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Neutrophil to Lymphocyte Ratio as a Prognostic Marker for Cardiovascular Outcomes in Patients with ST-Segment Elevation Myocardial Infarction after Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis

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Neutrophil to lymphocyte ratio as a prognostic marker for cardiovascular outcomes in patients with ST-segment elevation myocardial infarction after percutaneous coronary intervention

A systematic review and meta-analysis

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Abstract

Background: Neutrophil to lymphocyte ratio (NLR) has been considered a prognostic biomarker of mortality and other major cardiac events. This study investigates NLR's efficacy in predicting in-hospital and long-term outcomes in patients with ST-segment elevated myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).

Methods: Electronic databases (PUBMED, Cochrane CENTRAL, ERIC, Embase, Ovid, and Google Scholar) were searched till June 2022 to identify studies having STEMI patients who underwent PCI. Risk ratios and mean differences (MDs), along with their corresponding 95% confidence intervals (Cis) and standard deviations (SDs), were pooled using a random-effect model. This meta-analysis has been registered on Prospero (ID: CRD42022344072).

Results: A total of 35 studies with 28,756 patients were included. Pooled estimates revealed an increased incidence of primary outcomes; in-hospital all-cause mortality (RR = 3.52; 95% CI = 2.93–4.24), long-term all-cause mortality (HR = 1.07; 95% CI = 1.00–1.14), (RR = 3.32; 95% CI = 2.57–4.30); in-hospital cardiovascular mortality (RR = 2.66; 95% CI = 2.04–3.48), long-term cardiovascular mortality (RR = 6.67; 95% CI = 4.06–10.95); in-hospital major adverse cardiovascular events (MACE) (RR = 1.31; 95% CI = 1.17–1.46), long-term MACE (RR = 2.92; 95% CI = 2.16–3.94); length of hospital stay (WMD = 0.60 days; 95% CI = 0.40–0.79) in patients with high NLR compared to those with a low NLR.

Conclusion: NLR might be a valuable tool for prognostication (in-hospital) and stratification of patients with STEMI who underwent PCI.

Abbreviations: AF = atrial fibrillation, AHF = advanced heart failure, CVD = coronary vascular disease, HRs = hazard ratios, MACE = major adverse cardiovascular events, MI = myocardial infarction, NLR = neutrophil to lymphocyte ratio, PCI = percutaneous coronary intervention, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, STEMI = ST-segment elevated myocardial infarction, TVR = target vessel revascularization, WMD = weighted mean difference.

Keywords: Cardiovascular Disease, Mortality, Neutrophil to Lymphocyte Ratio, PCI, STEMI

1. Introduction

Coronary vascular disease (CVD) has been reported as one of the most common causes of mortality worldwide.[1] According to the World Health Organization (WHO), an estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke.[2] Among CVD, ST-elevation myocardial infarction (STEMI) carries the highest risk of morbidity and mortality.[3]

STEMI results from a series of events centered on developing intra-coronary thrombus, disrupting atherosclerotic plaque, and epicardial adipose tissue-related local

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This is a systematic review and meta-analysis then it doesn't need ethical approval

Supplemental Digital Content is available for this article.

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inflammation. While, percutaneous coronary intervention (PCI) has proven benefits in revascularizing the culprit lesions, the role of inflammation has been debated. A few studies have discussed the role of anti-inflammatory medications and their potential benefit in patients with STEMI, but little is known about the role of inflammatory markers in predicting secondary outcomes.[4]

Recent, non-cardiac and oncological studies have shown the role of neutrophils to lymphocytes ratio (NLR) in predicting worse clinical outcomes in patients with COVID-19.[5] Given the plausible overlap of mechanisms in patients with STEMI, the current systematic review and meta-analysis aim to determine the use of NLR to predict the in-hospital and long-term prognosis in patients with STEMI after PCI treatment.

2. Methods

This meta-analysis followed the guidelines set by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). PRISMA checklist is provided in Table S1 of File S1, Supplemental Digital Content, http://links.lww.com/MD/N22. This systematic review and meta-analysis has been registered with PROSPERO (ID: CRD42022344072). Our paper required no ethical approval since it is a systematic review and meta-analysis of already published paper.

2.1. Data sources and search strategy

Six databases, PUBMED, Cochrane CENTRAL, ERIC, Embase, Ovid, and Google Scholar were searched for studies showing in-hospital or long-term prognosis of NLR in STEMI patients who underwent PCI. No language and time restrictions were placed on the search, and the databases were searched until June 2022. Figure 1 shows the PubMed relevance keywords map produced via VOSviewer.[6]

We used the medical subject headings (MESH) "Neutrophils to lymphocytes ratio," "NLR ratio," "ST segment elevated myocardial infarction," "STEMI," "Percutaneous coronary intervention," "PPCI," "PCI." The search string was modified for each database, and the detailed search strategy for each database has been provided in Table S2 of File S2, Supplemental Digital Content, http://links.lww.com/MD/N23. We searched for gray and white; different data sources like list of the retrieved articles, editorials, conference proceedings for indexed abstracts, meta-analyses and systematic reviews, were also manually searched to identify any relevant studies that may have been missed during the search.

2.2. Study selection

Articles were included based on the following eligibility criteria: Experimental group consisted of STEMI patients receiving primary PCI; the study designs were prospective and retrospective cohorts; risk ratios between NLR levels and cardiovascular events occurring during hospital or follow-up were compared and studied; studies that showed the number of cardiovascular events occurring in a population instead of the risk ratios; studies that divided the patients on the basis of NLR tertiles or cutoffs.

All articles retrieved as a result of the systematic search were then exported to EndNote Reference Library Software (X7 v17.0.0.7072), where the duplicates were sought and removed. Only those articles which met the pre-specified eligibility criteria were selected. Two independent reviewers (HUH and KN) assessed the relevant articles, first based on title and abstract and then the full text was reviewed to confirm the relevance. Any discrepancies were resolved via group discussion till consensus. The concordance rate between reviewers was 96%. All studies having irrelevant population or studies consisting of non-PCI and Coronary Artery Bypass Grafting patients as experimental group, case reports, meta-analyses, letters, registries, or studies that were not released as published reports were excluded from the meta-analysis.

2.3. Outcomes

Our primary outcomes included in-hospital and long-term all-cause mortality, cardiovascular mortality, major adverse cardiovascular events (MACE), and length of stay in hospital. Secondary outcomes included non-fatal myocardial infarction (MI), in-stent thrombosis, and stroke as both in-hospital and long-term outcomes, while no-reflow, atrial fibrillation (AF), arrhythmia (all types), ventricular arrhythmia, advanced heart failure (AHF), reinfarction, target vessel revascularization (TVR), and angina only as in-hospital outcomes. Any revascularization was another long-term secondary outcome.

2.4. Data extraction and quality assessment

Study characteristics, baseline demographics, and outcome data were extracted on the basis of in-hospital and long-term mortality into a Microsoft Excel sheet. Quality assessment for the included observational studies was done using the New-castle Ottawa scale, based on the selection, comparability, and outcome/exposure criterion of included studies. A study can have a maximum score of 9 for cross-sectional studies and a score of 10 for case-control studies. Data extraction and quality assessment were conducted independently by 2 independent reviewers (H.U.H. and M.Z.) and conflicts were resolved by group discussion till consensus. Funnel plots, rank correlation, and Egger's regression test were used to assess the publication bias of 3 outcomes, including in-hospital all-cause mortality, in-hospital MACE, and long-term all-cause mortality. The symmetry of the funnel plot in the figures exhibits relevance of studies and rules out any small study bias or publication bias.

2.5. Statistical analysis

RevMan (version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The results of the report expressed as means ± SD were pooled using the random-effects model, and the results expressed as risk ratio (RR) with 95% confidence intervals were pooled using the number of events that occurred in experimental and control groups or inverse variance weighted random-effects model when events were not given. Forest plots were made to analyze the pooled results visually. Heterogeneity was evaluated using the I^2 statistics, with 25% to 50% of I^2 values being considered mild heterogeneity and 50% to 75% being considered moderate heterogeneity.[7] A value greater than 75% is considered severe heterogeneity. Sensitivity analysis was performed to assess individual study's influence on pooled effect size. The P value < .05 was considered statistically significant in all cases. Publication bias was investigated using funnel plots and assessing funnel plot asymmetry via rank correlation and Egger's regression tests using the Jamovi Desktop (version 2.3.13).[8–11]

3. Results

3.1. Literature search

The initial search of the following electronic databases yielded 12,435 citations, out of which 12,394 citations were left after the removal of duplicates. 12,302 articles were

ruled out after title and abstract screening. After a full-text review of 92 articles assessed for their eligibility, 57 articles were excluded which did not meet the inclusion criteria. Hence, 35 observational studies were finalized for this meta-analysis. The complete literature search has been outlined in Figure 2.

3.2. Study characteristics and patients' baseline characteristics

Study characteristics, patients' baseline characteristics, and detailed outcome information have been summarized in Tables S3 and S4, Supplemental Digital Content, http://links.lww.com/MD/N24, http://links.lww.com/MD/N25. respectively. Out of 35 observational studies, there were 34 retrospective or prospective studies[12–45] and 1 cross-sectional study.[46] These 35 observational studies enrolled a total population of 28,756 participants, out of which 9678 patients had high NLR and 13,105 patients had low NLR, while one study didn't specify high NLR and low NLR participants.[43] The mean age of patients ranged from 55.5 to 72.1 years with an average of 63.2 years. The percentage of males ranged from 59.7% to 86.3%, with a mean of 75.23%. About 42.8% of studies were from Asia, 37.1% from transcontinental countries (Turkey), 8.5% from South America, 5.7% from North America, and 5.7% from Europe.

