Cardiac Performance by Echocardiography, Cardiovascular Biomarker, Kidney Function, and Venous Oxygen Saturation as Mortality Predictors of Septic Shock

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ABSTRAK

Latar belakang: *fungsi jantung pada pasien dengan syok septik pada tingkat sel dapat dinilai dengan mengukur tingkat troponin I dan NT Pro BNP. Saturasi oksigen vena diukur untuk mengevaluasi pengiriman dan pengambilan oksigen oleh jaringan organ. Studi kami dapat memberikan pengetahuan dan pemahaman yang lebih besar tentang patofisiologi gangguan kardiovaskular pada pasien dengan syok septik. Penelitian ini bertujuan untuk mengevaluasi peran ekokardiografi, biomarker kardiovaskular, saturasi oksigen vena dan fungsi ginjal sebagai prediktor tingkat kematian pada pasien dengan syok septik.* ***Metode:*** *ini adalah studi kohort prospektif pada pasien dengan infeksi, hipotensi (MAP <65 mmHg) dan tingkat serum laktat >2 mmol/L. Pada hari pertama dan kelima, pasien septik menjalani pemeriksaan ekokardiografi dan darah. Analisis statistik yang digunakan dalam penelitian kami meliputi uji-t atau uji Mann-Whitney untuk data numerik dan uji chi-square untuk data nominal kelompok dua variabel; sedangkan untuk analisis multivariat, kami menggunakan model Cox Regression.* ***Hasil:*** *pada 10 hari pengamatan, kami menemukan 64 (58%) pasien meninggal dan 47 (42%) pasien selamat. Usia rata-rata pasien adalah 48 (SB 18) tahun. Pasien dengan fraksi ejeksi ventrikel kiri abnormal (LVEF) memiliki risiko kematian 1,6 kali lebih besar dibandingkan dengan LVEF normal (RR 1,6; p = 0,034). Pasien dengan level troponin I yang abnormal menunjukkan risiko kematian yang lebih tinggi sebanyak 1,6 kali (RR: 1,6; p = 0,004). Pasien dengan gangguan fungsi ginjal memiliki risiko kematian 1,5 kali (RR 1,5; p = 0,024). Pasien dengan tingkat troponin I yang abnormal dan / atau gangguan fungsi ginjal menunjukkan peningkatan risiko kematian; Namun, mereka yang memiliki kadar troponin I normal dan gangguan fungsi ginjal juga menunjukkan peningkatan risiko kematian. Analisis multivariat mengungkapkan bahwa fraksi ejeksi ventrikel kiri dan level troponin I dapat berfungsi sebagai prediktor mortalitas pada pasien dengan syok septik. (HR 1,99; 95% CI: 1,099–3,956; p = 0,047 dan HR: 1,83; 95% CI: 1,049–3,215; p = 0,043).* ***Kesimpulan:*** *fraksi ejeksi ventrikel kiri dan biomarker seperti level troponin I merupakan prediktor mortalitas pada pasien syok septik.*

Kata kunci: *ekokardiografi, kematian, NT Pro BNP, syok septik, troponin I.*

ABSTRACT

Background: *cardiac function in patients with septic shock at the cellular level can be assessed by measuring troponin I and NT Pro BNP levels. Venous oxygen saturation is measured to evaluate oxygen delivery and uptake by organ tissue. Our study may provide greater knowledge and understanding on pathophysiology of cardiovascular disorder in patients with septic shock. This study aimed to evaluate the roles of echocardiography, cardiovascular biomarkers, venous oxygen saturation and renal function as predictors of mortality rate in patients with septic shock.* ***Methods:*** *this is a prospective cohort study in patients with infections, hypotension (MAP < 65 mmHg) and serum lactate level of > 2 mmol/L. On the first and fifth days, septic patients underwent echocardiography and blood tests. Statistical analysis used in our study included t-test or Mann-Whitney test for numeric data and chi-square test for nominal data of two-variable groups; while for multivariate analysis, we used Cox Regression model.* ***Results:*** *on 10 days of observation, we found 64 (58%) patients died and 47 (42%) patients survived. The mean age of patients was 48 (SD 18) years. Patients with abnormal left ventricular ejection fraction (LVEF) had 1.6 times greater risk of mortality than those with normal LVEF (RR 1.6; p = 0.034). Patients with abnormal troponin I level showed higher risk of mortality as many as 1.6 times (RR: 1.6; p = 0.004). Patients with impaired renal function had 1.5 times risk of mortality (RR 1.5; p = 0.024). Patients with abnormal troponin I level and/or impaired renal function showed increased mortality risk; however, those with normal troponin I level and impaired renal function also showed increased mortality risk. Multivariate analysis revealed that left ventricular ejection fraction and troponin I level may serve as predictors of mortality in patients with septic shock. (HR 1.99; 95% CI: 1.099 − 3.956 ; p = 0.047 and HR: 1.83 ; 95%CI: 1.049 − 3,215 ; p = 0.043).* ***Conclusion:*** *left ventricular ejection fraction and biomarkers such as troponin I level are predictors of mortality in septic shock patients.*

