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Determination of the kidney injury in multiple myeloma according to the KDIGO 2012 acute kidney injury guideline and relationship between serum β2 microglobulin and free T3 levels and acute kidney injury

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Abstract

Renal failure is common in multiple myeloma (MM) and is one of the main causes of morbidity and mortality. Despite many advances in diagnosis and treatment, almost half of the patients present with renal failure at presentation. In our study, we aimed to examine the relationship between acute kidney injury (AKI) and serum B2 microglobulin (sB2M) levels, and free T3 (fT3) levels, which has been proven to change in patients with renal failure without thyroid disease. The data of MM patients who were newly diagnosed between 2012 and 2015 were retrospectively analyzed. Bone marrow biopsy had been performed in all cases for final diagnosis. Patients were staged according to the International Staging System (ISS). The AKI staging was performed according to the Kidney Disease Improving Global Outcomes guideline. Twenty-six patients (10 females,16 males) diagnosed with MM were included. The mean age of the patients was 69.33±14.372 years. AKI was found in 92% (n=24) of the patients. According to ISS: one patient was classified as stage-I, five as stage-II, and 20 as stage-III. There was no significant difference between the mean sB2M levels and the stages of AKI in MM patients. The mean sB2M levels of the patients who required hemodialysis due to renal failure were higher than those who did not. In addition, lower fT3 levels were associated with AKI and advanced stage of MM. High sB2M levels may be a risk factor for severe AKI and hemodialysis requirement in patients with MM, and low fT3 levels also may be an indicator of AKI in these patients.

Keywords: Acute kidney injury, β2-microglobulin, multiple myeloma, triiodothyronine

Introduction

Multiple myeloma (MM) is a malignant disease characterized by malignant proliferation of plasma cells and increase in monoclonal immunoglobulin or its fragments in the blood. MM constitutes 1% of all malignant diseases and more than 10% of hematological malignancies [1]. Bone pain in the waist, back or chest, weakness due to anemia, and recurrent infections are usually the initial symptoms; patients with renal failure, nephrotic syndrome, bone fractures, radiculopathy and hypercalcemia may consult physicians from different disciplines [1].

Renal failure is common in MM and is one of the main causes of morbidity and mortality. While it is seen in 20% of newly diagnosed MM patients, this rate can increase up to 50% during the course of the disease [1]. Renal failure is the second most common cause of death in MM patients after infectious complications. In addition, it is very important to detect it early, as it increases mortality by 2.5 times among all causes of mortality [2].

Prognosis in MM is usually related to the stage of the disease. With the developed staging systems, appropriate therapeutic approaches can be applied to MM patients. In current staging systems with proven validity, two easily measured parameters with obvious prognostic significance -albumin and serum β2

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microglobulin (sβ2M)- are used [3]. sβ2M is a 11000-molar protein with homology to the constant region of immunoglobulins and forms the light chain of class I major histocompatibility antigens found on the surface of all cells. Sβ2M is a reliable marker for predicting survival in MM. At the same time, since it is a low molecular weight uremic toxin, its serum level increases in renal failure. Its endogenous production is fairly constant and is filtered almost exclusively through the glomeruli. Approximately 99% of it is reabsorbed and metabolized in the proximal tubule. Therefore, sβ2M levels remain constant in normal individuals. Serum concentration is independent of muscle mass and age. Moreover, these values do not change in males and females [4].

The most synthesized hormone of the thyroid gland is thyroxine (T4), and the most active hormone is triiodothyronine (T3). T4 is seen as the precursor of T3. Only 20% of plasma total T3 is secreted by the thyroid gland, and the remaining 80% is formed as a result of deiodinization of T4 in the periphery. Most of the T3 and T4 in plasma circulate bound to proteins. A smaller part is free. It is only the free fractions that enter the cell and show bioactivity. Abnormalities in serum concentrations of thyroid hormones are frequently observed in patients with uremia, and these disorders appear to worsen as the disease progresses [5]. Total T4, T3 and free T3 (fT3) levels decrease when renal failure progresses. The degree of this is correlated with the severity and prognosis of the disease. Studies conducted in patients with uremia show that the rate of T3 synthesis decreases secondary to the impairment of the peripheral conversion of T4 to T3 [6,7].

In our study, it is aimed to examine the relationship between acute kidney injury (AKI) and sβ2M levels, which is an independent prognostic indicator and used in the staging of MM, and fT3 levels, which has been proven to change in patients with renal failure without thyroid disease.

Material and Methods

The data of MM patients who were diagnosed between 2012 and 2015 were retrospectively analyzed and enrolled to the study. Patients over 18 years old, diagnosed with MM according to the International Myeloma Working Group criteria, and without known hypo/hyperthyroidism or using thyroid hormone replacement therapy were included. Patients under 18 years old, without a definite diagnosis of MM, with thyroid disease and using thyroid hormone replacement therapy were excluded.

