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RENAL-METABOLIC RESERVE INDEX FOR CARDIORENAL RISK STRATIFICATION IN CRITICALLY ILL PATIENTS WITH SEPSIS

Hasan Burak İşleyen*[1], Ertuğrul Okuyan[2]

[1]Nisantasi University, Faculty of Medicine, Department of Cardiology, Istanbul, Türkiye.
[2]Istanbul Medipol University, School of Medicine, Department of Cardiology, Istanbul, Türkiye.

ORCID iD: Hasan Burak İşleyen: 0000-0002-4400-9715; Ertuğrul Okuyan: 0000-0002-0626-2939

***Corresponding Author**: Hasan Burak İşleyen **e-mail:** hasanburak.isleyen@nisantasi.edu.tr

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Abstract

Objective: To evaluate whether admission renal-metabolic reserve index (RMRI), defined as (blood urea nitrogen + glucose)/albumin, was associated with in-hospital mortality in ICU patients with sepsis and to compare its prognostic performance against BAR and GAR.

Methods: This retrospective cohort study used MIMIC-IV v3.1. Adults in the first ICU stay who met Sepsis-3 criteria near ICU admission and had blood urea nitrogen, glucose, and albumin measured from 6 hours before to 24 hours after ICU admission were eligible. Patients with end-stage renal disease or chronic dialysis were excluded. The primary outcome was in-hospital mortality. Logistic regression, restricted cubic splines, AUROC analysis, DeLong testing, calibration assessment, subgroup analyses, and sensitivity analyses were performed.

Results: The locked analytic cohort included 5,736 patients, and 1,251 (21.8%) died in hospital. RMRI was higher in non-survivors than survivors (64.7 [47.9-91.7] vs 52.1 [40.3-70.5]). RMRI remained associated with in-hospital mortality after multivariable adjustment (adjusted odds ratio per 1-SD, 1.33; 95% CI, 1.25-1.43; p<0.001). Quartile 4 had an adjusted odds ratio of 2.35 (95% CI, 1.91-2.90; p<0.001) versus quartile 1. Restricted cubic splines showed non-linearity (p=0.001). AUROC increased from 0.723 for the clinical base model to 0.735 after RMRI addition, to 0.729 after GAR addition, and to 0.744 after BAR addition.

Conclusion: Admission RMRI was independently associated with in-hospital mortality and improved discrimination beyond the clinical base model and GAR. BAR remained the strongest comparator.

Keywords: *Hypoalbuminemia, Stress hyperglycemia, Critical illness, Prognosis, Biomarker.*

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Introduction

Sepsis remains a major cause of death in critical care, and the Sepsis-3 framework defines it as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Rapid recognition of high-risk patients remains central to contemporary management because early deterioration is followed by higher organ failure burden and worse short-term outcome.[2]

Albumin-anchored ratios have attracted attention because they combine a routinely available acute biomarker with a marker of nutritional and inflammatory reserve. Blood urea nitrogen-to-albumin ratio (BAR) has been proposed as a mortality marker in critical illness, and related albumin-based ratios such as the C-reactive protein-to-albumin ratio have shown prognostic utility in sepsis.[3,4] A systematic review also supports lactate-to-albumin ratio as a mortality marker in adult sepsis.[5]

Three admission variables are clinically attractive in sepsis. Low albumin reflects capillary leak, inflammation, and catabolic stress.[6] Admission hyperglycemia reflects stress biology and altered host response.[7] Elevated blood urea nitrogen captures renal hypoperfusion, protein breakdown, and impaired clearance.[8]

The renal-metabolic reserve index (RMRI), defined as (blood urea nitrogen + glucose)/albumin, was constructed to summarize these domains in a single composite index. Its clinical value cannot be assumed from its components and should be tested directly against adjacent comparators. This study examined the association between admission RMRI and in-hospital mortality in ICU patients with sepsis, assessed non-linearity, and compared RMRI against BAR and glucose-to-albumin ratio (GAR) within the same analytic framework.

