RESEARCH

DIAGNOSTIC AND PREDICTIVE ROLE OF PLATELET/LYMPHOCYTE RATIO (PLR) IN PREDICTING OUTCOMES IN ELDERLY COVID-19 PATIENTS (A CROSS-SECTIONAL STUDY)

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Abstract

Introduction: In this study, we aimed to investigate the prognostic effects of platelet-to-lymphocyte ratio biomarker in the group of laboratory-confirmed Coronavirus Disease-19 (COVID-19) geriatric patients and compare them with the group of patients under 75 years of age.

Material and methods: The platelet-to-lymphocyte ratio were recorded for oxidative stress response when it is decided to transfer patients from the emergency room COVID-19/area to the COVID-19 /service, at the time of admission to intensive care unit due to arterial oxygen partial pressure (PaO2 mmHg) to fractional inspired oxygen (FiO2) < 200 mmHg, at the time of discharge from intensive care unit and exitus.

Results: It was found that the mean age of the survivors was significantly lower than those who had died (p = 0,016). In Post-hoc analysis, the platelet-to-lymphocyte ratio values at hospitalization of ≥ 75years old patients who had died were found to be significantly different compared to patients 75 < years (p = 0.006)who were survived and patients 75 ≥ years who had died (p = 0.043). Only hospitalization platelet-to-lymphocyte ratio value and age data were found to be associated with mortality. According to mortality;the cut-off value for platelet-to-lymphocyte ratio at the time of admission to the COVID-19/ service in patients 75 ≥ years at the time of admission to ICU in patients 75 < years was determined as 411.15 and 216.54, respectively.

Conclusion: The clinical use of the platelet-to-lymphocyte ratio may be a suitable marker in geriatric patients for determining disease severity and can be used as a predictive factor for determining the poor prognosis.

Keywords: Aged; Platelet Count; Lymphocytes; COVID-19.

INTRODUCTION

COVID-19 is a new disease which has become a global pandemic, and is caused by a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1,2). The disease is still not very well characterized, and factors associated with severe clinical course are not well known (1). Coronavirus disease has wide clinical parameters that require intensive care unit, ranging from asymptomatic carriers to mild pneumonia, respiratory failure requiring mechanical ventilation, sepsis, septic shock and multi-organ failure (usually in elderly and those with comorbidities) (2-4).

The production of reactive oxygen species (ROS) resulting in oxidative stress has been suggested to be the main cause of local or systemic tissue damage leading to severe COVID-19 (5).

It is important to identify markers suggestive of poor prognosis and mortality in COVID 19 patients in order to achieve important therapeutic goals. White blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and serum C reactive protein (CRP), which are biomarkers of peripheral blood-derived inflammation, have been investigated as independent predictors for the prognosis of systematic inflammatory diseases, particularly cardiovascular diseases and malignancies (6,7). Lymphopenia can be considered a cardinal laboratory finding with prognostic potential (8).

It has been suggested that a high platelet/lymphocyte ratio may indicate a more pronounced cytokine storm due to increased platelet activation (3). Therefore, PLR may have prognostic value in identifying severe cases and is associated with poor prognosis (8).

Studies provide optimal cutoffs for PLR for hospital stay and mortality in adult COVID-19 patients, but it is not known whether there are differences for the geriatric patient group. Identifying these factors associated with severe COVID-19 will assist physicians at all levels of healthcare in determining the patients for need of home care, hospital care, and admission to the intensive care unit (ICU). Thus, more rational use of scarce health care resources can be prioritized.

In this study, we aimed to investigate the prognostic effects of PLR biomarker in the group of laboratory-confirmed COVID-19 geriatric patients and compare them with the group of patients under 75 years of age.

MATERIAL AND METHODS

Ethical Approval

The current cross-sectional, retrospective investigation was conducted in compliance with the Declaration of Helsinki. The study was approved by the institutional Ethics Committee, which also gave consent for the use of electronic data (decision date: 14.02.2022, number: 26). Throughout the study, the authors followed good clinical practice guidelines.

