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Platelet-To-Lymphocyte Ratio as a Predictor of No-Reflow after Primary Percutaneous Coronary Intervention in Patients with ST Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: No-reflow increases the complications and mortality rate of primary percutaneous coronary intervention (PCI). Therefore, it is important to identify patients at a higher risk of developing no-reflow. This study aimed to systematically review the prognostic value of the platelet-to-lymphocyte ratio (PLR) to predict no-reflow.

Materials and Methods: The databases, such as Pubmed, EMBASE, and Web of Knowledge were searched for the relevant studies. Two authors independently performed data extraction and quality assessment of the included studies. In this meta-analysis, sensitivity and specificity of PLR, as well as the pooled odds ratio were calculated to predict no-reflow and compared with the pooled means of PLR in no-reflow and reflow groups.

Results: According to the results obtained from six out of eight studies in this systematic review, there was a significant association between PLR and no-reflow. Moreover, a pooled six-fold increase of no-reflow risk was observed in the high PLR group. Pooled sensitivity and specificity of PLR to predict no-reflow was 65% (CI95%: 61%-69%) and 77% (CI95%: 76%-79%), respectively. The mean pooled of PLR in the no-reflow group was significantly 65.2 (CI95%: 26.7-103.8) units higher than that in the reflow group.

Conclusion: The PLR is a significant predictor of no-reflow in STEMI patients subjected to primary PCI which can be used alone or in combination with other markers to identify patients at higher risk of developing no-reflow.

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Introduction

ST-elevation myocardial infarction (STEMI) is one of the leading causes of mortality worldwide (1). Mortality in STEMI has decreased substantially in recent years due to the development of reperfusion techniques. Thirty-day mortality rates are 13% with medication alone, 6-7% with fibrinolytic therapy, and 3-5% with the primary percutaneous coronary intervention (PCI) (2-6). However, despite the successful opening of the infarct-related artery, myocardial tissue perfusion does not occur in 12-39% of the patients due to a phenomenon called no-reflow (7-10). The term no-reflow is

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mainly used for patients with thrombolysis in myocardial infarction (TIMI) grades of 2 or

No-reflow complicates primary PCI and increases the mortality rate, malignant arrhythmias, and heart failure. Moreover, persistent no-reflow may result in the extension or recurrence of myocardial infarction (MI), worsening the long-term prognosis (12, 13). Given the considerable rate of no-reflow and its association with the prognosis of patients after primary PCI, an easily available predictor of this phenomenon is highly valuable for the better care of STEMI patients. The pathophysiology of no-reflow is not fully understood; however, it seems to have a multifactorial etiology (14). Inflammatory and thrombotic pathways are believed to play important roles in the development of no-reflow. Platelet-to-lymphocyte ratio (PLR) is an easily available marker that can represent both these pathways (15). A number of studies have investigated the association of this marker with the no-reflow phenomenon in STEMI patients who undergo primary PCI. The purpose of this study was to systematically review the role of PLR in predicting no-reflow qualitatively and quantitatively.

Materials and methods

This systematic review and meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (16).

Search Strategy and study selection

The databases, including Pubmed, EMBASE, and Web of Knowledge were searched for relevant studies published until December 2018 using keywords, such as "platelets", "lymphocytes", and "myocardial infarction". Subsequently, the results of the search in different databases were combined and the duplicate records excluded from this study. Two authors independently screened the titles and or abstracts of the obtained records to identify possibly relevant studies. The full text of these studies, if available, were retrieved and evaluated in detail to further eliminate studies that failed to meet the inclusion and exclusion criteria. All discrepancies between the two authors were resolved by consensus.

