

Dynamic Trajectory of the Neutrophil-to-Lymphocyte Ratio and Coagulation-Immune Crosstalk in Sepsis: A Latent Class Mixed Model Analysis of the MIMIC-IV Cohort

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Article

Keywords: sepsis, neutrophil-to-lymphocyte ratio, coagulation, immune crosstalk, trajectory analysis, MIMIC-IV

Posted Date: October 1st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10793017/v1>

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Additional Declarations: No competing interests reported.

Abstract

Sepsis remains a leading cause of mortality in intensive care units (ICUs). The neutrophil-to-lymphocyte ratio (NLR) and coagulation parameters are dynamic biomarkers of immune activation and hemostatic dysregulation, yet their temporal interplay and prognostic trajectories remain poorly characterized. In this retrospective MIMIC-IV (version 2.2) cohort study, 5,267 adult sepsis patients meeting Sepsis-3 criteria were analyzed, with NLR, platelet count, white blood cell (WBC) count, activated partial thromboplastin time, prothrombin time, and lactate measured daily from ICU day 1 (D1) through D7 and trajectory groups classified by change rate. Overall mortality was 26.7% and 28-day mortality 8.5%. Log-transformed NLR on D1 predicted overall mortality (HR = 1.270, $P = 0.002$) but was attenuated after multivariable adjustment (HR = 1.125, $P = 0.139$). Platelet trajectory was the strongest discriminator: decreasing trajectories carried 41.4% versus 20.2% overall mortality ($P < 0.001$), and the combined “decreasing platelet + increasing WBC” phenotype conferred 48.7% mortality. NLR correlated with fibrinogen ($\rho = 0.138$), platelet count ($\rho = 0.099$), and WBC ($\rho = 0.085$) (all $P < 0.001$). Platelet trajectory, rather than a single NLR measurement, emerges as the most robust coagulation-related prognostic marker, supporting coagulation-immune crosstalk as a dual-axis prognostic framework warranting prospective validation.

Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection¹, remains a global health challenge with an in-hospital mortality rate of approximately 10–35%². Despite advances in early recognition, antibiotic therapy, and supportive care, the identification of reliable dynamic biomarkers for risk stratification remains an unmet need.

The neutrophil-to-lymphocyte ratio (NLR) has emerged as a readily available composite inflammatory marker that captures the balance between innate (neutrophil-mediated) and adaptive (lymphocyte-mediated) immune responses³. In sepsis, NLR elevation reflects the paradoxical combination of neutrophil mobilization and infection-induced lymphocyte apoptosis, both hallmarks of immune dysregulation⁴. However, the majority of existing studies have utilized NLR as a static, single-timepoint measurement, failing to capture its dynamic trajectory over the critical early ICU period—a window during which both immune and coagulation systems undergo rapid, interdependent shifts⁵.

The interplay between coagulation and immunity in sepsis—termed “coagulation-immune crosstalk”—has garnered increasing attention⁶. Sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) represent a spectrum of hemostatic failure driven by tissue factor expression on monocytes, neutrophil extracellular trap (NET) formation, and depletion of anticoagulant pathways (antithrombin, protein C)⁷. Concurrently, platelets serve not only as hemostatic effectors but also as immune modulators, interacting with leukocytes via P-selectin and Toll-like receptors⁸. This bidirectional

crosstalk suggests that the temporal trajectories of coagulation and immune markers may be more informative than any single measurement.

Latent class mixed models (LCMM) and trajectory analysis methods offer a statistical framework for identifying heterogeneous subgroups within a population based on longitudinal biomarker patterns⁹. Such approaches have been successfully applied to identify distinct inflammatory¹⁰ and coagulation¹¹ phenotypes in critical illness, but the combined analysis of NLR and coagulation trajectories in sepsis has not been comprehensively explored using the MIMIC-IV cohort.

Therefore, this study aimed to: (1) characterize the dynamic trajectories of NLR, platelet count, and WBC count during the first 7 ICU days; (2) identify trajectory-based subgroups and their association with mortality; (3) quantify the coagulation-immune crosstalk through correlation and cross-trajectory analysis; and (4) evaluate the independent prognostic value of NLR and coagulation parameters using multivariable regression models.

Results

Baseline characteristics

A total of 5,267 sepsis patients were included in the analysis (Table 1). The median age was 66.0 years (IQR 54.0–76.0), and 59.5% (n = 3,132) were male. The racial composition was predominantly White (69.1%), followed by Other (18.4%), Black (6.9%), Hispanic (3.2%), and Asian (2.4%).

Table 1
Baseline Characteristics of the Study Cohort (N = 5,267)

Variable	Value
Demographics	
Age, years, median (IQR)	66.0 (54.0–76.0)
Male, n (%)	3,132 (59.5)
Race, n (%)	
White	3,642 (69.1)
Black	362 (6.9)
Asian	129 (2.4)
Hispanic	167 (3.2)
Other	967 (18.4)
Insurance, n (%)	
Medicare	2,762 (52.4)
Private	1,672 (31.7)
Medicaid	685 (13.0)
Other	148 (2.8)
Clinical characteristics	
SOFA score, median (IQR)	4.0 (3.0–6.0)
APSO, median (IQR)	38.0 (29.0–51.0)
SAPS II, median (IQR)	35.0 (27.0–44.0)
OASIS, median (IQR)	32.0 (26.0–39.0)
Charlson index, median (IQR)	4.0 (2.0–6.0)
GCS, median (IQR)	15.0 (8.0–15.0)
SIRS criteria, median (IQR)	3.0 (2.0–4.0)
ICU type, n (%)	
CVICU	1,574 (29.9)
MICU	803 (15.2)
SICU	766 (14.5)
TSICU	743 (14.1)

