Original Study



# Disease Characteristics and Treatment Outcomes of Myeloma Patients Under 50 Years of Age: An Analysis of the Balkan Myeloma Study Group

Despina Fotiou,[1] Sorina Nicoleta Badelita,[2] Eirini Katodritou,[3] Meral Beksac,[4] Jelena Bila,[5] Emmanouil Spanoudakis,[6] Josip Batinić,[7] Daniel Coriu,[8] Sinziana Barbu,[2] Catalin Danaila,[9] Dimitra Dalampira,[3] Angeliki Sevastoudi,[3] Guldane Cengiz Seval,[10] Selami Koçak Toprak,[10] Aleksandra Sretenovic,[5] Olivera Markovic,[11] Toni Valkovic,[12,13] Zorica Cvetkovic,[14] Fenia Theodorakakou,[1] Maria Gavriatopoulou,[1] Evangelos Terpos,[1] Meletios A. Dimopoulos,[1] Efstathios Kastritis[1]

## Abstract

**Younger multiple myeloma (MM) patients, representing 10% of cases, show distinct clinical features, including lower anemia and renal impairment rates but higher lytic bone disease and adverse cytogenetics. Retrospective analysis reveals better complete response and survival outcomes, with median OS exceeding 15 years. Key prognostic factors include anemia and high-risk cytogenetics, while autologous stem cell transplantation significantly improves outcomes, highlighting the importance of tailored, intensive treatment strategies.**

**Background:** Multiple myeloma (MM) is predominantly a disease of the elderly, but approximately 10% of patients are younger than 50 years at diagnosis. **Methods:** This study aimed to investigate the clinical characteristics, treatment outcomes, and prognostic factors in younger MM patients using retrospective data from the Balkan Myeloma Study Group registry. **Results:** A total of 350 patients under 50 years old were included, comprising 10.4% of the overall cohort. The study found that younger patients had lower rates of renal impairment and anemia but a higher incidence of lytic bone disease and adverse cytogenetics. Treatment regimens, including proteasome inhibitors and immunomodulatory agents, were comparable between younger and older patients, but younger patients had significantly better complete response rates and overall survival (OS). The 5- and 10-year OS rates were 76% and 64%, respectively, with a projected median OS exceeding 15 years. Factors such as anemia, hypercalcemia, and high-risk cytogenetics were associated with worse survival outcomes. Autologous stem cell transplantation (ASCT) emerged as a key contributor

[1]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[2]Department of Hematology, Fundeni Clinical Institute, Bucharest, Romania
[3]Department of Hematology, Theagenio Cancer Hospital, Thessaloniki, Greece
[4]Ankara Liv Hospital, Istinye University, Ankara, Turkey
[5]Clinic of Hematology, University Clinical Center of Serbia, Medical Faculty, University of Belgrade, Belgrade, Serbia
[6]Department of Hematology, University Hospital of Alexandroupolis, Alexandroupolis, Greece
[7]Department of internal medicine, Division of Hematology, University Hospital Centre Zagreb; Zagreb, Croatia
[8]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[9]Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania
[10]Department of Hematology, Ankara University School of Medicine, Ankara, Turkey
[11]Clinic of Hematology, Clinical Hospital Center "Bezanijska Kosa", Medical Faculty, University of Belgrade
[12]Special Hospital Medico, Rijeka, Croatia
[13]Faculty of Health Studies, University of Rijeka, Croatia
[14]Department of Hematology Clinical Hospital Center Zemun, Medical Faculty University of Belgrade, Belgrade, Serbia

Submitted: Nov 18, 2024; Revised: Dec 26, 2024; Accepted: Dec 27, 2024; Epub: 7 January 2025

Address for correspondence: Efstathios Kastritis, MD, Department of Clinical Therapeutics, Plasma Cell Dyscrasia Unit, National and Kapodistrian University of Athens, School of Medicine, 80 Vas. Sofias Ave, 115 28, Athens, Greece
E-mail contact: ekastritis@med.uoa.gr, ekastritis@gmail.com


https://doi.org/10.1016/j.clml.2024.12.017

to improved progression-free survival (PFS) and OS.**Conclusion:** In conclusion, younger MM patients exhibit distinct disease features and benefit from intensified treatment approaches, underscoring the need for tailored therapies to achieve potential disease cure.

*Clinical Lymphoma, Myeloma and Leukemia,* Vol. 25, No. 5, e310–e318 © 2025 The Author(s). Published by Elsevier Inc.

**Keywords:** Multiple Myeloma, Overall survival, Prognosis, Young patients with multiple myeloma, Balkan Myeloma Study Group

## Introduction

Multiple myeloma (MM) is mostly a disease of the elderly with a median age at diagnosis at approximately 69 years of age and a rather rare malignancy among young individuals. Patients younger than 50 years old constitute approximately 10% of all patients with multiple myeloma[1] and less than 2% of patients are diagnosed before the age of 40.[2] Young patients with MM are underrepresented in clinical trials and there remains a paucity of comprehensive data regarding their clinical features, prognostic factors, disease trajectory, and their long-term outcomes, given their young age.[3-5]

Previous studies suggest that patients younger than 65 years have better outcomes compared to older individuals with MM, likely attributed to enhanced physical fitness, fewer concurrent comorbidities and better treatment tolerability. However, despite a more favorable prognosis, younger patients experience a greater loss of potential life years due to MM and endure longer periods of treatment-related toxicities, including symptom burden, systemic effects on quality of life, and financial strain.[6] Access to novel agent combinations over the past decade has translated into a significantly improved overall survival for all patients with MM. We therefore need to better characterize young patients with MM in terms of disease biology, clinical characteristics, treatment administration and prognosis in order to provide a tailored treatment approach with a focus on disease "cure". We used retrospective data from the Balkan Myeloma Study Group registry to provide further insights into the distinct features of this subpopulation among MM patients.

