

IMPACT OF AGE AND COMORBODITY AS PROGNOSTIC FACTORS ON OVERALL SURVIVAL IN PATIENTS WITH MULTIPLE MYELOMA

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ABSTRACT

Background: Multiple myeloma is a heterogeneous disease with variable disease course, a wide range of clinical presentation and many subtypes, variable response to therapy and survival outcome that ranges from less than one year in patients with aggressive disease to more than ten years in patients with indolent disease presentation. It is very important to clearly define the risk profile of each patient during establishing the diagnosis, and to predict the eventual type of therapeutic approach, its depth, quality and length. The age >75 and presence of comorbidities at the start of therapy are risk factors which impact on the quality of life, therapy response and overall survival (OS) in patients with multiple myeloma (MM).

Aim: The aim of this study was to assess the influence of the two most important risk factors in myeloma patients, ageism and comorbidities, that complicate the management of MM and at the same time OS.

Patients and methods: We retrospectively analyzed a total of 296 myeloma patients (150 male and 146 female) with average age of 62 ±10.3 years. The most affected age group (58.1%) comprised patients at the age ranging between 60 and 88 years, diagnosed at the University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia in the period 2005-2015. The follow-up period was 24 months. We evaluated some parameters that could influence OS: age and comorbidity that could influence the overall clinical condition of the patient during his therapy and his eventual future disease behavior. OS was estimated on monthly basis including the period from the date of diagnosis to the time of death / time of last visit.

Results: In the study group 26% of patients ≥ 65 years have survived more than 60 months, and 40% younger than 65 years have survived more than 60 months. Survival time in group ≥65 years is 18.3 months, and in group <65 years is 43.4 months. It is evident that age had a significant effect on OS in myeloma patients, and 49% of patients with no registered comorbidity preceding the diagnostic procedures had survived more than 60 months, but only 16% of patients with registered comorbidity survived more than 60 months. Survival time in patients with registered comorbidity preceding the diagnostic procedures was 59.3 months and survival time in patients with registered comorbidity before the diagnostic procedures is 10.7 months.

Conclusions: The age-related changes in physiology combined with comorbid conditions, disability or frailty have important implications in the treatment of myeloma patients. Based on these risk factors our recommendation is tailored treatment for each MM patient.

Key words: multiple myeloma, prognostic factors, overall survival

INTRODUCTION

Multiple myeloma is a heterogeneous disease with variable disease courses, a wide range of clinical presentation and many subtypes, variable response to therapy and survival outcome that ranges from less than one year in patients with aggressive disease to more than ten years in patients with indolent disease presentation. Symptomatic myeloma requires a quick diagnostic procedure, which will help in defining the prognostic profile and adequate treatment with which we could achieve a disease remission. Therefore, it is very important to clearly define the risk profile of each patient during establishing the diagnosis, and to predict the eventual type of therapeutic approach, its depth, quality and length. In this way, we can predict the eventual speed of the disease relapse. Moreover, we have the need to define the risk factors with which we could predict the overall impact of overall survival in patients with MM [1, 2]. The International Myeloma Working Group has revised and defined the risk factors for MM in 2011. Many studies have been involved and a consensus has been accomplished with valid biomarkers and risk factors as well. The prevalence of MM is expected to rise over time because of the aging population [3, 4]. The age >75, and presence of comorbidities (hypertension - HTA, diabetes mellitus - DM, presence of carcinoma - Ca, status post acute myocardial infarction - AMI, and chronic myocardialopathy - CMP) at the start of therapy are risk factors which have impact on the quality of life, therapy response and overall survival in patients with MM [5, 6]. In recent years, the introduction of novel agents, which are associated with high dose therapy and autologous stem cell transplantation in young patients and standard chemotherapy in elderly patients, has changed the management of MM and OS. An estimate of the 5-year relative survival of patients with MM reported a significant survival increase, but the improvement was confined in patients <70years [7, 8].

The aim of this study was to assess the influence of the two most important risk factors in myeloma patients, ageism and comorbidities, that complicate the management of MM and at the same time OS, as well as to do appropriate screening for risk factors.

