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| **Running title:** | **Napitupulu et al.** NEUT-RI and SOFA score |
| **Title:** | **Neutrophil reactivity intensity correlates with the SOFA score in adults with sepsis: a cross-sectional study from an Indonesian tertiary hospital** |
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ORIGINAL ARTICLE

# Neutrophil reactivity intensity correlates with the SOFA score in adults with sepsis: a cross-sectional study from an Indonesian tertiary hospital

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**Running title: Napitupulu et al.** NEUT-RI and SOFA score

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## ABSTRACT

**Aim:** To assess the correlations of neutrophil reactivity intensity (NEUT-RI) and neutrophil granularity intensity (NEUT-GI) with the Sequential Organ Failure Assessment (SOFA) score in adults with sepsis.

**Methods:** This cross-sectional study included 52 adult inpatients with sepsis at H. Adam Malik General Hospital, Medan, Indonesia, in September 2025. NEUT-RI and NEUT-GI were measured using a Sysmex XN-1000 haematology analyser, and SOFA scores were obtained from medical records. Associations were analysed using Pearson correlation and linear regression. Receiver-operating-characteristic (ROC) analysis for SOFA ≥6 was exploratory because the cut-off was derived and evaluated in the same sample.

**Results:** The median age was 56 years (IQR 46–64), 29/52 (55.8%) participants were male, and the median SOFA score was 6 (IQR 4–8). NEUT-RI correlated strongly with the SOFA score ($r = 0.819$; 95% CI 0.704–0.893; $R^2 = 0.671$; $p < 0.001$) and remained independently associated after adjustment for age, sex, NEUT-GI, and log-transformed leukocyte count ($B = 0.370$; 95% CI 0.294–0.446; standardised $\beta = 0.82$; $p < 0.001$). Exploratory ROC analysis yielded an in-sample AUC of 0.994 for SOFA ≥6 at a cut-off of 49.9 FI. NEUT-GI was not significantly associated with SOFA ($r = 0.068$; $p = 0.631$).

**Conclusion:** NEUT-RI, but not NEUT-GI, was independently associated with concurrent organ-dysfunction severity in adults with sepsis. Prospective validation is required before clinical application.

**Keywords:** biomarkers; cross-sectional studies; neutrophils; organ dysfunction scores; sepsis

## INTRODUCTION

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, is a leading global cause of intensive-care mortality (1). The Global Burden of Disease study estimated 48.9 million incident cases and 11.0 million sepsis-related deaths in 2017, with a disproportionate burden in low- and middle-income regions including Southeast Asia (2), and the pooled intensive-care mortality of hospital-acquired sepsis approaches 42% (3). Conventional inflammatory markers such as the leukocyte count, C-reactive protein, procalcitonin, interleukin-6 and presepsin are limited by delay and by weak independent prognostic association after adjustment (4), motivating the search for rapid, low-cost severity markers that can guide early triage in hospitals with constrained resources, particularly in Indonesia, where the disease burden remains high (5).

Neutrophils are central effectors of the septic host response. Activated myeloid signatures define bacterial sepsis and scale with severity (6,7), and emergency granulopoiesis releases immature, metabolically active neutrophils with elevated nucleic-acid and organelle content (8). The physical correlates of this activation can be captured by fluorescence flow cytometry on Sysmex XN-Series analysers: Neutrophil Reactivity Intensity (NEUT-RI) is proportional to intracellular RNA and organelle content, whereas Neutrophil Granularity Intensity (NEUT-GI) is proportional to cytoplasmic granularity (9,10). These Extended Inflammatory Parameters (EIPs) are generated without additional laboratory testing and have been associated with sepsis diagnosis and mortality in heterogeneous cohorts (11-17); however, head-to-head evaluation against a continuous severity outcome remains uncommon, at least one study found NEUT-RI unable to discriminate severity at admission (12), and Indonesian data are scarce.

The aim of this study was to determine the correlations of NEUT-RI and NEUT-GI with the Sequential Organ Failure Assessment (SOFA) score and to quantify the magnitude,

independence, and exploratory discriminative performance of these associations in adults with sepsis at H. Adam Malik General Hospital, Medan, Indonesia.

