



UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
"CAROL DAVILA" din BUCUREȘTI



UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA" BUCHAREST
DOCTORAL SCHOOL
FIELD OF MEDICINE

***CARDIAC DYSFUNCTION IN SEPSIS AND
SEPTIC SHOCK***

PhD Thesis Summary

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Published Scientific Works and Research Activity

Full publications

➤ **Paraschiv C**, Popescu MR, Paduraru, LF, Palcau CA, Popescu AC, Balanescu SM, Current challenges in understanding, diagnosing and managing sepsis-induced cardiac dysfunction. *J. Crit. Care* 2026, 91, 155250. IF 2.9, Q1

<https://doi.org/10.1016/j.jerc.2025.155250>.

(Chapter 2, pp 8-30)

➤ **Paraschiv C**, Nicolaescu DO, Popescu RM, Barbalata L, Moisa E, Negoita S, Popescu AC, Balanescu SM. NT-proBNP, Echocardiography Patterns and Outcomes in Sepsis-Induced Cardiac Dysfunction. *Journal of Clinical Medicine*. 2025; 14(24):8714. FI 2.9, Q1

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(Chapter 5, pp 43-66)

➤ **Paraschiv C**, Nicolaescu DO, Popescu MR, Vasile CC, Moisa E, Negoita SI, Balanescu SM. Laboratory and Microbiological Considerations in Sepsis-Induced Cardiac Dysfunction. *Medicina*. 2025; 61(10):1765. IF 2.4, Q1

<https://doi.org/10.3390/medicina61101765>

(Chapter 7, pp 79-98)

Other publications

➤ **Paraschiv C**, Paduraru LF, Balanescu SM. An Extensive Review on Imaging Diagnosis Methods in Takotsubo Syndrome. *Rev Cardiovasc Med*. 2023 Oct 20;24(10):300. doi: 10.31083/j.rcm2410300.

➤ **Paraschiv C**, Paduraru LF, Balanescu SM. (2024). Coincidence or consequence? Single coronary artery in a dilated cardiomyopathy case. *Cardiac and Cardiovascular Research*. 5. 2868. doi:10.54517/ccr.v5i1.2868.



Abstracts and Presentations – National and International Congresses

- Post-operative Takotsubo Syndrome with incidental findings of an anomalous coronary artery and left ventricle: a diagnostic challenge – **Paraschiv C**, Popescu Moraru RM, Onciul S, Balanescu SM - EACVI Congress 2025
- Laboratory and Microbiological Considerations in Sepsis-Induced Cardiac Dysfunction - **Paraschiv C**, Nicolaescu DO, Popescu Moraru RM, Barbu E, Palcau CA, Radu C, Moisa E, Negoita S, Popescu AC, Balanescu SM –National Congress of the Romanian Society of Cardiology 2025
- Sepsis-induced cardiac dysfunction: echocardiographic patterns and outcome implications – **Paraschiv C**, Nicolaescu DO, Popescu Moraru RM, Barbu E, Matei AMA, Moisa E, Negoita S, Balanescu SM –European Society of Cardiology Congress 2025
- Invisible Infection: From Tiny Vegetation to Perforated Leaflet – Farrugia SL, Robinson NL, **Paraschiv C**, Pislaru SV, Villavicencio MA - European Society of Cardiology Congress 2025
- Varied Clinical Presentations of Mitral Annulus Calcification – Farrugia SL, Paraschiv C, Bird JG, Pislaru SV, Nkomo VT –American Society of Echocardiography Scientific Sessions 2025
- Aortic regurgitation and worsening ventricular function: surgical intervention – with a twist **Paraschiv C**, Memis H, Borlaug BA, Nath KA, Morrison JJ, Francois C, Geske JB, Pislaru SV American College of Cardiology Congress 2025
(<https://www.jacc.org/doi/abs/10.1016/S0735-1097%2825%2903454-0>)
- A papillary fibroelastoma hidden behind the curtain of new onset atrial fibrillation – Memis H, El Sabbagh A, **Paraschiv C**, Aboukhatwa O, Krishna M, Klarich K - American College of Cardiology Congress 2025
- Feasibility and Quality of Focused Cardiac Ultrasound (FoCUS) by Novice Scanners in an Obstetric Population – Greason CM, **Paraschiv C**, Tobah Butler, Kane GC, Bird JG, Young KA – American College of Obstetricians and Gynecologists Annual Clinical & Scientific Meeting 2025
(https://journals.lww.com/greenjournal/abstract/2025/06001/feasibility_and_quality_of_focused_cardiac.25.aspx)



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- Sub massive PTE's influence upon the intraventricular gradient in HCM: the hemodynamic effect of anticoagulation - **Paraschiv C**, Popescu Moraru MR, Palcau C, Zamfirescu B, Popescu AC, Balanescu SM - National Congress of the Romanian Society of Cardiology 2023
- What hides behind premature ventricular contractions? **Paraschiv C**, Popescu Moraru MR, Linte AL, Balanescu SM – European Society of Cardiology Congress 2023 (<https://esc365.escardio.org/presentation/270179>)
- Anterior mitral valve flail: an unexpected complication after a timely reperfused STEMI - **Paraschiv C**, Popescu Moraru M, Al Hassan A, Balanescu SM - European Society of Cardiology Acute CardioVascular Care 2023 (<https://esc365.escardio.org/presentation/260078?query=paraschiv>)

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List of Abbreviations

ICD - 20 - International Classification of Diseases

ICU - intensive care unit

IQR – interquartile range

LV - left ventricle

LVEF - left ventricular ejection fraction

MAPSE - mitral annular plane systolic excursion

RV – right ventricle

SD – standard deviation

SICD – sepsis-induced cardiac dysfunction

SOFA- The Sequential Organ Failure Assessment

TAPSE - tricuspid annular plane systolic excursion

VTI LVOT – left ventricular outflow tract velocity–time integral



Introduction

Sepsis is defined as an abnormal host response to a bacterial, viral, parasitic, or fungal infection, that leads to at least one severe organ dysfunction (1). Despite recent advances in the medical management of sepsis, including improvements in medical devices and development of new antibiotics, sepsis remains a clinical condition associated with high rates of morbidity and mortality worldwide. It is estimated that approximately 19.7% of all global deaths are caused by sepsis (2). Mortality among hospitalized patients with sepsis is substantial, exceeding 30%, and is even higher in patients requiring admission to intensive care units (ICU) (3).

