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The Scottish inflammatory prognostic score: A novel biomarker for predicting in-hospital mortality in acute heart failure with reduced ejection fraction

Alperen Taş [a], Çağatay Tunca [b], Veysel Ozan Tanık [b], Bülent Özlek [c,*]

[a] Department of Cardiology, Ahi Evran University Training and Research Hospital, Kirsehir, Turkey
[b] Department of Cardiology, Faculty of Medicine, Health Science University, Etlik City Hospital, Ankara, Turkey
[c] Department of Cardiology, School of Medicine, Mugla Sitki Kocman University, Mugla, Turkey

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ABSTRACT

Background: Acute heart failure with reduced ejection fraction (AHF) remains a leading cause of ED visits, hospitalizations, and in-hospital mortality.
Objectives: To evaluate the prognostic utility of the Scottish Inflammatory Prognostic Score (SIPS) in patients with AHF.
Methods: This retrospective study analyzed 508 patients admitted with AHF between November 2022 and November 2024. The SIPS was calculated based on albumin and neutrophil levels. Clinical and laboratory parameters were compared between survivors and non-survivors to identify predictors of all-cause in-hospital mortality.
Results: At a median follow-up of 10 days (range 4–28), 63 patients (12.4 %) died. The mean age of the study population was 63 years, with non-survivors being older on average. Multivariable Cox proportional regression analysis revealed high SIPS values (HR: 2.335, 95 % CI: 1.044 - 5.221, $p = 0.039$), advanced age, elevated NT-pro-BNP levels, chronic renal failure, and low serum sodium as independent predictors of in-hospital mortality. When patients were categorized by SIPS scores of 0, 1, and 2, the associated mortality rates were 5.1 %, 14.0 %, and 46.0 %, respectively ($p < 0.001$). Additionally, ROC curve analysis indicated that a SIPS threshold of 0.5 effectively predicted in-hospital mortality, demonstrating a sensitivity of 77 % and a specificity of 58 % (95 % CI: 0.661–0.803, $p < 0.001$).
Conclusions: This study is the first to analyze the association between SIPS and in-hospital mortality in patients with AHF. Integrating SIPS with other established risk factors may help improve the identification of high-risk AHF patients who could benefit from closer monitoring and intensified therapy, though further validation is warranted.

Introduction

Heart failure (HF) is a long-lasting and progressively worsening condition caused by problems in the heart's structure or function.[1] Although this clinical syndrome can show different forms, heart failure with reduced ejection fraction (HFrEF), defined as a left ventricular ejection fraction (LVEF) ≤40 % according to the European Society of Cardiology guidelines, makes up nearly half of all HF cases.[1] Acute heart failure (AHF) describes the sudden start or worsening of HF symptoms due to various triggers. It is the main reason for unplanned hospital stays, especially among people aged 65 and older.[2] A global review of HF risk factors found that ischemic heart disease is still the leading cause of AHF-related hospital stays in more than half of cases in high-income countries, as well as in Eastern and Central Europe.[3] Although therapeutic progress has been made in chronic HFrEF, AHF still results in adverse outcomes, with one-year mortality approaching 30 % and high rates of hospital readmissions.[4]

Myocardial injury caused by ischemia or hemodynamic overload triggers the heart's innate and adaptive immune systems.[5] If inadequately controlled, the inflammatory response may evolve into a chronic process, contributing to left ventricular dysfunction and adverse remodeling—hallmark features of HFrEF.[6] Patients with HFrEF show

* Corresponding author at: Mugla Sitki Kocman Universitesi Tip Fakultesi, Kötekli Mah. Marmaris Yolu, No: 48, MUĞLA 48000, Turkey.
E-mail address: bulent_ozlek@hotmail.com (B. Özlek).

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higher levels of pro-inflammatory cytokines and chemokines, along with rapid infiltration of neutrophils into the affected myocardial tissue.[7] Neutrophil levels are elevated in the blood of HF patients compared to those without HF.[5] Albumin is an essential liver protein that helps maintain blood volume and regulate fluid distribution in the body. Hypoalbuminemia, marked by low albumin levels in the blood, indicates malnutrition-inflammation syndrome.[8] Hospitalized patients with AHF and hypoalbuminemia are nearly twice as likely to die in the hospital compared to those with normal albumin levels.[9]

The Scottish Inflammatory Prognostic Score (SIPS) is a simple and original metric that combines albumin and neutrophil levels to evaluate inflammatory status. It has been suggested as a prognostic tool, especially for patients with cancer.[10] Since inflammation is increasingly recognized as a key factor in the pathophysiology of AHF,[11] using validated inflammation-based scoring systems like SIPS may provide new insights. Although initially developed for oncology, SIPS includes serum neutrophil count and albumin levels—both of which have shown strong independent prognostic value in HF populations.[12,13] Our study aimed to explore whether SIPS could be adapted for use in AHF as a practical inflammatory risk indicator, understanding that this is an initial exploratory attempt. To date, no research has assessed the predictive value of SIPS in AHF. This study seeks to evaluate how well SIPS can predict in-hospital mortality among patients with AHF.

Methods

Study population

This study is a single-center, retrospective analysis of HFrEF patients hospitalized with AHF between November 2022 and November 2024. During this period, 604 patients were identified as being admitted with a diagnosis of AHF, and 508 patients were included in the final cohort after applying exclusion criteria. Blood tests, demographic information, comorbid conditions, medications, and echocardiographic findings at admission were anonymously extracted from the hospital medical record system. The exclusion criteria include the following conditions: (1) patients under 18 years of age, (2) patients hospitalized for AHF with preserved (HFpEF) or mildly reduced ejection fraction (HFmrEF), (3) patients with HFrEF treated as outpatients, (4) patients with missing clinical data, (5) a history of active malignancy or chemo-radiotherapy, (6) chronic liver disease, (7) sepsis, (8) trauma or burns, (9) presence of acute coronary syndrome (ACS) concurrent with AHF. HF classifications were based on the ESC 2021 guidelines for HF,[1] which define HFrEF as LVEF $\leq$40 %, HFmrEF as LVEF 41–49 %, and HFpEF as LVEF $\geq$50 %. Since this was a retrospective observational study, no formal sample size calculation was performed. Instead, all eligible patients meeting the inclusion criteria during the specified study period were included in the final analysis to maximize statistical power and generalizability.

