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Original Article

Predictive value of endothelial activation and stress index for acute kidney injury in hospitalized patients with multiple myeloma

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Abstract: Background: To investigate the predictive value of Endothelial Activation and Stress Index (EASIX) for acute kidney injury (AKI) in hospitalized patients with multiple myeloma (MM). Methods: This retrospective study included 352 MM patients admitted to our hospital between January 2020 and December 2024. Patients were divided into a training set (n = 248) and a validation set (n = 104) using a time-based split. Patients were further classified into AKI (training n = 52, validation n = 22) and non-AKI groups (training n = 196, validation n = 82) according to occurrence of AKI during hospitalization. Factors associated with the development of AKI in MM patients were identified using logistic regression analysis. The predictive performance of EASIX for AKI was assessed by receiver operating characteristic (ROC) curve analysis. Results: In the training set, binary logistic regression analysis revealed that EASIX, International Staging System (ISS) stage, and bortezomib-lenalidomide-dexamethasone (VRD) chemotherapy regimen were independent factors influencing the development of AKI in MM patients during hospitalization (all $P < 0.05$). The area under the ROC curve (AUC) for EASIX predicting AKI was 0.897 (95% CI: 0.852-0.942). All 248 patients were followed up without loss to follow-up. The mortality rate was significantly different between the group with EASIX ≤ 3.16 (18.54%) and the group with EASIX > 3.16 (34.29%) ($P < 0.05$). Temporal validation in the time-split validation set confirmed higher EASIX in the AKI group ($P < 0.001$) and robust predictive performance (AUC = 0.893, 95% CI: 0.830-0.956), with consistent mortality differences between EASIX subgroups ($P = 0.016$). Conclusion: EASIX holds promise in predicting AKI in hospitalized MM patients, supporting its potential use in risk stratification and clinical decision-making.

Keywords: Endothelial activation and stress index, multiple myeloma, acute kidney injury

Introduction

Multiple myeloma (MM), a prevalent malignancy of the hematopoietic system, often presents with complex and severe complications, among which acute kidney injury (AKI) is particularly prominent, significantly affecting patients' quality of life and prognosis. Among the various mechanisms underlying MM-associated AKI, light-chain cast nephropathy represents the most common cause [1]. Monoclonal free light chains deposit in the distal renal tubules and tubular epithelium, triggering a cascade of pathophysiological events that lead to severe AKI. Early and accurate identification of AKI and its etiology is crucial for developing rational and effective treatment strategies and preventing progression to chronic kidney disease [2]. Current management for light-chain cast nephropathy includes several aggressive rehydration, correction of precipitating factors, and effective anti-plasma cell chemotherapy. Regimens combining the proteasome inhibitor bortezomib with high-dose dexamethasone are widely adopted as first-line treatment options for newly diagnosed patients [3, 4]. However, challenges persist during treatment, including drug resistance, optimization of free light-chain response, and the need for further define the role of emerging agents such as anti-CD38 monoclo-

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nal antibodies. Renal biopsy provides valuable information for guiding treatment decisions and assessing renal prognosis, while kidney transplantation has gradually emerged as a potential option for selected patients [5]. Despite these advances, the occurrence of AKI during hospitalization in MM patients remains common and clinically heterogeneous, making the search for effective predictive markers a clinical focus [6].

The Endothelial Activation and Stress Index (EASIX), calculated using lactate dehydrogenase (LDH), creatinine, and platelet count, is a composite biomarker that reflects endothelial dysfunction and systemic stress [7]. EASIX value has been closely associated with endothelial activation, inflammatory responses, and multiple organ injury. Each component of EASIX has a clear pathophysiological significance: elevated LDH suggests endothelial injury and metabolic disturbances, increased creatinine levels reflect impaired renal function (associated with endothelial dysfunction), and decreased platelet counts are associated with endothelial activation-related complications such as thrombotic microangiopathy [8, 9]. Previous studies have shown that EASIX can predict 28-day mortality in patients with sepsis [10]. In the context of AKI, renal tubular dysfunction caused by endothelial damage and decreased glomerular filtration may be reflected by EASIX. As a low-cost, easily accessible biomarker, EASIX has considerable potential for AKI risk stratification and individualized treatment, assisting clinical optimization of resource allocation and intervention strategies [11, 12].

However, the predictive value of EASIX for predicting AKI in MM patients during hospitalization has not been fully elucidated [13]. Therefore, this study aimed to investigate the utility of EASIX in predicting the occurrence of AKI, with the goal of providing a scientific basis for early risk identification and timely clinical intervention to improve patient outcomes.

