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Prognostic value of the platelet-to-lymphocyte ratio for outcomes of stroke: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The current study aimed to conduct a systematic literature search and pool data from individual studies to assess the relationship between platelet-lymphocyte ratio (PLR) and functional outcomes and mortality in stroke patients.

MATERIALS AND METHODS: The databases of PubMed, Embase and Google Scholar were searched for relevant studies up to 21st August 2021. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the association between PLR and poor functional outcomes and mortality.

RESULTS: Sixteen studies were included in the systematic review and nine in the meta-analysis. On analysis of eight studies, we noted no statistically significant relationship between PLR and poor functional outcomes in patients with stroke (OR: 1.00 95% CI: 1.00, 1.00 I^2=80% *p*=0.30). Data on mortality was reported by just two studies. Pooled analysis indicated no statistical relationship between PLR and mortality in patients with stroke (OR: 1.49 95% CI: 0.56, 3.98 I^2=76% *p*=0.43). Descriptive analysis of the remaining studies demonstrated conflicting results for the relationship between PLR and early neurological deterioration (END) and functional outcomes.

CONCLUSIONS: Our results indicate that PLR may not be a useful prognostic marker to predict functional outcomes after AIS. Evidence on the predictive power of PLR for mortality and END after stroke is scarce and contrasting. There is a need for further studies assessing the role of PLR in predicting outcomes of stroke patients while taking into account important confounders like baseline stroke severity and treatment modality.

Key Words:
Stroke, Platelets, Lymphocytes, Inflammation, Mortality, Function.

Introduction

Stroke can be defined as a sudden impairment in the function of a region of the brain mainly due to hemorrhage or ischemia. When combined, acute ischemic stroke (AIS) and hemorrhagic stroke are the second most common cause of death around the world[1]. A recent study from China[2] indicates that the incidence of stroke has been increasing over the past 30 years with age-standardized prevalence, incidence, and mortality rates of 1114.8, 246.8, and 114.8/100 000 person-years, respectively. Indeed, with high such high numbers, the need for refinement of management protocols and risk stratification of patients with stroke cannot be underestimated. Prediction of prognosis after stroke is important to provide optimal care and allocate scarce medical resources. Availability of reliable prognostic markers in the early period of stroke can help in clinical decision making[3]. Over the past few decades, there has been intense research over several factors to predict outcomes of stroke but with variable results[4,5].

In recent times, the role of inflammation in the pathophysiology of stroke is being increasingly recognized[6]. Inflammation is closely associated with the initiation and progression of atheroma which subsequently leads to the development of stroke[7]. During the inflammatory process, platelets cause thrombocyte activation and release of cytokines leading to a localized inflammatory process at the vascular site[8]. Contrastingly, lymphocytes are mononuclear blood cells that modulate cellular and humoral

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immunity. Preliminary research[9] suggests that lymphocytes may have an anti-atherosclerosis function as well. In this context, the platelet-lymphocyte ratio (PLR) has been used as a prognostic marker for various diseases wherein inflammation is involved in the pathophysiological process. Studies[10-14] have demonstrated that PLR can be a useful prognostic marker for several malignancies like gastric, oral, renal, pancreatic, and cervical cancer. Amongst non-cancer diseases, PLR has been reported[15,16] to be a simple biomarker to predict osteoporosis and exacerbations in chronic obstructive pulmonary disease as well. In the past few years, several studies[17-20] have attempted to assess the relationship between PLR and the prognosis of stroke patients. However, while some studies[17,18] have demonstrated a link between PLR and functional outcomes after stroke another has shown no such association[19,20]. Given the conflicting results of individual studies, there is a need for a systematic review of evidence to demonstrate if PLR is indeed a marker for predicting outcomes in stroke patients. Since no such review has been conducted to date, the current study aimed to conduct a systematic literature search and pool data from individual studies to assess the relationship between PLR and functional outcomes and mortality in stroke patients.

Materials and Methods

This systematic review and meta-analysis were carried out according to the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[21]. The PROSPERO registration number of the study is CRD42021269462.

