Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: A systematic review and meta-analysis

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Abstract
Prognostic predictors are of paramount interest for prompt intervention and optimal utilization of the healthcare system in the ongoing context of the COVID-19 pandemic. The platelet-to-lymphocyte count ratio (PLR), has emerged as a potential tool for risk stratification of critically ill patients with sepsis. The current systematic review explores the utility of PLR as a prognostic predictor of COVID-19 patients. We screened the electronic databases until May 15, 2021 after enrolling in PROSPERO (CRD42021220269). Studies evaluating the association between PLR on admission and outcomes in terms of mortality and severity among COVID-19 patients were included. We retrieved 32 studies, with a total of 2768 and 3262 COVID-19 patients for mortality and disease severity outcomes. Deceased and critically ill patients had higher PLR levels on admission in comparison to survivors and non-severe patients (mean differences [MD] = 66.10; 95% confidence interval [CI]: 47.75–84.44; p < 0.00001 and MD = 86.74; 95% CI: 67.7–105.7; p < 0.00001, respectively).

A higher level of PLR on admission in COVID-19 patients is associated with increased morbidity and mortality. However, the evidence is of low quality and further studies regarding the cut-off value of PLR are the need of the hour.

KEYWORDS
Coronavirus disease 2019, Platelet-lymphocyte count ratio, Severe acute respiratory syndrome coronavirus-2

1 | INTRODUCTION

Even after a year of emergence of the severe acute respiratory syndrome coronavirus-2 (SARS CoV-2), the coronavirus disease 2019 (COVID-19) pandemic still has overwhelmed the medical infrastructure around the globe. Thus, early detection of severe cases is of paramount importance in the context of this pandemic as a method of triage and optimal allocation of resources.

The platelet-to-lymphocyte ratio (PLR) is an easily obtainable ratio from complete blood count (CBC) panels. Recently, it has been proposed as a better indicator of inflammation when compared to white blood cell count (WBC) alone. Increased PLR has been observed in patients with chronic inflammatory conditions like autoimmune diseases, rheumatic disorders, cancers, and diabetes. Various studies have indicated a correlation between elevated PLR and mortality in acute pulmonary embolism, advanced cancers, and gynecologic malignancies.
Similarly, inflammation is central to the pathogenesis of COVID-19 and the progress of inflammation or dysfunctional immune response has been associated with severe COVID-19 disease.\textsuperscript{7,8} It is therefore conceivable that patients with a pre-existing chronic inflammatory state will be susceptible to severe COVID-19 disease. In this meta-analysis, we analyzed the studies which had reported PLR on admission and examined the outcome of COVID-19 disease (severity and mortality) and the ability of PLR to predict progression to severe COVID-19 disease.

PLR as a marker of pre-existing pro-inflammatory or chronic inflammatory state can be used as a predictor of COVID 19 disease progression. There have been several studies that have examined the relationship between admission PLR and its ability to predict mortality in COVID 19 disease. In this meta-analysis, we aim to systematically analyze the current evidence for the utility of PLR on admission as a prognostic predictor of SARS CoV-2 infection, as per the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines”.

2 | METHODS

2.1 | Protocol and registration

We prospectively registered the protocol of this systematic review in PROSPERO (ID: CRD42021220269). This study is without any divergence from the reported protocol.

2.2 | Search strategy

Independently, SS, SK, and PK searched the major electronic databases (PubMed, Medline, and Embase), Google Scholar (https://scholar.google.com), preprint platforms MedRxiv (https://www.medrxiv.org), and Clinical trial database (https://ClinicalTrials.gov) from January 1, 2020 to May 15, 2021, with the following keywords: “COVID-19” OR “SARS-CoV-2” AND “PLR" OR "Platelet-to-lymphocyte count ratio.”

2.3 | Inclusion and exclusion criteria

Prospective and retrospective comparative cohort studies, case series with a control group, cross-sectional studies, controlled clinical trials, case-control studies, and randomized controlled trials (RCT), evaluating PLR on admission in COVID-19 patients were looked for inclusion. We assessed mortality as the primary outcome and disease severity as the secondary outcome. The articles except in the English language, without full retrievable text or appropriate control group, were excluded (PRISMA flow diagram).\textsuperscript{9,10}

2.4 | Study selection

SS, SK, and PK screened all the available abstracts independently after removing the duplications to exclude the irrelevant articles. Then the full-texts of the eligible studies were screened to check the inclusion criteria. Any disagreements were resolved in consultation with a fourth researcher (AKS).

