

APACHE II Score, Rather Than Cardiac Function, May Predict Poor Prognosis in Patients With Stress-Induced Cardiomyopathy

Byung-Hyun Joe¹, Uk Jo¹, Hyun-Soo Kim¹,
Chang-Bum Park¹, Hui-Jeong Hwang¹,
Il-Suk Sohn¹, Eun-Sun Jin¹, Jin-Man Cho¹,
Jeong-Hwan Park², and Chong-Jin Kim¹

¹Department of Internal Medicine, Kyung-Hee University, School of Medicine, Seoul; ²Department of Cardiology, Incheon Sarang Hospital, Incheon, Korea

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Address for Correspondence:
Chong-Jin Kim, MD
Department of Internal Medicine, Kyung-Hee University, School of Medicine, 26 Kyungheedaero, Dongdaemun-gu, Seoul 130-701, Korea
Tel: +82.2-440-6106, Fax: +82.2-442-6638
E-mail: chongjinkim0316@yahoo.co.kr

While the disease course of stress-induced cardiomyopathy (SIC) is usually benign, it can be fatal. The prognostic factors to predict poorer outcome are not well established, however. We analyzed the Acute Physiology And Chronic Health Evaluation (APACHE) II score to assess its value for predicting poor prognosis in patients with SIC. Thirty-seven consecutive patients with SIC were followed prospectively during their hospitalization. Clinical factors, including APACHE II score, coronary angiogram, echocardiography and cardiac enzymes at presentation were analyzed. Of the 37 patients, 27 patients (73%) were women. The mean age was 66.1 ± 15.6 yr, and the most common presentation was chest pain (38%). Initial echocardiographic left ventricular ejection fraction (EF) was $42.5\% \pm 9.3\%$, and the wall motion score index (WMSI) was 1.9 ± 0.3 . Six patients (16%) expired during the follow-up period of hospitalization. Based on the analysis of characteristics and clinical factors, the only predictable variable in prognosis was APACHE II score. The patients with APACHE II score greater than 20 had tendency to expire than the others ($P = 0.001$). Based on present study, APACHE II score more than 20, rather than cardiac function, is associated with mortality in patients with SIC.

Key Words: APACHE II Score; Cardiac Function; Stress-Induced Cardiomyopathy

INTRODUCTION

Stress-induced cardiomyopathy (SIC) typically presents as transient cardiac dysfunction with unique apical ballooning (1). Management is generally supportive, and, because the cardiac dysfunction at presentation is almost transient and reversible, it is reasonably treated with standard medication for left ventricular systolic dysfunction (2). Although the prognosis for SIC is usually favorable, it can be fatal in up to 8% of hospitalized cases (3-6). In spite of the possibility of death, little effort has been made to identify predictive factors for poor prognosis in SIC.

The Acute Physiology And Chronic Health Evaluation (APACHE) II score is a well-known disease severity index for hospitalized adults that has a solid relationship with predicting the mortality of critically ill patients (7). We analyzed the value of the APACHE II score for predicting poor prognosis in hospitalized patients with SIC.

MATERIALS AND METHODS

Study patients

Between June 2006 and October 2010, 3,100 patients were seen in our institutions with suspected acute coronary syndrome (ACS). Of these, 37 patients fulfilled the following criteria (1, 8) for SIC: 1) older than 18 yr; 2) transient akinesia/dyskinesia be-

yond a single major coronary artery vascular distribution; 3) absence of significant coronary artery disease upon coronary angiogram (CAG) and 4) the presence of definite antecedent physical or mental trigger factors, identified by the attending physicians. No patients had a preexisting cardiomyopathy, intracranial bleeding, or pheochromocytoma. We applied ergonovine echocardiography to all patients diagnosed with SIC to rule out coronary vasospasm within two days after CAG, and there was no patient with positive finding on the test.

Clinical assessment

We reviewed medical records for chief complaint, smoking history, and co-morbidities. We also investigated the presence of physical stress (septic shock, surgery, or intubation, etc.) or mental stress (anger management issues, death of loved one, or interpersonal conflicts, etc.). Body mass index (BMI), level of cardiac enzymes (creatinine kinase MB fraction, CK-MB; troponin-I), high sensitive C-reactive protein (hsCRP), systolic and diastolic blood pressure (BP), heart rate (HR), and Killip class were evaluated at the time of diagnosis for SIC.