The patients' demographic data such as age and gender, medical history, blood samples and radiological examination results were examined. Bone marrow biopsy had been performed in all cases for final diagnosis and renal biopsy was performed 11 (42%) of the patients. MM staging was performed according to the International Staging System (ISS) by examining serum albumin and sβ2M levels. Additionally, AKI staging was performed according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline [8].

The required permissions for the data used in the study was obtained during patient admission, and no additional consent form has been taken.

Ethics Committee Approval

This study was carried out in accordance with the principles of the Declaration of Helsinki, after receiving approval from the ethics committee of the University of Health Sciences Hamidiye Scientific Research Ethics Board that is the center of the research (Date: 10.01.2025 / Number: 35010).

Statistical Analysis

SPSS 23.0 program was used for statistical analysis. While evaluating the study data, Kolmogorov-Smirnov distribution test was used to examine normal distribution as well as descriptive statistical methods (frequency, percentage, mean, standard deviation). In comparing quantitative data, Mann Whitney U test was used to compare parameters between two groups. Kruskal Wallis test was used for intergroup comparisons of quantitative data. A value of $p<0.05$ was considered statistically significant.

Results

Totally, twenty-six (10 female, 16 male) newly diagnosed MM patients were included. The mean age of the patients was 69.33±14.372 years. The laboratory results of the patients at initiation are given in Table 1.

Table 1. Laboratory parameters of the patients at admission

Parameter	Value, mean±SD
Sedimentation (mm/hour)	86.54±28.19 (29-150)
CRP (mg/dl)	5.56±4.21 (0.44-17.8)
Creatinine (mg/dl)	4.19±2.66 (0.6-10.65)
Total protein (gr/dl)	8.57±1.79 (5.6-12.8)
Albumin (gr/dl)	2.56±0.58 (1.3-4.1)
Uric acid (mg/dl)	8.72±2.82 (2-16.53)
BUN (mg/dl)	60.62±37.32 (10-200)
Calcium (corrected) (mg/dl)	11.14±2.93 (7.9-18.8)
Parathormone (pg/ml)	106.13±105.56 (8-331)
Hemoglobin (gr/dl)	8.56±1.60 (4.8-13.7)
Platelet (10^3µl)	209038±62644 (120000-426000)
Leukocyte (10^3/µl)	8927±5045 (1690-21700)
β2 microglobulin (mg/L)	7.49±6.54 (1.1-22)
LDH (U/L)	269.50±108.36 (130-577)
ALP (U/L)	82.15±25.47 (35-128)
Proteinuria (g/day)	3.65±5.19 (0.3-17.95)
Phosphorus (mg/dL)	5.10±1.55 (2.2-8.9)
Magnesium (mg/dL)	2.09±0.41 (1.19-2.84)

ALP: alkaline phosphatase, BUN: blood urea nitrogen, CRP: C- reactive protein, LDH: lactate dehydrogenase; Mean±SD: range

AKI was found in twenty-four (92%) of the patients. One of the patients (3%) had stage-1, 7 (27%) had stage-2, and 16 (62%) had stage-3 AKI. Patients according to MM-ISS; one (3%) was detected as stage-1, 5 (20%) as stage-2, and 20 (77%) as stage-3. The distribution of the patients according to AKI and MM stages are given in Table 2. The percentage distribution of patients' initial symptoms is also given in Figure 1.

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Table 2. Distribution of the patients according to AKI and MM stages

	AKI		MM	
	n	%	n	%
Stage-1	1	3	1	3
Stage-2	7	27	5	20
Stage-3	16	62	20	77

AKI: acute kidney injury, MM: multiple myeloma

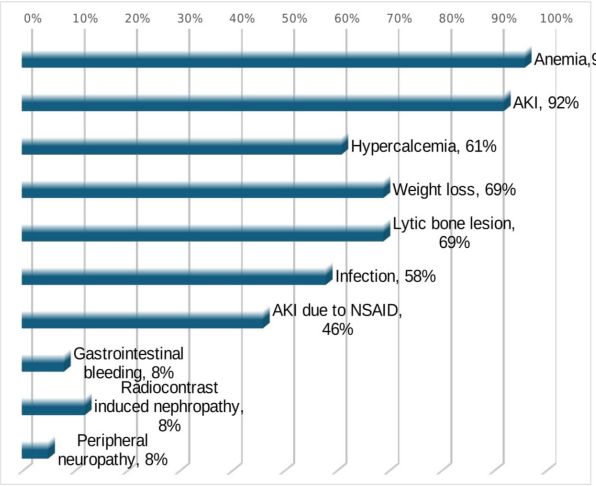

Figure 1. The percentage distribution of clinical findings detected in patients.; AKI: acute kidney injury, NSAID: non streoid anti inflammatory drugs

In MM patients with AKI, there was no significant difference between the mean sβ2M levels and AKI stages (p=0.930). Sβ2M levels in MM patients who required hemodialysis due to renal failure were higher than in those who did not require hemodialysis, but this result was not statistically significant (p=0.085). The results are shown in Table 3.

