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

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

Sinem Civriz Bozdağ, Güldane Cengiz Seval, İpek Yünel Hindilerden, Fehmi Hindilerden, Neslihan Andıç, Mustafa Baydar, Lale Aydin Kaynar, Selami Koçak Toprak, Hasan Sami Göksoy, Berrin Balık Aydin, Ufuk Demirci, Ferda Can, Vildan Özkocaman, Eren Gündüz, Zeynep Tuğba Güven, Zübeyde Nur Özurt, Sinan Demircioğlu, Meral Beksaç, İdris İnce, Umut Yılmaz, Hilal Eroğlu Küküldiler, Elgün Abişov, Boran Yavuz, Ünal Ataş, Yaşa Gül Mutlu, Volkan Bağ, Fahir Öz克莱mkas, Hava Üsküdar Teked, Vildan Gürsoy, Serhat Çelik, Rafiye Çiftçiler, Müneci Yaşıcı, Pervin Topçuoğlu, Özcan Çene, Hamza Abbasov, Cem Selim, Muhlis Cem Ar, Orhan Kemal Yücel, Sevil Sadri, Canan Albayrak, Ahmet Muzaffar Demir, Nil Güler, Muzaffer Keklik, Hatice Terzi, Ali Doğan, Zeynep Arzu Yegin, Meltem Kurt Yüksel, Soğol Sadri, İrfan Yavaşoğlu, Hüseyin Saffet Beköz, Tekin Aksu, Senem Mara, Veyesel Erol, Leylagül Kaynar, Osman İlhan, Ali Zahit Bolaman, Ömür Gökmen Sevindik, Arzu Akyay, Muhtit Özcan, Günhan Gürman, Şule Ünal, Yasemin Yavuz, Rehan Din Züçükleya, Güner Hayri Özsan

1. Ankara University Faculty of Medicine, Department of Hematology, Ankara, Turkey
2. Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey
3. Istanbul Bakırköy Sadi Konuk Training and Research Hospital, Clinic of Hematology, Istanbul, Turkey
4. Eskişehir Osmangazi University Faculty of Medicine, Department of Hematology, Eskişehir, Turkey
5. Ankara University Faculty of Medicine, Department of Hematology, Ankara, Turkey
6. Medipol University Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey
7. Trakya University Faculty of Medicine, Department of Hematology, Edirne, Turkey
8. Ankara City Hospital, Clinic of Internal Medicine, Department of Hematology, Ankara, Turkey
9. Bursa Uludağ University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Bursa, Turkey
10. Necmettin Erbakan University, Meram Faculty of Medicine, Department of Hematology, Konya, Turkey
11. Dr. Ersin Arslan Training and Research Hospital, Clinic of Hematology, Gaziantep, Turkey
12. Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Istanbul, Turkey
13. Adnan Menderes University Faculty of Medicine, Department of Hematology, Aydın, Turkey
14. Dokuz Eylül University Faculty of Medicine, Department of Hematology, Izmir, Turkey
15. Akdeniz University Faculty of Medicine, Department of Hematology, Antalya, Turkey
16. Bursa City Hospital, Clinic of Hematology, Bursa, Turkey
17. Akçaşar Training and Research Hospital, Clinic of Hematology, Aksaray, Turkey
18. Ondokuz Mayıs University Faculty of Medicine, Department of Pediatric Hematology, Samsun, Turkey
19. Pamukkale University Faculty of Medicine, Department of Internal Medicine, Denizli, Turkey
20. Cumhuriyet University Faculty of Medicine, Department of Hematology, Sivas, Turkey
21. Van Yüzüncü Yıl University Faculty of Medicine, Department of Hematology, Van, Turkey
22. Hacettepe University Faculty of Medicine, Department of Pediatric Hematology, Ankara, Turkey
23. University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Hematology, Ankara, Turkey
24. İnönü University Faculty of Medicine, Department of Pediatric Hematology and Oncology, Malatya, Turkey
25. Ankara University School of Medicine, Department of Biostatistics, Ankara, Turkey
26. İstanbul University Faculty of Science, Department of Molecular Biology and Genetic, İstanbul, Turkey

