RESEARCH ARTICLE

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Clinical Characteristics and Outcomes of COVID-19 in Turkish Patients with Hematological Malignancies

COVID-19 Geçiren Türk Hematolojik Malignite Hastalarının Klinik Özellikleri ve Sonuçları

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Abstract

Objective: Patients with solid malignancies are more vulnerable to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection than the healthy population. The outcome of SARS-CoV-2 infection in highly immunosuppressed populations, such as in patients with hematological malignancies, is a point of interest. We aimed to analyze the symptoms, complications, intensive care unit admissions, and mortality rates of patients with hematological malignancies infected with SARS-CoV-2 in Turkey.

Materials and Methods: In this multicenter study, we included 340 adult and pediatric patients diagnosed with SARS-CoV-2 from March to November 2020. Diagnosis and status of primary disease, treatment schedules for hematological malignancies, time from last treatment, life expectancy related to the hematological disease, and comorbidities were recorded, together with data regarding symptoms, treatment, and outcome of SARS-CoV-2 infection.

Results: Forty four patients were asymptomatic at diagnosis of SARS-CoV-2 infection. Among symptomatic patients, fever, cough, and dyspnea were observed in 62.6%, 48.8%, and 41.8%, respectively. Sixty-nine (20%) patients had mild SARS-CoV-2 disease, whereas moderate, severe, and critical disease was reported in 101 (29%), 71 (20%), and 55 (16%) patients, respectively. Of the entire cohort, 251 (73.8%) patients were hospitalized for SARS-CoV-2. Mortality related to SARS-CoV-2 infection was 26.5% in the entire cohort; this comprised 4.4% of those patients with mild disease, 12.4% of those with moderate disease, and 83% of those with severe or critical disease. Active hematological disease, lower life expectancy related to primary hematological disease, neutropenia at diagnosis of SARS-CoV-2, ICU admission, and first-line therapy used for coronavirus disease-2019 treatment were found to be related to higher mortality rates. Treatments with hydroxychloroquine alone or in combination with azithromycin were associated with a higher rate of mortality in comparison to favipiravir use.

Conclusion: Patients with hematological malignancy infected with SARS-CoV-2 have an increased risk of severe disease and mortality.

Keywords: COVID-19, SARS-CoV-2 infection, Hematological malignancy

Öz

Amaç: Solid malignite hastalarının şiddetli akut solunum yolu enfeksiyonu-koronavirüs-2 (SARS-CoV-2) enfeksiyonuna sağlıklı bireylerden daha yatkın oldukları gösterilmiştir. Bu verilerin ardından oldukça yoğun immünosupresif olan hematolojik malignite hastalarında SARS-CoV-2 infeksiyonu sonuçları ilgi konusu olmuştur. Biz de bu makalede Türkiye'de hematolojik malignite tanısı ile takip ve tedavi edilirken SARS-CoV-2 enfeksiyonu saptanan hastaların semptom, komplikasyon, yoğun bakım ünitesine yatış ve mortalite oranlarını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çok merkezli çalışmamıza Mart-Kasım 2020 tarihleri arasında SARS-CoV-2 enfeksiyonu tanısı alan erişkin ve pediatrik 340 hastayı dahil ettik. Hastaların hematolojik malignite tanıları, hastalık statusları, tedavileri, son tedaviden enfeksiyona kadar geçen süre, komorbiditeleri, yaşam beklentileri değerlendirildi. Semptomları, oluşan komplikasyonlar ve sonuçlar analiz edildi.

