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ORIGINAL ARTICLE

Observational Study

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

Sahil Kataria, Omender Singh, Deven Juneja, Amit Goel, Madhura Bhide, Devraj Yadav

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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 with hyperlactatemia in a hypoperfusion context (Group 1, n = 95) and patients with hyperlactatemia in a non-hypoperfusion context (Group 2, n = 40). Hypoperfusion context was defined by a central venous saturation less than 70%, central venous-arterial PCO_2 gradient [P(cv-a)CO_2] ≥ 6 mmHg, and capillary refilling time (CRT) ≥ 4 s. The patients were observed for various macro and micro hemodynamic parameters at regular intervals of 0 h, 3 h, 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 χ^2 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 cutoff values of lactate, CRT, and metabolic perfusion parameters to predict the 28-d all-cause mortality. A 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 h and 6 h, Sequential Organ Failure scores, need for invasive mechanical ventilation, days on mechanical ventilation, and renal replacement therapy-free days within 28 d, duration of intensive care unit stay, 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; $P = 0.234$). However, the patients within the hypoperfusion context with high P(cv-a)CO_2 and CRT ($P = 0.022$) 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 $P > 0.05$ 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 (18.88 ± 9.04 *vs* 21.08 ± 8.76; $P = 0.011$). The mean lactate levels and lactate clearance at 3 h and 6 h, CRT, P(cv-a)CO_2 at 0 h, 3 h, 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 exhibited similar 28-d all-cause hospital mortality, although patients with hypoperfusion 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)CO_2 (> 6 mmHg) or increased CRT (> 4 s) at 3 h and 6 h during 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; PCO_2 gap; Septic shock

Core Tip: Two different clinical patterns among hyperlactatemic septic shock patients can be effectively differentiated when utilizing three easily employable perfusion parameters. Lactate levels are still the best available tool, but persistence of high central venous-arterial PCO_2 gradient (> 6 mmHg) or raised capillary refill time (> 4 s) at 3 h and 6 h along with lactate metrics during early resuscitation can be valuable for guiding resuscitation of septic shock patients.

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INTRODUCTION

Septic shock remains the most frequent cause of mortality in patients admitted to the intensive care unit (ICU), contributing to 33%-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 edema, prolonged mechanical ventilation (MV), 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 Campaign (SSC) guidelines 2012 suggested fluid resuscitation guided by repeated measurement of blood lactate levels until normalization[11]. However, as per SSC 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 ($ScvO_2$), central venous-arterial PCO_2 gradient [$P(cv-a)CO_2$], and peripheral (skin) perfusion markers exhibit a very fast normalization rate concerning systemic flow optimization[14]. A concomitant low $ScvO_2$, high $P(cv-a)CO_2$, 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 and hyperlactatemic patients without hypoperfusion. The hypoperfusion context in the present study was defined similarly to the study by Alegría *et al*[15]: $ScvO_2$ less than 70%; $P(cv-a)CO_2$ greater than or equal to 6 mmHg; capillary refilling time (CRT) greater than or equal to 4 s; and hyperlactatemia after initial fluid resuscitation in septic shock patients admitted in the ICU.

MATERIALS AND METHODS

The present study was a prospective comparative observational study conducted in the medical ICU, Institute of Critical Care Medicine, Max Super Specialty 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 who were admitted to the medical ICU with septic shock (according to Sepsis-3 definition[1]), for whom concomitant values for $ScvO_2$, $P(cv-a)CO_2$, 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[15], which analyzed the mortality in septic shock patients with hypoperfusion *vs* those without hypoperfusion. 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 was in a ratio of 3:7. Thus, 135 patients in total were taken during the study period: 95 patients with hypoperfusion and 40 patients without hypoperfusion. Patients were enrolled and categorized as follows: Group 1. Patients with hypoperfusion; and Group 2. Patients without hypoperfusion.

Preload optimization was guided by an algorithm (Figures 1 and 2) that included early fluid loading, followed by vasopressor infusion as needed to maintain a mean arterial pressure > 65 mmHg. SSC guidelines 2016 were followed to guide the treatment of septic shock[1]. All patients were followed 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 d (asked by telephone if patient discharged earlier).

Secondary outcomes: (1) Macro hemodynamic variables measured at baseline including systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, norepinephrine (NE), or vasoactive drug doses; (2) Metabolic-related perfusion variables measured at 0 h (baseline), 3 h, and 6 h including $ScvO_2$ and $P(cv-a)CO_2$; (3) Lactate measurement and percentage of lactate clearance at 0 h (baseline), 3 h, 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 analyzer. The percentage of lactate clearance was defined as: Lactate clearance = (Lactate initial-Lactate time) × 100/Lactate initial; (4) CRT measured at 0 h (baseline), 3 h, and 6 h: Normal values were considered to be ≤ 4.0 s. It was measured by applying firm pressure to the ventral surface of the distal phalanx of the right index finger with a glass microscope slide. The pressure was increased until the skin blanched, was maintained for 10 s, and then released. The time for the return of the normal skin color was recorded using a chronometer, and a refill time greater than 3 s was defined as abnormal; (5) Amount of fluid administered measured at 0 h, 6 h, and 24 h; (6) Vasopressor dose measured at 0 h, 3 h, 6 h, 12 h, and 24 h; (7) Duration of vasopressor use in days; (8) Need of invasive MV, duration on invasive MV in days, and MV-free days within 28 d; (9) Need for renal replacement therapy and renal replacement therapy-free days within 28 d; and (10) ICU and hospital length of stay.

