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The Evaluation of Hematological Parameters and Their Correlation with Disease Prognosis in COVID-19 Disease in Iran

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ABSTRACT

Background: Since 2019, Coronavirus has been a highly contagious disease. The COVID-19 outbreak was declared a pandemic by the World Health Organization in March 2020. Variable laboratory findings are reported in COVID-19 patients, among which elevated levels of D-dimer, lactate dehydrogenase, as well as lymphopenia, have been reported to be associated with increased severity of disease symptoms requiring ventilator support, intensive care unit admission, and mortality.

Materials and Methods: In the current study, inclusion criteria were: patient age above 18 years and hospitalization in the Imam Khomeini hospital with COVID-19 disease confirmed with nasopharyngeal swab polymerase chain reaction tests. Levels of white blood cells, neutrophils, lymphocytes, hemoglobin, platelets, D-dimer, C-reactive protein, LDH, and ferritin were measured and their correlation with the final patients' outcome was evaluated.

Results: A total of 208 patients were included in the present study. Higher neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte, LDH, platelet to lymphocyte ratio, ferritin, and D-dimer were significantly related to O_2 dependency. Neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte and LDH were significantly related to higher rates of mortality. Higher Hb and lymphocyte count were significantly related to higher rates of survival.

Conclusion: Hematological parameters including neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte, LDH, platelet to lymphocyte ratio, ferritin, D-dimer, Hb, and lymphocyte count were significantly related to the prognosis of patients with COVID-19 disease. This could help decide which COVID-19 patients have priority for hospitalization and intensive medical care, particularly when the pandemic disease causes limitations in healthcare service.

Keywords: COVID-19; Hematological parameters; Disease prognosis; Final outcome; ICU admission

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious and pathogenic viral infection that is caused by a newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. The World Health Organization (WHO) declared the COVID-19 outbreak a pandemic, in March 2020[2]. COVID-19 has a wide spectrum of symptoms ranging from very mild to severe consisting of fever, dry cough, fatigue, and less commonly shortness of breath, sore throat, diarrhea, nausea or vomiting, muscle or body aches, and loss of taste or smell[3]. Most people who fall sick with COVID-19 will experience mild to moderate symptoms and recover without hospitalization and special treatment[4]. A small percentage of patients may become critically ill and require intensive care[4]. In such settings, complications including respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-organ failure, including injury of the heart, liver, or kidneys may occur and lead to death[5].

Several COVID-19 testing methods have been developed to diagnose the disease (6). The standard diagnostic method is by detection of the virus's nucleic acid by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab[6].

So far, Iran is ranked sixteenth in terms of prevalence and eleventh in terms of mortality in the world with 7227683 definite cases and 141216 deaths, respectively [7].

Variable laboratory findings have been reported in patients with COVID-19 disease including leukopenia, leukocytosis, lymphopenia, elevated level of lactate dehydrogenase (LDH), ferritin, D-dimer, troponin and creatinine, as well as increased inflammatory markers, impaired hepatic aminotransferases, and impaired coagulation tests (8, 9). Elevated levels of D-dimer, LDH as well as lymphopenia have been reported to be associated with an increased need for ventilation support, ICU admission, and mortality [8, 10-14].

The progression of COVID-19 is known to significantly be influenced by inflammatory reactions [15-17]. Rapid SARS-CoV-2 viral replication, cellular damage, and inflammatory responses can attract macrophages and monocytes and cause the release of cytokines and chemokines [15-17]. These cytokines and chemokines draw in immune cells and trigger immunological responses, which exacerbate the situation and cause cytokine storms [15-17]. Del Valle et al. showed that cytokine patterns are predictive of COVID-19 survival and mortality [18]. Furthermore, Zeng *et al.* explained the connection between inflammatory indicators and the severity of COVID-19, providing good and cost-effective biomarkers for clinicians to monitor and control the severity and prognosis of COVID-19 [19]. Various studies have found an association between the prognosis of systematic inflammatory diseases such as cancer and biomarkers of inflammation such as white blood cell (WBC) count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio, and serum C-reactive protein (CRP) levels [20, 21]. Moreover, these biomarkers are found to be potential biomarkers for the prediction of COVID-19 prognosis and severity[22,23].