Bulgular: Kırk-dört hasta semptomsuz olarak enfeksiyonu geçirirken, semptomatik hastaların ateş, öksürük, ve dispne oranları sırasıyla %62,6, %48,8 ve %41,8 idi. Altmış altı hasta (%20) hastalığı hafif geçirirken, orta, ciddi ve kritik hastalık tanısı alanların oranı sırasıyla %29, %20 ve %16 idi. Tüm kohortta ölüm oranı %26,6 idi; ölüm hafif hastalığı olanlarda %4,4 , orta derece hastalık geçirenlerde %12 ve ciddi/kritik hastalık geçirenlerde ise %83 olarak saptandı. Aktif hematolojik hastalık olması, primer hematolojik hastalığa bağlı düşük hayat beklentisi, SARS-CoV-2 tanısı aldığında nötropenik olmak, yoğun bakıma alınmış olmak ve ilk sıra koronavirüs hastalığı-2019 tedavisi yüksek ölüm riski ile ilişkilendirilen faktörlerdendi. Tek başına veya azitromisin ile kombine olarak hidroksiklorokin kullanan hastaların sadece favipiravir kullananlara göre ölüm riskleri daha yüksek saptandı.

Sonuç: SARS-CoV-2 infeksiyonu geçiren hematolojik malignite hastalarında daha yüksek oranda ciddi hastalık ve ölüm riski gözlenmektedir.

Keywords: COVID-19, SARS-CoV-2 enfeksiyon, Hematolojik malignite

Introduction

Millions of people have been infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) worldwide. Comorbidities like diabetes mellitus, hypertension, and chronic renal failure as well as older age have been identified as risk factors for the ensuing severity of coronavirus disease-2019 (COVID-19) [1,2,3,4]. Cancer patients were also found to be more vulnerable to SARS-CoV-2 infection than the healthy population in studies that mostly included solid malignancies [5,6,7].

The increased risk of viral infections of the respiratory tract in patients with hematological malignancy and hematopoietic stem cell transplantation (HSCT) has been previously reported [8,9,10]. The underlying diagnosis and the treatments may both influence humoral and cellular immune functions negatively and result in poor outcome. The clinical characteristics and risk factors that may be predictive for severity or mortality of COVID-19 in cases of hematological malignancy need to be addressed.

In this registry data analysis, we aimed to evaluate the symptoms, complications, intensive care unit (ICU) admissions, and mortality rates of SARS-CoV-2 infection in patients with underlying hematological malignancies and to clarify the risk factors associated with mortality in COVID-19 in Turkey. Additionally, the influence of national treatment protocols for SARS-CoV-2 infection on outcomes was analyzed.

Materials and Methods

On behalf of the Turkish Society of Hematology's Infectious Complications and Supportive Care Working Party, we

retrospectively collected data from 25 centers in Turkey from March to November 2020. The study was approved by both the Turkish Ministry of Health and the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (22-Sep-2020/80350), as well as locally by the participating centers.

Patients were included in the study according to the following criteria: a) SARS-CoV-2 polymerase chain reaction (PCR) positivity via nasal swabs or b) negative PCR results but symptoms related to SARS-CoV-2 with highly suggestive thoracic computerized tomography findings. Patients who were followed as both outpatients and inpatients for COVID-19 were eligible for the study. Forms for data collection were emailed to participating centers.

Diagnosis and status of the primary disease, treatment schedules for hematological malignancies, time from last treatment, and life expectancy related to the hematological disease were recorded. Data regarding symptoms related to SARS-CoV-2 infection, hospitalization and oxygen requirements, severity, complications and organ involvement, laboratory parameters on admission, and treatments given for COVID-19 were also investigated. Comorbidities, defined as diabetes mellitus, hypertension, chronic renal failure, chronic obstructive pulmonary disease, cardiovascular disease, or preexisting solid malignancy diagnosis, were also recorded.

Patients who had undergone autologous HSCT and were in the first 100 days after transplantation were grouped as "auto-HSCT." All patients who had undergone allogeneic HSCT were grouped as "allo-HSCT" irrespective of their primary diagnosis and the status of the disease.

The severity of SARS-CoV-2 infection was classified according to World Health Organization (WHO) definitions [11] as follows. Mild disease: Symptomatic patients without findings of pneumonia or hypoxia. Moderate disease: Patients with signs of pneumonia, like cough, fever, and dyspnea, without signs of severe pneumonia or SpO_2 of >90% on room air. Severe disease: Patients with symptoms of pneumonia and respiratory rate of >30/min, severe respiratory distress, or SpO_2 of <90% on room air. Critical disease: Patients with acute respiratory distress syndrome (ARDS), sepsis, and septic shock.