Literature Search

Two reviewers independently searched the electronic databases of PubMed, Embase, and Google Scholar for relevant articles. The search strategy was formalized with the aid of a medical librarian and the search limits were set from the inception of the above-mentioned databases to 21st August 2021. Only studies written in English were included. The search strings used for the literature search were: 1. "Platelet-lymphocyte ratio" AND "stroke" and 2. "PLR" AND "stroke". The primary search results were assessed initially by their titles and abstracts to identify citations requiring full-text analysis. The full texts of the articles were reviewed by the two reviewers independently based on the inclusion and exclusion criteria. The disagreements were resolved by discussion. We also carried out manual scoping of the bibliography in included studies for any additional articles.

Inclusion Criteria

The inclusion criteria were as follows: (1) All types of studies conducted on adult patients with stroke; (2) Studies were to measure PLR at admission or within 24 hours of admission; (3) Studies were to evaluate the relationship between PLR and mortality or functional outcomes.

Exclusion criteria were: (1) Studies not reporting outcomes of interest; (2) Studies with the unavailability of full texts; (3) Abstracts, editorials, review articles, and case reports; (4) Studies with a repeated or overlapping sample. If more than one study extracted their sample from the same database, the study including the maximum number of patients was selected for inclusion.

Data Extraction and Risk of Bias Assessment

A data extraction sheet was used by two reviewers to extract relevant data from the studies. Details of the first author, publication year, study type, study location, sample size, type of stroke, age and gender details, National Institutes of Health Stroke Scale (NIHSS) score, treatment modality used, the cutoff for PLR, sample collection time, study outcomes, and definition of outcomes were extracted. The outcome of interest for our review were mortality and functional outcomes. No prior definition was set for functional outcomes and definition as per the included study was used.

The methodological quality of studies was assessed using the Newcastle-Ottawa scale (NOS)[22]. It was conducted by two authors independent of each other. All disagreements were solved by a discussion. Studies were assessed for selection of study population, comparability, and outcomes, with each domain being awarded a maximum of four, two, and three points respectively. The maximum score which can be awarded was nine. Studies with nine points were considered to have a low risk of bias, seven to eight points were considered to have a moderate risk of bias and those with scores of six and below were with a high risk of bias.

Statistical Analysis

The software "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis. We extracted odds ratios (OR) with 95% confidence intervals (CI) of the association between PLR and outcomes from the included studies. These were then pooled using the generic inverse variance function of the meta-analysis software. The random-effects model was used for all the meta-analyses. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. Due to a limited number of studies in the meta-analysis (less than 10), funnel plots were not used to assess publication bias. We conducted a sensitivity analysis for the meta-analysis on poor functional outcomes. In the analysis, individual studies were excluded one at a time and the effect size was recalculated for the remaining studies in the meta-analysis software itself. Sub-group analysis was also carried out based on the location of studies, baseline NIHSS score, treatment modality, and definition of poor functional outcome.

Results

Search Results and Details of Included Studies

The number of search results at each stage is summarized in Figure 1. A total of 16 studies were included in this systematic review[17-20,23-34]. Details of all included studies are presented in Table I. The majority of the studies were from Asian countries while one was from Europe[20]. All studies were conducted on patients with AIS, except for one wherein 88.6% of patients had ischemic stroke[30]. The mean NIHSS score of the included studies varied from 3.7 to 13. In six studies[17,23,25,28,33,34], 100% of patients underwent intravenous thrombolysis (IVT) while in two studies[27,32] 100% of patients underwent endovascular therapy (EVT). All studies assessed the relationship between PLR and outcomes by using PLR as a continuous variable, except for two studies[24,27] wherein the cohorts were divided into two groups with PLR cutoff of either 163.12[24] or 145[27]. Four studies[20,24,25,33] recorded PLR within 24 hours of admission while the rest recorded it on admission. The NOS score of the included studies ranged from 5 to 8.