2.5 | Data extraction

SS and SK extracted the data regarding first author, year of publication, type of study, place, sample size, PLR on admission, disease severity, and mortality in COVID-19 patients in a pre-conceived data extraction sheet from all included studies individually. Dichotomous data were collected in terms of the number of incidents and the total number of patients in the respective group and means and SD were extracted for the continuous data. Studies with missing data have been described separately.

Due to lack of consensus regarding defining the severity of the disease among studies, any patient either requiring mechanical ventilation or with a ratio of the partial pressure of arterial blood oxygen (\(\text{PaO}_2\))/oxygen concentration (\(\text{FiO}_2\)) ≤ 300 mmHg was considered as severe/critically ill and the rest of the patients are defined as mild/moderate ill patients.

2.6 | Risk of bias assessment

SS and PK independently assessed the included studies for any potential bias. The difference of opinion was resolved by consulting with AKS. “The Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I)” tool\textsuperscript{11} was used for assessing the risk of bias in non-randomized studies. It includes the following seven domains: “bias due to confounding,” “selection of participants, classification of interventions,” “deviations from intended interventions,” “missing data,” “measurement of outcomes,” and “selection of the reported result.” Every domain is graded as “Low,” “Moderate,” “Serious,” and “Critical.”

2.7 | Quality of the evidence

Independently PK and SS used the "Grading of Recommendations Assessment, Development and Evaluation (GRADE)" tool, which has five downgrading factors ("study limitations, indirectness, imprecision, consistency of effect, and publication bias") and three upgrading factors ("dose-response relation, large magnitude of the effect, and plausible confounders or biases")\textsuperscript{12,13} for assessing the quality of evidence. Each outcome was graded in terms of either "High" or "Moderate" or "Low" or “Very low”\textsuperscript{14–19} The difference of opinion was resolved with the suggestion of AKS.
2.8 Data synthesis

SS and PK used Review Manager version 5 for conducting this frequentist meta-analysis. The odds ratio (OR) for dichotomous data, and mean differences (MDs) for continuous data along with the 95% confidence intervals (CIs) respectively were assessed as per the Cochrane Handbook for Systematic Reviews of Interventions. The $i^2$ statistic was used for evaluating the statistical heterogeneity, a value of >50% was accepted as significant heterogeneity. Publication bias was assessed with the help of a funnel plot.

3 RESULTS

3.1 Basic characteristics

Thirty-three studies out of 979 distinguished publications were incorporated as per the aforementioned inclusion criteria (Figure 1 and Table 1). Twenty-nine articles were peer-reviewed, and three were preprints. Although 20 articles evaluated PLR on admission to assess the severity of COVID-19 patients, 14 articles addressed PLR on admission between survivors and non-survivors. Among the included studies, six studies had a moderate degree of bias (Figure 2). The publication bias is represented qualitatively in the Funnel plot (Figure S1).

3.2 Meta-analyses

3.2.1 Mortality

Fourteen articles with a total of 2768 patients were evaluated for mortality in COVID-19. PLR on admission was significantly higher among the deceased in comparison to the survivors (MD = 66.10; 95% CI: 47.75-84.44; $i^2 = 89\%$, $p < 0.0001$) (Figure 3).