The COVID-19 treatments of patients were determined according to guidelines released by the Turkish Ministry of Health. Due to the antiviral potency of hydroxychloroquine (HCQ), it was introduced as the initial treatment schedule alone or in combination with azithromycin and favipiravir as salvage treatment. In subsequent months of the pandemic, favipiravir was moved to first-line treatment, consistent with the updated version of the guidelines.

The primary objective of this study was to identify the clinical outcomes and complications of COVID-19 in patients with hematological malignancies and to determine the rates of hospitalization, ICU admission, and overall 45-day mortality. The secondary objective was to identify additional risk factors for mortality specifically defined for this group of immunosuppressed patients.

Descriptive statistics were calculated as median and range for continuous and percentage for categorical variables. The Cox regression model was used for univariate analysis. Parameters achieving values of $p<0.20$ were added to the multivariate Cox regression model and significant factors were detected with the stepwise method. Analysis was performed with SPSS 20.0.

Results

The characteristics of 335 adult and 5 pediatric patients are summarized in Table 1. The median age was 59 years (range: 7-93). COVID-19 was more frequent in males (male-to-female ratio: 1.3). The most common underlying hematological diagnosis was multiple myeloma (MM), seen in 25% of cases, followed by acute myeloid leukemia (AML) (20%) and non-Hodgkin lymphoma (NHL) (18%). The hematological disease statuses of the patients are also shown in Table 1. Twenty-eight percent of the patients had active disease, and 28 of those patients were newly diagnosed but treatment could not be started as a consequence of SARS-CoV-2 infection. The treatment schedules for hematological malignancies are also summarized in Table 1. Treatment protocols for primary disease were changed before the diagnosis of COVID-19 for 21% of these patients.

Nasopharyngeal swab PCR positivity for SARS-CoV-2 was observed in 264 of 340 (77%) patients. Forty-four (12.9%) patients were asymptomatic at diagnosis. In symptomatic patients, fever, cough, and dyspnea were observed in 62.6%, 48.8%, and 41.8%, respectively. In the allo-HSCT group, 13% of the patients were asymptomatic. Fever was present in 55%, cough in 50%, dyspnea in 28%, and myalgia and malaise in 34% and 31% of the patients, respectively. In the auto-HSCT group, 9 patients (64%) had fever, 5 (35%) patients had cough and malaise, 4 (28%) patients had dyspnea, and 1 patient (7%) was asymptomatic.

The median number of febrile days was 3 (range: 1-20). Sixty-nine (20.2%) patients had mild disease, whereas moderate, severe, and critical disease was reported in 101 (29.7%), 71 (20.8%), and 55 (16.1%) patients, respectively. ARDS was reported in 11 patients while sepsis and septic shock were observed in 31 and 13 patients, respectively. Two of 5 pediatric patients were asymptomatic; 2 had severe and 1 had critical disease. Severity of COVID-19 was not found to be related to age, comorbidities, primary disease status, malignancy treatments, HSCT, or type of COVID-19 treatment.

Table 1. Patient characteristics, clinical outcomes, and treatments of hematological malignancy patients infected with SARS-CoV-2.

	n=340
Age, median (min-max)	59 (7-93)
Male/female ratio	196/144
Diagnosis	AML: 69 (20.3%) NHL: 64 (18.8%) MM: 85 (25%) ALL: 30 (8.8%) MDS: 27 (7.9%) HL: 18 (5.3%) CLL: 18 (5.3%) CMPD: 10 (2.9%) CML: 8 (2.4%) CMML: 4 (1.2%) HCL: 7 (2.1%)
Comorbidities	144 (42.4%)
Smoking status Active smoker/ex-smoker/nonsmoker/not available	 8 (2.4%)/84 (24.7%)/175(51.5%)/73 (21.5%)
Contact Yes/no/not available	 103/175/62
Disease status	New diagnosis: 65 (19.1%) CR: 135 (39.7%) PR: 13 (3.8%) Active disease: 98 (28.8%) Untreated: 20 (5.9%) Not available: 9 (2.6%)
Treatment Untreated Induction/consolidation/salvage/immunotherapy/maintenance Auto-HSCT/Allo-HSCT Steroids/rituximab/IvIG/GCSF	 48 134/19/68/13/14 14/38 100/57/42/55
Clinical presentation Asymptomatic Symptomatic	 44 (12.9%) 297 (87.1%)
Symptoms Fever Cough Dyspnea Myalgia Diarrhea Malaise Sore throat Headache Nausea Anosmia	 213 (62.6%) 166 (62.6%) 142 (41.8%) 64 (18.8%) 19 (5.6%) 75 (22.1%) 12 (3.5%) 9 (2.6%) 9 (2.6%) 8 (2.4%)
Days with fever Median (min-max)	 3 (1-20)

