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Central blood gases versus lactate level for assessment of initial resuscitation success in patients with sepsis in critical care

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ABSTRACT

Background: Central blood gas and lactate levels serve as goals for fluid resuscitation.
Objective: To evaluate the role of blood gases [the ratio of P(v-a)CO2/C(a-v)O2 and P(v-a)CO2)] and lactate clearance as indicators of initial fluid resuscitation in patients diagnosed with sepsis.
Study design: This study included three groups of patients according to the resuscitation effective predictors.
Patients: A total of 120 patients were divided into 3 groups, 40 patients in each. Group (A): ratio P(v-a)CO2/C(a-v)O2, group (B):: of Lactate clearance (LC), and group (C): P(v-a)co2.
Interventions: Variables were measured at the start of ICU arrival (T0) and after 8 hours of resuscitation (T8).
Main outcome measures: The ratio P(v-a)CO2/C(a-v)O2, difference of P(v-a)co2 and Lactate level and clearance (LC) recorded and calculated, a dose of dobutamine required, packed RBCs, length of stay, mortality, and any recorded complication. Measured at T0 and T8 time points
Results: In group A, the ratio of P(v-a)CO2/C(a-v)O2 was improved significantly at T8 when compared with values at baseline. Lactate (group B) showed a significantly lower level at T8 than at T0. In group C, the gradient of P(v-a)CO2 did not differ significantly at T8. After 28 days, group C had a higher mortality rate (55% in group C vs 25% in group A and 30% in group B).
Conclusion: The ratio of P(v-a)CO2/C(a-v)O2 calculation may be as good as, if not better than, lactate as an indicator of initial resuscitation success of patients with sepsis, this can improve the outcome and reduce mortality. Unfortunately, the P(v-a)CO2 gradient alone is not

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1. Introduction

Sepsis is caused by many etiologies and is usually diagnosed by clinical points and cultural results. Treatment of these life-threatening conditions includes early fluid resuscitation, antibiotic therapy, and excision of necrotic tissue [1]. Reduced tissue perfusion and failure of multiple body organs are major consequences in these groups of patients. Thus, early resuscitation is essential for severe sepsis or its shock, regardless of volume overload. Tissue perfusion can be measured directly using serum lactate. A co-measurement of oxygen saturation of central veins (ScvO2), and veno-arterial difference of pCO2 (Pcv-aCO2) was proposed as indicators of tissue hypoperfusion by many authors [2,3]. The objectives of initial resuscitation of this type of critically ill patient include MAP (main arterial pressure) at least (65–90 mmHg), CVP (central venous pressure) of (8–12 mmHg), the output of urine should not be below (0.5 mL/kg/hr), hematocrit >30%, and ScvO2 > 70% [4]. The ratio of {P (v-a)CO2/C(a-v)O2)} (central veno-arterial carbon dioxide difference over the arterio-venous oxygen content difference) is a measure that indicates the relationship between tissue oxygen delivery and consumption. The carbon dioxide produced anaerobically is buffered by bicarbonate when tissues are exposed to hypoxia. As a result, the amount elaborated of carbon dioxide (VCO2) exceeds the amount of oxygen consumed (VO2), causing the respiratory quotient (VCO2/VO2 ratio) to rise, indicating anaerobic metabolism [5]. Hyperlactatemia and acidosis can independently occur to a certain degree with higher predictive power for mortality in ICU [6]. Veno-arterial Co2 differences (P (v-a)CO2) can also be used to determine tissue perfusion status and has a link to the septic patient's death rate and other clinical outcomes [7,8]. Therefore, our research aimed to study the predictive value of central blood gases against lactate clearance (LC) for the outcomes of early resuscitation of patients admitted to ICU after sepsis clinically and laboratory diagnosis.

2. Patients and methods

One hundred and twenty patients were included in this study, aged (18–65 y) with clinical or/and laboratory criteria of sepsis, they were transferred to ICU, either from the emergency department or from ordinary hospital wards of Minia University Hospital, the

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patients were admitted to either postoperative intensive care or general intensive care units supervised by our department, between August 2021 and May 2022. All patients fulfilled the criteria of sepsis diagnosis according to Surviving Sepsis Campaign 2016 [9]. We excluded patients with previous organ dysfunction or who refuse consent to enrolment in the study.

