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Original Article

Clinical Findings and Mortality Rate of Patients with Multiple Myeloma Following COVID-19 infection: Report from Iranian Network for Research in Viral Diseases (INRVD)

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Abstract

Background and Aims: COVID-19 is a viral disease that spreads easily, caused by the SARS-CoV-2 virus. This illness has led to a worldwide pandemic and has caused many human fatalities. Patients with cancer have a weakened immune system, which makes them more susceptible to various infections. In this research, we wanted to compare mortality, hospitalization rate, and clinical findings in multiple myeloma (MM) patients.

Materials and Methods: This research examined the effect of COVID-19 on sixteen individuals diagnosed with MM. Four hospitals—Imam Khomeini, Rouhani, Shariati, and Sina—were included in the study. All participants in affiliated hospitals underwent Real-time PCR testing to determine whether they had a viral infection with SARS-CoV-2. According to Iranian CDC guidelines, the real-time reverse transcription-polymerase chain reaction (RT-PCR) test was performed on throat specimens using flocked swabs obtained immediately upon admission to confirm SARS-CoV-2 infection. Collaborative clinical virology necessitates the utilization of two pairs of primers, each designed to target two specific genes (the E gene and the RdRP gene).

Results: Patients with MM were found to have a considerably higher risk of hospitalization and mortality from COVID-19, as per the study results. Common symptoms observed in MM patients with COVID-19 included fever (87.5%), cough (87.5%), and dyspnea (62.5%). Moreover, the study revealed a substantial 17-fold increase in the odds of MM patients with COVID-19 positive compared to their counterparts without COVID-19.

Conclusion: The study results emphasize the critical significance of prompt identification of COVID-19 among patients with MM. It underscores the importance of implementing public health measures, vaccination efforts, and continued research to effectively prevent severe illness and fatalities related to COVID-19 within this vulnerable population.

Keywords: Multiple Myeloma, COVID-19, SARS-CoV-2, Respiratory Infection, Cancer

Introduction

The Coronavirus disease 2019 (COVID-19) has emerged due to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has become a major issue of concern. The World Health Organization (WHO) has repor-ted a total of 6,985,278 COVID-19 deaths worldwide as of November 2023 (1). Both individuals with underlying disorders and good health have been affected by this virus (2). Typically, individuals with COVID-19 experience symptoms such, as cough, fever, and fatigue (figure 1) (2).

Symptoms of COVID-19 can vary in their intensity, from mild to severe. Severe cases of the illness may present, pneumonia, low oxy-

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gen levels, respiratory failure, acute respiratory distress syndrome immune system imbalance, excessive cytokine release, blood clotting events, and dysfunction of organs may also happen. Certain factors have been identified as increasing the risk of severe COVID-19 disease. These include male gender, advanced age, smoking, and comorbidities such as hypertension and other underlying disorders. People with these risk factors should take extra precautions to avoid contracting the virus and stay vigilant about their health (3, 5).

Nowadays, many studies have investigated the relationship between cancer and viruses (6-8). These studies show that viral infections can increase the risk of some cancers and some viruses can increase the risk of developing cancer and autoimmune disease (9, 10). Multiple myeloma (MM), has become highly significant in the context of COVID-19 (7).

Those with multiple myeloma have compromised immune systems, making them more vulnerable to viral infections. Moreover, underlying diseases including diabetes, cardiovascular disease, and chronic lung disease have been linked to severe outcomes in COVID-19 patients (7, 11, 12). Recognizing the importance of multiple myeloma and underlying diseases in COVID-19 helps in tailoring strategies to protect this vulnerable population, implement timely interventions, and allocate resources appropriately (Figure 1) (13).

Detecting and controlling the spread of the virus is essential and requires a good understanding of its symptoms (14). In the context of the COVID-19 outbreak, clinicians have faced a diverse range of clinical manifestations. Some patients experienced mild symptoms like coughing and a runny nose, while others suffered from more severe complications like pneumonia and respiratory failure (Figure 2). Other serious complications included hypoxia, acute respiratory distress syndrome, thromboembolism, multi-organ failure, immune dysfunction, and cytokine release syndrome-related issues (15, 16). Throughout the observed time frame, there is a significant risk of health complications and death for individuals with MM who also contracted COVID-19 .

