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Higher AVCO2 and Lactate Gradient Combined with SOFA Score as a Mortality Predictor During the 6-hours of Resuscitation of Septic Shock

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ABSTRACT

Background: Sepsis is a severe and life-threatening condition leading to widespread inflammation and organ dysfunction. It is a medical emergency that requires immediate attention and treatment. One of the key indicators used to assess the severity and prognosis of sepsis is lactate level. Another key indicator of sepsis severity is a significant difference in the level of carbon dioxide (CO2) between veins and arteries.

Methods: In this study, we aimed to evaluate the differences in the venous and arterial PCO2 and lactate levels during the first 6 hours of treatment of septic shock. In this prospective observational-analytical study patients with septic shock admitted to the ICU were evaluated. Sepsis is defined as patients who had 1 or more of the SIRS criteria with a possible or proven source of infection and hypotension despite appropriate fluid therapy who needed to receive vasopressors.

Results: Among 85 patients the mean age was 64±17 years and 48 (56%) were men. Of these patients, 15 (17%) died, of them 8 (53.33%) were male, 14 (93%) were diabetic, 11(73.33%) were hypertensive, 11 (73.33%) had ischemic Heart disease and 9 (60%) patients had Chronic Obstructive Pulmonary Disease (COPD). The mean HR, SBP, and DBP were significantly higher in lived patients; the SOFA scores were significantly lower in these patients.

Conclusion: Overall, the gradient of AV PCO2 and lactate clearance combined with SOFA score can be a valuable tool for clinicians in predicting mortality risk in critically ill patients and guiding treatment decisions.

Introduction

Sepsis is a severe and life-threatening condition that occurs when the body's response to an infection becomes dysregulated, leading to widespread inflammation and organ dysfunction. It is a medical emergency that requires immediate attention and treatment [1].

One of the key indicators used to assess the severity and prognosis of sepsis is lactate level. Lactate is a byproduct of anaerobic metabolism, which occurs when there is insufficient oxygen supply to meet the energy demand of cells [2]. In sepsis, lactate levels rise due to tissue hypo perfusion, inadequate oxygen delivery, and impaired cellular metabolism [3-4]. Another key indicator of sepsis severity is a significant difference in the level of carbon dioxide (CO2) between veins and arteries [5].

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Understanding these differences is crucial for diagnosis and managing septic patients effectively [6]. Veins and arteries have distinct roles in the circulatory system. Arteries carry oxygenated blood back to the heart [7]. In sepsis, a severe infection that can lead to organ dysfunction, both veins and arteries are affected. One of the key differences between vein and arterial CO2 in sepsis is the partial pressure of carbon dioxide (PCO2) [8]. In normal conditions, arterial PCO2 is slightly higher than venous PCO2 due to CO2 production by tissue during metabolism [9]. However, in sepsis, this relationship can change significantly and often leads to tissue hypo perfusion or inadequate blood flow to organs and tissues [10]. When tissue perfusion is compromised, cells switch from aerobic metabolism to anaerobic metabolism [11]. As a result, arterial PCO2 decreases due to reduced CO2 production [12]. On the other hand, venous PCO2 increases in sepsis due to impaired clearance of CO2 by tissues [1,4]. This accumulation of CO2 leads to an increase in venous PCO2 levels [13-14]. The difference between arterial and venous PCO2 is known as the arteriovenous carbon dioxide gradient (AVCO2 gradient) [12]. In sepsis, this gradient becomes wider than normal due to decreased arterial PCO2 and increased venous PCO2 [7]. Monitoring and analyzing the AVCO2 gradient can provide information about tissue perfusion and the severity of sepsis [15]. Clinicians often use these differences in CO2 levels to guide resuscitation efforts in septic shock [11]. In this study, we aimed to evaluate the differences in the venous and arterial PCO2 and lactate levels during the first 6 hours of treatment of septic shock

Methods

Study design

This study is a prospective observational-analytical study on patients with septic shock admitted to the ICU of Imam Reza Hospital from 2018 to 2019. Sepsis is defined as patients who had 1 or more of the SIRS criteria with a possible or proven source of infection and hypotension despite appropriate fluid therapy who needed to receive vasopressors.

