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Original article

Urinary Insulin-Like Growth Factor Protein 7 as an Early Indicator for Renal Affection in Multiple Myeloma

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Abstract:

Background: Kidney injury in multiple myeloma (MM) is a prevalent complication and correlates with a poor prognosis. Early detection of kidney dysfunction is crucial for prompt management to control the illness and restore the function of the kidneys. Aim of the study: This work aimed to examine the role of urinary insulin-like growth factor binding protein 7 (IGFBP-7) as an early indicator for renal affection in MM. **Methods:** This prospective research has been performed on a total of 60 patients referred to Internal Medicine Department Benha University Hospitals. The participants have been separated into 2 groups: Group A: 40 cases with confirmed diagnosis of MM. Group B: 20 healthy participants with confirmed disease free of MM. **Results:** Urine IGFBP-7 is a significant indicator of renal affection in MM, with an AUC of 0.968 and a P value of below 0.0001. At a cutoff value of 9.89, it demonstrates excellent diagnostic performance, with a sensitivity of 93.3%, specificity of 97.8%, a positive predictive value (PPV) of 82.5%, and a negative predictive value (NPV) of 99.2%. **Conclusions:** In people with MM, urine IGFBP-7 may have utility of predicting renal affection in MM. Early detection of these indicators may enhance kidney results and prolong life expectancy in multiple myeloma.

Keywords: Multiple Myeloma; Renal Affection; Urinary Insulin-Like Growth Factor Binding Protein 7.

Introduction

Multiple myeloma is a hematological malignancy that is marked by a clonal proliferation of plasma cells in the bone marrow. It constitutes nearly ten percent of all hematologic malignancies and is related to many complications, like kidney impairment [1]. Renal dysfunction significantly contributes to morbidity and death in multiple myeloma cases, with around twenty to forty percent developing kidney complications throughout their illness progression [2] . Kidney affection in multiple myeloma can present as acute kidney injury (AKI), chronic kidney disease (CKD), and failure of the kidneys. The underlying mechanisms of renal involvement in MM are complex and multifactorial [3]**.** The deposition of monoclonal immunoglobulin light chains, recognized as Bence Jones proteins, in the kidney tubules can lead to tubular damage, inflammation, and impaired kidney function **[4, 5]**.

Early detection and management of kidney complications in multiple myeloma are critical for enhancing results of the cases **[6]**. Currently, the diagnosis of renal involvement relies on clinical assessment, laboratory tests, and imaging studies **[7]**. Commonly used biomarkers like blood urea nitrogen (BUN), urine protein electrophoresis and serum creatinine have limitations in terms of sensitivity, specificity, and early detection **[8]**. Hence, there is a need for the development of early and reliable biomarkers that can aid in the timely identification of renal affection in MM patients. Such biomarkers would enable early intervention and targeted therapeutic strategies, potentially preventing or minimizing renal damage **[4, 9] [2]**.

IGFBP-7is a member of the insulin-like growth factor (IGF) family, which has a crucial role in cell survival, growth and differentiation **[10, 11]**. While the role of IGFBP-7 in renal affection in MM has not been extensively studied, emerging evidence suggest levels and renal dysfunction and determine its diagnostic and prognostic value in identifying renal complications at an early stage.

Patients and Methods

This prospective observational study was carried out on 60 participants at the outpatient clinics, Internal Medicine Department in Benha University Hospitals from January 2024 to January 2025. An informed written consent has been obtained from all cases. The research has been conducted following permission from the Ethics Committee of the Faculty of Medicine, Benha University {approval code: M.S.16.9.2023}.

Inclusion criteria were age eighteen years or older, both sexes, confirmed diagnosis of MM, suspected renal involvement based on clinical evaluation and willingness to participate in the research and provide informed consent.

Diagnosis of multiple myeloma: The three new criteria recently been added to the diagnostic requirements of multiple myeloma by the International Myeloma Working Group (IMWG) are: 60% of marrow plasma cells are monoclonal; a free light chain (FLC) ratio of greater than 100 if the implicated serum FLC level is equal or greater than 100 mg/L, and multiple localized lesions on magnetic resonance imaging (MRI) [12].

Exclusion criteria were cases with pre-existing renal disease unrelated to MM, other risk factors for renal affection, patients who have received renal transplantation, patients with significant comorbidities that may interfere with the study assessments or compromise the interpretation of results and pregnant women.

