Covid-19 Related Fatality and Risk Factors in Multiple Myeloma: A Multicenter Cohort Study

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ABSTRACT

The distinctive clinical course and outcomes of COVID-19 infection in multiple myeloma patients are still not well established. In this study, we aimed to assess the clinical outcomes and associated factors of COVID-19 in patients with multiple myeloma (MM). This is a multi-center retrospective cohort study. Multiple myeloma patients treated in two tertiary centers were investigated, and the patients diagnosed with COVID-19 during follow-up were included. The main characteristics and clinical outcomes of patients were analyzed. A total of thirty patients were included for analysis. In this cohort, autologous hematopoietic stem cell transplantation (AHSCT) was performed in 63.3% of the patients, and 36.7% were in complete remission when COVID-19 was detected. The total fatality rate (FR) was 36%, and the COVID-19-related case fatality rate (CFR) was 30% for MM patients in our cohort. There was two non-COVID-related mortality. The CFR was associated with intensive care unit admission (26.7%, p< 0.001), mechanical ventilation (26.6%, p< 0.001), increased lactate dehydrogenase (p= 0.008) and lymphopenia (p= 0.042). Older age (> 65-years), stem cell transplantation, and comorbidities were not effective on the fatality rate. This study shows that the CFR rate was high in MM patients, irrespective of AHSCT status. Therefore, we suggest strict monitoring and adequate vaccination in this group. However, further studies, including vaccination data with a larger group of patients, are needed to clarify the literature.

Keywords: Multiple myeloma, COVID-19, Intensive care unit admission

INTRODUCTION

The COVID-19 caused by the SARS-CoV-2, first identified in January 2020 because of research among a group of patients who had respiratory symptoms in Wuhan Province, China, late December in 2019. On March 11 2020, the World Health Organization (WHO) announced the pandemic.[1]

It has been shown that COVID-19 has various clinical situations from asymptomatic to acute respiratory distress syndrome, which may result in morbidity and mortality. The risk factors such as age, male gender, cardiovascular disease, hypertension, and diabetes are effective in the clinical course.[2] There are also studies showing that the infection progresses more severely in patients with hematologic or oncologic diseases and especially hematological malignancies rather than solid tumors seem to cause higher rates of morbidity and mortality because most of the patients are in immunosuppressive state associated with immun defects.[3-5] Multiple myeloma is a plasma cell neoplasm that accounts for 1%-1.8% of all cancers and is the second most common hematological malignancy.[6]

Multiple myeloma and chronic lymphocytic leukemia (CLL) are associated with the most severe immune defects.[7] Multiple myeloma, disease itself and the treatment modalities cause humoral immunodeficiency and impared B-cell response against viruses like SARS-CoV-2. MM patients also have higher risks for secondary infections.

AHSCT recipients carry the same risk as MM patients about infections because of humoral and cellular immunosuppression states.[8] We have investigated the COVID-19 outcomes in multiple myeloma patients.

PATIENTS AND METHODS

This is a multi-center retrospective cohort study of patients treated at two university hospitals. Patients diagnosed with COVID-19 among the patients who were followed-up for the diagnosis of active multiple myeloma at Ondokuz Mayıs University and Hacettepe University Hospitals between April 1, 2020 and March 30, 2021 were included in the study. The International Myeloma Working Group criteria were used for the objective diagnosis of active multiple myeloma. COVID-19 was diagnosed with a positive result of reverse-transcriptase polymerase chain reaction (RT-PCR) test from upper respiratory tract swab samples or bronchoalveolar lavage fluids. Demographic data, comorbidities, myeloma response status, hospitalization after the diagnosis of COVID-19, ICU or mechanical ventilation needs, and final status (alive or dead) of the patients were noted from the electronic records of the hospitals. The ethical approvals were obtained from the Turkish Ministry of Health and the local ethics committee with decision number 2021/11-26.

Statistical Analysis

IBM SPSS Statistics for Windows V26 (IBM Corp., Armonk, NY, USA) were used for statistical analyses. Categorical data were analyzed using Chi-square or Fisher's exact test. The distribution of continuous data was examined using the Student t-test and Mann-Whitney U test. Mean ± standard deviation and median (minimum-maximum) values were given for normally distributed continuous and nonnormally distributed variables, respectively. The Kaplan–Meier method was used for overall survival analysis. The values in lymphocyte 1000 actuation were taken for the lymphopenia limit. The value of 250, which is the upper limit ot the LDH kit was used as the limit. Multivariable logistic regression was used to determine the risk factors that independently predict mortality among patients with COVID-19. The results are expressed as relative risk and 95% confidence interval (CI). A p value less than 0,05 was considered statistically significant.