Statistical analysis

Continuous variables were presented as mean ± standard deviation 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 χ^2 test or Fisher's exact test. Mann Whitney *U* test was performed to compare two group means. Receiver operating characteristic curve (ROC) analysis with the Youden index was performed to determine each the cutoff value of each parameter to predict the outcome. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were

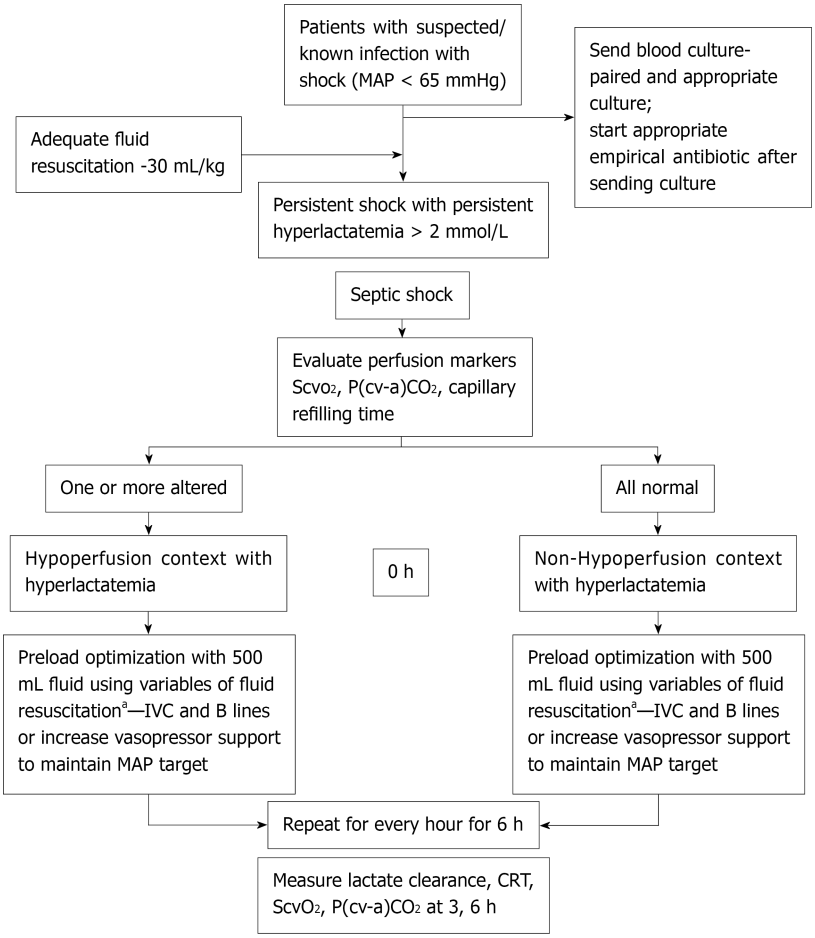

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Figure 1 Resuscitation algorithm. [a]Fluid resuscitation using inferior vena cava and lung ultrasound. CRT: Capillary refill time; IVC: Inferior vena cava; MAP: Mean arterial pressure; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; ScvO_2: Central venous oxygen saturation.

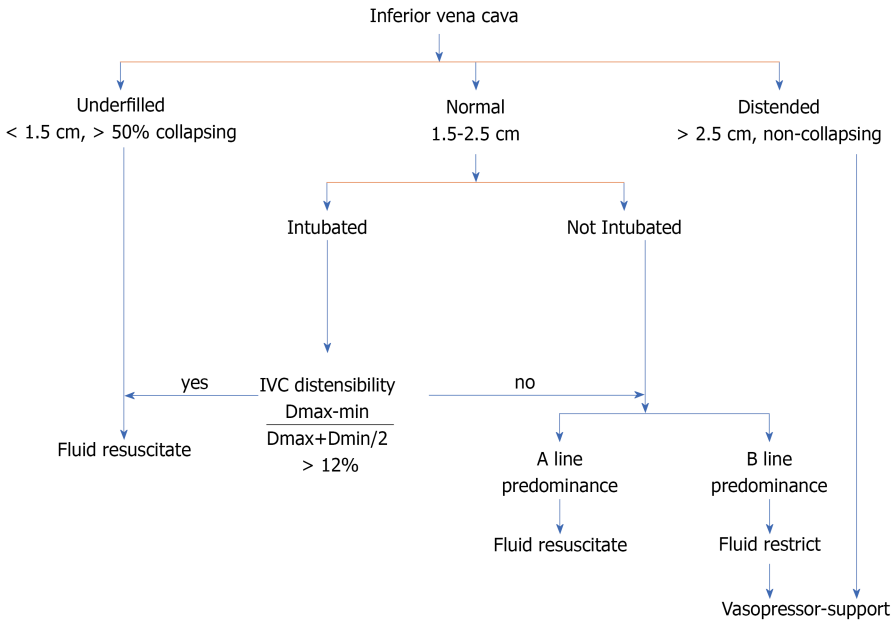

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Figure 2 Fluid resuscitation guide using inferior vena cava and lung ultrasound. IVC: Inferior vena cava.

calculated based on those cutoff values. For all statistical tests, a $P < 0.05$ indicated a significant difference.

RESULTS

A total of 148 patients met the inclusion criteria in the present study, out of which 7 patients had severe left ventricular systolic dysfunction, 1 patient was pregnant, and 5 patients refused to consent to participate. Therefore, 135 patients were included in the study; 95 patients were in the hypoperfusion context (Group 1), and 40 patients were in the 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). The Acute Physiology and Chronic Health Evaluation (APACHE) II score was higher in Group 2 (23.78 ± 5.414 *vs* 23.78 ± 5.414; $P < 0.002$). 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; $P = 0.594$) and all measured intervals. The primary and secondary outcomes of Group 2 were compared with Group 1 and with the subgroups of Group 1 (Supplementary Tables 1 and 2).

