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# Does the diagnosis of multiple myeloma show a seasonal difference?

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**Abstract**

**Aim:** Multiple myeloma (MM) is a heterogeneous disease caused by genetic and environmental factors. The present study aims to determine whether the diagnosis of MM exhibits a seasonal pattern.

**Materials and Methods:** Eighty new diagnosed patients with MM between January 2020 and July 2024 were included in the study. All data on gender, age and time of diagnosis were retrospectively analyzed from the files of patients.

**Results:** Eighty patients newly diagnosed with MM were included in the study. Thirty-four (42.5%) of them were female and 46 (57.5%) were male. The median age of the patients was 63 years (41-81). The month with the highest number of MM diagnoses was November, with nine patients (11.3%), while the month with the least number of diagnoses was July, with four patients (5%). The season with the highest number of diagnoses was winter, with 22 patients (27.5%) diagnosed, followed by spring and autumn, each with 20 patients (25%). The least number of MM diagnoses was observed in the summer, with 18 patients (22.5%). This observation did not reach statistical significance ($p>0.05$). Among the 80 patients, 44 were diagnosed between October and March, while 36 were diagnosed between April and September. The number of new cases was higher in the colder seasons.

**Conclusion:** In our study, the diagnosis of MM does not appear to show seasonal variation. We observed that new cases with MM increased in the cold months. Since infections are a common presenting feature in Multiple Myeloma (MM), clinicians should maintain a high index of suspicion for MM in patients with recurrent or unusual infections.



## Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of monoclonal plasma cells in the bone marrow. These plasma cells originate from post-germinal center B lymphocytes. MM represents approximately 1% of all cancers and is the second most common hematologic malignancy, following lymphoma. The median age at diagnosis is 66-70 years, with approximately 37% of cases occurring in individuals younger than 65. MM is rare in young individuals, particularly those under 30 years old. While familial cases are reported, MM is generally not considered a genetically inherited disease [1-3]. Studies on patients with MM have contributed to a better understanding of the pathophysiology of the disease. Mutations involving chromosome 14 are common in MM and lead to disease development. Mutations involving NRAS (Neuroblastoma RAS viral oncogene homolog), KRAS (Kirsten rat sarcoma viral oncogene homolog), and BRAF (B-Raf proto-oncogene, serine/threonine kinase) play a significant role in the uncontrolled proliferation of plasma cells.

Obesity, alcohol consumption, and exposure to environmental factors such as pesticides, organic solvents, and radiation have been associated with an increased risk of developing MM. The incidence of MM is known to be higher in individuals of Black ethnicity and in males [4,5]. The consumption of fruits, vegetables, whole grains, and seafood has been shown to reduce the risk of MM. MM is also more frequently observed in individuals with vitamin D deficiency [6]. Climate change, environmental pollution, aging, and anemic hypoxia are factors that contribute to an increased risk of MM [7,8]. Environmental and genetic factors play a role in the development of MM. The impact of seasonality on MM diagnosis has not been previously evaluated in Turkey. This study aims to determine whether MM diagnosis exhibits any seasonal variation.

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## Materials and Methods

We included 80 newly diagnosed patients with MM between January 2020 and July 2024. All patients underwent routine tests necessary for the diagnosis of MM, including complete blood count, biochemistry, sedimentation rate, immunoglobulins, free light chains, serum and 24-hour urine protein electrophoresis and immunofixation, as well as bone marrow aspiration and biopsy. Data regarding the age, gender, time of diagnosis, stage, and MM subtype for all the patients were retrospectively collected from the medical records. Renal involvement was defined as acute renal injury, chronic renal injury, proteinuria, hematuria, renal crystallopathy, and hypercalcemia.

Written informed consent was obtained from all patients, and the study was conducted under the principles of the Helsinki Declaration.

### *Statistical analysis*

Statistical analyses were performed using Statistical software Package for Social Sciences (SPSS) for Windows version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Categorical data were presented as frequencies and percentages, while continuous variables were summarized as mean ± standard deviation or median (min-max) based on their distribution. The study utilized a non-probability convenience sampling method. The sample size was calculated using a population proportion formula with a 95% confidence level, a margin of error of 5%, and an assumed prevalence of seasonal variation in diagnoses of hematologic malignancies based on the literature data. Based on these parameters, a minimum sample size of 73 was determined. To account for potential data inconsistencies, 80 patients newly diagnosed with multiple myeloma between January 2020 and July 2024 were included in the study.