This study aimed to assess clinical manifestations and outcomes of infection with COVID-19 in MM patients compared to those who were negative for COVID-19. The data for this study were collected from hospitals supervised by the Iranian Network for Research in Viral Diseases (INRVD).

Methods and Materials

Study Population

The study was conducted at four hospitals: Imam Khomeini, Rouhani, Shariati, and Sina, supervised by the INRVD. Of all our patients, there were an equal number of males and females, with 8 individuals (50%) in each category. All 16 patients were diagnosed with multiple myeloma (MM), a form of blood cancer, and exhibited respiratory symptoms upon hospital admission. Among these 16 patients, half (50%) tested positive for COVID-19, while the remaining 8 patients (50%) formed the control group as they did not have COVID-19. Data collection took place from March 2020 to May 2021. To confirm the presence of SARS-CoV-2 infection, Real-time PCR tests were performed on all participants in associated hospitals.

The RT-PCR test on throat specimens using flocked swabs, taken immediately upon admission, was used to confirm SARS-CoV-2 infection by Iranian CDC standards. To target two genes (the E and RdRP genes), collaborative clinical virology has to use two sets of primers. The dual-target detection kits and a procedure were supplied to all laboratories throughout the nation by the Iranian Pasture Institute.

A patient's respiratory sample would have been deemed positive and the illness would have been deemed laboratory-confirmed if tests for one or both genes had been satisfactorily completed (22). Ethical approval was obtained from the Ethics Committees of Tehran