Ethics: Afterof Minia University, No. 6,382,021. 15 August 2021 (The Instructional Review Board of Faculty of Medicine, Minia University is constituted and operating according to the Declaration of Helsinki, CIOMS, ICH-GCP guidelines, Egyptian law No. 214 (2020), and applicable local & institutional guidelines which govern EC operations) head of the ethical committee (Email: manalismail2000@yahoo.co.uk). ***clinical trial registration*** (NCT05049941), and written consent from the patient or responsible relative. We allocated the patients randomly (computer-generated) into three groups (40 for each) according to the calculated indicator of resuscitation which was the ratio of {P(v-a)CO2/C(a-v)O2} in the (A) group, lactate clearance (LC) in the (B) group, and the group (C) was P(v-a)co2.

The SIRS Criteria were evaluated on ICU admission including:

- WBC (white blood count) is > 12,000/ μL or < 4000/ μL

- Heart rate (HR) more than 90/min (UltraviewSL2700; Spacelaps, USA)

- RR (Respiratory rate) more than 20/min -PaCO2 less than 32 mmHg.

-Temperature less than 36°C or more than 38.3°C.

-Glasgow Coma Scale (GCS) is equal to or less than 13.

-Systolic blood pressure (SBP) less than 90 mmHg.

-Respiratory rate (RR) equal to or more than 22 bpm.

-Sequential Organ Failure Assessment (qSOFA) [10]

-(APACHE II) score [11]

Laboratory workup that included CBC, hepatic and kidney functions, C-reactive protein, blood sugar, and coagulation profile. Central jugular venous catheters were inserted under sonar guidance. (CVP) was measured before the start of resuscitation (T0) and at 8 hours after (T8). Venous and arterial gases were analyzed by the machine (the *RAPID Point SIEMENS machine*).

The following parameters were recorded at time points (T0) and at (T8):

- (Pvco2). -(ScvO2). -(Pvo2).

-An arterial cannula was inserted under sonar guidance and arterial gases were analyzed at (T0) and (T8) including (Pao2), (Cao2), (Paco2), (Sao2).

- Cvo2 = (1.34 × Svo2 × Hb) + (0.003 × Pvo2).

- Cao2 = (1.34 × Sao2 × Hb) + (0.003 × Pao2).

- Lactate level was measured using *(Microlab 300 German machine*).

- Lactate clearance (LC) was calculated: [(lactate(T0) – lactate(T8))/lactate(T0)] × 100%.

All patients received the same initial resuscitation protocol. An empirical antimicrobial was given till the results of microbial culture. The goals of resuscitation were as follows: MAP > 65 mm Hg, CVP of 8–12 cmH2O, urine output exceeding 0.5 mL/kg, and Scvo2 of 70% or above. 30 ml/kg crystalloids were given in the first 3 hours of resuscitation, then vasopressors can be used if needed until MAP is more than 65 mmHg by infusion of 0.25 mcg/kg/min norepinephrine or 2.5 mcg/min dobutamine with titration according to the response. Mechanical ventilation was initiated when needed with minimal sedation. Prophylactic anticoagulant and gut mucosa protector drugs were added. Regular control of blood sugar and early enteral nutrition was an important step in the protocol.

In group A, packed RBCs were transfused at T0 if the ratio {P(v-a)CO2/C(a-v)O2} exceeded 1.8, ScvO2 more than 70%, and the hematocrit (Hct) was <30%. If indicated, dobutamine was commenced and titrated at T8 until the ratio{P(v-a)CO2/C(a-v)O2} was less than 1.8 and ScvO2 was at least 70%.

In group B, the goal was to have an LC of at least 10%. Packed RBCs were transfused if the LC was <10% and the Hct was <30, while dobutamine was initiated and titrated if the LC remained <10% after the Hct was >30%.

In group C, packed RBCs were transfused at T0 if P (v-a)CO2 was more than 6 mm Hg, ScvO2 was less than 70% and the hematocrit was <30%, while dobutamine was initiated and titrated if ScvO2 was less than 70% or the gradient of P(v-a)CO2 remained >6 mmHg after Hct was 30% or higher at T8.

The assessed parameters included demographic data, the main source of sepsis, patient characteristics, and Systemic Inflammatory Response Criteria. Hemodynamic and vital parameters were reported at T0 and T8 including HR, Scvo2, MAP, CVP, and other variables in ABG. Other collected data included the APACHE II score and (qSOFA) score at time points of measurements and for 3 days, infused fluid volume, vasopressor doses, and required packed RBCs.