Table 1. Patients baseline characteristics

Variable	n (%)
Age	
> 65 years	14 (46.6%)
< 65 years	16 (53.4%)
Gender	
Female	10 (33.3%)
Male	20 (66.7%)
Co-morbidities	
No co-morbidity	7 (23.3%)
One co-morbidity	10 (33.3%)
2 ≤ co-morbidities	13 (43.4%)
AHSCT	
Prior COVID-19	15 (50%)
Post-COVID-19	4 (13.3%)
No transplantation	11 ((36.7%)
Myeloma subgroup	
IgG kappa	13 (43.3%)
IgG lambda	4 (13.3%)
IgA kappa	4 (13.3%)
IgA lambda	3 (10.0%)
Kappa light chain	5 (16.7%)
Lambda light chain	1 (3.3%)
Chemotherapy courses	
≤ 4	2 (6.7%)
5-9	21 (70%)
≥ 10	7 (23.3%)

RESULTS

Thirty-patients (20 male and 10 female) were included in the study. The mean age of the study population was 63.5 ± 8 years. 75% of the patients had one or more co-morbidities such as hypertension, diabetes, chronic renal failure or cardiovascular disease. Nineteen (63.7%) of the patients underwent autologous hematopoietic stem cell transplantation (AHSCT) and only three (10%) had active disease before the transplant procedure. The fatality rate (CFR) was 30% in MM patients. At the time of PCR positivity in the non-transplanted group, all patients were under active treatment. The

Table 2. Hospitalization and intensive care unit admission data

	Hospitalization n (%)	ICU admission n (%)	Mechanical ventilation n (%)	Covid-19 Exitus n (%)
Total	19 (63.3%	8 (26.7%)	8 (26.7%)	9 30%
Age				
< 65	11 (57.8%)	4 (50%)	4 (50%)	4 (44.4%)
> 65	8 (42.2%)	4 (50%)	4 (50%)	5 (55.6%)
Gender				
Female	5 (26.3%)	4 (50%)	4 (50%)	4 (44.4%)
Male	14 (73.6%)	4 (50%)	4 (50%)	5 (55.6%)
Co-morbidity				
No	5 (26.4%)	2 (25%)	2 (25%)	3 (33.3%)
One	7 (36.8%)	3 (37.5%)	2 (25%)	2 (22.2%)
2 ≤	7 (36.8%)	3 (37.5%)	4 (50%)	4 (44.5%)
AHSCT	12 (63.1%)	5 (62.5%)	5 (62.5%)	5 (55.5%)

total fatality rate (FR) was 36% and there was one non-COVID-related death in this group. Amongst the AHCST recipients CFR was 26% (5 patients) and 8 (42%) of these patients were on without any active treatment. The CFR of MM patients who did not recieve AHSCT was 36.3% (4 patients). The patients baseline characteristics are summarized in Table 1.

Table 3. Detailed p value table

Variable	p
Age	p= 0.694
Gender	p= 0.431
Co-morbidity	p= 0.596
Disease subtype	p= 0.260
Disease status	p= 0.607
Chemotherapy courses	p= 0.145
AHSCT	p= 0.687
Hospitalization duration	p= 0.169
ICU admission	p< 0.001
Mechanical ventilation	p= 0.001
Ferritin (> 500 µg/L)	p= 1.000
LDH (> 250 U/L)	p= 0.008
Leucocytosis (> 10000/ µL)	p= 0.555
Lymphopenia (< 1000/ µL)	p= 0.042
Neutrophenia (< 3000/ µL)	p= 0.419
Thrombocytopenia (< 150000/ µL)	p= 0.401

63% (19) of the patients were hospitalized. The ICU admission rate was 26.7% and invasive mechanical ventilation support needed for 23.3% of patients and noninvasive mechanical ventilation need was 3.3% in ICU. The fatality rate in ICU was high, up to 87%. Older age (> 65) (p= 0.011) and lactate dehydrogenase (LDH) level higher than 250 (p= 0.014) were statistically significant for ICU admission and ICU admission rate was higher in prolonged hospitalization. The need for mechanical ventilator support increased as the length of intensive care stay prolonged. Ferritin elevation, leukocytosis, neutropenia, thrombocytopenia was not effective in intensive care admissions. Hospitalization and intensive care unit admission data are summarized in Table 2.

