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Early piperacillin/tazobactam administration and sepsis-induced cardiomyopathy in emergency department patients: An observational study and exploratory prediction model

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Abstract: **Background**: Sepsis-induced cardiomyopathy (SICM), a significant cardiovascular complication of sepsis, necessitates prompt and effective management. While timely antimicrobial treatment forms the bedrock of early sepsis management, the relationship between the timing of piperacillin/tazobactam administration and the development of SICM remains incompletely characterized. **Objectives**: The primary objective of this study was to investigate the association between early piperacillin/tazobactam administration and SICM incidence and short-term outcomes. A secondary objective was to identify factors associated with SICM and to develop an exploratory model for its prediction. **Methods**: This single-center, retrospective observational study included 149 adults with sepsis admitted between January 2023 and January 2026. Patients were categorized into two groups: Early treatment (≤1 h; n=68) or delayed treatment (>1 h; n=81). SICM was assessed using echocardiographic criteria. Clinical outcomes were compared using univariate and multivariable logistic regression. Internal validation was performed using 1,000 bootstrap resamples. **Results**: SICM occurred in 15/68 (22.06%) early-treatment patients and 33/81 (40.74%) delayed-treatment patients (P=0.014). Twenty-eight-day mortality was 14.71% versus 29.63% (P=0.029) and ICU and total hospital stays were shorter in the early-treatment group (both P<0.001). Delayed treatment (OR=2.354, 95% CI 1.044–5.310), SOFA ≥8 (OR=2.762, 95% CI 1.215–6.279), NT-proBNP ≥1500 pg/mL (OR=3.019, 95% CI 1.320–6.906) and each 0.1-ng/mL elevation in cTnI (OR=1.208, 95% CI 1.037–1.408) were independently linked to SICM. The model AUC was 0.842 (95% CI 0.776–0.908); Hosmer–Lemeshow P=0.409. **Conclusion**: Early administration of piperacillin/tazobactam was associated with lower SICM incidence and improved short-term outcomes. However, because this study is retrospective, a causal relationship cannot be definitively established. Furthermore, the exploratory prediction model developed warrants external validation to confirm its generalizability and accuracy.

Keywords: Cardiomyopathies; Piperacillin; Risk factors; Sepsis

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INTRODUCTION

Sepsis, a life-threatening syndrome, is defined by organ dysfunction resulting from a dysregulated host response to infection (Seymour *et al*., 2026). Sepsis-induced cardiomyopathy (SICM), a significant cardiovascular complication of sepsis, can manifest as left or right ventricular systolic or diastolic dysfunction. The presence of SICM can complicate hemodynamic management and is associated with adverse patient outcomes (Cao *et al*., 2026; Kajal *et al*., 2023).

Early antimicrobial therapy is a crucial element of sepsis management (Prescott *et al*., 2026a). Piperacillin/tazobactam is frequently employed as empirical broad-spectrum therapy (Hagel *et al*., 2022). However, the timing of treatment initiation in emergency care can be affected by factors such as disease severity, diagnostic evaluation, intravenous access, emergency department workload, source-control strategies and other facets of healthcare delivery. Consequently, any observed association between antibiotic timing and SICM may partly reflect variation in the overall promptness and intensity of sepsis management.

Previous research has explored the relationship between early antimicrobial treatment and cardiovascular dysfunction in sepsis, with some studies even developing prediction models for septic cardiomyopathy (Knox *et al*., 2022; Sun *et al*., 2024). While these investigations highlight the importance of early risk identification, they do not definitively determine whether the timing of a particular empirical antibiotic, such as piperacillin/tazobactam, independently correlates with SICM in emergency department patients. Furthermore, the timing of antibiotic administration alone does not allow inferences about its appropriateness.

Consequently, this study's primary aim was to examine the association between the early administration of piperacillin/tazobactam and both the incidence of SICM and short-term clinical outcomes in septic patients presenting to the emergency department. A secondary objective was to identify independent risk factors for SICM and construct an exploratory nomogram-based prediction

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model. This model aims to estimate SICM risk using readily available clinical and laboratory data. Given its retrospective observational design, this study evaluated associations rather than establishing a causal link between early piperacillin/tazobactam administration and SICM.