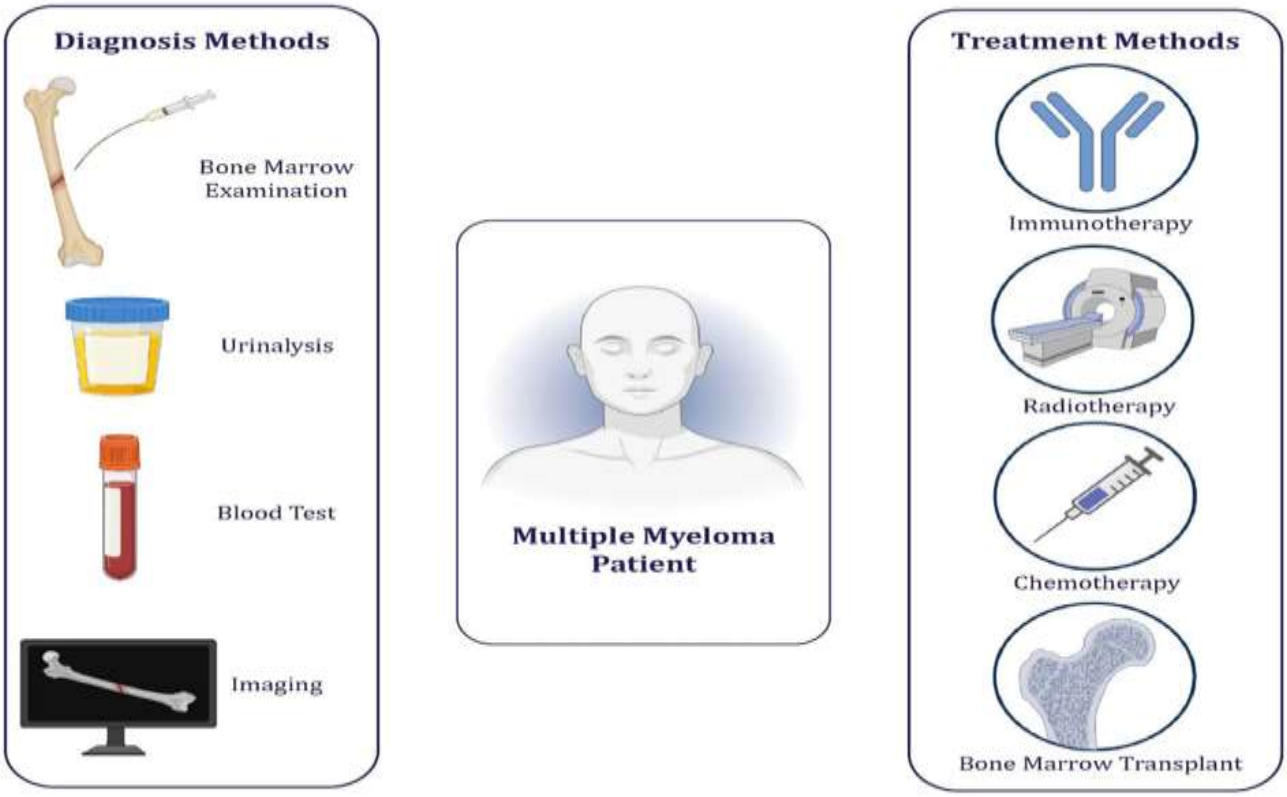


Fig 1. Detecting and treating multiple myeloma patients can be approached in different ways. Still, the most efficient method to diagnose it is by utilizing low-dose WB-CT, PET/CT scans using FDG, or MRI. These imaging techniques offer the best images for identifying MM (17). When diagnosing MM, two key criteria must be met: first, there must be at least 10% of bone marrow plasma cells or evidence of bone or extramedullary involvement; and second, there must be at least one myeloma-defining event (MDE), including hypercalcemia, renal insufficiency, anemia, bone lesions, and more. These criteria are essential for identifying and confirming the presence of MM (18). The treatment of MM is complicated and different based on the patient's situation such as chemotherapy, bone marrow transplantation immunomodulatory drugs, and radiotherapy (19-21).

University of Medical Sciences, Iran (IR.TUMS.VCR.REC.1399.599), and every patient involved provided informed consent.

Statistical Analysis

Here we used mean, standard deviation, and frequency to describe data. Mann-Whitney test was performed to test age equality in case and cancer-free groups. Fisher's exact test was employed to examine whether binary variables were associated with or independent of study groups. The analysis was conducted using the statistical software SPSS-27. Odds ratios were computed and assessed using the R package version 4.2.3.

Results

Demographic Data

This research examined multiple myeloma patients who had respiratory symptoms. There were 16 patients, of which 7 (43.75%) and 9 (56.25%) were female and male. The case group included 8 people with COVID-19, 4(50.0%) women and 4(50.0%) men, and 8 people without COVID-19 as the control group, which included 3(37.5%) women and 5(62.5%) men. We compared their clinical characteristics. The mean age in the multiple myeloma group was 69.0 years (standard deviation = 13.87), while in the other group, it was 70.3 years (standard deviation = 13.75). The age of patients in the two groups did not show any notable variation. (P-value = 0.878). Furthermore, the gender proportion was similar

in both the case and control groups (P-value = 1). The results are found in Table 1 and Figure 2.

Table 1. COVID-19 symptoms comparison in case and control group.

Symptom	Group N (%) of positive subjects		P-value[+]
	Case (n=8)	Control(n=8)	
Cough	7(87.5%)	5(62.5%)	0.589
Rhinorrhea	2(25.0%)	1(12.5%)	1.000
Sore throat	4(50.0%)	5(62.5%)	1.000
Breath shortness	5(62.5%)	4(50.0%)	1.000
Diarrhea	7(87.5%)	5(62.5%)	0.569
Myalgia	2(25.0%)	1(12.5%)	1.000
Fatigue	6(75.0%)	3(37.5%)	0.315
Nausea	3(37.5%)	0	0.200
Vomit	4(50.0%)	3(37.5%)	1.000
Diarrhea	4(50.0%)	1(12.5%)	0.282
Hospitalization	7(87.5%)	1(12.5%)	0.010*
Death	4(50.0%)	0	0.077**

[+] Fisher's exact test was performed.
* Significant at 5% type I error
** one-sided p-value is equal to 0.038

Clinical Manifestations

Most patients (87.5%) in the case group were hospitalized following COVID-19 infection. Only one (12.5%) subject in the control group, was hospitalized due to respiratory symptoms. Hospitalization was statistically related to having MM and COVID-19 (p-value=0.010). The odds of death due to COVID-19 in the multiple myeloma group were 17 times than the odds in the control group (Odds ratio=17, P-value=0.08). However, it was not statistically significant. The 95% confidence interval was very wide (95% CI: (0.7, 391.7)).