The most common infection sites leading to sepsis are the respiratory tract, followed by the genitourinary tract, the abdominal cavity, and wound or soft tissue infections (4). Approximately half of the hospitalized patients with sepsis have positive cultures obtained from various biological samples (blood, urine, stool, respiratory secretions, pleural, peritoneal, cerebrospinal fluid, etc.), with Gram-negative bacteria prevailing among culture-positive cases (5).

The natural progression of sepsis can lead to shock and multiple organ failure. One of the essential elements in improving outcomes for patients with sepsis is the prompt recognition of sepsis and its associated organ dysfunction (4,6).

Sepsis-induced cardiac dysfunction (SICD) is one of the most severe and still insufficiently understood organ dysfunctions described in sepsis. To date, no universal definition or standardized diagnostic criteria for sepsis-related cardiac dysfunction have been established. Cardiac dysfunction in septic patients was first described in 1984 in a small cohort of septic patients using radionuclide cine-angiography studies (7). In some patients, transient left ventricular (LV) dilation and reduced myocardial function, assessed by left ventricular ejection fraction (LVEF), were observed. Cardiac involvement was reversible within 7–10 days from documentation. Afterward, transient cardiac dysfunction has been reported in septic patients in multiple studies (8).



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The pathophysiology of SICD remains incompletely understood. Current research focuses on a complex mechanism involving the interaction of multiple factors, including pathogen-associated molecular patterns, inflammatory mediators (cytokines), mitochondrial dysfunction, calcium metabolism disturbances, all ultimately leading to myocardial cell injury (9).

The variability in reported incidence and prognosis of SICD can be explained by the use of different definitions for cardiac involvement. Generally, SICD has been considered a reduction in LV systolic function, with documented reversibility within 7–10 days of diagnosis. However, this definition has proven to be too limited to encompass the full spectrum of SICD. Transient right ventricular (RV) systolic dysfunction, either isolated or associated with LV systolic dysfunction (biventricular dysfunction), has also been described (10–13).

Multiple parameters have been used to assess ventricular function, ranging from longitudinal function parameters (mitral annular plane systolic excursion - MAPSE, tricuspid annular plane systolic excursion - TAPSE, S' wave) to LVEF and myocardial deformation assessed by global longitudinal strain. Furthermore, LV diastolic dysfunction has been observed, most commonly reported through parameters such as E and A wave velocities, E/A ratio, e' velocities, and the E/e' ratio.

A recent meta-analysis reported a prevalence of 20% for sepsis-associated LV systolic dysfunction (14). The prevalence of RV dysfunction in sepsis is approximately 35% (15). LV diastolic dysfunction has been reported in up to 46–57% of cases (16,17).

Integrating clinical, paraclinical, and imaging data gathered from septic patients with cardiac dysfunction could contribute to completing the clinical image of this complex and heterogeneous condition, improve prognostic understanding, and ultimately lead to the development of targeted therapeutic strategies.

The management of SICD requires a multidisciplinary team with close collaboration between intensive care physicians, cardiologists and infectious disease physicians. Early diagnosis of cardiac dysfunction leads to early initiation of sepsis treatment, maintenance of vital functions, and careful patient monitoring. Further research in this area is essential to better understand the complex



mechanisms leading to cardiac involvement and to identify a specific diagnostic and management algorithm for these patients.

Working Hypotheses and General Objectives

General Working Hypotheses

- Sepsis is a severe disorder, with a profound, systemic effect. Multiple inflammatory mechanisms are activated during sepsis, which leads to organ dysfunction, including cardiac dysfunction
 - SICD is a relatively common dysfunction among septic patients
 - SICD is not a homogenous type of cardiac dysfunction. Multiple types of SICD exist, requiring comprehensive echocardiographic evaluation for identification and characterization
 - Patients who develop SICD have more severe forms of sepsis
 - Patients who develop SICD have worse outcomes
 - Certain clinical and paraclinical parameters identifiable at admission are associated with the development of SICD
 - Cardiac biomarkers, troponin and NT-proBNP, are associated with the occurrence of SICD and have prognostic value
 - Patients who develop SICD have multiple inflammatory mechanisms activation, suggested by higher levels of inflammatory markers
 - Certain bacteria responsible for systemic infections and sepsis are risk factors for the developing SICD.

General Objectives

Primary Objective:

- Identification of risk factors for developing SICD and of prognostic markers

Secondary Objectives:



- Identifying the incidence of SICD and echocardiographic SICD types
- Echocardiographic characterization of cardiac dysfunction types observed in septic patients
- Characterization of the outcomes associated with different echocardiographic patterns of cardiac dysfunction
- Study cohort description, including comorbidities, clinical presentation at admission, and paraclinical findings at admission
- Identification of hospitalization length and mortality rate
- Description of echocardiographic parameters within the cohort
- Documentation of the relationship between cardiac biomarkers and prognosis
- Identification of clinical parameters predictive of SICD development.
- Identification of paraclinical parameters predictive of SICD development.
- Identification of parameters associated with unfavorable prognosis.

General Research Methodology

Study Design

A retrospective, observational study was conducted, which included patients hospitalized with a primary diagnosis of sepsis or septic shock at a tertiary university hospital—Elias Emergency University Hospital, Bucharest—between January 2023 and October 2024 (Figure 1). Patient selection was performed using ICD-10 codes corresponding to sepsis and septic shock.