## MATERIAL AND METHODS

### Patients and study design

An observational cross-sectional study was conducted in the Department of Clinical Pathology, H. Adam Malik General Hospital, Medan, Indonesia, during September 2025 and is reported in accordance with the STROBE statement for cross-sectional studies.

Consecutive adult inpatients (≥18 years) with sepsis defined by the Sepsis-3 criteria (suspected or documented infection plus an acute SOFA increase ≥ 2 points) (1) were eligible. In accordance with the Sepsis-3 convention, the baseline SOFA score was assumed to be zero in patients not known to have pre-existing organ dysfunction; in patients with documented pre-existing organ dysfunction, the baseline was reconstructed from the medical records, and the acute increase of ≥ 2 points was calculated relative to that baseline. Sample size was calculated for a correlation hypothesis with two-sided $\alpha = 0.05$ and power 0.80, assuming a moderate expected correlation ($r \approx 0.45$) between neutrophil-activation parameters and the SOFA score based on prior reports (11,12); the minimum required sample was approximately 36 patients. Patients with incomplete laboratory or clinical data required to compute the study variables or the SOFA score were excluded. Of 54 patients screened, two were excluded for incomplete data, leaving 52 patients (96.3% completeness) for analysis. All participants or legal representatives provided written informed consent.

The study was approved by the Health Research Ethics Committee of Universitas Sumatera Utara (Ethical Clearance No. 373/KEPK/USU/2025) and authorised by the Adam Malik General Hospital research committee (Research Permit No. DP.04.03/D.XXVIII/1818/2025), in compliance with the Declaration of Helsinki.

## Methods

Peripheral venous ethylenediaminetetraacetic acid (EDTA) samples were analysed on a Sysmex XN-1000 automated haematology analyser (Sysmex Corporation, Kobe, Japan), operating by fluorescence flow cytometry with a semiconductor laser and the Extended Inflammatory Parameters channel (9). All samples were processed within 4 hours of venipuncture at room temperature, within the validated EDTA stability window for NEUT-RI and NEUT-GI. NEUT-RI (fluorescence intensity, FI) and NEUT-GI (scatter intensity, SI) were retrieved together with the total leukocyte count and neutrophil percentage. Reference intervals were 39.8–51.0 FI for NEUT-RI and 142.8–159.3 SI for NEUT-GI. Internal quality control was satisfactory throughout, and the laboratory participated in external quality assessment. The SOFA score was abstracted from the medical record by personnel not involved in the haematology analysis, using the worst value within 24 hours of the blood draw across six organ systems (respiratory, coagulation, hepatic, cardiovascular, central nervous and renal), each scored 0–4. The primary outcome variable was the continuous SOFA score; a dichotomous high-severity category (SOFA ≥6 versus <6) was defined a priori as a predefined operational threshold for the supportive ROC analysis (18,19).

## Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are summarised as median and interquartile range (IQR), and categorical variables as frequency and percentage. Normality was assessed using the Kolmogorov–Smirnov test. NEUT-RI, NEUT-GI, leukocyte count, and SOFA score met the normality assumption ($p > 0.05$); therefore, Pearson correlation was used to quantify associations, and simple linear regression estimated the change in the SOFA score per unit increase in NEUT-RI. A multivariable linear regression model included NEUT-RI, NEUT-GI, age, sex, and log-transformed leukocyte count. Standardised regression coefficients (β)

were calculated to compare predictor effects. Multicollinearity was assessed using the variance inflation factor (VIF). Regression diagnostics included residual normality, homoscedasticity using the Breusch–Pagan test, and influential observations using Cook's distance, with a sensitivity analysis excluding observations with Cook's distance >1. The standardised mean difference between SOFA ≥6 and SOFA <6 groups was expressed as Cohen's d, and groups were compared using Welch's t test. Discriminative performance of NEUT-RI was evaluated using receiver operating characteristic (ROC) analysis, with the area under the curve (AUC) and optimal cut-off determined by the Youden index. The continuous SOFA score remained the primary outcome. Because the ROC cut-off was derived and evaluated in the same sample, the analysis was considered exploratory. All tests were two-tailed, with $p < 0.05$ considered statistically significant.