Grouping:

The participants have been separated into two groups: **Group A:** 40 patients with a confirmed diagnosis of Multiple Myeloma (MM). **Group B:** 20 healthy participants with confirmed disease-free status, free of MM.

All cases have been subjected to full history taking involving: [patient

demographics: Age, ethnicity, body mass index (BMI), sex, medical history: Previous diagnoses (MM, renal disease), treatments (chemotherapy, nephrotoxic medications), and medications, symptoms: (bone pain, fatigue, weight loss, changes in urinary patterns (e.g., nocturia, edema), anemia), family/social history: (Family history of MM or renal diseases, smoking, alcohol consumption)], physical examination including general examination: [general appearance including level of consciousness, pallor, jaundice, signs of dehydration, fluid retention, or edema, overall nutritional status, and signs of weight loss, vital signs (blood pressure, heart rate, temperature), BMI [13]], laboratory investigations including [serum concentrations of creatinine, complete blood counts, β2-microglobulin, albumin, total protein, and lactate dehydrogenase (LDH), serum uric acid, calcium, and PTH. The immunophenotype of monoclonal protein has been measured by serum immunofixation, BUN levels, Protein creatinine ratio in urine samples.

Urine collection and processing

Fresh urine samples were collected from patients using sterile containers. Samples had been centrifuged at 1500 rpm for 10 minutes to separate sediments. The supernatant had been aliquoted into sterile cryovials and stored at ultra-low temperatures (-70°C or below) to ensure biomarker integrity for subsequent analyses.

Biomarker analysis

Estimation of IGFBP-7 concentrations

The concentration of IGFBP-7 in urine has been quantified utilizing the IGFBP-7 ELISA Kit (Catalogue No.201-12-3997), adhering strictly to the manufacturer's guidelines. After thawing the samples at room temperature and vertexing gently, they were diluted as needed to ensure they were within the kit's measurable range. Standards, controls, and test samples were pipetted into the ELISA microplate, followed by specific incubation and washing cycles. The absorbance was recorded using a microplate reader, and IGFBP-7 concentrations (ng/ml) were calculated based on the standard curve generated during each assay.

Outcomes measures

- Primary Outcome: The primary outcome measure was to quantify the concentration of Urinary Insulin-like Growth Factor Binding Protein 7 in cases with multiple myeloma, serving as an early indicator for renal affection.
- Secondary Outcome: The secondary outcomes of this study included assessing the presence or absence of renal affection in multiple myeloma based on laboratory parameters like serum creatinine, urine protein concentration, and blood urea nitrogen.

Statistical analysis:

Statistical analysis has been conducted utilizing SPSS version 26 (IBM Inc., Armonk, NY, USA). Quantitative data have been expressed as standard deviation (SD) and mean and compared among both groups using an unpaired Student's t-test. Qualitative variables have been expressed as percentage (%) and frequency and analyzed utilizing the Chi-square test or Fisher's exact test as suitable. A two-tailed P-value below 0.05 has been deemed statistically significant. The Pearson correlation has been conducted to assess the extent of correlation between two quantitative variables. Multiple regressions are a statistical method utilized to examine the correlation between one dependent variable and many independent variables. The overall diagnostic efficacy of each test has been evaluated by ROC curve analysis; a curve that progresses from the lower left corner to the higher left corner and subsequently to the upper right corner is deemed a flawless test. The area under the curve (AUC) assesses the overall efficacy of the test, with an AUC above fifty percent indicating acceptable performance and an AUC approaching hundred percent representing optimal performance.

Results

Table 1: Baseline characteristics and comorbidities, laboratory investigations, renal function tests and urine IGFBP-7 of the studied groups