Inclusion and exclusion criteria

The inclusion criteria to include the studies in the systematic review were: 1) the STEMI patients who underwent primary PCI, 2) the measurement of platelet-to-lymphocyte ratio on admission, 3) the evaluation of no-reflow lower without the evidence of apparent obstruction in angiography (11).
after performing primary PCI, 4) the evaluation of the association between PLR with no-reflow. Conference proceedings, case reports, letters to the editor, comments, reviews, and animal studies were excluded from this systematic review. When duplicate reports of the same experiment were suspected, the one reporting more relevant data was included.

Data extraction and quality assessment

Two authors independently performed data extraction and quality assessment of the included studies. All discrepancies were resolved by consensus. The following data was extracted from the review: first author, year of publication, country, study design (i.e., prospective or retrospective), number of participants, mean age, gender, ratio, inclusion and exclusion criteria, PCI and medical treatment details, definition of no-reflow phenomenon and its rate, device and timing of PLR measurement, and statistical results.

Quality of the studies was assessed using a slightly modified version of Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) checklist which is originally designed for tumor markers; however, it can also be applied to other prognostic markers and other diseases (17). The REMARK criteria consisted of twenty items; however, since no-reflow was assessed immediately after primary PCI, following up the patients was not necessary and item 12 (i.e., reporting the flow of the patients) were removed.

Statistical analysis

We performed our meta-analysis using two effect sizes. The differences regarding the mean values of meta-analyses were determined using Comprehensive Meta-Analysis 2.2 (BioStat Inc., US). Studies reporting mean±SD or median and interquartile range (IQR) of PLR in the no-reflow and reflow groups were included. Moreover, the mean±SD values of the studies that reported median and IQR were estimated using a previously published spreadsheet (18). The random-effects model was used to calculate the pooled difference in mean values of PLR between no-reflow and reflow groups. Heterogeneity between the studies was assessed using the I^2 index and Cochran's Q test, where an $I^2 > 70\%$ or a significant Cochran's Q test represented substantial heterogeneity.

The diagnostic accuracy meta-analysis included the studies that reported the sensitivity and specificity of PLR to predict no-

reflow phenomenon, as well as the studies that reported the rate of no-reflow in high and low PLR groups. True positives, false negatives, true negatives, and false positives were calculated for each study using 2×2 tables and the sensitivity, specificity, and no-reflow rates.

Meta-DiSc 1.4 with a random effects model was used to calculate pooled sensitivity, specificity, odds ratio, positive likelihood ratio, and negative likelihood ratio (19). The symmetrical summary receiver operating characteristics (sROC) curve was also plotted and its area under the curve (AUC) was calculated. Good diagnostic performance is indicated by AUC > 0.80 (20). Similar to the differences regarding mean values of meta-analysis, heterogeneity was assessed using the I^2 index and the Cochran Q test. Since the cut-off used to stratify patients to low and high PLR groups was different across studies, the threshold effect analysis was performed to assess whether this difference has affected the results of the meta-analysis.

In the threshold effect analysis, Spearman correlation between the logit of true positive rates and logit of false positive rates was evaluated and threshold effect was assumed to exist when there was a significant correlation with a coefficient of 0.6 or higher (21). Since fewer than ten studies were included in both meta-analyses, publication bias tests, subgroup analyses, and meta-regression were not performed. P-value less than 0.05 was considered statistically significant (22, 23).

Results

Characteristics of the included studies

In total, eight studies with 4145 participants were included in this systematic review (Figure 1) (24-31).

The mean age of the participants was 59.7 years within the range of 57.0 to 64.1 years across studies. Overall, 3045 (73.4%) of the participants were male. Six studies were performed in Turkey and the other two were conducted in China and Iran. Regarding the study design, six studies were retrospective cohorts, one was a prospective cohort, and one was a case-control study. Similar standard PCI procedures with small variations were performed in the studies. In one study, only bare-metal stents were used (25); however, in the others, the choice of the stent type was at the discretion of the attending cardiologists. Tirofiban was utilized in selected patients in all studies.

In addition, four studies used thrombus aspiration at the discretion of the interventionist (24, 25, 27, 28); however, one had excluded patients with thrombus aspiration (31). In all studies, patients were similarly treated with aspirin, clopidogrel, and heparin prior to the PCI.

