Original Study

Prognostic Effect of Comorbidity Indices in Elderly Patients With Multiple Myeloma

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Abstract

In this study we analyzed the effect of the Charlson Comorbidity Index (CCI), age-adjusted CCI, and scale of Instrumental Activities of Daily Living on the course of disease in 110 patients newly diagnosed with multiple myeloma and older than 65 years of age. It was found that these comorbidity scores are of prognostic significance on the treatment outcome and course of disease.

Background: Consideration of comorbidity, disability, and frailty represents a significant part of the treatment of elderly multiple myeloma (MM) patients. The aim of study was to analyze the effect of the Charlson Comorbidity Index (CCI) and scale of Instrumental Activities of Daily Living (IADL) on the course of disease. **Patients and Methods:** The study included 110 newly diagnosed MM patients older than 65 years of age. According to the CCI most patients had at least 1 comorbidity (CCI score of 1) and most of them (51 of 110 patients; 46.4%) had an age-adjusted CCI (aaCCI) score of 5 to 6. Most of our patients were capable of performing routine daily activities (IADL $\geq$ 6). Patients were treated with thalidomide- and bortezomib- based combinations, or with conventional chemotherapy. **Results:** International Staging System (ISS) score 3 correlated with high scores of CCI or aaCCI ($R = 0.314$, $P < .003$; $R = .317$, $P < .002$, respectively), and lower IADL ($R = 0.259$, $P < .007$). The probability of adverse events was 70% greater for CCI score $\geq$ 2 (odds ratio [OR], 1.72); 28% for aaCCI $\geq$ 5 (OR, 1.28) and 22% higher for IADL < 3 (OR, 2.25). The patients with a CCI score of 0 to 1 had significantly longer overall survival (OS; log rank, 6.538; $P < .011$). The patients with aaCCI $\geq$ 5 had significantly shorter OS (log rank, 4.209; $P < .040$), and the patients with IADL > 3 had significantly longer OS (log rank, 6.62; $P < .001$). In the proposed model, aaCCI $\geq$ 5 and IADL > 3 scores had a major effect on the OS (χ^2, 8.46; $P = .037$). **Conclusion:** CCI, aaCCI, and IADL scale are clinical parameters of prognostic significance. A proposed model for a personalized treatment approach is based on variables such as scores for aaCCI $\geq$ 5 and IADL > 3.

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Introduction

Multiple myeloma (MM) is a disease of the elderly population with median age of 70 years at diagnosis.[1] Approximately 65% of the patients are older than 65 at the time of diagnosis and 30% of them are older than 75.[2-4] The elderly MM population is vulnerable because of different comorbidities that can mask the presentation of MM, and complicate management of the disease.[4] Most of the

patients older than 70 are ineligible for high-dose chemotherapy followed by the autologous stem cell transplantation (ASCT), and require personalized treatment.[4] In the recent years, novel agents have significantly improved the overall survival (OS) in the MM population.[5,6] The benefit of thalidomide, bortezomib, and lenalidomide has been confirmed in numerous clinical studies.[5-7] Further research is needed to define the best treatment approach for the vulnerable population of elderly patients because their inferior outcome might be the consequence of commonly used dosage reductions to avoid expected toxicity.[1,8] In an attempt to clinically define different groups of elderly MM patients and the best possible treatment approach for them, well known tools such as the Charlson Comorbidity Index (CCI) and Age-Adjusted CCI (aaCCI) are widely applied.[9,10] The Instrumental Activities of Daily Living

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(IADL), as a geriatric assessment, was used to indicate new disabilities in functional domains to prevent further disability and to promote a safe life time for older people.[11] The goal of this single-center study was to analyze the prognostic and treatment effect of the comorbidity indices CCI and aaCCI, and the ability to asses daily activities expressed using the IADL scale on the course and outcome of elderly MM patients.

Patients and Methods

The analyzed group consisted of 110 patients with newly diagnosed MM who were older than 65 years of age with an equal distribution of both sexes (55 men/55 women). The mean age was 71 (range, 65-81) years. According to the type of MM, distribution was as following: immunoglobulin (Ig)G myeloma, 68 patients (61.8%); IgA, 25 patients (22.7%); light chains, 15 patients (13.6%); IgD, 1 patient (0.9%); and nonsecretory, 1 patient (0.9%). Most patients (81 of 110; 75.7%) were in advanced III clinical stage (CS) of disease (Durie–Salmon). Five patients (4.7%) were in stage I on the CS scale, and 21 (19.6%) patients were in CS II. Regarding ISS score, 14 patients (12.7%) had an ISS score 1, 35 patients (31.8%) had an ISS score of 2, and 61 patient (55.5%) had an ISS score of 3. Renal impairment was present in 36 patients (34%).