Variable	Value
MICU/SICU	677 (12.9)
CCU	452 (8.6)
Other	152 (2.9)
Organ support	
Mechanical ventilation, n (%)	4,668 (88.6)
AKI, n (%)	3,826 (72.6)
AKI stage 1, n (%)	1,080 (20.5)
AKI stage 2, n (%)	3,539 (67.2)
AKI stage 3, n (%)	648 (12.3)
CRRT, n (%)	68 (1.3)
Length of stay	
ICU LOS, days, median (IQR)	2.4 (1.5–4.6)
Hospital LOS, days, median (IQR)	7.0 (4.8–11.4)
Outcomes	
28-day mortality, n (%)	446 (8.5)
ICU mortality, n (%)	285 (5.4)
Hospital mortality, n (%)	348 (6.6)
Overall mortality, n (%)	1,404 (26.7)

The median SOFA score on ICU admission was 4.0 (IQR 3.0–6.0), APsIII was 38.0 (IQR 29.0–51.0), SAPS II was 35.0 (IQR 27.0–44.0), and Charlson Comorbidity Index was 4.0 (IQR 2.0–6.0). The most common ICU type was CVICU (29.9%), followed by MICU (15.2%) and SICU (14.5%).

Mechanical ventilation was required in 88.6% of patients, AKI developed in 72.6% (AKI stage 2 in 67.2% of AKI cases), and CRRT was used in 1.3%. The median ICU LOS was 2.4 days (IQR 1.5–4.6), and the median hospital LOS was 7.0 days (IQR 4.8–11.4).

NLR and coagulation-immune markers: overall trajectories

The median NLR on D1 was 6.33, rising to a peak of 7.52 on D2, then gradually declining to 6.01 by D6 (Table 2). This biphasic pattern—initial neutrophil surge followed by gradual lymphocyte recovery—was consistent across the cohort.

Table 2
Longitudinal Laboratory Values (Days 1–7)

Variable	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
NLR							
Median	6.33	7.52	6.93	6.17	6.11	6.01	6.14
Platelet (×10⁹/L)							
Median	185.5	172.0	188.0	214.3	235.6	256.4	279.0
IQR Q1	141.3	128.0	137.0	165.0	203.0	—	—
IQR Q3	241.0	220.0	223.0	238.0	242.0	—	—
WBC (×10⁹/L)							
Median	12.0	11.2	10.5	10.0	10.0	10.5	10.9
IQR Q1	9.1	8.6	8.0	7.7	8.2	—	—
IQR Q3	15.1	13.6	12.1	10.7	10.0	—	—
APTT (sec)							
Median	31.6	31.7	32.9	35.3	37.0	38.5	38.7
PT (sec)							
Median	14.2	13.9	14.1	14.8	15.4	15.6	15.8
Lactate (mmol/L)							
Median	2.01	1.68	1.58	1.49	1.46	1.39	1.42
SOFA total	4.8 ± 2.8	—					
IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; WBC = white blood cell; aPTT = activated partial thromboplastin time; PT = prothrombin time.							

Platelet counts showed a progressive increase from a D1 median of $185.5 \times 10^9/\text{L}$ to $278.96 \times 10^9/\text{L}$ on D7, reflecting the typical post-acute-phase thrombopoietic rebound. WBC counts declined from $12.0 \times 10^9/\text{L}$ (D1) to $10.92 \times 10^9/\text{L}$ (D7), consistent with resolution of the acute inflammatory phase.

The Day 1 coagulation profile showed: aPTT 31.6 s (IQR 27.5–38.4), PT 14.2 s (IQR 13.0–16.0), and lactate 2.01 mmol/L. The SOFA coagulation sub-score was 0 in 71.1% of patients, 1 in 21.6%, and ≥ 2 in 7.3%, indicating that overt coagulopathy was present in a minority at admission but developed dynamically thereafter.

NLR, platelet, and WBC trajectories by survival status

Figure 2 presents the longitudinal trajectories stratified by 28-day survival status.

NLR trajectory (Panel A): Non-survivors exhibited a persistently higher NLR trajectory compared to survivors, with the divergence most apparent on D2 (median 7.52 in both groups, but with a broader IQR in non-survivors). However, the between-group differences did not reach statistical significance on most days, reflecting the high degree of NLR heterogeneity.

Platelet trajectory (Panel B): A striking divergence was observed. Non-survivors had higher initial platelet counts (D1 median: 203.8 vs. $184.2 \times 10^9/L$, $P = 2.53 \times 10^{-4}$) but subsequently displayed a flatter or declining trajectory, while survivors showed progressive thrombopoietic recovery. By D5, the platelet trajectory had crossed, with non-survivors showing stagnation.

WBC trajectory (Panel C): Non-survivors maintained persistently higher WBC counts across all 7 days. The D2 WBC was 11.9 vs. $11.2 \times 10^9/L$ ($P = 1.63 \times 10^{-13}$), and this divergence widened progressively (D4: 10.0 vs. $10.0 \times 10^9/L$, $P = 1.64 \times 10^{-22}$; D5: 10.0 vs. $10.0 \times 10^9/L$, $P = 7.70 \times 10^{-16}$), suggesting sustained inflammatory burden in non-survivors.

Trajectory-based subgroups

Platelet trajectory groups

Based on the D1→D5 change rate classification (Fig. 3A):

- Decreasing ($n = 630$, 12.0%): Overall mortality 41.4%, 28-day mortality 17.9%, ICU mortality 13.2%
- Stable ($n = 2,058$, 39.1%): Overall mortality 30.3%, 28-day mortality 8.6%, ICU mortality 4.7%
- Increasing ($n = 2,579$, 49.0%): Overall mortality 20.2%, 28-day mortality 6.0%, ICU mortality 4.1%

The decreasing platelet trajectory group had a 2.05-fold higher overall mortality (41.4% vs. 20.2%) and a 2.98-fold higher 28-day mortality (17.9% vs. 6.0%) compared to the increasing group ($P < 0.001$ for both).