The overall 28-d mortality was 21% in 135 patients, 24% in the hypoperfusion context group *vs* 15% in the non-hypoperfusion context ($P = 0.234$). However, the patients within the hypoperfusion context with high P(cv-a)CO_2 and CRT (P-value 0.022) at baseline had significantly higher mortality as compared to Group 2 (Supplementary Tables 1 and 2). The mean dose of noradrenaline at baseline in all the study patients was 0.19 ± 0.14 μg/kg/min. Although the NE requirement was higher in Group 1, it did not attain statistical significance at any specified interval ($P > 0.05$). 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; $P = 0.011$). Similarly, Group 1 had a higher fluid requirement than Group 2 at 0 h and 6 h ($P = 0.045$ 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 (Supplementary Table 2).

Univariate analysis of baseline variables and primary and secondary outcomes was also performed between the survivors and non-survivors (Table 3). We also analyzed the prognostic value of mean lactate levels, lactate clearance, $ScvO_2$, CRT, and P(cv-a)CO_2 at 0 h, 3 h, 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 ± 1.72 *vs* 4.74 ± 1.69; $P = 0.151$). Nevertheless, a significant association between lactate levels at 3 h and 6 h and lactate clearance at 3 h 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 h and 6 h: 0.776 and 0.845, respectively; AUROC for lactate clearance at 3 h and 6 h 0.754 and 0.834, respectively] (Figure 3). The optimal cutoff value for lactate values at 3 h in predicting 28-d mortality was ≥ 4.2 mmol/L, with a sensitivity of 55.2%, a specificity of 63.2%, a PPV of 29.1%, and an NPV of 83.8%. Similarly, the cutoff for the 6 h lactate levels was ≥ 4.1 mmol/L with a sensitivity of 74.2%, a specificity of 84.9%, a PPV of 55.6%, and an NPV of 92.8% (Tables 4 and 5).

A statistical significant ($P = 0.033$) difference in $ScvO_2$ at baseline between non-survivors and survivors was observed in the present study. However, mean $ScvO_2$ at 3 h and 6 h was comparable between non-survivors and survivors ($P = 0.304$ and 0.299, respectively) (Table 5).

In the current study, P(cv-a)CO_2 ≥ 6 mmHg at baseline was used as one of the criteria of hypoperfusion and was measured at baseline, 3 h, 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, and < 0.001, respectively. In the current study, the cutoff value of P(cv-a)CO_2 in predicting 28-d mortality at baseline was ≥ 7.6 mmHg (AUROC: 0.627; sensitivity: 44.8%; specificity: 81.1%; PPV: 39.4%; NPV: 84.3%; accuracy: 73.3%; $P = 0.004$). Similarly, cutoff values for P(cv-a)CO_2 at 3 h and 6 h were ≥ 5.9 and 6.45 mmHg, respectively (Tables 4 and 5).

Similarly, a statistically significant association was found between the 28-d mortality and CRT levels at baseline, 3 h, and 6 h. ($P = 0.004$, < 0.001, and < 0.001, respectively). The AUROC to estimate mortality for CRT at baseline was 0.623 [95% confidence interval (CI): 0.536-0.705) and at 3 h and 6 h was 0.768 (95%CI: 0.688-0.837) and 0.705 (95%CI: 0.675-0.827), respectively, with the asymptotic significance of < 0.001 and < 0.001, respectively. In the present study, the cutoff 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 cutoff point for CRT at 6 h was 7 s, with a sensitivity of 51.9% and a specificity of 94.3% ($P < 0.001$) (Tables 4 and 5).

