The Effect of CRAB Findings on the Prognosis of Multiple Myeloma Patients

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ABSTRACT

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by malignant proliferation of monoclonal plasma cells in the bone marrow. Interphase fluorescence in situ hybridization (I-FISH) required for revised international staging system (R-ISS) classification in MM risk classification is not available in every medical center. CRAB findings were suggested to be an easy and practically applicable marker for MM prognosis. In this study, we aimed to examine the effect of CRAB and SLiM factors, which are among the myeloma defining events, on progression-free survival and overall survival of the MM patients. Sixty six MM patients who applied to Diskapi Yildirim Beyazit Training and Research Hospital Hematology Clinic for treatment and follow up between 2012 and 2021 were included in the study. Patients in this study were between the ages of 39-86.The number of male patients in the study was 36 (54.5%). In the multivariate analysis, the most important factors affecting the overall survival of the patients were identified as M protein type, bone marrow plasma cell ratio ≥ 60% and autologous stem cell transplantation (p= 0.019, p= 0.007, p= 0.04, respectively). Multivariate analysis revealed that the only factor affecting the progression-free survival of the patients included in the study was the presence of extra medullary plasmacytoma (p= 0.014). In conclusion, CRAB criteria are not related to overall survival. CRAB criteria cannot replace R-ISS, contrary to what is suggested in some studies in the literature. Bone marrow plasma cell ratio,which is one of the SLiM criteria, affects overall survival. SLiM criteria may be more important than CRAB criteria as a practical and easy prognostic marker that can be substituted for R-ISS.

Keywords: Multiple myeloma, SLiM, CRAB, Prognosis

INTRODUCTION

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by the malignant proliferation of monoclonal plasma cells in the bone marrow.[1] MM diagnostic criteria were revised by the International Myeloma Working Group (IMWG) in 2014. The conversion of approximately 80% of Smoldering Multiple Myeloma (SMM) patients with certain markers to MM in the 2 year follow up has caused these criteria to be accepted by IMWG as findings defining active myeloma. In this last revision, three new markers were added to the findings of CRAB (hypercalcemia, kidney failure, anemia, bone disease), which previously defined myeloma that required treatment [(SLiM-clonal plasma cell presence over 60% in the bone marrow, free light chain ratio above 100) and the presence of more than one focal lesion of 5 mm or larger on whole-body MRI (magnetic resonance imaging)] and myeloma-defining findings requiring treatment have been termed myeloma-defining events (MDE).[2,3] Nakaya et al. examined the effect of CRAB findings on MM disease survival and found that the presence of bone disease and hypercalcemia indicated a poor prognosis.[4]

doi: 10.4999/uhod.226343

They found that anemia and renal failure had no effect on survival. They found that the new agents used to treat patients in the study had a more favorable outcome in patients with renal failure than the old treatments. However, the use of new agents in this study did not show any improvement in the prognosis of patients with bone disease.[4]

Many risk assessment systems have been developed for MM, and the most widely accepted one is the International Scoring System (ISS), which has recently been updated to include lactate dehydrogenase (LDH) and cytogenetic features. Palumbo et al. proposed a model that includes ISS, LDH and cytogenetic characteristics data to better guide data comparisons in clinical trials and studies, and to define subgroups of patients with different prognosis.[5] They introduced this new algorithm as the Revised International Scoring System (R-ISS) in 3.060 young and old patients with newly diagnosed MM.[5] The R-ISS staging system is a recently identified risk stratification algorithm with enhanced prognostic power. In the R-ISS classification; in addition to serum LDH, iFISH (interphase fluorescent in situ hybridization) chromosomal anomalies are examined in addition to ISS stage groups. We planned this study by using simpler prognostic markers such as CRAB and SLiM because chromosomal anomaly examination with iFISH required for R-ISS classification in MM risk classification is only available in certain large institutions and access to these tests is difficult. There are previous studies examining the relationship between CRAB findings and prognosis. We have aimed to examine the effect of both CRAB and SLiM factors on progression-free survival and overall survival in MM.

