Comparative Evaluation of Common Comorbidity Scores and Freiburger Comorbidity Index as Prognostic Variables in a Real Life Multiple Myeloma Population

Birgul Onec^{1,2} · Harika Okutan² · Murat Albayrak² · Esra Sarıbacak Can² · Vedat Aslan² · Ozge Soyer Kosemehmetoglu² · Basak Unver Koluman²

Received: 24 May 2015 / Accepted: 5 November 2015 / Published online: 16 November 2015
© Indian Society of Haematology & Transfusion Medicine 2015

Abstract Multiple myeloma (MM) is a disease of the geriatric population with a median age at diagnosis of 69 years but most clinicians consider performance status and comorbidities rather than chronological age in determining prognosis and treatment. The purpose of this study was to assess whether and which comorbidity indices predict survival in a real life population of MM. We calculated Charlson Comorbidity Index (CCI), age combined Charlson index (CCI-age), Hematopoietic cell transplantation-specific comorbidity index (HCT-SCI) and Freiburger comorbidity index (FCI) retrospectively for 66 MM patients and compared their impact on treatment responses and overall survival (OS). Treatment response was significantly worse in groups with high CCI, CCI-age, HCT-SCI scales ($p < 0.05$), but FCI's effect on treatment response was not significant. However, while no significant relationship was determined between other comorbidity indices with OS, it was related only with FCI-CI ($p = 0.006$). FCI, developed in this patient group, was the only prognostic index with a significant effect on OS in the evaluation of comorbidities in MM patients with different scores, but its relationship to treatment responses was not significant contrary to other indices. While this small patient group gave us hope regarding the use of FCI in practice, multi-center studies are still required.

Keywords Comorbidity scores · Freiburger comorbidity index · Multiple myeloma · Prognosis · Survival · Treatment response

Introduction

Multiple myeloma (MM) is a heterogeneous disease with 20 % of patients having a survival time of less than 2 years but more than 15 % having a survival time of more than 10 years [1]. Therefore, it is important to identify disease features and prognostic factors that may allow better tailored therapeutic intervention. Because it is a disease involving a relatively older population with a median age at diagnosis of 69 years [1], in addition to advanced age and poor performance status, comorbidities are also used empirically as prognostic factors in treatment determination. As not all comorbidities may affect the outcome, weighted comorbidity measurements are frequently used in older patients but it is not well known which of them are really prominent at MM [2]. We calculated Charlson Comorbidity Index (CCI), CCI age combined index (CCI-age), Hematopoietic cell transplantation-specific comorbidity index (HCT-SCI) and Freiburger comorbidity index (FCI) [3–6] retrospectively for 66 MM patients and compared their impact on treatment responses and overall survival in order to assess whether and which comorbidity indices predict survival in a real life population of MM.

Materials and Methods

After this study had been approved by the local ethics committee, records of 66 MM patients diagnosed in our clinic between 2009 and 2013 were reviewed, and their

✉ Birgul Onec
birgulonec@gmail.com

¹ Present Address: Department of Hematology, Duzce University Faculty of Medicine, 81000 Konuralp, Duzce, Turkey

² Department of Hematology, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey

age, MM type, staging (International Staging System = ISS and Durie-Salmon), biochemical prognostic factors, existing comorbidities, Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance scores (KPS) were recorded. CCI, CCI-age, HCT-SCI and FCI scores were calculated for each patient with these data. While risk groupings were determined as four risk groups for CCI, five risk groups for HCT-SCI, and three risk groups for FCI according to comorbidity scores in original sources [3–5, 7], three main groups, namely low, intermediate and high, were used in order to make comparisons as in previous studies [4, 5] (Table 1).

While age and biochemical parameters of the patients were grouped as “low” and “high” in terms of median values for analysis, beta-2 microglobulin levels were divided into three groups as <3.5 , between 3.5–5.5 and >5.5 in accordance with ISS staging, and into two groups as below and above albumin 3.5 g/dl. Karnofsky performance status was grouped into two as below and above 70 as in FCI scoring. Response levels of the patients evaluated in accordance with International Myeloma Working Group (IMWG) international response criteria were examined with these factors after the first line treatment (3–6 months), but stringent complete response, complete response, very good partial response and partial response groups were combined to establish “good response”, and stable disease, progressive disease and deaths occurring before first response evaluation were combined to establish “poor response” for statistical analysis due to lack of sufficient numbers of patients in total. Statistical analysis was carried out using IBM SPSS version 20 software. Compliance of variables for normal distribution was examined with visual (histogram and probabilistic graphics) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Descriptive analysis was given using mean and standard deviation ($\pm$ SD) for normally distributed variables, and using median and value intervals (minimum–maximum) for not normally distributed variables (Table 2). For cases where variables were not normally distributed, these parameters and ordinal response level variable were compared using Kruskal–Wallis test. Paired comparisons were made using Mann–Whitney

