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Research Article

Diagnostic Value of Serum Procalcitonin and Diastolic Dysfunction for Evaluating the Mortality of Sepsis Patients Admitted in the Intensive Care

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ABSTRACT

Background: Sepsis is a serious condition that can be fatal and has become more common in recent times. The impact of diastolic dysfunction on the early mortality rate of septic patients has not been extensively researched. This study aimed to assess the accuracy of serum procalcitonin (PCT) levels and diastolic dysfunction in predicting the mortality rate of patients diagnosed with sepsis and admitted to the intensive care unit.

Methods: In this cross-sectional study, 40 sepsis patients admitted to the ICU were examined. Their characteristics were meticulously recorded using the APACHE II and SOFA score questionnaires, and only those who met the criteria underwent echocardiography. In order to evaluate the serum levels of PCT, it was required to take 40 ml of venous blood samples from the patients on the first and fifth days of admission.

Results: Out of 40 patients, the average age was 63±17 years. Of these patients, 23 (57.5%) were discharged, while 17 (42.5%) unfortunately passed away. Results showed a notable correlation between diastolic dysfunction, CRP, SOFA score on days 1 and 2, APACHE II score, and PCT on day 5 ($P<0.05$). However, when analyzed using logistic regression, only PCT on day 5 showed a significant association with mortality.

Conclusion: Based on our research, we found that PCT is an essential indicator in predicting the mortality rate of sepsis patients. While there was no significant correlation between diastolic dysfunction and mortality, it should still be considered a critical factor in determining the mortality rate.

Introduction

Sepsis is a serious medical condition where the body's response to infection causes harm to tissues and organs, potentially leading to life-threatening consequences. This condition is hazardous for patients who are already ill, with a mortality rate of up to 70%. As a result, sepsis is one of the leading causes of death in intensive care units (ICUs) [1]. Annually, 600,000 cases of sepsis are diagnosed in the United States, with severe sepsis and septic shock showing an increase over the past two decades. Around two-thirds of these cases are

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reported in patients with significant underlying health conditions. The incidence and mortality rate of sepsis tends to rise with age and concurrent diseases [1-2]. Septic shock is an extremely grave condition that ensues when an individual suffers from continuous hypoperfusion or hypotension for more than an hour, even after receiving proper fluid therapy and prescribed inotropic drugs and vasopressors. It is an acute form of sepsis that demands immediate attention and intervention [3]. A significant issue that can arise from sepsis is multiple organ failure, including myocardial dysfunction. This dysfunction affects the ventricles during both the systolic and diastolic phases and is believed to be involved in developing sepsis-induced cardiac shock. However, this condition can be reversible. [3]. In the initial three days of septic shock, the ventricular function is likely to reduce by 20 to 60%. But it commonly reverts to normal within 7 to 10 days [4-5]. While this topic has not been extensively researched, it has been found that diastolic dysfunction is prevalent in patients with sepsis and has been linked to unfavorable outcomes [6-7].

Numerous biomarkers, such as IL-8, IL-1β, TNFα, and procalcitonin (PCT), have been proposed for the early identification of sepsis [2, 8]. PCT stands for prohormone calcitonin. It is a valuable diagnostic tool in infectious diseases and crucial in determining the severity of conditions like pneumonia. Additionally, it can predict mortality rates in cases such as ventilator-induced pneumonia [9-10]. Researchers have found that high levels of PCT are strongly linked to increased mortality in septic patients from any cause. As a result, it is believed that PCT levels can be used to predict the outcome of sepsis patients [10-11].

Although diastolic dysfunction may play a significant part in predicting the outcome of septic patients, its impact on the early mortality of such patients has not been thoroughly researched. On the other hand, identifying high-risk patients susceptible to death from sepsis early on can lead to prompt interventions. This study investigated the value of serum PCT and diastolic dysfunction as diagnostic factors in the ICU admitted sepsis patients to determine their mortality.

Methods

Patients

In this cross-sectional study, 40 sepsis patients who were admitted to the ICU within less than 12 hours of their admission request between 2017 and 2018.

Sample size calculation

In order to determine the sample size using the results of the study of Meisner et al. [4], considering the median of PCT in the group of living people was 5.83 (2.5-23.96) and in the group of deceased people 4.42 (1.99-32.14) and also $\alpha = 0.05$ and power 80%, the number of samples was determined to be 40 in each group as the following formula:

$$\frac{2(z_{1-\frac{\alpha}{2}}+z_{1-\beta})^2}{(P2-P1)^2}\bar{p}(1-\bar{p})$$

Inclusion and exclusion criteria

Inclusion criteria were age over 18 years and the presence of SIRS criteria with a proven cause (positive or possible microbial blood culture via PCT or positive C-reactive protein [CRP]).

