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Capillary lactate as a prognostic marker in sepsis: correlation with venous lactate and prediction of outcomes

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Abstract

Introduction Venous lactate (VL) measured by a blood–gas analyser is not widely available despite its importance in the management of sepsis. Capillary lactate (CL) measured via a hand-held lactate analyser is a feasible and less expensive option. The aim of this study was to determine the correlation between CL and VL in sepsis patients at 0 h (t_0) and 6 h (t_6) and identify the best CL and lactate clearance cut-off values that predicts a poor outcome.

Methods A descriptive study was conducted recruiting all patients with suspected sepsis (qSOFA ≥ 2 with evidence of infection) admitted to a tertiary care hospital in Sri Lanka between March and June 2022. “Lactate-plus”, a hand-held lactate analyser, was used to measure CL and VL at t_0 and t_6 of admission. The lactate analyser was tested for accuracy and calibrated in a pilot study of 30 patients by correlating to laboratory lactate values. Patient demographics, clinical data and outcomes during hospitalization and at 28 days were assessed.

Results There were 102 patients with suspected sepsis and a median age of 71.5 (interquartile range: 62–77) years were recruited. Majority were females ($n = 52$, 51%). Majority of the source of infection was pulmonary ($n = 57$, 55.9%) and urological ($n = 19$, 18.6%). Paired CL and VL values significantly correlated at both t_0 and t_6 ($p < 0.001$). CL at t_0 predicted 28-day mortality with a ROC curve AUC of 0.89 (95% CI: 0.82–0.95, $p < 0.05$) and 3.5 mmol/L was the best cut-off value with an 85% sensitivity and 78% specificity. CL ≥ 3.5 at t_0 was associated with increased intensive care unit (ICU) admission ($p < 0.01$), vasopressor requirement ($p < 0.0001$), and a higher mortality rate ($p < 0.001$) compared to CL < 3.5 . Additionally, a capillary lactate clearance greater than 64% predicted a good outcome, with a 97% sensitivity and 91% specificity.

Conclusions CL measured by a lactate meter correlates well with VL and effectively predicts sepsis outcomes. A CL cut-off ≥ 3.5 mmol/L at admission increases the risk of mortality, vasopressor requirement and ICU admission, making CL a useful tool for risk assessment in sepsis.

Keywords Capillary lactate, Lactate clearance, Mortality prediction, Point-of-care testing, Sepsis, Biomarker, Lactate

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Background

Sepsis is a time-sensitive life-threatening condition and a major cause of morbidity and mortality worldwide. Estimates suggest that 48.9 million cases of sepsis and 11 million deaths occur annually [1]. The burden is more severe in developing nations because of the scarcity of healthcare resources, resulting in alarmingly high case fatality rates [2]. The cost of treating sepsis is also substantial and takes a heavy toll on healthcare systems globally [3].

In this context, early identification of patients at risk of poor outcomes is crucial for early goal-directed resuscitation to reduce the disease burden [4]. The use of biomarkers for diagnosis, risk stratification, prognostication, and disease monitoring in sepsis has become increasingly popular. However, their effectiveness is often hindered by their low sensitivity and specificity [5]. Novel molecular markers, including metabolites, chemicals, genes and proteins, are gaining popularity, but their use is limited by their cost, availability and time-consuming nature [5]. This highlights the need for readily available and reliable biomarkers to guide the management of sepsis.

Lactate is a recognized biomarker for tissue hypoperfusion and organ dysfunction. In sepsis, infection-induced dysregulation of host immunity predisposes individuals to shock, compromising micro- and macro circulation, resulting in lactic acidosis [6]. However, this is not by any means the only basis. In fact, hyperlactataemia in sepsis is multifactorial and involves a complex interplay of haemodynamic and metabolic responses to infection and shock [6]. Studies have shown that the duration and degree of hyperlactataemia correlates well with poor outcomes in sepsis [7]. On the other hand, early lactate clearance has been linked to improved outcomes in sepsis [8]. Therefore, in practice, elevated serum lactate levels and lactate clearance are useful parameters for predicting sepsis severity and are therefore included in the surviving sepsis guidelines [9–11].

Although arterial lactate (AL) measurement is considered the gold standard, point-of-care (POC) venous lactate (VL) measurement has been found to yield reliable measurements at bedside and has largely replaced arterial blood gas sampling in emergency settings [9, 12]. Meanwhile, capillary lactate (CL) measurement via a handheld point-of-care lactate analyser is gaining popularity as a much faster, less invasive and inexpensive alternative. Moreover, unlike venous blood, capillary samples can be tested by any healthcare worker at admission. Hence, the utility of CL has been explored in recent years and was found to have a satisfactory correlation with venous and arterial lactate levels in several studies [13–18]. However, two systematic reviews evaluating POC lactate at presentation and its value in predicting adverse outcomes and mortality in septic patients, discouraged the use of

CL as a substitute for VL or AL. Available studies consists of small sample sizes and lacks high-quality evidence supporting the use of POC CL measurements for prognostication. Additionally, the propensity for CL to overestimate blood lactate levels results in false positives and unnecessary escalation of care [9, 19]. The significance of CL values in the assessment of lactate clearance has never been evaluated. Hence, the aim of this study was to explore the correlation between CL and VL in sepsis patients at 0 h (t_0) and 6 h (t_6) and to identify the best CL at t_0 and lactate clearance cut-off values that predicts a 28-day mortality in sepsis.