Methods

Study design and data source

This retrospective cohort study used the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1), a de-identified critical care database derived from Beth Israel Deaconess Medical Center admissions.[9] Reporting followed the STROBE and RECORD frameworks for observational studies based on routinely collected health data.[10,11]

Study population

Adults in the first ICU stay were screened. Sepsis was identified with the MIMIC Sepsis-3 concept table. Patients were retained when suspected infection time occurred from 6 hours before to 24 hours after ICU admission and the first valid blood urea nitrogen, glucose, and albumin measurements were all available within the same exposure window. Patients with end-stage renal disease or chronic dialysis were excluded by diagnosis coding. Because biomarker availability defined cohort eligibility, no imputation was performed for the exposure panel.

Ethics

The study used de-identified data from MIMIC-IV. Access to MIMIC-IV requires credentialing and completion of human research protections training. The project was additionally reviewed and approved by the Academic Board of the Department of Cardiology, Bezmialem Vakif University Faculty of Medicine (meeting no. 5, decision no. 1, dated 31 March 2026). Written informed consent was waived because all protected health information had been removed.

Exposure definitions

RMRI was defined as (blood urea nitrogen + glucose)/albumin. BAR was defined as blood urea nitrogen/albumin. GAR was defined as glucose/albumin. All indices were calculated from the first valid laboratory value obtained between 6 hours before and 24 hours after ICU admission. RMRI was analyzed as a continuous variable, a standardized variable per 1-SD, and quartiles. BAR and GAR were analyzed as standardized continuous comparators. Creatinine was extracted in the same time window and reserved for sensitivity adjustment.

Outcome definitions

The primary outcome was in-hospital mortality. Secondary outcomes were ICU mortality and prolonged ICU stay, defined as an ICU length of stay of at least 168 hours. Chronic kidney disease was not defined from admission creatinine because chronicity cannot be inferred from a single acute measurement; therefore, chronic kidney disease was handled as a coded baseline comorbidity in line with KDIGO guidance.[12]

Covariates and subgroup definitions

The prespecified adjustment set included age, sex, admission type group, diabetes, chronic kidney disease, chronic liver disease, heart failure or coronary artery disease, malignancy, vasopressor use within 24 hours, and invasive mechanical ventilation within 24 hours. The Sequential Organ Failure Assessment (SOFA) score was summarized as an illness-severity descriptor and was not included in the primary multivariable adjustment set. Prespecified subgroups were diabetes, chronic kidney disease, albumin below 3.0 g/dL, and glucose at least 180 mg/dL. The glucose threshold matched contemporary inpatient glycemic recommendations for hospitalized adults.[13] ICD-coded diabetic ketoacidosis or hyperosmolar hyperglycemic state was reserved for sensitivity exclusion because recent consensus criteria emphasize biochemical diagnosis rather than diagnosis labels alone.[14]

Statistical analysis

Continuous variables were summarized as median [interquartile range], and categorical variables were summarized as n (%). Group comparisons used the Mann-Whitney U test, chi-square test, or Fisher exact test, as appropriate. Logistic regression models estimated odds ratios (ORs) with 95% confidence intervals. Restricted cubic splines tested non-linearity. Discrimination was assessed with area under the receiver operating characteristic curves and compared with the DeLong method. Calibration was assessed with Brier score and calibration plots. Prespecified subgroup analyses used interaction terms. Sensitivity analyses added creatinine to the multivariable model, excluded diabetic ketoacidosis/hyperosmolar hyperglycemic state, and restricted the cohort to laboratory span of 6 hours or less. No imputation was performed for blood urea nitrogen, glucose, or albumin because availability of the biomarker panel defined cohort eligibility. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, NY, USA). Two-sided $p<0.05$ was considered statistically significant.

Results

Among 65,366 adult first ICU stays, 16,564 met the temporal Sepsis-3 cohort definition. Complete blood urea nitrogen, glucose, and albumin data within the exposure window were available in 6,035 patients. After exclusion of 299 patients with end-stage renal disease or chronic dialysis, the locked analytic cohort included 5,736 patients (Figure 1).