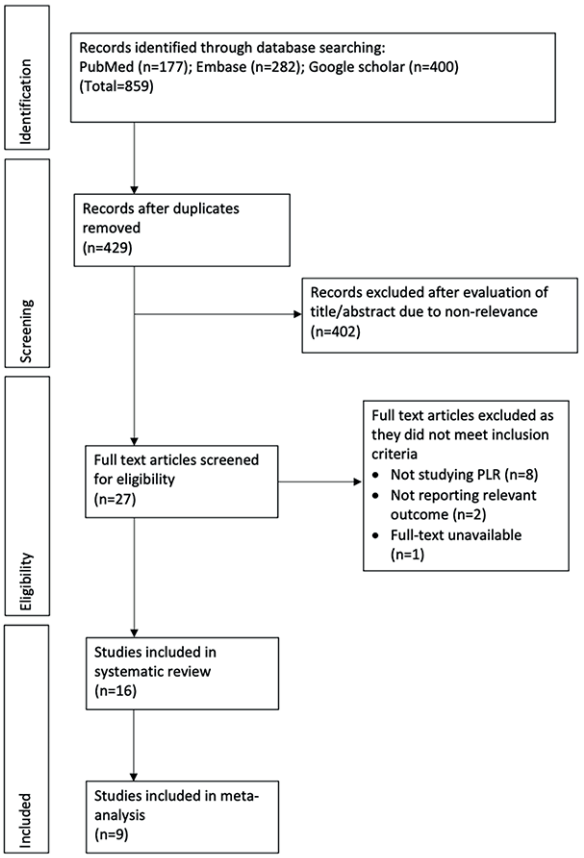

Figure 1. Study flow chart.

Analysis of Data

A total of eight studies[20,24-26,28,29,32,34] provided data on the association between PLR and poor functional outcomes at three months as ORs. On pooled analysis, we noted no statistically significant relationship between PLR and poor functional outcomes in patients with AIS (OR: 1.00 95% CI: 1.00, 1.00 I^2=80% p=0.30) (Figure 2). The results were stable on sensitivity analysis and there was no change insignificance of the results on the exclusion of any study. To explore the source of heterogeneity in the meta-analysis, we conducted multiple sub-group analyses (Table II). Dividing the studies based on the country of origin (Chinese and non-Chinese), we found that high PLR was associated with an increased risk of poor functional outcomes in Chinese studies but not in non-Chinese studies. Similarly, on classifying the studies based on baseline NIHSS scores, there was a statistically significant association between high PLR scores and poor functional outcomes when baseline NIHSS score was <8, but this was not significant for studies with a

Table I. Details of included studies.

Study	Location	Sample size	Ischemic stroke (%)	Age (years)	Male gender (%)	NIHSS score	IVT (%)	EVT (%)	Cutoff for PLR	Sample collection	Outcomes	Definition of outcome	NOS score
Sharma 2021[18]	India	100	100	60.8	69	10.8 ± 6.3	NR	NR	No cutoff	On admission	END	NR	5
Sha 2021[29]	China	210	88.6	66.9	64.8	NR	NR	NR	No cutoff	NR	Mortality at 6 months	–	8
Li 2021[30]	Taiwan	277	100	73.2	56.6	9.2 ± 7.8	37.2	12.6	No cutoff	On admission recovery at 3 months	Neurologica score compared with admission baseline	Improvement of mRS ≥ 1	8
Lee 2021[31]	Korea	282	100	69.5 ± 13.4	57.4	14.1 ± 6.5	52.5	100	No cutoff	On admission functional outcome at 3 months	Poor of ≥ 3	Defined as a mRS score	8
Gong 2021[17]	China	1060	100	69.7	66	7.2 ± NR	100	–	No cutoff	On admission	END	Increase in the NIHSS score by ≥ 4 points in the total score within 24 h after thrombolysis	7
Ferro 2021[20]	Portugal	325	100	75	49	13.7 ± 8.2	68	58	No cutoff	Within 24 hours of onset	1. Poor functional functional 2. END in NIHSS at 24 hours from the baseline	1. Defined as a mRS score of ≥ 3 2. Any increase	8
Chen C 2021[33]	China	448	100	66.8	64.7	3.7 ± 2.2	0	0	No cutoff	On admission	Poor functional outcome at 3 months	Defined as a mRS score of ≥ 3	8
Chen Y 2021[32]	China	280	100	69	63.9	NR	100	–	No cutoff	Within 24 hours of admission	1. Poor functional outcome at 3 months 2. Mortality	Defined as a mRS score of ≥ 3	6
Chen CT 2021[23]	Taiwan	100	100	71.3	46	12.7 ± 6.5	100	–	No cutoff	On admission	Poor functional outcome at 3,6 and 12 months	Defined as a mRS score of ≥ 3	8
Topcuoglu 2020[34]	Turkey	165	100	70	42	13 ± 5.6	100	–	No cutoff	On admission	Poor functional outcome at 3 months	Defined as a mRS score of ≥ 3	8
Cao 2020[24]	China	663	100	66.8	68	3.7 ± 2.9	3	NR	163.12	Within 24 hours of admission	Poor functional outcome at 3 months	1. Defined as a mRS score of > 2	

