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PLATELET-TO-LYMPHOCYTE RATIO AS A PROGNOSTIC BIOMARKER FOR COVID-19 SEVERITY: A SINGLE CENTER RETROSPECTIVE DATA ANALYSIS AND SYSTEMATIC REVIEW WITH META-ANALYSIS OF 187 STUDIES

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ABSTRACT

INTRODUCTION: This study aims to evaluate the prognostic value of the platelet-to-lymphocyte ratio in determining the severity and mortality of adults hospitalized for COVID-19 using retrospective data and a meta-analysis of previous studies on the platelet-to-lymphocyte ratio worldwide.

MATERIAL AND METHODS: A retrospective study was conducted at the Kırdar City Hospital (Istanbul, Turkey) and included 521 COVID-19 patients. A systematic literature search of EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar databases was performed for relevant trials relating to the PLR ratio in COVID-19 published before April 12, 2023.

RESULTS: In the retrospective part of the study, PLR values were found to predict COVID-19 severity at admission with an AUC of 0.61 (SE = 0.03; 95% CI: 0.56 to 0.65; p = 0.0003) as well as survival status in

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a statistically significant fashion with an AUC of 0.59 (SE = 0.03; 95% CI: 0.55 to 0.64; p = 0.0004). Results of our meta-analysis showed a significant relationship between PLR and COVID-19 severity, with a pooled standardized mean difference (SMD) of 1.34 (95% CI: 1.13 to 1.55; p < 0 .001), and that PLR was significantly lower among patients who survived compared to deceased patients (SMD = –1.32; 95% CI: 1.57 to –1.07; p < 0.001).

CONCLUSIONS: PLR is a valid, readily available marker that can distinguish COVID-19 individuals with distinct progression and survival outcomes.

KEYWORDS: platelet-to-lymphocyte ratio; PLR; SARS-CoV-2; COVID-19; prediction; biomarker; disease severity

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INTRODUCTION

SARS-CoV-2 is a virus that is a member of the family Coronaviridae. It is the primary cause of COVID-19, which is also known as severe acute respiratory syndrome coronavirus 2 [1]. The first case was discovered in December 2019 in the city of Wuhan, Hubei province which is located in China [2]. Not long after that, the virus, and therefore the sickness, began to spread over the rest of the globe. Since then, the World Health Organization (WHO) has received reports of 676 609 955 confirmed cases of COVID-19, including 6 881 955 fatalities (as of March 10, 2023) [3]. The clinical presentation varies from no symptoms to acute respiratory failure, shock, and multi-organ system dysfunction [4]. Pandemics provide a significant challenge to healthcare systems and the rapid identification of severe cases is of the utmost significance because of the requirement of appropriate medical workforce allocation, symptomatic treatment, timely access to the intensive care unit, and patient isolation in an attempt to prevent the illness from spreading [5–7]. According to the findings of immunological research, severe cases of COVID-19 are distinguished by very significant amounts of cytokines that promote inflammation. The term "cytokine storm" is used to describe this phenomenon rather often [8]. This cytokine storm causes a large proinflammatory response, which eventually leads to multiple organ dysfunction and acute respiratory distress syndrome, both of which ultimately result in death in COVID-19 patients [9, 10]. As a consequence, inflammatory markers might theoretically be used to measure the severity of COVID-19 patients' diseases as well as the risk that they might pass away as a result of their illness. The complete blood count (CBC) is a simple test that provides a wealth of information, including the number of leucocytes (neutrophils and lymphocytes), thrombocytes, erythrocytes, and specific ratios of these values [11]. The CBC of patients with COVID-19 infection at diagnosis shows shifts that correlate with the stage and severity of the disease [12]. The neutrophil is the leucocyte that best represents the features of a distinct and essential component of the immune system. It is well known that lymphocytes play a role in the infectious process. Furthermore, thrombocytes play an important role in the regulation of a number of inflammatory processes [13, 14]. Changes in white blood cells, lymphocyte, and platelet counts are strongly associated with COVID-19 pneumonia [15]. However, these biological parameters are still nonspecific, and the addition of a combination marker, such as the platelet-to-lymphocyte ratio (PLR), may provide an additional justification for better distinguishing between individuals at risk of having a severe SARS-CoV-2 infection and those who are not. During the incubation period and early phase of COVID-19, the lymphocyte count is normal or slightly decreased. However, after the onset of the main symptoms, there is a marked lymphopenia and hyperactivation of platelets, which leads to thrombocytopenia [16, 17]. The platelet-to-lymphocyte ratio is an easily obtainable ratio from the CBD panel. It has appeared as an advisory marker showing alterations in levels of absolute platelet count and absolute lymphocyte count and is considered economical and available in most clinical settings. Moreover, PLR has a positive correlation with CT severity score [18]. Nevertheless, the platelet-to-lymphocyte ratio of COVID-19 patients and differences between severe and non-severe cases still need to be investigated, which may have prognostic values and create important therapeutic targets [19]. Platelet-to-lymphocyte ratio 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 [20]. Affirmation of PLR as a good prognostic marker to discriminate the most severe patients infected with SARS-CoV-2 must be evaluated, however high PLR could be associated with excess mortality [21]. As a result, this study aims to evaluate the prognostic value of the platelet-to-lymphocyte ratio in determining the severity and mortality of adults hospitalized for COVID-19 using retrospective data from the Kartal Dr. Lütfi Kirdar City Hospital (Istanbul, Turkey) and a meta-analysis of previous studies on the platelet-to-lymphocyte ratio worldwide.