U test and evaluated using Bonferroni correction. Good and poor response rates in CCI, CCI-Age, HCT-SCI, and FCI risk groups were reviewed by Chi square and Kruskal–Wallis test. The effects of all factors studied on survival were reviewed using log rank test, and survival rate was calculated with Kaplan–Meier survival analysis. Total type 1 level of error was used as 5 % for statistical significance.

Results

Descriptive features of the patients are summarized in Table 2. Median survival was 39.01 months and 95 % CI was 95 % (29.4–48.6) in the group of 66 patients aged 34–90. No significant difference was determined between the survivals related to gender and diagnosis age. While heavy or light chain myeloma type, C reactive protein (CRP), lactate dehydrogenase (LDH), creatine, hemoglobin, and plasma cell ratio in bone marrow were not related to survival ($p > 0.05$), calcium (Ca), albumin, beta-2 microglobulin, and ISS staging were significantly related to survival ($p < 0.05$). While first treatment in low ISS stage patients had significantly better response ($p = 0.006$), no significant relation was determined between Durie-Salmon staging system and response rates ($p = 0.88$).

When ECOG performance status of the patients was assessed, median survival was 45.86 months for ECOG 0, 36.15 months for ECOG 1, 30.95 months for ECOG 2, 31.81 months for ECOG 3, and 16.76 months for ECOG 4 and this difference was statistically significant ($p = 0.028$). Similarly, while the survival was 39.92 months on average for the patients with good Karnofsky performance status, it was 27.04 months with poor Karnofsky performance status, and this effect on survival was significant ($p = 0.016$). While ECOG performance status had a relationship with response rate ($p = 0.026$), this relationship was not observed with Karnofsky performance status ($p = 0.07$).

When CCI risk groups were composed, a significant decrease was observed in response rates with high CCI scores ($p = 0.042$), but the relationship between CCI-age risk groups and response levels was not significant ($p = 0.081$, Fig. 1). While both CCI and CCI-age scores increase, survival decreases, this relationship was not statistically significant (p respectively 0.153 and 0.614, Fig. 2). Although there was a significant relationship between HCT-SCI risk groups and response rates (Fig. 1, $p = 0.03$), its significant relationship with survival was not available ($p = 0.244$, Fig. 2). No significant relationship was observed in the response rate distributions in the analysis made with FCI-CI risk groups ($p = 0.064$, Fig. 1), but survival decreased when risk score increased. Median survival was determined as 40.7 months in low risk group, 38.5 months in intermediate risk group, and 21.2 months in

Table 1 Risk group according to CCI, CCI-age, HCT-SCI and FCI comorbidity index

Risk groups	CCI	CCI-age	HCT-SCI	FCI
Low	0	0–1	0	0
Intermediate	1	2–4	1–2	1
High	≥ 2	≥ 5	≥ 3	2–3

CCI Charlson Comorbidity Index, CCI-age CCI-age combined index, HCT-SCI Hematopoietic cell transplantation-specific comorbidity index, FCI Freiburger comorbidity index

