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Observational Study
Hypoperfusion context as a predictor of 28-day all-cause mortality in septic shock
patients: A comparative observational study

Kataria Sahil et al. Hypoperfusion context in septic shock

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Abstract

BACKGROUND
As per the latest Surviving Sepsis Campaign guidelines, fluid resuscitation should be guided by repeated measurements of blood lactate levels until normalization. Nevertheless, raised lactate levels should be interpreted in the clinical context, as there may be other causes of elevated lactate levels. Thus, it may not be the best tool for real-time assessment of the effect of hemodynamic resuscitation, and exploring alternative resuscitation targets should be an essential research priority in sepsis.

AIM
To compare the 28-d mortality in two clinical patterns of septic shock: hyperlactatemic patients with hypoperfusion context and hyperlactatemic patients without hypoperfusion context.

METHODS
This prospective comparative observational study carried out on 135 adult patients with septic shock that met Sepsis-3 definitions, compared patients of hyperlactatemia with hypoperfusion context (Group 1, n = 95) and hyperlactatemia without hypoperfusion context (Group 2, n = 40). Hypoperfusion context was defined by a central venous saturation ($ScvO_2$) less than 70%; central venous-arterial PCO$_2$ gradient [P(cv-a)CO$_2$] ≥ 6 mmHg; capillary refilling time (CRT) ≥ 4 s. The patients were observed for various macro and micro-haemodynamic parameters at regular intervals of 0, 3, and 6 h. All-cause 28-d mortality and all other secondary objective parameters were observed at specified intervals. Nominal categorical data were compared using the Chi-square or Fisher’s exact test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test. Receiver operating characteristic curve analysis with the Youden index determined the cut-off values of lactate, CRT, and metabolic perfusion parameters to predict the 28-d all-cause mortality. P-value of < 0.05 was considered significant.
RESULTS

Patient demographics, comorbidities, baseline laboratory, vital parameters, source of infection, baseline lactate levels and lactate clearance at 3 and 6 h, Sequential Organ Failure scores, need for invasive mechanical ventilation (MV), days on MV, and renal replacement therapy-free days within 28 d, duration of intensive care unit, and hospital stay were comparable between the two groups. The stratification of patients into hypoperfusion and non-hypoperfusion context did not result in a significantly different 28-d mortality (24% vs 15%, respectively, P-value 0.234). However, the patients within the hypoperfusion context with high P(cv-a)CO₂ and CRT (P-value 0.022) at baseline had significantly higher mortality than Group 2. The norepinephrine dose was higher in Group 1 but did not achieve statistical significance with a P-value > 0.05 at all measured intervals. Group 1 had a higher proportion of patients requiring vasopressin and the mean vasopressor-free days out of the total 28 d were lower in patients with hypoperfusion context (18.88 ± 9.04 vs 21.08 ± 8.76, P-value 0.011). The mean lactate levels and lactate clearance at 3 and 6 h, CRT, P(cv-a)CO₂ at 0, 3, and 6 h were found to be associated with 28-d mortality in patients with septic shock, with lactate levels at 6 h having the best predictive value (Area under the curve lactate at 6 h: 0.845).

CONCLUSION

Septic shock patients fulfilling the hypoperfusion and non-hypoperfusion context exhibit similar 28-d all-cause hospital mortality, although patients with hypoperfusion context displayed a more severe circulatory dysfunction. Lactate levels at 6 h had a better predictive value in predicting 28-d mortality than other parameters. Persistently high P(cv-a)CO₂ (> 6 mmHg) or raised CRT (> 4 s) at 3 and 6 h during the early resuscitation can be a valuable additional aid for prognostication of septic shock patients.
**Key Words**: Capillary refill time; Central venous saturation; Hypoperfusion; Lactate; Mortality; PCO₂ gap; Septic shock.


**Core Tip**: Two different clinical patterns among hyperlactatemic septic shock patients can be effectively differentiated when utilising three easily employable perfusion parameters. Lactate levels are still the best available tool, but persistence of high P(cv-a)CO₂ (> 6 mmHg) or raised capillary refill time (> 4 s) at 3 and 6 h along with lactate metrics during the early resuscitation can be valuable for guiding resuscitation of septic shock patients.