To our knowledge, this is the largest study in Iran aiming to evaluate the hematological parameters that are indicators of the inflammatory response and damage to the immune system in hospitalized patients with COVID-19 disease and assess their correlation with the patient's final prognosis. The use of these easy, cost-effective, accessible, and rapid hematological tests as prognostic factors could help physicians design diagnostic protocols in determining the severity of COVID-19 disease, and ultimately decide whether the patient should be hospitalized or discharged, be admitted to an intensive care unit (ICU) or non-ICU (in cases that have the necessity for hospitalization), the need for more strict treatment as well as the timing of the patient's discharge. Furthermore, prompt and timely intervention could help to improve the affected patient's outcomes.

MATERIALS AND METHODS

Study population

In the current cross-sectional study, a total number of 208 patients with COVID-19 confirmed with PCR tests from nasopharyngeal swabs who were hospitalized in the Imam Khomeini Hospital in Tehran were included. The inclusion criteria were: a)

age above 18 years old, b) confirmed COVID-19 disease with nasopharyngeal swab PCR, and c) hospitalization in Imam Khomeini hospital. People who had another known disease affecting the count of blood cells (CBC) and/or those who were consuming cytotoxic drugs affecting CBC before COVID-19 infection were excluded from this study. The Ethics Committee of the Tehran University of Medical Sciences approved this study and written informed consent was obtained from all patients.

Data collection

A questionnaire was designed to retrospectively obtain all demographic information from the patient's medical records. Demographic and clinical data consisting of current age, presence of a medical disease, occurrence of, thrombosis, and outcome were included. The outcome was determined as a discharge without the need for O_2 therapy, discharge with the need for O_2 therapy, need for intensive care unit (ICU) admission, and death. Levels of white blood cells (WBC), neutrophils, lymphocytes, hemoglobin, platelets, Di-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin were measured at the beginning of hospitalization using standard techniques administered by highly authoritative technicians of Imam Khomeini hospital.

Statistical analysis

Statistical analysis was accomplished using SPSS software (SPSS Inc., version 24, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for the data normality. For quantitative variables, mean and standard deviation (SD) and for qualitative variables, frequency, and percentage were reported as the index of data exact tests. Logistic regression analysis was used for the evaluation of the correlation between laboratory parameters and disease prognosis. P-value <0.05 was considered statistically significant.

RESULTS

Demographic, clinical, and laboratory data

A total number of 208 patients were included in the current study. The mean ± SD age of the patients was 56.83 ± 14.21 years. The male-to-female ratio was 1:1.18. The outcome of the patients was as follows: 97 patients (46.6%) were discharged without need for O_2 therapy, 67 patients (25.9%) required O_2 therapy 54 numbers of which required ICU admission as well (26.1%) and 44 patients (21.1%) were dead. The detailed demographic and clinical data of the included patients are demonstrated in Table 1. Moreover, Table 2 shows the detailed laboratory data of these patients.

Evaluation of the relation between hematologic parameters and O2 dependency

Table 3 summarizes the correlation between variable hematologic parameters with O2 dependency. O2-dependent patients had significantly higher neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte, LDH, platelet to lymphocyte ratio, ferritin, and D-dimer compared to non-O2-dependent (mean: 17 to 4.8, 17.6 to 5.28, 1400 to 650, 240 to 114.28, 870 to 220 and 865 to 270, respectively, P-value <0.001). Furthermore, Hb and lymphocyte count were significantly higher in non-O2-dependent patients in comparison to O2-dependent patients (mean: 14 to 10.7 and 1400 to 500, respectively, P-value <0.001). We found no significant difference between Hb level and O2 dependency based on gender classification (Table S1). The correlation between different levels of platelets, neutrophils, lymphocytes, and neutrophil-to-lymphocyte ratio with O2 dependency is summarized in Tables S2-5.

