Clinical Course of Covid-19 in Hematological Disorders

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ABSTRACT

Hematology patients are extremely vulnerable to COVID-19 infection due to the immunosuppression arising from the direct effect of the disease and the medicines administered. Our purpose is to analyze the results of the patients that both have a hematological disease and receive treatment for COVID-19 infection in our hospital. Four hundred COVID-19 positive patients that received inpatient treatment between March 12, 2020 and October 1, 2020 in our center and got a diagnosis by using real -time polymerase chain reaction (RT-PCR) test were scanned retrospectively. Eighty one patients were included in the study. Nineteen patients had a hematological disease; 62 had a chronic disease but didn't have a hematological disease. We found that the group with hematological disease had a high level of ferritin (p= 0.0001). While the use of steroids in COVID-19 treatments is more frequent in the group with hematological disease (p= 0.01), the use of LMWH (low molecular weight heparin) is more frequent in the group with no hematological diseases (p= 0.02). Intensive care treatment and mechanical ventilatory support were required more for the patients with hematological disease than the others (p= 0.03. p= 0.008). While the mortality rate is 42.1% in the patients with hematological disease, it is 9.7% in the patients with chronic disease (p= 0.003). In cox regression analysis, the study found that hematological diseases (HR: 4.02, 95% CI: 1.7-1844.5, p= 0.02), cardiac diseases (HR: 2.28, 95% CI: 1.2-77.9, p= 0.03), and intensive care treatment (HR: 4.60, 95% CI: 3.1-3115.0, p= 0.009) are significant risk factors. Hematological patients infected with COVID-19 have a more severe and mortal clinical manifestation than the patients with other chronical disease.

Keywords: Hematological disease, Covid-19, Chronic disease, Treatment, Mortality

INTRODUCTION

Coronavirus-19 (COVID-19) which took hold of the world and causes severe respiratory distress was found in Wuhan city of China for the first time. World Health Organization (WHO) declared the virus as a pandemic on March 11, 2020 due to its spreading rate and severity.[1] The most frequent clinical findings of COVID-19 were found to be fever, coughing, and shortness of breath.[2]

There are many risk factors that affect the clinical course of COVID-19 disease. Old age, diabetes mellitus (DM), hypertension (HT), blood groups and cancer are the most significant factors among these risk factors.[3,4] It is shown that the patients diagnosed with cancer have an increased risk of SARS- CoV-2 infection, a more severe course of disease, and increased need for intensive care treatment and higher mortality rates.[5] Therefore, patients with hematologic disorders delay or interrupt their treatment due to the fear of getting infected with SARS-Cov2 in hospital. We noticed that, COVİD-19 outbreak and social arrangements by the government had deleterious effects on the compliance of cancer patients to chemotherapy treatment.[6]

Hematology patients are extremely vulnerable to COVID-19 due to the immunosuppression arising from the direct effect of the disease and the medicines administered. Infection management of the patients may be problematic and the patients may encounter management problems with respect to the treatments they receive, if any. There isn't any clear consensus on the use of cytotoxic drugs and particularly targeted therapy for COVID-19 infection. For this reason, it is recommended that intravenous therapies be continued orally, if possible, in order to reduce the mortality rate in the patients with hematological malignancy in COVID-19 pandemic, G-CSF be administered in order to shorten neutropenia time, the visits be minimized, and the contact of positive cases with negative cases be decreased in hospital environment.[7,8] Our purpose is to analyze the results of the patients that both have a hematological disease and receive treatment for COVID-19 infection in our hospital.

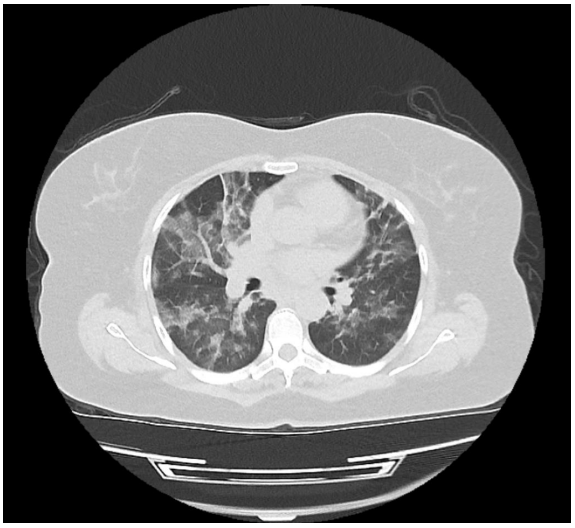

Figure 1. Radiological findings of COVID-19 patient with hematological disease. Bilateral diffuse involvement in the lung.

