Review Article

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Evaluation of Platelet-to-Lymphocyte Ratio in Predicting Early and Long Term Outcomes Following Acute Coronary Syndrome

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ABSTRACT

BACKGROUND AND OBJECTIVE: The platelet-to-lymphocyte ratio (PLR) might be an important and critical measure in evaluating and anticipating undesirable outcomes in patients with acute coronary syndrome (ACS). What was discussed in this study was systemic evaluation of the role of PLR in predicting adverse outcomes of ACS (including mortality and MACE) both in the short term and in the long term.

METHODS: In this systematic review, studies related to platelet counts, lymphocytes, acute coronary artery syndrome were searches in Medline, Web of knowledge, Google scholar, Scopus, and Cochrane databases. Finally, 15 related studies were reviewed, including 7 prospective studies and 8 retrospective studies.

FINDINGS: In a review of 15 articles, a total of 8304 patients in the group with low PLR and 5822 patients in the group with high PLR were considered. The increase in PLR can increase the risk of short-term and long-term mortality by 0.3 and 1.8 times, respectively.

CONCLUSION: Based on the results of this study, the increase in PLR can effectively predict early and long term adverse events in patients with ACS.

KEY WORDS: *Blood Platelets, Lymphocytes, Acute Coronary Syndrome*.

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Introduction

Despite development of therapeutic methods and diagnostic tools, cardiovascular disorders remain as a major leading cause of mortality and disability around the world. In this regard, the critical role of inflammatory processes in progression of atherosclerotic plaques and increasing the susceptibility to ischemic events has been clearly determined (1). In fact, accumulation of inflammatory cells along with adhesion and aggregation of platelets on plaques is the causative pathophysiology of coronary heart disease which mainly sourced from some genetic polymorphisms and variants (2-4).

In this regard, recent evidences have emphasized the major role of reducing plasma leukocytes count in predicting improper outcome in patients suffering coronary artery disease as well as congestive heart failure (5-7). In the cases of persistent inflammation, blood leukocyte count may reduce due to increase in lymphocytic apoptosis. In fact, leukocyte response to inflammatory processes is considerable. In addition, the progression of inflammation may lead to increased proliferation of megakaryocyte series as important components of thrombosis. Previous studies could demonstrate a close relationship between increase in platelet counts and poor coronary artery disease-related outcome (8-10).

In this regard, platelet to lymphocyte ratio has been recently identified as a prognostic marker for mortality and morbidity due to cardiac ischemic events, long-term patients' survival following acute coronary syndrome as well as need to revascularization (11-14). Moreover, a high value of platelet to lymphocyte ratio has been associated with the increased likelihood of in-hospital mortality in patients suffering from acute myocardial infarction (15-18). Recent studies have shown that increasing the platelet count may be a predictor of acute coronary syndrome. In some large trials, such as TIMI, abnormal platelet cells have been predictive of higher mortality, re-infarction, and heart failure within 30 days of ACS occurrence (19). However, some studies have not seen such a role in predicting the 60-day outcome of ACS (20).

Other parameters associated with platelet count may play a role in the development of adverse outcomes in ACS. In this regard, some platelet hyper reactivity based on collagen / ADP closure time indices predict cardiovascular events (21). Some studies have shown a significant relationship between platelet residual activity (platelet aggregation in response to arachidonic acid agonists, ADP, and PFA-100) and the consequences of ACS (22, 23). The role of both platelet count (through platelet aggregation and vascular atheroma formation) and leukocyte count (through activation of inflammatory processes and injury to atherosclerotic plaque) in the development of cardiovascular events is quite clear. The aim of this study was to systematically review the role of the ratio of platelets to lymphocytes in predicting the outcomes of patients with acute coronary artery syndrome.

Methods

Search strategy: This study was performed according to established methods and in compliance with PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis) Protocols with the ethics code IR.IUMS.FMD.REC.1396.9411160016 (24). We searched online databases including Medline, Web of knowledge, Google scholar, Scopus, and Cochrane for all eligible studies in accordance with the considered keywords including: "acute coronary syndrome", "platelet", and “lymphocyte”, “platelet to lymphocyte ratio“, “outcome” and “mortality” since 2000. The studies were restricted to English language. Inclusion criteria were the relationship between platelet-to-lymphocyte ratio and clinical outcomes in patients with acute coronary artery syndrome. In the absence of clear and reproducible results in the study, non-English studies, lack of access to the full text of article copies, 10 articles were deleted (Figure 1).