Charlson Comorbidity Index score was calculated according to the criteria reported by Charlson et al.[9,10] Adding 1 point to the CCI for each decade of the age over 40, it gives the possibility to calculate the aaCCI.[9,10] The median score for CCI was 1 (range, 0-5), and median aaCCI score was 5 (range, 3-9). Most of the patients had a CCI score of 0 to 1 (82 patients, 74.5%); 21 patients (19.1%) had scores of 2 to 3; and 7 patients (6.4%) had scores of 4 to 5. Regarding aaCCI, 49 patients (44.5%) had an aaCCI score of 3 to 4; 51 patients (46.4%) had scores of 5 to 6; and 10 patients (9.1%) had aaCCI scores $\geq$ 7. The IADL was scored according to the Lawton criteria for the geriatric assessment of elderly people.[11] The questionnaire of the IADL Scale was filled personally by the patient, who chose 1 of the offered answers to 8 questions. The median IADL score was 6 (range, 0-8), with IADL $\geq$ 6 in 70 patients (64.2%); 3 to 5 in 26 patients (23.9%); and 0 to 2 in 13 patients (11.9%; Table 1).

Treatment of the analyzed group of patients included thalidomide combinations in 63 patients (57.3%); 5 patients (4.6%) received bortezomib; and 42 patients (38.1%) received conventional chemotherapy.

Statistical Analyses

Descriptive statistics were used to characterize clinical features of the MM population as median values and ranges for continuous variables; and percentages and frequencies were used for categorical variables. OS was defined either as the time from diagnosis to death, or censored as of June 2013. The survival distribution was estimated using the Kaplan–Meier method. The association between comorbidity indices and OS in the univariate analyses with estimated hazard ratios (HRs) and 95% CIs were analyzed using the Cox regression model. Statistical significance was determined at a value of $P < .05$. The multivariate analyses included the factors of significance with the major influence on OS as comorbidity indices and ISS. All calculations were made using SPSS software version 16.0.

Ethics Standard

The study was performed according to the guidelines of the Declaration of Helsinki and Principles of Good Clinical Practice.
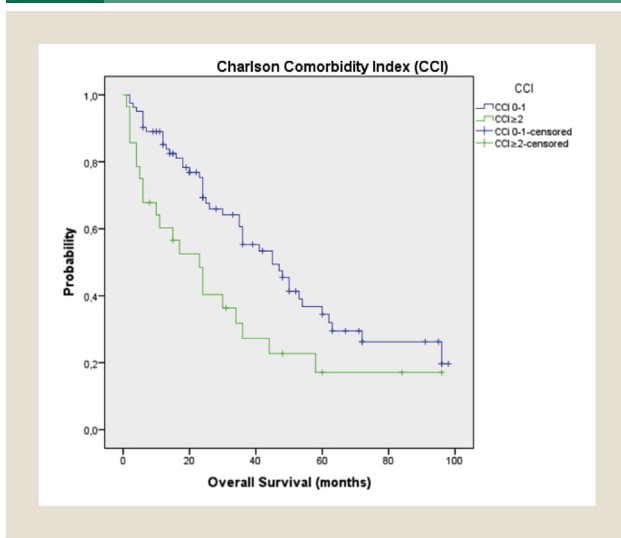
Results

Regarding clinical characteristics of patients, high values of ISS (International Staging System score 3) correlated with high scores of CCI or aaCCI ($R = 0.314$, $P < .003$; $R = 0.317$, $P < .002$), and lower IADL ($R = 0.259$, $P < .007$).

The probability of adverse events (AEs) such as neutropenia, thrombocytopenia, anemia, infections, and polyneuropathy were 70% greater for CCI score $\geq$ 2 (odds ratio [OR], 1.72; 95% confidence interval [CI], 0.62-4.75); and 28% for aaCCI $\geq$ 5 (OR, 1.28; 95% CI, 0.49-3.34). There was a 22% greater probability of AEs for patients with IADL < 3 (OR, 2.25; 95% CI, 0.65-7.79).

