ORIGINAL RESEARCH

A Prospective Observational Study to Determine Incidence and Outcome of Sepsis-induced Cardiomyopathy in an Intensive Care Unit

Sonali Bansal[1], Siddarth Varshney[2], Anupam Shrivastava[3]

Abstract

Introduction: Sepsis leads to left and/or right ventricular systolic and/or diastolic dysfunction resulting in adverse outcomes. Myocardial dysfunction can be diagnosed by echocardiography and early intervention can be planned. There are lacunae in Indian literature regarding the true incidence of septic cardiomyopathy and its impact on the outcome of patients admitted in the Intensive Care Unit (ICU).

Materials and methods: This prospective observational study was conducted on patients admitted with sepsis in the ICU of a tertiary care teaching hospital in North India. In these patients, ECHO was performed after 48–72 hours to establish left ventricular (LV) dysfunction, in whom the ICU outcome was analyzed.

Result: The incidence of left ventricular dysfunction was 14%. Moreover, 42.86% patients had isolated systolic dysfunction, 7.14% patient had isolated diastolic dysfunction, and 50.00% patients with combined systolic and diastolic dysfunction. The average days of mechanical ventilation in patients without LV dysfunction group (group I) were 2.41 $\pm$ 3.82 days as compared to 4.43 $\pm$ 4.27 days in patients with LV dysfunction (group II) (*p* value—0.034). Incidence of all-cause ICU mortality was 11 (12.79%) in group I and 3 (21.43%) in group II (*p*-value—0.409). Mean duration of ICU stay was 8.26 $\pm$ 4.41 days in group I as compared to 13.21 $\pm$ 6.83 days in group II.

Conclusion: We concluded that sepsis-induced cardiomyopathy in ICU is quite prevalent and clinically significant. All-cause ICU mortality and length of stay in the ICU is prolonged in patients with SICM.

Keywords: Sepsis, Sepsis-induced cardiomyopathy, Septic cardiomyopathy.

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Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis leads to a complex intramyocardial inflammatory response that results in sepsis-induced myocardial dysfunction. Sepsis-induced cardiomyopathy (SICM) is defined traditionally as intrinsic and reversible systolic and/or diastolic dysfunction involving left and/or right ventricle.[2] Myocardial dysfunction results in complications such as arrythmia, congestive heart failure, ischemic events, valvular dysfunctions, thrombus formation, etc., and these events further lead to worse outcomes. Routine screening with the use of bedside point of care tests like hemodynamics, electrocardiographic changes, and echocardiography (ECHO) may lead to an early diagnosis. Likewise early intervention with modified therapeutics such as fluid restriction, anticoagulation, vasopressor use, and vasopressor choice, etc., may lead to a better outcome. In Indian population, to the best of our knowledge, there is no data regarding the true incidence of septic cardiomyopathy and its impact on the outcome of patients admitted in the ICU. In the present study, we intended to determine the burden of sepsis-induced cardiomyopathy in the Indian population and its effect on all-cause mortality and length of stay in ICU admitted patients.

Materials and Methods

Study Design

This was a prospective observational study conducted on patients admitted with sepsis in the ICU of a tertiary care teaching hospital in North India from March 2020 to December 2020.

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Sample Size Calculation

The study of Narvaez et al.[3] observed that the incidence of sepsis-induced cardiomyopathy was 22.8%. Taking this value as reference, the minimum required sample size with 10% margin of error and 5% level of significance was 68 patients. To reduce the margin of error, the total sample size taken was 100.

Formula used:

$$N \geq (i(1-i))/(ME/Z_{\alpha})^2$$

where Z_{α} is the value of Z at two-sided alpha error of 5%, *ME* is the margin of error, and *i* is the incidence rate.