3.3. Quality assessment and publication bias

Observational studies were assessed for quality assessment on the New-castle Ottawa scale. All of the included observational studies have a low or moderate risk of methodological bias as outlined in Tables S5 and S6, Supplemental Digital Content, http://links.lww.com/MD/N26 and http://links.lww.com/MD/N27. The only prime bias reported in Sawant et al.[13] Ayça et al[28] and Gazi et al[31] was their failure to explain the reason for loss of follow-up and adequacy of follow-up. The quality assessment table in the supplementary file depicts a range of 6 to 9 out of a maximum score of 9. There was no publication bias in the studies that reported long-term all-cause mortality, as shown by the visual symmetry of the funnel plot and non-significant P value of the rank correlation test ($P = .1557$) and Egger's regression test (=0.1451) (Fig. 3). The rank correlation rank and Egger's regression tests' results for in-hospital all-cause mortality indicated asymmetry in the funnel plot and a publication bias ($P = .005$ and $P < .001$, respectively) (Fig. 4). Similarly, in-hospital MACE also revealed publication bias and demonstrated rank correlation and Egger's regression test indicating funnel plot asymmetry ($P = .381$; $P < .001$, respectively) (Fig. 5).

3.4. Outcome analysis

All 35 observational studies reported the association of NLR values with STEMI patients after undergoing PCI. The detailed information of the primary and secondary outcomes and the prevalence of in-hospital and long-term outcomes extracted from most studies are given in Figures 6 and 7. Detailed Forest plots with effect sizes of primary and secondary outcomes are given in Figures 8–30 respectively.

3.5. All-cause mortality

Out of 35 observational studies, 19 studies reported in-hospital all-cause mortality. It showed a significant association between raised NLR and the incidence of in-hospital all-cause mortality in patients after undergoing PCI as compared to patients with low NLR (RR = 3.52; 95% CI = 2.23–5.54; $P < .00001$; $I^2 = 91\%$). Sensitivity analysis was performed by removing a single study[41] which reported the same risk (RR = 3.52; 95% CI = 2.93–4.24; $P < .00001$) and revealed mild heterogeneity of the included studies ($I^2 = 7\%$; $P = .37$) as shown in Figure 8.

Eighteen studies reported long-term all-cause mortality. It showed a substantial correlation between patients with high NLR, and the occurrence of long-term all-cause mortality as compared to individuals with low NLR. (HR = 1.29; 95% CI = 1.08–1.56; $P = .006$; $I^2 = 86\%$), (RR = 3.12; 95% CI = 2.31–4.22; $P < .00001$; $I^2 = 71\%$). Sensitivity analysis was performed by removing 2[12,43] and 3 studies[13,37,41]

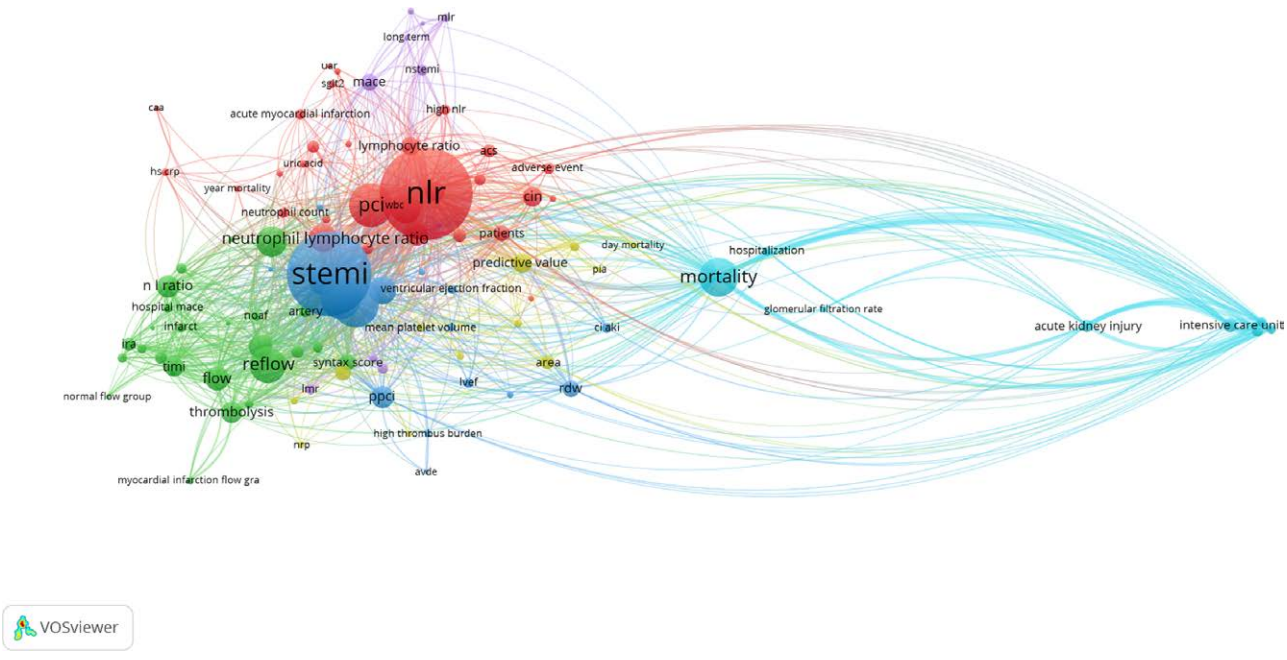

Figure 1. PUBMED relevance keywords map.

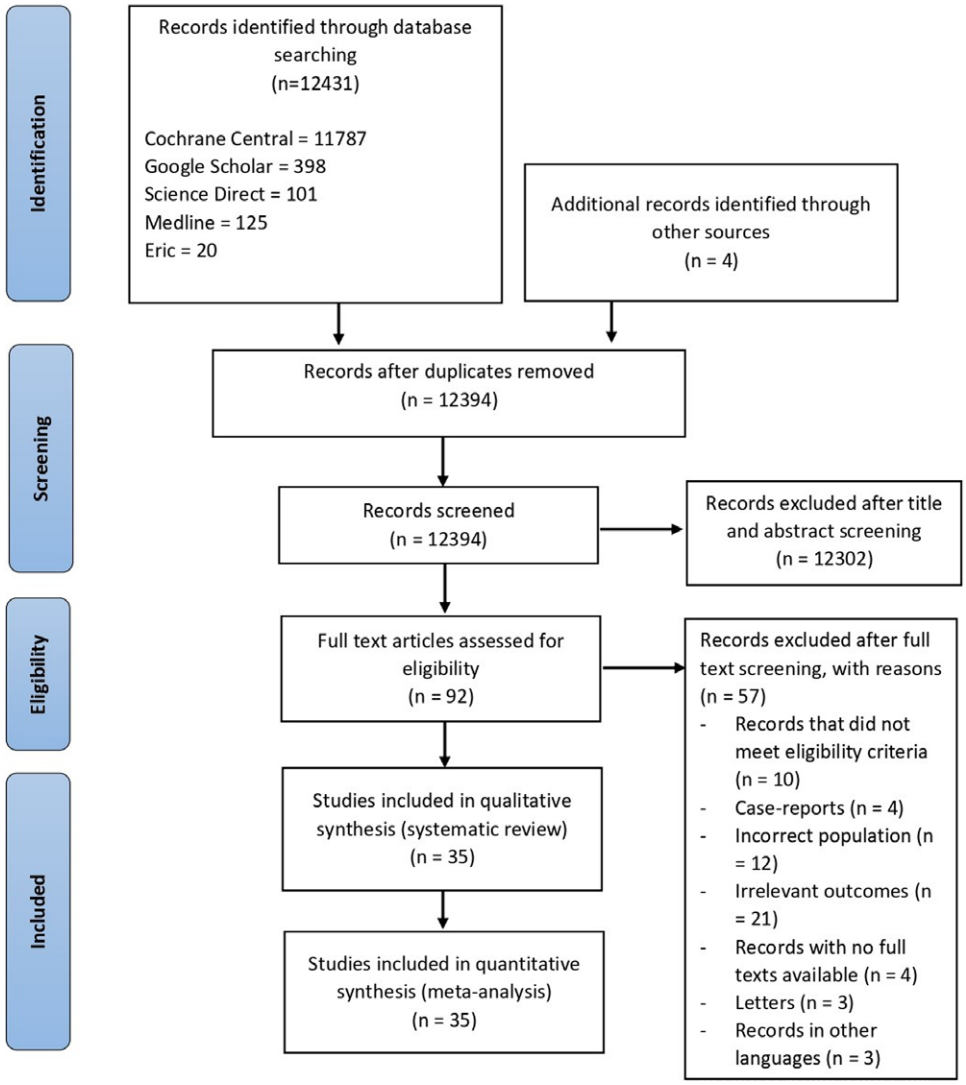

Figure 2. PRISMA flowchart summarizing results of literature search. PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis.

which resulted in a mild change in the risk (HR = 1.07; 95% CI = 1.00–1.14; $P = .05$), (RR = 3.32; 95% CI = 2.57–4.30; $P < .00001$) respectively, and revealed a mild heterogeneity of the included studies ($I^2 = 47\%$; $P = .05$), ($I^2 = 38\%$; $P = .11$), respectively (Figs. 9 and 10).

3.6. Cardiovascular mortality

Seven studies reported in-hospital cardiovascular mortality in patients having high NLR value. The pooled analysis revealed a significant interdependence between patients with high NLR and occurrence of in-hospital cardiovascular mortality in contrast to patients with low NLR (RR = 2.66; 95% CI = 2.04–3.48; $P < .00001$; $I^2 = 0\%$) (Fig. 11).

Five out of the 35 included studies provided adequate data for long-term cardiovascular mortality. There were significantly higher odds of cardiovascular mortality in patients with high NLR compared with low NLR (RR = 4.70; 95% CI = 1.88–11.71; $P = .0009$; $I^2 = 91\%$). Sensitivity analysis by exclusion of a single study[23] resulted in prime change in the result (RR = 6.67; 95% CI = 4.06–10.95; $P < .00001$) and revealed a mild heterogeneity of the included studies ($I^2 = 46\%$; $P = .13$) (Fig. 12).