MATERIAL AND METHODS

Retrospective study

Study design

This retrospective study was conducted at the Kartal Dr. Lütfi Kırdar City Hospital (Istanbul, Turkey) between January 1, 2022, and June 1, 2022. The institutional review board approved the analysis and issued a waiver of consent (ethics committee ruling number: 2022/514/228/25, date: 30.06.2022). All the patients with COVID-19 aged over 18 years, who presented to the emergency department between January 1, 2022, and June 1, 2022, were included in this study. The diagnosis of COVID-19 was determined based on the WHO guidelines. The digital records of the Hospital Information Management System were used to collect data. For the patients who were included in this study, age, gender, vital signs, chronic diseases, and laboratory test results, including platelets and lymphocytes values, were recorded in a format at the time of presentation to the emergency department. Patients with a negative reverse transcription-polymerase chain reaction test result, those with unknown mortality status, those who had been referred from another hospital, and those with unavailable platelets and lymphocytes values were not included in the study.

Case severity definitions were as per the interim guidance of WHO. Asymptomatic (patients are RT-PCR positive but do not show symptoms), mild (patients are RT-PCR positive but no hypoxia), moderate (RT-PCR positive patients who show signs of pneumonia and but no signs of severe hypoxia with $SpO_2 > 90\%$), severe (signs of severe pneumonia evident with respiratory rate more than 30 breaths/minute or $SpO_2 < 90\%$) and critical [with Acute Respiratory Distress Syndrome (ARDS) or septic shock]. We included both severe and critical patients under the category of severe.

The systemic inflammation index was determined from the first blood test result. The PLR was calculated using the equations below:

Statistical analysis

Statistical tests used in this study were Chi-Square and Kolmogorov-Smirnov tests to ensure data normality. However, Kruskall-Wallis would be used if the data had abnormal distribution.

Receiver operating characteristic (ROC) analysis was performed to investigate whether PLR values could predict COVID-19 severity at admission and survival. For this purpose, the area under the curve (AUC) was computed, using PLR values as variables and COVID-19 severity at admission and survival status as classification variables. Furthermore, Youden's J index was used to determine the best cutoff point to achieve acceptable sensitivity and specificity levels. Statistical analyses were performed using the commercial software "Statistical Package for Social Sciences" (SPSS v.28, IBM, NY, USA). Graphs were generated using MedCalc for Windows, (MedCalc Software, Ostend, Belgium).

Systematic review

To investigate the correlation of the platelet-to-lymphocyte ratio on COVID-19 severity, we did a systematic review and meta-analysis in line with the Preferred Publishing Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [22]. The study protocol was registered in the PROSPERO registry (CRD42023416385).

