

1 **1. Introduction**

2 The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
3 was first discovered in Wuhan, China and named as coronavirus disease 2019 (COVID-
4 19) then spread all over the world, and declared as a pandemic by World Health
5 Organization [1].

6 Clinical course of the disease varies from asymptomatic disease to significant morbidity
7 and mortality due to respiratory failure. Advanced age, male gender, hypertension,
8 diabetes mellitus, cardiovascular diseases and cancer have been shown as risk factors
9 worsening outcomes. There are studies that show higher mortality rates in hematologic
10 cancer patients [2, 3]. The characteristics of the disease course in immunosuppressive
11 patients are not exactly known yet [4]. Hematopoietic stem cell transplantation (HSCT)
12 recipients are considered to be at risk due to severe immunosuppressive therapy and
13 immune system dysregulation after HSCT [5]. There is as yet insufficient information
14 about the effects of COVID-19 on the clinical course of HSCT patients.

15 In the present study, we aimed to investigate the effects of COVID-19 in patients who
16 had undergone HSCT.

17 **2. Materials and methods**

18 According to the hospital medical records, thirty-three patients followed in the stem cell
19 transplantation unit of Hacettepe University Hematology Department were diagnosed
20 with COVID-19 between 11th March and 30th November 2020. The data of these patients
21 was analyzed retrospectively. COVID-19 was diagnosed with positive result of reverse-
22 transcriptase polymerase chain reaction (RT-PCR) test from upper respiratory samples
23 or bronchoalveolar lavage fluid. The disease with only mild symptoms (cough, fever,
24 anosmia, fatigue) was evaluated as mild disease. The disease with clinical or

1 radiological findings of pneumonia, but not requiring supportive oxygen therapy was
2 evaluated as moderate disease. Patients with pneumonia and oxygen saturation below
3 93% or respiratory rate above 30/min were considered to have severe COVID-19. The
4 condition of the patients with respiratory failure, shock or multi-organ failure was
5 evaluated as critical illness [6]. Some high-risk patients with mild COVID-19 were
6 hospitalized for observation purposes only.

7 The approvals were obtained from the Turkish Ministry of Health and the local ethics
8 committee with decision number 2020/20-54.

9 IBM SPSS Statistics for Windows, SPSS version 25.0 (IBM Corp., Armonk, NY, USA)
10 was used for statistical analyses. Categorical data was analyzed using Chi-square or
11 Fisher's Exact test. The distribution of continuous data was examined. Mean \pm standard
12 deviation and median (minimum-maximum) values were given for normally distributed
13 continuous and non-normally distributed variables, respectively. At the time of last
14 follow-up, patients who were alive were censored for overall survival analysis. Kaplan-
15 Meier method was used for overall survival analysis.

16 **3. Results**

17 Thirty-three patients were included in the study. Median age was 57 (27-71) years.
18 Nineteen (57.6%) of the patients underwent autologous hematopoietic stem cell
19 transplantation (AH SCT), and fourteen (42.4%) underwent allogeneic hematopoietic
20 stem cell transplantation (Allo-HSCT). Nine (27.3%) had uncontrolled primary disease,
21 and four (12.1%) were on calcineurin inhibitors at the time of COVID-19 diagnosis.
22 Twelve (85.7%) of allo-HSCT recipients were transplanted from 10/10 human
23 leukocyte antigen (HLA) matched related donors, two of them (14.3%) from
24 haploidentical donors. The patients baseline characteristics are outlined in Table-1.

1 Among the patients, twenty-three (69.7%) of them developed fever in the course of
2 COVID-19. Twenty (60.6%), nine (27.3%), and four (12.1%) of the patients had mild,
3 moderate and severe COVID-19 or critical illness, respectively. Fifteen (45.5%) were
4 hospitalized. Four (12.1%) required intensive care. Three patients (9.1%) needed
5 invasive mechanical ventilation. A patient, who refused hospitalization died at home.
6 Favipiravir, which is a ribonucleic acid polymerase inhibitor, was the most common
7 antiviral medication used by the patients. Detailed COVID-19 outcomes of the patients
8 are given in Table-2.

