Diagnostic and prognostic performance of the neutrophil--to-lymphocyte ratio in acute coronary syndromes: A meta-analysis of 90 studies including 45 990 patients

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Editorial
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ABSTRACT

Background: Cardiovascular disease is a leading cause of mortality worldwide and is likely to rise. Acute coronary syndrome (ACS) is consequent on inflammation. As a common and cost-effective inflammatory biomarker, the neutrophil-to-lymphocyte ratio (NLR) may be beneficial in cardiovascular medicine.

Aims: This meta-analysis examines the diagnostic and prognostic performance of the NLR in ACS.

Methods: We systematically searched PubMed Central, Medline, Scopus, EMBASE, Cochrane Central Register of Controlled Trials, and Clinicaltrial.gov databases. The search spanned from databases inception to January 10, 2024. The findings were aggregated into normalized mean differences with 95% confidence intervals.

Results: Ninety articles, with 45 990 participants, were included. Pooled analysis of the NLR varied and was higher in ST-segment elevation myocardial infarction (STEMI) vs. non-ST-segment elevation myocardial infarction patients (4.94 ± 3.24 vs. 3.24 ± 2.74), acute myocardial infarction vs. unstable angina (4.47 ± 3.43 vs. 2.97 ± 1.58), ACS vs. stable angina (SA) (5.45 ± 4.28 vs. 2.46 ± 2.15), and ACS vs. controls (5.31 ± 4.01 vs. 2.46 ± 2.45). The NLR also was associated with ACS mortality, with survivors having lower results (3.67 ± 2.72 vs. 5.56 ± 3.93). Subanalysis showed that differences in the NLR were observed in STEMI survivors (4.28 ± 3.24 vs. 6.79 ± 3.98). Of ACS patients with major cardiovascular events (MACE) vs. without MACE, the NLR was 6.29 ± 4.89 vs. 3.82 ± 4.12. In STEMI patients, the NLR differed between those with and without MACE (6.99 ± 5.27 vs. 4.99 ± 4.12).

Conclusions: The NLR is an effective tool for differentiating between different types of ACS. A high NLR is associated with ACS and increased MACE at 30 days. The NLR also appears to be a good predictor of MACE risk, at least in STEMI patients.

Key words: acute coronary syndrome, biomarkers, diagnostic techniques, neutrophil-to-lymphocyte ratio, prognosis

WHAT'S NEW?

Research published so far indicates that the neutrophil-to-lymphocyte ratio (NLR) may be an effective and cost-effective predictor of outcomes in conditions where inflammation has a crucial role. This meta-analysis aimed to determine the diagnostic and prognostic performance of the NLR in acute coronary syndromes (ACS). Our study showed that the NLR is an effective tool for differentiating between different types of ACS. The NLR is higher in acute myocardial infarction (AMI) vs. unstable angina (UA), ACS vs. stable angina (SA), ACS vs. controls, and between ACS survivors vs. ACS deceased. A high NLR is associated with ACS and increased major cardiovascular events (MACE) at 30 days. The NLR also appears to be a good predictor of MACE risk. Considering the above results, as well as the wide availability and cost-effectiveness of the NLR index, our meta-analysis has suggested the potential positive predictive and diagnostic properties of the NLR in ACS patients.

INTRODUCTION

The neutrophil-to-lymphocyte ratio (NLR) is a cost-effective potential inflammatory marker used to assess the prognosis in many diseases, such as COVID-19 [1], diabetes [2], head and neck cancer [3], multiple organ dysfunction syndrome [4], etc. The NLR is also recommended as a potentially useful indicator for assessing the response to neoadjuvant chemotherapy in triple-negative breast cancer [5]. The biomarker may also have applications in cardiovascular disease diagnosis and prediction. In a recently published retrospective observational study, Ha et al. showed that an NLR >3.4 is associated with worse one-year survival after percutaneous coronary intervention (91.4% vs. 95.4%, log-rank P <0.004) [6]. It is also recommended to use the NLR, rather than other hematological parameters, such as white blood cell count, for 30-day mortality risk stratification in elderly patients after acute coronary syndrome (ACS) [7]. Finally, in patients with heart failure, an increased NLR was associated with increased all-cause mortality during a median follow-up of 66 months [8].

Many mechanisms related to the functioning of the immune system have been well described in the development of atherosclerosis and atherothrombosis [9, 10]. Macrophages and T lymphocytes are involved in the process of formation and development of atherosclerotic plaque. Additionally, pro-inflammatory cytokines, e.g., interleukins (especially IL-1, IL-6, IL-12, and IL-18), accelerate the development of atherosclerotic lesions. Other pro-inflammatory proteins, including tumor necrosis factor-α (TNF-alpha) or macrophage colony-stimulating factor (M-CSF), have similar properties [11]. In patients with diagnosed heart failure (both with preserved and reduced ejection fraction), increased concentrations of inflammatory cytokines are observed. Elevated cytokine levels also correlate with increased risk of decompensation and negative outcomes [12, 13].

