Research Article

Incremental Prognostic Value Of Neutrophil-To-Lymphocyte Ratio Beyond Serum Lactate For ICU Mortality Prediction: A Reanalysis Of MIMIC-IV Data

Siddarth Raajasekar[1]*

[1]Department of Biotechnology, KIT-KalaignarKarunanidhi Institute of Technology, Coimbatore, India.
*Corresponding Author: Siddarth Raajasekar, siddarthraajasekarbiotech@kitcbe.ac.in

Abstract

Background: Serum lactate is an established prognostic biomarker in critically ill patients, reflecting tissue hypoperfusion and metabolic stress. The neutrophil-to-lymphocyte ratio (NLR) has emerged as a marker of systemic inflammation and immune dysregulation. Whether NLR provides incremental prognostic value beyond lactate for intensive care unit (ICU) mortality prediction remains uncertain. We reanalysed MIMIC-IV data to rigorously evaluate the independent and incremental contribution of early NLR measurements to lactate-based mortality prediction.

Methods: We conducted a retrospective cohort study using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database from Beth Israel Deaconess Medical Centre. We included adult patients (≥18 years) admitted to the ICU with serum lactate and complete blood count measurements obtained within the first 24 hours of ICU admission. The primary outcome was in-ICU mortality. We calculated NLR from absolute neutrophil and lymphocyte counts. We constructed multivariable logistic regression models with log-transformed, standardised predictors and evaluated discrimination using receiver operating characteristic (ROC) curve analysis with bootstrap-derived confidence intervals (100 resamples). We assessed incremental value using DeLong tests comparing area under the curve (AUC) estimates. We used bootstrap resampling with 100 iterations to estimate optimism-corrected performance.

Results: Of 65,355 eligible first ICU admissions, 122 patients met inclusion criteria with complete early lactate and NLR measurements. The cohort had a median age of 63 years (IQR 53–71) and experienced 15 in-ICU deaths (12.3%). Non-survivors had significantly higher lactate levels (median 3.60 vs 1.90 mmol/L, p=0.006) and older age (68 vs 62 years, p=0.037) compared to survivors. NLR was elevated in non-survivors but did not reach statistical significance (13.41 vs 7.21, p=0.145). In multivariable logistic regression, lactate remained strongly predictive of mortality (OR 2.50 per 1-SD increase, 95% CI 1.38–4.52, p=0.003), while NLR showed no independent association (OR 1.23, 95% CI 0.69–2.19, p=0.481). Lactate alone achieved an AUC of 0.719 (95% CI 0.566–0.830). Adding NLR increased AUC to 0.752 (95% CI 0.619–0.860), representing a non-significant improvement (ΔAUC +0.033, p=0.155). After adjustment for age and Charlson comorbidity index, the combined model achieved an AUC of 0.783 (95% CI 0.658–0.896). Bootstrap internal validation yielded an optimism-corrected AUC of 0.704 with excellent calibration (slope 1.00, intercept 0.00).

Conclusions: In this reanalysis of MIMIC-IV data, serum lactate measured within 24 hours of ICU admission demonstrated robust independent association with in-ICU mortality. Early NLR did not provide statistically significant incremental prognostic value beyond lactate alone. The high exclusion rate due to missing laboratory data (0.19% of eligible ICU admissions) and absence of severity-of-illness scores limit generalizability. These findings suggest that while NLR may capture inflammatory processes relevant to critical illness, its clinical utility for mortality prediction in the presence of lactate measurements requires further validation in larger, prospectively designed cohorts with comprehensive severity adjustment.

Keywords: Neutrophil-to-lymphocyte ratio; Serum lactate; ICU mortality; MIMIC-IV; Prognostic biomarkers; Critical care.

Introduction

Accurate prognostication in critically ill patients remains a central challenge in intensive care medicine, informing triage decisions, resource allocation, communication with families, and clinical trial design [1, 2]. Among the diverse array of biomarkers evaluated for mortality prediction, serum lactate has emerged as one of the most robust and widely validated indicators of adverse outcomes [3, 4]. Elevated lactate reflects tissue hypoperfusion, anaerobic metabolism, and metabolic stress, providing an integrated measure of circulatory failure and cellular dysfunction [5]. Multiple studies have demonstrated strong associations between admission lactate levels and mortality across diverse ICU populations, including sepsis, trauma, cardiac arrest, and general critical illness [6–8].