This methodology was designed to ensure diagnostic accuracy: only patients in whom the diagnosis of sepsis, established at admission, was subsequently confirmed during hospitalization by clinical and biological investigations and maintained at discharge were included. Thus, patients with false-positive diagnoses (sepsis suspected at admission but later ruled out) as well as those who developed sepsis during hospital stay were excluded. Infections occurring in hospitalized patients for another disease and leading to sepsis account for approximately 12–15% of all sepsis cases. Given the difficulty in identifying the exact time of onset of sepsis in patients admitted for other conditions,



this study included only patients presenting primarily for severe infection, thus allowing analysis from the time of admission.

The study protocol was approved by the Ethics Committee and the Ethics Commission of Elias Emergency University Hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients aged 18 to 89 years diagnosed with sepsis or septic shock who required admission to the intensive care unit or monitoring in a specialized acute care unit within other hospital departments were enrolled.

Only patients who underwent transthoracic echocardiography within the first 24 hours of admission were included.

Patients in whom echocardiography revealed newly developed LV systolic dysfunction were re-evaluated echocardiographically within 7–10 days to assess reversibility or persistence of dysfunction among survivors.

The complete inclusion and exclusion criteria are presented in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
Sepsis or septic shock as the main admission and discharge diagnosis	Cardiovascular: <ul style="list-style-type: none">○ History of cardiomyopathy with systolic dysfunction (LVEF<40%) or HF_rEF○ Preexistent or newly diagnosed severe aortic or mitral valve disease○ Infective endocarditis○ Acute coronary syndrome○ Acute intermediate or high risk PE

Age 18-89 years old	Oncological <ul style="list-style-type: none"> ○ Advanced or end stage cancer or hematological disease
TTE in the first 48 hours from admission Repeat TTE within 10 days if there is newly diagnosed LV dysfunction on first TTE	Preexistent end stage disease/ organ failure <ul style="list-style-type: none"> ○ Hepatic ○ Neurological ○ Renal (without any replacement therapy) ○ Pulmonary

Definitions and Parameters used in the analysis

Sepsis and septic shock were defined according to the Sepsis-3 criteria (1).

Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, with organ dysfunction evaluated using the SOFA score.

Cases were classified according to:

- **Source of infection:** community-acquired vs. healthcare-associated;
- **Primary site of infection:** pulmonary, urinary, abdominal, cutaneous/soft tissue, catheter-associated (venous/arterial), osteoarticular;
- **Type of pathogen:** Gram-positive bacteria, Gram-negative bacteria, polymicrobial, fungal.

In cases where multiple pathogenic microorganisms were isolated from different cultures, medical records were reviewed (clinical, imaging) to determine the primary source of infection.

The types of cultures collected included: blood cultures, urine cultures, stool cultures, respiratory cultures (sputum, bronchial aspirate), skin cultures, and joint cultures.



The laboratory parameters evaluated were: lactate; cardiac biomarkers (troponin, NT-proBNP); inflammatory markers (leukocyte count, neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio - NLR, platelets, C-reactive protein, procalcitonin).

Echocardiography parameters evaluated

a. LV systolic function was assessed using: LVEF (biplane Simpson method or visual estimation in cases of limited acoustic window), MAPSE, LVOT VTI (LV outflow tract velocity–time integral), lateral and septal s' wave velocities.

b. RV longitudinal systolic function was assessed using: TAPSE, S' wave velocity; in cases of inadequate alignment, visual assessment was performed.

c. LV diastolic function was assessed using: E and A wave velocities, E/A ratio, lateral e', septal e', and average e' velocities, lateral E/e', septal E/e', and average E/e' ratios.

SICD diagnosis

The diagnosis of SICD was established based on the following criteria:

- LV systolic dysfunction: previously unknown or new-onset LV systolic dysfunction with an LVEF of less than 50%, or, in patients with pre-existing LV systolic dysfunction, the diagnosis of SICD was established when a reduction of at least 10% from baseline was observed.
- RV systolic dysfunction: previously unknown or new-onset RV longitudinal, defined as TAPSE <17 mm or a decrease of at least 2 mm compared to a previously documented reduced longitudinal function;
- LV diastolic dysfunction: diastolic dysfunction defined by an increase in lateral, septal, or mean E/e' ratio above 10.

The reversible nature of cardiac dysfunction could only be assessed in patients who survived at least 7 days of hospital stay, by comparing echocardiographic findings at admission with those obtained at the 7–10-day reassessment.

All echocardiographic examinations were acquired and interpreted by experienced cardiologists.

The outcomes evaluated were:

- In-hospital mortality;



- Prolonged hospitalization, defined as a hospital stay >28 days;
- Prolonged ICU stay, defined as a duration >7 days.

The primary composite outcome included all three of the above.

Data Processing and Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Graphical representations were created using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA; version 2016).

The distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were reported as mean \pm standard deviation (SD). Non-normally distributed data were reported as median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Variables were presented in tables and illustrated using graphical representations.

Group comparisons were performed using: Student's t-test for normally distributed continuous variables, Mann–Whitney U test for non-normally distributed variables, Kruskal–Wallis test for comparisons involving more than two non-normally distributed groups, Chi-square test for categorical variables, and Fisher's exact test when expected cell frequencies were <5. A p-value <0.05 was considered statistically significant.

To identify risk factors associated with the development of SICD, univariate logistic regression analyses were performed. Odds ratios (ORs) with 95% confidence intervals (95% CI) were reported.

Statistical analyses and comparisons were performed according to:

- Presence or absence of SICD;
- In-hospital evolution (in-hospital mortality, prolonged hospitalization);
- In-hospital mortality;
- Composite outcome.



Results Summary

Study I Summary

NT-proBNP, Echocardiography Patterns and Outcomes in Sepsis-Induced Cardiac Dysfunction

Objectives

The main objective of this study was to determine the incidence and assess the prognosis of SICD. The secondary objectives included: characterization of the clinical and paraclinical profile of patients with SICD, analysis of different echocardiographic types of cardiac dysfunction, identification of risk factors associated with the development of SICD and prognostic factors in this cohort.

Materials and Methods

This study included retrospectively patients admitted to the ICU with a diagnosis of sepsis or septic shock who underwent transthoracic echocardiographic examination within the first 24 hours from admission, between January 2023 and September 2024. The exclusion criteria are detailed in Table 1.