Table 1. Continued.

	n=340
Extrapulmonary disease	
Myocarditis	6 (%)
Liver	2 (%)
Renal	2 (%)
Skin	1 (%)
Neurological	2 (%)
COVID-19 severity	
Asymptomatic/mild/pneumonia/severe pneumonia/ARDS/sepsis/septic shock	44/69/101/71/11/31/13
Asymptomatic/mild/moderate/severe/critical	44 (12.9%)/69 (20.2%)/101 (29.7%)/71 (20.8%)/55 (16.1%)
Thrombosis	7 (2%)
Hospitalization	251 (73.8%)
Ward/ICU	165 (48.5%)/86(25.3%)
Hospitalization days	
Median (min-max)	11 (1-49)
ICU days	
Median (min-max)	2 (1-63)
Laboratory variables	
Hemoglobin	10.1 (6.0-15.3)
White blood cell count	4300 (30-343000)
Lymphocytes	780 (0-326200)
Neutrophils	2500 (0-67480)
Platelets	1250000 (5000-654000)
Ferritin	1461 (17-40000)
Antiviral treatment	
HCQ	35 (10%)
Favipiravir	140 (41.2%)
HCQ + favipiravir	50 (14.7%)
HCQ + azithromycin	42 (12.4%)
HCQ + azithromycin + favipiravir	42 (12.4%)
Not available	31 (9.1%)
Anti-cytokine treatment	
Convalescent plasma	36 (12.3%)
Steroids	27 (7%)
Tocilizumab	24 (7%)
IvIG	21 (6%)
Anakinra	5 (1%)
Ruxolitinib	1 (2%)
Anticoagulant treatment	
Prophylactic dose	198 (58.2%)
Treatment dose	26 (7.6%)

AML: Acute myeloid leukemia; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; ALL: acute lymphocytic leukemia; MDS: myelodysplastic syndrome; CLL: chronic lymphocytic leukemia; HL: Hodgkin lymphoma; CMPD: chronic myeloproliferative disorder; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; HCL: hairy cell leukemia; CR: complete response; PR: partial response; auto-HSCT: autologous hematopoietic stem cell transplantation; allo-HSCT: allogeneic hematopoietic stem cell transplantation; IvIG: intravenous immune globulin; GCSF: granulocyte colony-stimulating factor; ICU: intensive care unit; HCQ: hydroxychloroquine.

In the allo-HSCT group, mild, moderate, severe, and critical COVID-19 was observed in 18%, 44%, 13%, and 10% of cases, respectively. Patients with graft-versus-host disease (GVHD) had more severe and critical disease in comparison to those without GVHD (p=0.03). In patients who were diagnosed with COVID-19 in the first 30 days after auto-HSCT, mild disease was observed in 4 of 14 patients, while moderate, severe, and critical disease was observed in 3, 4, and 2 patients, respectively.

Laboratory variables of the patients are summarized in Table 1. Neutropenia and lymphopenia were observed at diagnosis in 23% and 57%, respectively.

Treatment for COVID-19 was either with HCQ or favipiravir alone or in combination with other treatments (Table 1). Favipiravir alone was given to 41.4% of the entire cohort, while it was given in combination with HCQ to 14.7% and in combination with HCQ and azithromycin to 12.4% of the patients. Ten percent of the patients received HCQ alone while 12.4% received it in combination with azithromycin.