Methods

Study design

This was a prospective observational single-arm cohort study including consecutive consenting patients with suspected new-onset sepsis admitted from March to June 2022 to a tertiary care medical unit in Sri Lanka.

Study participants

Patients above 18 years of age with clinical evidence of infection and a qSOFA score ≥ 2 were recruited. The “quick Sepsis Related Organ Failure Assessment” (qSOFA) score is a bedside assessment tool that utilizes 3 criteria: a) low blood pressure (SBP ≤ 100), b) high respiratory rate (≥ 22 breaths/min), and c) altered mental status (GCS < 15). Those with alternative causes of shock (cardiogenic shock, dengue shock syndrome, hypovolaemia in the absence of infection) or hyperlactataemia (drug overdose) were excluded.

Lactate analysis

Paired blood samples were obtained for baseline CL and VL at admission (t_0) and subsequently repeated at 6 h after admission (t_6). Capillary blood was obtained through the same finger prick used for capillary glucose measurement with a disposable lancet, whereas venous blood was sampled through a forearm venepuncture performed for other blood investigations. These POC capillary and venous blood samples were then analysed via “Lactate-plus”, a hand-held lactate analyser.

The lactate analyser was tested for accuracy and calibrated in a pilot study of 30 patients by correlation with laboratory lactate values obtained by a general biochemistry analyser (BECKMAN COULTER AU 480). Standard medical care appropriate for the patient's condition was provided for all patients regardless of the CL level in accordance with the surviving sepsis guidelines [11]. The treating physicians were not directly involved in the recruitment process of the study and therefore were blinded to the lactate results. Lactate clearance was calculated with the formula $\frac{CL(t_0) - CL(t_6)}{CL(t_0)} \times 100$ [8].

Data extraction

Patient demographics, comorbidities and laboratory investigations were collected from medical records. The sources of sepsis were determined clinically and microbiologically. Patients were followed up until hospital discharge and subsequently reviewed at 28 days. The primary outcome was 28-day mortality. Secondary outcomes were the need for vasopressor therapy and Intensive Care Unit (ICU)/ High dependency unit (HDU) admission.

Ethics statement

Ethical approval was granted by the ethics review committee of the Colombo South Teaching Hospital. All study participants were recruited after obtaining written informed consent. Any patient without capacity to consent due to the illness, were recruited following proxy consent.

Statistical analysis

The data were analysed via the IBM Statistical Package for the Social Sciences (SPSS) version 27. Categorical variables such as patient characteristics, comorbidities, source of sepsis and outcomes are presented as frequencies with percentages. Chi-square tests of independence or Fisher's exact tests were used for comparison of categorical data. All continuous data were skewed in distribution; therefore, they are presented as median (interquartile ranges), and the Mann–Whitney U test was used to compare each predictive variable between the two outcome groups. A significance level of $p < 0.05$ was used. Spearman correlation coefficient was used to measure the strength and direction of the relationship between CL and VL. Receiver operator characteristic (ROC) analysis was used to assess the predictive capacity of CL at t_0 and the lactate clearance at t_6 using the area under the curve (AUC) and Youden's J statistic.

Results

Baseline characteristics of the study population

A total of 102 participants with suspected sepsis were recruited for the study. The baseline characteristics of the study population are described in Table 1. There were 52 females (51%), and the median age was 71.5 (IQR: 62–77) years. The comorbidity with the highest proportion was dyslipidaemia ($n=63$, 61.8%), followed by hypertension ($n=55$, 53.9%) and diabetes mellitus ($n=48$, 47.1%).