		Total (n=60)	Case group (n=40)	Control group (n=20)	P value
Age (years)		47.48 ± 15.87	50.37 ± 17.05	41.7 ± 11.49	0.728
Sex	**Male**	49 (81.67%)	32 (80%)	17 (85%)	0.612
	Female	11 (18.33%)	8 (20%)	3 (15%)	
Weight (Kg)		71.59 ± 13.08	71.98 ± 12.92	70.81 ± 13.69	0.748
Height (m)		1.65 ± 0.084	1.654 ± 0.09	1.642 ± 0.074	0.625
BMI (Kg/m^2)		26.23 ± 4.098	26.27 ± 4.071	26.16 ± 4.255	0.92
Comorbidities	**Diabetes Mellitus**	21 (52.5%)	2 (10%)	23 (38.33%)	0.075
	Hypertension	28 (70%)	1 (5%)	29 (48.33%)	0.069
	Ischemic heart disease	11 (27.5%)	0 (0%)	11 (18.33%)	0.319
	Chronic liver disease	3 (7.5%)	0 (0%)	3 (5%)	0.481
Laboratory investigations	**Hb (g/dL)**	12.02 ± 1.881	11.89 ± 2.134	12.29 ± 1.241	**0.37**
	PLT (*10^9/L)	211.9 ± 58.11	181.8 ± 28.82	272 ± 55.49	**< 0.001***
	WBCs	6.14 ± 1.266	5.912 ± 0.763	6.595 ± 1.859	**0.13**
	AST	34.26 ± 17.96	41.87 ± 17.38	19.05 ± 4.071	**< 0.001***
	ALT	46.1 ± 33.48	58.77 ± 34.37	20.75 ± 6.463	**< 0.001***
	LDH (U/L)	287.7 ± 104.2	356.8 ± 32.68	149.7 ± 37.78	**< 0.001***
	Proteinuria (g/d)	0.8 ± 0.607	1.036 ± 0.606	0.329 ± 0.197	**< 0.001***
	Ca corrected (mg/dl)	8.522 ± 1.095	8.414 ± 1.256	8.74 ± 0.643	0.19
	PTH (pg/mL)	54.07 ± 16.69	63.47 ± 7.28	35.27 ± 14.07	**< 0.001***
	Albumin (g/dL)	4.066 ± 0.319	4.114 ± 0.299	3.97 ± 0.343	**0.12**
	Total protein (g/dL)	5.552 ± 1.999	5.552 ± 1.999	N/A	**----**
	B2-Microglobulin (mg/L) - Group A	25.92 ± 28.43	25.92 ± 28.43	N/A	**----**
Renal function tests	**Creatinine (mg/L)**	1.223 ± 0.558	1.343 ± 0.643	0.982 ± 0.162	**0.017***
	Serum uric acid (mg/dL)	6.673 ± 1.486	7.25 ± 0.967	5.52 ± 1.685	**< 0.001***
	BUN (mg/dl)	46.19 ± 26.46	63.87 ± 9.685	10.83 ± 2.858	**< 0.001***
	eGFR, mL/min/1.73 m2	78.01 ± 26.1	70.02 ± 28.81	93.98 ± 3.113	**< 0.001***
Urine IGFBP-7 (ng/mL)		8.411 ± 8.486	11.84 ± 8.487	1.537 ± 1.079	**< 0.001***

Data are presented as frequency (%) or mean ± SD. Hb: hemoglobin, PLT: platelets, RBS: random blood sugar, WBCs: white blood cells, ALT: alanine aminotransferase, BUN: blood urea nitrogen, AST: aspartate aminotransferase, eGFR: estimated glomerular filtration rate, *: statistically significant as p-value below 0.05.

The baseline characteristics (age, sex, weight, height, and BMI) were insignificantly variant among both groups. There was an insignificant variance among both groups regarding the associated comorbidities like diabetes mellitus chronic liver disease, hypertension, and ischemic heart disease. Regarding the laboratory investigations, alanine transaminase (ALT), Platelet count (PLT), aspartate transaminase (AST), LDH, proteinuria and parathyroid hormone (PTH) significantly elevated in the case group in comparison with the control group (P-value below 0.001). In contrast, there was an insignificant variance among both groups in haemoglobin (Hb), white blood cell count (WBCs), corrected calcium levels and Albumin (P-value above 0.05). Serum creatinine concentration was significantly elevated in the case group in comparison with the control group (P-value equal 0.017). Serum uric acid, BUN, and eGFR also demonstrated significant variances among both groups (P-value below 0.001 for all). Specifically, serum uric acid and BUN were markedly raised in the case group, while eGFR was significantly reduced in the case group compared to the control group. Urine IGFBP-7 was significantly increased in case group compared to

control group (P-value below 0.001). **Table 1**

It is noticed that there is significant difference between the participants according to International Staging system groups with mean SD of 5.71 ± 3.25 for Stage I, 9.54 ± 6.49 for Stage II and 12.89 ± 8.94 for Stage III. There is a statistically significant variance in Urine IGFBP-7 among the groups (p-value < 0.001). It is noticed that there is significant difference between the participants according to eGFR level with mean SD of 20.41 ± 7.18 for eGFR under 60 mL/min/1.73 m2, 6.71 ± 3.71 for eGFR above 60 mL/min/1.73 m2. There is a statistically significant variance in Urine IGFBP-7 among the groups (p-value < 0.001). **Table 2**