Study selection

A systematic literature search of the Excerpta Medica Data Base (EMBASE), MEDLINE (using the PubMed interface), the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar databases was performed for relevant trials published before April 12, 2023.

The following search terms were used i.e.: "COVID-19", "SARS-CoV-2", "ncov", "novel coronavirus", "severe acute respiratory syndrome coronavirus 2", "severity", "mortality", "platelet-to-lymphocyte ratio", "platelet to lymphocyte ratio", "platelet lymphocyte ratio", "PLR". The references of the highlighted studies were also carefully searched.

The searches were limited to human subject trials with complete texts published in English.

Inclusion and exclusion criteria

Eligibility criteria for inclusion were as follows: (a) reporting continuous data on the platelet-to--lymphocyte ratio in COVID-19 patients, (b) investigating COVID-19 patients with different degrees of disease severity and/or survival status during follow-up; (c) adult patients, (d) English language, and (e) a full--text article is available. The exclusion criteria were: (1) review papers, guidelines, consensus of viewpoints, case reports, case series, background research, or other irrelevant items beyond the scope of this review; (2) descriptive studies, studies without an experimental/control group, and studies that are neither analytical nor experimental.

Data collection

Data were independently extracted using predefined extract forms from the included COVID-19 studies by two independent reviewers (M.M. and L.S.). When the preliminary conclusions were uncertain, the literature was reassessed by a third reviewer (N.L.B.). The information extracted from the studies included the following: (1) first author, publication date, country of origin, study design; (2) type of participant group; (4) case number; age, male sex; (5) COVID-19 severity outcomes.

Assessment of study quality

Two reviewers (M.M. and L.J.) independently assessed the quality of the included studies. Discussion with a third reviewer (L.S.), if there were any differences between the reviewers, resolved them. The risk of bias within an individual cohort study was determined using the Newcastle-Ottawa Scale (NOS) [23]. We examined each study for selection (4 points), comparability (2 points), and outcome/ /exposure (3 points) using the NOS scale rating system. A score of 1–3, 4–6, and 7–9 points, respectively, indicated low, moderate, and good quality.

Statistical analysis

All statistical analyses were performed using RevMan (ver. 5.4; Cochrane Collaboration, Oxford, UK) and "Statistical Package for Social Sciences" (SPSS v.28, IBM, NY, USA). Pooled prevalence was estimated using the Mantel-Haenszel method. The results are presented as forest plots using odds ratios (ORs) with 95% confidence intervals (CIs). For dichotomous data and the standardized mean difference (SMD) for continuous data, with 95% CI. When data were reported as median with interquartile range, estimated means, and standard deviations, with the formula described by Hozo, were used [24]. Heterogeneity between studies was assessed by the I^2 test and was assessed as low, moderate, or high when I^2 was $< 50\%$, 50–75%, or $\geq 76\%$, respectively [25]. The random-effects model was used for $I^2 > 50\%$; otherwise, the fixed-effect model was employed. Egger's test and funnel plots were used to assess potential bias and perform funnel plot tests for asymmetry to investigate potential publication bias if there were more than ten trials in a single meta-analysis. A 2-sided test was conducted to calculate all P values, and a P value was considered statistically significant when it was less than 0.05.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit it for publication.

RESULTS

Retrospective study

Characteristics of the study participants

The population of this study consisted of 521 patients, 280 women, and 241 men. The mean age of the patients included in the study was 72.4 years. The proportion of patients who ended up with in-hospital death was 37.8%. The mean age of study subjects was 72.4 ± 13.4 years. Clinical characteristics of all patients are summarized (overall and by severity and survivor status) and shown in Table S1 and S2.