Inclusion Criteria

- Patients aged 18 years and above
- Patient having sepsis defined as per 2016 sepsis-3 guidelines[1]
- Patients with normal echocardiography at the time of admission

Exclusion Criteria

Patients were excluded if they had any of the following criteria:

- Patients with pre-existing left ventricular (LV) dysfunction based on clinical history and previous echocardiography findings
- Patients without known LV dysfunction but clinical and baseline investigations suggestive of pre-existing cardiac disease
- Patients with abnormal echocardiogram at the time of admission
- Patients admitted with primary cardiac illness
- History of uncontrolled hypertension
- Absence of sinus rhythm such as atrial fibrillation, atrial flutter, any type of atrial-ventricular block, presence of pacemaker, etc.
- Pregnant patients
- Patients with poor transthoracic ECHO window
- Patients who left hospital or died before the second ECHO, i.e., 48–72 hours window
- Patients who developed acute coronary syndrome at any point of ICU or hospital stay

Methodology

After obtaining a written informed consent, in patients with sepsis, baseline characteristics like age, sex, personal history such as smoking, obstructive airway disease, diabetes mellitus, hypertension, alcoholism, opioid abuse, and site of infection were compared. Prognostic markers like Sequential Organ Failure Assessment (SOFA), Acute Physiological and Chronic Health Evaluation II (APACHE II) score, and lactate levels were compared with the worst documented value in the first 24 hours of admission. Index ECHO was done within first 24 hours of admission in ICU and another ECHO was performed after 48–72 hours to establish LV dysfunction (systolic or diastolic). Mortality and length of ICU stay was compared in both groups of patients, i.e., patients without LV dysfunction (group I) or with LV dysfunction (group II). Infection site documentation was done after reporting any sign of infection on imaging like chest X-ray, CT scans, ultrasonography, etc., or confirmation of growth of organism on blood, fluid, or tissue culture.

Statistical Analysis

The presentation of the categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the mean ± SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data were not normal, we used nonparametric tests. The following statistical tests were applied for the results:

- The comparison of the variables which were quantitative and not normally distributed in nature were analyzed using Mann-Whitney Test (for two groups) and Kruskal-Wallis test (for more than two groups), and independent *t*-test was used for comparison of normally distributed data between two groups.
- The comparison of the variables which were qualitative in nature were analyzed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. A *p*-value of less than 0.05 was considered statistically significant.

Results

The mean age in group I was 57.02 ± 14.47 years while in group II it was 58.64 ± 16.69. There were 27 females (31.40%) and 59 males (68.60%) in group I and 7 females (50%) and 7 males (50%) in group II. Table 1 lists all the demographic characteristics of the study subjects. Both the groups were comparable in terms of past medical history (Table 2) and infection site (Table 3). Diabetes mellitus was the most common comorbid condition in both the groups. The most common site of infection was the lung (29.07%)

Table 1: Comparison of baseline characteristics between patients without and with cardiac dysfunction

Baseline characteristics	*Without LV dysfunction (n = 86) group I*	*With LV dysfunction (n = 14) group II*	*Total*	*p value*
Age (years)				
Mean ± SD	57.02 ± 14.47	58.64 ± 16.69	57.25 ± 14.72	
Median (25th–75th percentile)	60 (47–67)	62.5 (40–73)	60 (46–68)	0.637†
Range	20–81	35–78	20–81	
Gender				
Female	27 (31.40%)	7 (50%)	34 (34%)	0.173§
Male	59 (68.60%)	7 (50%)	66 (66%)	
Body mass index (kg/m^2)				
<18.5	1 (1.16%)	1 (7.14%)	2 (2%)	
18.5–24.99	39 (45.35%)	5 (35.71%)	44 (44%)	0.426‡
25–29.99	29 (33.72%)	5 (35.71%)	34 (34%)	
≥30	17 (19.77%)	3 (21.43%)	20 (20%)	
Mean ± SD	25.7 ± 3.54	25.73 ± 4.03	25.7 ± 3.59	
Median (25th–75th percentile)	25.35 (23.45–28.1)	25.9 (24.2–28.3)	25.4 (23.55–28.1)	0.975*
Range	18.2–32.8	18.2–32	18.2–32.8	

*Independent *t*-test; †Mann-Whitney test; ‡Fisher's exact test; §Chi-square test

Table 2: Comparison of past medical history between patients without and with cardiac dysfunction

