







MM: Multiple Myeloma; ISS: International Staging System; R-ISS: Revised International Staging System

When the patients were divided into 2 groups as normal renal function (stage 0-1) and renal failure (stage 2-3-4-5) groups according to the Kidney Disease Quality Classification of the National Kidney Foundation, the rate of renal failure in ISS1, ISS2 and ISS3 patients were 21%, 20.7% and 50.9% respectively. The rate of renal failure in ISS3 patients were higher than those of the patients in ISS1 and ISS2 stages at a statistically significant level ( $p < 0.001$ ). While the rate of renal failure in patients at the age of  $\geq 65$  years was 56.5%, it was found 27.5% in patients under the age of 65 ( $p < 0.001$ ). OS of ISS1, ISS2 and ISS3 patients were 21 months, 20 months and 18 months respectively ( $p: 0.231$ ) (Table II).

**Table II:** The relationship between ISS stages and overall survival

MM Stage	OS (Overall Survival) months (%95 CI)	p value
ISS 1	21 (8,16-33,83)	0.231
ISS 2	20 (13,76-26,23)	
ISS 3	18 (4,69-8,80)	

ISS, International Staging System

OS according to renal failure stages were found as follows: 8 months in stage 0, 19 months in stage 1, 42 months in stage 2, 25 months in stage 3, and 23 months in stage 4 ( $p: 0.95$ ) (Table III).

**Table III:** The relationship between renal failure and overall survival

Stages of renal failure	OS (Overall Survival) months (%95 CI)	p value
Stage 0	8 (0-18,73)	0.950
Stage 1	19 (15,62-22,37)	
Stage 2	42 (13,94-70,05)	
Stage 3	25 (0-50,48)	
Stage 4	23	
Stage 0-1	18 (14,37-21,62)	0.606
Stage 2-3-4-5	30 (18,24-41,76)	

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OS in stage 0-1 patients was 18 months, it was 30 months in stage 2-3-4-5 patients. When the OS in stage 0-1 compared to OS in stage 2-3-4-5, there was no statistically significant difference regarding OS ( $p: 0.606$ ). OS according to ISS and renal failure stages were given in Table 4. There was no statistically significant difference regarding OS between patients with renal failure and normal renal function in all ISS stages (Table IV).

**Table IV:** The relationship between renal failure, ISS and OS

MM Stage	Renal Failure Stage	OS (Overall Survival) months (%95 CI)	p value
ISS 1	Stage 0-1	20 (13,21-26,79)	0.433
	Stage 2-3-4-5	42 (-)	
ISS 2	Stage 0-1	19 (15,21-22,78)	0.700
	Stage 2-3-4-5	47 (21,39-72,60)	
ISS 3	Stage 0-1	16 (6,28-25,71)	0.384
	Stage 2-3-4-5	23 (7,89-38,10)	

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## DISCUSSION

It has been considered that the patients with renal failure would be included in higher ISS stages due to increased B2M associated not with the tumor burden of myeloma but renal failure; therefore, they could possibly have different clinical expectations as compared to the patients at the same ISS stage without renal failure. Approximately 30% of MM patients have renal failure of some extent at the time of diagnosis<sup>5-9</sup>, and most of these patients are classified as ISS-3 due to increased levels of B2M; therefore, it is important to verify the survival predictive value of ISS in MM patients with renal failure.

In a previous study, in ISS-3 patients, they found out that renal failure, which was evaluated by GFR or serum creatinine levels, did not have any impacts over OS in univariate and multivariate analyses<sup>12</sup>. In our study, although the patients

with renal failure in all ISS stages had longer OS compared to the patients without renal failure, this did not create a statistically significant difference. This situation supports that the prognostic significance of ISS is independent from renal failure.

In a study, although renal failure was more prevalently observed in MM patients at the age of  $\geq 65$  than the MM patients under the age of 65 years, renal failure was found as an independent prognostic factor only in the patients at the age of  $\geq 65$  years<sup>12</sup>. Similarly, we found a statistically significant difference between the patients at the age of  $\geq 65$  years and the patients under the age of 65 years regarding the rate of renal failure ( $p < 0.001$ ). The frequency of renal failure in the MM patients at the age of  $\geq 65$  years was higher than those of the patients under the age of 65 years. Moreover, the cause of renal failure could be associated with accompanying comorbidities other than MM in myeloma patients. MM is an older age disease so the rate of accompanying chronic disease rate is also high. In a multicenter study including 3894 MM patients, it was shown that B2M significantly increased with age which may be related to renal failure whereas albumin decreased with age. In combination with the B2M increase there was an increase in the proportion of patients with higher ISS stages in the older groups but they showed that ISS remained its survival predictivity in all age groups<sup>13</sup>.

In a previous study, higher rate of renal failure was found in MM patients with high tumor burden when compared to the MM patients with lower tumor burden<sup>14</sup>. This also indicates that although increased B2M was associated with renal failure in ISS-3 patients with renal failure, it still continues to be a strong indicator of tumor burden. In our study, the rate of patients with renal failure in ISS3 was higher than those of the patients in ISS2 and ISS1 stages at a statistically significant level as well ( $p < 0.001$ ).

Furthermore, B2M is related with tumor burden, tumor-micro-environment interactions and various factors associated with patients (such as renal function and immune deficiency)<sup>4,15,16</sup>. In spite of ISS's significant prognostic value, we have to consider the fact that ISS only defines three prognostic groups. However, myeloma patients are characterized by significant heterogeneity which would not fit only three prognostic categories.

In conclusion, ISS was not developed for individual treatment decisions, but it is a beneficial tool for classification and comparisons in clinical trials, and it provides significant prognostic information for MM patients. Our data reveals that the significance of ISS to predict overall survival is independent from renal failure.

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