MATERIALS AND METHODS

Study design and population

This single-center, retrospective observational cohort study was conducted in the Department of Emergency Medicine at The First Affiliated Hospital of Soochow University. Medical records from January 2023 to January 2026 were retrospectively reviewed (Fig. S1).

Inclusion criteria: Age ≥18 years; sepsis diagnosed according to the Sepsis-3 consensus criteria (Prescott *et al.*, 2026b); presentation within 24 hours of symptom onset; echocardiography performed on admission with a repeat examination within 48 hours; complete imaging data; and complete records of piperacillin/tazobactam administration. *Exclusion criteria*: Established chronic heart failure or cardiomyopathy, New York Heart Association (NYHA) functional class ≥III (Bennji *et al.*, 2026); acute coronary syndrome, severe valvular or congenital heart disease, antibiotic use within 24 hours before admission and end-stage malignant disease.

Sample size

As this was a retrospective observational study, a formal a priori sample-size calculation was not performed. Instead, all consecutive eligible patients identified within the predefined study period were screened and subsequently included. The final cohort comprised 149 patients, among whom 48 experienced SICM events. The relatively limited number of outcome events inherently constrains the precision and stability of both multivariable and prediction-model estimates, simultaneously elevating the possibility of overfitting. Consequently, this model should be interpreted as exploratory.

Piperacillin/tazobactam timing

Piperacillin/tazobactam served as the empirical broad-spectrum antibiotic choice, aligning with both local protocols and the 2021 Surviving Sepsis Campaign recommendations (Evans *et al.*, 2021). The standard dose was 4.5 grams administered intravenously every 6–8 hours, with adjustments based on renal function. Subsequent modifications to this regimen were guided by the patient's clinical response and results from microbiological cultures and susceptibility testing, once available. For this study, T0 marked the patient's arrival and registration in the emergency department, while T1 denoted the initiation of the first intravenous infusion. Early treatment was defined as T1−T0 ≤1 hour and delayed treatment as >1 hour. This 1-hour cutoff was chosen for its clinical interpretability and its consistency with guideline recommendations emphasizing rapid antimicrobial administration. It is important to note that this threshold does not imply a causal link or establish the superiority of piperacillin/tazobactam.

Various factors were considered as potential confounders, including the severity of illness, the volume of fluid resuscitation, the use of vasoactive therapy, mechanical ventilation, infection source, any source-control interventions performed, the degree of emergency department crowding and the appropriateness of antimicrobial selection. While some of these variables were retrievable from the existing dataset, comprehensive details regarding crowding, the precise timing of source-control interventions and a systematic antimicrobial-appropriateness assessment were not fully documented.

SICM definition and assessment

SICM was assessed using expert-consensus criteria combined with echocardiographic findings from two independently certified echocardiographers. SICM was defined by any of the following: LVEF <50%; E/e' ≥14 or other evidence of left-ventricular diastolic dysfunction; or right-ventricular dysfunction, defined by right ventricular end-diastolic area/left ventricular end-diastolic volume >0.6, TAPSE <17 mm, or abnormal right-ventricular free-wall motion.

Data collection and outcomes

Data were extracted from electronic medical records, laboratory systems, PACS and nursing records. Variables included demographics, comorbidities, infection source, admission vital signs and GCS, SOFA (Hincapié-Osorno et al., 2026) and APACHE II scores (Yuksel et al., 2024), and laboratory indicators such as cTnI, CK-MB, NT-proBNP, inflammatory markers, coagulation parameters and organ-function measures. Data on antibiotic timing, combination therapy, fluid resuscitation, vasoactive therapy and mechanical ventilation were also extracted. The primary outcome was SICM incidence. Secondary outcomes included 28-day all-cause mortality, ICU length of stay, total hospital stay, vasoactive drug use, duration of mechanical ventilation and volume of fluid resuscitation.

Statistical analysis

Continuous variables were evaluated for normality using the Shapiro–Wilk test and subsequently compared using either the independent-samples t-test or Mann–Whitney U test, depending on their distribution. Categorical variables were compared using chi-square or Fisher's exact tests. Sex was included in the univariate SICM analysis. Variables with $P<0.05$ in the univariate analysis were then incorporated into a multivariable logistic regression model.

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Table 1: Comparison of baseline data between the two groups of patients.