3.7. MACE

Twelve studies reported in-hospital MACE in patients with high NLR. A significant association was observed amongst the patients with high NLR as compared to low NLR for developing in-hospital MACE before sensitivity analysis (RR = 1.31; 95% CI = 1.17–1.46; $P < .00001$; $I^2 = 87\%$). Exclusion of 5 studies on sensitivity analysis did not lead to a significant change in the high heterogeneity. On subgroup analysis based on the NLR cutoff value, low NLR cutoff subgroup (studies having NLR cutoff ranged between 2.3 and 6.97) showed a raised risk of the incidence of in-hospital MACE (RR = 2.12; 95% CI = 1.79–2.50; $P < .00001$) and revealed no heterogeneity ($I^2 = 0\%$; $P = .54$) whereas high NLR cutoff subgroup (studies having NLR cutoff ranged between 9.41 and 9.45) also reported an increased risk (RR = 1.01; 95% CI = 1.00–1.02; $P = .02$) and revealed no heterogeneity of the included studies ($I^2 = 0\%$; $P = .50$). Therefore, pooled subgrouping analysis showed a prime risk among high NLR patients in comparison with low NLR patients for developing in-hospital MACE (RR = 1.31; 95% CI = 1.17–1.46; $P < .00001$; $I^2 = 87\%$) (Fig. 13).

Out of 35 included studies, 8 studies reported long-term MACE. Pooled analyses demonstrated a significant association between patients with high NLR and the prevalence of long-term

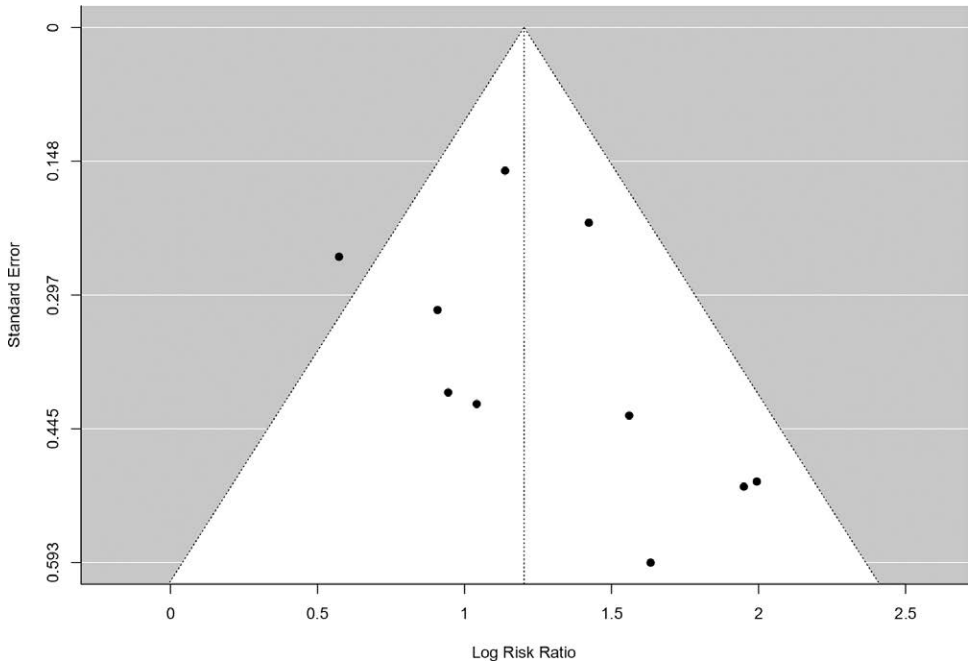

Figure 3. Funnel plot for long-term all-cause mortality.

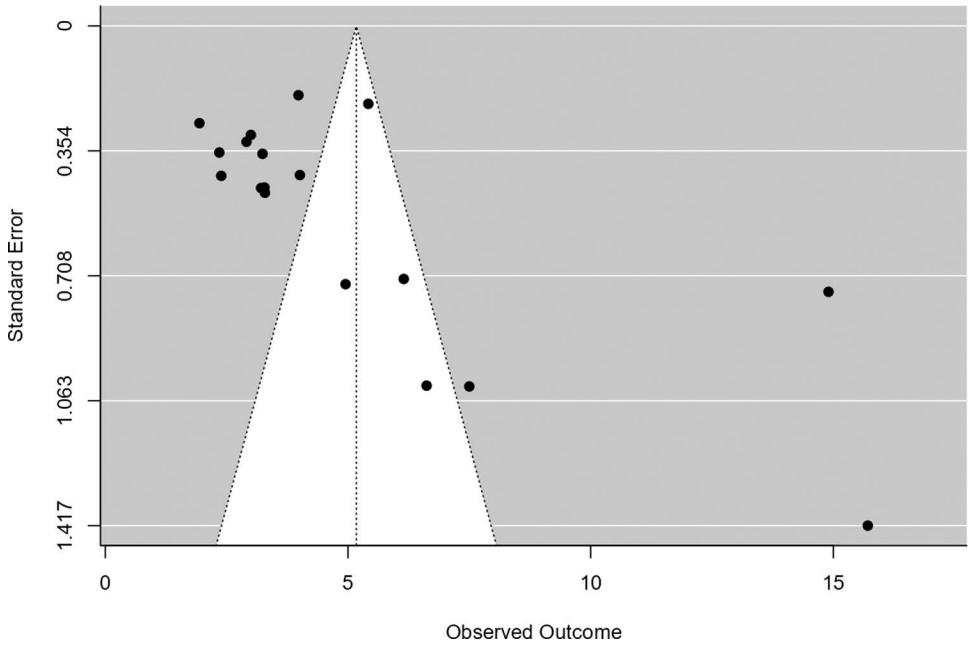

Figure 4. Funnel plot for in-hospital all-cause mortality.

MACE in comparison to patients with low NLR (RR = 2.05; 95% CI = 1.48–2.84; $P < .00001$; $I^2 = 88\%$). Sensitivity analysis was carried out by excluding 3 studies[23,30,39] that demonstrated a minor change in the risk (RR = 2.92; 95% CI = 2.16–3.94; $P < .00001$) and revealed a mild heterogeneity of the included studies ($I^2 = 41\%$; $P = .15$) (Fig. 14).

3.8. Length of hospital stay

Eight studies reported post-procedure length of stay in hospital in patients with high NLR. Pooled analysis showed a significant association between patients with high NLR in comparison with low NLR patients, and the length of hospital stay (WMD = 0.69 days; 95% CI = 0.01–1.36; $P = .05$; $I^2 = 95\%$). Exclusion of 2 studies[27,35] by sensitivity analysis, revealed only slight alteration in the result (WMD = 0.60 days; 95% CI = 0.40–0.79; P .00001), and there was no evidence of study heterogeneity among the included studies ($I^2 = 0\%$; $P = .53$) (Fig. 15).

3.9. AHF

Out of 35 included studies, 3 studies provided data on in-hospital AHF. Patients with high NLR were associated with a significantly higher risk of developing in-hospital AHF, in comparison to patients with low NLR (RR = 1.78; 95% CI = 1.45–2.18; $P < .00001$; $I^2 = 1\%$) (Fig. 16).

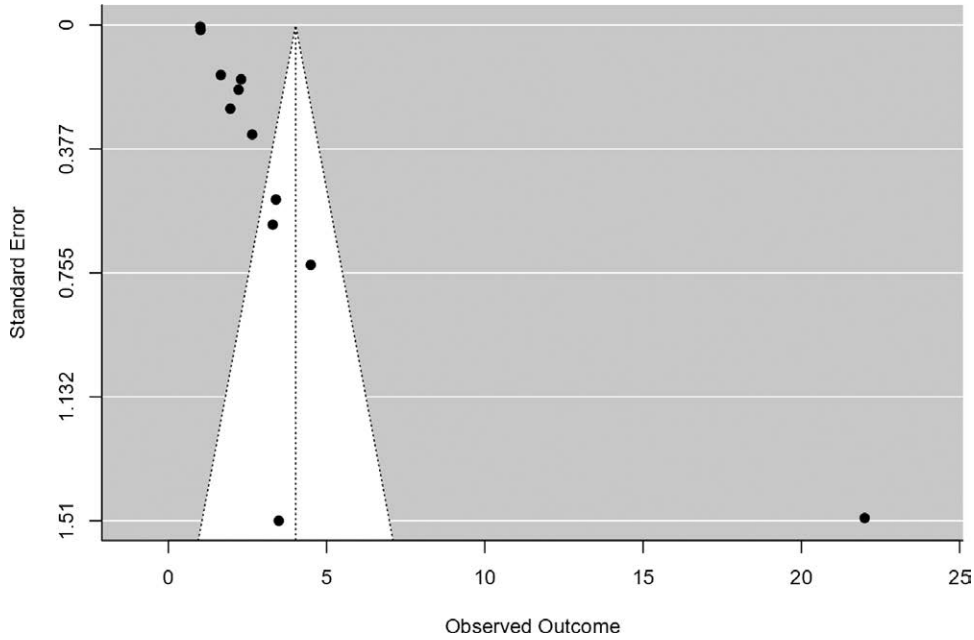

Figure 5. Funnel plot for in-hospital MACE. MACE = major adverse cardiovascular events.

3.10. Angina

Adequate data for in-hospital angina was provided in 2 out of 35 included studies. It showed that patients with high NLR had a higher risk of developing in-hospital angina in collation to the patients with low NLR (RR = 1.66; 95% CI = 1.15–2.40; $P = .007$; $I^2 = 0\%$) (Fig. 17).

3.11. Arrhythmia

Four studies reported in-hospital arrhythmia, and pooled analysis showed a significant interdependence between patients with high NLR, and the incidence of arrhythmia as compared to patients with low NLR (RR = 1.52; 95% CI = 1.14–2.03; $P = .004$; $I^2 = 34\%$) (Fig. 18).