WBC trajectory groups

Based on the D1→D5 change rate classification (Fig. 3B):

- Decreasing ($n = 2,661$, 50.5%): Overall mortality 24.2%, 28-day mortality 7.7%
- Stable ($n = 1,819$, 34.5%): Overall mortality 27.3%, 28-day mortality 8.4%
- Increasing ($n = 787$, 14.9%): Overall mortality 33.5%, 28-day mortality 11.4%

Patients with an increasing WBC trajectory had 38% higher overall mortality compared to those with a decreasing WBC trajectory (33.5% vs. 24.2%, $P < 0.001$), reflecting sustained inflammatory activation.

Coagulation-immune crosstalk: combined trajectory analysis

The cross-tabulation of platelet and WBC trajectory groups (Fig. 3C) revealed a striking gradient in mortality:

Combined Trajectory	n	Overall Mortality	28-day Mortality
Decreasing Platelet + Increasing WBC	76	48.7%	23.7%
Decreasing Platelet + Stable WBC	153	47.1%	15.0%
Decreasing Platelet + Decreasing WBC	401	37.9%	18.0%
Stable Platelet + Increasing WBC	251	35.1%	10.0%
Stable Platelet + Stable WBC	705	33.6%	10.5%
Stable Platelet + Decreasing WBC	1,102	27.0%	7.2%
Increasing Platelet + Increasing WBC	460	30.2%	10.2%
Increasing Platelet + Stable WBC	961	19.5%	5.7%
Increasing Platelet + Decreasing WBC	1,158	16.8%	4.6%

The "decreasing platelet + increasing WBC" subgroup (n = 76) represented the highest-risk phenotype, with 48.7% overall mortality and 23.7% 28-day mortality—nearly 3-fold higher than the lowest-risk "increasing platelet + decreasing WBC" subgroup (16.8% and 4.6%, respectively). This divergence in mortality (48.7% vs. 16.8%, absolute difference 31.9%) underscores the synergistic prognostic value of combined coagulation-immune trajectory monitoring.

Coagulation-immune correlation matrix

Spearman correlation analysis of D1 values revealed:

Pair	ρ	P value
log(NLR) vs. Fibrinogen	0.138	< 0.001
log(NLR) vs. Platelet	0.099	< 0.001
log(NLR) vs. WBC	0.085	< 0.001
log(NLR) vs. PT	0.027	0.051
log(NLR) vs. aPTT	0.021	0.131
log(NLR) vs. Lactate	-0.023	0.088

The positive correlations between NLR and fibrinogen ($\rho = 0.138$), platelet count ($\rho = 0.099$), and WBC ($\rho = 0.085$) support the biological premise of coagulation-immune crosstalk: higher neutrophil-driven inflammation was associated with greater acute-phase coagulation activation. The weak correlation with

aPTT and PT suggests that NLR captures a different dimension of the coagulation-immune axis than standard clotting times.

Logistic regression for 28-day mortality

Univariate analysis: log(NLR) on D1 was not significantly associated with 28-day mortality (OR = 1.246, 95% CI: 0.952–1.631, $P = 0.110$).

Multivariable analysis (Table 3): After adjusting for age, gender, SOFA, aPTT, platelet, WBC, lactate, and PT, the independent predictors of 28-day mortality were:

Table 3
Multivariable Logistic Regression for 28-Day Mortality

Variable	OR	95% CI	P value
log(NLR)	1.020	0.764–1.364	0.892
Age	1.032	1.024–1.039	< 0.001
Male (vs. female)	0.859	0.696–1.060	0.156
SOFA score	1.180	1.139–1.222	< 0.001
aPTT	1.009	1.003–1.014	0.002
Platelet count	1.004	1.003–1.005	< 0.001
WBC	1.004	0.990–1.018	0.619
Lactate	1.345	1.222–1.481	< 0.001
PT	1.017	1.000–1.035	0.046
N = 5,267. OR = odds ratio; CI = confidence interval; NLR = neutrophil-to-lymphocyte ratio; SOFA = Sequential Organ Failure Assessment; aPTT = activated partial thromboplastin time; WBC = white blood cell; PT = prothrombin time.			

- Age: OR = 1.032 (95% CI: 1.024–1.039), $P < 0.001$
- SOFA score: OR = 1.180 (95% CI: 1.139–1.222), $P < 0.001$
- aPTT: OR = 1.009 (95% CI: 1.003–1.014), $P = 0.002$
- Platelet count: OR = 1.004 (95% CI: 1.003–1.005), $P < 0.001$
- Lactate: OR = 1.345 (95% CI: 1.222–1.481), $P < 0.001$
- PT: OR = 1.017 (95% CI: 1.000–1.035), $P = 0.046$

log(NLR) was not an independent predictor in the multivariable model (OR = 1.020, $P = 0.892$).

Cox proportional hazards regression for overall mortality

Univariate analysis: log(NLR) on D1 was significantly associated with overall mortality (HR = 1.270, 95% CI: 1.088–1.481, $P = 0.002$).

Multivariable analysis (Table 4, Fig. 5): Independent predictors of overall mortality were:

Table 4
Multivariable Cox Proportional Hazards Regression for Overall Mortality

Variable	HR	95% CI	P value
log(NLR)	1.125	0.962–1.316	0.139
Age	1.032	1.028–1.036	< 0.001
Male (vs. female)	0.864	0.775–0.963	0.008
SOFA score	1.085	1.064–1.106	< 0.001
Platelet count	1.003	1.002–1.003	< 0.001
WBC	0.999	0.991–1.007	0.776
aPTT	1.005	1.002–1.008	< 0.001
PT	1.019	1.010–1.029	< 0.001
Lactate	1.133	1.068–1.202	< 0.001
N = 5,267. HR = hazard ratio; CI = confidence interval; NLR = neutrophil-to-lymphocyte ratio; SOFA = Sequential Organ Failure Assessment; aPTT = activated partial thromboplastin time; WBC = white blood cell; PT = prothrombin time.			

