/	/	9	1.41[1.13, 1.76]	0.003	77%	/	/	/	/
Case-Control	/	/	/	/	1	2.16 [0.63, 7.41]	0.22	NA	/	/	/	/

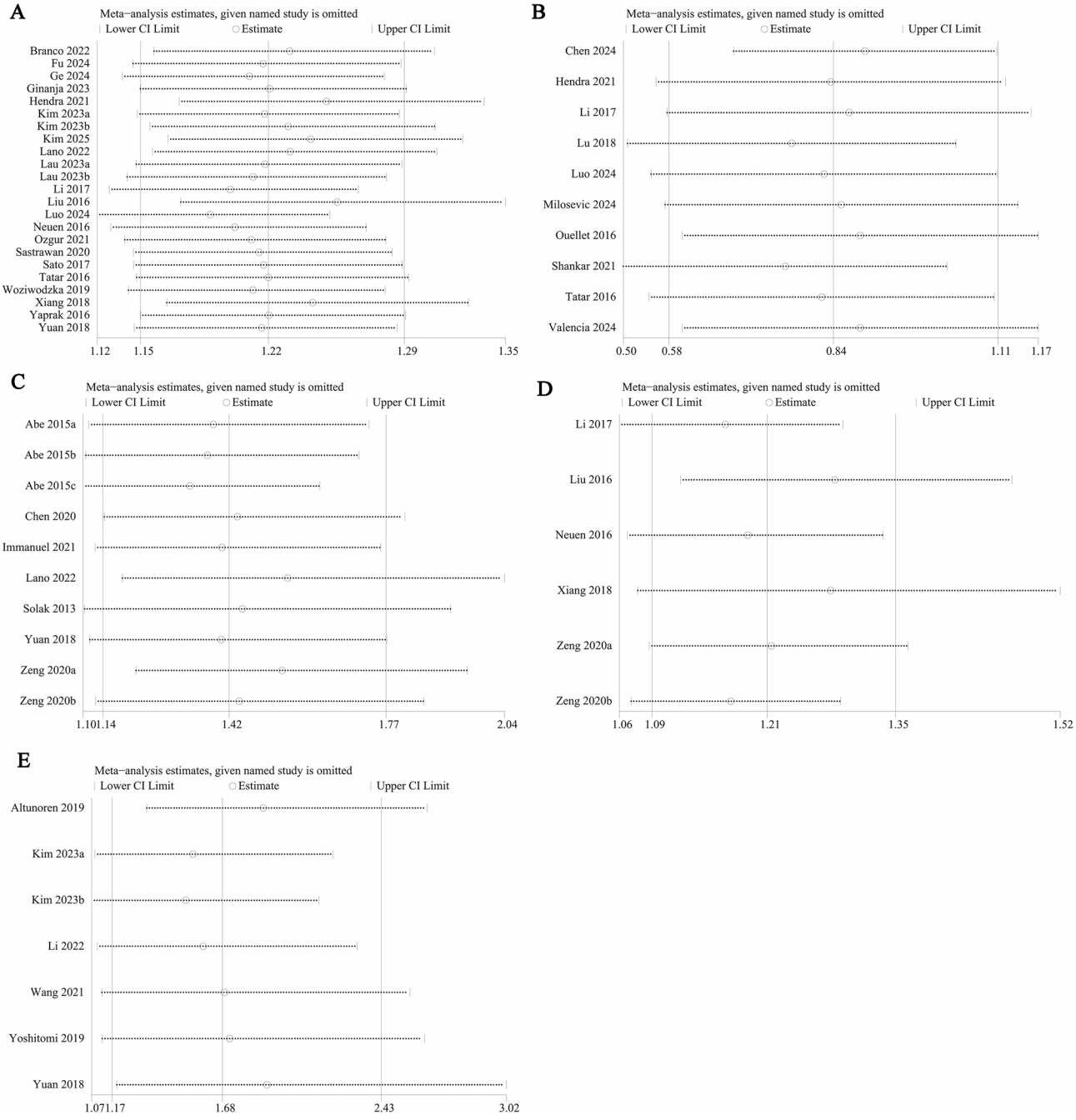

Fig. 3 Sensitivity analysis. (**A**) Dichotomous variables of all-cause mortality; (**B**) Continuous variables of all-cause mortality; (**C**) Dichotomous variables of MACE incidence; (**D**) Dichotomous variables of cardiovascular mortality; (**E**) Dichotomous variables of ESRD outcomes

GRADE rating

This study applied the GRADE system to evaluate the quality of evidence, with all outcomes rated as very low. Detailed results are presented in Table 3.