AHF and HFrEF were diagnosed based on the European Society of Cardiology guidelines for the diagnosis and treatment of HF.[1] The diagnosis of AHF required the presence of acute or worsening symptoms and signs of HF (e.g., dyspnea, orthopnea, pulmonary rales, peripheral edema), supported by objective evidence of cardiac dysfunction on echocardiography (LVEF $\leq$40 % for HFrEF) and elevated natriuretic peptide levels above the guideline-recommended thresholds. Additional supportive findings included chest X-ray evidence of pulmonary congestion and laboratory data consistent with HF decompensation. For this exploratory analysis, we limited inclusion to patients with HFrEF to ensure a pathophysiologically homogeneous study cohort. HFpEF and HFmrEF patients were excluded because these phenotypes differ substantially from HFrEF in underlying mechanisms, hemodynamic characteristics, and prognosis, as demonstrated in prior studies.[1] Including all HF phenotypes in a single analysis could introduce considerable heterogeneity and potentially obscure the prognostic impact of SIPS. Moreover, in the acute care setting, HFpEF diagnosis is more challenging than HFrEF, as it requires comprehensive echocardiographic evaluation and hemodynamic assessment, which may not always be feasible in the emergency department. For these reasons, we considered it methodologically sound to focus on HFrEF for this initial investigation. Each patient's SIPS score was calculated using serum albumin and neutrophil levels. The scoring was as follows: (i) low risk (0 points): serum albumin $\geq$ 3.5 g/dL and neutrophil counts $\leq 7.5 \times 10^9$/L; (ii) moderate risk (1 point): serum albumin $\geq$ 3.5 g/dL and neutrophil counts $> 7.5 \times 10^9$/L or serum albumin $<$ 3.5 g/dL and neutrophil counts $\leq 7.5 \times 10^9$/L; (iii) high risk (2 points): serum albumin $<$ 3.5 g/dL and neutrophil counts $> 7.5 \times 10^9$/L.[10]

Follow-up and endpoints

Patients who were hospitalized from the study's start date until November 30, 2024, were monitored until they were discharged or until they died. The follow-up period for each patient thus corresponded to their individual hospitalization duration. All follow-up data, including clinical outcomes and in-hospital events, were retrospectively collected from the hospital's electronic medical record system, ensuring accurate and complete documentation. The primary endpoint of the study was all-cause in-hospital mortality. Because all patients experienced a definitive in-hospital outcome (discharge or death), the follow-up duration did not influence outcome ascertainment.

This research followed the principles of the Declaration of Helsinki, and all study protocols received approval from the institutional review board at Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2025–106). Because of the study's retrospective nature, informed consent was not necessary.

Statistical analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed parameters are presented as mean $\pm$ standard deviation, while non-normally distributed data are expressed as median and interquartile range. Categorical variables are reported as frequency and percentage, with analyses conducted using the chi-square test. The statistical approach was selected to best address the study's retrospective nature and the time-to-event structure of in-hospital mortality. All analyses adhered to established methodological standards for clinical outcome research, ensuring internal consistency and robustness. For comparisons between groups with normally distributed data, Student's *t*-test was utilized. Analysis of Variance (ANOVA) was employed to evaluate groups of three or more. In contrast, the Mann-Whitney U test was applied to data that did not conform to normal distribution. Following a comprehensive analysis of deceased and surviving patients, a regression analysis was conducted to evaluate the predictive value of various clinical and laboratory parameters on all-cause in-hospital mortality. Independent variables included demographic characteristics, comorbidities, and key biomarkers, with the SIPS as a primary variable of interest. Age was analyzed as a continuous variable in all regression models, expressed per 1-year increment, without applying a specific cut-off value. Covariate selection was based on both clinical relevance and statistical significance in univariable analysis ($p < 0.05$), and multicollinearity was checked to ensure model validity. To avoid multicollinearity, all variables entered into the multivariable Cox model were tested using variance inflation factor analysis, with all values $<$2.5. Both univariable and multivariable Cox proportional hazards regression models were employed to evaluate the association between predictor variables and in-hospital mortality. The proportional hazards assumption was evaluated and satisfied for the included covariates. Cox proportional hazards regression was deemed appropriate given the time-to-event nature of the primary endpoint and its ability to adjust for multiple covariates simultaneously while assessing their independent associations with mortality. To assess the internal stability of the results, a non-parametric bootstrap procedure with 1000 resamples was performed for the multivariable Cox

regression model. The results were expressed as hazard ratios (HR) with corresponding 95 % confidence intervals (CI), allowing for a comprehensive assessment of each parameter's prognostic relevance. The optimal prognostic threshold value of the SIPS was determined through receiver operating characteristic curve (ROC) analysis. The prognostic implications of SIPS were evaluated by stratifying patients based on the predefined cut-off value and risk categories: 0 (low risk), 1 (moderate risk), and 2 (high risk). Kaplan-Meier survival curves were generated to compare survival probabilities among these groups, and statistical significance was assessed using log-rank p-values. A p-value of <0.05 was considered statistically significant in all analyses conducted. Statistical evaluations were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) for data analysis. A priori sample size estimation was not performed because of the retrospective design; all consecutive eligible patients within the study window were included. A post-hoc power analysis (Schoenfeld's method for Cox regression) was conducted for the primary endpoint by dichotomizing SIPS at 0.5 (SIPS ≥ 0.5 vs. < 0.5). With 63 events and an exposure prevalence of approximately 46.5 %, the achieved power to detect the observed effect was ~90 % at a two-sided α=0.05. The corresponding minimum detectable HRs were ~2.03 for 80 % power and ~2.27 for 90 % power.

