PROGNOSTIC VALUE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO IN CARDIOVASCULAR DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Basel Mohammad Hamad Khawaldeh[1], Dr. Farrukh Ameer[2], Basmalah Saeed Al-Hawadi[3], Saif Saeed Alhawadi[4], Ahmed Osman Hassan Ali[5], Khaled Mohamed Aly Eltamawy[6], Eman Mohamed Mahmoud Habib[7]

[1]Faculty of Medicine, Near East University, Mersin, Turkey, Khawaldehbassel@gmail.com , https://orcid.org/0009-0007-7731-8307

[2]Department of Adult Cardiology, Dr. Soliman Fakeeh Hospital, Fakeeh Care Group, Riyadh, Saudi Arabia, dr.farrukhameer@gmail.com , https://orcid.org/0009-0004-3095-3475

[3]School of Medicine, University of Jordan, Amman, Jordan, Basmalahalhawadi7@gmail.com , https://orcid.org/0009-0009-6561-1471

[4]School of Medicine, University of Jordan, Amman, Jordan, saifalhawadi6@gmail.com , https://orcid.org/0009-0009-3187-2753

[5]Faculty of Medicine, Benha University, Benha, Egypt, Ahmad.elmesary@gmail.com , https://orcid.org/0009-0008-4430-4053

[6]Cardiology Department, Faculty of Medicine, Merit University, Sohag, Egypt, khalid_eltamawey@yahoo.com , https://orcid.org/0000-0003-1549-6646

[7]Clinical Pathology Department, Faculty of Medicine, Kafrelsheikh University, Kafr El-Sheikh, Egypt, Eman.habeeb@yahoo.com , https://orcid.org/0009-0006-3764-8881

Abstract

Cardiovascular diseases (CVDs) remain the leading cause of death globally. The neutrophil-to-lymphocyte ratio (NLR), an inexpensive inflammatory biomarker derived from routine blood counts, has shown promise for risk stratification, yet pooled prognostic evidence across heterogeneous CVD populations remains limited. This study systematically synthesised the prognostic value of baseline NLR for mortality across the full spectrum of CVD. Following PRISMA 2020 guidelines, PubMed, Scopus, and Web of Science were searched (January 2011–March 2026). Studies reporting multivariable-adjusted hazard ratios (HRs) for mortality in CVD patients with NLR as a prognostic exposure were included. Random-effects meta-analysis (DerSimonian–Laird), subgroup analyses (ACS vs. non-ACS; heart failure vs. CAD/interventional), leave-one-out sensitivity analysis, and publication bias tests (Egger's, Begg's) were performed. Twenty studies met the inclusion criteria; 16 contributed to the primary mortality HR pool. The pooled adjusted HR was 1.30 (95% CI: 1.20–1.40; $p < 0.001$; $I^2 = 89.4\%$). The ACS/STEMI subgroup showed a higher pooled HR of 2.18 (95% CI: 1.15–4.13) compared with non-ACS conditions (HR = 1.30; 95% CI: 1.20–1.42). The association remained robust in all leave-one-out iterations. Egger's test indicated potential publication bias ($p = 0.031$). Elevated NLR independently predicts mortality across diverse CVD populations. As a universally available, zero-cost biomarker, NLR holds considerable promise as an adjunctive risk-stratification tool. Future research should establish standardised cutoffs and test NLR-guided management strategies.

Keywords: *Neutrophil-to-lymphocyte ratio; cardiovascular disease; mortality; meta-analysis; systematic review; inflammatory biomarker*

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in every region of the world, and this condition causes about one-third of all worldwide deaths (Roth et al., 2020). According to the Global Burden of Disease 2023 report, it was estimated that 437 million disability-adjusted life years were due to CVDs in 204 countries and territories, which is 1.4 times higher than in 1990 (Martin et al., 2024). More than 20.5 million people were killed by the cardiovascular disease in 2021, and about 80 percent of those deaths took place in low- and middle-income nations (Vos et al., 2024). The major causes of this burden still remain ischaemic heart disease and stroke, and other conditions such as heart failure, valvular disease, and peripheral arterial disease only make the problem more difficult to any healthcare system in the world (Tsao et al., 2023). Although tremendous therapeutic improvements have been made in the last 20 years, such as percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), transcatheter aortic valve implantation (TAVI), and pharmacological developments, the risk of an adverse outcome among CVD patients is still unacceptable (Libby et al., 2019). Consequently, a long-standing clinical requirement exists to have readily available, cost-effective biomarkers, which can be used to stratify the patients according to their risk at early stages of their disease progression, preferably at the time they first met a doctor.

A candidate that has arisen as a possible solution to this is the neutrophil-to-lymphocyte ratio (NLR) which is the number of neutrophils divided by the number of lymphocytes on a routine complete blood count. NLR is a combination of two immunological responses: the innate inflammatory response, which is represented by neutrophils, and the adaptive immune-regulatory response, which is represented by lymphocytes (Bhat et al., 2013). Physiologically, a high NLR is an indicator of a state of increased systemic inflammation along with a relative lack of immunosuppression, a dual imbalance that defines the pathobiology of atherosclerosis, plaque instability, myocardial injury, and adverse cardiac remodelling (Hansson, 2005; Frangogiannis, 2014). The mechanisms of neutrophilia in acute cardiovascular stress are catecholamine release, cortisol-induced demargination, and granulopoietic stimulation with the resultant lymphopenia caused by apoptosis-mediated lymphocyte depletion and redistribution under sympathetic-adrenal activation (Onsrud and Thorsby, 1981; Acanfora et al., 2001). Since NLR is calculated based on a routine haemogram, has a very low incremental cost, and no special lab resources are necessary, it is universally applicable in emergency departments, intensive care units, and primary care throughout the world (Forget et al., 2017).

Within the last 10 years, a significant amount of primary research studies has investigated the prognostic importance of NLR in diverse cardiovascular conditions, such as ST-elevation myocardial infarction (STEMI), non-ST-elevation acute coronary syndromes, stable coronary artery disease, acute and chronic heart failure, and structural heart disease necessitating TAVI or CABG (Park et al., 2013; Wasilewski et al., 2016; Merdler et al., 2 Nevertheless, the evidence base is still still in pieces due to the mixed populations, unequal NLR cutoff settings, and different outcome endpoints. A number of previous meta-analyses have been done to synthesize this literature, but most of them had focused on a single disease subtype. An example is Angkananard et al. (2018), which combined 38 studies that investigated NLR and overall CVD risk but concentrated more on odds ratios of disease incidence and not prognostic ratios of mortality. In more recent works, Vakhshoori et al. (2023) summarized NLR

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

evidence in heart failure, whereas Banahene et al. (2024) limited their study to myocardial infarction. A 90-study meta-analysis of NLR in acute coronary syndromes by Pruc et al. (2024) proved that it is a useful diagnostic and prognostic tool in the target population. However, the most recent synthesis has not adopted a cross-cutting approach to combine adjusted hazard ratios of mortality across the entire range of cardiovascular disease, in addition to using the larger cohort studies published between 2022 and 2025.

