Association of C-reactive Protein/Albumin, Procalcitonin/Albumin, Platelet/Lymphocyte, and Lymphocyte/Monocyte Ratio with Mortality in Hospitalised COVID-19 Patients

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ABSTRACT

Objective: To investigate and compare complete blood count and biochemistry parameters such as c-reactive protein/albumin (CRP/ALB) ratio, procalcitonin/albumin (PRO/ALB) ratio, lymphocyte/monocyte (LYM/MON) ratio, platelet/lymphocyte (PLT/LYM) ratio of the recovered/deceased, and ICU (intensive care unit) /ward patients with COVID-19.

Study Design: An observational study.

Place and Duration of Study: Department of Internal Medicine, Sakarya University Training and Research Hospital, Turkey, from April 2020 to January 2021.

Methodology: The study was conducted with 590 diagnosed patients with COVID-19. The patients were divided into 2 groups as deceased (n = 294) /survivor (n = 296) and those in need of ICU (n= 418) /ward (n = 172). The information was obtained from the hospital information system and analysed retrospectively. The relationships of crp/alb, pro/alb, lym/mon, and PLT/LYM ratios with patient groups were investigated.

Results: Of the total 590 patients in the study, 358 (60.6%) were males. The total mean age was 65.63 ±14.9 years. The mean age of survivor and deceased groups was 71.32±10.9 and 59.97±16.2 years, respectively (p<0.001). The mean CRP/ALBratio of the both groups was 2.32±2.42 and 5.02±3.66, respectively (p<0.001). The mean values of PRO/ALBratio for both groups were 0.096±0.53 and 0.180±0.55, respectively (p<0.001). The mean values of LYM/MONratio for both groups were 5.72±23.5 and 4.12±9.25, respectively (p<0.001). The cut-off values of crp/alb, pro/alb, LYM/MONfor the risk of mortality were found to be 2.832, 0.008, and 1.189, respectively.

Conclusion: Advanced age, elevated CRP/ALB, procalcitonin/albumin, and platelet/lymphocyte ratios were found to be associated with mortality.

Key Words: *Covid-19, CRP/ALBratio, PRO/ALBratio, LYM/MON, PLT/L ICU, Mortality.*

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INTRODUCTION

Although coronavirus is a zoonotic RNA virus, it has made shifts between species a few times to date. Coronaviridea, known to cause infectious diseases since 1949, caused an outbreak as "Middle Eastern Respiratory Syndrome (MERS)" in 2012.[1,2] *SARS CoV-2* outbreak, which has been going on since December 2019, have caused more than 3 million people to lose their lives to date.[3]

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The most common complaints of the infected people are cough, fever, sputum, shortness of breath, fatigue, loss of smell, and known clinical symptoms usually start to present 3-4 days after the encounter with the virus.[4] One of the most serious complications of the disease is stated as acute respiratory disease syndrome (ARDS), which can especially be seen in 8-12 days after the diagnosis. Another phenomenon was seen in COVID-19 is hypercoagulation. The high levels of D-dimer, a fibrin degradation product, are associated with disease severity and mortality. Moreover, thrombosis-related findings were detected, especially in the pulmonary vascular beds in the autopsy series of COVID-19 patients.[5,6] Besides, high levels of acute-phase reactants, such as interleukin (IL)-1, IL-6, CRP, ferritin, and ldh, are linked with ICU requirements and mortality in patients with COVID-19.[7] This study aimed to determine the relationship between the above laboratory parameters and outcomes of patients with COVID-19.

METHODOLOGY

Approval of the Sakarya University Medical Faculty Ethics Committee was obtained for this study (27/04/2020-E.4266) This study was conducted on 590 confirmed COVID-19 patients who were hospitalised in the internal medicine clinic due to symptomatic pneumonia between April 15, 2020 and January 15, 2021. The patients were divided into the 2 groups *i.e.* deceased (n = 294) /survivor (n = 296) and those in need of ICU (n = 418) /ward (n = 172). Both groups were compared according to the demographic features, comorbid conditions, and measurements of the CRP/ALBratio, PRO/ALBratio, LYM/-MONratio, and PLT/LYM ratio of the patients. The ROC analysis was performed for ICU-ward and survivor-deceased groups to determine the cut-off value of statistically significant findings. Information was recorded from the hospital's electronic system. The World Health Organisation's definition for critical illness was used to evaluate the ICU requirement of the patients. According to this criteria: patients with SpO_2: <90% while receiving 5 L/min oxygen therapy; paO_2/fiO_2: <300; systolic blood pressure (SBP): <90 mm Hg; more than 40 mm Hg decrease in SBP and/or mean arterial pressure (MAP): <65 mmHg; acute organ dysfunctions, such as acute kidney injury, acute changes in liver function tests, confusion, acute haemorrhagic diathesis, and immunosuppression, were included in the study.[8]

