THE PLANET

Original Article

Correlation of Serum β2-Microglobulin with Renal Function and Clinical Outcomes in Multiple Myeloma

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ARTICLE INFO

Received: 2 Feb 2026
Accepted: 9 Feb 2026
Published Online: 16 Feb 2026

DOI: 10.5281/zenodo.18662379

Volume: 8, Number: 2, Page: 127-131

e-ISSN: 2789-5912
ISSN: 2617-0817

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ABSTRACT

Background: Renal impairment is a frequent complication in multiple myeloma (MM) and significantly affects prognosis. Serum β2-microglobulin (β2-MG) is a well-recognized biomarker of tumor burden, yet its relationship with renal function and treatment response remains incompletely characterized. **Aim of the study:** To evaluate the correlation of serum β2-MG with renal function and clinical outcomes in patients with MM and to determine its predictive utility for post-treatment renal recovery. **Methods & Materials:** In this prospective observational study, 54 adult MM patients were stratified into two groups based on baseline serum β2-MG (<3.5 mg/L and ≥3.5 mg/L). Baseline demographic, clinical, and laboratory data—including urinary protein-to-creatinine ratio (PCR), estimated glomerular filtration rate (eGFR), κ/λ free light chain (FLC) ratio, and neutrophil gelatinase-associated lipocalin (NGAL)—were collected. Patients received standard anti-myeloma therapy and were followed for six months. Correlations between β2-MG and renal/clinical biomarkers were assessed using Spearman's correlation. Post-treatment outcomes were compared between groups, and receiver operating characteristic (ROC) analysis was performed to identify optimal β2-MG thresholds for predicting poor renal response. **Result:** Patients with β2-MG ≥3.5 mg/L exhibited significantly higher urinary PCR (median 1.60 vs. 0.68 g/g, p<0.001), κ/λ FLC ratio (median 2.20 vs. 1.28, p<0.001), and NGAL levels (median 1.55 vs. 1.12 pg/mL, p<0.001), along with lower eGFR (mean 45.3 vs. 65.2 mL/min, p<0.001). Post-treatment, the high β2-MG group had poorer renal recovery, with significantly lower odds of achieving urinary PCR <1.0 g/g, eGFR >60 mL/min, normalized κ/λ FLC ratio, and NGAL <1.5 pg/mL (all p<0.001). Serum β2-MG correlated strongly with urinary PCR (r=0.71), eGFR (r=–0.75), κ/λ FLC ratio (r=0.68), and NGAL (r=0.66; all p<0.001). ROC analysis identified β2-MG cut-offs of 3.75–3.95 mg/L for predicting poor renal response with high sensitivity (80–88%) and specificity (87–90%). **Conclusion:** Serum β2-MG is a robust biomarker reflecting both disease burden and renal impairment in MM. Elevated β2-MG levels predict poorer renal outcomes and may serve as a valuable tool for risk stratification and treatment monitoring.

Keywords: *Multiple myeloma, β2-microglobulin, renal function, proteinuria, κ/λ free light chains, NGAL, prognostic biomarker*

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Introduction

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by the uncontrolled proliferation of abnormal plasma cells within the bone marrow, leading to excessive production of monoclonal immunoglobulins or light chains [1]. Globally, MM accounts for nearly 1% of all cancers and about 10% of hematologic malignancies, with a prevalence that continues to rise due to improved diagnostic and survival rates [2,3]. This process results in a spectrum of clinical manifestations, including anemia, bone lesions, hypercalcemia, immunodeficiency, and—most importantly—renal dysfunction [4]. The pathophysiology of myeloma-related renal injury is multifactorial, involving light chain cast nephropathy, hypercalcemia, dehydration, amyloidosis, and direct tubular toxicity [5]. Once renal impairment develops, it substantially worsens patient outcomes, complicates therapeutic interventions, and reduces overall survival. Early identification of renal dysfunction and its underlying mechanisms is therefore essential to prevent irreversible kidney damage [6]. Traditional markers such as serum creatinine and blood urea nitrogen (BUN) are often insufficient for early detection, as they rise only after significant nephron loss. In this context, serum β2-microglobulin (β2M) has emerged as a promising biomarker for evaluating both renal function and disease burden in MM [7]. β2-microglobulin is a low-molecular-weight protein (approximately 11.8 kDa) that forms the light chain component of the class I major histocompatibility complex (MHC) present on all nucleated cells [8]. It is continuously shed into the circulation during cell turnover and is freely filtered by the glomeruli, with almost complete reabsorption and catabolism by the proximal renal tubules. Under normal conditions, serum β2M levels remain low (typically 1–3 mg/L) [9]. However, its levels increase markedly in conditions of high cellular proliferation (such as malignancy) and impaired renal clearance. Consequently, β2M serves as an integrated marker reflecting both tumor activity and renal function [10]. Elevated serum β2M has since been shown to predict advanced disease, poor response to therapy, and reduced overall survival. In addition, β2M levels are directly influenced by renal clearance; hence, their elevation may also signify renal dysfunction independent of tumor burden. This dual interpretative value makes β2M a uniquely informative biomarker in MM [11]. The relationship between serum β2M and various renal parameters, including estimated glomerular filtration rate (eGFR), serum creatinine,