Table 2 Descriptive features

		<i>n</i> (%)	Median (range)	Mean (SD)
Age	General	66 (100)		66.55 (12.149)
	Male	40 (60.6)		67 (13)
	Female	26 (39.4)		65 (11)
MM Type	IgG	35 (53)		
	IgA	15 (22.7)		
	IgM	0 (0)		
	Light chain	16 (24.2)		
	κ/λ	37 (56.1)/29 (43.9)		
Extramedullary		3 (4.56)		
ECOG	0	8 (12.1)		
	I	14 (21.2)		
	2	14 (21.2)		
	3	19 (28.8)		
	4	11 (16.7)		
KPS			60 (30–90)	
ISS Stage	I	8 (12.1)		
	II	19 (28.8)		
	III	38 (57.6)		
Durie-Salmon Stage	I	1 (1.5)		
	II	24 (36.4)		
	IIIA	23 (34.8)		
	IIIB	18 (27.3)		
Sedimentation (mm/h)			93.85 (33.65)	
Hemoglobin (g/dl)			9.68 (1.95)	
Total protein (g/dl)			8.73 (2.29)	
Albumin (g/dl)			3.6 (0.65)	
Creatinine (mg/dl)		1.15 (0.2–24)		
Calcium (mg/dl)		9.56 (4.2–14.9)		
LDH(U/l)		212 (3.7–842)		
Beta 2 microglob. (mg/l)		7.19 (2.1–52)		
Bone marrow plasma cell (%)		54 (10–90)		
CCI score		1(0–4)		
CCI-age score		3 (0–7)		
HCT-SCI score		3 (0–9)		
FCI score		1 (0–3)		

MM Multiple myeloma, *ECOG* Eastern Cooperative Oncology Group performance status, *KPS* Karnofsky performance status, *ISS* International Staging System, *LDH* Lactate Dehydrogenase, *CCI* Charlson Comorbidity Index, *CCI-age* CCI-age combined index, *HCT-SCI* Hematopoietic cell transplantation-specific comorbidity index, *FCI* Freiburger comorbidity index

high risk group, and this difference was statistically significant (Fig. 2, $p = 0.006$). This difference in survival in paired comparisons is due to the difference between low and high risk groups ($p = 0.005$). When factors composing FCI scoring are separately reviewed, it was observed that pulmonary and renal comorbidity scores separately do not have any significant affect on survival, but when Karnofsky performance status was coded as below and above 70, they separately had significant relationship with survival ($p < 0.001$).

Discussion

Clinical course and survival have a distinctive variability in myeloma patients. This variability is the result of both myeloma cell biology and various factors that belong to the patient. Several comorbidities and performance limitations are frequently involved as the disease has a higher incidence in elderly subjects. As for determining whether the patient is a candidate for autologous stem-cell supported high dose chemotherapy as a key step in the treatment, it is

Fig. 1 Bar charts demonstrating first line treatment responses and comorbidities calculated by different indices. CCI Charlson Comorbidity Index ($p = 0.042$), CCI-age CCI-age combined index ($p = 0.081$), HCT-SCI hematopoietic cell transplantation-specific comorbidity index ($p = 0.03$), FCI freiburger comorbidity index ($p = 0.064$). Good response Stringent complete response, complete

response, very good partial response, or partial response according to International Myeloma Working Group (IMWG) international uniform response criteria. Bad response Stable disease or progressive disease according to International Myeloma Working Group (IMWG) international uniform response criteria or death before response evaluation

important to examine the prognostic factors and comorbidities in these patients in accordance with the patient group.

In our study, the median age of the patients was 66.5 between 34 and 90, which had a normal distribution. It was thought that not observing any significant relationship between diagnosis age and prognosis might be due to the small size of the sample. It might be due to the existence of several factors which are more efficient on prognosis as well. Although age of diagnosis was reported to be determinant on overall survival in a recent analysis where data of more than 40,000 MM patients were evaluated, it should be kept in mind that the age limit in this analysis was

determined to be 75 [7]. In a study by Kleber et al. [6] with a focus on comorbidities, chronological patient age, which was observed as significant factor in a single variable analysis, was not as significant as other factors in multivariate analysis and the authors stressed that biological age can substantially differ from the chronological patient age, and that evaluation solely with chronological patient age may lead to false outcomes.

Traditionally staging systems are used for determining prognosis. In our study, median survival in stage II was approximately 40, 30 months in stage IIIA and 24 months in stage IIIB in compliance with the literature in Durie-Salmon stages and its relationship with survival was

Fig. 2 Overall survival and comorbidities calculated by different indices. *CCI* Charlson Comorbidity Index ($p = 0.153$), *CCI-age* CCI-age combined index ($p = 0.614$), *HCT-SCI* hematopoietic cell

transplantation-specific comorbidity index ($p = 0.244$) and *FCI* Freiburger comorbidity index ($p = 0.006$)

determined to be significant ($p = 0.037$). ISS staging system is also established on $\beta 2$ microglobulin and albumin, which is related to tumor burden. These two parameters were determined to be independent parameters with a powerful relationship with survival in the studies (8). Accordingly, median survival was 69 months for stage I, 44 months for stage II, and 29 months for stage III. In our study, both albumin and $\beta 2$ microglobulin had a relationship with prognosis as well. ($p = 0.013$). Median survival was 46 months for ISS stage I, 42 months for stage II, and 25 months for stage III.

