Original Article

Dynamic Changes in Parameters of Complete Blood Count Predict Disease Severity and Prognosis in Patients with COVID-19; A Prospective Study

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Abstract

Background: The pandemic of the coronavirus disease 2019 (COVID-19) is a major cause of death worldwide; thus, disease prediction is important. This study aimed to evaluate dynamic changes of complete blood count parameters in adult patients to predict disease severity.

Materials and Methods: Data from 980 consecutive hospitalized patients diagnosed with COVID-19 were analyzed prospectively. Patients were categorized into moderate disease-cured (n = 682), severe disease-cured (n = 136), and deceased (n = 162) groups. Clinical conditions at the admission and blood samples every other day were collected for each patient from hospital admission to discharge or death. Mean values of serum parameters were compared among the three groups; the Hazard ratio of different indices for death was calculated, and repeated measured ANOVA was employed to assess the prognostic importance of dynamic changes in blood parameters during the disease.

Results: Univariable and multivariable regression analysis showed that the only important clinical risk factor associated with death was needing invasive ventilation at admission (HR of 18.97 and 23.82 in univariable and multivariable regression analysis, respectively). Considering dynamic changes in blood elements, repeated measured ANOVA showed patients who survived had a decrease in WBC and Neutrophil count as well as Neutrophil to lymphocyte ratio (NLR) compared to expired patients; in contrast, platelet and lymphocyte count increased in survivors while dropped in deceased ones.

Conclusion: Dynamic changes in blood indices are prognostic indicators of an unfavorable prognosis for COVID-19 infection.

Keywords: COVID-19, Severity, Blood cell count, Mortality, Intensive care units

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Introduction

Coronavirus disease 2019 (COVID-19), also known as the 2019 novel Coronavirus (2019-n CoV), is the most critical health issue in today's world[1]. The pooled incidence of COVID-19 is reported at 20%, with a mortality rate of about 3%[2]. COVID-19 emerged from

Wuhan, China, in December 2019 as an epidemic with an R0 of 2.5-3.5. It spread rapidly by human-to-human transmission worldwide[3,4], resulting in the worst influential pandemic in a new era, without any definite treatment measure to date[5].

COVID-19 may have a long incubation period, up to 14 days, and asymptomatic patients in this phase can transmit the disease to others[6]. Some patients may remain completely asymptomatic (carriers); others present the disease symptoms in the next few days[7]. The symptoms of COVID-19 may be mild and unspecific, such as fever, headache, cough, shortness of breath, fatigue, and malaise in some patients. In contrast, in some other patients, it may affect several organs, resulting in a systemic disease that causes severe symptoms, such as severe pneumonia, multiple organ failure (MOF), and death[8]. Therefore, clinical symptoms are insufficient for diagnosis, and laboratory tests are required to screen for definite COVID-19, among which reverse transcriptase polymerase chain reaction (rRT-PCR) is considered the gold standard method[9,10].

The disease prognosis depends on several factors, including demographic characteristics of the patients, such as age and sex[2]. Comorbidities are important risk factors for poor clinical outcome; renal, respiratory, and cerebrovascular diseases are considered important predictors of severe COVID-19, and cardiovascular disease, hypertension (HTN), and diabetes mellitus (DM) are considered significant predictors of death related to COVID-19[11,12]. Laboratory findings have also been suggested as predictors of disease severity and death related to COVID-19, including hematologic parameters, such as lymphopenia, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)[13]. Others have also suggested decreased white blood cell (WBC) and platelet counts as predictors of disease severity in COVID-19[14]. However, the clinical value of these serum parameters in predicting disease severity and death related to COVID-19 has to be further investigated. Therefore, the present study aimed to investigate the clinical value of complete blood count (CBC) parameters for predicting COVID-19 disease severity. Significant results can introduce these parameters as an easy and available method for the prediction of patients' prognosis during COVID-19 infection.

Methods

Study design: In this single-centered study, adult patients admitted to the Shohada Tajrish Hospital, Tehran, Iran, with positive real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 from 20 February to 21 June 2020 were evaluated prospectively. Patients were categorized into three groups based on their clinical outcome: deceased patient group (intensive care unit (ICU) deceased, who died after at least three days of admission to the ICU, n=162), severe disease-cured patient group (ICU alive, patients with severe symptoms admitted to the ICU, who survived, n=136), and moderate disease-cured patient group (ward alive patients with moderate symptoms admitted to the ward, who survived=682).