Evaluation of relation between hematologic parameters and ICU admission need

Table 4 illustrates the correlation between variable hematologic parameters with ICU need in O2-dependent patients. ICU cases had significantly higher neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, LDH, CRP, ferritin, and D-dimer compared to non-ICU cases (mean: 30 to 21.25, 333.33 to 325, 1800 to 900, 110 to 91, 1300 to 954 and 2100 to 1400, respectively, P-value <0.05). Also, lymphocyte count was significantly higher in non-ICU cases compared to ICU cases (mean: 400 to 300, P-value =0.008).

Evaluation of the relation between hematologic parameters and mortality

Thirty-four (16%) patients were dead at the end of the current study. Neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte and LDH were significantly higher among the dead in comparison to patients who were alive at the end of the study (mean: 20 to 10, 480 to 9, and 1680 to 960, respectively, P-value <0.05). Interestingly, Hb and lymphocyte count were significantly higher among the alive patients compared to the dead ones (mean: 12.8 to 11.3 and 970 to 480, respectively, P-value <0.05). Table 5 shows detailed information on hematologic parameters in dead and alive patients.

The chance of mortality in ICU cases was 60% in case of ICU admission compared to 67% in case of non-ICU admission. Among ICU cases who were admitted to ICU, neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte and LDH were significantly higher in those who were finally dead compared to the alive ones (mean: 22.6 to 10, 21.66 to 9, and 1700 to 980, respectively, P-value <0.05), while Hb and lymphocyte count were significantly higher among the alive ones compared to the dead (mean: 11.2 to 10.1 and 980 to 450, respectively, P-value <0.05). Similarly, among ICU cases who were not admitted to ICU, neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte and LDH were significantly higher in those who were finally dead compared to the alive ones (mean: 18.4 to 10.87, 500 to 11.87 and 1600 to 950, respectively, P-value <0.05), while lymphocyte count was significantly higher in alive patients in comparison to the dead (mean: 800 to 500, P-value <0.05). Detailed information is summarized in Table 6.

Correlation between thrombosis with disease prognosis

Among the total number of patients, 20 cases (9.6%) had thromboembolic events. Among the hematologic parameters, only lymphopenia was found to be significantly associated with thromboembolic events (mean: 1100 in those with thrombotic events compared to 1300 in those without thrombotic events, P-value <0.05). Table 7 demonstrates more information about the association of hematologic parameters with thromboembolic events. Of interest, no significant correlation was found between thrombosis and disease prognosis.

Table 1. Demographic data of the patients

Number of patients (N=208)		Variable	
Percentage	Frequency		
45.7	95	Male	Sex
54.3	113	Female	
46.6	97	Discharged	Outcome
6.25	13	O_2-dependent non-ICU cases	
25.9	54	O_2-dependent ICU cases	
21.1	44	Dead	
9.6	20	Yes	Thrombosis
90.4	188	No	

N: Number; ICU: Intensive care unit

Table 2. Laboratory data of the patients

Variable	Number of patients (N=208)	
	Standard deviation	Mean
LDH	790.2	891.8
Hb	2.6	13.1
Age	14.2	56.8
WBC	4500.3	7651.7
Neutrophil	4153.7	6393.3
Lymphocyte	507.6	925.9
Platelet	92.8	185.0
Neutrophil/lymphocyte	9.5	9.2
Platelet/lymphocyte	722.6	277.4
(WBC count excluding lymphocyte)/lymphocyte	46.2	15.8
CRP	76.5	104.1
Ferritin	292.7	664.8
D-dimer	1571.8	1251.7

LDH: lactate dehydrogenase; Hb: hemoglobin; WBC: white blood cell; CRP: C-reactive protein; N**:** number

