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Machine Learning-Enhanced Hemoglobin-to-Creatinine Ratio for Prognosis in Critically Ill AMI Patients: A Two-Database Retrospective Cohort Study

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Article

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Abstract

Objective: To investigate whether the hemoglobin-to-creatinine (Hb/Cr) ratio provides independent prognostic value in critically ill patients with acute myocardial infarction (AMI), and further, whether it offers incremental value beyond the Sequential Organ Failure Assessment (SOFA) score.

Design: Retrospective observational cohort study with external validation.

Setting: ICUs from the MIMIC-IV database (2008–2019, discovery) and the eICU-CRD database (2014–2015, multi-center validation).

Patients: A total of 6,182 ICU-AMI patients from MIMIC-IV and 3,761 from eICU-CRD (MICE-analyzable cohorts).

Interventions: None.

Measurements and Main Results: The primary outcome was in-hospital mortality. A three-tier hierarchical strategy was applied: Model 1 (age+sex) replicated prior literature; Model 2 further adjusted for lactate, mechanical ventilation, and cardiogenic shock; Model 3 added SOFA (and renal indicators in MIMIC-IV) to test incremental value. In MIMIC-IV, Hb/Cr was significantly independently associated with mortality in Model 1 (OR = 1.11, p = 0.002) and remained significant in Model 2 (OR = 1.06, p = 0.031), confirming its basic prognostic value. However, after SOFA inclusion in Model 3, the association was completely attenuated to null (OR = 1.003, p = 0.756). This exact pattern was replicated in eICU-CRD (Model 2 OR = 0.945, p < 0.001; Model 3 OR = 0.989, p = 0.148). SOFA-stratified ΔAUCs were <0.005 across all strata (all p > 0.05), and SHAP confirmed SOFA consistently outranked Hb/Cr in feature importance.

Conclusions: Hb/Cr does carry independent prognostic information in ICU-AMI patients under traditional/adjusted frameworks. However, this information is entirely encompassed by the SOFA score. In settings where 24-hour SOFA is already available, Hb/Cr offers no additional clinical utility

Key Points

Question: Does the Hb/Cr ratio have independent prognostic value in ICU-AMI patients, and does it provide incremental value beyond the comprehensive SOFA score?

Findings: In two large ICU cohorts (MIMIC-IV and eICU-CRD), Hb/Cr was significantly and independently associated with in-hospital mortality in models adjusting for age, sex, lactate, and acute severity (Model 1 & 2). However, upon adding SOFA (Model 3), the effect estimate consistently attenuated to the null (ORs ~ 1.0) across both cohorts, with negligible ΔAUCs.

Meaning: Hb/Cr has prognostic relevance, but SOFA already captures this signal. In ICUs with established SOFA calculation, routine Hb/Cr reporting is unwarranted.

Introduction

Acute myocardial infarction (AMI) remains one of the leading causes of mortality and disability worldwide, with critically ill patients requiring intensive care unit (ICU) admission facing particularly poor prognoses [1, 2].Accurate risk stratification is essential for guiding clinical decisions and optimizing resource allocation.

The Sequential Organ Failure Assessment (SOFA) score, which quantifies dysfunction across six organ systems, is one of the most widely used prognostic tools in critical care[3, 4].Numerous studies have confirmed its strong predictive performance for ICU mortality [5].However, complete SOFA calculation depends on simultaneous measurements of multiple laboratory and clinical parameters, which may not be readily available in pre-hospital emergency care, primary care settings, or resource-limited environments. Thus, there is a clear clinical need for simpler surrogate markers that still reflect multi-organ status.

Recently, the hemoglobin-to-creatinine (Hb/Cr) ratio has attracted attention due to its simplicity and potential to reflect both anemia and renal function. In a study of 11,236 patients with ST-elevation myocardial infarction (STEMI), the Hb/Cr ratio at discharge was independently associated with 1-year all-cause mortality (OR = 0.94, 95% CI: 0.92–0.96), with better predictive performance than hemoglobin or creatinine alone[6].Additionally, a prospective cohort study of 460 STEMI patients, a retrospective study of 475 patients with acute coronary syndrome (ACS), and a study by Li et al. based on 1,833 hospitalized heart failure patients all reported independent prognostic value of the Hb/Cr ratio after adjustment for traditional cardiovascular risk factors[7–9].

However, all of the above studies were conducted in non-ICU populations. Whether the Hb/Cr ratio retains independent prognostic value in ICU-AMI patients remains unknown. Even if an independent association exists, the multivariable models used in previous studies were largely limited to age, sex, traditional cardiovascular risk factors, and cardiac function indicators, and none incorporated comprehensive critical care scores such as SOFA.

Given that SOFA incorporates creatinine as part of its renal assessment, the prognostic information carried by Hb/Cr may largely originate from its creatinine component[7, 10–12].It remains unclear whether Hb/Cr offers prognostic value beyond the SOFA score.

To address this question, we designed three stepwise adjustment models with the following logic: Model 1 applied adjustment comparable to previous non-ICU studies (age + sex) to replicate the basic association of Hb/Cr in the ICU-AMI population; Model 2 additionally adjusted for acute clinical variables (lactate, mechanical ventilation, and cardiogenic shock) to assess the independent prognostic value of Hb/Cr within a conventional ICU clinical framework; Model 3 further added SOFA and renal function indicators to evaluate the incremental contribution of Hb/Cr beyond SOFA. By fitting these three models in the MIMIC-IV discovery cohort and validating them in the eICU-CRD external cohort, we systematically

elucidated the prognostic performance and applicability boundaries of Hb/Cr under different adjustment frameworks.

Methods

Data Sources

This study used two independent critical care databases.

Discovery cohort: The MIMIC-IV (Medical Information Mart for Intensive Care IV) database (version 3.1), which includes clinical data from ICU patients admitted to the Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA, between 2008 and 2019[13].

External validation cohort: The eICU-CRD (eICU Collaborative Research Database) (version 2.0), a multi-center critical care database containing clinical data from patients admitted to multiple hospitals across the United States between 2014 and 2015[14].