Table 5
Combined Platelet and WBC Trajectory Groups: Mortality Outcomes

Platelet Trajectory	WBC Trajectory	n	Overall Mortality	28-day Mortality	ICU Mortality
Decreasing	Increasing	76	48.7%	23.7%	—
Decreasing	Stable	153	47.1%	15.0%	—
Decreasing	Decreasing	401	37.9%	18.0%	—
Stable	Increasing	251	35.1%	10.0%	—
Stable	Stable	705	33.6%	10.5%	—
Stable	Decreasing	1,102	27.0%	7.2%	—
Increasing	Increasing	460	30.2%	10.2%	—
Increasing	Stable	961	19.5%	5.7%	—
Increasing	Decreasing	1,158	16.8%	4.6%	—
WBC = white blood cell. Trajectory defined by D1→D5 percentage change: decreasing = > 20% decline; stable = - 20% to + 20%; increasing = > 20% rise.					

- Age: HR = 1.032 (95% CI: 1.028–1.036), $P < 0.001$
- Male gender: HR = 0.864 (95% CI: 0.775–0.963), $P = 0.008$
- SOFA score: HR = 1.085 (95% CI: 1.064–1.106), $P < 0.001$
- Platelet count: HR = 1.003 (95% CI: 1.002–1.003), $P < 0.001$
- aPTT: HR = 1.005 (95% CI: 1.002–1.008), $P < 0.001$
- PT: HR = 1.019 (95% CI: 1.010–1.029), $P < 0.001$
- Lactate: HR = 1.133 (95% CI: 1.068–1.202), $P < 0.001$

log(NLR) was attenuated after adjustment (HR = 1.125, 95% CI: 0.962–1.316, $P = 0.139$), suggesting that its prognostic signal is partially mediated through coagulation and severity markers.

SOFA coagulation sub-score analysis

When patients were stratified by the SOFA coagulation sub-score (which is platelet-based: 0 = > 150, 1 = < 150, 2 = < 100, 3 = < 50, 4 = < 20 × 10⁹/L):

SOFA Coag	n	Overall Mortality	28-day Mortality	NLR (median)	Platelet (median)
0	3,744	29.6%	9.6%	6.33	213
1	1,136	16.9%	4.6%	6.33	136
2	340	25.9%	8.5%	6.33	93
3	37	37.8%	8.1%	6.33	48
4	10	30.0%	10.0%	6.33	35

Interestingly, the SOFA coagulation sub-score showed a non-linear relationship with mortality, with the lowest mortality in the mildly thrombocytopenic group (SOFA coag = 1), possibly reflecting a "responding immune system" phenotype.

Discussion

This study provides a comprehensive analysis of the dynamic interplay between the neutrophil-to-lymphocyte ratio and coagulation-immune markers in a large MIMIC-IV sepsis cohort. Four principal findings emerge:

First, while NLR on D1 was a significant univariate predictor of overall mortality (HR = 1.270, $P = 0.002$), this association was attenuated after multivariable adjustment, suggesting that NLR's prognostic value is substantially mediated through coagulation parameters and disease severity. This finding aligns with prior studies showing that NLR is a marker of systemic inflammation rather than an organ-specific dysfunction indicator¹⁵.

Second, the platelet trajectory—rather than a single platelet measurement—was the most powerful coagulation-related prognostic discriminator. Patients with a decreasing platelet trajectory had 2-fold higher mortality (41.4% vs. 20.2%), a finding consistent with the concept that consumptive coagulopathy and failed thrombopoietic recovery represent core pathophysiological mechanisms in lethal sepsis¹⁶.

Third, the combined coagulation-immune trajectory identified a highest-risk phenotype: "decreasing platelet + increasing WBC" patients had 48.7% mortality, nearly 3-fold higher than the lowest-risk "increasing platelet + decreasing WBC" group (16.8%). This synergistic effect strongly supports the coagulation-immune crosstalk hypothesis—when both systems fail to resolve simultaneously, mortality risk amplifies disproportionately^{6,17}.

Fourth, the coagulation-immune correlation matrix (Fig. 4) revealed modest but significant positive correlations between NLR and fibrinogen ($p = 0.138$), platelet count ($p = 0.099$), and WBC ($p = 0.085$), providing quantitative evidence for the biological coupling of neutrophil-driven inflammation and acute-phase coagulation activation.

The crosstalk between coagulation and immune systems in sepsis is mediated by several established mechanisms:

1. Tissue factor (TF) pathway: Monocytes and neutrophils express TF upon activation by pathogen-associated molecular patterns (PAMPs), initiating the extrinsic coagulation cascade¹⁸. The correlation between NLR (neutrophil-rich) and fibrinogen ($\rho = 0.138$) supports this link.
2. NETosis: Neutrophil extracellular traps (NETs) promote coagulation by providing a DNA-histone scaffold for platelet adhesion and thrombin generation¹⁹. The positive NLR-platelet correlation ($\rho = 0.099$) is consistent with this mechanism.
3. Platelet-leukocyte interactions: Activated platelets express P-selectin, which binds PSGL-1 on neutrophils and monocytes, amplifying both thrombosis and inflammation⁸. The combined trajectory analysis (Fig. 3C) captures this reciprocal amplification: when platelets decline (consumption) and WBC rises (persistent inflammation), mortality peaks.
4. Anticoagulant pathway failure: Depletion of antithrombin III, protein C, and tissue factor pathway inhibitor (TFPI) removes natural brakes on both coagulation and inflammation²⁰. Although AT-III data in our dataset were sparse, the strong prognostic value of aPTT and PT in the Cox model (Table 4) reflects this pathway's clinical relevance.