Variable	Early (n=68)	Delayed (n=81)	Statistic	*P*
Age (years)	61.85 ± 14.02	62.83 ± 14.51	t=0.427	0.670
Male, n (%)	41 (60.29)	48 (59.26)	χ^2=0.017	0.897
BMI (kg/m²)	23.45 ± 3.12	23.68 ± 3.28	t=0.445	0.657
Hypertension, n (%)	26 (38.24)	32 (39.51)	χ^2=0.025	0.875
Diabetes, n (%)	18 (26.47)	24 (29.63)	χ^2=0.184	0.668
Coronary heart disease, n (%)	9 (13.24)	12 (14.81)	χ^2=0.076	0.782
Chronic kidney disease, n (%)	5 (7.35)	8 (9.88)	χ^2=0.294	0.588
COPD, n (%)	7 (10.29)	10 (12.35)	χ^2=0.153	0.696
SOFA score	7.15 ± 2.86	7.93 ± 3.04	t=1.618	0.108
APACHE II score	15.23 ± 5.17	16.04 ± 5.43	t=0.936	0.351
Infection source	Pulmonary 47.06%; abdominal 20.59%; urinary 13.24%; bloodstream 10.29%; skin/soft tissue 5.88%; other 2.94%	Pulmonary 46.91%; abdominal 19.75%; urinary 14.81%; bloodstream 7.41%; skin/soft tissue 7.41%; other 3.70%	χ^2=1.846	0.764

Note: BMI, body mass index; COPD, chronic obstructive pulmonary disease; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 2: Comparison of clinical outcomes between the two groups of patients.

Outcome	Early (n=68)	Delayed (n=81)	Statistic	P
SICM, n (%)	15 (22.06)	33 (40.74)	χ^2=5.989	0.014
28-day mortality, n (%)	10 (14.71)	24 (29.63)	χ^2=4.794	0.029
ICU stay, days	8.24 ± 3.76	11.58 ± 4.92	t=4.518	<0.001
Total hospital stay (days)	14.36 ± 5.28	18.74 ± 6.15	t=4.628	<0.001
Vasoactive drugs, n (%)	25 (36.76)	43 (53.09)	χ^2=3.980	0.046
Mechanical ventilation, n (%)	18 (26.47)	29 (35.80)	χ^2=1.498	0.221
Fluid volume first 6 h (mL)	1896.34 ± 598.27	2054.67 ± 648.35	t=1.562	0.120
Fluid volume first 24 h (mL)	3246.82 ± 986.34	3482.15 ± 1024.68	t=1.438	0.153

For this model, ORs and their corresponding 95% CIs were reported. Given that only 48 SICM events were observed, the final model was interpreted cautiously. Internal validation was performed using 1,000 bootstrap resamples. Model discrimination was assessed using the AUC and calibration was evaluated using the Hosmer–Lemeshow test. An external validation cohort was not available for this study.

RESULTS

Baseline characteristics

The study encompassed 149 patients, divided into two cohorts: 68 received early treatment and 81 received delayed treatment. Baseline characteristics were largely similar across both groups. No statistically significant differences existed between the early- and delayed-treatment groups in age, sex, BMI, comorbidities, infection source, SOFA score, or APACHE II score (all P>0.05) (Table 1).

Clinical outcomes

SICM occurred in 15/68 (22.06%) patients in the early-treatment group compared to 33/81 (40.74%) in the delayed-treatment group (χ^2=5.989, P=0.014; Fig. S2). Twenty-eight-day mortality was 14.71% in the early-treatment group versus 29.63% in the delayed-treatment group (χ^2=4.794, P=0.029). The early-treatment group also had shorter ICU and total hospital stays (both P<0.001) and lower vasoactive drug use (36.76% vs 53.09%, P=0.046). There were no significant differences in mechanical ventilation or fluid resuscitation volumes (Table 2).

Univariate analysis of SICM-associated factors

Patients with SICM were older than those without the condition. They also more frequently received delayed antibiotic treatment. Upon admission, individuals with SICM presented with higher SOFA and APACHE II scores, as well as elevated levels of cTnI, NT-proBNP, CK-MB, NLR, CRP, PCT, IL-6, RDW and lactate. Furthermore, this group received greater fluid resuscitation during the first six hours and more often required vasoactive drug support (P<0.05). Sex was not associated with SICM (P=0.633) (Table 3).

