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RESEARCH ARTICLE

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The outcome of COVID-19 in patients with hematological malignancy

Tugce N. Yigenoglu MD[1] | Naim Ata[2] | Fevzi Altuntas[1] | Semih Bascı MD[1] | Mehmet Sinan Dal[1] | Serdal Korkmaz[3] | Sinem Namdaroglu[4] | Abdulkadir Basturk[5] | Tuba Hacıbekiroglu[6] | Mehmet H. Dogu[7] | İlhami Berber[8] | Kursat Dal[9] | Mehmet A. Erkurt[8] | Burhan Turgut[10] | Mustafa Mahir Ulgu[11] | Osman Celik MD[12] | Ersan Imrat[11] | Suayip Birinci MD[13]

[1]Department of Hematology and Bone Marrow Transplantation Center, Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey

[2]Department of Strategy Development, Republic of Turkey, Ministry of Health, Ankara, Turkey

[3]Department of Hematology, Kayseri Training and Research Hospital, University of Health Sciences, Kayseri, Turkey

[4]Department of Hematology, Bozyaka Training and Research Hospital, University of Health Sciences, Izmir, Turkey

[5]Department of Internal Medicine, School of Medicine, Division of Hematology, Selcuk University, Konya, Turkey

[6]Department of Internal Medicine, School of Medicine, Division of Hematology, Sakarya University, Sakarya, Turkey

[7]Department of Hematology, İstanbul Training and Research Hospital, İstanbul, Turkey

[8]Department of Internal Medicine, School of Medicine, Division of Hematology, Inonu University, Malatya, Turkey

[9]Department of Internal Medicine, Kecioren Training and Research Hospital, Ankara, Turkey

[10]Department of Internal Medicine, School of Medicine, Division of Hematology, Namık Kemal University, Tekirdağ, Turkey

[11]General Directorate of Health Information Systems, Republic of Turkey, Ministry of Health, Ankara, Turkey

[12]Public Hospitals General Directorate, Republic of Turkey, Ministry of Health, Ankara, Turkey

[13]Republic of Turkey, Ministry of Health, Ankara, Turkey

Correspondence
Tugce N. Yigenoglu, MD, Department of Hematology and Bone Marrow Transplantation Center, Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey.
Email: dr.nuryigenoglu@gmail.com

Abstract

In this study, we aim to report the outcomes for COVID-19 in patients with hematological malignancy in Turkey. Data from laboratory-confirmed 188 897 COVID-19 patients diagnosed between 11 March 2020 and 22 June 2020 included in the Republic of Turkey, Ministry of Health database were analyzed retrospectively. All COVID-19 patients with hematological malignancy (n = 740) were included in the study and an age, sex, and comorbidity-matched cohort of COVID-19 patients without cancer (n = 740) at a 1:1 ratio was used for comparison. Non-Hodgkin lymphoma (30.1%), myelodysplastic syndrome (19.7%), myeloproliferative neoplasm (15.7%) were the most common hematological malignancies. The rates of severe and critical disease were significantly higher in patients with hematological malignancy compared with patients without cancer ($P = .001$). The rates of hospital and intensive care unit (ICU) admission were higher in patients with hematological malignancy compared with

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DM, diabetes mellitus; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; HT, hypertension; ICU, intensive care unit; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm; MV, mechanical ventilation; NHL, non-Hodgkin lymphoma.

the patients without cancer ($P = .023$, $P = .001$, respectively). The length of hospital stay and ICU stay was similar between groups ($P = .7$, $P = .3$, retrospectively). The rate of mechanical ventilation (MV) support was higher in patients with hematological malignancy compared with the control group ($P = .001$). The case fatality rate was 13.8% in patients with hematological malignancy, and it was 6.8% in the control group ($P = .001$). This study reveals that there is an increased risk of COVID-19-related serious events (ICU admission, MV support, or death) in patients with hematological malignancy compared with COVID-19 patients without cancer and confirms the high vulnerability of patients with hematological malignancy in the current pandemic.