Discussion

The neutrophil-to-lymphocyte ratio (NLR), an indicator of systemic inflammation, is linked to CKD progression and prognosis, including all-cause mortality, cardiovascular events, and adverse renal outcomes. Growing research interest reflects NLR's advantages of cost-effectiveness, simplicity, rapid availability, and ease of use in clinical settings. However, definitive evidence remains insufficient. This study aims to clarify the link between NLR and CKD outcomes through a comprehensive meta-analysis.

This study demonstrated that NLR predicts all-cause mortality, MACE incidence, cardiovascular mortality,

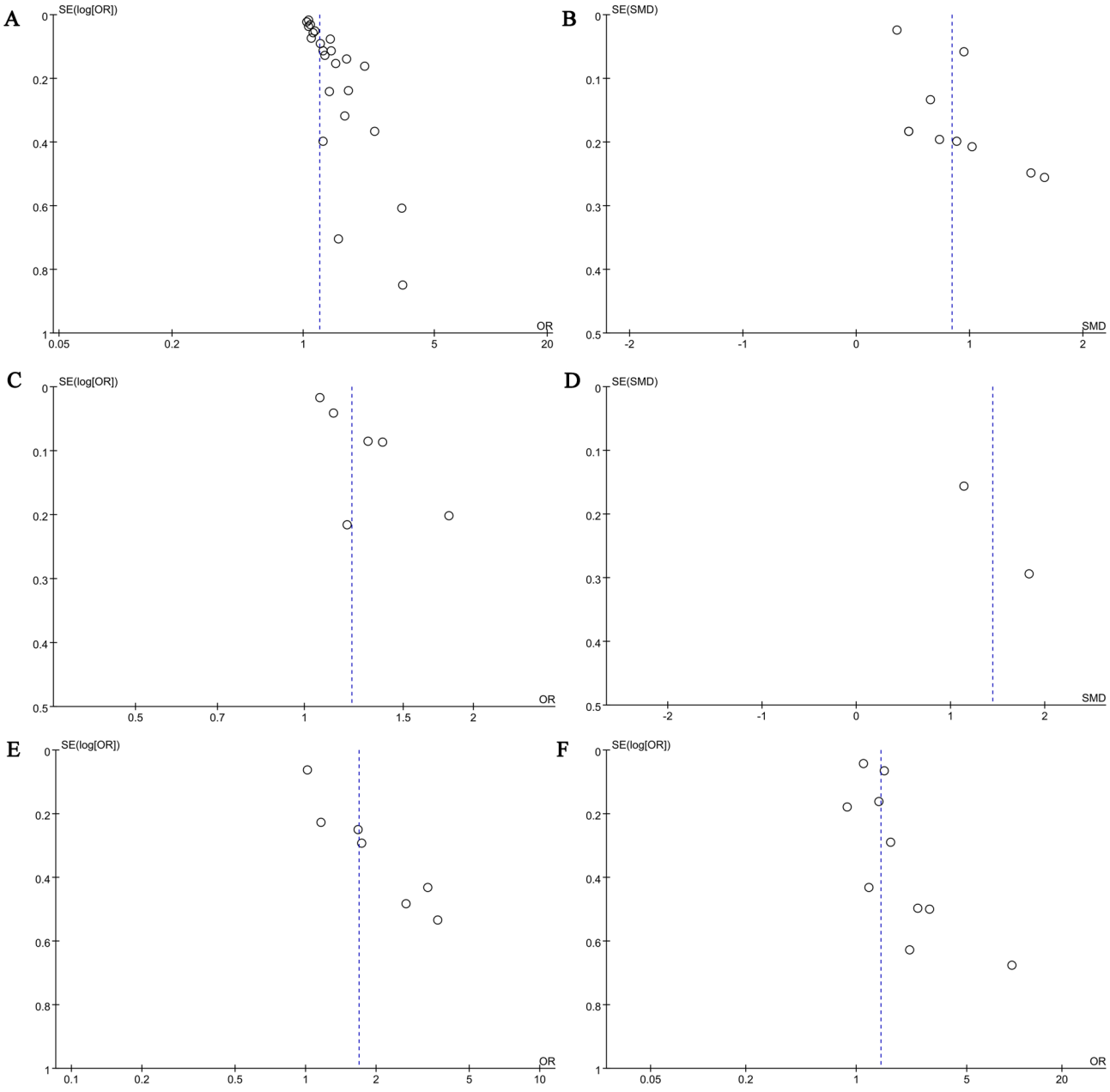

Fig. 4 Funnel plot. (**A**) Dichotomous variables of all-cause mortality; (**B**) Continuous variables of all-cause mortality; (**C**) Dichotomous variables of cardiovascular mortality; (**D**) Continuous variables of cardiovascular mortality; (**E**) Dichotomous variables of ESRD outcomes; (**F**)Dichotomous variables of MACE incidence