The descriptive analyses were performed to provide information on the general characteristics of the study population. Some laboratory parameters could not be found for some patients in the management system. Thus, the patients, who did not not have that certain parameter, were excluded from the related subanalysis. Visual (probability plots, histograms) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were used to determine whether or not they are normally distributed. Descriptive analyses were presented using mean and standard deviation for the normally distributed variables, non-normally distributed variables were represented with median and İQR. The Independent t-test was used for the parametric tests to compare these parameters. Mann-Whitney U-test were performed for non-parametric parameters. The categorical variables were presented as the frequency (% percentage), and chi-square test was performed. ROC analysis was performed for the cut-off values of CRP/ALB, PRO/ALB, PLT/LYM ratio, and LYM/MON ratios; and the area under the ROC curve, cut-off values, sensitivities, and specificities were calculated. A p-value <0.05 was considered significant. The analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

Of the total 590 patients in the study, 358 (60.6%) were males, and 232 (39.4%) were females. The mean age was 65.63±14.9 years. The mean age was higher in the deceased group (p<0.001). The mean CRP/ALB ratio was increased in the deceased group than the survivor group (p<0.001). The mean PRO/ALBratio was higher in both group (p<0.001). The mean LYM/MON ratio was lower in both groups (p<0.001). The mean age in the ICU group was 69.49±11.95 years while it was 56.24±17.13 years for in the ward group (p<0.001). The mean CRP/ALB ratio was higher in the ICU care group (p<0.001). Mean PRO/ALBratio was higher in the ICU care group (p<0.001). There was no statistically significant difference in the mean PRO/ALZB and LYM/MON ratios between the deceased and ICU care groups (p<0.001). All these subgroup analyses were statistically significant (Table I).

The cut-off value of CRP/ALB ratio for the risk of mortality, was found to be 2,832 (AUC:0.755, 95% CI:0.714-0.795, sensitivity:70.7, and specificity:70.6, p<0.001), while it was 0.008 for PRO/ALB ratio (AUC:0.811, 95% CI:0.774-0.847, sensitivity:73.9, and specificity:73.2, p<0.001), and 1.189 for LYM/MON ratio (AUC:0.730 95% CI:0.687-0.773, sensitivity:64.6, and specificity:64.3, p<0.001, Table II, and Figure 1) The cut-off value of CRP/ALB ratio for the risk of ICU admission was found to be 1.893 (AUC:0.838, 95% CI:0.799-0.877, sensitivity:77.7, and specificity:77.6, p<0.001), while it was 0.004 for PRO/ALB ratio (AUC:0.862, 95% CI:0.825-0.899, sensitivity:78.5, and specificity:78.3, p<0.001) and 0.045 for PLT/LYM ratio (AUC:0.833, 95% CI:0.815-0.849, sensitivity:80.3, and specificity:79.1, p=0.002, Table III, Figure 2).