Keywords: *echocardiography, death, NT Pro BNP, septic shock, troponin I.*

INTRODUCTION

According to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3 Consensus) in 2016, sepsis is a life-threatening organ dysfunction due to a disorder of host regulation in response to infections. In clinical practice, organ dysfunction is usually assessed using the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) and it is defined in patients with score of ≥ 2. The mortality rate of septic patients during hospitalization is more than 10%. Septic shock is a subset of sepsis with circulatory, cellular, and metabolic abnormalities associated with mortality risk. Septic shock can be clinically identified when the patients requires vasopressor to maintain mean arterial blood pressure (MAP) of 65 mmHg or more, and their serum lactate level is greater than 2 mMol/L (>18 mg/dL) in the absence of hypovolemia. The mortality rate of patients with sepsis during treatment is more than 40%.[1]

Patients with infectious diseases and possibility of worsening condition in spite of having treatment or those with condition that may lead to sepsis can be assessed rapidly using quickSOFA (qSOFA). It uses three criteria assigning one point for (1) respiratory rate >22 breaths/minute; (2) altered mental status; or (3) blood pressure ≤100 mmHg.[2] Moreover, there are at least two of those criteria may occur together in clinical setting. Using qSOFA, cardiovascular system is assessed by measuring mean arterial pressure; however, the mean arterial pressure does not reflect cardiac function, e.g. patients with peripartum cardiomyopathy may have normal mean arterial pressure but still have reduced cardiac function.[3]

The heart works as a pump to maintain blood circulation and the blood consists of oxygen, nutrition and substrate to protect cell integrity.[1] Cardiac dysfunction can be categorized into two groups, which are systolic dysfunction and diastolic dysfunction. The assessment of systolic function is based on observation of myocardial contractility by measuring Left Ventricular Ejection Fraction for the left heart[4] and Tricuspid Annular Plane Systolic Excursion

(TAPSE) for the right heart;[5] while diastolic dysfunction or reduced compliance can be assessed using echocardiography and measuring the E/e' ratio.[6] Diastolic dysfunction will increase pulmonary capillary wedge pressure and generate pulmonary edema. Cardiac index, a hemodynamic parameter associated with cardiac performance, can be assessed by measuring the amount of blood pumped from the heart to the whole body in each minute. Cardiac output is measured by multiplication of stroke volume and heart rate in one minute. Stroke volume can be assessed by measuring Time Velocity Integral and area of aortic valves opening.[7]

Cardiac function in patients with septic shock at the cellular level can be assessed by measuring troponin I and NT Pro BNP levels. Troponin I can be found in patients with sepsis shock due to changes in permeability or the presence of micro-circular thrombosis.[8] NT Pro BNP release occurs due to myocardial stretching in patients with septic shock.[9] The amount of troponin I and NT Pro BNP in blood circulation also depend on renal function.[10] Venous oxygen saturation is measured to evaluate oxygen delivery and uptake by organ tissue.[11] It is expected that our study may provide greater knowledge and understanding on pathophysiology of cardiovascular disorder in patients with septic shock. The study was aimed to identify the roles of cardiovascular parameters in order to initiate prompt and appropriate treatment for patients with septic shock and it may also serve as a complementary aid to the clinical practice guidelines.

METHODS

Our study was an observational study with a cohort prospective design and it was conducted at Tangerang District General Hospital, in Banten Province between December 2013 and February 2016. Sampling was done consecutively until the number of samples was reached.