3.12. In-stent thrombosis

4 studies reported data on in-hospital in-stent thrombosis. No statistically significant association was reported between patients with high NLR, and the risk of developing in-stent thrombosis following PCI, in collation to the patients with low NLR (RR = 1.56, 95% CI = 0.73–3.35, $P = .25$, $I^2 = 60\%$) However, sensitivity analysis was performed by removing a single study[30] which showed an increased risk of developing in-hospital in stent thrombosis (RR = 2.26; 95% CI = 1.25–4.10; $P = .007$), and mild heterogeneity of the included studies ($I^2 = 27\%$; $P = .25$) (Fig. 19).

Three studies provided data on long-term in-stent thrombosis. It showed an important correlation between patients with high NLR, and the prevalence of developing long-term in-stent thrombosis (RR = 1.81; 95% CI = 1.12–2.93; $P = .02$; $I^2 = 51\%$) (Fig. 20).

3.13. Non-fatal MI

Out of 35 included studies, 6 studies reported in-hospital non-fatal MI. In contrast to patients with low NLR, high NLR patients had a significantly higher chance of having an in-hospital non-fatal MI, as per pooled analyses (RR = 2.03; 95% CI = 1.50–2.75; P .00001; $I^2 = 7\%$). (Fig. 21).

4 studies reported data on long-term non-fatal MI. There was no statistically significant difference in the risk of non-fatal MI between patients with high and low NLR (RR = 1.32; 95% CI = 0.64–2.74; $P = .45$; I2 = 72%). There was a significant shift in the risk after performing sensitivity analysis by eliminating one study[23] (RR = 2.18; 95% CI = 1.37–3.47; $P = .001$) and revealed no heterogeneity of the included studies ($I^2 = 0\%$; $P = .45$) (Fig. 22).

3.14. No-reflow phenomenon

Adequate data regarding the in-hospital no-reflow was reported in 13 of 35 included studies. A statistically significant interrelation was observed among patients with high NLR in terms of developing in-hospital no-reflow after undergoing PCI, compared to patients with low NLR (RR = 2.07; 95% CI = 1.47–2.91; $P < .0001$ $I^2 = 94\%$). Sensitivity analysis was performed by removing 4 studies[17,19,28,37] that reported a mild change in the risk of developing in-hospital no-reflow (RR = 1.54; 95% CI = 1.29–1.84; $P < .00001$) and revealed mild heterogeneity of the included studies ($I^2 = 29\%$; $P = .19$) (Fig. 23).

3.15. AF

Three studies provided data for developing in-hospital AF. No significant association was noted between patients with high NLR, and the occurrence of AF after undergoing PCI in contrast to low NLR patients (RR = 1.17; 95% CI = 0.67–2.06; $P = .58$; $I^2 = 0\%$) (Fig. 24).

3.16. Ventricular arrhythmia

Out of 35 included studies, 6 reported data for the incidence of in-hospital ventricular arrhythmia. The pooled analyses showed a significant association between patients with high NLR and the occurrence of ventricular arrhythmia, as compared to patients with low NLR (RR = 3.18; 95% CI = 2.30–4.41; $P < .00001$; $I^2 = 0\%$) (Fig. 25).

3.17. Stroke

Three studies provided data for developing in-hospital stroke. It showed a significant correlation between patients with high NLR in

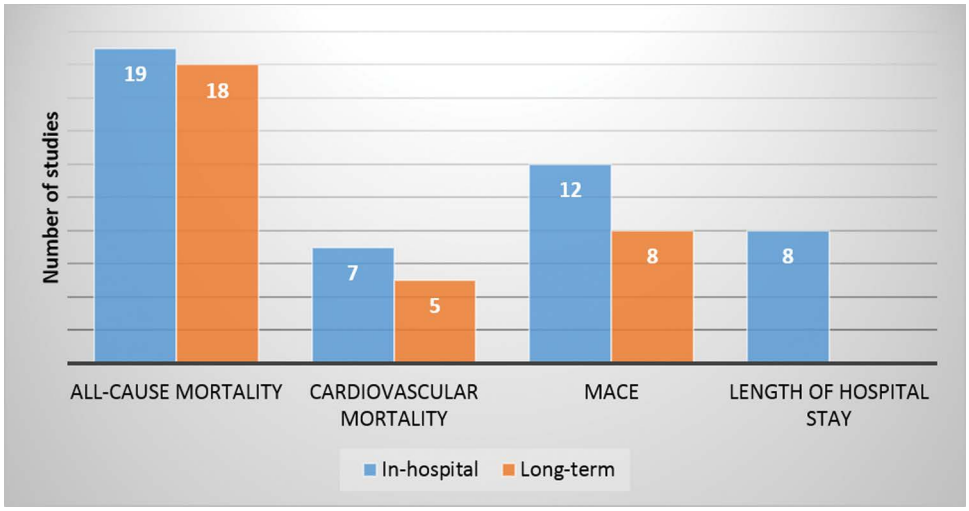

Figure 6. In-hospital and long-term primary outcomes reported by included studies.

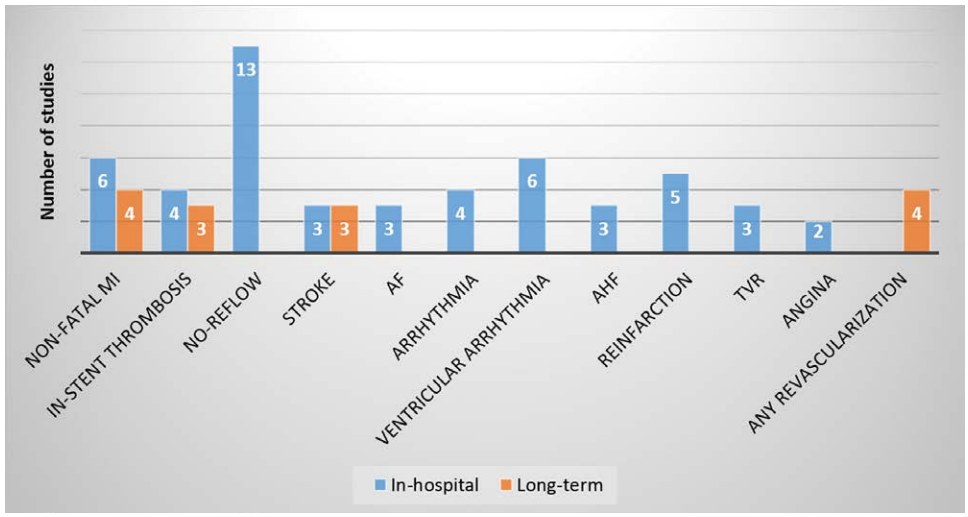

Figure 7. In-hospital and long-term secondary outcomes reported by included studies.

terms of developing in-hospital stroke as compared to those with low NLR (RR = 2.33; 95% CI = 1.09–5.00; P = .03; I^2 = 0%) (Fig. 26).

Three studies reported outcomes for long-term stroke, and pooled analysis revealed no significant difference between patients with high, and low NLR (RR = 2.11; 95% CI = 0.74–5.99; P = .16; I^2 = 0%) (Fig. 27).

3.18. Reinfarction

Five studies provided data on in-hospital reinfarction, and revealed a non-significant association between patients with high NLR, as compared to those with low NLR (RR = 1.26; 95% CI = 0.90–1.76; P = .18; I^2 = 0%) (Fig. 28).

3.19. TVR

Three out of 35 included studies reported outcomes for in-hospital TVR. No significant difference was observed between patients with high, and low NLR groups (RR = 1.17; 95% CI = 0.89–1.54; P = .25; I^2 = 0%) (Fig. 29).

3.20. Any revascularization

Out of 35 included studies, 4 studies provided data on long-term revascularization. The pooled analyses revealed a significant association among patients with high NLR for developing long-term revascularization, as compared to low NLR (RR = 1.17; 95% CI = 1.00–1.37; P = .05; I^2 = 19%) (Fig. 30).

4. Discussion

In this meta-analysis comprising 35 articles, raised NLR was associated with higher risk of the following in-hospital outcomes: all-cause mortality, cardiovascular mortality, MACE, length of hospital stays, AHF, angina, arrhythmia, non-fatal MI, no-reflow, ventricular arrhythmia, stroke. Raised NLR was also significantly associated with long-term outcomes: all-cause mortality, cardiovascular mortality, MACE, in-stent thrombosis, and revascularization. However, no significant association was observed between high NLR and in-hospital outcomes such as in-stent thrombosis, AF, reinfarction, TVR, and long-term outcomes non-fatal MI and stroke.

Zhang[47] has reported a previous meta-analysis with a similar objective in 2018. However, it had a couple of limitations such as the inclusion of small sample-sized observational studies, lack of a uniform counting standard for different cell counts, and the failure to correct for interference from several factors. Moreover, the authors overlooked some essential continuous and dichotomous outcomes.