To fill this gap, the current study will focus on updating and conducting a thorough systematic review and meta-analysis to assess the prognostic value of baseline NLR to predict mortality in heterogeneous CVD populations. In particular, the main aim is to combine multivariable-adjusted hazard ratios (HRs) of all-cause or cardiovascular mortality of all eligible observational studies published between 2011 and 2026 using a random-effects model to factor in future clinical and methodological heterogeneity. One of the secondary goals is to investigate possible sources of heterogeneity with the help of pre-specified subgroup analyses stratified by the cardiovascular condition (acute coronary syndromes versus non-acute conditions) and disease category (coronary artery disease/interventional cohorts versus heart failure). The results are supposed to explain the scale and stability of the NLR-mortality relationship in relation to CVD subtypes, guide clinical risk-stratification choices, and set the research agenda of future studies.

2. Methods

2.1 Protocol and Registration

This meta-analysis and systematic review was performed and presented in compliance with the Preferred Reporting Items of the Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). Review protocol was formulated a priori, where the research question, the eligibility criteria, search strategy, data extraction procedures, quality assessment tool, and statistical analysis plan were stated. The review was not prospectively enrolled in PROSPERO; though, all the methodological choices were made prior to the commencement of the literature search to reduce the risk of reporting bias.

2.2 Search Strategy

A systematic literature search was performed across three electronic databases: PubMed/MEDLINE, Scopus, and Web of Science, covering publications from January 1, 2011, to March 15, 2026. The search strategy was constructed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords organized around three conceptual blocks: (a) the exposure of interest *("neutrophil-to-lymphocyte ratio" OR "neutrophil lymphocyte ratio" OR "NLR"*), (b) the population *("cardiovascular disease" OR "coronary" OR "myocardial infarction" OR "acute coronary syndrome" OR "heart failure" OR "PCI" OR "CABG" OR "TAVI" OR "transcatheter aortic valve" OR "aortic stenosis"*), and (c) the outcome *("prognos*" OR "mortality" OR "death" OR "outcome*" OR "MACE" OR "MACCE"*). These blocks were combined using the Boolean AND operator. Database-specific adaptations were made for Scopus (TITLE-ABS-KEY field) and Web of Science (TS field). To maximise retrieval, backward and forward citation chasing was conducted on included articles and on recent relevant systematic reviews and meta-analyses.

2.3 Eligibility Criteria

Studies were eligible for inclusion if they met all of the following criteria: (1) peer-reviewed, original human research published between January 2011 and March 2026; (2) enrolled a population

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

with an established cardiovascular disease diagnosis; (3) evaluated baseline or peri-procedural NLR as a prognostic exposure; (4) reported mortality (all-cause or cardiovascular) or major adverse cardiovascular events as a primary or secondary outcome; and (5) provided an extractable adjusted effect estimate (hazard ratio [HR], odds ratio [OR], or relative risk [RR]) with a corresponding 95% confidence interval (CI) from a multivariable regression model. Studies were excluded if they were reviews, meta-analyses, editorials, conference abstracts without extractable data, or case reports; if the study population was not cardiovascular in nature; if no quantitative effect estimate with 95% CI was extractable; if the study presented data from an overlapping cohort; or if the publication fell outside the specified date window.

2.4 Study Selection and Data Extraction

The flow diagram used to determine the selection of the study was PRISMA 2020 (Figure 1). The initial search in the database provided 182 records, which were further added with 17 records found as a result of citation chasing, resulting in a total of 199 records. Following 56 duplicates, 143 unique records were screened in terms of titles and abstracts. Of them, 102 records were left out as obviously irrelevant. The other 41 full-text reports were evaluated in terms of eligibility. The full-text stage eliminated 21 reports, no extractable adjusted effect estimate with 95% CI (n = 8), wrong outcome (n = 5), review or commentary (n = 4), overlapping cohort (n = 3), and out of the date window (n = 1). The outcome of this process was 20 studies that passed all the inclusion criteria. Of these, 16 studies which provided adjusted hazard ratios of mortality were the main meta-analytic pool.

Data were extracted using a standardised form. Variables recorded included: first author, year, country, cardiovascular condition, study design, sample size, NLR definition and cutoff, follow-up duration, outcome, effect measure, adjusted estimate with 95% CI, and key covariates. For the primary meta-analysis, the natural logarithm of the HR (ln[HR]) and its standard error (SE) were computed from the reported HR and 95% CI using the formula: SE = (ln [upper CI] – ln [lower CI]) / 3.92.