Data abstraction was independently performed by two un-blinded reviewers on structure collection forms without divergences in data collection. The study quality was evaluated based on the following criteria: 1) the systematic review and meta-analysis based on the questions primarily described and formulated; 2) inclusion and exclusion criteria predefined in the studies as eligibility criteria; 3) searching the literature performed on a systematic and comprehensive approach; 4) to minimize the bias, the full texts of the articles were reviewed independently by two reviewers; 5) the quality of included studies was rated independently by the reviewers for appraising internal validity; 6) studies' characteristics and findings were comprehensively listed; 7)the publication and risk of bias were listed; and 8)heterogeneity was also assessed (25). The present study was conducted to determine the early and long-term odds of mortality and major adverse cardiac events (MACE) after acute coronary syndrome through determining Odds Ratio for determining this association.

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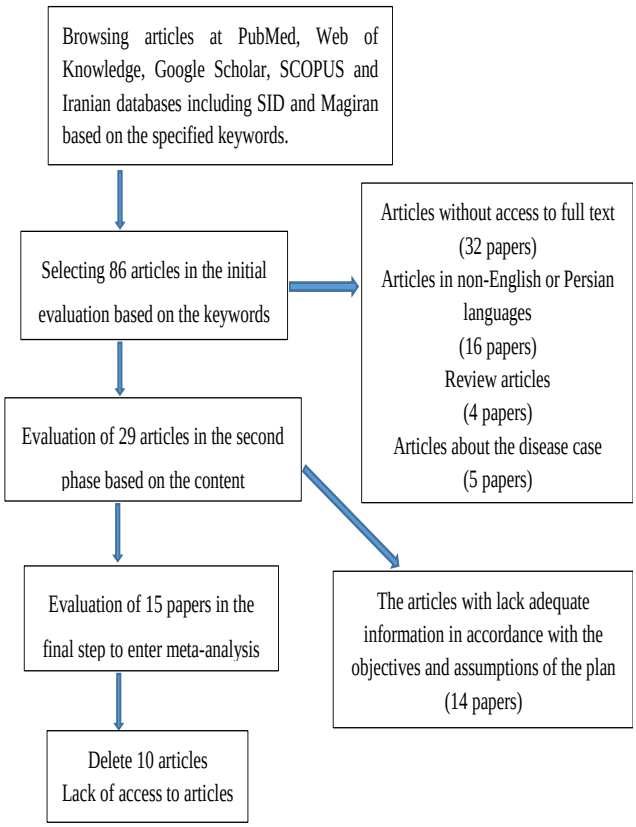

Figure 1. Flowchart for the selection of studies for final analysis

Statistical analysis: Dichotomous variables are reported as proportions and percentages, and continuous variables as mean values. Binary outcomes from individual studies were to be combined by the Mantel-Hansel fixed effect model. The odds ratio (OR) and 95% confidence interval (CI) were used as summary statistics for the comparison of dichotomous variables. Cochran's Q test was used to determine the statistical heterogeneity of this study.

This test was complemented with the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. An I^2 value of 0-25% indicates insignificant heterogeneity, 26-50% low heterogeneity, 51-75% moderate heterogeneity and 76-100% high heterogeneity.

Publication bias was assessed by the rank correlation test and also confirmed by the funnel plot analysis. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at p=0.05. Statistical analysis was performed using the Stata software (version 13.1, Stata Corp, College Station, TX, USA).

Results

In this study, 15 studies were evaluated which included 7 prospective studies and 8 retrospective studies (26-39). In these studies, the participants in the study were classified into low PLR and high PLR groups in terms of both short and long term outcomes. In total, 8304 patients in the low PLR group and 5822 in the high PLR group were considered. The mean age of patients in the two groups was 60.06±2.84 years and 63.27±3.17 years, respectively.

In a total of 15 studies, the population studied in 4 studies involving patients with UA, in one study included patients with NSTEMI and in 10 studies involving patients with STEMI. In summary, a wide range of cut-off values for PLR was considered for predicting ACS outcomes, reported in the range of 116 to 217. Only 11 studies followed the patients for a long time, and the follow-up period was between 6 and 60 months. In total, 8 studies were performed on in-hospital mortality, 10 studies on long-term mortality, 4 studies on in-hospital MACE and 6 studies on long-term MACE.