Study Design

Three hundred fifty-one patients, who were admitted to the intensive care unit due to COVID-19 severe ARDS (PaO2/FiO2< 200 mmHg), were evaluated retrospectively in this study. Age and gender were all obtained from the hospital records. Patients were randomized into 4 groups: Group I: Survivor 75<years, Group II: Survivor 75≥ years, Group III: Died 75< years, Group IV: Died 75≥ years. The PLR values were recorded for oxidative stress response when it is decided to transfer patients from the emergency room COVID area to the COVID service, at the time of admission to intensive care unit due to PaO_2/FiO_2< 200 mmHg, at the time of discharge from intensive care unit and exitus.

Inclusion Criteria

Patients above 18 years who were admitted to the ICU due to COVID-19 severe ARDS (PaO2/FiO2< 200 mmHg) were included in this study.

Exclusion Criteria

Patients below 18 years, patients who did not require ICU follow-up were excluded from this study.

Statistical Analysis

Statistics were analyzed using SPSS version 21.0 (IBM Corp, Armonk, NY, United States) software. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The normality of the distribution of the data was investigated with the Kolmogorov-Smirnov test. Continuous variables were expressed as Mean±SD, interval variables as median (min, max), and categorical variables as numbers (percent). The Kruskal-Wallis test was used for comparisons between groups of more than two quantitative variables that did not show normal distribution. Mann-Whitney U test was used to find the group that created the post-hoc difference. Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution. Friedmann Test was used in dependent multiple group analyses. Wilcoxon sign rank test was applied to the paired groups to find the group that created the post-hoc difference. Pearson Chi-square test was used to compare categorical data. Logistic regression analyzes were applied to identify factors associated with mortality. First of all, single logistic regression tests were applied for factors such as PLR value at hospitalization, PLR value at admission to intensive care unit, PLR value at discharge, age, PLR difference between hospitalization and discharge, and PLR difference between hospitalization and admission to intensive care unit. Then, multiple logistic regression analysis was applied to the significant values. *Youden index* was used by performing AUROC analyzes in order to establish optimal cut-off values for mortality estimation. Statistical significance was accepted as $p<0.05$.

RESULTS

Within the scope of the study, 351 patients (175 males, 176 females) between the ages of 18-92 were analyzed for PLR values at the time of admission to the service, at the time of admission to the intensive care unit, and at discharge (exitus or discharge). 195 of the patients were under the age of 75 and the remaining 156 patients were over the age of 75.

In the statistical analysis, it was determined that the age and PLR values of the data did not comply with the normal distribution. When the patients who survived (n=194) and those who died (n=157) were compared; the mean age of patients who survived (66.6±17) was found to be significantly lower than those who had died (71.5±13.3) (p=0.016). There was no significant difference between survivors and those who had died in terms of gender (p>0.05). In terms of PLR levels at the time of admission to the service; It was found that the PLR level of the patients who survived (211.2±155.5) was significantly lower than that of the patients who had died (290.5±347.7) (p=0.017).

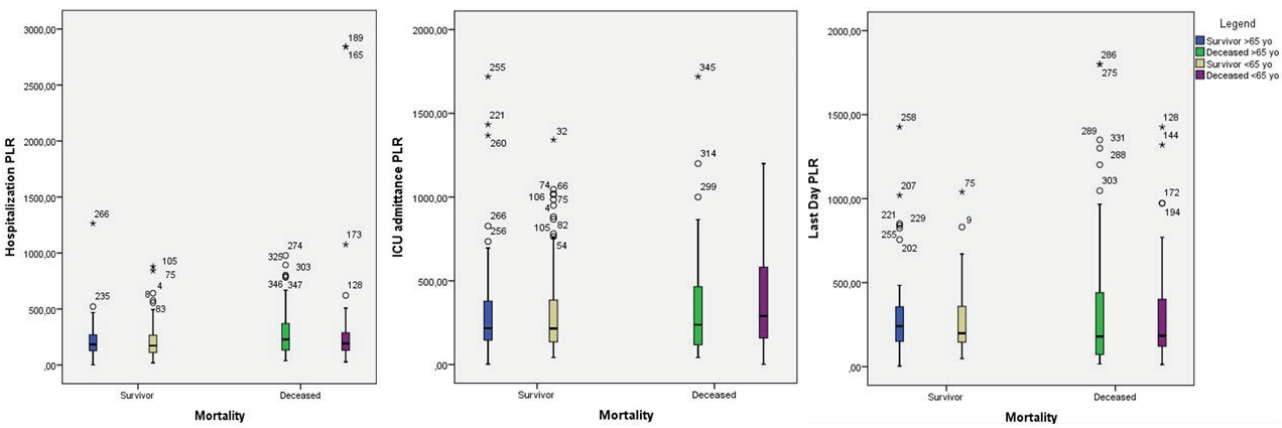
The difference between admission-discharge PLR values was found to be significantly higher in survivors compared to those who had died (p=0.019). It was found that the PLR value of patients at hospitalization were significantly different between the groups (p=0.040). In Post-hoc analysis, the PLR values at hospitalization of ≥75 years old patients who had died (Group IV) were found to be significantly different compared to patients under 75 years of age (p=0.006) who were survived and patients aged 75 years and over who had died (p=0.043). However, the PLR values of ≥75 years old patients who had died were similar to <75 years old patients who had died (p=0.117). (Table 1., Figure 1a-c.).

