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Original Article

# Septic cardiomyopathy phenotype in the critically ill may depend on antimicrobial resistance

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ABSTRACT

*Background:* Sepsis is a life-threatening organ dysfunction, and septic cardiomyopathy (SCM) may complicate the course of the disease. Infection with multidrug-resistant (MDR) pathogens has been linked with worse outcomes. This study aims to evaluate SCM in patients with infections caused by different antimicrobial-resistant phenotypes.

*Method:* This retrospective study included patients with sepsis/septic shock, hospitalized, and intubated in the intensive care unit of the University Hospital of Larissa between January 2022 and September 2023 with echocardiographic data during the first two days after infection onset. The patients were divided into two groups: non-MDR-SCM group and MDR-SCM group. The cardiac function was compared between the two groups.

*Result:* A total of 62 patients were included in the study. Forty-four patients comprised the MDR-SCM and 18 the non-MDR-SCM group. Twenty-six patients (41.9%) presented with left ventricular (LV) systolic dysfunction, and ≤35% right ventricular fractional area change (RVFAC) was present in 56.4%. LV systolic function was more severely impaired in the non-MDR-SCM group (left ventricular ejection fraction, 35.8% ±4.9% *vs.* 45.6%±2.4%, *P*=0.049; LV outflow tract velocity time integral, [10.1±1.4] cm *vs.* [15.3±0.74] cm, *P*=0.001; LV-Strain, –9.02%±0.9% *vs.* –14.02%±0.7%, *P*=0.001). The MDR-SCM group presented with more severe right ventricular (RV) dilatation (right ventricular end-diastolic area/left ventricular end-diastolic area, 0.81±0.03 *vs.* 0.7±0.05, *P*=0.042) and worse RV systolic function (RVFAC, 32.3%±1.9% *vs.* 39.6%±2.7%, *P*=0.035; tricuspid annular plane systolic excursion, [15.9±0.9] mm *vs.* [18.1±0.9] mm, *P*=0.165; systolic tissue Doppler velocity measured at the lateral tricuspid annulus, [9.9±0.5] cm/s *vs.* [13.1±0.8] cm/s, *P*=0.002; RV-strain, –11.1%±0.7% *vs.* –15.1%±0.9%, *P*=0.002).

*Conclusion:* SCM related to MDR infection presents with RV systolic dysfunction predominance, while non-MDR-SCM is mainly depicted with LV systolic dysfunction impairment.

## Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis is associated with a 10% mortality risk, while it exceeds 40% in patients presenting with septic shock.[2] Multidrug-resistant (MDR) pathogens have overwhelmed institutions dealing with the most severely ill patients. In 2017, the World Health Organization prioritized pathogens of great concern to incentivize research and development of new antibiotics. Among the identified pathogens were carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Acinetobacter* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).[3,4] Multidrug resistance has been extensively found to affect mortality outcomes. Patients with bloodstream infection caused by *Klebsiella pneumoniae* resistant to carbapenems are associated with a worse outcome compared to those infected with non-resistant strains, even adjusting for comorbidities and receipt of appropriate treatment according

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to *in vitro* activity of empirical and targeted therapy.[5] Moreover, the attributable mortality to carbapenem-resistant Gram-negative bacteria is affected by the pathogen and its mechanism of resistance. In a recent Italian multicenter study, the highest mortality was found among patients infected with CRAB, CRPA, and CRE-producing metallo-$\beta$-lactamases.[6]

Inherent to the progression of sepsis is the decompensation of organ function, which is mostly interdependent; failure of one organ may lead to the dysfunction of other organs.[7] This is especially true for the cardiovascular system responsible for tissue oxygenation of the whole body. Septic cardiomyopathy (SCM) can manifest as left ventricular (LV) and/or right ventricular (RV) impairment during systole and/or diastole, inadequate cardiac output (CO), and oxygen delivery.[8] The exact prevalence of SCM is unknown, and the reported incidence varies between 10% and 70%, due to the lack of clear SCM definition criteria, knowledge of pre-existing cardiac function, and criteria to promptly direct the investigation for its presence during a septic episode.[8] The diagnosis of heart failure is further complicated by the significant and dynamic alterations in systemic hemodynamics during sepsis (with variable preload and afterload conditions).[9] The SCM effect on mortality has long been debatable, and data support no mortality increase; SCM is mainly a transient myocardial impairment, lasting 7–10 days, during severe sepsis and septic shock.[10,11] On the other hand, the "afterload-related myocardial performance," indicating the specific myocardial contractility adjusted for the present degree of systemic vascular resistances, has been evaluated as a measure to unravel SCM presence in an apparently normal functioning heart;[9,12] the degree of afterload-related myocardial performance impairment has been linked to survival, even in patients with sepsis apart from septic shock.[12] To our knowledge, there are no data concerning the effect of antimicrobial resistance on the incidence and degree of SCM impairment.