## Methods

This is a retrospective, multi-institutional study conducted in 19 centers from 11 countries in Europe. Patients were identified through a search in the database of the Balkan Myeloma Study Group; participating institutions provide data and maintain this common database. Consecutive adult (≥ 18 years) patients with MM are included in the database and the main focus of the current analysis are those who were younger than 50 years of age at the time of diagnosis. Patients were enrolled between 1996 and 2003, only 7 patients were enrolled before 2000. Ethical committee approvals and consents were collected from each patient on admission depending on the local regulations of each country.

The diagnosis of symptomatic MM was made in accordance with the International Myeloma Working Group Guidelines[7-9] and response criteria were defined according to standard International Myeloma Working Group (IMWG) criteria.[10] Clinical data included age at the time of MM diagnosis, baseline laboratory investigations and disease characteristics, disease stage per R-ISS, R2-ISS and cytogenetic abnormalities, radiological findings (PET-CT/MRI/CT), number and types of therapies including chemotherapy/radiotherapy, autologous stem cell transplantation (ASCT), presence of extramedullary disease (EMD), response to therapy, PFS (progression free survival) and OS (overall survival). High risk cytogenetics were defined as the presence of translocation t(4;14), t(14;16) and del17p.

### *Statistical Analysis*

Categorical variables were compared with the use of the Fisher's exact test or the $\chi 2$ test. Continuous variables were analyzed using the Kruskal–Wallis test for independent samples. Survival probabilities were estimated by the Kaplan–Meier method, and the Log-Rank test was used for univariate comparison. Outcomes were determined as response to treatment, PFS and OS. To assess the multivariate factors for each end point, we used Cox proportional hazard model to estimate hazard ratios (HR) with 95% confidence intervals (CI). All tests were 2-sided, with the type 1 error rate fixed at $\alpha = 0.05$. All analyses and graphs were obtained using the statistical software SPSS Statistics 21 (SPSS; IBM Corp., Armonk, NY, USA).

## Results

### *Cohort Characteristics*

Among 3356 patients treated within centers of the BMSG and registered in the database, 350 patients (10.4%) were < 50 years of age at the time of diagnosis. In addition, 1.8% ($n = 59$) were younger than < 40 years. The median age of the < 50 years group was 45 years (range 26-49). At the time of diagnosis them main symptoms included anemia (hemoglobin < 10 gr/dl) in 37%, renal impairment (RI) (defined as eGFR < 60 ml/min/1.73 $m^2$) in 27% and severe RI (defined as < 30 ml/min/1.73 $m^2$ or requiring dialysis) in 15%, hypercalcemia (serum calcium ≥ 11 mg/dl) in 22% and lytic bone disease in 77% of patients. Among patients < 50 years old, applying the criteria proposed by Dimopoulos et al.,[11] 14 patients (4%) were detected that met the diagnostic criteria for macrofocal myeloma. When compared to patients ≥ 50 years of age, had more often light chain only disease (25% vs. 16%, $P = .005$) the young patient cohort presented less often with moderate RI ($P < .001$) or anemia ($P = .021$), thrombocytopenia ($P = .013$), more often with lytic bone disease ($P < .001$) but there was no significant difference in the frequency of hypercalcemia, severe RI or BM infiltration (Table 1). Among those with available data ($n = 247$), high risk cytogenetics were present in 15% (vs. 11% in the older patients, $P = .004$) but elevated LDH (above upper limit of normal) was similar in frequency between groups. Accord-

**Table 1** Baseline Patient Characteristics in the Database in Patients < 50 y Old and ≥ 50 y Old and Comparisons (P-Values)

| | Age < 50 y Old ($n = 350$) (%) | Age ≥ 50 y Old ($n = 3006$) (%) | P-Value |
|---|---|---|---|
| Male / Female (%) | 55 / 45 | 52 / 48 | .144 |
| BM infiltration (Median %) | 60 | 57 | .098 |
| IgG / IgA / LC only (%) | 54 / 17 / 25 | 57 / 23/ 16 | .001 |
| Lytic bone disease (%) | 77 | 68 | < .001 |
| Hb < 10 gr/dl (%) | 37 | 44 | .021 |
| PLT < 130 K/uL (%) | 4.5 | 8 | .013 |
| Calcium > 11 mg/dl (%) | 22 | 21 | .354 |
| LDH > ULN (%) | 19 | 18 | .412 |
| eGFR < 60 ml/min/1.73m$^2$ (%) | 27 | 42 | < .001 |
| eGFR < 30 ml/min/1.73m$^2$ (%) | 15 | 18 | .139 |
| HR cytogenetics (%) ($n = 247$) | 15 | 11 | .004 |
| ISS 1 /2 / 3 (%) ($n = 350$) | 44 / 24 / 33 | 27 / 32 / 41 | < .001 |
| R-ISS −1 / −2 / −3 (%) ($n = 247$) | 28 / 58 / 14 | 18 / 67 / 15 | .003 |
| R2-ISS-1 / −2/ −3 / −4 (%) ($n = 178$) | 26 / 26 / 30 / 18 | 15 / 24 / 48 / 13 | < .001 |
| Treatment type (%) Chemo only | 7.4 | 6.7 | .262 |
| PI±chemo | 48.5 | 46.1 | |
| IMiD±chemo | 14.6 | 19.2 | |
| PI+IMiD | 24.7 | 22.5 | |
| Dara-containing | 5.2 | 5.1 | |
| Response to treatment ($n =$ ) (%) ORR* | 89 | 87 | .693 |
| CR/sCR | 28 | 16 | < .001 |
| VGPR | 32 | 36 | .388 |
| ≥ VGPR | 60 | 52 | .015 |
| PR | 29% | 35% | .021 |

BM = bone marrow; CR/sCR = complete response and stringent CR; Dara = Daratumumab; eGFR = Estimated glomerular filtration rate assessed by the MDRD formula; Hb = Hemoglobin; HR = high risk; IMiD = immunomodulatory agent; ISS = international staging system; LDH = lactate dehydrogenase; ORR = overall response rate; PLT = Platelet count; PI = proteasome inhibitor; PR = partial response; R-ISS = first revision of the ISS; R2ISS = second revision of the ISS; ULN = upper limit of normal; VGPR = very good partial response. $n = 350$ for < 50 years of age and $n = 3006$ for ≥ 50 years old unless otherwise stated. *Evaluable patients at end of induction regimen.

ing to ISS ($n = 350$), 43%, 24% and 33% were stage 1, 2 and 3 respectively, per R-ISS ($n = 247$ patients) 28%, 58% and 14% of patients < 50 years were R-ISS-1, −2 and −3 respectively and per R2-ISS ($n = 178$ patients), 26% of patients < 50 years were low, 26% low-intermediate, 30% intermediate-high and 18% high risk respectively. Stage distributions were significantly different than in older patients ($P < .01$ for all) (Table 1).