Materials and methods

Study participants

A total of 248 patients diagnosed with multiple myeloma (MM), who were admitted to the Department of Hematology, Quzhou Affiliated Hospital of Wenzhou Medical University, between January 2020 and January 2024, were included as the training set. Additionally, 104 MM patients admitted between February 2024 and December 2024 were selected as the validation set. A time-based split was adopted to perform temporal validation rather than independent external validation. All enrolled patients received routine treatment at our hospital, and their clinical data were retrospectively collected from electronic medical records.

Inclusion criteria: (1) Meeting the diagnostic criteria for MM: Clonal bone marrow plasma cells ≥ 10% or biopsy-confirmed bone or extramedullary plasmacytoma, along with at least one myeloma-defining event, including evidence of end-organ damage attributable to plasma cell proliferative disorders (CRAB features): Hypercalcemia (serum calcium levels > 0.25 mmol/L above the upper limit of normal, or > 2.75 mmol/L (> 11 mg/dL)); Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 177 μmol/L (> 2 mg/dL)); Anemia (Hemoglobin > 20 g/L below the lower limit of normal or < 100 g/L); and Bone lesions (one or more osteolytic lesions detected by radiography, computed tomography [CT], or positron emission tomography-computed tomography [PET-CT]). Myeloma-defining biomarkers included any of the following: clonal bone marrow plasma cells ≥ 60%; involved/uninvolved serum free light chains ≥ 100; or > 1 focal lesion detected by magnetic resonance imaging (MRI). Definition of smoldering MM: Serum monoclonal protein (IgG or IgA) ≥ 30 g/L, urinary monoclonal protein ≥ 500 mg/24 h, and/or clonal bone marrow plasma cells accounting for 10%-60%, in the absence of myeloma-defining events or amyloidosis [14]; (2) Newly diagnosed patients; (3) Age ≥ 18 years; and (4) Complete clinical data.

Exclusion criteria: (1) Severe cardiac or hepatic dysfunction; (2) Other hematologic disorders; (3) Coexisting psychiatric disorders or cognitive impairments; (4) A history of primary kidney disease or chronic kidney disease unrelated to MM; (5) Autoimmune diseases or other malignancies; (6) Severe infections, clinically significant dehydration, or other conditions that could independently contribute to AKI. Patients with pre-existing renal diseases unrelated to MM and those with obvious dehydration were ex-

cluded to minimize potential confounding, as these conditions may independently increase the risk of AKI and thereby affect the assessment of the association between EASIX and MM-related AKI.

This study was conducted in accordance with the Declaration of Helsinki (2013) and was approved by the Ethics Committee of The Quzhou Affiliated Hospital of Wenzhou Medical University. Given the retrospective design of this study, all patient data were anonymized and de-identified before analysis, and the requirement for written informed consent was waived by the Ethics Committee.

Research methods

Grouping: In the training set (n = 248), patients were classified into the AKI group (n = 52) and the non-AKI group (n = 196) according to whether they developed AKI during hospitalization. In the validation set (n = 104), patients were likewise classified into the AKI group (n = 22) and non-AKI group (n = 82) using same diagnostic criteria. AKI diagnostic criteria [15, 16]: (1) an increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; or (2) an increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or (3) urine output < 0.5 mL/kg/h for 6 hours.

Data collection: Patient demographic and clinical data were extracted from electronic medical records.

EASIX [17] was calculated as: Lactate Dehydrogenase (LDH; U/L) * Creatinine (Cr; mg /dL)/ Platelet Count (PLT; 10^9/L).

Acute Physiology and Chronic Health Evaluation II (APACHEII) [18] comprises three components: acute physiology score, age score, and chronic health score. Higher scores indicate greater severe of illness and higher risk of mortality.

M protein typing: Immunofixation electrophoresis (IFE) was performed on serum or urine samples. Proteins were separated on agarose gels based on differences in protein charge and molecular weight. The gels were then overlaid with antisera containing antibodies against κ and λ light chains as well as various heavy chains (IgG, IgA, etc.). If the sample contains the corresponding M protein, the antibodies bind to the antigens to form complexes fixed at specific locations, and the gels were visualized as narrow, intense colored bands after staining. The position of the bands allowed determination of the type of light or heavy chain in the M protein.

Data analysis

All statistical analyses were performed using SPSS 27.0 (IBM, USA). The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation (SD), with group comparisons conducted using independent sample t-tests. Non-normally distributed data were represented as MQ2 (Q1, Q3), with calculations performed using the Mann-Whitney U test. Categorical data were presented as counts or percentages, with comparisons made using χ^2 test or Fisher's exact test.