Clinical, paraclinical, and echocardiographic data were collected. The primary outcome was a composite outcome including in-hospital mortality, prolonged hospital stay (>28 days), and prolonged ICU stay (>7 days).

Results

Baseline Characteristics of the Cohort

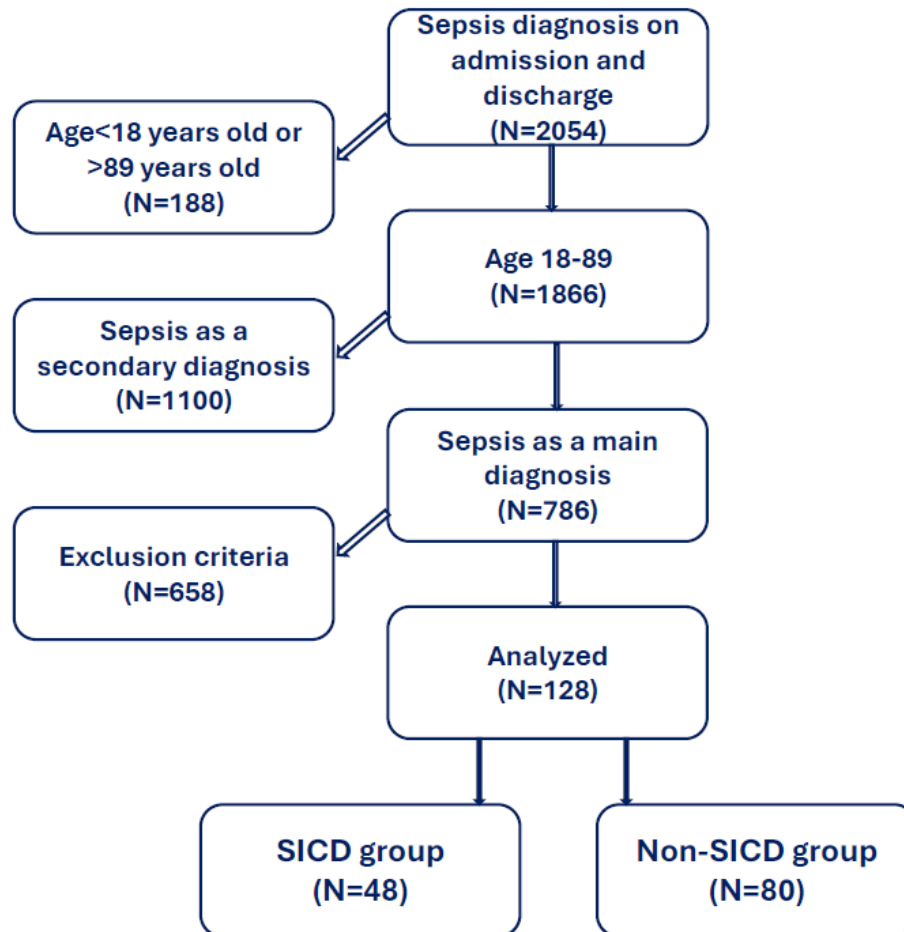
During the study period, 2024 patients were identified using ICD-10 codes for sepsis (Figure 1). Patients younger than 18 years and older than 89 years were excluded. Additionally, patients whom sepsis was a secondary diagnosis (sepsis developed during hospitalization) were excluded, as well as those who met the exclusion criteria according to Table 1.



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Figure 1. Study flowchart. SICD=Sepsis-induced cardiac dysfunction, non-SICD= Non-Sepsis-induced cardiac dysfunction



A total of 128 septic patients were included, with a median age of 72.5 years (IQR 63–81), 55% were male. SICD was diagnosed in 37% of patients.

Median age did not differ significantly between patients with and without SICD—74 years (IQR 66.5–82) versus 71.5 years (IQR 62.5–80), $p = 0.248$. No significant differences were observed regarding sex distribution between patients with and without SICD (52% male in the SICD group vs. 57% male in the non-SICD group).

The percentage of patients with documented ethanol abuse was higher in the SICD group compared with the non-SICD group. Further analysis showed that alcohol abuse was identified as a risk factor for developing isolated LV systolic dysfunction (OR = 6.250, 95% CI 1.8–21.8, $p = 0.004$), LV or RV systolic dysfunction (OR = 4.4, 95% CI 1.6–11.7, $p = 0.003$), and biventricular systolic



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dysfunction (OR = 5.4, 95% CI 1.01–28.9, $p = 0.048$). Alcohol abuse was not a predictor for developing isolated RV systolic dysfunction.

SOFA scores were elevated in both groups, with a median score of 7 in the SICD group versus 6 in patients without cardiac involvement, without reaching a statistically significant difference.

The most frequently identified infection sites were respiratory, urinary tract, and abdominal infections.

From a microbiological point, although specimens were collected at admission for all patients, 77% of patients with SICD and 80% of those without SICD had positive cultures. Positive cultures identified predominantly Gram-positive bacteria. A substantial proportion of patients presented with culture-negative infections - nearly one quarter (23% in the SICD group and 20% in the non-cardiac involvement group).

Patients with SICD experienced more severe clinical outcomes, showed by significantly higher rates of septic shock during hospitalization (75% vs. 56%, $p = 0.033$). The need for orotracheal intubation at admission was a risk factor for the development of SICD (OR 2.9; 95% CI 1.2–7.4; $p = 0.020$), and the initiation of vasopressor therapy at admission was also a predictor of SICD (OR 2.5; 95% CI 1.2–5.3; $p = 0.016$).

Length of hospitalization. Patients who developed cardiac dysfunction had longer hospital stays compared with those without cardiac dysfunction (12 days vs. 10 days), although the difference did not reach statistical significance. Similarly, patients with SICD had longer ICU stays compared with those without cardiac dysfunction (3.5 days vs. 2 days), without statistical significance.

Mortality. The overall mortality rate in this cohort was 44% (56 patients), with higher mortality observed in the SICD group (54% vs. 37%, $p = 0.066$), although the difference did not reach statistical significance.

