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Neutrophil-to-Lymphocyte Ratio and Systemic Immune-Inflammation Index as Predictors of Disease Severity and In-Hospital Outcomes in Acute Decompensated heart Failure: A Prospective Observational Study.

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Abstract

Background: Systemic inflammation contributes to the pathophysiology and clinical deterioration of acute decompensated heart failure (ADHF). The neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) are inexpensive indices derived from routine complete blood counts and may facilitate early risk stratification. ***Objectives:*** To evaluate the association of admission NLR and SII with disease severity and in-hospital outcomes among patients admitted with ADHF, and to compare their discriminatory performance for adverse in-hospital outcomes. ***Materials and Methods:*** This prospective observational study included 200 consecutive adults admitted with ADHF to a tertiary-care hospital. Clinical characteristics, comorbidities, vital signs, left ventricular ejection fraction and admission laboratory parameters were recorded. NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count, while SII was calculated as platelet count × neutrophil count/lymphocyte count. The primary outcome was a composite adverse in-hospital outcome comprising in-hospital death, need for invasive or non-invasive ventilatory support, vasopressor/inotrope requirement or intensive care unit transfer. Secondary outcomes included length of hospital stay and individual components of the composite outcome. Multivariable logistic regression and receiver operating characteristic analysis were performed. ***Results:*** The mean age of the 200 participants was 65.1 ± 12.4 years and 58.0% were male. The median NLR was 5.4 (IQR 3.5–8.2), while median SII was 1,185 $\times 10^9$/L (IQR 720–1,890). Fifty-eight patients (29.0%) experienced the composite adverse in-hospital outcome. Patients with adverse outcomes had higher NLR [8.7 (5.9–12.6) vs 4.4 (3.0–6.4), P<0.001] and SII [1,940 (1,280–2,880) vs 910 (610–1,430) $\times 10^9$/L, P<0.001]. After multivariable adjustment, elevated NLR and SII remained independently associated with adverse outcomes. SII showed an AUC of 0.79 and NLR an AUC of 0.76 for the composite outcome. ***Conclusion:*** Higher admission NLR and SII were associated with greater clinical severity and adverse in-hospital outcomes in ADHF. These readily available inflammatory indices may complement conventional bedside and laboratory risk assessment, although external validation and prospective outcome studies are required.

Keywords: acute decompensated heart failure; neutrophil-to-lymphocyte ratio; systemic immune-inflammation index; inflammation; mortality; prognosis.

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INTRODUCTION

Acute decompensated heart failure (ADHF) is a common cause of emergency presentation and hospitalization and remains associated with substantial short-term morbidity, mortality and early readmission. Although congestion is the dominant clinical manifestation, the biological processes accompanying acute heart failure are heterogeneous and include neurohormonal activation, renal dysfunction, endothelial injury, oxidative stress and systemic inflammation. Identifying patients at increased risk soon after admission is important because clinical deterioration may occur rapidly and may necessitate intensive monitoring, ventilatory support or vasoactive therapy. Inflammation has increasingly been recognized as an important component of heart failure pathophysiology. Activation of innate immune pathways can promote myocardial dysfunction, endothelial activation and adverse ventricular remodeling, while severe congestion may itself amplify inflammatory signaling. Conventional inflammatory biomarkers such as C-reactive protein have demonstrated prognostic associations in acute heart failure, but additional testing may increase cost and may not be immediately available in every setting.

Complete blood counts are routinely obtained at admission and contain potentially useful information regarding systemic inflammatory and immune responses. Neutrophilia may reflect acute stress and innate immune activation, whereas relative lymphopenia has been linked to neurohormonal stress and poorer outcomes. The neutrophil-to-lymphocyte ratio (NLR) combines these two components into a simple inflammatory index. Uthamalingam et al. demonstrated a graded increase in long-term mortality and 30-day readmission across increasing NLR tertiles among patients admitted with ADHF [1]. Subsequent studies and pooled analyses have supported an association between elevated NLR and both short- and long-term mortality in acute heart failure [2–5].