Anti-cytokine drugs may be a promising strategy in the development of cardiovascular pharmacotherapy, especially when included as part of a personalized approach [14, 15]. The introduction of these types of drugs is an additional argument in support of the pro-inflammatory etiology of cardiovascular diseases and to reduce inflammation-related residual CVD risk. Unfortunately, conducting a clinical trial with unambiguous results in this population has been a challenge. Clinical trials to date, in most cases, have been terminated prematurely due to lack of direct benefit to participants or lack of impact on endpoints such as major adverse cardiovascular events (MACE) [16].

Overall, given the potential usefulness of the NLR in assessing prognosis in patients after ACS, this meta-analysis aims to determine NLR utility as a prognostic and diagnostic biomarker.

MATERIAL AND METHODS

The present study employed a systematic review and meta-analysis approach, adhering to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol (Supplementary material, *Table S1*) [17]. There was no patient or public involvement in this study. A full study protocol is available for this review and can be accessed on PROSPERO, an international register of systematic reviews (Record number: CRD42023468529). The data underlying this article will be shared upon reasonable request.

Data sources and searches

Two authors (MP and MT) independently conducted a comprehensive systematic review of the literature, encompassing all publications cited on the PubMed, Medline, Scopus, Embase, the Cochrane Central Register of Controlled Trials, and Clinicaltrial.gov databases, from databases inception to January 10, 2024. The search phrase employed for this purpose was as follows: "neutrophil-to-lymphocyte ratio" OR "neutrophil-to-lymphocyte ratio" OR "neutrophil/lymphocyte ratio" OR "neutrophil-lymphocyte ratio" OR "neutrophil-lymphocyte ratio" OR "Neutrophils to lymphocytes ratio" OR "Neutrophils-to-lymphocytes ratio" OR "neutrophils lymphocytes ratio" OR "neutrophils/lymphocytes ratio" OR "NLR" AND "acute coronary syndrome" OR "ACS" or "ST Segment Elevation Myocardial Infarction" OR "ST Elevated Myocardial Infarction" OR "ST-elevation MI" OR "STEMI" OR "non-ST elevation myocardial infraction" OR "NSTEMI" OR "myocardial Infarction" OR "unstable angina". Moreover, we searched the bibliographies of the target studies for additional references. If multiple publications from partially or completely overlapping cohorts were found, only the most recent publication with the larger sample size was included.

Inclusion and exclusion criteria

The inclusion criteria were randomized and non-randomized trials, as well as studies that reported NLR values in adult participants (aged ≥18 years) with different ACS forms. Reviews, meta-analyses, editorials, conference papers, case series with <10 participants, studies of pediatric populations, and non-English language studies were excluded.

Data extraction and quality assessment

Data was extracted by three independent reviewers (MP, MT, and LS) into a structured pro forma in an Excel sheet. Any discrepancies were resolved by consensus following a discussion with all the reviewers. Data on study characteristics (author, country, region, study design, sample sizes), patient demographics (baseline characteristics, major cardiovascular event [MACE] [Supplementary material, *Table S2*]), and NLR values were extracted. We extracted the mean and standard deviation or median and interquartile range for continuous variables and the number of patients belonging to each category for dichotomous variables.

Observational studies were appraised using the modified Newcastle-Ottawa Scale [18]. In each study, the domains that were assessed included the representation of patients by the subjects, selection of comparative groups, ascertainment of exposure and outcomes, and duration and comprehensiveness of follow-up, if applicable. The quality assessment of articles ranged from low (0–4), moderate (5–6), to high scores (7–9), representing three different levels of study quality.

Statistical analysis

The statistical analysis was performed in accordance with the recommendations of the Cochrane Collaboration and the standards for reporting the quality of meta-analyses [19]. Statistical analyses were performed using Review Manager software (version 5.4, Nordic Cochrane Centre, Cochrane Collaboration, Denmark) and Stata (version 14, StataCorp, College Station, TX, US). Outcomes were reported as the pooled odds ratio (OR), standard mean difference (SMD), and the corresponding 95% confidence intervals (95% CI). When the continuous outcome was reported as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. [20]. Random-effects models were used for all analyses. Heterogeneity between studies was assessed quantitatively using the I2 statistic. I2 values of <50%, between 50% and 75%, and >75% were taken to represent low, moderate, and high degrees of heterogeneity, respectively. All tests were 2-sided and *P*-values <0.05 were considered statistically significant. We used Egger's test and funnel plots to check for potential bias and performed funnel plot tests for asymmetry to assess potential publication bias if there were more than ten trials in a single meta-analysis. Finally, in sensitivity analyses, leave-one-out analysis was performed.

RESULTS

Characteristics and quality assessments of included studies

The flow diagram of the study selection process is shown in Figure 1. In the primary search, a total of 1148 references were initially included. Of these, 443 articles were eliminated due to duplication, while additional 502 articles were omitted based on an assessment of their titles and abstracts. Following a comprehensive examination of 203 research studies, 113 were excluded due to their publication category (44 case reports/series, 18 abstracts, 17 letters/editorials, and 34 review articles). Finally, 90 articles were included in this meta-analysis [S1–S90].

Essential characteristics of the included studies are outlined in Supplementary material, *Table S3*. Overall, the 86 studies included in this meta-analysis provided a combined cohort of 45 990 patients. The sample size of studies varied from 59 to 6560 patients.

Of all analyzed studies, 90 were cohort studies, 34 were prospective studies, 42 were retrospective studies, and 14 were cross-sectional studies. The worldwide distribution of studies is presented in Figure 2. All studies had high quality based on Newcastle Ottawa Scale (Supplementary material, *Table S3*).