In assessing the relationship between the increase in PLR and the prediction of hospital mortality, we found that patients with high PLR were more likely to face hospital deaths than patients with low PLR with a relative risk of 3.08 (95%CI: 2.43 to 3.91). Studies regarding the relationship between high PLR and hospital mortality were found to be of acceptable homogeneity (homogeneity coefficient= 29.0, p=0.196) (Figure 2).

Moreover, the studies did not have a publication bias (p=0.216). In assessing the relationship between increased PLR and long-term mortality prediction, the increase in PLR in patients with ACS was associated with an increased risk for long-term death (relative risk: 1.83, 95% confidence interval: 1.62 to 2.8). In this regard, studies also had high degree of heterogeneity (homogeneity coefficient= 0.81, p= 0.001). Moreover, the studies had publication bias (p= 0.039) (Figure 2).

In total, 10 studies examined the relationship between high PLR and in-hospital MACE. In the analysis of these studies, the increase in PLR predicted the occurrence of in-hospital MACE with a relative risk of 2.52 (95% CI: 1.76 to 2.88). Studies also had high levels of heterogeneity (homogeneity coefficient equal to 67, p= 0.023) (Figure 2). However, studies did not have a significant publication bias (p= 0.999). Moreover, increased PLR was a strong predictor for

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long-term MACE after ACS (relative risk= 1.86, 95%CI: 1.64 to 1.21). However, studies also had high levels of heterogeneity (homogeneity coefficient equal to 0.81, p= 0.001). The studies did not have a significant publication bias (p= 0.255) (Figure 2). In total, the increase in PLR could increase the risk of short and long term mortality by 0.3 and 1.8 times, respectively. Furthermore, an increase in PLR increased the risk of occurrence of short-term and long-term MACE by 2. 2 and 1.8 times, respectively.