PATIENTS AND METHOD

This study included 66 MM patients who applied to the Dışkapı Yıldırım Beyazıt Training and Research Hospital Hematology Clinic for treatment and follow-up purposes between the years 2012-2021. Patients were between the ages of 39-86. Our study was planned as retrospective observational research. The data were obtained from the patient files and the hospital registry system. Seventy patients who applied to the hematology clinic and polyclinic for treatment and follow-up between 2012 and 2021 were included in the study, and 4 patients were excluded from the study due to lack of sufficient data because they did not continue their outpatient follow-ups regularly. An up-to-date database was created by examining the data of the remaining 66 patients. Age, gender, weight, diabetes mellitus, chronic kidney disease, heart failure and other comorbidity histories of the patients included in the study, date of disease diagnosis, laboratory result values at the time of diagnosis (hemoglobin, sedimentation, calcium, uric acid, phosphorus, BUN, creatinine), creatinine clearance, total protein, albumin, beta-2 microglobulin, LDH, serum M protein level, M protein type) bone involvement site at diagnosis, presence of osteolytic bone lesion at diagnosis, presence of CRAB factor and SLiM criteria at diagnosis, ISS at diagnosis stage, serum free light chain ratios at the time of diagnosis, presence of lesions larger than 5 mm in MRI, presence-description of cytogenetic test, cytogenetic risk, presence, location and size of plasmacytoma, presence of plasma cell leukemia, presence of AL amyloidosis, autologous bone marrow transplantation, transplantation date, preparation regimen, patient's performance status (ECOG), disease status before transplantation, mortality, the reason for treatment-related mortality (TRM), patients' last follow-up or death date, the disease status at the last follow-up, relapse and the relapse dates were recorded retrospectively from the patient files and the hospital registry system.

This study is accepted as internal medicine specialization thesis of Ahmet Faruk Kalkisim in 2021 with the title of "The effect of CRAB findings on the prognosis of multiple myeloma patients" and the thesis number of "678063". The ethics committee approval decision date of our research is 06.01.2020 and the decision no: 79/04.

Statistical Analyses

After file reviews and data collection with the hospital registry system, all statistical analyzes were performed with IBM© SPSS© Statistics Version 25.0 for Windows (Armonk, NY: IBM Corporation, 2017). First, descriptive statistics were performed for MM patients. For the overall and progression-free survival analysis of the patients, firstly, the Kaplan-Meier method was used for univariate

Table 1. Main parameters of the patients

Parameters	n
Gender (Male / Female)	36/30
History of Comorbidity (Diabetes Mellitus/Chronic Kidney Failure/Other Comorbidities / No Comorbidity)	19/9/10/28
Patients with Autologous Bone Marrow Transplantation	25/41
Hemoglobin ≤ 10 g/dl / Hemoglobin >10 g/dl	45/21
Calcium ≥ 11 mg/dl / Calcium < 11 mg/dl	11/55
Creatinine ≥ 2 mg/dl / Creatinine < 2 mg/dl	12/54
GFR < 40 / GFR ≥ 40 (ml/min)	16/50
Albumin < 3.5 g/dl / Albumin > 3.5 g/dl	31/35
Beta-2 microglobulin < 3.5 g/dl / 3.5-5.5 g/dl / ≥ 5.5 g/dl	20/17/29
IgA Lambda/ IgG Lambda/ IgA Kappa/ IgG Kappa/Kappa Light Chain/ Lambda Light Chain/ non-secretory (M protein type)	6/13/7/25/7/7/1
CRAB1+/CRAB2+/CRAB3+/CRAB4+	24/32/6/4
Osteolytic lesion Yes / No	39/27
SLIM Yes / No	31/35
Positivity of SLiM Criteria 1/2/3	26/5/0
S/Li/M/SLi/SM/MLi/SLiM	7/17/2/3/1/1/35
Bone Marrow Plasma Cell Ratio at Diagnosis ≥ 60% / < 60%	12/54
ISS Staging 1/2/3	13/25/28
R- ISS Staging 1/2/3/No R-ISS	3/12/3/48
Plasmacytoma at diagnosis Yes / No	12/54
≥ 5 mm Lesions on MRI Yes / No	5/61
Cytogenetic Test Yes / No	16/50
Risk classification of patients undergoing cytogenetic testing	
Normal Karyotype/Low Risk/High Risk	14/1/1
First Pre-Transplant Disease Status CR/VGPR/PR/SD	13/8/3/1
Exitus / Alive	10/56
Cause of Death Relapse/Infection/Relapse + Infection/ Metabolic Disorders	4/4/1/1
Treatment Related Mortality Yes / No	4/62
Disease Status at last follow-up CR/VGPR/PR/PD	20/32/12/2
Relapse Status Yes / No	7/59

analysis. Variables with a p value below < 0.1 in univariate analyzes were analyzed by multivariate analysis (Cox-Regression method). The order of importance of the parameters in the multivariate analysis was evaluated by logistic regression and forward similarity ratio. The limit of statistical significance in multiple variables was determined as $p< 0.05$.