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

Table 1 Comparison of Group 1 and Group 2

Variable	Group 1			Group 2			*P* value
	mean ± SD	Min-Max	Median (Q1-Q3)	mean ± SD	Min-Max	Median (Q1-Q3)	
Age	62.34 ± 14.32	20-92	64 (56-73)	61.03 ± 15.10	25-82	66.5 (52-72)	0.843
APACHE II	20.82 ± 5.47	9-32	20 (17-25)	23.78 ± 5.41	8-33	24 (21-28)	0.002[a]
SOFA score	9.26 ± 4.22	2-18	8 (6-13)	8.88 ± 3.44	4-16	8 (6-11.75)	0.751
Hemoglobin	11.24 ± 6.30	7.1-16.70	10.2 (9.10-12.20)	10.26 ± 1.93	7.1-16	10.25 (8.75-11.7)	0.299
TLC	12.37 ± 7.92	0.1-46.50	11.9 (6.70-16.70)	12.56 ± 9.34	1.4-42.80	9.65 (6.5-16.65)	0.668
Platelet count	2.17 ± 1.01	0.1-5.26	1.98 (1.63-2.78)	2.08 ± 0.72	0.25-3.18	2.02 (1.61-2.75)	0.904
Serum bilirubin	1.84 ± 2.78	0.16-18.57	0.8 (0.55-1.6)	1.68 ± 2.24	0.28-10.93	0.81 (0.41-1.84)	0.507
Serum albumin	3.0 ± 0.60	1.5-4.4	2.9 (2.60-3.50)	2.9 ± 0.60	1.7-4	2.9 (2.30.-3.40)	0.584
INR	1.35 ± 0.36	0.95-3.83	1.28 (1.12-1.49)	1.31 ± 0.30	1.01-2.52	1.26 (1.08-1.44)	0.323
Creatinine	1.59 ± 1.31	0.2-10.50	1.3 (0.70-1.90)	1.34 ± 0.91	0.20-4.20	1.15 (0.6-1.85)	0.265
Urea	51.68 ± 34.75	7.8-229	41.7 (29.70-64.60)	54.12 ± 35.30	3.3-157	44 (33.1-69.88)	0.565
Heart rate	104.15 ± 15.44	64-156	107 (94-114)	106.73 ± 15.65	70-137	112 (98-118.75)	0.216
SBP	101.6 ± 22.16	50-166	102 (90-117)	99.5 ± 21.53	60-133	102 (81-117.75)	0.629
DBP	56.92 ± 15.26	24-97	58 (45-66)	58.58 ± 15.65	36-90	59 (44-68.75)	0.685
MAP	71.62 ± 16.08	31-106	70 (64-82)	72.5 ± 16.47	44-103	70.5 (61.75-87)	0.808
Lactate at 0 h	4.87 ± 1.69	2.1-9.70	4.6 (3.50-5.90)	4.76 ± 1.75	2.3-9.8	4.15 (3.5-5.65)	0.594
Lactate at 3 h	4.22 ± 2.0	1.3-12.00	3.6 (2.80-5.20)	3.82 ± 2.06	1.9-12.40	3.4 (2.45-4.10)	0.16
Lactate at 6 h	3.91 ± 3.01	0.6-14.10	2.8 (2.0-4.60)	3.88 ± 3.48	0.9-16.70	2.7 (2.0-4.20)	0.7
CRT at 0 h	5.14 ± 2.16	2-12	5 (3-7)	2.25 ± 0.67	1-3	2 (2-3)	< 0.001[a]
CRT at 3 h	4.72 ± 2.68	1.0-13.00	4 (3-7)	3.55 ± 2	2-9	3 (2-4)	0.011[a]
CRT at 6 h	4.50 ± 3.30	1.0-13.00	3 (2-7)	3.88 ± 3.22	1-13	3 (2-4)	0.255
$ScvO_2$ at 0 h	64.5 ± 9.10	42.8-74.20	70.4 (56.40-71.80)	71.8 ± 1.30	68.1-74.0	71.8 (70.9-72.70)	< 0.001[a]
$ScvO_2$ at 3 h	60.1 ± 7.0	36.8-73.70	60.8 (56.70-64.70)	63.8 ± 4.70	52.8-73.50	63.6 (61.7-67.3)	0.002[a]
$ScvO_2$ at 6 h	58.6 ± 9.0	36.7-89.20	60.2 (52.30-64.90)	62.4 ± 6.80	42.3-71.0	63.7 (58.7-68.3)	0.010[a]
P(cv-a)CO_2 at 0 h	6.63 ± 1.78	2.9-9.80	7.2 (5-7.9)	4.24 ± 0.84	2.8-5.80	4.2 (3.6-4.86)	< 0.001[a]
P(cv-a)CO_2 at 3 h	5.81 ± 2.03	2.6-12.30	5.5 (4.10-7)	5.05 ± 1.51	2.7-10	4.4 (4-5.98)	0.035[a]
P(cv-a)CO_2 at 6 h	5.70 ± 2.30	2.6-12.40	5.1 (4-60.5)	5.88 ± 6.88	2.6-47	4.3 (3.6-6.375)	0.059
Lactate clearance at 3 h	10.2 ± 38.5	(-183.3-57.7)	22.7 (-7.30-36.0)	18.3 ± 29.8	(-103.3-58.2)	26.7 (5.4-36.4)	0.332
Lactate clearance at 6 h	15.3 ± 76.0	(-433.3-100.0)	39.6 (5.1-57.1)	20.3 ± 54.8	(-173.8-76.9)	39.1 (2.4-57.9)	0.973

[a]Denotes statistical significance.

Group 1 referred to patients with hyperlactatemia in a hypoperfusion context. Group 2 referred to patients with hyperlactatemia in a non-hypoperfusion context. APACHE: Acute Physiology and Chronic Health Evaluation; CRT: Capillary refill time; DBP: Diastolic blood pressure; INR: International normalized ratio; MAP: Mean arterial pressure; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; Q1: First quartile; Q3: Third quartile; SBP: Systolic blood pressure; $ScvO_2$: Central venous oxygen saturation; SOFA: Sequential Organ Failure Assessment; TLC: Total leukocyte count; SD: Standard deviation.

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, $ScvO_2$, and P(cv-a)CO_2, might be more pragmatic. A recent study by Algeria *et al*[15] used CRT, P(cv-a)CO_2, and $ScvO_2$ to define hypoperfusion context and demonstrated that patients with hyperlactatemia plus hypoperfusion context exhibited a severe circulatory dysfunction with increased morbidity. However, this study was retrospective and did not examine the superiority of

Table 2 Comparison of baseline patient characteristics between Group 1 and Group 2

Characteristics	Group 1		Group 2		Total		*P* value
	Frequency	%	Frequency	%	Frequency	%	
Sex							
Female	43	45%	20	50%	63	95%	0.614
Male	52	55%	20	50%	72	105%	
Comorbidities							
DM	30	32%	12	30%	42	31%	0.856
HTN	39	41%	15	38%	54	40%	0.700
COPD	6	6%	5	13%	11	8%	0.393
CLD	7	7%	4	10%	11	8%	0.868
CKD	12	13%	8	20%	20	15%	0.271
Malignancy	7	7%	4	10%	11	8%	0.868
CAD	8	8%	6	15%	14	10%	0.403
Others IMM	5	5%	2	5%	7	5%	1.000
Source of infection							
Intra-abdominal infection	27	28%	12	30%	39	29%	0.853
Bacteremia	11	12%	3	8%	14	10%	0.689
Pneumonia	30	32%	11	28%	41	30%	0.638
UTI	12	13%	8	20%	20	15%	0.271
Others	10	11%	2	5%	12	9%	0.484
Unknown	5	5%	4	10%	9	7%	0.529