Standardized electrocardiography (ECG) and echocardiographic studies were examined at the time of diagnosis and one or two weeks later to confirm the status of recovery. If regional wall motion abnormality (RWMA), observed on the first echocardiogram, was not definitely improved on the second one, a

third echocardiogram was performed a few weeks after the second one. All patients showed resolution of RWMA. In echocardiography studies, we measured the left ventricular ejection fraction (LVEF) and regional wall motion score index (WMSI) to determine the severity of cardiac dysfunction. The LVEF was measured using the modified Simpson's method, and WMSI was calculated using all views, including the parasternal short axis and long axis and apical four chamber views. We classified ventricular ballooning into two categories, typical and atypical apical ballooning, based on the location of ballooning. Standard 2-dimensional and Doppler echocardiography was performed using a 2.5 MHz transducer with harmonic imaging. We used a Philips iE33 system (Philips Medical Systems, USA) for patients admitted to the general ward and ViVid I (GE Ultrasound, Horten, Norway) for patients in the intensive care unit. We calculated the APACHE II score, with the worst physiologic parameters during the first 24 hr after the event, to measure the clinical severity of each patient's objective physical condition upon presentation. APACHE II is composed of vital signs, serum creatinine level, oxygen pressure in arterial blood gas analysis, blood acidity, degree of leukocytosis, level of hematocrit, severity of electrolyte imbalance, Glasgow coma scale (GCS; representing patient mental status), and age of patient, each recorded at the most severe level in 24 hr (7).

Statistical analysis

All statistical analyses were performed using SPSS software (version 18.0, SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean \pm SD or mean with interquartile ranges. Frequencies and percentages were used to describe categorical variables and were compared based on the result of ROC curve analysis with Fisher's exact test. Continuous variables of the two groups (Group I and II, divided by APACHE II score 20) were analyzed and compared using the student T-test. To estimate the sensitivity and specificity of the APACHE II score for predicting death, ROC curve analysis was done. Kaplan-Meier survival analysis was performed to estimate the mortality according to survival period. Statistical significance was defined as $P < 0.05$ in all of the analyses.

Ethics statement

The institutional review board of Kyung-Hee University Hospital approved the protocol of this prospective SIC registry (KH-NMC IRB 2011-026). The data were retrospectively reviewed and informed consents were provided by all patients.

RESULTS

Parameters associated with the outcome

To find out the variable which is able to predict the outcomes of patients exceedingly, we analyzed the baseline characteristics

and the clinical factors of patients, including the cardiac functions, in terms of LVEF and WMSI, cardiac enzymes, such as CK-MB and TnI, and APACHE II score based on survival (Table 1). And we figured out that APACHE II score was significantly different between the dead and the survived among multiple clinical variables (22.5 ± 1.6 vs 11.7 ± 6.2 , P value = 0.001). Even though SIC is a kind of cardiomyopathy, the abnormalities in ECG, the shape of apical ballooning, the heart functions and cardiac markers did not show any significant difference between two groups. And more male patients were included in the death group than survival group (67% vs 19%, P value = 0.035). Based on this result, we carried out receiver operating characteristics (ROC) curve analysis to confirm the availability of APACHE II score as a prognostic marker. According to the result of ROC curve analysis we divided the patients into group I (APACHE II score > 20) and group II (APACHE II score ≤ 20), because APACHE II score 20 showed higher sensitivity and specificity than any other scores (Fig. 1). The comparison between group I and group II was done to find out any other clinical factors, which is related to the prog-

Table 1. The comparisons of characteristics and clinical factors based on survival