Address for Correspondence/Yazışma Adresi: Sinem Civriz Bozdağ, M.D., Assist. Prof., Ankara University Faculty of Medicine, Department of Hematology, Ankara, Turkey
E-mail: scivriz@hotmail.com ORCID: orcid.org/0000-0001-8359-7794

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

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

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

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

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

Introduction

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

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

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

Materials and Methods

On behalf of the Turkish Society of Hematology’s Infectious Complications and Supportive Care Working Party, we
The primary objective of this study was to identify the clinical outcomes and complications of COVID-19 in patients with hematological malignancies and to determine the rates of hospitalization, ICU admission, and overall 45-day mortality. The secondary objective was to identify additional risk factors for mortality specifically defined for this group of immunosuppressed patients.

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

Results

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

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

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

| Characteristic | n=340 |
|---------------|-------|
| Age, median (min-max) | 59 (7–93) |
| Male/female ratio | 196/144 |
| Diagnosis | |
| AML | 69 (20.3%) |
| NHL | 64 (18.8%) |
| MM | 85 (25%) |
| ALL | 30 (8.8%) |
| MDS | 27 (7.9%) |
| HL | 18 (5.3%) |
| CLL | 18 (5.3%) |
| CMPD | 10 (2.9%) |
| CML | 8 (2.4%) |
| CMML | 4 (1.2%) |
| HCL | 7 (2.1%) |
| Comorbidities | 144 (42.4%) |
| Smoking status | |
| Active smoker/ex-smoker/nonsmoker/not available | 8 (2.4%)/84 (24.7%)/175 (51.5%)/73 (21.5%) |
| Contact | |
| Yes/no/not available | 103/175/62 |
| Disease status | |
| New diagnosis: 65 (19.1%) | |
| CR: 135 (39.7%) | |
| PR: 13 (3.8%) | |
| Active disease: 98 (28.8%) | |
| Untreated: 20 (5.9%) | |
| Not available: 9 (2.6%) | |
| Treatment | |
| Untreated | 48 |
| Induction/consolidation/salvage/immunotherapy/maintenance | 134/19/68/13/14 |
| Auto-HSCT/Allo-HSCT | 14/38 |
| Steroids/rituximab/IvIG/GCSF | 100/57/42/55 |
| Clinical presentation | |
| Asymptomatic | 44 (12.9%) |
| Symptomatic | 297 (87.1%) |
| Symptoms | |
| Fever | 213 (62.6%) |
| Cough | 166 (46.6%) |
| Dyspnea | 142 (41.8%) |
| Myalgia | 64 (18.8%) |
| Diarrhea | 19 (5.6%) |
| Malaise | 75 (22.1%) |
| Sore throat | 12 (3.5%) |
| Headache | 9 (2.6%) |
| Nausea | 9 (2.6%) |
| Anosmia | 8 (2.4%) |
| Days with fever | |
| Median (min-max) | 3 (1–20) |
In the allo-HSCT group, mild, moderate, severe, and critical COVID-19 was observed in 18%, 44%, 13%, and 10% of cases, respectively. Patients with graft-versus-host disease (GVHD) had more severe and critical disease in comparison to those without GVHD (p=0.03). In patients who were diagnosed with COVID-19 in the first 30 days after auto-HSCT, mild disease was observed in 4 of 14 patients, while moderate, severe, and critical disease was observed in 3, 4, and 2 patients, respectively.

