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The Prognostic Role of the Hematological Biomarkers is Questionable in Patients with COVID-19

Karakayalı M[1], Omar T[2] and Perincek G[3]*

[1]Department of Cardiology, School of Medicine, M.D. Kafkas University, Turkey

[2]Department of Cardiology, M.D. Kars Harakani State Hospital, Turkey

[3]Department of Chest Diseases, M.D. Kars Harakani State Hospital, Turkey

Abstract

Aim: During the COVID-19 pandemic, hematological biomarkers such as Red Cell Distribution Width (RDW), Mean Platelet Volume (MPV), and Neutrophil to Lymphocyte Ratio (NLR) have gained significant attention due to their ready availability, low invasiveness, and quick turnaround time. Reports produced confusing results that were at odds with each other. In this respect, we aimed to more precisely reveal the predictive value of hematological biomarkers in patients with COVID-19.

Methods: Demographics, comorbidities, and laboratory results on the admission of hospitalized patients with COVID-19 were analyzed. The study population was divided into two groups according to survival. Findings were compared between survivors and non-survivors.

Results: 501 patients with a median age of 60 (IQR, 40-74) were included. The in-hospital mortality rate was 24.5%. A total of 263 (52.5%) patients were male. A higher mortality rate for males and the elderly was observed. Regarding laboratory findings, medians of RDW, MPV, NLR and CRP were significantly higher in non-survivors compared to survivors according to univariate analysis (median (IQR), 14.6 (13.8-16) *vs.* 13.5 (13-14.6), 10.6 (9.7-11.5) *vs.* 10.1 (9.4-11), 11.42 (5.74-22.21) *vs.* 2.9 (1.82-5.75) and 95.15 (49-162.6) *vs.* 10.27 (2.3-33.21) all p values <0.05, respectively). However, none of them showed statistical significance in multivariate analysis. According to ROC curve analysis, the diagnostic performance of RDW, MPV, and NLR were lower than CRP.

Conclusion: In patients with COVID-19, the relationship between hematological biomarkers and in-hospital mortality is inconsistent. And the predictive role of the hematological biomarkers is questionable.

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Correspondence:
Muammer Karakayalı, Department of Cardiology, School of Medicine, M.D. Kafkas University, İsmail Aytemiz Bulvarı, Yeni Devlet Hastanesi Merkez, Kars, Turkey, Tel: +90-5356567912; Fax: +90-474 2125671

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Introduction

The COVID-19 pandemic has been still going ahead with a significant threat for human beings, resulting in many death tolls worldwide [1]. At this critical time, identifying at risk patients is crucial to facilitating the health professional's workload and ensuring optimal resource allocation. Furthermore, timely identification of patients at higher risk of progression towards unfavorable outcomes should be put at the center to enable an earlier and more appropriate therapeutic intervention, in this way focusing on limited healthcare resources on patients who would receive the most excellent benefits. In this context, identifying clinical, demographic, and laboratory factors predictive of clinical deterioration, prognosis and risk stratification is a top research priority in the ongoing pandemic [2,3]. Effective biomarkers would be helpful for screening, clinical management, and prevention of poor outcomes.

During the COVID-19 pandemic, among the multitude of laboratory parameters that might have a significant prognostic value, hematological biomarkers such as Red Cell Distribution Width (RDW) [4], Mean Platelet Volume (MPV) [5], and Neutrophil to Lymphocyte Ratio (NLR) [6,7] have gained significant attention due to their ready availability, low invasiveness and quick turnaround time [8].

However, the majority of studies relevant to the aforementioned hematological biomarkers included a smaller population. Moreover, reports produced confusing results that were at odds with each other. In this connection, we aimed to work with a relatively larger population to reveal the predictive value of hematological biomarkers more precisely in patients with COVID-19.

Materials and Methods

In this single-center retrospective study, the demographics, comorbidities, and laboratory findings of hospitalized patients with COVID-19 between April 22nd and December 30th, 2020, were analyzed. We included hospitalized COVID-19 patients (≥ 18 years old) who presented to the Kars Harakani State Hospital, a medical center designated as the pandemic hospital in the eastern city of Kars of Turkey. It was clear that the surveyed population died or was discharged with treatment. All patients were tested positive for SARS-CoV-2 with confirmed Polymerase Chain Reaction (PCR) and administered favipiravir and hydroxychloroquine when necessary for five days. The study population was divided into two groups according to survival. Findings were compared between survivors and non-survivors. The study protocol was approved by both Ministry of Health of Turkey and institutional review board of Kafkas University (Approval No and date 80576354-050-99/25, March 11th, 2020).

