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Original Article

Initial complete blood count score and predicting disease progression in COVID-19 patients

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Abstract: Introduction: Coronavirus has caused a pandemic since it was first detected in Wuhan in December 2019. The mortality rate is high in moderate and severe cases. Our study aimed to screen the CBC parameters as a useful predictive factor for COVID-19 resulting in critical illness. Methods: A total of 285 patients with positive PCR results were analyzed. The median age was 55 (24-90), and 64.2% of patients were male. Sixty-eight percent of cases were hospitalized with moderate, 32% with severe disease at initial admission. Results: We found that lymphocyte count <620/mcl, neutrophil-to-lymphocyte ratio (NLR) >6, and platelet to lymphocyte ratio (PLR) >350 were predictive of the outcome. We scored our cohort 0-3 for these three parameters. Patients with a score of 2-3 were more likely to have progressive disease, anti-cytokine treatment, intensive care admission, intubation, and death, compared to patients with a score of 0-1. Additionally, they tended to be hospitalized for longer (median 11.5 days, mean 15.6), compared to those with a score 0 or 1 (median 9 days, mean 11.3). Twenty-eight of 38 cases with scores of 2-3 were discharged (73.6%), whereas the rate was 89% for patients with a score of 0-1 (P=0.009). Conclusion: Based on the absolute lymphocyte count (<620/mcl, NLR >6, PLR >350), our three-parameter score was able to predict disease progression, and the likelihood of anti-cytokine treatment, intubation, and death. We think that COVID-19 patients presenting with moderate to severe pneumonia, and having scores of 2 or 3 on our scale, should be closely monitored and robustly supported.

Keywords: Coronavirus disease, peripheral blood, neutrophil-lymphocyte ratio, neutrophil-lymphocyte ratio

Introduction

Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-Cov-2) associated respiratory disease (COVID-19) has caused a pandemic since it was first detected in Wuhan in December 2019 [1]. Mild cases have a good prognosis. On the other hand, moderate and severe cases have variable outcomes, which can result in death. Mortality rates reported from China range between 4.3% and 14.6%, mainly increasing in elderly patients with comorbidities [2-4]. About 19% of cases are classified as severe or critical, and the mortality rate is 49% for the critical group [5].

The outcome of COVID-19 pneumonia is unpredictable, and it varies according to the individual characteristics. Although we know that the disease has more severe consequences in elderly patients with comorbidities, it can also cause death in younger people. Studies have focused on early detection of severe cases that should be hospitalized, and could need intensive care. Hematological markers were proposed to diagnose COVID-19 [6], as well as to predict the severity of the disease and the outcomes [7, 8].

An excessive inflammatory response constitutes the main pathophysiological mechanism,

and this could be predicted by hematological markers. The ratios of neutrophils, monocytes, and platelets to absolute lymphocyte count have been demonstrated to be useful in the diagnosis of COVID-19, and in predicting the severity of the disease [6]. Therefore, it is possible that CBC could predict disease's outcomes. This study will analyze CBC parameters to determine whether they can predict the severity of COVID-19 disease, and its outcomes.

Patients and methods

Study design, patients and treatment strategies

In this single-center retrospective analysis, all adult patients hospitalized during the COVID-19 pandemic between March and May 2020 were included. Patients with active malignancies or chronic diseases, which could affect the outcomes, were excluded from the analysis. As an institutional approach, patients who had typical radiological findings associated with COVID-19 pneumonia [9], and who had moderate, severe, or critically severe disease [5] were hospitalized.

We retrospectively screened the medical records of the patients, including files, electronic files, and laboratory results. Laboratory confirmation of COVID-19 was performed with reverse transcriptase-polymerase chain reaction (RT-PCR) assays [10].

The treatment protocol included hydroxychloroquine and azithromycin, and when patients were deteriorating under treatment, we switched to favipiravir or anti-cytokine treatment. The vast majority of patients had received anticoagulant therapy with low molecular weight heparins, and dipyridamole as bid 75 mg orally.