Participants

Patients with septic shock were enrolled in this study; inclusion criteria were confirmation of septic shock based on the criteria explained and patients under 18 years of age, pregnant, known heart disease, liver disease, severe pulmonary airway obstruction, and whom with the inability to insert a central venous catheter are excluded from the study.

Once the diagnosis was confirmed, 1 cc of arterial blood was taken as an ABG and checked lactate level, arterial carbon dioxide pressure, and a venous blood gas (VBG) sample was also taken from the central vein to for carbon dioxide pressure and oxygen pressure. Finally, the patient's outcome, daily SOFA score, length of stay in ICU, and 11-day mortality were determined.

It should be noted that blood cultures and other necessary cultures were taken. Broad-spectrum antibiotics were started in all patients in the first hour. Crystalloid was administered at the rate of 30 kg/cc in the first three hours up to mean arterial blood pressure (MAP) of more than 65.

Three hours later, fluid therapy was performed as a fluid challenge based on hemodynamic status.

Statistical Analysis and Sample Size

Descriptive statistical methods such as mean, standard deviation, frequency, and frequency percentage were used to describe the data. The quantitative variables were analyzed by T-test due to normality of data distribution, and qualitative variables with Fisher's exact test.

The sample size was calculated at 71-patients considering the correlation coefficient between the difference in venous and arterial carbon dioxide pressure with changes in central venous oxygen pressure ($r2=0.55$), and alpha 05 0.0 and beta 0.2; to increase the power of the study we considered 85-patients [7].

Results

Among 85 patients enrolled in this study with a mean age of 64±17 years 48 (56%) were men. Patient’s vital signs, length of ICU- admission, lactate level, and the differentiation between the vein and arterial PCO2 are summarized in Table 1.

Of these patients, 15 (17%) died, of them 8 (53.33%) were male, 14 (93%) were diabetic, 11(73.33%) were hypertensive, 11 (73.33%) had ischemic Heart disease and 9 (60%) patients had Chronic Obstructive Pulmonary Disease (COPD).

Patient’s vital signs and also lactate level and AVCO2 in both dead and lived groups were summarized in Table 2. The t-test showed that mean HR, SBP, and DBP were significantly higher in lived; on the other hand, mean RR was significantly lower in these patients.

In this study, we evaluated the patient's SOFA score for 13 days, in this way, we found that patients' SOFA scores were significantly lower in lived patients (Table-3).

Table 1- Study variables.

	Min	Max	Mean	Standard deviation
1. Patients Vital Sign				
Age(year)	37	95	64±17	17.00
Heart Rate (per minute)	36	140	112±25	25.00
SBP (mmhg)	61	133	68 ± 25	25.00
DBP (mmhg)	40	93	59 ± 16.08	16.00
RR (per minutes)	15	40	24 ± 9	9.02
O 2 saturation (%)	60	100	77 ± 12	12.00
2. Length of ICU Stay				
Length of stay at ICU (Day)	0	13	6	3
3. Laboratory findings				
Lactate at admission	1.0	3.1	1.00	0.00
Lactate after 6-hours	0.0	2.0	0.00	0.00
Lactate gradient (admission and after 6-hour)	0.02	4.10	1.00	0.00
AV PCO2 at admission	4.0	11.0	6.00	1.00
AV PCO2 after 6-hours	5.0	7.0	6.00	0.00
AV PCO2 gradient (admission and after 6-hour)	- 3.02	12.00	1.00	4.00

HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; RR: Respiratory Rate; ICU: Intensive Care units; AV PCO2: Arteria-venous PCO2