Results

Table 1 compares the demographic, clinical, comorbid, and laboratory data of patients who have died and those who survived in the entire study cohort. In the final cohort of 508 patients, 63 (12.4 %) succumbed during hospitalization. The median length of in-hospital follow-up was 10 days (range: 4–28 days). Among the entire cohort, 70.8 % of patients were female, with a mean age of 63 years. Deceased patients were notably older than survivors, with average ages of 72 and 62.5 years, respectively ($p < 0.001$). There was no significant difference in gender distribution between the two groups. When analyzing comorbid conditions, no significant disparities were found between deceased patients and survivors regarding diabetes mellitus, hypertension, hyperlipidemia, history of coronary artery bypass surgery, smoking, chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), and peripheral arterial disease. However, chronic renal failure (CRF) was significantly more prevalent among those who died, occurring in 46.0 % of deceased patients compared to 25.4 % of survivors ($p = 0.001$). Interestingly, the usage patterns of various medications were similar between the two groups, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, sodium-glucose cotransporter-2 inhibitors, mineralocorticoid receptor antagonists, acetylsalicylic acid, statins, and anticoagulants. The mean LVEF values were also comparable between deceased and surviving patients. Significant differences emerged in blood test results. Serum levels of glucose, creatinine, urea, and N-terminal B-type natriuretic peptide (NT-pro-BNP) (5493 vs. 2037 pg/mL, $p < 0.001$) were considerably higher in deceased patients. Additionally, levels of C-reactive protein (CRP), white blood cell (WBC) count, and neutrophil count (8.9 ± 6.8 vs. 5.9 ± 3.1 × 10^9/L, $p < 0.001$), regarded as inflammatory markers, were also elevated in deceased patients compared to survivors. Conversely, survivors had higher serum sodium, calcium, hemoglobin levels, and lymphocyte counts. Notably, serum albumin levels were significantly lower in deceased patients than survivors (3.3 ± 0.7 vs. 3.7 ± 0.5 g/dL, $p < 0.001$). Furthermore, when comparing SIPS values between the two groups, deceased patients had a significantly higher score than surviving patients (1.14 ± 0.75 vs. 0.48 ± 0.30, $p < 0.001$).

The results of univariable and multivariable regression analyses examining all-cause in-hospital mortality after controlling for potential confounders are summarized in Table 2. In the univariable analysis, factors such as increasing age, CRF, elevated serum urea, glucose, NT-pro-BNP, CRP, WBC, and neutrophil levels were found to be associated with mortality. Conversely, lower serum albumin, sodium, calcium, hemoglobin, and lymphocyte levels were also linked to increased mortality. Additionally, a higher SIPS score was associated with mortality ($p < 0.001$). In the multivariable analysis, the following factors were independently linked to higher in-hospital mortality: advanced age (HR: 1.067, 95 % CI: 1.032 - 1.103, $p < 0.001$), CRF (HR: 1.043, 95 % CI: 1.022 - 1.101, $p = 0.003$), elevated NT-pro-BNP levels (HR: 1.856, 95 % CI: 1.513 - 2.109, $p = 0.001$), increased SIPS score (HR: 2.335, 95 % CI: 1.044 - 5.221, $p = 0.039$), and low serum sodium levels (HR: 0.757, 95 % CI: 0.698 - 0.821, $p < 0.001$). In internal validation using 1000 bootstrap resamples, the HR for SIPS was 2.310 (95 % CI: 1.040–5.251), which was highly consistent with the original model estimates, indicating stability of the association.

ROC curve analysis was conducted to identify the optimal cut-off

Table 1
Demographic and clinical characteristics of study participants.

	Surviving ($n = 445$)	Deceased ($n = 63$)	p-value
Age, years	62.5 ± 14.1	72.0 ± 12.1	<0.001
Female sex, n (%)	315 (70.8)	45 (71.4)	0.878
Diabetes mellitus, n (%)	148 (33.3)	20 (31.7)	0.811
Hypertension, n (%)	280 (62.9)	41 (65.1)	0.740
Hyperlipidemia, n (%)	139 (31.2)	23 (36.5)	0.401
CABG, n (%)	122 (27.4)	22 (34.9)	0.216
Smoking, n (%)	194 (43.6)	24 (38.1)	0.275
COPD, n (%)	144 (32.4)	26 (41.3)	0.161
Atrial fibrillation, n (%)	87 (19.6)	16 (25.4)	0.280
Chronic renal failure, n (%)	113 (25.4)	29 (46.0)	0.001
Peripheral artery disease, n (%)	34 (7.6)	7 (11.1)	0.344
Medications			
ACEi, n (%)	346 (77.8)	42 (66.7)	0.053
ARB, n (%)	73 (16.4)	15 (23.8)	0.146
SGLT-2i, n (%)	148 (33.3)	16 (25.4)	0.212
MRA, n (%)	318 (71.5)	43 (68.3)	0.599
Acetylsalicylic acid (%)	271 (60.9)	39 (61.9)	0.878
P2Y12 inhibitor, n (%)	69 (15.5)	16 (25.4)	0.049
Statins, n (%)	210 (47.2)	28 (44.4)	0.683
Anticoagulant, n (%)	240 (53.9)	42 (66.7)	0.057
Laboratory data			
LVEF, %	26.3 ± 6.1	27.1 ± 4.7	0.221
Serum glucose, mg/dL	111 (94–152)	130 (110–178)	0.002
Serum creatinine, mg/dL	1.1 (0.9–1.9)	2.2 (1.2–3.0)	<0.001
Serum urea, mg/dL	38.3 ± 30.1	65.2 ± 47.4	<0.001
Serum sodium, mmol/L	138 (136–140)	132 (127–134)	<0.001
Serum potassium, mmol/L	4.5 (4.0–4.9)	4.6 (4.1–5.1)	0.108
Serum chloride, mmol/L	101 (98–104)	102 (99–103)	0.271
Serum calcium, mg/dL	9.0 (8.4–9.5)	8.6 (8.2–9.1)	0.006
NT-pro-BNP, pg/mL	2037 (696–5427)	5493 (1023–23,610)	<0.001
Total cholesterol, mg/dL	174.2 ± 54.4	172.3 ± 63.8	0.805
LDL-cholesterol, mg/dL	142.2 ± 80.1	139.3 ± 83.8	0.789
HDL-cholesterol, mg/dL	38.1 ± 11.7	35.5 ± 14.7	0.126
Trigliserid, mg/dL	120 (91–166)	123 (90–183)	0.593
AST, U/L	24 (11–41)	26 (15–45)	0.281
ALT, U/L	22 (10–38)	25(12–41)	0.109
C-reactive protein, mg/L	20 (8–42)	51 (38–67)	<0.001
Serum albumin, g/dL	3.7 ± 0.5	3.3 ± 0.7	<0.001
White blood cells, x10^9/L	8.5 ± 3.0	9.5 ± 3.4	0.021
Hemoglobin, g/dL	13.4 ± 2.2	12.4 ± 2.7	0.001
Platelet, x10^9/L	240 (190–294)	257 (184–306)	0.492
Neutrophil, x10^9/L	5.9 ± 3.1	8.9 ± 6.8	<0.001
Lymphocyte, x10^9/L	1.9 (1.3–2.5)	1.5 (1.0–2.1)	0.001
SIPS	0.48 ± 0.30	1.14 ± 0.75	<0.001
Follow-up time, days	10.0 ± 6.5	11.4 ± 6.1	0.113

Abbreviations: LVEF, Left Ventricular Ejection Fraction; CABG, Coronary Artery Bypass Grafting; COPD, Chronic Obstructive Pulmonary Disease; ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin II Receptor Blocker; SGLT-2i, Sodium-Glucose Cotransporter-2 inhibitors; MRA, Mineralocorticoid Receptor Antagonist; SIPS, Scottish Inflammatory Prognostic Score; NT-pro-BNP, N-terminal pro-B-type Natriuretic Peptide; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2
Univariable and multivariable Cox proportional hazards regression analysis for in-hospital mortality.