Definitions

The disease severity was defined as moderate if radiological pneumonia, fever, and respiratory symptoms were present. In cases of severe disease, patients presented with a respiratory rate equal to or above 30/minute, a pulse oxygen saturation level equal to or less than 93%, or an oxygenation index equal to or less than 300. Detection of 50% growth from a computerized tomography (CT) scan was defined as disease progression. The critically severe patients were defined as those who had required mechanical ventilation, had been in shock, or had suffered from any type of organ failure [5]. CT severity was defined and classified in our analysis as mild to moderate-severe according to the five lobe scores [11].

Statistical analysis

Continuous variables were presented as a median. The differences between groups were analyzed using the X^2 test. The risk factors were evaluated with univariate and multivariate logistic regression models. The variables found to be significant from univariate analysis were included in the logistic regression analysis. A two-sided α of less than 0.05 was considered statistically significant. We used receiver operating curve (ROC) analysis to evaluate the sensitivity and specificity of the parameters. Statistical analysis was performed using StataMP-64 software.

No funding source was used, and our study was approved by the Istanbul University, Istanbul Medical Faculty ethical committee (nr: 22/05/2020-84932).

Results

A total of 285 patients with positive PCR results were hospitalized between March 11 and May 5, 2020, and were included in the analysis. The median age was 55 (24-90), and 183 patients (64.2%) were male. The majority of patients were hospitalized with moderate disease (n=194), and about 32% of our cohort (n=91) had severe disease at initial admission. The demographic features, clinical presentation and comorbidities of our cohort is summarized in **Table 1**. The median hospitalization time was nine days (range: 2-61). There were no significant differences in the CBC parameters between patients with moderate disease, and those with severe disease (**Table 2**).

Sixty patients had progressive pneumonia. According to our treatment protocols, 33.7% of our cohort needed anti-cytokine agents. Forty-eight patients were transferred to the intensive care unit, and 41 of them were intubated. A total of 26 out of 285 hospitalized patients (9.1%) died.

Table 1. Demographic characteristics, initial signs and symptomatology

	n=285
Median Age (range)	55 (24-90)
Sex	
Female (%)	102 (35.8%)
Male (%)	183 (64.2%)
Disease severity	
Moderate	194 (68%)
Severe	91 (32%
Initial symptoms	
Fatigue and myalgia	273 (95.8%)
Cough	249 (87.4%)
Fever	219 (76.8%)
Dyspnea	127 (44.5%)
Nausea	44 (15.4%)
Diarrhea	37 (13%)
Anosmia	19 (6.7%)
Sputum	9 (3.16%)
Comorbid conditions	
Hypertension	109 (38.5%)
Diabetes mellitus	67 (23.6%)
COPD or Asthma	30 (10.5%)
Coronary artery disease	30 (10.5%)
Congestive heart failure	16 (5.6%)
History of solid malignancy	7 (2.5%)
History of hematologic malignancy	8 (2.8%)
Median number of comorbidities (range)	1 (0-6)
Anti-hypertensive exposure	106 (37.2%)
Angiotensin convertng enzyme inhibitor	22 (7.8%)
Angiotensin receptor blocker	51 (17.9%)

We analyzed the differences in initial CBC parameters for disease progression, the need for anti-cytokine treatment, intensive care, or intubation, and the likelihood of death. We evaluated the white blood cell (WBC), neutrophil, lymphocyte, monocyte, eosinophil, and platelet counts, and hemoglobin concentrations. We also measured neutrophil to lymphocyte, monocyte to lymphocyte, and platelet to lymphocyte ratios for the above outcomes.

The differential of WBC, hemoglobin, and platelets was similar in the groups presenting with moderate to severe COVID-19 pneumonia (**Table 2**). In the univariate analysis of CBC parameters, a lymphocyte count of less than 620/mcl, neutrophil to lymphocyte ratio (NLR) greater than 6, and platelet to lymphocyte ratio (PLR) greater than 350 were predictive of our outcomes (**Table 3**).