**INTRODUCTION**

Septic shock remains the most frequent cause of mortality in patients admitted to the intensive care unit (ICU), contributing 33% to 50% to the total inpatient hospital deaths[^1-3]. Early recognition and adequate resuscitation of patients with sepsis-associated circulatory dysfunction is a fundamental challenge for an intensivist. Undertreatment may lead to persistently impaired tissue oxygenation, whereas overtreatment may lead to a positive fluid balance that can result in pulmonary oedema, prolonged mechanical ventilation (MV), and death[^4-9].

Viewing the strong relationship between hyperlactatemia, lactate kinetics, and mortality[^10], and following the study results by Jansen et al[^10], surviving sepsis guidelines, 2012 suggested fluid resuscitation guided by repeated measurement of blood lactate levels until normalization[^11]. However, as per surviving sepsis guidelines 2021, lactate level interpretation should be based on the clinical context, and other causes of elevated lactate levels, such as adrenergic-driven aerobic lactate production and impaired hepatic lactate clearance, should be considered[^12]. Thus, lactate levels
might not be the best tool for real-time assessment of the effect of hemodynamic resuscitation\textsuperscript{[15,16]}, Therefore, exploring alternative resuscitation targets is an important research priority in sepsis.

Variables such as central venous saturation (ScvO\textsubscript{2}), central venous-arterial PCO\textsubscript{2} gradient [P(cv-a)CO\textsubscript{2}], and peripheral (skin) perfusion markers exhibit a very fast normalization rate concerning systemic flow optimization\textsuperscript{[14]}. A concomitant low ScvO\textsubscript{2} high P(cv-a)CO\textsubscript{2}, or abnormal peripheral perfusion define a “hypoperfusion context” in which increasing systemic blood flow may reduce blood lactate levels. Thus, multimodal perfusion monitoring could aid in identifying a hypoperfusion context.

This study aimed to analyze septic shock patients and compare the outcome in two clinical patterns: hyperlactatemic patients with hypoperfusion context and hyperlactatemic patients without hypoperfusion context. The hypoperfusion context in the present study was defined similarly to the study by Alegria et al\textsuperscript{[15]}; ScvO\textsubscript{2} Less than 70%; P(cv-a)CO\textsubscript{2} greater than or equal to 6 mmHg; capillary refilling time (CRT) greater than or equal to 4 s(s), together with hyperlactatemia after initial fluid resuscitation in septic shock patients admitted in ICU.

**MATERIALS AND METHODS**

The present study was a prospective comparative observational study conducted in the Medical Intensive care unit (MICU), Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi, from March 2021 to November 2021. Institutional Human Ethics Committee approval was obtained before the commencement of the study (Reference number: TS/MSSH/MHIL/SKT-1/MHEC/CC/20-14). All consecutive adult non-pregnant patients aged 18 years and above were admitted to the MICU with septic shock (according to sepsis-3 definition\textsuperscript{[11]}), for whom concomitant values for ScvO\textsubscript{2}, P(cv-a)CO\textsubscript{2}, and CRT could be obtained were considered eligible for this study. Patients with severe cardiorespiratory disease and active bleeding were excluded. Written informed consent was obtained from all the patients. Our estimated sample size was based on a previous study\textsuperscript{[15]}, which analysed the mortality in septic...
shock patients with hypoperfusion context vs those with non-hypoperfusion context. With reference to this previous study, we defined a relevant clinical difference of 11% (5% in non-hypoperfusion vs 16% in hypoperfusion) in mortality between the two groups. Thus, a sample size of 95 patients per group provided an 80% power for detecting a significant difference between the two groups at an alpha level of 0.05. As observed from the previous study,[9] the number of patients with and without hypoperfusion context is in the ratio of 3:7. Thus, 135 patients in total were taken during the study period—95 patients with hypoperfusion context and 40 patients without hypoperfusion context.

Patients were enrolled and categorised as follows: Group 1, patients with hypoperfusion context; Group 2, patients with non-hypoperfusion context.

Preload optimization was guided by an algorithm (Figures 1 and 2) which included early fluid loading, followed by vasopressor infusion as needed to maintain a mean arterial pressure (MAP) > 65 mmHg. Surviving Sepsis Campaign (SSC) guidelines 2016 were followed to guide the treatment of septic shock.[1] All patients were followed up for 28 d. The following primary and secondary outcomes were measured as part of the multimodal perfusion assessment:

Primary outcome, All-cause mortality at the 28th day (asked telephonically if patient discharged earlier).