ROC curve to detect optimal cut-off values of the hematological ratios

Platelet-to-lymphocyte ratio values were found to predict COVID-19 severity at admission with an AUC of 0.61 (SE = 0.03; 95% CI: 0.56 to 0.65; p = = 0.0003; Fig. 1). The Youden's J index was 0.18 (95% CI: 0.07 to 0.24), and its associated criterion was 210. Sensitivity and specificity yielded values of 51.32% and 66.67%, respectively. Stratifying according to sex/gender, the analysis holds statistical significance only among men (AUC of 0.63, SE of 0.04; 95% CI: 0.57 to 0.69), p = 0.0005; Fig. S1), with a sensitivity of 48.97% and a specificity of

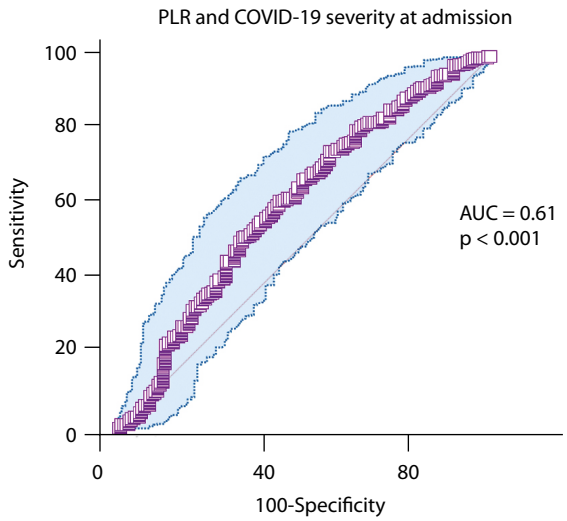

FIGURE 1. Platelet-to-lymphocyte ratio (PLR) and COVID-19 severity at admission; AUC — area under the curve

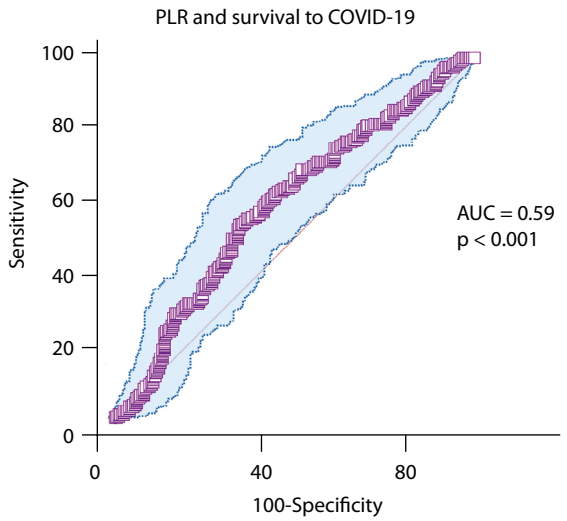

FIGURE 2. Platelet-to-lymphocyte ratio (PLR) and survival to COVID-19; AUC — area under the curve

72.50%. The Youden's J index and its associated criterion were computed at 0.21 (95% CI: 0.09 to 0.28) and 230, respectively. The analysis was not significant among women (AUC of 0.56, SE of 0.04; 95% CI: 0.49 to 0.62; p = 0.1958; Fig. S2). The Youden's J index and its associated criterion yielded a value of 0.14 (95% CI: 0.07 to 0.21) and 351, respectively, with a sensitivity of 80.00% and a specificity of 34.43%.

Platelet-to-lymphocyte ratio values could predict survival status in a statistically significant fashion, with an AUC of 0.59 (SE = 0.03; 95% CI: 0.55 to 0.64; p = 0.0004; Fig. 2). The Youden's J index was computed at 0.19 (95% CI: 0.10 to 0.26),