Vital parameters such as respiratory rate, heart rate, blood pressure, oxygen saturation, and blood sample results at the time of admission were collected from the hospital records. Regarding biochemical and hematological blood tests, albumin, C-Reactive Protein (CRP), D-dimer, ferritin, procalcitonin, B-type Natriuretic Peptide (pro-BNP), ferritin and creatinine, White Blood Cell count (WBC), hemoglobin, lymphocyte, neutrophil, platelet results on admission were analyzed. Further, blood cell Distribution Width-Coefficient of Variation (RDW-CV), MPV, was derived from complete blood count on admission. NLR was formulated as neutrophil count divided by lymphocyte count.

Comorbidities hypertension, diabetes, Chronic Obstructive Pulmonary Disease (COPD), Coronary Artery Disease (CAD), Cerebrovascular Disease (CVD), Chronic Kidney Disease (CKD), and Chronic Heart Failure (CHF) were interrogated. Smoking status was checked, as well. CHF was defined as a left ventricle ejection fraction <50% and patients with an estimated Glomerular Filtration Rate (eGFR) of less than 60 ml/minute were considered CKD. The history of hemorrhagic or ischemic cerebral attack was described as having a CVD. Patients lacking blood samples were excluded from the study.

Statistical analysis

Data obtained from this study was evaluated by using the SPSS 20 program. The normality test was maintained by using the Kolmogorov-Smirnov test. All continuous data in the study were not normally distributed thus expressed as the median with interquartile range. Categorical data were expressed as a percent and analyzed using the Chi-square test. Mann-Whitney U-test was used to analyze continuous variables. The statistical significance level was accepted as $p<0.05$. Multivariate logistic regression analysis was performed to identify the independent predictors of in-hospital mortality, using variables showing significant association in univariate analysis. Receiver Operating Characteristic (ROC) curve analysis was also used to indicate the diagnostic performance of RDW, MPW, NLR, and CRP for predicting in-hospital mortality.

Results

The study population comprised 501 patients with a median age of 60 (IQR, 40-74). While 378 patients survived the disease and were discharged with a cure, 123 (24.5%) patients died during the hospitalization. A total of 263 (52.5%) patients were male. Demographics are summarized in Table 1.

The frequency of male patients was significantly higher in non-survivor compared to survivors (63.4% *vs.* 48.9%, p=0.007). Also, dead patients were older than survivors (median age (IQR) 77 (68-84) *vs.* 32 (55-67), p<0.001). In addition, vital signs, heart rate and respiratory rate, were significantly higher and saturation was significantly lower in non survivors [median % (IQR), 26 (120-130) *vs.* 83 (78-90), 30 (28-34) *vs.* 20 (20-20), and 78 (72-82) *vs.* 94 (92-96), all p values <0.001, respectively).

Although the proportion of overall symptom did not show a significant difference between survivors and non-survivors, fever, cough, dyspnea, fatigue, nausea, anorexia, ageusia, sore throat, chest pain, abdominal pain, headache, arthralgia/myalgia were significantly higher in non-survivors (all p values <0.05). Diarrhea and anosmia were similar in both groups.

When comorbidities were compared between the two groups, the percentages of hypertension, diabetes, CAD, CHF, COPD, CKD, CVD, and Atrial Fibrillation (AF) were significantly higher in non-survivors. (62.6% *vs.* 29.9%, 30% *vs.* 9.5%, 17.9% *vs.* 7.4%, 9.8% *vs.* 2.6%, 44.7% *vs.* 22.2%, 13.8% *vs.* 3.4%, 16.3% *vs.* 8.1%, 8.1% *vs.* 1.9%, respectively, all p values <0.05). However, asthma and smoking showed similarities between two groups.