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and proteinuria. A strong inverse correlation between β2M and eGFR has been consistently reported, supporting its use as an early indicator of renal impairment [12]. Moreover, persistently elevated β2M levels after therapy have been linked to treatment resistance and inferior progression-free survival. These findings suggest that β2M measurement can provide valuable insight into both renal and hematologic recovery following therapy [13]. Despite its proven significance, the clinical utility of β2M as a predictor of renal outcomes in MM remains underexplored in certain populations, where genetic, environmental, and healthcare variations may influence disease expression [14]. Understanding the interplay between β2M, renal function, and clinical outcomes in these patients could help refine prognostic stratification and guide therapeutic decisions. Therefore, this study was undertaken to evaluate the correlation of serum β2-microglobulin with renal function and clinical outcomes in patients diagnosed with multiple myeloma.

Methods & Materials

This was a prospective observational study conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU, Dhaka, Bangladesh from April 2023 to September 2024. The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. A total of 54 patients meeting the inclusion criteria were enrolled. Patients were stratified into two groups based on serum β2-MG: Group I: <3.5 mg/L and Group II: ≥3.5 mg/L.

Inclusion and Exclusion criteria

Inclusion criteria:

1. Adult patients (≥18 years) with a confirmed diagnosis of multiple myeloma based on the International Myeloma Working Group (IMWG) criteria.
2. Availability of baseline serum β2-MG measurement prior to treatment initiation.
3. Willingness to participate and provide informed consent.

Exclusion criteria:

1. Patients with concomitant renal disorders unrelated to MM, such as chronic glomerulonephritis or diabetic nephropathy.
2. History of prior chemotherapy or hematopoietic stem cell transplantation.
3. Active infection or inflammatory conditions that could affect renal biomarkers.
4. Incomplete baseline or follow-up data.

Data Collection

Baseline demographic and clinical data—including age, sex, comorbidities (e.g., hypertension, diabetes mellitus), disease duration, and performance status—were collected using standardized case record forms. Clinical assessment included measurement of blood pressure, body weight, and grading of peripheral edema. Venous blood and spot urine samples were collected prior to initiation of therapy. Serum was separated within two hours of collection and stored at –80°C until analysis. Laboratory data, including hematological, biochemical, and renal function parameters, were entered into a secured electronic database and cross-checked for accuracy by two independent researchers. Follow-up data were collected at three- and six-month intervals to assess renal function and clinical outcomes. Patients were evaluated for anemia, categorized as none (hemoglobin >12 g/dL), mild (9–12 g/dL), or moderate–severe (<9 g/dL). Hypertension was defined according to JNC-8 criteria or ongoing antihypertensive therapy. Peripheral edema was graded as + or ++. Baseline comorbidities and clinical features were documented to explore associations with serum β2-microglobulin (β2-MG) and renal function.

Laboratory Investigations

Blood and spot urine samples were collected at baseline and after completion of first-line therapy. Serum β2-MG was measured using a validated enzyme-linked immunosorbent assay (ELISA). Renal function was assessed through serum creatinine and estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI equation, while proteinuria was evaluated via the urinary protein-to-creatinine ratio (PCR). Free light chains (κ and λ) were quantified using nephelometry to calculate the κ/λ ratio, and neutrophil gelatinase-associated lipocalin (NGAL) was measured by ELISA. All laboratory measurements were performed in duplicate to ensure reliability, with internal quality controls implemented throughout the study period.