This study aims to evaluate and compare the SCM features and outcomes in patients with septic shock resulting from MDR and non-MDR pathogens.

## Methods

In this retrospective study, we included mechanically ventilated patients with sepsis/septic shock caused by a known pathogen; they were admitted in the intensive care unit (ICU) of the University Hospital of Larissa between January 2022 and September 2023. The patients were included if there were available echocardiographic data on sepsis (day 0–day 2). Routinely, in our institution, echocardiography is performed in patients with sepsis/septic shock during the initiation of the episode. The study was approved by the local ethics committee (55944/2022). The inclusion criteria were as follows: age >18 years, signs of sepsis/septic shock presence according to Sepsis-3 definition,[2] and a known antimicrobial resistance of the isolated pathogen (antibiogram). The exclusion criteria were as follows: a pre-existing severe heart disease (valvular heart disease, dilated cardiomyopathy, coronary heart disease, myocardial infarction, and/or known heart failure) and/or obstructive shock (tamponade, massive pulmonary embolism, and/or tension pneumothorax).

### *Transthoracic echocardiography echocardiographic parameters*

A comprehensive transthoracic echocardiographic examination (GE VividTM E95, GE VINGMED ULTRASOUND Standpromenaden 45 3191 Horten, Norway; Philips iE33, Philips Ultrasound 22100 Bothell-Everett Highway Bothell, WA98021-8431 USA) was performed to assess LV and RV dimensions and function and the inferior vena cava (IVC), IVC diameter during inspiration (maximum) and expiration (minimum), and the distensibility index (assessed as the $[IVC_{max}-IVC_{min}]/IVC_{min}$).[13–17]

LV systolic function was assessed using Simpson's method to calculate the ejection fraction (EF).

RV dilation was estimated through planimetry at end-diastole from a four-chamber view quantification comparing the right ventricular end-diastolic area (RVEDA) to left ventricular end-diastolic area (LVEDA) to calculate their ratio (RVEDA/LVEDA). The RV contractility was estimated by measuring the RVEDA and right ventricular end-systolic area (RVESA); thereafter, right ventricular fractional area change (RVFAC%=100 × [RVEDA−RVESA]/RVEDA) was calculated. Further, we calculated the tricuspid annular plane systolic excursion (TAPSE) with M-MODE and RV tissue Doppler systolic excursion (RV S′) using tissue Doppler imaging. Two-dimensional speckle-tracking echocardiography (2D-STE) was used to characterize longitudinal systolic strain, excluding the septum.[14]

Using the simplified Bernoulli's equation, the right ventricular systolic pressure (RVSP) was estimated from the peak tricuspid regurgitation (TR) jet velocity. Pulmonary artery systolic pressure (PASP) was estimated from the sum of RVSP plus the central venous pressure.

Pulmonary vascular resistance (PVR) was indirectly estimated through quantification of the PASP (via TR velocity), the pulmonary acceleration time (AcT) of the right ventricular outflow tract (RVOT) flow velocity Doppler envelop, and the ratio of PASP to the RVOT velocity time integral ($PASP/VTI_{RVOT}$) as the ratio integrates PASP and CO and thus better expresses changes in PVRs.[18,19]

Right ventriculoarterial coupling ($VAC_R$) which is the coupling between the right ventricle and the pulmonary artery, was assessed through the TAPSE/PASP ratio.[20]

Three consecutive cycles (5–10 in case of non-sinus rhythm) were averaged for every parameter. Measurements were assessed offline (EchoPAC) by three cardiologists (NK, VV, and EZ) and trained doctors (competence in advanced critical care echocardiography [VT]). Two of these doctors evaluated each measurement. In case of >10% variability in the calculated parameters, re-evaluation was performed with two operators present, to reach an agreement.