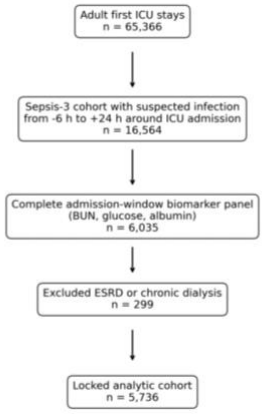


Figure 1. Cohort flow chart. Adult first ICU stays were screened, the Sepsis-3 cohort was aligned to ICU admission time, patients without blood urea nitrogen, glucose, or albumin in the exposure window were excluded, and end-stage renal disease or chronic dialysis was removed before model development.

In-hospital death occurred in 1,251 patients (21.8%). Median age was 66.0 [53.0-78.0] years, 58.2% were male, and median Sequential Organ Failure Assessment score was 3.0 [2.0-5.0]. Non-survivors had higher blood urea nitrogen, glucose, creatinine, BAR, GAR, and RMRI, whereas albumin was lower (Table 1).

Median RMRI was 52.1 [40.3-70.5] in survivors and 64.7 [47.9-91.7] in non-survivors. In-hospital mortality increased across RMRI quartiles from 13.0% in quartile 1 to 18.1% in quartile 2, 22.6% in quartile 3, and 33.6% in quartile 4.

RMRI was associated with in-hospital mortality in the unadjusted model (OR per 1-SD, 1.44; 95% CI, 1.36-1.54; p<0.001) and after multivariable adjustment (OR per 1-SD, 1.33; 95% CI, 1.25-1.43; p<0.001). In the quartile analysis, adjusted risk became evident from quartile 3 onward. Compared with quartile 1, quartile 3 had an adjusted OR of 1.42 (95% CI, 1.15-1.76; p=0.001), and quartile 4 had an adjusted OR of 2.35 (95% CI, 1.91-2.90; p<0.001) (Table 2).

Table 1. Baseline characteristics of survivors and non-survivors.

Variable	All patients	Survivors	Non-survivors	p value
Age, y	66.0 [53.0-78.0]	65.0 [53.0-77.0]	69.0 [57.0-80.0]	<0.001
SOFA score	3.0 [2.0-5.0]	3.0 [2.0-4.0]	4.0 [3.0-6.0]	<0.001
Blood urea nitrogen, mg/dL	23.0 [15.0-39.0]	21.0 [14.0-36.0]	31.0 [19.0-52.0]	<0.001
Glucose, mg/dL	129.0 [104.0-172.0]	128.0 [104.0-166.0]	137.0 [103.5-194.0]	<0.001
Albumin, g/dL	3.0 [2.6-3.5]	3.1 [2.6-3.5]	2.8 [2.3-3.3]	<0.001
Creatinine, mg/dL	1.1 [0.8-1.8]	1.1 [0.8-1.6]	1.4 [0.9-2.3]	<0.001
BAR	7.7 [4.7-14.1]	7.0 [4.4-12.4]	11.9 [6.6-20.4]	<0.001
GAR	44.1 [33.7-60.6]	42.7 [33.1-57.9]	50.0 [36.2-73.0]	<0.001
RMRI	54.5 [41.5-74.9]	52.1 [40.3-70.5]	64.7 [47.9-91.7]	<0.001
Blood urea nitrogen timing from ICU admission, h	1.1 [0.3-3.0]	1.1 [0.3-3.2]	0.9 [0.2-2.4]	<0.001
Glucose timing from ICU admission, h	0.9 [0.2-2.4]	0.9 [0.2-2.6]	0.7 [0.2-1.8]	<0.001
Albumin timing from ICU admission, h	2.0 [0.6-7.5]	2.1 [0.6-7.8]	1.6 [0.5-6.8]	0.002
Laboratory sampling span, h	0.0 [0.0-5.5]	0.0 [0.0-5.7]	0.0 [0.0-5.2]	0.783
Male sex	3338 (58.2)	2620 (58.4)	718 (57.4)	0.538
Diabetes	1633 (28.5)	1286 (28.7)	347 (27.7)	0.540
Chronic kidney disease	1036 (18.1)	790 (17.6)	246 (19.7)	0.104
Chronic liver disease	1282 (22.4)	889 (19.8)	393 (31.4)	<0.001
Heart failure or coronary artery disease	2428 (42.3)	1868 (41.6)	560 (44.8)	0.053
Malignancy	962 (16.8)	671 (15.0)	291 (23.3)	<0.001
Vasopressor within 24 h	2594 (45.2)	1753 (39.1)	841 (67.2)	<0.001
Invasive mechanical ventilation within 24 h	3165 (55.2)	2281 (50.9)	884 (70.7)	<0.001
Albumin <3.0 g/dL	2586 (45.1)	1878 (41.9)	708 (56.6)	<0.001
Glucose >=180 mg/dL	1274 (22.2)	900 (20.1)	374 (29.9)	<0.001
Admission type: urgent/emergent	5047 (88.0)	3922 (87.4)	1125 (89.9)	<0.001
Admission type: elective	243 (4.2)	215 (4.8)	28 (2.2)	
Admission type: other	446 (7.8)	348 (7.8)	98 (7.8)	