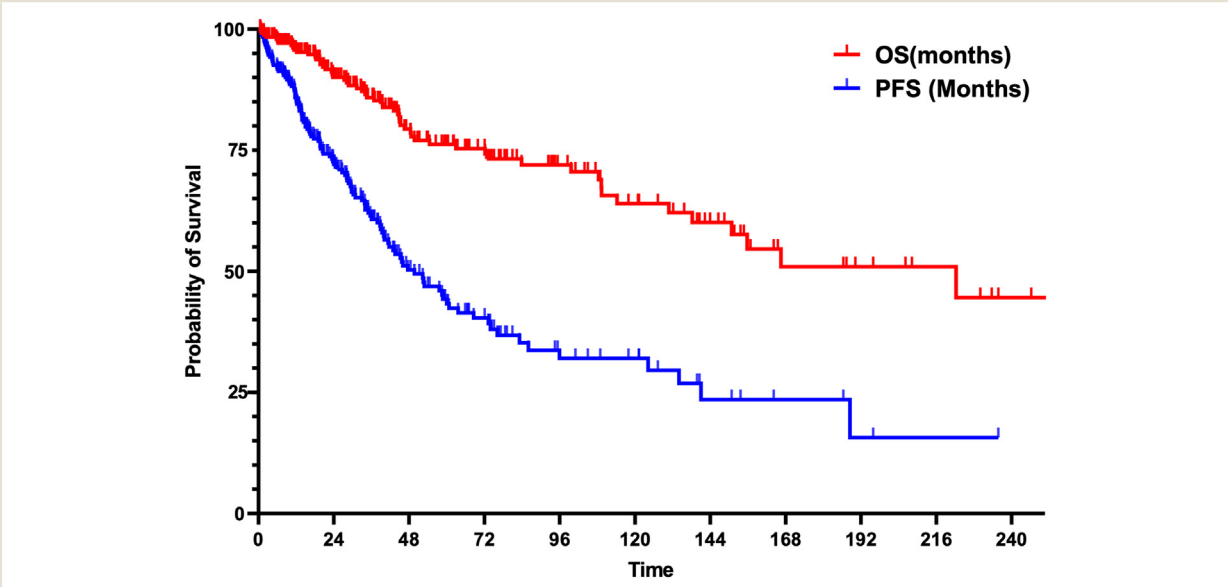
### *Treatment*

Among patients < 50 years of age first-line/induction therapy was based on proteasome inhibitor (PI) bortezomib (± chemotherapy) in 48.5%, Immunomodulatory agents (IMiDs) in 14.6%, PI + IMiDs in 24.7% and in 5.2% it was daratumumab-based. These regimens did not differ significantly than those used in patients ≥ 50 years. Overall response rate (ORR), defined as partial response or better, to induction treatment among evaluable patients was 89% (sCR/CR in 28%, VGPR in 32%, PR in 29%). Compared to patients ≥ 50 years old, ORR were comparable ($P = .693$) but CR/sCR rates were significantly higher ($P < .001$). Overall, 73% of the young patients received an ASCT (autologous stem cell transplant) as part of first line treatment. Nontransplanted young patients had more often severe RI (23% vs. 12%), lytic bone disease (91% vs. 56%), high risk cytogenetics (23% vs. 12%), failure to achieve at least partial response after induction (17% vs. 1%) and were mostly diagnosed after 2015.

### *Outcomes*

The median follow up for the whole cohort is 55 months (IQR 28-113); for those < 50 years was 60 months (IQR 25-100) and for patients ≥ 50 years of age was 54 months (IQR 24-93). The median progression free survival (PFS) was 50 months for patients < 50 years versus 31 months for patients ≥ 50 years ($P < .001$). Factors associated with longer PFS were ISS-1 (vs. ISS-2 or ISS-3) disease ($P = .0033$), light chain (LC) only disease ($P = .033$) and use of HDM-ASCT ($P < .001$). Hypercalcemia ($P < .001$), anemia ($P = .001$) and R2-ISS-3 or −4 (vs. −1 or −2) ($P = .018$) were

**Figure 1** Overall survival (OS) and Progression Free survival (PFS) curves for patients < 50 y of age.




associated with shorter PFS in univariate analysis. In the multivariate analysis the use of HDM-ASCT and the presence of hypercalcemia, anemia and of LC only disease were independently associated with PFS, even after adjustment for the year of diagnosis (either before/after 2010 or before/after 2015). Among patients with adequate follow up (ie, diagnosed at least before 2013) 16% had a PFS of at least 10 years. These patients had numerically (but not reaching statistical significance) less often hypercalcemia, eGFR < 30, anemia (Hb < 10 gr/dl) or high risk cytogenetics (none vs. 10.5% among evaluable patients with PFS <10 years) at presentation. Regarding treatment all had received ASCT and 73% among them additional consolidation versus 30% among evaluable patients with a PFS < 10years.