Table 2- Patients prognosis based on study variables

	Lived (N: 70)	Died (N:15)	P value
1. Vital Signs / Mean (Standard deviation)			
Heart Rate (per minute)	112 (27.00)	112 (14.00)	0.001
SBP (mmhg)	87 (25.00)	83 (23.00)	0.001
DBP (mmhg)	60 (16.00)	58 (13.00)	0.001
RR (per minutes)	24 (8.00)	26 (10.00)	0.001
O 2 saturation (%)	78 (12.00)	71 (11.00)	0.04
2. Length of ICU Stay/ Mean (Standard deviation)			
Length of stay at ICU (Day)	6 (3.00)	5 (3.00)	0.001
3. Laboratory findings/ Mean (Standard deviation)			
Lactate at admission	1 (0.00)	3.02 (0.04)	0.001
Lactate after 6-hours	0 (0.00)	-	-
Lactate gradient (admission and after 6-hour)	0 (0.00)	4.02 (0.04)	0.001
AV PCO2 at admission	6.01 (1.00)	9.00 (1.00)	0.001
AV PCO2 after 6-hours	6 (0.00)	-	-
AV PCO2 gradient (admission and after 6-hour)	0.00 (1.00)	10 (1.0)	0.001

Table 3- SOFA score from the first day of admission till 13 day

		N	Mean	Standard deviation	P value
Admission	Lived	70	3.00	0.00	0.001
	Dead	15	10.00	2.00	
Day-1	Lived	69	3.00	0.00	0.001
	Dead	13	10.07	2.00	
Day-2	Lived	64	3.00	1.03	0.001
	Dead	13	9.00	2.00	
Day-3	Lived	58	3.00	1.00	0.001
	Dead	12	9.00	1.00	
Day-4	Lived	51	3.07	1.00	0.001
	Dead	10	9.00	1.00	
Day-5	Lived	48	3.08	1.00	0.001
	Dead	8	9.00	1.00	
Day-6	Lived	42	2.00	1.00	0.001
	Dead	8	9.00	1.00	
Day-7	Lived	35	2.00	1.00	0.001
	Dead	7	8.00	1.00	
Day-8	Lived	27	2.00	1.00	0.001

	Dead	6	8.00	2.04	
Day-9	Lived	25	2.00	1.00	0.001
	Dead	5	8.00	2.00	
Day-10	Lived	19	2.00	1.00	0.001
	Dead	3	10.00	2.00	
Day-11	Lived	12	2.00	1.00	0.001
	Dead	2	10.00	2.00	
Day-12	Lived	8	2.00	2.00	0.001
	Dead	-			
Day-13	Lived	4	3.00	1.00	0.001
	Dead	-			

Discussion

Sepsis is a systemic inflammatory response to infection after the invasion of microbial pathogens into the bloodstream, which leads to suppression of the immune system, multiple organ failure, and susceptibility to hospital infections. It is very important to predict the risk of mortality, especially in high-cost departments such as the emergency department and ICU.

Estimating the patient's mortality risk, in addition to informing the patient's relatives, can be a useful tool to evaluate the quality of emergency department services, as well as evaluate the effectiveness of the treatments; therefore, a different scoring system has been designed. The present study is designed based on predicting hospital mortality of septic patients and includes changes in central venous and arterial carbon dioxide pressure, changes in lactate clearance, as well as daily SOFA score.

We showed that the mean lactate level and its changes in the dead patients were significantly higher than survived. These findings showed the importance of the lactate level by considering it as a prognostic factor due to the emphasis of recent studies on this factor [1].

Lactate level has been used in predicting the adverse outcomes of sepsis and trauma in patients [1-3]. Studies have shown that lactate secretion of more than 32% within 6 hours after resuscitation can reduce the survival rate of patients suffering from septic shock [4]. Researchers showed that a lactate level greater than 4 L/mmol was a criterion for trauma with a worse prognosis [5]. Others have proven that patients with higher lactate levels compared to normal levels had a higher risk of death [12].

Gustavo and colleagues studied 60 septic shock patients and found that persistent high-pressure differences in arterial-venous carbon dioxide (Pv-aCO2) are associated with a worse prognosis in these patients [11]. We found similar findings to them, patients with higher AVCO2 gradient were more likely to die, which was consistent with the results of the study by Gustavo et al.

In confirmation of our study, we can refer to the Huai-wu study in 2016 in China, which investigated the relationship between changes in the difference between Central venous and arterial carbon dioxide pressure (P (v-a) CO2/C (a-v) O2) and lactate clearance in septic shock patient's prognosis. In this study, 84 septic shock patients were monitored within 8 hours of resuscitation. They showed that higher P (v-a) CO2/C (a-v) O2) is associated with higher lactate clearance [13], like us.