## RESULTS

Of 54 patients screened, two were excluded because of incomplete data, leaving 52 patients (96.3% completeness) for analysis. Twenty-nine (55.8%) were male, the median age was 56 years (IQR 46–64), and the median SOFA score was 6 (IQR 4–8) (Table 1).

The median NEUT-RI was 52.3 FI (IQR 48.2–57.3) and exceeded the upper reference limit of 51.0 FI in 29/52 (55.8%) patients. The median NEUT-GI was 150.6 SI (IQR 146.7–155.1) and was within its reference interval. NEUT-RI, NEUT-GI, leukocyte count, and SOFA score met the normality assumption (Kolmogorov–Smirnov $p = 0.200$, $p = 0.092$, $p = 0.200$, and $p = 0.200$, respectively).

NEUT-RI showed a strong positive correlation with the SOFA score (Pearson $r = 0.819$; 95% CI 0.704–0.893; $p < 0.001$), with $R^2 = 0.671$. NEUT-GI was not significantly correlated with the SOFA score (Pearson $r = 0.068$; 95% CI −0.209 to 0.335; $p = 0.631$) (Table 2; Figure 1).

Simple linear regression yielded SOFA = −13.19 + 0.371 × NEUT-RI; each 1-FI increase in NEUT-RI corresponded to a 0.371-point increase in the SOFA score (95% CI 0.298–0.445; $p < 0.001$). NEUT-RI was higher in patients with SOFA ≥6 (56.70 ± 4.93 FI; n = 33) than in those with SOFA <6 (46.67 ± 2.32 FI; n = 19), with a mean difference of 10.03 FI (95% CI 8.05–12.01; $p < 0.001$; Cohen's d = 2.40). NEUT-GI did not differ significantly between severity groups. In the multivariable model, NEUT-RI remained independently associated with the SOFA score after adjustment for NEUT-GI, age, sex, and log-transformed leukocyte count (B = 0.370; 95% CI 0.294–0.446; standardised β = 0.82; $p < 0.001$) (Table 3). No other predictor was statistically significant. The model explained 69.2% of the variance (adjusted $R^2 = 0.658$; $F(5,46) = 20.64$; $p < 0.001$), and all VIF values were <2.5. Residuals were approximately normally distributed (Kolmogorov–Smirnov $p = 0.102$). The Breusch–Pagan test indicated heteroscedasticity in the full sample ($p = 0.011$), but not after exclusion of one influential observation with Cook's distance >1 ($p = 0.085$); this exclusion did not materially alter the NEUT-RI association. Exploratory ROC analysis yielded an in-sample AUC of 0.994 (95% CI 0.974–1.000) for SOFA ≥6 at a cut-off of 49.9 FI (sensitivity 97.0%; specificity 100%) (Figure 2).

## DISCUSSION

In this study, NEUT-RI correlated strongly and positively with the SOFA score, remained independently associated after multivariable adjustment, and showed high exploratory in-sample discrimination for SOFA ≥6, whereas NEUT-GI showed no meaningful association. Because the design is cross-sectional, these findings establish an association with concurrent organ-dysfunction severity rather than prognostic or predictive value for mortality, intensive-care admission, or progression of organ dysfunction. The contrast between the two Extended Inflammatory Parameters suggests that neutrophil metabolic reactivity may reflect concurrent organ dysfunction more closely than granularity in this cohort.

The strong NEUT-RI–severity association is consistent with and extends prior reports. Formenti et al. found NEUT-RI to be elevated in septic compared with non-septic critically ill patients, with higher values in non-survivors and a further rise in septic shock (11); in paediatric sepsis, NEUT-RI carried the highest mortality hazard among haematological parameters (13); in bloodstream infection, Morello et al. recently derived an optimal NEUT-RI cut-off of 50.7 FI (14), and multi-parameter EIP models incorporating NEUT-RI have achieved high discrimination (15). Importantly, Mantovani et al. reported that NEUT-RI discriminated the presence of sepsis well but did not discriminate severity at intensive-care admission (12).