Post-PCI angiography was employed to assess the presence of no-reflow. Two cardiologists, who were blinded to each other and the clinical data of the patients in six studies, reviewed the angiographic data in seven studies. The TIMI flow grade ≤ 2 was considered as no-reflow in all studies, and in two studies myocardial blush grade (MBG) score ≤ 1 in the presence of TIMI flow grade 3 was also defined as no-reflow (27, 29). No-reflow had an overall rate of 20.4% (807 patients) with a range of 12.5% - 34.1% across the studies. It should be noted that 98 patients with no-reflow in the case-control study were not considered in the calculation of the overall no-reflow rate. Blood samples were acquired on admission and complete blood counts were analyzed using a variety of autoanalysers manufactured by Beckman Coulter (Hialeah, Florida), Sysmex Corporation (Kobe, Japan), Abbott Laboratory (Abbott Park, Illinois), and Bayer Diagnostics (Tarrytown, New York).

The investigated studies commonly excluded patients with a history of conditions that could affect the platelets or neutrophils counts, including active infections, systemic inflammatory diseases, malignancies and hematologic diseases, as well as liver and renal diseases. The PLR was calculated using simply dividing platelets count by lymphocytes count.

Table 1 tabulates the mean values of PLR within the range of 138-211 across studies.

Table 1. Characteristics of the included studies.

Author	Year	Country	No. of participants	Age (mean ± SD)	Sex (male %)	No-reflow definition	No-reflow rate	PLR cut-off
Amirpour, A.[20]	2017	Iran	۱۹۶	۶۴	%۸۰,۶	TIMI ≤ 2	[b]%۵۰,۰	-
Ayça, B.[21]	2015	Turkey	۴۴۰	۸ ± ۵۷	%۶۶,۸	TIMI ≤ 2	%۱۲,۵	۱۳۷
Celık, T.[22]	2016	Turkey	۵۸۰	۱۲ ± ۵۹	%۷۷,۰	TIMI ≤ 2	%۳۴,۱	-
Kurtul, A.[23]	2017	Turkey	۱۲۰۶	۱۳ ± ۵۹	%۷۵,۳	TIMI ≤ 2 MBG ≤ 1	%۱۶,۴	۱۳۳
Kurtul, A.[24]	2014	Turkey	۵۲۰	۱۳ ± ۶۰	%۶۶,۲	TIMI ≤ 2	%۲۲,۵	۱۲۶
Toprak, C.[25]	2015	Turkey	۳۰۴	۱۰ ± ۶۰	%۸۰,۹	TIMI ≤ 2 MBG ≤ 1	%۲۶,۰	۲۱۷
Wang, Z.[26]	2018	China	۶۱۲	۱۴ ± ۶۲	%۷۱,۱	TIMI ≤ 2	%۱۵,۸	۱۴۲

[Yildiz, A.[27	2015	Turkey	۲۸۷	۱۴ ± ۶۱	%۷۴,۲	TIMI ≤ 2	%۲۲,۰	۱۶۰

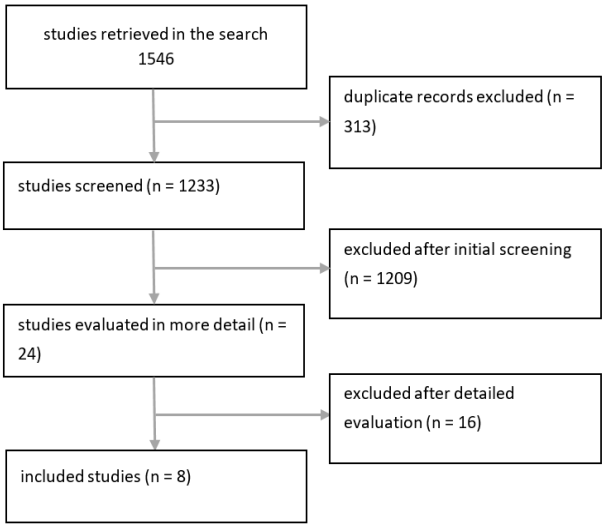


Figure 1. Flow chart summarizing the process of study selection.