Thirty-six patients (12.3%) received convalescent plasma and the rest of the anti-cytokine treatments are summarized in Table 1.

Of the entire cohort, 251 (73.8%) patients were hospitalized and 86 (25%) of those patients were admitted directly to the ICU. Median number of hospitalization days in the ward and ICU was 11 (range: 1-49) and 2 (range: 1-63), respectively.

Thrombotic events were observed in 7 (2%) patients. Three of them had thrombotic attacks while using prophylactic-dose low-molecular-weight heparin. One of those three patients had a history of previous pulmonary embolism.

PCR negativity could be achieved in a median of 11 days (range: 1-60). Patients who had received rituximab for the primary disease within 1 year before COVID-19 showed significantly prolonged viral shedding (median: 14 days (3-60) vs. 11 days (1-59), p=0.023).

Mortality was 26.5% in the entire cohort and 4.4% in cases of mild disease, 12.4% in cases of moderate disease, and 83% in cases of severe and critical disease. Nine of 38 (23.7%) patients who had undergone allo-HSCT and 3 (21%) of 14 patients who had undergone auto-HSCT died. No difference in mortality was observed according to the timing of HSCT or presence of GVHD.

Parameters analyzed for relationships with mortality in univariate analysis with Cox regression are shown in Table 2. Age, comorbidities, status of primary hematological disease, neutropenia and lymphopenia at diagnosis of SARS-CoV-2 infection, severity of COVID-19, hospitalization, admission to the ICU, intubation, type of COVID-19 treatment, convalescent plasma treatment, and decreased life expectancy related to primary hematological disease were all found to be associated with higher mortality rates. Patients with PCR positivity also had a higher mortality rate in comparison with patients who had only CT findings but negative PCR results (Table 2).

In multivariate Cox regression analysis by stepwise approach, all the significant parameters related to mortality in univariate analysis were included in multivariate analysis. Hematological disease status, decreased life expectancy related to primary hematological disease, neutropenia, ICU admission, and type of COVID-19 treatment were accordingly found to be associated with higher mortality (Table 3). Patients treated with HCQ alone had 4.9-fold higher mortality risk in comparison to patients treated with favipiravir alone, while those treated with HCQ plus favipiravir had 2.04-fold higher risk and those treated with HCQ plus azithromycin had 2.14-fold higher risk.

Discussion

We have reported the outcomes of 340 hematological malignancy patients who contracted SARS-CoV-2 infection from March to November 2020 in Turkey. Patients with hematological malignancies are a high-risk population for SARS-CoV-2 infection as a result of immunosuppression arising from both the disease and its treatment. In our study, severe/critical disease as defined according to the WHO classification was observed in 36% of patients [11]. Consistent with our results, another report from Turkey that included patients from the Turkish Ministry of Health database showed more severe and critical disease among hematological malignancy patients with COVID-19 compared to patients without cancer [12]. Piñana et al. [13] included patients grouped according to different severity criteria [14] in their study and observed severe disease in 55% of non-HSCT, 36% of auto-HSCT, and 43% of allo-HSCT patients.

We could not find a relation between the severity of COVID-19 and age, comorbidities, primary disease status, malignancy treatments, HSCT, or COVID-19 treatment. In allo-HSCT patients, however, GVHD was related to severe-critical disease status. Risk factors for severe disease were reported as hypertension, baseline lymphopenia, baseline C-reactive protein of >20 mg/dL, age, and comorbidities in different series [13,15,16].

Factors related to mortality in hematological malignancy patients are still debated. The mortality rate was 26% in our study, correlated with increasing COVID-19 severity. In a meta-analysis of 34 adult and 5 pediatric studies that predominantly included hospitalized patients, the risk of death was 34% and 4%, respectively [17]. Although there were only five pediatric patients in our study, all were alive at the end of follow-up. Piñana et al. [13] showed associations between mortality and age, performance score, neutropenia, uncontrolled disease, and increased C-reactive protein. In our study, hematological disease status, life expectancy related to the primary hematological disease, neutropenia, ICU admission, and type of COVID-19 treatment were risk factors for mortality in multivariate analysis. ICU admission closely reflected the disease severity and mortality increase irrespective of age, probably related to the primary hematological disease status.