The median overall survival (OS) for the whole cohort is 75 months, and it has not been reached for those < 50 years (5-year OS is 76% vs. 55% for those ≥ 50 years of age, $P < .001$). OS and PFS curves for patients < 50 years can be seen in Figure 1. Even in comparison with patients 50 to 65 years old, 5-year OS was 76% versus 71% and 10-year OS was 64% versus 51% ($P = .013$) (Figure 2). Notably the projected OS for younger patients at 10 years is 64% and the estimated median OS exceeds 15 years. Among the younger patients, the 5- and 10-year OS for patients with R-ISS-1 disease was 87% and 73% respectively, for patients with R-ISS-2 disease 70% and 62% and for R-ISS-3 disease it was 61% and 16% respectively. OS in patients with macrofocal myeloma ($n = 14$) was similar to that of the rest of the cohort.

Anemia (Hgb < 10 gr/dl) (HR: $P = .0015$), hypercalcemia ($P < .001$), high-risk cytogenetics ($P = .008$), eGFR < 60 ml/min/1.73 $m^2$ ($P = .0058$) and disease risk stage as assessed by ISS, R-ISS and R2-ISS were significant prognosticators for OS ($P < .001$ for all, see Figure 3 for details).

There was no significant difference in terms of OS according to the type of primary therapy but ASCT was the most important factor for better OS in univariate and multivariate analysis (HR: 0.412, $P < .001$) (Figure 4).

We also compared the OS in patients according to the year of diagnosis, using 2 cut-offs, 2010 and 2015. Although the follow-up of the more recently diagnosed patients is shorter, there was no significant improvement in the OS for patients < 50 years of age diagnosed before and after 2015 (Figure 5) or for patients diagnosed before or after 2010. In contrast, among patients aged 50 to 65 years of age, there was a significant improvement in OS compared to the year of diagnosis, after 2010 (compared to before) and after 2015 compared to before.

In a multivariate analysis that included only significant baseline variables (Anemia as Hgb < 10 gr/dl, hypercalcemia, high-risk cytogenetics, eGFR < 60 ml/min/1.73 $m^2$ and R2-ISS), the presence of hypercalcemia (HR:5.3, $P < .001$) and R2-ISS-3 or −4 (HR: 3.4, $P = .009$) were significant independent prognosticators for OS. When use of ASCT was also included in the model (excluding early deaths < 4 months from start of therapy), adjusting for < PR after induction, then again hypercalcemia (HR:5.2, $P < .001$) and R2-ISS-3 or −4 (HR: 4.9, $P = .003$) and use of HDM-ASCT (HR: 0.31, $P < .001$) were independently associated with OS.

## Discussion

MM remains a rare disease among young individuals with ~10% of patients being younger that 50 years. As outcomes improve in the era of novel treatments, there is a need for more data to tailor clinical practices to the characteristics of younger patients with MM. A small number of studies have attempted to evalute the characteristics and outcomes of younger patients with MM, using different age-

**Figure 2** Overall survival (OS) among different age groups.

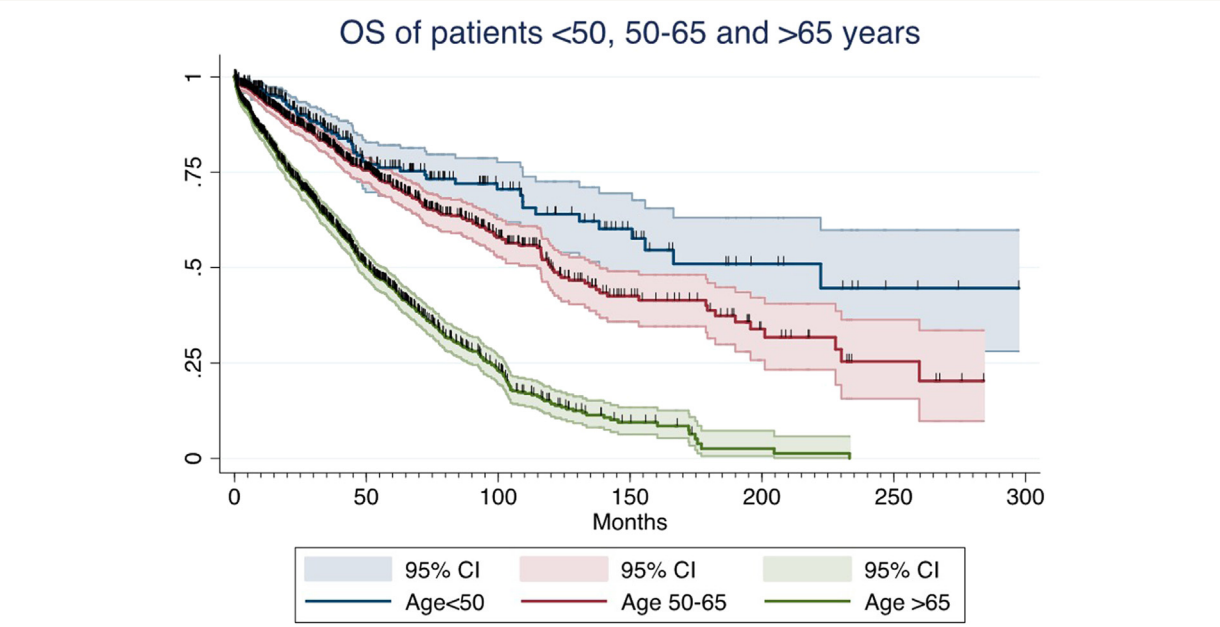
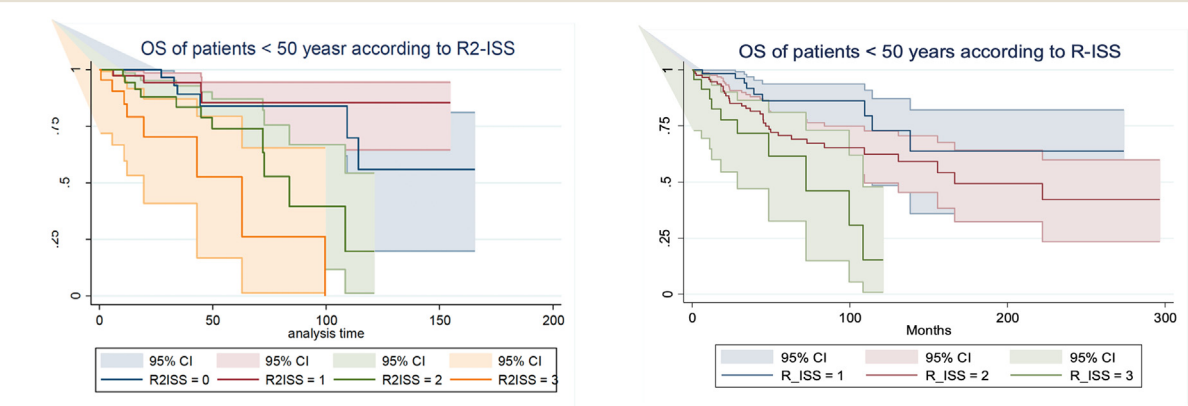