In the case group, the most common symptoms were cough (87.5%), diarrhea (87.5%), fatigue (75.0%), and Breath shortness (62.5%) and compared to the control group, most of the symptoms manifested with a higher intensity, except for sore throat, which had a higher percentage (62.5%) in the control group.

Discussion

SARS-CoV-2's significance stems from its effects on the world's health, economy, and society. (4, 21). SARS-CoV-2 is overwhelming the resources of the healthcare system and has a significant impact on medical care. In addition to generally decreasing the availability of medical treatment, the COVID-19 pandemic specifically affects oncological care. People with current cancer may be more susceptible to COVID-19, according to reports. A more severe course of COVID-19 may be independently associated with cancer (24).

This study compared the clinical characteristics of 16 patients suffering from multiple myeloma with respiratory symptoms. The case group included 8 people with COVID-19 and 8 people without COVID-19 as the control group. Following their COVID-19 infection, the majority of patients (87.5%) in the case group were admitted to the hospital. In the control group, hospitalization for respiratory symptoms occurred in just one person (12.5%). Hospitalization was significantly associated with COVID-19 and MM. The multiple myeloma group had 17 times greater risks of dying from COVID-19 than the control group did. It was not statistically significant, though. The study found that among clinical symptoms, cough and diarrhea had the highest prevalence at 87.5%. This was followed by fatigue at 75.0% and breath shortness at 62.5% in MM patients with COVID-19. Most of the symptoms were more intense in the MM patients with COVID-19 than in the control group. Research specifically examined the mortality rates for hospitalized patients with multiple myeloma and COVID-19. They found a mortality rate of 4% for outpatients, 31% for non-ventilated patients, and 80% for ventilated patients. These findings align with the mortality rates observed in our study, indicating consistency in the impact of COVID-19 on individuals with multiple myeloma (25).

A study conducted by Dhakal et al analyzed 7 patients with multiple myeloma who were infected with COVID-19. These patients' most common clinical symptoms were fever, dry cough, and shortness of breath. Furthermore, 71% of the patients were admitted to the hospital while suffering from COVID-19.