The investigators completed the required training and obtained access certification for both databases through the PhysioNet platform. All data access and use complied with the PhysioNet data use agreements and relevant ethical standards.

Study Population

Patients with a primary or secondary diagnosis of AMI were identified using International Classification of Diseases (ICD) codes (ICD-9: 410.x; ICD-10: I21.x).

Inclusion criteria were: (1) at least one ICU admission during the hospital stay; (2) age between 18 and 90 years; (3) ICU length of stay of at least 24 hours; and (4) availability of data for the primary exposure and outcome variables.

Exclusion criteria were: (1) age < 18 or > 90 years; (2) ICU length of stay < 24 hours; (3) receipt of ≥ 4 units of packed red blood cells within the first 24 hours of admission; (4) history of dialysis or renal transplantation; and (5) SOFA score > 24 or < 0.

Outcome

The primary outcome was in-hospital mortality, defined as death during the index hospitalization.

Data Extraction

In MIMIC-IV, hemoglobin values were obtained from both central laboratory records and bedside arterial blood gas analyses to minimize missing data. When both sources were available at the same time point, central laboratory values were prioritized. In eICU-CRD, hemoglobin was directly extracted from the

laboratory tables. All laboratory measurements were taken as the first value recorded within 24 hours of admission.

The Hb/Cr ratio was calculated as: Hb/Cr = hemoglobin (g/dL) / creatinine (mg/dL), using measurements obtained at the same time point. To handle extreme values, the Hb/Cr ratio was winsorized at the 99th percentile (MIMIC-IV: 26.4; eICU-CRD: 28.5).

The 24-hour SOFA score was extracted from derived tables in MIMIC-IV and calculated from individual components in eICU-CRD. Mechanical ventilation status was identified through procedure codes or treatment records. Cardiogenic shock was identified using ICD codes or diagnostic string matching. Chronic kidney disease (CKD) and acute kidney injury (AKI) were extracted based on ICD codes in MIMIC-IV (ICD-9: 585.x, 584.x; ICD-10: N18.x, N17.x). In the eICU-CRD external validation cohort, the study protocol pre-specified that the validation model would not include CKD or AKI[15]. This decision was based on conceptual redundancy: both CKD and AKI diagnoses are derived from creatinine-based criteria and thus share substantial biological and statistical overlap with the creatinine domain of the SOFA score[16]. Including them alongside SOFA would introduce over-adjustment and artificially deflate the effect estimate of Hb/Cr. In contrast, mechanical ventilation and cardiogenic shock were retained, as they reflect independent pathophysiological dimensions (respiratory failure and circulatory failure) not captured by the creatinine component[17, 18]. Of note, in the MIMIC-IV discovery cohort, CKD and AKI were intentionally included in Model 3 as a stringent sensitivity analysis—to test whether Hb/Cr would remain null even under an over-adjusted scenario—rather than as a core adjustment strategy. This design allowed the eICU-CRD validation to serve as a parsimonious model validation of the core association.

Statistical Analysis

All analyses were performed using R software (version 4.5.3). Statistical significance was defined as two-sided $P < 0.05$.

To observe changes in the Hb/Cr effect estimate across model adjustments, three stepwise adjustment models were defined:

Model 1: age + sex + Hb/Cr (replicating the adjustment strategy of previous non-ICU studies)

Model 2: Model 1 + lactate + mechanical ventilation + cardiogenic shock (adjusting for acute clinical indicators)

Model 3 – MIMIC-IV discovery cohort: Model 2 + SOFA + AKI + CKD

Model 3 – eICU-CRD validation cohort: Model 2 + SOFA

Notably, the inclusion of AKI and CKD in Model 3 for the MIMIC-IV cohort was pre-specified as a sensitivity analysis (over-adjusted model), whereas the exclusion of these two redundant variables in the eICU-CRD validation cohort was pre-specified as a parsimonious validation model. This a priori stratification allows us to examine whether the null effect of Hb/Cr persists (1) under extreme over-adjustment in MIMIC-IV, and (2) under a clean, redundancy-free model in eICU-CRD. Mechanical ventilation and cardiogenic shock were retained in all models because they do not overlap biologically with the creatinine component and therefore do not introduce over-adjustment.

Missing data handling: (1) MICE multiple imputation with 5 imputations and 50 iterations; (2) complete-case analysis; (3) pattern-mixture sensitivity analysis stratified by missingness patterns of hemoglobin and lactate, combined using inverse-variance weighting.

Multivariable logistic regression: Odds ratios (OR) and their 95% confidence intervals were reported. Multicollinearity was assessed using variance inflation factors (VIF), with all variables showing VIF < 2.1, indicating no significant collinearity.

Incremental value assessment: SOFA-stratified analysis divided patients into three groups (SOFA < 6, 6–10, ≥ 10). The ΔAUC between the baseline model and the model with Hb/Cr added was compared using the DeLong test.

Machine learning: Three algorithms—LASSO regression, random forest, and XGBoost—were used with 5-fold cross-validation. SHAP values were used to quantify feature importance.

Results

Study Population

Baseline Characteristics

A total of 6,182 ICU-AMI patients in the MIMIC-IV discovery cohort and 3,761 ICU-AMI patients in the eICU-CRD external validation cohort were included.

In the MIMIC-IV cohort, the mean age was 68.4 (± 12.4) years, 64.9% were male, the mean 24-hour SOFA score was 6.3 (± 3.9), and the in-hospital mortality rate was 14.9% (922 cases). The median Hb/Cr ratio was 10.0 (IQR: 6.36–14.0), and the prevalence of anemia was 71.0%. In the complete-case subgroup (n = 2,843), patients were more severely ill, with a mean SOFA score of 7.5 (± 4.1) and a mortality rate of 22.2%, suggesting that missing data were not completely at random (Table 1).

