AFMN BIOMEDICINE

ORIGINAL ARTICLE

CHARACTERISTICS AND MANAGEMENT OF PATIENTS WITH MULTIPLE MYELOMA: A SINGLE-CENTER EXPERIENCE

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Multiple myeloma is the second most common hematological malignancy, in which pathological plasma cells secrete monoclonal proteins, ultimately leading to end-organ damage. Albumin, β2-microglobulin, and LDH are considered highly relevant biomarkers for the diagnosis and prognosis of this disease. Different treatment options are available depending on age and eligibility for autologous stem cell transplantation.

The aim of this study was to investigate basic characteristics, prognostic biomarkers, and the use of different treatment protocols in newly diagnosed multiple myeloma patients.

The study included 50 patients with newly diagnosed multiple myeloma. Data were collected from their medical records, and the statistical analysis was performed using the SPSS 15.0 program. The average age of patients at the time of diagnosis was 64, with a predominance of female patients. The most common type of myeloma was IgG kappa. More than half of the patients had an advanced stage of multiple myeloma and a high-risk disease, according to the prognostic score at the time of the diagnosis. The results showed that almost all patients had elevated levels of β2-microglobulin. The most commonly used protocols in younger patients eligible for transplantation were VTD and CTD, whereas patients who were not suitable for transplantation were treated with melphalan-based protocols.

The results of this study indicate that basic characteristics, prognostic biomarkers, and the treatment modalities used in newly diagnosed multiple myeloma patients are similar to those described in global clinical practice.

Keywords: multiple myeloma, prognosis, treatment

Submitted: January 13, 2025 **Accepted:** May 13, 2025
Published online: December 22, 2025

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INTRODUCTION

Multiple myeloma (MM) is a hematological disorder characterized by the abnormal proliferation of plasma cells, which results in the pathological production of monoclonal proteins and end-organ damage (1). Multiple myeloma most commonly occurs in older people, with the median age at the time of the diagnosis being 69. It is 1.5 times more common in men than women. The highest incidence of the disease is in Australia, Western parts of Europe, and the United States. In 2018, there were more than 160,000 cases of MM worldwide. Also, in 2018, it was estimated that approximately 106,000 people died as a result of the disease (2).

Historically, end-organ damage in MM was once referred to as CRAB (hypercalcemia, renal failure, anemia, and bone lesions). More than two-thirds of patients with MM have bone pain and anemia at the time of diagnosis. Immunosuppression is a common state in patients with MM, due to the abnormal synthesis and function of immunoglobulins often accompanied by decreased complement activity. Patients usually have relative lymphocytosis, Rouleaux formation. Sometimes eosinophilia can be present as well (3). In MM patients, there are both structural and functional abnormalities of platelets which often cause bleeding, although some patients tend to develop thrombotic complications (3).

The most common type of M protein in patients with MM is IgG, followed by IgA and light chain type of the disease, and rarely other types of immunoglobulins. Only 15% of patients have MM with overproduction of light chains. This group of patients has a poorer prognosis compared to those with immunoglobulins as M protein, as well as a higher incidence of bone lesions, renal failure, and amyloidosis (4). The most commonly used staging system for MM was established by Durie-Salmon (5). It includes levels of M protein as well as CRAB criteria. At the beginning of the 21th century, a new staging system was developed. It was named the International Staging System (ISS) and it is calculated based on albumin and β2 microglobulin levels (5). One of the most important biomarkers in MM is β2-microglobulin, and its concentration in the serum correlates with the size of the tumor mass. Its values at the time of the diagnosis can predict the response to treatment and disease outcome (6). According to the ISS score, patients can be divided into three stages with different median overall survival (MOS): stage 1 (MOS—62 months), stage 2 (MOS—44 months), and stage 3 (MOS—29 months) (7). LDH is another significant biomarker and its increased levels indicate high proliferation rate, aggressiveness of the disease as well as the presence of tumor mass (7).