### *Definitions*

LV dysfunction was defined as an EF <40% and/or LV- longitudinal strain (LS) >−15.9% (defined as the lower normal level).[13,14]

RV dilation was present when RVEDA/LVEDA was >0.6.[14]

RV dysfunction was considered if one of the following indices were present: RVFAC ≤35%, RV S′≤10 cm/s, TAPSE ≤16 mm, or RV-LS >−17% (lower normal level).[14]

For ventriculoarterial coupling, values were compared to the mean value of 1.1, found in healthy adults above 60 years of age, according to previous reports.[20]

### *Clinical data recorded demographics*

The data include age, sex, illness severity scores (sequential organ failure assessment [SOFA] upon the index septic episode and acute physiology and chronic health evaluation [APACHE] II upon ICU admission), and type of isolate depending on antimicrobial resistance. The isolates were divided into MDR and non-MDR isolates as previously defined.[21] Moreover, we recorded laboratory data, hemodynamic variables, vasopressor dose during the echocardiographic study, and finally the outcome during the ICU stay (discharged alive or dead).

### *Statistical analysis*

The data were tested for normality with the Kolmogorov–Smirnov test, and variables were expressed as medians (minimum and maximum values) or means ± standard error of the mean, accordingly. Demographics, hemodynamic variables, and cardiac function variables were compared between the MDR-SCM and non-MDR-SCM groups using the Mann–Whitney *U* test or *t*-test. Statistical analyses were performed using SPSS version 26.0 (IBM, NY, USA), and $P<0.05$ was considered statistically significant.

## Results

During the study period, 142 patients presented with a septic episode. Of these, 96 had an echocardiographic examination, 16 had a known history of left heart failure, 12 had a history of pulmonary hypertension, and 5 patients were diagnosed with pulmonary embolism during the ICU admission, while 1 had pericardial effusion with signs of right atrial collapse, leaving 62 patients eligible for inclusion. Among the 62 patients included in the study, 44 patients presented with a septic episode with an MDR isolate and comprised the MDR-SCM group, and 18 had an infection due to a non-MDR pathogen (community-acquired), who were included in the non-MDR-SCM group. The baseline characteristics and severity scores upon admission (APACHE II) and the septic episode (SOFA score) are presented in Table 1. Patients in the MDR-SCM group tended to be older ([64.4±1.8] years *vs.* [57.7±4.0] years, $P=0.084$) and tended to have less multi-organ involvement upon ICU admission (APACHE II, 18.3±1.2 *vs.* 22.3±2.0, $P=0.086$).

The majority (88.6%) of the patients in the MDR-SCM group were admitted after hospitalization in the medical-surgical wards (mean hospitalization duration: [7.9±1.1] days), while the majority of the patients in the non-MDR-SCM group were admitted from the emergency department (ED) (72.2%, $P=0.030$). Only one patient was admitted from the operating room, transferred from the ED for acute gastric rupture. Sixteen patients (88.9%) in the non-MDR-SCM group were admitted in the ICU due to septic shock resulting from the index non-MDR pathogen that was isolated. The shock was present in the majority of the patients in both groups—86.4% (38/44) and 88.9% (16/18) in MDR-SCM and non-MDR-SCM groups, respectively. Hemodynamics and respiratory variables did not differ between the two groups (Table 2). Patients in the MDR-SCM group required fewer vasopressor doses (noradrenaline dose, [0.55±0.07] μg/(kg·min) *vs.* [0.79±0.12] μg/(kg·min), $P=0.056$). Concerning the global tissue oxygenation, both groups presented with reduced tissue oxygenation as depicted by the decreased oxygen saturation in the superior vena cava ($ScvO_2$) values (64.3%±2.4% *vs.* 65.3%±4.6%, $P=0.837$), increased arteriovenous partial dioxide pressure difference ($Pa\text{-}vCO_2$) values ([7.2±0.9] mmHg *vs.* [8.8±1.1] mmHg, $P=0.299$), and lactate levels ([6.3±1.3] mmol/L *vs.* [9.1±3.1] mmol/L, $P=0.333$). Atrial fibrillation occurred in 50% of the patients in the MDR-SCM group and 33.3% in the non-MDR-SCM group. Troponin, measured in 34 patients (54.8%), was equally increased in both groups ([1.15±0.60] ng/mL *vs.* [0.80±0.50] ng/mL, $P=0.681$).