Parameters	Survival (n = 31)	Death (n = 6)	P value
Age (yr)	65.4 \pm 15.8	69.7 \pm 15.6	0.546
Body mass index (kg/m ²)	21.5 \pm 3.5	21.2 \pm 3.2	0.850
Gender			0.035
Male, No. (%)	6 (19)	4 (67)	
Female, No. (%)	25 (81)	2 (33)	
Smoking			0.245
Never, No. (%)	27 (87)	4 (67)	
Current, No. (%)	4 (13)	2 (33)	
Stress type			0.561
Physical, No. (%)	25 (81)	6 (100)	
Mental, No. (%)	6 (19)	0 (0)	
Presenting symptoms/signs			0.258
Chest pain, No. (%)	13 (42)	1 (17)	
Dyspnea, No. (%)	7 (23)	4 (67)	
Altered mentality, No. (%)	5 (16)	1 (17)	
Hypotension, No. (%)	5 (16)	0 (0)	
Killip class			0.195
Class I, No. (%)	22 (71)	2 (34)	
Class II, No. (%)	6 (19)	3 (50)	
Class III, No. (%)	3 (10)	1 (17)	
Class IV, No. (%)	0 (0)	0 (0)	
Electrocardiographic abnormalities			0.470
T wave inversion, No. (%)	14 (45)	2 (34)	
ST elevation, No. (%)	5 (16)	1 (17)	
ST depression, No. (%)	5 (16)	0 (0)	
Apical ballooning			0.561
Typical, No. (%)	25 (81)	6 (100)	
Atypical, No. (%)	6 (19)	0 (0)	
CK-MB (ng/mL)	16.7 \pm 54.6	15.6 \pm 25.5	0.961
Troponin-I (ng/mL)	3.3 \pm 7.7	2.3 \pm 3.3	0.761
hsCRP (mg/L)	33.8 \pm 46.7	26.0 \pm 0.0	0.877
APACHE II score	11.7 \pm 6.2	22.5 \pm 1.6	0.001
LVEF (%)	42.9 \pm 9.5	40.5 \pm 8.5	0.563
WMSI	1.8 \pm 0.4	2.0 \pm 0.3	0.244

Mean \pm SD. CK-MB, creatine kinase-MB; hsCRP, high sensitive C-reactive protein; APACHE II, acute physiology and chronic health evaluation II; LVEF, left ventricular ejection fraction; WMSI, wall motion score index.

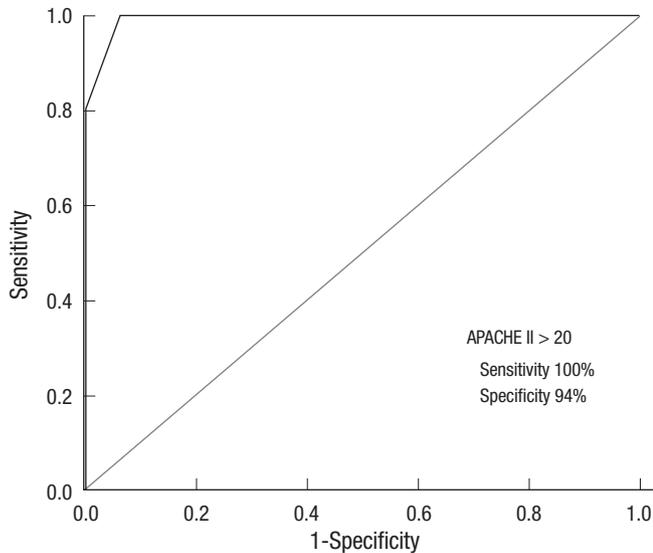


Fig. 1. ROC curve of APACHE II score in predicting death in patients with stress-induced cardiomyopathy.

nosis, as described beneath.

Baseline characteristics

The baseline characteristics of patients are presented in Table 2. The mean age was 66.1 ± 15.6 yr old, and the mean BMI was 21.5 ± 3.4 kg/m². Twenty-seven (73%) of 37 patients were female, and 31 (84%) were non-smokers. One third of the subjects had comorbidities, with cancer being most common ($n = 6$, 16%). Except for a few comorbidities, such as cancer or chronic obstructive pulmonary disease (COPD), most of them were not related to SIC itself.

Clinical characteristics and factors associated with survival

The comparisons of clinical characteristics of the subjects are presented in Table 3. Physical stress, such as sepsis, surgery, or acidosis, was reported more often than mental stress in both groups (100% vs 0% in group I and 79% vs 21% in group II, respectively). Even though not described in the tables, operation was largest number of physical stress, followed by severe pneumonia, acute pyelonephritis, and acute exacerbation of COPD. And The most frequent initial symptom on presentation was chest pain ($n = 14$, 38%), followed by dyspnea, altered mentality and hypotension, with dyspnea in group I and chest pain in group II being the most common respectively. ECG on presentation showed no remarkable arrhythmia. Among ECG abnormalities, T wave inversion was most common ($n = 16$, 43%), followed by ST elevation and ST depression. Corrected QT interval (QTc) was prolonged at the time of diagnosis (485.3 ± 55.5 ms). Serum cardiac enzymes were elevated in all patients, and were not statistically different between groups. In the echocardiographic study at the time of diagnosis, mean LVEF was $42.5\% \pm 9.3\%$, and mean WMSI was 1.9 ± 0.3 and those are not significantly different be-

