

Comparative Prognostic Performance of the Systemic Immune-Inflammation Index and Systemic Inflammation Response Index for In-Hospital Mortality in Acute Heart Failure with Sepsis

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Abstract

Background: The systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) were originally developed as prognostic markers in oncology and have subsequently been investigated in cardiovascular disease. Their validity for mortality prediction in acute heart failure (AHF) complicated by sepsis remains uncertain. We compared their prognostic performance for in-hospital mortality. **Methods:** This single-centre observational study included 150 adults with AHF and Sepsis-3-defined sepsis treated at the Integrated Heart Center, Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. Admission SII and SIRI were calculated from complete blood counts. Survivors and non-survivors were compared, discrimination was assessed using receiver operating characteristic analysis, and independent associations were explored using multivariable logistic regression. **Results:** Eighty-six patients (57.3%) died in hospital. Median SII was 2,393.0 in non-survivors and 2,776.5 in survivors ($p=0.701$); median SIRI was 59.00 and 53.68, respectively ($p=0.410$). SII showed poor discrimination (AUC 0.523, 95% CI 0.429-0.617; $p=0.640$; cut-off 2,555.29; sensitivity 54.7%; specificity 54.7%), and SIRI performed no better than chance (AUC 0.469, 95% CI 0.376-0.563; $p=0.528$; cut-off 33.76; sensitivity 47.7%; specificity 56.3%). Lower Glasgow Coma Scale score (adjusted OR 0.599, 95% CI 0.373-0.960; $p=0.033$), leukocyte count ($p=0.014$), and haemoglobin (adjusted OR 1.678, 95% CI 1.097-2.567; $p=0.017$) remained associated with mortality in the reported multivariable model. **Conclusions:** A single admission measurement of SII or SIRI was not a valid stand-alone discriminator of in-hospital mortality in this AHF-sepsis cohort. Neither index should be used alone for individual prognostication; external validation and assessment of incremental value within multimarker models are required.

Keywords: acute heart failure; sepsis; systemic immune-inflammation index; systemic inflammation response index; mortality; prognosis

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Highlights

- In-hospital mortality was 57.3% in this high-risk AHF-sepsis cohort.
- Neither SII nor SIRI differentiated survivors from non-survivors or demonstrated adequate stand-alone discrimination.
- The findings do not validate either index for individual mortality prediction in AHF with sepsis; haemodynamic and organ-dysfunction variables were more informative.

Introduction

Acute heart failure is a life-threatening syndrome characterised by new or worsening symptoms and signs of heart failure requiring urgent evaluation and treatment. Infection is a common precipitant and may progress to sepsis, in which a dysregulated host response causes organ dysfunction. When AHF and sepsis coexist, reduced cardiac reserve, vasoplegia, endothelial injury, microcirculatory failure, and inflammatory myocardial depression may converge, producing refractory congestion or shock and a high risk of death [1–6].

Inflammation is integral to both syndromes. Neutrophilia reflects innate immune activation, lymphopenia may indicate stress-related or sepsis-associated adaptive immune dysfunction, thrombocytopenia may accompany consumption

and immunothrombosis, and monocyte alterations reflect innate immune reprogramming [4,7]. Composite indices derived from routine blood counts may therefore summarise several inflammatory pathways at negligible additional cost. SII is calculated as platelet count $\times$ neutrophil count / lymphocyte count, whereas SIRI is calculated as neutrophil count $\times$ monocyte count / lymphocyte count [8,9].

The indices did not originate in cardiovascular populations. Hu et al. introduced SII in 2014 to predict recurrence and survival after curative resection for hepatocellular carcinoma, developing it in a retrospective cohort of 133 patients and evaluating it in a prospective cohort of 123 patients [8]. Qi et al. introduced SIRI in 2016 to predict time to progression and overall survival in patients

with pancreatic adenocarcinoma receiving gemcitabine-based chemotherapy, with evaluation across three independent cohorts [9]. Thus, both indices were initially oncology prognostic markers rather than sepsis diagnostic tests or established AHF mortality scores.

Their subsequent use in cardiovascular disease is biologically plausible because neutrophils, monocytes, lymphocytes, and platelets participate in endothelial injury, atherosclerosis, immunothrombosis, myocardial injury, and ventricular remodelling. Associations with outcomes have been reported in coronary disease, chronic heart failure, and broader cardiovascular cohorts [10-13]. However, transport from oncology or stable cardiovascular disease to AHF with sepsis cannot be assumed. The target population has rapidly changing immune phenotypes, severe haemodynamic instability, and competing pathways to death that may alter both index distributions and prognostic performance.