Table 2. Univariate analysis for mortality of the patients by Cox regression model (p<0.20 is statistically significant).

	n	p	Hazards ratio	95% confidence interval for hazards ratio	
				Lower	Upper
Gender					
Female			1		
Male	195	0.448	1.180	0.769	1.810
Age, years					
<60	170		1		
≥60	167	**0.094**	1.432	0.941	2.180
Diagnosis					
Acute leukemia	99	0.459			
Lymphoma	106	0.376	1.270	0.748	2.156
Myeloproliferative	22	0.251	1.599	0.718	3.561
Myeloma	84	0.548	0.827	0.444	1.539
Myelodysplastic syndrome	27	0.486	1.329	0.597	2.959
Hematological disease status					
Newly diagnosed	47	**0.000**			
Complete response	136	**0.001**	0.354	0.187	0.672
Partial response	21	0.963	1.020	0.440	2.365
Active disease	104	0.928	1.027	0.582	1.812
Untreated	21	**0.038**	0.212	0.049	0.918
Not available	9	**0.167**	0.241	0.032	1.812
Comorbidities					
No	194		1		
Yes	144	**0.016**	1.672	1.102	2.537
Smoking habit					
Nonsmoker	174	0.992			
Ex-smoker	83	0.975	1.008	0.616	1.648
Active smoker	8	0.903	0.916	0.222	3.773
Hematological treatment					
Induction	134	0.232			
Consolidation	21	0.248	0.546	0.196	1.525
Salvage	69	0.514	1.182	0.714	1.957
Immunotherapy	13	0.313	0.481	0.116	1.992
Maintenance	15	0.183	0.381	0.092	1.575
Allo-HSCT	32	0.103	0.462	0.182	1.168
Auto-HSCT	6	0.459	0.473	0.065	3.436
Untreated	48	0.201	0.636	0.318	1.272
Hematological treatment - COVID-19					
Untreated	17	0.205			
During treatment	152	0.979	0.988	0.392	2.488
<1 month	48	0.790	1.145	0.423	3.105
<3 months	24	0.917	0.941	0.299	2.965
3-6 months	16	0.500	1.484	0.471	4.677
6-12 months	15	0.122	0.183	0.021	1.570
≥12 months	19	0.183	0.328	0.064	1.691
>24 months	20	0.144	0.294	0.057	1.518

Table 2. Continued.

	n	p	Hazards ratio	95% confidence interval for hazards ratio	
				Lower	Upper
Steroids					
No	219				
Yes	100	0.244	0.745	0.453	1.223
GCSF before COVID-19					
No	281				
Yes	55	0.037	1.687	1.033	2.756
Rituximab before COVID-19					
No	281				
Yes	57	0.357	1.275	0.760	2.139
IvIG before COVID-19					
No	296				
Yes	42	0.382	1.300	0.722	2.343
COVID-19 diagnosis method					
PCR	95	**0.000**			
PCR + CT	169	**0.000**	3.514	1.852	6.669
CT	74	**0.196**	1.674	0.767	3.653
COVID-19 severity					
Asymptomatic	44	**0.001**			
Mild	69	**0.122**	2.071	0.822	5.219
Moderate	101	0.371	1.517	0.609	3.778
Severe	69	**0.078**	2.283	0.912	5.718
Critically ill	55	**0.001**	4.418	1.817	10.744
Lymphopenia					
No	126				
Yes	194	**0.058**	1.563	0.985	2.480
Neutropenia					
No	162				
Yes	78	**0.000**	2.546	1.553	4.175
Hospitalization					
ICU admission	84	**0.000**			
Outpatient	89	**0.005**	5.479	1.668	17.996
Ward hospitalization	165	**0.000**	30.986	9.684	99.149
Intubation					
No	260				
Yes	78	0.000	21.883	13.360	35.844
COVID-19 treatment					
HCQ	28	0.131			
Favipiravir	130	0.953	0.976	0.428	2.226
HCQ + favipiravir	43	0.226	1.724	0.714	4.161
HCQ + azithromycin	42	0.910	0.946	0.360	2.488
HCQ + azithromycin + favipiravir	42	**0.188**	1.799	0.751	4.309
Prophylactic anticoagulant					
No	141				