Mallat et al. investigated the relationship between lactate and Pv-aCO2 in septic patients responding to crystalloid therapy. This study which was conducted on 80 patients showed that central venous and arterial carbon dioxide pressure combined with changes in lactate can be used as a marker to check the effectiveness of resuscitation [14]. By combining these markers, clinicians can get a more comprehensive picture of a patient's response to resuscitation interventions. Improvements in central venous and arterial CO2 pressures, along with lactate clearance, can indicate successful resuscitation and tissue perfusion. Conversely, persistent abnormalities in these markers, as we showed in our study, may suggest ongoing tissue hypo perfusion need for further interventions and poor prognosis.

Zhu et al evaluated the relationship between Pv-aCO2/Ca-vO2 and lactate levels and prognosis of patients with septic shock. Their study was conducted on 144 patients and showed that the ratio of changes in Pv-aCO2/Ca-vO2 and lactate level is more accurate for estimating the prognosis and 11-day mortality of septic patients than each of these factors alone [15].

The results of all these studies are consistent with the results of our study and indicate the poor prognosis of patients with higher lactate gradients and differences in arterial and venous pco2.

Higher daily SOFA scores also were accompanied by poor outcomes. Balchi et al evaluated the value of SOFA in predicting the mortality of septic and non-septic patients, which was conducted on 120 ICU-admitted patients. They showed, that when SOFA scores increase, the patient's mortality increases. Therefore, examining the patients' SOFA Score increases the power of predicting the results of septic patients [16]. While the SOFA score can be a useful tool for predicting mortality in critically ill patients, it is important to note that it is just one of many factors that should considered when making treatment decisions. Therefore, combining the SOFA score with the gradient of lactate clearance and Pv-aCO2 may be helpful to better decisions.

Also, Sawika et al. conducted a study on 99 malignant hematologic ICU–admitted patients to investigate the effectiveness of SOFA in estimating their prognosis and analyzed the risk factors related to mortality using univariate logistic regression analysis. They found that SOFA was one of the independent risk factors of death [2]. Thakur et al. conducted a study on surgical patients with sepsis and used SOFA score and Apache- II to predict mortality. They studied 72 surgical patients with sepsis and showed that Apache- II, and SOFA scores were equally effective in the mortality assessment of surgical patients with sepsis [17].

Therefore, the predictive power of SOFA Score, like other common scoring systems such as Apache- II, has been mentioned as acceptable and excellent in most previous studies, such as ours. In a study aimed at investigating SOFA and Apache- II scores in predicting mortality in sepsis patients, Desal et al. examined SOFA scores on days 1, 3, 7, and Apache on the day of admission. Finally, they had 41% mortality, and 84% of their patients had multi-organ dysfunction syndrome (MODS), and the most affected organ was the lung. On the third day, 9.1% of patients with a SOFA score of less than 9 and 78% with a SOFA score of more than 9 had mortality; however, the Apache- II score had a slight difference in these patients. They showed that the Apache-II score was inefficient in determining the prognosis of patients and it was in line with our results [18].

Conclusion

Based on our study, it seems that the mean lactate, the gradient of AV PCO2 and lactate, and daily SOFA scores are important predictors for in-hospital death in patients with sepsis. We found that combining these three variables can provide a more accurate prediction of mortality in critically ill patients instead of using any single variable alone. This combined approach takes into account both tissue perfusion, providing a more comprehensive assessment of the septic shock patient's condition and prognosis. Overall, the gradient of AV PCO2 and lactate clearance combined with SOFA score can be a valuable tool for clinicians in predicting mortality risk in critically ill patients and guiding treatment decisions.

Strengths and limitations

This study had several strengths, including the simultaneous use of models to predict septic in-hospital mortality, as well as a new idea in the emergency department (ED) context.

Among the limitations of the current research, it can be mentioned that the research was conducted in a single center, which reduces the generalizability of the results. Since there were few studies in this field, the possibility of comparison with other studies was limited. It should be noted that few studies in this field have been conducted in the intensive care unit, and considering that the present study was conducted in the emergency department, this issue can be one of the limitations of our study and to some extent affect the results.

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