RESULTS

Sixty-six patients with MM included in the study were examined. Thirty-six (54.5%) of 66 patients were male. Main parameters of the patients were depicted in Table 1 and 2. The median age of the patients participating in the study was 65, although it varied between the ages of 39-86. The weight of the patients ranged between 50-110 kg, and the median weight was 75 kg. Nineteen patients had diabetes mellitus, 9 patients had chronic kidney failure, and ten patients had other comorbidities, 28 patients had no comorbidities. Autologous transplantation was performed in 25 patients. The number of patients with hemoglobin 10 g/dl and below was 45. The number of patients with a calcium level below 11 mg/dl was 55. Serum creati-

Table 2. Parameters of the study participants

Parameters	Median (Minimum-Maximum)
Age (years)	65 (39-86)
Weight (kg)	75 (50-110)
Hemoglobin (g/dl)	9.4 (6.2-15)
Sedimentation (mm/hour)	43 (2-140)
Calcium (mg/dl)	9.3 (7.5-13.1)
Uric acid (mg/dl)	7.4 (0.5-19.2)
Phosphorus (mg/dl)	3.85 (1.5-35)
BUN (mg/dl)	22.5 (10-120)
Creatinine (mg/dl)	1.05 (0.5-9)
Creatinine clearance (ml/min)	64.15 (3.4-128)
Albumin (g/dl)	3.52 (1.8-5.2)
Beta-2 microglobulin (mg/L)	4.98 (1.6-42.7)
LDH (U/L)	229 (26-1776)
M protein level (mg/dl)	11.17 (0-47)
Overall survival (days)	620 (4-2399)
Disease-free survival (days)	555 (4-2399)
Bone marrow plasma cell ratio (%)	40 (15-90)

nine levels of fifty-four patients were below 2 mg/dl. Creatinine clearance was found below 40 ml/min in 16 patients. The number of patients with albumin levels below 3.5 g/dl was 31. The number of patients with beta-2 microglobulin level below 3.5 mg/L was 20. Twenty-five patients with IgG kappa, 13 patients with IgG lambda, 7 patients with IgA kappa, 6 patients with IgA lambda, 7 patients with kappa light chain, 7 patients with lambda light chain, one patient with non-secretory were found in the study.

The number of patients with one positive CRAB finding was 24, the number of patients with 2 CRAB findings was 32, the number of patients with 3 CRAB findings was 6, and the number of patients with 4 CRAB findings was 4. Osteolytic lesions were detected in 39 of the patients. Osteolytic lesions were localized in the vertebral body in 23 patients (59%), in the face and skull bones in 6 (15%) patients, and in the ribs in 6 (15%) patients. The SLiM criteria were positive in 31 patients at the time of diagnosis and the SLiM criteria were not found in 35 patients. Serum free light chain ratio ≥ 100 was found in 17 of 31 patients with positive SLiM factors, and clonal bone marrow plasma cell ≥ 60% was found in 7 patients. 13 of 66 patients were found to be ISS stage I, 25 as ISS stage II, and 28 as ISS stage III. R-ISS staging was performed in 16 patients as genetic testing was performed only in 16 patients. Among the 16 patients, 2 were diagnosed as R-ISS stage I, 12 as R-ISS stage II, and 2 as R-ISS stage III. Among the 16 patients who underwent cytogenetic testing, 14 were found to have normal karyotype, 1 as low risk, 1 as high risk. FISH 17p del and 13q del (13q14.2-14.3) were detected in 1 patient. In one patient, -y (monosomy 7) was detected in 1 of 4 metaphases in bone marrow cytogenetic examination. No deletion or chromosomal anomaly was detected in the FISH and cytogenetic examination in the other 14 patients. At the time of diagnosis, plasmacytoma was detected in 12 of the patients. Plasmacytomas were located in the vertebrae in 5 (42%) patients and in the ribs in 3 (25%) patients. At the time of diagnosis, the number of patients with a lesion of 5 mm or more on MRI was found to be 5. Forty-four (66%) patients included in the study were given velcade-cyclophosphamide-dexamethasone as first treatment, 9 (14%) vincristine-adriamycin-dexamethasone, 6 (9%) velcade-lenalidomide-dexamethasone. 25 of the 66 patients in the study had autologous bone marrow transplantation. 18 of 25 patients were ECOG-1 before transplantation, 7 had ECOG-2 performance score. Ten patients were died during follow-up. The causes of death were found to be relapse in 4 of 10 patients and infection in 4 patients. Treatment-related death was detected in 4 of 10 patients. Relapse was detected in 7 patients.