Patients and Methods

Four hundred COVID-19 positive patients over the age of 18 that received inpatient treatment between March 12, 2020 and October 1, 2020 in the Ondokuz Mayıs University hospital and got a diagnosis by using real-time polymerase chain reaction (RT-PCR) test were scanned retrospectively. Eighty one patients were included in the study. Nineteen patients had a hematological disease; 62 had a chronic disease but didn't have a hematological disease. The study was accepted by the Local Ethics Committee with OMU KAEK2020/581 reference number.

The diagnosis of COVID-19 was confirmed by RT-PCR test of SARS-CoV-2 on nasal and pharyngeal swab samples from patients. The patients were split into two groups as the patients with hematological diseases and the patients with chronic disease and without any hematological disease. Demographic data and clinical symptoms, and biochemical parameters (hemoglobin, platelets, leucocytes, lymphocytes, neutrophil/lymphocyte ratio, clotting tests, serum lactate dehydrogenase, C-reactive protein (CRP), pro-calcitonin, D-dimer, ferritin), and hematological disease characteristics (disease type, therapy status) and pulmoner involvement and anticoagulant and COVID-19 treatment and underlying comorbidities and patient outcome results (hospitalization, complications (Specific organ damage, additional infection and vascular complication, need for intensive care, mortality, discharge) were obtained the electronic medical records (Figure 1).

Statistical Analysis

The study data were transferred to computer and analyzed with SPSS software (Version 15 for Windows, SPSS Inc, Chicago, IL, USA) after they were encoded. In data evaluation, continuous variables were expressed by median (min.-max.) and frequency data were expressed by percentage (%). In statistical analysis, fitness of the measurable variables to normal distribution was evaluated by Shapiro Wilk test. Mann Whitney U test was used in intergroup comparisons as they don't fit to normal distribution for measurable variables. Chi square test was used for comparison of the frequency data. Relationship of the independent variables with survival was evaluated by Cox regression analysis (Enter Method), and the results were expressed by hazard rates (HR) and suitable confidence intervals (95% CI). Significance level is considered as $p< 0.05$ in all statistical tests.

Tablo1. Distribution of hematological patients

Hematological Disease	n (%)
Acute myeloid leukemia (AML)	6 (23.5%)
Acute lymphocytic leukemia (ALL)	2 (10.5%)
Multiple Myeloma (MM)	3 (15.8%)
Chronic lymphocytic leukemia (CLL)	2 (10.5%)
Aplastic anemia	2 (10.5%)
Thalassemia	1 (5.3%)
Immune thrombocytopenia	1 (5.3%)
Mantle cell lymphoma	1 (5.3%)
Marginal zone lymphoma	1 (5.3%)
Total	19 (100%)

RESULTS

Age mean of 81 patients that were included in the study is 59.8 ±13.6. Of the patients, 54.3% are male. Nineteen (23.5%) of these patients were diagnosed with a hematological disease. Age mean of the patients with hematological disease is 57.2±18.2, and 47.4% of them are male. There isn't any statistically significant difference between the patients with hematological disease and the patients without any hematological disease in terms of age mean and gender distribution (p:0.85 and p:0.66 respectively). Distribution of the hematological patients is given in Table 1. In the recent month, two of the patients diagnosed with acute myeloid leukemia (AML) received cytotoxic treatment; one of them received a hypomethylating agent, and one received a targeted treatment in addition to the hypomethylating agent. The remaining two AML patients had just been diagnosed and didn't receive any medication at that time. Acute Lymphocytic leukemia (ALL) patients were in remission and they were being monitored. Chronic lymphocytic leukemia (CLL) patients weren't receiving any treatment. One of the patients with lymphoma were receiving a high dose of cytotoxic chemotherapy due to relapse, and the other one were in remission and being monitored. There were three patients with myeloma and they were receiving a targeted treatment. There were two patients with aplastic anemia and they were receiving an immunosuppressive treatment. The patients diagnosed with thalassemia and immune thrombocytopenia weren't receiving any treatment.