Subjects

Subjects included in the study were patients with sepsis shock, i.e. those with the identified infection, hypotension (MAP of <65mmHg) and serum lactate level of >2 mmol/L, who were recruited at Tangerang District Hospital. The exclusion criteria were patients with heart failure, acute coronary syndrome, heart valve disorders due to rheumatic heart disease or congenital heart disease and patients who were unable to undergo echocardiography procedures because the field of view was difficult to obtain or due to other technical aspects.

Protocol

Patients were examined on day 1, i.e. when they were first admitted to hospital; and on day 5 when the patients received treatment. The research methodology flow chart is described as follows:

Echocardiography was performed using Philip HD 15 (R). The assessment of diastolic function was carried out by evaluating the E/e' ratio according to the ASE /EACVI Guidelines and Standards Recommendation for the Evaluation of Left Ventricular Diastolic Function by Echocardiography, An Update from American Society of Echocardiography and European Association of Cardiovascular Imaging (2016).[5] The LVEF was measured using Simpson's method, which provided all four cardiac chamber views. The LVEF was calculated from the left ventricular chamber during diastole and systole following the guidelines issued by the Recommendation for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and European Association of Cardiovascular Imaging 2015.[5] The measurement of Cardiac Index (CI) was assessed by multiplying the Time Velocity Integral (TVI) and area of aorta, which was then multiplied by pulses per minute, and divided by body surface area. TAPSE was measured on four-chamber views. M-mode line was placed on the wall of tricuspid valve of the right cardiac chamber and the longitudinal systolic excursion distance was measured according to Guidelines for Echocardiographic Assessment of Right Heart in Adults issued by the American Society of Echocardiography in 2010.[5] Troponin I and NT Pro BNP levels were examined using RAMP 200 (R) and serum lactate level was measured using CobasAccutrend Plus (R). Venous oxygen saturation was assessed by blood gas analysis.

Ethics

All patients or families of patients included in the study were given oral and written explanations about the research activity and subsequently they gave their informed consent. The protocol of our study has been approved by the Medical Research Ethics Committee, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital with a reference number of 752/H2.F1/ETIK/2013 issued on December 9th, 2013.

Statistical Analysis

Data analysis was performed using SPSS program version 20.0. The obtained data were then analyzed for data normality. Hypothesis test was carried out on two variable groups using t-test for numerical data or Mann Whitney test for non-parametric data. Chi-square test was used for data on nominal group and whenever the requirements for its appropriate use had been met. Multivariate analysis was performed using Cox Regression model.

RESULTS

There were 111 study subjects consisting of 56 women and 55 men with mean age of 48 (SD 18) years. Patients were observed for 10 days. The number of patients who died were 64 (56.64%) subjects. (**Table 1**)

Table 1. Subject characteristics of patients with septic shock

Characteristics (n=111)	Total (%)
Gender	
- Male	55 (49)
- Female	56 (51)
Age, year, mean (SD)	48 (SD 18)
Infection marker / microorganism found	111 (100)
Temp > 38.3 ^{0}C or < 36 ^{0}C	61 (55)
Pulse > 90/min	83 (75)
Respiratory rate >20/min	81 (73)
Altered Mental Status	85 (77)
Leucocytes count of >12.000 or < 4000	104 (94)
Blood sugar level of > 120 mg/dL in non-DM patient	37 (433)
Mild Organ Dysfunction	14 (13)
Death	64 56.64)

Association Between Ventricular Function and Septic Shock Mortality

Low or abnormal left ventricle ejection fraction had increased the risk of mortality in patients with septic shock. (RR 1.6; 95%CI: 1.1 – 2.1; p=0.034).

There were no differences between those with abnormal and normal value of diastolic function, cardiac indexes, TAPSE in association with septic shock mortality. (**Table 2**)

