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Original Article

Impact of COVID-19 on Outcomes of Patients with Hematologic Malignancies: A Multicenter, Retrospective Study

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Abstract. ***Objectives*: Patients with hematological malignancies have a high risk of mortality from coronavirus disease 2019 (COVID-19). This study aimed to investigate the impact of COVID-19 on mortality rates in patients with various hematological malignancies and to determine risk factors associated with all-cause mortality.**

***Methods*: A multicenter, observational retrospective analysis of patients with hematological malignancies infected with COVID-19 between July 2020 and December 2021 was performed. Demographic data, clinical characteristics, and laboratory parameters were recorded. Patients were grouped as non-survivors and survivors. All-cause mortality was the primary outcome of the study.**

***Results*: There were 569 patients with a median age of 59 years. Non-Hodgkin lymphoma (22.0%) and multiple myelomas (18.1%) were the two most frequent hematological malignancies. The all-cause mortality rate was 29.3%. The highest mortality rates were seen in patients with acute myeloid leukemia (44.3%), acute lymphoid leukemia (40.5%), and non-Hodgkin lymphoma (36.8%). The non-survivors were significantly older ($p<0.001$) and had more comorbidities ($p<0.05$). In addition, there were significantly more patients with low lymphocyte percentage ($p<0.001$), thrombocytopenia ($p<0.001$), and high CRP ($p<0.001$) in the non-survived patients. Age ≥ 65years ($p=0.017$), cardiac comorbidities ($p=0.041$), and continuation of ongoing active therapy for hematological cancer ($p<0.001$) were the independent risk factors for the prediction of mortality.**

***Conclusions*: In patients with hematological malignancies, coexistent COVID-19 leads to a higher mortality rate in elderly patients with more comorbidities. Acute myeloid and lymphoid leukemia**

and non-Hodgkin lymphoma have the highest mortality rates. Older age, cardiac diseases, and continuation of ongoing active therapy for hematological cancer are the independent risk factors for mortality in hematological malignancy patients with COVID-19.

Keywords: Hematologic malignancies, COVID-19 virus disease, Mortality.

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Introduction. Following the declaration of COVID-19 as a global pandemic in March 2020 by the World Health Organization, several studies reported that the corrupted immunity seen in patients with COVID-19 infection causes poor outcomes in patients using chemotherapy, radiotherapy, and systemic immunosuppressive treatment.[1,2] It has been reported that the overall mortality rate of cancer patients with COVID-19 infection could be as much as 40%.[1,3-5] Hematological disorders such as myeloproliferative disorders, leukemia, lymphomas, and myelodysplastic syndromes are among the most vulnerable cohorts for COVID-19, considering the worse outcomes.[2,4,6-8] The development of severe infections leads to worsening clinical outcomes in these patients.[2,9,10] Hematological malignancies have been responsible for more severe clinical conditions due to COVID-19 infection than solid organ tumors.[11]

In patients with hematological malignancies, such as leukemia, lymphoma, and myeloma, humoral and cellular immunosuppression can be a leading factor for the significantly increased mortality rates following COVID-19 infection.[1] The immunosuppressive treatment modalities like chemotherapeutic agents or autologous or allogeneic hematopoietic stem cell transplantation may aggravate this situation.[1,10] Although there is a significant concern about the increased morbidity and mortality risk due to COVID-19 infection, each hematological malignancy does not pose the same risk.[9,12]

Previous studies have documented various high-risk factors for mortality, including the type of malignancy, advanced disease, comorbidity, age > 60 years, need for intensive care unit admission, and recent systemic chemotherapy in hematological cancer patients infected with COVID-19.[2,5,9,13] Because of the methodological heterogeneity, the reported outcomes show remarkable variations. However, determination of the prognostic factors for mortality of COVID-19 in hematological malignancy patients based on real-time data may be used to perform impactful decisions.[14] That way, risk assessment and decision-making for effective supportive care would be possible.

This study aimed to evaluate the impact of COVID-19 on the mortality rates in patients with various hematological malignancies and determine the risk factors associated with all-cause mortality.

Materials and Methods.