MATERIAL AND METHODS

We retrospectively analyzed a total of 296 myeloma patients (150 male and 146 female) with average age of 62 years \pm 10.3 years. The most commonly affected age group (58.1%) comprised patients at the age ranging from 60 years to 88 years, diagnosed at the University Clinic of Hematology, Ss Cyril and Methodius University, Skopje, Macedonia in the period 2005-2015. They were evaluated for age, comorbidity, frailty and disability, Charlson index⁸ at the start of treatment of MM. Observation time was 24 months. We evaluated some parameters that could influence OS: age and comorbidity that could influence the overall clinical condition of the patient during his therapy and his eventual future disease behavior. OS was estimated on monthly basis including the period from the date of diagnosis to the time of death/time of last visit.

Statistical analysis

The statistical analysis was performed using the statistical package SSPS 16.0. Range, mean and standard deviation are presented for the analyzed parameters or variables in this study. Differences among variables were evaluated by the Chi-square test. Overall survival was defined as the time interval between date of diagnosis and date of death. The probabilities of OS were estimated using the method of Kaplan and Meier. Cox proportional hazards regression models were used to assess the association between prognostic factors and OS.

comorbidity	no	%
yes	122	41.2
no	174	58.8
total	296	100.0

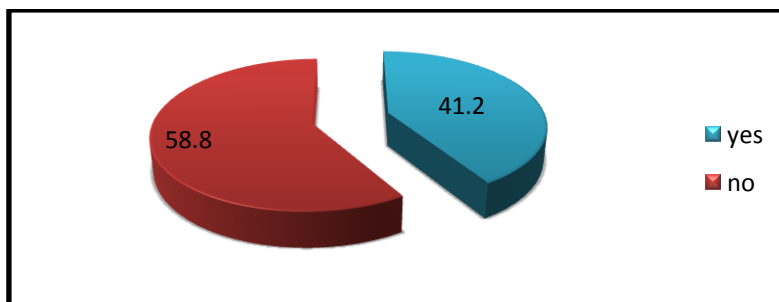


Fig. 1. Distribution of registered comorbidities in patients at time of diagnosis

In more than 58.8% of patients comorbidities were not registered, but in 41.2% there were comorbidities. The percentage difference between the registered and not registered comorbidities was statistically significant for $p < 0.05$ ($p = 0.0000$). Most of the comorbidities before diagnostic procedures included HTA in 6.8% of patients, followed by DM in 2.7%, Ca in 2.7%, St. Post AMI, cardiorespiratory events in 13.9% etc.