**Table 1**
Demographic and infection data in the MDR- and non-MDR-SCM groups.

| Measured value | MDR-SCM group ($n$=44) | Non-MDR-SCM group ($n$=18) | $P$-value |
|---|---|---|---|
| Age | 64.4±1.8 | 57.7±4.0 | 0.084 |
| Sex | 22 (50) | 13 (72) | 0.113 |
| Charlson comorbidity index | 0 (0, 6) | 0 (0, 2) | 0.394 |
| Arterial hypertension | 24 (54.5) | 5 (27.8) | 0.014 |
| Coronary artery disease | 6 (13.6) | 0 | 0.139 |
| Diabetes mellitus | 4 (9.1) | 4 (22.2) | 0.575 |
| COPD | 3 (6.8) | 0 | 0.269 |
| Cancer | 6 (13.6) | 0 | 0.139 |
| APACHE II score | 18.3±1.2 | 22.3±2.0 | 0.086 |
| SOFA score | 8.9±0.7 | 9.4±0.9 | 0.740 |
| Ward of admission | | | 0.030 |
| ED | 4 (9.2) | 13 (72.2) | |
| Medical ward | 24 (54.5) | 4 (22.2) | |
| Surgical ward | 15 (34.1) | 0 | |
| Operating room | 1 (2.3) | 1 (5.6) | |
| Length of hospital stay before ICU admission | 7.9±1.1 | 3.4±1.3 | 0.021 |
| Length of ICU stay upon SCM onset | 13.2±2.6 | 2.3±1.7 | 0.013 |
| Source of infection | | | 0.054 |
| Intra-abdominal infection | 0 | 4 (22.2) | |
| Pneumonia | 3 (6.8) | 6 (33.3) | |
| Bloodstream infection (primary) | 41 (93.2) | 4 (22.2) | |
| Urine tract infection | 0 | 4 (22.2) | |
| Isolated pathogens | | | 0.237 |
| *Klebsiella pneumonia* | 31 (70.5) | 5 (27.8) | |
| *Acinetobacter baumannii* | 11 (25.0) | 0 | |
| *Pseudomonas aeruginosa* | 1 (2.3) | 0 | |
| *Escherichia coli* | 0 | 5 (27.8) | |
| *Enterobacter aerogenes* | 0 | 3 (16.7) | |
| *Proteas mirabilis* | 0 | 1 (5.6) | |
| *Streptococcus pneumoniae* | 0 | 2 (11.2) | |
| *Staphylococcus aureus* | 1 (2.3) | 1 (5.6) | |
| *Candida albicans* | 0 | 1 (5.6) | |
| Outcomes | | | |
| Treatment | | | 0.025 |
| Noradrenaline-(±vasopressin) | 38 (86.4) | 16 (88.9) | |
| Dobutamine | 1 (2.3) | 0 | |
| Levosimendan | 8 (18.2) | 6 (33.3) | |
| Levosimendan + dobutamine | 1 (2.3) | 3 (16.7) | |
| LOS (days) | 28.2±5.6 | 21.9±5.2 | 0.506 |
| ICU survival | 21 (47.7) | 9 (50.0) | 0.873 |

Data are expressed as *n* (%), medians (minimum and maximum values), or mean ± standard error of the mean.
APACHE: Acute physiology and chronic health evaluation; COPD: Chronic obstructive pulmoriary disease; ED: Emergency department; ICU: Intensive care unit; LOS: Length of stay; MDR: Multidrug resistant; SCM: Septic cardiomyopathy; SOFA: Sequential organ failure assessment.

### *Echocardiographic findings*

Regarding the whole group of patients, 26 patients (41.9%) presented with LV systolic dysfunction, and 47 patients (75.8%)