**Figure 3** (A) Comparison of OS among patients < 50 y of age according to R-ISS stage. (B) Comparison of OS among patients < 50 y of age according to R2-ISS stage.




cutoffs. Most data are however retrospective and reflect treatment practices mostly before 2015.[2,5,12-14] In addition, most studies lack a comparator arm.

To address this gap, we analyzed data from the Balkan Myeloma Study Group Registry, which includes 19 centers across 11 countries. We used a 50-year age cut-off due to the lack of consensus on what defines "young" MM.[15] In our cohort, patients under 50 exhibited distinct characteristics compared to older patients, most notably a lower-risk disease profile and different presenting features. Importantly, the projected median overall survival (OS) for these younger patients exceeds 15 years but remains significantly shorter than that of the general population of similar age, and probably more than 2 decades of life may be lost for such a patient.[2] Our data, being largely consistent with previous research on young patients with MM, offer further new insights that expand our understanding of this population. The present study reflects clinical practice in different Balkan countries, uses a comparator arm to assess outcomes based on treatment practices up to 2017 and presents data regarding disease biology and risk status across all staging systems.

**Figure 4** Overall survival in patients < 50 y of age according to the use of Autologous stem cell transplant versus no ASCT.

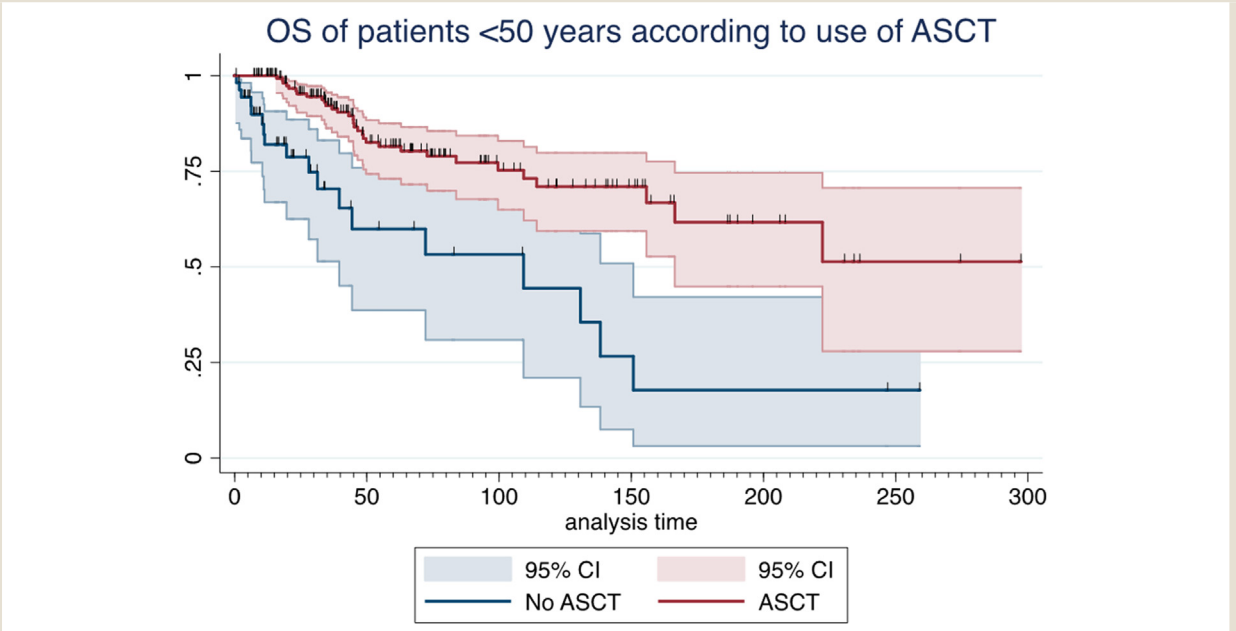
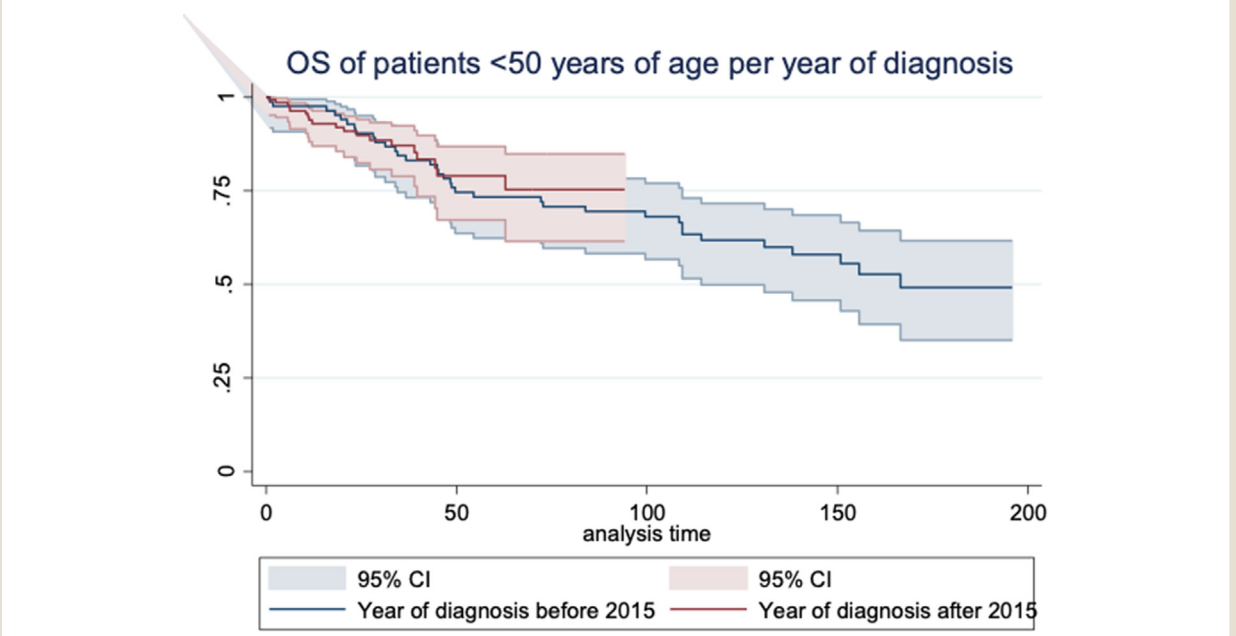