Study. This study was a multicenter, observational retrospective analysis of patients with hematological malignancies who had been diagnosed with COVID-19 between July 2020 and December 2021. Fourteen tertiary centers specialized in hematological diseases throughout Turkey participated in the study. The local ethical committee approved the study (Institutional Review Board of Memorial Sisli Hospital, Istanbul, Turkey, Jul 28, 2020, Number: 003). The researchers agreed to apply the principles of the Helsinki Declaration. However, written consent could not be taken due to the study's retrospective design and the unanimity of data.

Patients. The patients with newly diagnosed hematological malignancies or ongoing treatment/follow-up were evaluated. The specific hematological malignancies were Hodgkin and non-Hodgkin lymphoma, multiple myeloma, leukemia (acute myeloid, acute and chronic lymphoid, chronic myeloid, chronic myelomonocytic, hairy cell), myelodysplastic syndromes, polycythemia vera, essential thrombocytopenia, myelofibrosis, histiocytosis, and mastocytosis.[7] The severity and the treatment modality (home isolation, outpatient, and inpatient treatment) of COVID-19 and the remission status of the hematological malignancies were not considered for the inclusion of the cases. The diagnosis of COVID-19 was performed and proved via a positive qualitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) on the nasal and oropharyngeal swab samples. The inclusion criteria were as follows: age over 18 years, diagnosis of hematological malignancy before COVID-19, and RT-PCR proved diagnosis of COVID-19. The patients with clinical findings suspicious of COVID-19

but without positive RT-PCR (clinical diagnosis) and presumed second primary cancers were excluded. A standardized protocol for diagnosing and treating COVID-19 based on the Turkish Ministry of Health Guidelines was used for all patients.[15]

Variables. A Microsoft Excel spreadsheet format was used in collecting and recording the related data. All centers entered their data into this predetermined sheet and electronically submitted it in an anonymized form to the study's principal investigator/data processor. The entries were checked for duplicated data.

Demographic data (age, sex) and clinical characteristics (admission symptoms, severe obesity, comorbidities) were recorded. The body mass index value equal to or higher than 40 kg/m^2 was defined as class III obesity.[16] The patients' presenting symptoms at the time of admission for COVID-19 were also searched and recorded. The type of baseline hematological cancer and past and ongoing treatment details were collected using the hospital information system of each center and the patient's medical files. The ongoing treatment was defined as having the treatment within 30 days before COVID-19 diagnosis.[5,17]

The laboratory parameters at the diagnosis of COVID-19 [leukocyte and platelet counts, lymphocyte percentage, C-reactive protein (CRP), and D-dimer] were investigated and categorized as low, normal, or high using each laboratory's lower and upper limits. In addition, we categorized the treatment modalities for hematological malignancies as conventional chemotherapy, targeted therapies (small-molecule inhibitors and monoclonal antibodies), immunotherapy (checkpoint inhibitors), and immunomodulatory.[14] Any change in the chemotherapy protocols associated with COVID-19 was noted.

The antiviral drugs, broad-spectrum antibiotics, antifungal and antimalarial medications, glucocorticoids, immune-modulating agents (Interleukin-6 and Janus kinase inhibitors), immune plasma therapy, and other medical modalities for COVID-19 were recorded. In addition, the adverse effects due to COVID-19 treatment were noted.

Statistical analysis. All-cause mortality was the primary outcome of this study; therefore, the patients were grouped as the non-survivors and survivors. We compared the groups regarding demographic and clinical characteristics; however, the factors impacting the development of all-cause mortality were also analyzed.

For descriptive statistics, mean ± standard deviation was used to present continuous data with normal distribution. A Median with minimum-maximum values was applied for continuous variables without normal distribution. Numbers and percentages were used for categorical variables. The Shapiro-Wilk and Kolmogorov-Smirnov tests analyzed the normal distribution of the numerical variables. Q-Q plots and histograms also checked the normal distribution pattern.

The Mann-Whitney U test compared two independent groups for the variables without normal distribution. The Pearson Chi-Square, Fisher's Exact, and Fisher Freeman Halton tests were used to compare the differences between categorical variables in 2x2 and RxC tables.

Binary logistic regression was performed to analyze the factors that impact the development of mortality. In addition, statistically or clinically significant factors regarding hematological malignancies in the univariate analysis were included in the multivariate analysis.

For statistical analysis, IBM SPSS Statistics V.21 was used. All statistical analyses determined the significance level (p-value) at 0.05.