Univariate analyses were initially performed to identify variables associated with the development of AKI in MM patients during hospitalization. Variables with potential clinical or statistical significance were subsequently entered into a multivariate binary logistic regression model to identify independent risk factors for AKI. Prior to multivariate logistic regression, multicollinearity was assessed using the variance inflation factor (VIF). A VIF value > 5 was considered indicative of significant multicollinearity. All variables included in the final model were evaluated for collinearity.

The predictive performance of EASIX for AKI was evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) with corresponding 95% confidence intervals (CIs) was calculated. Survival analysis was performed using the Kaplan-Meier method. Post hoc power analysis was performed using G*Power software (version 3.1.9.7). Based on the observed AUC of 0.897 in the training cohort, a type I error rate (α) of 0.05, and a total sample size of 248 patients (52 AKI cases), the achieved power was 0.96, indicating sufficient statistical power to detect the observed effect. A two-sided *P* value < 0.05 was considered statistically significant.

Table 1. Univariate analysis of factors influencing AKI occurrence in MM patients during hospitalization

Indicator		AKI Group (n = 52)	Non-AKI Group (n = 196)	t/χ^2 Value	*P* Value
Age (years)		56.54±3.14	56.73±3.29	0.398	0.691
Sex	Male	26 (50.00)	101 (51.53)	0.048	0.826
	Female	26 (50.00)	95 (48.47)		
BMI (kg/m^2)		21.54±1.88	21.09±1.73	1.735	0.084
Hypertension	Yes	19 (36.54)	75 (38.27)	0.023	0.880
	No	33 (63.46)	121 (61.73)		
Diabetes	Yes	17 (32.69)	69 (35.20)	0.024	0.878
	No	35 (67.31)	127 (64.80)		
Drug Use	NSAID	18 (34.62)	51 (26.02)	1.532	0.216
	ACEI/ARB	1 (1.92)	6 (3.06)	0.206	0.650
	Diuretics	15 (28.85)	65 (33.16)	0.351	0.554
	Aminoglycosides	2 (3.85)	6 (3.06)	0.087	0.768
	Vancomycin	3 (5.77)	11 (5.61)	0.002	0.965
	Urate-Lowering Therapies	13 (25.00)	57 (29.08)	0.337	0.562
CRP		7.33±2.24	8.01±3.12	1.584	0.114
Hemoglobin		87.54±10.37	89.74±10.57	1.426	0.155
EASIX		6.34±2.05	2.21±0.70	23.590	< 0.001
APACHE II (score)		16.48±4.13	14.84±4.54	2.518	0.012
M Protein Type	IgG Type	22 (42.31)	72 (36.73)	1.340	0.720
	IgA Type	18 (34.62)	63 (32.14)		
	Light Chain Type	7 (13.46)	34 (17.35)		
	Others	5 (9.62)	27 (13.78)		
ISS Staging	I	6 (11.54)	51 (29.08)	9.027	0.011
	II	14 (26.92)	53 (30.10)		
	III	32 (61.54)	72 (40.82)		
Chemotherapy Regimen	VRD	30 (57.69)	79 (40.31)	5.043	0.025
	D-VRD	12 (23.08)	60 (30.61)	1.133	0.287
	VCD	10 (19.23)	57 (29.08)	2.023	0.155

Note: AKI, acute kidney injury; MM, multiple myeloma; BMI, body mass index; CRP, C-reactive protein; EASIX, endothelial activation and stress index; APACHE II, Acute Physiology and Chronic Health Evaluation II; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone; NSAID, nonsteroidal anti-inflammatory drug; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker.

Results

Univariate analysis of factors

In the training cohort, patients in the AKI group had significantly higher EASIX and APACHE II scores than those in non-AKI group (**Table 1**). Additionally, a greater proportion of patients in AKI group were classified as International Staging System (ISS) stage III and received conventional bortezomib, lenalidomide, and dexamethasone (VRD) chemotherapy regimen, compared with the non-AKI group ($P < 0.05$). Other demographic and clinical parameters, including age, sex, BMI, history of hypertension or diabetes, concomitant medications, C-reactive protein (CRP) levels, hemoglobin levels, and M protein type, did not differ notably between groups (all $P > 0.05$).