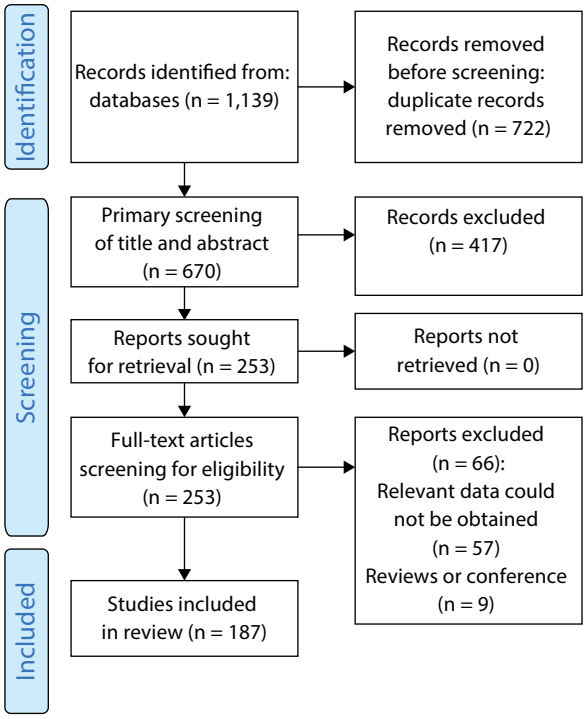

FIGURE 3. Flow diagram of the search strategy and study selection

whilst its associated criterion was calculated at 210, with a sensitivity of 53.56% and a specificity of 65.31%. Stratifying according to sex/gender, the analysis showed sex- and gender-specific differences. Among men, AUC yielded a value of 0.59 (SE = = 0.03; 95% CI: 0.53 to 0.65, p = 0.0071; Fig. S3), with the Youden's J index being computed at 0.17 (95% CI: 0.07 to 0.25). Its associated criterion was calculated at 241, with a sensitivity of 52.20% and a specificity of 65.22%. However, among women, AUC was computed at 0.57 (SE = 0.04; 95% CI: 0.50 to 0.63; p = 0.0911; Fig. S4). The Youden's J index yielded a value of 0.19 (95% CI: 0.09 to 0.29), with an associated criterion of 210, a sensitivity of 61.25%, and a specificity of 58.02%.

Systematic review and summary of evidence

The initial literature search yielded 2219 articles from all the databases. A final total of 187 articles concerning to 186 studies (82,957 COVID-19 patients) screening based on the inclusion criteria (Fig. 3) [S1–S187].

Finally, 125 studies reporting PLR among severe vs non-severe COVID-19 patients (49,392 patients), and 92 studies compare PLR in COVID-19 patients who survive vs decrease (46,009 patients). The main characteristics of the studies are summarized in Table S3. Most of the included studies were from Turkey,

