Correlation of central venous-to-arterial carbon dioxide difference to arterial-central venous oxygen difference ratio to lactate clearance and prognosis in patients with septic shock: A prospective observational cohort study

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ABSTRACT

**Background:** To assess the relationship between the ratio of difference of venoarterial CO₂ tension (P (v-a) CO₂) and difference of arterio-venous oxygen content (C (a-cv) O₂), i.e., ΔPCO₂/ΔCaO₂ with lactate clearance (LC) at 8 and 24 h, to define a cutoff for the ratio to identify LC >10% and >20% at 8 and 24 h, respectively, and its association with prognosis in septic shock.

**Methods:** Adult patients with septic shock were included in this prospective, observational cohort study. Blood samples for arterial lactate, arterial, and central venous oxygen and carbon dioxide were drawn simultaneously at time zero (T0), 8 h (T8), and 24 h (T24). At T8, patients were divided into Group 8A (LC ≥10%) and Group 8B (LC <10%). At T24, patients were divided into Group 24A (LC ≥20%) and Group 24B (LC <20%).

**Results:** Ninety-eight patients were included. The area under the curve of ΔPCO₂/ΔCaO₂ at T8 (0.596) and T24 (0.823) was the highest when compared to P(v-a) CO₂ and C(a-v) O₂. The best cutoff of P(v-a) CO₂/C (a-v) O₂ as predictor of LC >10% was 1.31 (sensitivity 70.6% and specificity 53.3%) and for LC >20% was 1.37 (sensitivity 100% and specificity 50%). At both T8 and T24, P(v-a) CO₂/C (a-v) O₂ showed a significant negative correlation with LC. Groups 8A and 24A showed lower intensive care unit mortality than 8B and 24B, respectively. Values of P(v-a) CO₂/C (a-v) O₂ at T8 were comparable, but at T24, there was a significant difference between the survivors and nonsurvivors (P < 0.001).

**Conclusion:** ΔPCO₂/ΔCaO₂ predicts lactate clearance, and its 24 h value appears superior to the 8-h value in predicting LC and mortality in septic shock patients.

**Key Words:** Carbon dioxide tension, lactate, septic shock

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INTRODUCTION

It had been estimated that globally sepsis afflicts a staggering 30 million people each year, of which about five million perish. In most fatal cases of sepsis, there is multiple organ dysfunction, which is commonly associated with the signs of accelerated anaerobic metabolism leading to tissue hypoxia. Serum lactate greater than 2 mmol L⁻¹ and hypotension necessitating vasopressor to preserve the mean arterial pressure (MAP) ≥65mm of Hg despite adequate volume resuscitation are the criteria for the diagnosis of diagnosis septic shock. This hyperlactatemia in septic shock is postulated to be the consequence of circulatory shock resulting in inadequate oxygen delivery, which leads to mitochondrial hypoxia. As a result, mitochondrial oxidative phosphorylation is hampered, leading to anaerobic glycolysis and elevated serum lactate level. However, other factors also contribute to hyperlactatemia, for instance, aerobic glycolysis stimulated by the adrenergic response to stress diminished clearance of lactate, mitochondrial dysfunction, which reduces the metabolism of pyruvate, etc. Thus, there is much complexity involved with lactate as a biomarker of physiological stress. Such intricacies rule out the utilization of absolute lactate level as a target of resuscitation in septic shock.

In septic shock, hyperlactatemia does not necessarily mean anaerobic metabolism. Moreover, when it is evident, hyperlactatemia results from inadequate delivery of oxygen to the tissues. Further, it is suggested that the ongoing hyperlactatemia in septic shock is more likely due to a decrease in clearance rather than an increased production. Lactate clearance (LC) (defined as the difference in concentration of lactate in blood specimens collected at different time points) is a dynamic measure that is often used to gauge response to resuscitation and suffers from several limitations. First, 20%–30% of patients who fulfil the norms for labelling septic shock might have normal serum lactate levels. Secondly, lactate measurement can be confounded by the resuscitation with ringer’s lactate solution, presence of cirrhosis, use of metformin, or administration of large volume of packed RBCs. Rivers et al. also reported that 33%–37% of patients who suffered from septic shock and had diminished central venous oxygen saturation (ScvO₂) had normal lactate levels.

