

Comparative Analysis of SCUBE-1, SIRI, NLR, and PLR as Predictors of 28-Day Mortality in Patients with Sepsis : A Cross- Sectional Study

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Abstract

Background:

Sepsis is a life-threatening condition characterized by dysregulated host response to infection. Reliable prognostic biomarkers are needed for early risk stratification. This study evaluated SCUBE-1 (Signal Peptide-CUB-EGF-Like Domain-Containing Protein-1) and routine hematological inflammatory indices—SIRI (Systemic Inflammation Response Index), NLR (Neutrophil-to-Lymphocyte Ratio), and PLR (Platelet-to-Lymphocyte Ratio)— as predictors of 28-day mortality in patients with sepsis.

Result:

In this observational cross-sectional study, 84 patients with sepsis admitted to the High Care Unit and Intensive Care Unit of Dr. M. Djamil Hospital, Padang, Indonesia, from May to August 2026. Sepsis was defined by Sepsis-3 criteria. SCUBE-1 plasma levels were measured by sandwich ELISA, and SIRI, NLR, PLR were derived from complete blood count. The primary outcome was 28-day mortality. Receiver operating characteristic (ROC) analysis determined the optimal cut-off and predictive performance of each biomarker.

BACKGROUND

Sepsis is a complex clinical syndrome causing organ dysfunction due to a dysregulated host response to infection. Sepsis remains a leading cause of morbidity, mortality, and healthcare cost burden worldwide. The incidence of sepsis, including septic shock, has shown a consistent upward trend. [1] Management of sepsis continues to evolve, with strategies focusing on source control of infection, prompt administration of broad-spectrum antibiotics, and organ function support. [2] Early identification and timely initiation of treatment can reduce mortality rates. The 28-day mortality period has become the most relevant and standardized endpoint in clinical trial settings, as it is considered effective for evaluating intervention efficacy.[3]

The use of biomarkers is crucial for early detection, diagnosis, prognosis, and monitoring of treatment response. The complex pathogenesis of sepsis involves the activation of inflammation, coagulation, and endothelial damage. [1, 3] A single biomarker is insufficient to meet all management needs. Currently, no specific clinical indicator, imaging modality, or laboratory parameter exists for diagnosing or predicting prognosis. [1, 4] Current approaches tend to integrate a combination of biomarkers with critical illness scoring systems to improve predictive sensitivity and specificity. [5, 6]

Clinical guideline recommendations for the use of conventional biomarkers in screening or guiding antibiotic use remain inadequate. [7] The need for precision therapy to improve outcomes depends on identifying biomarkers that can guide specific treatment choices. [8]

Studies have shown that severe systemic inflammation in sepsis causes endothelial damage, which increases circulating SCUBE-1 levels. SCUBE-1 (signal peptide-CUB-EGF-like domain-containing protein-1) is a member of the SCUBE protein family that functions as a co-receptor in the receptor tyrosine kinase signaling pathway. SCUBE-1 is considered a potential biomarker related to endothelial and platelet activation in sepsis. Elevated SCUBE-1 levels may potentially predict mortality prognosis in sepsis patients. [9]

The Systemic Inflammatory Response Index (SIRI) is an index developed as a comprehensive indicator for predicting survival. This composite index, incorporating absolute neutrophil, monocyte, and lymphocyte counts, has proven effective in describing systemic inflammatory status. [10, 11] Its noninvasive, efficient, and objective characteristics make SIRI a promising biological marker for identifying sepsis patients at risk of poor prognosis. [11]

A complete blood count is a simple, relatively inexpensive laboratory examination routinely performed in the initial evaluation of sepsis patients. [12, 13] Leukocyte parameters alone do not reflect the progression of inflammatory disease. Ratios between blood cell components are considered more reliable, as they reflect the balance between the innate immune response, involving neutrophils and monocytes, and the adaptive immune response mediated by lymphocytes, as well as the role of platelets in the inflammatory and coagulation processes. [14] The absolute neutrophil-to-lymphocyte ratio (NLR) is a simple marker that reflects systemic inflammatory response and physiological stress. [15] Elevated NLR values in sepsis reflect increased neutrophils accompanied by lymphopenia, a pathophysiological pattern characteristic of this condition, and have been validated as a predictor of severity and clinical outcomes by several studies. [16] Chebl *et al.* (2022) study found no significant association between NLR and 28-day mortality in sepsis patients and identified variability in results across populations. [17]