According to The National Multiple Myeloma Diagnostic and Therapeutic Guidelines, the first-line treatment for patients with newly diagnosed MM is largely based on whether the patient is eligible for autologous stem cell transplantation (ASCT). Key factors in deciding if a patient is eligible for ASCT are age, comorbidities, and overall performance status. Patients who are candidates for ASCT usually start treatment with four to six cycles of protocols which include a proteasome inhibitor in combination with immunomodulator or cytostatic drug. The most commonly used protocols are VTD (thalidomide, bortezomib, dexamethasone), CVD (cyclophosphamide, bortezomib, dexamethasone), VRD (lenalidomide, bortezomib, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone), CTD (thalidomide, cyclophosphamide and dexamethasone) and TAD (thalidomide, doxorubicin and dexamethasone) (8). In patients with high-risk disease (ISS score 2 or 3), it is recommended to use VTD or VRD protocol because they contain both an immunomodulator and a proteasome inhibitor (8). Older patients or those who are not eligible for ASCT are usually treated with VTD or VRD, or with protocols which contain melphalan in combination with an immunomodulator or a proteasome inhibitor such as MPT (thalidomide, melphalan and prednisone) or MPV (bortezomib, melphalan and prednisolone) (8).

The aim of this study was to determine whether basic characteristics, prognostic biomarkers and the treatment modalities used in newly diagnosed multiple myeloma coincide with those that are globally recognized.

METHODS

This research was conducted as a retrospective study. All data were obtained from the medical records of 50 newly diagnosed MM patients who were treated at the Clinic of Hematology, Allergology and Clinical Immunology, University Clinical Center Niš. The subjects were patients diagnosed with MM and treated between 2021 and 2023. The values of biomarkers used in the paper were the ones recorded at the time of the diagnosis.

Multiple myeloma was diagnosed according to the guidelines of the International Myeloma Working Group (9). The main diagnostic criteria for MM are ≥ 10% clonal plasma cells in the bone marrow and at least one of the

following myeloma-defining events: end-organ damage (hypercalcemia, renal insufficiency, anemia, osteolytic bone lesions), > 1 focal lesion detected on MRI, serum free light chain ratio ≥ 100 mg/L and ≥ 60% of bone marrow plasma cells (9).

For clinical staging and prognosis of patients with MM, Durie-Salmon and ISS staging systems were used. According to the ISS staging system, all patients were divided into three stages (8).

All types of treatment protocols used for multiple myeloma patients in this study were in accordance with The National Multiple Myeloma Diagnostic and Therapeutic Guidelines (8).

Statistical analysis was performed using SPSS version 15.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). The results are shown through mean values and standard deviation (SD). The Student's t-test was used to test the statistical significance of biomarkers ($p < 0,01$). This study was approved by the Ethics Committee of the University Clinical Center Niš, Serbia (date: December 12, 2024; number: 37288/7). The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

This study included 50 newly diagnosed multiple myeloma patients. There were 24 men (48%) and 26 women (52%). The average age of patients at the time of making the diagnosis was 64.22 ± 10.35 years (64.46 ± 10.78 for men and 64 ± 10.14 for women). There was no statistically significant difference in age between men and women (Table 1). The youngest patient was 39 and the oldest patient was 86 at the time of the diagnosis. There were 4 patients (8%) below the age of 50.

In 60% of patients, the levels of β2 microglobulin were higher than 5.5 mg/L, 14% had levels higher than 3.5 mg/L and lower than 5.5 mg/L, whereas in 26% of patients β2 microglobulin was below 3.5 mg/L at the time of the diagnosis (Figure 1). The mean value of β2 microglobulin was 11.8 ± 12 mg/L. The mean value of LDH at the presentation was 380.48 ± 175.41 U/L. LDH levels were elevated in 28% of patients. The mean value of albumin was 31.72 ± 5.61 g/L, and its levels were < 35 g/L in 74% of patients at the time of the diagnosis. There were no statistically significant differences in the parameters examined between genders ($p < 0.01$) (Table 1).

Table 1. *Age and biomarker concentrations at the time of establishing MM diagnosis*

Parameter	All patients	Men	Women	p
Number	50	24	26	-
Age	64.22 ± 10.35	64.46 ± 10.78	64 ± 10.14	p = 0.88
β2 microglobulin	11.8 ± 12.5	10.62 ± 10.32	12.9 ± 14.34	p = 0.52
Albumin	31.72 ± 5.61	30.96 ± 4.6	32.38 ± 6.48	p = 0.38
LDH	380.48 ± 175.41	365.13 ± 199.15	396.85 ± 152.35	p = 0.53

X±SD – mean value ± standard deviation; p – probability value

The most frequent type of myeloma was IgG kappa (42%), followed by IgG lambda(28%), IgAkappa (10%), kappa and lambda light chain MM (10%), and IgA lambda (8%). Only onepatient had the biclonal type of MM (IgG kappa and lambda) (Figure 2). According to the Durie-Salmon staging system, 34% were stagedas IIIA, 32% wereIIIB, 14% were IIA, 10% were IIB, and 10% were IA. There were no patients staged as IB (Figure 3). Most patients had ISS 3 (66%), 24% of patients had ISS 2, and 10% of patients had ISS 1 at the time of the diagnosis (Figure 4).

