Original Article

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Predictive Value of the Hematopoietic Stem Cell Transplantation - Comorbidity Index for Overall Survival in Patients with Multiple Myeloma

Tayfun Elibol*, Osman Kara**

*Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Clinic of Hematology, Istanbul, Turkey

**Bahcesehir University, Faculty of Medicine, Clinic of Hematology, Istanbul, Turkey

Abstract

Aim: The scoring system of the hematopoietic cell transplantation comorbidity index (HCT-CI) was used in patients with multiple myeloma (MM) undergoing autologous stem cell transplantation (ASCT), and it could predict progress-free survival and overall survival. Our study aims to determine the ideal cut-off value for the HCT-CI score, which can be effective in showing overall survival in patients with MM undergoing ASCT.

Methods: The files of all MM patients with ASCT between January 2015 and December 2020 were retrospectively scanned. The X-tile model was used to determine the cut-off values of the HCT-CI score. Survival probabilities were calculated using the Kaplan-Meier estimator. The Cox proportional hazard regression model was used for univariate and multivariate analyses.

Results: Patients were divided into two categories according to HCT-CI. Score ≤6 was defined as low-risk (n=93, 81.6%), and score >6 was defined as high-risk (n=21, 18.4%). The low-risk group had one-year and two-year OS rates of 96.7% and 86.9%, respectively, while the high-risk group had rates of 69.9% and 40.3% (p<0.001). In multivariate regression analysis, only being older than 70 years and having a HCT-CI >6 were found to be significant, with an HR of 3,718 and 5,543, respectively.

Conclusion: Hematopoietic stem cell transplantation - comorbidity index score >6 can aid physicians in deciding whether to perform ASCT in MM patients and predict the overall survival of those patients.

Keywords: Multiple myeloma, autologous stem cell transplantation, hematopoietic stem cell transplantation - comorbidity index, survival

Introduction

High-dose therapy with autologous stem cell transplantation (ASCT) is an effective treatment for patients with multiple myeloma (MM) who are eligible for transplantation (1). Choosing the appropriate patient for transplantation and anticipating issues that may occur during ASCT is still a paramount problem for patients of all ages; when it can be done, various studies (2,3) have stated that favorable results have been obtained with ASCT even in elderly patients with MM.

The scoring system of the hematopoietic cell transplantation comorbidity index (HCT-CI), developed by Sorror et al. (4) to show early non-relapse mortality in patients undergoing allogeneic stem cell transplant, was also used in patients undergoing ASCT and included patients with MM. Although it does not effectively show transplant-related early mortality in MM patients, some studies (5,6) in the past few years have shown that it could predict progress-free survival (PFS) and overall survival (OS).

As research conducted in the current treatment era uses many new medications, we intended to evaluate the impact of medical comorbidities on the outcome of MM patients undergoing ASCT using the HCT-CI. The current study determines the ideal cut-off value for the HCT-CI score, a value that can be effective in showing OS in patients

Address for Correspondence: Tayfun Elibol,
Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Clinic of Hematology, Istanbul, Turkey
Phone: +90 5396562942 E-mail: tayfunelibol@gmail.com ORCID: orcid.org/0000-0001-8738-5246
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with MM who are treated with ASCT. The secondary endpoints are comparing the patients' characteristics and comorbidities before ASCT, transplant outcomes, and OS according to the cut-off value determined by HCT-CI.

Materials and Methods

Compliance with Ethical Standards

The present study was approved by the University of Health Sciences Turkey, Istanbul Medeniyet University, Goztepe Training and Research Hospital Clinical Research Ethic Committee (date: 16.06.2021, approval no: 2021/0315). The ethics committee of the institution approved all protocols, experimental studies, and clinical trials involving human subjects before the study began. Protocols have been developed in accordance with the Helsinki Declaration of 1975.

