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Correlation Analysis of Mortality and Length of Stay in Sepsis Cases Among Heart Failure Patients with Low Ejection Fraction at Dr. Saiful Anwar General Hospital, East Java, Indonesia

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Abstract:

In Indonesia, heart failure (HF) prevalence reaches 5%, contributing to over 1.8 million annual hospitalizations, accompanied by a 29% readmission rate and a 30-day mortality rate of 17%. The burden of infectious diseases, notably sepsis, further complicates the clinical landscape. Patients with sepsis residing in tropical regions often exhibit mortality rates surpassing global averages. Sepsis-associated coagulopathy (SAC) serves as a significant complication in this context. This study investigates the correlation between SAC, indicated by international normalized ratio (INR) levels, and outcomes in patients with heart failure with reduced ejection fraction (HFrEF) who develop sepsis. Utilizing a retrospective cohort approach, we analyzed medical records from Saiful Anwar Regional General Hospital, Malang, East Java, involving adult HFrEF patients who underwent INR testing. Purposive sampling was applied. Statistical analyses, including the Mann-Whitney Test, Kaplan-Meier Analysis, Log-Rank Test, Cox Proportional Hazards Regression, and Multiple Linear Regression, were conducted employing SPSS software. Results revealed a mean survival of 7.69 days in the Non-SAC group compared to 6.78 days in the SAC group, though the difference was not statistically significant (p=0.080). Notably, additional clinical complications predominantly influenced survival outcomes. This study elucidates that elevated INR levels, indicative of SAC, correlate with increased mortality and decreased survival in HFrEF patients with sepsis. Furthermore, the exacerbating effect of clinical complications on mortality highlights the imperative for early SAC detection and management of cardiovascular implications to enhance patient prognosis.

Keywords: Heart Failure; Length of Stay; Mortality; Sepsis Associated Coagulopathy.

Introduction

Heart failure is a clinical syndrome characterized by typical symptoms such as dyspnea, fatigue, and edema, which result from structural or functional cardiac abnormalities, leading to increased intracardiac pressure and/or reduced cardiac output, both at rest and during activity. Based on left ventricular ejection fraction (LVEF), heart failure is classified into three phenotypes: HFrEF (LVEF ≤40%), HFmrEF (LVEF 41–49%), and HFpEF (LVEF ≥50%).[1]Although developed countries have seen a decline in heart failure incidence due to advances in cardiovascular management, the global prevalence of heart failure continues to rise, particularly in the elderly population.[2–4] In Indonesia, the prevalence of heart failure has been reported to reach 5% and accounts for more than 1.8 million hospitalizations annually, with a 29% readmission rate and a 30-day mortality rate of 17%.[5]

As a tropical country, Indonesia also bears a high burden of infectious diseases, including sepsis. International studies show that patients with sepsis in tropical countries have a higher mortality rate, even exceeding the global average.[6] This condition poses a particular challenge when sepsis occurs alongside heart failure, especially the HFrEF type. Sepsis and heart failure share a pathophysiological relationship that exacerbates each other: sepsis causes hemodynamic instability requiring aggressive fluid resuscitation and vasopressors, whereas heart failure management demands a reduction in preload and afterload.[7] Studies have shown that a history of heart failure increases the risk of mortality in septic patients and HFrEF specifically correlates with worse clinical outcomes in sepsis cases.[8–10]

One major complication of sepsis is coagulation disorder, known as sepsis-associated coagulopathy (SAC). SAC reflects hemostatic dysfunction due to systemic coagulation activation, with a high risk of progressing to disseminated intravascular coagulation (DIC). Although complex examinations such as thromboelastography are available, conventional coagulation tests remain relevant for the early detection of SAC. The international normalized ratio (INR) test is a simple yet potentially powerful parameter for predicting the prognosis of sepsis.[11,12]

Considering the high incidence of both heart failure and sepsis in Indonesia and the potential pathophysiological interaction between the two, this study aims to evaluate the relationship between SAC, assessed through INR levels and mortality and length of hospital stay in patients with heart failure with reduced ejection fraction (HFrEF) who develop sepsis. The findings from this study are expected to contribute significantly to the development of clinical strategies for early detection, risk monitoring, and optimal management of patients with the comorbidity of sepsis and HFrEF.