The systemic immune-inflammation index (SII) extends this concept by integrating platelet count with neutrophil and lymphocyte counts and is calculated as platelet count multiplied by neutrophil count and divided by lymphocyte count. Platelets participate in inflammatory signaling, endothelial interactions and thrombosis; therefore, incorporation of platelet count may provide additional information beyond NLR. Large observational studies have reported significant associations between elevated SII and short-term mortality in critically ill patients with heart failure [6,7]. More recently, Qiu et al. reported that an SII threshold of approximately 980 ×10⁹/L was useful for predicting 30-day mortality among patients with ADHF, with an area under the receiver operating characteristic curve of approximately 0.75 [8].

Despite growing evidence, direct evaluation of NLR and SII as pragmatic bedside markers of disease severity and in-hospital outcomes remains clinically relevant, particularly in settings where advanced biomarkers may not be uniformly accessible. A prospective study evaluating both indices using admission blood counts may clarify their relationship with immediate clinical deterioration and determine whether SII offers incremental discriminatory value over NLR. The present study was therefore designed to evaluate admission NLR and SII as predictors of disease severity and adverse in-hospital outcomes in patients admitted with ADHF.

Objectives

The primary objective was to determine the association of admission NLR and SII with adverse in-hospital outcomes among patients with ADHF. Secondary objectives were to evaluate their relationship with indicators of disease severity, including intensive care requirement, ventilatory support and duration of hospitalization, and to compare the discriminatory performance of NLR and SII for predicting the composite adverse in-hospital outcome.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of General Medicine, Navodaya medical college Raichur, Karnataka, after obtaining approval from the Institutional Ethics Committee. Consecutive adult patients aged 18 years or older admitted with a clinical diagnosis of acute decompensated heart failure during the study period were screened for eligibility. ADHF was defined as new-onset or worsening signs and symptoms of heart failure requiring hospital admission and treatment, supported by clinical examination and relevant investigations. A total of 200 eligible participants were included after written informed consent. Patients with active bacterial sepsis or other severe acute infection at presentation, active malignancy, hematological disorders substantially affecting leukocyte or platelet counts, chronic systemic inflammatory or autoimmune disease requiring immunosuppressive treatment, recent major surgery or trauma, and patients receiving systemic corticosteroids or other therapies likely to markedly alter differential leukocyte counts were excluded.

Demographic characteristics, cardiovascular risk factors, previous heart failure history, comorbidities, precipitating factors, admission blood pressure, heart rate, respiratory rate, oxygen saturation and relevant clinical signs of congestion were recorded using a structured proforma. Routine investigations included complete blood count with differential leukocyte count, serum creatinine, blood urea nitrogen, electrolytes, liver function tests and other clinically indicated biochemical tests. Echocardiography was performed or reviewed during hospitalization to document left ventricular ejection fraction and relevant structural abnormalities. The neutrophil-to-lymphocyte ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The systemic immune-inflammation index was calculated as platelet count multiplied by absolute neutrophil count and divided by absolute lymphocyte count and was expressed as ×10⁹/L.

Both indices were calculated from the first complete blood count obtained at admission before substantial inpatient treatment whenever feasible. The primary study outcome was a composite adverse in-hospital outcome defined as occurrence of any of the following during the index hospitalization: in-hospital death, transfer to an intensive care unit because of clinical deterioration, requirement for invasive or non-invasive ventilatory support, or requirement for vasopressor or inotropic support. Secondary outcomes included individual components of the composite endpoint and length of hospital stay. Data were analyzed using appropriate statistical software.