Study Design

The files of all MM patients who underwent high-dose melphalan with ASCT between January 2015 and December 2020 were retrospectively scanned. Treatments were selected by the hematologist who made the diagnosis of the patients, according to the current international guidelines (NCCN, ESMO, etc.), labels, and practices. In all patients included in the study, MM panel tests (serum biochemistry, serum protein electrophoresis, serum plasma, and spot urine immune electrophoresis), serum plasma free light chain kappa/lambda, and 24-hour urine total light chain kappa/lambda), beta-2 microglobulin analysis, and whole-body 18-fluorodeoxyglucose using positron emission tomography-computed tomography (PET-CT) were performed in the pre-transplant setting. ECOG performance scores and ISS stages were recorded before transplantation.

The HCT-CI score determined by Sorror et al. (4) was calculated for all patients before transplantation (Supplementary Table 1). If information about any comorbidity of the patient could not be reached, that patient was considered to have no comorbidity, and scoring was done accordingly.

Melphalan was administered at doses of 200 mg/m² or 140 mg/m² as a conditioning regimen on day -2 according to the measurements of creatinine clearance and the patients' ages. All patients received levofloxacin for bacterial prophylaxis, fluconazole for fungal prophylaxis, and valaciclovir for viral prophylaxis starting from day -2.

Myeloma panel tests and PET-CT imaging were repeated with all patients at the end of the third month after transplantation. Post-transplant response status was determined by comparing the results obtained on day 100 after transplantation with those obtained before transplantation. All patients who survived had at least a 100-day follow-up.

Statistical Analysis

The X-tile model (version 3.6.1) was used to determine the cut-off values of the HCT-CI score. The Kaplan-Meier method was used to plot survival curves, and the log-rank test was used to determine whether differences existed between the individual groups.

Descriptive statistics, frequency, and percentage were used to summarize the characteristics of the study population. Group comparisons were done using the Mann-Whitney U test, the chi-square test, and the Fisher's exact test. Based on Kaplan-Meier estimates, survival probabilities were calculated. To compare the survival of different groups, point-wise comparisons were made and log-rank analyses were conducted. The Cox proportional hazard regression model was used for univariate and multivariate analysis. Variables analyzed included HCT-CI (>2, and >6), age (>65 and >70 years), ECOG, gender, myeloma subgroup, ISS stage, melphalan dose, and biochemical parameters (albumin, LDH, creatinine, and B2-microglobulin at the time of transplantation). A univariate Cox regression was performed for variable selection at a .05 significance level was used to identify covariates; multivariate Cox regression analysis was performed using all significant covariates. IBM SPSS Version 25 was used for statistical analyses.

Results

Patients Characteristics

One hundred fourteen patients who had ASCT in concordance with a diagnosis of MM were included in the study. There was a predominance of males, with 64 patients (56.1%) examined, and the median age was 61 years (26-76). The median HCT-CI score was 4 for all patients (0-11). The distribution of patients due to the HCT-CI score is given in Figure 1, and the distribution of comorbidities among patients between the groups is given in Table 1.

X-tile Modeling & Group Comparisons

By using the X-tile model according to the HCT-CI score, patients were divided into 2 categories according to OS: HCT-CI scores ≤6 as low-risk (n=93, 81.6%), HCT-CI score >6 as high-risk (n=21, 18.4%).

Figure 1. Distribution of patients due to HCT-CI score
HCT-CI: Hematopoietic cell transplantation comorbidity index