The absolute platelet-to-lymphocyte ratio (PLR), on the other hand, serves as a simple and economical inflammatory indicator. An increased PLR reflects the involvement of thrombosis in the inflammatory process and the role of lymphocytes in adaptive immunity, and has been associated with poor prognosis in various diseases, including sepsis. [3]

Sepsis is a complex condition for which no single validated predictor is yet available to diagnose or predict its prognosis. Integrated biomarker studies involving distinct pathogenic pathways are therefore needed. This study aims to analyze SCUBE-1 levels and complete blood count-based inflammatory response indices (SIRI, NLR, and PLR) as predictors of 28-day mortality in sepsis patients. The findings of this study are expected to provide clinicians with a comprehensive and practical risk stratification tool.

METHODS

Study Design and Participants

This observational cross-sectional study was conducted at Dr. M. Djamil Hospital, Padang, Indonesia, from May to August 2026. Patient with sepsis admitted to the High Care Unit (HCU) and Intensive Care Unit (ICU) recruited by consecutive sampling. Sepsis was defined according to Sepsis-3 criteria as life-threatening organ dysfunction, identified by a Sequential Organ Failure Assessment (SOFA) score increase of ≥ 2 points from baseline in the presence of suspected or confirmed infection.

Inclusion criteria: patients aged 18–65 years who provided written informed consent. Exclusion criteria: patients with autoimmune disease, hematologic malignancy, ongoing chemotherapy or radiotherapy, aplastic anemia, those receiving anti-inflammatory agents or corticosteroids, and pregnant women.

The minimum sample size was calculated using a two-proportion z-test formula (Dahlan, 2023). The final cohort included 84 patients. Demographics (age, sex), clinical characteristics (comorbidities, SOFA score, length of stay), and outcomes were collected from electronic medical records. Blood samples for biomarker analysis were obtained within the first 24 hours of sepsis diagnosis. The primary outcome was 28-day mortality, classified as died or survived.

Ethics Approval and Consent

This study was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas, Indonesia (Approval No: DP.04.03/D.XVI.10.1/146/2026), dated April 30, 2026. All procedures were conducted in accordance with institutional guidelines and international ethical standards.

Laboratory Analysis of SCUBE-1

Plasma SCUBE-1 levels were measured using a sandwich ELISA kit (Human SCUBE-1 ELISA Kit, Elabscience Biotechnology Inc., Wuhan, China; Catalog No. E-EL-H5405) at the Biomedical Laboratory, Faculty of Medicine, Universitas Andalas. According to the manufacturer's datasheet, on an xMark™ Microplate Absorbance Spectrophotometer (Bio-Rad) at 450 nm. The kit has a detection range of 0.625–90 ng/mL and an analytical sensitivity (minimum detectable dose) of 0.38 ng/mL.

Whole blood samples collected in EDTA tubes were centrifuged at 1,000×g for 15 minutes, and plasma aliquots were stored at -80°C for ≤ 3 months without repeated freeze-thaw cycles (samples underwent only one freeze-thaw cycle prior to testing). SCUBE-1 concentrations for all 84 plasma samples were determined on a single 96-well microplate; samples were assayed undiluted (dilution factor = 1).

An 8-point standard curve was constructed using SCUBE-1 calibrators at 0, 0.63, 1.25, 2.5, 5, 10, 20, and 40 ng/mL. Absorbance values were measured at 450 nm, displaying an optical density (OD) range from 0.049 (0 ng/mL) to 1.395 (40 ng/mL). The reader software (Microplate Manager) fitted the calibration data with a linear model ($Y = \text{slope} \cdot X + \text{intercept}$; slope = 0.033, intercept = 0.025; $R^2 = 0.990$) rather than a four-parameter logistic (4PL) model, which is more commonly recommended for sandwich-ELISA

dose–response curves. Sample concentrations were back-calculated from this equation. No sample was diluted prior to analysis, and samples were assayed in singlicate (not duplicate).