KEYWORDS

COVID-19, hematological malignancy, SARS-CoV-2

1 | INTRODUCTION

Most of the coronaviruses (CoVs) are pathogenic to humans, but they rarely cause severe infections. However, in the last two decades, two CoVs have caused severe infections in humans: the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV).[1-3] At the end of 2019, a cluster of pneumonia patients of an unidentified cause was observed in Wuhan, China. After the genetic analysis of the virus, it was understood that these pneumonia cases were caused by the 2019 novel coronavirus (2019-nCoV), which was later named SARS-CoV-2.[4,5] The new disease presented with similar clinical findings to SARS-CoV and MERS-CoV, such as fever, dyspnea, and multilobed lesions in the computed tomography of the thorax. The disease caused by SARS-CoV-2 was named as COVID-19, by the World Health Organization (WHO). It was declared a pandemic, on 11 March 2020.[6,7]

Older age and comorbidities such as diabetes, hypertension, or cardiac disease are risk factors for a more aggressive clinical course in patients with COVID-19.[8] In addition, in a previous report, it was reported that 39% of COVID-19 patients with cancer had severe events such as intensive care unit (ICU) admission, need of mechanical ventilation (MV) and death during the COVID-19 course, whereas only 8% of COVID-19 patients without cancer had those severe events. The more aggressive clinical course of cancer patients with COVID-19 may be attributed to immunosuppression due to the chemotherapies, radiotherapy, or immunosuppressive drugs they are receiving or increased coexisting medical conditions or lung invasion by the primary tumor itself or metastasis. Patients with hematological malignancies may be more vulnerable than patients with solid tumors because of the immune system dysfunction that they have.[9,10] However, there are only a limited number of studies about COVID-19 in patients with hematological malignancy, and most of these data are based on case series. Therefore, in this study, we aim to report the outcome of COVID-19 in patients with hematological malignancies treated in Turkey.

2 | MATERIALS AND METHODS

Ethics committee approval was obtained from the Republic of Turkey, Ministry of Health.

2.1 | Patients

The data of laboratory-confirmed 188 897 COVID-19 patients diagnosed between 11 March 2020 and 22 June 2020 included in the Republic of Turkey, Ministry of Health database were analyzed retrospectively. All COVID-19 patients with hematological malignancy (n = 740) were included in the study and age, sex, and comorbidity-matched COVID-19 patients without cancer (n = 740) at 1:1 ratio was used for comparison.

2.2 | Laboratory analysis

Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 RNA were performed using nasopharyngeal swabs. Total nucleic acid extraction of nasopharyngeal swabs of viral isolates was performed using a Biospeedy and Coyote extraction system (Bioeksen Ltd and Coyote Bioscience Ltd). RT-PCR assays for SARS-CoV-2 RNA detection were performed using a Biospeedy COVID-19 RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey), a Direct Detect SARS-Cov2 Detection Kit (Coyote Bioscience Co Ltd, China), a Probe RT-PCR Kit in a LightCycler 960 real-time PCR system (Roche, Basel, Switzerland), a CFX96 Touch RT-PCR Detection System (Bio-Rad, CA), and a Rotor-Gene Q (Qiagen, Hilden, Germany).

2.3 | Disease severity

Severe COVID-19 was defined as the existence of dyspnea, blood oxygen saturation less than or equal to 93%, $PaO_2/FiO_2 < 300$ and

greater than 50% progression in lung infiltrates within 24 to 48 hours. Critical COVID-19 was defined as the existence of respiratory failure, septic shock, and/or multiple organ dysfunctions.[10]

2.4 | Statistical analysis

Data analysis was performed using IBM SPSS v26 software. Variables were assessed for normal distribution with the Kolmogorov-Smirnov test. Categorical data were presented as number-percentages, and numerical data were presented as the median, minimum, and maximum. Differences between categorical variables were analyzed with the χ^2 test, and numeric variables were compared with the Mann-Whitney *U* test.

3 | RESULTS

3.1 | Patients

In total, there were 1480 laboratory-confirmed COVID-19 patients; 740 of them had hematological malignancy and the other 740 comprised the age, sex, and comorbidity-matched cohort. The demographic and clinical characteristics of all patients in the study are given in Table 1.