Table 2. Baseline characteristics of patients

Parameters	Total (n = 37)	Group I (n = 8)	Group II (n = 29)	P value
Age (yr)	66.1 ± 15.6	68.5 ± 13.4	65.4 ± 16.3	0.627
Body mass index (kg/m ²)	21.5 ± 3.4	21.8 ± 3.1	21.4 ± 3.6	0.772
Female, No. (%)	27 (73)	4 (50)	23 (79)	0.174
Smoking				0.591
Never, No. (%)	31 (84)	6 (75)	25 (86)	
Current, No. (%)	6 (16)	2 (25)	4 (15)	
Comorbidities				0.815
None, No. (%)	13 (35)	2 (25)	11 (38)	
Cancer, No. (%)	6 (16)	2 (25)	4 (14)	
Diabetes mellitus, No. (%)	3 (8)	1 (13)	2 (7)	
COPD, No. (%)	3 (8)	1 (13)	2 (7)	
Hypertension, No. (%)	2 (5)	0 (0)	2 (7)	
Hyperthyroidism, No. (%)	1 (3)	0 (0)	1 (3)	
Liver cirrhosis, No. (%)	1 (3)	1 (13)	0 (0)	
ESRD, No. (%)	1 (3)	0 (0)	1 (3)	

Mean \pm SD. COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease.

tween two groups (P value = 0.573 and 0.516, respectively). There was no significant difference in the proportion of typical ballooning between groups, although all patients in group I had typical ballooning at presentation (100% vs 79%, P value = 0.305). ROC curve indicated a high sensitivity (100%) and specificity (94%) of the APACHE II score for predicting death, with a threshold score of greater than 20 (Fig. 1). The APACHE II score at diagnosis was significantly higher in group I as compared to group II (22.1 ± 1.6 vs 11.0 ± 5.9 , $P = 0.001$). Among multiple components of the APACHE II score, only maximal heart rate and Glasgow coma scale were higher in group I. Six in group I and no one in group II died during hospitalization, all with physical stress and 4 of them were male (Table 4). Their mean APACHE II score and LVEF were 22.5 (range 21-25) and 40.5% (range 26%-49%), respectively. Mean time to death from diagnosis was 25 days (range 2-111 days). Kaplan-Meier survival curve shows significant difference in cumulative survival between two groups divided by APACHE II score 20 (Fig. 2).

DISCUSSION

In this prospective observational study, we could identify a few findings, as follows. First, the most frequent symptom was chest pain. This observation, similar result with another study in Korea (9), suggests that SIC should be one of the differential diagnoses for chest pain in conjunction with ACS. Second, the prevalence of SIC was much higher in women than men, even though there is no proven study about the reason of this preponderance associated with gender. The last, in spite of its old name 'broken heart syndrome', the patients were more connected with physical stress than mental stress.

We also found that the APACHE II score more than 20, rather than cardiac functions, was associated with mortality in patients

Table 3. Clinical characteristics and comparisons of two groups divided by APACHE II score 20