## Results

The study included 80 newly diagnosed patients with multiple myeloma (MM), comprising 34 females (42.5%) and 46 males (57.5%). The median age of the patients was 63 years, ranging from 41 to 81 years. The median hemoglobin level was 9.8 g/dl, with values ranging from 5.5 to 15.8 g/dl. The median sedimentation rate was 88 mm/h, ranging from 28 to 159 mm/h. According to the Revised International Staging System (R-ISS), 14 patients (17.5%) were classified as stage I, 28 patients (35%) were classified as stage II, and 38 patients (47.5%) were classified as stage III. Renal involvement at diagnosis was observed in 33 patients (41.3%). The most common type of MM was IgG Kappa. The characteristics of the patients are presented in Table 1.

**Table 1.** Characteristics of Patients with Multiple Myeloma.

| | n=80 |
|---|---|
| Age (median, min-max) | 63 (41-81) |
| Gender | |
| Female | 34 (42.5 %) |
| Male | 46 (57.5 %) |
| Leukocytes ($mm^3$ ) (median, min-max) | 6520 (2540-15540) |
| Hemoglobin (gr/dl) (median,min-max)gr/dl | 9.8 (5.5-15.8) |
| Platelets ($mm^3$) (median, min-max) | 215.000 (16.000-551.000) |
| Sedimentation (mm/h) | 88 (28-159) |
| B2 microglobulin (mg/L) | 7.06 (2.01-20.4) |
| Stage (R-ISS) (I,II,III) | 14 (17.5%), 28 (%35%), 38(47.5%) |
| Presence of renal involvement | 33 (41.3%) |
| MM type | |
| Ig G Kappa | 45 (56.25%) |
| Ig G Lambda | 22 (27.5%) |
| Ig A Kappa | 6 (7.5%) |
| Ig A Lambda | 4 (5%) |
| Nonsecretory | 3 (3.75%) |

**Table 2.** Distribution of Patients Diagnosed with Multiple Myeloma According to Months and Seasons.

| Months | n=80 | Seasons | n=80 |
|---|---|---|---|
| December | 7 ( 8.8%) | | |
| January | 7 (8.8%) | Winter | 22 (27.5 %) |
| February | 8 (10%) | | |
| March | 8 (10%) | | |
| April | 7 ( 8.8%) | Spring | 20 (25 %) |
| May | 5 (6.3%) | | |
| June | 7 (8.8%) | | |
| July | 4 (5%) | Summer | 18 (22.5 %) |
| August | 7 (8.8%) | | |
| September | 6 (7.5%) | | |
| October | 5 (6.3%) | Autumn | 20 (25 %) |
| November | 9 (11.3%) | | |

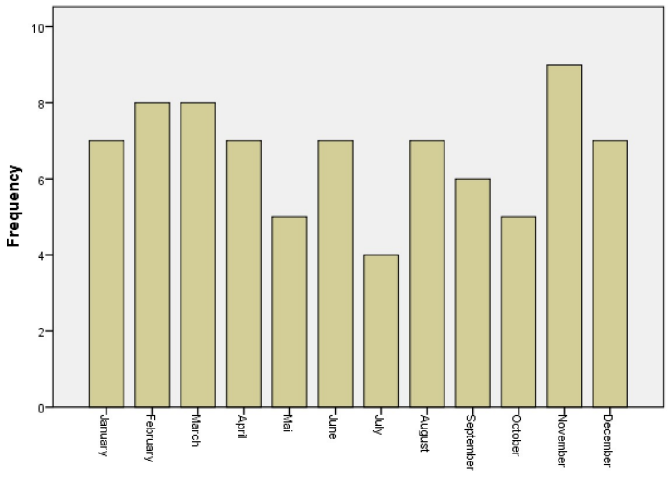


**Figure 1.** Monthly Distribution of newly diagnosed patients with MM.

The distribution of MM diagnoses by month is illustrated in Figure 1, and the monthly and seasonal distribution of diagnoses is detailed in Table 2. November had the highest number of MM diagnoses with 9 patients (11.3%), whereas July had the fewest diagnoses with 4 patients (5%). Winter recorded the highest number of diagnoses with 22 pa-

tients (27.5%), followed by spring and autumn, each with 20 patients (25%). Summer had the lowest number of MM diagnoses with 18 patients (22.5%). An evaluation of newly diagnosed MM patients based on the season of diagnosis revealed no significant difference ($p>0.05$) (Table 2). Furthermore, 44 patients were diagnosed between October and March, while 36 patients were diagnosed between April and September, indicating a higher number of diagnoses during colder seasons.