Continuous variables were assessed for distribution and summarized as mean ± standard deviation when approximately normally distributed or median with interquartile range when skewed; categorical variables were expressed as frequency

and percentage. Continuous variables between patients with and without adverse outcomes were compared using the independent-samples t-test or Mann–Whitney U test as appropriate, while categorical variables were compared using the chi-square test or Fisher's exact test. Associations of NLR and SII with clinical severity measures were assessed using appropriate correlation and trend analyses. Multivariable logistic regression was performed to identify independent predictors of the composite adverse in-hospital outcome after adjustment for clinically relevant covariates including age, systolic blood pressure, renal function, left ventricular ejection fraction and major comorbidities. Receiver operating characteristic curves were constructed to evaluate the discriminatory performance of NLR and SII, and areas under the curve with 95% confidence intervals were reported. A two-sided P value <0.05 was considered statistically significant.

RESULTS

A total of 200 patients with ADHF were included. The mean age was 65.1 ± 12.4 years and 116 (58.0%) were male. Hypertension was present in 142 (71.0%), diabetes mellitus in 94 (47.0%), chronic kidney disease in 48 (24.0%) and ischemic heart disease in 86 (43.0%). The median NLR at admission was 5.4 (IQR 3.5–8.2) and median SII was 1,185 ×10⁹/L (IQR 720–1,890).

Table 1. Baseline characteristics of the study population

Parameter	Overall (n=200)
Age, years	65.1 ± 12.4
Male sex	116 (58.0%)
Hypertension	142 (71.0%)
Diabetes mellitus	94 (47.0%)
Ischemic heart disease	86 (43.0%)
Chronic kidney disease	48 (24.0%)
Systolic BP, mmHg	126.8 ± 24.5
Heart rate, beats/min	96.4 ± 18.7
LVEF, %	38.6 ± 12.8
Hemoglobin, g/dL	11.8 ± 2.1
Serum creatinine, mg/dL	1.42 (1.05–1.96)
NLR	5.4 (3.5–8.2)
SII, ×10⁹/L	1,185 (720–1,890)

Fifty-eight patients (29.0%) experienced at least one component of the composite adverse in-hospital outcome. This included ICU transfer in 39 (19.5%), ventilatory support in 35 (17.5%), vasopressor or inotropic support in 25 (12.5%) and in-hospital death in 13 (6.5%). Patients experiencing the composite endpoint had lower systolic blood pressure, lower ejection fraction and higher creatinine at admission. Both inflammatory indices were substantially higher in this group.

Table 2. Comparison according to composite adverse in-hospital outcome

Parameter	No adverse outcome (n=142)	Adverse outcome (n=58)	P value
Age, years	63.9 ± 12.1	68.0 ± 12.7	0.032
Systolic BP, mmHg	131.4 ± 22.8	115.6 ± 24.9	<0.001
LVEF, %	40.5 ± 12.5	34.0 ± 12.3	0.001
Creatinine, mg/dL	1.31 (1.00–1.72)	1.82 (1.28–2.45)	<0.001
NLR	4.4 (3.0–6.4)	8.7 (5.9–12.6)	<0.001
SII, ×10⁹/L	910 (610–1,430)	1,940 (1,280–2,880)	<0.001
Hospital stay, days	5 (4–7)	9 (7–12)	<0.001

Increasing NLR and SII tertiles were associated with progressively greater rates of adverse events. The composite outcome occurred in 13.6% of patients in the lowest SII tertile, 25.8% in the middle tertile and 47.8% in the highest tertile (P for trend <0.001). A similar graded pattern was observed across NLR tertiles.

Table 3. Adverse outcomes across inflammatory-index tertiles

Outcome	Lowest tertile	Middle tertile	Highest tertile	P for trend
Composite adverse outcome: NLR	12.1%	27.3%	47.0%	<0.001
Composite adverse outcome: SII	13.6%	25.8%	47.8%	<0.001
Ventilatory support: SII	6.1%	13.6%	32.8%	<0.001
ICU transfer: SII	7.6%	18.2%	32.8%	<0.001

On multivariable logistic regression, both elevated NLR and elevated SII remained independently associated with the composite endpoint after adjustment for age, systolic blood pressure, creatinine, LVEF, diabetes and chronic kidney disease. When entered in separate adjusted models to avoid collinearity between the two related indices, high NLR was associated with an adjusted odds ratio of 2.64 and high SII with an adjusted odds ratio of 3.08 for the composite adverse outcome.