Results. There were 569 patients in the study group with a median age of 59 years (18-91 years). There was a higher prevalence of elderly (≥65 years) (61.3%) and male patients (57.6%). Non-Hodgkin lymphoma and multiple myelomas were the two most common hematological malignancies in 125 (22.0%) and 103 patients (18.1%). Hypertension was the most frequent comorbidity (28.3%), followed by respiratory diseases (16.5%) and diabetes mellitus (16.0%) in the study group. The study cohort's baseline demographic and clinical characteristics are given in **Table 1**.

One hundred and sixty-seven patients did not survive, with an all-cause mortality rate of 29.3%. Considering all cases, 154 cases (92.2%) were COVID-related mortality. We hospitalized 410 patients (72.1%) for COVID-19 treatment. The hospitalization rate was significantly higher in the non-survived group (99.4% vs.60.7%, p<0.001). The highest mortality rates were seen in patients with acute myeloid leukemia (44.3%), acute lymphoid leukemia (40.5%), non-Hodgkin lymphoma (36.8%), and multiple myeloma (31.1%), and myelodysplastic syndromes (29.5%).

The comparison of the demographic and clinical characteristics of the patients revealed that the non-survivors were significantly older (median age 64 vs. 57 years, p<0.001) than the survivors. The proportion of patients aged 65 years or more was significantly higher in the non-survived group (p=0.001). Sex distribution was similar in the groups (p=0.780). Comparing the frequencies of the hematological malignancies revealed no significant difference in the survived and non-survived patients (p=0.781). The incidences of hypertension (p=0.019), respiratory diseases (p=0.047), cardiac diseases (p=0.003), and chronic renal failure (p=0.026) were significantly higher in patients who were non-survived. The survival and non-survived patients' clinical characteristics were similar (**Table 1**).

The distribution of the presenting symptoms is detailed in **Table 2**. Fever (76.3%), fatigue (58.3%),

Table 1. Demographic and clinical characteristics of the study group.

		Overall (n=569)	Survivors (n=402)	Non-survivors (n=167)	p
Age †, ‡		57.2 ±17.6 (59, 18-91)	55±18 (57, 18-91)	62±16 (64, 20-89)	<0.001
Age group §	<65 years	349 (61.3)	264 (65.7)	85 (50.9)	0.001
	≥65 years	220 (38.7)	138 (34.3)	82 (49.1)	
Sex §	Female	241 (42.4)	172 (42.8)	69 (41.3)	0.780
	Male	328 (57.6)	230 (57.2)	98 (58.7)	
Type of hematological cancer §	Non-Hodgkin lymphoma	125 (22)	79 (19.7)	46 (27.5)	0.781
	Multiple myeloma	103 (18.1)	71 (17.7)	32 (19.2)	
	AML	79 (13.9)	44 (10.9)	35 (21.0)	
	CLL	66 (11.6)	57 (14.2)	9 (5.4)	
	MDS	44 (7.7)	31 (7.7)	13 (7.8)	
	ALL	42 (7.4)	28 (7.0)	14 (8.4)	
	CML	27 (4.7)	23 (5.7)	4 (2.4)	
	Hodgkin lymphoma	25 (4.4)	21 (5.2)	4 (2.4)	
	Polycythemia vera	15 (2.6)	13 (3.2)	2 (1.2)	
	Essential thrombocythemia	14 (2.5)	10 (2.5)	4 (2.4)	
	Myelofibrosis	13 (2.3)	11 (2.7)	2 (1.2)	
	Others	16 (2.9)	14 (3.5)	2 (1.2)	
Obesity Class III §		8 (1.4)	6 (1.5)	2 (1.2)	1.0
Cancer §		7 (1.2)	3 (0.7)	4 (2.4)	0.203
Previous hematopoietic stem cell transplant §		4 (0.7)	3 (0.7)	1 (0.6)	1.0
Immune deficiency §		15 (2.6)	12 (3.0)	3 (1.8)	0.570
Comorbidities §	Hypertension	161 (28.3)	102 (25.4)	59 (35.3)	0.019
	Respiratory diseases	94 (16.5)	58 (14.4)	36 (21.6)	0.047
	Diabetes mellitus	91 (16.0)	59 (14.7)	32 (19.2)	0.209
	Cardiac diseases	79 (13.9)	44 (10.9)	35 (21.0)	0.003
	Chronic renal failure	26 (4.6)	13 (3.2)	13 (7.8)	0.026
	Cerebrovascular diseases	7 (1.2)	4 (1.0)	3 (1.8)	0.424
	Psychiatric disorders	13 (2.3)	7 (1.7)	6 (3.6)	0.217

†: mean ± standard deviation, ‡: median [min-max], §: n (%). Others: Hairy cell leukemia (n=6), histiocytosis (n=5), CMML (n=4), mastocytosis (n=1). AML: acute myeloid leukemia, CLL: chronic lymphoid leukemia, MDS: myelodysplastic syndromes, ALL: acute lymphoid leukemia, CML: chronic myeloid leukemia.