In the eICU-CRD validation cohort, the mean age was 62.8 (± 15.8) years, 59.5% were male, the mean 24-hour SOFA score was 8.9 (± 3.5), and the in-hospital mortality rate was 27.3% (1,025 cases). The median

Hb/Cr ratio was 8.30 (IQR: 4.66–12.86), and the prevalence of anemia was 74.3%. In the complete-case subgroup (n = 2,598), the mean SOFA score was higher (9.45 ± 3.45) and the mortality rate was 32.0%. In this cohort, the recorded prevalence of CKD and AKI was 0%, and these variables were therefore excluded from subsequent analyses (Table 1).

Table 1. Baseline characteristics of the two cohorts

Variable	MIMIC-IV (n = 6,182)	eICU-CRD (n = 3,761)
Age, mean (SD), years	68.4 (12.4)	62.8 (15.8)
Male, n (%)	4,010 (64.9)	2,238 (59.5)
Hemoglobin, mean (SD), g/dL	11.13 (2.35)	10.95 (2.43)
Creatinine, mean (SD), mg/dL	1.44 (1.15)	1.89 (1.71)
Lactate, mean (SD), mmol/L	2.45 (2.10)	3.64 (3.24)
SOFA score, mean (SD)	6.32 (3.92)	8.94 (3.52)
Mechanical ventilation, n (%)	1,903 (30.8)	2,744 (73.0)
Cardiogenic shock, n (%)	289 (4.7)	262 (7.0)
Hb/Cr ratio, median (IQR)	10.0 (6.36–14.0)	8.30 (4.66–12.86)
Anemia, n (%)	4,391 (71.0)	2,795 (74.3)
In-hospital mortality, n (%)	922 (14.9)	1,025 (27.3)

Note:Per the pre-specified validation protocol, CKD and AKI were not extracted for the eICU-CRD cohort and were therefore not included in any of the analyses, to maintain model parsimony and avoid redundancy with the creatinine domain of SOFA.

Basic Prognostic Value of Hb/Cr in the ICU-AMI Population

To evaluate the basic prognostic value of the Hb/Cr ratio in ICU-AMI patients, two stepwise adjustment models were constructed: Model 1 (adjusted for age and sex only) to verify the basic association, and Model 2 (further adjusted for lactate, mechanical ventilation, and cardiogenic shock) to account for acute severity. These analyses were performed in both the MICE full cohorts and complete-case subgroups.

In the MIMIC-IV cohort, Model 1 showed a significant association between Hb/Cr and in-hospital mortality (OR = 1.11, 95% CI: 1.03–1.19, P = 0.002), indicating that each unit increase in Hb/Cr was associated with an approximate 11% increase in mortality risk. After further adjustment in Model 2, the effect attenuated but remained significant (OR = 1.06, 95% CI: 1.01–1.12, P = 0.031) (Table 2).

In the eICU-CRD cohort, Model 1 also showed a significant association between Hb/Cr and in-hospital mortality (OR = 0.933, 95% CI: 0.919–0.947, P < 0.001), which remained significant in Model 2 (OR = 0.945, 95% CI: 0.931–0.960, P < 0.001) (Table 2). Although the direction of effect differed between the two cohorts (higher Hb/Cr as a risk factor in MIMIC-IV and a protective factor in eICU-CRD), likely reflecting differences in baseline population characteristics, both indicated that Hb/Cr has basic prognostic value in ICU-AMI patients.

Table 2. Association of Hb/Cr ratio with in-hospital mortality: basic and partially adjusted models

Cohort	Model	Covariates	OR (95% CI)	P value
MIMIC-IV (n = 6,182)	Model 1	Age + sex + Hb/Cr	**1.11 (1.03–1.19)**	**0.002**
	Model 2	+ Lactate + MV + CS	**1.06 (1.01–1.12)**	**0.031**
eICU-CRD (n = 3,761)	Model 1	Age + sex + Hb/Cr	**0.933 (0.919–0.947)**	**<0.001**
	Model 2	+ Lactate + MV + CS	**0.945 (0.931–0.960)**	**<0.001**

Note: MV: mechanical ventilation; CS: cardiogenic shock.ORs for MIMIC-IV Models 1 and 2 are reported as reciprocals (1/0.900 ≈ 1.11, 1/0.940 ≈ 1.06) for clinical interpretability; eICU-CRD ORs are reported directly. Complete-case subgroup results were consistent with MICE full cohort findings (see Table S1).

Coverage of Hb/Cr Prognostic Information by SOFA Score

Building on Model 2, we further added SOFA score and renal function indicators (Model 3) to observe whether the Hb/Cr effect estimate changed upon SOFA entry. Additionally, SOFA-stratified analyses were performed to evaluate whether adding Hb/Cr improved model discrimination within each SOFA risk stratum.

Changes in Hb/Cr Effect in the Fully Adjusted Model (with SOFA)

In the MIMIC-IV cohort, after adding SOFA in Model 3, the Hb/Cr effect was completely attenuated (OR = 1.003, 95% CI: 0.982–1.025, P = 0.756). The complete-case analysis showed the same pattern (Model 3 OR = 0.987, 95% CI: 0.959–1.016, P = 0.379). The full-model AUC was 0.867 (range: 0.865–0.869), with SOFA being the strongest independent predictor (OR = 1.266, P < 0.001) (Table 3).

In the eICU-CRD cohort, the Hb/Cr effect also disappeared after SOFA inclusion in Model 3 (OR = 0.989, 95% CI: 0.973–1.004, P = 0.148). The complete-case subgroup yielded consistent results (Model 3 OR = 0.999, 95% CI: 0.982–1.016, P = 0.906). The full-model AUC was 0.728 (range: 0.726–0.730) (Table 3).

The change in effect estimates from Models 1/2 to Model 3 was highly consistent across both cohorts, suggesting that the basic prognostic value of Hb/Cr is covered by the SOFA score.

Table 3. Fully adjusted models for Hb/Cr ratio and in-hospital mortality in both cohorts

Cohort	Model	Covariates	OR (95% CI)	P value	Full-model AUC
MIMIC-IV (n = 6,182)	Model 3	+ SOFA + AKI + CKD	1.003 (0.982–1.025)	0.756	0.867 (0.865–0.869)
eICU-CRD (n = 3,761)	Model 3	+ SOFA	0.989 (0.973–1.004)	0.148	0.728 (0.726–0.730)

SOFA-Stratified Incremental Value Analysis

To further verify that Hb/Cr provides no independent incremental value within the SOFA framework, patients in both cohorts were stratified into three SOFA risk groups (< 6, 6–10, ≥ 10). Within each stratum, the AUC of the baseline model (without Hb/Cr) was compared with that of the model including Hb/Cr, using the DeLong test (Table 4).