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

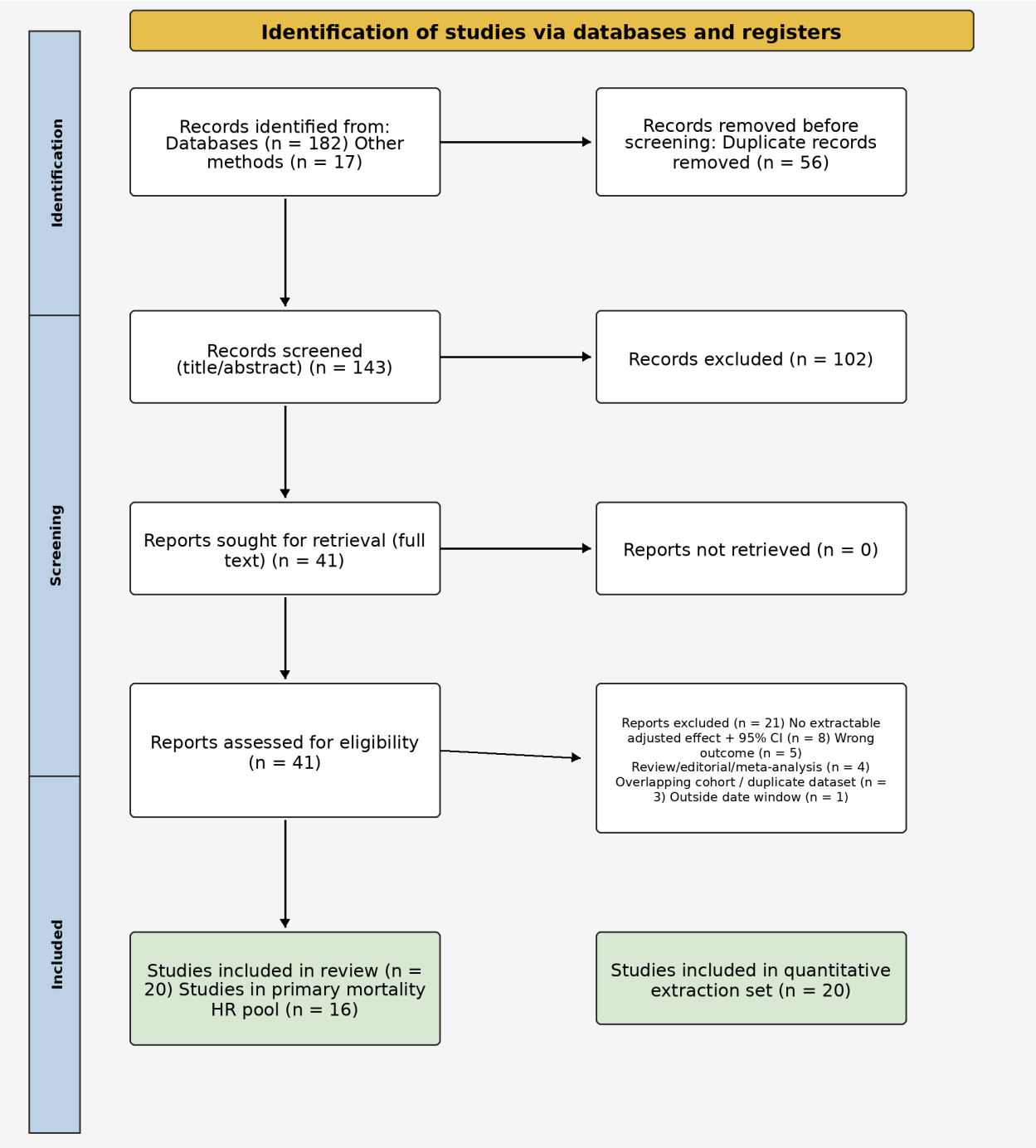


Figure 1. *PRISMA 2020 flow diagram illustrating the identification, screening, eligibility, and inclusion process for studies evaluating the prognostic value of NLR in cardiovascular disease. Adapted from Page et al. (2021).*

2.5 Quality Assessment

A cohort study using the Newcastle-Ottawa Scale (NOS) was used as a methodological quality tool of each of the included studies (Wells et al., 2000). The NOS evaluates quality of studies on three levels, namely, selection (up to four stars), comparability (up to two stars), and outcome ascertainment (up to three stars), producing a total possible score of nine stars. The articles that had a score of seven and above were of high quality, four to six was moderate quality, and three or less was low quality

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

(Stang, 2010). Each study was examined by two reviewers who then agreed on all issues via discussion.

2.6 Statistical Analysis

The primary mortality HR pool of 16 studies was used to conduct all the statistical analyses. Effect sizes were in the form of ln(HR) having standard errors. The random-effects model of DerSimonian and Laird (1986) was used to come up with the pooled estimate, which included both within-study and between-study variance. The heterogeneity was evaluated based on Cochran Q test (significance level at $p < 0.10$) and I^2 statistics (Higgins et al., 2003), which were divided into low (< 25%), moderate (25-75%), and high (> 75%). Stratification was done based on cardiovascular condition (ACS/STEMI [k = 5] vs. non-ACS [k = 11]) and disease category (heart failure vs. CAD/interventional). The sensitivity analyses involved a leave-one-out method. Publication bias was measured through funnel plot analysis, Egger regression test (Egger et al., 1997) and Begg rank correlation test (Begg and Mazumdar, 1994). Python 3.11 and the statsmodels and scipy libraries were used to perform all the analyses. A p value of less than 0.05 was taken as significant.

3. Results

3.1 Study Selection

The PRISMA 2020 flow diagram summarizing the study selection process is presented in Figure 1. The initial systematic search yielded 182 records, supplemented by 17 from citation chasing (total 199). Following removal of 56 duplicates, 143 unique records underwent title and abstract screening, of which 102 were excluded. Forty-one full-text reports were assessed for eligibility; 21 were excluded (eight lacking extractable estimates, five with wrong outcomes, four reviews/commentaries, three overlapping cohorts, and one outside the date window). Twenty studies met all inclusion criteria; 16 reporting adjusted HRs for mortality constituted the primary meta-analytic pool.

3.2 Study Characteristics

The characteristics of the 16 primary-pool studies are summarized in Table 1. Studies were published between 2013 and 2025 and collectively contributed 30,874 participants to the primary mortality pool. Most were observational cohort studies, with additional retrospective and registry-based cohorts. The included populations spanned STEMI/primary PCI, acute or chronic heart failure, stable or interventional coronary artery disease, TAVI, CABG, CHD with hypertension, and broad cardiovascular disease cohorts. NLR was modelled either continuously or using predefined cutoffs or quantiles, and all studies reported multivariable-adjusted estimates.

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

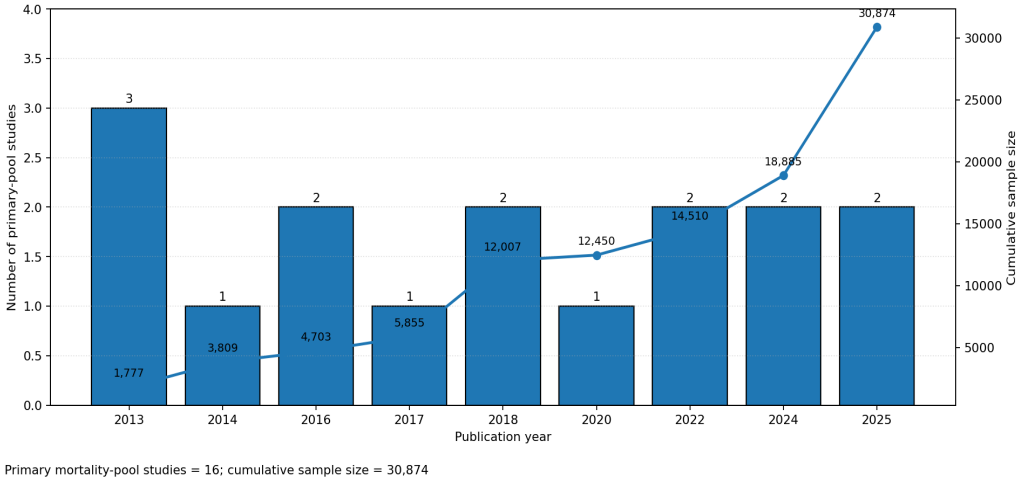


Figure 2. Temporal distribution of the 16 primary mortality-pool studies by publication year (bars) and cumulative sample size (line). The primary mortality pool spans 2013–2025, with accelerating evidence accumulation from 2022 onward.

As illustrated in Figure 2, the body of evidence has grown substantially over the review period, with nearly half of all included studies (n = 8) published between 2022 and 2025. The detailed characteristics of the 16 studies contributing to the primary mortality HR pool are presented in Table 1 below.