Binary logistic regression analysis

Variables with statistical significance in the univariate analysis were entered into a binary logistic regression model, with AKI occurrence during hospitalization in MM patients as the dependent variable (AKI = 1, non-AKI = 0). Multivariate logistic regression analysis identi-

Table 2. Variable assignments

Factor	Assignment
EASIX	Original Value
APACHE II	Original Value
ISS Staging	I = 0, II = 1, III = 2
VRD Chemotherapy Regimen	No = 0, Yes = 1

Note: EASIX, endothelial activation and stress index; APACHE II, Acute Physiology and Chronic Health Evaluation II; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone.

fied EASIX, ISS staging, and the VRD chemotherapy regimen AS independent factors influencing AKI development in MM patients during hospitalization ($P < 0.05$, **Tables 2**, **3**).

Collinearity diagnostics revealed that all variables included in the multivariate model had VIF values < 2 (EASIX: 1.23, ISS staging: 1.18, VRD chemotherapy regimen: 1.09), indicating no significant multicollinearity among these predictors.

ROC curve analysis

ROC analysis showed that AUC for EASIX was 0.897 (95% CI: 0.852-0.942). The optimal cutoff value of EASIX, determined by the maximum Youden index (sensitivity + specificity - 1), was 3.16, corresponding to a Youden index of 0.66, with a sensitivity of 94.52% and a specificity of 71.24%. For ISS staging, the AUC was 0.654 (95% CI: 0.575-0.734), with a Youden's index of 0.31, yielding a sensitivity of 52.04% and specificity of 78.85%. Regarding VRD chemotherapy regimen, the AUC was 0.624 (95% CI: 0.540-0.708), with a Youden's index of 0.25, a sensitivity of 55.61% and specificity of 69.23% (**Table 4**; **Figure 1**).

1-year survival analysis stratified by EASIX values

Among the 248 patients, there was no lost follow-ups. The 1-year overall survival rate was 81.46% (95% CI: 75.2%-87.7%) in the EASIX ≤ 3.16 group and 65.71% (95% CI: 55.8%-75.6%) in the EASIX > 3.16 group. The median survival time was not reached in either group during the 12-month follow-up, as the survival probability remained above 50% in both groups. Kaplan-Meier survival analysis showed a significant difference in survival distribution between two groups (Log-rank $\chi^2 = 6.810$, $P = 0.009$), with better survival observed in the EASIX ≤ 3.16 group (**Figure 2**).

Baseline comparability between training set and validation set

As shown in **Table 5**, there were no significant differences between the training set (n = 248) and the validation set (n = 104) regarding all baseline characteristics, indicating good baseline comparability between two temporally split cohorts (all $P > 0.05$).

Time-split validation

EASIX levels were significantly higher in the AKI group compared with the non-AKI group ($P < 0.001$). Notable distinctions were also noted in ISS staging and VRD chemotherapy regimen (both $P < 0.05$), whereas other variables showed no notable differences between two groups (**Table 6**).

As shown in **Table 7**, ROC curve analysis in the validation set demonstrated that EASIX maintained good discriminative ability for predicting AKI during hospitalization in MM patients (AUC: 0.893). For ISS staging and VRD chemotherapy regimen, the AUCs were 0.675 and 0.645, respectively. Compared with training set (EASIX AUC = 0.897), the predictive performance of EASIX remained stable in the validation set, further confirming its robustness and generalizability as a risk predictor for AKI in MM patients. In contrast, the predictive value of ISS stage and the VRD regimen remained limited.

In the validation set, 29 patients had EASIX > 3.16, of whom 11 died (mortality rate of 37.93%). Among 75 patients with EASIX ≤ 3.16, 12 died, corresponding to a mortality rate of 16.00%. The difference in mortality rates between the two groups reached statistical significance ($\chi^2 = 5.84$, $P = 0.016$; **Table 8**), consistent with findings in the training set.

Discussion

This retrospective study investigated the predictive value of EASIX for AKI in MM patients during hospitalization. The results revealed significant differences in EASIX, APACHE II score, ISS staging, and VRD chemotherapy regimens between the AKI and non-AKI groups. Multivariate logistic regression analysis further identified EASIX, ISS staging, and VRD chemothera-

Table 3. Multivariate logistics regression analysis of factors influencing AKI occurrence in MM patients during hospitalization

Factor	β	Standard Error	Wald	P	Exp (β)	95% CI	
						Lower Limit	Upper Limit
EASIX	0.751	0.246	9.318	< 0.001	2.119	1.308	3.432
APACHE II	0.114	0.124	0.848	0.213	1.121	0.879	1.429
ISS Staging	0.704	0.256	7.554	< 0.001	2.021	1.224	3.338
VRD Chemotherapy Regimen	0.560	0.212	6.982	< 0.001	1.751	1.156	2.653

Note: EASIX, endothelial activation and stress index; APACHE II, Acute Physiology and Chronic Health Evaluation II; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone; CI, confidence interval.