Distribution of the determined clinical symptoms of the both two patient groups diagnosed with COVID-19, their existing chronic disease history, the distribution of the medicines administered to them for COVID-19 treatment are given in Table 2. There isn't any difference between the groups in terms of the distribution of clinical symptoms and the existence of chronic diseases (p= 0.05). The prevalence of cardiac diseases (66.1%), and the prevalence of endocrinological diseases (48.4%) in the patients without any hematological disease are statistically significant and higher (p= 0.04 and p= 0.02 respectively). Infection and vascular complications were more common in patients with hematological conditions compared to those without hematological conditions, however, that difference was not statistically significant (p= 0.06). Typical pulmonary involvement of COVİD-19 was more common in patients without hematological conditions and atypical pulmonary involvement of COVİD-19 was more common in patients with hematological conditions, however, the difference was not statistically significant, either (p= 0,42). While the use of steroids is more frequent in the group with hematological diseases (73.7%), the use of LMWH (low molecular weight heparin) is more frequent in the group with no hematological diseases (91.9%) (p= 0.01 and p= 0.02 respectively).

Mean length of hospital stay of all patients was found 10.4±7.4 days. Mean length of hospital stay of the patients with hematological disease is 14.7 ±9.1 days, and it is statistically and significantly higher than that of the group without any hematological disease (p= 0.01). In comparison of the groups in terms of laboratory parameters, while mean hemoglobin and platelet values of the patients with hematological diseases were statistically lower (p= 0.0001 and p= 0.01 respectively), their ferritin levels were found much higher (p= 0.0001). Similarly, while before treatment CRP, D-dimer and pro-calcitonin values of the patients with hematological disease were higher, the difference wasn't statistically significant (p= 0.15, p= 0.052 and p= 0.054 respectively). Post-treatment CRP levels of the patients with hematological con-

Tablo 2. Distribution of symptoms, chronic disease histories, pulmoner involment, complications and drugs used by patients diagnosed with COVID-19

	Total (n= 81) n (%)	Patients without hematological disease (n= 62) n (%)	Patients with hematological disease (n= 19) n (%)	P
Clinical symptoms				
Fever	28 (34.6)	23 (37.1)	5 (26.3)	0.55
Cough	49 (60.5)	41 (66.1)	8 (42.1)	0.10
Shortness of breath	20 (24.7)	16 (25.8)	4 (21.1)	0.90
Loss of sense of taste	10 (12.3)	8 (12.9)	2 (10.5)	1.00
Headache	30 (37.0)	26 (41.9)	4 (21.1)	0.16
Throat ache	22 (27.2)	19 (30.6)	3 (15.8)	0.32
Runny nose	6 (7.4)	6 (9.7)	0 (0.0)	0.36
Stuffy nose	4 (4.9)	4 (6.5)	0 (0.0)	0.59
Diarrhea	9 (11.1)	6 (9.7)	3 (15.8)	0.74
Myalgia	25 (30.9)	21 (33.9)	4 (21.1)	0.43
Weakness	13 (16.0)	6 (9.7)	7 (36.8)	**0.01**
Chronic Diseases				
Cardiological disease	48 (59.3)	41 (66.1)	7 (36.8)	**0.04**
Respiratory illness	7 (8.6)	6 (9.7)	1 (5.3)	0.89
Endocrological disease	33 (40.7)	30 (48.4)	3 (15.8)	**0.02**
Neurological disease	7 (8.6)	4 (6.5)	3 (15.8)	0.42
Oncological disease	7 (8.6)	6 (9.7)	1 (14.3)	0.89
Rheumatological disease	3 (3.7)	2 (3.2)	1 (5.3)	1.00
Nephrological disease	3 (3.7)	3 (4.8)	0 (0.0)	0.77
Pulmoner Involment *				
Typical for COVID-19	50 (65.8)	39 (68.4)	11 (57.9)	0.42
Atypical for COVID-19	16 (21.1)	10 (17.5)	6 (31.6)	
Negative	10 (13.2)	8 (14.0)	2 (10.5)	
Complications				
Spesific organ damage	15 (18.5)	13 (21.0)	2 (10.5)	0.30
Additional Infection	28 (34.6)	18 (29.0)	10 (52.6)	0.06
Vasculer complication	8 (9.9)	4 (6.5)	4 (21.1)	0.058
Intensive care unit admission	18 (22.2)	10 (16.1)	8 (42.1)	**0.03**
Mechanical ventilation	7 (8.6)	2 (3.2)	5 (26.3)	**0.0008**
Medicines used to treat COVID-19				
Hydroxychloroquine	17 (21.0)	13 (21.0)	4 (21.1)	1.00
Azithromycin	11 (13.6)	10 (16.1)	1 (5.3)	0.40
Favipiravir	73 (90.1)	56 (90.3)	17 (89.5)	1.00
LMWH	70 (86.4)	57 (91.9)	13 (68.4)	**0.02**
Steroid	38 (46.9)	24 (38.7)	14 (73.7)	**0.01**
Plasma	2 (2.4)	1 (1.6)	1 (5.3)	0.95
Tocilizumab	5 (6.2)	5 (8.1)	0 (0.0)	0.46
Aspirin	15 (18.5)	11 (17.7)	4 (21.1)	1.00
Daily LMWH doses used by patients**				
1 x 0.4	32 (45.7)	29 (50.9)	3 (23.1)	**0.033**
2 x 0.4	10 (14.3)	7 (12.3)	3 (23.1)	
1 x 0.6	7 (10.0)	7 (12.3)	0 (0.0)	
2 x 0.6	16 (22.9)	9 (15.8)	7 (53.8)	
1 x 0.8	4 (5.7)	4 (7.0)	0 (0.0)	
2 x 0.8	1 (1.4)	1 (1.8)	0 (0.0)	