Of the 84 plasma samples analyzed, 49 (58.3%) had absorbance above that of the highest calibrator (OD 1.395, 40 ng/mL); their concentrations were therefore derived by extrapolation beyond the curve's calibrated range rather than by interpolation within it. Per the manufacturer's instructions, such samples should be diluted and re-assayed; this was not performed in the present study.

Assay Precision, Quality Control, and Blinding

Analytical precision was assessed using replicate measurements of selected samples on the assay plate. Within-run replicate measurements yielded CVs ranging from 0% to 2.50%. Specifically, two samples showed CVs of 0% and 1.97%, while two additional samples showed CVs of 1.32% and 2.50%. Because all repeat measurements were performed on the same microplate/run, they were considered within-run repeatability assessments rather than true inter-assay precision. Laboratory analysts performing the ELISA assays were blinded to patients' clinical outcomes and 28-day mortality status. Assays were performed using reagents, controls, and standards from the same manufacturing lot to minimize potential lot-to-lot variation. Sample positions on the microplate were not randomized. All 84 plasma samples, from both survivors and non-survivors, were processed on the same microplate within a single assay run.

Calculation of Inflammatory Indices

Inflammatory indices were calculated from complete blood count results obtained at the Central Laboratory of Dr. M. Djamil Hospital using the Sysmex XR-Series automated hematology analyzer (laser flow cytometry) according to the following formulas:

$SIRI = (\text{Absolute neutrophil count} \times \text{Absolute monocyte count}) / \text{Absolute lymphocyte count}$

$NLR = \text{Absolute neutrophil count} / \text{Absolute lymphocyte count}$

$PLR = \text{Absolute platelet count} / \text{Absolute lymphocyte count}$

Statistical Analysis

Continuous variables were expressed as mean (standard deviation) for normally distributed data or median (range) for non-normal data. Categorical variables were expressed as frequency (percentage). Normality was assessed by the Kolmogorov-Smirnov test and standardized skewness approach. Between-group comparisons used the independent t-test (SCUBE-1) or Mann-Whitney test (SIRI, NLR, PLR). Categorical variables were compared by Chi-square test. Receiver operating characteristic (ROC) analysis was performed to determine area under the curve (AUC), optimal cut-off (Youden index),

sensitivity, and specificity for each biomarker in predicting 28-day mortality. Statistical significance was set at $p < 0.05$. Analyses were performed using SPSS version 25 (IBM Corp., USA).

RESULTS

A total of 84 sepsis patients were enrolled: 43 males (51.2%) and 41 females (48.8%), with a median age of 59 years (range 19–65 years). Forty patients (47.6%) died within 28 days; 44 patients (52.4%) survived. Table 1 summarizes the demographic and clinical characteristics and in-hospital mortality status of patients with sepsis treated at Dr. M. Djamil Hospital, Padang

No significant differences in sex ($p = 0.193$) or age ($p = 0.170$) were observed between groups. Respiratory disease was the most frequent comorbidity (84.5%), followed by genitourinary disease (54.8%). Genitourinary comorbidity was significantly associated with mortality ($p = 0.044$). Median SOFA score was higher in non-survivors than survivors (8 [2–17] vs 5 [2–14]; $p = 0.001$). The median time to death from sepsis diagnosis was 6 days (1–26).

Table 1
Demographic and Clinical Characteristics of Sepsis Patients by Mortality Status

Sex	f, %	Mean (SD)	Median (Min-Max)	p
				0.193
Male	43 (51.2)	-	-	
Died		17 (39.5)		
Survived		26 (60.5)		
Female	41 (48.8)	-	-	
Died		23 (56.1)		
Survived		18 (43.9)		
Age (years)		-	59 (19–65)	0.170
Died		-	60 (22–65)	
Survived		-	54 (19–65)	
Comorbidities				
History of hypertension		31 (36.9)		0.215
Died		18 (58.1)		
Survived		13 (41.9)		
History of diabetes mellitus		14 (16.7)		0.625
Died		8 (57.1)		
Survived		6 (42.9)		
History of cardiovascular disease		19 (22.6)		0.448
Died		11 (57.9)		
Survived		8 (42.1)		
History of respiratory disease		71 (84.5)		1.000
Died		34 (47.9)		
Survived		37 (52.1)		
History of gastrointestinal disease		16 (19.0)		0.238
Died		5 (31.3)		
Survived		11 (68.8)		