Table 2. Continued.

	n	p	Hazards ratio	95% confidence interval for hazards ratio	
				Lower	Upper
Yes	197	0.238	0.778	0.513	1.180
Anticoagulant treatment					
No	215				
Yes	26	0.477	1.291	0.639	2.609
Life expectancy					
<3 months	10	**0.000**			
3-6 months	9	**0.002**	0.089	0.019	0.416
6-12 months	38	**0.001**	0.275	0.124	0.608
>12 months	208	**0.000**	0.075	0.036	0.158

Auto-HSCT: Autologous hematopoietic stem cell transplantation; allo-HSCT: allogeneic hematopoietic stem cell transplantation; GCSF: granulocyte colony-stimulating factor; IvIG: intravenous immune globulin; PCR: polymerase chain reaction; CT: computerized tomography; ICU: intensive care unit; HCQ: hydroxychloroquine.

Table 3. Multivariate analysis for mortality of the patients by Cox regression model (p<0.20 is statistically significant).

	$\hat{\beta}$	SE ($\hat{\beta}$)	p	HR	95% CI for HR	
					Lower	Upper
COVID treatment						
Favipiravir			0.037			
HCQ	1.608	0.537	**0.003**	**4.992**	1.741	14.313
HCQ + favipiravir	0.715	0.370	0.053	2.044	0.989	4.224
4= HCQ + azithromycin	0.744	0.440	0.091	2.104	0.888	4.981
5= HCQ + azithromycin + favipiravir	0.270	0.356	0.448	1.310	0.652	2.630
ICU admission	1.116	0.536	0.038	3.051	1.066	8.731
Intubation	2.484	0.472	0.000	11.987	4.756	30.210
Neutropenia	0.670	0.278	0.016	1.954	1.132	3.372
Life expectancy						
≥12 months			0.021			
<6 months	0.907	0.409	0.026	2.476	1.112	5.514
6-12 months	0.755	0.324	0.020	2.127	1.127	4.015
Hematological disease status (active disease)	0.880	0.320	0.006	2.410	1.287	4.512

HR: Hazards ratio; CI: confidence interval; HCQ: hydroxychloroquine; ICU: intensive care unit.

Thirteen percent of our patients were asymptomatic at diagnosis, a rate lower than that seen in the general population. The most prominent symptoms at diagnosis were fever, cough, and dyspnea. In an Italian study that included only adult patients, fever was reported in 75%, dyspnea in 51%, cough in 45%, and malaise in 39% of cases [15]. He et al. [18] observed more fever, cough, and dyspnea in hematology patients in comparison to healthcare professionals. Consistent with our findings, Piñana et al. [13] failed to show a difference in the symptoms of patients with different HSCT statuses. Hospitalization was required for 73% of our patients and 25% were admitted to the ICU, similar to the findings of other series [13,15]. In Italy, among patients with severe or critical COVID-19, those who were admitted to the ICU were younger and had a lower comorbidity index [15].

In our study, AML, NHL, and MM were the most frequent hematological malignancies, consistent with previous studies [16,17,19]. Chronic myeloproliferative neoplasms (CMPNs) were the least frequent in this patient population. In another Turkish study, in contrast to our data, besides NHL, myelodysplastic syndrome and myeloproliferative diseases were the most commonly diagnosed malignancies [12].