**Table 2**
Hemodynamic and respiratory parameters.

| Measured value | MDR-SCM group ($n$=44) | Non-MDR-SCM group ($n$=18) | $P$-value |
|---|---|---|---|
| Hemodynamic variables | | | |
| Heart rate | 102.9±4.1 | 104.7±5.4 | 0.563 |
| Noradrenaline (μg/(kg·min)) | 0.55±0.07 | 0.79±0.12 | 0.056 |
| Shock | 38 (86.4) | 16 (88.9) | 0.776 |
| MAP (mmHg) | 67.53±1.80 | 68.20±8.70 | 0.817 |
| CVP (mmHg) | 14.2±1.8 ($n$=26) | 11.4±1.8 ($n$=13) | 0.286 |
| $ScvO_2$ (%) | 64.3±2.4 ($n$=26) | 65.3±4.6 ($n$=13) | 0.837 |
| Pa-$vCO_2$ (mmHg) | 7.2±0.9 ($n$=26) | 8.8±1.1 ($n$=13) | 0.299 |
| Lactate (mmol/L) | 6.3±1.3 ($n$=36) | 9.1±3.1 ($n$=16) | 0.333 |
| ECG | | | 0.326 |
| Sinus rhythm | 22 (50.0) | 12 (66.7) | |
| Atrial fibrillation | 22 (50.0) | 6 (33.3) | |
| Respiratory variables | | | |
| Mode of ventilation | | | 0.928 |
| Volume control | 36 (81.8) | 15 (83.3) | |
| Pressure support | 4 (9.1) | 1 (5.6) | |
| T-piece | 3 (6.8) | 2 (11.2) | |
| High-flow nasal cannula | 1 (2.3) | 0 | |
| Tidal volume* | 417.0±9.5 | 458.0±13.7 | 0.022 |
| PEEP* | 9.4±0.4 | 9.2±0.5 | 0.772 |
| Respiratory rate* | 25.6±0.9 | 22.6±0.9 | 0.057 |
| $PaO_2/FiO_2$ | 172.4±13.6 | 174.4±15.9 | 0.929 |

Data are expressed as $n$ (%) or mean ± standard error of the mean.
CVP: Central venous pressure; ECG: Electrocardiography; MAP: Mean arterial pressure; MDR: Multidrug resistant; $PaO_2/FiO_2$: Ratio of partial oxygen pressure to the fraction of inspired oxygen; Pa-$vCO_2$: Arteriovenous partial dioxide pressure difference; PEEP: Positive end expiratory pressure; SCM: Septic cardiomyopathy; $ScvO_2$: Oxygen saturation in the superior vena cava.
*For the patients on controlled mode.

presented with LV-LS >−15.9%. Moreover, 56.4% of the patients had a $VTI_{LVOT}$ <15 cm. RV systolic dysfunction was also common: RVFAC of ≤35% was present in 56.4%, TAPSE of ≤1.6 cm in 48.2%, RV S′ of <10 cm in 44.6%, and RV-LS of >−17 in 81.5%. Biventricular systolic dysfunction was present in 22.6%. PVRs were increased in 38% (assessed with PASP >38 mmHg), while the $VAC_R$ was <0.8 mm/mmHg in 53%.

MDR-SCM group presented with a higher incidence of RV systolic dysfunction (77.3% *vs.* 44.4%, $P$=0.022), while more patients in the non-MDR-SCM group (36.4% *vs.* 77.8%, $P$=0.003) presented with worse LV systolic function and a higher incidence of biventricular dysfunction compared to MDR-SCM patients (15.9% *vs.* 38.9%, $P$=0.051) (Table 3). LV systolic function was more severely impaired in the non-MDR-SCM group (left ventricular ejection fraction [LV EF; Simpson's method], 35.8%±4.9% *vs.* 45.6%±2.4%, $P$=0.049; $VTI_{LVOT}$, [10.1±1.4] cm *vs.* [15.3±0.7] cm, $P$=0.001; LV-LS, −9.02%±0.90% *vs.* −14.02%±0.70%, $P$=0.001), and so was the LV diastolic function (E/E′, [11.9±1.3] cm/s *vs.* [8.5±0.8] cm/s, $P$=0.025; deceleration time, [146.9±12.0] ms *vs.* [212.5±15.2] ms, $P$=0.019).

The right ventricle was dilated in both groups. Yet, patients in the MDR-SCM group presented with more severe RV dilatation (RVEDA/LVEDA, 0.81±0.03 *vs.* 0.70±0.05, $P$=0.042) and a worse RV systolic function (RVFAC, 32.3%±1.9% *vs.* 39.6%±2.7%, $P$=0.035; TAPSE, [15.9±0.9] mm *vs.* [18.1±0.9] mm, $P$=0.165; RV S′, [9.9±0.5] cm/s *vs.* [13.1±0.8] cm/s, $P$=0.003; RV-LS, −11.1%±0.7% *vs.* −15.1%±0.9%, $P$=0.002). The coupling between $VAC_R$ was more impaired in patients in the MDR-SCM group ($VAC_R$, [0.56±0.07] mm/mmHg *vs.* [0.72±0.01] mm/mmHg, $P$=0.276).

### *Treatment and outcome*

Inotropic agents (levosimendan and/or dobutamine) were administered to 22.8% of the patients in the MDR-SCM group *vs.* 50.0% in the non-MDR-SCM group ($P$=0.025). ICU survival did not differ between the two SCM groups.