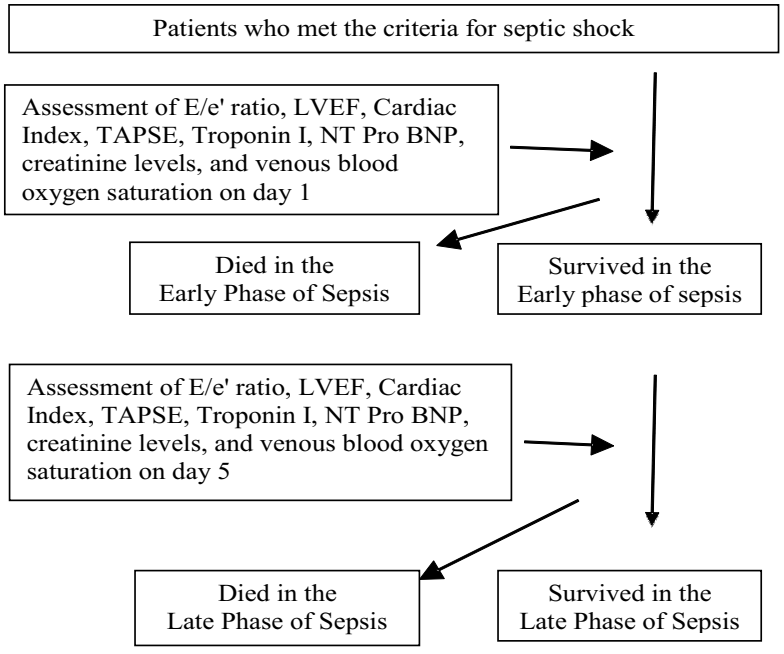

Figure 1. Flow chart of the study protocol

Association Between Cardiovascular Biomarkers, Venous Oxygen Saturation, Creatinine Levels on Day 1 and Septic Shock Mortality

The relative risk of mortality in patients with abnormal troponin I level was 1.6 and abnormal creatinine level was 1.5 (RR: 1.6; CI95%: 1.2 – 2.1; p = 0.004 and RR: 1.5; CI95%: 1.1 – 2.1; p = 0.024). The relative risk of mortality in patients between those with abnormal and normal NT Pro BNP level and venous oxygen saturation was not different. (**Table 3**)

Patients with abnormal troponin I and abnormal creatinine level had a 5.7 times greater mortality risk compared to patients with normal troponin I and creatinine levels. (RR: 5.7; CI95%: 1.7–18.5; p = 0.004). Patients with sepsis who have abnormal NT Pro BNP and abnormal creatinine levels had not been statistically proven to have greater risk of mortality.

Association Between Ventricular Function, Biomarker Cardiovascular and Time of Measurement with Death

The E/e' ratio reflecting diastolic function, left ventricle ejection fraction and cardiac indexes were not different when they were measured on day 1 and day 5 (p = 0.531; p = 0.620 and p = 0.933). The TAPSE, which demonstrated the function of right heart, was found greater when it was measured on day 5 compared to day 1 (p = 0.04).

There were no differences found regarding cardiovascular biomarkers, troponin I and NT

Table 2. Association of ventricularfunction on day 1 with septic shock mortality.

Ventricular Function	n (%)		RR (95% CI)	P value
	Death	Life		
Diastolic function (E/e') (n=95)				
- Abnormal (n=19)	10 (52.6)	9 (47.4)	0.98 (0.6 – 1.6)	0.918
- Normal (n=76)	41 (53.9)	35 (46.1)		
Left Ventricular Ejection Fraction (LVEF) (n=102)				
- Abnormal (n=15)	12 (80.0)	3 (20.0)	1.6 (1.1 – 2.1)	0.034
- Normal (n=87)	44 (50.6)	43 (49.4)		
Cardiac Index (n=97)				
- Abnormal (n=17)	7 (41.2)	10 (58.8)	0.7 (0.4 – 1.4)	0.349
- Normal (n=80)	44 (55.0)	36 (45.3)		
TAPSE (n=102)				
- Abnormal (n=15)	9 (60.0)	6 (40.0)	1.1 (0.7 – 1.8)	0.667

Table 3. Association between cardiovascular biomarkers, venous oxygen saturation, creatinine level on day 1 and septic shock mortality

Variables	n (%)		RR (95% CI)	P value
	Death	Life		
Troponin I level (n=111)				
- Abnormal (n = 38)	29 (76.3)	9 (23.7)	1.6 (1.2 – 2.1)	0.004
- Normal (n = 73)	35 (47.9)	38 (52.1)		
NT Pro BNP (n=111)				
- Abnormal (n = 104)	60 (57.7)	44 (42.3)	1.0 (0.5 – 2.0)	1.000
- Normal (n = 7)	4 (57.1)	3 (42.9)		
Venous O2 Saturation (n = 111)				
- Abnormal (n=40)	24 (60.0)	16 (40.0)	1.1 (0.8 – 1.5)	0.708
- Normal (n=71)	40 (56.3)	31 (43.7)		
Creatinine level (n=109)				
- Abnormal (n=53)	36 (67.9)	17 (32.1)	1.5 (1.1 – 2.1)	0.024
- Normal (n=56)	26 (46.4)	30 (53.6)		

Pro BNP levels between those which were measured on day 1 and day 5. (P = 0.600 and p = 0.058). There were also no different results regarding echocardiography and cardiovascular biomarkers of patients who died prior to day 5 compared to those who died after day 5.