Central venous-arterial carbon dioxide gap (P (v-a) CO₂ or ∆PCO₂) had been defined as the difference between the partial pressures of carbon dioxide (pCO₂) in central venous blood and that in arterial blood. It was considered a marker of venous blood flow or cardiac output (CO) in turn. Elevated value (>6mm of Hg) was related to absolute or relative inadequacy of systemic blood flow or CO. Persistent high ∆PCO₂ in septic shock is associated with poor outcomes. However, it suffered from several disadvantages. ∆PCO₂ can rise in the presence of hyperoxia or because of the Haldane effect or even hyperventilation. In addition to acute changes in respiratory status, ∆PCO₂ also rises in ischemic hypoxia and could be lower in patients with high cardiac index.

Mekontso-Dessap et al. hypothesized that ∆PCO₂/C(a-v)O₂ ratio, where (C (a‑cv) O₂ or ∆CaO₂ is the difference in oxygen content of arterial and venous blood), is a more sensitive indicator of anaerobic metabolism occurring at a macro level in critically ill patients. It has been proposed that a value of ∆PCO₂/∆CaO₂ >1 may suggest anaerobic metabolism. However, there is no unanimity regarding the exact threshold value with the best sensitivity and specificity for detecting the persistence of oxygen debt. It was also found that changes in P(v-a) CO₂/D (a‑v) O₂ ratio occur more rapidly than lactate kinetics, enabling it to monitor the correction of anaerobic metabolism.

Data are lacking regarding the correlation of the value of ∆PCO₂/C(a-v)O₂ with survival either early (within 8 h) or at 24 h after initiation of resuscitation in patients with septic shock. Thus, the present study was carried out to evaluate the association between ∆PCO₂/C(a-v) O₂ with LC at eight and 24 h, to define a cut-off value for ∆PCO₂/∆CaO₂ to identify LC values of 10% and 20% at eight and 24 h, respectively, after the start of resuscitation and the association of ∆PCO₂/∆CaO₂ with survival in patients of septic shock.

METHODS

This prospective, observational cohort study was conducted in the intensive care unit (ICU) of the Department of Anesthesiology and Critical Care at a tertiary care center from August 15 to December 30, 2021. The Institutional Ethical Committee approved the study protocol. The trial was registered prospectively at the Clinical Trial Registry-India (CTRI/2021/08/035506). Before enrolling patients in this study, written informed consent was acquired from the patient’s guardian. The manuscript adheres to the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the CONSORT 2010 statement, during the conduct of this research project.

The primary objective of the study was to assess the relationship between the ratio of difference of venoarterial CO₂ tension (P (v-a) CO₂) and difference of arterio-venous oxygen content (C (a-cv) O₂), i.e., ∆PCO₂/∆CaO₂ with LC at 8 and 24 h. The secondary objectives were to define a cutoff value for the ratio to identify LC >10% and >20% at 8 and 24 h, respectively, and its association with prognosis.
The clinical criteria of septic shock (Sepsis 3) were the need for vasopressor infusion(s) to sustain a mean arterial blood pressure of (MAP) of 65 mm Hg or higher and having a serum lactate level >2 mmol/L even after fluid resuscitation.\[^{[15]}\]

**Inclusion criteria**
Consenting adult patients (18 to 65 years) with a new episode of septic shock were admitted to our ICU during the study period were included.

**Exclusion criteria**
Those who had survived a previous episode of septic shock within the last 3 months, pregnant women and patients with severe co-existing diseases such as cirrhosis (Child-Pugh class C), severe chronic obstructive airway disease (GOLD 3 and 4 categories), end-stage renal disease, left ventricular dysfunction (moderate to severe, i.e., ejection fraction <40%) were excluded from the study.