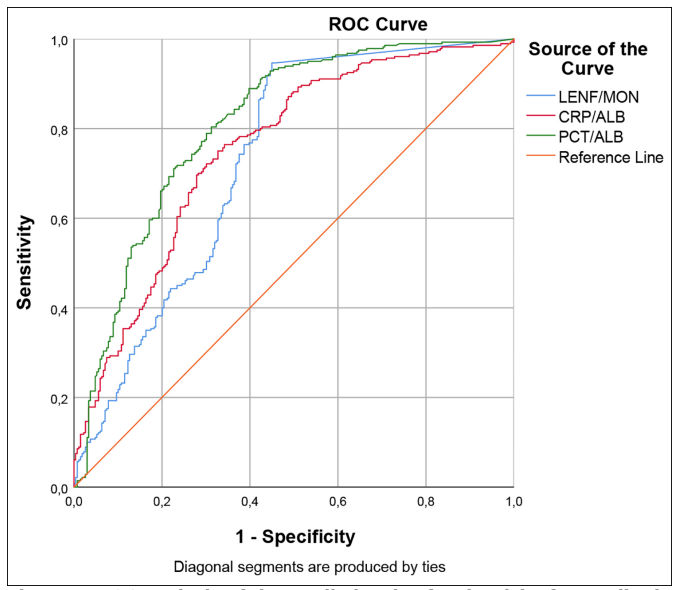

Figure 1: ROC analysis of the studied ratios for the risk of mortality in patients with COVID-19.

DISCUSSION

The advanced age is a risk factor in patients with COVID-19. In a retrospective study conducted in Wuhan, 50.2% of the 269 patients with severe disease were greater than or equal to the age of 65 years, whereas only 26% of the 279 patients, with mild to moderate diseases were greater than or equal to the age of 65 years.[9] In this study, the mean age of the patients in need of intensive care is 13.2 years more than the mean age of the patients followed in the ward, and the mean age of the deceased patients is 11.4 years more than the survivor patients. Both differences were statistically significant (Table I).

Table I: Comparison of deceased *vs.* survivor patients and ICU care *vs.* ward patients in terms of demographic features, MPV/PLT, CRP/ALB, PRO/ALB, LYM/MON, and PLT/LYM ratios.

Parameter	Decasead	Survivor	p	ICU	Ward	p
Age	71.32 ±10.92	59.97±16.24	<0.001	69.49±11.95	56.24 ±17.13	<0.001
Gender (n)	M:193 (65.6%) F:101 (34.4%)	M:165 (55.9%) F:130 (44.1%)	<0.001	M: 271 (64%) F: 147 (36%)	M: 87 (50.5%) F: 85 (49.5%)	<0.001
CRP/ALB	5.02±3.66	2.32±2.42	<0.001	4.561±3.41	1.407±2.00	<0.001
PRO/ALB	0.180±0.55	0.096±0.53	<0.001	0.181±0.61	0.0299 ±0.292	<0.001
LYM/MON	4.12±9.25	5.72±23.5	<0.001	4.35±3.36	5.11±21.41	<0.001
LLT/LYM	377.32±282.1	238.09±197.7	<0.001	374.31±263.46	148.0±92.2	<0.001

Table II: ROC analysis of the studied ratios for the risk of mortality in patients with COVID-19.

Parameter	AUC(95%)	Cut-off	Sensitivity	Specificity	p
CRP/ALB	0.755(0.714-0.795	2.832	70.7	70.6	<0.001
PRO/ALB	0.811(0.774-0.847)	0.008	73.9	73.2	<0.001
LYM/MON	0.730(0.687-0.773)	1.189	64.6	64.3	<0.001

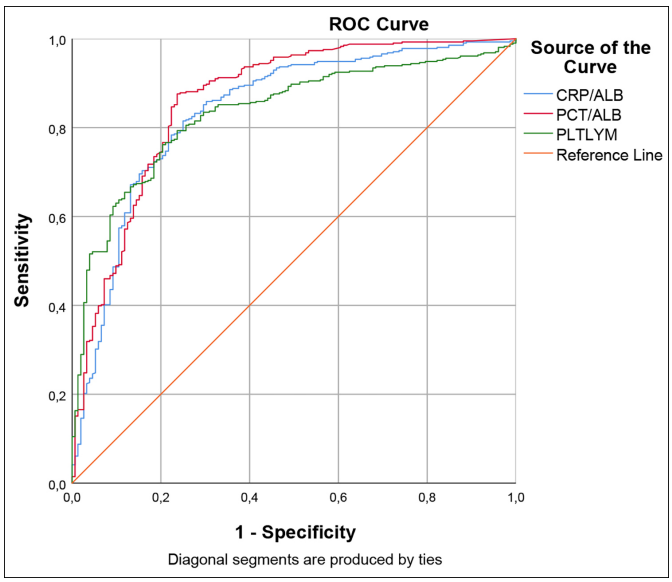

Figure 2: ROC analysis of the studied ratios for the risk of ICU admission in patients with COVID-19.