Multivariable logistic regression

Delayed treatment, SOFA ≥8, NT-proBNP ≥1500 pg/mL and higher cTnI remained independently associated with SICM. Age, APACHE II, CK-MB, NLR, CRP, PCT, IL-6, RDW, lactate, fluid resuscitation and vasoactive drug use were not significant in the adjusted model (Table 4). The risk nomogram derived from the multivariable analysis is presented in fig. 1.

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Table 3: Univariate analysis of factors influencing the occurrence of SICM.

Variable	SICM (n=48)	Non-SICM (n=101)	Statistic	P
Age (years)	66.28 ± 12.47	60.75 ± 14.58	t=2.247	0.026
Male, n (%)	30 (62.50)	59 (58.42)	χ^2=0.228	0.633
Delayed treatment, n (%)	33 (68.75)	48 (47.52)	χ^2=5.989	0.014
SOFA	9.35 ± 2.78	6.82 ± 2.41	t=5.683	<0.001
APACHE II	18.46 ± 5.23	14.27 ± 4.86	t=4.832	<0.001
cTnI (ng/mL)	0.38 ± 0.21	0.14 ± 0.09	t=9.184	<0.001
NT-proBNP (pg/mL)	2136.48 ± 1124.37	847.26 ± 523.48	t=8.954	<0.001
CK-MB (U/L)	24.86 ± 10.34	16.42 ± 7.85	t=5.478	<0.001
NLR	12.38 ± 5.26	6.85 ± 3.42	t=7.452	<0.001
CRP (mg/L)	124.56 ± 48.23	86.34 ± 35.67	t=5.348	<0.001
PCT (ng/mL)	8.46 ± 4.23	4.28 ± 2.56	t=7.125	<0.001
IL-6 (pg/mL)	126.38 ± 58.46	68.24 ± 36.18	t=7.248	<0.001
RDW (%)	15.28 ± 1.86	13.94 ± 1.52	t=4.704	<0.001
Lactate (mmol/L)	3.86 ± 1.52	2.34 ± 1.08	t=6.989	<0.001
Fluid first 6 h (mL)	2156.48 ± 678.34	1846.27 ± 562.18	t=2.938	0.004
Vasoactive drugs, n (%)	31 (64.58)	40 (39.60)	χ^2=8.159	0.004

Note: SICM, sepsis-induced cardiomyopathy; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK-MB, creatine kinase-MB; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; RDW, red blood cell distribution width.

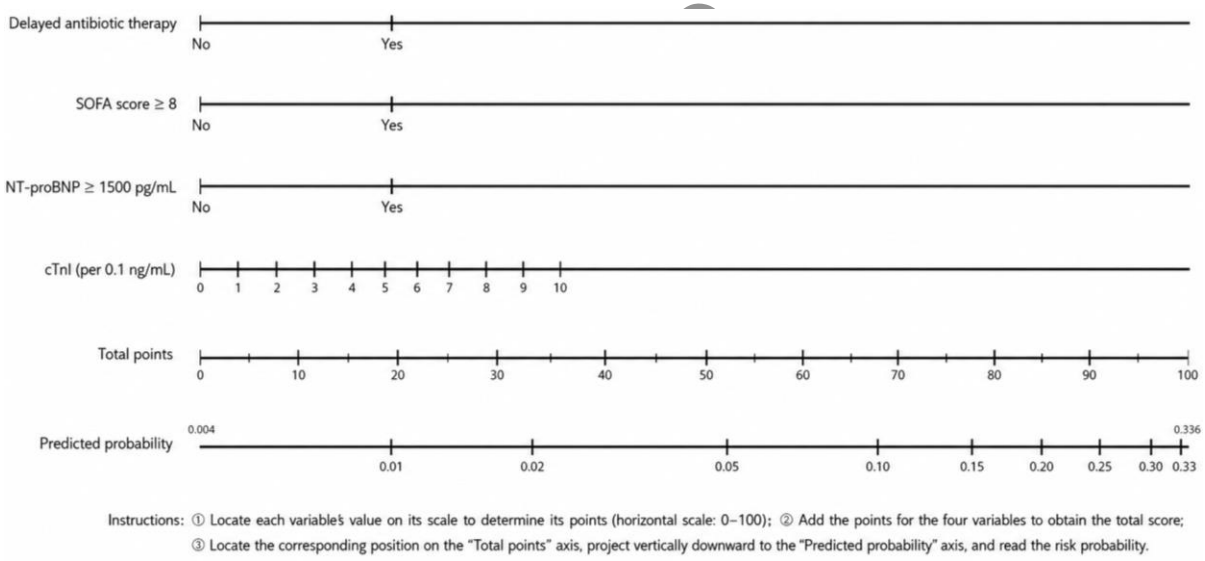


Fig. 1: Nomogram for predicting SICM risk.