Table 2. COVID-19 symptoms and signs at diagnosis.

Admission symptoms §	Overall (n=569)	Survivors (n=402)	Non-survivors (n=167)	p
Fever	434 (76.3)	290 (72.1)	144 (86.2)	<0.001
Fatigue	332 (58.3)	223 (55.5)	109 (65.3)	0.032
Coughing	297 (52.3)	202 (50.2)	95 (56.9)	0.167
Myalgia	273 (48.0)	197 (49.0)	76 (45.5)	0.462
Dyspnea	269 (47.3)	155 (38.6)	114 (68.3)	<0.001
Arhtralgia	186 (32.7)	135 (33.6)	51 (30.5)	0.494
Headache	144 (25.3)	108 (26.9)	36 (21.6)	0.205
Sore throat	137 (24.1)	100 (24.9)	37 (22.2)	0.520
Irritability/confusion	105 (18.5)	62 (15.4)	43 (25.7)	0.006
Anosmia	69 (12.1)	46 (11.4)	23 (13.8)	0.481
Diarrhea-nausea/vomiting	47 (8.3)	27 (6.7)	20 (12.0)	0.045
Chest pain	45 (7.9)	21 (5.2)	24 (14.4)	0.001
Abdominal pain	19 (3.3)	11 (27.0)	8 (4.8)	0.211
Disgusia	14 (2.5)	10 (2.5)	4 (2.4)	1.0
Rinorrhea	2 (0.4)	2 (0.5)	0 (0)	1.0

§: n (%).

Table 3. Details of ongoing active therapy for hematologic cancer (n=329).

		Overall (n=329)	Survivors (n=214)	Non-survivors (n=115)	p
Type of therapy §	Conventional chemotherapy	225 (68.4)	139 (65.0)	86 (74.8)	0.082
	Targeted therapy	71 (21.6)	49 (22.9)	22 (19.1)	0.483
	Immunotherapy	93 (28.3)	57 (26.6)	36 (31.3)	0.372
	Monoclonal antibody	49 (14.9)	32 (15.0)	17 (14.8)	1.0
Impact of COVID on therapy §	On-therapy	31 (9.4)	26 (6.5)	5 (3.0)	0.028
	Off-therapy	299 (90.6)	187 (46.5)	52 (31.1)	

§: n (%).

Table 4. Laboratory investigations of the survived and non-survived patients.

		Survivors (n=402)	Non-survivors (n=167)	p
Leukocyte count (x10^{3}L) ‡		5120 (0.05-198200)	3800 (0-188000)	0.053
Leukocyte groups §	Low	122 (30.3)	73 (43.7)	0.461
	Normal	200 (49.8)	53 (31.7)	
	High	80 (19.9)	41 (24.6)	
Lymphocyte (%) ‡		15 (0-100)	10 (0-95)	<0.001
Lymphocyte groups §	Low	212 (52.7)	113 (67.7)	0.008
	Normal	190 (48.3)	54 (32.3)	
Platelet count (x10^{3}L) ‡		146000 (2-2760000)	40000 (23-993000)	<0.001
Platelet groups §	Low	196 (48.8)	141 (84.4)	<0.001
	Normal	206 (51.2)	26 (15.6)	
C-reactive protein (mg/dL) ‡		30 (1-257)	130 (2-560)	<0.001
C-reactive protein groups §	Normal	53 (13.1)	3 (1.8)	<0.001
	High	349 (86.9)	164 (98.2)	
D-dimer (ng/mL) ‡		939 (0-19000)	4200 (9-85000)	<0.001
D-dimer groups §	Normal	91 (22.6)	20 (12.0)	0.166
	High	311 (77.4)	174 (88)	

‡: median [min-max], §: n (%).

coughing (52.3%), myalgia (48.0%), and dyspnea (47.3%) were the most common symptoms at the admission of the patients. There were significant differences in the frequencies of the admission symptoms between the survivors and non-survivors. The non-survived patients more frequently have had fever (p<0.001), fatigue (p=0.032), dyspnea (p<0.001), irritability/confusion (p=0.006), gastrointestinal symptoms (p=0.045), and chest pain (p=0.001).