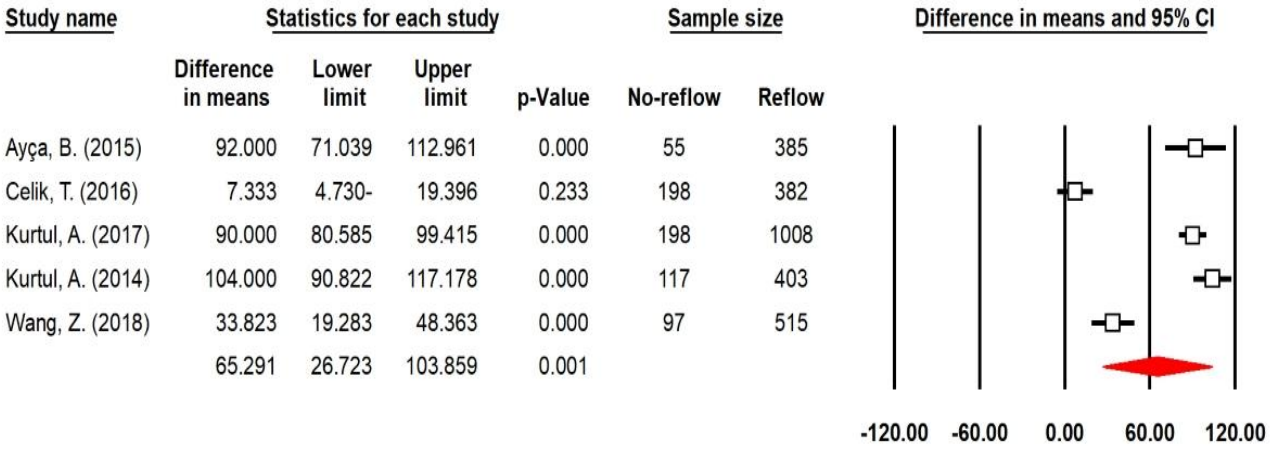
Prognostic value of platelet-to-lymphocyte ratio

The PLR was significantly associated with the no-reflow rate in six out of eight studies. Of the total studies, six of them compared PLR values between no-reflow and reflow groups and four reported a significant difference. These studies were included in the meta-analysis regarding differences in mean values, with the exception of one study that failed to report the standard deviation or interquartile range of PLR (24). In this meta-analysis, 3358 patients were included and was significantly 65.2 (CI95%: 26.7-103.8) units higher than that of reflow group (Figure 2).

The studies included in this meta-analysis were highly heterogeneous (I^2 = 98%, P<0.001).

Six studies with 3369 patients were included in the meta-analysis of diagnostic accuracy and odds ratio. The pooled sensitivity and specificity was 65% (CI 95%: 61%-69%) and 77% (CI 95%: 76%-79%), respectively (Figure 3a, b). In the high PLR group, the ratio of no-reflow to reflow rate was 2.81 (95% CI: 2.22-3.56), whereas this ratio was 0.45 (95% CI: 0.35-0.59) in the low PLR group (Figure 3c,d). A pooled odds ratio of 6.29 (95% CI: 3.98 to 9.95) indicates a six-fold higher odds of no-reflow in high PLR, compared to low PLR group (Figure 3e). The area under the summary receiver operating characteristic (SROC) curve was 0.805 (CI95%: 0.723-0.887), which indicates a good prognostic performance of PLR for prediction of no-reflow (Figure 3f).