2.1. Sample size

Based on previously published data that 8% of patients admitted to the ICU had septic shock during their ICU stay([31), a minimum sample size of 102 patients was determined at a margin of error of 5%, a confidence level of 95%, and a population size of 1000. We added 15% of attrition for missing participants to get the final size of 120 septic shock patients.

2.2. Statistical analysis

By using SPSS (Statistical Package for Social Sciences), (version 20.0) software. Quantitative parameters were expressed as Means ± SD (Standard deviation), while numbers and percentages described categorical parameters. Chi-square and Fisher-exact tests were used to compare percentages between categorical parameters. For normally distributed quantitative data, one-way ANOVA was used for the comparison of multiple means, an independent t-test was used for the comparison between every two means of quantitative data, and Paired t-test was also used for intragroup comparisons of related means. Mann–Whitney test was used for non-parametric data to compare the two groups in the study, the Wilcoxon Signed-Rank test wa,s used to compare intragroups and the Kruskal–Wallis H-test for differences between more than two groups of patients. Pearson test was used to examine the correlation of both the qSOFA score and the APACHE II score. Receiver Operating Characteristic (ROC) curve was used to evaluate the diagnostic value of the parameter. After each statistical test, whenever P-value <0.05, it was considered significant.

3. Results

One hundred twenty patients were included after the enrolment of 151 patients and the exclusion of (12; 13) patients who had septic shock before 24 h of ICU admission [8], refused central-line insertion, and [8] died during the first 24 h [Figure 1]. Chest infection is the most common source of sepsis. Regarding demographic data, sources of sepsis, and comorbidities, there were no recorded significant differences [Table 1]. Regarding the Systemic Inflammatory Response criteria, there were no significant differences [Table 2]. The relevant hemodynamic parameters of all groups T are shown in [Table 3], regarding CVP, MAP, and Scvo2, there was significant improvement at T8 after initial resuscitation without significant intergroup differences. {P(v-a)CO2/C(a-v)O2} at T8 was different significantly when compared to T0, in group A [Table 3]. In lactate group B, lactate level was reduced significantly at T8 when compared to its level at T0 baseline, but P(v-a)CO2 in the third group C was s improved and reduced at T8 time point compared to T0 but statistically nonsignificant ($p > 0.5$) [Table 3].

However, there was a significant difference when doses of dobutamine between 5 and 20 μg/kg/min were increased during initial resuscitations with a decrease in P(v-a)CO2 at T8.

There is a statistically non-significant difference between the studied group A, B, and C, regarding the qSOFA score and the APACHE II, score at times of measurements ($P > 0.05$) for 3 days after the initial resuscitation. Also, the difference in the fluid volume and the number of patients who received packed RBCs transfusion in the three groups showed statistically nonsignificant ($p > 0.5$).

Regarding vasopressors [Table 3], the number of patients that still needed NE (norepinephrine) at T8 was reduced without any statistical difference (10%, 16%, 10% in A, B, and C groups respectively) when