Accordingly, describing SII or SIRI as an independent predictor in a previous cohort does not establish universal clinical validity. A useful prognostic marker should demonstrate reproducible discrimination and calibration, clinically meaningful sensitivity and specificity, incremental value beyond established predictors, and external validity in a comparable target population. Universal cut-offs for SII and SIRI have not been established, and evidence directly comparing both indices in concurrent AHF and sepsis remains limited. We therefore compared their admission values and discrimination for in-hospital mortality and examined why performance might differ in this high-risk population.

Methods

Study design and setting

This observational analytical study was conducted at the Integrated Heart Center of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from March to May 2025. Consecutive eligible patients were enrolled using purposive sampling and followed until hospital discharge or death. Although the source protocol described the design as cross-sectional, the analysis used a clearly defined in-hospital outcome and is reported here as an observational prognostic cohort.

Participants and definitions

Adults with a clinician-confirmed diagnosis of AHF and concurrent sepsis were eligible. AHF was established from compatible symptoms and signs supported by electrocardiography, chest radiography, natriuretic peptides, and/or echocardiography in accordance with contemporary guideline principles [1,2]. Sepsis was defined as suspected or confirmed infection with an acute increase in Sequential Organ Failure Assessment score of at least 2 points, consistent with Sepsis-3 [3]. Patients declining participation, with

incomplete outcome ascertainment, or with major systemic conditions considered likely to confound the study measurements were excluded. The source document contains an age-range inconsistency; therefore, no unsupported age restriction is reproduced in this manuscript.

Data collection and index calculation

Demographic characteristics, comorbidities, AHF phenotype, vital signs, Glasgow Coma Scale (GCS), vasopressor/inotrope use, left ventricular ejection fraction (LVEF), cardiac output, systemic vascular resistance (SVR), and admission laboratory results were recorded. SII and SIRI were calculated from the first available complete blood count using the formulas above. The primary outcome was all-cause in-hospital mortality.

Statistical analysis

Continuous variables were summarised as mean $\pm$ standard deviation or median (minimum–maximum), as appropriate; categorical variables were reported as n (%). Between-group comparisons used the independent-samples t test or Mann–Whitney U test and the χ^2 or Fisher exact test. Associations were evaluated using logistic regression. Receiver operating characteristic (ROC) analysis provided the area under the curve (AUC), 95% confidence interval (CI), optimal threshold, sensitivity, and specificity. Spearman correlation assessed relationships among indices, C-reactive protein (CRP), and mortality. Two-sided $p < 0.05$ was considered significant. Analyses were performed in SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Ethics

The study was reviewed by the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University. Written informed consent was obtained from participants or legally authorised representatives. The approval number should be inserted before journal submission: [ETHICS APPROVAL NUMBER TO BE COMPLETED].

Results

Cohort characteristics and outcomes

A total of 150 patients with AHF and sepsis were included; 86 (57.3%) died during hospitalisation and 64 (42.7%) survived to discharge. Mean age was 60.10 ± 14.18 years, 104 (69.3%) were men, and coronary artery disease was present in 118 (78.7%). Cardiogenic shock was the predominant AHF presentation (61.3%), and 95 patients (63.3%) received vasopressor or inotropic support. The cohort consequently represented a severely ill population with substantial haemodynamic compromise.

Study cohort and analytical framework

Patients with clinician-confirmed acute heart failure and Sepsis-3-defined sepsis

Analytical cohort: n = 150
Admission clinical, haemodynamic, and laboratory assessment
SII and SIRI calculation from complete blood count
In-hospital outcome: 86 deaths (57.3%) 64 survivors (42.7%)

Table 1. Baseline characteristics of the study cohort

Characteristic	Overall (n=150)
Age, years	60.10 ± 14.18
Male sex	104 (69.3)
Body mass index, kg/m ²	23.07 ± 4.38
Hypertension	72 (48.0)
Diabetes mellitus	37 (24.7)
Chronic kidney disease	10 (6.7)
Coronary artery disease	118 (78.7)
Atrial fibrillation	24 (16.0)
Previous heart failure	125 (83.3)
Cardiogenic shock	92 (61.3)
Vasopressor/inotrope use	95 (63.3)
LVEF, %	39.61 ± 11.07
GCS score	13.61 ± 3.40
Creatinine, mg/dL	1.85 ± 1.23
Urea, mg/dL	88.02 ± 59.19
Lactate, mmol/L	4.08 ± 2.92
CRP, mg/L	166.39 ± 115.43
SII	3916.57 ± 4234.04
SIRI	77.37 ± 76.51
In-hospital death	86 (57.3)