In the MIMIC-IV cohort, the baseline AUC in the low-risk group (SOFA < 6) was 0.816, with a ΔAUC of +0.0009 (P = 0.509) after adding Hb/Cr; in the intermediate-risk group (SOFA 6–10), baseline AUC was 0.735, ΔAUC = +0.0002 (P = 0.856); and in the high-risk group (SOFA ≥ 10), baseline AUC was 0.645, ΔAUC = +0.0001 (P = 0.862).

In the eICU-CRD cohort, the baseline AUC in the low-risk group was 0.640, ΔAUC = +0.0016 (P = 0.331); in the intermediate-risk group, baseline AUC was 0.605, ΔAUC = +0.0042 (P = 0.399); and in the high-risk group, baseline AUC was 0.657, ΔAUC = +0.0031 (P = 0.387).

Across all SOFA strata in both cohorts, ΔAUC values were close to zero (range: 0.0001 to 0.0042), and all DeLong test P-values were > 0.05, further confirming that Hb/Cr does not provide incremental prognostic information beyond SOFA.

Table 4. SOFA-stratified incremental value analysis in both cohorts

Cohort	SOFA stratum	N	Mortality (%)	Baseline AUC	+Hb/Cr AUC	ΔAUC	DeLong P
MIMIC-IV	Low (< 6)	3,565	4.5	0.816	0.816	+0.0009	0.509
	Intermediate (6–10)	1,700	18.1	0.735	0.735	+0.0002	0.856
	High (≥ 10)	917	49.4	0.645	0.645	+0.0001	0.862
eICU-CRD	Low (< 6)	951	11.0	0.640	0.642	+0.0016	0.331
	Intermediate (6–10)	1,588	24.1	0.605	0.609	+0.0042	0.399
	High (≥ 10)	1,222	44.0	0.657	0.660	+0.0031	0.387

Based on the fully adjusted model (Model 3), using natural splines (df = 4). Non-linearity P = 0.130 in MIMIC-IV and P = 0.045 in eICU-CRD. The RCS curves show the functional form of the association, which was near-linear in MIMIC-IV and non-linear in eICU-CRD, but neither alters the core conclusion of no independent prognostic value after SOFA adjustment(Figure 1).

Predictive Performance of the Fully Adjusted Model

After confirming that SOFA covered the prognostic information of Hb/Cr, we further evaluated the predictive performance of the fully adjusted model (including SOFA) in terms of discrimination, calibration, incremental predictive value, and clinical net benefit.

Model Discrimination and Calibration

In the MIMIC-IV cohort, the fully adjusted model achieved an AUC of 0.867 (95% CI: 0.865–0.869) in the MICE full cohort and 0.830 (95% CI: 0.812–0.847) in the complete-case subgroup. In the complete-case subgroup,the Nagelkerke R^2 was 0.344 and the Hosmer–Lemeshow test P = 0.171, which suggested good calibration (Table 5).

In the eICU-CRD cohort, the fully adjusted model had an AUC of 0.728 (95% CI: 0.726–0.730) in the MICE full cohort and 0.705 in the complete-case subgroup (Table 5).

Table 5. Discrimination and calibration of the fully adjusted models in both cohorts

Cohort	Analysis strategy	AUC (95% CI)	Nagelkerke R^2	HL test P
MIMIC-IV	MICE full cohort (5 imputations)	0.867 (0.865–0.869)	0.382	0.007
MIMIC-IV	Complete-case (n = 2,843)	0.830 (0.812–0.847)	0.344	0.171
eICU-CRD	MICE full cohort (5 imputations)	0.728 (0.726–0.730)	0.183	0.936
eICU-CRD	Complete-case (n = 2,598)	0.705	0.159	0.214

Note: AUCs for MICE full cohorts are reported as ranges across 5 imputed datasets; HL P-values are reported as min–max ranges.

MICE AUC = 0.866 (95% CI: 0.854–0.877), complete-case AUC = 0.830 (95% CI: 0.812–0.847), DeLong P = 0.0006(Figure 2).

Calibration showed good agreement between predicted and observed probabilities; Hosmer–Lemeshow P = 0.171(Figure 3).

Incremental Predictive Value (NRI/IDI)

To quantify the incremental predictive value of adding SOFA, we calculated the integrated discrimination improvement (IDI) and net reclassification improvement (NRI_total) from Model 2 (without SOFA) to Model 3 (with SOFA), using bootstrap with 1,000 resamples (Table 6).

In the MIMIC-IV cohort, adding SOFA yielded an IDI of 0.085 (P < 0.001) and NRI_total of 0.657 (P < 0.001). In the eICU-CRD cohort, IDI was 0.045 (P < 0.001) and NRI_total was 0.428 (P < 0.001). Both were significantly > 0, confirming that SOFA significantly improved model prediction and was the key factor accounting for the attenuation of the Hb/Cr effect.

Table 6. Incremental predictive value after adding SOFA (NRI/IDI)

Cohort	Metric	Estimate	P value
MIMIC-IV	IDI	0.085	<0.001
	NRI_total	0.657	<0.001
eICU-CRD	IDI	0.045	<0.001
	NRI_total	0.428	<0.001

Net clinical benefit of the fully adjusted model (with SOFA) exceeded the "treat all" and "treat none" strategies across a wide range of threshold probabilities, indicating clinical utility(Figure 4).

Machine Learning and SHAP Feature Importance

To cross-validate the core findings within a non-parametric framework, we applied LASSO, random forest, and XGBoost with 5-fold cross-validation to predict in-hospital mortality in both cohorts, and quantified feature importance using SHAP values (Table 7).