** Five patients without hematological disease did not have lung tomography; ** These are the distributions of 70 patients using LMWH*

Tablo 3. Hospitalization day and measurement values of some blood parameters of patients diagnosed with Covid-19

	Total (n= 81) mean ± SD	Patients with Hematological disease (n= 19) mean ± SD (median)	Patients without Hematological disease (n= 62) mean ± SD (median)	P
Hospitalization day	10.4 ±7.4	9.1 ±6.4 (8)	14.7 ±9.1 (13)	**0.01**
White blood	7.6 ±12.7	5.9 ± 3.0 (5.5)	13.0 ±25.5 (5.4)	0.81
Hemoglobin	11.6 ±2.4	12.2±2.0 (12.2)	9.7±2.5 (9.1)	**0.0001**
Platelet	172.8 ±78.7	190.2±62.1 (191.5)	116.2±100.2 (83)	**0.001**
Lymphocyte	1.5 ±1.9	1.3±1.4 (1.0)	2.2 ±3.1 (1.2)	0.78
N/L ratio	5.1 ±6.4	5.4±6.8 (2.7)	4.1±5.2 (1.9)	0.19
PT	12.8 ±1.7	12.6±1.6 (12.3)	13.5±2.0 (12.5)	0.25
APTT	29.0 ±4.8	28.6 ±4.2 (28)	30.2±6.2 (27)	0.44
LDH	335.8 ±242.6	295.7±115.5 (270)	466.6± 439.1 (294)	0.22
Ferritin	881.2 ±1408.6	539.3±906.2 (278.5)	1996.7±2078.3 (1277)	**0.0001**
D-dimer	1718.2 ±2455.5	1433.1±2220.8 (554)	2648.5±2981.5 (1667)	0.052
Before treatment CRP	49.5 ±61.2	40.0±47.0 (28)	80.4±88.5 (41)	0.15
After treament CRP	50.1±76.2	39.2±6.2 (10)	85.5±96.2 (50)	**0.009**
Procalsitonin	0.3 ±0.8	0.2±0.7 (0.08)	0.5±0.9 (0.1)	0.054

ditions was higher than that of the patients without hematological disease (p= 0.009) (Table 3).

Of the 81 patients included in the study, 18 patients (22.2%) were in intensive care unit (ICU); 7 patients (8.6%) received mechanical ventilation (MV) support. In conclusion, while 14 (17.3%) of the patients died, 67 (82.7%) were discharged. While 8 (42.1%) of the patients with hematological diseases were in ICU, 5 (26.3%) of them received MV support. The rates were 16.1% and 3.2% respectively in the patients without any hematological disease, and the results were statistically significant (p= 0.03 and p= 0.008). 42.1% of the patients with hematological disease and 9.7% of the patients without any hematological disease died. As a result, statistically significant differences were found (p= 0.003) (Table 2).