Data are mean ± SD or n (%). CRP, C-reactive protein; GCS, Glasgow Coma Scale; LVEF, left ventricular ejection fraction; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

Between-group comparisons

Non-survivors had lower systolic and diastolic blood pressure, lower mean arterial pressure and GCS, greater vasopressor/inotrope use, and higher creatinine, urea, and lactate. Cardiogenic shock and atrial fibrillation were more frequent among non-survivors, whereas acute pulmonary oedema was

more frequent among survivors. LVEF and cardiac output did not differ significantly.

Table 2. Selected characteristics according to in-hospital survival

Variable	Non-survivors (n=86)	Survivors (n=64)	p value
Age, years	61.14 ± 14.30	58.70 ± 14.00	0.373
Atrial fibrillation, n (%)	20 (23.3)	4 (6.2)	0.005
Acute pulmonary oedema, n (%)	12 (14.0)	18 (28.1)	0.032
Cardiogenic shock, n (%)	60 (69.8)	32 (50.0)	0.014
Systolic BP, mmHg	101.35 ± 30.02	118.23 ± 34.27	<0.001
Diastolic BP, mmHg	67.97 ± 19.75	79.25 ± 24.09	0.001
Mean arterial pressure, mmHg	78.62 ± 23.52	94.98 ± 27.91	<0.001
GCS score	12.87 ± 4.08	14.61 ± 1.80	0.002
Vasopressor/inotrope, n (%)	61 (70.9)	34 (53.1)	0.025
LVEF, %	40.13 ± 10.91	38.91 ± 11.33	0.551
Cardiac output, L/min	3.71 ± 1.60	3.64 ± 1.40	0.971
SVR, dyn·s/cm ⁵	1755.21 ± 940.94	2044.52 ± 938.32	0.037
Creatinine, mg/dL	2.21 ± 1.41	1.37 ± 0.69	<0.001
Urea, mg/dL	105.86 ± 61.13	64.05 ± 47.18	<0.001
Lactate, mmol/L	4.70 ± 3.29	3.22 ± 2.03	0.002
CRP, mg/L	182.24 ± 119.96	143.38 ± 106.21	0.178

Data are mean ± SD or n (%). BP, blood pressure; CRP, C-reactive protein; GCS, Glasgow Coma Scale; LVEF, left ventricular ejection fraction; SVR, systemic vascular resistance.

SII and SIRI performance

Median SII did not differ between non-survivors and survivors (2,393.0 [228–23,718] vs 2,776.5 [155–17,741]; p=0.701). SIRI was likewise similar (59.00 [8.34–290.00] vs 53.68 [1.27–764.00]; p=0.410). SII correlated moderately with SIRI

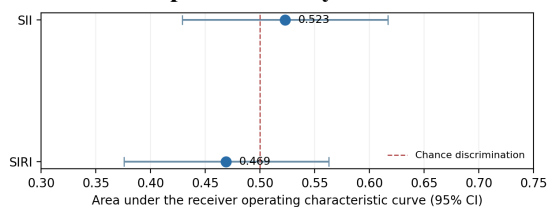
($p=0.561$; $p<0.001$) and weakly with CRP ($p=0.263$; $p=0.022$); SIRI was not correlated with CRP ($p=0.005$; $p=0.965$).

Table 3. Discrimination of SII and SIRI for in-hospital mortality

Index	AUC (95% CI)	p value	Cut-off	Sensitivity, %	Specificity, %
SII	0.523 (0.429–0.617)	0.640	2,555.29	54.7	54.7
SIRI	0.469 (0.376–0.563)	0.528	33.76	47.7	56.3

AUC, area under the receiver operating characteristic curve; CI, confidence interval. Thresholds were those reported in the source analysis.

Figure 1. Comparative discrimination of SII and SIRI for in-hospital mortality



Points represent AUCs and horizontal bars represent 95% CIs. This is a summary of reported AUC estimates, not a reconstructed ROC curve.