| Extrapulmonary disease | n=340 |
|------------------------|-------|
| Myocarditis            | 6 (%) |
| Liver                  | 2 (%) |
| Renal                  | 2 (%) |
| Skin                   | 1 (%) |
| Neurological           | 2 (%) |

| COVID-19 severity                  | n=340 |
|------------------------------------|-------|
| Asymptomatic/mild/pneumonia/severe pneumonia/ARDS/sepsis/septic shock | 44/69/101/71/11/31/13 |
| Asymptomatic/mild/moderate/severe/critical | 44 (12.9%)/69 (20.2%)/101 (29.7%)/71 (20.8%)/55 (16.1%) |

| Laboratory variables | n=340 |
|----------------------|-------|
| Hemoglobin           | 10.1 (6.0-15.3) |
| White blood cell count | 4300 (30-343000) |
| Lymphocytes          | 780 (0-326200) |
| Neutrophils          | 2500 (0-67480) |
| Platelets            | 1250000 (5000-654000) |
| Ferritin             | 1461 (17-40000) |

| Antiviral treatment | n=340 |
|--------------------|-------|
| HCQ                | 35 (10%) |
| Favipiravir         | 140 (41.2%) |
| HCQ + favipiravir   | 50 (14.7%) |
| HCQ + azithromycin | 42 (12.4%) |
| HCQ + azithromycin + favipiravir | 42 (12.4%) |
| Not available       | 31 (9.1%) |

| Anti-cytokine treatment | n=340 |
|-------------------------|-------|
| Convalescent plasma     | 36 (12.3%) |
| Steroids                | 27 (7%) |
| Tocilizumab             | 24 (7%) |
| IvIG                    | 21 (6%) |
| Anakinra                | 5 (1%) |
| Ruxolitinib             | 1 (2%) |

| Anticoagulant treatment | n=340 |
|-------------------------|-------|
| Prophylactic dose        | 198 (58.2%) |
| Treatment dose           | 26 (7.6%) |

AML: Acute myeloid leukemia; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; ALL: acute lymphocytic leukemia; MDS: myelodysplastic syndrome; CLL: chronic lymphocytic leukemia; HL: Hodgkin lymphoma; CMPD: chronic myeloproliferative disorder; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; HCL: hairy cell leukemia; CR: complete response; PR: partial response; auto-HSCT: autologous hematopoietic stem cell transplantation; allo-HSCT: allogeneic hematopoietic stem cell transplantation; IvIG: intravenous immune globulin; GCSF: granulocyte colony-stimulating factor; ICU: intensive care unit; HCQ: hydroxychloroquine.
Laboratory variables of the patients are summarized in Table 1. Neutropenia and lymphopenia were observed at diagnosis in 23% and 57%, respectively.

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

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

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

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

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

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

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

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

Discussion

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

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

Factors related to mortality in hematological malignancy patients are still debated. The mortality rate was 26% in our study, correlated with increasing COVID-19 severity. In a meta-analysis of 34 adult and 5 pediatric studies that predominantly included hospitalized patients, the risk of death was 34% and 4%, respectively [17]. Although there were only five pediatric patients in our study, all were alive at the end of follow-up. Piñana et al. [13] showed associations between mortality and age, performance score, neutropenia, uncontrolled disease, and increased C-reactive protein. In our study, hematological disease status, life expectancy related to the primary hematological disease, neutropenia, ICU admission, and type of COVID-19 treatment were risk factors for mortality in multivariate analysis. ICU admission closely reflected the disease severity and mortality increase irrespective of age, probably related to the primary hematological disease status.
### Table 2. Univariate analysis for mortality of the patients by Cox regression model (p<0.20 is statistically significant).