Considered criteria for SIRS include fever >38° C or hypothermia <36° C, tachypnea (respiratory rate>24), tachycardia (heart rate>90), and leukocytosis (white blood cells [WBCs]>12000) or leukopenia (WBCs less than 4000).

Also, patients treated with antibiotics one week before hospitalization and other causes of sepsis except for SIRS (such as pancreatitis, trauma, adrenal insufficiency, pulmonary embolism, myocardial infarct, bleeding, cardiac tamponade, and drug-induced) were excluded from this study.

Clinical information Record

All patients who met the inclusion criteria were clinically examined. Their characteristics, including age, gender, axillary temperature, respiratory rate per minute, systolic and diastolic blood pressure, state of consciousness, the presence of underlying diseases, need for resuscitation measures in and during hospitalization, need for vasopressor drugs, were recorded in the APACHE II and SOFA scoring questionnaires. APACHE II score was determined as described previously [12] by using PaO2 rate, rectal temperature, mean arterial pressure, arterial pH, heart rate, respiration rate, serum sodium, potassium, and creatinine levels, hematocrit, WBCs count, and calculated Glasgow coma score (GCS). The SOFA score is also calculated based on its standard parameters, PaO2 to FiO2 ratio, GCS score, administration of inotropic drugs (e.g., dobutamine, epinephrine, and norepinephrine), mean arterial pressure, bilirubin, platelet, and creatinine levels [13].

Serum PCT levels measurement

To determine Serum PCT levels, 1 ml of venous blood samples were taken from 40 patients on the first day of admission and five days later. PCT levels were evaluated using commercial ELISA kits (Biolegend, Germany).

Evaluation of diastolic dysfunction

All the patients underwent echocardiography with Konica Minolta ultrasound with a 2-4 S4 MHz probe, and the apical and parasternal view was examined. The criteria of atrial contracture, early diastolic filling, E-wave deceleration time, and mitral inflow velocity of propagation with M-mode were investigated.

Data analysis

The data were analyzed using SPSS version 21 (IBM Corporation, Armonk, NY, USA). The Chi-square test was utilized to determine the connection between mortality and qualitative variables, while the odds ratio of diastolic dysfunction grade and mortality rate was calculated through logistic regression. To evaluate the relationship between quantitative variables and mortality, we measured the normality of variables using the Komolov-Smirnov test, followed by the independent t-test and Mann-Whitney test. A p-value of less than 0.05 determined significance.

Ethical considerations

The ethics committee of Tabriz University of Medical Sciences approved this study with the code IR.TBZMED.REC.1397.880. Also, informed consent was obtained from patients, and all the procedures adhered to Helsinki's ethical principles during the study.

Results

The patients' mean age was 63±17 years, with males accounting for 52% (n=21) and females accounting for 48% (n=19) of the total patient population. Finally, 57.5% (23) were discharged, and 42.5% [17] expired.

According to (Table 1), the mean age of patients in the discharged and expired groups were 62.53±17.1 and 64.57±17.6 years, respectively, which was not statistically significant (P =0.71). The level of day 1 PCT among discharged and expired patients was 5.92±3.48 and 9.02±5.99 ng/ml, respectively, in which there was no statistically significant difference. In comparison, the PCT day 5 level in the expired patients was significantly higher than in discharged patients.

The criteria for diastolic dysfunction are given in (Table 2). Among these, there were significant associations between ejection fraction (EF), DDT, E wave, E/A, SOFA scores of days 1 and 2, and APACHE II scores with mortality. In contrast, there was no statistically significant association between LVDD, LVSD, and A wave with mortality rate (P>0.05). Overall, 25% of patients were normal in terms of diastolic dysfunction, and 43% of patients had grade 1 diastolic dysfunction. The most common diastolic dysfunction grade among discharged and expired patients was 1 and 3, respectively, which was statistically significant (31.8% vs. 41.2%) (Table 3). The logistic regression test showed that the mortality rate was statistically associated only with the PCT of day 5 (Table 4).