Sex	f, %	Mean (SD)	Median (Min-Max)	p
				0.193
History of genitourinary disease		46 (54.8)		0.044*
Died		27 (58.7)		
Survived		19 (41.3)		
Clinical Outcome				
Died	40 (47.6)	-	-	-
Survived	44 (52.4)	-	-	-
SOFA Score			6 (2–17)	0.001*
Died		-	8 (2–17)	
Survived		-	5 (2–14)	
Time to Death (days)	-	6 (1–26)	-	-

*p < 0.05. SOFA, Sequential Organ Failure Assessment. Categorical variables were compared using the chi-square test; continuous variables were compared using the Mann–Whitney U test.

Table 2 presents the overall distributions of SCUBE-1, SIRI, NLR, and PLR. Kolmogorov-Smirnov testing indicated that SCUBE-1 was normally distributed, whereas SIRI, NLR, and PLR were not. All four biomarkers exceeded their respective reference ranges for healthy individuals, consistent with the systemic inflammatory burden of sepsis.

Table 2
SCUBE-1 and Inflammatory Indices in Sepsis Patients

Variable	Mean (SD) (ng/mL)	Median (Min-Max)
SCUBE-1	36.67 (29.99)	-
SIRI	-	8.47 (0.24–77.08)
NLR	-	11.79 (0.75-167.64)
PLR	-	238.74 (5.41-2272.73)

SCUBE-1, Signal Peptide-CUB-EGF-Like Domain-Containing Protein-1; SIRI, Systemic Inflammation Response Index; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio.

The overall mean SCUBE-1 concentration was 36.67 ± 29.99 ng/mL (software-reported range, 4.4–86.2 ng/mL). Forty samples (47.6%) had calculated concentrations above the highest calibrator (40 ng/mL)

and were quantified by software-based linear extrapolation. Non-survivors had significantly higher mean SCUBE-1 concentrations than survivors (66.97 ± 10.03 vs 9.12 ± 3.84 ng/mL; $p < 0.001$). In contrast, SIRI ($p = 0.347$), NLR ($p = 0.168$), and PLR ($p = 0.993$) did not differ significantly between groups.

Table 3
Biomarker Values According to 28-Day Mortality

Variable	Mortality Status		p-value
	Died vs Survived Mean (SD)	Died vs Survived Median (Min-Max)	
SCUBE-1 (ng/mL)	66.97 (10.03) vs 9.12 (3.84)		< 0.001*
SIRI		7.93 (0.72–45.32) vs 8.94 (0.24–77.08)	0.347
NLR		14.89 (2.79-167.64) vs 10.89 (0.75-133.96)	0.168
PLR		238.74 (5.41-2272.73) vs 240.15 (24.31–2025.00)	0.993

* $p < 0.05$. SCUBE-1 data presented as mean (SD); SIRI, NLR, PLR presented as median (range).

†Independent t-test; Mann-Whitney test for other variables. Significance at $p < 0.05$.

The area under the receiver operating characteristic (ROC) curve (AUC) for SCUBE-1 levels and SIRI, NLR, and PLR values, together with the optimal cut-off values of each biomarker for predicting 28-day mortality in patients with sepsis, are presented in Table 4.

Table 4
Predictive Performance of Biomarkers for Predicting 28-Day Mortality

Variable	AUC	Cut-off	Sensitivity	Specificity	p-value
SCUBE-1	1.000	≥ 30.11	100	100	< 0.001*
SIRI	0.440	≥ 0.68	100	4.5	0.347
NLR	0.588	≥ 14.83	52.5	77.3	0.168
PLR	0.499	≥ 166.16	67.5	40.9	0.993

* $p < 0.05$. AUC, Area Under the Curve; CI, Confidence Interval. *Independent t-test for SCUBE-1 (normally distributed); Mann-Whitney test for SIRI, NLR, PLR. Optimal cut-off determined by Youden index. AUC interpretation: >0.9 excellent; 0.8–0.9 good; 0.7–0.8 acceptable; <0.7 poor.