	Univariable regression analysis			Multivariable regression analysis		
	HR	%95 CI	p-value	HR	%95 CI	*p*-value
Age, 1 year increase	1.058	1.034–1.082	<0.001	1.067	1.032–1.103	<0.001
Chronic renal failure	1.085	1.033–1.184	0.001	1.043	1.022–1.101	0.003
Serum glucose	1.010	1.005–1.016	0.004	1.004	0.998–1.010	0.102
Serum urea	1.018	1.011–1.025	<0.001	1.004	0.994–1.015	0.421
Serum sodium	0.767	0.720–0.817	<0.001	0.757	0.698–0.821	<0.001
SIPS	3.958	2.653–5.907	<0.001	2.335	1.044–5.221	0.039
Sarum calcium	0.579	0.392–0.853	0.006	0.564	0.313–1.014	0.056
NT-pro-BNP, 1000 pg/mL increase	2.143	1.918–2.687	<0.001	1.856	1.513–2.109	0.001
C-reactive protein	1.013	1.006–1.020	<0.001	1.009	1.000–1.018	0.055
White blood cells	1.094	1.013–1.183	0.022	1.088	0.969–1.223	0.153
Hemoglobin	0.827	0.736–0.928	0.001	1.084	0.913–1.287	0.358
Lymphocyte	0.942	0.865–0.985	0.001	1.056	0.921–1.134	0.257
Serum albumin	0.340	0.221–0.523	<0.001	0.972	0.447–2.113	0.943
Neutrophil	1.152	1.077–1.232	<0.001	1.024	0.908–1.154	0.701

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; SIPS, Scottish Inflammatory Prognostic Score; NT-pro-BNP, N-terminal pro-B-type Natriuretic Peptide.

value of the SIPS score for predicting in-hospital mortality. The Youden index determined 0.5 as the ideal threshold. This cutoff was then used to categorize patients for Kaplan-Meier survival analysis and risk stratification. The findings showed that SIPS had strong sensitivity in predicting mortality, with an area under the curve of 0.732 (95 % CI: 0.661–0.803, $p < 0.001$). For the optimal cut-off value of 0.5, the sensitivity and specificity of SIPS for predicting in-hospital mortality were 77 % and 58 %, respectively, with a positive predictive value of 20.6 %, a negative predictive value of 94.7 %, a positive likelihood ratio of 1.83, and a negative likelihood ratio of 0.40 (Fig. 1). It should be noted that the ROC-derived cut-off value of 0.5 does not correspond to an actual category within the SIPS system, but represents the statistically optimal threshold. Clinically, this is equivalent to separating patients with a SIPS score of 0 from those with a score of ≥1. When using a SIPS cut-off of 0.5, the in-hospital mortality rate was higher in patients with SIPS scores of 0.5 and above compared to those with scores below 0.5 (log-rank $p < 0.001$). The Kaplan-Meier survival curves for these groups are shown in Fig. 2.

Table 3 shows a comparison of clinical and laboratory data among patients categorized into low (0), moderate (1), and high-risk (2) scores based on the SIPS assessment. The analysis indicates that individuals in the high-risk SIPS group tend to be older and have higher rates of COPD, AF, and CRF compared to those in the low-risk group. Notably, there were no significant differences in the proportions of medications prescribed for HF across the different SIPS risk groups. Additionally, serum urea, creatinine, NT-pro-BNP, WBC, and CRP levels increased with higher SIPS scores, while serum calcium and sodium levels decreased among patients with higher scores. Hemoglobin and lymphocyte levels were also lower in the high SIPS group. The average follow-up duration was similar across all patient groups, and in-hospital mortality rates rose

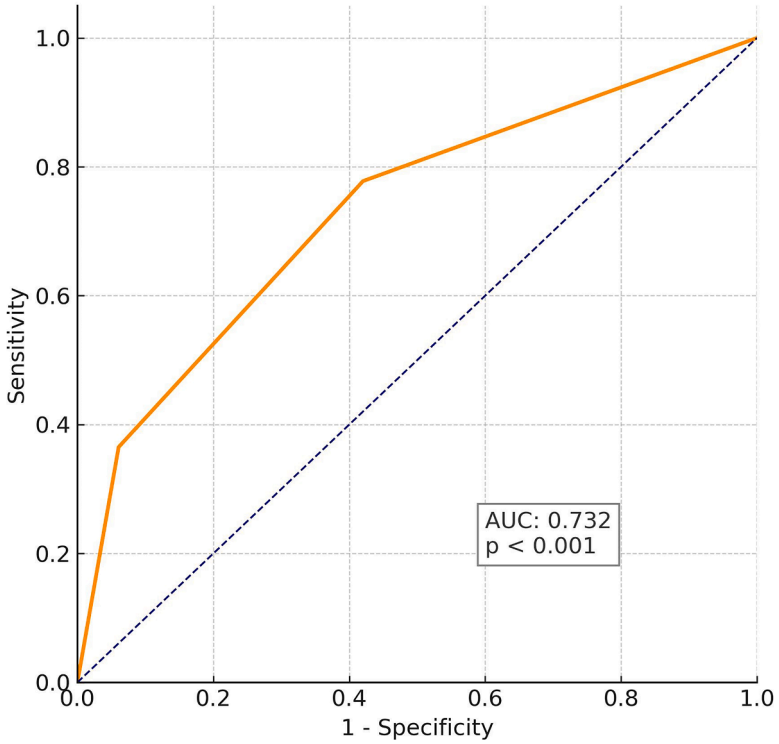
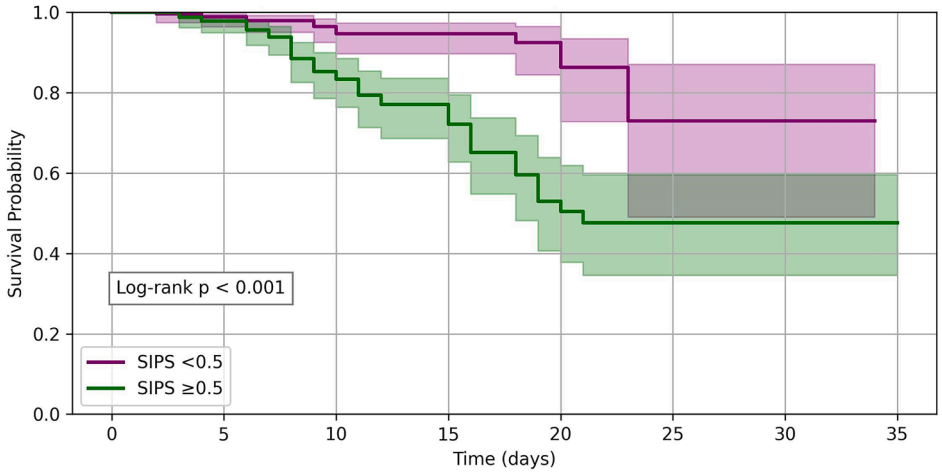