Demographic information extracted from the medical records included patients' sex, age, time of admission, time of discharge, and comorbidities. Several routine blood tests were taken for each patient during hospitalization. The results of complete blood count parameters (by using an automatic cell counter, Sysmex - KX-21 system), including WBC, Red Blood Cell (RBC), neutrophil, lymphocyte, monocyte, platelet, NLR, and PLR, were recorded at admission, on day 1, 3, 5, and 7, as well as day discharge or death. The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study protocol (IR.SBMU.RETECH.REC.1399.391).

Statistical analysis: The mean ± standard deviation (SD) of the serum parameters were reported and compared among the three groups using one-way ANOVA. Then, univariable and multivariable analysis was done using the COX regression method to estimate the Hazard Ratio (HR) of different factors related to death or survival. Repeated measured ANOVA was also employed to assess the value of dynamic changes in predicting the outcome of patients. Finally, ROC curve analysis was done to find the survival prediction's best cutoff value for NLR and PLR.

Results

A total of 980 patients were evaluated: 162 patients in the deceased patient group, 136 patients in severe

disease-cured patient group, and 682 in moderate disease-cured patient group. The demographic data are shown in Table 1. The maximum time between symptom onset and referral to the hospital was 25 days in the deceased and severe disease-cured (ICU alive) groups and 15 days in the moderate disease-cured (ward alive) group. The mean time interval from symptom onset and hospitalization was 2.89±4.68 among expired patients, which was significantly higher than that in ICU alive patients (0.88±3.24, P<0.001) and from ward alive patients (2.02±3.49, P=0.002).

There were significant differences in mean subject value of the serum parameters, including WBC, RBC, neutrophil, lymphocyte, monocyte, platelet, Neutrophil/Lymphocyte ratio (NLR), and Platelet/lymphocyte ratio (PLR) among the three study groups, with patients who passed away tend to have lower RBC, Monocyte and Lymphocyte and higher WBC, Neutrophile, Platelet, NLR and PLR at the time of admission (Table 2).

Univariable and multivariable regression analysis showed that the only important risk factor associated with death was needing invasive ventilation at admission (HR=18.97 and 23.82 in univariable and multivariable regression analysis, respectively) (Table 3).

Considering dynamic changes in blood elements, repeated measured ANOVA analysis showed that patients who survived showed at least a decrease in WBC, neutrophil count, and NLR compared to expired patients during disease (Figure 1). In contrast, platelet and lymphocyte counts increased in survivors compared to deceased ones. (Figure 2).

ROC curve analysis was done to find the optimal cutoff for NLR and PLR, which revealed a cutoff point of 4.79 with a Sensitivity of 76% and a Specificity % of 68 for NLR (Figure 3A) and a cutoff point of 12.03 with a Sensitivity of 62% and Specificity of 72% for PLR (Figure 3B).

Table 1. Demographic features of the patients.

Group	Mean age	Number of female patients	Number of male patients
Deceased	69.8± 16.64	65	97
ICU Alive (Severe disease -cured)	59.8±19.02	59	77
Ward Alive (Moderate disease -cured)	50.4±17.49146	255	427

Discussion

The present study showed that the serum parameters significantly differed among the three groups. There was a reduction in the count of RBC, lymphocyte, and monocyte with an increase in disease severity (lowest in the deceased group). In contrast, WBC, neutrophil count, NLR, platelet, and PLR were increased (highest in the deceased group). The same findings have been observed in previous studies and systematic reviews[15-18].

Lymphopenia has been suggested as one of the first biomarkers since the emergence of COVID-19, observed in most infected patients[19]. This finding has been justified by the fact that COVID-19 enters the body's cells by binding to the angiotensin-converting enzyme (ACE) receptor, a type I membrane protein that mainly helps in blood pressure regulation[20], whichis also expressed in lymphocytes[21].

Table 2. Comparison of mean subject values of the serum parameters among the three study groups.