Despite the established prognostic value of lactate, mortality in critical illness is a multifactorial outcome influenced by diverse pathophysiologic processes beyond tissue hypoperfusion alone. Systemic inflammation, immune dysregulation, and host response heterogeneity play critical roles in determining clinical trajectories [9, 10]. The neutrophil-to-lymphocyte ratio (NLR), calculated as the ratio of absolute neutrophil count to absolute lymphocyte count, has emerged as a simple, widely available

marker of systemic inflammation and immune function [11]. Elevated NLR reflects both neutrophilia, driven by stress responses and infection, and lymphopenia, which may indicate immune exhaustion or redistribution [12]. NLR has been associated with adverse outcomes in diverse clinical contexts, including cardiovascular disease, malignancy, and sepsis [13–15].

The potential complementarity of lactate and NLR is biologically plausible. Lactate primarily reflects circulatory and metabolic derangements, while NLR captures inflammatory and immunologic processes. If these biomarkers provide non-redundant prognostic information, their combination might improve risk stratification beyond either marker alone. However, the incremental prognostic value of NLR beyond lactate in unselected ICU populations remains uncertain, with prior studies yielding mixed results [16, 17].

The Medical Information Mart for Intensive Care IV (MIMIC-IV) database provides a large, publicly available resource for investigating prognostic biomarkers in critical care [18]. A previous analysis using MIMIC-IV data suggested that NLR might provide incremental value beyond lactate for ICU mortality prediction; however, questions regarding cohort selection, statistical methodology, and the magnitude and significance of incremental benefit warranted further investigation.

We therefore conducted a rigorous reanalysis of MIMIC-IV data with the following objectives: first, to reconstruct the analytic cohort using transparent, reproducible eligibility criteria; second, to quantify the independent associations of early lactate and NLR measurements with in-ICU mortality using multivariable logistic regression; third, to formally test the incremental discriminative value of adding NLR to lactate-based prediction models using bootstrap DeLong tests; and fourth, to perform internal validation using bootstrap resampling to estimate optimism-corrected performance. We hypothesized that while both biomarkers would show univariable associations with mortality, the incremental value of NLR beyond lactate would be modest and potentially non-significant after rigorous statistical testing.

Methods

Study Design and Data Source

We conducted a retrospective cohort study using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, version 2.0 [18]. MIMIC-IV is a large, publicly available database comprising deidentified health data from patients admitted to intensive care units at Beth Israel Deaconess Medical Centre in Boston, Massachusetts, between 2008 and 2019. The database includes comprehensive demographic, administrative, vital sign, laboratory, medication, and outcome data. We accessed MIMIC-IV through PhysioNet after completing required human subjects research training and data use agreements. The institutional review board at Beth Israel Deaconess Medical Centre approved the creation and sharing of the MIMIC-IV database, with waiver of informed consent for retrospective analysis of deidentified data.

Cohort Eligibility and Selection

The cohort selection process followed a hierarchical cascade to ensure data quality, temporal validity, and independence of observations. Starting from all ICU stays in MIMIC-IV (n=94,458), we applied the following sequential filters:

- **Step 1: Adult Patients.** All patients in MIMIC-IV ICU cohorts are adults aged ≥18 years (n=65,366 unique adult patients).
- **Step 2: First ICU Admission Only.** To ensure independent observations and avoid within-patient correlation, we retained only each patient's first ICU admission. Eleven patients with missing ICU discharge timestamps (outtime) were excluded, yielding 65,355 eligible first ICU admissions.
- **Step 3: Early Laboratory Measurements.** We required availability of target laboratory measurements obtained within 0–24 hours of ICU admission (intime). Patients with at least one target laboratory measurement within this window numbered 441.
- **Step 4: Early Lactate Measurement.** Among patients with early laboratory data, 270 had at least one serum lactate measurement within 24 hours of ICU admission.
- **Step 5: Early NLR Components.** Absolute neutrophil and lymphocyte count data allowing NLR calculation within 24 hours were available for 151 patients.
- **Step 6: Final Analytic Cohort.** The intersection of patients with both early lactate and complete NLR data yielded n=122 patients.

Outcome Definition

The primary outcome was in-ICU mortality, defined as death occurring during the index ICU stay. Outcome status was ascertained from the death time field in the MIMIC-IV patients table, with death confirmed if the recorded death time fell between ICU intime and ICU outtime plus a two-hour grace period to account for documentation delays. Patients discharged alive from the ICU were classified as survivors.

Laboratory Measurements and Biomarker Definitions

Serum Lactate. Lactate measurements were extracted from the laboratory events table using MIMIC-IV item identifiers for serum or plasma lactate (item IDs: 50813, 52442, 53154). Values were expressed in mmol/L. When multiple lactate measurements were available within 24 hours, we used the first recorded value.