Table 2. Average age of patients

	No.	Average	Minimum	Maximum	St. Deviation
age	296	62.0	31.0	88.0	10.3

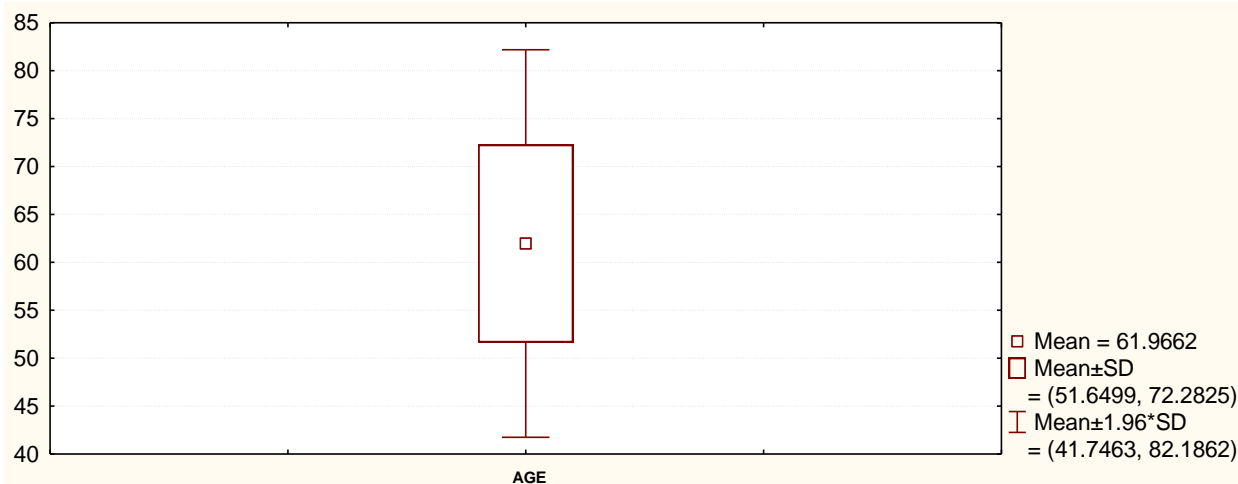


Fig. 2. Average age of patients

Table 3. Distribution of patients as per age groups

Age	No.	%
<40	4	1.4
40-59	120	40.5
>60	172	58.1
total	296	100.0

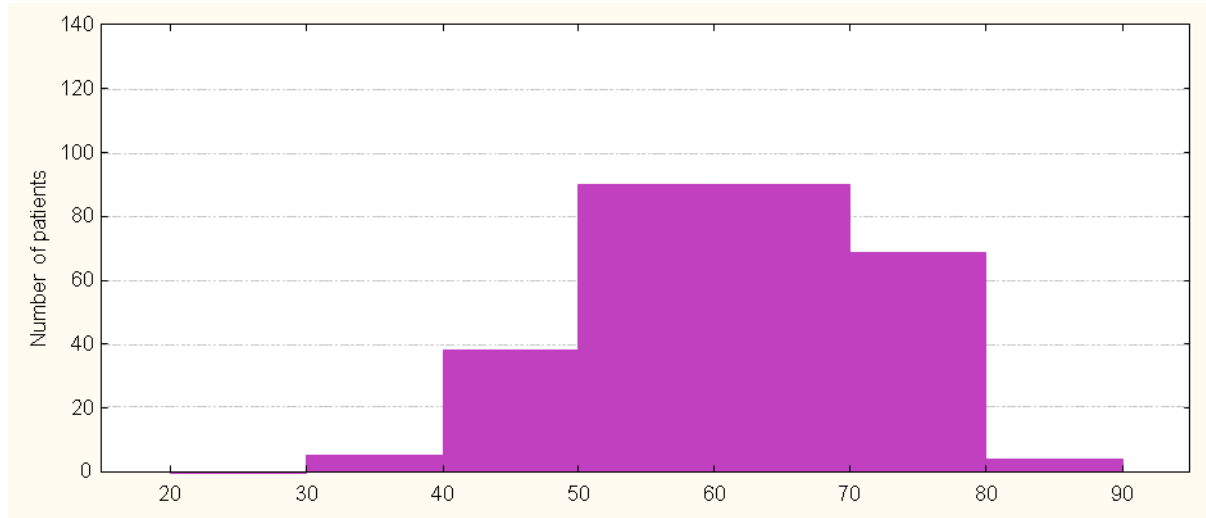


Fig. 3. Distribution of patients as per age groups

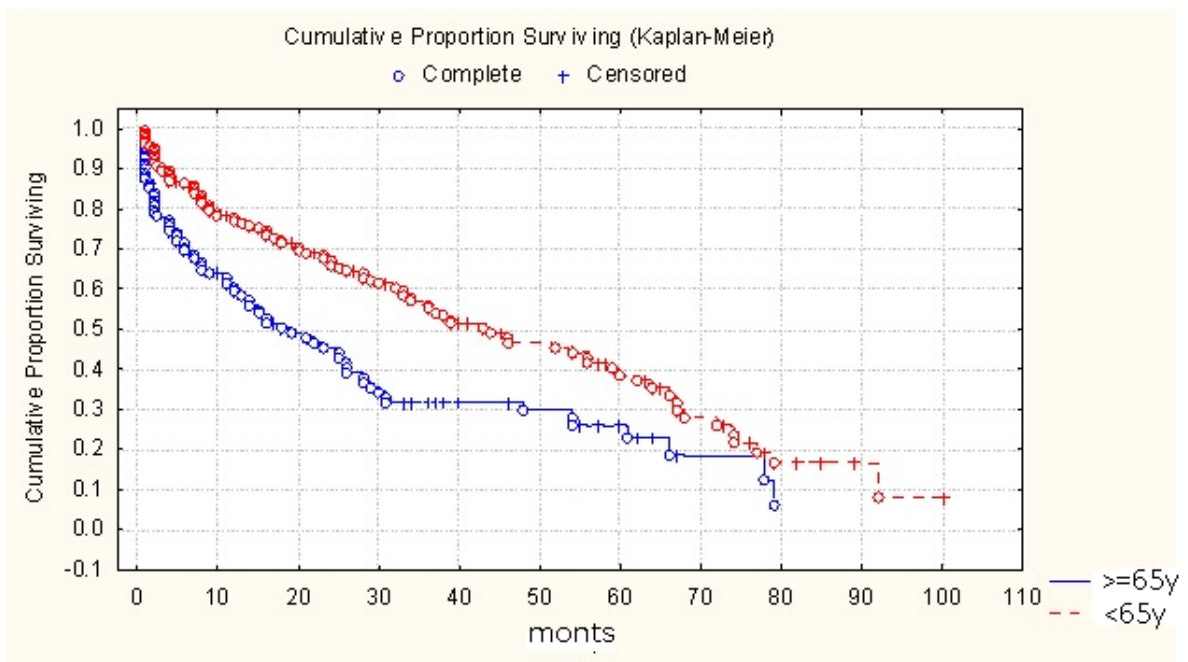


Fig. 4. Overall time of survival of patients in relation to age above and below 65 years

In this study 26% of patients ≥ 65 years have survived more than 60 months, and 40% younger than 65 years have survived more than 60 months. According to Log-Rank test ($p=0.00047$) difference between the two subgroups in relation to survival in patients younger than 65 years and older than 65 years was statistically significant. Survival time of group ≥ 65 years was 18.3 months, and of group <65 years 43.4 months. It is evident that age had a significant effect on OS in myeloma patients, and it is most important to adjust the therapy according to the age of the patients. In addition, it is also important to adjust the performance score since we have older patients who are fit and we do not have frailty and they are eligible for more aggressive or adequate treatment with adequate doses.



Fig. 5. Overall time of survival of patients in relation to comorbidity

In this study 49% of patients with no registered comorbidity preceding the diagnostic procedures have survived more than 60 months. 16% of patients with registered comorbidity have survived more than 60 months. According to Log-Rank test ($p=0.00000$) the difference between subgroups in relation to present and not present comorbidity preceding the diagnostic procedures in relation to survival was statistically significant. Survival time of patients with registered comorbidity before the diagnostic procedure was 59.3 months and survival time in patients with registered comorbidity before the diagnostic procedures was 10.7 months. It is important to compare these two risk factors with the actual physical condition and clinical state of the patients as well as to make the best treatment choice for them.

