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Hematologic malignancies and COVID-19 infection: A monocenter retrospective study

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Abstract

Introduction: Hematologic malignancies are risk factors for severe COVID-19 infection. Identification of risk factors correlated with mortality in these groups of patients is important in the assessment strategy. We studied the characteristics of patients with hematologic malignancies and COVID-19 and then analyzed the predictors of mortality.

Methods: Eligible for the analysis were hospitalized patients with hematologic malignancies and confirmed COVID-19 infection observed between January 2020 and March 2021. Patients were categorized based on the type of malignancy and phase of the treatment.

Results: A total of 194 COVID-19 infected patients with hematologic malignancies were included. The median age was 44 (15–81) years; 135 of them were males and 59 were females. Acute myeloid leukemia was the most frequent cancer type (43.8%). A total of 119 patients had severe COVID-19 and 61 patients were admitted to the intensive care unit. A total of 92 deaths occurred in all cases for an overall case-fatality rate of 47%. Male gender, preinduction and induction phase of the treatment, intensive care admission, low levels of oxygen saturation, Rhesus (RH) factor positivity, and higher fibrinogen level correlated with mortality.

Conclusion: This study focuses on the epidemiology, risk factors, outcomes, and predictors of mortality of COVID-19 among patients with hematologic malignancies. Patients with hematologic malignancies are at high risk of mortality.

KEYWORDS

cancer, case fatality rate, epidemiology, hematology, mortality, SARS-CoV-2

1 | INTRODUCTION

Patients with hematological malignancies are at high risk of developing severe infections including COVID-19 because of immunodeficiency status due to underlying malignancy and immunosuppressive treatments.[1] In these patients, there are several issues, including comorbidities and compromised immune status,[2] which can promote or interfere with the classical course of COVID-19 infection. These patients usually had one or several courses of chemotherapy that predispose them to pancytopenia. This phase of immunosuppression takes usually about 2–3 weeks, so viral infections and opportunistic infections can cause severe and life-threatening infections. On the other hand, COVID-19 promotes its infectivity through immune-related changes, especially cytokine release and also endothelial injury-related thrombotic reactions. Leukocyte and platelet counts are both decreased during chemotherapy,[3] so one of the hypotheses is that in patients with leukopenia and thrombocytopenia, cytokine release cannot promote inflammatory reactions and also endothelial injury.[4] In this study, we evaluated the characteristics of patients with hematologic malignancies and COVID-19 infection and analyzed the predictors of mortality.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

From January 2020 to March 2021, this single-center retrospective study was conducted in Taleghani Hospital, affiliated with Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran. This study was approved by the ethics committee of SBMU (IR.SBMU.MSP.REC.1400.001). Written informed consent was obtained from all the patients. Two investigators independently reviewed the data collection forms to verify data accuracy.

2.2 | Data collection

For each patient, demographic data, past medical history, comorbidities, chemotherapeutic regimens, and also the phase of the hematologic malignancy treatment, such as preinduction, induction, consolidation, maintenance, and refractoriness were recorded and analyzed. Eligible for the analysis were hospitalized adult patients with confirmed COVID-19 and hematologic malignancies. Patients with a previous or current history of allogeneic or autologous hematopoietic stem cell transplantation or the existence of other explanations for pneumonia were excluded. Patients included in this study had a computed tomography scan (CT scan) compatible with COVID-19 pneumonia.

Laboratory data for each patient included complete blood count (CBC), hepatic and renal function tests, inflammatory markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and fibrinogen. Also, clinical data such as oxygen (O_2) saturation, vital signs, and medications for the management of COVID-19 pneumonia were included.