Secondary outcomes, Macro-hemodynamic variables measured at baseline: systolic blood pressure, diastolic blood pressure, MAP, heart rate, norepinephrine (NE) or vasoactive drug doses; Metabolic-related perfusion variables measured at 0 (baseline), 3 and 6 h: SvO₂ and P(cv-a)CO₂. Lactate measurement and percentage of lactate clearance at 0 (baseline), 3 and 6 h: The normal level was defined as less than 2 mmol/L. Lactate was assessed using an arterial sample and processed by a point of care common gas analyser. The percentage of lactate clearance was defined as Lactate clearance = (Lactate initial-Lactate time) × 100 / Lactate initial; CRT measured at 0 (baseline), 3 and 6 h: Normal values were considered to be ≤ 4.0 s. It was measured by applying firm pressure to the right index finger's ventral surface of the distal phalanx with a glass
microscope slide. The pressure was increased until the skin blanched, was then maintained for 10 s and then released. The time for the return of the normal skin colour was recorded using a chronometer, and a refill time greater than 3 s was defined as abnormal; Amount of fluid administered measured at 0, 6 and 24 h; Vasopressor dose measured at 0, 3, 6, 12 and 24 h; Duration of vasopressor use in days; Need of invasive MV and duration on invasive MV in days, MV-free days within 28 d; Need for renal replacement therapy (RRT) and RRT-free days within 28 d; ICU and hospital length of stay.

**Statistical analysis**

Continuous variables were presented as mean ± SD for normally distributed data, and median ± interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's t-test. Nominal categorical data between the groups were compared using the Chi-square test or Fisher's exact test. Mann Whitney U test was done to compare two group means. Receiver operating characteristic curve (ROC) analysis with the Youden index was done to determine each parameter's cut-off value to predict the outcome. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated based on those cut-off values. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

**RESULTS**

A total of 148 patients met the inclusion criteria in the present study, out of which 7 had severe left ventricular systolic dysfunction, 1 was pregnant, and 5 refused to consent to participate. So, 135 patients were included in the study, 95 patients with hypoperfusion context (Group 1) and 40 patients with non-hypoperfusion context (Group 2). Patient demographics, comorbidities, baseline laboratory and vital parameters, source of infection, and Sequential Organ Failure scores were comparable between the two
groups (Tables 1 and 2). APACHE II score was higher in Group 2 (23.78 ± 5.414 vs 23.78 ± 5.414, P-value < 0.002). The baseline lactate levels were 4.84 ± 1.7 mmol/L and were comparable in both the groups at baseline (4.87 ± 1.69 vs 4.76 ± 1.75 mmol/L, P-value 0.594) and all measured intervals. The primary and secondary outcomes of Group 2 were compared with Group 1 and also with the sub-groups of Group 1 (Table 3).

The overall 28-d mortality was 21% in 135 patients, 24% in the hypoperfusion context group vs 15% in the non-hypoperfusion context (P-value 0.234). However, the patients within the hypoperfusion context with high P(cv-a)CO2 and CRT (P-value 0.022) at baseline had significantly higher mortality as compared to Group 2. The mean dose of noradrenaline at baseline in all the study patients was 0.19 ± 0.14 mcg/kg/min. Although the NE requirement was higher in Group 1, it did not attain statistical significance at any specified interval (P-value > 0.05). Group 1 had a higher proportion of patients requiring vasopressin, with lower mean vasopressor-free days out of the total 28 d (18.88 ± 9.04 vs 21.08 ± 8.76, P-value 0.011). Similarly, Group 1 had a higher fluid requirement than Group 2 at 0 and 6 h (P-value 0.045 and 0.008, respectively). The need for invasive MV, days on MV, renal replacement therapy-free days within 28 d, and ICU and hospital stay duration were comparable between the groups (Table 3).

Univariate analysis of baseline variables and primary and secondary outcomes were also done between the survivors and non-survivors (Table 4). We also analyzed the prognostic value of mean lactate levels, lactate clearance, ScvO2, CRT, P(cv-a)CO2 at 0, 3, and 6 h for 28-d all-cause mortality. In the current study, although the lactate levels at baseline were higher in non-survivors than the survivors, they were statistically insignificant (5.2 ± 2.72 vs 4.74 ± 1.69, P-value 0.151). Nevertheless, a significant association between lactate levels at 3 and 6 h and lactate clearance at 3 and 6 h was observed with the 28-d mortality, with lactate levels at 6 h having a better predictive value than lactate clearance at 6 h [area under the ROC (AUROC) for lactate at 3 and 6 h: 0.776 and 0.845, respectively; AUROC for lactate clearance at 3 and 6 h 0.754 and 0.834, respectively] (figure 3). The optimal cut-off value for lactate values at 3 h in predicting 28-d mortality was ≥ 4.2 mmol/L, with a sensitivity of 55.2% and specificity 8 / 16
of 63.2%, PPV of 29.1%, and NPV of 83.8%. Similarly, the cut-off for the 6 h lactate levels was ≥ 4.1 mmol/L with a sensitivity of 74.2%, specificity of 84.9%, PPV of 55.6%, and NPV of 92.8% (Tables 5 and 6).