Table 4. ROC curve analysis of independent predictors

Indicator	AUC (95% CI)	SE	Youden	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%)	NPV (%)
EASIX	0.897 (0.852-0.942)	0.023	0.66	94.52% (84.6-98.7)	71.24% (64.5-77.4)	46.5	98.1
ISS Staging	0.654 (0.575-0.734)	0.041	0.31	52.04% (38.2-65.6)	78.85% (72.5-84.3)	39.1	86.5
VRD Chemotherapy Regimen	0.624 (0.540-0.708)	0.043	0.25	55.61% (41.8-68.9)	69.23% (62.3-75.6)	32.6	85.2

Note: EASIX, endothelial activation and stress index; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

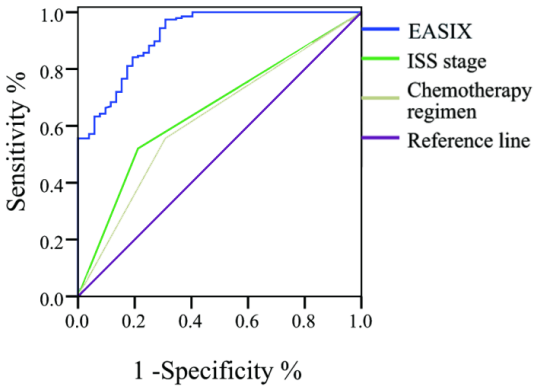

Figure 1. ROC curve analysis for independent predictors for AKI in MM patients. Note: EASIX, endothelial activation and stress index; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone; ROC, receiver operating characteristic; AKI, acute kidney injury; MM, multiple myeloma.

py regimen as independent factors associated with AKI occurrence in MM patients. EASIX exhibited excellent predictive performance, with an AUC of 0.897, a sensitivity of 94.52%, and a specificity of 71.24%. In contrast, the predictive performance of ISS staging and the VRD chemotherapy regimen was relatively limited. Furthermore, patients with EASIX > 3.16 had a significantly higher 1-year mortality rate than those with EASIX ≤ 3.16 (34.29% vs. 18.54%). These findings suggest that EASIX may serve as a valuable biomarker for identifying MM patients at high risk of AKI and adverse clinical outcomes.

The predictive value of EASIX may be attributed to its integration of LDH, creatinine, and platelet counts, which are closely associated with endothelial dysfunction and systemic stress responses [19, 20]. Patients with MM are prone to renal tubular damage and cast obstruction due to factors such as monoclonal immunoglobulin deposition and hypercalcemia, which in turn leads to AKI. Endothelial dysfunction plays a critical role in the pathogenesis of both MM progression and renal injury.

Several interrelated pathophysiological mechanisms may explain the association between elevated EASIX and AKI in MM patients. First, endothelial injury is a common feature of both MM and AKI. Malignant plasma cells produce cytokines and growth factors, including vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α), which promote endothelial activation, increased vascular permeability, and microvascular thrombosis. Elevated LDH reflects endothelial injury and increased cellular turnover, while thrombocytopenia may indicate endothelial activation-related platelet consumption and microangiopathic processes. Second, cast nephropathy - the hallmark of MM-related AKI - is exacerbated by endothelial dysfunction. Injured endothelium impairs tubular perfusion and reduces the clearance of filtered light chains, promoting intratubular cast formation and obstruction [21, 22]. Third, systemic inflammation in MM triggers a cascade of inflammatory mediators (IL-6, IL-1β) that further