There were 329 patients (57.8%) in the study group with ongoing active oncological treatment. We found a significant difference considering the use of any treatment. The proportion of non-survived patients with on-therapy was significantly higher than those of the survived patients (58.9% vs.46.8%, p=0.001). The distribution of the oncological treatment modalities revealed no significant difference (**Table 3**). The oncological treatment was stopped in 299 patients (90.6%) due to COVID-19. The proportion of patients with ongoing therapy after COVID-19 was significantly lower in the non-survived patients (p=0.028).

The results of the laboratory investigations at the admission are given in **Table 4**. There were significant differences in leukocyte count, lymphocyte percentage, platelet count, CRP, and D-Dimer between the survived and non-survived patients. The median values of platelet counts and the percentage of lymphocytes were significantly lower in the non-survived patients (p<0.001 and p<0.001, respectively). In addition, we found significantly higher CRP and D-dimer values in the non-survived group (p<0.001 and p<0.001).

Table 5 presents the details of the treatment used for COVID-19. 77.9% of the patients received antiviral medications, and glucocorticoids were used in 299 patients (52.5%). Other details are summarized in **Table 5**.

We detected a total of 84 side effects in the study group. Nausea/vomiting, elevated liver enzymes, and neutropenia were the most frequent complications in 23, 18, and 11 patients. The development of side effects

Table 5. Summary of received treatments for COVID-19 infection.

Treatment modalities [§]		Overall (n=569)	Survivors (n=402)	Non-survivors (n=167)
Supportive treatment only		60 (10.5)	56 (13.9)	4 (2.4)
Antiviral drugs		443 (77.9)	307 (76.4)	136 (81.4)
Antifungal drugs		10 (1.8)	4 (1.0)	6 (3.6)
Antibacterial drugs		62 (10.9)	39 (9.7)	23 (13.8)
Antimalarial drugs		68 (12.0)	42 (10.4)	26 (15.6)
IL-6 inhibitors	Tocilizumab	28 (4.9)	11 (2.7)	17 (10.2)
JAK inhibitors	Tofasitinib, baricitinib, upadacitinib	12 (2.1)	8 (2.0)	4 (2.4)
Glucocorticoids		299 (52.5)	160 (39.8)	139 (8.2)
Intravenous immunglobulin		53 (9.3)	25 (6.2)	28 (16.8)
Convalescent immune plasma therapy		80 (14.1)	19 (4.7)	61 (36.5)
High-dose vitamin C		51 (9.0)	23 (5.7)	28 (16.8)
Anakinra		3 (0.5)	1 (0.2)	2 (1.2)

[§]: n (%).

Table 6. Binary logistic regression analysis of variables impacting on development of mortality.

	Odds ratio	95% Confidence interval		p
		Lower	Upper	
Age: <65 years vs. ≥65years	1.669	1.096	2.542	0.017
Respiratory diseases: Absent vs. present	1.517	0.927	2.484	0.097
Hypertension: Absent vs. present	1.209	0.777	1.880	0.400
Cardiac diseases: Absent vs. present	1.748	1.024	2.984	0.041
Chronic renal failure: Absent vs. present	1.940	0.838	4.494	0.122
Conventional chemotherapy: Absent vs. present	2.510	1.707	3.691	<0.001
Impact of COVID on therapy: Off-therapy/no chemotherapy vs. on-therapy	0.425	0.157	1.150	0.092

associated with COVID-19 treatment was more frequently seen in non-survived patients (p<0.001).

Binary logistic regression analysis revealed that age ≥ 65years (OR=1.669, CI 95%:1.096-2.542, p=0.017), cardiac diseases (OR=1.748, CI 95%:1.024-2.984, p=0.041), and the continuation of ongoing active therapy for hematological cancer (OR=2.510, CI 95%:1.707-3.691, p<0.001) were the independent risk factors for the prediction of mortality in hematological cancer patients with COVID-19 infection (**Table 6**).