Meta-analysis

Pooled analysis of the NLR varied and was higher in ST-segment elevation myocardial infarction (STEMI) vs. non-ST elevation myocardial infarction (NSTEMI) patients; 4.94 ± 3.24 vs. 3.24 ± 2.74 (SMD = 0.61; 95% CI, 0.39–0.83; *P* <0.001; Figure 3). It also showed a difference between acute myocardial infarction (AMI) vs. unstable angina (UA) (4.47 ± 3.43 vs. 2.97 ± 1.58; SMD = 1.19; 95% CI, 0.80–1.59; Figure 4), ACS vs. stable angina (SA) (5.45 ± 4.28 vs. 2.46 ± 2.15; SMD = 1.67; 95% CI, 1.29–2.04; *P* <0.001; Figure 5), and ACS vs. controls (SMD = 5.31 ± 4.01 vs. 2.46 ± 2.45; SMD = 0.93; 95% CI, 0.70–1.16; *P* <0.001; Figure 6).

The NLR also was associated with mortality in ACS, with survivors having lower results; 3.67 ± 2.72 vs. 5.56 ± 3.93 (SMD = –2.55; 95% CI, –3.90 to –1.19; *P* <0.001). Subanalysis showed that differences in the NLR were observed in STEMI survivors (4.28 ± 3.24 vs. 6.79 ± 3.98; SMD = –1.94; 95% CI, –2.82 to –1.07; *P* <0.001) but not observed in those with NSTEMI (SMD = –0.63; 95% CI, –2.54 to 1.28; *P* = 0.52; Figure 7). No bias was found in the results of the studies in funnel plots of mortality risk.

Twenty-three studies also reported the relationship between NLR levels and MACE occurrence. Of ACS patients with MACE, the NLR was 6.29 ± 4.89, compared to only 3.82 ± 4.12 for those without MACE (SMD = 2.80; 95% CI, 1.28 to 4.32; *P* <0.001). In the subgroup of patients with STEMI, the NLR was different between patients with and without MACE; 6.99 ± 5.27 vs. 4.99 ± 4.12, respectively (SMD = 1.85; 95% CI, 0.90 to 2.80; *P* <0.001). In NSTEMI patients, the NLR ratio for those with and without MACE