Group 1 referred to patients with hyperlactatemia in a hypoperfusion context. Group 2 referred to patients with hyperlactatemia in a non-hypoperfusion context. CAD: Coronary artery disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; HTN: Hypertension; IMM: Immunocompromised diseases; UTI: Urinary tract infection.

serial measurements of CRT, P(cv-a)CO_2, and $ScvO_2$ 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 analyzed: hypoperfusion context *vs* non-hypoperfusion context. Similar to the results by Algeria *et al*[15], the stratification of patients in the present study into hypoperfusion and non-hypoperfusion contexts 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(cv-a)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 comorbidities, 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 at all intervals compared to Group 2, it did not achieve statistical significance. These results differ from Algeria *et al* [15], who reported significantly higher NE requirements ($P < 0.005$) 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 h 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* [16] showed a significant difference between the lactate values at baseline, 6 h, 12 h, or 24 h between the survivors and non-survivors group ($P < 0.05$ for each time interval). Analysis of the AUROC for lactate levels at baseline, 3 h, and 6 h to predict the 28-d mortality revealed that initial lactate levels had a poor predictive value compared to those at 3 h and 6 h. These results were similar to the study by Lee *et al*

Table 3 Comparison of survivors and non-survivors

Variable	Non-Survivors			Survivors			*P* value
	mean ± SD	Min-Max	Median (Q1-Q3)	mean ± SD	Min-max	Median (Q1-Q3)	
Age	62.41 ± 14.61	28-82	66 (55.5-74.0)	61.82 ± 14.55	20-92	64 (53.75-71.25)	0.653
APACHE II	23.93 ± 4.91	14-32	24 (20.5-28.0)	21.08 ± 5.64	8-33	21 (17.00-25.25)	0.012[a]
SOFA score	10.38 ± 4.71	2-17	11 (6-15)	8.81 ± 3.73	2-18	8 (6-11)	0.094
HB	12.2 ± 11.0	7.2-16.7	10 (8.8-12.0)	10.6 ± 2.0	7.1-16.9	10.3 (9.1-12.0)	0.493
TLC	10.0 ± 6.9	0.2-24.3	8.5 (5.4-13.8)	13.1 ± 8.6	0.1-46.5	11.9 (6.8-16.7)	0.101
PLT	1.99 ± 0.89	0.25-4.08	1.83 (1.58-2.01)	2.18 ± 0.95	0.10-5.26	2.10 (1.65-2.78)	0.188
SBIL	1.02 ± 0.84	0.28-4.70	0.78 (0.57-1.27)	2.00 ± 2.90	0.16-18.57	0.8 (0.5-2.0)	0.489
SALB	2.4 ± 0.4	1.6-3.1	2.3 (2.1-2.7)	3.1 ± 0.6	1.5-4.4	3.1 (2.7-3.5)	< 0.001[a]
INR	1.28 ± 0.29	0.97-2.14	1.18 (1.09-1.31)	1.36 ± 0.36	0.95-3.83	1.30 (1.12-1.48)	0.099
CREAT	2.08 ± 0.95	0.50-4.90	1.80 (1.50-2.40)	1.36 ± 1.23	0.20-10.50	1.10 (0.60-1.80)	< 0.001[a]
Urea	61.24 ± 44.91	9.90-229.00	45.60 (30.50-86.70)	49.99 ± 31.30	3.30-168.90	41.83 (30.10-61.60)	0.280
HR	107.00 ± 15.22	70-128	112 (98-118)	104.34 ± 15.58	64-156	106.50 (94.00-116.00)	0.228
SBP	94.66 ± 22.81	60-138	90 (74-116)	102.71 ± 21.45	50-166	102 (90-118)	0.065
DBP	52.41 ± 14.21	26-87	50 (41-60)	58.77 ± 15.41	24-97	60.00 (46.00-69.25)	0.060
MAP	66.24 ± 16.61	31-101	67.0 (53.0-76.5)	73.42 ± 15.74	33-106	71 (64-85)	0.057
Lactate at 0 h	5.20 ± 1.72	2.10-9.40	5.20 (4.0-5.70)	4.74 ± 1.69	2.30-9.80	4.40 (3.40-5.90)	0.151
Lactate at 3 h	5.54 ± 2.14	2.40-10.70	5.20 (3.80-6.70)	3.71 ± 1.80	1.30-12.40	3.40 (2.50-4.20)	< 0.001[a]
Lactate at 6 h	6.61 ± 3.35	2.10-14.60	6.30 (3.90-8.60)	3.21 ± 2.70	0.60-16.70	2.45 (1.90-3.30)	< 0.001[a]
CRT at 0 h	5.07 ± 2.46	2-12	5 (3-7)	4.07 ± 2.18	1-9	3 (2-6)	0.040[a]
CRT at 3 h	6.38 ± 2.95	2-13	6 (4-8)	3.82 ± 2.14	1-10	3 (2-5)	< 0.001[a]
CRT at 6 h	7.10 ± 4.10	2-13	9 (3-11)	3.63 ± 2.64	1-13	2.5 (2.0-5.0)	< 0.001[a]
$ScvO_2$ at 0 h	68.30 ± 7.80	43.20-73.90	71.9 (70.2-72.8)	66.20 ± 8.50	42.80-74.20	70.80 (58.90-71.90)	0.033[a]
$ScvO_2$ at 3 h	61.90 ± 7.10	45.80-73.50	62.8 (58.9-66.2)	61.00 ± 6.50	36.80-73.70	61.70 (57.80-64.90)	0.304
$ScvO_2$ at 6 h	58.10 ± 11.80	36.70-89.20	58.9 (49.7-66.2)	60.2 ± 7.60	37.90-71.0	61.90 (56.10-65.90)	0.299
$P(cv\text{-}a)CO_2$ at 0 h	6.50 ± 1.90	2.80-9.40	7.3 (4.9-7.9)	5.70 ± 1.90	2.80-9.80	5.50 (4.20-7.40)	0.036[a]
$P(cv\text{-}a)CO_2$ at 3 h	7.00 ± 2.10	3.40-12.30	6.5 (5.6-8.6)	5.20 ± 1.60	2.7-11.0	4.8 (4.0-6.2)	< 0.001[a]
$P(cv\text{-}a)CO_2$ at 6 h	7.10 ± 2.50	2.60-10.80	7.4 (4.9-9.2)	5.40 ± 4.50	2.60-8.70	4.70 (3.60-5.80)	< 0.001[a]
Lactate clearance at 3 h	(-10.20 ± 35.10)	(-88.10-40.40)	(-8.6) (-37.1-24.7)	18.80 ± 34.20	(-183.30-58.20)	26.80 (7.30-37.20)	< 0.001[a]
Lactate clearance at 6 h	(-28.70 ± 72.80)	(-187.0-100.0)	(-46.4) (-61.5-29.9)	29.20 ± 64.40	(-433.80-81.30)	44.90 (23.40-58.70)	< 0.001[a]