Continued

Table I *(Continued)*. Details of included studies.

Study	Location	Sample size	Ischemic stroke (%)	Age (years)	Male gender (%)	NIHSS score	IVT (%)	EVT (%)	Cutoff for PLR	Sample collection	Outcomes	Definition of outcome	NOS score
Xu 2019[25]	China	286	100	69.5	59.1	8.7 ± 8.9	100	–	No cutoff	Within 24 hours of onset	1. Poor functional outcome at 3 months 2. Mortality at 3 months	1. Defined as a mRS score of > 2	8
Sung 2019[26]	Taiwan	99	100	64.1	59.6	8.6 ± 8.5	NR	NR	No cutoff	On admission	Poor functional outcome	Defined as a mRS score of ≥ 3	6
Chen 2019[28]	China	241	100	66.5	67.6	9 ± 5.9	100	–	No cutoff	On admission	Poor functional outcome at 3 months	Defined as a mRS score of ≥ 3	8
Inanc 2018[19]	Turkey	56	100	58.2	62.5	16.9± 3.3	–	NR	No cutoff	On admission	END, Poor functional outcomes	NR	5
Altintas 2016[27]	Turkey	57	100	61.9	36.8	NR	–	100	145	On admission	Poor functional outcome at 1 and 3 months	Defined as a mRS score of ≥ 3	6

CC: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IVT, intravenous thrombolysis; EVT, endovascular therapy; NOS, Newcastle Ottawa Scale; NR, not reported; END, early neurological deterioration; PLR, platelet lymphocyte ratio or comorbidities.

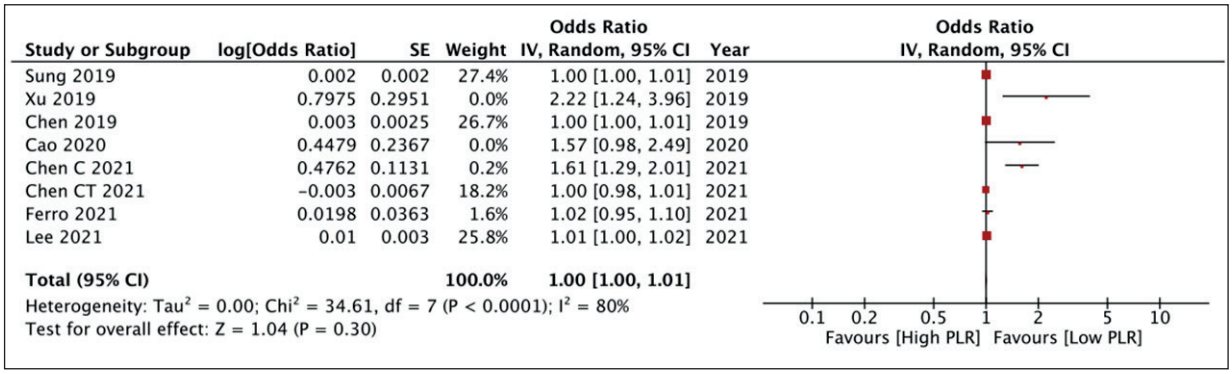

Figure 2. Meta-analysis of the relationship between PLR and poor functional outcomes.

