The Relationship of Hematological Disorders in SARS-CoV-2 Patients with Intensive Care Needs and Survival

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Abstract

Objective: It was aimed to retrospectively examine the clinical and survival results of patients who were consulted with the hematology clinic due to hematological disorders related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Materials and methods: In this study, the data of patients who were hospitalized and consulted to the hematology clinic due to hematological disorders related to COVID-19 infection diagnosed by radiological findings and/or PCR results in the Ministry of Health Istanbul Training and Research Hospital between April 1 2020 and May 21 2020, were evaluated, retrospectively.

Results: Of the 48 patients evaluated in the study, 25 (52%) were female and 29 (60%) were 60 years old and above. Leukocytosis in 5(10%) patients, leukopenia in 19 (39%) patients, and D-Dimer ≥2ng/mL and Ferritin ≥500ml/ng in 32(66%) patients were remarkable. D-Dimer was found to be ≥2ng/mL and Ferritin ≥500ml/ng in 9 out of 10 patients in intensive care. A total of seven (14%) patients died.

Conclusion: Patients who are over the age of 60, and have lymphocyte count <1000μl/ml, D-Dimer value above 2ng/mL, and ferritin over 500ml/ng are more likely to need a follow-up in the intensive care. For this reason, vaccination of people over the age of 60, moreover, the high antibody response obtained with the vaccine seems to be the most important precaution that can be taken against this disease.

Keywords: COVID-19; SARS-CoV-2; Gender; Hematology; Lymphopenia; Thrombocytopenia; Survival; Intensive care; D-dimer; Ferritin

Introduction

Coronavirus Disease (COVID-19) is the clinical syndrome associated with SARS-CoV-2 infection and characterized with an extent from a mild upper respiratory tract disease to severe interstitial pneumonia or an Acute-Respiratory-Distress-Syndrome (ARDS) [1]. Symptoms of COVID-19 infection can be asymptomatic depending on the immune response of the host and comorbid diseases, as well as mild, moderate, severe, or critical status of patients [2]. In the early stage of infection, mild symptoms, dry cough, diarrhea, headache, etc. may be encountered with other complaints. During this period, there is an increase in lymphopenia, increased prothrombin time, D-dimer, and Lactate Dehydrogenase (LDH) values. In the second phase, shortness of breath, hypoxia, $PaO_2/FiO_2 \leq 300mmHg$, abnormalities in lung imaging, increased transaminases, low/normal procalcitonin levels are seen. In the third phase, the inflammatory response of the host gradually increases. ARDS, Systemic Inflammatory Response Syndrome (SIRS), shock, heart failure, and multi-organ dysfunction may be encountered. Inflammatory markers (c-reactive protein (CRP), LDH, IL-6, D-dimer, ferritin, etc.) increase during this period. Troponin and pro-BNP heights can be seen as well. Chen et al. [3] reported that the increase in the neutrophil ratio, C-reactive protein, and procalcitonin values is related to cytokine storm induced by virus invasion or accompanied by other infections in severe Covid-19 cases [3]. Gao et al. [4] revealed that the D dimer values were significantly higher in severe patients compared to mild and moderate patients [4]. In the study of Zhou et al. [5] D-dimer values were found to be approximately nine times higher in patients who died. A D-dimer value greater than 1μg/ml may help to identify patients with a poor prognosis at the early stage [5]. Studies have found that a low lymphocyte count, high D-dimer, and acute phase reactants (CRP, ferritin) levels are associated with a more severe outcome of the disease [6-8]. Therefore, it was aimed to conduct the study to retrospectively examine the

clinical and survival results of patients who were consulted with the hematology clinic due to hematological disorders related to SARS-CoV-2.