Table-1- Association of patients' characteristics, PCT, and CRP with mortality

Variables	Mortality		P value
	Discharged	Expired	
Age, y (mean SD)	64.57±17.6	62.53±17.1	0.717
Gender, n(%)			
Male	10 (45.5)	11(64.7)	0.331
Female	12 (54.5)	6 (35.3)	
PCT day1, ng/ml (mean SD)	5.92± 3.48	9.02± 5.99	0.51
PCT day 5, ng/ml (mean SD)	1.68 ±1.28	12.45± 10.48	<0.001
CRP, n (%)			
1+	7 (31.8)	0 (0)	0.006
2+	12 (54.5)	8 (47.1)	
3+	3 (13.6)	9 (52.9)	

Table-2- Association of diastolic parameters with mortality

Variables	Mortality		95% CI		P value
	Discharged	Expired	Lower	Upper	
LVDD, cm	4.7 ±0.53	4.62± 0.54	-0.43	0.27	0.648
LVSD, cm	3.58± 0.53	3.82± 0.6	-0.11	0.6	0.18
EF, %	46.74± 11.24	40± 9.18	-13.49	-0.01	0.05
DDT, msec	188.41 ±21.91	153.53 ±28.54	-51.23	-18.52	<0.001
E wave, cm/s	188.4± 21.91	153.52± 28.53	-51.23	-18.52	<0.001
A wave	61.91± 12.05	53.07± 16.66	-18.15	0.46	0.062
E/A ratio	0.94± 0.44	1.53± 0.72	0.2	0.97	0.003
SOFA day 1	7.35± 2.26	10.12± 2.47	1.24	4.29	0.001
SOFA day2	5.17± 2.26	12.71± 2.95	5.86	9.2	<0.001
APACHE II	14.65± 4.52	25.88± 6.32	7.76	14.7	<0.001

Table-3- Association of diastolic status with mortality

Variables	Mortality		P value
	Discharged	Expired	
Normal	7 (31.8)	3 (17.6)	0.01
Grade 1	13 (59.1)	4 (23.5)	
Grade 2	1 (4.5)	3 (17.6)	
Grade 3	1 (4.5)	7 (41.2)	

Table-4- Multivariate logistic regression modeling associated with mortality in patients with sepsis

Variables	B	S.E.	OR	95% CI		P value
				Lower	Upper	
Age	-0.074	0.083	0.929	0.790	1.092	0.372
Gender	2.847	2.543	17.243	0.118	2519.909	0.263
PCT day1	1.551	0.882	4.717	0.837	26.568	0.079
PCT day5	-1.578	0.783	0.206	0.045	0.958	0.044
CRP	-0.856	1.195	0.425	0.041	4.418	0.474
LVDD grade	1.439	2.080	4.216	0.072	248.485	0.489

Discussion

This cross-sectional study was conducted on 40 sepsis patients admitted to the ICU with an average age of 63 years. Previous research has shown diastolic dysfunction to be a risk factor for mortality in sepsis patients [7]; however, in the present study, though there was a statistically significant difference between discharged and expired patients, it was not indicated as a risk factor after multivariate analysis. In contrast, the study conducted by Rolando et al. [14] showed that diastolic dysfunction had no significant association with mortality. The reason for this discrepancy was the higher mean age of patients (74 years old) in this study compared to other studies.

Also, some evidence revealed E wave as a factor associated with diastolic dysfunction and patients' mortality [7]. The present study also showed a significant association between E wave and mortality. On the other hand, some animal studies reported that systolic dysfunction, which leads to left ventricle dilation, was associated with improved stroke volume and cardiac output, resulting in significantly improved survival [15-16]. However, its mechanism is not yet known.

The present study showed no significant association between A wave and mortality. Also, in several studies, the E/A ratio has been recognized as a factor associated with diastolic dysfunction and mortality [7, 17]. The present study demonstrated the same result.

Sevilla Berrios et al. found that EF was a predictor for mortality and associated with diastolic dysfunction. At the same time, it has been noted that this factor does not have highly sensitive and specific [18]. Also, in another study with a sample size of 7599, EF of less than 45% was considered an important risk factor in mortality among patients with sepsis [19]. In our study, also EF was not recognized as a predictor but as a mortality-related factor.

The SOFA score is a prognostic factor and a vital tool in determining the probability of mortality in patients diagnosed with sepsis [14]. Our study also presented a significant association between the SOFA score of days 1 and 2.

Although PCT of day five and CRP have a significant association with mortality rate, the multivariant analysis revealed that these variants were not risk factors for mortality of sepsis patients. Despite studies that demonstrated the ratio of CRP to albumin as a predictor for mortality, this study showed that CRP was not identified as a predictor but as an important factor associated with mortality [17]. In addition, studies suggest that serum PCT was preferred to CRP not only for predicting mortality but also for presenting the severity of the infection [2].

In this study, multivariate regression was used to reduce the effect of confounders. In addition, one of the limitations of this study was the small sample size, which can be a source of type I error and failure to identify risk factors. Future studies are suggested to reduce this error possibility by using multicenter studies with a larger sample size.

Conclusion

In the present study, although CRP, SOFA score, APACHE II, E/A ratio, E wave, DDT, EF, and PCT of day five were significantly associated with mortality, after multivariate analysis, only PCT of day5 was considered as a risk factor for mortality of patients with sepsis.

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