Treatment and Follow-up

All patients received standard anti-myeloma therapy based on institutional protocols, typically incorporating bortezomib-based triplet regimens (e.g., bortezomib, lenalidomide, and dexamethasone) or cyclophosphamide-containing combinations. Supportive care included bisphosphonates, erythropoiesis-stimulating agents, and appropriate infection prophylaxis. Patients were followed for a minimum of six months post-initiation of therapy. Renal response was evaluated according to the IMWG renal response criteria: **complete response** (urinary PCR <0.5 g/g and eGFR >60 mL/min), **partial response** (≥50% reduction in urinary PCR), and **no response** (<50% reduction). Biochemical response was assessed using the κ/λ FLC ratio normalization and NGAL improvement (<1.5 pg/mL).

Statistical Analysis

All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and compared between β2-MG groups using Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were expressed as counts and percentages and compared using Chi-square or Fisher's exact test. Effect sizes were calculated using Cohen's d for continuous variables and odds ratios with 95% confidence intervals for categorical outcomes. Spearman's correlation coefficients were used to assess associations between β2-MG, renal function, and myeloma biomarkers. Receiver operating characteristic (ROC) curves were constructed to determine optimal β2-MG cut-off values for predicting poor post-treatment outcomes, with the Youden index employed to maximize sensitivity and specificity. A two-sided p-value of <0.05 was considered statistically significant.

Result

Table I showed that the mean age of participants was 55.7 ± 11.8 years, with no significant difference between patients with β2-MG <3.5 mg/L (53.2 ± 12.1) and β2-MG ≥3.5 mg/L (56.5 ± 11.5, p=0.42). Gender distribution was nearly equal (males 51.85%, females 48.15%), with no significant difference between groups (p=0.78).

Table I
Baseline demographic and clinical characteristics of the study population (*n*=54).

Variable	Total (n=54)	β2-MG <3.5 mg/L (n=15)	β2-MG ≥3.5 mg/L (n=39)	p-value
Age (years)				
Mean ± SD	55.7 ± 11.8	53.2 ± 12.1	56.5 ± 11.5	0.42
Gender				
Male	28 (51.85)	7 (46.67)	21 (53.85)	0.78
Female	26 (48.15)	8 (53.33)	18 (46.15)	
Hypertension, n (%)	25 (46.30)	5 (33.33)	20 (51.28)	0.27
Anemia				
None (Hb >12 g/dL)	3 (5.56)	0 (0.00)	3 (7.69)	0.63
Mild (Hb 9–12 g/dL)	39 (72.22)	12 (80.00)	27 (69.23)	
Moderate–Severe (<9 g/dL)	12 (22.22)	3 (20.00)	9 (23.08)	
Edema				
+	18 (33.33)	4 (26.67)	14 (35.90)	0.51
++	3 (5.56)	0 (0.00)	3 (7.69)	

Hypertension was present in 46.3% of patients, lower in the β2-MG <3.5 mg/L group (33.33%) than in the ≥3.5 mg/L group (51.28%, p=0.27). Most patients had mild anemia (Hb 9–12 g/dL, 72.22%), and 33.33% had edema, with no significant differences between groups (p>0.05). Median urinary protein-to-creatinine ratio was higher in this group (1.60 g/g [IQR 0.95–2.30] vs 0.68 g/g [0.42–0.90], d=1.25, p<0.001). Mean eGFR was lower (45.3 ± 12.5 vs 65.2 ± 11.8 mL/min, d=1.75, p<0.001). The κFLC/λ FLC ratio and NGAL levels were also elevated (2.20 [1.68–3.10] vs 1.28 [1.05–1.50], d=1.58; 1.55 [1.40–1.70] vs 1.12 [0.95–1.33], d=1.45; p<0.001 for both) (*Table II*).

Table II
Baseline renal and myeloma biomarkers according to serum β2-microglobulin status among the study population.

Parameter	β2-MG ≤3.5 mg/L (n=15)	β2-MG >3.5 mg/L (n=39)	Effect Size (Cohen's d)	p-value
Urinary PCR (g/g), median (IQR)	0.68 (0.42–0.90)	1.60 (0.95–2.30)	1.25	<0.001
eGFR (mL/min), mean ± SD	65.2 ± 11.8	45.3 ± 12.5	1.75	<0.001
κFLC/λ FLC ratio, median (IQR)	1.28 (1.05–1.50)	2.20 (1.68–3.10)	1.58	<0.001
NGAL (pg/mL), median (IQR)	1.12 (0.95–1.33)	1.55 (1.40–1.70)	1.45	<0.001

Patients with β2-MG ≤3.5 mg/L exhibited significantly better responses across all parameters. Good response rates, defined as urinary PCR <1.0 g/g, eGFR >60 mL/min, κFLC/λ FLC ratio <1.65, and NGAL <1.5 pg/mL, were notably higher in the low β2-MG group (86.7%, 80.0%, 80.0%, and 86.7%, respectively) compared to the high β2-MG group (48.7%, 25.6%, 33.3%, and 30.8%, respectively; all p<0.01). The corresponding odds ratios ranged from 0.10 to 0.18 (*Table III*).