SII provided only marginal discrimination (AUC 0.523), while SIRI was below the 0.50 chance benchmark (AUC 0.469). Neither AUC differed significantly from chance. Sensitivities and specificities at the reported data-derived cut-offs were close to 50%, producing substantial potential for both false-negative and false-positive classification. These findings did not support either index as a valid stand-alone mortality discriminator in this cohort.

Regression analyses

In univariable logistic regression, creatinine (OR 2.405 per mg/dL, 95% CI 1.527–3.789; $p<0.001$), urea (OR 1.016 per mg/dL, 95% CI 1.008–1.023; $p<0.001$), and lactate (OR 1.256 per mmol/L, 95% CI 1.073–1.470; $p=0.005$) were associated with mortality. Neither SII ($p=0.131$) nor SIRI ($p=0.915$) was significant in the reported univariable model.

Table 4. Reported multivariable logistic regression model for in-hospital mortality

Variable	Adjusted OR	95% CI	p value
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Variable	Adjusted OR	95% CI	p value
GCS score	0.599	0.373–0.960	0.033
SVR, dyn·s/cm ⁵	0.999	0.997–1.000	0.128
Leukocyte count, /μL	1.000	0.999–1.000	0.014
Lymphocytes, %	0.382	0.110–1.328	0.130
Haemoglobin, g/dL	1.678	1.097–2.567	0.017
Urea, mg/dL	1.016	0.997–1.035	0.107
CRP, mg/L	1.008	0.998–1.018	0.140
Lactate, mmol/L	1.354	0.925–1.982	0.119
SII	1.000	1.000–1.001	0.110
SIRI	0.958	0.911–1.008	0.099

Reported model: $-2 \log$ likelihood 38.62; Cox–Snell R^2 0.455; Nagelkerke R^2 0.608; McFadden R^2 0.440. The unit-dependent ORs for leukocyte count and SII round to 1.000 and should be rescaled (e.g., per 1,000 cells/μL) in any re-analysis.

Discussion

In this single-centre cohort of patients with AHF and sepsis, admission SII and SIRI did not distinguish survivors from non-survivors and showed poor discrimination for in-hospital mortality. SII was numerically higher by AUC than SIRI, but this difference was clinically negligible: both confidence intervals crossed 0.50 and sensitivities and specificities were close to chance. The study therefore did not validate either index for stand-alone individual prognostication. Conversely, non-survivors exhibited more profound hypotension, impaired consciousness, renal dysfunction, and hyperlactataemia, suggesting that circulatory failure and established organ dysfunction dominated prognosis.

These results differ from reports in chronic heart failure and broader cardiovascular populations, where higher SII or SIRI was independently associated with mortality [10–13]. This discrepancy is clinically credible because those studies largely evaluated chronic, elderly, ischaemic, or broadly defined cardiovascular populations rather than patients with the simultaneous acute insults of AHF and sepsis. In stable disease, persistent low-grade inflammation may retain prognostic separation over

months or years. In this cohort, 61.3% had cardiogenic shock and nearly two-thirds required vasoactive support; haemodynamic collapse, microcirculatory dysfunction, mitochondrial injury, and multiorgan failure may therefore have overwhelmed the signal captured by a single differential blood count [4-7].

Several additional mechanisms may explain the non-significant findings. First, a ceiling effect is plausible because all participants already had AHF and sepsis, creating substantial inflammation in both outcome groups and reducing between-group separation. Second, only one admission value was analysed, although hyperinflammation and immunosuppression may coexist and evolve rapidly. Third, neutrophils vary with bacterial infection, catecholamines, corticosteroids, and physiological stress; lymphocytes with apoptosis, redistribution, malnutrition, chronic disease, and immunosuppressive therapy; platelets with immunothrombosis, disseminated intravascular coagulation, bleeding, and transfusion; and monocyte count may not reflect monocyte function or antigen presentation [4,7]. Fourth, the wide and skewed distributions of both indices increased overlap and reduced precision. Fifth, treatment before sampling may have altered cell counts. Finally, differences among studies in source populations, outcome definitions, sampling time, laboratory units, formulas, and data-derived cut-offs limit direct comparison.

A non-significant association should not be interpreted as proof that SII and SIRI have no biological relationship with outcome. Rather, the present data provide insufficient evidence that a single measurement separates survivors from non-survivors in this clinical setting. The AUCs near 0.50 and low sensitivity and specificity are more directly relevant to clinical validity than the absence of statistical significance alone.