9 A total of six patients had concomitant graft versus host disease (GVHD) (acute
10 gastrointestinal and cutaneous: two patients, chronic cutaneous and gastrointestinal: two
11 patients, chronic cutaneous: two patients) at the time of COVID-19 diagnosis. The
12 course of the GVHD did not get worse in these patients.

13 Among the hospitalized patients, thirteen (86.7%) of them were male, and the remaining
14 two (13.3%) were female. The difference was statistically significant ($P < 0.05$).
15 Hospital admission rates according to gender, HSCT type, remission status and presence
16 of GVHD are given in Table-3.

17 Median follow-up time was 28 days (2-262 days). During this time, 3 of 33 patients
18 (9.1%) died. The case fatality rate was 9.1% in all HSCT recipients, 22.2% in patients
19 with active hematologic malignancy, 4.2% in patients without active hematologic
20 malignancy, and 25.0% in who was on immunosuppressive drugs. The mortality rates
21 according to gender, HSCT type, remission status, presence of GVHD and use of
22 immunosuppressive drugs are given in Table-4.

23 The mortality and hospitalization rates were calculated separately for the treatments.

24 The detailed data on COVID-19 treatments received by the patients are given in Table-

1 5. The treatment records of a patient who refused hospitalization and treated at home
2 were not available. In univariate survival analysis, there was not statistically significant
3 difference between the AHSCT and allo-HSCT recipients ($P = 0.39$). Kaplan-Meier
4 survival curve of AHSCT and allo-HSCT recipients is shown in Figure.

5 **4. Discussion**

6 Information on the course of COVID-19 in HSCT recipients remained scarce, and
7 mostly derived from case series involving limited number of patients. Survival rate of
8 the HSCT recipients is a matter of debate. Sultan et al. and Haroon et al. did not report
9 any mortality among seven and eleven HSCT recipients, respectively [3, 5]. However,
10 Varma et al. published the outcomes of HSCT recipients with COVID-19 where 32%
11 of the patients were treated in intensive care unit, and 21% died [7]. In another case
12 series, 2 of 7 HSCT recipients died due to COVID-19 [8]. In another study conducted
13 in Spain, mortality was 20% in allo-HSCT recipients, and 24% in AHSCT recipients
14 [9].

15 In another study, the CFR was 15.6% in HSCT recipients. The CFR of the HSCT
16 recipients who were receiving immunosuppressive treatment was reported as 33% in
17 that study [10]. The patients on immunosuppressive treatment can be considered at high
18 risk for COVID-19 as well as other viral infections.

19 In a cohort study examining the results of 318 HSCT recipients, overall survival 30 days
20 after the COVID-19 diagnosis was 68% (95% CI 58-77) in allo-HSCT recipients and
21 67% (95% CI 55-78) in AHSCT recipients [11].

22 In the present study, case fatality rate (CFR) is 9.1% (3/33) in all HSCT recipients,
23 22.2% (2/9) in patients with active hematologic malignancy, and 4.2% (1/24) in patients
24 without active hematologic malignancy.

1 All of the patients received favipiravir as soon as the diagnosis was made which could
2 lead to favorable outcome in the present study [12, 13].

3 This study reflects our experience though with a limited number of HSCT recipients,
4 given insight in the outcome of HSCT patients with COVID-19 infection.

5 CFR was 9.1% in all patients, and 4.2% in patients with primary disease in remission.

6 Based on the data above presented, it can be concluded that mortality of HSCT
7 recipients is lower in patients whose primary disease is in remission compared to ones
8 that are not in remission. Further studies with large group patients are needed in order
9 to delineate the effects of COVID-19 in HSCT patients.