Table 1 Characteristics of the 16 Studies Included in the Primary Mortality HR Meta-Analysis Pool

Study	Country	CVD Condition	Design	N	NLR Definition	F/U	Outcome	EM	Estimate (95% CI)
Park (2013)	Korea	STEMI / Primary PCI	Observational cohort	325	Cutoff ≥5.44	~3 years	All-cause mortality	HR	3.12 (1.14–8.55)
Han (2013)	Korea	STEMI / Primary PCI	Observational cohort	326	Tertiles: >6.53	12 months	Death	HR	4.10 (1.17–14.46)
Azab (2013)	USA	CABG	Observational cohort	1,126	Continuous	5 years	All-cause mortality	HR	1.05 (1.01–1.10)
Arbel (2014)	Israel	STEMI / Primary PCI	Observational cohort	2,032	Cutoff ≥6.5	3 years	All-cause mortality	HR	2.20 (1.04–4.80)
Yan (2016)	China	Chronic HF (elderly)	Observational cohort	339	Tertiles: >2.5	29 months	Cardiac death	HR	1.75 (1.03–2.96)

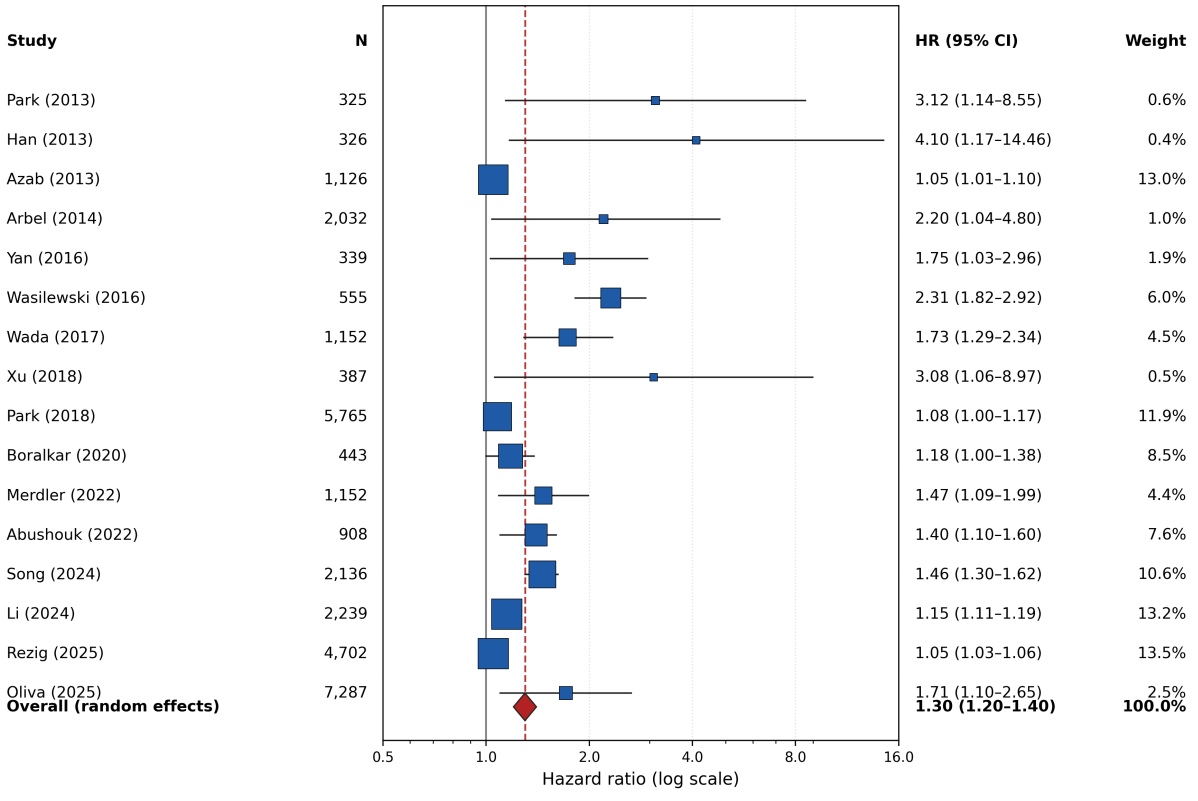
Wasilewski (2016)	Poland	HF (LVEF ≤35%)	Observational cohort	555	Tertiles: >3.1	36 months	All-cause mortality	HR	2.31 (1.82–2.92)
Wada (2017)	Japan	Stable CAD / PCI	Observational cohort	1,152	Cutoff ≥3.39	4 years	All-cause mortality	HR	1.73 (1.29–2.34)
Xu (2018)	China	AMI / Multi-vessel PCI	Retrospective cohort	387	Median ≥4.1	12 months	All-cause mortality	HR	3.08 (1.06–8.97)
Park (2018)	Korea	STEMI survivors / PCI	Retrospective cohort	5,765	Continuous	5 years	All-cause mortality	HR	1.08 (1.00–1.17)
Boralkar (2020)	USA	Acute HFpEF	Retrospective cohort	443	Continuous	2.2 years	All-cause mortality	HR	1.18 (1.00–1.38)
Merdler (2022)	Israel	TAVI	Registry cohort	1,152	Median cutoff 4.1	3 years	All-cause mortality	HR	1.47 (1.09–1.99)
Abushouk (2022)	USA	TAVI	Retrospective cohort	908	Elevated NLR	Mid-term	All-cause mortality	HR	1.40 (1.10–1.60)
Song (2024)	USA	CHD + Hypertension	Retrospective cohort	2,136	Cutoff >2.65	76 months	All-cause mortality	HR	1.46 (1.30–1.62)
Li (2024)	USA	Broad CVD cohort	Population-based cohort	2,239	Continuous; cutoff 2.89 explored	6.7 years	All-cause mortality	HR	1.15 (1.11–1.19)

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

Rezig (2025)	UK/Italy	Chronic HF outpatients	Observational cohort	4,702	Continuous	54 months	All-cause mortality	HR	1.05 (1.03–1.06)
Oliva (2025)	USA	CAD / PCI	Retrospective cohort	7,287	Quartile 4 >5.0	1 year	All-cause mortality	HR	1.71 (1.10–2.65)

Note. *CVD = cardiovascular disease; NLR = neutrophil-to-lymphocyte ratio; F/U = follow-up; EM = effect measure; HR = hazard ratio; STEMI = ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; TAVI = transcatheter aortic valve implantation; CAD = coronary artery disease; CHD = coronary heart disease; AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction. All estimates are multivariable-adjusted.*

The primary random-effects meta-analysis of 16 studies is presented in Figure 3. The pooled adjusted HR was 1.30 (95% CI: 1.20–1.40; z = 6.62; p < 0.001), indicating that elevated NLR was significantly associated with a 30% higher mortality risk overall among CVD patients. All 16 individual estimates were in the direction of increased risk (HR > 1.00), with point estimates ranging from 1.05 (Azab, 2013; Rezig, 2025) to 4.10 (Han, 2013). Substantial heterogeneity was observed (Q = 142.1, df = 15, p < 0.001; I^2 = 89.4%; τ^2 = 0.0116), indicating that approximately 89% of observed variability was attributable to between-study differences.



Random-effects model (DerSimonian–Laird): Q = 142.1, I^2 = 89.4%, τ^2 = 0.0115.