## Discussion

In this study, we evaluated the cardiac function in consecutive intubated and mechanically ventilated patients presenting with sepsis/septic shock. We found that cardiac function was impaired during a septic episode, as LV and RV systolic dysfunction was present in more than half of the patients. Interestingly, we observed two different SCM phenotypes: patients with a non-MDR community-acquired infection, who tended to present with severely depressed LV function, and patients with hospital-acquired MDR infection, who were more likely to present with an RV SCM pattern. Although various forms of cardiac dysfunction, including RV/LV systolic dysfunction, LV diastolic dysfunction, and takotsubo cardiomyopathy, have been reported in sepsis, our study provides a novel insight. Specifically, we found a correlation between the type of cardiac dysfunction in sepsis and the microbiological pattern of infection, considering factors such as antimicrobial resistance and the setting of infection acquisition. This association, to our knowledge, has not been previously reported.

SCM is a well-identified entity presenting in sepsis/septic shock patients, although there is no consensus regarding the definition of the syndrome. Systolic LV and/or RV dysfunction and LV diastolic dysfunction have been described to characterize SCM presence.[8] Yet, to our knowledge, there are no data attributing the presence of SCM phenotypes to different microbiologic patterns/settings. In the present study, we identified two SCM subphenotypes, according to the type of the isolated pathogen and setting. The first phenotype was SCM that occurred during a severe infection leading to ICU admission due to a community-based non-MDR infection. This type of SCM was characterized by LV systolic dysfunction predominance; patients had a severe circulatory failure and required increased vasopressor support. The right ventricle was also dilated but with no signs of dysfunction. The second identified phenotype in our cohort concerned patients presenting with an MDR hospital-acquired infection (MDR-SCM phenotype); it was mainly depicted by severe RV dilation and systolic dysfunction. The LV systolic function was mainly preserved, although LV-LS was severely decreased. The right ventriculoarterial coupling was also severely impaired.

This study reported different SCM phenotypes, depending on the antimicrobial resistance of the pathogenic phenotype. We believe that increased virulence of the non-MDR pathogens (leading to the index hospitalization in ICU) affected LV performance. On the other hand, MDR infections (mainly occurring in patients being already hospitalized in the ICU for other reasons) are not that aggressive to impact LV function. The RV dysfunction predominance might be a distinct SCM phenotype in MDR infections or could present with a combined result of SCM and increased RV afterload due to acute respiratory distress syndrome (ARDS) presence and the impact of mechanical ventilation on RV afterload.[22] Certainly, the lat-