Table 3. Correlation of variable hematologic parameters with O_2 dependency

Parameter mean	O2 dependency in general ward admitted patients N=208		
	Non-O_2-dependent N=97	O_2-dependent N=111	P-value
WBC	8800	9300	0.755
Lymphocyte	1400	500	0.001*
Neutrophil	6800	8500	0.501
Neutrophil/lymphocyte	4.8	17	0.001*
(WBC count excluding lymphocyte)/lymphocyte	5.28	17.6	0.001*
Platelet	160000	120000	0.609
Platelet/lymphocyte	114.28	240	0.001*
LDH	650	1400	0.001*
Hb	14	10.7	0.001*
CRP	77	98	0.763
Ferritin	220	870	0.001*
D-dimer	270	865	0.001*

LDH: lactate dehydrogenase; Hb: hemoglobin; WBC: white blood cell; CRP: C-reactive protein; N: number
**P-value* <0.05 is statistically significant

Table 4. Correlation of variable hematologic parameters with ICU needs in O_2-dependent patients

Variable mean	ICU need in O_2-dependent cases N=111		
	ICU Case N=52	Non-ICU case N=59	*P*-value
WBC	9300	9100	0.787
Lymphocyte	300	400	0.008*
Neutrophil	9000	8500	0.663
Neutrophil/lymphocyte	30	21.25	0.001*
(WBC count excluding lymphocyte)/lymphocyte	30	21.75	0.002*
Platelet	100000	130000	0.742
Platelet/lymphocyte	333.33	325	0.002*
LDH	1800	900	0.007*
Hb	10.2	11	0.07
CRP	110	91	0.003*
Ferritin	1300	954	0.001*
D-dimer	2100	1400	0.001*

ICU: intensive care unit; LDH: lactate dehydrogenase; Hb: hemoglobin; WBC: white blood cell; CRP: C-reactive protein; N: number
**P-value* <0.05 is statistically significant

Table 5. Relation between hematologic parameters and mortality

Variable mean	All cases		
	Dead N=34	Discharged N=177	*P*-value
WBC	9600	9700	0.783
Lymphocyte	480	970	0.003*
Neutrophil	8990	10100	0.548
Neutrophil/lymphocyte	20	10	0.004*
(WBC count excluding lymphocyte)/lymphocyte	480	9	0.001*
Platelet	91800	96000	0.608
LDH	1680	960	0.007*
Hb	11.3	12.8	0.012*
CRP	100	55	0.562

LDH: lactate dehydrogenase; Hb: Hemoglobin; WBC: white blood cell; CRP: C - reactive protein; N: Number
**p-value* <0.05 is statistically significant

Table 6. Relation between hematologic parameters and mortality. Among ICU cases who were admitted to ICU

Variable mean	ICU Cases					
	Admitted N=15			not admitted N=37		
	Dead N=9	Discharged N=6	*P*-value	Dead N=25	Discharged N=12	*P*-value
WBC	10200	9800	0.896	9200	9500	0.708
Lymphocyte	450	980	0.026*	500	800	0.014*
Neutrophil	8900	8200	0.941	9100	9000	0.228
Neutrophil/lymphocyte	22.66	10	0.005*	18.4	10.87	0.002*
(WBC count excluding lymphocyte)/lymphocyte	21.66	9	0.003*	500	11.87	0.001*
Platelet	90000	98000	0.807	92000	95000	0.692
LDH	1700	980	0.002*	1600	950	0.009*
Hb	10.1	11.2	0.001*	10.6	11.5	0.37
CRP	90	9800	0.868	110	9500	0.288

ICU: intensive care unit; LDH: lactate dehydrogenase; Hb: hemoglobin; WBC: white blood cell; CRP: C-reactive protein; N: number
**P-value* <0.05 is statistically significant

Table 7. Correlation of thrombosis with disease prognosis

Variable mean	Thrombotic event N=20	No thrombotic event N=188	*P*-value
WBC	8800	9200	0.512
Lymphocyte	1100	1300	0.032*
Neutrophil	7800	8100	0.671
Neutrophil/lymphocyte	7.9	6.23	0.078
(WBC count excluding lymphocyte)/lymphocyte	7.79	8.01	0.065
Platelet	140000	125000	0.673
Platelet/lymphocyte	390	350	0.511
LDH	1400	1100	0.06
Hb	10.9	11.4	0.708
CRP	87	65	0.541
Ferritin	680	900	0.06
D-dimer	1700	1500	0.065