Past medical history	*Group I*	*Group II*	*Total*	*p value*
No significant history	21 (24.42%)	2 (14.29%)	23 (23%)	
Alcoholic	6 (6.98%)	2 (14.29%)	8 (8%)	
Chronic kidney disease	8 (9.30%)	1 (7.14%)	9 (9%)	
Chronic liver disease	10 (11.63%)	0 (0%)	10 (10%)	
Chronic obstructive airway disease	3 (3.49%)	0 (0%)	3 (3%)	
Stroke	3 (3.49%)	0 (0%)	3 (3%)	
Diabetes mellitus	27 (31.40%)	5 (35.71%)	32 (32%)	
Hypertension	1 (1.16%)	1 (7.14%)	2 (2%)	
Hypothyroid	1 (1.16%)	0 (0%)	1 (1%)	
Opium addiction	4 (4.65%)	1 (7.14%)	5 (5%)	
Psychiatry	0 (0%)	2 (14.29%)	2 (2%)	
Other thyroid illness	2 (2.33%)	0 (0%)	2 (2%)	
Total	86 (100%)	14 (100%)	100 (100%)	0.127‡

‡Fisher's exact test

Table 3: Comparison of infection site between patients without and with cardiac dysfunction

Infection site	*Group I*	*Group II*	*Total*	*p value*
Abdomen	11 (12.79%)	0 (0%)	11 (11%)	
Blood	9 (10.47%)	2 (14.29%)	11 (11%)	
Bone	2 (2.33%)	0 (0%)	2 (2%)	
Brain	14 (16.28%)	0 (0%)	10 (14%)	
Lung	25 (29.07%)	7 (50%)	32 (32%)	
Pancreas	3 (3.49%)	0 (0%)	3 (3%)	
Skin	1 (1.16%)	0 (0%)	1 (1%)	
Spine	1 (1.16%)	1 (7.14%)	2 (2%)	
Soft tissue	6 (6.98%)	1 (7.14%)	7 (7%)	
Renal infections except urinary tract infection	2 (2.33%)	0 (0%)	2 (2%)	
Urinary tract infection	12 (13.95%)	3 (21.43%)	15 (15%)	
Total	86 (100%)	14 (100%)	100 (100%)	0.573‡

‡Fisher's exact test

followed by the urinary tract (13.95%) and abdomen (12.79%) in group I. In group II, the most common site of infection was lung (50%) followed by urinary tract (21.43%) and blood (14.29%). The mean SOFA score in group I was 6.55 ± 3.5 and 9.14 ± 3.06 in group II, which was statistically significant ($p = 0.013$). The mean APACHE II score was 13.73 ± 5.74 in group I and 18.86 ± 6.02 in group II ($p = 0.007$). Figure 1 shows comparison of SOFA and APACHE II score between groups. Mean lactate was 2.69 ± 1.4 mmol/L in group I and 3.46 ± 2.08 mmol/L in group II (*p*-value: 0.174). The average days of mechanical ventilation in group I were 2.41 ± 3.82 and 4.43 ± 4.27 in group II (p value = 0.034). The number of patients without septic shock during study period was 38 (44.19%) in group I and 4 (28.57%) in group II ($p = 0.384$). Incidence of all-cause ICU mortality was 11 (12.79%) in group I and 3 (21.43%) in group II ($p = 0.409$). Mean duration of ICU stay was 8.26 ± 4.41 days in group I and 13.21 ± 6.83 days in group II.

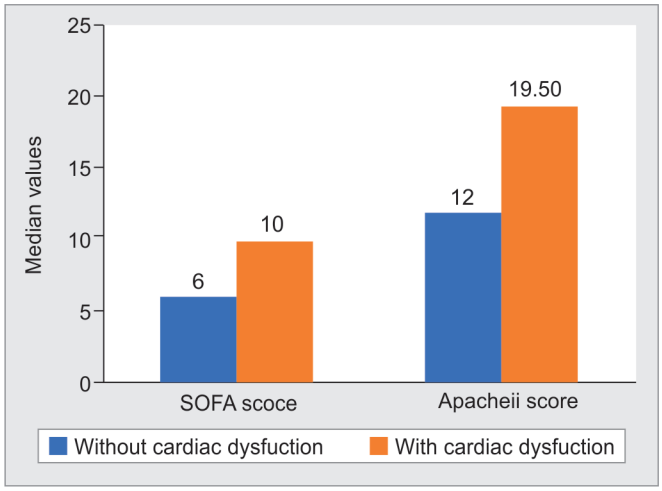

Fig. 1: Graphical presentation showing comparison of SOFA and APACHE II score between patients without and with cardiac dysfunction

Table 4: Comparison of echocardiography parameters after 48 hours between patients without and with left ventricular dysfunction