## Discussion

Multiple Myeloma (MM) is an incurable disease characterized by relapses despite improved survival and response rates with proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibody treatments [9,10]. As our understanding of the tumor microenvironment and genetic landscape deepens, the pathogenesis and treatment response risk factors for MM will become clearer. MM is a heterogeneous disease, and the impact of seasonality on MM remains uncertain. This study aims to present single-center analysis data to determine if a seasonal variation in MM exists.

Several studies have evaluated seasonality in hematologic malignancies. Factors such as aging, air pollution, dry seasons, and global warming have been identified as significant determinants of hematologic malignancies among African patients [11]. Hassan et al. [12] assessed 1982 cases of hematologic diseases over a 10-year period. They observed a seasonal relationship with acute leukemia, aplastic anemia, and immune thrombocytopenia, with an increased number of cases during the southwest monsoon period. However, no specific seasonal relationship was found with acute promyelocytic leukemia. Borchmann et al. [13] conducted a study involving 41,405 cases of Hodgkin lymphoma and identified a seasonal relationship, suggesting a protective role for vitamin D in Hodgkin lymphoma.

Data from Atlanta, evaluating seasonality in 120 MM patients, showed significant seasonal variation in MM frequency. Over five years, an average of 10 cases were diagnosed per month. From October to March, monthly diagnoses exceeded 10, while from April to September, they were 10 or fewer. In total, 77 cases were diagnosed between October and March, whereas only 43 cases were diagnosed between April and September. When correlating these data with Atlanta's average monthly temperatures, an increase in MM diagnoses during colder months was observed. However, this correlation was deemed inconclusive. For instance, April, with only five diagnoses, was on average two degrees colder than October, which had 14 diagnoses. While the winter predominance in the entire cohort cannot be fully explained, it suggests that acute respiratory infections may accelerate MM diagnosis [14]. In the present study, 44 of the 80 patients were diagnosed between October and March, while 36 were diagnosed between April and September. Specifically, 22 cases were diagnosed during winter, 20 each in spring and autumn, and 18 during summer. November had the highest number of diagnoses (9 cases), while July had the fewest (4 cases). More cases were observed during the colder months.

MM is characterized by bone involvement, renal failure, anemia and cytopenias, elevated sedimentation rate, hypercalcemia, coagulation abnormalities, neurological symptoms, hyperviscosity, and increased susceptibility to infections [4,5]. Infections are frequently observed in MM patients due to age-related immune dysfunction, changes in immunoglobulin production, and treatment-related immunosuppression. The risk of opportunistic bacterial and viral infections, including seasonal influenza viruses, increases by 7-10 times in MM patients. Deaths in MM often result from disease progression or infections [5,6]. Patients presenting with infection-related symptoms facilitate the diagnosis of MM. Both the Atlanta data and the present study have shown increased MM diagnoses during periods of heightened respiratory tract infections.

Climate change, excessive ultraviolet radiation exposure, and vitamin D deficiency contribute to immune system impairment in MM. A study at the Mayo Clinic evaluated vitamin D deficiency in 148 newly diagnosed MM patients and found no seasonal variation in vitamin D status. Given that vitamin D levels can be significantly influenced by skin pigmentation, sun exposure, geographic location, and diet, the lack of a seasonal correlation is understandable [15]. Vitamin D levels were not evaluated in the present study, which is a limitation to be considered.

## Conclusion

Our study found no seasonal variation in the diagnosis of multiple myeloma (MM). However, there was an increase in new MM cases during the colder months, specifically with patients presenting infection findings, leading to faster diagnoses. MM is a hematologic malignancy associated with higher morbidity and mortality. Understanding the factors that increase susceptibility to MM requires prioritizing improvements in lifestyle habits, diagnostic capacity, and treatment availability. Future research should investigate the underlying causes of these trends.

### *Disclosures*

**Ethics Committee Approval:** We performed our study with the approval of the institutional review board (Date: 23.07.2024; Decision Number: E-60116787-020-556369).

**Informed Consent:** Not necessary for this manuscript.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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