and ESRD outcomes, with higher NLR levels associated with increased risks of these events. While continuous NLR values showed statistically significant differences across groups, their precise clinical application requires further validation. Sensitivity analyses confirmed the stability of these findings. Publication bias was detected for most outcomes except MACE incidence. Subgroup analyses indicated that NLR's predictive value remained significant and consistent across various sample sizes, patient ages, geographic regions, and cut-off values. Regarding study design, cohort studies showed robust predictive value, whereas the single included case-control study did not. Future research should prioritize cohort designs, while additional evidence is needed to evaluate the utility of case-control studies in this context.

For MACE incidence, when the NLR cut-off is ≥ 3, its predictive value is no longer significant ($p > 0.05$), indicating that the NLR level influences its predictive ability. Therefore, the NLR value level affects prediction. In future predictive model development, the cut-off value

Table 3 GRADE rating of each outcome

No. of study groups	Outcomes	OR/SMD	95%CI	I^2; *P* value	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible confounding	Magnitude of effect	Dose-response gradient	GRADE
23	All-cause Mortality (Dichotomous Variables)	1.22	1.15, 1.29	70%; $P < 0.00001$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Strongly suspected	Would not reduce effect	No	No	Very low
10	All-cause Mortality (Continuous Variables)	0.84	0.58, 1.11	93%; $P < 0.00001$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Strongly suspected	Would not reduce effect	No	No	Very low
10	MACE (Dichotomous Variables)	1.42	1.14, 1.77	74%; $P < 0.0001$	No serious risk	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Would not reduce effect	No	No	Very low
6	Cardiovascular Mortality (Dichotomous Variables)	1.21	1.09, 1.35	75%; $P = 0.001$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	Strongly suspected	Would not reduce effect	No	No	Very low
2	Cardiovascular Mortality (Continuous Variables)	1.44	0.77, 2.11	77%; $P = 0.04$	No serious risk	Serious inconsistency	No serious indirectness	No serious imprecision	NA	Would not reduce effect	No	No	Very low
7	ERSD (Dichotomous Variables)	1.68	1.17, 2.43	72%; $P = 0.001$	No serious risk	Serious inconsistency	No serious indirectness	Serious imprecision	Strongly suspected	Would not reduce effect	No	No	Very low

can be set above 3. Further studies should explore more refined subgroupings of NLR cut-off values to identify the optimal threshold and improve the accuracy of clinical decision-making. Most current studies use receiver operating characteristic (ROC) curve analysis to determine optimal cut-off values. For instance, Tang et al. [50] identified an NLR cut-off of 4.9 (AUC = 0.634) for predicting survival in patients with liver cirrhosis after TIPS surgery. Some studies have adjusted cut-off values based on clinical outcomes such as mortality and complications. For example, Li et al. [51] used a restricted cubic spline model in a cardiovascular disease study and found a non-linear relationship between NLR and all-cause mortality, identifying 2.89 as the optimal cut-off value.

Various factors may impact NLR values, including age, diet, medications, and chronic conditions, such as coronary heart disease, stroke, diabetes, obesity, mental illness, solid organ cancer, anemia, and hypertension. All of these affect neutrophils and lymphocyte function and dynamics. In future predictive models, the NLR cut-off value should be determined by integrating statistical methods with clinical context, considering disease type, patient characteristics, and research methodology. Dynamic evaluation and personalized application are essential to improve predictive accuracy.

In the subgroup analysis of ESRD outcomes, age and region were identified as sources of heterogeneity. NLR significantly predicted ESRD outcomes in the Asian region subgroup but not in the European subgroup, likely due to the only one European study being included. The results suggest that this indicator is applicable to the Asian population; however, additional studies are needed to confirm its applicability in the European population. Future studies should establish more refined subgroups based on age and region to identify where NLR's predictive value is most reliable, thereby improving the accuracy of ESRD outcome prediction. For instance, age-stratified studies in Asian populations could be combined with CKD staging, proteinuria levels, and other clinical indicators to enable more in-depth research on predicting ESRD outcomes.

