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

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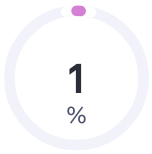

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INTRODUCTION

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, and death[4-8].

Viewing the strong relationship between hyperlactatemia, lactate kinetics, and mortality[9] 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[13,14]. Therefore, exploring alternative resuscitation targets is an important research priority in sepsis.

Variables such as central venous saturation (ScvO2), central venous- arterial PCO2 gradient (P(cv-a) CO2), and peripheral (skin) perfusion markers exhibit a very fast normalization rate concerning systemic flow optimization [14]. A concomitant low ScvO2, high P(cv-a)CO2, 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 Algeria L et al.[15]: ScvO2 less than 70%; P(cv-a) CO2 greater than or equal to 6 mm Hg; capillary refilling time (CRT) greater than or equal to 4 seconds(s), together with hyperlactatemia after initial fluid resuscitation in septic shock patients admitted in ICU.

MATERIAL 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[1]), for whom concomitant values for ScvO2, P(cv-a)CO2, 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[15], which analyzed the mortality in septic shock patients with the hypoperfusion context versus those with the 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[15], 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 categorized 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 days. The following primary and secondary outcomes were measured as part of the multimodal perfusion assessment:

Primary outcome

1. All-cause mortality at the 28th day (asked telephonically if the patient was discharged earlier).

Secondary outcomes

1. Macro-hemodynamic variables measured at baseline: systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, heart rate (HR), norepinephrine (NE) or vasoactive drug doses.
2. Metabolic-related perfusion variables measured at 0 (baseline), 3 and 6 hours: ScvO2, and P (cv-a) CO2.
3. Lactate measurement and percentage of lactate clearance at 0 (baseline), 3 and 6 hours: 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 analyzer. The percentage of lactate clearance was defined as Lactate clearance = (Lactate initial- Lactate time) x 100 / Lactate initial.
4. Capillary refill time measured at 0 (baseline), 3 and 6 hours: Normal values were considered to be ≤ 4.0 seconds. 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 seconds 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 seconds was defined as abnormal.
5. Amount of fluid administered measured at 0, 6 and 24 hours.
6. Vasopressor dose measured at 0, 3, 6, 12 and 24 hours.
7. Duration of vasopressor use in days.
8. Need of invasive mechanical ventilation and duration on invasive mechanical ventilation in days, mechanical ventilation–free days within 28 days.
9. Need for renal replacement therapy (RRT) and RRT–free days within 28 days.
10. ICU and hospital length of stay.

Statistical methods

Continuous variables were presented as mean ± SD for normally distributed data and median ± IQR 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 appropriate 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 (Table 1 and Table 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 the sub-groups of Group 1(Table 3). The 28-day mortality in group 1 was (24% vs 15%, respectively, p-value of 0.234) in the two groups. 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 mean dose of noradrenaline at baseline in all the study patients was 0.19 ± 0.14 mcg/kg/min. Although the norepinephrine (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 days (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 hours (p- values 0.045 and 0.008, respectively). The need for invasive mechanical ventilation (MV), days on MV, renal replacement therapy-free days within 28 days, 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, and P(cv-a) CO2 at 0, 3, and 6 hours for 28-day 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±1.72 vs 4.74±1.69, p-value 0.151). Nevertheless, a significant association between lactate levels at 3 and 6 hours and lactate clearance at 3 and 6 hours was observed with the 28-day mortality, with lactate levels at 6 hours having a better predictive value than lactate clearance at 6 hours (area under the receiver operating curve (AUROC) for lactate at 3 and 6 hours: 0.776 and 0.845, respectively; AUROC for lactate clearance at 3 and 6 hours 0.754 and 0.834, respectively) (figure 3). The optimal cut-off value for lactate values at 3 hours in predicting 28-day 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 hours 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% (Tables 5 and 6).

Regarding ScvO2, a statistical significance at baseline between non-survivors and survivors, a p-value of 0.033 was observed in the present study. However, the mean ScvO2 at 3 and 6 hours was comparable between non-survivors and survivors (p-value 0.304 and 0.299, respectively) (Table 5).