[a]Denotes statistical significance.

APACHE: Acute Physiology and Chronic Health Evaluation; CREAT: Creatinine; CRT: Capillary refill time; DBP: Diastolic blood pressure; HB: Hemoglobin; HR: Heart rate; INR: International normalized ratio; MAP: Mean arterial pressure; $P(cv\text{-}a)CO_2$: Central venous-arterial pCO_2 gradient; PLT: Platelet; Q1: First quartile; Q3: Third quartile; SALB: Serum albumin; SBIL: Serum bilirubin; SBP: Systolic blood pressure; $ScvO_2$: Central venous oxygen saturation; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; TLC: Total leukocyte count.

[17], conducted in 2021, in which the lactate levels at 6 h had a better prognostic performance. In the present study, the optimal cutoff value for lactate values in predicting 28-d mortality was ≥ 4.2 mmol/L, with a sensitivity of 55.2%, specificity of 63.2%, PPV of 29.1%, and NPV of 83.8%. Similarly, the cutoff value for the lactate levels at 6 h 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 cutoff 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%)].

Table 4 Area under the curve to predict 28-d mortality for various perfusion markers at specified intervals

Test result variable	Area	Std. Error	*P* value	Asymptomatic 95%CI	
				Lower bound	Upper bound
Lactate at 0 h	0.587	0.058	0.133	0.499	0.671
Lactate at 3 h	0.776	0.048	< 0.001[a]	0.696	0.843
Lactate at 6 h	0.845	0.04	< 0.001[a]	0.772	0.902
Lactate clearance at 3 h	0.754	0.053	< 0.001[a]	0.672	0.824
Lactate clearance at 6 h	0.834	0.041	< 0.001[a]	0.76	0.893
CRT at 0 h	0.623	0.056	0.028[a]	0.536	0.705
CRT at 3 h	0.768	0.047	< 0.001[a]	0.688	0.837
CRT at 6 h	0.757	0.054	< 0.001[a]	0.675	0.827
$ScvO_2$ at 0 h	0.630	0.062	0.035[a]	0.542	0.711
$ScvO_2$ at 3 h	0.562	0.064	0.325	0.474	0.648
$ScvO_2$ at 6 h	0.565	0.072	0.367	0.476	0.651
P(cv-a)CO_2 at 0 h	0.627	0.060	0.033[a]	0.540	0.709
P(cv-a)CO_2 at 3 h	0.754	0.052	< 0.001[a]	0.673	0.824
P(cv-a)CO_2 at 6 h	0.736	0.060	< 0.001[a]	0.652	0.808

[a]Denotes statistical significance.

CI: Confidence interval; CRT: Capillary refill time; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; $ScvO_2$: Central venous oxygen saturation.

Table 5 Cutoff values of perfusion markers at specified intervals

Marker	Cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy	*P* value
Lactate at 0 h	> 4.9	55.2%	63.2%	29.1%	83.8%	61.5%	0.074
Lactate at 3 h	> 4.2	65.5%	77.4%	44.2%	89.1%	74.8%	< 0.001[a]
Lactate at 6 h	> 4.1	74.1%	84.9%	55.6%	92.8%	82.7%	< 0.001[a]
Lactate clearance at 3 h	≤ -20.6 (≥ 20.6% from baseline)	44.8%	93.4%	65.0%	86.1%	83.0%	< 0.001[a]
Lactate clearance at 6 h	≤ -46.4 (≥ 46.4% from baseline)	55.6%	94.3%	71.4%	89.3%	86.5%	< 0.001[a]
CRT at 0 h	> 4	55.2%	67.9%	32.0%	84.7%	65.2%	0.022[a]
CRT at 3 h	> 4	69.0%	70.8%	39.2%	89.3%	70.4%	< 0.001[a]
CRT at 6 h	> 8	51.9%	94.3%	70.0%	88.5%	85.7%	< 0.001[a]
$ScvO_2$ at 0 h	> 71.7	55.2%	71.7%	34.8%	85.4%	68.2%	0.007[a]
$ScvO_2$ at 3 h	> 61.7	69.0%	53.8%	29.0%	86.4%	57.0%	0.03[a]
$ScvO_2$ at 6 h	≤ 58.9	55.6%	65.1%	28.9%	85.2%	63.2%	0.05
P(cv-a)CO_2 at 0 h	> 7.6	44.8%	81.1%	39.4%	84.3%	73.3%	0.004[a]
P(cv-a)CO_2 at 3 h	> 5.9	72.4%	73.6%	42.9%	90.7%	73.3%	< 0.001[a]
P(cv-a)CO_2 at 6 h	> 6.4	63.0%	83.0%	48.6%	89.8%	79.0%	< 0.001[a]