The median overall survival of the patients participating in the study was 620 days, and the median of progression-free survival was 555 days. Univariate analyzes were performed (Table 3). Overall survival of the patients who received autologous bone marrow transplantation was higher than the patients who did not receive autologous bone marrow transplantation (2116±131 days versus 1737±216 days, p= 0.074). Overall survival of the patients with serum albumin level of 3.5 g/dl and above was found to be higher than the patients with albumin level below 3.5 g/dl (2174±123 days ver-

Table 3. Progression-free survival and overall survival results in univariate analysis

Parameters		Progression Free Survival (days)	P	Overall Survival (days)	P
Gender	Male	735 ± 557	0.009	1785 ± 177	0.376
	Female	799 ± 746		2107 ± 161	
Autologous Bone	Yes	1714 ± 144	0.168	2116 ± 131	0.074
Marrow Transplantation	No	2252 ± 133		1737 ± 216	
Comorbidity	Diabetes Mellitus	1832 ± 190	0.106	1828 ± 199	0.131
	Chronic renal failure	1870 ± 246		1896 ± 228	
	Other	1080 ± 169		1368 ± 367	
Hemoglobin	Below 10 g/dl	1652 ± 149	0.498	1847 ± 175	0.285
	10 gr/dl and above	2078 ± 165		2106 ± 150	
Calcium	Less than 11 mg/dl	*637 (36-2399)	0.292	1969 ± 134	0.591
	11 mg/dl and above	*391 (4-2140)		1557 ± 336	
Creatinine	Less than 2 mg/dl	777 ± 655	0.26	1903 ± 142	0.609
	2 mg/dl and above	710 ± 622		2022 ± 187	
Creatinine Clearance	Less than 40 ml/min	1986 ± 189	0.473	1873 ± 206	0.735
	40 ml/min and above	1949 ±156		1909 ± 151	
Serum albumin	Less than 3.5 g/dl	1603 ± 205	0.048	1556 ± 193	0.053
	3.5 gr/dl and above	2216 ± 122		2174 ± 123	
Beta 2 microglobulin	Less than 3.5 g/dl	1487 ± 157	0.328	1561 ± 158	0.86
	3.5-5.5 g/dl	2008 ± 233		1925 ± 234	
	Above 5.5 g/dl	2051 ± 152		2065 ± 166	
M Protein type	Free light chain	1501 ± 203	0.031	1813 ± 98	0.015
	IgG	2186 ± 134		2086 ± 145	
	IgA	1109 ± 218		973 ± 202	
Osteolytic Bone Lesion	Yes	1923 ± 132	0.583	1889 ± 131	0.815
	No	1833 ± 246		1832 ± 217	
SLIM Criteria for Diagnosis	Yes	1654 ± 143	0.833	1383 ± 173	0.068
	No	2006 ± 147		2101 ± 132	
Bone Marrow Plasma Cell Ratio	60% and Above	*234 (4-1293)	0.562	865 ± 201	0.018
	Less than 60%	*668 (34-399)		2024 ± 125	
Light Chain Ratio	100 or more	1580 ± 184	0.414	1481 ± 197	0.646
	Under 100	2038 ± 137		1972 ± 141	
Magnetic resonance	Lesions 5 mm or more	*532 (43-1871)	0.493	1505 ± 327	0.682
	Lesions under 5 mm	*637 (4-2399)		1943 ± 132	
Plasmacytoma at diagnosis	Yes	1249 ± 276	0.024	1231 ± 257	0.085
	No	2108 ± 126		2043 ± 131	

Note: * stands for median (minimum-maximum) values. Other values are depicted as mean ± standard deviation

sus 1556±193 days, p= 0.053). The patients with M protein type IgG had higher overall survival than the patients with M protein type IgA (2086±145 days versus 973±202 days, p= 0.015). The patients with M protein type IgG had higher overall survival than patients with M protein type light chain (2086±145 days versus 1813±98 days, p= 0.015). The patients without SLiM criteria at diagnosis were found to have higher overall survival than the patients with SLiM criteria (2101±132 days versus 1383±173 days, p= 0.068). Overall survival of the patients with a bone marrow plasma cell ratio below 60% was higher than those with a bone marrow plasma cell ratio of 60% or higher (2024±125