The treatment started in 45 patients right after establishing MM diagnosis. One patient did not meet the requirements for the beginning of the treatment. In four patients, it was decided to begin the treatment with high doses of dexamethasone due to the impaired kidney function, before making definite decision about which MM treatment protocol should be used. Out of those 45 patients who began their treatment right after establishing MM diagnosis, 42.2% of them received VTD, followed by CTD (24.4%), CVD(9%), TAD(2.2%), and Vel-Dex(2.2%). In older patients and/or those who were not candidates for ASCT, melphalan-based protocols were used, most commonly MPT (13.4%), followed by MP (4.4%) and MPV (2.2%) (Figure 5).

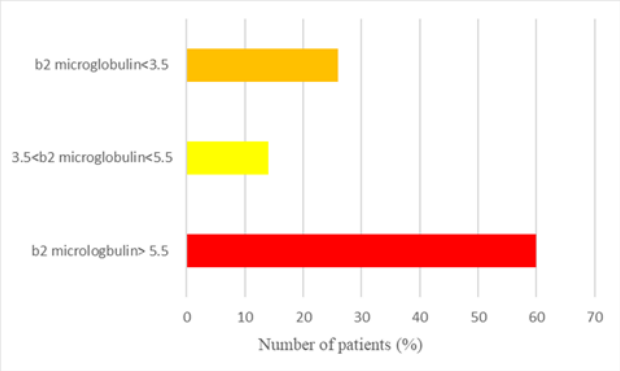

Figure 1. *Levels of β2 microglobulin (mg/L) in newly diagnosed MM patients*

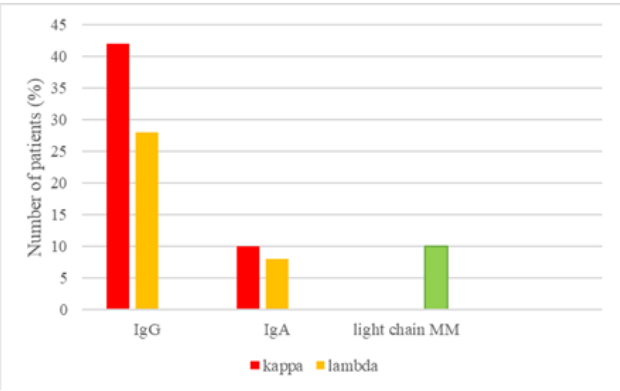

Figure 2. *Types of multiple myeloma*

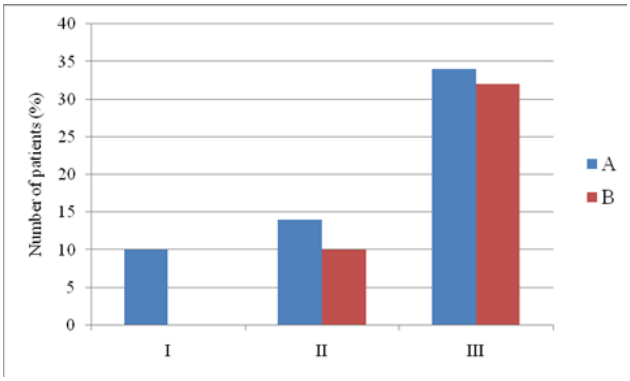

Figure 3. *Stages of MM according to Durie Salmon staging system*

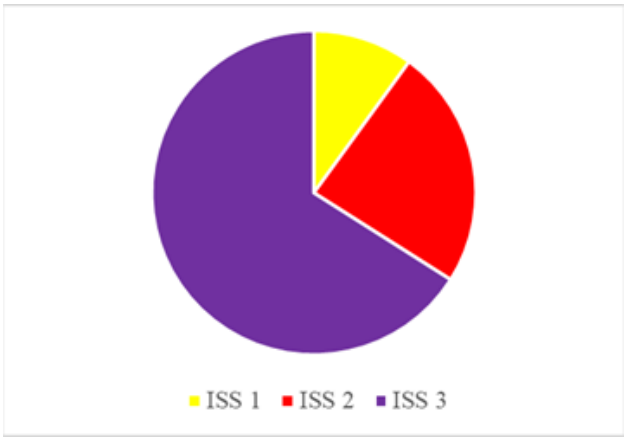

Figure 4. *ISS score at the time of the MM diagnosis*

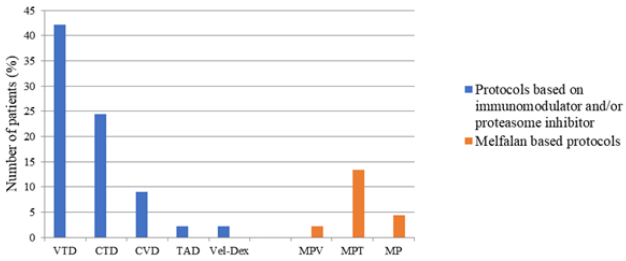

Figure 5. *Protocols used in newly diagnosed MM patients*

DISCUSSION

Multiple myeloma is the second most common blood cancer and it accounts for 1% of all malignancies (10). According to the International Agency for Research on Cancer, in 2020, there were 474 newly diagnosed MM cases in Serbia (226 men and 248 women). The results from the same year showed that there were 332 death cases (160 men and 172 women) from this disease in the whole country (11). Multiple myeloma is 1.5 times more common in males than females (2). In our study, there were 4% more women than men newly diagnosed with MM.

The average age of patients with MM diagnosis is 69 worldwide, with approximately 40% of patients being older than 75 at the time of making the diagnosis (12). In this study, the average age at the time of establishing the MM diagnosis was 64.22 ± 10.35, with 14% of patients being 75 or older. This is in correlation with the global median age for MM diagnosis. It is very unusual to diagnose MM in younger patients, and it seems to occur more frequently in males than in females (10). One study

reported that almost half of the patients diagnosed with MM younger than 40 had low-risk disease and better overall survival rate, probably due to a lower number of comorbidities and better ability to tolerate treatment protocols (13). Other studies have also confirmed that patients with MM below the age of 50 were mostly males with lower ISS score and Durie-Salmon stage, more favorable prognostic features, longer life expectancy, and better response to different lines of therapy (14). In our study, there were four patients (8%) younger than 50 at the time of the diagnosis, three males, and one female. The female patient had ISS 1 and was staged as IA. Two of the male patients had ISS 3 and were staged as IIIA and IIIB, respectively, whereas the third male patient had ISS 2 and was staged as IIA.