Regarding Svo2, a statistical significance at baseline between non-survivors and survivors, a P-value of 0.033 was observed in the present study. However, mean Svo2 at 3 and 6 h was comparable between non-survivors and survivors (P-value 0.304 and 0.299, respectively) (Table 5).

In the current study, \( P_{(cv-a)CO_2} \geq 6 \text{ mmHg} \) at baseline was used as one of the criteria of hypoperfusion and was measured at baseline, 3 and 6 h. At baseline, the mean \( P_{(cv-a)CO_2} \) was 5.92 ± 1.91 mmHg. \( P_{(cv-a)CO_2} \) was higher in survivors than non-survivors at baseline, 3 h, and 6 h, which achieved statistical significance with a P-value of 0.036, < 0.001, < 0.001, respectively. In the current study, the cut-off values of \( P_{(cv-a)CO_2} \) in predicting 28-d mortality at baseline was ≥ 7.6 mmHg (AUC: 0.627; sensitivity: 44.8%; specificity: 81.1%; PPV: 39.4%; NPV: 84.3%; accuracy: 73.3%; P-value: 0.004). Similarly, cut-off for \( P_{(cv-a)CO_2} \) at 3 and 6 h was ≥ 5.9 and 6.45 mmHg, respectively (Tables 5 and 6).

Similarly, a statistically significant association was found between the 28-d mortality and CRT levels at baseline, 3 and 6 h. (P-value of 0.004, < 0.001, and < 0.001, respectively). The area under the ROC curve to estimate mortality for CRT at baseline was 0.623 (95% CI, 0.536-0.705), while for CRT at 3 and 6 h, it was 0.768 (95% CI, 0.688-0.837) and 0.705 (95% CI, 0.675-0.827) with the asymptotic significance of < 0.001 and < 0.001, respectively. In the present study, the cut-off point to predict 28-d mortality for CRT at baseline was 4 s, with a sensitivity of 55.2% and specificity of 67.9%, while the cut-off point for CRT at 6 h was 7 s, with a sensitivity of 51.9%, and a specificity of 94.3% (P-value < 0.001) (Tables 5 and 6).

We also performed a multivariate logistic regression analysis to predict variables associated with 28-d mortality. Only lactate levels at 6 h [odds ratio (OR) = 1.344, 95% CI, 1.168 to 1.546, P < 0.001] and baseline serum creatinine [OR = 1.515, 95% CI,
1.036-2.216, \( P < 0.001 \) were identified as independent risk factors of 28-d mortality (Table 7).

**DISCUSSION**

Although serum lactate has been established as an objective surrogate marker for tissue hypoxia and disease severity in septic shock, an absolute dependence on serial lactate levels to guide fluid resuscitation may lead to over-resuscitation in some cases. Hence, alternative measures for assessing perfusion such as CRT, ScvO₂, and \( P(\text{cv-a})\text{CO}_2 \) might be more pragmatic. A recent study by Algeria et al[13], used CRT, \( P(\text{cv-a})\text{CO}_2 \), and ScvO₂ to define hypoperfusion context and demonstrated that patients with hyperlactatemia plus hypoperfusion context, exhibit a severe circulatory dysfunction with increased morbidity. However, this study was retrospective and did not examine the superiority of serial measurements of CRT, \( P(\text{cv-a})\text{CO}_2 \), and ScvO₂ over serial lactate measurements in predicting poor outcome in patients with septic shock. In the present prospective observational study involving 135 patients with septic shock, the outcome in two different clinical patterns of septic shock was analysed: hypoperfusion context vs non-hypoperfusion context. Similar to the results by Algeria et al[13], the stratification of patients in the present study into hypoperfusion and non-hypoperfusion context did not result in a significant difference in 28-d mortality. However, in the present study, the subgroup of patients within the hypoperfusion context with a high \( P(\text{cv-a})\text{CO}_2 \) and CRT exhibited significantly higher mortality than those in the non-hypoperfusion context.