**General management**
Measurements of vital parameters and clinical procedures were done according to the existing protocols for managing septic shock. Patients admitted to the ICU with septic shock either from the ward or the community were resuscitated and treated as per recommendations for treating septic shock (Sepsis 3).\[^{[3]}\] Broad-spectrum antibiotics were given at the earliest (preferably within 1 h) after detection of septic shock. An arterial catheter was inserted in the radial artery, and a central venous catheter was introduced through the right internal jugular vein. The position of the tip of the catheter was verified to be above the junction of superior vena cava and right atrium, on the chest radiograph, before sampling of blood. All patients were continuously monitored (Infinity 700 of Dragger Medical Systems, Lubeck, Germany). Fluid resuscitation was achieved with lactate-free balanced salt solution, guided by pulse pressure variation (PPV). The first line vasopressor used to maintain the MAP above 65 mm Hg was norepinephrine. Patients who needed mechanical ventilatory support received an infusion of fentanyl and midazolam. The ventilatory settings were; tidal volume 6–8 mL.kg\(^{-1}\) ensuring plateau pressures less than 30 cm H\(_2\)O. Hydrocortisone (50 mg intravenous (IV) every 6 h) was started if there was no significant reduction in the need for vasopressor within the first 6 h of resuscitation despite confirming sufficient intravascular volume. The intensivist, who was not a part of the study team, determined the magnitude and duration of resuscitation.

**Study procedure and data collection**
The study team evaluated all patients admitted to ICU with the diagnosis of sepsis and who developed septic shock. Patients were enrolled if they followed the inclusion criteria for the study.

Time 0 (T0) was defined as the central venous catheter insertion time. Blood samples for arterial lactate, arterial, and central venous blood gases were drawn simultaneously at T0, 8 h (T8), and 24 h (T24) from T0. Blood gas samples were collected in 3 mL heparinized syringes, ensuring the absence of any air bubble and analyzed. The same blood gas analyzer (RAPID Lab 1265 of Siemens Healthcare Diagnostics, New York, USA) was used to analyze all samples. Each set of central venous and arterial blood samples was drawn at the same time for the determination of the required measured and calculated variables, which are as follows:

All the data were collected and recorded electronically by a single observer. Patients with inadequate data were excluded [Figure 1]. The hemodynamic assessment, organ dysfunction assessment using sequential organ failure assessment (SOFA) score, analysis of arterial and central venous samples for oxygen and CO\(_2\) concentrations were carried out on all the patients at 0 h (T0), 8 h (T8), and 24 h (T24). The outcome was defined by survival or death on day 28. Table 1 lists all the measured and calculated variables.

**Definitions of four groups**
In the first step, depending on the LC from T0 to T8, the patients were allocated to two groups: Group 8A (those who had 8-h LC ≥10%) and Group 8B (those who had 8-h LC < 10%). In the second step, subject to the LC rate from T0 to T24, the same patients were again assigned to two groups: Group 24A (24-h LC ≥ 20%) and Group 24B (24-h LC < 20%). The flow diagram of the study is depicted in Figure 1.

**Statistical analysis**

**Sample size estimation**
From a previous study,\[^{[16]}\] the ratio of $\Delta$PCO\(_2$/ΔCaO\(_2\) (mm Hg mL\(^{-1}\)) at 8 h after the start of resuscitation had a mean of 2.1 and standard deviation (SD) of 1.0 in the non-LC Group ($n = 34$) and mean 1.4 and SD of 1.0 in the LC Group ($n = 50$). Thus, the allocation ratio is 50/34 = 1.47, i.e., approx. 1.5. For a two-tailed test with a level of significance fixed at 5% and a power of 90%, the calculated effect size from the values of mean and SD was 0.70, the minimum sample size required to conduct this study was 92. The sample size was estimated using GPower, version 3.1.9.6. We included 98 patients in the present study.

A descriptive analysis was carried out. All figures were expressed as the mean ± SD or medians (25\(^{th}\)–75\(^{th}\) percentiles). Any departure from this format is explicitly mentioned. Independent sample t-test and Mann–Whitney U test was used for continuous variables. For repeated measures, the Friedman test was employed to check significance. The discrimination values of the
variables were assessed with the receiver operating characteristic (ROC) analyses. The optimal cutoff values to dichotomize the population were calculated according to Youden’s method. All comparisons were two-tailed, and \( P < 0.05 \) was required to exclude the null hypothesis. Statistical evaluations were carried out with the SPSS 21.0 software package (SPSS Inc., Chicago, Ill, USA) and R software version 4.0.3.