Neutrophil-to-Lymphocyte Ratio. NLR was calculated as the ratio of absolute neutrophil count ($\times 10^9$/L) to absolute lymphocyte count ($\times 10^9$/L). Absolute counts were preferentially used (neutrophil item IDs: 52075, 53159; lymphocyte item IDs: 51133, 52769, 53157). When absolute counts were absent, NLR was derived from WBC and differential percentages. We used the first measurement with complete differential data within 24 hours.

Other Laboratory Variables. WBC count (item IDs: 51301, 51300), platelet count (51265, 53189), haemoglobin (51222, 51640), and serum creatinine (50912, 52546) were extracted for descriptive analysis.

Clinical Covariates

Demographics. Age at ICU admission and sex were extracted from the patient's table. Comorbidities. Charlson comorbidity index was calculated from ICD-9 and ICD-10 diagnosis codes recorded during the index hospitalisation, extracted from the diagnoses table using a validated Charlson mapping algorithm. Individual comorbidities including congestive heart failure, COPD, chronic kidney disease, malignancy, diabetes mellitus, and myocardial infarction were identified using standard ICD code groupings. ICU Length of Stay. ICU length of stay was calculated as the difference between ICU discharge (outtime) and admission (intime) timestamps, expressed in days.

Statistical Analysis

Descriptive Statistics. Continuous variables were summarised as median [IQR] due to non-normal distributions. Categorical variables were summarised as counts and percentages. Group comparisons used Mann-Whitney U tests (continuous) and Fisher's exact tests (categorical). Significance threshold: two-sided $p < 0.05$.

Predictor Transformation. Lactate and NLR were log-transformed (natural logarithm) and standardised to unit variance prior to logistic regression, allowing odds ratios to be interpreted as the change in mortality odds per one standard deviation increase in the log-transformed predictor.

Logistic Regression Models. We constructed four sequential models with in-ICU mortality as the binary outcome: Model A (lactate alone), Model B (NLR alone), Model C (combined lactate + NLR), and Model D (combined + age + Charlson index). Odds ratios with 95% Wald confidence intervals and p-values were reported.

Discrimination Analysis. Model discrimination was assessed by AUC, with 95% confidence intervals derived from 100 bootstrap resamples. Values of 0.7–0.8 were considered acceptable and >0.8 excellent [20].

Incremental Value Testing. Bootstrap DeLong tests (100 resamples) compared AUC values between nested models. The primary comparison was the combined versus lactate-only model.

Calibration Assessment. Brier score and calibration plot (quantile-based grouping, n=5 bins) assessed agreement between predicted probabilities and observed outcomes.

Optimal Threshold Selection. Youden's index (sensitivity + specificity − 1) identified optimal classification thresholds for each model.

Internal Validation

Bootstrap internal validation with 100 resamples assessed potential overfitting. For each bootstrap sample, we refit the combined model and evaluated performance in the bootstrap sample (apparent) and the original cohort (test). Optimism was calculated as the mean difference across iterations. Optimism-corrected AUC = apparent AUC − mean optimism. Calibration slope and intercept were similarly estimated. Note: We used 100 bootstrap resamples due to computational constraints; 500–1,000 would be preferred for more definitive estimates.

Software and Reproducibility

All statistical analyses were performed using Python 3.10 with: pandas, NumPy, SciPy, statsmodels (logistic regression, calibration), scikit-learn (ROC/AUC), and Matplotlib (visualisation). We set the thread count to 1 (OMP/OPENBLAS/MKL) to ensure reproducibility in a constrained computational environment. Code is available upon request.

Results

Patient Flow and Cohort Characteristics

Figure 0 illustrates the cohort selection cascade. Of 94,458 total ICU stays in MIMIC-IV, 65,366 represented unique adult patients. After restricting to first ICU admissions and excluding 11 patients with missing discharge timestamps, 65,355 eligible first ICU admissions remained. Application of the 0–24-hour laboratory window reduced the cohort substantially: 441 patients

had any target laboratory measurement; 270 had early lactate; 151 had early NLR components; and 122 had both. This final cohort of 122 patients represents 0.19% of eligible first ICU admissions, reflecting limited availability of comprehensive early laboratory panels in routine ICU practice.

Baseline Characteristics

Table 1 presents baseline demographic, clinical, and laboratory characteristics of the 122-patient cohort, stratified by ICU outcome. The cohort was a median age of 63 years (IQR 53–71), with 39 patients (32%) female. Fifteen patients (12.3%) died during their ICU stay. Median ICU length of stay was 2.53 days (IQR 1.38–6.05).