Materials and Methods

In this study, the data of patients who were hospitalized and consulted to the hematology clinic due to hematological disorders related to COVID-19 infection diagnosed by radiological findings and/or PCR results in the Ministry of Health Istanbul Training and Research Hospital between April 1 2020 and May21 2020, were evaluated in terms of the relationship between hematological disorders and the need for intensive care and survival, retrospectively. The gender, age, leukocyte, lymphocyte count, eosinophil count, thrombocyte count, D-Dimer and ferritin levels, intensive care status, and survival status of the patients were recorded. In order to statistically evaluate the hematological values of the patients, reference values were categorically 3,500-11,000µl/ml for the definition of normal leukocyte value, >1,000µl/ml for the lympphocyte value, >40µl/ml for the normal eosinophil value, 100,000µl for the normal platelet value. Under 60 years old and above for age, female and male for gender, between 3,500 and 11,000µl/ml for the normal range of leukocyte counts, >1000µl/ml, between 500 and 1000µl /ml, and <500µl/ml for the normal lymphocyte counts, >40µl/ml and <40µl/ml for the eosinophil counts, <100,000µl/ml and >100,000µl/ml for the thrombocyte counts, >2ng/mL and <2ng/mL for the D-dimer values, >500mL/ng and <500mL/ng for the ferritin values were categorized for the better statistical evaluation of valuables and values that were width in the normal ranges [2,3]. While only the patients who were consulted with the hematology clinic due to disorders in their hematological parameters were included in the study, those who had incomplete data were excluded from the study. This study was approved by the Ministry of Health authorized board on 06.12.2020. Nominal data of the patients were categorized and classified as normal, low, and high. Numerical data were presented up to decimal percent. The data were categorized taking into account the width in the normal range of blood cell numbers and laboratory tests. With the categorized data, it was aimed to reveal the clustering of the patients more clearly. For the statistical evaluation of the study, Chi-square or Fischer's exact tests were used to compare nominal data, Pearson correlation coefficient and Odd's ratio were used to evaluate the levels of the relationship between them, while the confidence interval was taken as 95%.

Result

Of the 48 patients evaluated in the study, 25(52%) were female, 23(48%) were male, and 29(60%) were 60 years old and above. Leukocytosis in 5(10%) patients, leukopenia in 19(39%) patients, D-Dimer ≥2ng/mL and Ferritin ≥500ml/ng in 32(66%) patients were remarkable. D-Dimer was found to be ≥2ng/mL and Ferritin ≥500ml/ng in 9 out of 10 patients in intensive care. A total of seven (14%) patients were deceased. Of the 7 mortal patients, 4 (57%) were female, followed by thrombocytopenia in 5(71%), eosinophilopenia (<40/µL) in 20(41), lymphocyte count <1,000µl/ml in 5(71%) and <500µl/ml in 2 (28%), leukopenia (<3.500/µL) in 3(42%), normal leukocyte count in 4 (57%), and 5 (71%) over 60 years old. Of the 16 patients with D-dimer value >2ng/mL and ferritin >500ml/ng, 13 (81%) were over 60 years old, 9(56%) were male, 9(56%) were under intensive care follow-up. As lymphocyte count was <1,000µl/ml in 11 (68%) patients, 7 (43%) died. The parameters of 48 patients evaluated by the hematology clinic are given in Table 1. In the statistical analysis of the study, no significant relationship was found between survival and gender (Fischer's exact test p: 0,771). In terms of survival, no significant difference was found between patients under 60 years of age and above (Fischer's exact test p: 0.687). There was no significant difference in terms of survival in terms of leukocyte count, lymphocyte count, eosinophil count, platelet count (Chi-Square test p: 0.813, p: 0.438, p: 0.429, p: 0.086, respectively). A significant difference was found in terms of survival and need for intensive care (Fischer's exact test p: 0.0001; Pearson correlation coefficient: -0.805; Odd's ratio: 13.66; Confidence Interval 4.59-40.62). A significant correlation was found between low survival rates and high D-Dimer and Ferritin values (Fischer exact test p: 0.0001; Pearson correlation coefficient: -0.584; Odd's ratio: 4.55; Confidence Interval: 2.55-8, 11th). A significant correlation was found between the increased need for ICU and high D-Dimer and Ferritin values (Fischer exact test p: 0.0001; Pearson correlation coefficient: 0.617; Odd's ratio: 39.85; Confidence Interval: 4.35-368).

Table 1: The hematological parameters of patients with COVID-19 by gender.