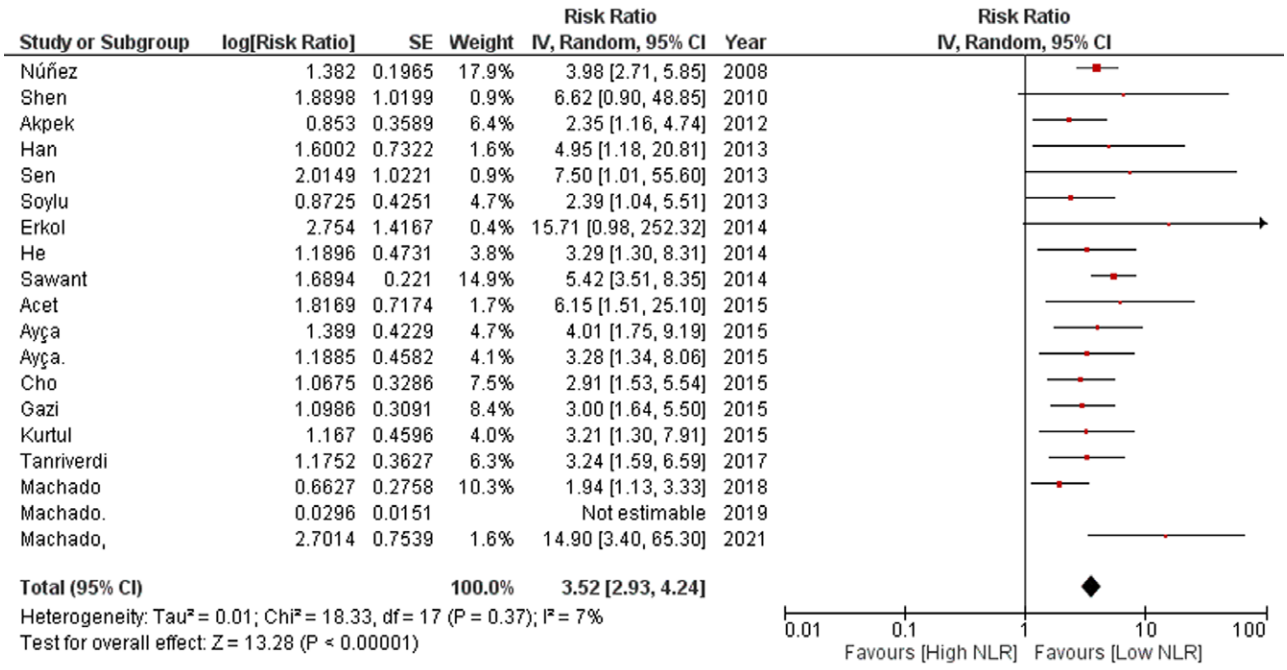

Figure 8. Forest plot for in-hospital all-cause mortality after sensitivity analysis.

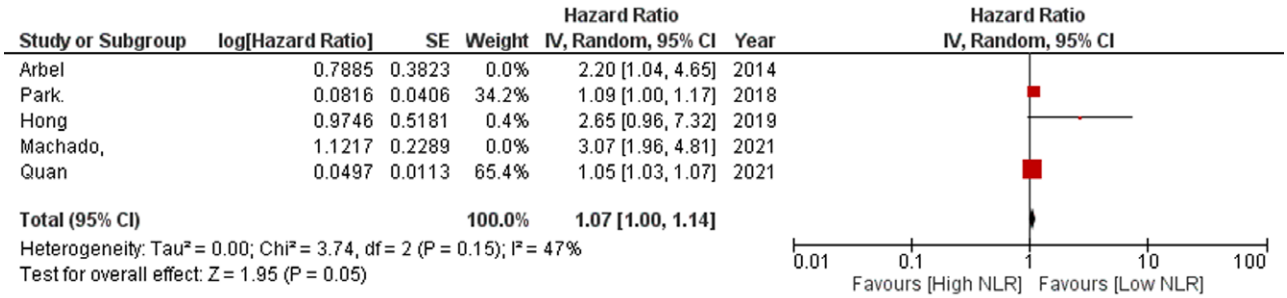

Figure 9. Forest plot for long-term all-cause mortality after sensitivity analysis in terms of HR. HRs = hazard ratios.

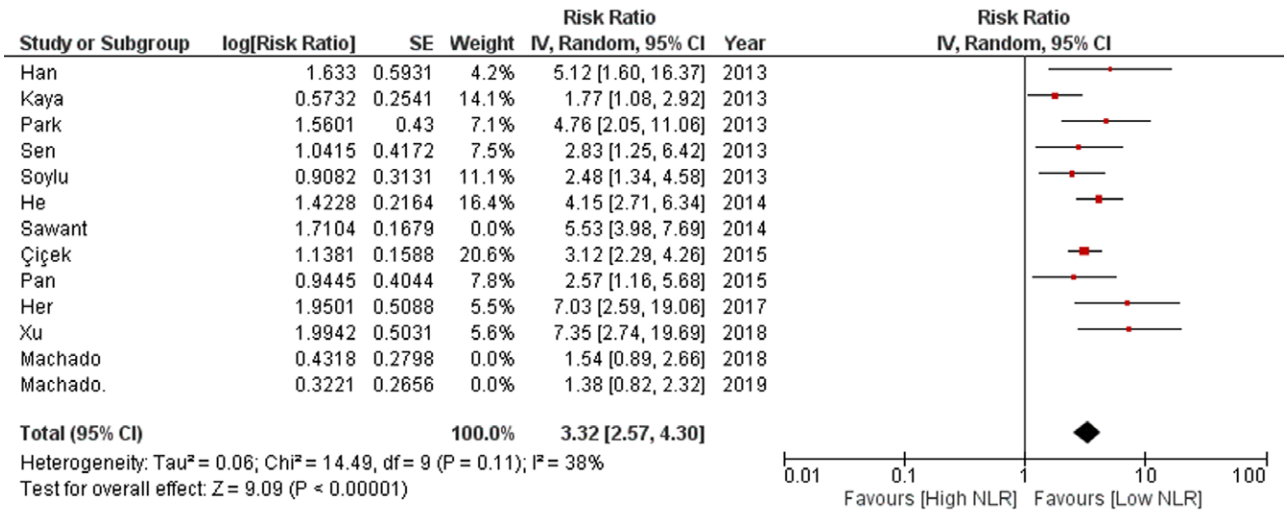

Figure 10. Forest plot for long-term all-cause mortality after sensitivity analysis in terms of RR. RR = risk ratios.

The neutrophil to lymphocyte ratio (NLR) is the number of neutrophils divided by the number of lymphocytes. The neutrophil and lymphocyte count may increase or decrease under physiological stress. The NLR pools both individual changes, making it a more powerful diagnostic tool than either of them alone.[48] NLR has been extensively evaluated and associated with predicting disease course and mortality among patients with major cardiac events.[49] Duffy et al showed that elevated preprocedural NLR was associated with an increased risk of long-term mortality in patients undergoing PCI.[14]

Evidence suggests that hematological cells, notably leukocytes, neutrophils, and lymphocytes, accelerate the

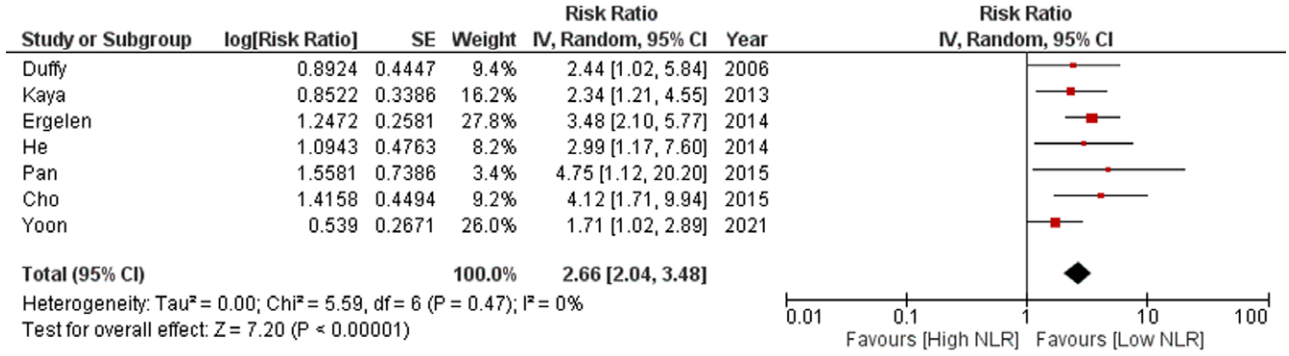

Figure 11. Forest plot for in-hospital cardiovascular mortality.

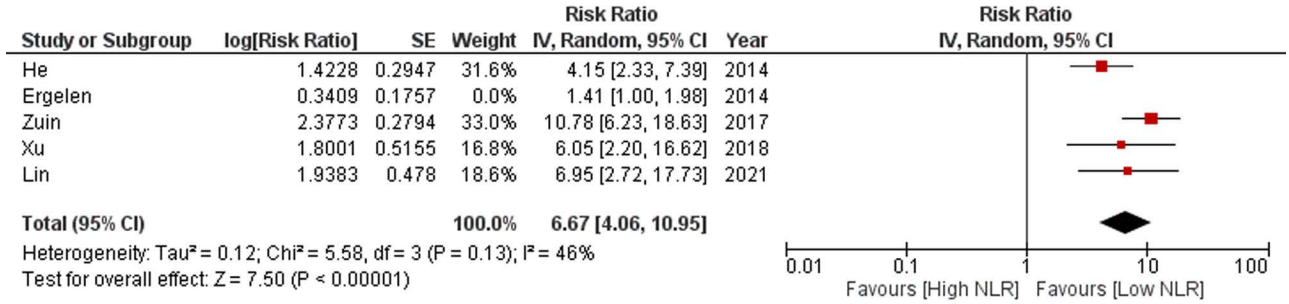

Figure 12. Forest plot for long-term cardiovascular mortality after sensitivity analysis.