### RESULTS

Overall, 98 adult patients diagnosed to be in septic shock and admitted to the ICU were included in this study. Based on LC at 8 h (T8), patients were allocated to either of the two groups - Group 8A (LC >10%, \( n = 68 \)) and Group 8B (LC <10%, \( n = 30 \)). Six patients expired between 8 and 24 h. After 24 h of resuscitation (T24), the remaining 92 patients were assigned to one of the two groups - Group 24A (LC >20% \( n = 62 \)) and Group 24B (LC <20%, \( n = 30 \)). No patient was dialyzed or received blood or blood products or showed evidence of limb ischemia during the study period. Since we included patients with septic shock, all needed vasopressor infusion and were mechanically ventilated.

Demographic and hemodynamic variables among different groups at baseline (T0) are shown in Table 1. The age, gender, baseline heart rate, MAP, SOFA score, P(v-a) CO\(_2\)/C (a-v) O\(_2\), and ∆PCO\(_2\)/∆CaO\(_2\) ratio were
found comparable among different groups. However, 8B (LC < 10%) and 24B (LC < 20%) showed significantly higher lactate levels at baseline when compared to 8A (LC >10%) and 24B (LC >20%), respectively.

Table 2 represents the distribution of probable sites of sepsis among the participants.

The comparison of relevant global oxygen metabolic parameters among groups 8A and 8B at T8 and among groups 24A and 24B at T24 is shown in Table 3. At T8, comparison among groups 8A and 8B revealed no significant differences in C(a-v)O₂ (P = 0.502) and also between ∆PCO₂/∆CaO₂ (P = 0.051). However, Group 8A showed a significantly lower P(v-a)CO₂ value than 8B (P = 0.037). At T24, comparison between 24A and 24B groups revealed significantly differences in C(a-v)O₂ (P = 0.003), P(v-a)CO₂ (P = 0.0006), and ∆PCO₂/∆CaO₂ (P < 0.0001) values.

Table 2: Site of probable infection among the included subjects

| Site of infection among cases (n = 98) | n (%) |
|--------------------------------------|-------|
| Lungs                                | 36 (36.73) |
| Bloodstream infection                | 26 (26.53) |
| Urinary tract                        | 18 (18.36) |
| Abdomen                              | 11 (11.22) |
| Skin and soft tissue infection       | 7 (7.14) |

Table 3: Comparison of various oxygen-derived variables and the volume of fluid used for resuscitation among different groups

| Variable | Group (n) | Mean ± SD | P   | Group (n) | Mean ± SD | P   |
|----------|-----------|-----------|-----|-----------|-----------|-----|
| C(a-v)O₂ (ml/dl of blood) | 8A        | 8.369 ± 3.087 | 0.5018 | 24A        | 11.25 ± 6.597 | 0.0032 |
|          | n=68      | 8.853 ± 3.673 |       | n=62      | 7.44 ± 2.764 |     |
|          | n=30      |            |       | n=30      |            |     |
| P(v-a)CO₂ (mm of Hg)       | 8A        | 9.482 ± 3.303 | 0.0371 | 24A        | 7.289 ± 3.432 | 0.0006 |
|          | n=68      | 11.17 ± 4.327 |       | n=62      | 10.253 ± 4.312 |     |
|          | n=30      |            |       | n=30      |            |     |
| P(v-a)CO₂/C(a-v)O₂         | 8A        | 1.179 ± 0.307 | 0.0513 | 24A        | 0.75 ± 0.335 | 0.0001 |
|          | n=68      | 1.33 ± 0.431 |       | n=62      | 1.5 ± 0.698 |     |
|          | n=30      |            |       | n=30      |            |     |
| Volume of fluid used (ml)  | 8A        | 1865.83 ± 459.17 | 0.11 | 24A        | 738.54 ± 394.95 | 0.0054 |
|          | n=68      | 2045.65 ± 604.32 |       | n=62      | 982 ± 358.49 |     |
|          | n=30      |            |       | n=30      |            |     |