Figure 3. *Forest plot of the random-effects meta-analysis showing the association between elevated NLR and mortality risk across 16 cardiovascular disease studies. Square sizes are proportional to study weight; the diamond represents the pooled HR.*

3.4 Subgroup Analyses

Subgroup analyses are summarized in Figure 4 and Table 2. The ACS/STEMI subgroup (k = 5) yielded a pooled HR of 2.18 (95% CI: 1.15–4.13; I^2 = 73.5%), whereas the non-ACS subgroup (k = 11) yielded a pooled HR of 1.30 (95% CI: 1.20–1.42; I^2 = 92.1%). Although the ACS point estimate was notably higher, the test for subgroup difference was non-significant (Q = 0.75, p = 0.386), likely due to the wide confidence interval in the ACS subgroup. The heart failure subgroup (k = 4) had a pooled HR of 1.45 (95% CI: 1.04-2.02; I 2 = 93.8%), and the CAD/interventional subgroup (k = 12) had a pooled HR of 1.31 (95% CI: 1.18-1.44; I2 = 83.7%). Both subgroups showed statistically significant relationships, which proved that NLR-mortality signal is similar in the key categories of CVDs.

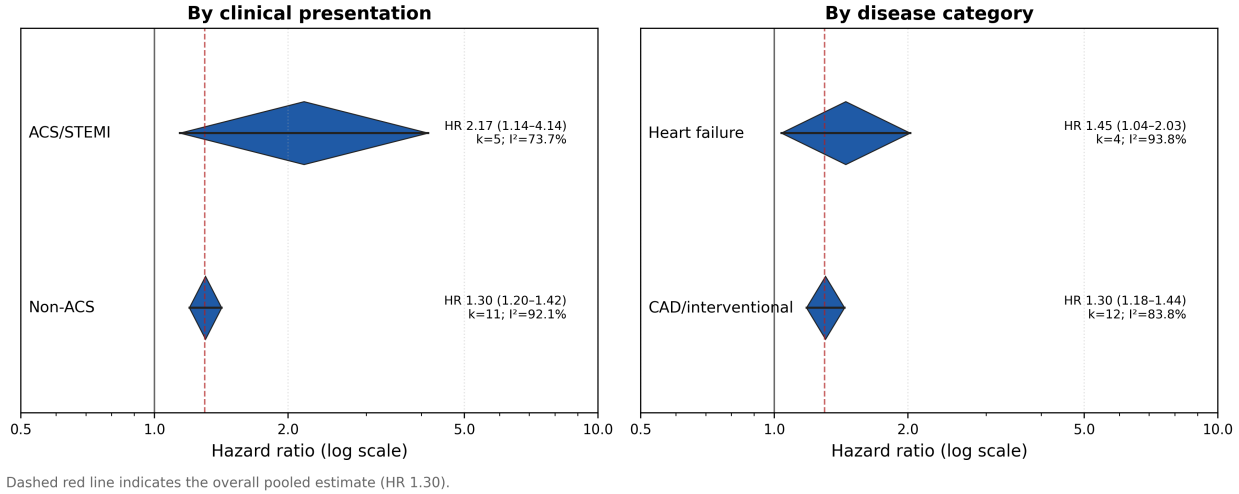


Figure 4. *Subgroup forest plot showing pooled hazard ratios stratified by cardiovascular condition type (ACS/STEMI vs. non-ACS) and disease category (heart failure vs. CAD/interventional).*

3.5 Sensitivity Analysis

The sensitivity analysis with leave-one-out showed that the pooled HR was also strong and significant irrespective of the study that was not included (Figure 5). The pooled HR was 1.23 (95% CI: 1.15-1.32, excluding Wasilewski, 2016) to 1.39 (95% CI: 1.25-1.54, excluding Rezig, 2025). There was no disproportional impact of none of the studies on the overall estimate because all the recalculated pooled HRs were in the confidence interval of the initial analysis. All the researches were excluded, and the two largest researches Rezig (2025, 13.5%) and Li (2024, 13.2%) each shifted the estimate by the opposite directions, which confirms the stability.

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

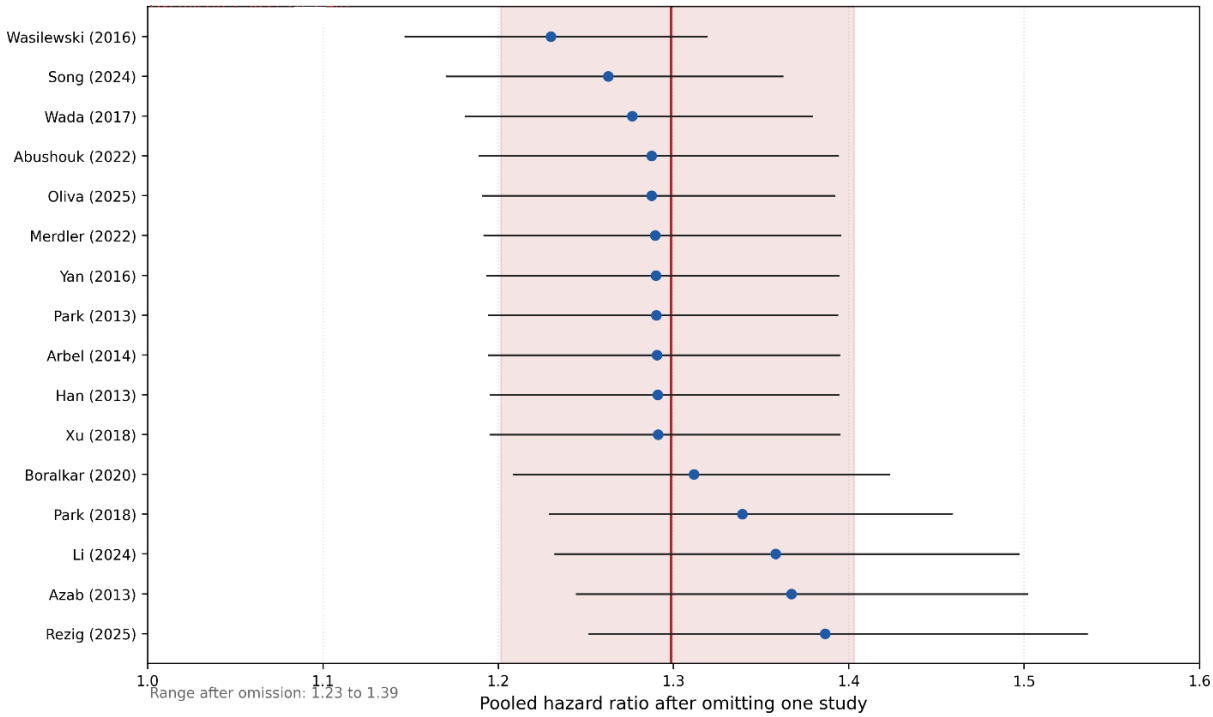


Figure 5. *Leave-one-out sensitivity analysis. Each row shows the pooled HR when the named study is omitted. The red vertical line and shaded band represent the overall pooled HR and its 95% CI.*

3.6 Publication Bias

The funnel plot displayed visual asymmetry, with smaller studies tending to report larger effects (Figure 6). Egger's regression test yielded an intercept of 2.86 ($p = 0.031$), and Begg's rank correlation test was also significant ($\tau = 0.795$, $p < 0.001$). These results suggest potential publication bias or small-study effects. However, funnel plot asymmetry in the presence of high heterogeneity ($I^2 = 89.4\%$) may also reflect genuine clinical diversity rather than selective publication alone (Sterne et al., 2011).