Regarding laboratory findings, level of WBC, neutrophil, RDW, MPV, NLR, pro-BNP, CRP, creatinine, D-Dimer, ferritin and procalcitonin were statistically higher (median (IQR), 11.09 (7.27-14.68) *vs.* 7.27 (5.48-10.59), 9.32 (5.68-12.64) *vs.* 4.8 (3.2-7.98), 14.6 (13.8-16) *vs.* 13.5 (13-14.6), 10.6 (9.7-11.5) *vs.* 10.1 (9.4-11), 11.42 (5.74-22.21) *vs.* 2.9 (1.82-5.75), 1124 (319-2525) *vs.* 57 (18-277), 95.15 (49-162.6) *vs.* 10.27 (2.3-33.21), 1.39 (0.93-2.16) *vs.* 0.84 (0.73-1.05), 2153 (942-4811) *vs.* 407 (219-953), 716 (277-1203) *vs.* 127 (53-251) and 0.433 (0.192-0.997) *vs.* 0.057 (0.39-0.112) all p values <0.05, respectively) and level of hemoglobin, platelet, lymphocyte and albumin were significantly lower [median (IQR), 13.4 (11.7-14.9) *vs.* 14.4 (13.1-15.8), 191 (133-265) *vs.* 208 (174-264), 0.46 (0.07-1.40) *vs.* 1.56 (1.11-2.13), and 30.9 (25.7-34.6) *vs.* 2.3 (39.4-44.9), all p values <0.05, respectively) in non-survivors in comparison to survivors. Of note, among these, hemoglobin (normal range, 11-16 g/dL), platelet (normal range, 100-300 10 × 3 uL) and procalcitonin (normal range, <0.5 ug/L) were within the normal ranges in both groups.

For multivariate analysis, the variables of age, gender, AF, COPD, hypertension, CAD, diabetes, CHF, CKD, CRP, D-dimer, ferritin, lymphocytes, neutrophils, pro-BNP, creatinine, WBC, RDW, MPV, and NLR were all included. Age and ferritin were found to be independent predictors of in-hospital mortality (Table 2).

A Receiver Operating Characteristic curve (ROC curve) was applied to show the performances of hematological biomarkers compared to conventional markers CRP. Area under curve for RDW, MPV, NLR, and CRP were 0.697 (p<0.001), 0.596 (p=0.51), 0.814 (p<0.001), and 0.844 (p<0.001), respectively (Figure 1).

Discussion

Our results showed a higher mortality rate for men and the elderly, consistent with previous reports [9,10]. A significant difference between survivors and non-survivors was observed for all blood parameters examined, including biochemical and hematologic biomarkers. Furthermore, rates of comorbidity other than malignancy and asthma were also higher for deceased patients. Although it is well documented that COVID-19 is primarily manifested as a

Table 1: Demographic, clinical, and laboratory characteristics.