Nevertheless, the occurrence of SICD was a significant predictor of the composite outcome (OR 2.211; 95% CI 1.0–4.6; $p = 0.037$), even after adjustment for age and sex (OR 2.2; 95% CI 1.0–4.7; $p = 0.039$).

Echocardiographic Data



All the patients included in the study underwent echocardiographic assessment at admission (performed within the first 24 hours of hospital admission). Patients diagnosed with cardiac dysfunction were subsequently reevaluated to assess for reversibility.

Based on echocardiographic findings, four distinct patterns of cardiac dysfunction were identified (Figure 2), highlighting the heterogeneous spectrum of sepsis-related cardiac dysfunction:

- isolated LV systolic dysfunction,
- isolated RV systolic dysfunction,
- biventricular systolic dysfunction,
- isolated LV diastolic dysfunction.

LV systolic function was assessed using LVEF, RV longitudinal systolic function using TAPSE, and LV diastolic function using lateral, septal, and average E/e' ratios.

Patients with isolated LV systolic dysfunction were significantly younger (median age 57 vs. 73 years, $p = 0.039$) and predominantly male (58%).

A total of 12 patients presented with isolated LV systolic dysfunction. The median LVEF at admission was 42%, which subsequently normalized during follow-up (Figure 2).

Six patients presented with biventricular systolic dysfunction. Median LVEF at admission was 30%, lower than in the isolated LV systolic dysfunction group (30% vs. 42%). Similarly, median TAPSE at admission was lower in the biventricular dysfunction group compared with the isolated RV dysfunction group (14 vs. 16 mm).

The group with isolated RV systolic dysfunction consisted of 9 patients and was predominantly female, as opposed to the other groups. Slightly reduced median TAPSE values were observed at admission (16 mm), which increased to 18 mm on reassessment.

The most frequent type of cardiac dysfunction identified in this analysis was isolated LV diastolic dysfunction, affecting 21 patients (16%). LV diastolic function was assessed using the following parameters: E, A, E/A ratio, lateral, septal, and averaged e' velocities, and E/e' ratios. Compared with the non-SICD group, patients with cardiac involvement exhibited lower e' velocities and higher E/e' ratios, irrespective of the type of cardiac dysfunction.



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Patients with any type of SICD demonstrated reduced lateral and septal e' velocities and increased E/e' ratios, indicating significant diastolic impairment, regardless of the specific SICD pattern.

Mortality rates did not differ significantly among the four groups. The highest mortality was observed in the isolated diastolic dysfunction group (66%), suggesting a population of older patients with increased frailty and multiple comorbidities.

LVEF using the Simpson method was reported for 72 patients (56%), and TAPSE was measured in 101 patients (79%). In the remaining patients, LVEF was visually estimated due to the difficulty in accurately measuring ventricular volumes in critically ill patients, and RV systolic function was visually assessed because of challenges in image alignment required for longitudinal function measurements.

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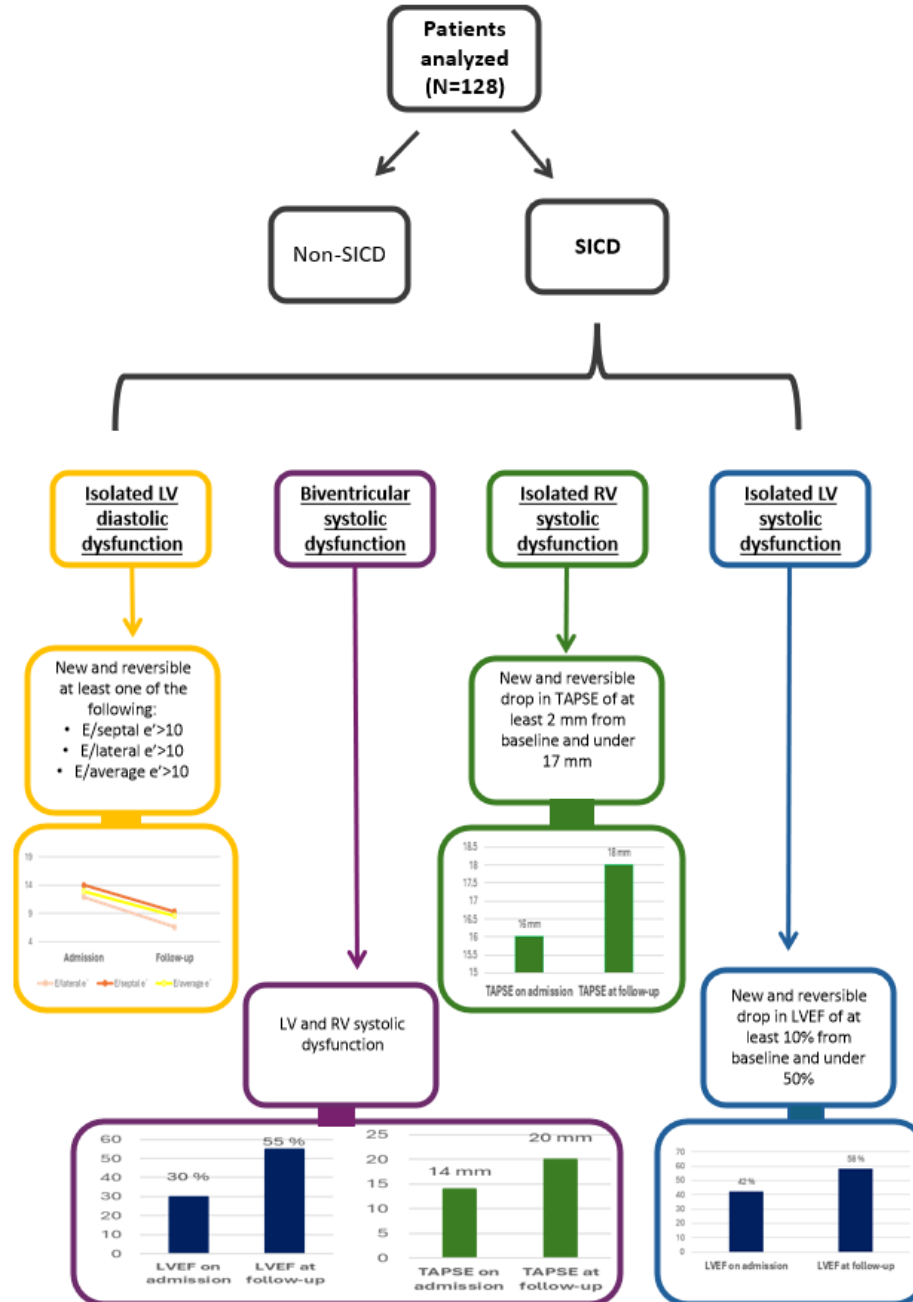