LDH: Lactate dehydrogenase; HB: Hemoglobin; WBC: White blood cell; CRP: C - reactive protein; N: Number
**P-value* <0.05 is statistically significant

DISCUSSION

In the current study, we evaluated the hematological parameters in Iranian patients with COVID-19 disease and assessed their correlation with the final prognosis of the patients. According to our findings, neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte, LDH, platelet to lymphocyte ratio, ferritin, D-dimer, Hb, and lymphocyte count were significantly related to the prognosis of patients with COVID-19 disease and could be considered as prognostic factors. Another study about the correlation between hematological parameters with disease severity was conducted on 189 COVID-19 patients in Iran, which did not find a significant association between lymphocyte count, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio, and disease severity [24]. Herein, we have enrolled more patients, also we have investigated more hematological parameters in comparison to the previous study.

In a study by Huang *et al.* on 41 patients with COVID-19 disease, lymphocytopenia, and higher D-dimer and LDH levels were significantly associated with increased risk of ICU admission[14]. Similarly in another study, Yao *et al.* showed a significant relationship between elevated D-dimer levels and increased risk of mortality [11]. Similar to these studies, we observed that lymphopenia, higher LDH, and D-dimer were correlated with poorer disease prognosis, and patients with lymphopenia, and higher LDH and D-dimer were significantly more dependent on O_2 and required ICU care. Also, higher LDH and lymphopenia were associated with an increased risk of mortality. Other studies have also reported the association between lymphopenia and COVID-19 disease severity [8, 14, 25-27], which could be linked with the ability of T lymphocytes essential for the destruction of infected viral particles [28].

Wu *et al.* evaluated the risk factors for the clinical outcomes of COVID-19 patients who developed acute respiratory distress syndrome (ARDS) or died[8]. They concluded that older age, neutrophilia, lymphocytopenia, higher LDH, and D-dimer are associated with an increased risk of developing ARDS[8]. Moreover, neutrophilia and higher LDH and D-dimer were associated with higher mortality in COVID-19 patients[8]. Contrarily, the absolute count of neutrophils and neutrophilia were not statistically associated with disease prognosis in our study. Of interest, according to our findings, a higher neutrophil-to-lymphocyte ratio was determined as a poor prognostic factor in COVID-19 disease and associated with higher O_2 dependency, ICU admission as well as mortality. This finding shows that a higher neutrophil-to-lymphocyte ratio is a more sensitive factor compared to an increased absolute neutrophil count in predicting the disease prognosis. Several studies have reported a significant association between neutrophil to lymphocyte ratio, as well as platelet to lymphocyte ratio, and the disease severity and prognosis [23, 25, 29]. Our findings follow these studies. COVID-19 causes a systemic inflammatory response through the production of inflammatory factors by lymphocyte and endothelial cells including interleukin IL-6 and IL-8, tumor necrosis factor-alpha (TNF-α), granulocyte colony-stimulating factor (G-CSF) and interferon-gamma factor (INF-γ), which trigger activation of neutrophils[30-33]. Conversely, systematic inflammation and immune response significantly decrease cellular immunity, notably the helper T lymphocytes [34]. Thus, the neutrophil to lymphocyte ratio is elevated as a result which itself prompts the COVID-19 disease progression. In our study, platelet to lymphocyte ratio was significantly correlated with higher O_2 dependency and ICU admission. Our findings are in line with the findings of Waris *et al.* and Yang *et al.* reporting a significant association between a higher platelet-to-lymphocyte ratio and COVID-19 severity [23, 35]. Furthermore, some studies have concluded that the platelet-to-lymphocyte ratio is a predictor of inflammation in some diseases such as autoimmunity, inflammatory bowel syndrome, and cardiovascular diseases [23, 36, 37]. Thus, platelet to lymphocyte ratio could be used as a cost-effective predictor of COVID-19 severity and prognosis due to the involvement of inflammatory processes in COVID-19.