Multiple myeloma can be classified into several different types depending on which immunoglobulin and/or light chain is mostly present: IgG (52%), IgA (21%), light chains only (16%), biclonal (2%), and other forms (IgM, IgD and IgE which are extremely rare) (15). Our study demonstrated similar findings, showing that the most common type was IgG (70%), followed by IgA (18%) and kappa and lambda light chain MM (10%). Only one patient (2%) had the biclonal type of MM (IgG kappa and lambda). IgA type of MM is thought to have a poorer prognosis compared to IgG type. In about 15% of patients, MM cells secrete only light chains of immunoglobulins (kappa or lambda) (4). These free light chains are detectable in the serum by using the light chain assay, which has greatly replaced the quantification of Bence Jones proteins in urine (16). Light chains MM is more common in younger patients and has a worse prognosis compared to IgG and IgA types (17). Biclonal gammopathies are extremely rare and account for less than 5% of all MM patients. They are more symptomatic compared to their monoclonal counterpart. However, there are no significant differences in prognosis and how the patients respond to therapy (18).

Durie-Salmon score was the first established staging system for MM. It includes levels of M protein as well as CRAB criteria, and it is still widely used in clinical practice worldwide. Further substaging into A and B is based on the levels of serum creatinine (cut off value 177 µmol/l) (6,8). In our study, most patients were staged as IIIA (34%) and IIIB (32%). A 10-year period prospective study found that median survival for stage I was 53 months, 31 months for stage II, and 24 months for stage III. There was a significant difference in survival period between substages of stage III, with IIIA having median survival of 38 months and IIIB 18 months (19). Calculating ISS before the beginning of the treatment is very important because this score can help determine the overall prognosis of the disease. According to a major study that collected data from 11 worldwide multicenter clinical studies, out of 3,060 individuals, 38% had ISS 1, 38% had ISS 2, and 24% had ISS 3 (7). Another study found that 29% of the 1,516 newly diagnosed myeloma patients had ISS 1, 38% had ISS 2, and 33% had ISS 3 (20). However, in this study, 66% of patients had ISS 3, 24% of patients had ISS 2 and 10% of patients had ISS 1 at the time of the diagnosis. Both Durie-Salmon score and ISS are effective in differentiating patients with worse prognosis from those with better prognosis and are widely used in clinical practice (21).