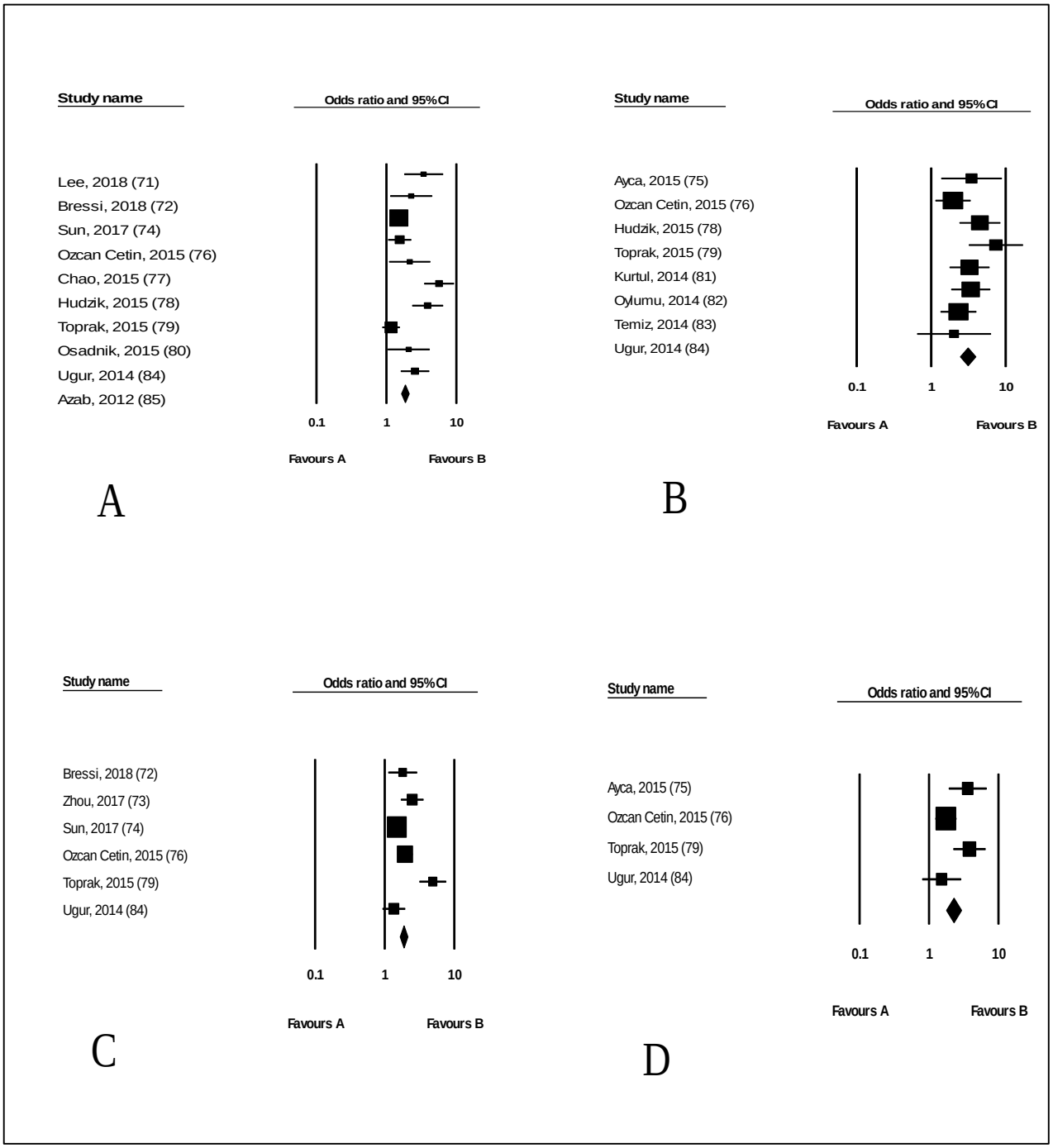

Figure 2. Results of the meta-analysis of the relationship between increased PLR and the relative risk of mortality and short- and long-term MACE in patients with ACS

A: long-term mortality

B: in-hospital mortality

C: long-term cardiac complications

D: in-hospital cardiac complications

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Table 1. Details of the studies systematically assessed

Author	Study type	Country	Comparison	Number	Age (year)	Male (%)	ACS	Cutoff/PLR	Intervention
Lee, 2018 (71)	PC	Australia	Low/high PLR	342/172	63/65	67/72	UA	137	PCI
Bressi, 2018 (72)	PC	Italy	Low/high PLR	314/157	66/69	84/67	STEMI	164	PCI
Zhou, 2017 (73)	RC	China	Low/high PLR	426/213	58/60	61/61	STEMI	171	PCI
Sun, 2017 (74)	RC	China	Low/high PLR	1470/1484	58/63	77/78	STEMI	163	PCI
Ayca, 2015 (75)	RC	Turkey	Low/high PLR	281/159	56/59	68/65	STEMI	137	PCI
Ozcan Cetin, 2015 (76)	PC	Turkey	Low/high PLR	1292/646	60/60	66/66	STEMI	148	PCI
Cho, 2015 (77)	RC	Korea	Low/high PLR	508/290	60/62	66/61	UA	128	PCI
Hudzik, 2015 (78)	RC	Poland	Low/high PLR	349/174	63/65	41/43	STEMI	124	PCI
Toprak, 2015 (79)	PC	Turkey	Low/high PLR	318/217	60/59	83/76	STEMI	217	PCI
Osadnik, 2015 (80)	RC	Poland	Low/high PLR	986/987	62/65	76/66	STEMI	121	PCI
Kurtul, 2014 (81)	PC	Turkey	Low/high PLR	521/495	58/65	76/67	UA	116	PCI
Oylumu, 2014 (82)	RC	Turkey	Low/high PLR	391/196	60/65	44/66	UA	127	PCI
Temiz, 2014 (83)	RC	Turkey	Low/high PLR	474/212	61/64	74/73	STEMI	144	PCI
Ugur, 2014 (84)	PC	Turkey	Low/high PLR	426/213	55/60	85/85	STEMI	175	PCI
Azab, 2012 (85)	PC	USA	Low/high PLR	206/207	61/68	74/61	NSTEMI	176	PCI

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Table 2. Details of hospital and long-term consequences of ACS in various studies