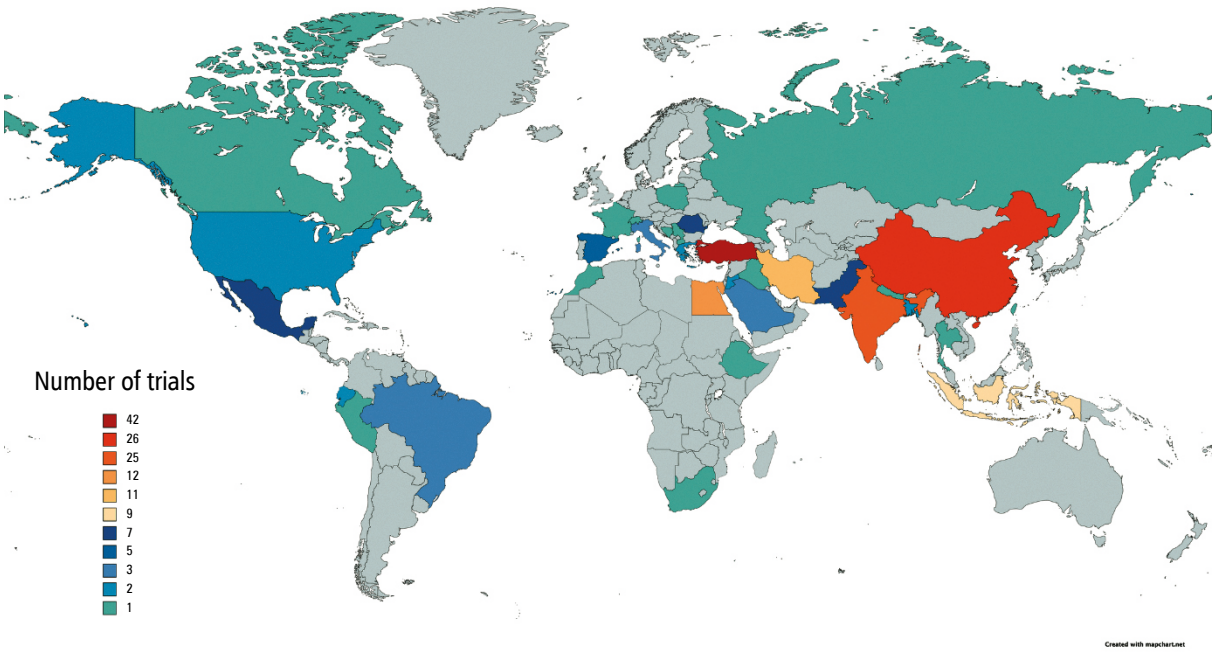

FIGURE 4. Worldwide distribution of studies included in the meta-analysis

China, India, Egypt, and Iran (Fig. 4). Newcastle-Ottawa Scale was used to assess the quality of the eligible studies and indicated overall good quality (Tab. S3).

One hundred and twenty-five articles reported PLR in severe and non-severe COVID-19 patients. The forest plot outcome for the connection between PLR and the severity of patients with COVID-19 can be found in Figure 5. The pooled data were calculated with the random effect model as a high heterogeneity within the studies. Our results showed a significant relationship between PLR and COVID-19, with a pooled standardized mean difference (SMD) of 1.34 (95% CI: 1.13 to 1.55; $p < 0.001$; Fig. S5).

A total of ninety-two studies reported data on PLR among COVID-19 patients who survived or deceased, giving a total sample size of 44315 patients for evaluation. Pooled analysis of all 92 studies showed that PLR was significantly lower among patients who survived compared to deceased patients (SMD = –1.32; 95% CI: 1.57 to –1.07; $p < 0.001$; Figure 6). Significant heterogeneity was present across the included studies ($I2 \geq 80\%$; Fig. S6).

DISCUSSION

In our retrospective study, we found that PLR values could significantly predict COVID-19 severity at hospital admission and survival status, pointing out the clinical importance and meaning of this novel inflammatory marker, which was confirmed and corroborated by our systematic review of the literature with meta-analysis. However, when stratifying our series according to the patient's sex and gender, PLR values were found to be predictive only among men. These findings underline the importance of a gender-sensitive approach in the management of the COVID-19 patient.

Platelet-to-lymphocyte ratio is a systemic inflammation index that has been associated with the prognosis of several impairments of the human immune system as well as with communicable and non-communicable diseases with inflammatory/ /immune backgrounds.

The physiopathology of PLR alteration in COVID-19 patients is quite complex and involves several mechanisms, such as: i) a reduced peripheral production of platelets, as well as ii) a decreased release of platelets from lungs (which are a major site of platelet production), and probably iii) biogenesis aberration induced by diffuse lung interstitial changes and parenchymal damage.

Thrombocytopenia is one of the hallmarks of COVID-19, being experienced by approximately one-quarter of COVID-19 patients. Half of these patients die because of coagulopathy [26]. However, PLR has been inconsistently linked to COVID-19 severity: some studies have failed to find a statistically significant association, whilst other investigations

reported an association [21, 27]. Some systematic reviews and meta-analyses have been published: however, they are based on a lower number of studies concerning the investigations we were able to retrieve, include, and synthesize in the present me-ta-analytical review. For instance, Simadibrata et al. [28] have summarized seven studies, totaling 998 participants, 316 (32%) of which had severe COVID-19. Severity was linked with higher PLR levels on hospital admission [SMD 0.68 (95% CI: 0.43–0.93), I2 = 58%], pointing out the cost-effectiveness and readily availability of PLR as a prognostic biomarker [28]. Sarkar and colleagues [20] have synthesized 32 studies, with a total of 2768 and 3262 COVID-19 patients for COVID-19 mortality and severity outcomes, finding that deceased and critically ill patients displayed higher PLR levels on admission in comparison to survivors and non-severe patients, respectively [mean differences of 66.10 (95% CI: 47.75–84.44) and 86.74 (95% CI: 67.7–105.7)] [20]. As such, our systematic review and meta-analysis represent the most comprehensive and updated synthesis of the studies that have explored the clinical meaning of PLR in COVID-19 patients.