All included studies were cohort or case-control in design, and the GRADE assessment indicated that the overall quality of evidence was very low. In the future, multicenter, large-sample, prospective randomized controlled trials should be conducted to generate higher-quality evidence for clinical practice.

Previous meta-analyses, such as those by Ao et al. [7] and Zhao et al. [8], reported that NLR predicted all-cause mortality (Ao: HR 1.93, 95% CI 1.87–2.00, Zhao: HR 1.45, 95% CI 1.20–1.75) and cardiovascular events (Ao: HR 1.45, 95% CI 1.18–1.79 all-cause mortality, Zhao: HR 1.52, 95% CI 1.33–1.72 for cardiovascular events) in patients with CKD. These results are support those of the

present study. However, Ao et al. did not investigate the association between NLR and ESRD or MACE, nor did they adequately adjust for potential confounders such as baseline eGFR or serum creatinine (Scr). The sample size in Zhao et al.'s study was relatively small ($n = 1,442$) and did not evaluate ESRD outcomes.

To address these gaps, the present meta-analysis incorporated studies published up to 2025, including newly available cohort studies since 2021, and for the first time demonstrated a clear link between NLR and ESRD (OR 1.42, 95% CI: 1.14—1.77), thereby extending the clinical prognostic value of NLR. Notably, stratified analysis revealed that the predictive efficacy of NLR varied by region—showing significance in Asian populations but not in European cohorts—and by NLR cut-off value, as its predictive ability for MACE was not significant when the threshold was ≥ 3. These findings highlight the importance of refining NLR thresholds, a topic insufficiently explored in previous studies. Furthermore, the inclusion of updated data and adherence to rigorous methodology—including compliance with PRISMA 2020 guidelines, sensitivity testing, and subgroup analyses—enhanced the robustness of the findings and helped control for potential sources of heterogeneity. This comprehensive evaluation deepens the understanding of NLR's role in CKD progression, supports its integration into CKD risk stratification frameworks, and provides critical evidence to inform early risk assessment and clinical decision-making in CKD management.

Recent studies have demonstrated a consistent link between elevated NLR levels and increased all-cause mortality, underscoring its potential as an independent prognostic marker. Woziwodzka et al. [43] found that among patients with end-stage renal disease (ESRD), an NLR ≥ 3.9 significantly predicted 5-year all-cause mortality (HR = 2.23, 95% CI: 1.10–4.50, $p = 0.025$). Elevated NLR may reflect either lymphopenia or neutrophilia—conditions with distinct pathophysiological implications. Zamora et al. [52] reported that decreased lymphocyte counts impair infection resistance and adaptive immunity, while excessive neutrophils may cause tissue damage through an overactive innate immune response. Elevated inflammatory markers are associated with poorer prognosis, and observing NLR values can facilitate the identification of individuals at high risk of mortality.

Schuett et al. [53] reported that cardiovascular diseases account for 40–50% of total mortality in ESRD patients. Matsushita et al. [54] emphasized that microinflammation is a key factor in the onset and progression of CVDs within this population. Supporting this, Zhu et al. [55] demonstrated that NLR levels were significantly higher in hemodialysis patients with cardiovascular complications compared to those without, and were correlated with increased myocardial injury markers, including cTnI and CK-MB, suggesting NLR's potential as a predictor of myocardial injury. Additionally, Roumeliotis et al. [56] observed a significant positive correlation between NLR and dp-ucMGP ($r = 0.43$, $p < 0.0001$) in CKD patients. Sabbagh et al. [57] further confirmed that dp-ucMGP, an inactive form of matrix Gla protein induced by vitamin K deficiency or antagonists, is a reliable marker of vascular calcification (VC) and predicts the incidence and mortality of cardiovascular diseases. These results collectively demonstrate that NLR serves as a valuable predictor of the development, progression, and prognosis of cardiovascular diseases in patients with CKD. Additionally, NLR is also a predictor of adverse renal outcomes. Yoshitomi et al. [46] reported that in non-dialysis patients, elevated NLR was significantly associated with reduced eGFR (β = -0.23, $p < 0.01$) and a 1.67-fold increased risk of progression to dialysis [95% CI (1.02–2.77)].