Parameters	Total (n = 37)	Group I (n = 8)	Group II (n = 29)	P value
Stress type				0.305
Physical, No. (%)	31 (84)	8 (100)	23 (79)	
Mental, No. (%)	6 (16)	0 (0)	6 (21)	
Presenting symptoms/signs				0.496
Chest pain, No. (%)	14 (38)	1 (13)	13 (45)	
Dyspnea, No. (%)	11 (30)	4 (50)	7 (24)	
Altered mentality, No. (%)	6 (16)	1 (13)	5 (17)	
Hypotension, No. (%)	5 (14)	2 (25)	3 (10)	
Killip class				0.179
Class I, No. (%)	24 (65)	3 (38)	21 (72)	
Class II, No. (%)	9 (24)	4 (50)	5 (17)	
Class III, No. (%)	4 (11)	1 (13)	3 (10)	
Class IV, No. (%)	0 (0)	0 (0)	0 (0)	
Electrocardiographic abnormalities				0.521
T wave inversion, No. (%)	16 (43)	3 (38)	13 (45)	
ST elevation, No. (%)	6 (16)	1 (13)	5 (17)	
ST depression, No. (%)	5 (14)	1 (13)	4 (14)	
Corrected QT interval (ms)	485.3 ± 55.5	482.5 ± 68.8	486.0 ± 52.7	0.877
Cardiac enzymes				
CK-MB (ng/mL)	16.5 ± 50.6	49.2 ± 103.7	7.2 ± 11.3	0.290
Troponin-I (ng/mL)	3.2 ± 7.1	6.8 ± 13.7	2.1 ± 3.5	0.368
hsCRP (mg/L)	33.1 ± 44.3	26.0 ± 0.0	33.8 ± 46.7	0.877
Echocardiogram on diagnosis				
LVEF (%)	42.5 ± 9.3	40.9 ± 7.7	43.0 ± 9.7	0.573
WMSI	1.9 ± 0.3	1.9 ± 0.3	1.8 ± 0.4	0.516
Apical ballooning				0.305
Typical, No. (%)	31 (84)	8 (100)	23 (79)	
Atypical, No. (%)	6 (16)	0 (0)	6 (21)	
APACHE II score	13.4 ± 7.0	22.1 ± 1.6	11.0 ± 5.9	0.001
Blood temperature (°C)	36.8 ± 0.6	36.7 ± 0.3	36.9 ± 0.6	0.403
Mean arterial blood pressure (mmHg)	81.9 ± 20.3	77.9 ± 23.5	83.0 ± 19.7	0.535
Maximum heart rate (rate/min)	106.2 ± 26.6	126.6 ± 16.9	100.6 ± 26.2	0.012
Maximum respiratory rate (rate/min)	25.7 ± 6.0	28.4 ± 6.8	24.9 ± 5.7	0.155
Oxygenation score	0.8 ± 1.2	1.0 ± 1.6	0.7 ± 1.1	0.536
Acidity score	0.8 ± 1.1	1.3 ± 1.3	0.7 ± 1.1	0.218
Serum sodium (mEq/L)	138.7 ± 4.7	137.9 ± 6.1	138.9 ± 4.4	0.596
Serum potassium (mEq/L)	3.8 ± 0.7	3.6 ± 0.6	3.8 ± 0.7	0.435
Serum creatinine (mg/dL)	1.2 ± 1.5	1.4 ± 0.8	1.2 ± 1.7	0.791
Kidney function score	0.6 ± 1.5	1.8 ± 2.5	0.2 ± 0.8	0.133
Leukocytes (/ μ L)	11,924.3 ± 5,196.1	11,400.0 ± 4,535.3	12,069.0 ± 5,428.8	0.752
Hematocrit (%)	32.3 ± 5.3	30.0 ± 3.6	32.9 ± 5.6	0.173
Glasgow coma scale	2.2 ± 3.0	5.5 ± 3.5	1.3 ± 2.2	0.001
Age score	3.9 ± 2.1	4.4 ± 1.5	3.8 ± 2.3	0.379
Length of hospital stay from diagnosis (days)	17.1 ± 21.5	30.5 ± 35.9	13.3 ± 14.4	0.224
Death during hospitalization, No. (%)	6 (16)	6 (75)	0 (0)	0.001

Mean ± SD. APACHE II, acute physiology and chronic health evaluation II; CK-MB, creatine kinase-MB; hsCRP, high sensitive C-reactive protein; LVEF, left ventricular ejection fraction; WMSI, wall motion score index.

with SIC, even though there was no study which proposed any prognostic factors using any kind of scoring systems. Most of studies with SIC were about its epidemiology, and the studies, interested in prognostic factor, were focusing only to cardiac findings, such as EKG results or cardiac markers. Based on our results, we suggest that outcomes may depend more upon the physical conditions of the patients than the severity of the symptoms or signs of cardiac dysfunction.