Substantial heterogeneity was observed in these meta-analyses. The cut-off values used to stratify patients to low and high PLR groups varied in a range of 126 to 217 across studies. However, the threshold effect analysis showed no significant correlation between true positive and false positive rates, indicating that the results of this meta-analysis were not significantly affected by the difference in cut-off values (r=0.371, P=0.468).



the pooled mean of PLR in the no-reflow group

Figure 2. Forest plot of difference of PLR means between no-reflow and reflow.

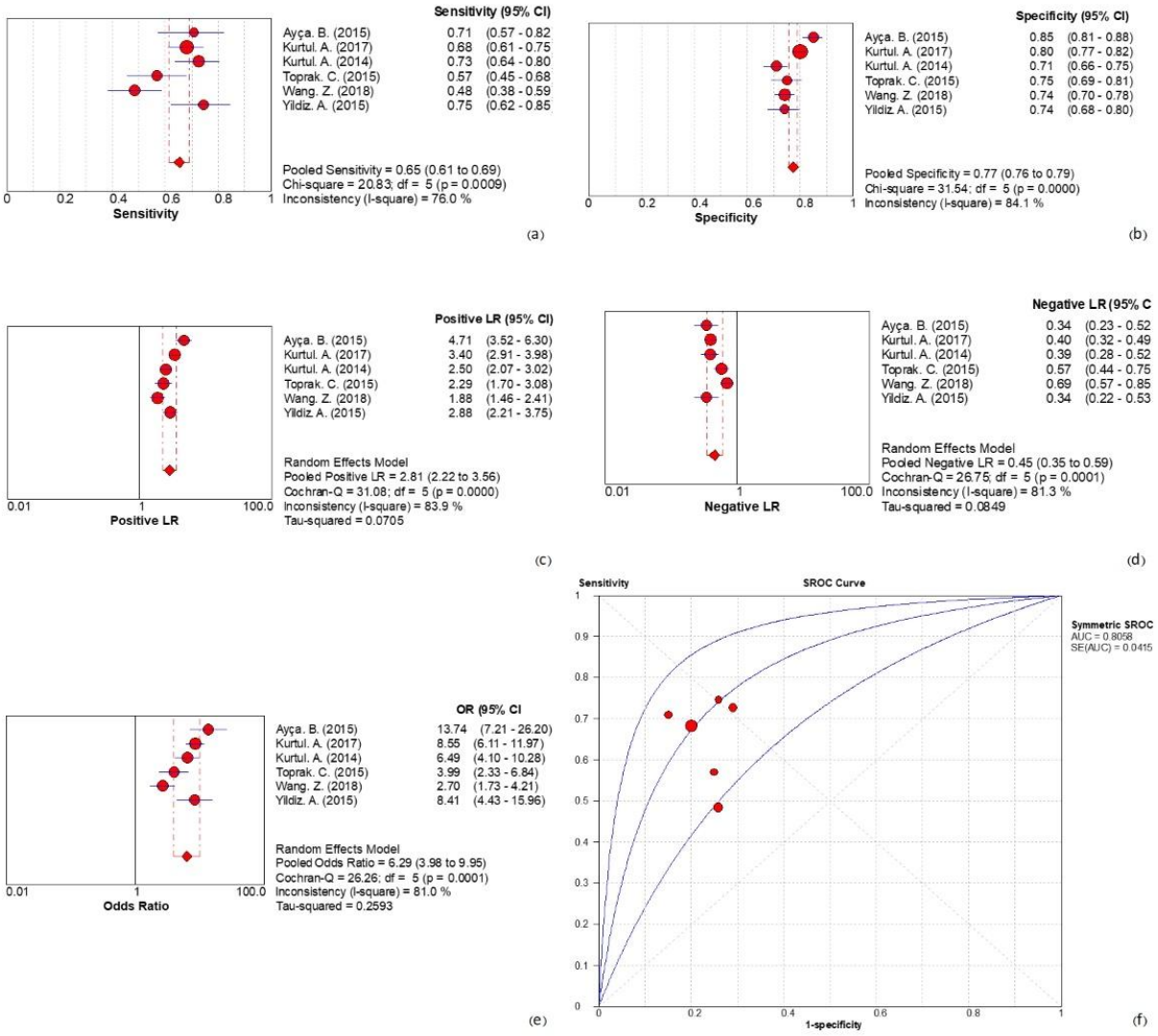


Figure 3. Forest plots of sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), diagnostic odds ratio (e) of PLR to predict no-reflow with its SROC curve (f).