Table II. Subgroup analysis of association between PLR and poor functional outcomes.

Variable	Groups	Number of studies	Pooled OR
Location	Chinese	4	1.46 95% CI: 1.20, 2.13 I^2 =89% p = 0.05
	Non-Chinese	4	1.00 95% CI: 1.00, 1.01 I^2 =52% p = 0.17
NIHSS score	≥ 8	6	1.00 95% CI: 1.00, 1.01 I^2 =63% p = 0.18
	< 8	2	1.60 95% CI: 1.31, 1.96 I^2 = 0% p < 0.00001
IVT	100%	3	1.00 95% CI: 0.98, 1.02 I^2 = 75% p = 0.90
	Others	5	1.01 95% CI: 0.99, 1.03 I^2 = 85% p =0.25
Definition of poor functional outcome	mRS ≥ 3	6	1.00 95% CI: 1.00, 1.01 I^2 = 79% p = 0.28
	mRS > 2	2	1.79 95% CI: 1.25, 2.58 I^2 = 0% p = 0.02

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IVT, intravenous thrombolysis.

baseline NIHSS score of ≥8. Sub-group analysis based on the use of IVT demonstrated no change in the significance of results. However, we noted that high PLR was associated with increased risk of poor functional outcomes when defined as modified Rankin scale (mRS) >2, but not for studies that defined it as ≥3.

Data on mortality was reported by just two studies[25,30]. Pooled analysis indicated no statistical relationship between PLR and mortality in patients with stroke (OR: 1.49 95% CI: 0.56, 3.98 I^2=76% p=0.43) (Figure 3).

Since many studies could not be included in the meta-analysis for want of data, a descriptive analysis was performed for these studies. Details of study results not included in the meta-analysis are presented in Table III. Early neurological deterioration (END) was assessed by four studies[17-20] in the review but with variable definitions and conflicting results. Sharma et al[18] and Gong et al[17] noted a statistically significant relationship between high PLR and END, but Ferro et al[20] and Inanc et al[19] noted no such difference. Li et al[31] also noted no relationship between PLR and neurological recovery at 1, 3, 6, and 12 months post-stroke. Amongst the four studies[19,23,27,33] reporting relationship between PLR and poor functional outcomes at three months, two[27,33] showed

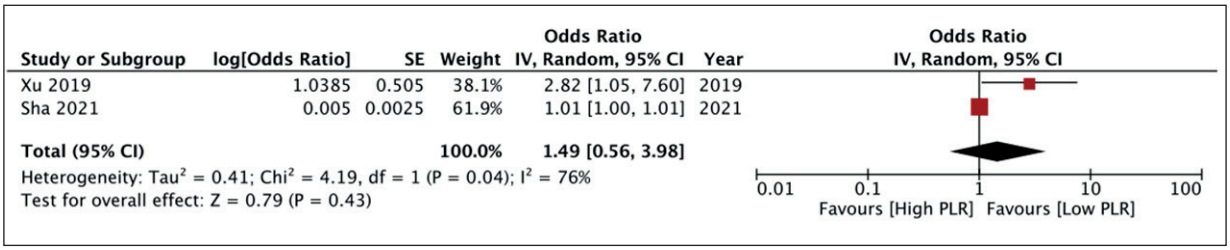

Figure 3. Meta-analysis of the relationship between PLR and mortality.

Table III. Descriptive analysis of study outcomes not included in the meta-analysis.