	Overall (n=501)	Survivors (n=378)	Non-survivors (n=123)	*P*-value
Male, n (%)	263 (52.5)	185 (48.9)	78 (63.4)	0.007
Age (years), median [IQR]	60 (40-74)	32 (55-67)	77 (68-84)	<0.001
Intensive care unit, n (%)	142 (28.3)	24 (6.3)	118 (95.9)	<0.001
Initial Vital Signs				
Heart Rate, median [IQR]	86 (80-110)	83 (78-90)	126 (120-130)	<0.001
Saturation (%), median [IQR]	92 (85.5-95)	94 (92-96)	78 (72-82)	<0.001
RR/minute, median [IQR]	20 (20-24)	20 (20-20)	30 (28-34)	<0.001
Symptoms at arrival				
Symptomatic, n (%)	446 (89)	335 (88.6)	111 (90.2)	0.74
Fever, n (%)	117 (23.4)	66 (17.5)	51 (41.5)	<0.001
Cough, n (%)	186 (37.1)	118 (31.2)	68 (55.3)	<0.001
Dyspnea, n (%)	201 (40.1)	90 (23.8)	111 (90.2)	<0.001
Fatigue, n (%)	170 (33.9)	88 (23.3)	82 (66.7)	<0.001
Nausea, n (%)	39 (7.8)	39 (10.3)	0 (0)	<0.001
Diarrhoea, n (%)	9 (1.8)	9 (2.4)	0 (0)	0.121
Anosmia, n (%)	11 (2.2)	11 (2.9)	0 (0)	0.073
Anorexia, n (%)	47 (9.4)	15 (4)	32 (26)	<0.001
Ageusia, n (%)	12 (2.4)	12 (3.2)	0 (0)	0.044
Sore throat, n (%)	58 (11.6)	54 (14.3)	4 (3.3)	0.001
Chest pain, n (%)	67 (13.4)	34 (9)	33 (26.8)	<0.001
Abdominal pain, n (%)	19 (3.8)	19 (5)	0 (0)	0.006
Headache, n (%)	75 (15)	69 (18.3)	6 (4.9)	<0.001
Arthralgia/Myalgia, n (%)	112 (22.4)	47 (12.4)	65 (52.8)	<0.001
Laboratory findings at admission				
Hgb (g/dL), median [IQR]	14.2 (12.7-15.7)	14.4 (13.1-15.8)	13.4 (11.7-14.9)	<0.001
WBC (× 103/μL), median [IQR]	7.87 (5.64-11.86)	7.27 (5.48-10.59)	11.09 (7.27-14.68)	<0.001
PLT (× 103/μL), median [IQR]	206 (164-264)	208 (174-264)	191 (133-265)	0.004
Lymphocyte (× 103/μL), median [IQR]	1.46 (0.85-2.01)	1.56 (1.11-2.13)	0.46 (0.70-1.40)	<0.001
Neutrophil (× 103/μL), median [IQR]	5.52 (3.53-9.45)	4.80 (3.20-7.98)	9.32 (5.68-12.64)	<0.001
RDW (%), median [IQR]	13.8 (13.1-14.9)	13.5 (13-14.6)	14.6 (13.8-16)	<0.001
MPV (fl)	10.3 (9.4-11.2)	10.1 (9.4-11)	10.6 (9.7-11.5)	0.001
NLR	3.88 (2.02-8.79)	2.9 (1.82-5.75)	11.42 (5.74-22.21)	<0.001
ProBNP (pg/mL), median [IQR]	85 (22-540)	57 (18-277)	1124 (319-2525)	<0.001
CRP (mg/L), median [IQR]	17.93 (3.91-72.74)	10.27 (2.43-33.21)	95.15 (49-162.6)	<0.001
Creatinine (mg/dL), median [IQR]	0.90 (0.73-1.18)	0.84 (0.73-1.05)	1.39 (0.93-2.16)	<0.001
D-Dimer (μg/mL), median [IQR]	488 (237-1283)	407 (219-953)	2153 (942-4811)	<0.001
Albumin (g/L), median [IQR]	40.6 (34.6-44)	42.3 (39.4-44.9)	30.9 (25.7-34.6)	<0.001
Ferritin (ug/L), median [IQR]	145 (59-344)	127 (53-251)	716 (277-1203)	<0.001
Procalcitonin (ug/L), median [IQR]	0.065 (0.042-0.196)	0.057 (0.39-0.112)	0.433 (0.192-0.997)	<0.001
Comorbidities				
Hypertension, n (%)	190 (37.9)	113 (29.9)	77 (62.6)	<0.001
Diabetes, n (%)	66 (13.2)	36 (9.5)	30 (24.4)	<0.001
Cigarette smoking, n (%)	184 (36.7)	138 (36.5)	46 (37.4)	0.914
Coronary artery disease, n (%)	50 (10)	28 (7.4)	22 (17.9)	0.002
Chronic heart failure, n (%)	22 (4.4)	10 (2.6)	12 (9.8)	0.002
COPD, n (%)	139 (27.7)	84 (22.2)	55 (44.7)	<0.001

Asthma, n (%)	26 (5.2)	17 (4.5)	9 (7.3)	0.243
CKD (eGFR <60 mL/min/m2), n (%)	30 (6)	13 (3.4)	17 (13.8)	<0.001
Cancer, n (%)	10 (2)	5 (1.3)	5 (4.1)	0.071
Previous CVD, n (%)	28 (5.6)	8 (2.1)	20 (16.3)	<0.001
Previous atrial fibrillation, n (%)	17 (3.4)	7 (1.9)	10 (8.1)	0.002

RR: Respiratory Rate; Hgb: Hemoglobin; WBC: White Cell Blood Count; PLT; Platelet; RDW: Red Cell Distribution Width; MPV: Mean Platelet Volume; NLR: Neutrophil to Lymphocyte Ratio; BNP: B Type Natriuretic Peptide; CRP: C-Reactive Protein; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; CVD: Cerebrovascular Disease

Table 2: Predictors in univariable and multivariable analysis.