In the univariate logistic regression models made for the research of mortality-related data; only the PLR value at admission (p=0.01, OR:1.002 95% confidence interval 1.000-1.003) and age (p=0.004 OR: 1.021 95% confidence interval 1.007-1.036) data

Table 1. Demographic data and Platelet Lymphocyte Ratios (PLR) of the study population (n=351)

	Survivors (Age group)			Nonsurvivors (Age group)		
	Group I 75< (n=120)	Group II 75≥ (n=74)	Total (n=194)	Group III 75< (n=75)	Group IV 75≥ (n=82)	Total (n=157)
Age (in years) (Mean±SD)	56.8±14.0	82.6±4.6	66.6±17	60.7±10.7	81.4±5.3	71.5±13.3
Gender						
Male	65 (%33.5)	37 (%19.3)	102 (%53.1)	38 (%36.9)	35 (%22.3)	73 (%46.5)
Female (n,%)	55 (%28.6)	37 (%19.3)	92 (%47.9)	37 (%23.6)	47 (%29.9)	84 (%53.5)
Hospitalization PLR(Mean±SD)	209.5±150.4	214.6±163.5	211.2±155.5	294±455.7	287.4±207,5	290.5±347.7
ICU Admittance PLR (Mean±SD)	305.7±257.3	321.8±300.1	312.3±274.4	390.5±300.7	335.2±292.2	361.6±296.6
Last Day PLR (Mean±SD)	258.8±169.1	295.5±234.3	272.9±196.8	297.2±285.8	334.2±391.7	316.6±344.6

Figure 1a-c. a.PLR values of the groups at hospitalization, b. Admission, c. Last day



were found to be associated with mortality. The PLR values during hospitalization in patients older than 75 years of age, who had died (p=0.022, OR: 1.002, 95% confidence interval 1.000-1.004), and the PLR values at admission to intensive care unit in patients younger than 75 years of age, who had died (p=0.04, OR:1.001 95% confidence interval 1.000-1.002) were found to be associated with mortality. The PLR value of the cases with mortality at the time of hospitalization was found to be statistically significantly higher than the cases without mortality (p=0.007; p<0.01). According to mortality; the cut-off value for PLR at the time of admission to the COVID-19 service in patients 75 years was determined as 411.15 and over (sensitivity 24%, specificity 95%). On the other hand, the cut-off value for PLR at the time of admission to the intensive care unit in patients under 75 years of age was determined as 216.54 and over (sensitivity 68%, specificity 52%) (Table 2).

For young patients, the area under the curve for the PLR value at admission to ICU was 0.584 (0.498-0.669; p=0.049) in ROC analysis.The area under the curve for the PLR value at hospitalization for all patients was 0.574 (0.513-0.635; p=0.017). For elderly

Table 2. ROC analyzes associated with mortality and optimal cut-off values

	AUC (%95 CI)	Cut-off value	% Sensitivity	%Specificity	p
Hospitalization PLR (All Patients)	0.574 (0.513-0.635)	271.9450	51	64	0.017*
Hospitalization PLR (75≥)	0.594 (0.505-0.683)	411.1500	24	95	0.043*
ICU Admittance PLR (75<)	0.584 (0.498-0.669)	216.5400	68	52	0.049*
LastDay-Hospitalization PLR	0.573(0.508- 0.637)	-3.8550	71	53.5	0.019*

* p<0.05 , CI: Confidence interval, AUC: Area under curve, ROC: Receiver operating characteristic

patients, the area under the curve for the PLR value at hospitalization was 0.594 (0.505-0.683; p=0.043), (Figure 2.). The area under the curve for the difference in PLR value at hospitalization - discharge was 0.573 (0.508-0.637; 0.019), (Figure 3.).