Mean ±SD subject value	*Deceased*	*ICU Alive (Severe disease -cured)*	*Ward Alive (Moderate disease -cured)*	*P-value**
Red blood cell	4.05±1.02	4.19±0.85	4.59±0.69	<0.001
White blood cell	10.81±6.65	8.48±8.81	7.14±4.25	<0.001
Neutrophil	82.06±12.46	75.70±12.48	71.21±12.97	<0.001
Lymphocyte	13.81±10.67	19.34±9.34	24.60±11.76	<0.001
Monocyte	3.09±2.89	5.49±7.92	4.14±4.62	0.006
Platelet	199.79±109.42	186.43±79.18	187.36±74.53	0.02
Neutrophil/Lymphocyte	9.23±6.12	5.49±4.15	4.25±3.69	<0.001
Platelet/lymphocyte	23.62±25.74	12.91±9.25	10.79±10.56	<0.001

Table 3. Factors associated with survival in patients with COVID-19, using Cox regression**.**

Variables (Time of admission)	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age	1.04	1.02 - 1.05	1.01	0.99 - 1.04
Heart rate	1.01	1.004- 1.02	0.99	0.98 - 1.01
GCS	0.78	0.74 - 0.83	0.93	0.82 - 1.06
O2SAT	0.95	0.93- 0 .96	0.99	0.95 - 1.03
Invasive Ventilation	18.97	11.76 - 30.59	23.82	8.70 -65.21
RBC	0.86	0.71- 1.04	-	-
WBC	1.04	1.02- 1.06	1.08	1.02 -1.15
PLT	1.0008	0.99- 1.002	-	-
Neutrophil	1.04	1.02- 1.06	0.93	0.75 - 1.17
Monocyte	0.78	0.68 - 0 .89	0.90	0.68 - 1.19
Lymphocyte	0.94	0.91 - 0.96	0.92	0.73 - 1.15
NLR	1.07	1.05 -1.10	0.93	0.84 - 1.04
PLR	1.01	1.007- 1.01	1.01	0.96 -1.05

GCS: Glasgow Coma Scale, RBC: Red Blood Cell, WBC: White Blood Cell, PLT: Platelet, NLR: eutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio.

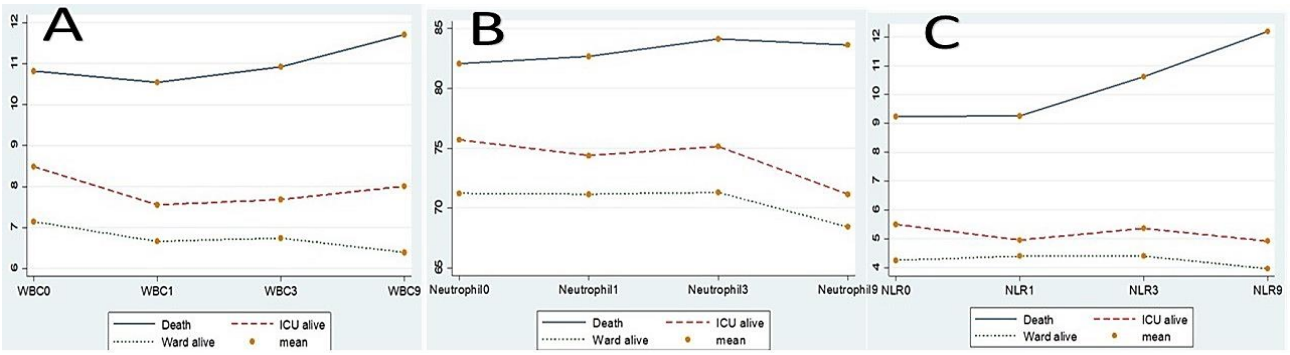

Figure 1. *A: Dynamic WBC change IN 3 groups based on repeated measured ANOVA; P value: 0.04.B: Dynamic Neutrophil change based on repeated measured ANOVA; P value: 0.02.C: Dynamic NLR change based on repeated measured ANOVA; P value: 0.01*.