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

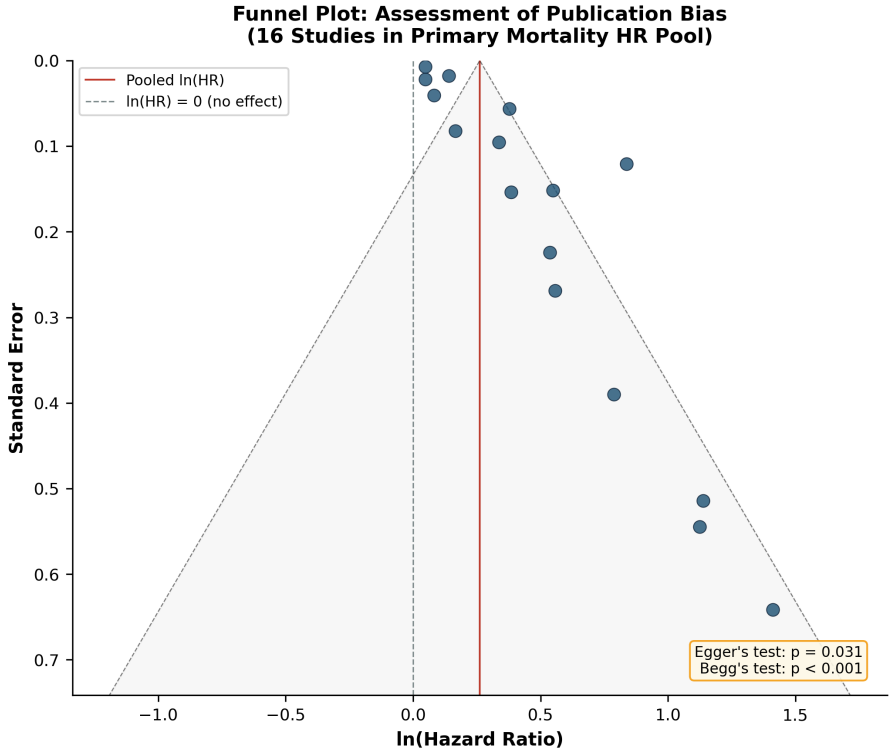


Figure 6. *Funnel plot of standard error against ln(HR) for 16 studies. The red vertical line represents the pooled ln(HR). Dashed lines indicate pseudo-95% confidence limits. Asymmetry was confirmed by Egger's ($p = 0.031$) and Begg's ($p < 0.001$) tests.*

A comprehensive summary of all primary and subgroup meta-analytic results, including pooled hazard ratios, heterogeneity statistics, and publication bias test outcomes for each stratum, is provided in Table 2.

Table 2 *Summary of Primary and Subgroup Meta-Analysis Results*

Analysis	k	Pooled HR (95% CI)	I^2 (%)	τ^2	Q (p-value)	Egger p	Begg p
Overall mortality	16	1.30 (1.20–1.40)	89.4	0.0116	142.1 (< 0.001)	0.031	< 0.001
ACS/STEMI	5	2.18 (1.15–4.13)	73.5	0.3491	15.1 (0.005)	0.374	0.083
Non-ACS	11	1.30 (1.20–1.42)	92.1	0.0116	126.3 (< 0.001)	0.134	0.005
Heart failure	4	1.45 (1.04–2.02)	93.8	0.0985	48.0 (< 0.001)	0.456	0.333
CAD/Interventional	12	1.31 (1.18–1.44)	83.7	0.0137	67.5 (< 0.001)	0.053	< 0.001

Note. k = number of studies; HR = hazard ratio; CI = confidence interval; I^2 = percentage of variability due to heterogeneity; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; CAD = coronary artery disease. Egger's and Begg's tests are shown where estimable and should be interpreted cautiously in subgroup strata with few studies.

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

4. Discussion

The present systematic review and meta-analysis, encompassing 20 studies, with 16 studies (30,874 participants) contributing to the primary mortality meta-analysis, demonstrates that elevated baseline neutrophil-to-lymphocyte ratio is a significant and independent predictor of mortality across heterogeneous CVD populations. The adjusted hazard ratio of 1.30 (95% CI: 1.20-1.40; $p < 0.001$) shows that high NLR was 30 percent more likely to represent the risk of overall mortality. This correlation was also strong in all the sensitivity analyses, and the leave-one-out method verified that there was no study that had a disproportionate effect on the summary estimate. These results support the idea that NLR is an easy to calculate ratio that can be derived based on any standard complete blood count and has a significant prognostic value in the cardiovascular risk assessment.

These findings are generally consistent with, but go beyond the findings of previous meta-analyses. Angkananard et al. (2018) combined 38 articles and indicated strong correlations between high NLR and CVD risk with odds ratios between 1.62 and 3.86, but they did not control the occurrence but mortality of the disease. Pruc et al. (2024) have shown that NLR is useful in acute coronary syndromes with a meta-analysis of 90 studies involving 45,990 patients, which confirmed the use of this tool in the specified setting, and Banahene et al. (2024) have reported a pooled odds ratio of 2.29 of all-cause mortality in myocardial infarction. The current work is distinguished by combining adjusted hazard ratios particularly to mortality in the entire range of CVD, such as heart failure, stable CAD, TAVI and CABG groups, and integrating a large number of large cohort studies that were published within the last 2 years (2022-2025) and were not available to the previous syntheses.

The subgroup analyses depicted interesting trends. The pooled HR of the ACS/STEMI subgroup was significantly larger than the non-ACS subgroup (2.18 vs. 1.30), which was however not found to be significantly different between the two subgroups. This trend can be explained by pathophysiological considerations: acute coronary events are defined by the high inflammatory response with neutrophil infiltration into ruptured plaques, reactive neutrophilia with catecholamine and cortisol releases, and the simultaneous lymphopenia caused by stress (Frangogiannis, 2014). The NLR signal is increased after acute inflammatory milieu, yielding larger effect sizes in STEMI populations. On the other hand, in chronic diseases like stable CAD and heart failure, the inflammatory condition is of lower grade and diffuse and leads to a less dramatic yet significant prognostic signal. The subgroup of heart failures ($k = 4$; HR = 1.45; 95% CI: 1.04-2.02) validates the previous results indicating the contribution of the continuous neurohormonal activation and immune deregulation to the progression of heart failure.