Study	Outcome	Results
Sharma 2021[18]	END	The mean PLR value increased significantly from the baseline in patients who deteriorated (263.42 ± 108.98 to 346.28 ± 125.35; $p = 0.016$), decreased drastically in patients who improved (242.27 ± 75.14 to 167.19 ± 57.91; $p = 0.0001$) and did not change much in patients who tend to remain static (181.35 ± 105.40 to 183.36 ± 111.61; $p = 0.955$)
Li 2021[30]	Neurological recovery	PLR did not predict neurological recovery at 3 months (OR: 0.997 95% CI: 0.994-1.000). There was no difference was observed in PLR values upon admission between patients with AIS and neurological recovery and patients with no improvement at 1, 3, 6, and 12 months post-stroke.
Gong 2021[17]	END	PLR was an independent factor predicting END (OR: 1.013; 95% CI: 1.009-1.016)
Ferro 2021[20]	END	PLR did not predict END (OR: 1.06; 95% CI: 0.83, 1.34)
Chen Y 2021[32]	Poor functional outcome and mortality at months	The mean PLR was significantly higher in patients with poor functional outcomes [143.46 (106.41-192.04) *vs.* 121.30 (91.59-162.93)] and in patients who dies within 3 months [153.64 (100.00-242.86) *vs*.125.00 (94.15-164.59)]
Topcuoglu 2020[34]	Poor functional outcome at 3 months	No statistically significant difference in PLR between patients with poor functional outcomes vs those with favorable outcomes (147 ± 92 *vs.* 130± 79)
Inanc 2018[19]	END and Poor functional outcomes	No significant relationship between PLR and NIHSS scores at 24 hours ($p = 0.07$) and mRS scores at 3 months ($p = 0.101$)
Altintas 2016[27]	Poor functional outcome at 3 months	Patients with low-PLR values had better functional outcomes as compared with the patients with high-PLR values at 1 month ($p = 0.004$) and 3 months ($p = 0.014$)

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; END, early neurological deterioration; PLR, platelet lymphocyte ratio; OR, odds ratio; CI, confidence intervals.

a significant relationship between high PLR and poor functional outcomes while the other two[19,23] showed no such association.

Discussion

In recent years, there has been a spurt in research focusing on hematological prognostic markers for various diseases[10-14]. Amongst several investigations prescribed for the diagnosis and management of different illnesses, measurements of complete blood counts are a relatively common and routine practice around the world. Indeed, if such counts could provide early prognostic information for major diseases like stroke, it would not only empower clinicians with a low-cost and easy-to-use biomarker but also enable early risk stratification and aid in clinical decision-making. However, a plethora of ratios has been evaluated by researchers in a bid to find the most optimal biomarker to predict the prognosis of stroke. To name a few, the neutrophil-lymphocyte ratio (NLR), neutrophil-eosinophil ratio, PLR, lymphocyte-monocyte ratio, eosinophil-leucocyte ratio, and eosinophil-monocyte ratio have all been analyzed by clinicians but with variable results, and to date there is no consensus on what constitutes the most optimal prognostic marker for patients with stroke[17,33,35,36]. Considering the variability of results amongst individual studies, a pooled analysis by means of a systematic review would provide better evidence on the clinical utility of the biomarker.

Amongst the enumerated factors, NLR and PLR have received maximum attention in the literature. In a recent meta-analysis of nine studies, Zhang et al[37] have demonstrated that higher NLR was predictive of poor functional outcome in stroke patients at 3 months (OR: 1.55 95% CI: 1.21-2.00) but not for mortality at 3 months (OR: 2.35 95% CI: 0.40-13.78) or functional outcomes at discharge (OR: 2.38 95% CI: 0.49-11.69). In another review focusing only on AIS patients receiving IVT, Wang et al[38] showed that high NLR was significantly associated with an increased risk of hemorrhagic transformation (OR: 1.33 95% CI: 1.14-1.56) and poor functional outcomes

at 3 months (OR: 1.64 95% CI: 1.38-1.94). In contrast, to date, no review has attempted to assess the relationship between PLR and stroke outcomes. It should be noted that despite broad inclusion criteria, the majority of the included studies were conducted on AIS patients. The only study[30] with a mixed cohort included just 11.8% of hemorrhagic stroke patients. This is important as circulating platelets are directly involved in the genesis of arterial thromboembolism in the case of AIS. Furthermore, the disintegration of platelet granules leads to the release of a variety of chemokines and cytokines which mediate mobilization of other peripheral blood cells at the site of the thrombus[39]. Excessive activation and accumulation of platelets may therefore lead to worse clinical outcomes after AIS[39]. Contrastingly, higher lymphocytes could be beneficial owing to their neuroprotective function[9]. Thus, hypothetically high PLR could lead to worse outcomes after stroke.