To the best of our knowledge, there have been few attempts to evaluate a scoring system, like the APACHE II, for patient phys-

ical condition and SIC prognosis. We hypothesized that the APACHE II score would correlate with patient prognosis, particularly mortality, and sought to identify other factors with prognostic value. After confirmation that APACHE II score on diagnosis was related to prognosis, we also found that an APACHE II score greater than 20 had a high sensitivity (100%) and specificity (94%) for predicting in-hospital death in patients with SIC (Fig. 1).

Among the components of the APACHE II score, maximal heart rate and GCS (a marker of consciousness regardless of inotropic or sedative use) were increased more in patients who had

Table 4. Clinical characteristics of the dead patients

Patients	Gender	Age	Smoking	Comorbidities	Trigger (stress)	Killip class on diagnosis	LVEF (%)	APACHE II score	Time to death after diagnosis (days)
Case 1	Male	47	Never	None	Infectious colitis	I	49	25	6
Case 2	Male	71	Never	Liver cirrhosis	Hepatic encephalopathy	III	46	21	14
Case 3	Male	73	Current	COPD	Acute exacerbation of COPD	II	26	22	111
Case 4	Female	92	Current	Lung cancer	Lung cancer	I	40	21	8
Case 5	Male	77	Never	None	Hospital acquired pneumonia	II	46	24	9
Case 6	Female	58	Never	Breast cancer	Breast cancer with multiple metastasis	II	36	22	2

LVEF, left ventricular ejection fraction on echocardiogram; APACHE II, acute physiology and chronic health evaluation II; COPD, chronic obstructive pulmonary disease.

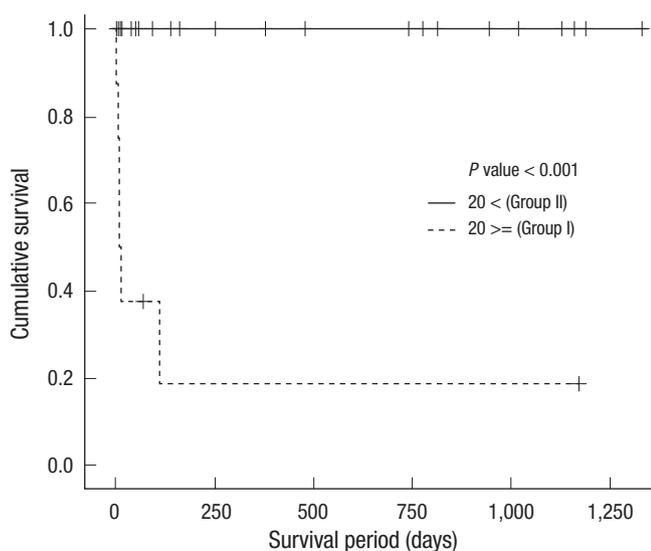


Fig. 2. Kaplan-Meier survival curve shows significant difference in cumulative survival between two groups divided by APACHE II score 20.

APACHE II score greater than 20. ECG could potentially offer information about the prognosis of SIC patients. Our findings were in agreement with previous research, however, showing no link between electrocardiographic abnormalities and poor outcome (10). Overall, we saw that the prevalence of SIC was higher in females, as expected (1, 4, 6).

There are a few limitations in our study. Despite the prospective enrollment of SIC patients, we could only offer a single center experience with a relatively small number of subjects, which was inevitable due to the low prevalence of SIC. Above this, we could not measure the relation between stress and prognosis, because there was no proven method for quantitative analysis of the physical and mental stress. And the cardiac functions were not evaluated with echocardiography in daily routine follow-up and at the time of death, nevertheless Lee et al. (11). suggested that the absence of left ventricular function recovery within a week could predict the poor outcome of patients. And the follow-up echocardiography was not done at right time, because of many reasons concerned with their refusals, short hospitalization and cost problems.

The prospective study comparing the characteristics, clinical factors and prognosis according to the threshold score of APACHE II score 20 should be performed, to confirm that it would be high sensitive and specific standard in predicting prognosis. The proper echocardiographic and cardiac marker follow-up should be considered, to make sure that the cardiac function and myocardial damages are not related to the prognosis of SIC. Given the small size of our study population, larger, prospective long-term observational studies are needed to confirm and validate these findings.

The APACHE II score is higher in SIC patients who was dead, and the score of greater than 20, rather than cardiac function, is associated with mortality. It is able to give more information to physicians, regarding to the prognosis of SIC patients.

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