3.2.2 Severity

Twenty studies with an aggregate of 3262 patients were evaluated for the severity of COVID-19. Critically ill patients are associated with increased PLR on admission (MD = 86.74; 95% CI: 67.7-105.7; $i^2 = 95\%$, $p < 0.0001$) (Figure 4A).
| SN | Author, year | Type of study, center | Country | Total no. of patients | PLR cut off value | Outcome |
|----|--------------|-----------------------|---------|----------------------|------------------|---------|
| 1. | Fois et al. (2020) | Retrospective, SC | Italy | 119 | 240 | Nonsurvivors had a higher PLR in comparison to the surviving COVID-19 patients (AUC: 0.57; 95% CI: 0.47–0.66). |
| 2. | Abrishami et al. (2020) | Prospective, MC | Iran | 100 | NS | An elevated PLR has a positive correlation with mortality and it can be one of the cost-effective prognostic markers of COVID-19 |
| 3. | Pan et al. (2020) | Retrospective, SC | China | 120 | NS | High PLR associated with risk of in hospital death in persons with COVID-19 |
| 4. | Rokhni et al. (2020) | Retrospective, SC | Iran | 233 | 200 | Nonsurvivors had a high level of PLR (14.84) in comparison to survivors (13.9) at admission. |
| 5. | Asgar et al. (2020) | Retrospective, SC | Pakistan | 191 | 201.16 | Elevated PLR is positively correlated with morbidity and mortality of COVID-19 patients (AUC: 0.703, PPV: 81.8%) |
| 6. | Wang et al. (2020) | Retrospective, SC | China | 450 | NS | The mortality rate of COVID-19 positively correlated with higher neutrophil-to-lymphocyte ratio, PLR |
| 7. | Wang et al. (2020) | Retrospective, SC | China | 131 | NS | Mortality is associated with higher variation of PLR [187.33, IQR: 139.24–332.76] in comparison to surviving patients [169.23, IQR: 115.23–222.96] |
| 8. | Allahverdiyev et al. (2020) | Retrospective, SC | Turkey | 455 | NS | The mortality rate of COVID-19 positively correlated with higher PLR, NLR, RDW |
| 9. | Güneysu et al. (2020) | Retrospective, SC | Turkey | 169 | 148.85 | NLR, PLR, and CRP values can be used as early predictors of mortality in Covid-19 patients (AUC: 0.660; 95% CI: 0.577–0.743). |
| 10. | Jimeno et al. (2021) | Retrospective, SC | Spain | 119 | NS | Deceased COVID-19 patients had a higher PLR (200; IQR: 336.7–131.7) on admission in comparison to the survivors (193.3; IQR: 284.1–147) |
| 11. | Kalabin et al. (2021) | Retrospective, SC | USA | 184 | NS | No significant difference in PLR was found among the deceased in comparison to the survivors. |
| 12. | Arachana et al. (2021) | Cross Sectional, SC | India | 302 | 205 | The cut-off of PLR > 205 for predicting the mortality had a 42% sensitivity and 49% specificity |
| 13. | Nasir et al. (2021) | Retrospective, SC | Bangladesh | 99 | NS | No significant difference in PLR was found among the deceased in comparison to the survivors |
| 14. | Ashgar et al. (2020) | Retrospective, SC | Pakistan | 100 | 153.65 | Elevated PLR on admission is associated with disease severity (AUC: 0.696, 95% CI: 0.576–0.816), and mortality (AUC: 0.671, 95% CI: 0.535–0.808). |
| 15. | Bastug et al. (2020) | Retrospective, SC | Turkey | 191 | 175.78 | PLR is a prognostic predictor for patients with severe COVID-19 (AUC: 0.715, 95% CI: 0.61–0.81). |
| 16. | Ai-Ping Yang et al. (2020) | Retrospective, SC | China | 93 | 180 | Elevated age, PLR, and NLR can be independently associated with advancing COVID-19 severity (AUC: 0.784, 95% CI: 0.666–0.901) |
| 17. | Zeng et al. (2020) | Retrospective, MC | China | 217 | NS | Higher PLR was associated with severe COVID-19. |
| 18. | Xue et al. (2020) | Retrospective, SC | China | 114 | NS | PLR > 229 has a positive predictive value of 69.8% for disease severity |
| 19. | Gong et al. (2020) | Retrospective, MC | China | 381 | NS | PLR and RDW help to predict the severity of COVID-19 patients. |
| SN | Author, year | Type of study, center | Country | Total no. of patients | PLR cut off value | Outcome |
|----|--------------|----------------------|---------|----------------------|------------------|---------|
| 20 | Wang et al. (2020) | Retrospective, SC | China | 61 | 200.8 | The PLR was significantly elevated in the severe group compared with the group with common symptoms (OR: 0.112; 95% CI: 0.032–0.387) |
| 21 | Kong et al. (2020) | Prospective, SC | China | 40 | 191.7 | A higher PLR was associated with poor outcome. |
| 22 | Kazancioglu et al. (2020) | Retrospective, SC | Turkey | 120 | 230 | The elevated PLR during follow-up may be more useful compared to NLR to predict the disease severity. |
| 23 | Sha lin et al. (2020) | Retrospective, SC | China | 68 | NS | High PLR, low monocyte counts, and low lymphocyte counts were independent correlates of severe illness in SARS-CoV-2 infection. |
| 24 | Huang et al. (2020) | Prospective, SC | China | 415 | 222.5 | Elevated NLR, and PLR are independent risk factor of severe COVID-19 patient |
| 25 | Sun et al. (2020) | Retrospective, SC | China | 116 | 226.67 | Severe COVID-19 patients had a higher PLR at presentation |
| 26 | Weili Wang et al. (2020) | Retrospective, SC | China | 123 | 189.11 | PLR is a potential predictor of poor clinical outcome in Covid-19 patients (AUC: 0.788, 95% CI: 0.826–0.944) |
| 27 | Yan Zhao et al. (2020) | Retrospective, SC | China | 285 | 274 | Initial PLR is found to be higher in SARS-CoV-2 virus-infected group than in influenza A. |
| 28 | Yutian Zhou et al. (2020) | Retrospective, SC | China | 304 | NS | Critically ill COVID-19 patients had an elevated PLR. It is an important predictor for severity grading. |
| 29 | Waris et al. (2021) | Retrospective, SC | Pakistan | 101 | NS | A significant association was observed in platelet-lymphocyte ratio and disease severity |
| 30 | Erdogan et al. (2021) | Retrospective, SC | Turkey | 304 | NS | PLR can be used as a significant biomarker for predicting prognosis of patients. |
| 31 | Ok et al. (2021) | Retrospective, SC | Turkey | 139 | NS | PLR can help identify high-risk cases with COVID-19. |
| 32 | Zhu et al. (2021) | Retrospective, SC | China | 111 | NS | PLR can play an important role in the severity of COVID-19 and had a potential value for monitoring the process of severe cases. (OR: 1.004; 95% CI: 1.000–1.008; p = 0.06) |
| 33 | Seyit et al. (2020) | Retrospective, SC | Turkey | 233 | 100.8 | Baseline PLR was significantly higher in COVID-19 patients in comparison to COVID-19 negative patient. AUC: 0.669 (0.590–0.747) |