In our study, lower levels of Hb and higher amounts of ferritin were significantly correlated with O_2 dependency, ICU admission, and mortality. Similar to our findings, Tao *et al.* (38) and Lin *et al.*[39] respectively found that anemia and higher amounts of serum ferritin are two independent risk factors

associated with COVID-19 severity. Hemoglobin is known as one of the main determinants of blood's oxygen-carrying capacity [40]. Lower hemoglobin level is accompanied by the lesser ability to support the elevated oxygen demands of peripheral tissues brought on by hypermetabolic conditions during COVID-19 infection, thereby being correlated with disease severity [41,42]. An elevated level of circulating ferritin is not only a sign of an acute-phase response but also is crucial for the development of an inflammatory cytokine storm [41,42]. The H-chain of ferritin may be crucial for stimulating macrophages to release more inflammatory cytokines, as seen in COVID-19 patients [41, 42]. Thus, serum ferritin could be used as a screening biomarker for the severity of the inflammatory state in patients with COVID-19.

CRP is a liver-made protein and an early indicator of inflammation and infection. After the commencement of the disease, CRP rises quickly within several hours and reaches its greatest peak after 48 hours. CRP concentration decreases when tissue damage or inflammation is repaired, making it a helpful marker for evaluating the severity of the disease [43]. Some studies have reported a significant association between higher levels of CRP and severe forms of COVID-19 in the affected patients [44.] Similar to these reports, we observed higher CRP levels among the patients who were admitted to the ICU and the difference was statistically significant.

Thrombocytopenia is reported to be another poor prognostic factor in COVID-19 disease [25, 45]. Similarly, we observed lower platelet count in O_2-dependent cases, ICU cases, and/or deceased cases compared to the non-O_2-dependent, non-ICU cases, and/or the alive ones; however, this difference was not statistically significant. This might be due to the small sample size and the fact that our data were obtained from a single clinical center. The exact mechanism of thrombocytopenia in COVID-19 is unknown and further evaluation is required; however, thrombin generation, immunological destruction of platelets, impaired megakaryopoiesis, and inappropriate platelet consumption are among the proposed mechanisms [46, 47]. Thus, thrombocytopenia should be considered another poor prognostic factor in COVID-19 disease.

Various studies have reported a hypercoagulable state in COVID-19 leading to both arterial and venous thrombosis, however, the exact pathophysiology of this state is not well understood. To date, multiple hypotheses regarding the pathophysiology of the hypercoagulation state in COVID-19 have been proposed including a severely heightened inflammatory response originating in the alveoli leading to thrombo-inflammation of local small pulmonary vessels followed by more generalized endothelial dysfunction and thrombo-inflammation in the microvasculature of the brain, kidneys and other organs leading to a hypercoagulable state and multiple organ failure, other mechanisms such as cytokine storm, complement activation, renin-angiotensin system dysregulation, macrophage activation syndrome, antiphospholipid antibody syndrome, hyperferritinemia, endotheliitis, and the virus itself could activate the coagulation cascade [14, 45, 48-50]. Several studies have reported a higher frequency of thrombotic complications and their contribution to higher mortality and morbidity rates in COVID-19 patients [51, 52]. In our study, 20 patients (9.6%) experienced thromboembolic events, although no significant correlation was found between thrombosis occurrence and disease prognosis. Further studies on more patients are required to determine thrombosis and thromboembolic events as prognostic factors in COVID-19 disease.

CONCLUSION

Hematological parameters including neutrophil to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte, LDH, platelet to lymphocyte ratio, ferritin, D-dimer, Hb, and lymphocyte count were significantly related to the prognosis of patients with COVID-19 disease. Our findings show that these hematological parameters could be considered as prognostic values in determining the severity of COVID-19 disease in the affected patients, also could help decide which COVID-19 patients have priority for hospitalization, get sufficient and intensive medical care, particularly when there are limitations in healthcare service, although further studies are required to come to a definite conclusion and design proper diagnostic and

therapeutical protocols for using these parameters in guiding the clinicians on early interventional strategies and focusing healthcare resources towards the group of patients with worse outcomes, who are candidates for intensive care intervention.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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