In the MIMIC-IV cohort, cross-validated AUCs for the three algorithms in the MICE full cohort were: LASSO 0.845 ± 0.002, random forest 0.837 ± 0.002, and XGBoost 0.848 ± 0.002; in the complete-case subgroup, they were 0.803, 0.777, and 0.789, respectively.

In the eICU-CRD cohort, cross-validated AUCs were: LASSO 0.703 ± 0.003, random forest 0.693 ± 0.006, and XGBoost 0.701 ± 0.002.

SHAP importance analysis showed that in MIMIC-IV, the top five variables were SOFA (0.728), mechanical ventilation (0.541), age (0.317), AKI (0.225), and lactate (0.197), with Hb/Cr ranking 6th (0.074)(Figure 5A). In eICU-CRD, SOFA (0.346) and lactate (0.288) ranked first and second, and Hb/Cr ranked 3rd (0.147)(Figure 5B). Although Hb/Cr ranked slightly higher in eICU-CRD than in MIMIC-IV, it did not surpass SOFA as the predominant predictor in either cohort.

Table 7. Predictive performance of machine learning algorithms

Cohort	Analysis strategy	LASSO AUC	Random forest AUC	XGBoost AUC
MIMIC-IV	MICE full cohort (mean ± SD)	0.845 ± 0.002	0.837 ± 0.002	0.848 ± 0.002
MIMIC-IV	Complete-case	0.803	0.777	0.789
eICU-CRD	MICE full cohort (mean ± SD)	0.703 ± 0.003	0.693 ± 0.006	0.701 ± 0.002

Based on XGBoost model, SHAP values were averaged across absolute contributions. SOFA was the most important predictor in both cohorts, and Hb/Cr did not enter the top two, consistent with logistic regression results(Figure 5).

Sensitivity Analysis for Missing Data

In the MIMIC-IV cohort, the missing proportion was 31.35% for hemoglobin and 50.68% for lactate. To assess the potential impact of missing-data handling on the core conclusions, we applied three strategies: (1) MICE multiple imputation (full cohort, n = 6,182); (2) complete-case analysis (n = 2,843); and (3) pattern-mixture modeling for non-random missingness (MNAR).

Under all three strategies, the Hb/Cr effect estimate in the fully adjusted model (Model 3) remained centered around the null: MICE full cohort OR = 1.003 (95% CI: 0.982–1.025, P = 0.756), complete-case OR = 0.990 (95% CI: 0.962–1.019, P = 0.500), and pattern-mixture pooled OR = 0.995 (95% CI: 0.971–1.020, P = 0.690) (Table 8). The effect estimates (OR range: 0.990–1.003) and directions were fully consistent, indicating that the results were robust to missing-data handling strategies.

Table 8. Sensitivity analysis for missing data (MIMIC-IV fully adjusted model)

Strategy	Sample size	OR (95% CI)	P value
MICE full cohort (MAR assumption)	6,182	1.003 (0.982–1.025)	0.756
Complete-case analysis (MCAR assumption)	2,843	0.990 (0.962–1.019)	0.500
Pattern-mixture model (MNAR assumption)	2,843	0.995 (0.971–1.020)	0.690

Note: The pattern-mixture model stratified by missingness patterns of Hb and lactate (complete, Hb only, lactate only, both missing) and pooled stratum-specific ORs using inverse-variance weighting.

Discussion

This study used the MIMIC-IV discovery cohort and the eICU-CRD external validation cohort to construct three stepwise adjustment models, systematically evaluating the prognostic value of the hemoglobin-to-creatinine (Hb/Cr) ratio in critically ill patients with AMI.

The Hb/Cr ratio has been shown to have independent prognostic value in various cardiovascular diseases. In patients with STEMI, the discharge Hb/Cr ratio independently predicted 1-year all-cause mortality with better performance than hemoglobin or creatinine alone[6].A lower Hb/Cr ratio was also independently associated with 30-month major adverse cardiovascular events (MACE) [19].Among patients undergoing PCI, each unit increase in Hb/Cr was associated with a 14.2% reduction in 3-year all-cause mortality[20].Furthermore, in coronary artery disease (CAD) populations, a non-linear association between Hb/Cr and all-cause mortality has been reported[21].This prognostic value was also validated in heart failure patients, with multiple retrospective cohort studies showing that admission Hb/Cr was independently associated with 6-month all-cause readmission and could independently predict post-discharge mortality[7, 22].

Our study replicated the basic prognostic value of Hb/Cr in the ICU-AMI population. In models adjusting only for demographic variables and further adjusting for acute clinical indicators, Hb/Cr was significantly associated with in-hospital mortality, with effect directions consistent with previous studies. This suggests that even in the more severely ill ICU-AMI population with prominent organ dysfunction, Hb/Cr still has prognostic significance.

From a pathophysiological perspective, hemoglobin reflects tissue oxygen delivery reserve, and creatinine reflects glomerular filtration function, representing two well-established prognostic dimensions: anemia and renal impairment[23–25].Anemia is associated with higher mortality risk in cardiovascular diseases, and renal dysfunction is an independent predictor of adverse outcomes in ACS patients [26–28].By combining these two dimensions into a single indicator, the Hb/Cr ratio inherently carries prognostic information.

However, when SOFA was introduced into the model, the Hb/Cr effect disappeared in both databases. This attenuation occurred primarily upon SOFA entry rather than when acute indicators such as lactate or

mechanical ventilation were added, suggesting that SOFA is the key factor responsible for the loss of significance. SOFA integrates assessments across six organ systems, whereas Hb/Cr covers only two dimensions, and both are more comprehensively evaluated within SOFA. Therefore, its effect is likely already accounted for by SOFA[6, 28–31].

A critical distinction must be made regarding which variables were excluded and why. Mechanical ventilation and cardiogenic shock were retained in all models, despite also being identified via ICD or procedure codes, because they reflect pathophysiological dimensions—respiratory failure and circulatory failure—that are orthogonal to the creatinine component of Hb/Cr[17, 18, 32, 33]. Excluding them would have introduced genuine confounding by acute illness severity, whereas excluding CKD/AKI only removed redundant diagnostic labels already captured by the creatinine domain of SOFA[16, 34, 35]. This selective exclusion is therefore methodologically justified and does not represent selective reporting.