The overall treatment response (complete response [CR]/very good partial response/partial response/minimal response) was achieved in 81 patients (73.6%) with a median duration of 14 (range, 3-85) months. The median OS for the group was 36 (range, 6-98) months. Patients with a CCI score of 0-1 had significantly longer OS (log rank 6.538; $P < .011$; Figure 1). The patients with aaCCI $\geq$ 5 had significantly shorter OS (log rank, 4.209; $P < .040$; Figure 2). The OS was significantly longer in patients with IADL > 3 (log rank, 6.62; $P < .001$; Figure 3). Furthermore, aaCCI $\geq$ 5 and IADL > 3 scores were indicated as major variable cutoff values in the proposed model for the personalized treatment approach with a clear effect on the OS of elderly MM patients ($\chi^2 = 8.46$, $P = .037$; HRs: IADL $\geq$ 3 = 0.46; 95% CI, 0.24-0.9; aaCCI $\geq$ 5 = 1.43; 95% CI, 0.76-2.71).
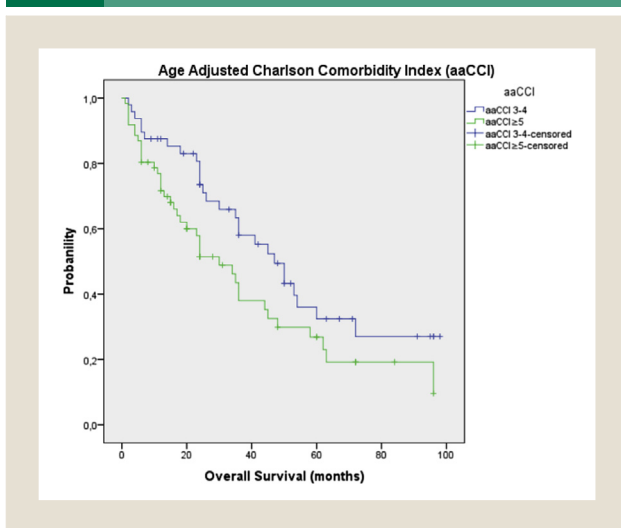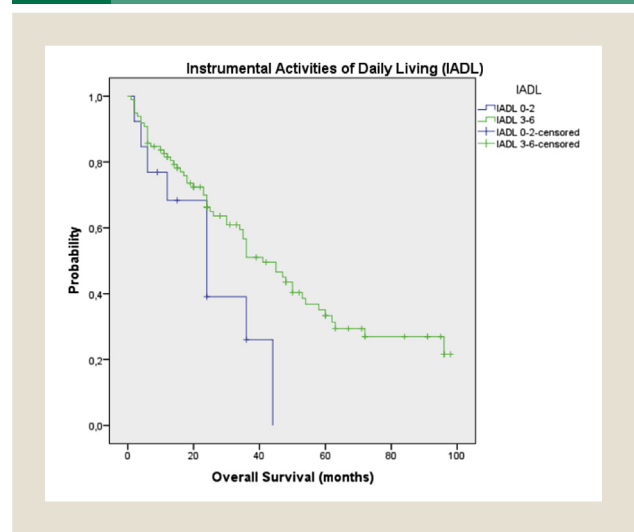
Discussion

An increased incidence of MM in the elderly population has been reported, which is mainly due to improvement of life conditions and consequently life expectancy.[1,12,13] Today, the management of the elderly population with MM becomes a real challenge, especially because of the fact that 40% of patients belong to the so-called "very elderly patients" group.[8-14]

Table 1	Patient Clinical Characteristics and Comorbidity Scores (n = 110)		
Comorbidity Index	**Score**	**n (% of Patients)**	**Median Score (Range)**
Charlson Comorbidity Score	0-1	82 (74.5)	1 (0-5)
	2-3	21 (19.1)	
	4-5	7 (6.4)	
Age Adjusted Charlson Comorbidity Score	3-4	49 (44.5)	5 (3-9)
	5-6	51 (46.4)	
	$\geq$7	10 (9.1)	
Instrumental Activities of Daily Living Scale	0-1	13 (11.9)	6 (0-8)
	3-5	26 (23.9)	
	$\geq$6	70 (64.2)	

Figure 1	Overall Survival in Patients ≥ 65 Years of Age According to Charlson Comorbidity Index (CCI)

Figure 3	Overall Survival in Patients ≥ 65 Years of Age According to Instrumental Activities of Daily Living Scale (IADL)