Figure 2: Types of SICD: isolated LV dysfunction, isolated RV dysfunction, biventricular dysfunction, and isolated LV diastolic dysfunction and their respective echocardiographic parameters at admission and follow-up.

LV= left ventricle, LVEF= LV ejection fraction, RV= right ventricle, TAPSE= Tricuspid Annular Plane Systolic Excursion

Cardiac Biomarkers: NT-proBNP and Troponin

A total of 90% of patients had NT-proBNP on admission. Of these, 99% had values above the upper reference limit; only one patient had NT-proBNP values within normal range. Thus, NT-proBNP elevation was also noted in patients who did not develop cardiac dysfunction detectable by echocardiography.

Patients with SICD had noticeably higher median NT-proBNP values compared with patients without cardiac dysfunction (9022 vs. 4000 pg/mL), although this difference did not reach statistical significance. NT-proBNP level >9000 pg/mL was a significant predictor for developing SICD of any type (OR 3.1, 95% CI 1.4–6.8; $p = 0.04$).

An NT-proBNP level >9000 pg/mL was also a significant predictor of both the composite outcome and mortality, even after adjustment for age and sex (OR 7.7, 95% CI 3.3–17.8; $p < 0.001$, and OR 7.8, 95% CI 3.2–18.7; $p < 0.001$, respectively).

These findings highlight an important prognostic value of NT-proBNP in sepsis, even in the absence of echocardiographic evidence of cardiac dysfunction.

Troponin I was measured at admission in 58% of patients; 43% had elevated values, most values were only mildly increased. Patients with SICD had higher troponin levels compared with those without SICD, but this difference did not reach statistical significance (0.16 vs. 0.06 ng/mL).

Median troponin levels were significantly higher in non-survivors compared with survivors (0.223 [0.07–1.1] vs. 0.0 [0.0–0.2], $p = 0.02$), showing the prognostic value of troponin elevation observed in other severe non-cardiovascular organ dysfunctions (e.g., chronic kidney disease, chronic obstructive pulmonary disease).



Study I Conclusions

In conclusion, this analysis describes the incidence and echocardiographic spectrum of SICD in a cohort of septic patients admitted to the intensive care unit of a tertiary hospital. Ethanol abuse was identified as a predictor for developing LV systolic dysfunction and biventricular systolic dysfunction.

SICD, regardless of echographic pattern, as well as elevated NT-proBNP levels, showed important prognostic implications. The presence of any type of cardiac dysfunction was revealed to be a significant predictor of the composite outcome. Notably, mortality was particularly high in the group with isolated LV diastolic dysfunction, with 66% of patients dying during hospitalization. Additionally, elevated NT-proBNP levels (>9000 pg/mL) were a significant predictor of SICD development, mortality, and the composite outcome.

Study II Summary

Clinical, paraclinical and echocardiographic insights in critically ill patients with sepsis-induced cardiac dysfunction: more than just a systolic impairment

Objectives

The main objective of this analysis was to describe the dynamic changes in echocardiographic parameters at admission and at 7–10 days follow-up in a group of patients diagnosed with SICD. Secondary objectives included the characterization of clinical and laboratory features of the cohort. By identifying predictors of severity and prognosis, this study aimed to improve early diagnosis and guide management strategies in critically ill septic patients.

Materials and Methods

Patients admitted to the ICU with sepsis or septic shock who developed LV systolic dysfunction, with or without concomitant RV systolic dysfunction, between January 2023 and



September 2024 were retrospectively included. Only patients without a prior history of LV systolic dysfunction were included.

Exclusion criteria were acute myocardial infarction, severe left-sided valvular heart disease, pre-existing cardiomyopathy, and severe or end-stage disease previously diagnosed.

Results

A total of 18 patients were included, with a mean age of 64 ± 17 years; 72% were male. Half of the patients (9/18) had a history of chronic alcohol consumption.

Total in-hospital mortality in this group was 50%, and two patients died before the 7–10 day follow-up echocardiographic assessment.

The most frequent comorbidities identified were neurocognitive disorders, type 2 diabetes mellitus and obesity. Non-survivors had higher rates of atrial fibrillation and required a greater number of days of mechanical ventilation compared with survivors.

One-third of patients presented with culture-negative sepsis. The most frequent infection sites were respiratory, urinary, and abdominal/gastrointestinal, while the most commonly identified microorganisms were *Escherichia coli*, *Klebsiella pneumoniae*, and streptococci.

Elevated inflammation markers levels were observed. Inflammation biomarkers analyzed included: complete blood count (leukocyte, neutrophil, lymphocyte counts, and neutrophil-to-lymphocyte ratio), C-reactive protein and procalcitonin.

A significant difference was noted between median LVEF at admission and at 7–10 day reassessment (40% vs. 58%; $p < 0.001$). The lowest reported LVEF at admission was 20%, which subsequently improved to 60% at follow-up.

Regarding regional wall motion abnormalities patterns, all patients exhibited diffuse LV hypokinesia at admission. Six patients (one-third of the cohort) presented with biventricular dysfunction.

Stroke volume SV and lateral e' velocity were significantly higher at admission among survivors compared with non-survivors (mean stroke volume: 34.2 ± 7.8 vs. 24.1 ± 5.0 ; $p = 0.012$;



mean rank septal e' : 10.25 vs. 5.43; $p = 0.037$). Lower lymphocyte counts were associated with reduced stroke volume ($r = -0.709$, $p = 0.03$).