Research Method

Study Design

This study is an analytical observational study with a retrospective cohort approach. Data were obtained from the medical records of patients diagnosed with heart failure with reduced ejection fraction (HFrEF) who underwent international normalized ratio (INR) testing

Population and Sample

The study population included adult patients diagnosed with heart failure with reduced ejection fraction who were admitted to Saiful Anwar Regional General Hospital, Malang, East Java, between January 2022 and January 2024. Sampling was conducted using purposive sampling,

which involves selecting research subjects based on specific criteria or considerations. This technique is appropriate for quantitative studies that do not aim for broad generalization but rather focus on the relationship between clinical variables. Inclusion and exclusion criteria were applied to determine eligible subjects for analysis.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were adult patients diagnosed with heart failure with reduced ejection fraction who were hospitalized at Saiful Anwar Hospital and had complete medical records, including INR test results. Exclusion criteria included patients under 18 years of age, those with clinical conditions affecting the coagulation system such as chronic liver disease, hematologic disorders, long-term use of immunosuppressants, anticoagulant therapy, and patients with incomplete medical records.

Study Location and Duration

This study is planned to be conducted at Saiful Anwar Regional General Hospital, Malang, East Java, from January to March 2025.

Statistical Analysis

Data analysis was performed using SPSS software. The statistical methods employed in this study include Mann-Whitney Test, Kaplan-Meier Analysis, Log-Rank Test, Cox Proportional Hazards Regression and Multiple Linear Regression.

Results

Sample Characteristics

A total of 223 patients with heart failure with reduced ejection fraction (HFrEF) who developed sepsis were analyzed and divided into two groups: Non-SAC (n=86) and SAC (n=137). The mean age and body mass index (BMI) did not differ significantly between the two groups. However, the proportion of male patients was significantly higher in the SAC group (p=0.030). Several clinical and laboratory parameters showed significant differences. Respiratory rate (p=0.042), leukocyte count (p=0.016), bilirubin levels (p=0.001), and INR values (p=0.000) were higher in the SAC group, reflecting more severe inflammation and coagulation dysfunction. Clinical complications such as pulmonary edema, malignant arrhythmias, and cardiogenic shock were more frequently observed in the SAC group (each $p<0.05$). Mortality was also substantially higher in the SAC group compared to the Non-SAC group (63.5% vs. 9.3%; p=0.000), indicating a significant impact of SAC on clinical outcomes. The key demographic and clinical characteristics are presented in Table 1.