The null result for NEUT-GI aligns with emergency-department cell-population-data studies in which granularity-based parameters showed only modest or absent sepsis discrimination (20) and with paediatric data in which reactivity, not granularity, tracked outcome (13).

Several factors may explain the absence of an association for NEUT-GI in the present cohort. NEUT-GI reflects the side-scatter signal determined by cytoplasmic granule content and intracellular complexity (9,10), which during sepsis is shaped by competing influences: increased granule production on the one hand and degranulation together with the release of hypogranular immature neutrophils during emergency granulopoiesis on the other (8,10,20). These opposing effects may offset one another, so that mean NEUT-GI remains within its reference interval despite ongoing neutrophil activation, and the parameter may also vary according to analyser methodology and calibration (9,10,20). By contrast, NEUT-RI quantifies the fluorescence signal proportional to intracellular RNA and organelle content, which rises as neutrophils become metabolically activated (9). Emergency granulopoiesis releases immature, transcriptionally and metabolically active neutrophils (8), and single-cell studies have defined activated neutrophil states that scale with severity (6,7,21). NEUT-RI may therefore provide a more direct readout of transcriptional–metabolic activation

associated with organ dysfunction than NEUT-GI. Its persistence after adjustment for leukocyte count suggests that NEUT-RI may capture information beyond simple neutrophilia; leukocyte count and conventional inflammatory markers may have limited value as standalone severity indicators in sepsis (4,22,23).

These findings may be relevant to Indonesian and similar resource-constrained settings where XN-Series analysers are available. NEUT-RI is generated automatically with the routine complete blood count without an additional assay and is operator-independent. If prospectively validated, a flagged NEUT-RI value could be evaluated as an adjunct to established clinical assessment and sepsis pathways, together with other automated cell-population indices such as monocyte distribution width, the delta neutrophil index, and the neutrophil-to-lymphocyte ratio (24-26). The Bali cohort of Herawati et al. showed that integrating routine and extended haematological parameters may improve sepsis diagnosis and prognosis in Indonesian hospitals (5), and the present results add exploratory severity data from a North Sumatran referral centre. NEUT-RI should not replace clinical assessment or recommendations of the Surviving Sepsis Campaign (27).

Several limitations warrant caution. The single-centre, cross-sectional design and single time-point measurement preclude causal or temporal inference and limit generalisability. The modest sample and absence of a non-septic comparison group restricted subgroup analyses and reduced the precision, stability, and external validity of the multivariable estimates. The 49.9-FI ROC cut-off was derived and evaluated in the same sample without internal or external validation; therefore, the very high AUC is likely optimistic and the threshold should be considered exploratory rather than clinically applicable. Important potential confounders—including septic shock, infection source, comorbidity burden, immunosuppressive or corticosteroid therapy, recent granulocyte-colony-stimulating-factor exposure, timing of blood sampling, microbiological findings, immature granulocyte fraction,

and mortality—were not recorded or modelled, so residual confounding cannot be excluded. With five predictors and 52 observations, the model was also vulnerable to overfitting; smaller coefficients may be unstable and may shrink in independent samples, and non-significant effects of age, sex, and leukocyte count should not be interpreted as evidence of no association. Prospective multicentre studies with serial NEUT-RI measurements, outcome linkage, comprehensive confounder adjustment, and internal and external cut-off validation are needed.

## CONCLUSION

In adults with sepsis at an Indonesian tertiary hospital, NEUT-RI correlated strongly and independently with the SOFA score, whereas NEUT-GI showed no significant association. Because the study is cross-sectional, these findings demonstrate an association with concurrent organ-dysfunction severity rather than validated prognostic performance. NEUT-RI may be evaluated as an adjunctive severity marker in similar settings where XN-Series analysers are available, pending prospective multicentre studies with internal and external validation.