The CRP/ALB ratio can be used as an inflammatory marker like MPV/PLT ratio. High crp and low albumin are the two independent risk factors for Covid-19.[10] While the CRP/ALB ratio is used for disease severity in inflammatory diseases such as acute pancreatitis and ulcerative colitis.[11] CRP/ALB ratio was found to be a better predictor than CRP level alone in determining 28-day mortality in intensive care patients.[12]

In COVID-19, the CRP/ALB ratio measured in 12 patients can be used to determine disease mortality.[13] Concurrently, in this study, it was found to be significantly higher in deceased and ICU groups compared to the survivor and ward groups (p<0.001 and p<0.001, respectively). Additionally, ROC analysis revealed that the cut-off value of CRP/ALB ratio was 2.832, for predicting mortality in this study group while the cut-off value of the same ratio was 1.893 for predicting ICU need.

The PRO/ALB ratio is another inflammatory marker that was found to be an independent predictor of the disease in a study in which patients with urosepsis were compared to pyelonephritis patients with fever. In the same study, it was determined that this ratio was a more sensitive predictor than CRP, procalcitonin, and leukocyte levels alone.[14] The literature search did not reveal any study regarding the use of the PCT/ALB ratio in COVID-19. In this study, it was found to be significantly higher in deceased and ICU groups compared to the survivor and ward groups (both p<0.001, respectively). Moreover, the cut-off value of PRO/ALB ratio for predicting mortality in this study group was found as 0.008, and for predicting ICU requirement was determined as 0.004.

The LYM/MON ratio was found to be a potential prognostic factor in a cohort study of upper urothelial system carcinomas such as renal pelvis cancer.[15] In a study performed on 476 patients with classic Hodgkin lymphoma, the LYM/MON ratio was found to be an independent prognostic factor.[16] In a regression analysis performed in another study conducted on 93 cirrhotic patients with septic shock, the LYM/MON ratio was found to be a prognostic factor for mortality. In a study, it was determined that the LYM/MON ratio was lower in patients with severe COVID-19 compared to the control group.[17] Accordingly, this study results revealed that deceased patients and patients with ICU need have significantly lower LYM/MON ratio values than survivors and ward patients (p<0.001 for both). The cut-off value of LYM/MON ratio for predicting mortality in this study group was found as 1.189. These results showed that the LYM/MON ratio could be used as a predictive marker, for mortality and ICU need, in patients with COVID-19.

The PLT/LYM ratio is also an easy-to-calculate marker used for an acute inflammation and prothrombotic conditions. It is generally used in neoplasia and a very useful marker for inflammatory rheumatological diseases, especially giant cell arthritis.[18] In a meta-analysis performed on patients with pulmonary embolism, PLT/LYM ratio was found to be a good marker in determining the prognosis.[19] It is known that inflammation and thrombosis progress together in COVID-19, therefore, in the study conducted with COVID-19 patients, it was stated that the PLT/LYM ratio might be a predictor for the excessive cytokine release in the disease.[20] In a meta-analysis, a high PLT/LYM ratio was determined as

a predictor of disease severity.[21] Compatible with these data, the authors' analyses revealed that the deceased and the patients treated in the ICU have significantly higher PLT/LYM values than survivors and ward patients ($p<0.001$ and $p<0.001$, respectively). Additionally, ROC analysis revealed that the cut-off value of PLT/LYM ratio for predicting ICU requirement in this study group was 0.045.

CONCLUSION

The advanced age, elevated CRP/ALBUMIN ratio, procalcitonin/albumin, and platelet/lymphocyte ratios are found to be associated with mortality. These important results show that a high PLT/LYM ratio is a good indicator for both determining the mortality and need for intensive care.

ETHICAL APPROVAL:
Ethical approval was obtained from Sakarya University Ethical Committee (Aapproval on 27 April 2020, document No. 183).

PATIENTS' CONSENT:
Consents for participation in this study were not obtained from the patients as the data were collected from the medical record system of the Hospital without disclosing the identity of the participants.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
DC: Designing, data curation, and drafting the work.
KI: Data curation and drafting the work.
ACG: Analysis and interpretation of data.
ABG, SY, AT: Final approval of the version to be published.
All the authors have approved the final version of the manuscript to be published.

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