Abbreviations: AUC, area under curve; IQR, interquartile range; MC, multi-center; NLR, neutrophil-to-lymphocyte ratio; NS, not specified; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; SC, single-center.
3.2.3 | Subgroup analysis

In subgroup analyses, the baseline PLR was found to be significantly elevated in COVID-19 patients in comparison to healthy controls (MD = 57.48; 95% CI: 52.95–62; $I^2 = 0\%$) (Figure 4B), as well as similar patients with influenza (MD = 36.29; 95% CI: 32.23–40.35; $I^2 = 1\%$) (Figure 4C). However, there was no significant difference in similarly ill patients with community-acquired pneumonia (CAP) (MD = 62.54; 95% CI: −57.5–182.58; $I^2 = 95\%$) (Figure 4D).

3.2.4 | Significant heterogeneity is found among studies assessing mortality, severity, and subgroup analysis in patients with CAP

3.3 | Quality of evidence

We found a low quality of evidence on the impact of raised PLR on COVID-19 mortality and severity (Table 2).
Publication bias was assessed for the studies on COVID-19 mortality. As per the Funnel plot, qualitatively a publication bias is likely in view of some smaller studies with large effects (Figure S1).

4 | DISCUSSION

We have identified low-quality evidence with variability that PLR value on admission has the potential ability of discrimination in COVID-19 patients predicting the mortality and severity.

The PLR, a nonspecific inflammatory marker, implies concurrent interaction between platelet count and lymphocyte count, reflects aggregation, as well as inflammatory pathways. It has been found to be elevated in response to many acute as well as chronic proinflammatory conditions and associated with a poor prognosis in patients with COPD and carcinomas.

A recent study found an correlation between raised PLR and poor prognosis of sepsis-induced acute kidney injury, and mortality (OR: 1.02, 95% CI: 1.003–1.039).

Another recent systematic review also echoed that an elevated PLR is associated with severe illness in COVID-19 patients than in those with mild disease (SMD: 0.68; 95% CI: 0.43–0.93; I² = 58%).