Table 1. Distribution of comorbidities among patients between the groups				
	All patients	**HCT-CI ≤6**	**HCT-CI >6**	**p-value**
Psychiatric disturbance	47 (41.2%)	33 (35.5%)	14 (66.7%)	0,009
Peptic ulcer	34 (29.8%)	21 (22.6%)	13 (61.9%)	0.000
Heart valve disease	21 (18.4%)	12 (12.9%)	9 (42.9%)	0,003
Pulmonary disease	51 (44.7%)	34 (36.6%)	17 (81%)	0.000
Diabetes/steroid-induced hyperglycemia	36 (31.6%)	24 (25.8%)	12 (57.1%)	0.005
Infection	26 (22.8%)	19 (20.4%)	7 (33.3%)	0.250
Renal disease	9 (7.9%)	3 (3.2%)	6 (28.6%)	0.001
Cardiac disease	17 (14.9%)	12 (12.9%)	5 (23.8%)	0.305
Arrhythmia	5 (4.4%)	1 (1.1%)	4 (19%)	0.004
Hepatic disease	21 (18.4%)	17 (18.3%)	4 (19%)	1,000
Prior solid tumor	9 (7.9%)	4 (4.3%)	5 (23.8%)	0.010
Inflammatory bowel disease	0 (0%)	0 (0%)	0 (0%)	
Cerebrovascular disease	1 (0.9%)	1 (1.1%)	0 (0%)	1,000
Obesity	10 (8.8%)	5 (5.4%)	5 (23.8%)	0.018
Rheumatologic disease	2 (1.8%)	1 (1.1%)	1 (4.8%)	0.336

According to the new risk score, most patients in the high-risk group were female (12 patients, 57.1%). The median ages were 58 (26-76), and 66 (35-72) in the low-risk and high-risk groups, respectively. The number of patients with an ECOG score of zero showed a significant difference between the groups (50 patients (53.8%) in low-risk vs. a total of 2 (9.5%) in high-risk groups, p <0.001). The number of patients with left ventricular ejection fraction above 50% was similar between the groups (89 patients (95.7%) in the low-risk group vs. 19 patients (90.5%) in the high-risk group, respectively), but there were statistically significantly more patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 in the high-risk group (10 patients, 47.6%) than the low-risk group (21 patients, 22.6%) (p=0.020).

Myeloma subgroups, ISS stages of patients, and pre-transplant and post-transplant response rates were similar among both groups. Although a decreased tendency was observed without significant statistical difference in stem cell mobilization success with G-CSF in the high-risk group (p=0.255), in most of the patients it was successfully mobilized with G-CSF: 84 patients (90.3%) in the low-risk group, and 17 patients (81%) in the high-risk group, respectively. As expected, melphalan dose reduction was performed more frequently in the high-risk group (10 patients in the high-risk group; 47.6% and 24 patients in the low-risk group; 25.8%, p=0.048) (Table 2).

Concerning the post-transplant complications presenting on the 100th day after the transplantation, death due to septic shock was observed in one patient from each risk group, while death due to cardiorenal toxicity was observed in one patient in the high-risk group. Renal toxicity and hepatobiliary toxicities were more frequent in high-risk patients [p=0.020, hazard ratio (HR): 3.72, 95% confidence interval (CI): 1,236-11,244], but cardiac toxicity, pulmonary toxicity, bleeding, and deep vein thrombosis were comparable between groups (Table 3).

Survival Analysis

Patients were followed for an average of 21 months (0-79). The median duration of survival could not be reached for the low-risk group and the entire cohort, but it was 22 months for high-risk patients. One-year and 2-year OS rates were 96.7% and 86.9% in the low-risk group; 69.9% and 40.3% in the high-risk group (p<0.001), respectively (Figure 2).

In univariate cox-regression analysis, being more than 70 years old, HCT-CI >6, ECOG >0, reduced melphalan dose, and creatinine levels of patients before ASCT were found to be significant in terms of decreased OS. In multivariate regression analysis, only being older than 70 years and having an HCT-CI >6 were found to be significant with an HR of 3.718 (p=0.011, 95% CI: 1,344-10,291) and 5.543 (p=0.001, 95% CI: 2,072-14,833), respectively (Supplementary Table 2).