Baseline characteristics were comparable between the groups, apart from the APACHE II score, which was higher in Group 2. As the APACHE II score calculation involves chronic co-morbidities, a higher APACHE II score in the non-hypoperfusion context could be attributed to more patients with cirrhosis and dialysis dependence.

Although the dose requirement of NE was higher in patients with hypoperfusion context at all intervals compared to Group 2, it did not achieve statistical significance. These results differ from Algeria et al[13], who reported significantly higher NE.
requirements (P-value < 0.005) in the hypoperfusion context group. This difference
could be due to a higher proportion of patients requiring vasopressin in the
hypoperfusion context group in the present study. The present study also observed a
higher fluid requirement in Group 1 at 0 and 6 h. Consequently, this signifies the
presence of more severe circulatory dysfunction in Group 1 than in Group 2. The rest of
the secondary outcomes were comparable between Group 1 and Group 2.

Serum lactate has been established to be of prognostic value in patients with septic
shock. Marty et al[14] showed a significant difference between the lactate values at
baseline, 6, 12, or 24 h between the survivors and non-survivors group (P-value < 0.05
for each time interval). Analysis of AUROC for lactate levels at baseline, 3 and 6 h to
predict the 28-d mortality revealed that initial lactate levels had a poor predictive value
compared to those at 3 and 6 h in the current study. These results are similar to the
study by Lee et al[17], conducted in 2021, in which the lactate levels at 6 h had a better
prognostic performance. In the present study, the optimal cut-off value for lactate
values in predicting 28-d mortality was ≥ 4.2 mmol/L with a sensitivity of 55.2% and
specificity of 63.2%, PPV of 29.1%, and NPV of 83.8%. Similarly, the cut-off for the 6 h of
lactate levels was ≥ 4.1 mmol/L with a sensitivity of 74.2%, specificity of 84.9%, PPV of
55.6%, and NPV of 92.8%. These findings differ from the study mentioned above by Lee
et al[17], where the optimal cut-off of 6 h lactate levels was ≥ 2 mmol/L with the highest
sensitivity [89.2% (95% CI, 83.0%-93.7%)], but the specificity was relatively lower [35.3%
(95% CI, 29.0%-42.1%)].

Lactate clearance is defined as the rate of decline in lactate concentration. It has been
extensively studied and is a strong independent predictor of survival in patients with
septic shock, with lactate non-clearance consistently linked to increased mortality[16]. In
our study, lactate clearance remained higher in survivors than non-survivors at all time
intervals in the study period. Although the prognostic value of lactate clearance at 6 h
was better than at 3 h, the metrics were inferior to the static lactate levels at the
corresponding time intervals. Similar results were observed in a study by Ryoo et al[18]
in which lactate and lactate clearance at 6 h was associated with higher mortality;
lactate levels had significantly higher prognostic value than lactate clearance. On multivariate analysis to evaluate mortality, among all variables assessed, only lactate at 6 h and baseline serum creatinine was independently associated with 28-d mortality (Table 7).

ScvO2 trends correlate well with mixed central venous oxygen saturation and have been independently associated with mortality in septic shock\textsuperscript{19,20}, with threshold values supporting those published in SSC guidelines 2012\textsuperscript{21}. Normalization of ScvO2 does not rule out persistent tissue hypoperfusion, and the latter can still occur due to severe microcirculatory disorders and mitochondrial dysfunction\textsuperscript{21,22}. Moreover, if ScvO2 < 70% is associated with mortality\textsuperscript{23}, it does not mean that ScvO2 ≥ 70% is associated with survival\textsuperscript{24}. Thus, in some circumstances, the use of ScvO2 might mistakenly drive an intensivist to conclude that the patient’s physiologic state has improved when, in fact, it may have not. According to the results of the current study, ScvO2 appears to be a valuable tool for initial resuscitation but cannot distinguish between survivors and non-survivors after initial resuscitation.