Diastolic dysfunction parameters—including E/A ratio, lateral E/ e' ratio, and septal E/ e' ratio—showed significant positive correlations with NT-proBNP levels ($r = 0.857$, $p = 0.014$; $r = 0.613$, $p = 0.026$; $r = 0.674$, $p = 0.012$).

Conclusions of Study II

This analysis describes a lot of critically ill patients with SICD, who were relatively young, predominantly male, and exhibited elevated rates of in-hospital mortality (50%). A substantial percentage of chronic ethanol consumers was identified (50%). Non-survivors had higher rates of atrial fibrillation and lower admission stroke volume and lateral e' velocity, underlining the importance of both systolic and diastolic echocardiographic parameters and supporting their potential role as prognostic markers.

Study III Summary

Microbiological and Laboratory Considerations in Sepsis-Induced Cardiac Dysfunction

Objectives

The main objective of this study was to analyze laboratory markers—particularly inflammatory and cardiac biomarkers—and microbiological findings in septic patients who developed LV systolic dysfunction or biventricular systolic dysfunction within a lot of patients with positive cultures.

Materials and Methods

Patients who were admitted to the ICU for sepsis at a tertiary hospital between January 2023 and September 2024 were retrospectively included. The diagnosis of sepsis was established according to the Sepsis-3 Criteria and was characterized based on clinical, laboratory, microbiological, and



imaging data. Patients were categorized according to the source of infection, primary site of infection, and causative microorganism.

All patients who had laboratory markers, microbiological cultures, and transthoracic echocardiography performed within the first 24 hours of admission were enrolled. Only patients with positive cultures were included in the final analysis.

Exclusion criteria are detailed in Table 1. Cardiac function was assessed using transthoracic echocardiography. LV systolic dysfunction was defined as newly diagnosed LVEF $\leq 45\%$ with a decrease of at least 10% from baseline, with or without concomitant RV systolic dysfunction. RV systolic dysfunction was defined as a TAPSE < 17 mm.

In surviving patients with cardiac dysfunction, follow-up echocardiographic examinations were reviewed. SICD was confirmed if systolic dysfunction was reversible within 7–10 days.

Results

A total of 100 patients with positive cultures were identified, with a median age of 73 years (IQR 64–81), 55% were male.

All patients underwent transthoracic echocardiography within the first 24 hours from admission. SICD was diagnosed in 14% of patients. In this group, the median age was 73 years (IQR 54–82), and 71% were male.

Among patients with SICD, mean LVEF increased from 40% (IQR 30–44) at admission to 58% (IQR 42.5–63) on day 7-10 follow-up. Similarly, mean TAPSE increased from 16.5 mm (IQR 14–19) at admission to 19 mm (IQR 17–20.5) at follow-up.

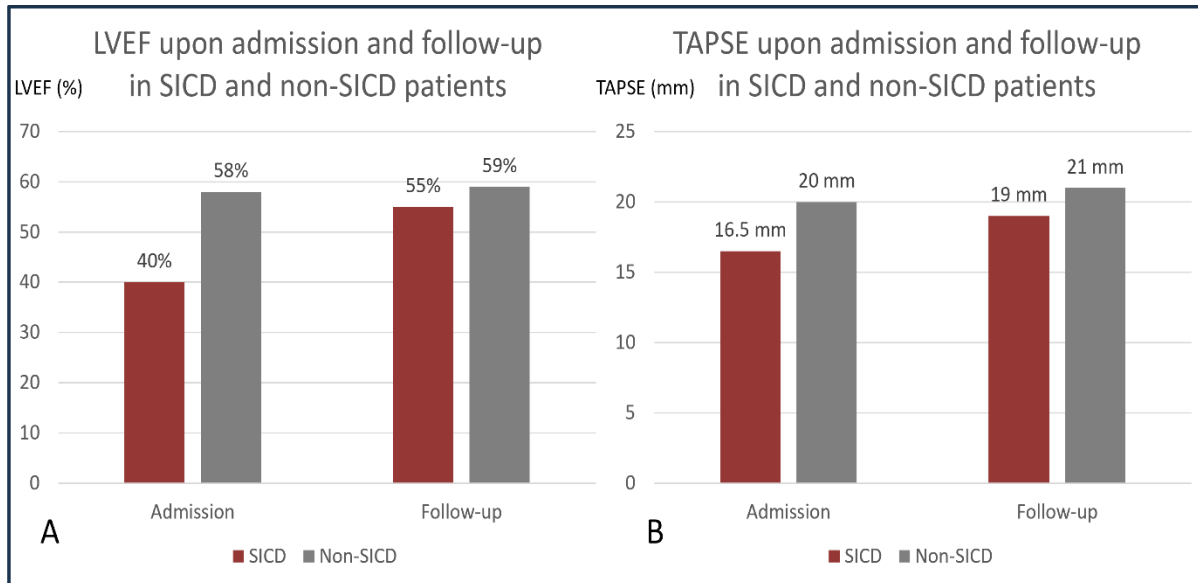


Figure 3: Progression of left and right ventricular function in SICD and non-SICD patients. Panel (A): comparison between LVEF upon admission and LVEF at follow-up in patients with and without SICD; (B): comparison between TAPSE upon admission and TAPSE at follow-up in patients with and without SICD.

LVEF = left ventricular ejection fraction; SICD = sepsis-induced cardiac dysfunction; TAPSE = tricuspid annular systolic excursion.

Patients with SICD developed septic shock more frequently compared to those without SICD.

Patients with SICD had longer hospital stays and longer ICU stays. The median length of hospitalization for patients who developed cardiac dysfunction was 14 days, compared to 10 days for patients without SICD.

Total in-hospital mortality was 44%, with no statistically significant difference between patients with and without SICD (in-hospital mortality 43% in the SICD group versus 44% in the non-SICD group).