Table 4: Multivariate logistic regression analysis of factors influencing the occurrence of SICM.

Variable	OR	95% CI	P
Delayed treatment >1 h	2.354	1.044–5.310	0.039
SOFA ≥8	2.762	1.215–6.279	0.015
cTnI per 0.1 ng/mL	1.208	1.037–1.408	0.015
NT-proBNP ≥1500 pg/mL	3.019	1.320–6.906	0.009

Exploratory prediction model

The model equation was Logit(P)=−5.546 + 0.856×X1 + 1.016×X2 + 1.105×X3 + 0.189×X4, where X1=delayed treatment, X2=SOFA ≥8, X3=NT-proBNP ≥1500 pg/mL and X4=cTnI per 0.1-ng/mL increase. The AUC was 0.842 (95% CI 0.776–0.908) after 1,000 bootstrap resamples. The Hosmer–Lemeshow test was χ^2=8.246, P=0.409. No external validation was conducted.

DISCUSSION

Sepsis is characterized by life-threatening organ dysfunction resulting from a dysregulated host response to infection. In emergency department patients, rapid progression may lead to severe multiorgan dysfunction, and the cardiovascular system is particularly vulnerable. SICM is an important complication associated with adverse outcomes and increased complexity of hemodynamic management (Sato et al., 2023; Caracioni et al., 2025). In the present study, early piperacillin/ tazobactam administration was associated with a lower incidence of SICM and more favorable short-term clinical outcomes. However, because this was a retrospective observational study, these findings show association rather than causation and do not establish that early piperacillin/tazobactam administration prevents SICM.

The study's findings reveal a significantly lower incidence of SICM (22.06%), 28-day all-cause mortality (14.71%) and rate of vasopressor use (36.76%) in the early treatment group compared to the delayed treatment group (40.74%, 29.63% and 53.09%, respectively; $P < 0.05$). Furthermore, the early treatment group had shorter ICU length of stay and total hospitalization duration ($P < 0.05$). These results align with previous research (Sun *et al*., 2025; Nan *et al*., 2026; Chen *et al*., 2026) and underscore the critical role of prompt antimicrobial treatment in early sepsis management. However, this study cannot definitively attribute the observed associations solely to piperacillin/tazobactam. Instead, the improvements likely reflect the broader benefits of earlier overall sepsis management. Patients who received antibiotics sooner may also have benefited from earlier fluid resuscitation, more rigorous hemodynamic monitoring, quicker source-control interventions and other comprehensive elements of sepsis-bundle care. Consequently, the reduced SICM incidence and improved short-term outcomes in the early-treatment group should not be interpreted as direct evidence of a specific cardioprotective effect of piperacillin/tazobactam. Nonetheless, these findings suggest that early intervention with piperacillin/tazobactam in sepsis patients could mitigate myocardial damage from the systemic inflammatory response, thereby reducing SICM risk and improving patient prognosis. Research indicates (Nan *et al*., 2026) that the early inflammatory cytokine storm in sepsis is a primary driver of myocardial dysfunction. Timely infection control and interruption of the inflammatory cascade can reduce myocardial cell apoptosis and necrosis, thus better preserving cardiac function.

Multivariate logistic regression analysis identified several independent risk factors for SICM: delayed treatment with piperacillin/tazobactam (OR = 2.354, 95% CI: 1.044–5.310, P = 0.039), an admission SOFA score ≥ 8 (OR = 2.762, 95% CI: 1.215–6.279, P = 0.015), NT-proBNP ≥ 1500 pg/mL (OR = 3.019, 95% CI: 1.320–6.906, P = 0.009) and a 0.1 ng/mL increase in cTnI (OR = 1.208, 95% CI: 1.037–1.408, P = 0.015). These findings suggest that both the overall severity of illness and specific markers of myocardial stress or injury are crucial for identifying patients at elevated risk of SICM. However, it is important to interpret the term "independent risk factors" with caution, as statistical adjustments in a retrospective study cannot entirely eliminate residual confounding. A more in-depth exploration of the underlying causes and mechanisms is warranted, as detailed below:

(1) Delayed initiation of piperacillin/tazobactam was associated with a higher risk of SICM in the study cohort. This observation is consistent with the concept that delayed effective antimicrobial therapy may prolong exposure to uncontrolled infection and systemic physiological stress. A positive correlation between worsening left ventricular longitudinal strain in early sepsis and delayed antibiotic initiation has been reported (Knox et al., 2022), consistent with the association observed in the present study.