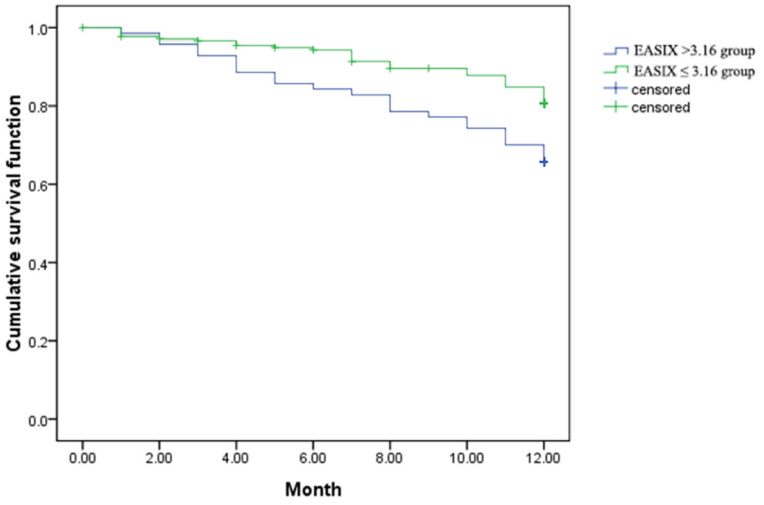

Figure 2. Survival curve analysis of 1-year mortality rate in patients with different EASIX values. Note: Median survival time was not reached in either group within the 12-month follow-up period (survival probability > 50% at 12 months for both groups). EASIX, endothelial activation and stress index. Log Rank (Mantel-Cox): $\chi^2 = 6.810$, $P = 0.009$.

disrupt glomerular endothelial integrity, enhance vascular permeability, and promote tubulointerstitial injury. Because EASIX incorporates both LDH and platelet count, it may partially reflect the inflammatory burden and endothelial activation associated with these pathological processes. Fourth, renal microcirculation disturbance - including vasoconstriction, capillary leakage, and loss of autoregulation - contributes to ischemia-reperfusion injury and amplifies AKI severity. Serum creatinine, a key component of EASIX, directly reflects declining glomerular filtration rate and therefore captures the functional consequences of these microvascular alterations [23]. Collectively, EASIX serves as a composite readout of these interconnected pathways, enabling early risk stratification.

In this study, although APACHE II score differed significantly between groups in univariate analysis, it did not remain an independent predictor in multivariate analysis. This is likely because APACHE II shares variance with EASIX, as both include or correlate with markers of disease severity (e.g., creatinine, LDH). When EASIX is included in the regression model, the unique contribution of APACHE II becomes non-significant, suggesting that EASIX may more specifically capture endothelial dysfunction related to AKI in MM patients. ISS stage and VRD chemotherapy regimen also showed some association with AKI occurrence in MM patients during hospitalization; however, their predictive performance, as indicated by AUC, was lower than that of EASIX. ISS staging stratifies MM patients based on serum levels of β2-microglobulin and albumin, which reflect overall disease burden but provide only indirect information about renal function [24]. Similarly, VRD chemotherapy regimens may affect renal function through nephrotoxic effects or hemodynamic alterations, but these impacts are multifactorial and patient-dependent [25, 26]. In contrast, EASIX directly integrates laboratory markers related to endothelial injury, inflammation, and renal function, thereby demonstrating higher sensitivity and specificity in predicting AKI [27].

Furthermore, this study demonstrated a correlation between elevated EASIX levels and patient mortality rates, with significantly higher mortality rates in the EASIX > 3.16 group compared to the EASIX ≤ 3.16 group. This finding highlights the clinical relevance of EASIX in assessing disease severity in MM patients. AKI is a common complication in MM patients, and in severe cases, it can lead to multiple organ dysfunction syndrome, thereby increasing mortality risk. By predicting the occurrence of AKI, EASIX indirectly reflects overall patient prognosis. Elevated EASIX levels may indicate more severe metabolic disturbances and organ dysfunction, corresponding to higher mortality rates. These findings suggest that EASIX could serve as a practical prognostic marker, aiding in timely interventions to improve patient outcomes [8, 28].

By measuring EASIX levels, clinicians can identify MM patients at high risk of developing AKI during hospitalization at an early stage. For these patients, intensified monitoring of renal function, electrolytes, and acid-base balance can be implemented, allowing for timely adjustments to treatment plans. For instance, in patients receiving nephrotoxic chemotherapy agents, an elevated EASIX level may indicate a

Table 5. Comparison of baseline characteristics between the training and validation sets