The P(cv-a)CO\textsubscript{2} gap represents an excellent surrogate indicator of the adequacy of cardiac output and tissue perfusion under a given condition of CO\textsubscript{2} production. Recently, Osprina-Tascón et al\textsuperscript{25} showed that the persistence of high P(cv-a)CO\textsubscript{2} (≥ 6 mmHg) during the first 6 h of resuscitation of septic shock patients is associated with severe multiple organ dysfunction and increased mortality rate (Relative Risk = 2.23, \(P = 0.01\)). There is a strong agreement between P(cv-a)CO\textsubscript{2} and P(cv-a)CO\textsubscript{2}, though it should not be interchanged. In the present study, it was observed that P(cv-a)CO\textsubscript{2} was higher in survivors than non-survivors at all time intervals, and persistence of PCO\textsubscript{2} gap > 6.5 mmHg at 3 and 6 h during early resuscitation of septic shock patients was associated with higher mortality rates. The cut-off values of P(cv-a)CO\textsubscript{2} in predicting 28-d mortality at baseline was ≥ 7.6 mmHg (AUC: 0.627; sensitivity: 44.8\%; specificity: 81.1\%; PPV: 39.4\%; NPV: 84.3\%; accuracy: 73.3\%; \(P\)-value:0.004). Similarly, cut-off at 6 h was ≥ 6.45 mmHg (AUC: 0.689; sensitivity: 58.6\%; specificity: 83.0\%; PPV: 48.6\%; NPV: 88.0\%; accuracy: 77.8\%; \(P\)-value: <0.001). A study by Helmy et al\textsuperscript{26} observed P(cv-a)CO\textsubscript{2}
cut-off of ≥ 8.4 mmHg at 0 h and ≥ 7.8 mmHg at 6 h as a predictor of all-cause hospital mortality. The difference in cut-off may be because of the increased specificity of later. Consequently, high P(\text{cv-a})CO₂ > 6 mmHg at 6 h could identify patients with septic shock at high mortality risk in apparently resuscitated patients.

CRT has emerged as a reasonable alternative to guide septic shock resuscitation. The skin territory lacks auto-regulatory flow control, therefore, sympathetic activation can impair skin perfusion during circulatory dysfunction, a phenomenon that can be assessed by measuring CRT. CRT can be easily measured at the bedside with no additional equipment required beyond a chronometer (i.e., a clock or the stopwatch on your phone). Measurement of CRT upon admission assesses the alteration in microcirculation at 3 and 6 h; it also evaluates the response to resuscitation. The present study found a statistically significant association between the 28-d mortality and CRT at baseline, 3 and 6 h. Similar results were described by Morocho et al., who concluded that the measurement of CRT at baseline, 3 and 6 h was a strong predictor of mortality in septic shock, even above the widely studied markers such as lactate. Castro et al. demonstrated that CRT-targeted fluid resuscitation was associated with a higher and faster achievement of resuscitation targets and exhibited similar improvement in hypoxia surrogates and regional blood flow to those observed with lactate-targeted fluid resuscitation. These results were in contradiction with that of the ANDROMEDA-SHOCK trial. It may be due to the difference in the duration of intervention periods of both studies and the different kinetics of CRT and Lactate. In accordance with the current literature and the results of the present study, CRT is a reliable marker for assessing the severity of clinical perfusion. Its frequent bedside assessment alone can improve resuscitation in septic shock, especially in low-resource settings.

In the present study, it was observed that the cut-off point to predict 28-d mortality for CRT at baseline was 4 s, with a sensitivity of 55.2% and specificity of 67.9%, while the cut-off point for CRT at 6 h was 7 s, with a sensitivity of 51.9%, and a specificity of 94.3%. The corresponding CRT cut-offs by Morocho et al. at admission and 6 h were 4.5 s at admission, and 3.5 s at 6 h post-resuscitation. This cut-off at 6 h was different
from the present study, which may be because of temperature associated variation, inter-rater variability and high melanin concentration in our population. In dark-skinned people (phototypes V and VI), the high concentration of melanin in the epidermis absorbs much of the light, so the reflected light contribution comes mainly from the melanin contribution and not from the perfusion change caused in the dermis during compression, causing an error in the CRT measurement. This can be overcome by newly developed optical devices to objectively assess CRT. Recently the role of melanin pigment in controlling the immune response has been increasingly recognized. Melanocytes containing little melanin produce more cytokines, such as TNF, IL-1β, IL-6, and IL-10, and thus can cause fluctuation in the immune response levels.