In the current study, P(cv-a) CO2 ≥ 6mmhg at baseline was used as one of the criteria of hypoperfusion and was measured at baseline, 3 and 6 hours. At baseline, the mean P(cv-a) CO2 was 5.92 ± 1.91 mmHg. P(cv-a) CO2 was higher in survivors than non-survivors at baseline, 3 hours, and 6 hours, 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) CO2 in predicting 28-day 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, the cut-off for P(cv-a) CO2 at 3 and 6 hours was ≥5.9 and 6.45 mmHg, respectively (Tables 5 and 6)

Similarly, a statistically significant association was found between the 28-day mortality and CRT levels at baseline, 3 and 6 hours. (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 hours, it was 0.768 (95% CI, 0.688-0.837) and 0.705 (95% CI, 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-day mortality for CRT at baseline was 4 seconds, with a sensitivity of 55.2% and specificity of 67.9%. In comparison,

the cut-off point for CRT at 6 hours was 7 seconds, 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-day mortality. Only lactate levels at 6 hours (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 to 2.216, p < 0.001) were identified as independent risk factors of 28-day 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(cv-a) CO2, might be more pragmatic. A recent study by Algeria et al. used CRT, P(cv-a) CO2, and ScvO2 to define the hypoperfusion context. It demonstrated that patients with hyperlactatemia plus hypoperfusion context exhibit a severe circulatory dysfunction with increased morbidity[15]. However, this study was retrospective and did not examine the superiority of serial measurements of CRT, P(cv-a) CO2, and ScvO2 over serial lactate measurements in predicting poor outcomes 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 analyzed: hypoperfusion context vs non- hypoperfusion context. The overall 28-day mortality rate was 21% in 135 patients. Similar to

the results by Algeria et al., the stratification of patients in the present study into hypoperfusion and non-hypoperfusion context did not result in a significant difference in 28-day mortality. However, in the present study, the subgroup of patients within the hypoperfusion context with a high P(cv-a) CO2 and CRT exhibited significantly higher mortality than those in the non-hypoperfusion context.

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

Although the difference in NE doses between the two groups was not statistically significant, the dose requirement was higher in patients with hypoperfusion context at all intervals. These results differ from Algeria et al. [15], 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 hours. Hence, 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. It is utilized as a more objective surrogate marker for tissue hypoxia and disease severity, independent of the blood pressure.

In a previous study by Godinjak A et al., the initial lactate levels in non-survivors were 4.88 mmol/l vs 3.64 mmol/l in survivors (p-value 0.021). Marty P et al. showed a significant difference between the lactate values at baseline, 6, 12, or 24 hours 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 hours to predict the 28-day mortality revealed that initial lactate levels had a poor predictive value compared to those at 3 and 6 hours in the current study. These results are similar to the study by Lee SG et al., conducted in 2021, in which the lactate levels at 6 hours had a better prognostic performance[16]. In the present study, the optimal cut-off value for lactate values in predicting 28-day 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 hours 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 SG et al., where the optimal cut-off of 6 hours 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%)] [16].

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. Lactate clearance remained higher in survivors than non-survivors at all time intervals in the study period. However, lactate clearance at 6 hours had lower AUC than static lactate levels at 6 hours (AUC: 0.619 vs 0.706). Although the prognostic value of lactate clearance at 6 hours was better than at 3 hours, the metrics were inferior to the static lactate levels at the

corresponding time intervals. Similar results were observed in a study by Ryoo SM et al. in which lactate and lactate clearance at 6 hours was associated with higher mortality; lactate levels had significantly higher prognostic value than lactate clearance[17]. On multivariate analysis to evaluate mortality, among all variables assessed, only lactate at 6 hours and baseline serum creatinine was independently associated with 28-day mortality (Table 7).

In patients with septic shock, the causes of elevated serum lactate can be multifactorial. Apart from acute tissue hypoperfusion and anaerobic metabolism, hyperlactatemia can be attributed to other causes: 1) sepsis-induced impairment of pyruvate-dehydrogenase enzyme activity, 2) increased lactate production via catechol-amine-driven pathways, and 3) decreased lactate clearance due to hepatic dysfunction69. Hence, alternative measures for assessing perfusion (such as CRT, P(cv-a) CO2, and ScvO2) might be more pragmatic, as absolute dependence on serial lactate levels to guide fluid resuscitation may lead to over-resuscitation in some cases.