[a]Denotes statistical significance.

CRT: Capillary refill time; NPV: Negative predictive value; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; PPV: Positive predictive value; $ScvO_2$: Central venous oxygen saturation.

Table 6 Stepwise logistic regression to predict 28-d all-cause mortality

Step		*B*	S.E.	Wald test	df	Significance	Exp(B)	95%CI for Exp(B)	
								Lower	Upper
1[a]	Lactate at 6 hours	0.302	0.073	17.230	1	0.000	1.353	1.173	1.561
	Constant	-2.731	0.421	42.115	1	0.000	0.065		
2[b]	Creatinine	0.416	0.194	4.595	1	0.032	1.515	1.036	2.216
	Lactate at 6 hours	0.295	0.071	17.091	1	0.000	1.344	1.168	1.546
	Constant	-3.416	0.552	38.348	1	0.000	0.033		

[a]Variable(s) entered on step 1: lactate at 6 h.
[b]Variable(s) entered on step 2: baseline creatinine. CI: Confidence interval; df: Degree of freedom; S.E.: Standard error.

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 were independently associated with 28-d mortality (Table 6).

$ScvO_2$ trends correlate well with mixed central venous oxygen saturation and have been independently associated with mortality in septic shock[19,20], with threshold values supporting those published in the SSC guidelines 2012[11]. Normalization of $ScvO_2$ does not rule out persistent tissue hypoperfusion, and the latter can still occur due to severe microcirculatory disorders and mitochondrial dysfunction[21,22]. Moreover, if $ScvO_2$ < 70% is associated with mortality[23], it does not mean that $SvcO_2$ ≥ 70% is associated with survival[24]. Thus, in some circumstances, the use of $ScvO_2$ might mistakenly drive an intensivist to conclude that the patient's physiologic state has improved when, in fact it has not. According to the results of the current study, $ScvO_2$ appeared to be a valuable tool for initial resuscitation but cannot distinguish between survivors and non-survivors after initial resuscitation.

The P(cv-a)CO_2 gap represents an excellent surrogate indicator of the adequacy of cardiac output and tissue perfusion under a given condition of CO_2 production. Recently, Ospina-Tascón *et al*[25] showed that the persistence of high P(v-a)CO_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(v-a)CO_2 and P(cv-a)CO_2, though it should not be interchanged. In the present study, it was observed that P(cv-a)CO_2 was higher in survivors than non-survivors at all time intervals, and persistence of the PCO_2 gap > 6.5 mmHg at 3 h and 6 h during early resuscitation of septic shock patients was associated with higher mortality rates. The cutoff values of P(cv-a)CO_2 in predicting 28-d mortality at baseline was ≥ 7.6 mmHg (AUROC: 0.627; sensitivity: 44.8%; specificity: 81.1%; PPV: 39.4%; NPV: 84.3%; accuracy: 73.3%; P = 0.004). Similarly, the cutoff value at 6 h was ≥ 6.45 mmHg (AUROC: 0.685; sensitivity: 58.6%; specificity: 83.0%; PPV: 48.6%; NPV: 88.0%; accuracy: 77.8%; P < 0.001). A study by Helmy *et al*[26] observed a P(cv-a)CO_2 cutoff 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 cutoff values may be because of the increased specificity. Consequently, high P(cv-a)CO_2 > 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 autoregulatory flow control; therefore, sympathetic activation can impair skin perfusion during circulatory dysfunction, a phenomenon that can be assessed by measuring CRT[27]. 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 h 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 h, and 6 h. Similar results were described by Morocho *et al*[28], who concluded that the measurement of CRT at baseline, 3 h, and 6 h was a strong predictor of mortality in septic shock, even above the widely studied markers such as lactate.

Castro *et al*[29] demonstrated that CRT-targeted fluid resuscitation was associated with 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

