

## Single Centre Experience: Benign and Malign Hematological Patients with COVID-19/

*Tek Merkez Deneyimi: Benign ve Malign Tanılı Hematoloji Hastalarında COVID-19*

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### Abstract

**Introduction:** In this study, we aimed to contribute to the literature by analyzing the data of our patients who were followed up with malignant or benign hematological diagnoses and diagnosed with COVID-19, determining the distribution of this infection according to patient groups and examining its course in hematological patients. **Patients and methods:** Patients followed in our hospital with benign and malignant hematological diagnoses and with a history of COVID-19 were retrospectively examined. **Results:** Seventy seven patients had been followed by hematologic malignancies and eleven patients had been followed by benign hematological disease. In the group with malignancy, COVID was found most frequently in patients diagnosed with myeloproliferative neoplasms (22%). Immune thrombocytopenia (64%) was the most common disease in patients with benign hematological disorder who had COVID history. Almost all of the patients in the moderate and severe disease group were followed up in patients diagnosed with malign disease. Sixteen (18%) patients were transferred to the intensive care unit and all required mechanical ventilation. All of the patients who were intubated and needed intensive care



were diagnosed with malign group. The mortality rate was 22% in patients with malign hematological diseases, and 19% when all patients (malign and benign) were included.

Discussion: In conclusion, the COVID-19 pandemic is a problem all over the world. Determining the course of the disease in certain diagnostic groups is important in the management of both the main disease and the COVID-19 infection. Therefore, the contribution of such recording studies to the literature is important and valuable.

*Keywords: Coronavirus, Hematological malignancy, Pandemic, Severe acute respiratory syndrome coronavirus 2*

### Öz

Giriş: Bu çalışma ile malign veya benign hematolojik tanılarla takip edilen ve COVID-19 tanısı alan hastalarımızı analiz edip; bu enfeksiyonun hasta gruplarına göre dağılımını belirleyerek ve hematolojik hastalardaki seyrini inceleyerek tanımlayıcı istatistikler oluşturup literatüre katkı sağlamayı amaçladık. Gereç ve yöntemler: Hastanemizde benign ve malign hematolojik tanılarla takip edilen ve COVID-19 öyküsü olan hastalar retrospektif olarak incelenmiştir. Bulgular: Yetmiş yedi hasta hematolojik maligniteler, 11 hasta da benign hematolojik tanılar ile takip ediliyordu. Malign tanılarla izlenen grupta COVID en sık Philadelphia kromozomu negatif miyeloproliferatif neoplazm (%22 tanılı hastalarda görüldü. Benign hastalık grubunda ise ITP (%64), COVID öyküsü olan hastalarda en sık görülen hastalıktı. Orta ve ağır hastalık grubundaki hastaların tamamına yakını malign hematolojik hastalık grubunda idi. On altı (%18) hasta yoğun bakım ünitesine devredildi ve tümünün mekanik ventilasyon ihtiyacı oldu. Entübe edilen ve yoğun bakım ihtiyacı olan hastaların tamamı malign hematolojik hastalık tanısı olan hastalardı. Mortalite oranı malign hematolojik hastalık grubunda %22, tüm hastalar (malign ve benign) dahil edildiğinde ise %19 idi. Tartışma: Sonuç olarak, COVID-19 pandemisi dünya genelinde sorun teşkil etmektedir. Belirli tanı gruplarında hastalığın seyrinin belirlenmesi hem ana hastalığın hem de COVID-19 enfeksiyonunun yönetiminde önemlidir. Bu nedenle bu tür kayıt çalışmalarının literatüre katkısı önemli ve değerlidir.

Anahtar kelimeler: Hematolojik malignite, Koronavirüs, Pandemi, Şiddetli akut solunum sendromu koronavirüsü 2

### 1.Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) caused by this virus were declared as pandemic and public health emergency by World Health Organization (WHO) (Wang, Horby, Hayden, & Gao, 2020).