**Figure 5** OS of patients less than 50 y of age diagnosed before and after 2015.




Our study found a 5-year OS rate of 76%, a 10-year OS rate of 64%, and a projected median OS over 15 years for patients under 50. These outcomes are consistent with other studies using similar cut-offs,[16,4] and are significantly better than those for patients aged 50 or older. In the literature, all studies with a comparator arm, report a longer 5years OS in younger patients[3,5,17] and median OS, reported in 4 studies ranges from 61 to 175 months.[12,18,19] Importantly we present a 15-year median OS projection, raising the issue of "curability" to highlight the evolving treatment landscape and the potential for "cure".

In our cohort, younger patients were more likely to present with adverse cytogenetics and lytic bone disease but less likely to have renal impairment (< 60 ml/min/1.73 m2) or anemia compared to older patients. However, even mild RI (< 60 ml/min/1.73 m2) was associated with worse outcome in univariate analysis probably because such levels of eGFR indicate a significant loss of renal function in younger patients. Regarding cytogenetics, other research groups have not consistently identified significant differences in the incidence of high-risk cytogenetics between age groups.[4,5] Coulier et al. reported cytogenetic abnormalities in 52.4% of patients, with high-risk cytogenetics in 18% of cases[12] and Nakaya et al. also found a higher frequency of del(17p) in patients < 40 years of age.[17] Duek et al. also noted a high incidence of t(11;14) in patients under 50, which was linked to more unfavorable disease characteristics and outcomes.[13] The incidence of light chain only disease in MM is approximately 15%. Our analysis, in agreement with the results of several other studies[13,14,20-22] has demonstrated a higher incidence of light-chain-only disease among young MM patients, ranging from 18% to 45%.

Overall, the most consistent feature regarding disease biology in younger MM patients is the presence of lower-risk disease[4,12,14,17,22] though other disease characteristics appear to vary across studies. Our findings also confirm the finding that stage distributions differ compared to older patients with 67% of younger patients classified as stage I/II per the ISS, 87% as stage I/II per the R-ISS, and 51% as low or low-intermediate risk per the R2-ISS. Our study presents detailed data regarding risk distribution in younger patients with MM across all 3 currently used staging systems. Young age is consistently associated with better OS compared to older patient groups, both after conventional and high-dose therapies. This is likely due to a combination of baseline factors, such as lower-risk disease, and time-dependent variables, including response to first-line therapy and time to progression. Additionally, younger patients often tolerate treatments better and have fewer comorbidities compared to older cohorts, further contributing to their improved outcomes.

In our study, major baseline factors influencing OS included the presence of anemia, hypercalcemia, disease risk stage. These factors likely indicate a more aggressive disease and higher tumor burden. Importantly, our data indicate that ASCT remains critical for younger patients and should not be omitted, even in the era of newer therapies. Painuly et al.[23] compared outcomes over 5 decades in patients under 40 and found that OS improved in the post-ASCT era, with similar survival rates for patients receiving both ASCT and novel agents versus ASCT alone. Additionally, a study using the 65-year-old cut-off from the Center for International Blood and Marrow Transplant Research[24] demonstrated that ASCT prolonged progression-free survival (PFS) in both younger and older groups equally. High-dose therapy appears to have an even greater effect on OS in younger patients.[4]

Our findings should be interpreted in the context of treatment practices from 2010 to 2017. For example, Kristinsson et al.[25] reported improvements in 5-year and 10-year survival rates for patients younger than 60 and 70 years between 1973 and 2003 and similar data were seen in a study that used the SEER database.[26] In our study, we did not observe significant differences in outcomes when comparing the 2010 and 2015 cut-offs for younger patients, likely due to the pivotal role of ASCT as the primary determinant of outcomes during this period. Improvements in OS observed in older patients may be attributed to advancements in clinical practices, including supportive care, toxicity management, and the broader use of ASCT in older patients over time.

Since 2017, numerous novel agents have emerged for treating newly diagnosed MM, with triplet and quadruplet combinations becoming the standard induction regimen. The impact of these newer regimens and immunotherapies is yet to be fully assessed, but they are expected to improve OS in both younger and older MM patients. ASCT remains the standard of care, although bispecific antibodies are being studied as potential maintenance therapies, and CAR T-cell therapies are being explored as alternatives to ASCT. With a projected OS exceeding 15 years for MM patients under 50, the concept of "curability" becomes increasingly relevant for these patients. Many MM patients now survive beyond 10 years, but MM is still considered an incurable disease.[27,28,29] The term "operational cure" is often used to describe patients who remain in complete response for an extended period but who remain on continuous therapy and face a persistent risk of relapse, with no clear plateau in OS or PFS curves.[30,31] Additionally, patients must be monitored for long-term complications, and preventive measures should be incorporated into clinical practice.[32] Issues related to quality of life, as well as the impact of the disease on patients' professional, financial, and social lives, also need to be addressed. Especially for younger patients, and with the emergence of more effective therapies, these issues are becoming important and should be investigated in the context of dedicated research.