Discussion. This study presented the outcomes of 569 COVID-19 patients treated due to hematological malignancies in 14 tertiary centers in Turkey. The all-cause mortality rate was 29.3% in the study group. The older patients with comorbidities were the most susceptible group to mortality. Older age, cardiac comorbidities, and continuation of ongoing active therapy for hematological cancer during the COVID-19 pandemic were the independent risk factors for mortality in the binary logistic regression model.

Several studies have focused on the outcomes of COVID-19 in hematological malignancy patients.[5,7,9,13] The European Hematology Association Survey (EPICOVIDEHA) published the outcomes of 3801 patients with hematological malignancy. Non-Hodgkin lymphoma, multiple myeloma, chronic lymphoid leukemia, acute myeloid leukemia, and myelodysplastic syndromes were more frequent than other diseases.[2] The frequency rank of the diseases in our study was almost similar to the findings of this cohort. In population-based data from the Turkey Ministry of Health, non-Hodgkin lymphoma was the most frequent malignancy seen in almost one-third of 1480 laboratory-confirmed COVID-19 patients.[18] Other studies documented many COVID-19 cases with non-Hodgkin lymphoma and multiple myeloma.[7,19] In the EPICOVIDEHA study, the incidence of acute myeloid leukemia was 12.5%, like 13.9% in our study. Although the authors thought this disease was a rare malignancy compared to the other types, Wood et al.[20] reported that acute leukemia was the most common type of cancer, followed by non-Hodgkin lymphoma in the ASH Research Collaborative COVID-19 Registry for Hematology. So, it should be kept in mind that the heterogeneity of the hematological diagnoses and their treatment modalities leads to difficulty in evaluating the outcomes.

In the studies investigating the mortality rate of

hematological malignancy patients after they were infected with COVID-19, the overall mortality rates were reported to be up to 40%.[2,5,7,9,17,21,22] Vijenthira et al.[4] reviewed the outcomes of 3377 patients with hematological malignancies and COVID-19 in a systematic review and meta-analysis. They found a higher mortality risk in older and hospitalized patients. Recent cancer treatment was not associated with mortality. Several authors used different time points to determine mortality rates ranging from 14 to 45 days leading to conflicting evaluations.[9,13,22] The overall mortality rate in the European Hematology Association Survey was 31.2%.[2] The current study's all-cause mortality rate was 29.3% during the in-hospital follow-up period. We think our mortality rate was similar to the previously published studies. Higher mortality rates have been explicitly detected in patients with severe COVID-19.[9] It has also been mentioned that COVID-19 caused higher mortality rates in patients with hematological cancer than those with solid tumors.[18] So, the methodological differences, different study date intervals regarding the various waves of the COVID-19 pandemic, and the evaluation periods for mortality should be considered when comparing the outcomes.[13] In light of these data, we may think that COVID-19 leads to higher mortality rates in patients with hematological malignancies.[2,5,7,14]

The possible association between the type of hematological cancer and mortality is another speculated issue. According to the European Survey, the highest mortality rates were detected in patients with acute myeloid leukemia and myelodysplastic syndromes.[2] In the UK Coronavirus Cancer Monitoring Project (UKCCMP), acute leukemia and myeloma had the highest mortality compared to the other hematological cancer types.[14] A subgroup analysis of hematological malignancies was not performed in Vijenthira's review paper.[4] However, the variances according to the type of malignancy have been studied by others.[6] The relatively lower or higher mortality rates have been reported in patients with lymphoma or acute myeloid leukemia infected with COVID-19.[2,6,14] In the current study, the five diseases with the highest mortality rates (acute myeloid leukemia, acute lymphoid leukemia, non-Hodgkin lymphoma, multiple myeloma, and MDS) were similar to the previous studies. There should be several explanations for the worst outcome and highest mortality rates in these specific hematological malignancies. Age, profound immunodeficiency status due to the underlying disease or its treatment, and any possible delay in the treatment have been speculated to explain the poor outcomes in these patients.[2,22]