The two factors with a distinctive effect on survival were ECOG and Karnofsky performance status of the patients. While median survival of the patients was 45.86 months for ECOG 0, 36.15 months for ECOG 1,

approximate for ECOG 2 and ECOG 3 (30.95 and 31.81 months), and 16.76 months for ECOG 4, this difference was statistically significant ($p = 0.028$). Similarly, while the survival was 39.92 months on average for the patients with good Karnofsky performance status, it was 27.04 months with poor Karnofsky performance status, and this effect on survival was significant ($p = 0.016$). Indeed, while the performance status is set forth as a patient related prognostic factor in the 2013 guide of the Mayo Clinic, the performance status is not included either in ISS or Durie–Salmon staging or Mayo Clinic risk classification, which is mainly based on genetic features [8–10]. In new studies, performance status was reported to have significant effect on the survival in a similar manner with our findings. The study of Offidani et al. on 266 MM patients reported that

poor performance status (ECOG 2–4) is an independent factor that deteriorates survival [2]. Kleber et al. [6] achieved the same result by measuring the performance status with KPS. Although clinicians generally accept that performance status is important for the selection of treatment and prognosis, performance status leads to difficulties for estimating prognosis and making practical clinical decisions as it is not included in objective staging and risk classifications. Therefore, KPS is also a parameter in addition to pulmonary and renal functions in the FCI index developed by Kleber et al. [6] which can allow objective use of performance status in the survival estimation.

As MM has a higher incidence in elderly subjects, it is expected that comorbidities that increase with the age accompany this disease. Two or more comorbidities are reported in 35 % of males and 45 % of females aged 60–69 in our society. These rates increase to 53 and 70 %, respectively above the age of 80 [11]. The same rate was reported to be 36.4 % in our patient group. Different comorbidity indices can be used for evaluating comorbidities. The relationship of CCI, which is one of these comorbidity indices, with survival is analyzed in several solid malignancies; however their data in hematological malignancy are limited. Therefore, our study is of importance with this regard as well. In the studies with myelodysplastic syndrome and acute myeloid leukemia, it was reported that survival deteriorated with increased numbers of comorbidity [12, 13]. HCT-SCI was developed in studies where patients had undergone hematopoietic cell transplantation [5]. Kleber et al. recently compared various comorbidity scales in MM and reported that the effects of KPS, eGFR and lung disease had more impact on progression-free survival and overall survival in their analysis. They proposed a distinctive comorbidity index, based on these factors, called the Freiburger comorbidity index (FCI) for MM [6]. In this study, survival was reported as 118 months with low score (0), and 25 months with high scores (2–3) in MM patients according to this comorbidity index, validation of which was also carried out. Kleber et al. [14] recently proved the relationship between FCI and survival once again on 466 MM patients and they claimed that a more powerful prognostic index might be established when FCI is merged with ISS. Offidani et al. [2] reported that CCI score was among independent factors that deteriorated overall survival together with performance status (ECOG) in 266 MM patients. In multivariate analysis of this study, ISS was reported to have an effect on survival as well, but effects of ECOG and CCI were analyzed independently from this effect. In a study on patients with relapsed or refractory MM receiving lenalidomide treatment, HCT-SCI, FCI and Kaplan Feinstein comorbidity indices were compared, and only FCI was reported to have an effect on progression-free and overall survival [15, 16].

While all comorbidity indices presented graphics related to survival, only the FCI index has a statistically significant effect on survival in our study as well ($p = 0.006$). In this study, FCI developed in MM patients was reported to be the only comorbidity with a significant effect on the overall survival in comorbidity measurements of patients.

Selection of treatment and response to treatment may be a significant factor that needs to be taken into account for the effects of performance status and comorbidity scores on survival. As good response to the first treatment was reported to be the most important factor on survival ($p < 0.001$) in our study, comorbidity scoring, one of the factors which may affect the level of response, and first treatment responses were compared. While CCI, HCT-SCI scores, ISS stage, and ECOG performance status had a statistically significant distribution difference on the response, this effect was not observed in FCI. In clinical practice, initiation of chemotherapy protocols with low toxicity in patients with poor performance and comorbidities and their low therapeutic efficiency might lead to these results. We could not find any other study in the literature that examines the performance status in myeloma patients and the effect of comorbidities on the treatment responses. It will be more accurate if evaluation is made in higher scale studies with multivariate analysis in order to clarify this issue.