Although it has been widely acknowledged that both lymphopenias, as well as, thrombocytopenia are associated with poor outcomes in SARS-COV-2 infection, the exact mechanism of elevated PLR is still not clear. Platelets play a crucial role in the inflammatory response particularly at the endothelial injury and mortality (OR: 1.02, 95% CI: 1.003–1.039).

A cut off of 126.7 for difference in PLR had 100% sensitivity and 81.5% specificity (p = 0.014). Similarly, Kazancıoğlu et al. also reported a decline of PLR in the non-severe group in contrast to a sharp rise of PLR in critically ill COVID-19 patients from admission till the finishing of treatment.

Although Mousavi et al. have reported a strong correlation betwenn PLR (>233) and mortality in Covid-19 patients (p = 0.034), Zhao et al. reported an elevated PLR of 274 (AUC: 0.69) activity of platelets leads to the release of cytokines. Direct viral invasion of the hematopoietic cells or bone marrow stromal cells, injury of pulmonary endothelial cells leading to activation, and aggregation of platelets resulting into thrombus may lead to alteration of platelets and megakaryocytes.

A recent study found after an initial elevation subsequent decline of platelet count in critically ill COVID-19 patients. The activated platelets not only augment lymphocyte adhesion to the endothelium, orients the lymphocytes towards endothelial veins of various inflammatory sites but also release the platelet factor 4 to hinder the agglutinin-A, thereby impeding lymphocyte generation.

On the contrary, the abundance of ACE 2 receptors in lymphocytes makes vulnerable to SARS-COV-2 invasion, acute tissue sequestration similar to previous outbreaks of the severe acute respiratory syndrome, increased utilization by the elevated interleukin-6, or SARS-COV-2 mediated direct stimulation of NLRP3 inflammasome resulting in pyroptosis in lymphocytes may predispose significant lymphocytopenia. Probably, a more severe lymphocytopenia than thrombocytopenia leading results in an elevated PLR.

The change in PLR during the hospital course from baseline seems to be linearly correlated with disease severity and period of hospital stay in COVID-19 patients. More difference is associated with prolongation of hospitalization along with severe pneumonia. A cut off of 126.7 for difference in PLR had 100% sensitivity and 81.5% specificity (p = 0.014). Similarly, Kazancıoğlu et al. also reported a decline of PLR in the non-severe group in contrast to a sharp rise of PLR in critically ill COVID-19 patients from admission till the finishing of treatment.

Although Mousavi et al. have reported a strong correlation between elevated PLR (>233) and mortality in Covid-19 patients (p = 0.034), Zhao et al. reported an elevated PLR of 274 (AUC: 0.69).
has a specificity: 79% and sensitivity: 57%. Similarly, another study with 233 hospitalized COVID-19 patients also reported raised PLR > 102.8 (AUC: 0.669) with sensitivity: 70% and specificity: 50%.53

Irrespective of different cut-off values of PLR at admission, it cannot be ignored that elevated PLR is associated with increased morbidity and mortality in SARS-COV2 infection.

4.1 | Strengths and limitations

Our study is one of the extensive and comprehensive systematic reviews of the effectiveness of PLR on admission in patients with COVID-19 for predicting the mortality and severity, and may be considered at the moment as important evidence for decision-making.

The majority of the included studies are retrospective in nature and from Asian countries. Although in the current scenario, the prognostic role of PLR in COVID-19 is promising, our findings are heterogeneous, medium in effect, and of low-quality evidence. We also acknowledged that the cut-off value of PLR and the point of evaluation is yet to be standardized, and information in this regard is still evolving.

5 | CONCLUSION

PLR is a potential predictive biomarker for stratifying risk and aiding prompt decisions about an escalation of management, and further large-scale prospective studies in this context are the need of the hour.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Soumya Sarkar: Conceptualization, search strategy, study selection, data extraction, data synthesis, risk of bias assessment, and drafted the manuscript. Sundara Kannan: Study selection and data extraction. Puneet Khanna: Conceptualization, search strategy, study selection, risk of bias assessment, quality of the evidence assessment, and editing. Akhil Kant Singh: Study selection, data extraction, risk of bias assessment, quality of the evidence assessment, and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Sarkar S, Kannan S, Khanna P, Singh AK. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: A systematic review and meta-analysis. J Med Virol. 2022;94:211-221. https://doi.org/10.1002/jmv.27297