	Female n (%)	Male n (%)	Total
The number of patients	25(52)	23(48)	48(100)
Age >60 years	14(56)	15(65)	29(60)
Lymphocyte ≥1000/µL	0(0)	2(8)	2(4)
Lymphocyte <500/µL	6(24)	5(21)	11(22)
Eosinophil <40/µL	12(48)	8(34)	20(41)
Platelet <100,000/µL	6(24)	12(52)	18(62)
Leukocyte ≥11.000/µL	2(8)	3(13)	5(10)
Leukocyte <3.500/µL	12(48)	7(30)	19(39)
ICU admission	4(16)	6(26)	10(20)
D-dimer ≥2ng/mL and Ferritin ≥500ml/ng	18(72)	14(60)	32(66)

Discussion

In our study, the female-male ratio was almost similar and more than half of them were over the age of 60. The female-male ratio was similar in the conducted studies as well [9,10]. On the other hand, the number of male cases among critical patients with COVID-19 was higher according to the data reported from China, and 82% of the patients requiring critical care were male in the ICU in Italy [8,11,12]. Leukopenia, lymphopenia, platelet (100,000μl/ml) and D-dimer >2ng/mL and ferritin> 500ml/ng were mainly remarkable values in our cases. In a study conducted by Cömert et al. [13] the common laboratory findings at the time of diagnosis were low albumin (75%), high CRP, lymphopenia (43%), and high D-dimer, ferritin, and liver enzymes. High CRP, D-dimer, serum ferritin, prolonged prothrombin time, troponin elevation, creatinine phosphokinase elevation, and hypoxemia have been identified as poor prognostic factors as well [12,13]. In other studies, about COVID-19, neutrophil count, D-Dimer, blood urea, and creatinine levels increased, and lymphocyte count continued to decrease until death [5,12,14]. Leukocytosis, lymphopenia, thrombocytopenia, hypoalbuminemia, creatinine, D-dimer, and ferritin levels were also found to be more prominent in severe disease in a study when compared with patients without severe disease and laboratory findings [15]. In the severe cases neutrophil ratio, CRP, and procalcitonin were found high, as lymphocyte ratio and number were found to be low. In addition, leukocyte and neutrophil counts increased numerically in severe cases, but the difference was not found to be significant, statistically [16]. In a study conducted in China, there was no difference in leukocyte count between severe cases and non-severe cases [17]. It was reported that 109 Covid-19 patients who died in Wuhan city were admitted with higher leukocyte counts than 116 patients who recovered. The patients in the death group had a lower lymphocyte count and the lymphocyte/leukocyte ratio continued to decrease, significantly [18]. In the study of Yuan et al. [19] leukocyte and neutrophil values were significantly higher in the severe and critical patients with COVID-19 compared to the normal group. Erythrocyte and hemoglobin values have been reported to decrease in critical conditions, as the platelet count was often found to be normal. While ferritin and D-dimer values were more pronounced in critically ill patients, the blood was hypercoagulable and critical levels of D-dimer and fibrinogen were higher in those cases than in normal patients [19,20]. Another study reported that 71.4% of non-survivors and 0.6% of survivors met the criteria for the disseminated intravascular coagulation during their hospital follow-up and significantly elevated D-dimer and FDP were cases who died of COVID-19 (20). Moreover, 71.4% of mortal cases and 0.6% of survivors had the diffuse intravascular coagulation (DIC) criteria and abnormal coagulation, especially with more markedly elevated D-dimer and fibrin washed-out [21]. In a meta-analysis conducted by Huang et al. [22] 11 of 25 studies revealed high D-dimer values related to the poor result. Subgroup analysis found that a higher D dimer values are associated with increased mortality rates. A higher serum ferritin level was found to be independently associated with ARDS, mortality, and severe COVID-19, as well as other biomarkers included in this study. Non-survival had higher levels of ferritin as a result of SARS-CoV-2 infection that can trigger hemostatic dysfunction and result in mortality in cases with a severe COVID-19 course. That supports the hypothesis about hypercoagulation [22]. In conclusion, patients who are over the age of 60, and have lymphocyte count <1000μl/ml, D-dimer value >2ng/mL, and ferritin >500ml/ng are most likely to need an intensive care, moreover;... moreover, patients who have thrombocytopenia, lymphopenia, D-dimer >2ng/mL and ferritin >500ml/ng are more likely to result in mortality. Therefore, the vaccination of people over the age of 60, moreover, the high antibody response to be obtained with the vaccine seems to be the most important measure that can be taken against this disease.

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