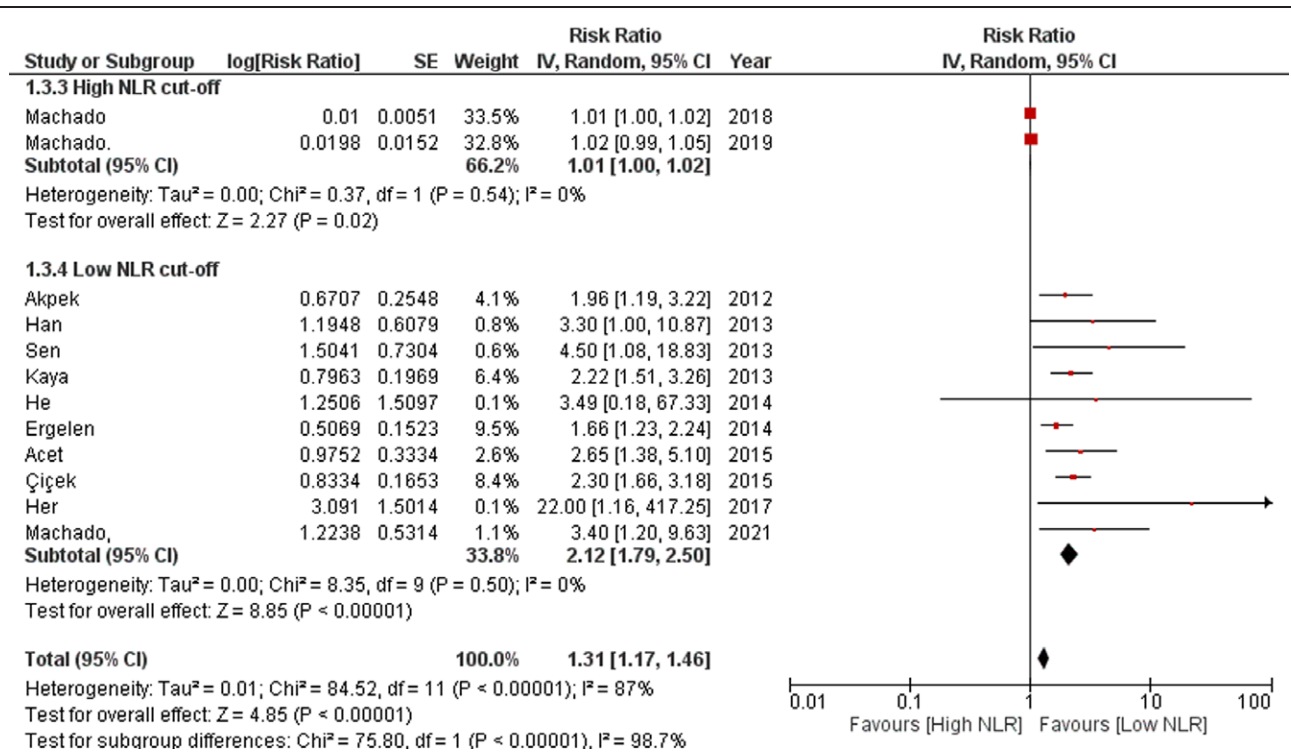

Figure 13. Forest plot for in-hospital MACE after subgroup analysis. MACE = major adverse cardiovascular events.

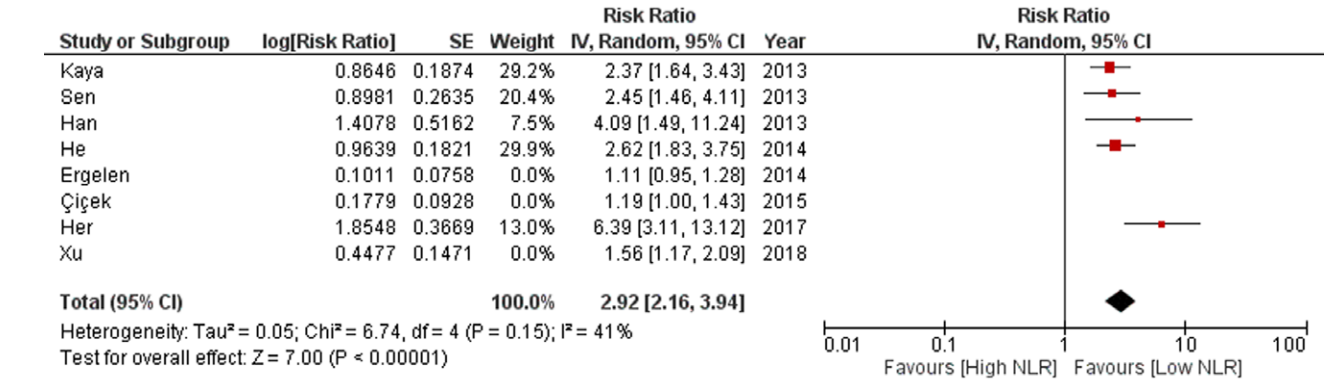

Figure 14. Forest plot for long-term MACE after sensitivity analysis. MACE = major adverse cardiovascular events.

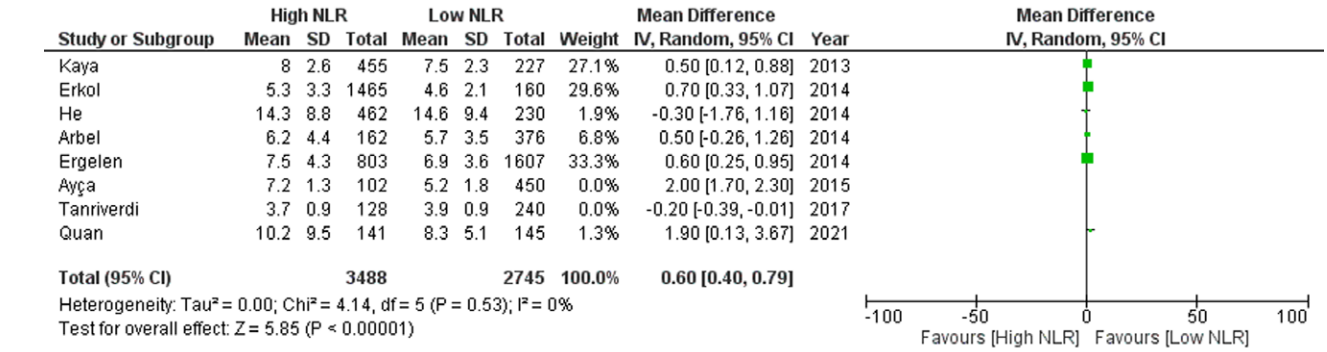

Figure 15. Forest plot for the length of hospital stay.

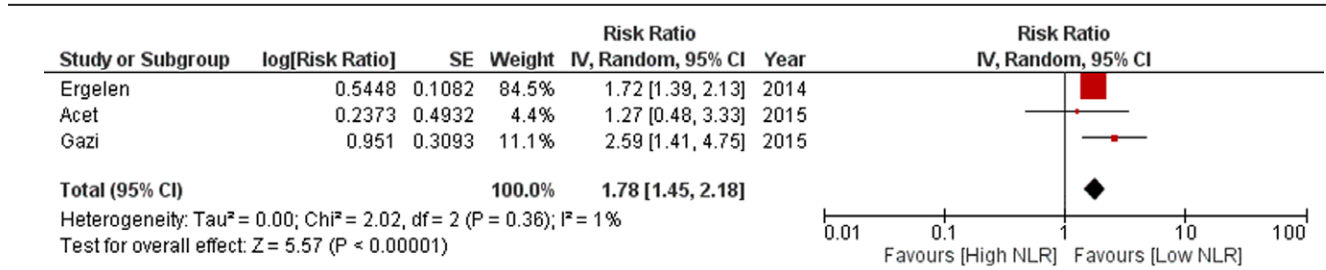

Figure 16. Forest plot for in-hospital advanced heart failure.

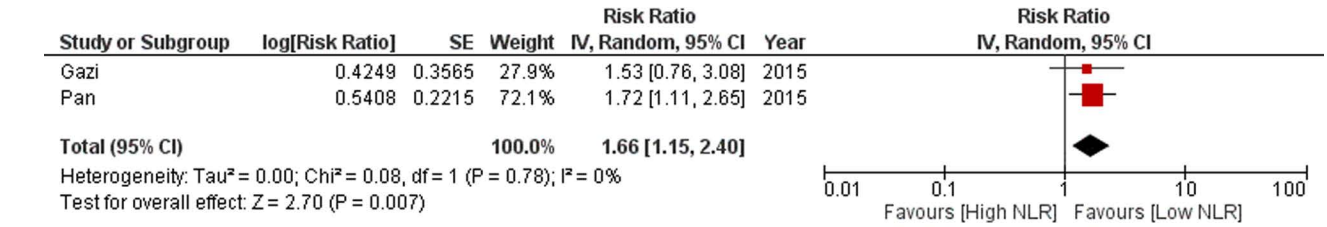

Figure 17. Forest plot for in-hospital angina.

development of cardiovascular injury in acute myocardial infarction.[50] Neutrophils are linked to cardiac disease development due to their ability to propagate thrombosis and destabilize atherosclerotic plaques.[50–52] By contrast, lymphocytes reduce inflammation and stabilize atherosclerotic plaques.[53,54] A study of 1037 post-PCI patients concluded that a lower lymphocyte count is associated with an increased risk of long-term mortality.[55] A strong link between lower circulating T-lymphocyte function and worsening of ischemia-reperfusion injury following an episode of myocardial infarction has been established.[56]

As hematological indicators such as neutrophils and lymphocytes are essential during cardiac injury, the combined neutrophil-to-lymphocyte ratio has been proven to be a stronger predictor of cardiovascular disease than each individual parameter.[14] NLR has been demonstrated to have a

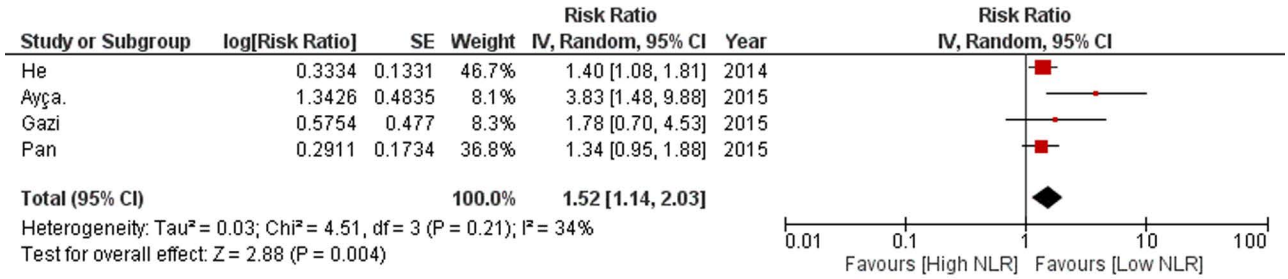

Figure 18. Forest plot for in-hospital arrhythmia.