**Table 3**
Echocardiographic variables in patients with MDR-SCM *vs.* those in patients with non-MDR-SCM.

| Measured value | MDR-SCM group (*n*= 44) | Non-MDR-SCM group (*n*=18) | *P*-value |
|---|---|---|---|
| Echocardiographic variables: left ventricle | | | |
| LVEDD (cm) | 4.6±0.1 | 4.7±0.2 | 0.733 |
| Left atrial diameter (cm) | 3.8±0.1 | 3.7±0.1 | 0.873 |
| LVEDA ($cm^2$) | 26.6±0.8 | 27.2±1.4 | 0.678 |
| LVEDV (mL, 2D) | 90.6±3.7 | 94.7±8.9 | 0.609 |
| LVESV (mL, 2D) | 50.1±3.6 | 63.8±9.6 | 0.103 |
| EF (%) | 45.6±2.4 | 35.8±4.9 | 0.049 |
| LVOTd (cm) | 2.0±0.03 | 1.9±0.03 | 0.140 |
| $VTI_{LVOT}$ (cm) | 15.3±0.7 | 10.1±1.4 | 0.001 |
| SV (mL, Simpson's) | 39.5±2.7 | 30.9±3.8 | 0.081 |
| SV (mL, VTI) | 44.3±3.6 | 25.3±3.7 | 0.003 |
| CO (Simpson's, L/min) | 3.7±0.3 | 3.1±0.4 | 0.290 |
| CO (VTI, L/min) | 4.3±0.4 | 2.6±0.4 | 0.018 |
| LV-LS (%) | −14.02±0.70 (*n*=35) | −9.02±0.90 (*n*=12) | 0.001 |
| LV S′ (cm/s) | 8.5±0.7 | 6.6±0.8 | 0.111 |
| Echocardiographic variables: transmitral flow | | | |
| E (cm/s) | 79.3±4.7 | 73.6±6.7 | 0.513 |
| A (cm/s) | 78.1±4.3 | 64.4±8.1 | 0.110 |
| E′ (cm/s) | 9.7±0.5 | 6.7±0.7 | 0.002 |
| E/E′(cm/s) | 8.5±0.8 | 11.9±1.3 | 0.025 |
| DT (ms) | 212.5±15.2 | 146.9±12.0 | 0.019 |
| Echocardiographic variables: right ventricle | | | |
| RVEDA/LVEDA | 0.81±0.03 | 0.70±0.05 | 0.042 |
| RVEDA ($cm^2$) | 20.9±0.9 | 18.4±1.2 | 0.103 |
| RVESA ($cm^2$) | 14.3±0.7 | 10.9±0.8 | 0.010 |
| RVFAC (%) | 32.3±1.9 | 39.6±2.7 | 0.035 |
| PASP (mmHg) | 33.4±2.2 | 31.5±3.6 | 0.641 |
| $PASP/VTI_{LVOT}$ (mmHg/cm) | 2.3±0.3 | 3.6±0.7 | 0.051 |
| $VTI_{RVOT}$ (cm) | 12.2±1.1 | 9.1±1.5 | 0.106 |
| Pulmonary AcT (ms) | 69.9±4.5 | 73.5±3.4 | 0.605 |
| $VAC_R$ (mm/mmHg) | 0.56±0.07 | 0.72±0.01 | 0.276 |
| TAPSE (mm) | 15.9±0.9 | 18.1±0.9 | 0.165 |
| RV S′ (cm/s) | 9.9±0.5 | 13.1±0.8 | 0.003 |
| IVC* (cm) | 2.20±0.07 | 2.04±0.07 | 0.076 |
| ΔIVC | 11.1±2.3 | 7.4±1.6 | 0.282 |
| RV-LS (%) | −11.1±0.7 (*n*=35) | −15.1±0.9 (*n*=15) | 0.002 |

Data are expressed as mean ± standard error of the mean.
ΔIVC: Respiratory variability in inferior vena cava diameter [$(IVC_{max}-IVC_{min})/IVC_{min}$]; A: Left ventricular late diastolic filling velocity with atrial contraction; AcT: Acceleration time; CO: Cardiac output; DT: Deecceleration time; E: Left ventricular early diastolic peak velocity; E′: Early diastolic tissue Doppler velocity at the lateral wall; EF: Ejection fraction; IVC: Inferior vena cava; LV S′: Systolic tissue Doppler velocity measured at the lateral mitral annulus; LVEDA: Left ventricular end-diastolic area; LVEDD: Left ventricular end-diastolic diameter; LVEDV: Left ventricular end-diastolic volume; LVESA: Left ventricular end-systolic area; LVESV: Left ventricular end-systolic volume; LV-LS: Longitudinal strain of the left ventricle; LVOTd: Left ventricular outflow tract diameter; MDR: Multidrug resistant; $PASP/VTI_{LVOT}$: Pulmonary artery systolic pressure to left ventricular outflow tract velocity time integral ratio; PASP: Pulmonary artery systolic pressure; RV S′: Right ventricular tissue Doppler systolic excursion; RVEDA/LVEDA: Right ventricular end-diastolic area to left ventricular end-diastolic area; RVESA: Right ventricular end-systolic area; RVFAC: Right ventricular fractional area change; RV-LS: Right ventricular free wall longitudinal strain; SCM: Septic cardiomyopathy; SV: Stroke volume; TAPSE: Tricuspid annular plane systolic excursion; $VAC_R$: Right ventricular to pulmonary artery coupling; VTI: Velocity time integral; $VTI_{LVOT}$: Left ventricular outflow tract velocity time integral.
*Maximum diameter measured during inspiration in mechanical ventilation.

ter is not supported by our findings as both groups did not differ in terms of oxygenation impairment; mechanical ventilator settings were comparable. Yet, we cannot exclude that mechanical ventilator duration and severe organ dysfunction in the MDR-SCM group, resulting from the higher length of hospital and ICU stay, might have an impact on RV function. Indeed, PVRs in our study were evaluated through PASP and $PASP/VTI_{LVOT}$. We found that PVRs were higher in the non-MDR-SCM group, although with borderline significance, indicating that MDR-SCM patients did not present higher PVRs either from ARDS or mechanical ventilation. MDR pathogens affect mainly RV performance, which is a finding that needs further investigation. The right ventriculoarterial coupling was severely impaired in the MDR-SCM group with RV dysfunction predominance. Early and pronounced RV-PA uncoupling has been recently reported in COVID-19 ARDS patients; survivors presented with a TAPSE/PASP of [0.89±0.29] mm/mmHg *vs.* [0.51±0.22] mm/mmHg in non-survivors.[23]