Several potential confounding factors merit careful consideration. Disease severity at presentation could influence both the urgency of antibiotic administration and the subsequent risk of SICM. Emergency department overcrowding and variations in healthcare delivery might delay antibiotic administration while simultaneously affecting patient monitoring and other critical aspects of sepsis care. Similarly, the timing and adequacy of source-control interventions, fluid resuscitation, vasopressor therapy, mechanical ventilation and subsequent antimicrobial adjustments could influence SICM development. Although some treatment variables were available in the dataset, these factors were not comprehensively characterized or adjusted for; therefore, residual confounding cannot be excluded. Furthermore, antimicrobial susceptibility and the appropriateness of the initial piperacillin/tazobactam regimen were not systematically evaluated. Accordingly, it cannot be determined whether the observed association reflects early administration of an appropriate antimicrobial regimen rather than a drug-specific effect of piperacillin/tazobactam. (2) An admission SOFA score of ≥8 was independently associated with SICM. A higher SOFA score reflects greater organ dysfunction and may identify patients with more severe systemic illness who are more susceptible to cardiovascular complications. This association therefore supports the clinical utility of organ-dysfunction severity for early SICM risk stratification rather than establishing a specific mechanistic pathway. Exercise-induced histone lactylation in monocyte-derived macrophages has been reported to restore cardiac immune homeostasis in sepsis-induced cardiomyopathy (Sun et al., 2025), suggesting a potential role for metabolic reprogramming in cardiac protection. However, these

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mechanisms were not directly examined in the present study and cannot be established from the current dataset.

(3) NT-proBNP ≥1500 pg/mL, along with elevated cTnI levels, were independently associated with SICM. These observations are clinically reasonable, as NT-proBNP indicates myocardial wall stress and cTnI serves as a marker for myocardial injury. However, in sepsis, these biomarkers can be elevated due to various factors, including ventricular loading, kidney dysfunction, systemic inflammation and critical illness. Therefore, their elevation should not be solely attributed to a single pathological mechanism. Given that ventricular myocytes synthesize and release NT-proBNP in response to increased ventricular wall pressure, elevated levels (≥1500 pg/mL) directly signify increased cardiac preload or impaired myocardial diastolic function during sepsis. This aligns with research by Xie and pang (Xie *et al*., 2026; Pang *et al*., 2024) regarding the role of disrupted copper homeostasis in SICM pathogenesis. Copper imbalance, as a cofactor for crucial myocardial respiratory chain enzymes, may worsen myocardial energy metabolism by affecting mitochondrial function. Consequently, an elevated NT-proBNP might reflect a compensatory response by myocardial cells to insufficient energy supply and increased workload. Furthermore, the systemic inflammatory response in sepsis can heighten vascular permeability and reduce effective circulating blood volume, thereby activating the renin-angiotensin-aldosterone system. This activation further increases ventricular wall pressure, leading to a substantial release of NT-proBNP.

Conversely, cTnI is a marker of myocardial injury; in the present analysis, each 0.1-ng/mL increase was associated with higher odds of SICM (OR=1.208). Inflammatory signaling, oxidative stress and mitochondrial dysfunction have been described as important mechanisms contributing to myocardial injury in SICM (Shangzu et al., 2026; Jiang et al., 2026). Dynamic changes in left ventricular ejection fraction have also been reported in relation to cardiac biomarkers in patients with sepsis (Ghazal et al., 2026). These findings support the potential utility of NT-proBNP and cTnI for clinical risk assessment but do not establish the molecular mechanisms responsible for biomarker elevation in the present cohort.