The impact of hematological cancer treatment and its type is another conflicting issue. The features of treatment modalities for hematological malignancies are thought to be associated with the outcomes of COVID-19.[9] However, in the UKCCMP cohort, the authors found no association between cytotoxic chemotherapy, anti-CD 20 therapy, and mortality.[14] Although there were no significant differences in the frequencies of the cancer types and the ongoing active treatment modalities for hematological cancer between the survivors and non-survivors, the continuation of the ongoing active therapy for hematological cancer was one of the independent risk factors for mortality in our study. It is not easy to show the exact cause-and-effect relationships in a retrospective study. Besides, comparing the mortality rates in the different studies may be problematic regarding the patients' different demographic and clinical characteristics. So, prospective studies are needed to overcome the controversies between the studies,

Previous studies reported various risk factors for mortality. Older patients were more susceptible to mortality.[2,13,14,22] Although different cut-off values to define elderly people have been used, we may conclude that patients over 65 or 70 have higher mortality rates. In the present study, older age (≥65 years) was significantly associated with the development of mortality. We think that as the patient's age increases, comorbidities and other clinical situations might reflect the increased mortality risk more appropriately. Age, comorbidities, neutrophilia, lymphopenia, and high CRP were significant predictors of mortality in the UKCCMP cohort.[14] Thrombocytopenia was another significant factor associated with higher mortality risk.[24] However, others found no significant impact on mortality of age, sex, comorbidity, leukocyte, and lymphocyte counts.[7] In the current study, older age, cardiac comorbidities, and continuation of ongoing active therapy for hematological cancer were the independent risk factors for mortality in the multivariate model. It is unsurprising to obtain controversial findings due to the different patient and tumor characteristics.[22]

Different treatment modalities based on the severity and remission status of COVID-19 may impact the outcomes of patients with hematological malignancies. Although we did not use the severity grading of the infection, the inclusion criteria for COVID-19 infection were well-standardized based on the national treatment protocols. Besides, various factors, including the intensity of immunosuppressive treatment and the type of hematological cancer and its treatment modalities, might contribute to the differences in the outcomes of the patients infected with COVID-19.[9] Several authors also proposed that in their treatment's pre-induction, induction, and refractory phases, hematological malignancy patients might have weaker immunity than those in the maintenance phase.[23] Azhdari Tehrani et al. found that the pre-induction and induction phases of the treatment for hematological cancer were significantly associated with increased mortality for different hematological cancers.[23] A systematic review and meta-

analysis by Naimi et al. analyzed that the weakening of the immune system is a common consequence of anti-tumor therapies.[24] Previous studies showed that anti-tumor therapies during the first 14 days of COVID infection caused poor prognosis in cancer patients.[25,26] Avoidance of the treatment modalities leading to an immunosuppressive status has been recommended.[25] Although the types of ongoing active therapy for hematological cancer were not associated with the development of mortality in this patient group, the continuation of these therapies was the independent risk factor for mortality. We also could not discriminate between the different phases of the therapies. So, we think the treatment strategies for patients with hematological cancer should be tailored considering the current status of cancer and COVID infection simultaneously.

The patients' symptoms may show variations considering the underlying malignancy and COVID-19. The most frequent symptoms were fever, weakness, cough, and dyspnea.[7,13,20,22,27] We detected significant differences in the incidences of the admitting symptoms between the survivors and non-survivors. Fever, fatigue, dyspnea, irritability/confusion, gastrointestinal complaints, and chest pain were more frequently seen in the non-survivors. However, the triad of "malignancy, infection, and treatment" may lead to complexity in this patient group. So, we may not be sure of the exact role of these significant symptoms and signs of mortality.

The multicenter design and large sample size were the study's major strengths. Nevertheless, retrospective data analysis might be the main limitation of incomplete data. We could not evaluate the exact reasons for the mortality attributable and contributable to either hematological malignancy or COVID-19.[2] The clinical benefits of the treatment modalities for COVID-19 were not analyzed in this study, considering the study's retrospective nature. Besides, the side effects developed during the COVID-19 treatment would be due to the viral exposure that could not be differentiated using this retrospective data. Although a predetermined worksheet was used, incomplete data entry was considered possible.

In conclusion, coexistent COVID-19 was significantly associated with a higher mortality rate in elderly patients with more comorbidities in patients with hematological malignancies. Acute myeloid and lymphoid leukemia and non-Hodgkin lymphoma had the highest mortality rates. Older age, cardiac diseases, and continuation of ongoing active therapy were the independent risk factors for mortality in hematological malignancies with COVID-19.

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