Outcomes of patients with initial lymphocyte count less than 620/mcl

Patients presenting with a lymphocyte count of less than 620/mcl were more likely to have progressive pneumonia (AUC 0.55; 95% CI 0.49-0.60), anti-cytokine treatment (AUC 0.55, 95% CI 0.51-0.60), intensive care admission (AUC 0.60; 95% CI 0.53-0.67), intubation (AUC 0.58; 95% CI 0.51-0.65), and it was more likely that their illness would result in death (AUC 0.58; 95% CI 0.49-0.67).

Outcomes of patients with initial neutrophil to lymphocyte ratio more than six

An NLR of more than 6 was similarly predictive of progressive pneumonia (AUC 0.59; 95% CI 0.52-0.66), anti-cytokine treatment (AUC 0.62, 95% CI 0.56-0.67), intensive care admission (AUC 0.68; 95% CI 0.60-0.75), and intubation (AUC 0.64; 95% CI 0.56-0.72). Although the *p*-value was not significant for death (AUC 0.58; 95% CI 0.48-0.68), almost 15% of patients who had an NLR≥6 died, whereas only 7.3% of those with an NLR≤6 died.

Outcomes of patients with initial platelet to lymphocyte ratio more than 350

A PLR of more than 350 was predictive of progressive pneumonia (AUC 0.55; 95% CI 0.49-0.61), anti-cytokine treatment (AUC 0.54, 95% CI 0.49-0.59), intensive care admission (AUC 0.61; 95% CI 0.54-0.68), intubation (AUC 0.58; 95% CI 0.51-0.65), and death (AUC 0.58; 95% CI 0.49-0.68).

Outcomes of patients according to CBC score

We gave our cohort a score of 0-3 for the three parameters. Patients with scores of 2 or 3 were more likely to have progressive disease (AUC 0.55; 95% CI 0.49-0.60), require anti-cytokine treatment (AUC 0.55, 95% CI 0.51-0.60), intensive care admission (AUC 0.61; 95% CI 0.54-0.68), or intubation (AUC 0.57; 95% CI 0.50-0.65), and were at increased risk of death (AUC 0.57; 95% CI 0.48-0.66) compared to patients with a score of 0 or 1 (**Table 3**). The patients with scores of 2 or 3 tended to be hospitalized for longer (median 11.5 days, mean 15.6,

Table 2. Initial complete blood counts of patients according to disease severity

Median (range)	Moderate disease (n=194)	Severe disease (n=91)	P
White blood cells (/mcl)	5800 (2310-12710)	6630 (1510-97110)	0.584
Neutrophils (/mcl)	3790 (1020-10290)	5000 (1100-18500)	0.281
Lymphocytes (/mcl)	1255 (100-3230)	1000 (160-81150)	0.283
Monocytes (/mcl)	500 (150-1340)	420 (10-6520)	0.197
Eosinophils (/mcl)	0 (0-310)	0 (0-740)	0.346
Hemoglobin (g/dl)	13.7 (9.1-17.3)	13 (6.1-17.7)	0.266
Platelets (/mcl)	191050 (75000-552000)	222000 (85900-515000)	0.445

range: 4-49) compared to those with a score of 0 or 1 (median nine days, mean 11.3, range: 2-61). Twenty-eight out of 38 cases with scores of 2 or 3 were externalized (73.6%), whereas the rate was 89% for patients with a score of 0 or 1 (P=0.009).

Discussion

We have followed the progress of COVID-19 since December 2019, and have experienced it face to face since March 2020. We are now able to recognize the signs, symptoms, and radiological features of COVID-19. However, the current problem is identifying which patients will have progressive pneumonia and need more robust treatment. The aim might not be treating the disease, but supporting the patient to overcome the excessive inflammatory period.