In our study, the vast majority of included patients presented with septic shock. LV systolic dysfunction was present in 41.9% of the patients, and 64.5% presented with at least one abnormal RV systolic function variable; biventricular dysfunction was present in 22.6%. The exact incidence of sepsis cardiomyopathy is not fully elucidated, due to the lack of standardized evaluation of the cardiac function in all patients presenting with septic shock.[8] Yet, our findings of SCM presence in at least half of the septic patients corroborate previous findings. Concerning the LV function, various cut-off levels of the LV EF, ranging between 45% and 55%, have been used to denote LV systolic impairment.[10,24,25] In our study, we used a more strict criterion to define LV systolic function impairment (LVEF: <40%), considering the effects of afterload on LV performance.[9] Despite this, we could still identify increased SCM incidence in critically ill patients with sepsis/septic shock. Moreover, we found that strain imaging might be more sensitive to identify systolic dysfunction in patients with apparently preserved EF. Dalla et al.[26]

found that among patients with shock requiring vasopressors, only septic patients presented with an abnormal LV strain, despite the preserved EF.[26] Similarly, Orde et al.[10] found that 69% of the evaluated septic patients presented with decreased LV strain, although only half of them presented with an LV EF of <55%.

Traditionally, SCM was thought to mainly affect the LV systolic and/or diastolic function, while the performance of the right ventricle during sepsis has only recently been the center of attention. In our cohort, we identified more than half of the patients who presented with RV systolic dysfunction, while RV-LS was impaired in 81.5% of the patients. RV dilation was present in 77% of the patients as well. Lanspa et al.[27] recently identified the increased incidence of RV dysfunction in sepsis, while they also noted a clear association with survival, independently of LV dysfunction. Additionally, in a large meta-analysis of 1373 patients with sepsis and septic shock, RV dysfunction was noted in nearly 35% of the patients, while ARDS was not more frequent in RV dysfunction patients.[28] On the contrary, to the abovementioned studies, we did not find a correlation of RV or LV dysfunction presence on the mortality of the patients. The assumption of increased virulence of the non-MDR pathogens, which mainly led to the index ICU admission in the majority of the non-MDR patients, may explain the increased mortality rate observed.

Our study is limited due to its retrospective analysis. Secondly, although we tried to include consecutive patients presenting with sepsis/septic shock, we failed to include all of them as some patients lacked echocardiographic examinations. This may have impacted the reported incidence of SCM. On the other hand, we present data in almost half of the patients who presented with sepsis in this particular study period, thus we believe our analysis may somehow depict the incidence of SCM in ICU patients. Yet, we decided to use rather strict criteria to define LV systolic dysfunction and also report the incidence of severe LV strain impairment (>−15.9) to avoid LV dysfunction overestimation.

## Conclusions

In this study, two different SCM phenotypes were observed. The non-MDR-SCM, community-acquired pattern, was characterized by LV systolic dysfunction impairment, while the MDR-SCM, hospital-acquired pattern, was mainly depicted by RV dysfunction predominance, with severely impaired right ventriculoarterial coupling. Both phenotypes did not differ in terms of mortality. Yet, the non-MDR-SCM phenotype was associated with more severe circulatory failure. Our novel observation links cardiac dysfunction in sepsis with the microbiologic pattern of infection, based on antimicrobial resistance and setting. This finding warrants further studies for validation.

## Author Contributions

**Vasiliki Tsolaki:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kyriaki Parisi:** Writing – original draft, Investigation, Data curation, Conceptualization. **Efrosini Gerovasileiou:** Investigation, Data curation. **Nikitas Karavidas:** Investigation. **Vassileios Vazgiourakis:** Investigation, Data curation. **Epaminondas Zakynthinos:** Writing – review & editing, Writing – original draft, Formal analysis. **Demosthenes Makris:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

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## Ethics Statement

The study was approved by the Institutional Review Board of the University Hospital of Larissa (approval number: 55944/2022).

## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data Availability

The data analyzed in the study shall be available upon reasonable request.

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