Fig. 1. The sensitivity and specificity of the Scottish Inflammatory Prognostic Score in predicting all-cause in-hospital mortality were determined using the Receiver Operating Characteristic curve analysis.
Abbreviations: AUC, area under the curve.



SIPS <0.5								
At risk	272	208	98	51	23	8	5	0
Censored	0	61	165	212	237	250	253	258
Events	0	3	9	9	12	14	14	14
SIPS ≥0.5								
At risk	236	177	82	52	18	6	3	0
Censored	0	54	128	148	170	181	184	187
Events	0	5	26	36	48	49	49	49

Fig. 2. Kaplan-Meier survival curves comparing patients in the low-risk (SIPS $<$ 0.5) and high-risk (SIPS $\geq$ 0.5) groups, based on the Scottish Inflammatory Prognostic Score (SIPS) threshold of 0.5.

significantly with increasing SIPS values (5.1 % for SIPS = 0, 14.0 % for SIPS = 1, and 46.0 % for SIPS = 2, respectively, $p < 0.001$) (Fig. 3). The Kaplan-Meier survival curve stratified by SIPS risk group is shown in Fig. 4.

Discussion

To the best of our knowledge, this analysis represents the first investigation in the literature demonstrating the in-hospital prognostic significance of SIPS in patients with AHF and HFrEF. The key findings of the current study can be summarized as follows: (i) a high SIPS value is an independent prognostic factor for all-cause mortality among patients hospitalized with AHF; (ii) patients with a SIPS value of 2 face a relative 9-fold increased risk of in-hospital mortality compared to those with a SIPS value of 0, while patients with a SIPS value of 1 have a relative 2.7-fold increased risk; (iii) additional risk factors associated with mortality in hospitalized AHF patients include advanced age, CRF, elevated NT-pro-BNP levels, and low serum sodium levels. The prognostic value of SIPS was preserved when analyzed both as a binary variable (SIPS $\geq$1 vs. 0) and in its original categorical form (0, 1, and 2), supporting the robustness of our findings.

Advancements in the treatment of various cardiac conditions, including ACS and congenital heart diseases, have markedly reduced short-term mortality rates in HF.[1] The widespread adoption of effective oral therapies and medical devices for patients with HFrEF has also improved long-term survival.[1] On the other hand, demographic shifts, particularly increased life expectancy, have significantly contributed to the growing number of individuals living with HF.[14] In developed countries, HF affects approximately 2 % of the adult population, and hospitalization rates for HF have tripled since the 1990s.[14] Despite significant progress in the treatment of chronic HFrEF, AHF continues to be associated with poor outcomes, with in-hospital mortality rates generally ranging from 4 % to 9 %.[15] The in-hospital mortality rate in our cohort (12.4 %) was higher than some reported estimates—such as approximately 5.8 % in broader AHF populations[16]—but similar to more severe AHF/HFrEF cohorts with rates around 12.7 %.[17] This difference is likely attributable to our inclusion of exclusively HFrEF patients hospitalized with AHF, many of whom presented with advanced comorbidities such as CRF. Such a selection bias toward more severe clinical profiles may partly explain the higher observed mortality and underscores the importance of precise risk stratification tools like SIPS in this subgroup.

The development and worsening of systemic congestion leading to AHF can occur over hours to days. This may be initiated directly by activating pathophysiological processes that cause fluid buildup or redistribution, or indirectly through diastolic or systolic cardiac function deterioration.[18] Common causes for the onset of AHF include factors such as arrhythmias (especially AF), ACS, uncontrolled hypertension, infections (particularly respiratory ones), and failure to adhere to prescribed dietary or medication guidelines.[18] In addition to these clinical factors, recent evidence has made it increasingly clear that immune and inflammatory mechanisms play a significant role in developing AHF.[19] A recent study documented that inflammation, endothelial dysfunction, and mechanical stress are linked to severe congestion.[20] The presence of inflammatory markers, including tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), myeloperoxidase, and CRP, typically remains normal or low in patients with chronic HFrEF.[21] However, these markers become elevated during acute decompensation and remain elevated for a certain period.[21] This pattern serves as an important indicator of the cellular mechanisms underlying the development of AHF. Although patients with sepsis were excluded from our analysis, elevated CRP and neutrophil levels may also reflect subclinical infections or sterile inflammatory responses triggered by hemodynamic stress in AHF. Therefore, SIPS may serve as a surrogate for overall inflammatory burden rather than an infection-specific marker. Furthermore, research indicates that TNF-α and IL-6 levels serve as independent predictors of mortality and hospitalizations in patients with AHF.[22] Both pro-inflammatory cytokines and chemokines, the complement system, macrophages, T and B cells, mast cells, natural killer cells, and dendritic cells are involved in the inflammatory process in AHF.[6] The activation of all these systems leads to an increase in neutrophils in the peripheral blood.[23] While specific pro-inflammatory markers offer direct insights into inflammation and can indirectly indicate the prognosis of AHF, obtaining this data in clinical practice may not always be feasible. Therefore, it seems more logical to start with neutrophil data derived from a complete blood count, particularly given that previous studies

Table 3
Analysis of patients stratified by low, moderate, and high-risk scores based on the Scottish Inflammatory Prognostic Score (SIPS).