The biological plausibility of NLR-mortality relationship is established well. Neutrophils discharge reactive oxygen species, myeloperoxidase and neutrophil extracellular traps that facilitate oxidative stress, endothelial dysfunction, and destabilisation of plaque (Hansson, 2005). At the same time, lymphopenia especially with T-lymphocytes suggests that adaptive immunity is impaired and that immunity is exhausted, which is accompanied by undesirable remodelling and decreased recovery capacity (Acanfora et al., 2001). NLR combines these two opposite immune responses into one measure that reflects the balance between harmful inflammation and protective immune response, which may be the reason why it is a better prognostic measure than individual counts of cell types (Bhat et al., 2013).

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

On a clinical note, there are several implications of the findings. First, NLR is calculated using a routine haemogram that is universally ordered in the emergency department and cardiac ward, i.e. its prognostic data is already included in the existing workflows at no incremental cost (Forget et al., 2017). In contrast to high-sensitivity CRP or natriuretic peptides, NLR does not need a specific immunoassay, which will be especially useful in resource-limited environments where the CVD burden is concentrated (Roth et al., 2020). Second, the uniform prognostic indicator is that NLR might be used as an adjunct to existing risk stratification instruments, including the GRACE score or the MAGGIC score, and enhance the level of discriminative validity. Third, patient diagnosis of high NLR may inform clinical judgments on disease monitoring, timely follow-up, and anti-inflammatory or cardioprotective therapy escalation.

There are a number of constraints that need to be recognized. First, all these studies were observational, which excluded any possibility of causation and presented potential confounding factors that remain unadjusted by multivariate analysis. Second, there is a significant lack of homogeneity in definitions of NLR cutoff (between 2.65 and 6.5) being a significant obstacle to defining a clinically actionable value. Third, the pooled estimate is not very accurate because of the high statistical heterogeneity (I2 = 89.4%). Fourth, both Egger and Begg tests revealed publication bias, but the asymmetry of funnel plot should be carefully interpreted under the situation of high heterogeneity (Sterne et al., 2011). Fifth, the majority of the studies evaluated NLR at one time point, lacking the dynamic nature of inflammation. Sixth, only publications in English language were reviewed and the topography of the studies in East Asia, the United States and Israel restricts the generalisability to under-represented populations.

The next-generation studies should focus on defining the standardised NLR-thresholds using the data on individual patients by meta-analysis or employing big prospective groups with ROC-optimisation. Research studies on serial NLR patterns can enhance the accuracy of prognostic estimates. Composite biomarker panel: The use of NLR in combination with other inflammatory indicators deserves a study. The most powerful evidence of clinical utility would be randomised controlled trials comparing NLR-guided management strategies. Lastly, research in under-represented areas and other population groups is required to establish generalisability.

5. Conclusion

This meta-analysis and systematic review of 20 included studies and 16 of them yielded to the primary mortality meta-analysis showing that high baseline neutrophil-to-lymphocyte ratio has a significant and independent association with high mortality risk with a pooled adjusted hazard ratio of 1.30 (95% CI: 1.20-1.40; $p < 0.001$). This prognostic relationship can be found throughout acute coronary syndromes, heart failure, stable coronary artery disease, and structural heart disease that needs intervention. NLR is a biomarker that is universally accessible, free of charge, and can be calculated using routine haematology, and it has significant potential to be used as an adjunctive risk-stratification instrument in cardiovascular medicine. Future research must be aimed at standardisation of NLR cutoff values, serial NLR monitoring strategies, and NLR-guided therapeutic strategies by well-designed randomised controlled trials.

Gland Surg
VOL-11 NO 1 (2026)
ISSN:2227-684X | E-ISSN:2227-8575

References

Acanfora, D., Gheorghiade, M., Trojano, L., Furgi, G., Pasini, E., Iannuzzi, G. L., Bonow, R. O., & Rengo, F. (2001). Relative lymphocyte count: A prognostic indicator of mortality in elderly patients with congestive heart failure. American Heart Journal, 142(1), 167–173. https://doi.org/10.1067/mhj.2001.115792

Abushouk, A. I., Agrawal, A., Hariri, E., Dykun, I., Kansara, T., Saad, A., Abdelfattah, O., Badwan, O., Jaggi, C., Farwati, M., Harb, S. C., Puri, R., Reed, G. W., Krishnaswamy, A., Yun, J., & Kapadia, S. (2022). Association between haematological parameters and outcomes following transcatheter aortic valve implantation at mid-term follow-up. Open Heart, 9(2), e002108. https://doi.org/10.1136/openhrt-2022-002108

Angkananard, T., Anothaisintawee, T., McEvoy, M., Attia, J., & Thakkinstian, A. (2018). Neutrophil lymphocyte ratio and cardiovascular disease risk: A systematic review and meta-analysis. BioMed Research International, 2018, Article 2703518. https://doi.org/10.1155/2018/2703518

Arbel, Y., Shacham, Y., Ziv-Baran, T., Laufer-Perl, M., Finkelstein, A., Halkin, A., Revivo, M., Berliner, S., Herz, I., Keren, G., & Banai, S. (2014). Higher neutrophil/lymphocyte ratio is related to lower ejection fraction and higher long-term all-cause mortality in STEMI patients. Canadian Journal of Cardiology, 30(10), 1177–1182. https://doi.org/10.1016/j.cjca.2014.05.010

Azab, B., Shariff, M. A., Bachir, R., Nabagiez, J. P., & McGinn, J. T., Jr. (2013). Elevated preoperative neutrophil/lymphocyte ratio as a predictor of increased long-term survival in minimal invasive CABG compared to sternotomy. Journal of Cardiothoracic Surgery, 8, 193. https://doi.org/10.1186/1749-8090-8-193

Banahene, N. O., Owusu-Agyemang, N., & Mensah, K. A. (2024). Effect of elevated NLR on adverse outcomes in patients with myocardial infarction: A systematic review and meta-analysis. Cureus, 16(6), e62880. https://doi.org/10.7759/cureus.62880

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. Biometrics, 50(4), 1088–1101. https://doi.org/10.2307/2533446

Bhat, T., Teli, S., Rijal, J., Bhat, H., Raza, M., Khoury, G., Meghani, M., Akhtar, M., & Costantino, T. (2013). Neutrophil to lymphocyte ratio and cardiovascular diseases: A review. Expert Review of Cardiovascular Therapy, 11(1), 55–59. https://doi.org/10.1586/erc.12.159

Boralkar, K. A., Kobayashi, Y., Amsallem, M., Ataam, J. A., Moneghetti, K. J., Cauwenberghs, N., Horne, B. D., Knowlton, K. U., Maecker, H., Kuznetsova, T., Heidenreich, P. A., & Haddad, F. (2020). Value of neutrophil to lymphocyte ratio and its trajectory in patients hospitalized with acute heart failure and preserved ejection fraction. The American Journal of Cardiology, 125(2), 229–235. https://doi.org/10.1016/j.amjcard.2019.10.020

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. Controlled Clinical Trials, 7(3), 177–188. https://doi.org/10.1016/0197-2456(86)90046-2

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Forget, P., Khalifa, C., Defour, J.-P., Latinne, D., Van Pel, M.-C., & De Kock, M. (2017). What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Research Notes, 10(1), Article 12. https://doi.org/10.1186/s13104-016-2335-5