The clinical course of the disease varies from mild symptoms such as very weakness, joint pain, to severe respiratory failure (Wiersinga, Rhodes, Cheng, Peacock, & Prescott, 2020). 5% of patients need intensive care due to acute respiratory distress syndrome or multiple organ failure (García-Suárez et al., 2020). The overall mortality rate of the disease ranges from 4% to 15% (Rate, 2020; D. Wang et al., 2020). Patients with comorbidities such as hypertension, diabetes mellitus, cardiovascular disease and cancer have more aggressive clinical course (Meng et al., 2020; Yang et al., 2020). Altered immune system caused by the biology of the disease in hematological disorders, especially in malignancies, treatments such as chemotherapy, radiotherapy or other immunosuppressive agents make patients vulnerable against infections (Hirsch et al., 2013). Based on this information, COVID-19 disease in hematological patients may be associated with worse outcomes. With this study, we aimed to define our patients who were followed up with malign or benign hematological diagnoses and diagnosed with COVID-19; determine the distribution of this infection in patient groups and contribute to the literature by creating descriptive statistics with its



clinical and demographic features. In addition, we aimed to reveal the effect of COVID-19 infection on the clinical course and mortality rates of our patients.

## 2. Materials and Methods

**2.1 Type of research:** A descriptive study

**2.2 Research place and time:** Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, 01.04.2020-31.12.2020

**2.3 Universe, sample and sampling Method:** It was planned to retrospectively examine patients with a history of COVID-19 who were followed up in Hematology Department of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital with benign and malign diagnoses. All patients who had COVID-19 disease and admitted to our hematology-followed-up patient clinic from 01.04.2020 until 31.12.2020 were included in the study.

**2.4 Data collection tools:** Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital records, Public Health Management System (HSYS) patient files and the MERNIS death notification system were used to collect data.

**2.5 Data collection:** Demographic data (age, gender, comorbidities), clinicopathological characteristics related to hematological diagnoses (hematological diagnoses / disease status at time of COVID-19 infection/ treatments), data about COVID-19 diseases (PCR results-dates / computerized tomography findings / symptoms / severity of infection/ hospitalization, need of mechanic ventilation, transferred to intensive care unit / COVID-related treatments / recovery, mortality) and the final status of the patients (alive / ex) will be recorded. Severity was defined as mild (outpatient), moderate (hospitalization), or severe (intensive care unit-ICU). The diagnosis of COVID-19 was confirmed with a polymerase chain reaction (PCR)-based test of a specimen collected on a nasopharyngeal swab or typical findings for COVID-19 infection on thorax computerized tomography (CT).

**2.6 Ethical approval and informed consent:** All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and / or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The study was approved by the Ethics Committee of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey (11.01.2021-102/07)

## 2.7 Statistical analysis

Data obtained in the study were analyzed statistically using SPSS 27.0 software. Descriptive statistics were stated as mean  $\pm$  standard deviation, median, minimum and maximum values or number (n) and percentage (%). The conformity of variables to normal distribution was assessed with the Kolmogorov Smirnov test. The Mann-Whitney U test, Kruskal-Wallis test, and ANOVA test were used in the analysis of quantitative independent data. A value of  $p < 0.05$  was accepted as statistically significant.

## 3. Results

The demographic and clinical characteristics of the patients are given in Table 1. Since the malign disease group in this study was used in a published study, the mentioned study was cited for the demographic and disease-related characteristics of the malign hematologic disease group in this study (Tığlıoğlu et al., 2022).