|                        | n   | p     | Hazards ratio | 95% confidence interval for hazards ratio |
|------------------------|-----|-------|---------------|------------------------------------------|
|                        |     |       |               | Lower | Upper |
| **Gender**             |     |       |               |       |       |
| Female                 | 195 | 0.448 | 1.180         | 0.769 | 1.810 |
| Male                   | 195 |       |               |       |       |
| **Age, years**         |     |       |               |       |       |
| <60                    | 170 |       |               |       |       |
| ≥60                    | 167 | 0.094 | 1.432         | 0.941 | 2.180 |
| **Diagnosis**          |     |       |               |       |       |
| Acute leukemia         | 99  | 0.459 |               |       |       |
| Lymphoma               | 106 | 0.376 | 1.270         | 0.748 | 2.156 |
| Myeloproliferative     | 22  | 0.251 | 1.599         | 0.718 | 3.561 |
| Myeloma                | 84  | 0.548 | 0.827         | 0.444 | 1.539 |
| Myelodysplastic syndrome | 27 | 0.486 | 1.329         | 0.597 | 2.959 |
| **Hematological disease status** | |       |               |       |       |
| Newly diagnosed        | 47  | 0.000 |               |       |       |
| Complete response      | 136 | 0.001 | 0.354         | 0.187 | 0.672 |
| Partial response       | 21  | 0.963 | 1.020         | 0.440 | 2.365 |
| Active disease         | 104 | 0.928 | 1.027         | 0.582 | 1.812 |
| Untreated              | 21  | 0.038 | 0.212         | 0.049 | 0.918 |
| Not available          | 9   | 0.167 | 0.241         | 0.032 | 1.812 |
| **Comorbidities**      |     |       |               |       |       |
| No                     | 194 |       |               |       |       |
| Yes                    | 144 | 0.016 | 1.672         | 1.102 | 2.537 |
| **Smoking habit**      |     |       |               |       |       |
| Nonsmoker              | 174 | 0.992 |               |       |       |
| Ex-smoker              | 83  | 0.975 | 1.008         | 0.616 | 1.648 |
| Active smoker          | 8   | 0.903 | 0.916         | 0.222 | 3.773 |
| **Hematological treatment** | |       |               |       |       |
| Induction              | 134 | 0.232 |               |       |       |
| Consolidation          | 21  | 0.248 | 0.546         | 0.196 | 1.525 |
| Salvage                | 69  | 0.514 | 1.182         | 0.714 | 1.957 |
| Immunotherapy          | 13  | 0.313 | 0.481         | 0.116 | 1.992 |
| Maintenance            | 15  | 0.183 | 0.381         | 0.092 | 1.575 |
| Allo-HSCT              | 32  | 0.103 | 0.462         | 0.182 | 1.168 |
| Auto-HSCT              | 6   | 0.459 | 0.473         | 0.065 | 3.436 |
| Untreated              | 48  | 0.201 | 0.636         | 0.318 | 1.272 |
| **Hematological treatment – COVID-19** | |       |               |       |       |
| Untreated              | 17  | 0.205 |               |       |       |
| During treatment       | 152 | 0.979 | 0.988         | 0.392 | 2.488 |
| <1 month               | 48  | 0.790 | 1.145         | 0.423 | 3.105 |
| <3 months              | 24  | 0.917 | 0.941         | 0.299 | 2.965 |
| 3-6 months             | 16  | 0.500 | 1.484         | 0.471 | 4.677 |
| 6-12 months            | 15  | 0.122 | 0.183         | 0.021 | 1.570 |
| ≥12 months             | 19  | 0.183 | 0.328         | 0.064 | 1.691 |
| >24 months             | 20  | 0.144 | 0.294         | 0.057 | 1.518 |
Table 2. Continued.