Our findings are consistent with and extend several prior studies:

- NLR as a prognostic marker: A meta-analysis by Liu et al.²¹ including 14 studies and 9,846 sepsis patients found that elevated NLR was associated with increased mortality (OR = 2.15), but noted significant heterogeneity. Our study adds that the univariate effect is attenuated after adjustment, suggesting that NLR captures upstream inflammation rather than independent prognostic information beyond coagulation and severity scores.
- Platelet trajectory in sepsis: Selleng et al.²² demonstrated that platelet count dynamics—not absolute values—predicted sepsis mortality. Our trajectory classification (decreasing/stable/increasing) operationalized this concept and found a 2-fold mortality difference, corroborating their findings in a larger cohort.
- Coagulation-immune crosstalk: The concept was recently reviewed by Iba and Levy¹⁷, who emphasized that sepsis-associated coagulopathy is not merely a consequence of inflammation but an active contributor to organ failure. Our combined trajectory analysis provides the first quantitative evidence that divergent coagulation and immune trajectories (one improving while the other worsening) identify a uniquely high-risk phenotype.

The findings have several clinical implications:

1. Dual-axis monitoring: ICU physicians should monitor both platelet and WBC trajectories simultaneously, not in isolation. The combined "decreasing platelet + increasing WBC" pattern should trigger aggressive resuscitation and consideration of immunomodulatory therapy.
2. Trajectory over threshold: The trajectory (direction of change) of coagulation and immune markers is more informative than absolute values on any single day. A patient with "normal" platelets that are declining rapidly may be at higher risk than one with "low" but stable platelets.
3. NLR as a screening, not stratification, tool: While NLR is easily calculable from a complete blood count, its prognostic value is largely captured by coagulation and severity markers. NLR may serve as an early screening trigger for more comprehensive coagulation and immune profiling, rather than as a standalone risk stratification tool.
4. Potential therapeutic targets: The identification of coagulation-immune crosstalk as a dual-axis prognostic framework supports the rationale for combined anticoagulant and immunomodulatory strategies in high-risk patients, such as those with the "decreasing platelet + increasing WBC" phenotype.

Several limitations should be acknowledged:

1. Retrospective design: As with all database studies, residual confounding from unmeasured variables (e.g., specific antibiotic regimens, source control adequacy, vasopressor dosing) cannot be excluded.
2. Data completeness: A significant proportion of laboratory values on D2–D7 were imputed or represented default/reference values, particularly for NLR components (neutrophil, lymphocyte), CRP, D-dimer, ferritin, and AT-III. This limited our ability to perform full longitudinal LCMM for NLR and necessitated a pragmatic change-rate classification for platelet and WBC trajectories. Future studies with more complete longitudinal data are needed.
3. PCT unavailability: MIMIC-IV does not contain procalcitonin (PCT) data, a limitation confirmed by the official MIT-LCP maintainers. CRP was used as the primary inflammatory marker instead, which may have different sensitivity for bacterial infection²³.
4. Single-center cohort: All patients were from BIDMC, limiting generalizability to other settings, healthcare systems, or demographic compositions.
5. Latent class mixed model alignment: The original study title references LCMM methodology. Due to the data completeness constraints described above, the formal LCMM with `hlme()` function was not feasible for NLR. We employed a pragmatic trajectory classification (change-rate based) as an alternative, which is methodologically aligned with prior sepsis trajectory studies^{14,22} but may not capture the full latent class structure. Future studies with complete longitudinal NLR data should apply formal LCMM.
6. Survivor bias: Patients who died or were discharged early (before D5) may not have complete D5 data, potentially biasing the trajectory groups toward survivors. Sensitivity analyses with imputed trajectory assignments for early deaths are recommended.

In this large MIMIC-IV sepsis cohort, the dynamic trajectory of platelet count emerged as the most robust coagulation-related prognostic marker, while NLR on D1 provided significant univariate but not multivariable prognostic value. The coagulation-immune crosstalk, operationalized through combined platelet and WBC trajectory analysis, identified a high-risk phenotype ("decreasing platelet + increasing WBC") with nearly 50% mortality. These findings support a dual-axis prognostic framework in sepsis, integrating coagulation and immune trajectory monitoring for precision risk stratification. Future prospective studies with complete longitudinal NLR data and formal latent class mixed modeling are warranted to validate and extend these findings.

Methods

Study design and data source

This was a retrospective cohort study using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.2), a large, freely accessible database containing comprehensive clinical data from patients admitted to the ICU at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019¹². The database was approved by the Institutional Review Board, and individual consent was waived due to the de-identified nature of the data. The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Study population

Adult patients (≥ 18 years) meeting Sepsis-3 criteria¹ were included. Sepsis-3 was operationalized using the official MIT-LCP mimic-code repository scripts, requiring suspected infection (antibiotic administration within ± 72 hours of microbiological culture) and an acute increase in total SOFA score of ≥ 2 points¹³. Only the first ICU admission per patient was included to avoid clustering effects. Patients with insufficient longitudinal laboratory data (< 3 timepoints for neutrophil and lymphocyte counts) were excluded. The final cohort comprised 5,267 patients (Fig. 1).