The number and percentages of the hematological malignancies in COVID-19 patients were as follows: 223 (30.1%) non-Hodgkin lymphoma (NHL), 116 (15.7%) myeloproliferative neoplasm (MPN), 146 (19.7%) myelodysplastic syndrome (MDS), 77 (10.4%) multiple myeloma (MM), 54 (7.3%) chronic lymphocytic leukemia (CLL), 40 (5.4%) acute myeloid leukemia (AML), 30 (4.1%) chronic myeloid leukemia (CML), 27 (3.6%) Hodgkin's lymphoma (HL), 18 (2.4%) acute lymphoblastic leukemia (ALL), and 9 (1.2%) hairy cell leukemia (HCL).

Hypertension was the most common comorbid disease in COVID-19 patients with hematological malignancy and was observed in 51.2% of the patients. The rate of lopinavir/ritonavir use was higher in patients with hematological malignancy compared with the control group ($P = .013$) (Table 1).

TABLE 1 Demographic and clinical characteristics of the patients

	Patients with hematological malignancy (n = 740)	Patients without cancer (n = 740)	*P* value
Sex			
Male, n (%)	397 (53.6)	400 (54.1)	.9
Female, n (%)	343 (46.4)	340 (45.9)	
Age, y	56 (18-94)	56 (18-87)	
Comorbidity, n (%)			
Hypertension	379 (51.2)	378 (51.1)	1
Diabetes mellitus	198 (26.8)	198 (26.8)	1
Cardiovascular diseases	156 (21.1)	135 (18.2)	.2
Respiratory system diseases	175 (23.6)	164 (22.2)	.5
Additional treatment, n (%)			
Favipiravir	189 (27.4)	193 (26.1)	.6
Oseltamivir	309 (44.8)	349 (47.2)	.4
Lopinavir/ritonavir	35 (5.1)	19 (2.6)	.013*
Hydroxychloroquine	508 (73.6)	541 (73.1)	.8
High-dose vitamin C	118 (17.1)	109 (14.7)	.2
Not available	50	0	

*$P \leq .05$, statistically significant.

3.2 | Outcome

A severe course of COVID-19 was observed in 15.5% of patients with hematological malignancy whereas it was observed in 13% of patients without cancer. In addition, the rate of critically ill COVID-19 patients was 13.2% among patients with hematological malignancy whereas it was 6.6% among patients without cancer. The rates of severe and critical diseases were significantly higher in patients with hematological malignancy compared with patients without cancer ($P = .001$). The rates of hospital and ICU admission were higher in patients with hematological malignancy compared with the patients without cancer ($P = .023$, $P = .001$, respectively). The length of hospital stay and ICU stay was similar between groups ($P = .7$, $P = .3$, retrospectively). The rate of MV support was higher in patients with hematological malignancy compared with the control group ($P = .001$). The case fatality rate (CFR) was 13.8% in patients with hematological malignancy, and it was 6.8% in the control group ($P = .001$) (Table 2). The highest CFR among COVID-19 patients with hematological malignancy was observed in HCL (44%) followed by AML (20%) and MM (19.5%). When hematological malignancies were classified into two groups according to their origins as lymphoid malignancies (NHL, HL, ALL, CLL, HCL, MM) and myeloid malignancies (AML, MDS, MPN, CML), no significant difference was observed regarding CFR ($P = .6$). The distribution of the deceased patients according to their hematological malignancies is given in Table 3. No significant difference was observed between deceased patients with hematological malignancy and deceased patients without cancer regarding sex, age, number of comorbidities, and COVID-19 treatment they received (Table 4).