The most commonly identified comorbidities in this group were diabetes mellitus, obstructive lung disease (including asthma and chronic obstructive pulmonary disease), chronic kidney disease, chronic hepatitis (viral or toxic-nutritional) and obesity.



The respiratory tract was the most frequent source of infection leading to sepsis (37%), followed by the urinary tract (29%), digestive (14%), wounds and soft tissues (12%), catheter-related infections (5%), bone and joint infections (1%), and ear, nose, and throat infections (1%).

Laboratory markers at admission revealed significantly higher lactate levels and transaminases—aspartate aminotransferase (AST) and alanine aminotransferase (ALT)—in patients with SICD compared with those without SICD.

Serum lactate was a predictor for developing SICD, even after adjustment for age and sex (OR 1.5, 95% CI 1.17–1.94; $p = 0.002$).

Cardiac biomarkers, troponin and NT-proBNP, had higher admission values in the SICD group compared to patients without SICD; however, these differences were not statistically significant.

Similarly, inflammatory markers (leukocyte count, neutrophils, neutrophil-to-lymphocyte ratio, C-reactive protein, and procalcitonin) were higher in patients with SICD than in those without SICD, but without reaching statistical significance.

Blood cultures were obtained in 80% of patients, with positive results in 37% of cases. In patients with negative blood cultures, microbiological diagnosis was established based on respiratory cultures (26%), urine cultures (24%), skin or soft tissue cultures (9%), cultures from surgical wounds following abdominal surgery (3%), and stool cultures (1%).

Polymicrobial cultures were identified in 5 patients (35%) with SICD and in 9 patients (10%) without SICD ($p = 0.025$) - a significant risk factor for SICD (OR 4.7, 95% CI 1.3–17; $p = 0.018$).

Patients with SICD had significantly higher rates of streptococcal infections: positive cultures for *Streptococcus* spp. were obtained in 29% of patients with SICD compared with 9% of those without SICD ($p = 0.040$). The distribution of streptococcal infections among patients with SICD included two cases of *Streptococcus pneumoniae*, one case of *Streptococcus viridans*, and one case of *Streptococcus pyogenes*. Streptococcal infections were associated with an increased risk of developing SICD (OR 3.9, 95% CI 1–15), with a p -value of 0.051, suggesting a trend toward statistical significance.



No patients in the SICD group had positive cultures for *Staphylococcus* spp., including methicillin-sensitive *Staphylococcus aureus* (MSSA) or methicillin-resistant *Staphylococcus aureus* (MRSA).

Conclusions of Study III

In this study, LV or biventricular systolic dysfunction was identified in 14% of patients. Although no differences in mortality were observed between patients with and without SICD, patients who developed cardiac dysfunction experienced higher rates of septic or mixed shock, longer hospital stays and longer ICU stays, contributing to important long-term prognostic implications.

Higher admission levels of lactate, transaminases, and inflammatory markers were observed in patients with SICD, with lactate identified as a predictor for developing SICD, even after adjustment for age and sex. These findings suggest that septic patients with higher inflammatory markers and positive cardiac biomarkers at admission may be at increased risk of developing cardiac dysfunction, and early cardiac imaging should be considered in these cases.

Notably, patients with SICD had a significantly higher frequency of streptococcal infections, highlighting possible specific mechanisms implicated in the development of systolic dysfunction during sepsis.

Conclusions and Personal Contributions

The impact of sepsis and septic shock on healthcare systems is profound, being associated with high rates of morbidity and mortality, as well as poor short and long-term prognosis. Sepsis is one of the most common medical conditions requiring hospital care worldwide, particularly in intensive care units. Current management and treatment principles rely on early recognition and diagnosis of sepsis, prompt initiation of fluid resuscitation and antimicrobial therapy, and close monitoring with supportive care of vital organs.

Sepsis-induced systolic dysfunction is a complex condition that is relatively common in clinical practice among septic patients. Further research efforts are required to establish a universally



accepted definition, standardized diagnostic criteria and the implementation of an early diagnostic algorithm for this disease.

This analysis aimed to describe the incidence of cardiac dysfunction in sepsis, identify echocardiographic patterns of dysfunction, characterize and compare the clinical and paraclinical profiles of patients with and without cardiac dysfunction and identify risk factors for the development of sepsis-induced dysfunction. In addition, the outcomes and prognostic markers were analyzed.

The previously presented methodology, incorporating multiple exclusion criteria, was designed to eliminate alternative causes of cardiac dysfunction (reversible or irreversible) and to establish as clearly as possible the association between cardiac dysfunction and poor outcomes.

The major findings of this study are as follows:

1. **Identification of a relatively high incidence of cardiac dysfunction** in the study cohort. More than one-third of patients (37%) developed a type of cardiac involvement. This group was divided into four echocardiographic types: isolated LV systolic dysfunction, isolated RV systolic dysfunction, and isolated LV diastolic dysfunction. Patients with isolated LV diastolic dysfunction had the most advanced age and had the highest mortality rate, whereas the youngest patients were identified in the isolated LV systolic dysfunction group. Alcohol abuse was identified as a risk factor for developing LV systolic dysfunction and biventricular dysfunction.
2. **Prognosis of SID patients**, expressed through a composite outcome consisting of in-hospital mortality, prolonged hospitalization, and prolonged intensive care unit stay.
3. **Identification of elevated NT-proBNP levels as a risk factor** for developing SICD, mortality, and composite outcome. Additional risk factors for SICD included the need for orotracheal intubation at admission and the initiation of vasopressor therapy at admission.
4. **A significant original contribution of this work** was the identification of significantly higher rates of streptococcal infections and polymicrobial cultures among culture-positive patients who developed LV systolic dysfunction.

This work aims to contribute to a more comprehensive clinical and paraclinical characterization of septic patients who develop SICD, providing valuable findings for early diagnosis and prognostic stratification. Furthermore, it highlights the importance of a multidisciplinary



approach in the management of septic patients with cardiac dysfunction and highlights the crucial role of the intensive care team, which manages—at least temporarily—the majority of critically ill patients with sepsis or septic shock.

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