Table 3. Comparison of sβ2M levels according to AKI stages and hemodialysis requirement

	n=24	sβ2M	p
AKI Stage			
Stage-1	1	4.37±0.64	
Stage-2	7	6.98±6.73	0.930
Stage-3	16	7.73±6.99	
Hemodialysis requirement			
Yes	8	10.020±7.413	0.085
No	16	6.361±5.988	

AKI: acute kidney injury, sβ2M: serum β2 microglobulin; Mean±SD

In our study, a total of 11 (42%) patients had been undergone renal biopsy, and the biopsy findings belong to a patient required hemodialysis is shown in Figure 2 and Figure 3.

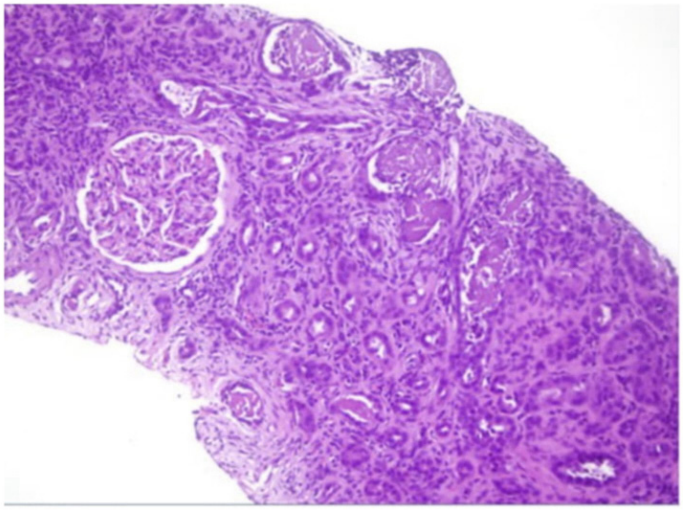

Figure 2. Tubuler casts and inflammatory cells in dilated renal tubules (Hematoxylin eosin x 400)

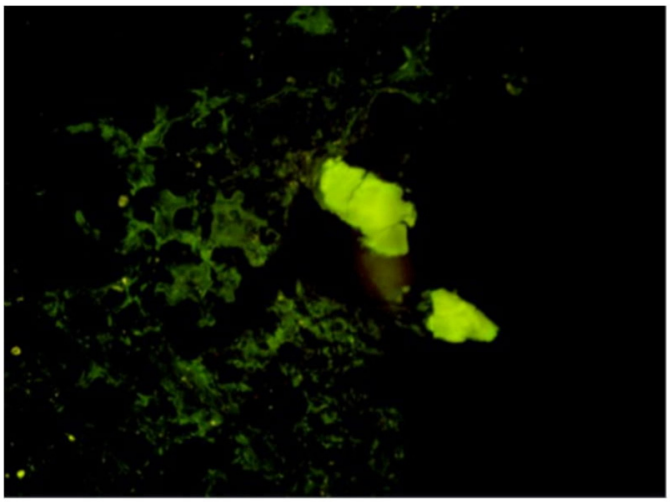

Figure 3. Lambda and kappa light chains accumulated in renal tubular cells (Immunofixation electrophoresis)

The patients were divided into two groups based on the stages of AKI and MM: stages 1-2 and stage 3. Then, the relationship between fT3 levels and the AKI/MM stages were investigated. When the relationship between the mean serum fT3 levels and AKI stages was evaluated in patients with AKI, no statistically significant result was found (p=0.061). Afterwards, the relationship between the mean fT3 levels and the MM stages of the patients was evaluated, there was also no significant difference was found in this statistical evaluation (p=0.86). The results are shown in Table 4.

Table 4. Relationship between fT3 levels and AKI/MM stages

	AKI Stage 1-2	AKI Stage 3	p
fT3	1.984±0.268	1.723±0.562	0.061
	MM Stage 1-2	**MM Stage 3**	
fT3	1.908±0.568	1.806±0.453	0.860

AKI: acute kidney injury, fT3: free triiodothyronine, MM: multiple myeloma, Mean±SD

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Discussion

In the present study, we examined the relationship between sβ2M level (which is an independent prognostic indicator used in the staging of MM), fT3 level (serum levels may vary without thyroid disease in patients with renal failure, as in many systemic diseases) and AKI/MM stages of the newly diagnosed MM patients.

AKI was detected in most of the patients, and a large portion of them were in stage 3. Renal dysfunction may develop in MM by many mechanisms, including hypercalcemia, hyper viscosity, hyperuricemia, and light chains causing proximal tubule damage [9,10].