Indicator		Training set (n = 248)	Validation set (n = 104)	t/χ^2 Value	*P* Value
Age (years)		56.73±3.28	56.87±3.33	0.362	0.718
Sex	Male	127 (51.21)	54 (51.92)	0.015	0.902
	Female	121 (48.79)	50 (48.08)		
BMI (kg/m^2)		21.18±1.75	21.28±1.80	0.489	0.625
Hypertension	Yes	94 (37.90)	40 (38.46)	0.010	0.921
	No	154 (62.10)	64 (61.54)		
Diabetes	Yes	86 (34.68)	35 (33.65)	0.035	0.852
	No	162 (65.32)	69 (66.35)		
Drug Use	NSAID	69 (27.82)	28 (26.92)	0.031	0.860
	ACEI/ARB	7 (2.82)	3 (2.88)	0.001	0.975
	Diuretics	80 (32.26)	33 (31.73)	0.009	0.924
	Aminoglycosides	8 (3.23)	3 (2.88)	0.030	0.862
	Vancomycin	14 (5.65)	6 (5.77)	0.002	0.964
	Urate-Lowering Therapies	70 (28.23)	31 (29.81)	0.091	0.763
CRP (mg/L)		7.87±2.98	8.00±3.11	0.367	0.714
Hemoglobin (g/L)		89.28±10.55	88.73±10.62	0.440	0.660
EASIX		3.08±1.85	3.16±1.92	0.367	0.714
APACHE II score		15.18±4.53	15.31±4.61	0.244	0.808
M Protein Type	IgG Type	94 (37.90)	39 (37.50)	0.112	0.990
	IgA Type	81 (32.66)	34 (32.69)		
	Light Chain Type	41 (16.53)	17 (16.35)		
	Others	32 (12.90)	14 (13.46)		
ISS Staging	I	57 (22.98)	27 (25.96)	0.442	0.802
	II	67 (27.02)	28 (26.92)		
	III	124 (50.00)	49 (47.12)		
Chemotherapy Regimen	VRD	109 (43.95)	45 (43.27)	0.014	0.905
	D-VRD	72 (29.03)	30 (28.85)	0.001	0.972
	VCD	67 (27.02)	29 (27.88)	0.028	0.867

Note: AKI, acute kidney injury; MM, multiple myeloma; BMI, body mass index; CRP, C-reactive protein; EASIX, endothelial activation and stress index; APACHE II, Acute Physiology and Chronic Health Evaluation II; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone; NSAID, nonsteroidal anti-inflammatory drug; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker.

higher risk of renal injury, prompting consideration of dose reduction or treatment plan modification to reduce the likelihood of AKI occurrence [21, 29]. EASIX not only serves as a predictive marker for AKI but also aids in treatment decision-making [17]. When formulating treatment plans for MM patients, EASIX levels should be considered in addition to disease staging and M protein type. Patients with higher EASIX values warrant cautious selection of chemotherapy agents, prioritizing those with lower nephrotoxicity. Moreover, in supportive care measures such as fluid management and electrolyte correction, dynamic adjustments based on EASIX changes can enhance treatment efficacy and safety. Early detection and intervention for AKI are critical for improving patient prognoses, and the use of EASIX enables timely preventive measures to mitigate the occurrence or severity of AKI, thereby decreasing the risk of multi-organ dysfunction and AKI-related mortality [22, 30]. Furthermore, EASIX can serve as an indicator for evaluating treatment response. Persistently elevated or rising EASIX levels during treatment may indicate poor treatment response, necessitating prompt adjustment of treatment strategies.

It is noteworthy that EASIX demonstrated robust discriminative ability in the time-split

Table 6. Analysis of factors influencing AKI occurrence in mm patients during hospitalization in the validation set

Indicator		AKI Group (n = 22)	Non-AKI Group (n = 82)	t/χ^2 Value	*P* Value
Age (years)		56.72±3.21	56.91±3.35	0.242	0.809
Gender	Male	11 (50.00)	43 (52.44)	0.041	0.839
	Female	11 (50.00)	39 (47.56)		
BMI (kg/m^2)		21.63±1.92	21.18±1.78	1.032	0.305
Hypertension	Yes	8 (36.36)	32 (39.02)	0.052	0.820
	No	14 (63.64)	50 (60.98)		
Diabetes	Yes	7 (31.82)	28 (34.15)	0.042	0.837
	No	15 (68.18)	54 (65.85)		
Drug Use	NSAID	7 (31.82)	21 (25.61)	0.352	0.553
	ACEI/ARB	0 (0.00)	3 (3.66)	0.818	0.366
	Diuretics	6 (27.27)	27 (32.93)	0.258	0.611
	Aminoglycosides	1 (4.55)	2 (2.44)	0.298	0.585
	Vancomycin	1 (4.55)	5 (6.10)	0.077	0.781
	Urate-Lowering Therapies	7 (31.82)	24 (29.27)	0.056	0.813
CRP (mg/L)		7.52±2.31	8.13±3.24	0.819	0.414
Hemoglobin (g/L)		86.93±10.52	89.22±10.68	0.896	0.372
EASIX		6.58±2.19	2.28±0.76	9.045	< 0.001
APACHE II score		16.62±4.25	14.95±4.61	1.536	0.128
M Protein Type	IgG Type	9 (40.91)	30 (36.59)	0.723	0.868
	IgA Type	8 (36.36)	26 (31.71)		
	Light Chain Type	3 (13.64)	14 (17.07)		
	Others	2 (9.09)	12 (14.63)		
ISS Staging	I	2 (9.09)	25 (30.49)	6.368	0.041
	II	7 (31.82)	21 (25.61)		
	III	13 (59.09)	36 (43.90)		
Chemotherapy Regimen	VRD	14 (63.64)	31 (37.80)	4.715	0.030
	D-VRD	4 (18.18)	26 (31.71)	1.546	0.214
	VCD	4 (18.18)	25 (30.49)	1.306	0.253