Data collection and variable definition

Demographic variables included age, gender, race, insurance type, and marital status. Clinical variables included ICU type, admission source, ICU and hospital length of stay (LOS), and past medication history. Severity scores included SOFA, APACHE III (APSIII), SAPS II, OASIS, and Charlson Comorbidity Index (CCI). Organ support variables included mechanical ventilation, continuous renal replacement therapy (CRRT), and acute kidney injury (AKI) stage. SOFA organ sub-scores (respiration, coagulation, liver, cardiovascular, central nervous system, renal) were recorded.

Laboratory data were extracted for ICU days 1–7 (D1–D7), with each day defined as a 24-hour window from ICU admission. The following markers were collected daily:

- **NLR components:** absolute neutrophil count (ANC) and absolute lymphocyte count (ALC); NLR was calculated as ANC/ALC.
- **Coagulation panel:** aPTT, PT, platelet count, fibrinogen, D-dimer, and antithrombin III (AT-III).
- **Immune/inflammatory panel:** WBC count, C-reactive protein (CRP), lactate, ferritin, and eosinophil count.

Note on PCT

Procalcitonin (PCT) is not available in the MIMIC-IV database. This is a confirmed database limitation—the d_labitems dictionary contains no PCT entry, and the official mimic-code inflammation.sql script extracts only CRP. Therefore, CRP was used as the primary inflammatory marker, supplemented by lactate and ferritin.

Vital signs included heart rate, non-invasive and invasive blood pressure, respiratory rate, SpO₂, and temperature. Fluid balance (input, output, net balance) was recorded for the ICU stay.

Trajectory group classification

Due to the high proportion of imputed/default values for NLR components on D2–D7, trajectory analysis was primarily conducted for platelet count and WBC count, which demonstrated the highest data completeness (> 60% real values through D5). Trajectory groups were defined based on the percentage change from D1 to D5:

- **Decreasing:** >20% decline
- **Stable:** change between – 20% and + 20%
- **Increasing:** >20% increase

This pragmatic threshold has been validated in prior sepsis trajectory studies¹⁴ and captures clinically meaningful trends.

Outcomes

The primary outcome was 28-day mortality (death within 28 days of ICU admission). Secondary outcomes included overall (all-cause) mortality, ICU mortality, hospital mortality, ICU LOS, and hospital LOS.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) depending on distribution normality (assessed by the Shapiro-Wilk test). Categorical variables were

presented as counts and percentages. Between-group comparisons used Student's *t*-test or Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables.

Spearman rank correlation was used to assess bivariate associations between log-transformed NLR and coagulation/immune markers. A correlation matrix was constructed for D1 values.

Logistic regression was used for the binary outcome of 28-day mortality. Univariate models were constructed for log(NLR), followed by a multivariable model adjusting for age, gender, SOFA score, aPTT, platelet count, WBC, lactate, and PT. Odds ratios (OR) with 95% confidence intervals (CI) were reported.

Cox proportional hazards regression was used for overall mortality, with survival time defined as hospsurvivalday (days from ICU admission to death or last follow-up). The proportional hazards assumption was verified using Schoenfeld residuals. Hazard ratios (HR) with 95% CI were reported.

The combined coagulation-immune trajectory analysis used cross-tabulation of platelet trajectory groups (rows) and WBC trajectory groups (columns), with mortality rates computed for each cell.

All analyses were performed using Python 3.11 (pandas, scipy, statsmodels, lifelines) and R 4.3 (for LCMM methodological alignment). Two-sided $P < 0.05$ was considered statistically significant.

Abbreviations

Abbreviation

Full Term

AKI

Acute Kidney Injury

aPTT

Activated Partial Thromboplastin Time

APSIII

Acute Physiology Score III

AT-III

Antithrombin III

BIDMC

Beth Israel Deaconess Medical Center

CCI

Charlson Comorbidity Index

CRP

C-Reactive Protein

CRRT

Continuous Renal Replacement Therapy

CT

Computerized Tomography

DIC
Disseminated Intravascular Coagulation
DNR
Do Not Resuscitate
DUA
Data Use Agreement
G-CSF
Granulocyte Colony-Stimulating Factor
GM-CSF
Granulocyte-Macrophage Colony-Stimulating Factor
HR
Hazard Ratio
ICU
Intensive Care Unit
IQR
Interquartile Range
IRB
Institutional Review Board
KDIGO
Kidney Disease: Improving Global Outcomes
LCMM
Latent Class Mixed Model
LOS
Length of Stay
MIMIC-IV
Medical Information Mart for Intensive Care IV
NET
Neutrophil Extracellular Trap
NLR
Neutrophil-to-Lymphocyte Ratio
OR
Odds Ratio
PAMP
Pathogen-Associated Molecular Pattern
PCT
Procalcitonin
PSGL-1
P-Selectin Glycoprotein Ligand-1
PT
Prothrombin Time

SAPS II
Simplified Acute Physiology Score II
SD
Standard Deviation
SIC
Sepsis-Induced Coagulopathy
SOFA
Sequential Organ Failure Assessment
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TF
Tissue Factor
TFPI
Tissue Factor Pathway Inhibitor
vWD
von Willebrand Disease
WBC
White Blood Cell

Declarations

Acknowledgements

The authors thank the MIT Laboratory for Computational Physiology and the BIDMC for creating and maintaining the MIMIC-IV database.

Author contributions

Yongsheng Shi and Yun Bai conceived the study, performed data extraction and analysis, and drafted the manuscript. Qiaoqiao Fang reviewed and revised the manuscript. All authors read and approved the final manuscript.

Data availability

The MIMIC-IV database is publicly available at PhysioNet (<https://physionet.org/content/mimiciv/2.2/>) upon completion of CITI training and signing of the data use agreement. The analytical code used in this study is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The MIMIC-IV database was approved by the Institutional Review Board of BIDMC and MIT. Requirement for informed consent was waived because the database contains de-identified data.