Studies conducted on renal failure biomarkers have reported that renal failure can be observed in 20% of newly diagnosed MM patients, and this rate can increase up to 50% during the course of the disease [1]. In our study, we found the frequency of AKI to be higher than these rates. The frequency of renal failure in MM patients may vary depending on the patient's age, comorbidities, and medications used. Additionally, definitions of renal failure based on serum urea, creatinine or GFR levels are controversial today. AKI classification according to the KDIGO guideline may be more sensitive than these units in indicating renal dysfunction. It is extremely important to detect renal involvement early, which can seriously affect the prognosis in MM, and to organize the treatment algorithm accordingly. Therefore, we suggest that it would be more useful to use KDIGO-AKI staging in the evaluation of renal dysfunction in MM patients.

In our study, according to the ISS staging based on albumin and sβ2M levels, which is an indicator of the tumor burden of the patients, the MM stage was more advanced in patients with AKI. Also, sβ2M levels in MM patients who required hemodialysis due to renal failure were higher than in those who did not. Additionally, sβ2M levels were higher in patients with advanced AKI stages. β2 microglobulin is a molecule that reflects tumor burden, determines the ISS stage, and its serum level is known to increase in renal failure because it is metabolized by the kidneys. Sβ2M level, an indicator of proximal tubular damage and glomerular filtration, has been found to be associated with AKI defined according to KDIGO criteria in many studies and has been associated with the severity of AKI [11,12]. In our study, we also found a higher frequency of AKI in patients with advanced MM stage and higher sβ2M levels in MM patients requiring hemodialysis. Based on this, we argue for the sβ2M level in MM patients is related to the severity of AKI and higher sβ2M levels may be predictor of hemodialysis requirement in MM patients.

When we evaluated the relationship between AKI/MM stage and fT3 levels, we detected that fT3 levels were lower in patients with advanced stage AKI and MM. Although we did not find a statistically significant result, our result is consistent with the literature. As in many systemic diseases, fluctuation in thyroid functions is observed in more than 80% of AKI patients, and low fT3 levels have been reported to be the most common disorder [13]. The reason for this is thought to be a defect in the response to serum thyroid hormone levels in the pituitary, a disorder in hormone secretion, hormone-genesis or a metabolic disorder in the conversion of T4 to T3 in the periphery [14,15].

In this study, we also investigated the relationship between sβ2M, fT3 levels and AKI in MM patients. We observed that the MM stage of patients who developed AKI was more advanced. We found that sβ2M levels to be higher in patients with advanced AKI stages and in patients requiring hemodialysis due to renal failure. This relationship has also been investigated in other diseases such as MM, and particularly a study conducted by Yuan L. et al. revealed that the sβ2M level was detected at higher levels in both urine and blood in patients who developed AKI in the course of acute pancreatitis [16]. In this context, it can be stated that the sβ2M level, which is an independent prognostic parameter for MM, is an effective parameter in indicating the severity of AKI not only in MM patients diagnosed with AKI but also in other diseases such as acute pancreatitis. This study and our study demonstrate that the use of sβ2M in assessing the severity of AKI is a highly reliable parameter.

We also found that fT3 levels were lower in patients with advanced AKI and MM stages. There are studies that support our preliminary findings and show that lower fT3 levels even have an impact on survival in MM patients. In a study conducted by Pan Q. et al. in 2022, serum fT3 level was found to be positively associated with blood hemoglobin and albumin and negatively correlated with sβ2M and creatinine: Statistical significance was found for all parameters ($p<0.005$). Additionally, this study demonstrated that fT3 level was also associated with overall and progression-free survival, revealing that patients with lower fT3 levels had shorter overall survival [17].

In this context, we hypothesize that the serum fT3 level of the patients can also be used as a determining laboratory parameter, in addition to the serum creatinine level and the patient's urine output, which are the two important parameters used in the KDIGO guideline for staging AKI. Also considering that fT3 levels may even affect overall and progression-free survival in MM patients, the early detection of lower fT3 levels and closer attention to the treatment and follow-up of these patients may be beneficial for improving survival.

Conclusion

Renal failure is a common complication in MM, and it is associated with poor prognosis. Renal functions can be improved with early diagnosis and treatment. We observed that the MM stages of the patients with AKI were more advanced.

High sβ2M level may be a risk factor for the development of AKI in patients with MM, and low serum fT3 may be an indicator of AKI in these patients. More comprehensive, multicenter and prospective designed studies are needed to clarify these issues.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This study was carried out in accordance with the principles of the Declaration of Helsinki, after receiving approval from the University of Health Sciences Hamidiye Scientific Research Ethics Board that is the center of the research (date: 10.01.2025 / number: 35010).

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