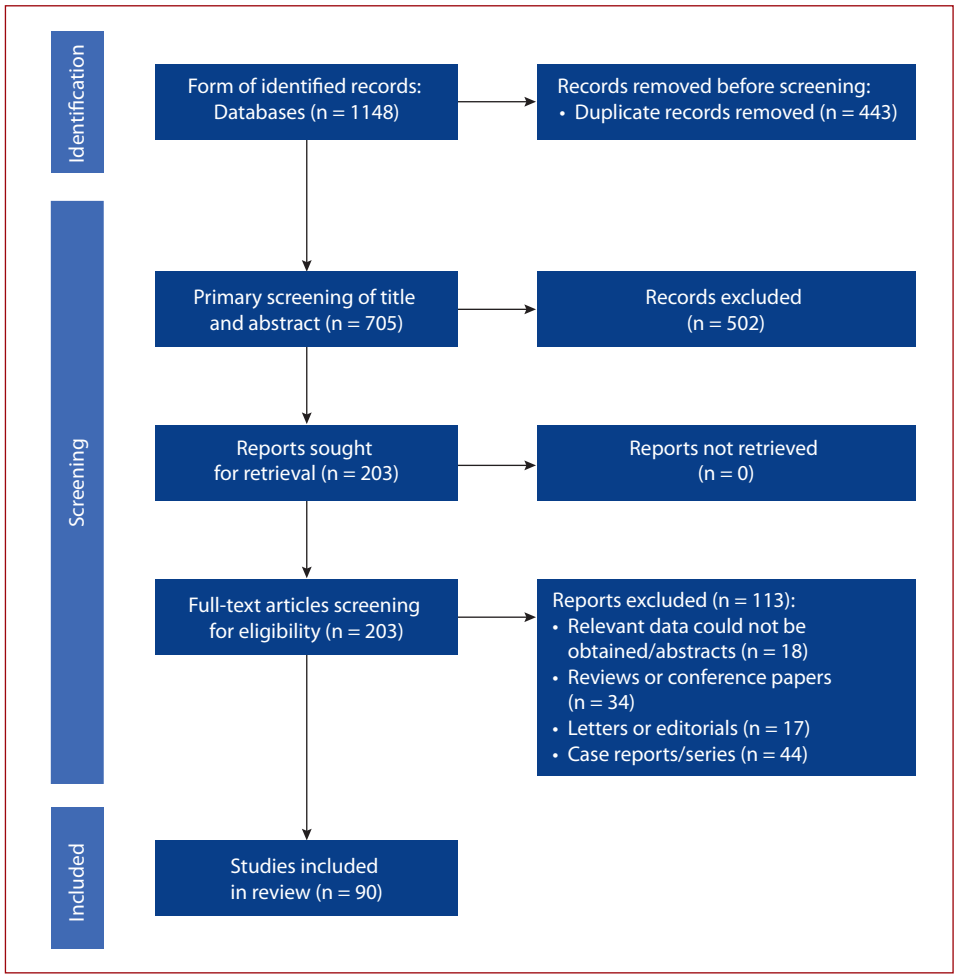

Figure 1. Flow diagram of study selection

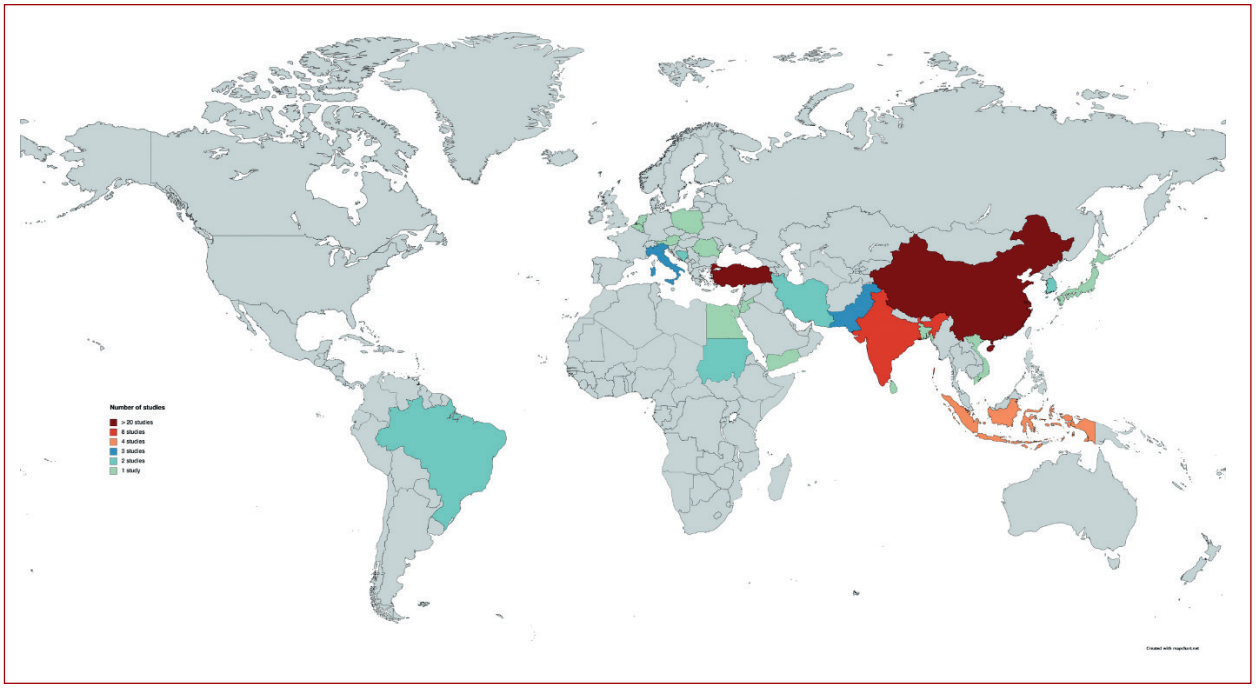

Figure 2. Worldwide distribution of studies included in the meta-analysis

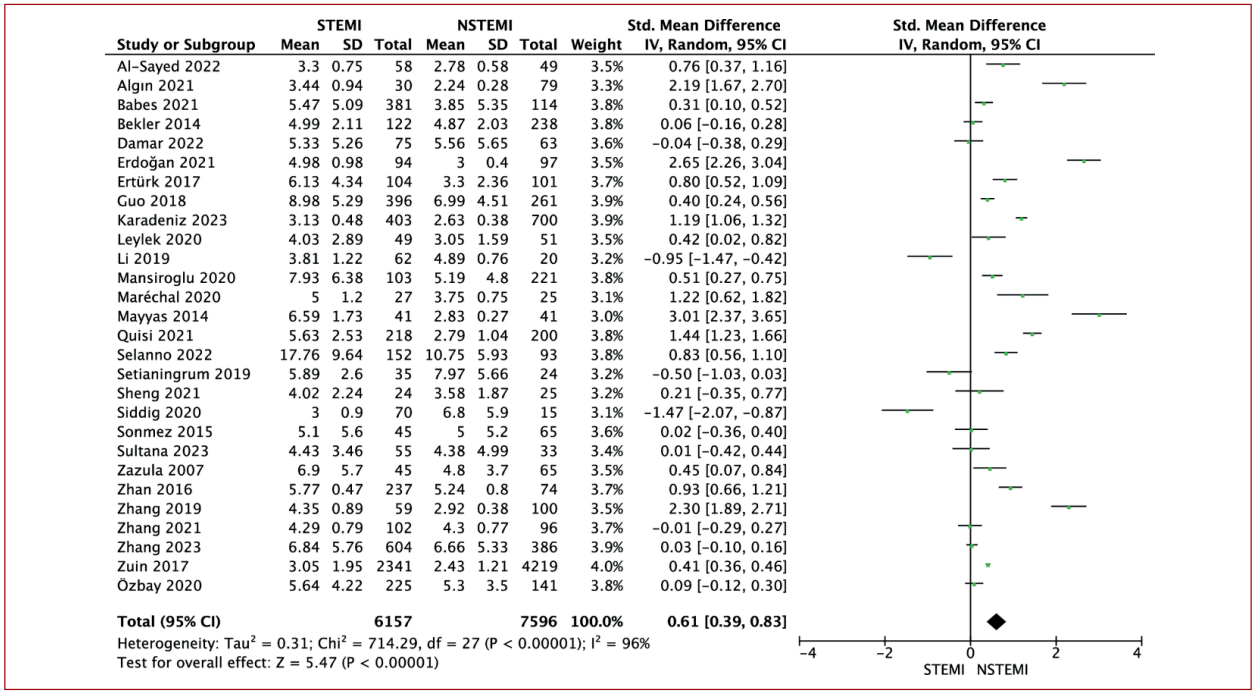

Figure 3. Forest plot of the neutrophil-to-lymphocyte ratio in STEMI and NSTEMI patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line represents a 95% confidence interval. The diamonds represent pooled results

Abbreviations: CI, confidence interval; NSTEMI, non-ST-segment elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction

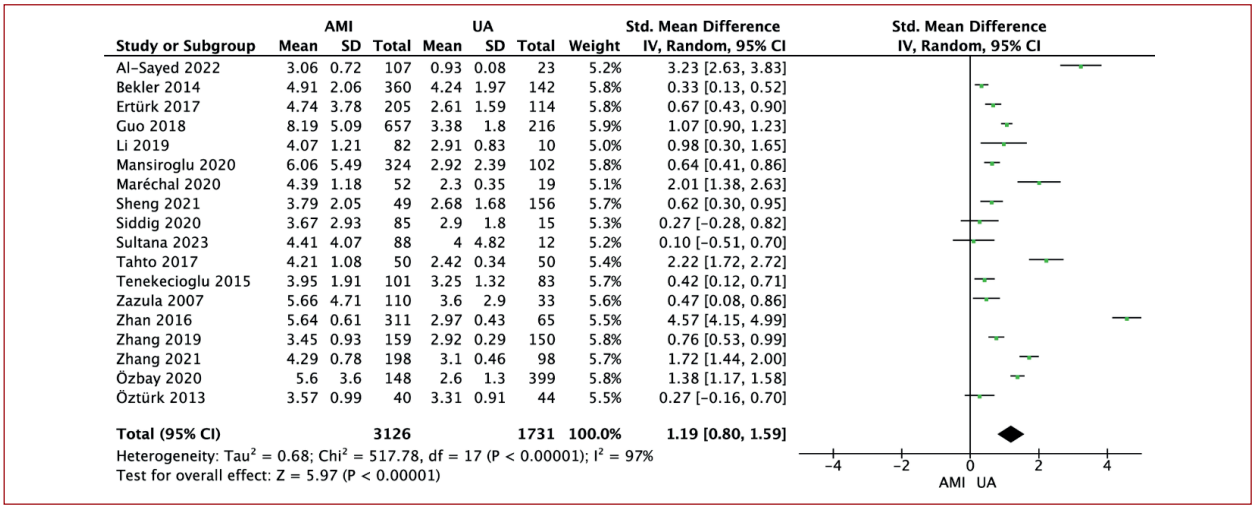

Figure 4. Forest plot of the neutrophil-to-lymphocyte ratio in acute myocardial infarction (AMI) vs. unstable angina (UA) patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line represents a 95% confidence interval. The diamonds represent pooled results

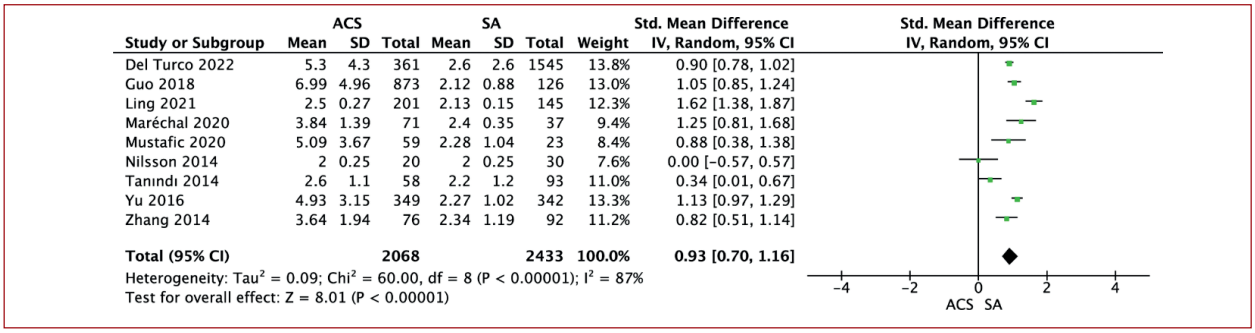

Figure 5. Forest plot of the neutrophil-to-lymphocyte ratio in acute myocardial infarction (ACS) vs. stable angina (SA) patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line represents a 95% confidence interval. The diamonds represent pooled results