In this study, there were patients with acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), Hodgkin and non-Hodgkin lymphoma (HL and NHL), multiple myeloma (MM), myelodysplastic syndromes (MDS), hairy cell leukemia (HCL), and hemophagocytic lymphohistiocytosis (HLH). We divided patients based on the treatment phase, namely preinduction, induction, consolidation, maintenance, and refractory. Preinduction refers to patients who were eligible to start chemotherapy; however, they had active COVID-19 disease and had not received any chemotherapeutic regimen. In the induction phase, patients had received chemotherapy; however, they became COVID-19 positive during the course of their chemotherapy or in the nadir phase of chemotherapy in which they had cytopenia. Consolidation refers to patients with AML, ALL in which patients were in postinduction phase of treatment. In the consolidation phase, patients usually were in remission for primary disease; however, if they had received chemotherapy recently, they had cytopenia. Maintenance refers to long-term chemotherapy in patients with a remission state in ALL, AML-M3, and also MM. Also, we have noted CLL and lymphoma patients' induction and maintenance phases. In these patients, induction refers to first-time chemotherapy and maintenance refers to second, third, and more rounds of chemotherapy; however, they were responsive to treatments and were not refractory. Refractory patients were referred to patients that were unresponsiveness to any type of chemotherapy and had active disease. Patients who had criteria for hospitalization were managed according to National Institutes Of Health (NIH) COVID-19 guidelines based on disease severity.

2.3 | Outcome assessment

Analyzed endpoints were frequency of COVID-19 among hematological patients, the severity of disease based on ICU admission, which therapies for COVID-19 they had received, assess preexisting comorbidities, outcomes of these patients, and length of hospital stay. Duration of hospitalization for COVID-19 infection was defined as the onset of clinical symptoms or the day with positive polymerase chain reaction (PCR) until the time of discharge from COVID-19 service. The case-fatality rate was defined as the proportion of deaths for any cause compared to the total number of patients.

2.4 | Statistical analysis

Data were analyzed using the SPSS version 21.0 Statistical package (SPSS Inc.). Quantitative and qualitative data were presented as mean ± SD, median (minimum–maximum), and frequency

(percentage). Data preparation were done based on the study protocol. Descriptive statistics were applied to explore and describe the data. The normality of continuous data was evaluated using the Kolmogorov–Smirnov test. We used the independent sample *t*-test and χ^2 (or fisher's exact test) for comparison between alive and deceased patients. Mann–Whitney nonparametric tests were applied for biomarkers analysis between two groups.

A binary logistic regression model was fitted to identify the associated parameters with mortality. Variables were selected primarily based on a theoretical conceptual framework predefined in the study proposal. Among the independent factors, which were candidates to be entered into the multivariable modeling, those with a *p* value of <0.3 were selected and entered into the statistical modeling procedure. A backward Wald elimination technique was applied for modeling. Accordingly, the odds ratio (OR) and its 95% confidence interval (CI) were estimated for each factor associated with mortality. Type I error was predefined at 0.05.

3 | RESULTS

In this single-center retrospective study, we included 194 hospitalized patients with hematological malignancies and COVID-19 infection. Demographic and clinical characteristics were shown in (Table 1). Chemotherapeutic regimens and mortality rates of each cancer type were shown in (Table 2) and an analysis of the variables was shown in (Table 3).

TABLE 1 Demographic and clinical characteristics based on gender of patients.

Characteristic	All (*n* = 194)	Male (*n* = 135)	Female (*n* = 59)	*p* Value
Age (years)				
Mean ± SD	43.78 ± 15.25	43.98 ± 15.05	43.32 ± 15.80	0.781
Median (min-max)	44 (15–81)	47 (15–68)	44 (20–81)	
Past medical history, n (%)				
HTN	21 (10.8)	10 (7.4)	11 (18.6)	**0.020**
DM	26 (13.4)	13 (9.6)	13 (22.0)	**0.020**
IHD	11 (5.7)	11(8.1)	0 (0.0)	**0.024**
Habitual history, n (%)				
Smoking	35 (18.0)	33 (24.4)	2 (3.4)	**<0.001**
Alcohol consumption	0 (0.0)	0 (0.0)	0 (0.0)	-
Hematological cancer type, n (%)				
ALL	31 (16.0)	17 (12.6)	14 (23.7)	**0.045**
AML (NM3)	85 (43.8)	56 (41.5)	29 (49.2)	
AML (M3)	16 (8.2)	16 (11.9)	0 (0.0)	
HL AND NHL	31 (16.0)	23 (17.0)	8 (13.6)	
MM	16 (8.2)	12 (8.9)	4 (6.8)	
OTHER	15 (7.7)	11 (8.1)	4 (6.8)	
Phase of treatment, n (%)				
Preinduction	45 (23.2)	30 (22.2)	15 (25.4)	**0.002**
Induction	82 (42.3)	52 (38.5)	30 (50.8)	
Consolidation	11 (5.7)	11 (8.1)	0 (0.0)	
Maintenance	21 (10.8)	21 (15.6)	0 (0.0)	
Refractory	35 (18.0)	21 (15.6)	14 (23.7)	
ICU admission, n (%)				
Yes	61 (31.4)	43 (31.9)	18 (30.5)	0.853

Note: **p* Values resulted from independent samples *t*-test and χ^2 (or Fisher's exact test) for continuous and categorical variables, respectively. Bold values Indicate statistical significance.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease.