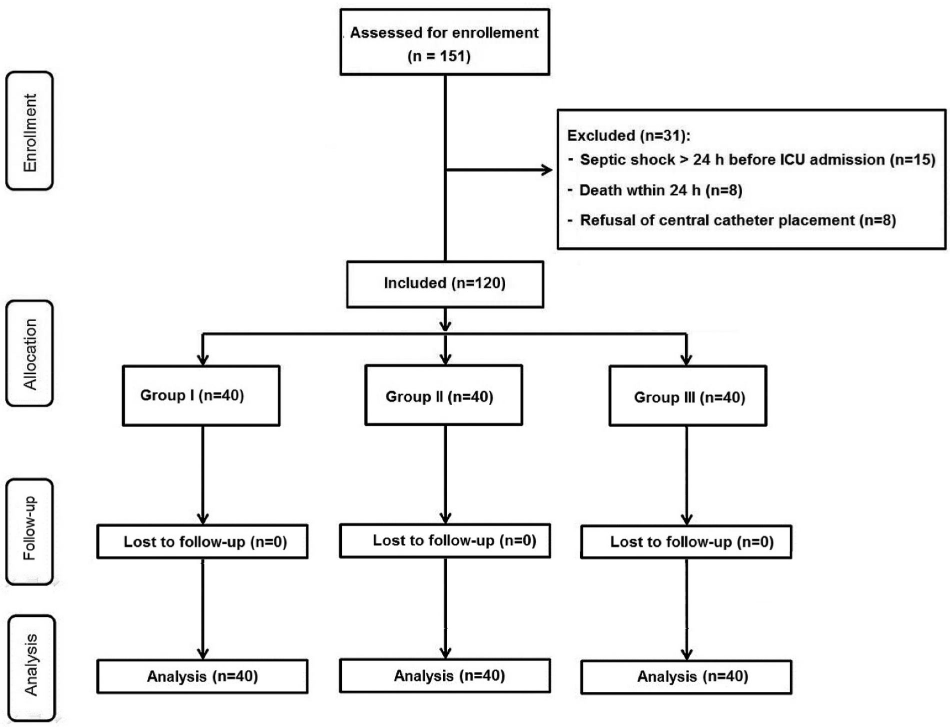

Figure 1. Flow chart of patients' enrollment.

Table 1. Patients' data, baseline clinical characteristics, and causes of sepsis.

Parameters	Group [A] 40 patient	Group [B] 40 patient	Group [C] 40 patient	(P-value)
Age in years	59.9 ± 10.5	57.3 ± 14.6	59.9 ± 10.5	0.53
Female gender	22(55%)	20(50%)	23(56%)	0.79
Comorbidities:				
DM	16(40%)	10(25%)	16(40%)	0.26
Malignancy	16(40%)	8(20%)	16(40%)	0.09
COPD	4(10%)	8(20%)	4(10%)	0.31
Source of sepsis:				
Pulmonary infection	15(37.5%)	13(32.5%)	15(37.5%)	0.86
Urinary tract infection	2(5%)	2(5%)	2(5%)	1
Soft tissue infection	2(5%)	8(20%)	3(7.5%)	0.06
Abdominal infection	4(10%)	6(15%)	4(10%)	0.72
Blood infection	2(5%)	2(5%)	2(5%)	1
Unknown	15(37.5%)	9(22.5%)	14(35%)	0.30
Severe sepsis	12(30%)	18(45%)	15(37.5%)	0.38

Data were expressed as mean ± SD or number and %.
DM;(diabetes mellitus), COPD;(chronic obstructive pulmonary disease.)

Table 2. Systemic inflammatory response criteria.

Parameters	Group [A] 40 patient	Group [B] 40 patient	Group [C] 40 patient	(P-value)
Abnormal white blood cell count	28(70%)	26(65%)	24(60%)	0.64
Elevated heart rate	25(62.5%)	26(65%)	27(67.5%)	0.89
Elevated respiratory rate	24(60%)	21(52.5%)	23(57.5%)	0.78
Abnormal body temperature	15(37.5%)	16(40%)	15(37.5%)	0.96
Organ dysfunction:**				
Respiratory	21(53%)	19(49%)	22(54%)	0.79
Liver	11(26%)	18(47%)	10(25%)	0.11
Cardiovascular	28(58%)	27(56%)	26(55%)	0.88
Neurological	12(24%)	15(27%)	14(26%)	0.77
Renal	23(54%)	19(49%)	18(47%)	0.49
Coagulation	13(25%)	12(24%)	11(26%)	0.88

Data are expressed as numbers and percentages. **One patient might have multiple organ dysfunctions

compared to T0 (15%, 21%, 15% in A, B, and C groups respectively), also the number of patients that still needed dobutamine at T8 (3%, 3%, 8% in group A, B, and C, respectively) is reduced without any statistical difference when compared to T0 (6%, 5%, 10% in A, B, and C group respectively), the doses of NE and dobutamine increased at T8 when compared to T0 but with no significant differences, except in group C, doses of dobutamine were increased significantly ($p < 0.5$) at T8 to reach the target of P(v-a)CO2 ≤ 6 mmHg

When comparing the three groups in the achievement of initial resuscitation parameters as a target indicator, we found that CVP was achieved in 90% of patients in the three groups and MAP was achieved in 100% of patients in the three groups. However, the ratio of P(v-a)CO2/C(a-v)O2 in group A was achieved in 85% of patients. Lactate clearance in group B was achieved in 80% of patients, whereas 70% of patients in the C group achieved the targeted P(v-a)CO2 difference with a significant statistical difference between the three groups (P-value = 0.03) [Figure 2].