In cox regression analysis, the independent variables affecting survival were evaluated. Accordingly, hematological diseases (HR: 4.02, 95% CI: 1.7-1844.5, p= 0.02), cardiac diseases (HR:2.28.95% CI: 1.2-77.9, p= 0.03) and intensive care treatment (HR: 4.60, 95% CI: 3.1-3115.0, p= 0.009) were found to be statistically significant risk factors (Table 4).

Table 4. The Cox regression analyses to determine independent prognostic factors affecting overall survival

	Multivariate Cox Regression Analysis	
	HR (95% CI)	P
> 60 years (vs < 60 years)	0.07 (0.1-11.1)	0.94
Male sex (vs female)	0.04 (0.1-10.4)	0.97
Hematological disease	4.02 (1.7-1844.5)	**0.02**
Cardiological disease	2.28 (1.2-77.9)	**0.03**
Endocrological disease	0.17 (0.1-10.1)	0.87
ICU admission	4.60 (3.1-3115.0)	**0.009**
Mechanical ventilation	0.69 (0.1-21.6)	0.56
Hemoglobin	-0.79 (0.1-1.2)	0.13
Platelet	-0.01 (0.9-1.0)	0.27
Ferritin	-0.001 (0.9-1.0)	0.30
LMWH use	0.18 (0.1-9.7)	0.86

ICU= intensive care unit

DISCUSSION

In this study, we examined the clinical results of the group of COVID-19 positive patients with hematologic disease and the group of COVID-19 positive patients without any hematologic disease.

We indicated that the COVID-19 patients with hematological diseases have an increased risk in terms of ICU admission and mortality rate. Complications caused by respiratory viruses develop frequently in hematological diseases due to damaged immune system and the cytotoxic drugs administered.[8] Infection related mortality rate was reported to be 70% in hematological patients that receive immunosuppressive treatment in the last 3 months during COVID-19 pandemic.[9] The mortality rate of the patients is 42.2% in this study, which is pretty high. Two of the dead patients received a high dose of cytotoxic chemotherapy due to AML; one of the patients received the same therapy due to lymphoma; one of the patients received targeted treatment due to multiple myeloma, and two of the patients received immunosuppressive treatment due to aplastic anemia in the recent month. Some of the patients were diagnosed with COVID-19 while receiving a treatment in the hospital. We think that forbidding the visit of patients, the hospital attendants' attention to isolation, and ensuring air circulation in patient rooms may decrease the risk of transmission of COVID-19 in hematological patients.

While 42% of the hematological patients receiving inpatient treatment needed support for intensive care, the rate is 16% in the patients without any hematological diseases. The need for MV support is 26.3% and 3.2% respectively. While the mortality rate is 42.1% in the patients with hematological disease, it was 9.7% in the other group. The severe clinical course of the hematological patients compared to the other group can be explained by three hypotheses. First of all, B, T, NK lymphocytes, histiocytes, and antigen-presenting cells play an essential role in pathophysiology in hematological malignancies. Secondly, hematological malignancy cells circulate in the blood and lymphatic system, and release cytokine by getting into the relevant organs. Thirdly, SARS-CoV-2 virus spreads more easily due to immune system damage in cases of aplasia and infiltration in bone marrows.[10]

High level of ferritin causes irregularity in the immune system. Immune system irregularity takes place by inflammatory and direct immunosuppressive impact, and this leads to cytokine storm.[11] Cytokine storm causes COVID-19 infection to have a more mortal course.[12] In this study, ferritin level is statistically significant in hematological patients compared to the other group. We think that high level of ferritin can be a factor that leads to severe clinical course of the hematological patients.

The study found that the use of steroids is more frequent in the hematological patients in COVID-19 treatment. There isn't any randomized study on the use of steroids in COVID-19 treatment. The use of steroids is not recommended as they may cause reactivation of the virus in the beginning of COVID-19 infection. However, it is reported to be useful and decrease the mortality risk in the treatment if lung involvement and acute respiratory distress syndrome (ARDS) develop due to the increase in cytokine levels in the later stages.[10,13]

World Health Organization recommends heparin or low molecular weight heparin as a prophylactic treatment against venous thromboembolism in severe SARS Cov-2 patients.[14] Additional risk factors increase the risk of thrombosis in hematological patients due to COVID-19 disease. Therefore, the need for using anticoagulants may arise. The use of anticoagulants was lower in some of the patients compared to the other group as they receive an active cytotoxic chemotherapy and low level of thrombocytes.