These findings establish NLR as a reliable predictor of renal function decline in CKD patients. Lan et al. [58] and Rashi et al. [59] further demonstrated that elevated NLR is significantly linked to a more rapid decrease in eGFR and serves as an independent predictor of renal function decline, outperforming other markers such as PLR and SII. Gupta et al. [60] reported that neutrophil activation leads to DNA depolymerization and histone citrullination, mediated by histone deaminases such as peptidyl arginine deiminase 4 (PAD4). This process and serves as an independent predictor of renal function decline the formation and release of neutrophil extracellular traps (NETs), which consist of DNA, histones, and neutrophil-derived proteases such as neutrophil elastase (NE) and myeloperoxidase (MPO). NETs contribute to the activation of the NLRP3 inflammasome, promote glomerular endothelial cell injury and dysfunction, and accelerate renal function decline in patients with CKD [58, 60]. Lymphocytes also play a crucial role in CKD progression by disrupting immune homeostasis. An imbalance in T cell subsets, characterized by a reduced Th17/Treg ratio-caused by STAT5 inhibition (leading to decreased Treg cells) and AhR activation (promoting Th17 polarization)—along with Breg dysfunction, drives IL-17-mediated renal interstitial inflammation and autoimmune damage, thereby accelerating CKD-associated fibrosis [61–64]. As a result, elevated NLR levels are associated with increased renal damage.

Finally, future clinical studies should consider setting the NLR cutoff value above 3 and further investigate its optimal threshold. Such research is expected to provide robust evidence supporting the incorporation of NLR into existing CKD risk stratification systems, thereby improving clinical management strategies. However, relying solely on NLR to predict prognosis is insufficient. A more comprehensive predictive model should integrate additional patient data, including age, disease stage,

other laboratory parameters, and immune-inflammatory markers (e.g., PLR, SI). Among these, NLR should be recognized as one of the more important and informative indicators. Furthermore, due to its low cost and ease of measurement, NLR has potential as a dynamic monitoring tool during hospitalization or follow-up to help identify CKD patients at increased risk of poor outcomes, such as all-cause mortality, major adverse cardiovascular events (MACE), and renal deterioration. This approach may contribute to the development of a more precise and adaptive prognostic model, facilitating early identification of high-risk individuals and enabling timely, targeted interventions.

Strengths and limitations

This study represents the largest meta-analysis to date in terms of sample size, incorporating research published up to 2025. It also provides an in-depth evaluation of the quality of evidence through sensitivity and subgroup analyses.

However, several limitations should be acknowledged. First, the subgroup analysis failed to identify the sources of heterogeneity in MACE outcomes. It is speculated that this variability may be attributed to factors such as geographic region, serum creatinine levels, and study design. Second, the included studies are subject to various biases, including design, selection, and treatment biases. All studies were cohort or case-control in design, and the GRADE assessment indicated that the overall quality of evidence was very low. Moreover, some studies had relatively small sample sizes, which limits the generalizability of the results. Third, potential confounding factors and selection bias may have influenced the results. The lack of detailed data on lifestyle factors, comorbidities, and treatment regimens could affect NLR values, weaken its association with key CKD indicators, and reduced the accuracy of predictions. Finally, the absence of individual patient data prevents the determination of an optimal NLR cut-off value. Given these limitations, the results should be interpreted with caution and in the context of clinical practice.

Conclusion

Our findings demonstrate that NLR is significantly associated with all-cause mortality, MACE incidence, cardiovascular mortality, and adverse renal outcomes in CKD. Sensitivity and subgroup analyses confirmed the robustness of these results. Since publication bias was detected in several outcomes, excluding MACE, the results, although promising, should be interpreted with caution. Given the high heterogeneity, regional imbalance (predominantly from Asia), and insufficient classification of NLR cutoff values, future studies should involve multicenter, large-sample, prospective randomized controlled trials. These studies should refine NLR cutoff values to determine the optimal threshold, thereby providing more precise evidence for clinical practice. Incorporating NLR into the existing CKD risk stratification system could optimize clinical management strategies and serve as a dynamic monitoring tool to identify CKD patients at high risk of poor prognosis. This approach would enhance the precision of prognosis assessments and treatment decision-making, enabling early identification of high-risk patients and the development of targeted intervention strategies.

Supplementary Information

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Supplementary Material 1

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Author contributions
All authors contributed to the study conception and design. Yangjing Xu: Conceptualization, Methodology, Software, Writing- Original draft, Data curation, Visualization were performed; Yongtong Chen and Xiaolu Mai: Investigation, Writing - Original Draft, Writing - Reviewing and Editing were performed; Min Zhang: Conceptualization, Supervision, Project administration were performed. All authors read and approved the final manuscript.

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Data availability
The data used to support the findings of this study are included within the article.

Declarations

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Not applicable.

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The authors declare no competing interests.

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