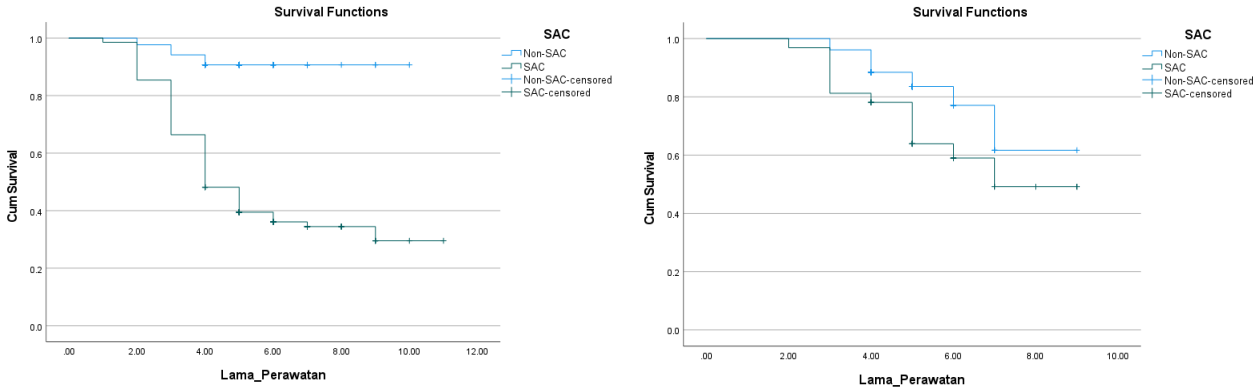
Table 1 Sample Characteristics

Characteristics	SAC		p-value
	Non-SAC (n = 86)	SAC (n = 137)	
Age	60.2 ± 13.7	58.4 ± 12.7	0.331
Sex			
Male	48 (55.8%)	96 (70.1%)	0.030*
Female	38 (44.2%)	41 (29.9%)	
BMI	23.6 ± 3.2	24.5 ± 4.9	0.105
BMI Category			
Underweight	3 (3.5%)	5 (3.6%)	0.087
Normal	33 (38.4%)	55 (40.1%)	
Overweight	16 (18.6%)	24 (17.5%)	

Characteristics	SAC		p-value
	Non-SAC (n = 86)	SAC (n = 137)	
Obesity 1	33 (38.4%)	39 (28.5%)	
Obesity 2	1 (1.2%)	14 (10.2%)	
Systolic Blood Pressure (mmHg)	119.3 ± 22.4	118.7 ± 24.2	0.487
Diastolic Blood Pressure (mmHg)	74 ± 14.1	74.3 ± 14.8	0.896
Heart Rate (x/min)	87.8 ± 23.1	90.4 ± 20.8	0.385
Temperature (ºC)	36.6 ± 0.4	36.6 ± 0.4	0.488
Respiratory Rate (x/min)	21.2 ± 3.2	22.7 ± 5.5	0.042*
SpO2 (%)	98.1 ± 2.5	97.6 ± 8.7	0.909
Hemoglobin (g/dL)	12.7 ± 2.3	13.2 ± 2.2	0.150
Hematocrit (%)	38.7 ± 6.8	40.1 ± 6.4	0.112
Leukocytes (cellss/uL)	11007.7 ± 5242.2	12922.3 ± 6336.8	0.016*
Platelets (thousand/uL)	186.8 ± 70.3	193.6 ± 85.9	0.974
Bilirubin	0.6 ± 0.4	1 ± 0.6	0.001*
Pulmonary Edema			
No	72 (83.7%)	88 (64.2%)	0.002*
Yes	14 (16.3%)	49 (35.8%)	
Hypertensive Crisis			
No	73 (84.9%)	100 (73%)	0.038*
Yes	13 (15.1%)	37 (27%)	
Malignant Arrhythmia			
No	75 (87.2%)	89 (65%)	0.000*
Yes	11 (12.8%)	48 (35%)	
Shock			
No	79 (91.9%)	108 (78.8%)	0.010*
Yes	7 (8.1%)	29 (21.2%)	
INR	0.8 ± 0.2	1.7 ± 0.5	0.000*
SOFA Score	2.9 ± 1.5	5.7 ± 2.3	0.000*
Mortality			
Alive	78 (90.7%)	50 (36.5%)	0.000*
Deceased	8 (9.3%)	87 (63.5%)	

Table 2 Cox Regression Analysis of the Impact of Complications on Patients with Heart Failure with Reduced Ejection Fraction

Complication	B	p-value	HR	95% CI
Pulmonary Edema	-1.029	0.000	0.357	0.23 - 0.55
Hypertensive Crisis	-0.399	0.150	0.671	0.39 - 1.16
Malignant Arrhytmia	-1.154	0.000	0.315	0.21 - 0.48
Shock	-1.150	0.000	0.317	0.19 - 0.52



(a) (b)

Figure 1 Survival Function Analysis: (a) Population With Complications; and (b) Population Without Complications

Discussion

Mortality in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF) With and Without SAC

This study demonstrates that the presence of Sepsis-Associated Coagulopathy (SAC) is associated with increased mortality in patients with heart failure with reduced ejection fraction (HFrEF) who develop sepsis. The cumulative survival rate was significantly lower in SAC patients compared to the non-SAC group, with most deaths occurring within the first few days of hospitalization. However, survival analysis between uncomplicated SAC and non-SAC groups showed no significant difference.