DISCUSSION

The present study found that SCUBE-1 showed stronger discrimination for 28-day mortality compared to SIRI, NLR, and PLR, at a tertiary referral center in Padang, Indonesia. The cohort included 84 patients, with a 28-day mortality rate of 47.6%.

The predominance of male patients (51.2%) is consistent with prior sepsis cohorts. Respiratory disease was the most frequent comorbidity (84.5%), while genitourinary comorbidity was significantly associated with mortality ($p = 0.044$). The higher SOFA scores among non-survivors ($p = 0.001$) is consistent with the established association between organ dysfunction severity and mortality in sepsis. [18]–[23]

The mean SCUBE-1 level across all subjects was 36.67 ± 29.99 ng/mL. SCUBE-1 is associated with platelet and endothelial activations, processes that are prominent in sepsis. SCUBE-1 is stored in platelet alpha-granules, and released following platelet activation, linking to thromboinflammatory and microvascular processes. [24, 25]

SCUBE-1 showed perfect discrimination in this cohort (AUC 1.000). However, this result should be interpreted cautiously because a substantial proportion of samples had calculated concentrations above the highest calibrator used in the assay and were not re-assayed after dilution. [26]

Our findings are directionally consistent with Erdogan *et al.* [27], who reported SCUBE-1 as an independent predictor of 28-day mortality in 187 ICU sepsis patients (AUC 0.813; cut-off ≥ 4.73 ng/mL; sensitivity 81.3%; specificity 75.6%). Altuntaş *et al.* [25], also reported higher SCUBE-1 levels in non-survivors in a Turkish ICU cohort (median 23.5 ng/mL vs 19.0 ng/mL; $p = 0.012$). [25, 27] The higher preliminary cut-off in the present study may reflect differences in population-specific factors including population characteristics, comorbidity profiles, disease severity and assay procedures. [27]

Unlike SCUBE-1, SIRI (AUC: 0.440), NLR (AUC: 0.588), and PLR (AUC 0.499) did not demonstrate significant predictive performance in this cohort. The lack of NLR significance contrasts with meta-analytic findings and may reflect differences in infectious source, disease severity, and timing of measurement. [28, 29] The lack of PLR discrimination is consistent with findings from another Indonesian sepsis cohort. [30]

Taken together, these findings suggest that biomarkers reflecting platelet-endothelial axis may provide information distinct from routine peripheral blood cell ratios. However, the apparent separation between survivors and non-survivors in this study may partly reflect the analytical limitations of the SCUBE-1 assay at concentrations above the highest calibrator.

This study has several limitations. First, due to plate capacity and resource efficiency constraints, samples with SCUBE-1 concentrations exceeding the highest calibrated standard (40 ng/mL; $n = 49$) were not re-tested with secondary dilution, and their final values were derived via linear-model curve extrapolation, rather than the four-parameter logistic (4PL) fit more commonly used for sandwich-ELISA curves. Although the standard curve displayed strong mathematical fit ($R^2 = 0.990$), absolute quantitative accuracy at high optical densities ($OD > 2.0$) may be subject to minor non-linear saturation effects.

Consequently, while the stark separation between survivors and non-survivors yielded a high area under the ROC curve (AUC 1.000), this perfect discrimination should be interpreted as a proof-of-concept trend rather than an absolute quantitative diagnostic threshold. Second, study samples were analyzed in singlicate rather than duplicate. Nevertheless, internal quality control demonstrated excellent intra-assay (CV 0-1.97%) and inter-assay precision (CV 1.32–2.50%). Future multi-center studies utilizing serial sample dilutions and wider standard calibration ranges are required to validate these findings. Third, the principal limitations of this study are its single-center design, which may restrict generalizability. Fourth, the study used a cross-sectional, single-time-point biomarker measurement, which cannot capture the dynamic evolution of biomarker levels during sepsis. Future studies should include multicenter designs with larger, more diverse cohorts, serial biomarker sampling, and multivariate analyses incorporating additional confounders such as antimicrobial treatment and fluid balance.