Table 4. Progression-free survival results in multivariate analysis

Parameters	B	p value	Exp (B)	95% CI Exp (B)	
				Low	High
Gender	32.428	0.878	1.212E	0	7.809E
Serum albumin level ≥ 3.5 g/dl	-2.159	0.361	0.115	0.001	11.869
M protein type (light chain)		0.789			
M protein type (IgG)	-20.982	0.862	0	0	4.036E
M protein type (IgA)	-19.703	0.870	0	0	1.404E
ISS Stage 1		0.442			
ISS Stage 2	-23.225	0.953	0	0	
ISS Stage 3	1.948	0.202	7.017	0.352	139.780
Presence of plasmacytoma	-2.916	0.014	0.054	0.005	0.548

days versus 865±201 days, p= 0.018). The patients without plasmacytoma were found to have higher overall survival than the patients with plasmacytoma (2043±131 versus 1231±257, p= 0.085). In the univariate analysis, other parameters were not statistically significant. No statistically significant correlation was found between the number of CRAB findings at the time of diagnosis and overall survival (p= 0.52). No statistically significant correlation was found between the number of CRAB findings at the time of diagnosis and progression-free survival (p= 0.542). The patients with SLiM criteria at the time of diagnosis had a lower progression-free survival than the patients without SLiM criteria (1654±143 days versus 2006±147 days, p= 0.833). The patients without plasmacytoma at the time of diagnosis had a higher progression-free survival than patients with plasmacytoma (2108±126 days versus 1249±276 days, p= 0.024). Progression-free survival was found to be higher in female patients than in male patients (799±746 days versus 735±557 days, p= 0.009). Progression-free survival was found to be higher in the patients with a serum albumin level of 3.5 g/dl and above than in the patients with a serum albumin level of less than 3.5 g/dl (2216±122 days versus 1603±205 days, p= 0.048). The patients with serum M protein type IgG had a higher progression-free survival than the patients with serum M protein type light chain or IgA (2186±134 days versus 1501±203 days, 1109±218 p= 0.031).

Those with p< 0.1 in univariate analyzes were included in multivariate analysis. Gender, serum albumin level of 3.5 g/dl and above at the time of diagnosis, M protein type, ISS staging at the time of diagnosis, presence of plasmacytoma were analyzed by multivariate analysis. Among these parameters, only the presence of plasmacytoma was found to be related with progression-free survival (p= 0.014) (Table 4). For the overall survival, autologous bone marrow transplantation with p< 0.1 in univariate analyzes, serum albumin level of 3.5 g/dl and above at the time of diagnosis, M protein type, presence of SLiM criteria at diagnosis, presence of plasmacytoma, the rate of bone marrow plasma cell ratio of %60 and above at diagnosis and autologous stem cell transplantation were examined by multivariate analysis (Table 5). As a result of this analysis, M protein type IgA (p= 0.019), M protein type light chain (p= 0.036), bone marrow plasma cell ratio of 60% and above (p= 0.007) and autologous bone marrow transplantation (p= 0.04) was found to be statistically significant.

DISCUSSION

MM accounts for 1-2% of hematological malignancies. In USA, 32 thousand new MM cases are diagnosed annually, and in our country, approximately 8.000 MM cases are diagnosed. iFISH is used as the genetic test in the revised ISS staging. Deletion of t(11;14), t(4;14), t(6;14), t(14;16),

Table 5. Overall survival results in multivariate analysis

Parameters	B	p value	Exp (B)	95% CI Exp (B)	
				Low	High
Serum albumin level ≥ 3.5 g/dl	1.166	0.143	3.21	0.673	15.314
M protein type (light chain)		0.036			
M protein type (IgG)	-1.875	0.089	0.153	0.018	1.327
M protein type (IgA)	-1.593	0.019	0.203	0.054	0.771
SLIM criteria at diagnosis	0.203	0.873	1.226	0.101	14.897
Plasmacytoma at diagnosis	-1.687	0.118	0.185	0.022	1.536
Bone marrow plasma cell ratio ≥ 60%	-2.213	0.007	0.109	0.022	0.551
Autologous bone marrow transplantation	1.709	0.040	5.524	1.081	28.222

t(14;20), 17p13 on the bone marrow is studied with iFISH for risk stratification in the initial diagnosis of myeloma patients. Among these genetic tests, t(4;14), t(14;16), t(14;20), 17p13 deletion has a high risk. These complicated genetic tests used in R-ISS staging can only be performed in large centers and not all myeloma patients can access these large centers. For this reason, we aimed to investigate the effect of CRAB and SLiM findings, which are an easier and more practical method compared to R-ISS, on overall survival and progression-free survival in MM patients.