	Low risk (SIPS=0) (*n* = 272)	Moderate risk (SIPS=1) (*n* = 186)	High risk (SIPS=2) (*n* = 50)	*p*-value
Age, years	62.2 ± 14.1 [a]	65.0 ± 13.9 [b]	67.1 ± 15.1 [b]	0.024
Female sex,n (%)	190 (69.9)	135 (72.6)	35 (70.0)	0.354
Diabetes mellitus, n (%)	78 (28.7)	69 (37.1)	21 (42)	0.063
Hypertension, n (%)	167 (61.4)	121 (65.1)	33 (66.0)	0.663
Hyperlipidemia, n (%)	81 (29.8)	65 (34.9)	16 (32.0)	0.507
CABG, n (%)	75 (27.6)	55 (29.6)	14 (28.0)	0.896
Smoking, n (%)	122 (44.9)	80 (43.0)	16 (32.0)	0.226
COPD, n (%)	82 (30.1) [a]	64 (34.4) [a.b]	24 (48.0) [b]	0.046
Atrial fibrillation, n (%)	43 (15.8) [a]	50 (26.9) [b]	10 (20.0) [a.b]	0.015
Chronic renal failure, n (%)	64 (23.5) [a]	58 (31.2) [a.b]	20 (40.0) [b]	0.027
Peripheral artery disease, n (%)	25 (9.2)	13 (7.0)	3 (6.0)	0.594
Medications				
ACEi, n (%)	216 (79.4)	139 (74.7)	33 (66.0)	0.098
ARB, n (%)	45 (16.5)	34 (18.3)	9 (18.0)	0.882
SGLT-2i, n (%)	93 (34.2)	56 (30.1)	15 (30.0)	0.614
MRA, n (%)	197 (72.4)	131 (70.4)	33 (66.0)	0.636
Acetylsalicylic acid, n (%)	181 (66.5) [a]	96 (51.6) [b]	33 (66.0) [a.b]	0.004
P2Y12 inhibitor, n (%)	44 (16.2)	31 (16.7)	10 (20.0)	0.801
Statins, n (%)	124 (45.6)	87 (46.8)	27 (54.0)	0.549
Anticoagulant, n (%)	147 (54.0)	110 (59.1)	25 (50.0)	0.398
Laboratory data				
LVEF, %	23 (15–38)	26 (10–40)	26 (20–37)	0.652
Serum glucose, mg/dL	108 (73–373)	104 (60–361)	109 (79–368)	0.196
Serum creatinine, mg/dL	1.0 (0.6–6.8) [a]	1.2 (0.5–4.1) [b]	1.4 (0.7–3.5) [c]	0.001
Serum urea, mg/dL	26 (9–147) [a]	55 (10–139) [b]	63 (10–156) [b]	<0.001
Serum sodium, mmol/L	138 (127–147) [a]	136 (118–156) [b]	135 (125–145) [b]	<0.001
Serum potassium, mmol/L	4.3 (3–5.1)	4.3 (2.7–6.2)	4.2 (3.3–5.6)	0.055
Serum chloride, mmol/L	101 (97–112)	101 (83–111)	100 (92–112)	0.877
Serum calcium, mg/dL	9.2 (6.5–10.2) [a]	8.9 (7.1–9.2) [a]	8.3 (6.9–9.7) [b]	0.002
NT-pro-BNP, pg/mL	1597 (488–2388) [a]	6576 (1207–29,842) [b]	7300 (2642–34,367)[c]	<0.001
LDL-cholesterol, mg/dL	109.5 (44–265)	97.0 (45–199)	101.5 (49–146)	0.105
HDL-cholesterol, mg/dL	35 (12–68)	34 (13–77)	36.5 (13–89)	0.096
Trigliserid, mg/dL	114 (19–475)	99 (40–359)	97 (47–242)	0.088
C-reactive protein, mg/L	11 (4–96) [a]	32 (2–249) [b]	38 (7–230) [b]	<0.001
White blood cells, 10^9/L	8.1 (4.9–15.7) [a]	8.7 (3.4–18.8) [a]	11.7 (8.4–20.3) [b]	<0.001
Hemoglobin, g/dL	12.8 (8.9–16.5) [a]	11.7 (8.2–16.7) [b]	11.5 (8.7–15.3) [c]	<0.001
Platelet, x10^9/L	240.2 ± 72.1	256.8 ± 88.1	261.8 ± 116.3	0.056
Lymphocyte, x10^9/L	2.1 (0.4–8.9) [a]	1.4 (0.2–13.1) [b]	1.4 (0.4–4.0) [b]	<0.001
Follow-up time, days	8 (2–28)	6 (3–25)	8 (3–19)	0.921
In-hospital mortality, n (%)	14 (5.1) [a]	26 (14.0) [b]	23 (46.0) [c]	<0.001

Different superscripts indicate the statistical difference between groups.
Abbreviations: LVEF, Left Ventricular Ejection Fraction; CABG, Coronary Artery Bypass Grafting; COPD, Chronic Obstructive Pulmonary Disease; ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin II Receptor Blocker; SGLT-2i, Sodium-Glucose Cotransporter-2 inhibitors; MRA, Mineralocorticoid Receptor Antagonist; NT-pro-BNP, N-terminal pro-B-type Natriuretic Peptide; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein.

have shown a correlation between elevated neutrophil counts, the severity of HF, and mortality rates.[24] Given that various factors can affect neutrophil counts, many studies have examined the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in patients with AHF to establish it as a more reliable inflammatory marker. A recent extensive meta-analysis demonstrated that an elevated NLR is independently associated with short- and long-term mortality in AHF patients.[25]

Albumin is a hepatic protein frequently used to evaluate nutritional status, even though its serum levels are influenced more by factors like infection, injury, and trauma than protein intake. Serum albumin levels decrease during acute illness but increase during recovery.[26] However, the degree of injury or illness can negatively impact appetite, gastrointestinal motility, and hemodynamic stability, further affecting nutritional status.[27] In HFrEF, reduced plasma albumin levels may result from malnutrition, hemodilution, decreased synthesis due to liver congestion, inflammation, increased metabolic activity, and proteinuria.[28] Severe hypoalbuminemia reduces plasma oncotic pressure, promoting fluid retention and edema, which can exacerbate AHF and renal failure.[28] Moreover, human serum albumin may be a marker of protein metabolism disorders and low-grade inflammation in patients with HF.[29] Clinical studies support these physiopathologic mechanisms, and prior research has shown that hypoalbuminemia is associated with both in-hospital and long-term mortality in AHF.[30] Consistently, the recent ALBIMED-HF study demonstrated that lower serum albumin levels independently predicted 1-year mortality in older patients hospitalized for AHF, reinforcing the prognostic relevance of this simple laboratory marker in this high-risk population.[31]