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.09 (1.07-1.11)	<0.001	1.11 (1.01-1.23)	0.026
Gender	0.55 (0.36-0.84)	0.007	1.4 (0.24-8)	0.705
Atrial fibrillation	0.21 (0.079-0.57)	0.002	0.36 (0.012-11.7)	0.572
COPD	0.35 (0.64-0.85)	<0.001	0.65 (0.108-3.99)	0.649
Hypertension	0.25 (0.16-0.39)	<0.001	0.87 (0.15-7.2)	0.898
Coronary artery disease	0.36 (0.20-0.67)	0.002	5.2 (0.35-76.9)	0.229
Diabetes	0.32 (0.19-0.55)	<0.001	8.06 (0.79-81)	0.077
Chronic heart failure	0.25 (0.106-0.597)	0.002	0.45 (0.006-37)	0.728
CKD	0.22(0.105-0.472)	<0.001	0.94 (0.015-60)	0.977
Cerebrovascular disease	0.11 (0.048-0.26)	<0.001	20 (0.48-822)	0.114
CRP	1.015 (1.011-1.018)	<0.001	1 (0.98-1.01)	0.956
D-Dimer	1 (1-1.001)	<0.001	1 (0.99-1)	0.734
Ferritin	1.002 (1.002-1.003)	<0.001	1.003 (1.001-1.005)	0.001
Lymphocyte	0.57 (0.50-0.64)	<0.001	9 (0.4-1666)	0.409
Neutrophil	1.16 (1.11-1.21)	<0.001	6.3 (0.04-985)	0.475
Pro-BNP	1 (1-1)	0.006	1 (1-1)	0.373
Creatinine	1.54 (1.28-1.86)	<0.001	1.3 (0.6-2.86)	0.496
WBC	1.11 (1.07-1.16)	<0.001	0.13 (0.001-16.8)	0.42
RDW	1.39 (1.23-1.57)	<0.001	0.92 (0.5-1.68)	0.795
MPV	1.32 (1.12-1.56)	0.001	1.05 (0.59-1.86)	0.865
NLR	1.14 (1.1-1.17)	<0.001	1.06 (0.8-1.41)	0.655

COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; CRP: C Reactive Protein; BNP: B Type Natriuretic Peptide; WBC: White Cell Blood Count; RDW: Red Cell Distribution Width; MPV: Mean Platelet Volume; NLR: Neutrophil to Lymphocyte Ratio

respiratory tract infection, emerging data indicate that it should be regarded as a systemic disease [11-13]. Thus, various inflammatory markers, including hematological indices, possibly concerning the hyperinflammatory state with cytokine, might be involved in the process.

Leukocytosis is noted in COVID-19 infected patients, especially in those complicated with superimposed bacterial infection [2]. Similarly, the WBC level in our study was higher, just above the upper limit of the normal range, in non-survivors. In a review article, leukocytosis was the main hematological finding in COVID-19 infection [14]. However, Huang et al. reported the opposite [15]. They observed a lower WBC in severe patients with COVID-19.

Neutrophilia was associated with unfavorable outcomes in the setting of COVID-19 [16]. According to a correspondence letter, ICU patients tend to develop neutrophilia during the hospitalization with a median peak Absolute Neutrophil Count (ANC) of 11.6×10^9/L, compared to 3.5×10^9/L in the non-ICU group (P-value <0.001) [17]. Moreover, Fan et al. noted that neutrophilia is common in patients treated in the ICU during hospitalization [17]. Our findings concerning the number of neutrophils are in agreement with these reports. Neutrophilia may also indicate superimposed bacterial infection [2]. Given the high levels of WBC and neutrophilia in our study population, a bacterial superinfection is being questioned and may contribute to increased mortality in COVID-19.

In our study, lymphopenia was observed dominantly among non-survivors. In a similar vein, reports showed lymphopenia might correlate with COVID-19 infection severity. Yang et al. reported lymphopenia in the majority of critically ill adult COVID-19 patients [18]. Chen et al. reported a rate of 25% of patients with mild COVID-19 infection [19]. Besides, the study by Huang et al. found low lymphocytes and WBC counts in most patients [15].

The NLR, calculated simply by the ratio of neutrophils count/lymphocytes count, is an inflammatory marker that can predict the probability of death in COVID-19 patients [20]. Furthermore, it was an independent risk factor for severe disease [21]. NLR, in our study, was higher in non-survivors according to univariate analysis.