DISCUSSION

In this study, the platelet lymphocyte ratio at the time of hospitalization, admission to the intensive care unit, and discharge from the intensive care unit (exit or discharge) in patients over 75 years of age, who were hospitalized due to SARS CoV-2 PCR test positivity within 3 months and then admitted to the intensive care unit because of moderate-to-severe ARDS, were compared with patients under 75 years of age. Optimal cut-off analysis for PLR was performed for disease progression and poor prognosis.

In COVID-19 patients, the lymphocyte count decreases and the neutrophil count increases due to inflammation. Studies have shown that the neutrophil lymphocyte ratio (NLR) and platelet lymphocyte

Figure 2. For elderly patients, the area under the curve for the PLR value at hospitalization (75≥) 0.594 (0.505-0.683; p=0,043).

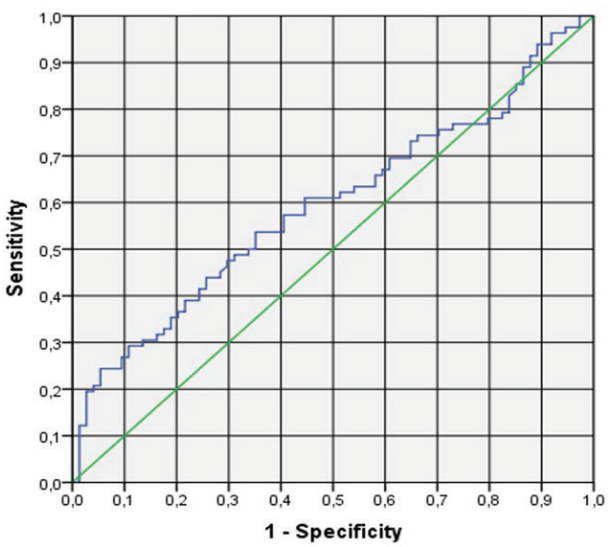
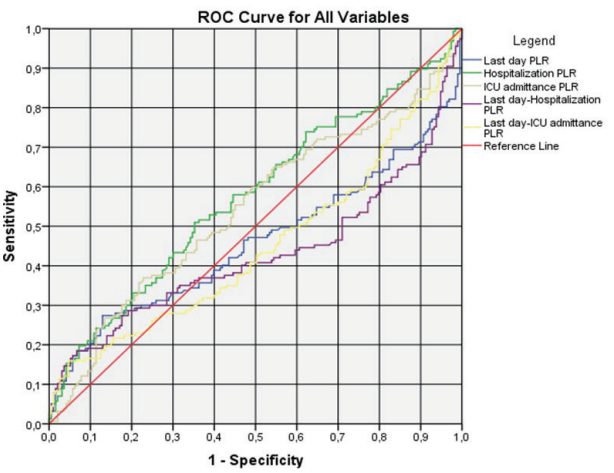


Figure 3. The area under the curve for the difference in PLR value at hospitalization - discharge was 0.573 (0.508-0.637; 0,019).



ratio (PLR) reflect inflammation more effectively and strongly than the individual lymphocyte, platelet, and neutrophil counts (9).

In the study of Seyit et al. PLR was found to be 156.47 ± 112.51 in positive SARS CoV-2 patients (n=110) presenting to the emergency department. The PLR value was found to be 109.14 ± 38.6 in those who were not infected at the same time. The rate of decrease in PLR indicates that the decrease in platelet count is greater than that of lymphocytes. This will require greater attention to thrombocytopenia in the follow-up of COVID-19 patients. The mean age of the patients in this study was 44.16 ± 18.56 years, and 75 of these patients were admitted to the service (10). In our study, patients with shortness of breath, respiratory rate >28/min, SaO2 <93% in room air, PaO2/FiO2 <300, who were admitted to the hospital due to >50% increase in lung infiltration within 24 to 48 hours and whose treatment was appropriate to continue in the service were included. Indications for admission to the service are the same as our protocol. In this study, the cut-off value for PLR at admission to the service was 102.8 (70% sensitivity, specificity 52%). In our patient group, the mean age of surviving patients (66.6±17) was significantly lower than those who had died (71.5±13.3) (p=0.016). Of the patients, 195 were under the age of 75 and 156 were over the age of 75. PLR value at hospitalization (p=0.01) and age (p=0.004) were found to be associated with mortality. It was found that the PLR level at the time of admission to the service was significantly lower in patients who survived at the end of study than in patients who had died (211.2±155.5 vs 290.5±347.7) (p=0.017).