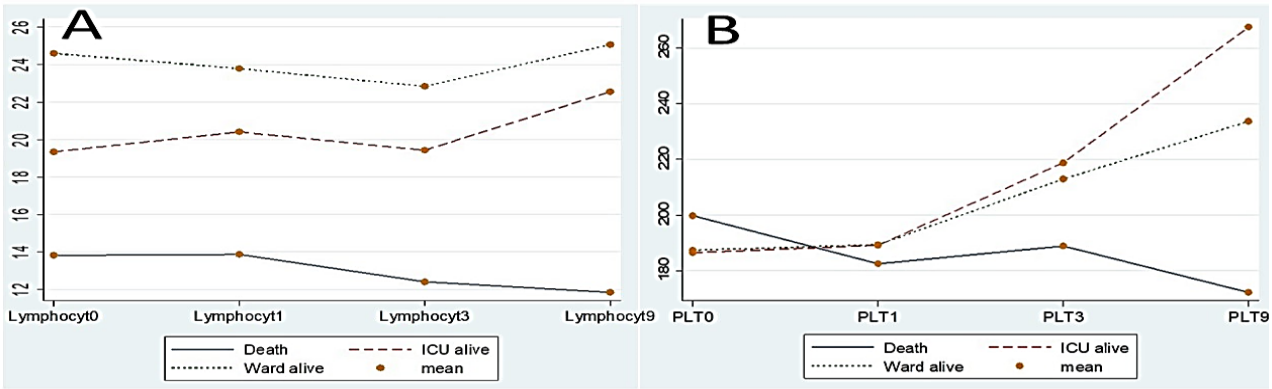

Figure 2. A: Dynamic Lymphocyte change in 3 groups based on repeated measured ANOVA, P value: 0.02.B: Dynamic Platelet change based on repeated measured ANOVA; P value: 0.005.

Furthermore, lymphopenia has been attributed to the disease severity in several studies that can be attributed to inflammation due to the dysregulated immune response in patients with severe COVID-19[22]. Comparison of the general serum parameters between survivors and non-survivors of COVID-19 has shown

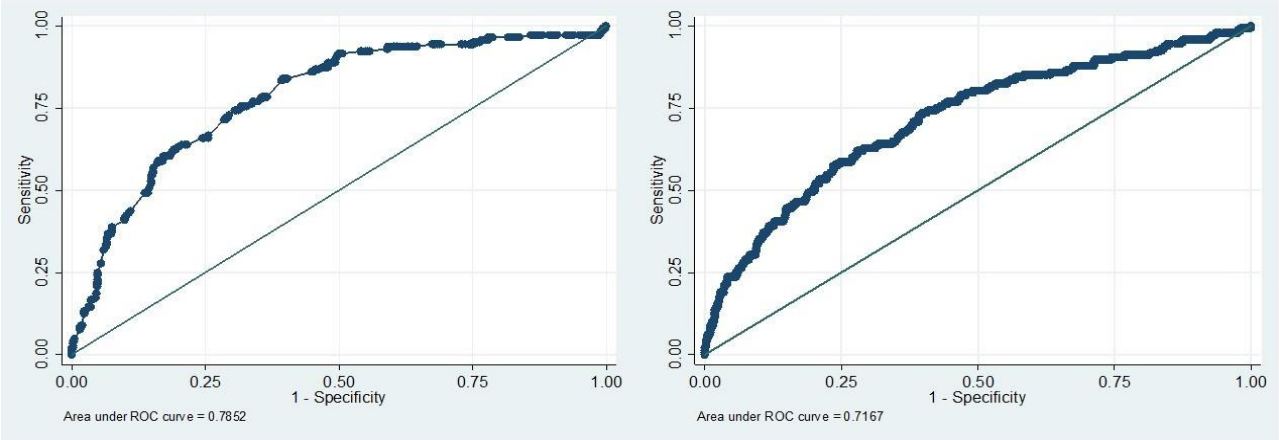

Figure 3. A: A: ROC curve analysis for NLR. The optimal cut-point for NLR on admission day was 4.79, and the sensitivity at cut point was 0.76. Specificity at cut point: 0.68, Area under ROC curve at cut point: 0.72. B: ROC curve analysis for PLR. Optimal cut-point for PLR0: 8911 12.03, Sensitivity at cut point: 0.62, Specificity at cut point: 0.72, Area under ROC curve at cut point:0.67.