Table 4 shows logistic regression models. The strongest predictor of reporting death was ICU admission, which had an OR of 23.35 and showed that patients who were admitted to ICU are 23.35 times more likely to die than others (OR = 23.35, 95% CI: [8.024–67.945]). Females are 3.48 times more likely to die than males (OR = 3.477, 95% CI: [1.528–7.909]). In addition, patients with induction treatment had lower odds of death than those alive (OR = 0.210, 95% CI: [0.074–0.598]). In contrast, severe cases had upper odds of death than those alive (OR = 1.887, 95% CI: [0.892–3.995]). Age was associated with an increased likelihood of exhibiting mortality. On the contrary, length of hospital stay was associated with a decrease in mortality.

In Table 5, the main laboratory parameters of these patients are illustrated. As shown, ESR in ALL patients and others (MDS, HLH, and HCL), LDH in CLL patients, fibrinogen in patients with CLL, lymphoma, and MM, ferritin in MM were statistically significant with mortality. Also, we concluded that a higher fibrinogen level was statistically significant with a higher mortality rate ($p = 0.002$). ESR, LDH, and fibrinogen were significantly associated with lower oxygen saturation ($p = 0.031$, 0.005, 0.00, respectively).

TABLE 2 Mortality rate attributed to COVID-19 according to cancer types, phases, and types of chemotherapy.

Cancer types	Phases	Therapies	Mortality rate Per phase	Total
ALL (31 cases)	Preinduction	***(4 cases)	0/4 (0%)	51.6%
	Induction	Hyper CVAD[a] (5 cases)	8/19 (42.1%)	
		CALGB[b] (14 cases)		
	Consolidation	None	-	
	Maintenance	None	-	
	Refractory	EMA[c] (3 cases)	8/8 (100%)	
		FLAG[d] (5 cases)		
AML-nonM3 (69 cases)	Preinduction	***(15 cases)	4/15 (26.7%)	47.8%
	Induction	7 + 3[e] (33 cases)	19/33 (57.6%)	
	Consolidation	HiDAC[f] (7 cases)	0/11 (0%)	
		Cytarabine SQ (4 cases)		
	Refractory	EMA[c] (10 cases)	10/10 (100%)	
AML-M3 (16 cases)	Preinduction	***(5 cases)	5/5 (100%)	81.2%
	Induction	ATRA[g] + Idarubicin 5 cases ATRA + arsenic + Idarubicin (3 cases)	5/8 (62.5%)	
	Consolidation	None	-	
	Maintenance	ATRA (3 cases)	3/3 (100%)	
	Refractory	None	-	
CLL (16 cases)	Preinduction	None	-	62.5%
	Induction[h]	FRC[i] (1 case)	0/1 (0%)	
	Maintenance[j]	RB[k] (8 cases) FRC (4 cases)	10/12 (83.3%)	

TABLE 2 (Continued)