Frangogiannis, N. G. (2014). The inflammatory response in myocardial injury, repair, and remodelling. Nature Reviews Cardiology, 11(5), 255–265. https://doi.org/10.1038/nrcardio.2014.28

Han, Y.-C., Yang, T.-H., Kim, D.-I., et al. (2013). Neutrophil to lymphocyte ratio predicts long-term clinical outcomes in patients with STEMI undergoing primary PCI. Korean Circulation Journal, 43(2), 93–99. https://doi.org/10.4070/kcj.2013.43.2.93

Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. New England Journal of Medicine, 352(16), 1685–1695. https://doi.org/10.1056/NEJMra043430

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. BMJ, 327(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Li, X., Liu, M., & Wang, G. (2024). The neutrophil-lymphocyte ratio is associated with all-cause and cardiovascular mortality in cardiovascular patients. Scientific Reports, 14(1), 26692. https://doi.org/10.1038/s41598-024-76836-6

Libby, P., Buring, J. E., Badimon, L., et al. (2019). Atherosclerosis. Nature Reviews Disease Primers, 5(1), Article 56. https://doi.org/10.1038/s41572-019-0106-z

Martin, S. S., Aday, A. W., Almarzooq, Z. I., et al. (2024). 2024 heart disease and stroke statistics: A report from the American Heart Association. Circulation, 149(8), e347–e913. https://doi.org/10.1161/CIR.0000000000001209

Merdler, I., Frydman, S., Sirota, S., Halkin, A., Steinvil, A., Toledano, E., Konigstein, M., Litmanowicz, B., Bazan, S., Wenkert, A., Sadon, S., Banai, S., Finkelstein, A., & Arbel, Y. (2022). Neutrophil-to-lymphocyte ratio as a prognostic marker in transcatheter aortic valve implantation (TAVI) patients. Israel Medical Association Journal, 24(4), 229–234.

Oliva, A., Vogel, B., Sartori, S., Cao, D., Smith, K. F., Bay, B., Sweeny, J., Di Muro, F. M., Danias, M., Moreno, P., Gitto, M., Stefanini, G. G., Pocock, S. J., Bhatt, D. L., Dangas, G., Ridker, P. M., Kini, A., Sharma, S., & Mehran, R. (2025). Association of neutrophil-to-lymphocyte ratio with clinical outcomes after percutaneous coronary intervention. European Journal of Preventive Cardiology. Advance online publication. https://doi.org/10.1093/eurjpc/zwaf597

Onsrud, M., & Thorsby, E. (1981). Influence of in vivo hydrocortisone on some human blood lymphocyte subpopulations. Scandinavian Journal of Immunology, 13(6), 573–579. https://doi.org/10.1111/j.1365-3083.1981.tb00171.x

Page, M. J., McKenzie, J. E., Bossuyt, P. M., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71

Park, J.-J., Jang, H.-J., Oh, I.-Y., et al. (2013). Prognostic value of NLR in patients presenting with STEMI undergoing primary PCI. The American Journal of Cardiology, 111(5), 636–642. https://doi.org/10.1016/j.amjcard.2012.11.012

Park, J. S., Seo, K. W., Choi, B. J., et al. (2018). Importance of prognostic value of NLR in patients with STEMI. Medicine, 97(48), e13471. https://doi.org/10.1097/MD.0000000000013471

Pruc, M., Kubica, J., Banach, M., et al. (2024). Diagnostic and prognostic performance of NLR in acute coronary syndromes: A meta-analysis of 90 studies. Polish Heart Journal, 82(3), 276–284. https://doi.org/10.33963/v.phj.99554

Rezig, A. O. M., Morsy, M. I. M., Caiazzo, E., Iaconelli, A., Ialenti, A., Hunter, D., Cuthbert, J. J., Kazmi, S., Guzik, T. J., Bruzzese, D., Cleland, J. G. F., Clark, A. L., Maffia, P., & Pellicori,

P. (2025). Neutrophil-to-lymphocyte ratio: Link to congestion, inflammation, and mortality in outpatients with heart failure. ESC Heart Failure, 12(3), 1571–1582. https://doi.org/10.1002/ehf2.15240

Roth, G. A., Mensah, G. A., Johnson, C. O., et al. (2020). Global burden of cardiovascular diseases and risk factors, 1990–2019. Journal of the American College of Cardiology, 76(25), 2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010

Song, S., Chen, L., Yu, R., & Zhu, J. (2024). Neutrophil-to-lymphocyte ratio as a predictor of all-cause and cardiovascular mortality in coronary heart disease and hypertensive patients: A retrospective cohort study. Frontiers in Endocrinology, 15, 1442165. https://doi.org/10.3389/fendo.2024.1442165

Stang, A. (2010). Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology, 25(9), 603–605. https://doi.org/10.1007/s10654-010-9491-z

Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., et al. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ, 343, d4002. https://doi.org/10.1136/bmj.d4002

Tsao, C. W., Aday, A. W., Almarzooq, Z. I., et al. (2023). Heart disease and stroke statistics—2023 update. Circulation, 147(8), e93–e621. https://doi.org/10.1161/CIR.0000000000001123

Vakhshoori, M., Nemati, S., Sabouhi, S., Yavari, B., Shakarami, M., Bondariyan, N., Emami, S. A., & Shafie, D. (2023). Neutrophil to lymphocyte ratio (NLR) prognostic effects on heart failure; a systematic review and meta-analysis. BMC Cardiovascular Disorders, 23(1), 555. https://doi.org/10.1186/s12872-023-03572-6

Vos, T., Lim, S. S., Abbafati, C., et al. (2024). Global burden of cardiovascular diseases: Projections from 2025 to 2050. European Heart Journal, 45(40), 4268–4281. https://doi.org/10.1093/eurheartj/ehae475

Wada, H., Dohi, T., Miyauchi, K., et al. (2017). Pre-procedural NLR and long-term cardiac outcomes after PCI for stable coronary artery disease. Atherosclerosis, 265, 35–40. https://doi.org/10.1016/j.atherosclerosis.2017.08.007

Wasilewski, J., Pyka, Ł., Hawranek, M., et al. (2016). Prognostic value of NLR in predicting long-term mortality in patients with ischemic and nonischemic heart failure. Polish Archives of Internal Medicine, 126(3), 166–173. https://doi.org/10.20452/pamw.3316

Wells, G. A., Shea, B., O'Connell, D., et al. (2000). The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Xu, N., Tang, X. F., Yao, Y., et al. (2018). Predictive value of NLR in AMI patients with left main and/or three-vessel disease treated with PCI. Heart and Vessels, 33(9), 1031–1038. https://doi.org/10.1007/s00380-018-1155-8

Yan, W., Liu, C., Li, R., Mu, Y., Jia, Q., He, K., & Sun, G. (2016). Usefulness of NLR in predicting adverse events in elderly patients with chronic heart failure. International Heart Journal, 57(5), 615–621. https://doi.org/10.1536/ihj.16-049