In case of severe infection or systemic inflammation, the NLR increases, and the absolute lymphocyte count decreases as a response to pneumonia [12]. The NLR was found to be higher in severe COVID-19 cases [13, 14]. Several studies have found that increased NLR was an independent factor in predicting progression to critical illness [15-17]. Ma et al. found that an NLR >9.2 could be used to predict acute respiratory distress syndrome and the need for ventilation support [18]. A recent analysis from Wuhan demonstrated that higher NLR, along with hypertension and increased NT-proBNP, was associated with poorer prognosis in hospitalized cases [19]. In a recent meta-analysis, severe cases were found to have higher NLR and PLR values [20]. Several studies have found a relationship between thrombocytopenia and poor outcomes in COVID-19 [21, 22]. We could not define a stable cut-off for the platelet count to predict our outcomes.

The main limitation of this study was its retrospective nature. We excluded all patients with known active malignancies, which could have affected the outcomes. We noted the initial CBC of all hospitalized cases. Hospitalization was decided on objective criteria. Although the number of patients may be relatively small, we would like to emphasize that we included moderate and severe cases only and we performed a detailed analysis including diverse outcome parameters such as the need for anti-cytokine treatment, intensive care, or intubation, and the likelihood of death.

We have hospitalized all cases of moderate and severe pneumonia in our center since identifying COVID-19 in our country. In the literature, there are many studies emphasizing the importance of cytopenia and cellular ratios to predict the outcome of COVID-19 pneumonia. However, our method which is only based on CNC parameters and does not include any biochemical parameters, is concise and easy to perform even in emergency setting. Based on the absolute lymphocyte count (<620/mcl, NLR >6, PLR >350), the three-parameter score was able to predict disease progression, and the likelihood of anti-cytokine treatment, intubation, and death. We think that COVID-19 patients presenting with moderate to severe pneumonia, and having scores of 2 or 3 on our scale, should be closely monitored and robustly supported.

Disclosure of conflict of interest

None.

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Table 3. Detailed analysis of the initial complete blood count ratios of patients

n (%)	All patients (n=285)	Patients with progressive disease (n=60)	*P*	Patients who needed anticytokine treatment (n=96)	*P*	Patients who needed intensive care (n=48)	*P*	Patients who needed intubation (n=41)	*P*	Patients who died (n=26)	*P*
Lymphocyte											
<620/mcl	34 (11.9%)	12 (35.2%)	*0.03*	19 (55.9%)	*0.004*	14 (41.2%)	*<0.001*	11 (32.4%)	*0.002*	7 (20.6%)	*0.013*
≥620/mcl	251 (88.1%)	48 (19.1%)		77 (30.7%)		34 (13.5%)		30 (11.9%)		19 (7.6%)	
Neutrophil to lymphocyte ratio											
>6	67 (23.5%)	23 (34.3%)	*0.002*	38 (56.7%)	*<0.001*	26 (38.8%)	*<0.001*	20 (29.9%)	*<0.001*	10 (14.9%)	*0.059*
≤6	218 (76.5%)	37 (16.9%)		58 (26.6%)		22 (10%)		21 (9.6%)		16 (7.3%)	
Platelet to lymphocyte ratio >350											
>350	42 (14.7%)	14 (33.3%)	*0.034*	20 (47.6%)	*0.042*	16 (38%)	*<0.001*	12 (28.6%)	*0.005*	8 (19%)	*0.016*
≤350	243 (85.3%)	46 (18.9%)		76 (31.3%)		32 (13.2%)		29 (11.9%)		18 (7.4%)	
Complete Blood Count Score											
0-1	247 (86.6%)	47 (19%)	*0.033*	76 (31%)	*0.009*	32 (13.2%)	*<0.001*	30 (12.2%)	*0.006*	19 (7.7%)	*0.032*
2-3	38 (13.4%)	13 (34.2%)		20 (52.6%)		16 (42.1%)		11 (28.9%)		7 (18.4%)	

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