The introduction of immunomodulatory drugs such as thalidomide or lenalidomide, and bortezomib as the proteasome inhibitor, has dramatically improved the survival of the patients with MM regardless of age.[4,15-17] The inferior outcome of elderly MM patients is mainly influenced by the presence of comorbidities, and consequently dose-reduced therapy.[1,8] This is in accordance with the assumption that biological age expressed by an individual performance status despite chronological age, should be a major determinant for the treatment approach.[18]

The presence of comorbidities has a major influence on the performance status in the elderly population, which leads to the necessity of revising functional status scores.[4,19,20] Up to 30% of elderly patients with good performance status are not able to completely perform all daily activities.[20,21] IADL was developed as a more sensitive tool that can detect earlier less complex dysfunction.

Figure 2	Overall Survival in Patients ≥ 65 Years of Age According to Age Adjusted Charlson Comorbidity Index (aaCCI)

According to the IADL scale, most of our patients were able to perform most of the daily activities. All of the patients with low IADL were in CS III (Durie–Salmon) with disseminated bone disease, and had inferior outcome.

Palumbo et al defined patient vulnerability according to frailty, comorbidity, and disability.[4] The wide usage of CCI in practice is mainly caused by its simplicity.[10,19,22] Several studies on different cancer patients indicated that comorbidities compared with the outspread of cancer, are independent factors associated with increased risk of mortality.[22-24] However, the influence of comorbidities on OS was studied in a few hematological disorders.[4,25] In our study, patients with a low CCI score of 0 to 1, and the patients with higher functional abilities (IADL > 3) had significantly longer OS. The patients with aaCCI ≥ 5 had significantly shorter OS. These results confirm the influence of different comorbidity conditions on the outcome of MM patients. Moreover, the CCI retains its ability to classify vulnerable population of patients.

Regarding current treatment recommendations, high-dose therapy followed with ASCT is considered standard therapy for younger patients.[26,27] However, some studies recommend ASCT in fit patients up 70 years of age with dose-reduced conditioning regimens.[1,4] Patients aged older than 75 years, or younger patients with comorbidities, should be treated with adjusted therapy to reduce treatment-related toxicity accompanied with therapy interruptions. In combination with melphalan and prednisone as the cornerstone of the treatment of the elderly population, the application of new drugs has led to the extension of survival in correlation with achievement of a durable CR, although associated with the increase of the rate of AEs.[4,18,28-30] In our group of patients, the occurrence of hematological AEs and polyneuropathy were associated with high scores of comorbidity indices and low IADL scores. In the analyzed group of patients with high comorbidity scores, dose-reduced chemotherapy was applied resulting in inferior outcome. In a "very elderly population," initially high values of the aaCCI score are based

predominantly on the patients age. In accordance with this, it was found that an aaCCI score ≥ 5 was the factor of poor prognosis despite the lack of comorbidities. In the proposed model for the personalized treatment approach, in our study, scores on the aaCCI of ≥ 5 and the IADL of > 3 were indicated as major variable cutoff values with clear effect on the OS of elderly MM patients. These data are in accordance with the previously reported necessity of caution in making treatment decisions for the vulnerable population of elderly MM patients, with a final goal to complete treatment and prolong OS, independent of hospitalization services and with improved quality of life.[4]

Conclusion

Our study showed that CCI, aaCCI, and scale of the IADL represented important clinical parameters with prognostic effects on the treatment outcome and course of disease in elderly MM patients. The variables such as aaCCI score ≥ 5 and IADL score > 3 are noted as significant importance for appropriate treatment choice and possible dose adjustment.

Clinical Practice Points

- Most of the current prognostic systems in MM are based on the biological characteristics of disease, frequently unfairly neglecting the importance of the clinical presentation of the patients.
- Considering that MM is an illness of a predominantly elderly population, the prognostic effect of the comorbidity indices should be clarified in a view of the personalized treatment approach.
- Analyzed CCI, aaCCI, and the scale of the IADL, have a clear prognostic effect on the OS of elderly MM patients.
- Based on the results of our study, the proposed prognostic model indicates a score on the aaCCI of ≥ 5 and IADL > 3 as the variable cutoffs at which an individualized treatment approach and possible dose adjustment are warranted.
- Such clinical prognostic models together with molecular biological findings of major prognostic significance, could be the variables of a unique prognostic system for personalized treatment, resulting in improved survival or eventually cure of patients with MM.

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Disclosure

The authors have stated that they have no conflicts of interest.

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