Our study is limited by its retrospective nature and reflects treatment practices in Balkans, which differ significantly among countries. Nevertheless, it provides valuable insights into the characteristics and outcomes of a large cohort of younger MM patients. On the other hand although there are differences in the induction regimens used, HDM-ASCT is commonly used across Balkans; thus, our findings regarding the important role of ASCT in the young patients are further emphasized. Our study is also limited by the absence of MRD data given that this is an older cohort of patients and we recognize the significance of MRD testing in defining depth of response and particularly in the context of evaluating potential cure definitions in MM.

In conclusion, it is essential to better understand the distinct biology of the disease in young MM patients and to identify major determinants of outcome. Prospective data from clinical trials and real-world settings will be crucial in developing a tailored, intensified approach to therapy that could move us beyond "operational" cure and toward true disease eradication.

### *Clinical Practice Points*

- What is already known about this subject?
  Multiple myeloma (MM) is predominantly a disease of the elderly, but approximately 10% of patients are younger than 50 years at diagnosis. Existing literature suggests that MM in younger individuals (< 50 years) may differ in biological and clinical features compared to older cohorts
- What are the new findings?

In a cohort of 350 patients from the Balkan Myeloma Study Group registry patients under 50 years of age, had lower rates of renal impairment and anemia but a higher incidence of lytic bone disease and adverse cytogenetics. Treatment regimens used were comparable across age groups but younger patients had significantly better complete response rates and overall survival (OS). The 5- and 10-year OS rates were 76% and 64%, respectively, with a projected median OS exceeding 15 years. Autologous stem cell transplantation (ASCT) emerged as a key contributor to improved outcomes.

- How might it impact on clinical practice in the foreseeable future? Overall it is essential to better understand the distinct biology of the disease in young MM patients and to identify major determinants of outcome. Prospective data from clinical trials and real-world settings will be crucial in developing a tailored, intensified approach to therapy that could move us beyond "operational" cure and toward true disease eradication.

## Disclosure

**Kastritis:** GSK: Honoraria, Research Funding; Pfizer: Honoraria, Research Funding; Janssen: Honoraria, Research Funding; Sanofi: Honoraria. **Beksac:** Sanofi: Speakers Bureau; Menarini**:** Membership on an entity's Board of Directors or advisory committees; BMS: Speakers Bureau; Janssen: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Takeda: Speakers Bureau. **Katodritou:** Janssen Cilag, Amgen, Abbvie, Pfizer, GSK, Takeda, Sanofi, Karyopharm: Honoraria, Research Funding. **Dalampira:** Pfizer: Research Funding. **Coriu:** Genesis BioPharma. **Gavriatopoulou:** Celgene/Genesis: Honoraria; Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees; Sanofi: Honoraria; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees; Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; GSK: Honoraria; X4 Pharmaceuticals: Research Funding; Karyopharm: Honoraria, Research Funding. **Terpos:** BMS: Honoraria; Takeda: Honoraria, Other: Travel expenses, Research Funding; Menarini/Stemline: Honoraria; Janssen: Honoraria, Research Funding; GSK: Honoraria, Research Funding; EUSA Pharma: Honoraria, Other: Travel expenses; ASTRA/Zeneca: Honoraria, Other: Travel Expenses; Amgen: Honoraria, Other: Travel Expenses, Research Funding; Pfizer: Honoraria; Sanofi: Honoraria, Other: Travel expenses, Research Funding. **Dimopoulos:** Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; Sanofi: Honoraria, Membership on an entity's Board of Direc- tors or advisory committees; Regeneron: Honoraria, Membership on an entity's Board of Directors or advisory committees; Menarini: Honoraria, Membership on an entity's Board of Directors or advisory committees; Janssen: Honoraria, Membership on an entity's Board of Directors or advisory committees; GlaxoSmithKline: Honoraria, Membership on an entity's Board of Directors or advisory committees; BeiGene Inc: Honoraria, Membership on an entity's Board of Directors or advisory committees; Bristol Myers Squibb: Honoraria, Membership on an entity's Board of Directors or advisory committees; Amgen: Honoraria, Membership on an entity's Board of Directors or advisory committees; AbbVie: Honoraria, Membership on an entity's Board of Directors or advisory committees**. Fotiou:** Sanofi: Honoraria, Janssen: Honoraria. **Batinić:** Janssen: Honoraria; Takeda: Honoraria; Amgen: Honoraria. The other authors have no relevant COIs to declare.

## CRediT authorship contribution statement

**Despina Fotiou:** Writing – original draft, Resources, Methodology, Formal analysis, Data curation. **Sorina Nicoleta Badelita:** Writing – review & editing, Resources, Data curation. **Eirini Katodritou:** Writing – review & editing, Resources, Data curation. **Meral Beksac:** Writing – review & editing, Resources, Data curation. **Jelena Bila:** Writing – review & editing, Resources, Data curation. **Emmanouil Spanoudakis:** Writing – review & editing, Resources. **Josip Batinić:** Writing – review & editing, Resources, Data curation. **Daniel Coriu:** Writing – review & editing, Resources, Data curation. **Sinziana Barbu:** Writing – review & editing, Resources, Data curation. **Catalin Danaila:** Writing – review & editing, Resources, Data curation. **Dimitra Dalampira:** Writing – review & editing, Resources, Data curation. **Angeliki Sevastoudi:** Writing – review & editing, Resources, Data curation. **Guldane Cengiz Seval:** Writing – review & editing, Resources, Data curation. **Selami Koçak Toprak:** Writing – review & editing, Resources, Data curation. **Aleksandra Sretenovic:** Writing – review & editing, Resources, Data curation. **Olivera Markovic:** Writing – review & editing, Resources, Data curation. **Toni Valkovic:** Writing – review & editing, Resources, Data curation. **Zorica Cvetkovic:** Writing – review & editing, Resources, Data curation. **Fenia Theodorakakou:** Writing – review & editing, Resources, Data curation. **Maria Gavriatopoulou:** Writing – review & editing, Resources, Data curation. **Evangelos Terpos:** Writing – review & editing, Resources, Data curation. **Meletios A. Dimopoulos:** Writing – review & editing, Resources, Data curation. **Efstathios Kastritis:** Writing – original draft, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

## Acknowledgments

No funding was received for this work.