SD: Standard deviation

Table 4: Comparison of receiver operating characteristic curves among variables for the putative predictors of lactate clearance >10% at 8 h and (lactate clearance)>20% at 24 h

| Variable pair | Difference | SE   | LCL (95%) | UCL (95%) | Z    | P   |
|---------------|------------|------|-----------|-----------|------|-----|
| At 8 h        |            |      |           |           |      |     |
| P (v-a)CO₂/C(a-v)O₂ versus P (v-a)CO₂ | 0.0027 | 0.0290 | -0.0542 | 0.0596 | 0.0929 | 0.9260 |
| P (v-a)CO₂/C(a-v)O₂ versus C (a-v)O₂ | 0.0676 | 0.0206 | 0.0272 | 0.1081 | 3.2816 | 0.0010 |
| At 24 h       |            |      |           |           |      |     |
| P (v-a)CO₂/C(a-v)O₂ versus P (v-a)CO₂ | 0.0938 | 0.0163 | 0.0619 | 0.1258 | 5.7582 | <0.001 |
| P (v-a)CO₂/C(a-v)O₂ versus C (a-v)O₂ | 0.5180 | 0.0333 | 0.4528 | 0.5832 | 15.5705 | <0.001 |

LC >10%-LC >10% from T0 to T8 among Groups 8A and 8B. LC >20%-LC >20% from T0 to T24 among Groups 24A and 24B. SE: Standard error, LCL: Lower control limit, UCL: Upper control limit, LC: Lactate clearance
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has maximum AUC. At T24 also, the area under ROC of ∆PCO₂/∆CaO₂ (AUC = 0.823) has the maximum value when compared to P(v-a)CO₂ (AUC = 0.729) and C(a-v)O₂ (AUC = 0.305).

The best cutoff values and the AUC for predicting LC >10% (LC >10% from T0 to T8 among groups 8A and 8B) at T8 and LC >20% (LC rate >20% from T0 to T24 among groups 24A and 24B) at T24 is shown in Table 5. The best cutoff value of ∆PCO₂/∆CaO₂ ratio as a predictor of LC >10% was 1.31, with a sensitivity of 70.6% and specificity of 53.3%. The best cutoff value of ∆PCO₂/∆CaO₂ ratio as a predictor of LC >20% was 1.37, with a sensitivity of 100% and specificity of 50%.

Table 6 depicts the relationship between ∆PCO₂/∆CaO₂ ratio and LC. At both T8 and T24, ∆PCO₂/∆CaO₂ ratio showed a negative correlation with LC (at T8 $r = -0.264$ and T24 $r = -0.531$). However, the correlation among these two variables was significant both at T8 ($P < 0.01$) and T24 ($P < 0.001$). Furthermore, the correlation was more significant at T24. The scatter plot at T8 and T24 is shown in Figures 4 and 5, respectively.

The mortality among the study patients was 35.7% (35/98) at T8, and at T24, it was 31.5% (29/92). Those who demonstrated LC ≥10% and LC ≥20% had lower ICU mortality than those with LC <10% and LC <20%, respectively. The mean ± SD of ∆PCO₂/∆CaO₂ ratio at T8 among survivors and nonsurvivors was 1.21 ± 0.29 and 1.24 ± 0.45, respectively. At T24 ∆PCO₂/∆CaO₂ ratio among survivors and nonsurvivors was 0.77 ± 0.33 and 1.48 ± 0.74. There were no differences observed in ∆PCO₂/∆CaO₂ ratio at T8 ($P = 0.69$), but at T24, there was a considerable difference ($P < 0.001$) in ∆PCO₂/∆CaO₂ between the survivors and nonsurvivors.

**DISCUSSION**

We found that a high ∆PCO₂/∆CaO₂ ratio was related to poor LC at both 8 h and 24 h after initiation of resuscitation [Table 6 and Figures 4, 5]. The correlation between ∆PCO₂/∆CaO₂ ratio and LC was more robust at 24 h than 8 h. The cutoff value of ∆PCO₂/∆CaO₂ ratio observed as a surrogate marker of LC >10% and LC >20% was 1.31 and 1.37 at 8 and 24 h, respectively. This study evaluated the correlation of ∆PCO₂/∆CaO₂ ratio to the arterial LC at 8 and 24 h after the beginning of resuscitation in septic shock patients.