Data are presented as median [interquartile range] or n (%). p values were derived from the Mann-Whitney U test, chi-square test, or Fisher exact test, as appropriate. BAR indicates blood urea nitrogen-to-albumin ratio; GAR, glucose-to-albumin ratio; ICU, intensive care unit; RMRI, renal-metabolic reserve index; SOFA, Sequential Organ Failure Assessment.

Restricted cubic splines showed a global RMRI-mortality association (p<0.001) and evidence of non-linearity (p=0.001) (Figure 2).

The curve was relatively flat in the lower range and steepened across the upper RMRI distribution.

AUROC of the clinical base model was 0.723. AUROC increased to 0.735 after RMRI addition, to 0.729 after GAR addition, and to 0.744 after BAR addition. RMRI improved AUROC over the base model (p<0.001) and over GAR (p<0.001), whereas BAR exceeded RMRI (p=0.006). Brier score improved from 0.152 for the base model to 0.150 with RMRI, 0.151 with GAR, and 0.148 with BAR (Table 3, Figure 3).

Subgroup analyses showed a consistent RMRI signal across all prespecified strata. Interaction was significant for diabetes and high glucose, with stronger relative association in patients without diabetes and in patients with glucose below 180 mg/dL. Interaction was not significant for chronic kidney disease or low albumin (Supplementary Table S2, Supplementary Figure S2).

Table 2. Association of RMRI with in-hospital mortality.

Model term	OR (95% CI)	p value
RMRI per 1-SD, unadjusted	1.44 (1.36-1.54)	<0.001
RMRI per 1-SD, adjusted	1.33 (1.25-1.43)	<0.001
RMRI quartile 2 vs quartile 1, adjusted	1.19 (0.96-1.48)	0.110
RMRI quartile 3 vs quartile 1, adjusted	1.42 (1.15-1.76)	<0.001
RMRI quartile 4 vs quartile 1, adjusted	2.35 (1.91-2.90)	<0.001

Adjusted models included age, sex, admission type group, diabetes, chronic kidney disease, chronic liver disease, heart failure or coronary artery disease, malignancy, vasopressor use within 24 hours, and invasive mechanical ventilation within 24 hours. OR indicates odds ratio; CI, confidence interval; RMRI, renal-metabolic reserve index.

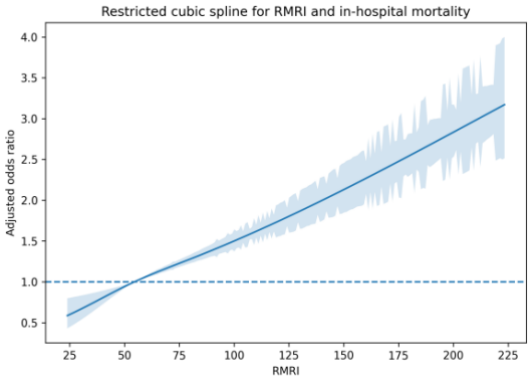


Figure 2. Restricted cubic spline for RMRI and in-hospital mortality. Odds ratios are displayed relative to the cohort median RMRI after multivariable adjustment. Shaded bands indicate 95% confidence intervals.