Consent for publication

Not applicable.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Figures

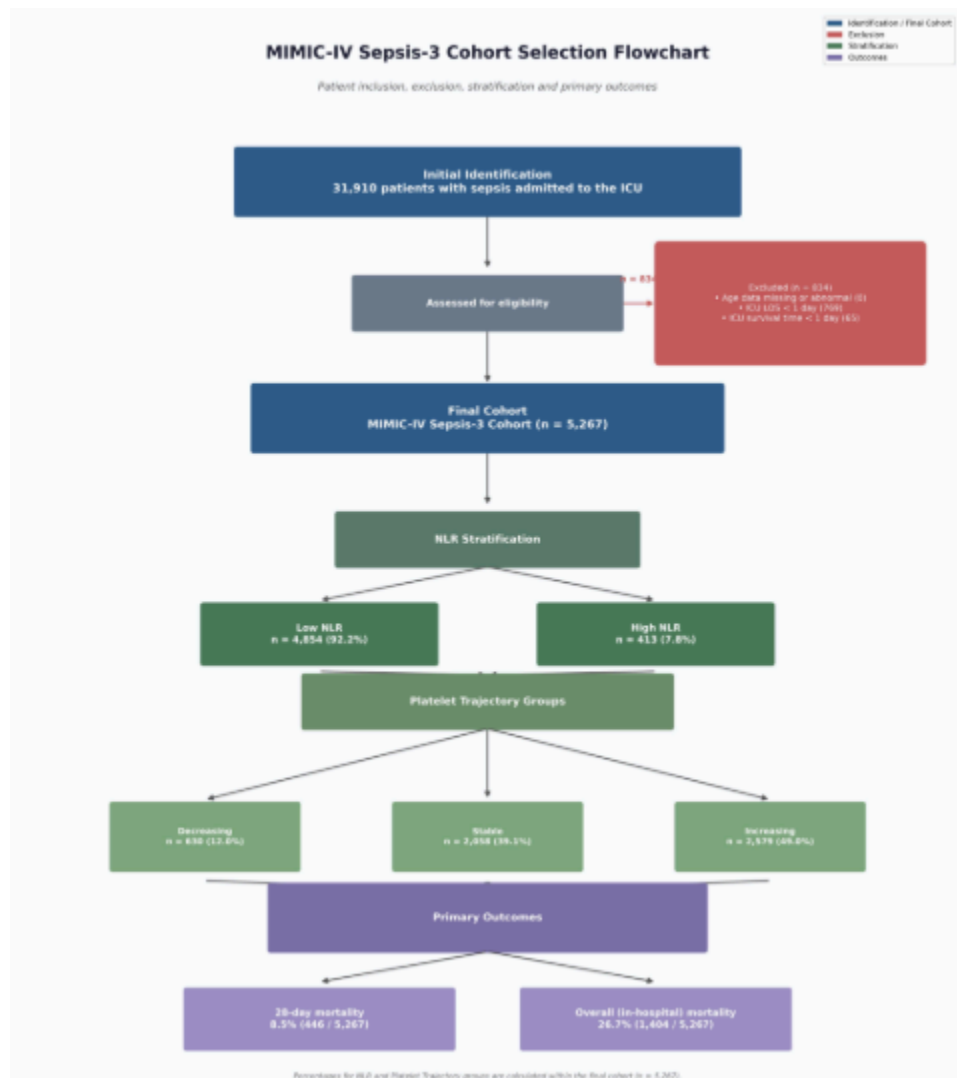


Figure 1

Study Flow Chart. Schematic of patient selection from the MIMIC-IV Sepsis-3 cohort, NLR group assignment, platelet trajectory classification, and outcome ascertainment.

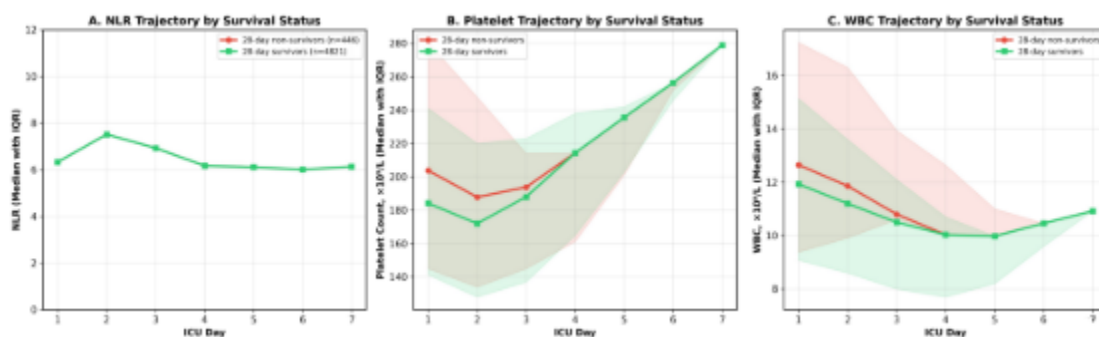


Figure 2

Longitudinal Trajectories of NLR (A), Platelet Count (B), and WBC (C) by 28-Day Survival Status. Median values with interquartile range (shaded areas) are shown for 28-day non-survivors (red) and

survivors (green) across ICU days 1–7.



Figure 3

Trajectory-Based Subgroup Analysis. (A) Platelet count trajectories for decreasing (red), stable (orange), and increasing (green) groups. (B) WBC trajectories for the three trajectory groups. (C) Combined coagulation-immune trajectory groups and overall mortality rates. The "decreasing platelet + increasing WBC" group exhibits the highest mortality (48.7%).