DISCUSSION

Multiple myeloma (MM) is the second most common hematologic cancer, with a higher incidence in elderly subjects: 26% are aged 65 to 74 years, and 37% are older than 75 years [9]. In our study elderly patients (58.1%) have a higher risk of death, shorter overall survival, which correspond to results in the world medical literature. Therefore, it is very important elderly patients to have a less aggressive protocol applications and its dosage reduction in relation with their performance score and in correlation with other risk factors which depend on patient's condition. These include comorbidities, socio-economic class, occupation, lifestyle factors and family support [10, 11]. The presence of comorbidities in our group has shown a shorter overall survival in patients with MM, with limited therapeutic possibilities, with less aggressive treatment, especially in patients with cardiac diseases, and those with secondary Ca. It is clear that the survival is shorter because the overall treatment is disturbed and consequently the therapy response is lower and because we could not apply more aggressive treatments such as autologous stem cell transplantation [12, 13, 14]. The question is - are these patients primarily non-responsive to the MM treatment, or they have a decreased response due to non-adequate treatments of this disease, or they have shorter overall survival due to presence of other disease? We should be very careful with these patients because with these two poor prognostic factors we have limited management of the entity called MM. Therefore, it is very important to have a personalized approach, along with a personalized treatment, in order to have a longer and more quality OS [9].

CONCLUSION

The age-related changes in physiology combined with comorbid conditions, disability or frailty have important implications in treatment of myeloma patients. Based on these risk factors our recommendation is tailored treatment to help clinicians ensure the most appropriate care for MM patients during everyday clinical practice.

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