Author	Follow-up	Comparison	Early mortality	Long-term mortality	Early MACE	Long-term MACE
Lee, 2018 (71)	60.0	Low/high PLR	-	5.0/15.0	-	-
Bressi, 2018 (72)	60.0	Low/high PLR	-	5.4/11.5	-	15.0/24.2
Zhou, 2017 (73)	42.0	Low/high PLR	-	-	-	17.3/34.2
Sun, 2017 (74)	81.6	Low/high PLR	-	13.3/18.7	-	12.2/17.2
Ayca, 2015 (75)	In-hospital	Low/high PLR	2.5/8.2	-	6.0/18.9	-
Ozcan Cetin, 2015 (76)	31.6	Low/high PLR	2.1/4.0	5.0/7.6	5.7/9.6	12.0/21.1
Cho, 2015 (77)	62.8	Low/high PLR	-	3.1/6.6	-	-
Hudzik, 2015 (78)	12.0	Low/high PLR	11.2/17.8	8.3/33.9	-	-
Toprak, 2015 (79)	24.0	Low/high PLR	2.0/14.0	8.0/25.0	7.0/22.0	11.0/38.0
Osadnik, 2015 (80)	37.0	Low/high PLR	-	9.6/11.0	-	-
Kurtul, 2014 (81)	In-hospital	Low/high PLR	2.7/8.3	-	-	-
Oylumu, 2014 (82)	In-hospital	Low/high PLR	4.9/14.8	-	-	-
Temiz, 2014 (83)	In-hospital	Low/high PLR	5.9/12.7	-	-	-
Ugur, 2014 (84)	6.0	Low/high PLR	1.4/2.6	4.0/8.0	5.4/8.0	22.1/27.7
Azab, 2012 (85)	48.0	Low/high PLR	-	16.0/33.0	-	-

Discussion

The role of both platelet counts (through the process of adhesion and platelet aggregation and the formation of vascular atheroma) and the leukocyte counts (by activating inflammatory processes and injuring atherosclerotic plaque) in the development of cardiovascular events have been clearly revealed. In recent years, the PLR index has been considered as an important and critical measure in evaluating and anticipating undesirable outcomes in patients with inflammatory and ischemic diseases (such as cardiovascular diseases, cerebrovascular accidents, and cancers). What was discussed in this study was the systemic evaluation of the role of PLR in predicting adverse outcomes of ACS (including mortality and MACE) both in the short term and in the long term. In this regard, a systematic analysis of studies aimed at comparing the two groups of patients with ACS with low PLR and high PLR was conducted to calculate the relative risk of occurrence of mortality and MACE in patients with increased PLR. What we finally found in this systematic analysis was that, first, increased PLR can increase the risk of short and long term mortality by 0.3 and 1.8 times, respectively. Second, an increase in PLR increases the risk of occurrence of short and long-term MACE by 2.2 and 1.8 times, respectively. Therefore, this index can be used as a prognostic parameter in predicting adverse outcomes in ACS patients. However, the studies were accompanied by some potential limitations. Firstly, the PLR cut-off points had a wide range in studies in such a way that these cut-off points varied from 116 to 217, which would make it difficult to take advantage of a specific cut-off points in predicting the outcomes in a clinical setting. Perhaps the use of averaged cut-off points can be exploited clinically, which requires more studies. On the other hand, due to the variety of sample sizes in studies, differences in the design of studies (prospective or retrospective) and significant differences during the follow up of patients, high heterogeneity was observed. In fact, heterogeneity in these studies is mainly

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influenced by the nature of the study, the choice of criteria for entering and leaving the study, the length of follow-up of patients, and most importantly the number of patients enrolled in the study. Each of these indicators may have contributed to the increase in heterogeneity. As a result, in the results of various studies, the publication bias in studies (except studies based on the evaluation of long-term mortality) was significantly lower. In terms of definition, publication bias means achieving both positive and negative results in studies. Therefore, in our analysis, studies had high similarity regarding the value of high PLR in the prediction of hospital mortality as well as short and long-term MACE and thus the studies had coherence in the publication of the results related to the predictability of PLR. In total, there are several reasons for publication bias. First of all, writers are usually interested in the significant results of their work and to publish these results, which can cause some irresponsible results never to be sent to magazines. Secondly, some editors and reviewers of journals tend to publish more positive and significant results in their journals because they have less significant readers. In sum, what can be deduced from the heterogeneity of the system and the high publication bias is that, first, studies should be carried out in different societies, taking into account racial and geographical differences, and second, the evaluation and analysis of articles published in journals with the above profiles is preferable.

Increased PLR in predicting early and long-term outcomes (including mortality and MACE) in patients with ACS has a high prognostic value. In this regard, increasing PLR increases the risk of short-term and long-term mortality by 0.3 and 1.8 times, respectively. Also, increasing PLR increases the risk of short-term and long-term MACE by 2.2 and 1.8 times, respectively.

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