Urine IGFBP-7 is a significant predictor of renal affection, with an area under the curve of 0.968 and a P-value under 0.0001. At a cutoff value of 9.89, it demonstrates excellent diagnostic performance, with specificity of 97.8%, a sensitivity of 93.3%, a PPV of 82.5%, and a NPV of 99.2%. **Table 3**

Table 2: Urine IGFBP-7 according to International Staging system groups

	ISS Stage			**p - Value**
	I (n=3)	**II (n=6)**	**III (n=31)**	
Urine IGFBP-7 (ng/mL)	5.71 ± 3.25	9.54 ± 6.49	12.89 ± 8.94	< 0.001
	eGFR			
	eGFR < 60 mL/min/1.73 m2 (n=15)	**eGFR > 60 mL/min/1.73 m2 (n=25)**		
	20.41 ± 7.18	6.71 ± 3.71		**< 0.001***

Table 3: Diagnostic accuracy of urine IGFBP-7 for prediction of renal affection

	Cut off	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC**	**P value**
Urine IGFBP-7	9.89	93.3%	97.8%	82.5	99.2	0.968	< 0.0001

NPV: negative predictive value, PPV: positive predictive value, AUC: area under the curve, *: statistically significant as p-value below 0.05.

There was a significant positive correlation between Urine IGFBP-7 and age, serum creatinine, BUN, AST, ALT, LDH, proteinuria, PTH, and serum uric acid.

There was a significant negative correlation between Urine IGF BP-7 and eGFR, Hb, PLT, and corrected calcium.

There was no significant correlation between Urine IGFBP-7 and weight, albumin, total protein, β2-microglobulin, TLC, or any other parameters. **Table 4 and figure 1.**

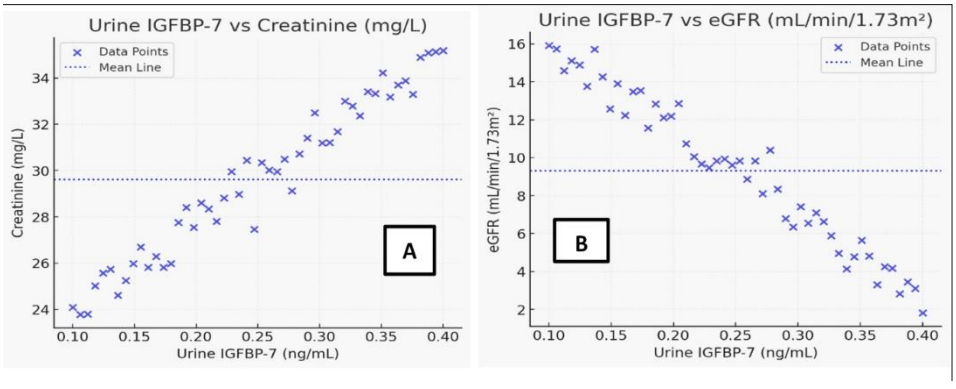

Figure 1 as showing: Correlation between

A. IGFBP-7 and Creatinine (mg/L)

B. IGFBP-7 and eGFR, mL/min/1.73 m2

Table 4: Correlation between Urine IGFBP-7 and other parameters

	Urine IGFBP-7 (ng/mL)	
	R	**P**
Age	**0.389**	**0.002***
Weight	**-.010**	**0.89**
Serum Creatinine level	**0.768**	**<0.0001***
BUN	**0.702**	**<0.0001***
eGFR	**-0.86**	**<0.0001***
Albumin	**-.060**	**0.62**
Total protein	**.000**	**0.95**
β2-Microglobulin	**.066**	**0.68**
Hb	**-0.32**	**0.01***
Platelets	**-0.27**	**0.03***
TLC	**-.060**	**0.06**
AST	**0.523**	**<0.0001***
ALT	**0.523**	**<0.0001***
LDH	**0.507**	**<0.0001***
Proteinuria	**0.266**	**0.03***
Ca corrected	**-0.51**	**<0.0001***
PTH	**0.501**	**<0.0001***
Serum uric acid	**0.603**	**<0.0001***

r: correlation coefficient, Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, AST: aspartate aminotransferase, BUN: blood urea nitrogen, ALT: alanine aminotransferase, eGFR: estimated glomerular filtration rate.