Since neutrophil count and serum albumin levels serve as indicators of the inflammatory process in AHF, combining these two parameters can enhance predictive accuracy and reduce uncertainties surrounding prognostic assessments. Evaluating these independent markers together accounts for the impact of various confounding factors on their individual levels. However, only one study in the literature has evaluated outcomes in AHF using neutrophil and albumin parameters. In a recent investigation by Hu et al. ,[32] 2942 patients with HF who were hospitalized in a coronary intensive care unit were analyzed for all-cause mortality based on the neutrophil to albumin ratio (NPAR). The study revealed that when a cut-off value of 27.64 for the NPAR was employed, the 30-day mortality rate was higher in patients exceeding this threshold.[32] The study conducted by Hu et al. included not only patients with HFrEF but also all HF phenotypes. In contrast, our research represents the first comprehensive analysis focusing specifically on this area. Moreover, while the NPAR is derived from neutrophil and albumin levels, establishing a standard optimal threshold value is challenging due to its nature as a ratio. The reference NPAR value may vary depending on the population being studied. In this regard, the SIPS classification offers greater clarity and convenience. Additionally, Hu et al.'s study[32] did not exclude clinical conditions that could influence neutrophil and albumin levels in a short time frame, such as ACS, sepsis,

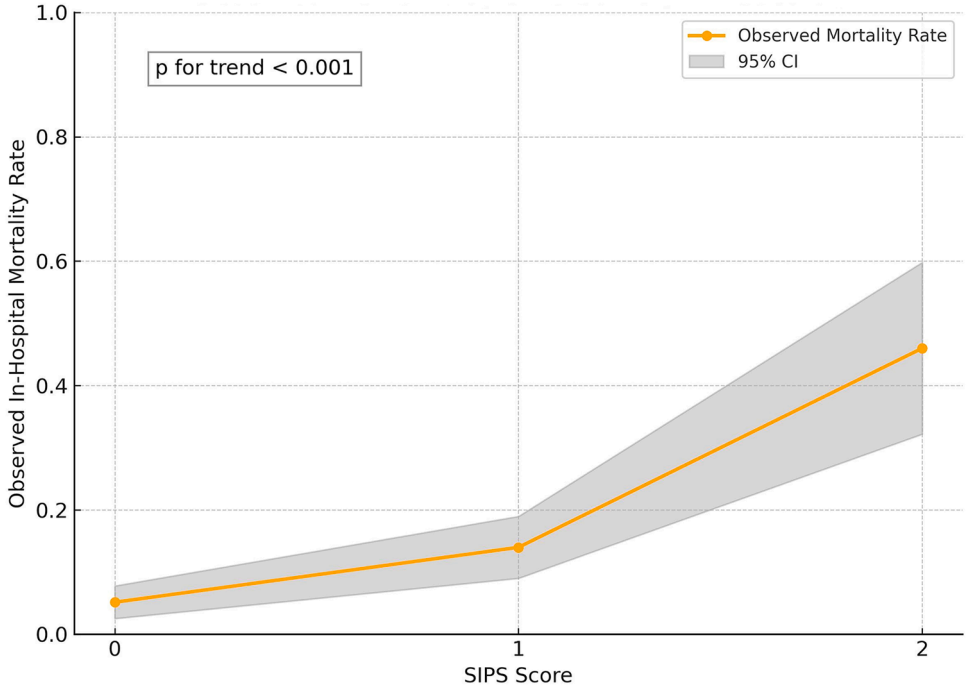
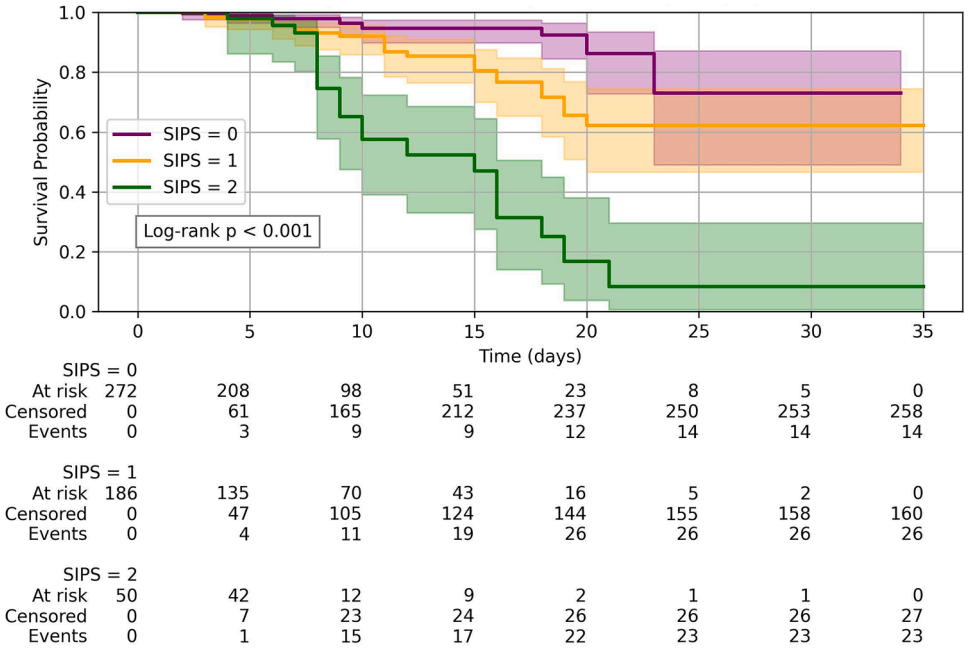


Fig. 3. Observed in-hospital mortality rates stratified by Scottish Inflammatory Prognostic Score (SIPS) score. A progressive increase in mortality was observed with rising SIPS values. The shaded area represents the 95 % confidence interval calculated using binomial approximation.