## References

1. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78(1):21–33.
2. Ludwig H, Bolejack V, Crowley J, et al. Survival and years of life lost in different age cohorts of patients with multiple myeloma. *J Clin Oncol*. 2010;28(9):1599–1605.
3. Pal I, Illes A, Varoczy L. Multiple myeloma of the young- a single center experience highlights future directions. *Pathol Oncol Res*. 2020;26(1):419–424.
4. Ludwig H, Durie BG, Bolejack V, et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. *Blood*. 2008;111(8):4039–4047.
5. Jurczyszyn A, Nahi H, Avivi I, et al. Characteristics and outcomes of patients with multiple myeloma aged 21-40 years versus 41-60 years: a multi-institutional case–control study. *Br J Haematol*. 2016;175(5):884–891.
6. van der Poel MW, Oerlemans S, Schouten HC, et al. Elderly multiple myeloma patients experience less deterioration in health-related quality of life than younger patients compared to a normative population: a study from the population-based PROFILES registry. *Ann Hematol*. 2015;94(4):651–661.

7. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538–e548.
8. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging system for Multiple Myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863–2869.
9. D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second revision of the International Staging System (R2-ISS) for overall survival in multiple myeloma: a European Myeloma Network (EMN) report within the HARMONY Project. *J Clin Oncol*. 2022;40(29):3406–3418.
10. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328–e346.
11. Dimopoulos MA, Pouli A, Anagnostopoulos A, et al. Macrofocal multiple myeloma in young patients: a distinct entity with favorable prognosis. *Leuk Lymphoma*. 2006;47(8):1553–1556.
12. Caulier A, Roussel M, Morel P, et al. Epidemiological landscape of young patients with multiple myeloma diagnosed before 40 years of age: the French experience. *Blood*. 2021;138(25):2686–2695.
13. Duek A, Trakhtenbrot L, Avigdor A, et al. Multiple myeloma presenting in patients younger than 50 years of age: a single institution experience. *Acta Haematol*. 2021;144(1):58–65.
14. Blade J, Kyle RA, Greipp PR. Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. *Br J Haematol*. 1996;93(2):345–351.
15. Steinbach M, Neupane K, Aziz M, et al. Multiple myeloma in young patients: a scoping review. *Clin Lymphoma Myeloma Leuk*. 2024;24(1):15–22.
16. Ravi P, Kumar SK, Cerhan JR, et al. Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies. *Blood Cancer J*. 2018;8(3):26.
17. Nakaya A, Kohara T, Shibayama H, et al. Retrospective multi-center study of adolescent and young adult (AYA) multiple Myeloma in Kansai Myeloma Forum registry. *Int J Hematol*. 2020;112(4):435–438.
18. Tanguay M, Dagenais C, LeBlanc R, et al. Young myeloma patients: a systematic review of manifestations and outcomes. *Curr Oncol*. 2023;30(6):5214–5226.
19. Bao A, Zhao Q, Merritt E, et al. Racial differences as predictors of outcomes in young patients with multiple myeloma. *Blood Cancer J*. 2022;12(7):114.
20. Corso A, Klersy C, Lazzarino M, et al. Multiple myeloma in younger patients: the role of age as prognostic factor. *Ann Hematol*. 1998;76(2):67–72.
21. Pydi VR, Bala SC, Kuruva SP, et al. Multiple myeloma in young adults: a single centre real world experience. *Indian J Hematol Blood Transfus*. 2021;37(4):679–683.
22. Lu J, Lu J, Chen W, et al. More frequent IgD and reduced CD200 expression in Chinese patients younger than 50 years old with multiple myeloma: a multicenter analysis. *Drug Des Devel Ther.*. 2016;10:3673–3679.
23. Painuly U, Pandey S, Kumar S, et al. Survival outcomes of very young (< 40 years) myeloma patients. *Blood*. 2013;122(21):2136.
24. Huang LW, Bacon W, Cirrincione C, et al. Efficacy and safety of high–dose chemotherapy with autologous stem cell transplantation in senior versus younger adults with newly diagnosed multiple myeloma. *Hematol Oncol*. 2017;35(4):752–759.
25. Kristinsson SY, Landgren O, Dickman PW, et al. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol*. 2007;25(15):1993–1999.
26. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood*. 2008;111(5):2521–2526.
27. Barlogie B, Mitchell A, van Rhee F, et al. Curing myeloma at last: defining criteria and providing the evidence. *Blood*. 2014;124(20):3043–3051.
28. Roschewski M, Korde N, Wu SP, et al. Pursuing the curative blueprint for early myeloma. *Blood*. 2013;122(4):486–490.
29. Alexanian R, Delasalle K, Wang M, et al. Curability of multiple myeloma. *Bone Marrow Res*. 2012;2012:916479.
30. Sirohi B, Powles R. International myeloma grand round. *Lancet Oncol*. 2001;2(9):571–579.
31. Tricot G, Spencer T, Sawyer J, et al. Predicting long-term (>or = 5 years) event-free survival in multiple myeloma patients following planned tandem autotransplants. *Br J Haematol*. 2002;116(1):211–217.
32. Gibson S, Thornton J, Sunderland K, et al. Multiple myeloma in adolescent and young adults: an ASCO CancerLinQ and SEER analysis. *Clin Lymphoma Myeloma Leuk*. 2023;23(10):e335–e340.