Echocardiography parameters after 48 hours	*Without LV dysfunction (n = 86) group I*	*With LV dysfunction (n = 14) group II*	*Total*	*p value*
Diastolic grade				
No diastolic dysfunction	86 (100%)	6 (42.86%)	92 (92%)	<.0001‡
Grade I	0 (0%)	0 (0%)	0 (0%)	
Grade II	0 (0%)	3 (21.43%)	3 (3%)	
Grade III	0 (0%)	5 (35.71%)	5 (5%)	
LVEF (%)				
Mean ± SD	58.26 ± 2.4	35.71 ± 9.58	55.1 ± 8.88	<.0001†
Median (25th–75th percentile)	60 (55–60)	35 (30–40)	60 (55–60)	
Range	55–60	25–60	25–60	

†Mann-Whitney test; ‡Fisher's exact test

The incidence of left ventricular dysfunction was 14%. Mean left ventricular ejection fraction after 48–72 hours of ICU admission in group I was 58.26 ± 2.4% and 35.71 ± 9.58% in group II. There were 86 (100%) patients without diastolic dysfunction in group I and 6 (42.86%) in group II. There were three (21.43%) and five (35.71%) patients with grade II and grade III diastolic dysfunction, respectively, in group II patients. No patient in either group had grade I diastolic dysfunction. Table 4 shows comparison of echocardiography parameters after 48 hours between patients without and with cardiac dysfunction. Distribution of LV dysfunction is shown graphically in Figure 2. There were six (42.86%) patients with isolated systolic dysfunction, one (7.14%) patient with isolated diastolic dysfunction, and seven (50.00%)

patients with combined systolic and diastolic dysfunction. There were 13 patients who developed systolic dysfunction at 48 hours of admission. Of these, two (15.38%) died during follow-up. Of the remaining 11 patients, 9 (69.38%) had complete recovery of systolic dysfunction and 2 (15.38%) had persistent systolic dysfunction. There were eight patients who developed diastolic dysfunction at 48 hours of ICU admission. Of these, three (37.50%) died during follow-up. Of remaining five patients, four (50.0%) had complete reversal and one (12.50%) had persistent diastolic dysfunction at the time of discharge. There was no ICU mortality in isolated systolic dysfunction patients, 100% ($n = 1$) mortality in isolated diastolic dysfunction, and 28.57% ($n = 2$) mortality in combined dysfunction ($p = 0.154$). There was no hospital mortality in isolated systolic dysfunction patients, 100% ($n = 1$) mortality in isolated diastolic dysfunction, and 28.57% ($n = 2$) mortality in combined dysfunction. The mean duration of ICU stay was 13 ± 7.27 in isolated systolic dysfunction, 18 days in isolated diastolic dysfunction, and 12.71 ± 7.27 days in combined dysfunction. The mean duration of hospital stay was 16.67 ± 8.16 days in isolated systolic dysfunction, 18 days in isolated diastolic dysfunction, and 17.57 ± 10.53 days in combined dysfunction. Table 5 shows association of outcome with left ventricular dysfunction.

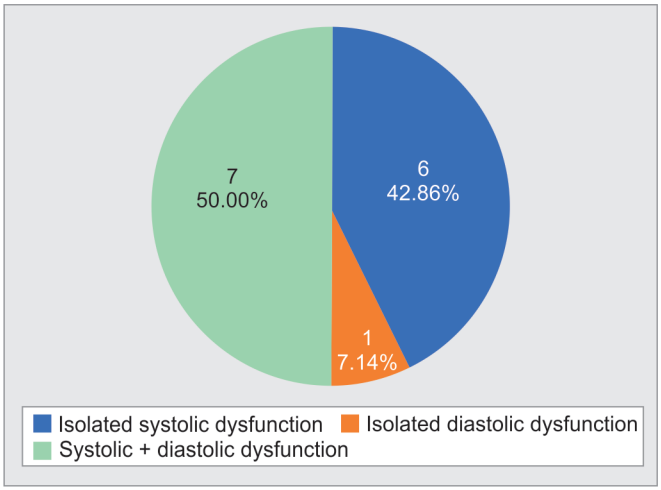

Fig. 2: Graphical presentation showing distribution of LV dysfunction among patients of group II