The current study had a few limitations. This non-experimental observational study could only demonstrate an association between hypoperfusion context and 28-d mortality but could not establish the cause-and-effect relationship. We used all-cause in-hospital mortality as our primary outcome; patients might have died from non-sepsis-related causes. Given the various aetiologies of hyperlactatemia, drugs or comorbidities causing hyperlactatemia of any clinical significance could not be accounted for, making interpretation of hyperlactatemia challenging. Although the personnel were thoroughly trained to assess CRT using a standardized technique, we did not consider the interrater variability and skin temperature, which could alter CRT values. Lastly, this was a single-centre study with a small sample size. Future multicentre prospective studies with larger sample sizes must conclusively establish the endpoints of early resuscitation in septic shock to reduce patient mortality.

CONCLUSION
Septic shock patients fulfilling the hypoperfusion and non-hypoperfusion context exhibit similar 28-d all-cause hospital mortality, although patients with hypoperfusion context displayed a more severe circulatory dysfunction. Targeting ScvO2 may not be desirable as normalization of ScvO2 does not rule out persistent tissue hypoperfusion.
Lactate levels at 6 h had a better prognostic value in predicting 28-d mortality than other parameters. Persistently high P(cv-a)CO₂ (> 6 mmHg) or raised CRT (> 4 s) at 3 and 6 h during the early resuscitation can be a valuable additional aid for prognostication of septic shock patients.

**ARTICLE HIGHLIGHTS**

**Research background**

As per the latest Surviving Sepsis Campaign guidelines, fluid resuscitation should be guided by repeated measurements of blood lactate levels until normalization.

**Research motivation**

Serum lactate is a non-specific biomarker which may be raised in a myriad of clinical conditions. Thus, it may not be the best tool for real-time assessment of the effect of hemodynamic resuscitation, and exploring alternative resuscitation targets should be an essential research priority in sepsis.

**Research objectives**

To compare the 28-d mortality in two clinical patterns of septic shock: hyperlactatemic patients with hypoperfusion context and hyperlactatemic patients without hypoperfusion context.

**Research methods**

This prospective comparative observational study carried out on 135 adult patients with septic shock that met Sepsis-3 definitions, compared patients of hyperlactatemia with hypoperfusion context (Group 1, n = 95) and hyperlactatemia without hypoperfusion context (Group 2, n = 40). The patients were observed for various macro and micro-haemodynamic parameters at regular intervals of 0, 3, and 6 h. All-cause 28-d mortality and all other secondary objective parameters were observed at specified intervals.
Research results

The stratification of patients into hypoperfusion and non-hypoperfusion context did not result in a significantly different 28-d mortality (24\% vs 15\%, respectively, \(P\)-value 0.234). However, the patients within the hypoperfusion context with high P(c-v)aCO\(_2\) and CRT (\(P\)-value 0.022) at baseline had significantly higher mortality than Group 2. Group 1 had a higher proportion of patients requiring vasopressin and the mean vasopressor-free days out of the total 28 d were lower in patients with hypoperfusion context (18.88 ± 9.04 vs 21.08 ± 8.76, \(P\)-value 0.011). The mean lactate levels and lactate clearance at 3 and 6 h, CRT, P(c-v)aCO\(_2\) at 0, 3, and 6 h were found to be associated with 28-d mortality in patients with septic shock, with lactate levels at 6 h having the best predictive value (AUC 0.845).

Research conclusions

Septic shock patients fulfilling the hypoperfusion and non-hypoperfusion context exhibit similar 28-d all-cause hospital mortality, although patients with hypoperfusion context displayed a more severe circulatory dysfunction. Lactate levels at 6 h had a better predictive value in predicting 28-d mortality. Persistently high P(c-v)aCO\(_2\) (> 6 mmHg) or raised CRT (> 4 s) at 3 and 6 h during the early resuscitation can be a valuable additional aid for prognostication of septic shock patients.

Research perspectives

Multicenter large scale trials should be conducted to further evaluate the role of CRT and PCO\(_2\) gap as markers for resuscitation in patients with septic shock.
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<td>Matthias Jacob, Daniel Chappell, Bernhard F. Becker. &quot;Regulation of blood flow and volume exchange across the microcirculation&quot;, Critical Care, 2016</td>
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<td>Pouya Farokhnezhad Afshar, Elisabeth H. Wiig, Seyed Kazem Malakouti, Behnam Shariati, Sara Nejati. &quot;Reliability and validity of a quick test of cognitive speed (AQT) in screening for mild cognitive impairment and dementia&quot;, BMC Geriatrics, 2021</td>
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