One of the most significant biomarkers in both the diagnosis and prognosis of MM is β2 microglobulin. Its levels are usually elevated in MM patients at the presentation of the disease (7). Also, β2 microglobulin is closely related to kidney function. Studies reported that β2 microglobulin levels were significantly higher in patients with poor renal function and GFR lower than 60 mL/min at the time of diagnosis (22). In this study, 88% of patients had elevated levels of β2 microglobulin at the time of diagnosis. In 60% of patients, β2 microglobulin levels were higher than 5.5 mg/L, indicating a high-risk disease (ISS 3).

The levels of albumin in serum are also considered to be a relevant prognostic factor in MM. The levels of albumin lower than 35 g/L are associated with a more severe form of the disease and poorer performance status, as well as kidney failure (23). In this study, 74% of patients had serum albumin levels lower than 35 g/L at the time of the diagnosis. LDH is another important biomarker, and its high levels correlate with the aggressiveness of the tumor (8). However, its levels are rarely elevated at the time of the diagnosis (24). This is in correlation with the results obtained in this study, where only 28% of patients had elevated levels of LDH. As the disease progresses, LDH levels usually rise, which is an indicator of a poorer prognosis (24). Other studies have also confirmed the normality of LDH at the time of the diagnosis and its elevation with the progression of the disease. It is suggested that LDH levels in combination with ISS score could be very useful in determining the overall survival of MM patients (25).

The most commonly used treatment protocols for a newly diagnosed MM patients eligible for ASCT are VTD, CVD, PAD and VRD, whereas melphalan-based protocols such as MPV and MPT are usually used in patients who are not eligible for ASCT (8). In this study, most patients were treated with VTD as the first-line protocol (42.2%),

followed by CTD (24.4%) and MPT (13.4%). Other first-line protocols included were CVD, MPV, TAD, MP and VEL-Dex. This choice of treatment complies with worldwide recommendations for the management of multiple myeloma. According to the EHA-ESMO clinical practice guidelines for treatment of multiple myeloma, the most frequently used first-line protocols for ASCT eligible patients are VTD, VRD and VCD. Prior to 2019, MPV and Rd (lenalidomide and dexamethasone) were the recommended treatment protocols for patients who were not candidates for ASCT. However, compared to MPV and Rd, VRD has shown a notable advantage in clinical trials, and it is currently the recommended first-line protocol for those ineligible for ASCT (26). Autologous stem cell transplantation is still considered to be the treatment of choice for young and fit older patients. The upper age limit for ASCT is usually 65, although sometimes doctors can approve transplantation in older patients if they are fit and with few comorbidities. The best induction protocols for patients who are eligible for ASCT are those based on three different medications. VTD protocol has been proven to be a treatment of choice before transplantation, with usually 4-6 cycles given before the procedure (27). The combination of proteasome inhibitors and immunomodulatory drugs is still considered the best therapy option for both ASCT eligible and ineligible patients (8). The introduction of daratumumab, an anti-CD38 monoclonal antibody, used in combination with proteasome inhibitors and immunomodulatory drugs, has significantly improved the depth of response and progression-free survival rate both in newly diagnosed and relapse/refractory MM patients (28). The combination of daratumumab and VTD is approved as the first option for the induction therapy for patients who are candidates for ASCT (26). The first-line treatment of choice for individuals ineligible for ASCT is the combination of daratumumab with MPV and Rd; VRD is given only in case that the aforementioned combinations are not available. (26). However, it should be noted that it is required to develop a specific treatment plan for each multiple myeloma patient individually, based on their diagnostic and prognostic characteristics.

The results of this retrospective study indicate that basic characteristics of the newly diagnosed multiple myeloma patients correlate with those which are described in the global clinical practice. Biomarkers measured at the clinical presentation of the disease and protocols used for the treatment of MM patients are fully consistent with the internationally accepted guidelines for the diagnosis and treatment of multiple myeloma.

Acknowledgements

This study was not supported by any sponsor or funder.

Statement of Ethics

This study was approved by the Ethics Committee of the University Clinical Center Niš, Serbia (date: December 12, 2024; number: 37288/7).

Competing Interest

The authors declare no relevant conflicts of interest.

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