The P(cv-a) CO2 gap represents an excellent surrogate indicator of the adequacy of cardiac output and tissue perfusion under a given condition of CO2 production. Recently, Ospina-Tascon GA et al. showed that the persistence of high P(v-a) CO2 (> 6 mmHg) during the first 6 hours of resuscitation of septic shock patients is associated with severe multiple organ dysfunction and increased mortality rate (Relative Risk = 2.23, P = 0.01)57. There is a strong agreement between P(v-a) CO2, and P(cv-a) CO2, though it should not be interchanged. In the present study, it was observed that P(cv-a) CO2 was higher in survivors than non-survivors at all time intervals, and persistence of PCO2

gap > 6.5 mmHg at 3 and 6 hours during early resuscitation of septic shock patients was associated with higher mortality rates. The cut-off values of P(cv-a) CO2 in predicting 28-day 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 hours was ≥ 6.45 mmHg (AUC:0.685; sensitivity: 58.6%; specificity: 83.0%; PPV: 48.6%; NPV: 88.0%; accuracy: 77.8%; p-value: <0.001). A study by Helmy AT et al. observed P(cv-a) CO2 cut-off of ≥8.4 mmHg at 0 hours (AUC: 0.668; sensitivity: 43.75%; specificity: 91.67%; PPV: 77.8%; NPV: 71%; p-value: <0.07); and at 6 hours cut-off of ≥7.8 mmHg (AUC: 0.979; sensitivity: 87.5%; specificity: 100%; PPV: 100.0%; NPV: 92.3%; p-value: <0.001) as a predictor of all-cause hospital mortality[24]. **The difference in cut-off may be because of the increased specificity of later.** Accordingly, high P(cv-a) CO2 >6 mmHg at 6 hours could identify patients with septic shock at high mortality risk in apparently resuscitated patients.

Capillary refill time (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 capillary refilling time[25]. 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 can assess the alteration in microcirculation and evaluate the response to resuscitation. The present study found a statistically significant association between the 28-day mortality and CRT at baseline, 3 and 6 hours. Similar results were described by Morocho JP et al., who concluded that the measurement of CRT at baseline, 3 and 6 hours was

a strong predictor of mortality in septic shock, even above the widely studied markers such as lactate[26]. Castro R et al. demonstrated that CRT-targeted fluid resuscitation was associated with the 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.

The present study observed that the cut-off point to predict 28-day mortality for CRT at baseline was 4 seconds, with a sensitivity of 55.2% and specificity of 67.9%. In contrast, the cut-off point for CRT at 6 hours was 7 seconds, with a sensitivity of 51.9% and a specificity of 94.3%. The corresponding CRT cut-offs by Morocho JP et al. at admission and 6 hours were 4.5 seconds at admission and 3.5 seconds at 6 hours post-resuscitation[26]. This cut-off at 6 hours 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 limitation can be overcome by using newly developed optical devices to 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.

.[37]

ScvO2 trends correlate well with mixed central venous oxygen saturation and have been independently associated with mortality in septic shock[18,19], with threshold values supporting those published in SSC guidelines 2012[11]. Normalization of ScvO2 does not rule out persistent tissue hypoperfusion, and the latter can still occur due to severe microcirculatory disorders and mitochondrial dysfunction[20,21]. Moreover, if ScvO2 <70% is associated with mortality[22], it does not mean that SvcO2 ≥70% is associated with survival[23]. 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 not have. 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 current study had a few limitations. This non-experimental observational study could only demonstrate an association between hypoperfusion context and 28-day 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 etiologies 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, and the small sample size may be an issue in physiologically focused studies. 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-day 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 hours had a better prognostic value in predicting 28-day mortality than other parameters. Persistently high P(cv-a)CO2 (> 6mm Hg) or raised CRT (>4 seconds) at 3 and 6 hours during the early resuscitation can be a valuable additional aid for the prognostication of septic shock patients.

1.	*According to the results of the current study,*	Assessing the Ovarian Accessory Glands to Determine the Parity of Phlebotomus papatasi, Vector of Zoonotic Cutaneous Leishmaniasis, under Laboratory Condition	Originality