Table 4. Multivariable predictors of composite adverse in-hospital outcome

Predictor	Adjusted OR	95% CI	P value
High NLR	2.64	1.35–5.17	0.005
High SII	3.08	1.56–6.07	0.001
Age, per year	1.02	0.99–1.05	0.18
Systolic BP, per 10 mmHg increase	0.82	0.71–0.95	0.008
Creatinine, per 1 mg/dL increase	1.49	1.10–2.03	0.011
LVEF, per 5% increase	0.88	0.78–0.99	0.038

Receiver operating characteristic analysis demonstrated useful discrimination for both indices. The AUC for SII was 0.79 (95% CI 0.72–0.85), compared with 0.76 (95% CI 0.69–0.83) for NLR. An illustrative SII threshold of approximately 1,350 ×10⁹/L provided 74% sensitivity and 70% specificity, while an NLR threshold of approximately 6.2 provided 72% sensitivity and 68% specificity for the composite outcome.

Table 5. Discriminatory performance for composite adverse in-hospital outcome

Marker	AUC	95% CI	Illustrative cut-off	Sensitivity	Specificity
NLR	0.76	0.69–0.83	6.2	72%	68%
SII	0.79	0.72–0.85	1,350 ×10⁹/L	74%	70%

DISCUSSION

In this prospective observational study, admission NLR and SII were significantly associated with adverse in-hospital outcomes among patients admitted with ADHF. Patients who required intensive care, ventilatory or vasoactive support, or who died during hospitalization had substantially higher values of both inflammatory indices. A graded increase in event rates was observed across increasing NLR and SII tertiles, and both indices retained independent associations with the composite endpoint after adjustment for important clinical variables. SII demonstrated numerically greater discrimination than NLR in the illustrative receiver operating characteristic analysis.

The findings are consistent with the established prognostic relevance of NLR in acute heart failure. Uthamalingam et al. analyzed 1,212 consecutive patients admitted with ADHF and demonstrated progressively greater mortality across increasing NLR tertiles; patients in the highest tertile also had a markedly higher 30-day readmission rate [1]. Benites-Zapata et al. reported that NLR remained an independent predictor of in-hospital mortality in patients with acute heart failure and reduced ejection fraction [2]. In another study of 439 patients hospitalized for ADHF, NLR values were substantially higher among 30-day non-survivors, and NLR remained independently associated with mortality after adjustment [3].

More contemporary evidence has reinforced these observations. An individual-patient analysis from the BLAST-AHF, Pre-RELAX-AHF and RELAX-AHF studies demonstrated that higher NLR independently predicted 30-day mortality, 60-day heart failure or renal failure rehospitalization or cardiovascular death, and 180-day mortality [4]. A 2024 meta-analysis incorporating 15 studies and nearly 16,000 patients with acute heart failure found that high NLR was associated with both increased in-hospital mortality and long-term all-cause mortality [5]. These data provide a strong rationale for evaluating NLR as an inexpensive adjunct to routine clinical risk stratification.

The present study also emphasizes the potential utility of SII. Unlike NLR, SII incorporates platelet count and may therefore reflect interactions between inflammation, immune status and platelet-mediated vascular processes. Tang et al. reported that higher SII independently predicted hospital, 30-day and 90-day mortality among critically ill patients with congestive heart failure [6]. Yang et al., using a large intensive-care database, similarly observed higher mortality across increasing SII groups in heart failure [7]. Most directly relevant to ADHF, Qiu et al. studied 1,452 hospitalized patients and found that SII ≥980 ×10⁹/L was associated with approximately twofold higher adjusted 30-day mortality; SII achieved an AUC of 0.748 for 30-day mortality [8].

Recent evidence continues to support the prognostic signal of SII. A 2026 MIMIC-IV analysis of 5,482 patients with acute heart failure reported a dose-response association between increasing SII and 28-day mortality, with the highest SII tertile

carrying substantially greater adjusted risk than the lowest tertile [9]. Although differences in population, endpoint definitions and illness severity make direct comparison of cut-offs inappropriate, these studies are directionally consistent with the higher SII values and adverse outcome rates demonstrated in the current manuscript.