The two cohorts differed markedly in baseline characteristics:eICU-CRD had substantially higher SOFA scores, mortality rates, and mechanical ventilation use than MIMIC-IV. This heterogeneity strengthens the external validity of our findings: across two distinct ICU populations (single-center vs. multi-center, different geographic regions, and different severity profiles), Hb/Cr consistently showed a null effect in Model 3, supporting the robustness of the conclusion. Although the direction of the Hb/Cr effect in Models 1 and 2 was opposite between the two cohorts (OR > 1 in MIMIC-IV, OR < 1 in eICU-CRD), reflecting effect modification by extreme differences in baseline risk profiles, the consistent convergence to a null effect in Model 3 across both cohorts underscores that SOFA coverage is stable across populations.

Our findings do not contradict previous literature. The distinction lies solely in the adjustment variables used; previous studies did not test the incremental value of Hb/Cr beyond SOFA[6–8, 19].Our study specifically examined its independent value relative to SOFA, which had not been previously assessed.

This finding has clear clinical applicability: in the post-24h ICU setting where SOFA is already available, Hb/Cr offers no additional value and does not need to be routinely reported. However, it may still have screening value in pre-hospital emergency or resource-limited settings where SOFA cannot be rapidly obtained.

Several limitations should be acknowledged.:

First, this was a retrospective study, and prospective validation is needed.

Second, the missing rate for hemoglobin in MIMIC-IV was 31.35%; although three missing-data strategies confirmed the robustness of the conclusions, the underlying missingness in the source data remains a concern.

Third, we only assessed in-hospital mortality and did not evaluate long-term outcomes.

Fourth, the potential value of Hb/Cr in resource-limited settings remains inferential and requires dedicated studies.

Conclusions

Through three-tier hierarchical modeling in the MIMIC-IV discovery cohort and external validation in the eICU-CRD cohort, this study observed changes in the effect estimates of the hemoglobin-to-creatinine (Hb/Cr) ratio across different adjustment frameworks in critically ill AMI patients.

Key findings are as follows: (1) Hb/Cr has basic prognostic value in the ICU-AMI population, with effect directions consistent with previous non-ICU studies, suggesting that it retains prognostic significance even in more severely ill patients with prominent organ dysfunction; (2) SOFA already provides strong prognostic value, and Hb/Cr does not offer incremental information beyond SOFA; (3) These findings remained robust across multiple sensitivity analyses, with Hb/Cr effect estimates consistently centered near the null (OR range: 0.987–1.003), ruling out substantial influence from missing-data mechanisms.

Taken together, our findings clarify that Hb/Cr has independent prognostic value in ICU-AMI patients, but in the post-24h ICU assessment setting where SOFA is already available, Hb/Cr does not provide independent prognostic information beyond SOFA and does not warrant routine calculation.

Declarations

Conflicts of Interest and Source of Funding

Conflicts of Interest and Source of Funding: The authors declare no conflicts of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability

The data supporting the findings of this study are derived from the MIMIC-IV (version 3.1) and eICU-CRD (version 2.0) databases, which are hosted and managed by the PhysioNet platform.

These are credential-restricted datasets. Access is granted to researchers who complete formal human research subject protection training and sign the PhysioNet Credentialed Health Data Use Agreement. Eligible researchers may apply for access via the official database pages:

- MIMIC-IV v3.1: https://physionet.org/content/mimiciv/3.1/

- eICU-CRD v2.0: https://physionet.org/content/eicu-crd/2.0/

The authors confirm that they have completed all required training and obtained official access approval for both databases. Per the signed Data Use Agreements, the authors are not permitted to publicly redistribute the original raw datasets.

For inquiries regarding data access or the analytical code used in this study, please contact the corresponding author at qqkylin@126.com.

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Contributor Roles Taxonomy

First Author: Formal analysis, Data curation, Writing-original draft, Visualization, Investigation.

Second Author: Methodology, Validation, Software, Writing-review & editing.

Corresponding Author: Conceptualization, Supervision, Project administration, Writing-review & editing.

All authors read and approved the final manuscript.

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Figures

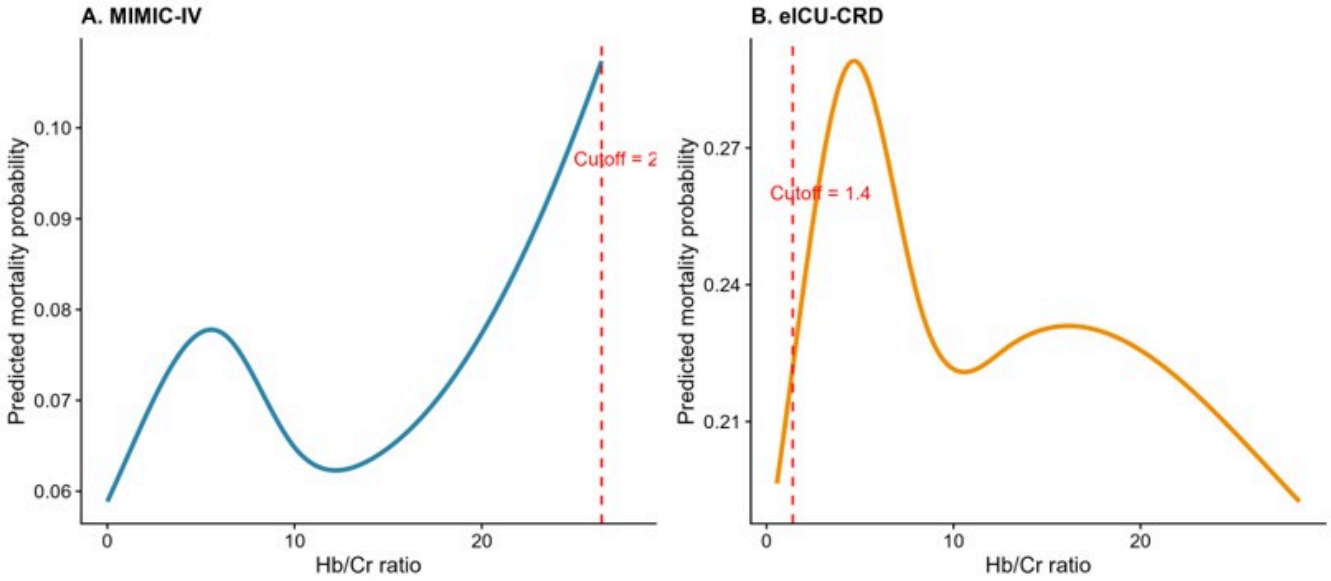


Figure 1

Restricted cubic spline curves of Hb/Cr ratio and in-hospital mortality risk (A: MIMIC-IV; B: eICU-CRD)