Cancer types	Phases	Therapies	Mortality rate Per phase	Total
	Refractory[l]	Off treatment	0/3	
		(3 cases)	(0%)	
Hodgkin lymphoma (13 cases)	Preinduction	*** (3 cases)	0/3	0%
			(0%)	
	Induction[m]	ABVD[n] (4 cases)	0/4	
			(0%)	
	Maintenance[o]	None	-	
	Refractory	Nivolumab[p]	0/6	
		(4 cases)		
		GEMOX[q]	(0%)	
		(2 cases)		
Non-Hodgkin lymphoma (18 cases)	Preinduction	*** (5 cases)	0/5	61.7%
			(0%)	
	Induction[m]	R-CHOP[r] (6 cases)	4/6	
			(66.7%)	
	Maintenance[o]	R-CHOP (4 cases)	4/4	
			(100%)	
	Refractory	R-ICE[s] + Nivolumab	3/3	
			(100%)	
Multiple myeloma (16 cases)	Preinduction	*** (5 cases)	5/5	31.25%
			(100%)	
	Induction	VCD[t] (1 case)	0/4	
		VRD[u] (3 cases)	(0%)	
	Maintenance	VD[v] (2 cases)	0/2	
			(0%)	
	Refractory	VCD[t] (4 cases)	0/5	
		VD[v] (1 case)	(0%)	
MDS (4 cases)	Preinduction[w]	*** (2 cases)	2/2	100%
			(100%)	
	Induction[x]	7 + 3[e] (2 cases)	2/2	
			(100%)	
	Maintenance	-	-	
	Refractory	-	-	
Hairy-cell leukemia (7 cases)	Preinduction	*** (4 cases)	0/4	0%
			(0%)	
	Induction	Cladirabine (3 cases)	0/3	
			(0%)	
	Maintenance	-	-	
	Refractory	-	-	

(Continues)

TABLE 2 (Continued)

Cancer types	Phases	Therapies	Mortality rate Per phase	Total
Hemophagocytic lymphohistiocytosis (4 cases)	Preinduction	*** (3 cases)	0/3 (0%)	0%
	Induction	Etoposide (1 case)	0/1 (0%)	
	Maintenance	-	-	
	Refractory	-	-	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; MS, myelodysplastic syndromes.
***No chemotherapy regimen were recieved.
[a]Hyper CVAD (cyclophosphamide + mesna + doxorubicin + dexamethasone + vincristine alternating with high dose cytarabine and high dose MTX).
[b]CALGB 9911 (cyclophosphamide + mesna + daunorubicin + vincristine as induction treatment).
[c]EMA (etoposide + mitoxantrone + cytarabine).
[d]FLAG (fludarabine + cytarabine + G-CSF).
[e]7 + 3 (7 days cytarabine + 3 days anthracycline).
[f]HiDAC (high dose cytarabine on one alternate day for 3 days).
[g]ATRA (type of retinoic acid).
[h]Induction in CLL is considered the first-time chemotherapy in patients with CLL.
[i]FRC (fludarabine + rituximab + cyclophosphamide).
[j]Maintenance in CLL is considered second time or third or more chemotherapy.
[k]RB (rituximab + bendamustine).
[l]Refractory in CLL is considered patients who are unresponsive to chemotherapy or targeted therapies.
[m]Induction in lymphoma is the first-time chemotherapy in this table.
[n]ABVD (adriamycin + bleomycin + vinblastine + dacarbazine).
[o]Maintenance in lymphoma refers to second or more times chemotherapy.
[p]Nivolumab (a PD-1 targeted therapy).
[q]GEMOX (gemcitabine + oxaliplatin).
[r]R-CHOP (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone).
[s]R-ICE (rituximab + ifosfamide + carboplatin + etoposide).
[t]VCD (Bortezomib + cyclophosphamide + dexamethasone)
[u]VRD (bortezomib + lenalidomide + dexamethasone).
[v]VD (bortezomib + dexamethasone).
[w]Preinduction in patients with MDS refers to patients who were indicated for chemotherapy (MDS with excess blast type) but did not receive chemotherapy.
[x]Induction in patients with MDS refers to patients who were indicated for chemotherapy (MDS with excess blast type).

4 | DISCUSSION

Cancer is a severe underlying condition besides other known risk factors for COVID-19 infection. Also, patients with malignancy almost have other risk factors, especially older age and chronic diseases. Besides other risk factors, the state of the current malignancy, recent administration of myeloablative chemotherapy or immunosuppressive therapies, recent surgery, and also radiotherapy, altogether have an impact on the possible increase in infectivity and severity of COVID-19 disease.[5] Also, patients with malignancy need to be regularly visited by their physicians, so they are more prone to contact COVID-19 patients and facilities.[6] Hematological malignancies rather than malignant solid tumors, almost always had chemotherapeutic options that affect the bone marrow environment and also the productivity of stem cells. So these patients had longer episodes of immunosuppression than patients with malignant solid tumors. Moreover, in hematological malignancies, patients who are in preinduction, induction, and refractory phases, have weak immunity.[7] So, the exact phase of treatment besides cytopenia significantly impacts the outcome of infections and also COVID-19 infection.