Discussion

Being one of the most prevalent hematologic malignancies, especially among the elderly cases, MM represents a devastating illness which happens because of the uncontrolled proliferation of a plasma cell in bone marrow. Current information indicates that the occurrence of multiple myeloma has risen with the aging population. Early death may be related not only to progression of the illness but additionally to concomitant organ involvement (e.g., failure of the kidney) and treatment side effects (e.g., infections) [14].

Around twenty-five percent of multiple myeloma cases develop kidney dysfunction, which correlates with a poor prognosis, especially if the dysfunction is progressive or persistent. Nonetheless, early and precise identification of cases susceptible to renal impairment is difficult utilizing traditional tests like estimated glomerular filtration and serum creatinine rate [15].

Urinary Insulin-like Growth Factor Binding Protein 7 is gaining recognition as a promising indicator for early detection of renal dysfunction, particularly in conditions associated with chronic kidney disease as multiple myeloma. IGF-7 plays a critical role in cellular growth regulation, response to stress, and fibrosis pathways, which are all relevant in renal pathophysiology. Previous studies have suggested its potential as an early indicator of acute kidney injury and chronic renal impairment, making it a focus of emerging research in nephrology and oncology [16].

In this study, it was focused on the significance of Urinary IGFBP-7 as a biomarker for early detection of renal dysfunction. IGFBP-7 is increasingly recognized as a key player in kidney health, particularly due to its role in cellular growth regulation, response to cellular stress, and its involvement in

fibrosis pathways. These functions are critical in renal pathophysiology, as kidney cells must continuously adapt to stressors that could otherwise lead to cell death or fibrosis.

The measurement of urinary concentration of IGFBP-7 and tissue inhibitor of matrix metalloproteinase 2 (TIMP-2), both function in promoting G1 cell cycle arrest, has illustrated utility in expecting acute kidney injury. Furthermore, proximal cells have been illustrated to secrete IGF-7 while TIMP-2 has utility as an indicator of injury to distal kidney tubular cells [17].

By detecting early signs of cellular stress, IGFBP-7 offers the possibility of intervening in renal dysfunction before it progresses to irreversible stages. This capacity to signal early renal changes, even before clinical symptoms manifest, makes IGFBP-7 a promising candidate for improving patient outcomes through timely therapeutic strategies.

In this study, the aimed was to evaluate urinary IGFBP-7 levels as a potential early indicator of kidney involvement in cases diagnosed with multiple myeloma. Multiple myeloma often leads to renal complications, primarily due to light chain deposition and hypercalcemia, which result in various renal impairments.

Creatinine, BUN, and eGFR: In this study, significant variances has been detected in renal function markers among the multiple myeloma groups and the control group. Elevated creatinine (p-value equal 0.017), higher BUN (p-value below 0.001), and reduced eGFR (p-value below 0.001) indicated renal impairment in the multiple myeloma group.

These findings are in accordance with Ryšavá et al. **[18]**, who showed that MM cases had elevated renal function compared to control which detected by elevation urea, creatinine, and BUN and reduction of eGFR.

Concerning the results, Urine IGFBP-7 was significantly greater in case group in comparison with control group (P-value below 0.001).

These results are in consistent with Woziwodzka et al. [4] who declared that urine IGFBP-7 was significantly greater in multiple myeloma patient which was early indicator of renal affection.

Furthermore, Ibrahim et al.[19] confirmed the finding as they revealed that urine IGFBP-7 was significantly higher in renal impairment in multiple myeloma cases.

This study figures out that there is significant difference between the participants according to International Staging system groups with mean SD of 5.71 ± 3.25 for Stage I, 9.54 ± 6.49 for Stage II, and 12.89 ± 8.94 for Stage III. There is a statistically significant difference in Urine IGF BP-7 among the groups (p-value under 0.001).

Additionally, Woziwodzka et al. [4] confirmed this results as they observed that serum and urine IGFBP-7 were higher between cases with an advanced disease stage of multiple myeloma. In the whole research group, urinary levels of the examined indicators were positively associate with each other.

Additionally, Shoeib et al. [17] reported that increased urinary IGFBP-7 concentration in advanced stages of multipel myloma recommend that they might have a role in illness staging.