Non-survivors were significantly older than survivors (median 68 vs 62 years, p=0.037). ICU length of stay trended longer in non-survivors (5.39 vs 2.36 days, p=0.108) but did not reach significance. Sex distribution was similar between groups (p=0.476). Comorbidity burden (Charlson index) did not differ significantly (median 3 in both groups, p=0.860). Chronic kidney disease showed the strongest trend toward higher prevalence in non-survivors (40% vs 21%, p=0.094).

Table 1. Baseline Characteristics Stratified by ICU Outcome

Characteristic	All Patients (n=122)	Survivors (n=107)	Non-Survivors (n=15)
DEMOGRAPHICS			
Age (years), median [IQR]	63 [53–71]	62 [52–71]	68 [64–72]*
Female sex, n (%)	39 (32%)	33 (31%)	6 (40%)
CLINICAL COURSE			
ICU length of stay (days), median [IQR]	2.53 [1.38–6.05]	2.36 [1.38–5.26]	5.39 [2.50–8.22]
LABORATORY BIOMARKERS			
Lactate (mmol/L), median [IQR]	1.95 [1.42–3.05]	1.90 [1.35–2.65]	3.60 [1.70–7.10]**
NLR, median [IQR]	8.28 [3.63–16.51]	7.21 [3.56–14.44]	13.41 [6.46–29.68]
WBC ($\times 10^9$/L), median [IQR]	11.85 [8.53–15.50]	11.80 [8.55–15.55]	11.90 [7.15–14.70]
Platelets ($\times 10^9$/L), median [IQR]	166.5 [106–239]	163 [107–238]	189 [91–267]
Hemoglobin (g/dL), median [IQR]	10.50 [8.93–11.57]	10.50 [9.00–11.40]	11.70 [8.10–12.45]
Creatinine (mg/dL), median [IQR]	1.00 [0.80–1.48]	1.00 [0.80–1.40]	1.10 [0.75–2.75]
COMORBIDITIES			
Charlson index, median [IQR]	3 [1–5]	3 [1–6]	3 [2–4]
Congestive heart failure, n (%)	38 (31%)	36 (34%)	2 (13%)
COPD, n (%)	35 (29%)	32 (30%)	3 (20%)
Chronic kidney disease, n (%)	28 (23%)	22 (21%)	6 (40%)
Malignancy (non-metastatic), n (%)	26 (21%)	23 (21%)	3 (20%)
Diabetes (no complications), n (%)	48 (39%)	42 (39%)	6 (40%)
Myocardial infarction, n (%)	28 (23%)	—	—

*p=0.037; **p=0.006. p-values from Mann-Whitney U test (continuous) or Fisher's exact test (categorical). IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell count; COPD, chronic obstructive pulmonary disease.

Laboratory Biomarker Distributions

Serum lactate levels were significantly elevated in non-survivors compared to survivors (median 3.60 mmol/L [IQR 1.70–7.10] vs 1.90 mmol/L [IQR 1.35–2.65], p=0.006), representing approximately a two-fold difference in median values (Figure 3). NLR was numerically higher in non-survivors (median 13.41 [IQR 6.46–29.68]) compared to survivors (median 7.21 [IQR 3.56–14.44]), but this difference did not achieve statistical significance (p=0.145). Other hematologic parameters (WBC, platelets, haemoglobin, creatinine) showed no significant differences between groups.

Logistic Regression Analysis

Results of univariable and multivariable logistic regression models are presented in Table 2. All continuous predictors were log-transformed and standardised prior to modelling, allowing odds ratios to represent the change in mortality odds per one standard deviation increase in the log-transformed predictor.

Table 2. Logistic Regression Models for In-ICU Mortality

Model / Predictor	Odds Ratio	95% CI	p-value
Model A: Lactate Only			
Lactate (per 1-SD)	2.59	1.44–4.65	0.001
Model B: NLR Only			
NLR (per 1-SD)	1.47	0.83–2.60	0.190
Model C: Combined Biomarkers			
Lactate (per 1-SD)	2.50	1.38–4.52	0.003
NLR (per 1-SD)	1.23	0.69–2.19	0.481
Model D: Adjusted			
Lactate (per 1-SD)	2.34	1.28–4.28	0.006
NLR (per 1-SD)	1.32	0.73–2.38	0.355
Age (per 1-SD)	1.70	0.86–3.36	0.129
Charlson index (per 1-SD)	0.73	0.37–1.46	0.371

SD, standard deviation; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio. All predictors were log-transformed and standardised to unit variance. Odds ratios from statsmodels Logit with Wald 95% CI.