The stronger unadjusted associations of renal indices and lactate are biologically coherent. AHF lowers forward perfusion and may cause renal venous congestion, whereas sepsis produces vasodilatation, endothelial injury, capillary leak, and heterogeneous microvascular flow. Creatinine and urea therefore integrate cardiorenal dysfunction, while lactate reflects the balance between production and clearance under hypoperfusion, adrenergic stimulation, hepatic dysfunction, and mitochondrial stress [5-7,14]. Lower GCS similarly captures cerebral hypoperfusion, sepsis-associated encephalopathy, hypoxaemia, and metabolic derangement. These variables represent downstream physiological injury rather than inflammatory activation alone.

The reported adjusted association between higher haemoglobin and mortality should be interpreted cautiously. It may reflect haemoconcentration, residual confounding, non-linear effects, or model

instability rather than a direct harmful effect. Likewise, the leukocyte OR rounded to 1.000 despite statistical significance because the model used a one-cell unit. Re-expression per 1,000 cells/ μ L, assessment of non-linearity, evaluation of collinearity, and internal validation would improve interpretability. The relatively large number of candidate predictors for 86 deaths also raises a risk of overfitting, particularly because the source document does not describe a prespecified variable-selection strategy.

Clinical implications

Admission SII and SIRI should not be used as stand-alone mortality tests or as sole grounds for escalation, limitation of therapy, or prognostic counselling in AHF with sepsis. Their low cost and immediate availability may justify evaluation as adjunctive variables, but only if they improve discrimination, calibration, or clinical decision-making beyond established assessment. A multimarker model integrating neurological status, blood pressure, lactate, renal function, cardiac phenotype, and validated organ-failure scores is more consistent with the multisystem pathobiology of this population. Serial trajectories may also be more informative than a single baseline value, but require prospective testing and external validation.

Strengths and limitations

This study directly compared two inexpensive composite inflammatory indices in a clinically important and under-studied overlap syndrome and included detailed haemodynamic and organ-function measurements. The negative findings are clinically valuable because they discourage overinterpretation of readily calculated indices in a population where predictive signals may be dominated by shock and organ failure.

Several limitations require emphasis. First, the single-centre design, purposive sampling, short recruitment window, and high prevalence of cardiogenic shock limit external validity. Second, the sample size was modest for multivariable modelling, and no calibration, internal validation, external validation, or formal comparison of incremental predictive value was reported. Third, the reported cut-offs were selected from the same dataset and should therefore be considered exploratory rather than transportable clinical thresholds. Fourth, only admission values were analysed; treatment before sampling and changes during hospitalisation were not captured. Fifth, the timing of blood sampling relative to infection onset, AHF presentation, antibiotics, vasoactive agents, corticosteroids, or transfusion was unavailable. Sixth, residual confounding from infection source, microbiology, SOFA severity, mechanical ventilation, renal replacement therapy, and treatment heterogeneity is likely. Seventh, the source protocol contains inconsistencies in age eligibility, sampling terminology, and univariable

versus multivariable estimates; these should be resolved against the original database and statistical output before submission. Finally, the ethics approval identifier and complete author contact details were unavailable in the supplied document.

Conclusion

SII and SIRI were originally developed as oncology prognostic markers and have biological plausibility in cardiovascular disease, but their validity cannot be assumed in AHF with sepsis. In this cohort, a single admission measurement of either index showed poor, non-significant discrimination for in-hospital mortality. SII was numerically superior to SIRI, but neither achieved clinically useful sensitivity or specificity and neither should be used alone to determine individual outcome. The non-significant findings may reflect ceiling effects, dynamic sepsis immunobiology, treatment-sensitive blood-cell counts, wide index distributions, and the dominance of haemodynamic compromise and organ dysfunction. Prospective multicentre studies should assess serial trajectories, calibration, external validity, and incremental value beyond established clinical and organ-failure measures.

Declarations

Ethics approval and consent to participate

Approval was obtained from the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University; approval number: [TO BE COMPLETED]. Written informed consent was obtained from participants or legally authorised representatives.

Consent for publication

Not applicable.

Availability of data and materials

De-identified data may be available from the corresponding author on reasonable request and subject to institutional and ethics approval.

Competing interests

The authors declare no competing interests.

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Author contributions

Arisal conceived the study, collected the data, performed the initial analysis, and drafted the manuscript. AHA and AFM supervised the clinical study and critically revised the manuscript. PK and KS contributed to interpretation and critical revision. AAZ contributed to methodological and statistical review. All authors approved the final manuscript. Author roles should be confirmed by all contributors before submission.

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