Although there are several drawbacks regarding the use of LC, it has been commonly recognized as a guide of oxygen debt inaccessible. LC is the parameter that reflected the best 28-day mortality in septic patients. Although several parameters were derived from either oxygen or carbon dioxide, including the ∆PCO₂/∆CaO₂ ratio, the latter had shown the best correlation with the arterial lactate level [Table 3 and Figures 2, 3]. The P(v-a)CO₂/C(a-v)O₂ ratio is computed from several easily derived values like central venous oxygen saturation (ScvO₂), hemoglobin (Hb), arterial oxygen saturation (SaO₂), and P(v-a)CO₂ utilizing the formula.

![Figure 3: Comparison between the ROC curves of P(v-a)CO₂/C(a-v)O₂, P(v-a)CO₂ and C(a-v)O₂ at T24](image)

![Figure 4: Scatter plot showing the correlation between P(v-a)CO₂/C(a-v)O₂ ratio and Lactate clearance at T8](image)

**Table 5: Areas under the receiver operating characteristic curve for the putative predictors of lactate clearance >10% at 8 h and lactate clearance >20% at 24 h**

| Variable: P (v-a) CO₂/C (a-v) O₂ | Mean ± SD | AUC  | SE   | Cut-off value | Sensitivity | Specificity |
|---------------------------------|-----------|------|------|--------------|-------------|-------------|
| 8A and 8B at 8 h ($n = 98$)     | 1.2247 ± 0.3540 | 0.5963 | 0.0606 | 1.3134       | 0.7059      | 0.5333      |
| 24A and 24B at 24 h ($n = 92$) | 0.9970 ± 0.5953 | 0.8231 | 0.0427 | 1.3729       | 0.0000      | 1.0000      |

LC >10% LC >10% from T0 to T8 among Groups 8A and 8B. LC >20% LC >20% from T0 to T24 among Groups 24A and 24B. SD: Standard deviation, AUC: Area under the curve, SE: Standard error, LC: Lactate clearance
Thus, the ratio calculation is rapid and straightforward, so detecting a high $\Delta$PCO$_2$/ΔCaO$_2$ ratio would provide a considerable advantage. Further, the causes leading to high $\Delta$PCO$_2$/ΔCaO$_2$ ratio deserve attention to reduce mortality in patients afflicted with septic shock.\cite{20}

$P$(v-a) CO$_2$/C(a-v)O$_2$ ratio was related with LC at 8 h after resuscitation in patients suffering from septic shock.\cite{16} A longer duration of observation of $\Delta$PCO$_2$/ΔCaO$_2$ might result in better outcomes, but there is a dearth of data regarding $\Delta$PCO$_2$/ΔCaO$_2$ in ICU after the first 8 h of treatment for sepsis. In our study, at T8, the patients in Group 8A exhibited a lower $\Delta$PCO$_2$/ΔCaO$_2$ ratio than those in Group 8B, but this disparity lacked statistical significance. However, the $\Delta$PCO$_2$/ΔCaO$_2$ ratio at 24 h (T24) was considerably lower in Group 24A than 24B. We observed a negative correlation between $\Delta$PCO$_2$/ΔCaO$_2$ and LC values, which was significant at both T8 and T24. Elevated $\Delta$PCO$_2$/ΔCaO$_2$ ratio was associated with low LC at T8 and T24. A similar negative correlation was seen with a high $\Delta$PCO$_2$/ΔCaO$_2$ ratio is related to poor LC at T8 in patients of septic shock after resuscitation.\cite{16} Authors reported that patients with LC ≥10% at 8 h after resuscitation showed significantly lower $\Delta$PCO$_2$/ΔCaO$_2$ ratios and ICU deaths than those with 8-h LC <10%. A retrospective study investigating the prognostic significance of $\Delta$PCO$_2$/ΔCaO$_2$ along with serum lactate in patients with septic shock during the early phase of resuscitation (6 h) supported the inverse correlation between $\Delta$PCO$_2$/ΔCaO$_2$ and serum lactate.\cite{21} It also revealed that patients with serum lactate ≥2mmol L$^{-1}$ and Cv-aCO$_2$/Da-vO$_2$ >1 had the worst outcome in terms of SOFA score and 28-day mortality. The best outcome was with serum lactate <2mmol L$^{-1}$ and Cv-aCO$_2$/Da-vO$_2$ value <1. At 6 h of resuscitation, the serum lactate levels independently predicted the 28-day mortality. When Cv-aCO$_2$/Da-vO$_2$ and serum lactate were combined, they had a higher area under ROC of 0.91, significantly greater than that of serum lactate or Cv-aCO$_2$/Da-vO$_2$ alone.\cite{22} Thus, the combination of the two at 6 h was a better marker of prognosis in septic shock.