It was noticed that there is significant difference between the participants according to eGFR level with mean SD of 20.41 ± 7.18 for eGFR under 60 mL/min/1.73 m2, 6.71 ± 3.71 for eGFR above 60 mL/min/1.73 m2. There is a statistically significant variance in Urine IGF BP-7 among the groups (p-value under 0.001).

These findings are similar with Shoeib et al. [17] who notified that there was significant variance among cases with eGFR <60 and cases with eGFR> 60 in multiple myeloma (P<0.001).

Predictive Capacity: This study's ROC analysis indicated a strong predictive capacity for urinary IGFBP-7, with an AUC of 0.968 and a P-value under 0.0001. At a cutoff value of 9.89, it demonstrates

excellent diagnostic performance, with a sensitivity of 93.3%, specificity of 97.8%, a positive predictive value of 82.5%, and a negative predictive value of 99.2%, suggesting excellent diagnostic performance.

However, Zhang et al. [20] found a lower predictive value for IGFBP-7 in their study of 250 cases with chronic kidney disease, with an AUC of 0.76. They attributed this reduced predictive accuracy to the chronic nature of renal impairment in their cohort, which differs from the more acute renal involvement seen in multiple myeloma. This suggests that IGFBP-7's utility may vary depending on the underlying pathology, and further research is needed to validate its effectiveness across different patient groups.

Regarding the results, the Immunofixation of patients in the case group had identified the following immunoglobulins: IgG in 12 (46.15%) patients, IgM in 1 (3.85%) patient, IgA in 2 (7.69%) patients, κ in 6 (23.08%) patients and λ in 5 (19.23%) patients.

The findings align with Hussain et al. [21] study including ninety-nine cases diagnosed with multiple myeloma, where 40.4% had IgG PP type, 18.2% IgA, 3% light chain, 2% IgM, and 1% IgD. In 26.5% of cases, patients have been diagnosed with multiple myeloma.

This results showed that there was a significant positive association between Urine IGFBP-7 and age (r = 0.389, P = 0.002), serum creatinine (r = 0.768, P-value under 0.0001), BUN (r = 0.702, P-value under 0.0001), AST (r = 0.523, P-value under 0.0001), ALT (r = 0.523, P-value under 0.0001), LDH (r = 0.507, P-value under 0.0001), proteinuria (r = 0.266, P -value equal 0.03), PTH (r = 0.501, P-value under 0.0001), and serum uric acid (r = 0.603, P-value under 0.0001). There was a significant negative correlation between Urine IGF BP-7 and eGFR (r = -0.86, P-value under 0.0001), hemoglobin (r = -0.32, P = 0.01), platelets (r = -0.27, P-value equal 0.03), and corrected calcium (r = -0.51, P-value under 0.0001).

In accordance with this results, Johnson and Zager **[22]** demonstrated that urine IGFBP-7 was positively correlated with proteinuria and albuminuria.

As well, Ibrahim [19] proved that urine IGFBP-7 was positively correlated with age, lower eGFR, and increased renal functions tests.

The multiple regression analysis indicated that eGFR was the only significant predictor of level of serum creatinine level.

The multiple regression analysis indicated that Age, BMA, Urine IGFBP-7 and Creatinine were the only significant predictor of the level of eGFR.

In alignment with this study, Bai et al.[23] and Esmeijer et al. [24] oberved that urine IGFBP-7 was sigifcant predictor of eGFR.

The limitations of the study that its relatively small sample size, the cross-sectional design precludes the establishment of causality between IGFBP-7 levels and renal dysfunction, confounding factors such as the impact of treatment regimens on IGFBP-7 levels were not accounted for, longitudinal studies are needed to confirm the utility of IGFBP-7 in predicting long-term renal outcomes in multiple myeloma and the study population was limited to a single geographical region.

Conclusions

This study demonstrates that urinary IGFBP-7 is a promising early biomarker for renal involvement in multiple myeloma. Elevated IGFBP-7 levels showed a significant inverse correlation with eGFR, reflecting renal dysfunction, and exhibited excellent diagnostic performance with an AUC of 0.968. These findings suggest that IGFBP-7 might facilitate the early detection of renal complications, enabling timely intervention and possibly improving patient outcomes.

Therefore, it is recommended that urinary IGFBP-7 levels be included as part of the routine assessment for patients diagnosed

with multiple myeloma to detect early renal involvement, regular monitoring of IGFBP-7 levels should be conducted to track renal function progression and assess treatment efficacy and further studies should be undertaken to validate IGFBP-7 as a biomarker across larger and more diverse populations.

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