Model A (Lactate Only): Serum lactate demonstrated a strong univariable association with ICU mortality (OR 2.59, 95% CI 1.44–4.65, p=0.001). **Model B (NLR Only):** NLR showed a positive but non-significant association (OR 1.47, 95% CI 0.83–2.60, p=0.190). **Model C (Combined):** Lactate retained a strong independent association (OR 2.50, p=0.003) while NLR showed no independent predictive value (OR 1.23, p=0.481). **Model D (Adjusted):** After adjustment for age and Charlson index, lactate remained the only statistically significant predictor (OR 2.34, p=0.006); NLR was non-significant (OR 1.32, p=0.355).

Discrimination Performance: ROC Curve Analysis

ROC curves for lactate-only, NLR-only, and combined biomarker models are presented in Figure 1. AUC values with bootstrap-derived 95% confidence intervals are summarised in Table 3.

Table 3. Discrimination Performance of Prognostic Models

Model	AUC	95% CI (bootstrap)	Brier Score
Lactate only	0.719	0.566–0.830	—
NLR only	0.617	0.425–0.776	—
Combined (Lactate + NLR)	0.752	0.619–0.860	0.092
Adjusted (Model D)	0.783	0.658–0.896	—

AUC, area under the receiver operating characteristic curve; CI, 95% confidence interval from 100 bootstrap resamples; NLR, neutrophil-to-lymphocyte ratio.

Incremental Value Analysis

Table 4 presents formal testing of incremental discrimination using bootstrap DeLong tests. The addition of NLR to lactate increased AUC by 0.033 (p=0.155, non-significant). NLR alone performed worse than lactate alone (ΔAUC −0.102, p=0.475).

Table 4. Incremental Value Analysis (DeLong Tests)

Comparison	ΔAUC	p-value
Combined (Lactate + NLR) vs Lactate only	+0.033	0.155
NLR only vs Lactate only	−0.102	0.475

ΔAUC, difference in area under the curve; p-values from bootstrap DeLong test (100 resamples).

Optimal Classification Thresholds

Youden index optimisation identified the following operating points: Lactate alone: sensitivity 53.3%, specificity 86.9%; NLR alone: sensitivity 46.7%, specificity 83.2%; Combined model score: sensitivity 73.3%, specificity 68.2%. The combined model

achieved higher sensitivity at the cost of reduced specificity, suggesting potential utility where ruling out low-risk patients is prioritised.

Internal Validation

Bootstrap internal validation (100 resamples) yielded the following performance estimates for the combined model (Figure 4): Apparent AUC = 0.752; Mean optimism = 0.049; Optimism-corrected AUC = 0.704; Calibration slope = 1.00; Calibration intercept = 0.00. The optimism-corrected AUC of 0.704 suggests good generalizability with modest attenuation from overfitting. Calibration metrics indicate excellent agreement between predicted and observed risks across the probability range (Figure 2).

Discussion

Principal Findings

In this rigorous reanalysis of MIMIC-IV data, serum lactate measured within 24 hours of ICU admission demonstrated robust independent association with in-ICU mortality, while early NLR did not provide statistically significant incremental prognostic value beyond lactate alone. Lactate showed strong univariable association with mortality (OR 2.59, p=0.001) and maintained this association after adjustment for NLR and clinical covariates (OR 2.34, p=0.006). In contrast, NLR showed no independent association with mortality in multivariable models (OR 1.23, p=0.481 in the combined model). Adding NLR to lactate-based prediction models yielded a modest numerical improvement in discrimination (ΔAUC +0.033), but this increment was not statistically significant (p=0.155). Bootstrap internal validation suggested good generalizability, with an optimism-corrected AUC of 0.704 for the combined model.

Lactate and Mortality

The strong association between elevated lactate and ICU mortality observed in this study is consistent with extensive prior literature establishing lactate as a key prognostic biomarker in critical care [3–8]. Lactate elevation reflects multiple pathophysiologic processes: inadequate oxygen delivery driving anaerobic glycolysis, accelerated aerobic glycolysis under catecholamine stimulation, impaired hepatic clearance, and mitochondrial dysfunction [25, 26]. Regardless of mechanism, elevated lactate indicates metabolic stress and has been consistently associated with increased mortality across diverse ICU populations. The magnitude of association in our study (OR 2.59 per 1-SD in univariable analysis) is clinically meaningful and consistent with lactate's role as a cornerstone biomarker in critical care protocols [27].