In univariate cox-regression analysis, the HCT-CI score > 2 was also found to be significant in terms of OS, with an HR of 3.457 (p=0.023, 95% CI: 1.19-10,043) compared with HCT-CI ≤2. Considering this information, patients were divided into 3 risk groups for OS according to their HCT-CI scores: 0-2 (very low risk), 3-6 (low risk), and more than 6 (high-risk). The median OS of patients was 58 months in low-risk patients and 22 months in high-risk patients; it could not be reached in the very low-risk group. One-year and two-year OS of patients were 100%

Table 2. Patients, disease and treatment characteristics between groups				
	All patients	**HCT-CI ≤6**	**HCT-CI >6**	**p-value**
HCT-CI	4 (0-11)	3 (0-6)	8 (7-11)	0.000
Male (n,%)	64 (56.1%)	55 (59.1%)	9 (42.9%)	0.174
Age (years, range)	61 (26-76)	58 (26-76)	66 (35-72)	0.410
18-39	8 (7%)	7 (7.5%)	1 (4.8%)	0.395
40-49	15 (13.2%)	14 (15.1%)	1 (4.8%)	
50-59	34 (29.8%)	28 (30.1%)	6 (28.6%)	
60-65	9 (7.9%)	7 (7.5%)	2 (9.5%)	
66-69	25 (12.9%)	17 (18.3%)	8 (38.1%)	
70-80	23 (20.2%)	20 (12.5%)	3 (14.3%)	
ISS				
Stage I	54 (47.4%)	48 (51.6%)	6 (28.6%)	0.080
Stage II	25 (21.9%)	17 (18.3%)	8 (38.1%)	
Stage III	35 (30.7%)	28 (30.1%)	7 (33.3%)	
Myeloma subgroups				
IgG	76 (67.9%)	63 (68.5%)	13 (65%)	0.460
IgA	22 (19.6%)	18 (19.6%)	4 (20%)	
Light Chain	9 (8%)	6 (6.5%)	3 (15%)	
Other	5 (4.5%)	5 (5.4%)	-	
Lines of chemotherapy	1 (1-5)	1 (1-3)	1 (1-5)	0.973
Response before transplant				
CR	17 (14.9%)	15 (16.1%)	2 (9.5%)	0.634
VGPR	64 (56.1%)	53 (57%)	11 (52.4%)	
PR	32 (28.1%)	24 (25.8%)	8 (38.1%)	
SD	1 (0.9%)	1(1.1%)	-	
ECOG				
0	52 (45.6%)	50 (53.8%)	2 (9.5%)	**0.000**
≥1	62 (54.4%)	43 (46.2%)	19 (90.5%)	
LVEF				
≥%50	108 (94.7%)	89 (95.7%)	19 (90.5%)	0.305
<%50	6 (5.3%)	4 (4.3%)	2 (9.5%)	
eGFR				
≥60 mL/min	83 (72.8%)	72 (77.4%)	11 (52.4%)	**0.020**
<60 mL/min	31 (27.2%)	21 (22.6%)	10 (47.6%)	
Stem cell mobilization				
G-CSF	101 (88.6%)	84 (90.3%)	17 (81%)	0.077
Cyclo & G-CSF	9 (7.9%)	5 (5.4%)	4 (19%)	
Plerixafor & G-CSF	4 (3.5%)	4 (4.3%)	-	
Melphalan dose				
<200 mg/m^2	34 (29.8%)	24 (25.8%)	10 (47.6%)	0.048
200 mg/m^2	80 (70.2%)	69 (74.2%)	11 (52.4%)	

Table 3. Outcomes of patients after ASCT				
	All patients	**HCTCI ≤6**	**HCT-CI >6**	**p-value**
Treatment-related mortality	3 (2.6%)	1 (1.1%)	2 (9.5%)	0.087
Febrile neutropenia	61 (53.5%)	47 (50.5%)	14 (66.7%)	0.181
Renal toxicity	18 (15.8%)	11 (11.8%)	7 (33.3%)	**0.023**
Cardiac toxicity	7 (6.1%)	5 (5.4%)	2 (9.5%)	0.611
Pulmonary toxicity	1 (0.9%)	1 (1.1%)	0	1,000
Hepatobiliary toxicity	25 (21.9%)	16 (17.2%)	9 (42.9%)	**0.018**
Bleeding	11 (9.6%)	7 (7.5%)	4 (19%)	0.117
Deep vein thrombosis	7 (6.7%)	5 (5.9%)	2 (10.5%)	0.609
Response after transplant				
CR	37 (33.9%)	32 (35.2%)	5 (27.8%)	0.186
VGPR	67 (61.5%)	55 (60.4%)	12 (66.7%)	
PR	2 (1.8%)	2 (2.2%)	-	
SD	3 (2.7%)	2 (2.2%)	1 (5.6%)	