**Table 1: Demographic and clinical data of the patients regarding their hematological diagnosis**

	Malign (n:77)	Benign (n:11)
Diagnosis (n)	ALL: 2 AML:5 NHL:15 HL:5 CLL:11 CML:3 MPN (Ph negative):17 MDS:7 MM:12	ITP: 7 AIHA: 2 Congenital TTP: 1 CDA: 1
Age median [min-max]	60 [27-93]	36 [22-62]
Sex, n (%)		
▪ <b>Female</b>	37 (48%)	5 (45%)
▪ <b>Male</b>	40 (52%)	6 (55%)
Comorbidity n (%)		
▪ <b>No</b>	31 (40%)	10 (%91)
▪ <b>Yes</b>	46 (60%)	1 (%9)
Comorbidities, n		
▪ <b>Hypertension</b>	28	1
▪ <b>Diabetes</b>	22	1
▪ <b>CAD</b>	13	
▪ <b>Congestive heart failure</b>	2	
▪ <b>Hyperlipidemia</b>	10	
▪ <b>Lung disease (COPD, asthma)</b>	14	1
▪ <b>CKD (eGFR &lt; 60 mL/min)</b>	1	
▪ <b>Chronic hepatitis</b>	2	
▪ <b>Rheumatoid arthritis</b>	2	
▪ <b>History of other malignancy</b>	2	
Disease status, n		
▪ <b>Active disease (include relapse-refractory or progressive disease)</b>	25 (33%)	3 (27%)
▪ <b>Remission (complete response, partial response)</b>	52 (67%)	8 (73%)
Active chemotherapy/immunotherapy/ immunosuppression, n, %		
▪ <b>Yes</b>	40 (52%)	1 (9%)
▪ <b>No</b>	37 (48%)	10 (91%)

AIHA: autoimmune hemolytic anemia, ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, CAD: coronary artery disease, CDA: congenital dyserythropoietic anemia, CKD: chronic kidney disease, CLL: chronic lymphocytic leukemia, CML: chronic myeloid leukemia, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, HL: Hodgkin lymphoma, MDS: myelodysplastic syndrome, MM: multiple myeloma, MPN: Myeloproliferative neoplasms, NHL: non-Hodgkin lymphoma, Ph: Philadelphia chromosome, TTP:Thrombotic thrombocytopenic purpura

Eighty eight patients who had COVID-19 infection while being followed in our clinic due to hematological diseases were included in the study. Seventy seven patients had been followed by hematologic malignancies and eleven patients had been followed by benign hematological disease. COVID-19 infection was identified in 78 patients by COVID-19 PCR assay. Ten patients were diagnosed with COVID-19 with CT scan findings.

In the group with malignancy, COVID-19 was found most frequently in patients diagnosed with Philadelphia chromosome (Ph) negative myeloproliferative neoplasms (MPN) (22%), nonhodgkin lymphoma (NHL) (19%) and multiple myeloma (MM) (16%). The median age of the patients who had malign disease was 60 (range, 27-93) years. Fourty (52%) of the patients were male. forty six (60%) of the patients had at least one comorbidity. The most common comorbidities were HT, diabetes and COPD, respectively (Tiğlioğlu et al., 2022) . Immune thrombocytopenia (ITP) (64%) was the most common disease in patients with benign hematological disorder who had COVID history. The median age of the patients with benign hematological disease were 36 (range, 22-62) and 6 (55%) were male. Only 1 (10%)



of these 11 patients had comorbidity. 52 (67%) of the malign cases and 8 (73%) of the benign cases were found to be followed up with the disease in remission. A total of 52% of malign patients were receiving active chemotherapy or immunosuppressive therapy. The most common treatments used by patients with hematological malignancies diagnosed with COVID-19 -in accordance with the frequency of diagnosis- were hydroxyurea (HU) (10 patients), R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, prednisone) chemotherapy regimen (3 patients) and lenalidomide and dexamethasone with one of the proteasome inhibitor (9 patients). Ninety one percent of the patients with benign diagnosis were followed up without concurrent cytotoxic/immunosuppressive therapy or corticosteroid treatment. The only patient in the benign disease group who received active treatment was receiving eltrombopag. Most common symptoms of all patients at COVID-19 diagnosis were fever (77%), cough (70%) and weakness (65%). CT scan of the chest was performed in 55 patients and COVID-19 specific findings were detected in 38 patients. Clinical data of patients on the course of COVID-19 infection are given in Table 2.