COVID-19 related fatality in MM patients was associated with ICU admission (p< 0.001), mechanical ventilation (p= 0.001), lymphopenia (p= 0.042) and lactate dehiyrogenase level (p= 0.008). We have emphasized that age, gender, stem cell transplantation prior or post-COVID-19 (p= 0.687), having co-morbidities, disease status or type, ferritin level, cytosis or cytopenias excluding lymphopenia were not predictors of fatality. Detailed p value table is stated below in Table 3.

In Kaplan- Meier analysis, the survival in MM patients who had COVID-19 was associated with the ICU admission (p< 0.001), lymphopenia (p= 0.039), mechanical ventilation (p< 0.001) and lac-

tate dehydrogenase (p= 0.007), however gender (p= 0.380), age (> 65 years) (p= 0.511), having co-morbidities (p= 0.460), subgroup of MM (p= 0.381), ferritin level (p= 0.455), thrombocytopenia (p= 0.208) or neutropenia (p= 0.330) was not effective in adverse outcomes.

DISCUSSION

Multiple myeloma patients are one of the most risky subgroups among malignancies contracting COVID-19 in terms of morbidity and mortality due to the immunosuppressive status. Although many studies have been done in MM patients during COVID-19, the results are unclear and inconsistent in terms of risk profile and factors affecting mortality. The experience in MM patients with COVID-19 was shared in this study.

In the literature many studies reported FR related to COVID-19 in hematological malignancies between 18% and 45%.[8-11] CFR in myeloma patients was 57% in a study done by Dhakal et al.[12] According to another study by Wang. et al. patients with hematological malignancies requiring frequent visits to hospitals are also at high risk of getting infected due to their immunocompromised state.[13] In our study CFR in MM patients was 30%. J. Martínez et al. reported increased fatality in male sex but Chari et al. demonstrated sex was not associated with worse outcomes.[14,15] The gender was not statistically different between groups in this study. CFR in MM patients was similar to recent studies.

The determined factors related to mortality were higher age, having co-morbidities, hospitalization and intensive care unit admission. Chari et al. reported 60 and 80 years old patients FR as 31.43% and 49.3%, respectively.[15] In a study by Hultcrantz et al age was not significantly associated with a worse outcome.[16] We reported that higher age (> 65 years) was not an independent predictor of mortality in MM patients. According to the recent studies stem cell transplantation, having active or recent chemotherapy, primary disease status was not effective in the clinical course of COVID-19 in myeloma patients and patients with hematological malignancy.[16,17] In a study including 7 MM patients the outcomes were not associated with disease activity.[12]

Krejci et al. reported having two and more co-morbidities was an independent risk factor for poor prognosis (p= 0.007).[11] In a cohort study in which 167 MM patients were examined, FR was 37% in patients with at least one co-morbidity and 22% in with no co-morbidity.[14] Chari et al. also reported that co-morbidies were significant in fatality (p= 0.040).[15] We have shown that having comorbidities were not related to the CFR in MM patients (p= 0.590).

In a multicentre retrospective cohort study, hospitalization rate was between 27% and 57% in different centers consisting of 650 MM patients.[15] The hospitalization rate was higher in this study, it may be due to insufficient knowledge and experience about COVID-19 at the beginning. ICU admission was also an independent risk factor for fatality. In a short by Krejci et al., 50 MM patients were analyzed and the most important factor affecting the worse outcome was ICU need (p= 0.001). Another study by Atay et al. showed that patients with hematological malignancies had the fatality rate due to COVID-19 infection as 42.2% and also detected ICU admission was a significant risk factor.[18] We demonstrated that ICU admission rate was 26% and fatality was 87% in the patients in ICU (p< 0.001).

A retrospective study reported increased mortality rate in higher ferritin level (32%), neutrophilia (43%) and lymphopenia (43%).[14] According to another study, 201 COVID -19 infected patients were detailed by Wu et al. and higher lactate dehydrogenase level was related to FR (p= 0.010).[19] Lymphopenia (p= 0.042) and higher lactate dehydrogenase (p= 0.008) were statistically significant, lactate dehydrogenase was also an independent factor for ICU admission in the present study (p= 0.014).

In summary, we have demonstrated a high fatality rate in MM patients with COVID-19. The ICU admission, mechanical ventilation, LDH and lymphopenia were the independent risk factors for the CFR. The CFR was 26% in AHSCT recipients while the CFR of MM patients who did not recieve AHSCT was 36.3% in this small group of MM patients with COVID-19.

There are some limitations of our study, mainly due to its retrospective nature, the small number

of patients, the short follow-up period and the fact that it was conducted before the vaccination process. Further studies with larger subgroups including vaccination data are needed to clarify the factors that effect outcomes in patients with MM.

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