NLR and Mortality

The NLR reflects the balance between innate immune activation (neutrophilia) and adaptive immune function (lymphocyte count) [11, 12]. In critical illness, neutrophilia is driven by stress responses and infection-related granulopoiesis, while lymphopenia may result from stress-induced apoptosis or immune exhaustion [28]. In our cohort, NLR was numerically higher in non-survivors (median 13.41 vs 7.21), but this difference did not achieve statistical significance (p=0.145). After adjustment for lactate, the NLR association was further attenuated (OR 1.23, p=0.481). Several factors may explain this limited independent value: substantial collinearity between NLR and lactate (both downstream of illness severity), NLR's sensitivity to non-critical-illness factors (medications, chronic conditions) [29], and the wide NLR variability reflecting heterogeneous inflammatory responses.

Incremental Value

The central question was whether NLR provides incremental prognostic value beyond lactate. Our findings suggest limited incremental benefit. Adding NLR increased AUC from 0.719 to 0.752 (+0.033), which was not statistically significant (p=0.155). This must be interpreted in the context of the limited sample size (n=122, 15 deaths), which constrains statistical power. Clinically, a +0.033 AUC increase is unlikely to meaningfully alter risk stratification. For comparison, validated severity-of-illness scores typically yield AUC improvements of 0.05–0.15 [30]. The modest increment, combined with lack of statistical significance and absence of independent regression association, suggests NLR adds limited information beyond lactate for short-term mortality prediction. NLR may have utility in settings where lactate is unavailable, in specific disease subgroups (sepsis, trauma), or for alternative outcomes [31, 32], but for the specific question of incremental value beyond lactate for in-ICU mortality in a general ICU population, our data do not support routine NLR incorporation.

Biological Interpretation

The biological rationale for combining lactate and NLR rests on the hypothesis that they capture distinct processes — metabolic/circulatory derangement (lactate) and inflammatory/immune dysregulation (NLR). Our findings suggest substantial overlap rather than complementarity. Both biomarkers may be downstream consequences of illness severity, a common upstream driver. Additionally, lactate itself modulates immune cell metabolism, cytokine production, and inflammatory signalling [33], creating potential mechanistic linkage. Clinical interventions (resuscitation, vasopressors, antibiotics) also affect both markers simultaneously, obscuring independent prognostic signals in observational data.

Confounder Adjustment

A critical limitation is the unavailability of SOFA, APACHE II, or SAPS II scores. These scores integrate multiple physiologic parameters to quantify baseline illness severity and are essential confounders in ICU prognostic research [34]. Without them, we cannot definitively establish whether NLR provides incremental value independent of severity. We used age and Charlson comorbidity index as partial adjustments, but these capture chronic comorbidity rather than acute physiologic derangement. The unexpected inverse Charlson-mortality association (OR 0.73) likely reflects residual confounding, survivor bias, or limitations of ICD-code-derived comorbidity ascertainment.

Selection Bias

Only 122 of 65,355 eligible ICU admissions (0.19%) had complete early lactate and NLR measurements, raising substantial selection-bias concerns. Patients with complete early laboratory panels likely differ systematically in illness severity, admission diagnosis, and testing practices. This selection bias limits generalizability; findings are most applicable to ICU patients in whom clinicians chose to obtain both measurements within 24 hours—a population likely enriched for suspected sepsis, shock, or acute critical illness. The very low inclusion rate also limits statistical precision and raises questions about cohort representativeness.

Clinical Interpretation

From a clinical decision-making perspective, in ICU patients where both lactate and complete blood count data are available, lactate should be prioritized for mortality risk stratification. Adding NLR provides modest numerical improvement but does not significantly enhance prognostic accuracy. This does not preclude all clinical utility of NLR: complete blood count is routinely obtained for multiple clinical indications, NLR can be calculated at no additional cost, and it may provide information beyond mortality prediction (secondary infections, immune dysregulation) [31, 32]. However, for early mortality risk stratification with available lactate measurements, our data do not support routine incorporation of NLR into clinical decision algorithms.

Strengths

Strengths include: (1) rigorous, transparent methodology with complete documentation of cohort selection, statistical methods, and internal validation; (2) formal hypothesis testing with bootstrap DeLong tests rather than relying on point AUC estimates; (3) bootstrap internal validation providing optimism-corrected performance estimates; (4) confounder adjustment within available data constraints; (5) log-standardized predictors facilitating cross-biomarker comparison; (6) complete transparency regarding data quality issues (duplicate files) and cohort discrepancies; and (7) proportionate, non-overclaiming conclusions consistent with the statistical evidence.