The hematologic patients with any malignancy, in particular, are vulnerable to infections and susceptible to thrombosis.[15,16] The rate of additional infections and vascular complications were higher in the group with hematologic disease during COVID-19 treatment process. Also, post-treatment CRP value was found significantly higher in the group with hematologic disease. Therefore, the high level of CRP after COVID-19 treatment in the group with hematologic disease can be explained by higher prevalence of additional infections.

The study found that hematological diseases cardiovascular diseases, and intensive care treatment are statistically significant risk factors. Granulocyte count is very low in the patients with acute leukemia, myelodysplastic syndromes, and aplastic anemia. Bacterial infections are frequently monitored in these patients due to the effect of COVID-19 virus and the granulocyte count. The additional cytotoxic treatment leads to a serious decrease in the

granulocyte count.[17] For these reasons, the need for intensive care of patients with hematological disorders increases and the length of hospital stay is prolonged. Consequently, the mortality rate in the intensive care unit is higher in COVID-19 patients with hematological disease, especially acute leukemia, as in this study.

Weaknesses of this study are as follows: the hematological patients in this study were a heterogeneous group and failure to compare them among themselves due to insufficient number of patients.

In consequence, COVID-19 patients with hematological diseases have a more mortal clinical course compared to the patients with other chronic diseases. COVID-19 treatments of the patients that receive systemic chemotherapy particularly in the recent month are more intensive and take longer. The mortality rates in COVID-19 patients with hematological diseases in the hospital, particularly the elder patients, are relatively higher compared to the patients with chronic diseases and without any hematological diseases. However, not all the patients with hematological diseases are affected by the virus equally. For the hematological patients infected with COVID-19, it is more appropriate to plan their treatments by making a risk-benefit analysis carefully by an experienced team consisting of the specialists in the fields of hematology, infection, chest disease, and intensive care. We think that the use of medicines as an alternative treatment (such as targeted therapy) which causes less immunosuppression and postponing their treatment, if possible, may be better options for hematology treatments.

REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1054-1062, 2020.
2. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382: 1708-1720, 2020.
3. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 22: 369, 2020.
4. Aktimur SH, Sen A, Yazicioglu B, at al. The assessment of the relationship between ABO blood groups and Covid-19 infection. UHOD - Int J Hematol Oncol 30: 121-125, 2020.
5. Martín-Moro F, Marquet J, Piris M, et al. Survival study of hospitalised patients with concurrent COVID-19 and haematological malignancies. Br J Haematol 190: 16-20, 2020.
6. Beypinar I, Muslih U. Intravenous chemotherapy adherence of cancer patients in time of Covid-19 crisis. UHOD - Int J Hematol Oncol 30: 133-138, 2020.
7 . Brissot E, Labopin M, Baron F, et al. Management of patients with acute leukemia during the COVID-19 outbreak:practical guidelines from the acute leukemia working party of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant 56: 532-535, 2021.
8. Hirsch HH, Martino R, Ward KN, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. Clin Infect Dis 56: 258-266, 2013.
9. Booth S, Willan J, Wong H, et al. Regional outcomes of severe acute respiratory syndrome coronavirus 2 infection in hospitalised patients with haematological malignancy. Eur J Haematol 105: 476-483, 2020.
10. Sica A, Casale D, Rossi G, et al. The impact of the SARS-CoV-2 infection, with special reference to the hematological setting. J Med Virol 93: 223-233, 2021.
11. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. Research J Med Sci 19: 164-174, 2014.
12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506, 2020.
13.. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020:e200994. JAMA Intern Med 180: 934-943, 2020.
14. Aktas G. A comprehensive review on rational and effective treatment strategies against an invisible enemy; SARS Cov-2 infection. Exp Biomed Res 3: 293-311, 2020.
15. Dai M, Liu D, Liu M, at al. Patients with cancer appear more vulnerable to SARS-CoV-2: A multicenter study during the COVID-19 Outbreak. Cancer Discov 10: 783-791, 2020.
16. Kekre N, Connors JM. Venous thromboembolism incidence in hematologic malignancies. Blood Rev. 33: 24-32, 2019
17. He W, Chen L, Yuan G, et al. COVID-19 in persons with haematological cancers. Leukemia 34: 1637-1645, 2020.

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