We also found that the $\Delta$PCO$_2$/ΔCaO$_2$ ratio produced the greatest area under the curve in the prediction of LC. The cutoff value of $\Delta$PCO$_2$/ΔCaO$_2$ varied in the studies published earlier. We observed $\Delta$PCO$_2$/ΔCaO$_2$ with cut-off 1.31 at T8, and 1.37 at T24 was related to LC ≥10% and LC >20%, respectively. Mekontso-Dessap\ et al. conducted a retrospective study of patients with septic shock reported that the delta PCO$_2$/C (a-v) O$_2$ ratio was greater in those with raised lactate levels, showing a good correlation. Further, with a cutoff value of 1.4, the $\Delta$PCO$_2$/ΔCaO$_2$ ratio predicted hyperlactatemia with PPV and NPV of 86% & and 80%, respectively.\cite{13} He et al. stated that assuming the values of $\Delta$PCO$_2$/ΔCaO$_2$, ratio and Da-vO$_2$ to be normal (i.e. 6 mm of Hg and 6 – 8 mm of Hg, respectively), the value of delta PCO$_2$/C (a-v) O$_2$ ratio would be between 0.75 to 1. They postulated that multiple factors could influence the exchange relationships between Pv-aCO$_2$ and Cv-aCO$_2$ for instance, metabolic acidosis, Haldane effect, hemodilution, hypoxic hypoxia, arterial hyperoxia, and acute hyperventilation. Thus, using $P$(v-a)CO$_2$ to replace C(v-a)CO$_2$ could be misleading in clinical practice in these cases.\cite{16} P(v-a)CO$_2$/C(a-v)O$_2$ of more than 1.23 at T8 has been associated with a poor 8-h LC rate (LC <10%) even in patients whose ScvO$_2$ values have returned to normal levels (≥70%) after resuscitation.\cite{16} Ahmad et al. also reported that the P(v-a)CO$_2$/C(a-v)O$_2$ ratio cutoff value of 1.4 at 6 h had an area under the ROC curve of 0.793 for predicting mortality.\cite{22} The threshold value of 1.4 of $\Delta$PCO$_2$/ΔCaO$_2$ ratio predicted a significantly better outcome than other parameters.\cite{24} C (v-a) CO$_2$/D (a-v) O$_2$ >1.0 signifies anaerobic metabolism and would lead to poor clinical outcomes.\cite{14} Thus, $\Delta$PCO$_2$/ΔCaO$_2$ ratio may provide valuable information regarding LC.

In our study, the patients with LC ≥10% and ≥20% showed lower mortality than those with LC <10% and LC <20%, respectively. We did not find any significant

### Table 6: Correlation between $P$ (v-a) CO$_2$/C (a-v) O$_2$ and lactate clearance at 8 h and 24 h

| Pearson’s correlations | Lower 95% CI | Upper 95% CI |
|------------------------|--------------|--------------|
| $P$ (a-v) CO$_2$/C (a-v) O$_2$ ratio at 8 h versus lactate clearance (8 h) | -0.009** | -0.009 | -0.009* |
| $P$ (a-v) CO$_2$/C (a-v) O$_2$ ratio at 24 h versus lactate clearance (24 h) | <0.001 | -0.001 | -0.001 |