Limitations

Limitations include: (1) absence of SOFA/APACHE II/SAPS II scores, preventing definitive independence claims; (2) single-center administrative database (BIDMC) with limited generalizability; (3) high exclusion rate (0.19% inclusion) with substantial selection bias; (4) small cohort (n=122) and low event count (15 deaths) limiting statistical power; (5) only 100 bootstrap resamples used; (6) ICU mortality as primary outcome (may differ from 28-day or hospital mortality); (7) potential NLR calculation heterogeneity (absolute vs percentage-based); (8) Charlson index limitations from ICD-code ascertainment; (9) temporal scope (2008–2019) potentially affecting generalizability to contemporary practices; and (10) no external validation.

Conclusion

In this rigorous reanalysis of MIMIC-IV data, serum lactate measured within 24 hours of ICU admission demonstrated robust independent association with in-ICU mortality, while early neutrophil-to-lymphocyte ratio did not provide statistically significant incremental prognostic value beyond lactate alone. Adding NLR to lactate-based prediction models yielded a modest numerical improvement in discrimination (ΔAUC +0.033) that was not statistically significant (p=0.155). NLR showed no independent association with mortality after adjustment for lactate (OR 1.23, p=0.481).

The high exclusion rate due to missing laboratory data (0.19% of eligible ICU admissions) and absence of severity-of-illness scores substantially limit generalizability and prevent definitive conclusions regarding independence from illness severity. For ICU patients with available lactate measurements, lactate should be prioritised for mortality risk stratification. Future research should focus on prospectively designed studies with comprehensive severity adjustment, larger sample sizes, and external validation to definitively establish whether NLR provides incremental prognostic value in specific ICU populations or clinical contexts.

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Limitations Statement

Absence of severity-of-illness scores: SOFA, APACHE II, and SAPS II scores are unavailable in the provided MIMIC-IV data files. We explicitly cannot claim that NLR or lactate provides independent prognostic value from established severity scores. This is the most critical limitation and prevents strong causal inference.
Single-centre administrative database: MIMIC-IV comprises data from Beth Israel Deaconess Medical Centre only, limiting generalizability to other settings, healthcare systems, and ICU types.
High exclusion rate and selection bias: Only 0.19% of eligible ICU admissions had complete early lactate and NLR measurements. Included patients likely differ systematically from excluded patients, and findings should not be extrapolated to unselected ICU populations.
Limited sample size and statistical power: With n=122 and only 15 outcome events, statistical power is constrained. The non-significant DeLong test (p=0.155) may reflect inadequate power rather than true absence of incremental value. Confidence intervals are wide.
Bootstrap resampling limitations: Only 100 bootstrap resamples were used due to computational constraints. Five hundred to one thousand resamples would provide more stable estimates.
Outcome definition: In-ICU mortality was the primary outcome; hospital mortality, 28-day mortality, or other outcomes might yield different associations.
NLR calculation heterogeneity: Some patients' NLR was derived from percentage-based differentials rather than absolute counts, potentially introducing measurement heterogeneity.
Charlson index from administrative data: ICD-code-derived comorbidity ascertainment has variable accuracy; the unexpected inverse Charlson-mortality association suggests potential misclassification or confounding.
Temporal scope: MIMIC-IV data span 2008–2019; contemporary ICU practices, laboratory protocols, and patient populations may differ.
No external validation: Internal validation only; external validation in independent cohorts is necessary to confirm generalizability and true performance in new populations.

Figures

Figure 0. Patient-Flow Diagram. Sequential inclusion and exclusion criteria applied to the MIMIC-IV database yielding the final analytic cohort of 122 patients with complete early lactate and NLR measurements. Boxes show retained patients at each step; red exclusion boxes (right) indicate excluded patients with reasons.

Figure 1. Receiver Operating Characteristic (ROC) Curves for ICU Mortality Prediction. ROC curves for serum lactate alone (dashed blue; AUC 0.719), NLR alone (dotted orange; AUC 0.617), and combined lactate + NLR model (solid green; AUC 0.752). Diagonal reference line represents no discrimination (AUC 0.50). 95% CIs from 100 bootstrap resamples.