Discussion

There has been significant advancement in the treatment of sepsis and septic shock, but it remains a major cause of morbidity and mortality. SICM is an increasingly recognized entity and no gold standard diagnostic criteria exist for diagnosis of SICM. A recent review article by L'Heureux et al. in 2020–2021 laid down a few fundamental features of SICM.[4] These included:

- Acute and reversible within 7–10 days
- Global, biventricular dysfunction (systolic and diastolic) with reduced contractility
- Left ventricular dilatation
- Diminished response to fluid resuscitation and catecholamines
- Absence of acute coronary syndrome as etiology

As per this definition, the patient must survive the event to document the reversibility of dysfunction. The incidence of SICM in our study was 14%. Narvaez et al.[3] studied the incidence of SICM in 57 consecutive patients and reported a higher incidence of 22.8%. The mean left ventricular ejection fraction (LVEF) was 34 ± 10.6% within the first 24 hours of admission, with complete recovery in survivors. The mean LVEF in our study was similar (35.71 ± 9.58%). This study by Narvaez et al. considered the first echocardiography as the basis of diagnosis of SICM so the pre-existent LV dysfunction could not be ruled out. Further, they did not include diastolic dysfunction as the inclusion criteria for the diagnosis of SICM. Another recent study by Hanumanthu et al.

Table 5: Association of clinical outcome with left ventricular dysfunction

Outcome	*Isolated systolic dysfunction (n = 6)*	*Isolated diastolic dysfunction (n = 1)*	*Systolic + diastolic dysfunction (n = 7)*	*Total*	*p value*
ICU mortality					
No	6 (100%)	0 (0%)	5 (71.43%)	11 (78.57%)	0.154‡
Yes	0 (0%)	1 (100%)	2 (28.57%)	3 (21.43%)	
Hospital mortality					
No	6 (100%)	0 (0%)	5 (71.43%)	11 (78.57%)	0.154‡
Yes	0 (0%)	1 (100%)	2 (28.57%)	3 (21.43%)	
Duration of ICU stay (days)					
Mean ± SD	13 ± 7.27	18 ± 0	12.71 ± 7.27	13.21 ± 6.83	
Median (25th–75th percentile)	12.5 (7.25–17)	18 (18–18)	10 (7.5–16)	12.5 (6.75–18)	0.681¶
Range	5–24	18–18	6–26	5–26	
Duration of hospital stay (days)					
Mean ± SD	16.67 ± 8.16	18 ± 0	17.57 ± 10.53	17.21 ± 8.78	
Median (25th–75th percentile)	16 (10.5–20)	18 (18–18)	14 (10–22.5)	15 (10–20.25)	0.823¶
Range	8–30	18–18	9–35	8–35	

‡Fisher's exact test; ¶Kruskal-Wallis test

studied 168 patients with septic shock.[5] They followed the findings of index echocardiography within 72 hours of admission and were considered as SICM if they had a reversible decline in the ejection fraction of more or equal to 10%. Incidence of SICM in their study was 9.5% with the mean LVEF of 25%. This study characteristically considered reversibility as the inclusion criteria for 42 SICM patients. They included a large sample size; however, as it was a retrospective data analysis, they could not firmly exclude pre-existing LV dysfunction on the basis of previous history and echocardiography findings. They did not include isolated diastolic dysfunction as criteria for diagnosing SICM either. This study included patients with septic shock only. However, this was not the case in our study as we included all patients with sepsis irrespective of presence or absence of shock. Many other studies including a study by Li et al.[6] conducted a retrospective analysis and reported an incidence of 18.8%. A wide range of incidence rate can be attributed to the lack of any consensus definition of SICM. Another explanation could be the varied timing of echocardiography done for the diagnosis, as examination findings may vary at different point of time either because of the reversibility of infective process or the use of vasopressors like norepinephrine. The baseline characteristics like age, sex, and body mass index were comparable in patients with or without LV dysfunction. The study subjects in both the groups of our study were having the lung infection in majority and the result was not statistically significant. We could not establish any linear relationship of site of infection with SICM with present data.