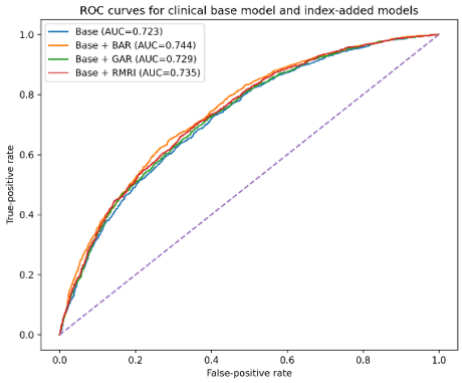


Figure 3. Receiver operating characteristic curves for the clinical base model and the three index-added models. BAR achieved the highest AUROC, RMRI exceeded GAR, and all three index-added models exceeded the base model.

Table 3. Comparative discrimination of the clinical base model, BAR, GAR, and RMRI.

Model	AUROC	Brier score
Clinical base model	0.723	0.152
Base model + BAR	0.744	0.148
Base model + GAR	0.729	0.151
Base model + RMRI	0.735	0.150
DeLong AUROC comparisons.		
Comparison	**p value**	
Base + RMRI vs clinical base model	<0.001	
Base + BAR vs clinical base model	<0.001	
Base + GAR vs clinical base model	<0.001	
Base + RMRI vs base + GAR	<0.001	
Base + RMRI vs base + BAR	0.006	
Base + BAR vs base + GAR	<0.001	

The clinical base model included age, sex, admission type group, diabetes, chronic kidney disease, chronic liver disease, heart failure or coronary artery disease, malignancy, vasopressor use within 24 hours, and invasive mechanical ventilation within 24 hours. Calibration plots are shown in Supplementary Figure S1. AUROC indicates area under the receiver operating characteristic curve; BAR, blood urea nitrogen-to-albumin ratio; GAR, glucose-to-albumin ratio; RMRI, renal-metabolic reserve index.

Sensitivity analyses were directionally stable. RMRI remained associated with mortality after additional creatinine adjustment (OR, 1.29; 95% CI, 1.21-1.38; p<0.001), after exclusion of diabetic ketoacidosis/hyperosmolar hyperglycemic state (OR, 1.42; 95% CI, 1.31-1.53; p<0.001), and after restriction to a laboratory sampling span of 6 hours or less (OR, 1.41; 95% CI, 1.30-1.53; p<0.001). Exploratory mutual-challenge models suggested that RMRI retained signal beyond GAR and BAR, although these models were interpreted cautiously because RMRI correlated strongly with GAR (r = 0.969) (Supplementary Tables S3-S4).

Discussion

Admission RMRI was independently associated with in-hospital mortality in this locked sepsis ICU cohort. Mortality increased across RMRI quartiles, and the spline analysis showed that risk acceleration was concentrated in the upper range of the distribution. RMRI improved discrimination beyond the clinical base model and outperformed GAR, whereas BAR remained the strongest single comparator.

The BAR comparison defines the boundary of the present claim. Prior sepsis-specific BAR studies have shown robust associations between higher BAR and worse short-term outcomes in ICU patients with sepsis.[15,16] The current data agree with that literature and indicate that RMRI should not

be presented as a replacement benchmark. Its practical role is more limited: RMRI may provide an adjunctive view of renal-metabolic reserve when glucose burden is clinically relevant, whereas BAR remains the stronger comparator for discrimination in this cohort.The GAR comparison was more favorable to RMRI. Recent sepsis analyses have linked GAR to short-term and medium-term mortality, yet the signal has varied across adjustment sets and outcome horizons.[17,18] In the present cohort, RMRI produced higher discrimination than GAR when both were added separately to the same clinical base model.

Albumin still anchors the biological interpretation of RMRI. Low albumin reflects capillary leak, impaired hepatic synthesis, inflammation, and catabolic stress, whereas the renal component captures perfusion and clearance failure.[19,20] RMRI may therefore summarize cardiorenal-metabolic stress more broadly than GAR alone.

The subgroup pattern adds context. Relative RMRI effect size was stronger in patients without diabetes and in those with glucose below 180 mg/dL. Similar context-dependent behavior has been described for stress hyperglycemia indices in sepsis, where risk is not uniform across glycemic strata.[21,22] The present data support the same interpretation.