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**Conflicts of interest:** None to declare.

**Author contributions (CRediT):** Conceptualization—E.M.N.; Methodology—E.M.N., M.R.N., and N.S.A.; Formal analysis—E.M.N.; Investigation—E.M.N., M.R.N., and N.S.A.; Data curation—E.M.N. and M.R.N.; Validation—A.P.L.; Resources—A.P.L.; Writing—original draft—E.M.N.; Writing—review and editing—R.P., E.M.N., M.R.N., A.P.L., and N.S.A.; Supervision—R.P.; Project administration—R.P. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

**Ethics statement:** The study was approved by the Health Research Ethics Committee of Universitas Sumatera Utara (Ethical Clearance No. 373/KEPK/USU/2025) and authorised by the H. Adam Malik General Hospital Human Resources, Education and Research Committee (Research Permit No. DP.04.03/D.XXVIII/1818/2025). Written informed consent was obtained from all participants or their legal representatives in accordance with the Declaration of Helsinki.

**Data availability statement:** The de-identified dataset and statistical output generated and analysed during the current study are available from the corresponding author upon reasonable request, subject to institutional data-governance approval.

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## TABLES AND FIGURES

**Table 1. Demographic and baseline characteristics of the study population**

| Variable | N (%) or Median (IQR) |
|---|---|
| Sex | |
| Male | 29 (55.8) |
| Female | 23 (44.2) |
| Age (years) | 56 (46–64) |
| Leukocyte (cells/μL) | 21,100 (17,725–25,950) |
| Neutrophil (%) | 86.9 (83.0–90.4) |
| NEUT-RI (FI) | 52.3 (48.2–57.3) |
| NEUT-GI (SI) | 150.6 (146.7–155.1) |
| SOFA score | 6 (4–8) |

FI, fluorescence intensity; IQR, interquartile range; NEUT-GI, neutrophil granularity intensity; NEUT-RI, neutrophil reactivity intensity; SI, scatter intensity; SOFA, Sequential Organ Failure Assessment.

**Table 2. Bivariate, severity-group, and exploratory receiver-operating-characteristic (ROC) analyses of neutrophil reactivity intensity (NEUT-RI) and neutrophil granularity intensity (NEUT-GI)**

| | Estimate | p |
|---|---|---|
| | **Pearson *r* (95% CI)** | |
| NEUT-RI vs SOFA | 0.819 (0.704 – 0.893)* | < 0.001 |
| NEUT-GI vs SOFA | 0.068 (− 0.209 to 0.335)† | 0.631 |
| | Mean difference (95% CI) | |
| NEUT-RI: SOFA ≥6 vs <6 | 10.03 FI (8.05 – 12.01)‡ | < 0.001 |
| NEUT-GI: SOFA ≥6 vs <6 | 0.75 SI (− 3.88 to 5.39)§ | 0.751 |
| | **AUC (95% CI)** | |
| NEUT-RI for SOFA ≥6 | 0.994 (0.974 – 1.000)¶ | < 0.001 |

*$R^2 = 0.671$; †$R^2 = 0.005$; ‡Cohen's d = 2.40; §Cohen's d = 0.08; ¶optimal cut-off, 49.9 FI, with 97.0% sensitivity and 100% specificity in the present sample.

AUC, area under the receiver-operating-characteristic curve; CI, confidence interval; FI, fluorescence intensity; NEUT-GI, neutrophil granularity intensity; NEUT-RI, neutrophil reactivity intensity; SI, scatter intensity; SOFA, Sequential Organ Failure Assessment. Confidence intervals for Pearson's r were calculated using Fisher's z transformation.