There are previous studies investigating the prognostic effect of CRAB scoring. Nakaya A. et al. conducted a study at Kansai University Hospital that included the association of CRAB findings with survival.[4] 113 patients who followed between 2006 and 2014 were included in the study, and 51% of these patients were male. The mean age of the patients was 72 years. The M protein types of the patients were found to be 69% IgG, 14% IgA, and 14% light chain. According to ISS staging, 45% of 113 patients were identified as stage I, 21% as stage II, and 34% as stage III. Nakaya A et al. determined that the presence of osteolytic bone disease and hypercalcemia from CRAB findings indicate a poor prognosis.[4] In our study, however, the effect of osteolytic bone disease and hypercalcemia on survival was not found. Nakaya A et al. found that anemia and renal failure had no effect on survival. Similarly, no effects of anemia and renal failure on survival were observed in our study. The authors identified osteolytic bone disease as the strongest and most prognostic factor in their study and suggested that this was the case because it showed tumor burden.[4] On the other hand, in our study bone marrow plasma cell infiltration rate of 60% and above was found to be more valuable. Nakaya A et al, found anemia did not show tumor burden because it was related to kidney failure and myeloma.[4] Similarly, no relationship was found between anemia and survival in our study. Nakaya et al, found that hypercalcemia reduces survival in MM.[4] However, we found no correlation between hypercalcemia and survival in our study.

Bean H et al, conducted a study regarding the effect of CRAB score on survival.[6] The study included 314 patients followed for 6 years in the UK. According to the results of the study, 5-year survival was found to be 81% in patients with a CRAB score of 0, 58% in patients with a CRAB score of 1, 41% in a patient with a CRAB score of 2, 22% in a patient with a CRAB score of 3, and 0% in a patient with a CRAB score of 4. According to the authors, CRAB scoring is more valuable than ISS in evaluating survival.[6] They have suggested that there should be more prognostic categories in CRAB scoring. The authors stated that there are 5 prognostic categories in CRAB scoring while there are 3 prognostic categories in ISS staging.[6] CRAB is an easier method as it is more accessible. In our study, the effect of CRAB score on both overall

survival and progression-free survival was investigated. According to our study, no correlation was found between CRAB score and overall and progression-free survival. Herein, we have found that the S parameter in SLiM scoring was associated with overall survival in MM patients, although we found that the CRAB score was not associated with prognosis. Bone marrow plasma cell ratio of 60% and above is associated with overall survival in our study can be attributed to the fact that this situation is related to the aggressiveness of the disease and tumor burden. In addition, we have showed in our study that M protein type and autologous bone marrow transplantation are associated with overall survival. There are many studies showing that M protein type affects overall survival. Qian J et al. conducted a study on the clinical features and prognosis of MM on 787 MM patients followed between 2006 and 2014.[7] The median age of the MM patients was 61 years and 62.4% of the patients were male. IgG type was the most common type with 46.5% of 787 MM patients. This was followed by 26.4% IgA, then 23.1% light chain type.[7] In our study, 57.6% of the patients were found to have IgG, 19.7% to IgA, and 21.2% to light chain type MM. Wang L. et al. studied the clinical course and prognosis of 129 patients with IgA type MM followed between 2011 and 2015 at Beijing Chao-Yang Hospital.[8] In the study, 75 of 129 patients were male and 54 were female, and the median age of the patients was 62.9. Extra medullary plasmacytoma was detected in 31.9% of newly diagnosed MM patients in the study. 17p13 deletion was found in 15 patients and chromosomal 1q21 gain abnormalities were found in 28 patients. In this study, it was determined that patients with IgA type MM had a worse prognosis than other M protein type MMs ($p< 0.05$).[8] Similarly, in the multivariate analysis performed in our study, IgA type MM was found to be associated with shorter overall survival ($p= 0.019$). Wang L, et al, reported that higher-risk cytogenetic abnormalities and the presence of extra medullary plasmacytoma in IgA type MM may explain the lower survival of IgA type MM.[8]