Table III
Post-treatment renal and clinical outcomes by serum β2-microglobulin level.

Outcome	β2-MG ≤3.5 mg/L (n=15)	β2-MG >3.5 mg/L (n=39)	Odds Ratio (95% CI)	p-value
Urinary PCR <1.0 g/g (Good Response)	13 (86.67)	19 (48.72)	0.18 (0.04–0.70)	0.004
eGFR >60 mL/min (Good Response)	12 (80.00)	10 (25.64)	0.10 (0.03–0.38)	<0.001
κFLC/λ FLC ratio <1.65 (Good Response)	12 (80.00)	13 (33.33)	0.13 (0.04–0.42)	<0.001
NGAL <1.5 pg/mL (Good Response)	13 (86.67)	12 (30.77)	0.10 (0.03–0.34)	<0.001

As demonstrated in *Table IV*, serum β2-MG levels showed a strong positive correlation with urinary PCR (r=0.71, p<0.001), κFLC/λ FLC ratio (r=0.68, p<0.001), and NGAL (r=0.66, p<0.001), while inversely correlating with eGFR (r=–0.75, p<0.001).

Table IV
Correlation of serum β2-microglobulin with renal and clinical outcomes among the study population.

Variable	Spearman r	p-value
Urinary PCR	0.71	<0.001
eGFR	–0.75	<0.001
κFLC/λ FLC ratio	0.68	<0.001
NGAL	0.66	<0.001

β2-MG demonstrated excellent discriminative ability, with area under the curve (AUC) values of 0.912 for urinary PCR >1.0 g/g, 0.934 for eGFR <60 mL/min, and 0.895 for κFLC/λ FLC ratio >1.65. Optimal cut-off values ranged from 3.75–3.95 mg/L, with sensitivities of 80–88%, specificities of 87–90%, and overall accuracy of 83–89% (*Table V*).

Table V
ROC analysis of serum β2-microglobulin predicting poor renal response.

Outcome	AUC (95% CI)	Optimal Cut-off (mg/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Urinary PCR >1.0 g/g	0.912 (0.842–0.982)	3.75	82	88	83	87	85
eGFR <60 mL/min	0.934 (0.875–0.993)	3.95	88	90	92	84	89
κFLC/λ FLC ratio >1.65	0.895 (0.818–0.972)	3.8	80	87	81	86	83