4 | DISCUSSION

The prevalence of cancer in patients with COVID-19 is uncertain. Previous studies from China reported that 1% to 2% of COVID-19 patients had cancer, and a study from the United States reported that 6% of hospitalized patients with COVID-19 had cancer. In Lombardy, Italy, they observed that 8% of the patients admitted to the ICU for COVID-19 had cancer. In a meta-analysis, the prevalence of cancer was 2% among COVID-19 patients.[11-14] Although there are reports about the prevalence of cancer among COVID-19 patients, the data about the prevalence of hematological malignancies among

TABLE 2 The outcome of COVID-19 patients with hematological malignancy and control group

	Patients with hematological malignancy	Patients without cancer	*P* value
COVID-19 severity, n (%)			
Severe	115 (15.5)	96 (13)	.001*
Critical	98 (13.2)	49 (6.6)	
Hospital admission, n (%)	452 (61.1)	409 (55.3)	.023*
ICU admission, n (%)	140 (18.9)	85 (11.5)	.001*
MV, n (%)	102 (13.8)	53 (7.2)	.001*
Duration in hospital, d	10 (2-57)	10 (2-61)	.7
Duration in ICU, d	6 (1-37)	8 (1-57)	.3
CFR, n (%)	102 (13.8)	50 (6.8)	.001*

Abbreviations: CFR, case fatality rate; COVID-19, coronavirus disease 2019; ICU, intensive care unit; MV, mechanical ventilation.
*$P \leq .05$, statistically significant.

COVID-19 patients are very limited. In our study, we found that 0.39% of the laboratory-confirmed COVID-19 patients had hematological malignancy. The most common hematological malignancies in COVID-19 patients were NHL (30.1%) followed by MDS (19.7%).

There is also less knowledge existing in the literature about the disease course in COVID-19 patients with hematological malignancies. In a previous study, researchers analyzed the data of 105 patients with cancer hospitalized for COVID-19 and compared their results to patients without cancer. Among 105 COVID-19 patients with cancer, nine had hematological malignancy. When compared with patients without cancer, they found that patients with cancer had higher death rates, higher rates of ICU admission, and a more severe COVID-19 course and had a higher rate of MV support. In addition, they observed that patients with hematologic malignancies, lung cancer, and metastatic cancer had the highest frequency of severe events.[15] In a study conducted by Mehta et al,[16] the ICU admission rate and MV support rate were higher in patients with hematological malignancy (26%) compared with patients with solid tumors (19%); however, this did not achieve statistical significance. In our study, a severe course of COVID-19 was observed in 15.5% of patients with hematological malignancy whereas it was observed in 13% of patients without cancer. In addition, the rate of critically ill COVID-19 patients was 13.2% among patients with hematological malignancy whereas it was 6.6% among patients without cancer. We found that the rates of severe and critical diseases were significantly higher in patients with hematological malignancy compared with patients without cancer. The rates of ICU and hospital admission and MV support were higher in COVID-19 patients with hematological

TABLE 3 The distribution of deceased patients according to their hematological malignancies

Disease	All (n)	Deceased (n)	CFR (%)
HL	27	4	14.8
CLL	54	9	16.6
MM	77	15	19.5
ALL	18	3	16.6
MPN	116	10	8.6
CML	30	3	10
NHL	223	24	10.8
MDS	146	22	15
AML	40	8	20
HCL	9	4	44
Total	740	102	13.8

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CFR, case fatality rate; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma.

TABLE 4 Clinical and demographic features of the deceased patients

	Patients with hematological malignancy (n = 102)	Patients without cancer (n = 50)	*P* value
Sex, n (%)			
Male	65 (63.7)	38 (76)	.13
Female	37 (36.3)	12 (24)	
Age, median (y)	69 (24-92)	71.5 (48-87)	.44
Comorbidity, n (%)			
≥2	59 (57.8)	26 (52)	.8
1	28 (27.5)	16 (32)	
0	15 (14.7)	8 (16)	
Treatment, n (%)			
Favipiravir	66 (65.3)	36 (72)	.4
Lopinavir/ritonavir	10 (9.9)	7 (14)	.5
Hydroxychloroquine	77 (76.2)	41 (82)	.4
Azithromycin	51 (50.5)	34 (68)	.4
Not available	1	0	

malignancy compared with the control group. This finding supports the hypothesis of the high probability of immunopathogenic damage due to a cytokine storm because of the increased risk of an immunological hyperactivation induced by SARS-CoV-2 in hematological malignancies involving T lymphocytes, natural killer cells, histiocytes and antigen-presenting cells.[17]

In a previous study, the mortality rate in myeloid malignancies (MDS/AML/MPN) was higher than that of the lymphoid neoplasms (NHL/CLL/ALL/MM/HL) (43% vs 35%).[16] In contrast to their results, we did not find a significant difference between lymphoid malignancies (NHL, HL, ALL, CLL, HCL, MM) and myeloid malignancies (AML, MDS, MPN, CML) regarding CFRs. In their study, there were 14 patients with myeloid malignancies and 40 patients with lymphoid malignancies; however, in our study, there were 332 patients with myeloid malignancies and 408 patients with lymhoid malignancies, therefore, this contrast between the two studies may be attributed to the different sizes of the studies.