In this first systematic review and meta-analysis on the role of PLR for predicting prognosis after stroke, we detected no statistically significant association between PLR and poor functional outcomes at 3 months or mortality. On examination of the forest plot, one can note that of the eight studies reporting data on the relationship between PLR and functional outcomes, only two studies[25,34] reported that high PLR was significantly associated with poor functional outcomes. A similar divergence of results was also noted in the descriptive analysis of the remaining studies. Such contrasting results are difficult to explain but could be attributed to the variability amongst studies for several important factors like the patient population, the time of sample collection from the onset of the event, the severity of the stroke, the treatment modality used, and the definition of the outcome. Given the high heterogeneity of our meta-analysis, we conducted various subgroup analyses to better understand the impact of PLR on stroke outcomes. Taking into account the reduced number of studies in the subgroup analysis, we noted that PLR may predict poor functional outcomes in stroke patients with lower NIHSS scores or when functional outcomes were defined as mRS >2 instead of ≥3. However, due to scarce data, these results could be significantly biased and need to be supported by further research.

The relationship between PLR and early mortality or END was reported by even fewer studies with contrasting results. On one hand, Xu et al[25] reported a 2.8 times increased risk of mortality with high PLR, the ORs with narrow 95% CI reported by Sha et al[30] showed no relation between the two (OR: 1.01 95% CI: 1.00, 1.01). Given such scarce data, it is important to compare the association of PLR and stroke with other ischemic vascular diseases to gain insights into the predictive power of this biomarker. Dong et al[40] in a recent systematic review and meta-analysis of eleven studies assessing the relationship between PLR and outcomes of ST-elevated myocardial infarction have demonstrated that high preprocedural PLR was associated with increased risk of major adverse cardiovascular events, all-cause mortality, and no-reflow phenomenon after primary percutaneous coronary intervention. Another review[41] has shown PLR as an independent predictor of adverse outcomes in acute coronary syndrome patients. Thus, according to the literature, PLR can predict outcomes for ischemic cardiac diseases, but it may not be a useful biomarker in the case of AIS. Such divergence is difficult to comprehend and could be attributed to the subtle differences in the pathophysiology of cerebrovascular and cardiovascular diseases which require further research.

Limitations

There are limitations to this review that need to be mentioned. Firstly, all studies were retrospective in nature with inherent selection bias. Based on the NOS score, not all studies were of high quality. Secondly, despite including 16 studies in the review, we could include a limited number of studies in the meta-analysis due to variable reporting of data. This may have reduced the statistical power of our meta-analysis. The number of studies in the subgroup analysis was even fewer, which compromises the persuasiveness of the results. Thirdly, there was variation in the included studies concerning the baseline severity of the stroke and in the treatment modality offered. These are important factors that could modify outcomes of stroke patients. Therefore, future studies must take into account these factors while assessing the relationship between PLR and outcomes. Lastly, the majority of studies assessed outcomes based on a single point of evaluation of PLR and it is unclear at this point if variations of PLR at different time points have an impact on outcomes.

Despite these limitations, the novelty of our study rests on the fact that it is the first review to pool evidence on the association between PLR

and stroke outcomes. A large number of studies were reviewed to present comprehensive evidence to clinicians. The stability of our results on sensitivity analysis adds to the credibility of our results.

Conclusions

Our results indicate that PLR may not be a useful prognostic marker to predict functional outcomes after AIS. Evidence on the predictive power of PLR for mortality and END after stroke is scarce and contrasting. There is a need for further studies assessing the role of PLR in predicting outcomes of stroke patients while taking into account important confounders like baseline stroke severity and treatment modality. Future studies should also take into account if variations in the timing of PLR measurements can predict outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

YY conceived and designed the study, HH, DL, ZA and XL collected data and performed data analysis. YY wrote the draft of this manuscript. ZS edited the manuscript.

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