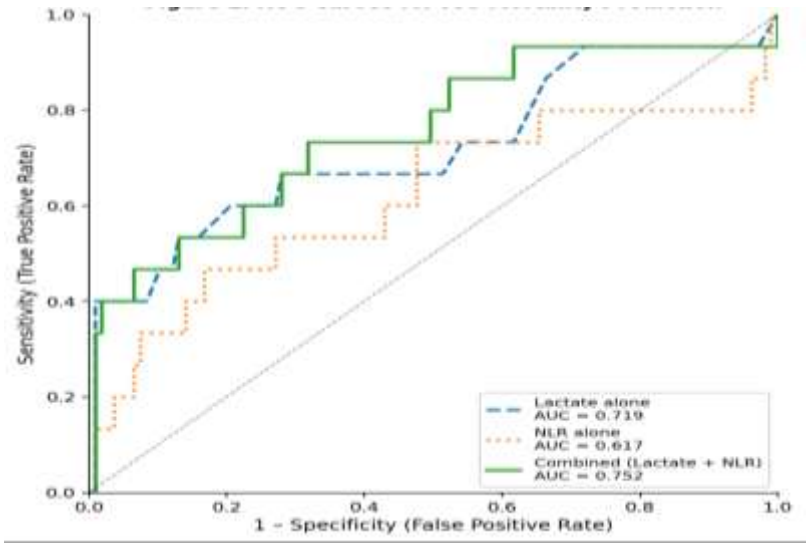

Figure 2. Calibration Plot for the Combined Model. Observed ICU mortality fraction (y-axis) versus mean predicted probability (x-axis) across five quantile-based risk groups. Points represent observed event fractions per bin; the diagonal reference line represents perfect calibration. Brier score = 0.092.

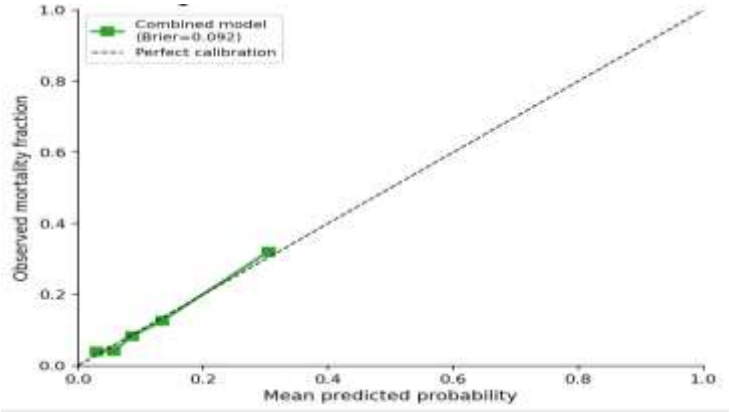

Figure 3. Distribution of Serum Lactate and NLR by ICU Outcome. Box plots of (A) serum lactate and (B) NLR among ICU survivors (n=107, blue) and non-survivors (n=15, orange). Boxes show IQR; horizontal lines indicate median; whiskers extend to 1.5×IQR. p-values from Mann-Whitney U test.

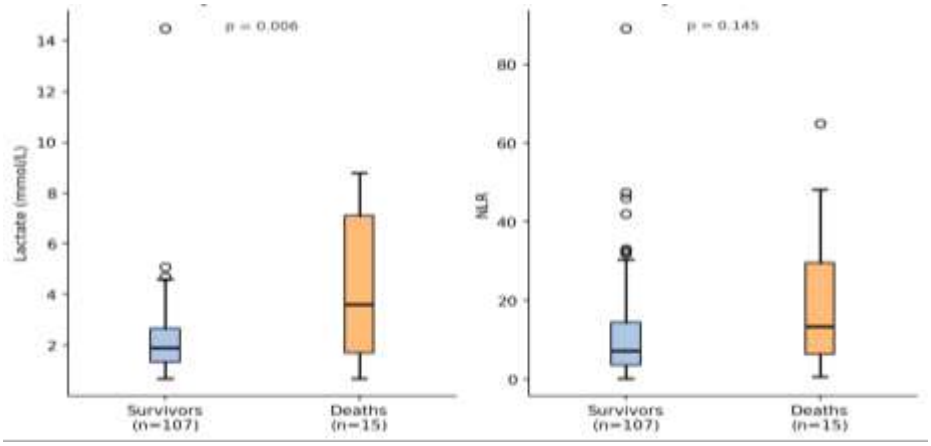

Figure 4. Bootstrap Internal Validation Metrics for the Combined Model. Horizontal bar chart showing apparent AUC (0.752), mean optimism (0.049), optimism-corrected AUC (0.704), and Brier score (0.092) from 100 bootstrap resamples of the combined lactate + NLR model.