**Table 2: Clinical data of patients on the course of COVID-19 infection**

	Malign (n:77)	Benign (n:11)	All patients (n:88)
Clinical course, n (%)			
▪ <b>symptomatic</b>	58 (75%)	8 (73%)	66 (75%)
▪ <b>asymptomatic</b>	19 (25%)	3 (27%)	22 (25%)
Symptoms, n (%)			
▪ <b>fever</b>	47 (61%)	4 (36%)	51 (58%)
▪ <b>cough</b>	43 (56%)	3 (27%)	46 (52%)
▪ <b>dyspnea</b>	19 (24%)	0	19 (22%)
▪ <b>weakness</b>	40 (52%)	3 (27%)	43 (49%)
▪ <b>arthralgia</b>	13 (17%)	2 (18%)	15 (17%)
▪ <b>myalgia</b>	9 (12%)	2 (18%)	11 (13%)
▪ <b>loss of taste and smell</b>	5 (6%)	2 (18%)	7 (8%)
▪ <b>throat sore</b>	4 (5%)	1 (9%)	5 (6%)
▪ <b>headache</b>	4 (5%)	1 (9%)	5 (6%)
Positive CT findings n/ Patient who performed CT n	36 / 50	2 / 5	38 / 55
Hospitalization, n (%)			
▪ <b>Yes</b>	39 (51%)	1 (9%)	40 (45%)
▪ <b>No</b>	38 (49%)	10 (91%)	48 (55%)
Median Length of stay in the hospital, day [min-max]	8 (1-30)	0	9 (1-30)
Need for intensive care, n (%)			
▪ <b>Yes</b>	16 (21%)	0 (0%)	16 (18%)
▪ <b>No</b>	61 (79%)	11 (100%)	72 (82%)
Invasive mechanical ventilation n (%)			
▪ <b>Yes</b>	16 (21%)	0 (0%)	16 (18%)
▪ <b>No</b>	61 (79%)	11 (100%)	72 (82%)
Severity of infection, n (%)			
▪ <b>Mild</b>	38 (49%)	10 (91%)	48 (55%)
▪ <b>Moderate</b>	21 (27%)	1 (9%)	22 (25%)
▪ <b>Severe</b>	18 (24%)	0	18 (20%)
Recovery, n (%)	60 (78%)	11 (100%)	71 (81%)
Mortality, n (%)	17 (22%)	0 (0%)	17 (19%)
Treatment, n (%)			
Favipravir	72 (94%)	10 (91%)	82 (93%)
Hydroxychloroquine	11 (14%)	2 (18%)	13 (15%)
Pulse corticosteroids	4 (5%)		4 (5%)
Tocilizumab	1 (1%)		1 (1%)
Anakinra	1 (1%)		1 (1%)
Convalescent plasma	3 (4%)		3 (3%)
IVIg	2 (3%)		2 (2%)
Unknown	2 (3%)	1 (9%)	3 (3%)

CT: computerized tomography , IVIG: intravenous immunoglobulin



Forty five percent of the patients were isolated at home, 48% were required hospitalization. Median duration of hospitalization is 9 (1-30) days. While the rate of hospitalization was higher in patients with a diagnosis of malignancy (51%), there was only 1 indication for hospitalization in patients with benign diagnoses. In total, 49% of patients had mild; 27% had moderate and 24% had severe COVID-19 infection. Almost all of the patients in the moderate and severe disease group were followed up in patients diagnosed with malign hematological disease. Favipiravir and hydroxychloroquine were the most preferred treatments for COVID-19 treatment. Data from 3 patients were not available. Detailed information on treatments are given in Table 2. All of the patients who needed pulse steroid, tocilizumab or anakinra due to cytokine storm were in the malign disease group. Sixteen (18%) patients received mechanical ventilation and all of them was transferred intensive care unit. All of the patients who were intubated and needed intensive care were diagnosed with malign hematological disease.

Seventeen patients died due to COVID-19 infection. The mortality rate was 22% in patients with diagnosis of malign hematological diseases, and 19% when all patients with malign and benign hematological diseases. The median time between COVID-19 diagnosis and death is 8 (3-53) days. When the hematological diagnoses of the patients who died were examined; 2 acute myeloid leukemia (AML), 4 MPN, 2 MM, 4 chronic lymphocytic leukemia (CLL), 2 myelodysplastic syndrome (MDS) and 3 NHL patients were detected. While 10 of these patients received active treatment, 7 of them did not receive any treatment excepted for supportive treatment (blood transfusion etc.).