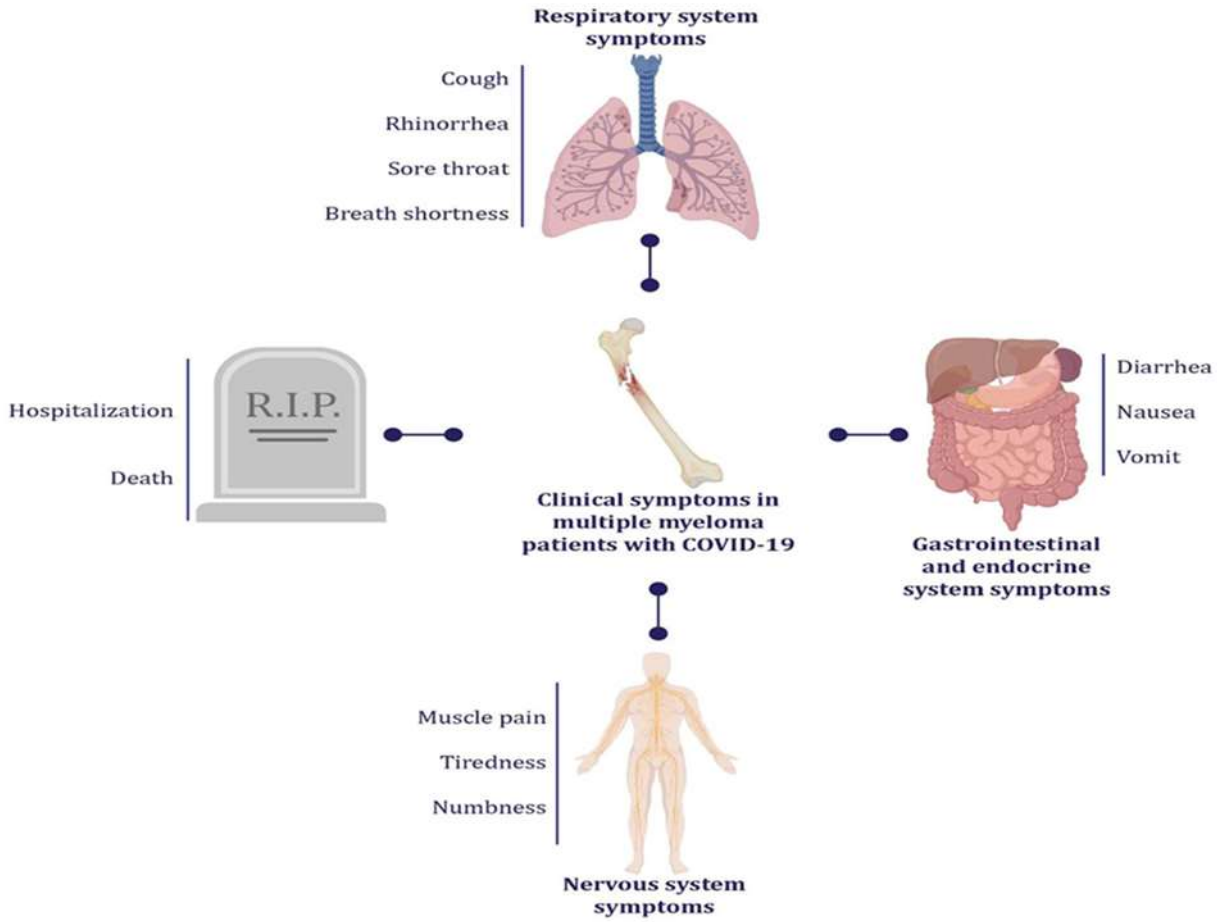


Fig 2. There are several clinical symptoms associated with COVID-19, including fever, cough, myalgia, fatigue, expectoration, and dyspnea. Some patients may also experience gastrointestinal issues like diarrhea, nausea, and vomiting (23). [Created with BioRender. com]

The outcomes of our investigation align with the observations made by Binod Dhakal et al. Our study revealed similar symptoms in the case group, including fever, cough, myalgia, fatigue, expectoration, and dyspnea.

Additionally, we observed that some individuals in the case group also presented with gastrointestinal symptoms such as diarrhea, nausea, and vomiting (26). In the study of Hultcrantz et al, 100 patients with COVID-19 who had the underlying disease of multiple myeloma were examined. Many factors were investigated in this study, including the death rate due to COVID-19 and the number of people who were admitted to the hospital. Out of 100 individuals diagnosed with both multiple myeloma and COVID-19, 75 required hospitalizations. Among them, 13 patients (17%) needed invasive mechanical ventilation, and 22 patients (29%) passed away. In our investigation, following COVID-19 infection, 87.5% of patients in the case group required hospitalization. Although the statistical population of Hultcrantz'study is about 10 times larger than the statistical population of our study, there is consistency between the results (27).

Some studies have indicated that patients with both multiple myeloma (MM) and COVID-19 who are hospitalized may have a higher risk of mortality than those without myeloma. Recent research conducted in Spain showed that MM patients with COVID-19 had a higher mortality rate (34%) than non-MM patients with COVID-19 of the same age and sex (23%). The multiple myeloma group had 17 times the chance of dying from COVID-19 in our study compared to the control group (28).

According to a study, patients with MM have higher rates of hospitalization and mortality from SARS-CoV-2 than the general population. This is especially true for patients under-

going aggressive chemotherapy. Advanced age, high-risk myeloma, renal disease, inadequate disease management, and COVID-19 are independent predictors of unfavorable outcomes. in our inquiry Following their COVID-19 infection, the majority of patients (87.5%) in the case group were admitted to the hospital. In the control group, hospitalization for respiratory symptoms occurred in just one person (12.5%). A significant relationship was found between hospitalization and both COVID-19 and MM (p-value = 0.010) (29).

An additional inquiry was carried out to analyze the impact of COVID-19 on individuals with pre-existing neurological conditions. The results showed that among clinical symptoms, cough was most common (79%), followed by fever (62%), and fatigue (57%). It is interesting that in the current study, the prevalence rates of fatigue and cough were comparable. However, diarrhea was far more common in those who had multiple myeloma (30).