**P<0.05, *P<0.01. CI: Confidence interval

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**Figure 5:** Scatter plot showing the correlation between $P$(v-a)CO$_2$/C(a-v)O$_2$ ratio and Lactate clearance at T24
difference between ΔPCO₂/ΔCaO₂ ratios between the survivors and nonsurvivors at T8. However, at T24, the difference was statistically significant (P < 0.001) between the survivors and nonsurvivors. Thus, ΔPCO₂/ΔCaO₂ ratio at 24 h may have prognostic implications. There are limited reports that assessed the impact of ΔPCO₂/ΔCaO₂ on the prognosis of patients diagnosed with septic shock. Mekontso-Dessap et al. found that ΔPCO₂/ΔCaO₂ ratio of less than 1.4 at baseline had a higher overall 1-month survival rate. Value of ΔPCO₂/ΔCaO₂ ratio at baseline (relative risk [RR] 3.85; 95% confidence interval [CI] 1.60–9.27) as well as 6 h (RR 3.97; 95% CI 1.54–10.24) of resuscitation independently predicted for mortality at day 28. Sarker et al. also mentioned that a higher value of Cv-aCO₂/Da-vO₂ was associated with higher mortality, but the study lacked adequate power to explore the predictive value of Cv-aCO₂/Da-vO₂ in septic shock. Similarly, Mesquida et al. found that the nonsurvivors had Cv-aCO₂/Da-vO₂ of 1.9 ± 0.9, whereas the value for survivors was 1.4 ± 0.45.

Studies have shown that persistent hyperlactatemia and high C(v-a)CO₂/D(a-v)O₂ were linked to the most severe organ dysfunction and poor clinical outcomes. In contrast, patients had the best results in patients in whom serum lactate and C (v-a) CO₂/D (a-v) O₂ were corrected concurrently. He et al. found that the ScvO₂ and ΔPCO₂/ΔCaO₂ ratio were comparable at T8 among the survivors and nonsurvivors. However, there was lower ICU mortality and low ΔPCO₂/ΔCaO₂ ratio after resuscitation in those patients with LC ≥ 10%. However, the authors could not demonstrate a significant correlation between ΔPCO₂/ΔCaO₂ ratio and survival because they observed the patients only for 8 h. Our findings did not find any significant difference in ΔPCO₂/ΔCaO₂ ratios at T8 between the survivors and nonsurvivors, but the difference became substantial at T24. Therefore, we recommend that more studies be planned to expound on the relationship between the ΔPCO₂/ΔCaO₂ ratio and mortality among septic patients.

Limitations
This study has several limitations. First, ΔPCO₂/ΔCaO₂ as a pointer of anaerobic metabolism has fallacies. The LC and ΔPCO₂/ΔCaO₂ ratio parameters are global variables and may not be reliable to identify regional or local perfusion disorders. In situations with high CO, e.g., septic shock, ΔPCO₂/ΔCaO₂ ratio may be normal despite significant hypoperfusion. This is because high CO effectively prevented the accumulation of CO₂ in venous blood. Second, as we utilized central venous blood parameters as a surrogate of mixed venous blood, there is a possibility that we have missed the estimation of oxygenation of important organs like kidneys and spleen. Third, the relationship between PCO₂ and CCO₂ is dependent on multiple factors, like oxygen saturation, arterial-venous pH difference, temperature, and hemoglobin concentrations. Thus, this relationship may become nonlinear when any of these parameters become abnormal. Further, the Pv-aCO₂ value may arise in situations other than hypoperfusion, for example, due to the Haldane effect. Finally, the small sample size.

CONCLUSION
ΔPCO₂/ΔCaO₂ ratio is a close substitute for LC. A cutoff value of 1.31 at T8 and 1.37 at T24 was related to LC ≥ 10% and LC > 20%, respectively. Further, 24 h cutoff value of the ΔPCO₂/ΔCaO₂ ratio is superior to the 8-h value in predicting LC in septic shock patients. Moreover, the 24 h ΔPCO₂/ΔCaO₂ ratio had a better predictive value than 8 h.

Research quality and ethics
This study was approved by the Institutional Review Board/Ethics Committee at Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, INDIA, (Approval No 55/18, approval date: February 1, 2021. The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the CONSORT 2010 statement, during the conduct of this research project. The trial was prospectively registered at Clinical Trial Registry - India (CTR1/2021/08/035506).

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Conflicts of interest
There are no conflicts of interest.

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