#### 4. Discussion

In hematological diseases, especially malignancies, the suppressed immune system caused by the biology of the disease and the chemotherapy, radiotherapy or other immunosuppressive agents used in the treatment (because of effects on humoral and cell-mediated immunity) of these patients, make them vulnerable to infections. In addition, these patients also have risk factors such as advanced age, additional comorbidity, neutropenia or lymphopenia. Based on this information, it can be predicted that the outcomes of COVID-19 disease for hematologic patients may be worse.

According to the ASH Research Collaborative COVID-19 Registry report, the most common hematological diagnoses of patients diagnosed with COVID-19 were acute leukemia (33%), NHL (27%), and myeloma or amyloidosis (16%) respectively (Wood et al., 2020). Recent, multicentre cohort study, it was reported that CLL (39.4%) and MM (33.3%) were the most common type of hematologic malignancy, in COVID-19 records (Passamonti et al., 2020). In our study, COVID-19 was most commonly detected among patients with MPN, NHL and MM (respectly 17, 15 and 12 of 77) diagnoses. This result is not surprising as these diseases are among the common hematological malignancies. The common symptom was fever in both the malign disease group and the benign disease group, similar to general population.

In a multicentre study from Italy, mortality due to COVID-19 was found to be 37% in 536 patients with hematological malignancies. Advanced age, progressive disease and severe COVID-19 infection were found to be related with mortality (Passamonti et al., 2020). In another study, COVID-19-related mortality rate was found to be 37% in patients with malign hematological disease (Mehta et al., 2020).

In the current study, 17 deaths (19% of a total of 88 patients) were observed. All patients who died had a malign hematological diagnosis. From this point of view, the fatality rate



due to COVID-19 was detected as 22% in the malign patient group in our observation. Although the fatality rate we found was lower than the studies reported in the literature, it was higher than the overall mortality of general population. Moreover, all of the patients who needed mechanical ventilation or transferred to intensive care unit were also in the malign disease group. These results demonstrate that the clinical course of COVID-19 patients with hematological malignancies may be more aggressive than both patients with benign hematologic diagnosis and the general population.

With this study, we aimed to evaluate the COVID-19 perspective of our patients who we follow in our hematology clinic. The most important limitation of the study was that we were insufficient in statistical analysis due to the wide range of patient diagnosis.

## 5. Conclusion

In conclusion, the COVID-19 pandemic is a problem all over the world. Determining the course of the disease in certain diagnostic groups such as hematological diseases is important in the management of both the main disease and the COVID-19 infection. Therefore, the contribution of such recording studies to the literature is important and valuable. With active vaccination, the effect of the pandemic is gradually decreasing today, but examining the long-term effects of COVID-19 infection and even vaccination in hematology patients may be the subject of new studies.

## Declarations

This article was not produced from the thesis study. It was not presented as a verbal / poster presentation at any meeting. No kind of support has been received from any institution / organization / person. There are no conflicts of interest between the authors in this study. The malignant disease group in this study was used in another study. The mentioned article (Tiğlioğlu et al., 2022) was cited in the Results section. The study was approved by the Ethics Committee of Ankara Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi Training and Research Hospital, Ankara, Turkey (11.01.2021-102/07). This study was conducted in accordance with the Helsinki Declaration principles. Author contributions: Idea: PT, MA, MT, HBAÖ, MRA, FY, SM, BS, ÜYM. Design: PT, MA, HBAÖ, BS, ÜYM. Data Collection or Processing: PT, MT, BS, FY. Analysis / Interpretation: PT, MA, FY, Literature Search: HBAÖ, MRA. Writer: PT, HBAÖ, MT, BS, MRA, FY, ÜYM., Critical Review: PT, MA, MT, HBAÖ, MRA, FY, SM, BS, ÜYM.

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