Albumin-based composite ratios continue to expand across critical care. Prognostic associations have also been reported for serum albumin-creatinine ratio and BAR in sepsis-associated acute kidney injury.[23,24] RMRI belongs to this same family, but its value lies in comparative testing rather than score invention.

This study has limitations. The design was retrospective and single-center. Exposure availability depended heavily on albumin measurement, which selected a sicker complete-case biomarker cohort and limits transportability to all ICU patients with sepsis. Residual confounding remains possible despite prespecification of the adjustment set. Strong correlation between RMRI and GAR complicates mechanistic separation of the metabolic component. Laboratory timing variability may have affected exposure classification, particularly because albumin timing was broader than glucose and blood urea nitrogen timing in some patients. Serial change was not modeled, even though albumin trajectory itself carries prognostic information in sepsis.[25] The next step should be external validation in independent sepsis cohorts with harmonized laboratory timing and direct comparison against parsimonious clinical models.

Conclusion

Admission RMRI was independently associated with in-hospital mortality in critically ill patients with sepsis, showed a non-linear risk pattern, and improved discrimination beyond the clinical base model and GAR. BAR remained the strongest comparator, which places RMRI as an adjunctive prognostic index rather than a replacement benchmark.

Ethics Committee Approval

This study used de-identified data from the Medical Information Mart for Intensive Care IV database. Access to the database requires credentialing and completion of human research protections training. The project was additionally reviewed and approved by the Academic Board of the Department of Cardiology, Bezmialem Vakif University Faculty of Medicine (meeting no. 5, decision no. 1, 31 March 2026). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent

Written informed consent was waived because all protected health information had been removed from the de-identified database.

Author Contributions

H.B.İ., E.O.: Concept and design; Data acquisition and cohort construction. Statistical planning, analysis interpretation; methodological review; Literature Review; Critical revision and final approval; H.B.İ.: Drafting of the manuscript.

Declaration of Interests

The authors have no conflicts of interest to declare.

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No specific funding was received for this work.

Data Availability

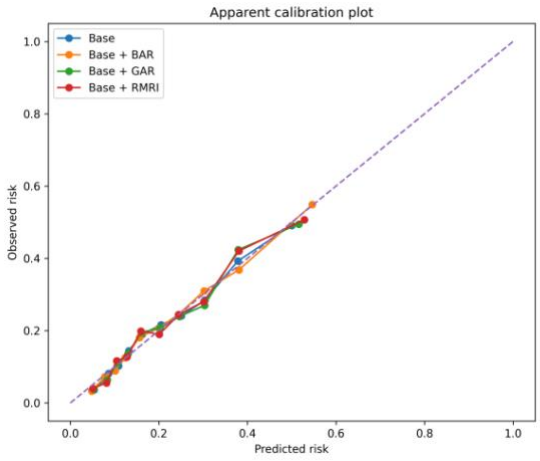
The data analyzed in this study were obtained from MIMIC-IV (version 3.1), a publicly available but credentialed critical care database hosted on PhysioNet. Access to raw data requires completion of the required training and approval through PhysioNet. The analytic dataset generated for this study is available from the corresponding author upon reasonable request.

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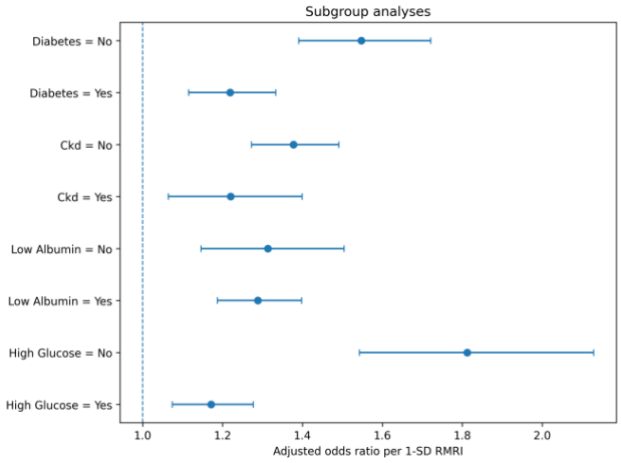
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Supplementary Results



Supplementary Figure S1. Apparent calibration plots for the clinical base model and index-added models.