Quality assessment

The quality of the included studies was assessed using a modified version of the REMARK score. The included studies failed to satisfy a median of six quality items (IQR: 5.75-6.5). Most of the studies failed to list the study variables in the methods, specify the rationale for the sample size, specify whether the PLR was included in the analysis as a continuous or binary variable, describe the relation of the marker to standard prognostic variables, and include all variables in the multivariable analysis regardless of their statistical significance in the univariate analysis. On the other hand, most of the studies specified the objectives and prospective or retrospective design of their studies as well as the statistical analyses in detail, described the study population, inclusion and exclusion criteria, and the method of measuring PLR, defined no-reflow clearly, and reported the population demographics (Table 2).

Table 2. Quality of the included studies.

.No	Item	Amirpour 2017 [20]	Ayca 2015 [21]	Celik 2015 [22]	Kurtul 2014 [23]	Kurtul 2017 [24]	Toprak 2015 [25]	Wang 2018 [26]	Yildiz 2015 [27]
١	Objectives specified	Y	Y	Y	Y	P	Y	Y	Y
٢	Inclusion/exclusion criteria reported	Y	Y	Y	Y	Y	Y	Y	Y

۳	Interventions reported	Y	Y	Y	Y	Y	Y	Y	Y
۴	Specimen characteristics clarified	Y	Y	Y	Y	Y	Y	Y	Y
۵	Assay methods clarified	N	Y	Y	Y	Y	Y	Y	Y
۶	Study design (prospective/retrospective) specified	Y	Y	Y	N	Y	P	Y	P
۷	No-reflow definition clarified	Y	Y	Y	Y	Y	Y	Y	Y
۸	Possible confounding variables listed	N	Y	P	Y	N	Y	N	Y
۹	Sample size rationale specified	Y	N	N	N	N	N	N	N
۱۰	Statistical analysis and model verification methods clarified	Y	P	P	Y	N	P	Y	P
۱۱	Clarified how marker values were handled (continuous (vs discrete	NA	N	N	N	N	N	N	N
۱۳	Baseline characteristics reported	Y	Y	Y	Y	P	Y	Y	Y
۱۴	Relation of marker to standard prognostic variables analyzed	N	P	N	N	N	P	N	Y
۱۵	Univiariable analysis performed	P	Y	N	Y	N	Y	Y	Y
۱۶	Multivariable analysis performed	N	Y	Y	Y	N	Y	Y	Y
۱۷	Variables included in the model regardless of statistical significance	N	N	N	N	N	N	N	N
۱۸	Checking assumptions, sensitivity analysis or internal validation performed	N	N	N	Y	N	N	N	N
۱۹	Interpretations of the results and study limitations discussed	Y	Y	Y	Y	P	Y	Y	Y
۲۰	Implications for future research and clinical values discussed	Y	N	Y	N	P	Y	Y	Y

Y: fully satisfied, P: partially satisfied, N: not satisfied

Discussion

No-reflow phenomenon complicates primary PCI with higher mortality and morbidity rates and its treatment and prevention are associated with a better outcome of primary PCI (12). Various pharmaceutical and mechanical interventions, including aspiration thrombectomy, distal protection with filters or balloons, and direct stenting (rather than predilation with a balloon) have been suggested to prevent no-reflow (32, 33). The utilization of these interventions would not be beneficial for all the patients and it is important to apply them selectively to the patients at a higher risk of developing no-reflow. Some of the identified risk factors for no-reflow include large thrombus burden, the duration and extent of ischemia, neutrophil count, diabetes, acute hyperglycemia, hypercholesterolemia, and lack of preconditioning (34).