The article discusses the varying severity and mortality rates among individuals with both multiple myeloma and COVID-19. Although our study was conducted in several hospitals, the limited sample size and the potential influence of chemotherapy and other treatments on patients may affect our results, which need further investigation. Also, comparison of clinical symptoms in COVID-19 patients compared to other types of cancers and stage of the cancer must be investigated in future studies.

Conclusions

The findings obtained from this study emphasize the importance of knowing the different impacts of COVID-19 on patients with multiple myeloma. Due to COVID-19, most patients (87.5%) in the case group required hospita-lization. In the control group, hospitalization for respiratory symptoms occurred in just one patient. Except for sore throat, which was more common in the control group, the case group displayed the majority of symptoms more severely than the control group. Chemotherapy or other systemic anticancer medications may make these patients more susceptible to severe infections and other symptoms. It is crucial to implement appropriate strategies for the clinical management of COVID-19 patients who have a history of cancer, particularly multiple myeloma. Having a better understanding of the unique characteristics of these patients can help in creating more precise diagnostic and treatment plans.

Moreover, the higher incidence of specific symptoms in people with underlying multiple myeloma highlights their increased vulnerability to the effects of COVID-19. This research highlights the necessity, amid an ongoing pandemic, to give priority to early detection, prevention strategies, and specialized treatment for individuals with cancer, including multiple myeloma. In the end, a thorough comprehension of these relationships will enhance therapeutic results and guide public health initiatives targeted at safeguarding susceptible groups.

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Authors' Contributions

None

Disclosure

None

Conflict of Interest

No conflict of interest is declared.

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committees of the Tehran University of Medical Sciences in Iran. (IR.TUMS.VCR.REC.1399.599), and we obtained consent from every participant.