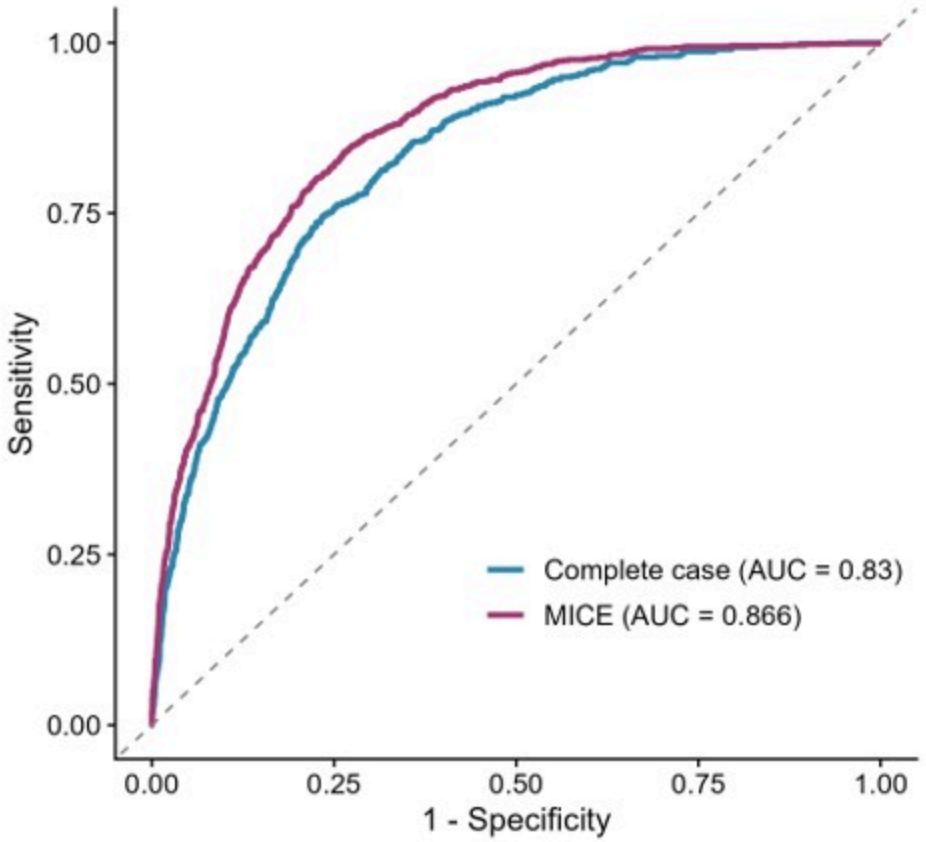


Figure 2

ROC curves comparing MICE full cohort and complete-case analysis (MIMIC-IV fully adjusted model)

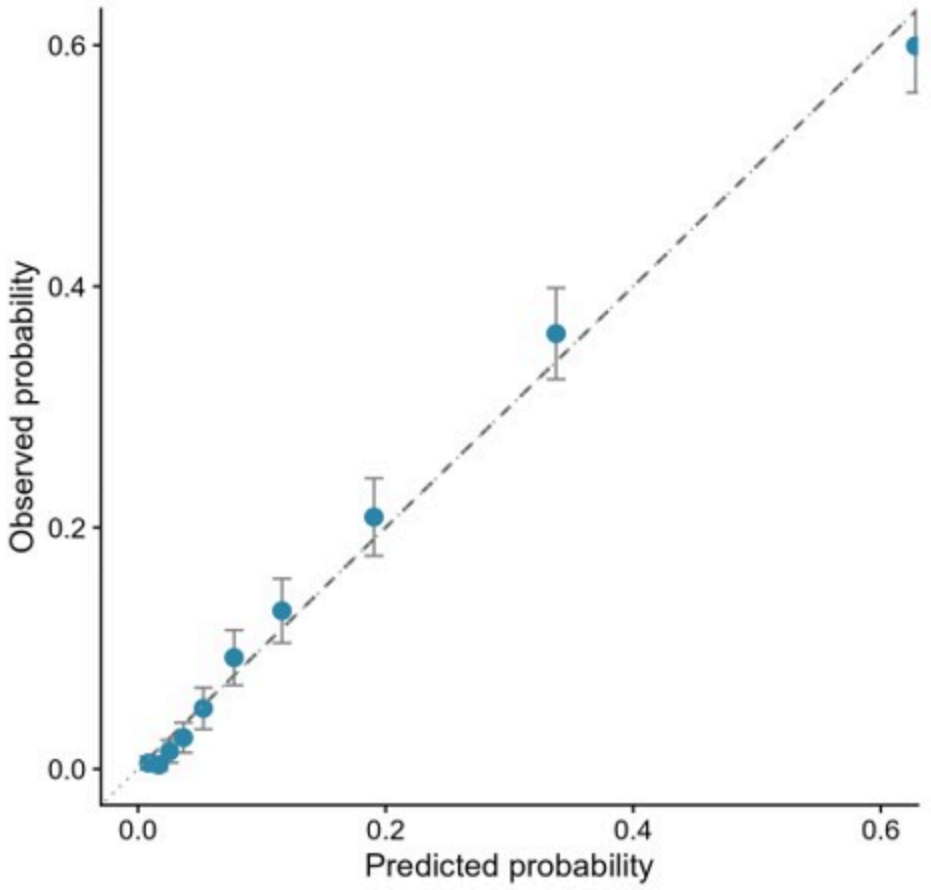


Figure 3

Calibration curve of the MICE full cohort fully adjusted model (MIMIC-IV)