**Table 3. Multivariable linear regression with the SOFA score as the dependent variable**

| Predictor | B (95% CI) | Standardised β | p |
|---|---|---|---|
| NEUT-RI (FI) | 0.370 (0.294 – 0.446) | 0.82 | < 0.001 |
| NEUT-GI (SI) | 0.050 (− 0.011 to 0.111) | 0.16 | 0.105 |
| Age (years) | −0.004 (− 0.039 to 0.032) | − 0.02 | 0.822 |
| Male sex | −0.196 (− 1.164 to 0.771) | − 0.03 | 0.685 |
| Log-transformed leukocyte count | −0.320 (− 1.041 to 0.401) | − 0.06 | 0.377 |

Model $R^2$=0.692; adjusted $R^2$=0.658; F(5,46)=20.64; p<0.001. All variance inflation factors were < 2.5.

B, unstandardised coefficient; β, standardised coefficient; CI, confidence interval; FI, fluorescence intensity; NEUT-GI, neutrophil granularity intensity; NEUT-RI, neutrophil reactivity intensity; SI, scatter intensity; SOFA, Sequential Organ Failure Assessment.

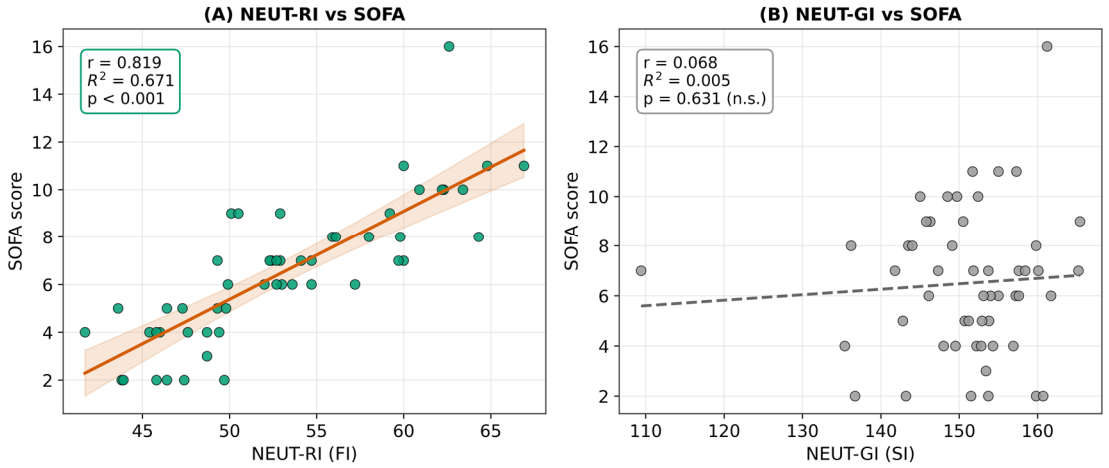


**Figure 1. Scatter plots with fitted regression lines for (A) neutrophil reactivity intensity (NEUT-RI) versus Sequential Organ Failure Assessment (SOFA) score and (B) neutrophil granularity intensity (NEUT-GI) versus SOFA score**

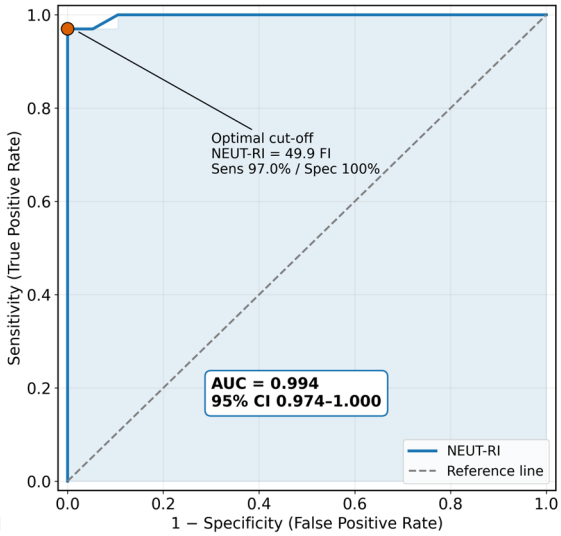


**Figure 2. Receiver-operating-characteristic (ROC) curve of neutrophil reactivity intensity (NEUT-RI) for a Sequential Organ Failure Assessment (SOFA) score ≥ 6**