SIPS = 0								
At risk	272	208	98	51	23	8	5	0
Censored	0	61	165	212	237	250	253	258
Events	0	3	9	9	12	14	14	14
SIPS = 1								
At risk	186	135	70	43	16	5	2	0
Censored	0	47	105	124	144	155	158	160
Events	0	4	11	19	26	26	26	26
SIPS = 2								
At risk	50	42	12	9	2	1	1	0
Censored	0	7	23	24	26	26	26	27
Events	0	1	15	17	22	23	23	23

Fig. 4. Kaplan-Meier survival curves for patients stratified by Scottish Inflammatory Prognostic Score (SIPS) 0 to 2.

trauma, and burns, which may occur concurrently with AHF. Despite these differences, our findings align with the analysis of Hu et al. In our study, SIPS was found to be an independent predictor of in-hospital all-cause mortality, with in-hospital mortality rates being at least 2.7 times higher in patients with an SIPS value of 1 or above compared to those with a value of 0. Only two analyses have examined the prognostic impact of the combination of neutrophils and albumin in chronic HF patients. Both studies utilized NPAR and included all HF phenotypes, finding that increased NPAR was independently associated with long-term mortality.[33,34] Although chronic patients and HF phenotypes other than HFrEF are not the focus of our study, considering the significant role of inflammation in chronic HF and other HF phenotypes,[35] the findings of these studies align with our study's results, albeit indirectly.

Beyond NPAR, several inflammation- and nutrition-based prognostic indices—such as the Glasgow Prognostic Score and the Prognostic Nutritional Index—have been evaluated in HF populations.[36,37] While these scores have demonstrated independent associations with short- and long-term mortality, their calculation often involves CRP measurements or more complex formulas, which may not be universally

available in acute settings. In contrast, SIPS is derived solely from albumin and neutrophil count, both routinely included in standard admission laboratory panels. This simplicity may offer an advantage for early risk stratification, particularly in resource-limited or emergency care environments. Furthermore, unlike NPAR, SIPS categorizes patients into discrete risk groups, facilitating clinical interpretation and potentially aiding decision-making in high-turnover acute care units.

While SIPS has not previously been validated in cardiologic cohorts, its components—serum neutrophil count and albumin—are well-established markers associated with mortality and disease severity in AHF.[12,13] Rather than asserting its immediate clinical applicability, our objective was to investigate whether this simple, pre-existing inflammatory score might provide incremental prognostic information when applied to an AHF population. As such, this study should be viewed as hypothesis-generating, laying the groundwork for future validation efforts. In addition to the primary focus, other clinical and laboratory parameters with significant prognostic implications for patients diagnosed with AHF are of considerable importance. Integrating these parameters with the SIPS value will enhance its predictive capacity. Moreover, our investigation underscores additional prognostic indicators. Prior research has indicated that factors such as advanced age, elevated levels of NT-pro-BNP, CRF, and hyponatremia correlate with heightened mortality rates.[38] From a clinical perspective, the incorporation of SIPS into existing triage and management pathways could enable earlier identification of high-risk patients who might benefit from intensified monitoring, more aggressive decongestive strategies, or early referral to specialized HF teams. Given that both of its components are available within hours of hospital admission, SIPS could be calculated in real time at the point of care, complementing established biomarkers such as NT-pro-BNP.

The rationale for focusing on SIPS lies in the central role of inflammation and nutritional status in the pathogenesis and progression of HF. Neutrophils are key mediators of the acute immune response and contribute to myocardial injury, endothelial dysfunction, and ventricular remodeling through the release of reactive oxygen species and pro-inflammatory cytokines.[39] Conversely, hypoalbuminemia reflects both systemic inflammation and catabolic stress, and has been linked to impaired cardiac contractility and increased vascular permeability.[28] These pathophysiologic mechanisms help explain the strong association between SIPS and short-term mortality in our cohort. By integrating two routinely available laboratory parameters, SIPS may offer a practical and biologically plausible tool for risk stratification in acute settings.

Study limitations

Due to the retrospective nature of our study, several limitations must be acknowledged. First, although the SIPS score has been validated in oncological settings, it has not undergone formal recalibration or validation in patients with cardiovascular disease. Therefore, the use of SIPS in our study should be interpreted as exploratory, and the findings require confirmation through external validation in prospective multicenter studies. Second, although our sample size is sufficient for meaningful statistical analysis, it remains relatively small. Third, while SIPS serves as an indirect marker of inflammation, we lacked direct measurements of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, limiting our ability to assess the correlation between SIPS and these mediators. In addition, our study exclusively included patients with AHF in the HFrEF subgroup. Given that nearly half of the HF population presents with alternative HF phenotypes, our findings may not be generalizable across the entire HF spectrum. While CRF was significantly more prevalent in the deceased group and included in the multivariable analysis, the potential contribution of renal protein loss to hypoalbuminemia cannot be entirely ruled out. Additionally, despite our efforts to refine exclusion criteria and minimize confounding factors that could contribute to inflammation beyond AHF, unidentified variables may have influenced the inflammatory response. Furthermore, although extensive exclusion criteria were applied to minimize bias, the possibility of residual confounding due to unmeasured variables cannot be entirely ruled out. Nevertheless, the absence of significant differences in baseline demographic and clinical characteristics between the deceased and surviving groups strengthens the validity of our findings.

Conclusions

This study illustrates that SIPS serves as an independent predictor of all-cause in-hospital mortality in patients admitted with AHF and HFrEF. As a standardized, readily accessible, and broadly applicable inflammatory marker, SIPS demonstrates significant prognostic value across various patient populations and healthcare settings. Integrating this parameter—alongside established clinical factors—can enhance the evaluation of AHF severity and assist in identifying patients who may benefit from more aggressive therapeutic interventions. Nonetheless, our findings necessitate validation through prospective, multicenter, and larger-scale studies to further confirm the clinical utility of SIPS in this context. Future research is warranted to validate SIPS across diverse HF phenotypes and clinical contexts before its routine implementation in cardiologic risk stratification.

Author declaration template

We wish to draw the attention of the Editor to the following facts, which may be considered potential conflicts of interest and significant financial contributions to this work.

We wish to confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that no other persons satisfied the criteria for authorship but are not listed. We further confirm that all have approved the order of authors listed in the manuscript.

We confirm that we have given due consideration to protecting the intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript

We understand that the Corresponding Author is the sole contact for the Editorial process (including the Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs. We confirm that we have provided a current, correct email address that is accessible by the Corresponding Author and has been configured to accept email from (bulent_ozlek@hotmail.com)

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Ethics approval and consent to participate

The Ethics Committee of Ankara Etlik City Hospital approved this retrospective study and waived the requirement for informed consent.

CRediT authorship contribution statement

Alperen Taş: Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Çağatay Tunca:** Writing – original draft, Validation, Supervision, Methodology,

Investigation, Conceptualization. **Veysel Ozan Tanık:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Bülent Özlek:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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