The CFR in COVID-19 patients with hematological malignancy also differs in the limited published studies. In a study conducted by Mehta et al,[16] CFR in COVID-19 patients with hematological malignancy was 37%.[16] He et al, in their study, compared the outcome of hospitalized COVID-19 patients with hematological malignancy to the healthcare providers with COVID-19. They found that hospitalized COVID-19 patients with hematological malignancy had more severe disease and a higher CFR compared with hospitalized healthcare providers. More complications including acute respiratory distress syndrome, acute renal failure, and sepsis were observed in COVID-19 patients with hematological malignancy compared with healthcare providers with COVID-19; none of the healthcare providers and eight patients with hematologic malignancy died at the end of observation (P =.001)[18] In a study from Spain, Martin-Moro et al investigated 34 hospitalized COVID-19 patients with hematological malignancy and observed that the CFR was 32%. They concluded that hematologic malignancy status at the time of COVID-19 is related to mortality; patients with no active cancer presented better outcomes.[19] Additionally, Aries et al[20] also reported CFR as 40% in hemato-oncology patients in their small cohort study including 35 patients. In the study conducted by Yang et al,[21] among 52 COVID-19 patients with solid tumors or hematological malignancies, the rate of severe/critical disease was 36.5% and CFR of severe/critical patients was 57.8%. In our study, CFR was 13.8% in COVID-19 patients with hematological malignancy. The lower CFR in our study compared with the other studies may be attributed to a high number of MPN patients in our study who were thought to be less immunocompromised compared with leukemia, MM, or lymphoma patients. Also, our study included both hospitalized and nonhospitalized patients.

To the best of our knowledge, this is the first large-scale population-based study investigating the COVID-19 patients with hematological malignancies and comparing their results to an age, sex, and comorbidity-matched cohort of COVID-19 patients without cancer. The main findings of the current study were that (a) hypertension was the most common comorbid disease in both of the groups; (b) the rates of severe and critical diseases, hospital and ICU admission, and MV support were higher in patients with hematological malignancy compared with the COVID-19 patients without cancer; (c) length of hospital stay and ICU stay was similar between groups; (d) CFR was higher in patients with hematological malignancy compared with the control group; (e) no significant difference was observed between lymphoid malignancies and myeloid malignancies regarding CFRs.

A retrospective design and lack of information about anticancer treatments and the hematological disease status are the limitations of our study. The merits of our study are that the control group was composed of age, sex, and comorbidity-matched patients, however, in most studies, control groups are not comorbidity-matched.

In conclusion, it is important to consider that patients with hematological malignancy are immunocompromised, and our study reveals that there is an increased risk of COVID-19-related serious events (ICU admission, requirement for MV, or death) in patients with hematological malignancy compared with COVID-19 patients without cancer and supports the high vulnerability of patients with hematological malignancy in the current pandemic. Therefore, physicians should pay great attention to the management of COVID-19 patients with hematological malignancy. A triage performed by telephone or other online technologies should be used to verify the need for treatment or follow-up in inpatient or outpatient clinics. In non–life-threatening diseases, hospitalization should be postponed. Patients who have a fever or any other symptoms that may be related to COVID-19 should be tested to detect SARS-CoV-2 RNA and they should not be accepted into the hematology ward before ruling out the possibility of COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Concept and design: TNY, FA; acquisition, analysis, or interpretation of data: MMU, EI; drafting of the manuscript: TNY, FA; statistical analysis: SB; critical revision of the manuscript for important intellectual content: all authors.

ORCID

Tugce N. Yigenoglu http://orcid.org/0000-0001-9962-8882

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