Table 3. Relevant hemodynamic variables in the studied groups at two different time points (T0 and T8).

Variables	T0	T8	P-value
Group [A]:			
C(a-v)O2	3.48 ± 2.05	3.7 ± 1.6 *	0.004
P(v-a) CO2	8.0 ± 5	6.0 ± 4 *	0.0001
Ratio of P(v-a) CO2/C(a-v)O2	2.1 ± 1.0	1.3 ± 1.15 *	0.0001
Patients with NE (%)	15%	10%	0.28
NE does µg/kg/min	0.18 ± 0.25	0.22 ± 0.6	0.47
Patients with dobutamine (%)	6%	3%	0.30
Dobutamine µg/kg/min	2.95 ± 0.10	3.01 ± 0.29	0.053
Group [B]:			
Lactate level (mmol/L)	2.9 ± 2.2	1.7 ± 1.3 *	0.0001
Lactate clearance%	-	41.4 ± 32	-
Patients with NE (%)	21%	16%	0.36
NE does µg/kg/min	0.15 ± 0.25	0.24 ± 0.61	0.12
Patients with dobutamine (%)	5%	3%	0.47
Dobutamine µg/kg/min	2.50 ± 0.75	2.57 ± 0.50	0.08
Group[C]:			
Paco2 (mmHg)	31 ± 5	31 ± 6	1
Pvco2 (mmHg)	40 ± 7	40 ± 8	1
P (v-a) co2 mmHg	7.0 ± 1.2	6.9 ± 1.8	0.29
Patients with NE (%)	15%	10%	0.28
NE does µg/kg/min	0.18 ± 0.25	0.23 ± 0.6	0.37
Patients with dobutamine (%)	10%	8%	0.62
Dobutamine µg/kg/min	2.50 ± 0.25	7.50 ± 0.25 *	0.0001

SaO2: arterial saturation of oxygen. – ScvO2: central venous saturation of oxygen.
(P(v-a)co2: the difference in venous-arterial co2 pressure. – (C(a − v)O2): arterio-venous difference in O2 content.
*P-value was statistically significant inside group 3 at T8. – NE: norepinephrine
T0: before the start of resuscitation T8: at 8 hours after resuscitation

The receiver operating curve (ROC) curves at T8 after resuscitation showed a higher area under the curve (AUC) for $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in comparison to that for other groups (0.721 vs 0.68 and 0.52) [Figure 3]. The cutoff of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio was 1.16; this cutoff resulted in a sensitivity of 94.1% and a specificity of 48%.

Table 4 showa the 30-day in-hospital mortality rate in the three groups A, B, and C (25%, 30%, and 55%, respectively) during the follow-up of 30 days after ICU admission, with lower mortality in A and higher mortality in C group. Time of ICU stay, total hospital stay, and also days of mechanical ventilation among the three groups showed differences but were statistically nonsignificant ($P > 0.05$).

4. Discussion

Sepsis and its different clinical varieties are life-threatening medical major problems [14]. Identification with correction of the hypoperfusion status in patients with sepsis is crucial for fluid resuscitation and improved outcomes [15]. We aimed to detect the optimal resuscitation predictor at this point of debate among authors. The old concepts considered hemodynamic parameters, especially CVP, but studies did not confirm that [13,16]

In the present study, using the ratio of (P(v-a)CO2/C(a-v)O2) to indicate resuscitation success when exceeding 1.8 is more applicable and reliable than P