The pathophysiological mechanism underlying increased mortality in HFrEF patients with SAC likely involves a combination of cardiac dysfunction and coagulatory system impairment. Left ventricular (LV) dysfunction in heart failure leads to reduced preload and cardiac output, while right ventricular (RV) dysfunction contributes to diminished venous return. Previous studies have shown that RV dysfunction is significantly associated with higher mortality in septic patients, whereas the impact of LV dysfunction remains complex and depends on volume status, inotropic drug use, and systemic vascular resistance. [14–17]

In the context of clinical complications, data indicate that SAC patients who developed complications such as pulmonary edema, malignant arrhythmias, and cardiogenic shock experienced a significantly sharper and more rapid decline in survival compared to the non-SAC group, with statistical significance. This suggests that SAC may act as an "amplifier" of pre-existing pathological processes in heart failure, particularly through coagulation system activation, systemic inflammation, and endothelial damage—though it may not be the direct cause of death in this patient population. [18–21]

In contrast, in critically ill patients with severe infections (e.g., COVID-19), where coagulopathy is a key pathophysiological feature, SAC has been shown to significantly contribute to thrombotic events and increased mortality. [22,23]

Mortality Based on Occurrence of Complications

Clinical complications play a critical role in determining the outcomes of HFrEF patients with sepsis. The study found that pulmonary edema, malignant arrhythmia, and shock significantly increased the risk of

death in both univariate and multivariate Cox regression analyses.

Pulmonary edema is a typical manifestation of decompensated heart failure due to elevated pulmonary venous pressure and congestion. It causes fluid accumulation in the alveoli and interstitial space, impairing oxygen diffusion and increasing the work of breathing. In sepsis, increased capillary permeability worsens fluid buildup and can lead to acute respiratory failure.[24,25] In this study, pulmonary edema reduced the likelihood of survival by up to 64.3%, with fatal effects occurring as early as the second day of treatment.

Malignant arrhythmia is a critical complication associated with electrical disturbances in the heart due to inflammation, electrolyte imbalances, and myocardial remodeling. HFrEF patients with sepsis are highly susceptible to arrhythmias due to autonomic dysregulation and hypoperfusion.[26,27] This study found that malignant arrhythmias decreased survival probability by 68.5%, with a very short mean survival time (4.31 days).

Cardiogenic shock also had a significant impact on reduced survival. This condition is marked by decreased systemic perfusion due to pump failure, eventually resulting in multiorgan failure.[15,28,29] In the shock group, only 12% of patients survived until the end of observation, with a mean survival of just 4.58 days.

On the other hand, hypertensive crisis, although not statistically significant in multivariate analysis (p=0.150), still contributed to clinical deterioration. A sudden spike in blood pressure can increase left ventricular workload, exacerbate congestion symptoms, and trigger arrhythmias or end-organ dysfunction.[30–32] Kaplan-Meier analysis showed that the mean survival for patients with hypertensive crisis dropped to 7.23 days, lower than in the group without this complication.

These findings underscore that the interaction between SAC and cardiovascular complications significantly worsens patient prognosis. Kaplan-Meier and Cox proportional hazard regression analyses in this study identified pulmonary edema, malignant arrhythmia, and shock as strong predictors of mortality. Therefore, early identification and aggressive management of these complications are crucial in efforts to reduce mortality in HFrEF patients with sepsis.[33–36]

Conclusions

This study demonstrates that the presence of sepsis-associated coagulopathy (SAC), as indicated by elevated INR values, is associated with increased mortality and reduced survival in patients with heart failure with reduced ejection fraction (HFrEF) who develop sepsis. Patients with SAC exhibited shorter mean survival times and higher mortality rates compared to the non-SAC group. Furthermore, the presence of clinical complications significantly exacerbated mortality. Patients with both SAC and these complications experienced a sharp and significant decline in survival, particularly within the first 3–5 days of hospitalization. These findings underscore the critical importance of early SAC detection and prompt management of cardiovascular complications to improve clinical outcomes.

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