and 89.9% in the very low-risk group; 94.2% and 84.6% in the low-risk group; and 69.9% and 40.3% in the high-risk group (Figure 3). While the HCT-CI score between 2 and 6 appeared to be associated with worse OS compared to the HCT-CI 0–1 score, it did not reach statistical significance (p=0.182, HR: 2.18, 95% CI: 0.694-6.849) in cox-regression analysis. HCT-CI Score >6 had a statistically significantly worse OS compared to both HCT-CI scores of 0-2 and 3-6 (with an HR of 8.7, p<0.001, 95% CI 2.74-27.6; HR 4, p=0.001, 95% CI 1.7-9.34).

Discussion

The largest study showing the effects of the HCT-CI score on OS in 1154 MM patients was conducted by Saad et al. (5) in 2014. They reported that in univariate analysis, the patients with HCT-CI scores of 1 to 2 had a worse OS with an HR of 1.37 and HCT-CI >2 with an HR of 1.5 compared with an HCT-CI score of 0. In multivariate analysis, HCT-CI scores greater than 0 had a HR of 1.33 (p=0.04) compared to HCT-CI scores less than 0. In another study, Jaglowski et al. (7) reported that there was no statistical difference between groups with HCT-CI scores <3 vs. ≥3 (p=0.92). Obiozor et al. (8) also reported that an HCT-CI score >2 also appeared to be associated with worse OS than HCT-CI 0-1, but the difference did not reach statistical significance (HR 1,311, 95% CI: 0.72 to 2.76), similar to patients with an HCT-CI score between 2 and 6 in our study. We found that all patients with an HCT-CI >2 had a worse OS with an HR 3.45 than patients with a score ≤2; however, this difference was mostly due to the patients with an HCT-CI >6, not those with an HCT-CI between 3 and 6 (with an HR 8.7 compared to an HCT-CI score 0-2; p<0.001, and an HR 4 compared to an HCT-CI score 3-6; p=0.001).

In our study, we reported that the 2-year OS of patients with HCT-CI scores 0-2 was 89.9%. In Saad et al.'s (5) study, it was 89%, and only in patients with an HCT-CI score of 0. In patients with an HCT-CI score of 1-2, it was 84%. We reported that patients with higher HCT-CI scores (between 3-6) had a 2-year OS of 84.6%. HCT-CI score did not influence OS in patients aged >65 years at the time of transplant in Saad et al.'s (5), but HCT-CI score >6 influenced OS in all age groups in our study (data not shown). When comparing the comorbidities of patients in two studies, it was observed that pulmonary dysfunction (44.7% vs. 22.6%), psychiatric disturbances (41.2% vs. 12.2%), diabetes/steroid-induced hyperglycemia (31.6% vs. 13.7%), peptic ulcus (29.8% vs. 2.5%), and all other comorbidities were higher in our study. In both studies, the melphalan dose was reduced similarly in about 26-28% of patients, especially those with high HCT-CI scores. Although HCT-CI scores were higher and comorbidities were more common in our study, OS in patients with an HCT-CI score of 6 was comparable to that of patients in Saad's study with an HCT-CI score between 0 and 2. This was speculated to be because OS has significantly improved in patients with MM. Several factors contribute to this progress, including better biological insights into the disease, more sensitive tests and technologies allowing for easier detection of relapses, better combination therapies, and increased access to supportive care measures (6). So now, high-risk patients could be defined as patients with an HCT-CI score >6.

In Saad et al.'s (5) study, there was no difference in OS among patients who received a reduced melphalan dose. In our study, reduced melphalan was associated with worse outcomes in univariate cox-regression analysis but not in multivariate analysis. TRM was similar in both studies (1-2%). Saad et al. (5) also reports that age greater than 65 years did not influence OS as much as our study, although we found that age greater than 70 years influenced OS with an HR 3.7.