Moreover, our study adds to the literature in that only a few studies have explored the sex-dependent performance of PLR in discriminating COVID-19 severity and survival status. Fors et al. [29] have carried out a single-center observational cross-sectional study consisting of 3,280 confirmed COVID-19 cases and have found sex-dependent differences in the contribution of this biomarker to COVID-19 morbidity and mortality. While overall speaking, severe COVID-19 pneumonia and non-surviving patients exhibited a higher level of PLR, its median values, and cut-offs were higher and lower in men, respectively, with better sensitivity. Specificity, however, was more enhanced among women than in men. These findings are different from ours, which revealed a higher sensitivity among women, whilst the AUC, the specificity, and Youden's J index were higher in men. Cut-offs were higher in women for COVID-19 severity, but lower for survival status.

Several scholars have called for a sex and gender-specific lens in the field of COVID-19-related research, stressing the importance of understanding sex and gender disparities observed in COVID-19 vulnerability in terms of epidemiology (incidence and prevalence rates) and clinics (co-morbidity and case fatality of the disease) [30]. This would enable individualize and tailor treatment according to sex and gender. However, only a few studies have included sex- and gender-sensitive analyses, stratifying patients according to their sex and gender.

Given the contrasting findings and paucity of data in this regard, further studies are warranted to better explore the role and clinical impact of sex-specific differences in COVID-19 severity and survival status.

Limitations

Our research is the most complete and in-depth examination of its kind to date since it includes both a retrospective investigation and a meta-analysis of the efficacy of PLR in predicting mortality and severity in patients who have COVID-19. Due to the fact that it has both of these components, it has the potential to be considered important evidence for decision-making at this time. However, our investigation does have certain restrictions. A limited number of patients who visited our emergency department provided the data for the retrospective study, and those patients' responses provided the study's findings. When we performed the meta-analysis, we restricted ourselves to only include articles that were published in the English language. Furthermore, the majority of the included studies were conducted in Turkey, China, India, Egypt, and Iran; nonetheless, the United States and Europe were responsible for the large majority of the confirmed cases and deaths. The possibility that PLR levels might differ dramatically across groups is a strong indicator that the discovery's usefulness may be constrained to a certain extent.

CONCLUSIONS

This research demonstrates that PLR is a valid, and readily available marker that may substantially differentiate between COVID-19 patients with varied progression and survival outcomes.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author (L.S.).

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Kartal Dr. Lütfi Kırdar City Hospital (Istanbul, Turkey; protocol code 2022/514/228/25, date: 30.06.2022).

Informed Consent Statement: Not applicable.

Author contributions

Conceptualization, L.S. and M.M.; methodology, M.M., L.S. and M.K.; software, L.S., M.K., R.A. and N.L.B.; validation, L.S., M.M. and F.C.; formal analysis, L.S., M.K., R.A. and N.L.B.; investigation, L.S., M.M., M.P., M.K., R.A. and N.L.B.; resources, L.S., M.P., M.M., M.K. and R.A.; data curation, L.S. and M.K.; writing — original draft preparation, L.S., M.M., M.P., M.K., R.A. and N.L.B.; writing — review and editing, L.S., M.M., M.P., M.K., R.A., L.J., N.L.B., A.P.H., S.L., M.G.M., A.P.W., M.C. and F.C..; visualization, L.S. and N.L.B.; supervision, L.S., M.K. and F.C..; project ad-ministration, L.S. and M.M. All authors have read and agreed to the published version of the manuscript.

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None.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Figure S1. Platelet to lymphocyte ratio and COVID-19 severity at admission in men population

Figure S2. Platelet to lymphocyte ratio and COVID-19 severity at admission in women population

Figure S3. Platelet to lymphocyte ratio to COVID-19 survival among men population

Figure S4. Platelet to lymphocyte ration to COVID-19 survival among women population

Figure S5. Pooled characteristics of platelet-to-lymphocyte ratio among severe vs. non-severe COVID-19 groups

Figure S6. Pooled characteristics of platelet-to--lymphocyte ratio among survive vs. decrease COVID-19 groups

Studies included in meta-analysis

Table S1. Baseline characteristics of studies included in meta-analysis

Table S2. Pooled characteristics of analyzed in articles variables among studies referred to severe and non-severe COVID-19 groups

Table S3. Pooled characteristics of analyzed in articles variables among studies referred to survive vs. decrease COVID-19 groups

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