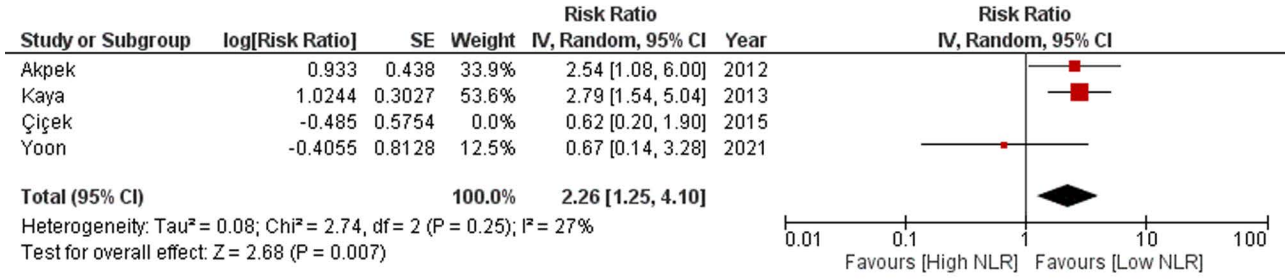

Figure 19. Forest plot for in-hospital in-stent thrombosis after sensitivity analysis.

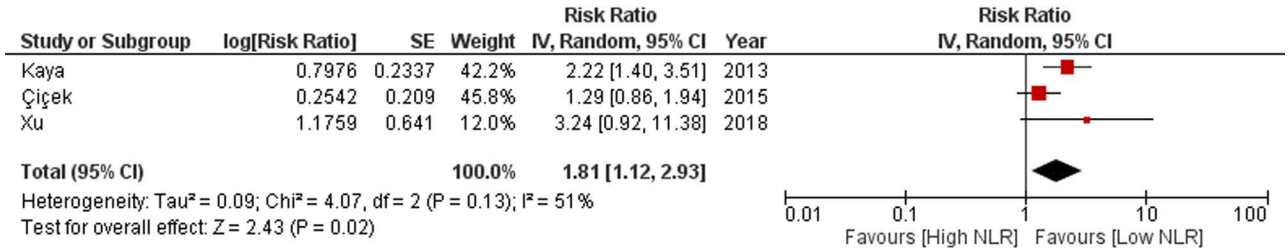

Figure 20. Forest plot for long-term in-stent thrombosis.

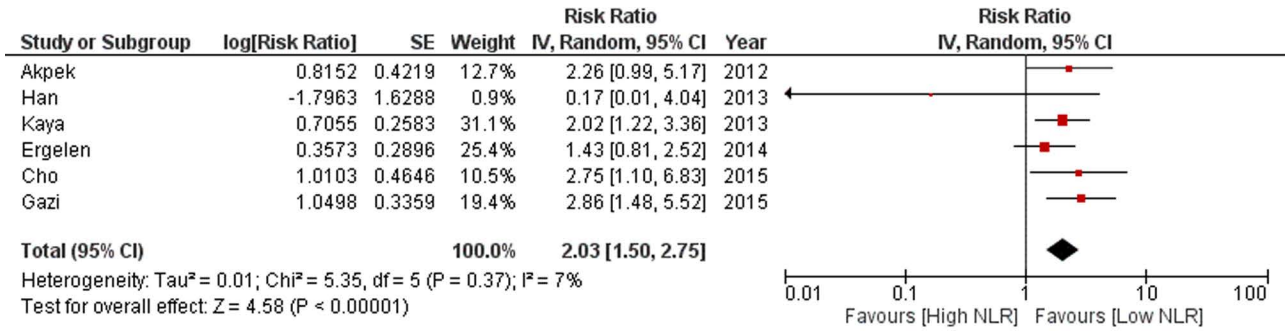

Figure 21. Forest plot for in-hospital non-fatal myocardial infarction.

significant connection with predicting short and long-term mortality, reinfarction, and heart failure in STEMI and non-STEMI patients.[15,57,58] Elevated NLR is also associated with an increased risk of in-stent thrombosis and mortality in STEMI patients.[27] An association is also observed between CVD mortality, MACE, and high NLR.[59,60]

Our findings are consistent with earlier meta-analyses by Zhang et al[61] and Zhang et al,[47] which aimed to discern the relationship between NLR and cardiovascular problems after coronary intervention. We observed that high NLR in STEMI patients after PCI is associated with a higher risk of all-cause mortality, MACE, AHF, in-stent thrombosis, angina, arrhythmia, non-fatal MI, no-reflow, ventricular arrhythmia, stroke, any revascularization as compared to low NLR. Similarly, a study observed that the NLR ratio is substantially associated with no-reflow in STEMI patients after PCI.[47] Another study reached similar conclusions, stating that a high neutrophil and lymphocyte count in circulation is predictive of angina, AHF, arrhythmia, MACE, cardiac mortality, all mortality, in-stent thrombosis, non-fatal MI, and no-reflow following coronary intervention.[61] However, our study observed no significant association between NLR and AF, reinfarction, and TVR.

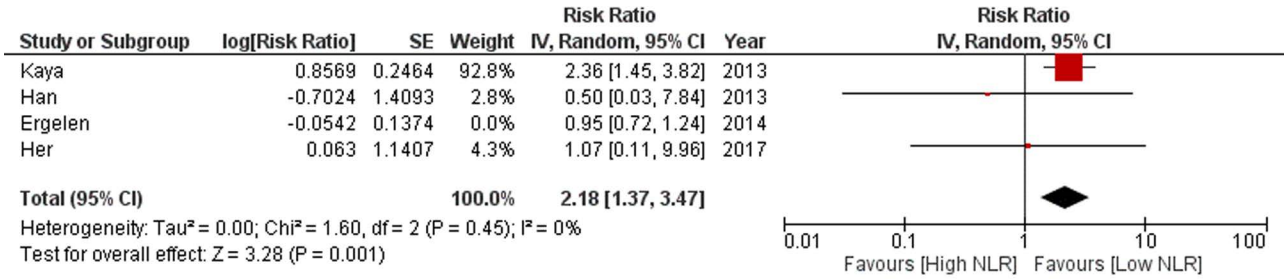

Figure 22. Forest plot for long-term non-fatal myocardial infarction after sensitivity analysis.

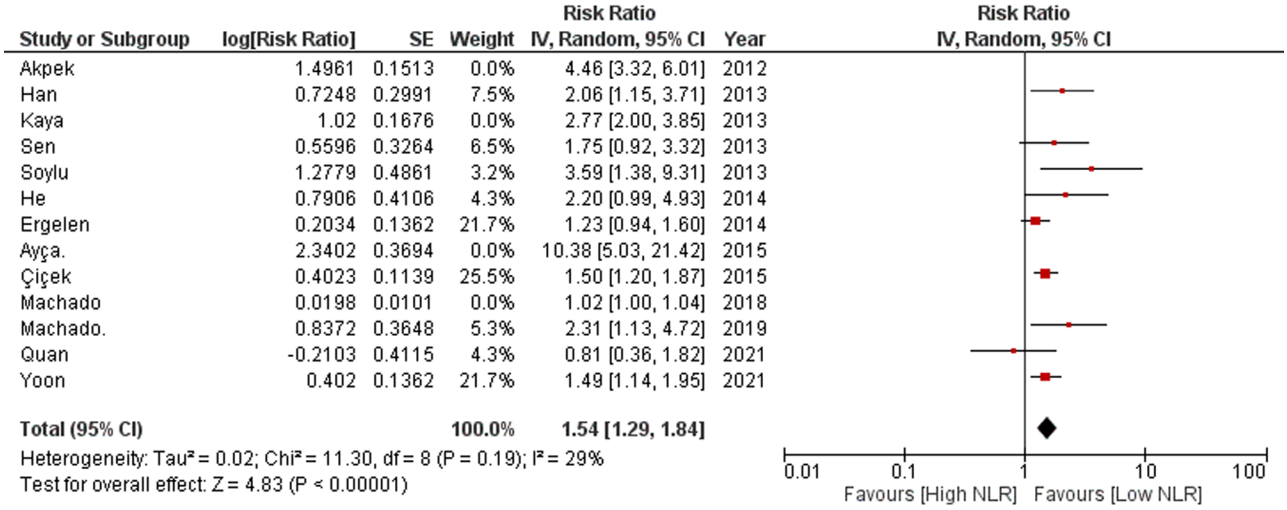

Figure 23. Forest plot for in-hospital no-reflow phenomenon.

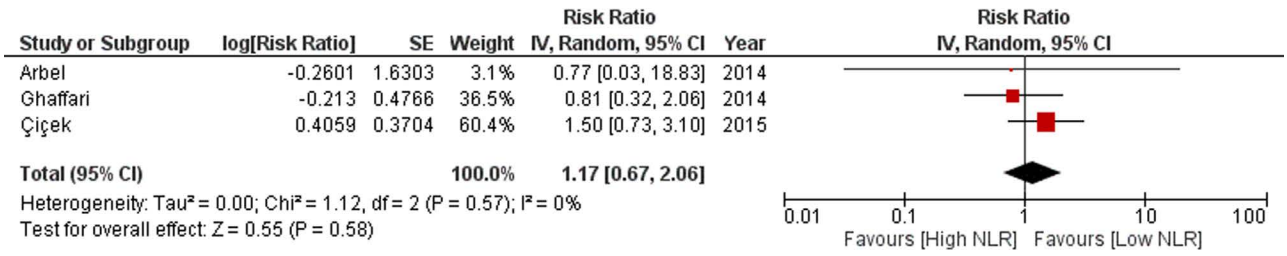

Figure 24. Forest plot for in-hospital atrial fibrillation.