higher WBC and neutrophil count and lower lymphocyte count in non-survivors of COVID-19 compared to patients who recovered from the disease[23], which confirms the results of the present study. In a meta-analysis of 21 studies on hematologic parameters in patients with COVID-19, a comparison between survivors and non-survivors of COVID-19 showed higher WBC count and lower lymphocyte and platelet count among the deceased cases, compared to non-severe cases and survivors[13]. These results align with the results of our study and highlight the important role of WBC and lymphocytes in predicting the severity of the disease during COVID-19 infection. Although in regression analysis, none had any effect on death or ICU admission, which may question the clinical benefit of serum parameters for prediction of COVID-19 prognosis, following the trend of these markers in the course of disease showed in survivors, contrary to non-survivors, platelet and lymphocyte count rise in rhythm with improvement on the other hand total WBC and neutrophil count as well and NLR goes up with disease exacerbation (Figs 1 and 2). These results suggest that to get a proper insight into the prognostic utility of blood indices in COVID-19 patients and risk stratification, not only initial values are important but their trends in the time may have a more crucial role.

The higher platelet count in the deceased patients of the present study at the admission time can also be justified by liver activation and thrombopoietin release. Also, platelets are considered an acute phase reactant[24], so a higher platelet count probably means higher degrees of inflammation. However, as noted in repeated ANOVA tests, patients who died showed a decline in platelets numbers, probably due to excessive activation of the coagulation cascade and consumption of platelets[25] during thrombosis, hemostasis[13,26] and disseminated intravascular coagulation (DIC), observed in the majority of COVID–19 non–survivors[27,28]. Other studies have also shown thrombocytopenia as a predictor of severe COVID-19[29], confirming the present study's results. RBC count is another serum parameter rarely compared among patients with different COVID-19 severity[30]. Deceased patients in our study had a lower RBC level at the time of admission, similar to the results of Taneri et al., who also showed lower RBC levels in patients with severe COVID-19 compared to patients with moderate disease[31]; however, in regression or repeated measured ANOVA analysis, RBC level at the time of admission or trend of RBC in patients did not affect severity of disease or death prediction. Populational studies have also shown no difference in RBC levels of patients with mild and severe COVID-19 or between survivors and non-survivors[21,30]. It has to be mentioned that the RBC count of the patients may vary based on the underlying diseases in the patients, including anemia and other comorbidities. Therefore, we may not be able to determine the effect of COVID-19 on RBC, without having the pre-disease values of the patients.

Neutrophil count and NLR were significantly increased in the deceased group of our study at the admission time

and rose during disease (Figure 1B and 1C, P value:0.02 and:0.01, respectively). Neutrophilia has been associated with increased odds of development of acute respiratory distress syndrome (ARDS) and progression to death in COVID-19 in other studies as well[32].NLR is also suggested as an important and independent predictor of in-hospital mortality[33] and is suggested to be considered for determining the prognosis of COVID-19 in several studies[34-36]. The results of the ROC curve analysis in our study showed that a cutoff of 4.79 for NLR predicted death with sensitivity of 76% and specificity of 68%(Fig 3A). In Contrast, PLR showed less importance, with sensitivity and specificity of 62% and 72%, respectively, for predicting death at the cutoff point 12.03 (Figure 3B)**.** Previous studies have also addressed the applicability of NLR and PLR as an important predictor of COVID-19 severity[37,38]. Yang and colleagues calculated the AUC of NLR at 74% and that of PLR at 78% at the optimal cutoff values of 3.3 and 18, respectively[36], which is in line with the results of the present study. The two easily calculated indices, PLR and especially NLR, are suggested valuable predictors of COVID-19-related mortality and are thus suggested to be considered in estimating patients' prognosis. It must be noted that finding the best cut-point for the blood parameters in the prediction of death is a scientific issue, rather than a statistical issue. The calculated index includes loss of function and decision problem. Therefore, caution must be taken in interpreting the cut points in a clinical setting.

One of the strengths of the present study was a comparison of all hematologic parameters among the study groups and considering different analyses, including comparison among the groups, calculation of hazard ratio, and AUC of the parameters. However, as a limitation, it should be mentioned that several other factors could have affected our study, rather than COVID-19, which may confound the results.

Conclusion

In conclusion, the results of this study highlight the important role of following dynamic changes in blood parameters to predict prognosis in COVID-19 infection so that a drop in lymphocyte and platelet count accompanied by a rise in WBC, Neutrophile, and NLR would be regarded as unfavorable prognostic markers. Patients with these characteristics would be given more intensive care.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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