Furthermore, the SICM prediction model for patients with acute sepsis developed in this study—based on delayed piperacillin/tazobactam treatment, SOFA score, NT-proBNP and cTnI—demonstrated an AUC of 0.842 (95% CI: 0.776–0.908). This model incorporates delayed piperacillin/tazobactam treatment, SOFA score, NT-proBNP and cTnI. The Hosmer–Lemeshow test yielded a P-value of 0.409, indicating acceptable discrimination within the current cohort. However, it is important to note that the Hosmer–Lemeshow test alone offers limited insight into calibration. A more comprehensive evaluation of model performance would necessitate a calibration plot, calibration slope/intercept, or Brier score. While the model appears to possess good discriminatory power and calibration, suggesting its ability to predict SICM risk in emergency sepsis patients with reasonable accuracy, these findings should be interpreted as preliminary evidence of performance rather than definitive proof of robust calibration or clinical accuracy.

This model effectively integrates readily available clinical indicators: delayed piperacillin/tazobactam treatment, admission SOFA score, NT-proBNP levels and cTnI levels. This integration provides clinicians with a practical tool for the rapid identification of high-risk groups for SICM within the emergency department. Beyond identifying high-risk patients, the model also implies that timely piperacillin/tazobactam administration may mitigate this risk, offering significant guidance for clinical practice (Liu *et al*., 2025). However, careful consideration is warranted regarding the clinical application of this model. Delayed antibiotic administration, being a treatment-related variable rather than an intrinsic baseline characteristic, presents a challenge. Given that antibiotic timing is determined during initial management and can be influenced by disease severity, diagnostic uncertainty, emergency department workload and healthcare-delivery factors, the model's utility for risk stratification before treatment decisions are made may be limited. Additionally, the model's development was based on a relatively small cohort of 149 patients, with only 48 SICM events. This increases the potential for overfitting and limits the precision of the estimated effects. Although internal bootstrap validation was performed, an external validation cohort was not available. Consequently, this model should be regarded as exploratory and is not yet suitable as a validated clinical decision-support tool. Future multicenter studies with larger sample sizes are essential to assess external discrimination, calibration and overall clinical utility.

Several limitations warrant acknowledgment. First, the study's retrospective, single-center design inherently limits the generalizability of the findings and introduces potential selection and information biases. Second, the relatively modest sample size and limited number of SICM events may compromise the stability of the multivariable regression and prediction model, increasing the risk of overfitting. Third, although the multivariable model included variables associated with SICM from the univariate analysis, residual confounding cannot be entirely ruled out. Fourth, the study did not systematically assess the microbiological appropriateness of piperacillin/tazobactam or compare it with alternative antimicrobial regimens; therefore, the results cannot definitively establish its superiority over other antibiotics. Fifth, the study did not comprehensively capture factors

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such as emergency department overcrowding, precise source-control timing, and the thoroughness of sepsis-bundle implementation, which may have affected both antibiotic timing and patient outcomes. Sixth, the records lacked documentation on whether echocardiographers were blinded to treatment timing, so detection bias cannot be entirely excluded. Seventh, the study assessed only 28-day mortality, with long-term outcomes unavailable. Finally, the prediction model underwent only internal validation and lacked external validation; consequently, its generalisability and practical clinical utility remain uncertain.

CONCLUSION

In summary, the findings indicate an association between earlier antimicrobial administration and more favorable outcomes within this cohort. Furthermore, baseline disease severity and cardiac biomarkers may serve as indicators for identifying patients at elevated risk of SICM. However, these findings necessitate cautious interpretation and should not be construed as establishing a causal or drug-specific cardioprotective effect of piperacillin/tazobactam. Future research should prioritize prospective, multicenter studies with larger sample sizes, comprehensive assessments of antimicrobial appropriateness, detailed timing of source control and sepsis-bundle implementation and external validation of the prediction model.

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Authors' contributions
Lu Liu: Designed the study, collected and analyzed the data, interpreted the results and drafted the manuscript. Jian Huang: Supervised the study, provided methodological guidance and critically revised the manuscript. Both authors read and approved the published version of the manuscript.

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Data availability statement
The datasets generated during and/or analysed in the current study are available from the corresponding author on reasonable request.

Ethical approval
This retrospective observational study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Ethics Approval No. (2022) Lun Approval No. 411). The requirement for informed consent was waived because of the retrospective design and use of anonymized clinical data. The study was conducted in accordance with the Declaration of Helsinki. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest
The authors declare no conflicts of interest.

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