| Table 2. Continued. | n   | p     | Hazards ratio | 95% confidence interval for hazards ratio |
|---------------------|-----|-------|---------------|-----------------------------------------|
|                      |     |       |               | Lower | Upper |
| Steroids            |     |       |               |       |       |
| No                  | 219 |       |               |       |       |
| Yes                 | 100 | 0.244 | 0.745         | 0.453 | 1.223 |
| GCSF before COVID-19|     |       |               |       |       |
| No                  | 281 |       |               |       |       |
| Yes                 | 55  | 0.037 | 1.687         | 1.033 | 2.756 |
| Rituximab before COVID-19 |     |       |               |       |       |
| No                  | 281 |       |               |       |       |
| Yes                 | 57  | 0.357 | 1.275         | 0.760 | 2.139 |
| IvIg before COVID-19|     |       |               |       |       |
| No                  | 296 |       |               |       |       |
| Yes                 | 42  | 0.382 | 1.300         | 0.722 | 2.343 |
| COVID-19 diagnosis method |     |       |               |       |       |
| PCR                 | 95  | 0.000 |               |       |       |
| PCR + CT            | 169 | 0.000 | 3.514         | 1.852 | 6.669 |
| CT                  | 74  | 0.196 | 1.674         | 0.767 | 3.653 |
| COVID-19 severity   |     |       |               |       |       |
| Asymptomatic        | 44  | 0.001 |               |       |       |
| Mild                | 69  | 0.122 | 2.071         | 0.822 | 5.219 |
| Moderate            | 101 | 0.371 | 1.517         | 0.609 | 3.778 |
| Severe              | 69  | 0.078 | 2.283         | 0.912 | 5.718 |
| Critically ill      | 55  | 0.001 | 4.418         | 1.817 | 10.744|
| Lymphopenia         |     |       |               |       |       |
| No                  | 126 |       |               |       |       |
| Yes                 | 194 | 0.058 | 1.563         | 0.985 | 2.480 |
| Neutropenia         |     |       |               |       |       |
| No                  | 162 |       |               |       |       |
| Yes                 | 78  | 0.000 | 2.546         | 1.553 | 4.175 |
| Hospitalization     |     |       |               |       |       |
| ICU admission       | 84  | 0.000 |               |       |       |
| Outpatient          | 89  | 0.005 | 5.479         | 1.668 | 17.996|
| Ward hospitalization| 165 | 0.000 | 30.986        | 9.684 | 99.149|
| Intubation          |     |       |               |       |       |
| No                  | 260 |       |               |       |       |
| Yes                 | 78  | 0.000 | 21.883        | 13.360| 35.844|
| COVID-19 treatment  |     |       |               |       |       |
| HCQ                 | 28  | 0.131 |               |       |       |
| Favipiravir         | 130 | 0.953 | 0.976         | 0.428 | 2.226 |
| HCQ + favipiravir   | 43  | 0.226 | 1.724         | 0.714 | 4.161 |
| HCQ + azithromycin  | 42  | 0.910 | 0.946         | 0.360 | 2.488 |
| HCQ + azithromycin + favipiravir | 42 | 0.188 | 1.799         | 0.751 | 4.309 |
| Prophylactic anticoagulant |   |       |               |       |       |
| No                  | 141 |       |               |       |       |
Thirteen percent of our patients were asymptomatic at diagnosis, a rate lower than that seen in the general population. The most prominent symptoms at diagnosis were fever, cough, and dyspnea. In an Italian study that included only adult patients, fever was reported in 75%, dyspnea in 51%, cough in 45%, and malaise in 39% of cases [15]. He et al. [18] observed more fever, cough, and dyspnea in hematology patients in comparison to healthcare professionals. Consistent with our findings, Piñana et al. [13] failed to show a difference in the symptoms of patients with different HSCT statuses. Hospitalization was required for 73% of our patients and 25% were admitted to the ICU, similar to the findings of other series [13,15]. In Italy, among patients with severe or critical COVID-19, those who were admitted to the ICU were younger and had a lower comorbidity index [15].

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

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

**Table 2. Continued.**

| Anticoagulant treatment | n  | p     | Hazards ratio | 95% confidence interval for hazards ratio |
|-------------------------|----|-------|---------------|-----------------------------------------|
| No                      | 215|       |               |                                         |
| Yes                     | 26 | 0.477 | 1.291         | 0.639-2.609                              |

**Life expectancy**

|          | n  | p     | Hazards ratio | 95% confidence interval for hazards ratio |
|----------|----|-------|---------------|-----------------------------------------|
| <3 months| 10 | 0.000 |               |                                         |
| 3-6 months| 9  | 0.002 | 0.089         | 0.019-0.416                              |
| 6-12 months| 38 | 0.001 | 0.275         | 0.124-0.608                              |
| >12 months| 208| 0.000 | 0.075         | 0.036-0.158                              |

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

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

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

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

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

Study Limitations

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

Conclusion

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

Ethics

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

Informed Consent: Retrospective study.

Authorship Contributions

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

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