Note: AKI, acute kidney injury; MM, multiple myeloma; BMI, body mass index; CRP, C-reactive protein; EASIX, endothelial activation and stress index; APACHE II, Acute Physiology and Chronic Health Evaluation II; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone; NSAID, nonsteroidal anti-inflammatory drug; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker.

Table 7. ROC curve analysis of independent predictors in the validation set

Indicator	AUC (95% CI)	SE	Youden	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%)	NPV (%)
EASIX	0.893 (0.830-0.956)	0.032	0.63	90.91% (70.8-98.9)	72.00% (61.1-81.3)	46.5	96.8
ISS staging	0.675 (0.557-0.793)	0.060	0.31	59.09% (36.4-79.3)	72.00% (61.1-81.3)	36.1	86.8
VRD chemotherapy regimen	0.645 (0.523-0.767)	0.062	0.29	63.64% (40.7-82.8)	65.85% (54.8-75.8)	33.3	87.1

Note: EASIX, endothelial activation and stress index; ISS, International Staging System; VRD, bortezomib, lenalidomide, and dexamethasone; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 8. Survival analysis of 1-year mortality rate in patients with different EASIX values in the validation set

Indicator	EASIX > 3.16 (n = 29)	EASIX ≤ 3.16 (n = 75)	t/χ^2 Value	*P* Value
Mortality rate	11(37.93)	12(16.00)	5.84	0.016

Note: EASIX, endothelial activation and stress index.

validation cohort. The association between EASIX > 3.16 and higher 1-year mortality rates was also confirmed in the validation set. These findings indicate that the predictive value of EASIX for AKI is stable across different time periods and patient populations, supporting its potential as a practical bedside tool. However, the validation cohort was derived from a single center and was of moderate size; Multicenter external validation is needed to further confirm these findings.

Several limitations should be acknowledged. First, this was a single-center retrospective study with a relatively limited sample size, which may have introduced selection bias and restricted the generalizability of the findings. Patients with pre-existing renal diseases and clinically significant dehydration were excluded to minimize confounding factors affecting renal function. While this approach improved the internal validity of the analysis, it may limit the generalizability of our conclusions to MM patients with baseline renal impairment or dehydration. Second, the small number of AKI events, particularly in the validation set, may have affected the stability of some estimates. Therefore, our findings should be interpreted with caution and regarded as exploratory. Although post hoc power analysis indicated sufficient statistical power for the primary analysis in the training cohort, future studies should incorporate a priori sample size calculations and larger cohorts to further validate our results. Third, the retrospective nature may have resulted in incomplete or missing clinical data, which could have influenced the accuracy of study results. Fourth, our study did not compare EASIX with established AKI biomarkers, such as cystatin C, NGAL, or KIM-1. It remains unclear whether the simplicity and low cost of EASIX translate into comparable or superior predictive performance relative to these established biomarkers. Future multicenter prospective studies with larger and more diverse patient populations are warranted to validate the predictive value and clinical utility of EASIX in unselected MM populations. Furthermore, mechanistic investigations are needed to clarify the biological links between EASIX, endothelial dysfunction, inflammation, and renal injury in MM. The integration of EASIX with other established biomarkers, including serum creatinine, cystatin C, NGAL, and KIM-1, may facilitate the development of more comprehensive risk prediction models and further improve the accuracy of AKI prediction.

Conclusion

EASIX is a promising predictor of AKI occurrence in hospitalized MM patients. By integrating LDH, serum creatinine, and platelet count, EASIX reflects endothelial dysfunction and systemic stress, both of which are closely associated with renal function. EASIX exhibits robust predictive performance, with high discriminative ability, sensitivity, and specificity for identifying MM patients at risk of AKI. Temporal validation further confirmed the strong discriminative ability of EASIX across different time periods within the study population, supporting its satisfactory generalization ability. Nevertheless, future multicenter prospective studies are warranted to further validate these findings, clarify the underlying biological mechanisms, and establish the clinical utility of EASIX in the management of MM patients.

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Disclosure of conflict of interest

None.

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