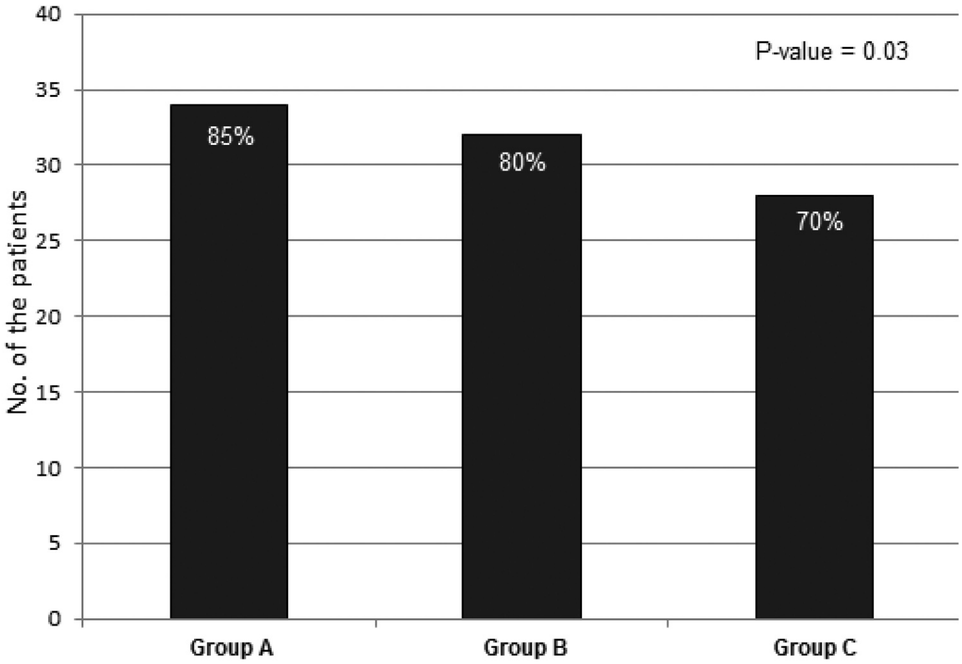

Figure 2. Achievement of initial resuscitation using target indicator of initial resuscitation. The indicator is the ratio of {P(v-a)CO2/C (a-v)O2} in group [a], Lactate clearance in group [b], also, P(v-a)CO2 gradient in group [c].

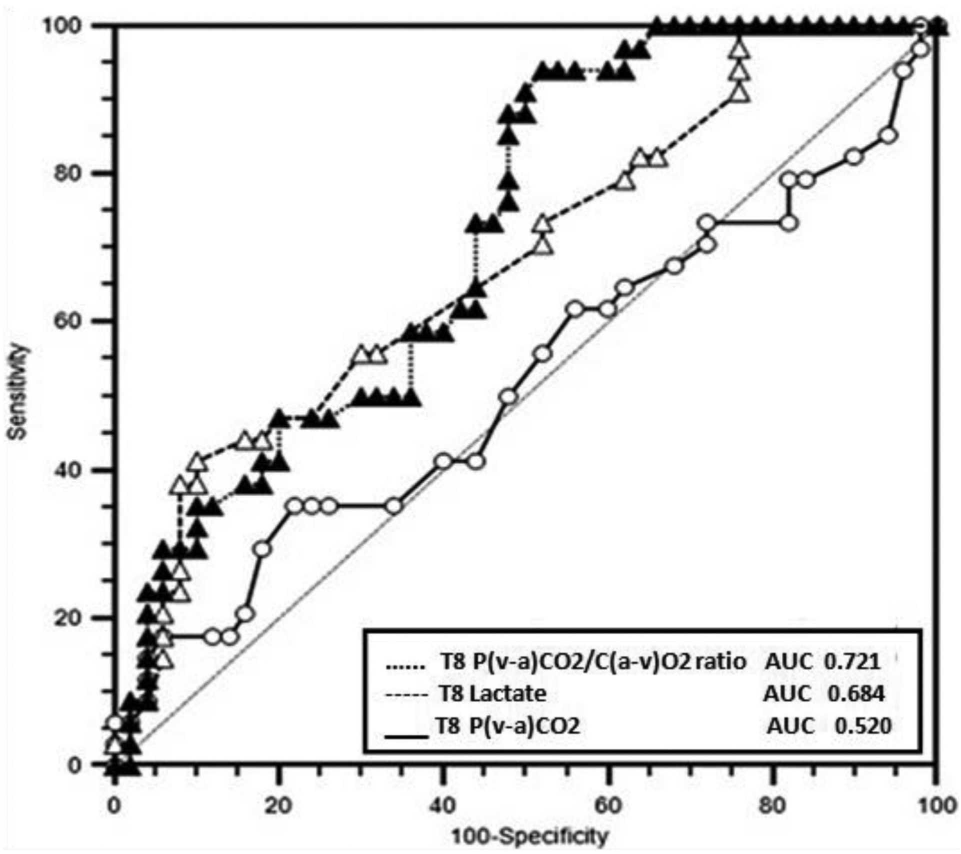

Figure 3. Receiver operating characteristic curves for $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio, lactate level, and $P(v\text{-}a)CO_2$ at T8 to discriminate between the three groups after resuscitation.