PLR is widely used as a marker of changes in platelet and lymphocyte counts observed in the systemic inflammatory response and pro-thrombotic states (6,11,12). In cases accompanied by immune suppression and thrombosis such as neoplastic, cardiovascular, inflammatory rheumatic diseases; changes in PLR have been shown to have high predictive values in assessing the severity of systemic inflammation and response to treatment and have been associated with poor prognosis (6,7,9,11-14). Because of the presence of more neutrophils and fewer lymphocytes in severe COVID-19 patients than in non-severe patients, markers in routine blood tests have been the subject of research to monitor and predict the severity and prognosis of COVID 19 (14,15).

As in 351 patients (175 males, 176 females) aged between 18 and 92, whom we included in our study, coronavirus disease has wide clinical parameters that require intensive care unit, ranging from asymptomatic carriers to mild pneumonia, respiratory failure requiring mechanical ventilation, sepsis, septic shock and multi-organ failure (16).

As mentioned in many studies, coronavirus generally affects the elderly population (17). On the other hand, the second step of our study was that all patients included in the study were admitted to the intensive care unit due to the development of one or more of the severe pneumonia, moderate to severe ARDS, sepsis, septic shock, or multiple organ failure.

In the study of Asghar et al. which included all patients over the age of 18, the initial PLR value of the patients hospitalized in the service was found to be lower than the PLR value of the patients hospitalized in the intensive care unit (169.81±105.30 vs 271.84±179.47). In the same study, the PLR value of the patients who survived (n=78) was found to be lower than the patients who died (n=22) (186.38±130.34 vs 267.11±168.05) (18). These data were very similar to our study. In our patient group, PLR values at the time of hospitalization were similar in patients over 75 years of age and younger (287.4±207.5 / 294±455.7 respectively) (p=0.117). According to mortality, the cut-off point for the PLR value during hospitalization in patients over 75 years of age was determined as 411 and above (sensitivity 24%, specificity 95%). It was found that the hospitalization PLR values of the patients over 75 years of age who died (Group IV 287.4±207.5) were signifi-

cantly different compared to the surviving patients under the age of 75 (Group I 214.6±163.5). In most severe cases, different comorbid conditions such as diabetes, hypertension, heart failure and renal failure, have been found. The PLR value was found to be higher in patients with one or more of these comorbid conditions compared to non-severe patients (255.8±226.1 vs 436.5±329.2) (19). In our study, it was observed that the PLR values in patients over 75 years of age at service admission (p=0.022) and in patients under 75 years of age at intensive care unit admission were found to be higher in mortal patients when compared to survivors (390.5±300.7 vs 305.7±257.3) and found to be related to mortality. The cut-off value for mortality-related PLR in patients under 75 years of age was found to be 216 and above (sensitivity 68%, specificity 52%). In the last laboratory data at the time of discharge from the intensive care unit or at the time of exitus, which we took as the endpoint of our study, the final PLR value of the patients who survived was 272.9±196.8, while it was 316.6±344.6 for the patients who died. While the PLR value of the patients over the age of 75 who died was 334.2±391.7; it was found to be 297.2±285.8 in patients under 75 years of age. In the study of Asghar et al. while the final PLR value of the patients who survived was 305.63±466.06, it was found to be 340.48±428.64 in the patients who died. In that study, the cutoff value for ICU hospitalization was 153.65 (sensitivity 72.7, specificity 65.1), while the cutoff value for death was 153.65 (72.7 sensitivity, 59.5 specificity) (18). On the other hand, ICU admission was associated with mortality in patients younger than 75 years of age in our study (cutoff value 216.54, 68% sensitivity, 52% specificity).

CONCLUSION

The clinical use of the platelet-to-lymphocyte ratio may be a suitable marker in geriatric patients for determining disease severity and can be used as a predictive factor for determining the poor prognosis.

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