Not only was OS short, but treatment-related toxicities were more common in high-risk patients. Labonté et al. (9) report in their study that patients with an HCT-CI score ≥1 had severe organ toxicity 2.5 times higher than patients with an HCT-CI score 0. Also, parallel with our study, high-risk patients had more pulmonary and hepatotoxicity compared with the low-risk patients (with an HR of 3.7).

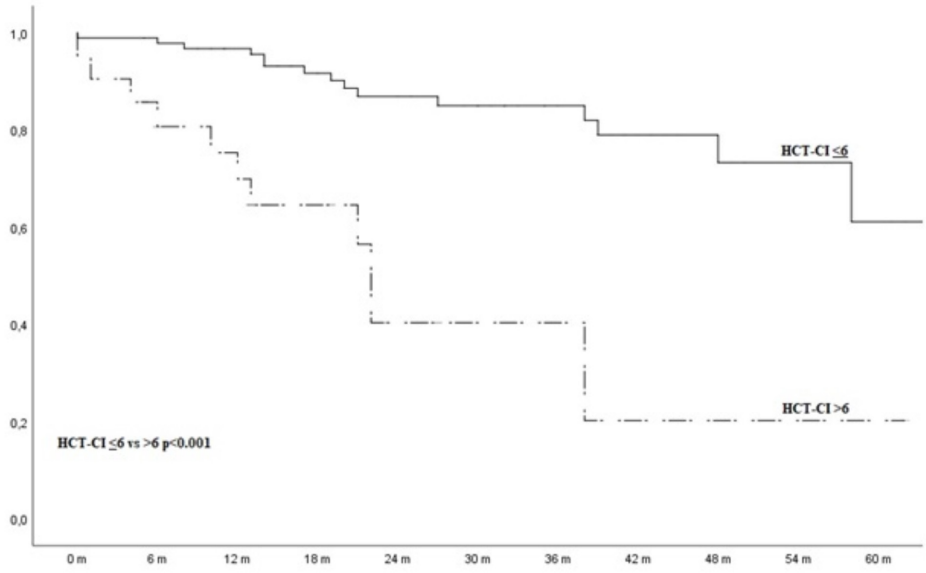

Figure 2. OS according to risk groups calculated from HCT-CI score (low risk vs. high-risk)
OS: Overall survival, HCT-CI: Hematopoietic cell transplantation comorbidity index

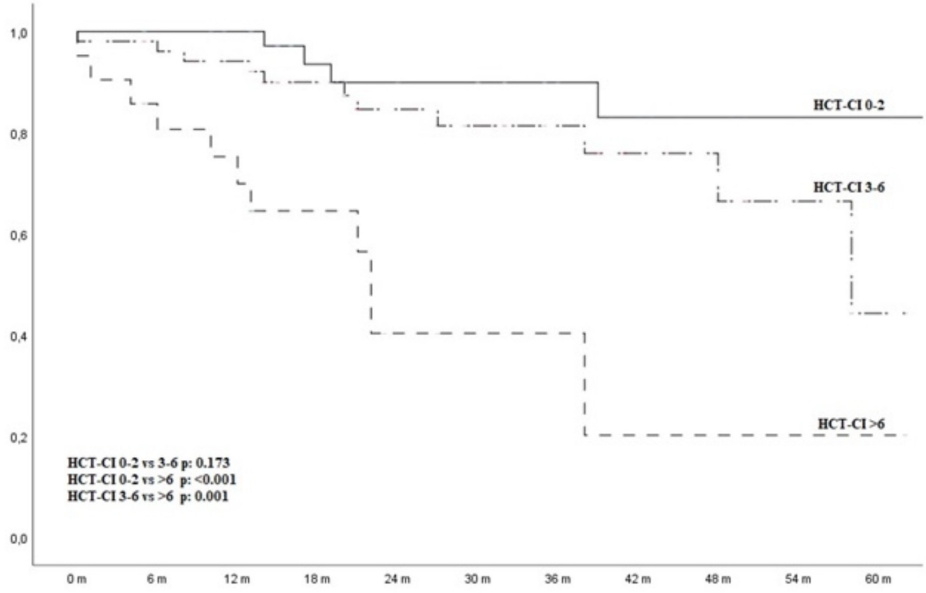

Figure 3. OS according to 3 risk groups calculated from HCT-CI score (very low-risk vs. low-risk vs. high-risk)
OS: Overall survival, HCT-CI: Hematopoietic cell transplantation comorbidity index