Li L, et al, conducted a study to examine the relationship between serum free light chain ratio and prognosis in 479 MM patients followed between 2012 and 2016.[9] According to the serum light chain ratio, patients were divided into 3 groups which are patients with a light chain ratio of ≤ 14.828, patients with a light chain ratio of 14.828 to 364.597, and a light chain ratio of ≥ 364.597. The overall survival of the first group was significantly better than the other two groups (61 versus 47 months, $p= 0.019$); the progression-free survival light chain ratio was not statistically significant from the 14.828-364.597 group ($p= 0.227$).[9] Overall survival was longer and statistically significant ($p= 0.024$) compared with the first group compared with the group with a light chain ratio ≥ 364.597. Univariate and multivariate analysis found that the light chain ratio was only significantly associated with overall patient survival. Compared to the 4-year overall survival rate in the study, the 4-year overall survival rate of patients in the light chain ratio ≤ 14.828 was 90.84%, which was significantly higher than the other two groups (59.29% versus 62.26%) ($p= 0.646$).[9] In our study, the patients were divided into two groups as those with a serum light chain ratio of 100 and above and those with a serum light chain ratio of less than 100. The progression-free survival of patients with serum light chain ratio of 100 and above was found to be shorter than that of patients with serum light chain ratio below 100, and it was not statistically significant ($p= 0.414$). Although overall survival was shorter in patients with serum light chain ratio of 100 and above, it was not statistically significant. In the multivariate analysis performed in our study, light chain M protein type was found to be associated with shorter overall survival ($p= 0.036$). Snozek C. et al. aimed to determine whether the FLC ratio has prognostic value in symptomatic MM patients.[10] The FLC test was studied from the serum of 790 newly diagnosed MM patients. In this study, overall survival was significantly lower in the patients with an abnormal FLC ratio < 0.03 or > 32 ($n= 479$) compared with those with an FLC ratio between 0.03 and 32 ($n= 311$), with a median survival of 30 months versus 39 months, respectively ($p< 0.001$).[10] In another study, Meddour Y. et al, aimed to evaluate the roles of serum free light chain (sFLC) and kappa/lambda free light chain ratio (sFLCR) in MM diagnosis and prognosis, sFLC levels and kappa/lambda ratios were measured in 112 newly diagnosed MM patients.[11] Abnormal sFLC or sFLCR levels were detected in 99.1% of patients. Serum free light

chain levels predicted overall survival. Patients were divided into 2 groups based on low sFLC (sFLC-Kappa < 132 mg/L or sFLC-Lambda < 342 mg/L) and high sFLC (sFLC-Kappa ≥ 132 mg/L or sFLC-Lambda ≥ 342 mg/L, respectively). Overall survival was longer in the low sFLC group (p< 0.001). Similarly, patients with a free light chain ratio of 32 and above and patients with a free light chain ratio of less than 32 were divided into two groups. Overall survival was higher in the group with patients with a free light chain ratio of less than 32 (p< 0.001).[11] Kyrtsonis MC et al., investigated the prognostic value of sFLCR at the time of diagnosis of MM patients was investigated on 94 MM patients.[12] According to the results of the study, 5-year disease-specific survival was found to be lower in patients with low serum free light chain ratio (p= 0.0001).[12] On the other hand, one of the SLiM criteria, a bone marrow plasma cell ratio of 60% or more, was found to be significant in our study similarly with the literature, while the other two SLiM criteria were not associated with overall survival and progression-free survival.