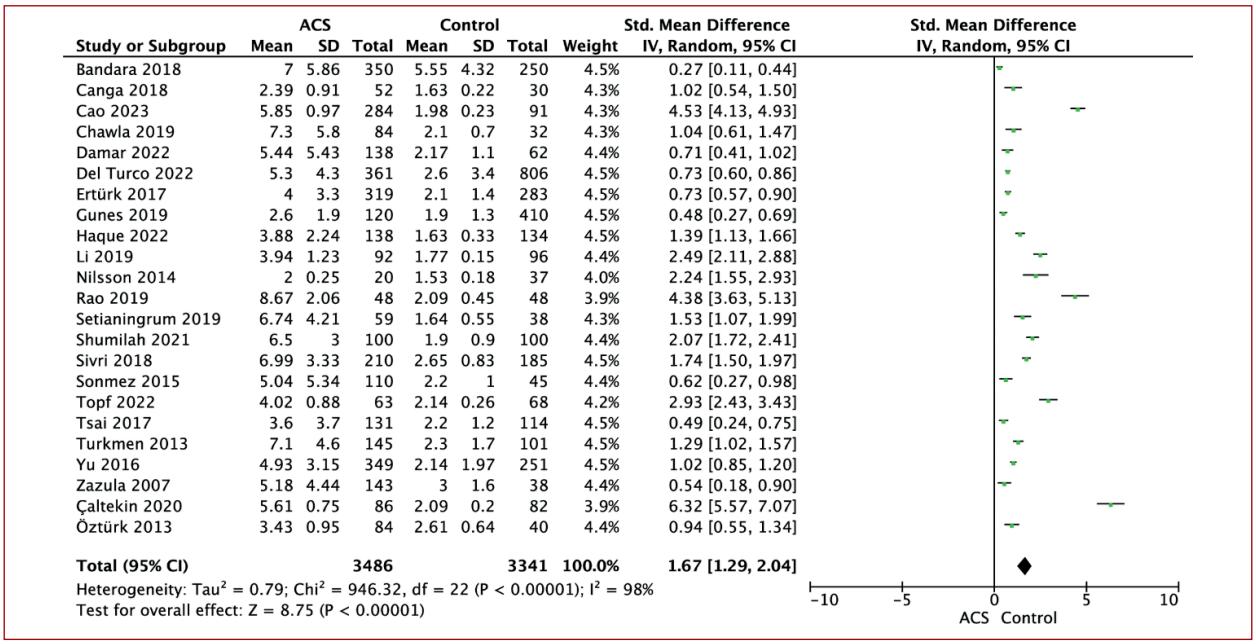

Figure 6. Forest plot of the neutrophil-to-lymphocyte ratio in acute coronary syndrome (ACS) vs. control patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line represents a 95% confidence interval. The diamonds represent pooled results