Supplementary Figure S2. Forest plot of prespecified subgroup analyses for RMRI and in-hospital mortality.

Supplementary Table S1a. Cohort assembly and data completeness.

Cohort stage	n
Adult first ICU stays	65,366
Temporal Sepsis-3 cohort	16,564
Complete admission-window BUN, glucose, and albumin	6,035
Excluded ESRD or chronic dialysis	299
Locked analytic cohort	5,736

The locked analytic cohort was defined by complete availability of admission-window blood urea nitrogen, glucose, and albumin, followed by exclusion of end-stage renal disease or chronic dialysis.

Supplementary Table S1b. Mortality by albumin availability and complete-trio status.

Group	n	Deaths	Mortality (%)
Albumin available	6,044	1,320	21.8
Albumin missing	10,520	1,276	12.1
Complete biomarker trio	6,035	1,319	21.9
Incomplete biomarker trio	10,529	1,277	12.1

These values show that biomarker availability defined a sicker analytic subset. No imputation was performed for the exposure panel.

Supplementary Table S2. Prespecified subgroup analyses.

Subgroup	Level	n	Deaths	OR (95% CI)	P value	P interaction
Diabetes	No	4103	904	1.55 (1.39-1.72)	<0.001	<0.001
Diabetes	Yes	1633	347	1.22 (1.11-1.33)	<0.001	<0.001
Chronic kidney disease	No	4700	1005	1.38 (1.27-1.49)	<0.001	0.086
Chronic kidney disease	Yes	1036	246	1.22 (1.06-1.40)	0.004	0.086
Albumin <3.0 g/dL	No	3150	543	1.31 (1.15-1.50)	<0.001	0.799
Albumin <3.0 g/dL	Yes	2586	708	1.29 (1.19-1.40)	<0.001	0.799
Glucose >=180 mg/dL	No	4462	877	1.81 (1.54-2.13)	<0.001	<0.001
Glucose >=180 mg/dL	Yes	1274	374	1.17 (1.07-1.28)	<0.001	<0.001

Odds ratios represent the adjusted association of RMRI per 1-SD with in-hospital mortality within each subgroup. Interaction terms were tested in the full cohort.

Supplementary Table S3a. Sensitivity and exploratory mutual-challenge analyses.

Sensitivity analysis	n	Deaths	OR (95% CI)	P value
Creatinine-adjusted model	5735	1251	1.29 (1.21-1.38)	<0.001
Exclusion of DKA/HHS	5613	1232	1.42 (1.31-1.53)	<0.001
Laboratory span <=6 h	4396	975	1.41 (1.30-1.53)	<0.001

Sensitivity analyses tested robustness of the RMRI signal in prespecified alternative models.

Supplementary Table S3b. Exploratory mutual-challenge analyses.

Exploratory model	RMRI OR (95% CI)	Likelihood ratio P
Add RMRI beyond GAR	4.15 (3.16-5.44)	<0.001
Add RMRI beyond BAR	1.19 (1.11-1.28)	<0.001

Mutual-challenge models were interpreted cautiously because RMRI and GAR were strongly correlated.

Supplementary Table S4a. Correlation structure of RMRI and related biomarkers.

Correlation pair	Pearson r
RMRI with BUN	0.30
RMRI with glucose	0.83
RMRI with albumin	-0.39
RMRI with BAR	0.40
RMRI with GAR	0.97

Pearson correlation coefficients were derived from the locked analytic cohort.

Supplementary Table S4b. Variance inflation factors.

Covariate	VIF
C(admission_type_group)[T.urgent_emergent]	2.68
C(admission_type_group)[T.other]	2.67
age	1.29
heart_failure_or_cad_flag	1.24
invasive_mechanical_ventilation_24h	1.24
vasopressor_use_24h	1.21
ckd_flag	1.15
diabetes_flag	1.08
chronic_liver_disease_flag	1.06
malignancy_flag	1.05
male	1.02

All variance inflation factors in the prespecified adjustment set remained below 3.0.