According to the results of our study, bone marrow plasma cell ratio is a very important parameter that affects overall survival in MM patients. There are previous studies in the literature examining the relationship between bone marrow plasma cell ratio and survival. AS Al Saleh et al. conducted by Mayo Clinic in Rochester MN in 1426 patients with MM between 2004 and 2018, they conducted a retrospective study of the survival of bone marrow plasma cell ratio in MM patients.[13] The patients were divided into 2 groups as bone marrow plasma cell ratio of 60% and above and below 60%. The median age of the patients was 66. Bone marrow plasma cell ratio was 60% or higher in 39% of the patients. The probability of having advanced disease was found to be higher in the group with a bone marrow plasma cell ratio of 60% and above (p< 0.001). Serum M protein, serum free light chain and beta-2 microglobulin levels were higher in this group (p< 0.001). The probability of having a high-risk FISH result was found to be higher in the group with a bone marrow plasma cell ratio of 60% and above (p< 0.001). Progression-free survival was found to be shorter in the group with a bone marrow plasma cell ratio of 60% and above. The median progression-free survival was 22.6 months in the group with a bone marrow plasma cell ratio of 60% and above, and 32.1 months in the group with a bone marrow plasma cell ratio of less than 60%, which is statistically significant (p< 60% patients were 28 months) (p= 0.002). For the second time interval, median progression-free survival was shorter for the high bone marrow plasma cell ratio group (24.4 versus 36.1 months; mean overall survival for patients with p< 60% was 2024±125 days (p= 0.018). Qian J et al, in a study involving 787 MM patients between 2006 and 2014, examined the clinical features of MM and the effect of various prognostic factors on survival.[7] Of the 787 patients (median age, 61 years, range 29-89 years) in the study, 491 (62.4%) were male. The median overall survival of patients with a bone marrow plasma cell ratio ≥ 30% was 44 months, and the median overall survival of patients with a bone marrow plasma cell ratio of <30% was 65 months (p= 0.005). The percentage of plasma cells in the bone marrow has been found to be associated with disease burden, and a proportion of plasma cells ≥ 30% has been found to be associated with poor prognosis, although reduced overall survival.[7] On the other hand, it was shown in our study that progression-free survival was associated with the presence of plasmacytoma. However, the presence of plasmacytoma did not affect overall survival in our patients.

There are studies showing the presence of extramedullary plasmacytoma with progression-free survival in MM patients. Ciftciler R. et al. designed a retrospective study about the relationship between the presence of plasmacytoma in the diagnosis of MM and survival on 180 MM patients followed in their centers between 2003 and 2017 at Hacettepe University Medical Faculty Hospital.[14] Among the 180 patients with MM, 141 were patients with no plasmacytoma at the diagnosis of MM, 22 patients with extramedullary bone associated plasmacytoma, and 17 patients with extramedullary soft tissue associated plasmacytoma. These 3 groups of patients were analyzed for overall survival and progression-free survival. The 5-year overall survival rate was 80% in patients without plasmacytoma, 63% in patients with extramedullary bone-associated plasmacytoma, and

63% in patients with extramedullary soft tissue associated plasmacytoma (p= 0.02). In their study, 5-year progression-free survival was found to be 54% in patients without plasmacytoma, 47% in patients with extramedullary bone-associated plasmacytoma, and 35% in patients with extramedullary soft tissue-associated plasmacytoma, which was not statistically significant (p= 0.15).[14] In our study, the progression-free survival was found to be 1249±276 days in MM patients with plasmacytoma and 2108±126 days in those without plasmacytoma, which was statistically significant (p= 0.024). Retrospective design is a limitation of both our study and this study conducted at Hacettepe University Faculty of Medicine.[14] In another study, Varettoni et al. analyzed 1003 patients who showed the presence of an extramedullary plasmacytoma at any time during the course of the disease and found that it was associated with shorter overall survival and shorter progression-free survival.[15]

The limitations of our study include the relatively small number of patients and a retrospective design. However, our study is important in terms of containing real-life data and finding findings compatible with the literature. In addition, our study differs from the literature in terms of evaluating the effect of previously unexplored SLiM criteria on overall survival and progression-free survival and emphasizing the importance of the effect of bone marrow plasma cell ratio on overall survival.

Conclusion

In conclusion, our study showed that CRAB criteria were not associated with overall survival. Our study emphasizes that CRAB criteria cannot replace R-ISS, contrary to what has been suggested in some studies in the literature. However, in our study, bone marrow plasma cell ratio, which is one of the SLiM criteria, was shown to affect overall survival. Moreover, in our study, other factors affecting overall survival were found to be M protein type and autologous stem cell transplantation, which are consistent with the literature. The presence of extramedullary plasmacytoma affects progression-free survival in our study, which is similar with the literature. Although our study is based on real-life data, it is not appropriate to apply our data to all patients with multiple myeloma because of its retrospective design and limited number of patients. However, the findings in our study suggest that SLiM criteria may be more important than CRAB criteria as a practical and easy prognostic marker that can be substituted for R-ISS. There is a need for prospective randomized controlled studies with more patients which will reveal the importance of SLiM criteria on the prognosis of myeloma.

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