We used the backward method for multivariate analysis. Variables with p value of less than 0.25 were involved in the analysis including LVEF, troponin I and creatinine levels and combination of abnormal troponin and creatinine levels. The multivariate analysis revealed that some variables had influence over patients' mortality and they could be used as predictors of mortality in patients with septic shock, which were left ventricle ejection fraction and troponin I level. (HR: 1.99; CI95% 1.009 − 3.956; p = 0.047 and HR 1.83; CI95% 1.049 − 3.125; p = 0.043).

DISCUSSION

The E/e' ratio of diastolic function reflects cardiac compliance. Any mean value of E/e' of >14 indicates the occurrence of diastolic dysfunction. The value of E/e' ratio can serve as a predictor for pulmonary capillary wedge pressure. Our study has demonstrated that the E/e' ratio of diastolic dysfunction did not increase mortality risk; while a previous study conducted by Landesberg showed that patients whose diastolic function with E/e' of < 8 may have increased risk of death by 6.0 times greater compare to normal patients.[8] Sturgess et al[12] who studied 20 hospitalized patients in an intensive care unit (ICU) showed that patients who died from septic shock had high E/e' ratio of diastolic function. The different results found between our study and previous studies may be due to differences in time measurement. The Left Ventricle Ejection Fraction (LVEF) represents the amount of blood transferred compared to the initial blood volume during diastole. There is an increased risk of mortality in patients with sepsis who have low LVEF. A previous study conducted by Landesberg et al[8] revealed that patients who suffer from severe sepsis and septic shock accompanied with systolic dysfunction (LVEF ≤ 50%) had 2.9 greater mortality risks compared to normal patients. Patients with normal right heart function, which are represented by TAPSE measurement, have the same risk of mortality with patients who had abnormal right heart functions. Right heart function depends on pulmonary artery pressure and left ventricular end diastolic pressure. A previous study, which measured differences between area of right cardiac chamber during systole and diastole, showed that right heart function do not affect sepsis mortality.[8] The study result is similar to our result.

The cardiac Index is assessed by multiplying Time Velocity Integral and area of Aorta, which is then multiplied by heart rate per minute, and divided by body surface area. Patients with sepsis usually have increased heart rate to maintain perfusion requirements to the tissues. It is suspected that troponin I is released by myocytes due to impaired permeability and necrosis of myocytes as a consequence of microcircular thrombosis.[13-15]

Myocardial dysfunction occurs in patients with septic shock.[16] NT Pro BNP level increases due to myocardial stretching.[17,18] Troponin I and NT Pro BNP increase in patients with impaired renal function due to biomarker release by the kidneys. The right cardiac chamber function, which was assessed with TAPSE, was greater on the fifth day compared to the first day. Such results showed that patients who survived had improved right heart chamber function.

Results on troponin I, NT Pro BNP, and cardioivascular biomarkers level suggest that there was no difference found between those results measured on the first day and the fifth day. It indicates that the cellular mechanism involved on the first and fifth day has no difference. Patients with abnormal venous oxygen saturation had similar risks of mortality to patients with normal venous oxygen saturation. Such results indicate that venous oxygen saturation obtained from femoral vein or the femoral venous oxygen saturation could not represent regional oxygenation.

The limitation of this study are patients who had been hospitalized probably had already had septic shock condition before hospitalization; therefore, the target population in our study may have more severe condition. Comorbidities had not been considered in our study; while they may

have some effects on the mortality prediction model of septic shock patients.

CONCLUSION

Echocardiography variables (LVEF and troponin I biomarker), which were measured on day 1, have been demonstrated to be useful as predictors of mortality in patients with septic shock; however, other variables including the E/e' ratio, cardiac index, TAPSE, NT ProBNP and creatinine levels as well as venous saturation are not useful as predictors.

Further studies are necessary to validate our study, particularly studies that involve comorbidities; moreover, further studies with additional variable of urine output will be useful to improve the accuracy of the mortality model prediction of septic shock patients. A 24-hour measurement of LVEF and troponin I level can serve as predictors of mortality risk in patients with septic shock.

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