Discussion

Multiple myeloma (MM) remains a complex hematologic malignancy where renal impairment frequently complicates disease progression and adversely affects survival [15]. Given that β₂-microglobulin (β₂-MG) reflects both tumor burden and renal clearance, its dual role as a biochemical and prognostic marker has attracted increasing attention [16]. In this context, the present study evaluated the correlation between serum β₂-MG and renal function parameters, as well as post-treatment outcomes, in patients with MM. In our study , patients with elevated β₂-MG levels (≥3.5 mg/L) demonstrated markedly higher urinary protein-creatinine ratio (PCR), lower estimated glomerular filtration rate (eGFR), and elevated κ/λ free light chain (FLC) ratios and neutrophil gelatinase-associated lipocalin (NGAL) levels compared with those having lower β₂-MG concentrations. These findings are consistent with previous reports demonstrating that elevated β₂-MG reflects both impaired renal clearance and increased tumor burden in multiple myeloma, correlating with reduced eGFR and markers of tubular injury such as NGAL [17]. Moreover, renal impairment has been shown to alter the serum κ/λ FLC ratio, reinforcing the association between β₂-MG elevation and dysregulated FLC homeostasis [18]. The observed increase in PCR in our study further underscores the link between β₂-MG and glomerular or tubular proteinuria, highlighting the utility of β₂-MG as a combined biomarker for both renal dysfunction and disease burden in multiple myeloma patients [19]. In our study, a strong inverse relationship between β₂-microglobulin (β₂-MG) and estimated glomerular filtration rate (eGFR) was observed ($r = –0.75$, $p < 0.001$), aligning with findings from previous investigations. Ortega et al. reported that elevated β₂-MG levels were significantly associated with both renal impairment and poorer survival outcomes in newly diagnosed multiple myeloma (MM) patients, underscoring its dual role as a marker of tumor burden and renal dysfunction [20]. Similarly, Savuliak et al. identified a robust negative correlation between β₂-MG and eGFR, further supporting its predictive value for renal impairment in MM [21]. In the context of chronic kidney disease, Siddiqui et al. demonstrated a progressive increase in β₂-MG with declining eGFR across disease stages [22], while Argyropoulos et al. highlighted the mechanistic basis for β₂-MG accumulation due to impaired renal filtration [23]. Furthermore, Dimopoulos et al. (2010) emphasized that the prognostic significance of β₂-MG reflects both myeloma cell burden and renal excretory capacity, justifying its inclusion in the Revised International Staging System (R-ISS) [24]. Comparable negative correlations have been reported by Yun et al. ($r = –0.787$, $p < 0.001$) and in a high vascular risk study ($r = –0.62$, $p < 0.01$), confirming the consistency of these findings across diverse patient populations [25,26]. Moreover, the strong positive association between β₂-MG and NGAL ($r = 0.66$, $p < 0.001$) observed in this study underscores the significance of β₂-MG in indicating concurrent tubular stress. NGAL, a sensitive marker of early tubular injury, has been recognized as a key indicator of MM-related kidney disease [27]. The parallel rise of both markers suggests that β₂-MG elevation may mirror not only tumor burden but also renal tubular compromise, thereby broadening its interpretive value in clinical assessment. Post-treatment analysis demonstrated that patients with lower baseline β₂-microglobulin (β₂-MG) levels achieved superior renal recovery, reflected by higher rates of estimated glomerular filtration rate (eGFR) >60 mL/min and normalization of the κ/λ free light chain (FLC) ratio. Notably, a β₂-MG threshold >3.95 mg/L was associated with poor renal response, exhibiting excellent predictive performance (AUC = 0.934, 95% CI: 0.875–0.993). These observations align with prior evidence highlighting an inverse relationship between β₂-MG and renal function in multiple myeloma (MM). Kastritis et al. (2010) identified lower baseline β₂-MG as an independent predictor of dialysis independence and renal recovery in MM patients with cast nephropathy [28]. Additionally, numerous studies and reviews have confirmed β₂-MG as a reliable surrogate of glomerular filtration and residual renal function, reflecting both disease burden and renal impairment [23,29]. In our study, both group identified a β₂-microglobulin (β₂-MG) threshold of approximately 4.0 mg/L as the optimal predictor of renal dysfunction, lending the robustness and external validity of these findings. Notably, β₂-MG demonstrated a strong correlation with the κ/λ free-light-chain (FLC) ratio ($r = 0.68$, $p < 0.001$), reflecting its sensitivity to disease activity. This aligns with previous data in 34 multiple myeloma (MM) patients, where baseline κ/λ FLC ratios correlated positively with β₂-MG ($r = 0.755$, $p < 0.0001$) and inversely with estimated glomerular filtration rate ($r = –0.448$, $p = 0.0078$), indicating that elevated FLC production is associated with higher β₂-MG levels and impaired renal clearance [18]. Additional studies have similarly linked abnormal FLC ratios at diagnosis with elevated serum creatinine and reduced renal function [30]. Collectively, these observations reinforce β₂-MG's dual role as a marker of both MM disease burden and renal impairment.

Limitations

This study was conducted at a single tertiary care center, which may limit generalizability to broader populations. Follow-up was restricted to six months, potentially underestimating long-term renal outcomes and late treatment effects. Additionally, variations in therapy regimens and supportive care could introduce confounding effects. Biomarker measurements, though standardized, were limited to selected time points, preventing dynamic assessment of β2-MG fluctuations during disease progression and treatment response.

Conclusion & Recommendations

Serum β2-microglobulin is a reliable biomarker reflecting both tumor burden and renal dysfunction in multiple myeloma. Elevated β2-MG levels are strongly associated with increased proteinuria, impaired eGFR, abnormal κ/λ free light chain ratios, and higher NGAL levels, indicating compromised renal and clinical outcomes. Patients with β2-MG ≥3.5 mg/L demonstrate significantly poorer post-treatment renal recovery. These findings underscore the utility of β2-MG not only for disease monitoring but also for early identification of patients at high risk for renal impairment, enabling tailored therapeutic strategies and optimized clinical management.

Funding: No funding sources
Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

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