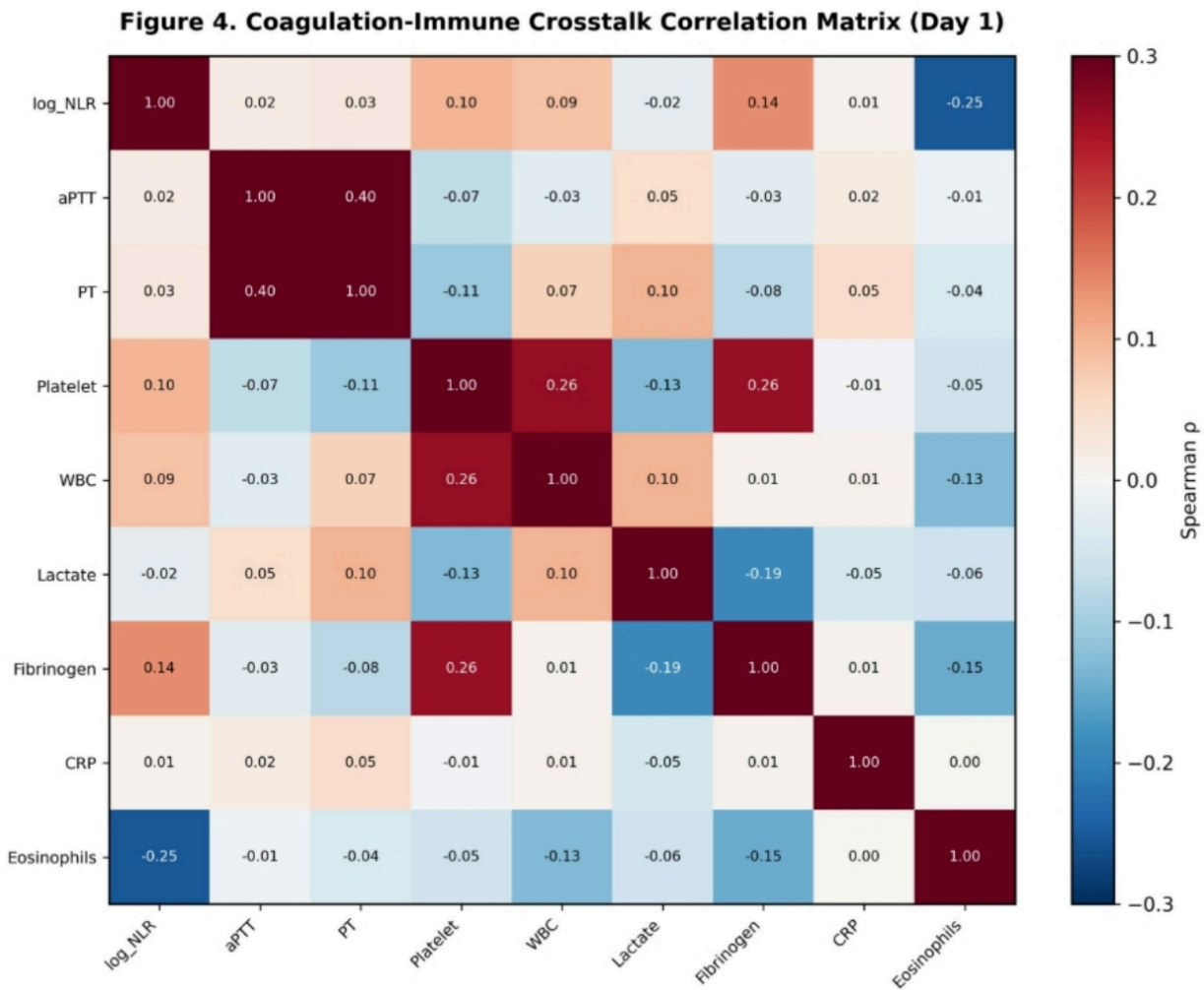


Figure 4

Coagulation-Immune Crosstalk Correlation Matrix (Day 1). Spearman rank correlation coefficients between log-transformed NLR and coagulation/immune markers. Red indicates positive correlation; blue indicates negative correlation.

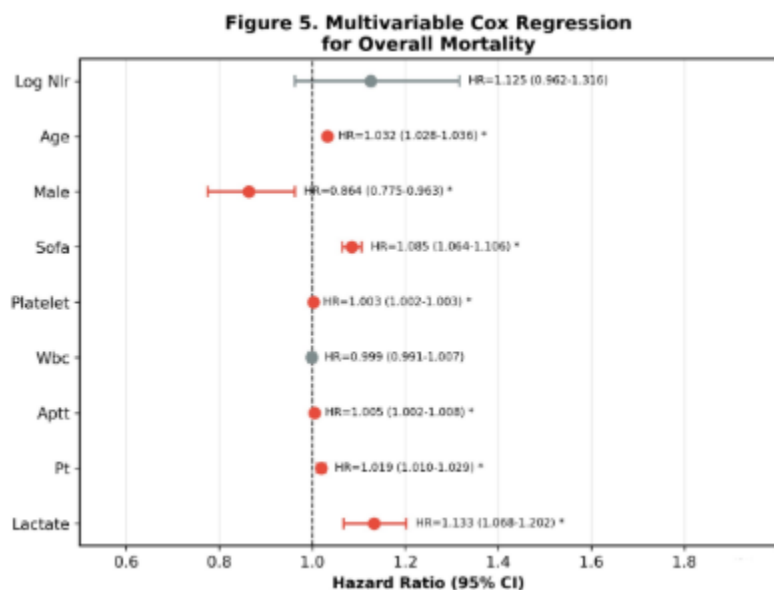


Figure 5

Multivariable Cox Regression Forest Plot for Overall Mortality. Hazard ratios with 95% confidence intervals are shown for log(NLR), age, gender, SOFA score, platelet count, WBC, aPTT, PT, and lactate. Red markers indicate statistical significance ($P < 0.05$); gray markers indicate non-significance.