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Table 1 – Baseline characteristics of the patients*

Median Age (min-max)	57 (27-71) years
Gender, n (%)	
Male	21 (63.6%)
Female	12 (36.4%)
Time from HSCT to COVID-19	
Median (min-max)	868 (31-2368) days
Primary Disease (Requiring HSCT), n (%)	
MM	9 (27.3%)
HL	1 (3.0%)
NHL	8 (24.2%)
AML	5 (15.2%)
ALL	3 (9.1%)
PID	2 (6.1%)
MF	1 (3.0%)
MDS	3 (9.1%)
ITP	1 (3.0%)
HSCT, n (%)	
AHSCT	19 (57.6%)
Allo-HSCT	14 (42.4%)
Uncontrolled Primary Disease, n (%)	9 (27.3%)
Use of Immunosuppressive Drugs, n (%)	
(Calcineurin inhibitors)	4 (12.1%)

Donor (n=14)	
Full matched donor, n (%)	12 (83.3%)
Haploidentical, n (%)	2 (16.7%)
GVHD, n (%)	6 (18.2%)
Chronic Diseases, n (%)	
CAD	4 (12.1 %)
CKD	7 (21.2%)
HT	8 (24.2 %)
COPD	1 (3.0 %)
DM	3 (9.1 %)
Non-hematologic malignancy	2 (6.1 %)

1 * MM: Multiple Myeloma, HL: Hodgkin-Lymphoma: NHL: Non-Hodgkin
2 Lymphoma, AML: Acute Myeloid Leukemia, ALL: Acute Lymphoblastic
3 Leukemia, PID: Primary Immunodeficiency, MF: Mycosis Fungoides, MDS:
4 Myelodysplastic Syndrome, ITP: Immune Thrombocytopenia, GVHD: Graft
5 versus Host Disease, CAD: Coronary Artery Disease, CKD: Chronic Kidney
6 Disease, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, DM:
7 Diabetes Mellitus

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Table 2 – The clinical findings in HSCT patients

Symptoms	
Fever	23 (69.7%)
Cough	14 (42.4%)
Myalgia	18 (54.6%)
Headache	19 (57.6%)
Anosmia	14 (42.4%)
Diarrhea	5 (15.2%)
Sore throat	4 (12.1%)
Shortness of Breath	10 (30.3%)
COVID-19 Severity	
Mild	20 (60.6 %)
Moderate	9 (27.3 %)
Severe or Critical Disease	4 (12.1 %)
Hospitalization	
n (%)	15 (45.5%)
Days, median (min-max)	12 (1-57) days
Treatment for COVID-19 (n, %)	
Hydroxychloroquine + Favipiravir	5 (15.6%)
Favipiravir	24 (75%)
Azithromycin + Hydroxychloroquine	3 (9.4%)

Intensive Care Unit Admission	
n (%)	4 (12.1%)
Days (mean \pm SD)	15.2 \pm 12.7
Mechanical Ventilation, n (%)	3 (9.1%)
Case Fatality Rate	3/33 (9.1%)
Duration to Death from COVID-19 (days)	
(mean \pm SD)	14.6 \pm 6.8

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Table 3 – Hospitalization rates according to parameters

Patients	Hospitalized	Non-Hospitalized	P-value
Gender			
Female (n = 12)	2 (13.3%)	10 (55.6 %)	0.01
Male (n = 21)	13 (86.7%)	8 (44.4 %)	
HSCT			
AHSCT	8 (53.3%)	11 (61.1 %)	0.65
Allo-HSCT	7 (46.7%)	7 (38.9 %)	
Remission Status of Primary Disease			
Yes	7 (46.7%)	2 (11.1%)	0.47
No	8 (53.3%)	16 (88.9%)	
GVHD (in Allo-HSCT patients, n = 14)			
Yes (n = 6)	2 (28.6 %)	4 (57.1 %)	0.59
No (n = 8)	5 (71.4 %)	3 (42.9 %)	