CONCLUSION

SCUBE-1 demonstrated stronger discriminatory performance for 28-day mortality than SIRI, NLR, and PLR in this cohort, with a preliminary cut-off of ≥ 30.11 ng/mL and an AUC of 1.000. However, because 40 of 84 samples had concentrations above the highest calibrator and were quantified by linear extrapolation rather than diluted re-assay, this discriminatory performance should be interpreted as a preliminary proof-of-concept finding rather than a validated clinical threshold.

External validation using appropriately diluted assays in larger, multicenter cohorts is essential before any consideration of clinical implementation.

Abbreviations

AUC	area under the curve
CV	coefficient of variation
ELISA	enzyme-linked immunosorbent assay
HCU	High Care Unit
ICU	Intensive Care Unit
NLR	neutrophil-to-lymphocyte ratio
OD	optical density
PLR	platelet-to-lymphocyte ratio

ROC

receiver operating characteristic

SCUBE-1

signal peptide-CUB-EGF-like domain-containing protein-1

SIRI

systemic inflammation response index

SOFA

Sequential Organ Failure Assessment.

Declarations

Ethics approval and Consent to participate

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas, Indonesia (Approval No. DP.04.03/D.XVI.10.1/146/2026), dated April 30, 2026. Written informed consent was obtained from participants.

Consent for Publication

Not applicable. The manuscript does not contain individually identifiable data, images, or other information requiring consent for publication.

Competing Interests

The authors declare that they have no competing interests.

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Author Contribution

Corresponding author: EConception or design: all authorsAcquisition, analysis, or interpretation of data: all authorsDrafting the work or revising: all authorsFinal approval of the manuscript: all authors

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable ethical and institutional restrictions.

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Figures

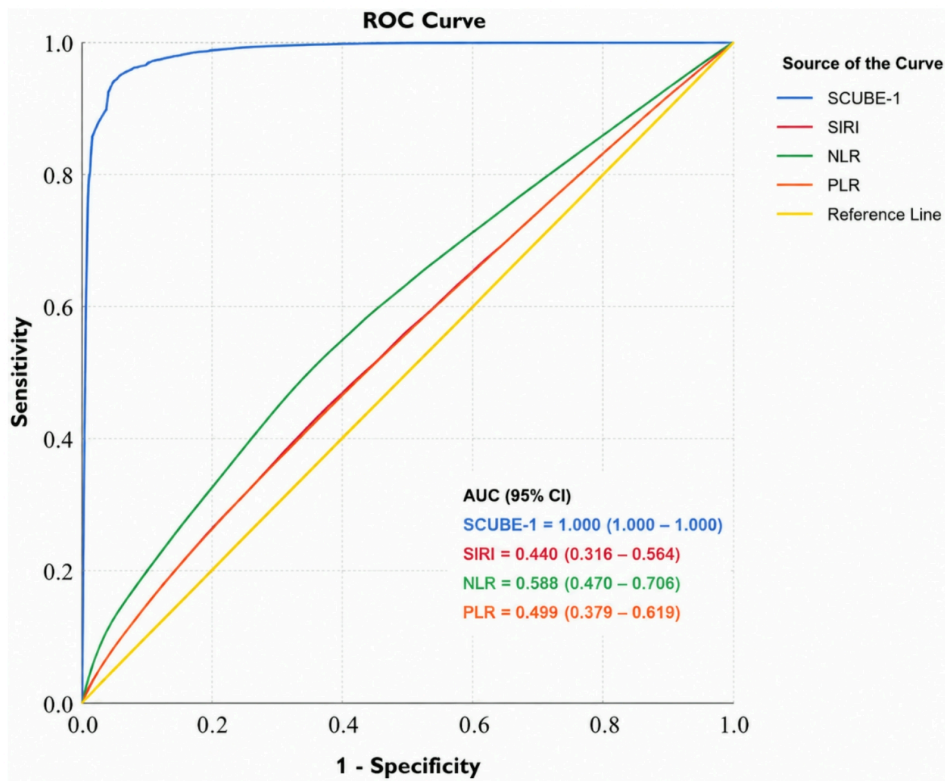


Figure 1. Receiver Operating Characteristic Curves for SCUBE-1, SIRI, NLR, and PLR in Predicting 28-day Mortality

Figure 1

Receiver Operating Characteristic Curves for SCUBE-1, SIRI, NLR, and PLR in aPredicting 28-day Mortality