There are several studies that point to these malignancies-related issues. In a study published in Lancet in May 2020, 928 patients were studied. Thirteen percent had died in 30 days of COVID-19 diagnosis. They found several risk factors that increase the 30-day mortality after adjustment for a multivariate model, such as higher age, male sex, smoking, cancer status and response to anticancer therapy, performance status, and comorbidities. In this study, patients who were progressive in their

TABLE 3 Univariable Analysis of association between all parameters and mortality.

Characteristic	Alive (*n* = 102)	Deceased (*n* = 92)	OR	95% CI	*p* Value[a]
Age, years			1.011	0.993–1.030	0.239
Mean (SD)	42.56 (14.9)	45.14 (15.6)			
Gender, n (%)					
Male (ref)	78 (57.8)	57 (42.2)	1.996	1.072–3.716	**0.029**
Female	24 (40.7)	35 (59.3)			
History of HTN, n (%)					
Positive	10 (47.6)	11 (52.4)	1.249	0.504–3.094	0.630
Negative (ref)	92 (53.2)	81 (46.8)			
History of DM, n (%)					
Positive	15 (57.7)	11 (42.3)	0.788	0.342–1.815	0.575
Negative (ref)	87 (51.8)	81 (48.2)			
History of IHD, n (%)					
Positive	7 (63.6)	4 (36.4)	0.617	0.175–2.18	0.453
Negative (ref)	95 (51.9)	88 (48.1)			
History of smoking, n (%)					
Positive	23 (65.7)	12 (34.3)	0.515	0.240–1.106	0.089
Negative (ref)	79 (49.7)	80 (50.3)			
Cancer types, n (%)					
AML	39 (45.9)	46 (54.1)	1.615	0.912–2.860	0.100
Others (ref)	63 (57.8)	46 (42.2)			
Phase of treatment, n (%)					
Induction	29 (64.4)	16 (35.6)	0.530	0.266–1.056	0.071
Others (ref)	73 (49.0)	76 (51.0)			
Blood groups					
O	36 (45.0)	44 (55.0)	1.681	0.944–2991	0.078
Others (ref)	66 (57.9)	48 (42.1)			
RH					
Negative(ref)	20 (39.2)	31 (60.8)	0.480	0.250–0.922	**0.027**
Positive	82 (57.3)	61 (42.7)			
CT scan involvement					
<50% (ref)	49 (53.3)	43 (46.7)	1.054	0.599–1.853	0.860
≥50%	53 (52)	49 (48)			
O_2 saturation at admission					
≥94% (moderate) (ref)	54 (72)	21 (28)	3.804	2.040–7.092	**<0.001**
<94% (severe)	48 (40.3)	71 (59.7)			
Length of hospital stay, day					
Mean (SD)	8.26 (5.8)	9.36 (4.9)	1.039	0.984–1.095	0.166
ICU admission					
Yes	10 (16.4)	51 (83.6)	11.44	5.292–24.749	**<0.001**
No(ref)	92 (69.2)	41 (30.8)			

Note: Bold values Indicate statistical significance.

Abbreviation: CI, confidence interval; OR, odds ratio; Ref, reference group; RH, Rhesus (RH) factor.

[a]*p* Values resulted from independent samples *t*-test and χ^2 (or Fisher's exact test) for continuous and categorical variables, respectively.

cancer had a higher rate of mortality; however, recent cytotoxic chemotherapy did not have any impact on the outcome of these patients.[8] In a survey conducted by Lee et al.,[9] those with cancers had higher age, higher comorbidities, and also majority were males and had more obesity. When they are older than 65 or when they are males rather than females, they have more positive PCR test. Milano et al.[10] showed that patients with a history of malignancy had 24% mortality rather than 3% mortality in patients without it. Also, these patients shed viral particles longer than others.

The overall mortality rate in this study was 47%, which is related especially to the preinduction and induction phases of the treatment. However, patients with hematologic malignancies receive several chemotherapeutic agents, and also these patients, especially those who are not in the remission phase, are rendered to opportunistic infection and also COVID-19; hence, along with the several studies that we have mentioned in this section, it seems that the mortality for this group of patients with COVID-19 is much higher rather than other groups of patients.