References

1. Creecy A, Awosanya OD, Harris A, Qiao X, Ozanne M, Toepp AJ, et al. COVID-19 and Bone Loss: A Review of Risk Factors, Mechanisms, and Future Directions. Curr Osteoporos Rep. 2024;22(1):122-34.
2. Haybar H, Kazemnia K, Rahim F. Underlying chronic disease and COVID-19 infection: a state-of-the-art review. Jundishapur J Chronic Dis Care. 2020;9(2): e103452.
3. Aslaner H, Aslaner HA, Gökçek MB, Benli AR, Yıldız O. The effect of chronic diseases, age and gender on morbidity and mortality of COVID-19 infection. Iran J Public Health. 2021;50(4):721-7.
4. Gasmi A, Peana M, Pivina L, Srinath S, Benahmed AG, Semenova Y, et al. Interrelations between COVID-19 and other disorders. Clin Immunol. 2021;224: 108651.
5. Kharroubi SA, Diab-El-Harake M. Sex-differences in COVID-19 diagnosis, risk factors and disease comorbidities: A large US-based cohort study. Front Public Health. 2022;10:1029190.
6. Letafati A, Aghamirmohammadali FS, Rahimi Foroushani A, Hasani SA, Mokhtari Azad T, Yavarian J. No human respiratory syncytial virus but SARS-CoV-2 found in children under 5 years old referred to Children Medical Center in 2021, Tehran, Iran. J Med Virol. 2022;94(7):3096-100.
7. Ghorbani S, Letafati A, Khatami A, Farzi R, Shabani S, Moradi P, et al. Association between human herpesvirus-6 and primary brain tumors: a systematic review and meta-analysis. Future Virol. 2022;17(5):305-14.
8. Maskouni EJ, Jamalvandi T, Tabatabaei F, Shirazi SB, Saadati H, Letafati A, et al. Association between Epstein-Bar virus and colorectal cancer: A systematic review and meta-analysis. Microb Pathog. 2023:106087.
9. Ghorbani S, Tambrchi V, Farzi R, Khatami A, Samiei RN, Saadati H, et al. Association between human Epstein–Barr virus and brain cancer: a systematic review and meta-analysis. Future Virol. 2023;18(8):537-45.
10. Letafati A, Sakhavarz T, Khosravinia MM, Ardekani OS, Sadeghifar S, Norouzi M, et al. Exploring the correlation between progression of human papillomavirus infection towards carcinogenesis and nutrition. Microb Pathog. 2023:106302.
11. Liu C, Zhao Y, Okwan-Duodu D, Basho R, Cui X. COVID-19 in cancer patients: risk, clinical features, and management. Cancer Biol Med. 2020;17(3):519-27.
12.Terpos E, Engelhardt M, Cook G, Gay F, Mateos M-V, Ntanasis-Stathopoulos I, et al. Management of patients with multiple myeloma in the era of COVID-19 pandemic: a consensus paper from the European Myeloma Network (EMN). Leukemia. 2020;34(8):2000-11.
13. Martinez Lopez J, Hernandez Ibarburu G, Alonso R, Sanchez Pina J, Zamanillo I, Lopez Muñoz N, et al. Impact of COVID-19 in patients with multiple myeloma based on a global data network. Blood Cancer J. 2021;11(12):198.
14. Anderson RM, Fraser C, Ghani AC, Donnelly CA, Riley S, Ferguson NM, et al. Epidemiology, transmission dynamics and control of SARS: the 2002–2003 epidemic. Philos Trans R Soc Lond B Biol Sci. 2004; 359(1447):1091-105.
15. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med. 2020;382(18):1708-20.
16. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-9.
17. Gerecke C, Fuhrmann S, Strifler S, Schmidt Hieber M, Einsele H, Knop S. The Diagnosis and Treatment of Multiple Myeloma. Dtsch Arztebl Int. 2016;113(27-28):470-6.
18. Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma. American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting. 2016;35:e418-23.
19. Barlogie B, Alexanian R, Dicke KA, Zagars G, Spitzer G, Jagannath S, et al. High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. Blood. 1987;70(3):869-72.
20. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood. 1986;67 (5):1298-301.
21. Mose S, Pfitzner D, Rahn A, Nierhoff C, Schiemann M, Böttcher HD. [Role of radiotherapy in the treatment of multiple myeloma]. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2000; 176(11):506-12.
22. Sedighi I, Fahimzad A, Pak N, Khalili M, Shokrollahi MR, Heydari H, et al. A Multi-Center Retrospective Study of Clinical features, Laboratory Characteristics, And Outcomes of 166 Hospitalized Children with Coronavirus Disease 2019 (COVID-19); A Preliminary Report from Iranian Network for Research in Viral Diseases (INRVD). Pediater Pulmonol. 2022;57(2):498-507.
23. Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz R, et al. COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. J Clin Med. 2020;9(6): 1753.
24. de Joode K, Dumoulin D, Engelen V, Bloemendal H, Verheij M, van Laarhoven H, et al. Impact of the

coronavirus disease 2019 pandemic on cancer treatment: the patients' perspective. Eur J Cancer. 2020;136:132-9.
25. Chari A, Samur MK, Martinez-Lopez J, Cook G, Biran N, Yong K, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. Blood. 2020;136(26):3033-40.
26. Dhakal B, D'Souza A, Chhabra S, Hari P. Multiple myeloma and COVID-19. Leukemia. 2020;34(7):1961-3.
27. Hultcrantz M, Richter J, Rosenbaum CA, Patel D, Smith EL, Korde N, et al. COVID-19 infections and clinical outcomes in patients with multiple myeloma in New York City: a cohort study from five academic centers. Blood Cancer Discov. 2020;1(3):234-43.
28. Martínez-López J, Mateos M-V, Encinas C, Sureda A, Hernández-Rivas JÁ, Lopez de la Guia A, et al. Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality. Blood Cancer J. 2020;10(10):103.
29. Zheng R, Mieth K, Bennett C, Miller C, Anderson Jr LD, Chen M, et al. Clinical Features and Risk Stratification of Multiple Myeloma Patients with COVID-19. Cancers (Basel). 2023;15(14):3598.
30. Aboofazeli A, Sarrafzadeh S, Najafabadi AQ, Hammami B, Soheili R, Sadeghi A, et al. A Survey on respiratory and neurological symptoms in Alzheimer's, Schizophrenia, Bipolar, and Migraine patients following COVID-19 infection. Arch Neurosci. 2023;10(4): e140959.