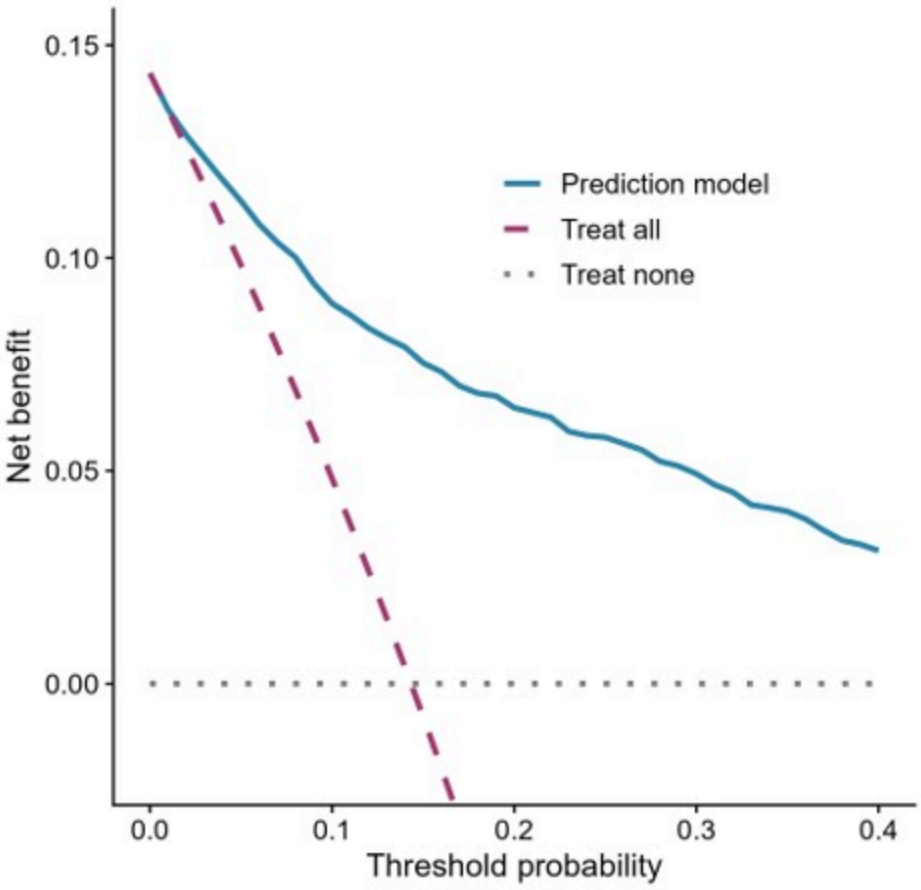


Figure 4

Decision curve analysis of the MICE full cohort fully adjusted model (MIMIC-IV)

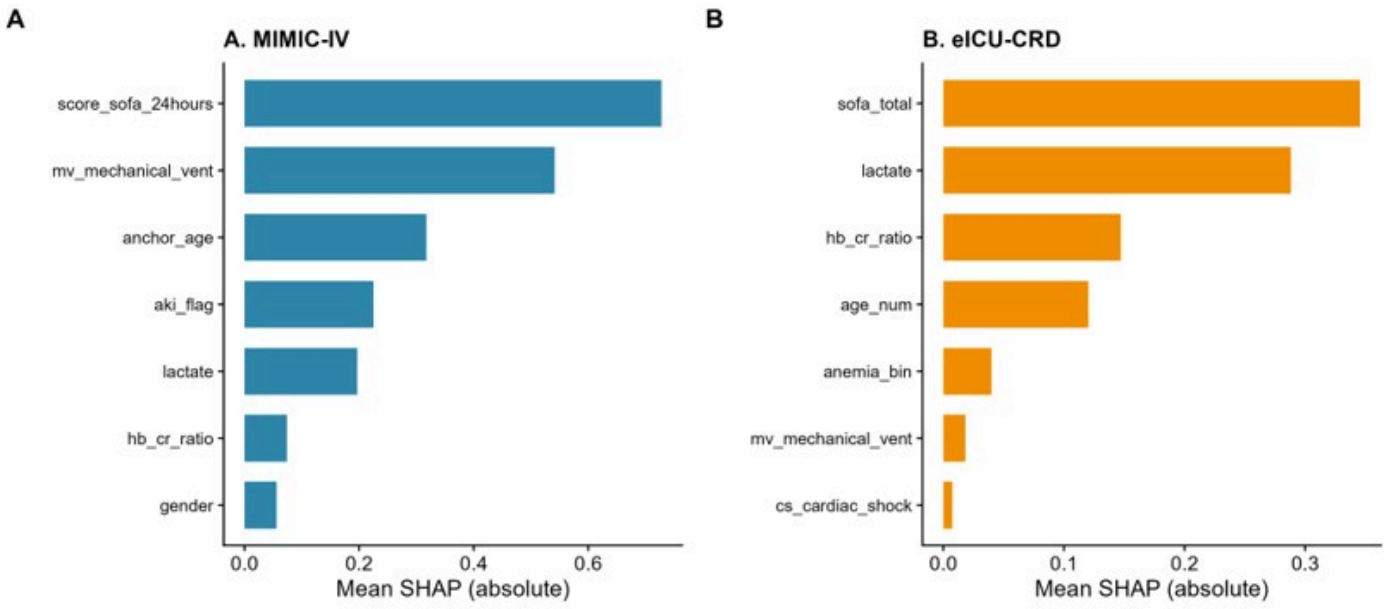


Figure 5

SHAP feature importance rankings (A: MIMIC-IV; B: eICU-CRD)

Supplementary Files

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- SupplementaryMaterials.docx