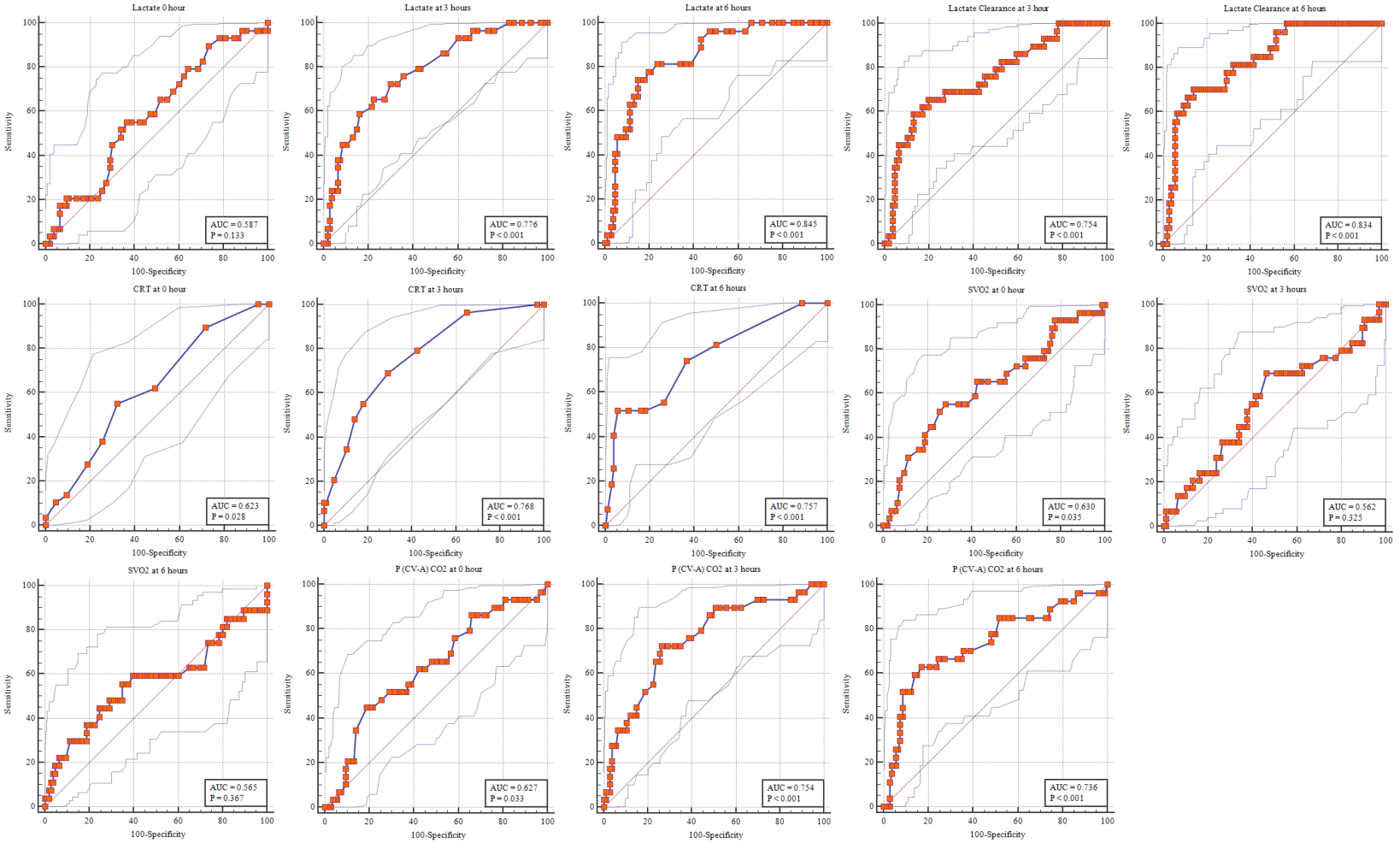

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Figure 3 Graphs of area under the receiver operating characteristic curve for capillary refill time, central venous oxygen saturation, and central venous-arterial pCO_2 gradient. AUC: Area under the curve; CRT: Capillary refill time; $P(cv\text{-}a)CO_2$: Central venous-arterial pCO_2 gradient; $ScvO_2$: Central venous oxygen saturation.

contradiction with that of the ANDROMEDA-SHOCK trial[30]. 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 cutoff 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 cutoff point for CRT at 6 h was 7 s, with a sensitivity of 51.9%, and a specificity of 94.3%. The corresponding CRT cutoffs by Morocho *et al*[28] at admission and 6 h were 4.5 s at admission and 3.5 s at 6 h post-resuscitation. This cutoff 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[31,32]. 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[33]. 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 can cause fluctuation in the immune response levels[34].

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 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 inter-rater variability and skin temperature, which could alter CRT values. Lastly, this was a single-center study with a small sample size. Future multicenter 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 displayed a more severe circulatory dysfunction. Targeting $ScvO_2$ may not be desirable as normalization of $ScvO_2$ 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)CO_2 (> 6 mmHg) or increased CRT (> 4 s) at 3 h and 6 h during early resuscitation can be a valuable additional tool 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 that may be increased by 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 in the hypoperfusion context and hyperlactatemic patients in the non-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 (Group 1, n = 95) and hyperlactatemia without hypoperfusion (Group 2, n = 40). The patients were observed for various macro and micro hemodynamic parameters at regular intervals of 0 h, 3 h, 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 did not result in a significantly different 28-d mortality (24% *vs* 15%, respectively; P = 0.234). However, the patients within the hypoperfusion context with high P(cv-a)CO_2 and CRT (P = 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 (18.88 ± 9.04 *vs* 21.08 ± 8.76; $P = 0.011$). The mean lactate levels and lactate clearance at 3 h and 6 h, CRT, and P(cv-a)CO_2 at 0 h, 3 h, 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 receiver operating characteristic: 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 displayed a more severe circulatory dysfunction. Lactate levels at 6 h had a better predictive value in predicting 28-d mortality. Persistently high P(cv-a)CO_2 (> 6 mmHg) or increased CRT (> 4 s) at 3 h 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.

FOOTNOTES

Author contributions: Kataria S, Singh O, and Juneja D designed the study; Kataria S, Bhide M, and Yadav D collected the data and analyzed the results; Kataria S and Juneja D performed the majority of the writing and prepared the tables; Singh O, Goel A, Devraj Y, and Bhide M provided input in writing the paper and reviewed the manuscript; All authors read and approved the final manuscript.

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