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Table 4 – The mortality rates according to parameters

Patients (n = 33)	Death (n = 3)	Survivor (n = 30)	P- value
Gender			0.2
Male	3 (100.0%)	18 (60.0%)	
Female	0 (0.0%)	12 (40.0%)	
HSCT			0.56
AHSCT	1 (33.3%)	18 (60.0%)	
Allo-HSCT	2 (66.7%)	12 (40.0%)	
Remission of Primary Disease			0.174
Yes (n = 9)	2 (66.7%)	7 (23.3%)	
No (n = 24)	1 (33.3%)	23 (76.7%)	
Use of Immunosuppressive Drug			0.33
Yes (n = 4)	2 (66.7%)	27 (90.0%)	
No (n = 29)	1 (33.3%)	3 (10.0%)	
GVHD (n=14)			1.0
Yes (n = 6)	1 (50.0%)	5 (41.7%)	
No (n = 8)	1 (50.0%)	7 (58.3%)	

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1 **Table 5 – Death and hospitalization rates according to COVID-19 treatment***

	Hydroxychloroquine + Favipiravir n = 5	Azithromycin + Hydroxychloroquine n = 3	Favipiravir n = 24
Hospitalization	4 (80.0%)	1 (33.3%)	13 (54.2%)
Non-Hospitalized	1 (20.0%)	2 (66.7%)	11 (45.8%)
Dead	0 (0.0%)	0 (0.0%)	3 (12.5%)
Survivor	5 (100.0%)	3 (100.0%)	21 (87.5%)

2 ***For this table n = 32, since the treatment records of a patient were not available.**

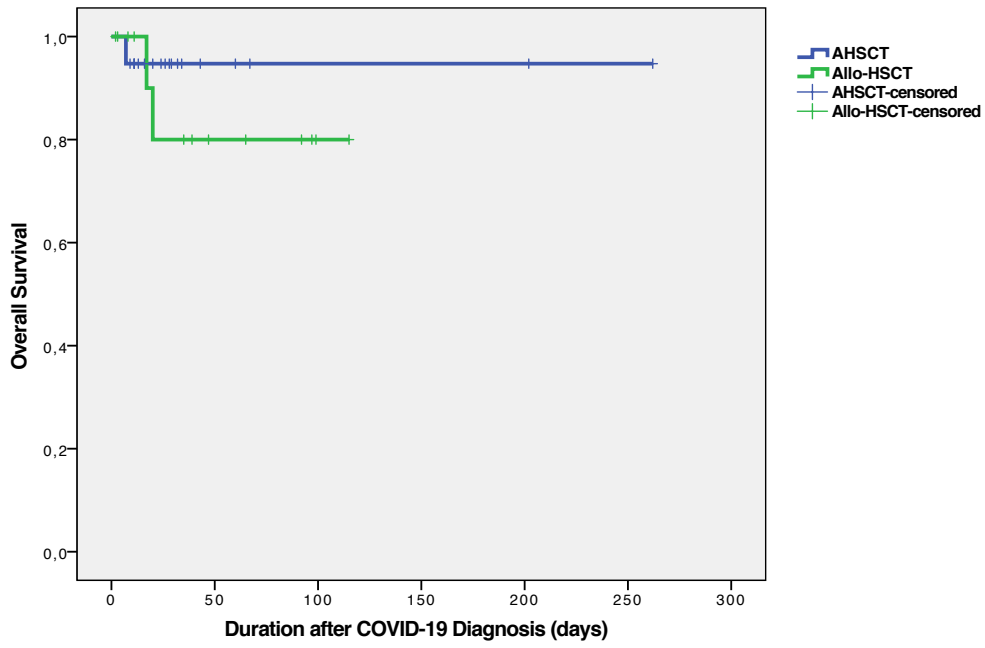
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Figure – Overall survival after COVID-19 diagnosis