Recently a meta-analysis showed that higher PLR was associated with a higher risk of in-hospital and long-term adverse events after acute coronary syndrome (35). In this systematic review, PLR was found to be a significant and independent predictor of no-reflow in most of the included studies. We showed that the pooled risk of no-reflow in

patients with high PLR was six-fold compared to the patients with low PLR, and PLR can predict no-reflow with a pooled sensitivity of 65% and a pooled specificity of 77%. The area under the sROC curve also shows a good prognostic performance for PLR.

The pathophysiology of no-reflow seems to be multifactorial, and the inflammatory and thrombotic status play important roles in the development of this phenomenon (36). Increased platelets count is a marker of inflammatory status, as several inflammatory mediators have been shown to stimulate megakaryocytes proliferation. Moreover, activated platelets are involved in inflammatory processes and release inflammatory mediators (37). On the other hand, lymphocytes regulate the inflammatory process and are associated with increased plaque stability (38, 39).

Additionally, increased platelets count reflects an excessive thrombotic status which is the other major mechanism involved in no-reflow. Antithrombotic therapies improve myocardial perfusion and no-reflow is often associated with a larger thrombus burden (40).

The PLR is a combined marker of inflammatory and thrombotic status and is easily measured with a complete blood count test which is inexpensive and available in most healthcare facilities. However, the results of complete blood counts may not be ready until after primary PCI has been performed. Ideally, the risk of no-reflow should be assessed before performing PCI to guide the decision for using additional preventive measures. The PLR has limited clinical utility if the results are not ready before performing primary PCI.

Limitations

The limitations of the studies in this systematic review included the retrospective design of most studies. Moreover, most of the studies were conducted in Turkey, making the results less representative of the global population. In addition, the patients with conditions that could affect platelets and or lymphocyte counts were excluded from the studies, which may lead to overestimation of the specificity of PLR in predicting no-reflow.

This meta-analysis also suffers from several limitations. Although multivariate logistic regressions were performed in the studies, there was no possibility to adjust for confounding variables in our meta-analysis. The included studies performed logistic regressions with PLR as a continuous and not a binary variable, and the best practice was to avoid pooling continuous odds ratios. Moreover, the confounding variables varied between the included studies. Therefore, we performed our meta-analysis using diagnostic statistical methods, which are by nature limited in adjusting for confounding variables.

Our meta-analysis was profoundly limited by the small number of the included studies, which not only makes the results less powerful but also imposes several issues on performing the meta-analysis (i.e., the assessment of publication bias and heterogeneity and performing subgroup analyses). Moreover, the results of the included studies were all in the same directions, indicating that publication bias was an issue in our meta-analysis. However, publication bias tests were not performed since they are not useful when a small number of studies are included (41).

Finally, although minimal heterogeneity was observed in our meta-analysis (with the exception of the meta-analysis of specificities), there were some differences between the included studies. Subtle differences were evident in the details of primary PCI procedure and other periprocedural interventions. For instance, some of the studies administered tirofiban, or utilized thrombus aspiration catheter selectively, while other studies did not mention using these interventions. Additionally, there were differences within the studies regarding the cut-off values which were used to stratify patients too high and low PLR groups. To assess the effect of this difference on the results of our meta-analysis, we performed threshold effect analysis which showed no evidence of this effect.

Conclusion

The PLR is a significant predictor of no-reflow in STEMI patients undergoing primary PCI. It can be used alone or in combination with other predictors to identify patients at higher risk of developing no-reflow; therefore, preventive measures would be applied to these patients. Large studies evaluating a combination of known risk factors is suggested for the ideal goal of developing models to stratify the patients based on the risk of developing no-reflow.

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