Conclusions

In the light of these findings, it was thought that performance status and presentation of comorbidities are significant tools in addition to staging for the estimation of prognosis during the first evaluation of patients. It was concluded that FCI, which clarifies performance and comorbidity status with simplicity to be used in clinical practice, might be an objective prognostic index. While this study presented a sampling of the prognostic benefit of the use of FCI in MM patients in real life as a single center experience, many questions could not be addressed due to the limited numbers of patients. For instance, the effect of renal and lung functions, which are components of FCI, on the survival could not be reported to be statistically significant or OS increases even if FCI does not have any effect on the treatment responses, are interesting findings that could not be clarified due to the small number of patients. Multi-centered randomized large studies are required in order to clarify these issues and to develop a simple comorbidity index such as FCI.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

References

1. Munshi NC, Jagannath S (2013) Plasma cell neoplasms. In: Hoffman R, Benz EJ, Silberstein L, Heslop H, Weitz J, Anastasi J (eds) Hematology, basic principles and practice, 6th edn. Saunders, Philadelphia, pp 1303–1337
2. Offidani M, Corvatta L, Polloni C, Centurioni R, Visani G, Brunori M et al (2012) Assessment of vulnerability measures and their effect on survival in a real-life population of multiple myeloma patients registered at Marche Region Multiple Myeloma Registry. *Clin Lymphoma Myeloma Leuk* 12(6):423–432
3. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40(5):373–383
4. Charlson M, Szatrowski TP, Peterson J, Gold J (1994) Validation of a combined comorbidity index. *J Clin Epidemiol* 47(11):1245–1251
5. Sorrow ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG et al (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 106(8):2912–2919
6. Kleber M, Ihorst G, Terhorst M, Koch B, Deschler B, Wasch R et al (2011) Comorbidity as a prognostic variable in multiple myeloma: comparative evaluation of common comorbidity scores and use of a novel MM-comorbidity score. *Blood Cancer J* 1(9):e35
7. Kaya H, Peressini B, Jawed I, Martincic D, Elaimy AL, Lamoreaux WT et al (2012) Impact of age, race and decade of treatment on overall survival in a critical population analysis of 40,000 multiple myeloma patients. *Int J Hematol* 95(1):64–70
8. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J et al (2005) International staging system for multiple myeloma. *J Clin Oncol* 23(15):3412–3420
9. Mikhael JR, Dingli D, Roy V, Reeder CB, Buadi FK, Hayman SR et al (2013) Mayo clinic. management of newly diagnosed symptomatic multiple myeloma: updated mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc Mayo Clin* 88(4):360–376
10. Durie BG, Salmon SE, Moon TE (1980) Pretreatment tumor mass, cell kinetics, and prognosis in multiple myeloma. *Blood* 55(3):364–372
11. Palumbo A, Bringhen S, Ludwig H, Dimopoulos MA, Blade J, Mateos MV et al (2011) Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). *Blood* 118(17):4519–4529
12. Wang R, Gross CP, Halene S, Ma X (2009) Comorbidities and survival in a large cohort of patients with newly diagnosed myelodysplastic syndromes. *Leuk Res* 33(12):1594–1598
13. Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E et al (2006) Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer* 106(5):1090–1098
14. Kleber M, Ihorst G, Gross B, Koch B, Reinhardt H, Wasch R et al (2013) Validation of the Freiburg Comorbidity Index in 466 multiple myeloma patients and combination with the international staging system are highly predictive for outcome. *Clin Lymphoma Myeloma Leuk* 13(5):541–551
15. Kaplan MH, Feinstein AR (1974) The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *J Chronic Dis* 27(7–8):387–404
16. Kleber M, Ihorst G, Udi J, Koch B, Wasch R, Engelhardt M (2012) Prognostic risk factor evaluation in patients with relapsed or refractory multiple myeloma receiving lenalidomide treatment: analysis of renal function by eGFR and of additional comorbidities by comorbidity appraisal. *Clin Lymphoma Myeloma Leuk* 12(1):38–48