The biological basis for these associations is plausible. Neutrophils participate in innate immune activation and may increase in response to acute hemodynamic stress, tissue injury and neurohormonal activation. Lymphopenia may reflect elevated endogenous cortisol, sympathetic activation and impaired adaptive immune balance. Platelets interact with leukocytes and the vascular endothelium and can amplify inflammatory and thrombotic signaling. SII therefore integrates three cellular components that may capture a broader inflammatory phenotype than any single cell count.

Inflammation and congestion may also reinforce one another. Recent work in acute heart failure has shown correlations between NLR, high-sensitivity C-reactive protein and multiple measures of congestion, with inflammatory and congestion indices independently contributing to mortality risk [10]. This may explain why high inflammatory indices identify patients with more severe clinical deterioration even when infection is excluded. Similarly, inflammatory-marker combinations incorporating NLR have shown prognostic value for long-term mortality in acute heart failure [11].

An important clinical advantage of NLR and SII is accessibility. Both are calculated from a routine complete blood count and require no additional blood sampling or specialized assay. In resource-limited settings, they may provide a rapid signal of increased risk while more comprehensive assessment is being completed. They should not, however, be interpreted as replacements for established clinical evaluation, natriuretic peptides, renal function, echocardiography or validated heart failure risk models. Their greatest potential may be as supplementary variables that identify patients requiring closer monitoring.

The numerically higher AUC observed for SII compared with NLR in this study is clinically interesting but should be interpreted cautiously. The two indices share neutrophil and lymphocyte counts and are therefore strongly related. Formal comparison of predictive performance requires adequate sample size, prespecified thresholds and external validation. Furthermore, platelet counts may be influenced by comorbid disease and treatment, which can alter SII independently of heart failure severity.

The study has several strengths, including prospective enrollment, calculation of inflammatory indices from admission blood counts, assessment of clinically meaningful in-hospital endpoints and adjustment for important conventional risk factors. Nevertheless, causality cannot be inferred from an observational design. NLR and SII are nonspecific inflammatory markers and may be influenced by occult infection, medications, smoking, stress and comorbid conditions despite exclusion criteria. Single admission measurements do not capture biomarker trajectories during decongestion, and recent evidence suggests that changes in NLR over time may also contain prognostic information [12,13]. Finally, a single-center sample limits generalizability and the proposed thresholds require validation in independent cohorts.

Overall, the findings support admission NLR and SII as pragmatic markers associated with severity and short-term adverse outcomes in ADHF. Their low cost and immediate availability make them attractive candidates for incorporation into multimarker risk-assessment approaches, but larger prospective studies are required to determine whether they meaningfully improve clinical decision-making beyond established predictors.

Strengths and Limitations

The prospective design, use of admission blood counts, simultaneous evaluation of NLR and SII, and assessment of clinically relevant in-hospital outcomes are important strengths. The study is limited by its single-center nature, observational design and use of single baseline inflammatory measurements. NLR and SII are nonspecific and may be altered by occult inflammatory conditions, medications and comorbidities. The composite endpoint combines outcomes of differing clinical severity, and the sample size may be insufficient for stable analysis of in-hospital mortality alone. Serial measurements and external validation would strengthen future work.

CONCLUSION

Higher admission neutrophil-to-lymphocyte ratio and systemic immune-inflammation index were associated with greater disease severity and adverse in-hospital outcomes in patients with acute decompensated heart failure. Both indices remained associated with the composite adverse outcome after adjustment for conventional clinical variables, with SII showing modestly greater discriminatory performance in this illustrative analysis. Because NLR and SII can be calculated from a routine complete blood count, they may represent inexpensive adjuncts for early risk stratification. Larger multicenter prospective studies are needed to establish validated thresholds and determine their incremental value over established heart failure risk markers.

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