There are controversial results about the impact of the underlying hematological diagnosis on mortality in cases of COVID-19. We suggest that not the diagnosis but rather the disease status before COVID-19 is the significant factor. In population-based registry data analysis of 833 patients, besides age and comorbidities, the diagnosis of AML was found to be

related to the highest mortality rate, whereas patients with Philadelphia-negative CMPNs had the lowest risk [16]. Passamonti et al. [15] showed worse survival in cases of uncontrolled disease and among AML, NHL, and plasma cell dyscrasia patients. In a study that included only chronic lymphocytic leukemia (CLL) patients, 79% presented with severe COVID-19 findings. No difference was observed regarding the presence of three or more comorbidities or hypogammaglobulinemia [10]. Predictors of adverse outcome in MM patients were revealed as age, high-risk MM, renal disease, and suboptimal control of the disease [20,21].

Treatment schedules for various hematological malignancies have been suggested to be modified during the pandemic in order to reduce immunosuppression and the admission of patients to the hospital [22,23,24]. In our cohort, the data revealed that hematological malignancy treatments were modified for 21% of our patients before COVID-19 diagnosis. There are controversial data about the impact of hematological malignancy treatment on COVID-19 outcomes. Vijenthira et al. [17] could not show the impact of recent hematological malignancy treatment on the risk of death irrespective of the type of therapy. In cases of CLL, the severity of COVID-19 increased among untreated patients and those who were treated within the last year, but administration of Bruton kinase inhibitors exerted a protective effect against the virus [10]. In myeloma patients, no anti-myeloma treatments including transplantation were found to be associated with outcome [25]. We could not show a significant impact of either the type or the timing of the last hematological malignancy treatment on mortality in our study.

Study Limitations

In our study, the treatment schedules designed by Turkish health authorities were followed. Favipiravir was moved to the first line of treatment as a consequence of studies that could not show benefits of HCQ [25,26,27]. Patients treated with HCQ alone had 4.9-fold increased mortality risk compared to patients treated with favipiravir alone, while those treated with HCQ plus favipiravir had 2.0-fold increased risk and those treated with HCQ plus azithromycin had 2.1-fold increased risk. The group receiving HCQ plus favipiravir mainly included patients who had received HCQ initially and favipiravir with the further progression of pneumonia. In a multicenter randomized superiority trial, conventional therapy in combination with favipiravir or arbidol was investigated and favipiravir was found to be significantly superior to arbidol in terms of 7-day clinical recovery rates [28,29]. Data on the impact of these drugs in immunosuppressive patients are limited. The lowest mortality was observed in patients who received favipiravir alone in our study, which may be a valuable finding for further studies.

Conclusion

Hematological malignancy patients infected with SARS-CoV-2 have an increased risk of mortality. Having active hematological malignancy, neutropenia, admission to the ICU, and/or lower life expectancy related to the primary disease increases the mortality rates in these patients.

Ethics

Ethics Committee Approval: The study was approved by both the Turkish Ministry of Health and the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (22-Sep-2020/80350), as well as locally by the participating centers.

Informed Consent: Retrospective study.

Authorship Contributions

Medical Practice: S.C.B., G.C.S., İ.Y.H., F.H., N.A., M.B., L.A.K., S.K.T., H.S.G., B.B.A., U.D., F.C., V.Ö., E.G., Z.T.G., Z.N.Ö., S.D., M.B., İ.İ., U.Y., H.E.K., E.A., B.Y., Ü.A., Y.G.M., V.B., F.Ö., H.Ü.T., V.G., S.Ç., R.Ç., M.Y., P.T., Ö.Ç., H.A., C.S., M.C.A., O.K.Y., S.S., C.A., A.M.D., N.G., M.K., H.T., A.D., Z.A.Y., M.K.Y., S.S., İ.Y., H.S.B., T.A., S.M., V.E., L.K., O.İ., A.Z.B., Ö.G.S., A.A., M.Ö., G.G., Ş.Ü., Y.Y., R.D.K., G.H.Ö.; Concept: S.C.B., G.H.Ö., M.C.A., M.K.Y., Ş.Ü., N.A.; Design: S.C.B., G.H.Ö., M.C.A., M.K.Y., Ş.Ü., N.A.; Data Collection: S.C.B., G.C.S.; Analysis: S.C.B., G.C.S., Y.Y.; Literature Search: S.C.B.; Writing: S.C.B., G.H.Ö., M.C.A., M.K.Y., Ş.Ü., N.A.

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