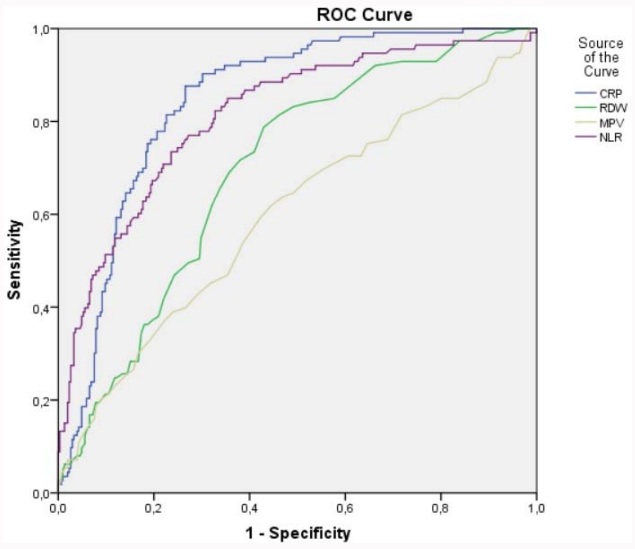

Figure 1: Diagnostic accuracy of CRP, RDW, MPV, and NLR on in-hospital mortality in patients with COVID-19 by ROC curve.
CRP: C-Reactive Protein; RDW: Red Cell Distribution Width; MPV: Mean Platelet Volume; NLR: Neutrophil to Lymphocyte Ratio

However, in multivariate analysis, it was insignificant as a predictor.

Recently, RDW has gained significant attention due to its capability to efficiently predict the risk of death in the general population, as well as in patients with non-cardiovascular critical illness, sepsis, pneumonia, and other respiratory tract infections [22,23]. Regarding COVID-19 disease, Henry et al. showed that RDW was significantly associated with mortality [4]. In addition, they described it as an independent predictor of mortality. Conversely, Sharma et al. concluded that there was no significant association between RDW and mortality [24]. The univariate analysis of our study indicated that the RDW was significantly higher in the non-living population than in the surviving population. However, in multivariate analysis, it did come out as a predictor of in-hospital mortality.

The predictive role of MPV in the context of COVID-19 infection has been the subject of a diversity of perspectives. It was not significantly associated with mortality, according to Gawda et al. [25], While Güçlü et al. [5] showed that every one unit increase in MPV increased mortality by 1.76 times in patients with COVID-19. Similarly, we found an increased median of MPV in non-survivors.

Elevated ferritin has become a prominent biomarker in COVID-19, with elevations associated with the development of severe disease [8]. In our study, a higher level of ferritin was observed in non-survivors. Additionally, ferritin was found to be an independent predictor of in-hospital mortality alongside advanced age.

CRP is an acute-phase reactant that is increased in a wide range of inflammatory conditions. Lippi et al. showed an increase in most patients with COVID-19 infection, particularly in severe disease [26]. Farther, it was correlated with poor outcomes in COVID-9 patients [27]. Tan et al. proposed that it might be used as an early predictor for severe COVID-19 [28]. Along these lines, the CRP level in our study also showed a higher median in non-survivors than survivors.

Another important point concerning our study, according to the ROC analysis, the RDW, MPV, and NLR performed below the CRP. Additionally, in the multivariate analysis, the parameters that differed significantly between survivors and non-survivors in univariate analysis, including hematological biomarkers, did not show association with in-hospital mortality except for ferritin and advanced age. We estimated that this was probably because our study population was highly heterogeneous, including patients of all adult age groups and hospitalized patients in intensive care and non-intensive care services.

Consequently, given the discrepancy among previous reports and considering our findings, the prognostic role of the hematological biomarkers in the context of COVID-19 infection has become controversial. This uncertainty points to an inconsistent relationship between hematologic biomarkers and fatality.

Conclusion

The prognostic role of hematological biomarkers in COVID-19 infection is questionable, given the discrepancy among past reports and considering our findings. This ambiguity indicates that the relationship between hematological biomarkers and in-hospital mortality is inconsistent and that more in-depth research, particularly in specific population groups, is warranted.

Limitations

Significant limitations must be acknowledged as follows: 1) our study population was widely heterogeneous, including patients of all adult age groups and hospitalized patients in intensive care and non-ICU wards. 2) Since we were lack of detailed data about pharmacological therapy for comorbidities, we could not calculate how treatment affected the survival.

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