A study by Sato et al.[7] showed a higher SOFA (median 10 vs 7) and APACHEII scores (median 27 vs 21) in patients with SICM versus without SICM. Higher APACHE II and SOFA scores at the time of admission were associated with a higher incidence of SICM. Havaldar et al.[8] concluded that Mitral annular pansystolic excursion (MAPSE) APACHE II score combined is a good predictor of mortality. Another similar study by Bergenzaun et al.[9] studied 50 patients prospectively and concluded that MAPSE and SOFA scores are good predictors of outcome in shock patients. The results of our study were comparable to previous studies. The mean lactate was higher in SICM group; however, it was not statistically significant. This is comparable to other studies. Li Yuting et al.[6] concluded lactate levels >4 mmol/L at the time of admission as an independent risk factor for SICM.

Average days of mechanical ventilation were 4.43 ± 4.27 in SICM patients. Incidence of septic shock was 71.43% in patients with LV dysfunction. However, the difference was not statistically significant. All-cause ICU mortality was 21.43% in patients with SICM and average length of stay in the ICU was 12.5 days (6.75–18). Length of hospitalization was longer and statistically significant ($p = 0.007$) as compared to patients with normal LV function. Sato et al.[7] reported an average length of ICU stay of 8 days (6–20) and in-hospital mortality of 24.1% in SICM patients which is comparable to our study. Length of stay in the ICU is influenced by multiple factors such as varied hospital policies, facilities of monitoring in wards, primary disease, complications, monitoring of therapy, etc. There is lack of data available on length of stay in the ICU in SICM patients especially from India.

In our study we had six (42.8%) patients of isolated systolic dysfunction, one (7.14%) patient of isolated diastolic dysfunction, and seven (50%) patients with combined systolic and diastolic dysfunction. Of the total 14 patients, 2 patients died were having combined systolic and diastolic dysfunction and 1 patient of isolated diastolic dysfunction as depicted in Table 5. There was 100% recovery in isolated systolic dysfunction. Earlier studies by Parker et al.[10] suggested the occurrence of septic cardiomyopathy as protective as 10 out of the 13 survivors had LVEF of 40%. Other recent studies have shown worse outcomes. The relationship between systolic dysfunction and outcome is still not clearly defined. Landesberg et al.[11] reported an incidence of isolated diastolic dysfunction 38%, combined systolic and diastolic dysfunction 14.1%, and isolated systolic dysfunction 9.1%. This study reported worse outcomes in patients with SICM. Another study by Sturgess et al.[12] concluded diastolic dysfunction as an independent predictor of mortality better than cardiac biomarkers.

We have shown the incidence of SICM, and its presence leads to worse outcomes in our study. All patients were studied by transthoracic echocardiography. As echocardiogram is considered as "point of care" test for ICU patients and with a modest learning curve, it can provide valuable information regarding myocardium status and treatment modifications need to be done by intensivists.

Prognostic scores in the ICU like SOFA and APACHEII already exist and provide valuable information regarding predictive outcome of patients. Echocardiography, which is available bedside, can provide valuable information about the myocardium status. More research is needed to consider it as an independent predictor of mortality and include it in various ICU prognostic scores. These imaging techniques and derived parameters may prove fruitful as dynamic variables for therapy modification.

Highlights

This is the first study from India that has evaluated incidence and outcome of SICM. We have used echocardiography as standard for the diagnosis of LV dysfunction (systolic and diastolic). We have excluded any pre-existing pathology of the myocardium by echocardiography before considering them as a part of study. Furthermore, the parameters used to assess systolic and diastolic dysfunction are easily done on bedside and are reproducible.

Limitations of Study

This study being a single center study and the sample size was small so findings cannot be applied to general population. All observations were collected by a single observer. Any patient developed LV dysfunction after 72 hours of admission was not included in the study. We could not study the impact of different therapeutic interventions on ECHO findings over a period of time. During hospitalization period in patients with global left ventricular dysfunction, we could not definitely rule out the evidence of acute coronary syndrome (Type II MI)[13] as coronary angiography was not performed. However, best efforts were done on the basis of clinical, ECG, and echocardiographic findings to rule out myocardial infarction.

Conclusions

After going through various aspects of the study, we may conclude the following:

- Sepsis-induced cardiomyopathy in intensive care unit is quite prevalent and clinically significant
- SICM patients have higher SOFA and APACHE II scores at the time of admission
- All-cause ICU mortality and length of stay in ICU are prolonged in patients with SICM

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