The limitation of this study was the study sample size. This was a single-center retrospective study and participants were from one center rather than multiple centers. With a larger sample size, some factors, especially laboratory findings, would be helpful to better evaluate and correlate disease severity and mortality.

TABLE 4 Logistic regression of related risk factors in patients with confirmed COVID-19 and hematologic malignancies.

Characteristic	*β*	SE	OR	95% CI	*p* Value
Age, years	0.029	0.013	1. 029	1.003–1.055	**0.028**
Gender	1.246	0.419	3.477	1.528–7.909	**0.003**
Phase of treatment	−1.562	0.535	0.210	0.074–0.598	**0.003**
O_2 saturation at admission	0.635	0.383	1.887	0.892–3.995	0.097
Length of hospital stay, day	−0.114	0.043	0.892	0.820–0.971	**0.009**
ICU admission	3.151	0.545	23.35	8.024–67.945	**<0.001**

Note: Bold values Indicate statistical significance.

Abbreviations: *β*, estimated coefficient; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

TABLE 5 Comparison of patients with COVID-19 by mortality status and serum biomarkers.

		Median (min–max)				
Cancer types		CRP	ESR	Ferritin	LDH	Fibrinogen
ALL	Alive	33 (6–63)	51 (2–89)	345 (200–450)	471 (331–3177)	245 (136–531)
	Deceased	30 (6–75)	63 (15–93)	364 (102–535)	869 (270–3694)	285 (120–486)
	p Value	0.84	**0.09**	0.27	0.41	0.66
AML	Alive	19 (2–90)	50 (9–125)	389 (65–753)	933 (274–2988)	235 (105–690)
	Deceased	20.5 (2–110)	38.5 (6–93)	397 (98–834)	739.5 (190–2712)	240 (110–593)
	p Value	0.97	0.19	0.61	0.36	0.47
CLL	Alive	28 (8–73)	34.5 (18–57)	276 (264–630)	1402 (809–2586)	205 (110–260)
	Deceased	13 (5–67)	33.5 (18–63)	424 (300–495)	625 (354–915)	305 (182–575)
	p Value	0.35	0.66	0.27	**0.01**	**0.02**
Lymphoma	Alive	13.5 (3–93)	40 (12–86)	349 (210–705)	630 (302–1340)	184 (76–440)
	Deceased	26.3 (4–50)	33 (14–81)	385 (192–855)	700 (356–3030)	275 (156–403)
	p Value	0.71	0.88	0.47	0.38	**0.03**
MM	Alive	30 (2–85)	43 (4–111)	325 (102–488)	780 (306–1153)	260 (100–379)
	Deceased	7.5 (5–73)	53 (39–86)	400 (351–590)	413 (413–939)	380 (170–459)
	p Value	0.25	0.46	**0.07**	0.12	**0.03**
Others	Alive	31 (3–69)	40 (26–85)	440 (269–610)	870 (598–3759)	200 (165–293)
	Deceased	30 (10–65)	11 (4–45)	443 (180–676)	975 (680–1356)	258 (196–369)
	p Value	0.94	**0.03**	0.99	0.79	0.19

Note: Bold values Indicate statistical significance.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; MM, multiple myeloma.

5 | CONCLUSION

This study focuses on the epidemiology, risk factors, outcomes, and predictors of mortality of COVID-19 among patients with hematologic malignancies. These groups of patients have a high mortality rate. Male gender, preinduction and induction phase, ICU admission, low levels of oxygen saturation at the onset of infection, Rhesus (RH) factor positivity, and higher fibrinogen levels were associated with mortality.

AUTHOR CONTRIBUTIONS

Hamed Azhdari Tehrani: Conceptualization; investigation; methodology; writing—original draft. **Soodeh Ramezaninejad**: Conceptualization; methodology. **Masoud Mardani** and **Shervin Shokouhi**: Conceptualization; supervision; writing—review and editing. **Maryam Darnahal**: Conceptualization; methodology. **Atousa Hakamifard**: Conceptualization; investigation; methodology; supervision; writing—review and editing.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

TRANSPARENCY STATEMENT

The lead author (manuscript guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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