(v-a)CO2 and LC. Moreover, a protocol targeting the ratio P(v-a)CO2/C(a-v)O2 for the indication of adequate tissue oxygen delivery is an effective prognostic value compared with LC. In agreement with our results, some authors consider the superiority of the ratio P(v-a)CO2/ C(a-v)O2 measurements over LC [17], or suggested more additive and confirming values when measured together as predictor[5]. According to our findings, the aim of 10% or higher lactate clearance was achieved in 80% of the lactate

Table 4. Mortality, length of hospital and ICU stay.

Parameters	Group [A] (n = 40)	Group [B] (n = 40)	Group [C] (n = 40)	(P-value)
Hospital stay (days)	7.4 ± 5.3	8.8 ± 9.8	7.6 ± 5.8	0.64
ICU stay (days)	6.3 ± 4.3	5.7 ± 3.5	6.7 ± 4.2	0.53
Mechanical ventilation (days)	3.3 ± 2.9	3.5 ± 3.2	3.4 ± 3.1	0.95
Mortality (30-day)	10 (25%)	12 (30%)	22 (55%)*	0.01

Data are expressed as mean ± SD or number and %.
* P-value is significant

group, we can consider this percentage as an adequate resuscitation predictor, and more convenient as a target goal of resuscitation than P(v-a)CO2 which achieved in 70% of patients with significantly higher doses of dobutamine and significantly higher mortality ($p < 0.05$). This consideration was enforced by the agreements with many studies[18–20], which concluded that lactate clearance is more convenient than P (v-a)CO2 for outcome prediction. So, P(v-a) CO2 difference when exceeds 6 mmHg, can be put as one of the multiple targets, not a predictor of prognosis or mortality [21]. Puskarich et al22] found that achieving the P (v-a)CO2 as a single predictor for outcome in septic patients is loaded with a 41% mortality rate. Many investigators concluded that the Pv-aCO2 was an inferior predictor when compared to {P (v-a)CO2/C(a-v)O2} [23,24].

When we compared the three groups to evaluate the ratio of P (v-a)CO2/C(a-v)O2, clearance of lactate, and the gradient of P(v-a)CO2 as targets for initial resuscitation management and outcome, the ratio of P (v-a)CO2/C(a-v)O2 is considered the most suitable marker than lactate (LC) and P(v-a)CO2 difference with least mortality coinciding with results of Zhang et al. [25].

Contrary to our study, the results of some studies found that the P(v-a)CO2/C(a-v)O2 may be calculated using factors that are mostly dependent on the clinical condition, resulting in a complicated relationship between the {P(v-a)CO2/C(a-v)O2} and related calculated values. Also, the lactate level did not differ significantly between the low and high values of the ratio P(v-a)CO2/ C(a-v)O2, suggesting that it could be a false or weak indicator of early resuscitation of sepsis and anaerobic metabolism [26,27].

The 30-day in-hospital mortality, in our results, recorded 55% of patients in the C group, which was significantly higher than the % of deaths in the A (25%) and B (30%) groups. This supports the findings of Troskot et al. [28] and they reported that the difference in P(v-a)CO2 when targeted as the goal of resuscitation was associated with higher deaths in non-ventilated septic patients and was shown to be higher among non-survivors than survivors; thus, the authors concluded weakness of the parameters' predictive usefulness. Also, many authors showed that P(v-a) CO2 > 6 mmHg 4 h after admission exhibited a significant increase in in-hospital mortality [29,30].

4.1. Study limitations

Some limitations of our study were observed, including a relatively small sample size with a short period of study, and also the parameter measurements should be continuous within 24 hours after initial resuscitation not 8 hours only to assess more accurate variations between parameters and indicate prognosis.

4.2. Study conclusion

The ratio of P(v-a)CO2/C(a-v)O2 calculation may be better than lactate as an indicator of initial resuscitation success of patients with sepsis, this can improve the outcome and reduce mortality. P(v-a)CO2 gradient alone is not an efficient parameter for effective resuscitation prediction.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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