In Waszczuk-Gajda et al.'s (10) study on infection complications in 1374 patients with MM, Waszczuk-Gajda reported that 336 of the 1374 patients (24.4%) had infection episodes during ASCT, whereas Gil et al. (11) reported that 56 of 64 patients with MM had infection complications during neutropenia after ASCT. Febrile neutropenia was observed in 53.5% of our patients, with a tendency to occur more frequently in high-risk patients. Different rates of febrile neutropenia in these studies and our study may be related to the different comorbidity rates of the patients in these studies.

Study Limitations

The first and most important limitation is the retrospective nature of the study. Most of the patients included in the study were treated with different induction regimens (vincristine-doxorubicin-dexamethasone, bortezomib-cyclophosphamide-dexamethasone, bortezomib-thalidomide-dexamethasone, etc.) and variable use of maintenance therapy, thereby affecting the OS homogeneity. Because the genetic makeup of the majority of our patients was unknown, genetic analyses

could not be included in our study. We could also not make any comments on the PFS for most of the patients due to the lack of information beyond 100 days post-transplant.

Conclusion

Successful results in studies conducted with both the elderly and patients with comorbidities showed that ASCT can be a treatment option for people of all ages with MM, as long as an accurate patient selection can be done. HCT-CI scores greater than 6 can help physicians make this difficult decision by predicting both overall patient survival and treatment-related toxicity incidence. Since similar survival times can be achieved with current combination therapies (monoclonal antibodies, etc.) in these patients, ASCT may not be considered. Randomized, controlled studies are needed on this subject. Also, there is still a need to develop a scoring system that can be easily performed and is more effective in showing morbidity and mortality in MM patients.

Ethics

Ethics Committee Approval: The present study was approved by the University of Health Sciences Turkey, Istanbul Medeniyet University, Goztepe Training and Research Hospital Clinical Research Ethic Committee (date: 16.06.2021, approval no: 2021/0315).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.E., O.K., Design: T.E., O.K., Data Collection or Processing: T.E., O.K., Analysis or Interpretation: T.E., O.K., Literature Search: T.E., O.K., Writing: T.E., O.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary Table 1. The HCT-CI score		
Comorbidities	**Definitions**	**HCT-CI Score**
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, and ventricular arrhythmias	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or ejection fraction ≤50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression/anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin >ULN - 1.5 x ULN, or AST/ALT >ULN - 2.5 x ULN	1
Obesity	Patients with a body mass index >35 kg/m2	1
Infection	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine >2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and/or FEV1 >65%-80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and/or FEV1 <65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin >1.5 x ULN, or AST/ALT > 2.5 x ULN	3

ULN: Upper limit of normal, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, CTD: Connective tissue disease, DLco: Diffusion capacity of carbon monoxide, FEV1: Forced expiratory volume at 1 second

Supplementary Table 2. Multivariate cox regression analysis for							
	Mean	**B**	**SE**	**p-value**	**HR**	**95% CI for Exp (B)**	
HCT-CI ≤6 vs. >6	**0.184**	**1,713**	**0.502**	**0.001**	**5,543**	**2,072**	**14,833**
ECOG	0.544	-0.281	0.547	0.608	0.755	0.258	2,209
Age ≤70 vs. >70 years old	**0.175**	**1,313**	**0.519**	**0.011**	**3,719**	**1,344**	**10,291**
Melphalane dose	0.298	0.499	0.493	0.312	1,646	0.627	4,324
Creatinine	1,026	0,43	0.443	0.332	1,537	0.645	3,658