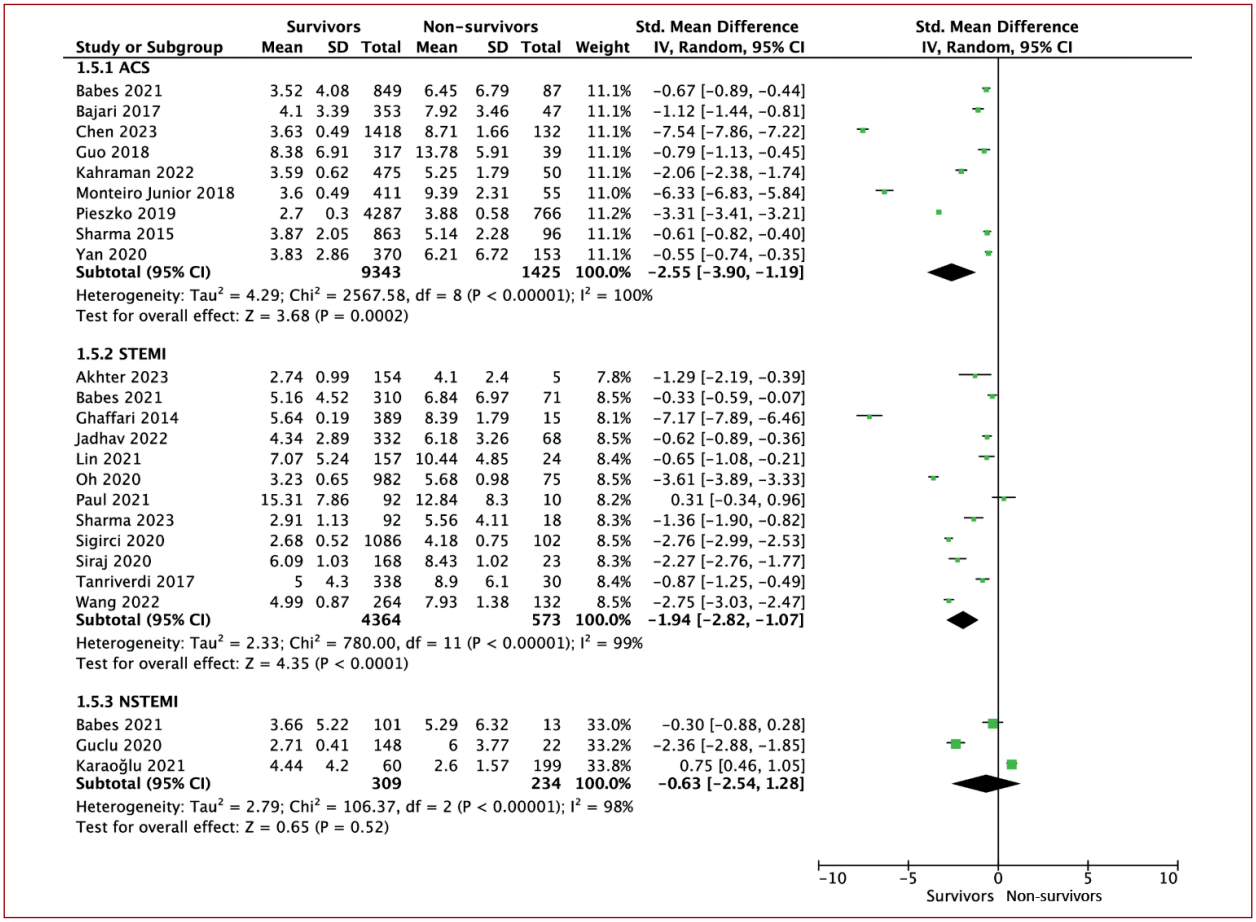

Figure 7. Forest plot of the neutrophil-to-lymphocyte ratio in survivors vs. non-survivors in ACS, STEMI, and NSTEMI patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line represents a 95% confidence interval. The diamonds represent pooled results

Abbreviations: see Figure 3

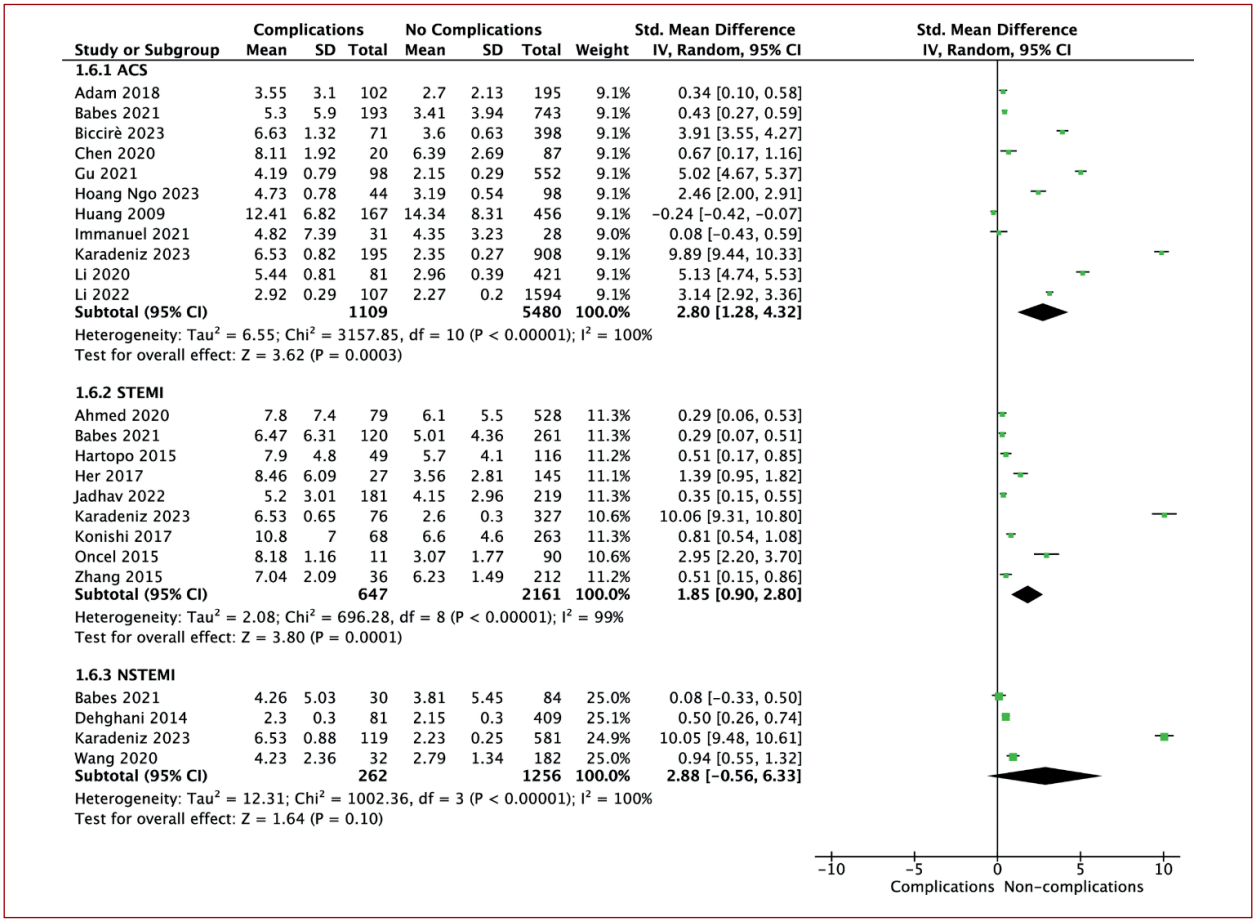

Figure 8. Forest plot of the neutrophil-to-lymphocyte ratio for major cardiovascular events (MACE) and non-MACE in ACS, STEMI, and NSTEMI patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line represents a 95% confidence interval. The diamonds represent pooled results

Abbreviations: see Figure 3

was 4.86 ± 2.69 vs. 2.39 ± 1.59, respectively (SMD = 2.88; 95% CI, 2.88; 95% CI, –0.56 to 6.33; *P* = 0.10; Figure 8). No bias was found in the results of the studies on funnel plots of MACE risk.