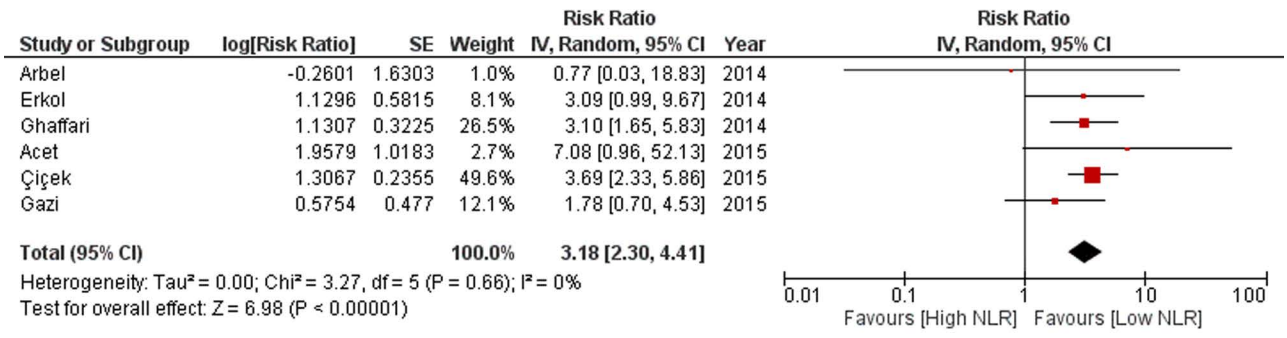

Figure 25. Forest plot for in-hospital ventricular arrhythmia.

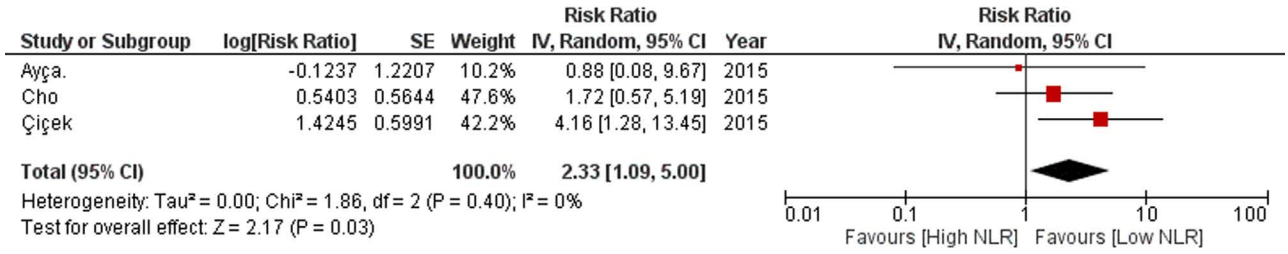

Figure 26. Forest plot for in-hospital stroke.

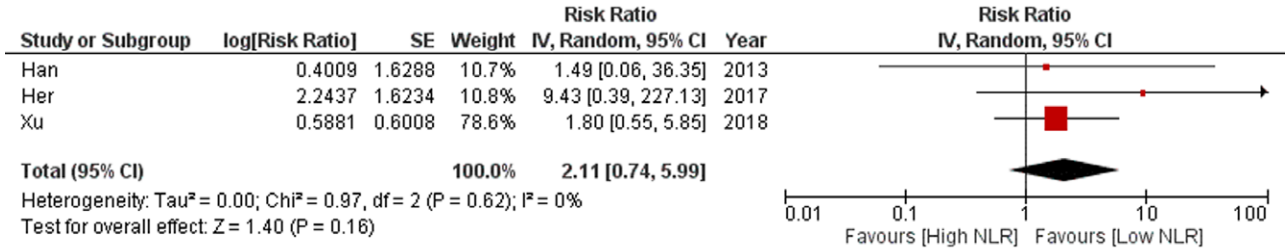

Figure 27. Forest plot for long-term stroke.

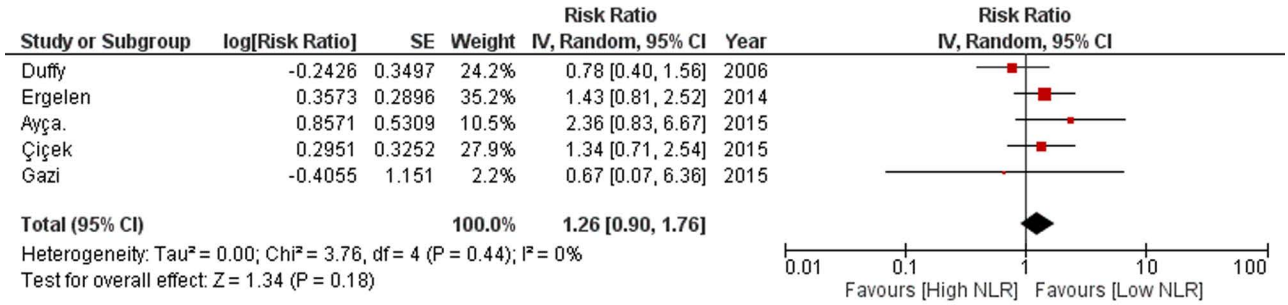

Figure 28. Forest plot for in-hospital reinfarction.

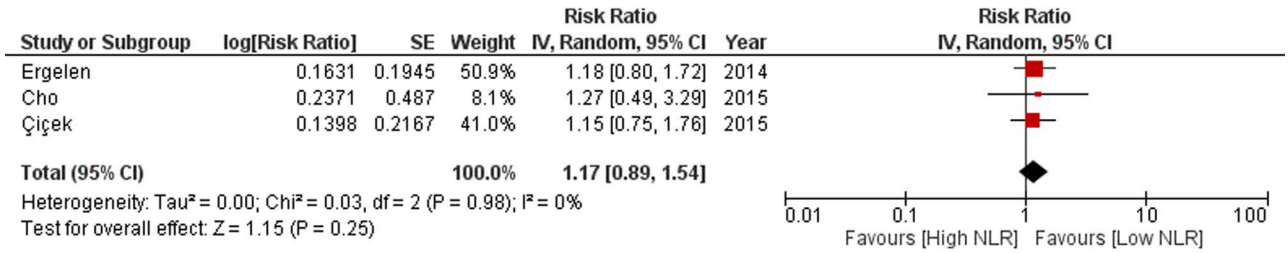

Figure 29. Forest plot for in-hospital target vessel revascularization.

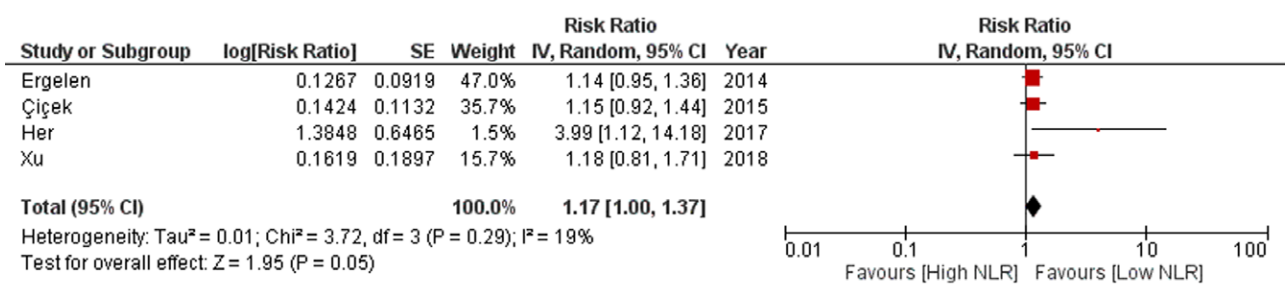

Figure 30. Forest plot for long-term any revascularization.

The findings of Wang et al further solidify the predictive function of high NLR in predicting the risk of all-cause mortality, MACE, and cardiovascular death.[62] Regarding inclusion and exclusion criteria, the current meta-analysis differs from a previous study, since they included patients who have undergone coronary and angiographic interventions, not just PCI.

Despite significant variabilities amongst the included studies in our meta-analysis, these results can have important clinical implications in the therapeutic management of STEMI patient's post-coronary interventions. In patients with a high NLR, strict surveillance can help in early identification of cardiovascular emergencies and aid in decision-making in treating such patients. High on-admission NLR has been directly linked with MACE and stricter surveillance practices can lead to better treatment plans.

To the best of our knowledge, this is the most comprehensive meta-analysis evaluating the relationship between elevated NLR and in-hospital and long-term cardiovascular risks in patients with ST-segment elevation following PCI. Our study incorporated data from numerous studies that had been corrected for potential confounders, which is more credible than data from single studies. Furthermore, the sensitivity and subgroup analyses were consistent with the overall results, suggesting the robustness of the findings.

This study has limitations, just like any other meta-analysis. Firstly, this meta-analysis only includes observational studies, leading to selection and recall bias. Secondly, the included studies had slightly different inclusion and exclusion criteria, and each study has a different NLR value, therefore we were unable to determine a consistent NLR cutoff value. Furthermore, the follow-up times in the included studies vary, which may lead to confounding biases. More extensive clinical trials are therefore required to investigate better and support the current findings of a link between NLR and cardiovascular problems in STEMI after coronary treatments. Because the included studies were done mainly in Asian nations, particularly China and Turkey, the clinical implications of the current study should be studied further in large-scale trials in other nations as well.

5. Conclusion

NLR might be a powerful predictor of cardiovascular risks in STEMI patients undergoing PCI. However, more large-scale trials are required to prove NLR as a significant therapeutic target in reducing the risk of in-hospital and long-term cardiovascular outcomes in STEMI patients.

Author contributions

Supervision: Waqas Ullah, M. Chadi Alraies.

Writing – original draft: Hassan ul Hussain, Kanwal Ashok Kumar, Marium Zahid, Muhammad Husban Burney, Zayeema Khan, Muqaddus Asif, Syeda Tayyaba Rehan, Huzaifa Ahmad Cheema, Sarya Swed, Farah Yasmin.

Writing – review & editing: Hassan ul Hussain, Kanwal Ashok Kumar, Marium Zahid, Muhammad Husban Burney, Zayeema Khan, Muqaddus Asif, Syeda Tayyaba Rehan, Huzaifa Ahmad Cheema, Sarya Swed, Farah Yasmin.

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