DISCUSSION

Our meta-analysis showed that the NLR was higher in AMI vs. UA, ACS vs. SA, ACS vs. controls, and ACS survivors vs. ACS deceased. The NLR was also higher for patients suffering a MACE compared to those without a MACE-based endpoint. Considering the above results as well as the wide availability and cost-effectiveness of the NLR index, our meta-analysis has suggested the potential good predictive and diagnostic properties of the NLR in ACS patients. Furthermore, our meta-analysis showed that the NLR may be a good predictor of MACE risk, at least in STEMI patients. The latter may be particularly useful in routine clinical settings.

Other meta-analyses conducted to date have provided results similar to our findings. In a 2018 meta-analysis that included 14 studies and 10 245 post-STEMI patients after percutaneous coronary intervention, the authors found NLR differences in numerous parameters (mortality, MACE, stent thrombosis, long-term mortality, etc.). Furthermore, compared to other meta-analyses, as well as ours, the population included in the just-mentioned analysis was more homogeneous [21]. Moreover, in a meta-analysis by Dong et al, the authors reported that an increased NLR before ACS treatment was associated with poor long-term prognosis and higher in-hospital mortality compared to patients with lower NLR values. Importantly, their work proposed an NLR cut-off of 5.0 as a risk estimation after ACS [22]. Taking into account the results of our meta-analysis and the previously presented meta-analyses [23], a 5.0 risk stratification cut-off point seems reasonable.

Other meta-analyses have indirectly suggested NLR value in predicting cardiovascular risk, thus supporting its use in cardiovascular medicine. For example, the NLR may predict cardiovascular or all-cause mortality in patients with chronic kidney disease as shown by a 2021 meta-analysis in which a higher NLR rate was associated with increased risk of cardiovascular mortality (HR 1.45; 95% CI, 1.18–1.79; *P* <0.001) [24]. The same conclusion was reported in another meta-analysis [25]. The NLR may also be a useful biomarker in differentiating patients requiring in-depth diagnostics for coronary artery abnormalities and in patients with Kawasaki disease [26]. In the context

of acute pulmonary embolism, the NLR turned out to be a good predictor of short-term (in-hospital and 30-day) mortality and long-term mortality [27]. Additionally, when assessing the predictive properties of the NLR, it should be taken into account that recognized cardiovascular risk factors are also associated with an increased NLR value. Thus, poor glycemic control, as indicated by elevated HbA1c, leads to increased NLR values [28]. A similarly elevated NLR is observed in patients with hypertension [29].

Compared to other biomarkers of the systematic inflammatory response, the NLR is easier to obtain; a basic blood count is sufficient [30, 31]. Moreover, compared to other leukocyte subtypes, it is a more stable biomarker [32]. Thus, the NLR is an effective and cost-effective alternative to other biomarkers. As with most biomarkers, studies are needed to demonstrate the true prognostic value of the cut-off.

Considering the above, the predictive properties of the NLR in the context of MACE risk seem to be the most clinically useful. Identifying patients at the highest risk of developing MACE within a predictable and well-defined time frame remains a significant clinical challenge. Identification of patients at risk of MACE may lead to more optimized care for this group of patients. However, our meta-analysis showed some limitations in this context, primarily the lack of statistical significance for patients with NSTEMI (NLR for those with and without MACE was 4.86 ± 2.69 vs. 2.39 ± 1.59, respectively; SMD = 2.88; 95% CI, 2.88; 95% CI, –0.56 to 6.33; $P = 0.10$). Therefore, the clinical usefulness of the NLR would be limited to STEMI patients, for whom statistical significance was obtained. This difference seems justified on the basis of basic science. Since in the course of STEMI, myocardial damage and microvascular obstruction are usually more prominent compared to NSTEMI, activation of the immune system is more expected, leading to an increased NLR value [33, 34]. Further research, in particular, to confirm the usefulness of the predictive properties of the NLR in the context of MACE, is needed. Research should also define the time interval in which NLR-based prediction is most accurate as well as indicate for which outcomes (defined variously in studies as components of the composite MACE endpoint) the predictive properties of the NLR may be most useful.

Limitations of the study

Some limitations of the current meta-analysis should be highlighted. As the summation of the totality of the data was derived from retrospective analyses, prospective validation would still be of value to determine the impact of interventions applied to patients identified by the NLR as high-risk. Finally, although others have evaluated a broader spectrum of cardiovascular diseases, our analysis was limited to only adult patients with acute coronary syndromes; therefore, our conclusions must be restricted to this cohort. Ultimately, despite these limitations, the large sample size analyzed in this study suggests that the NLR is an excellent predictor of outcomes in selected patients with specific cardiovascular pathology.

CONCLUSIONS

Overall, we evaluated 86 studies, involving 44 486 patients and concluded that NLR is an effective tool for differentiating between different types of ACS. A high NLR is associated with ACS and increased MACE at 30 days. The NLR also appears to be a good predictor of MACE risk, at least in STEMI patients. Further research should aim to confirm in which patient population the NLR has the best predictive properties, what time frame is acceptable, and for which MACE the NLR shows predictive properties.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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