Most frequent sources of sepsis in the study sample were pulmonary ($n=57$, 55.9%) or urological ($n=19$, 18.6%) in origin. In our sample, 34 patients succumbed to illness, whereas 68 survived, resulting in a 28-day mortality rate of 33.3%. Only 31.4% ($n=32$) required

Table 1 Demographic factors, comorbidities, potential septic foci and outcomes of the study sample

Parameters	Frequency (%)
Age in years, median (IQR)	71.5 (62–77)
Male gender, n (%)	50 (49.0)
Comorbidities, n (%)	
Dyslipidaemia	63 (61.8)
Hypertension	55 (53.9)
Diabetes mellitus	48 (47.1)
Ischemic Heart Disease	36 (35.3)
Stroke/TIA	23 (22.5)
Chronic kidney disease	20 (19.6)
Lung diseases (BA/COPD/ILD)	19 (18.6)
Malignancy	14 (13.7)
Chronic liver cell disease	12 (11.8)
Septic focus, n (%)	
Pulmonary	57 (55.9)
Urological	19 (18.6)
Gastrointestinal	7 (6.9)
Skin and soft tissue	8 (7.9)
Central nervous system	3 (2.9)
Musculoskeletal	1 (1.0)
Miscellaneous	8 (7.9)
Outcomes, n (%)	
ICU/HDU admission	15 (14.7)
Vasopressor Therapy	32 (31.4)
Mortality at 28-days	34 (33.3)

Abbreviations: BA bronchial asthma, COPD chronic obstructive pulmonary disease, HDU high-dependency unit, ICU Intensive Care Unit, ILD Interstitial Lung Disease, TIA transient ischaemic attack

vasopressor support during the hospital stay and 14.7% ($n=15$) required ICU/HCU care.

Lactate measurements and correlation between CL and VL

The median CL and VL at t_0 were 3.4 mmol/L (IQR: 2.5–4.2) and 3.6 mmol/L (IQR: 2.6–4.6), respectively. The median CL and VL at t_6 were 0.85 mmol/L (IQR: 0.4–1.8) and 0.85 mmol/L (IQR: 0.6–1.8), respectively (Table 2). CL had an excellent correlation with the paired VL levels at t_0 ($r=0.95$) and t_6 ($r=0.92$), both of which were statistically significant ($p < 0.001$). The median capillary lactate clearance and venous lactate clearance rates at t_6 were 75% (IQR: 54.2–80) and 72.6% (IQR: 55.4–79.3), respectively (Table 2). These two parameters strongly correlated ($r=0.77$) with each other (Fig. 1). Bland–Altman plots did not reveal a significant variation of CL values from VL at t_0 or t_6 (Figure S1).

Lactate levels in predicting poor outcomes

The median CL at t_0 was significantly greater among non-survivors than among survivors (4.3 mmol/L vs

Table 2 Lactate measurements and lactate clearance among the study participants and comparisons between survivors and non-survivors at 28-day follow-up

Lactate Parameter	Total sample <i>n</i> = 102	Survivors <i>n</i> = 68	Non-survivors <i>n</i> = 34	<i>p</i> value
CL at t_0	3.4 (2.5–4.2)	2.9 (2.1–3.4)	4.3 (3.8–5.2)	< 0.001
VL at t_0	3.6 (2.6–4.6)	3.0 (2.3–3.8)	4.8 (4.0–5.7)	< 0.001
CL at t_6	0.85 (0.4–1.8)	0.6 (0.4–0.9)	2.6 (1.8–3.4)	< 0.001
VL at t_6	0.85 (0.6–1.8)	0.8 (0.53–0.9)	2.8 (1.8–3.7)	< 0.001
CL clearance (%)	75.0(54.2–80.0)	76.7(74.6–81.6)	42(34.1– 56.1)	< 0.001
VL clearance (%)	72.6(55.4–79.3)	77.1(71.6–81.3)	46(33.0– 56.0)	< 0.001

All values are expressed as medians (IQR)

2.9 mmol/L, $p < 0.001$). Similarly, the median CL at t_6 was significantly higher (2.6 vs 0.6, $p < 0.001$) and percentage lactate clearance was lower (42 vs 76.7, $p < 0.001$ in the non-survivor group compared to survivors (Table 2).

The best cut-off value of CL at t_0 for predicting 28-day mortality was 3.5 mmol/L, with 85% sensitivity, 78% specificity. The ROC curve analysis revealed an area under the curve (AUC) of 0.89 (95% CI: 0.82–0.95) (Fig. 2). This cut-off was associated with increased ICU admission ($p < 0.01$) and vasopressor requirements ($p < 0.0001$) (Table 3). Lactate clearance predicted mortality with a ROC curve AUC of 0.94 (95% CI: 0.87–1, $p < 0.001$). The optimal capillary lactate clearance cut-off for predicting

the primary outcome was 64%. It had excellent sensitivity (97%) and specificity (91%) (Fig. 2).

Logistic regression revealed that CL at $t_0 \geq 3.5$ (adjusted OR 9.1, 95% CI 2.2–36.8), age (adjusted OR 1.1, 95% CI 1.04–1.2) and serum creatinine (adjusted OR 1.01, 95% CI 1.0–1.01) predicted 28-day mortality in this group of patients with sepsis (Table S1).

Discussion

In clinical practice, arterial and venous lactate levels are frequently used as surrogate markers for assessing disease severity, poor outcomes in sepsis and to measure responsiveness to treatment interventions [9]. However,

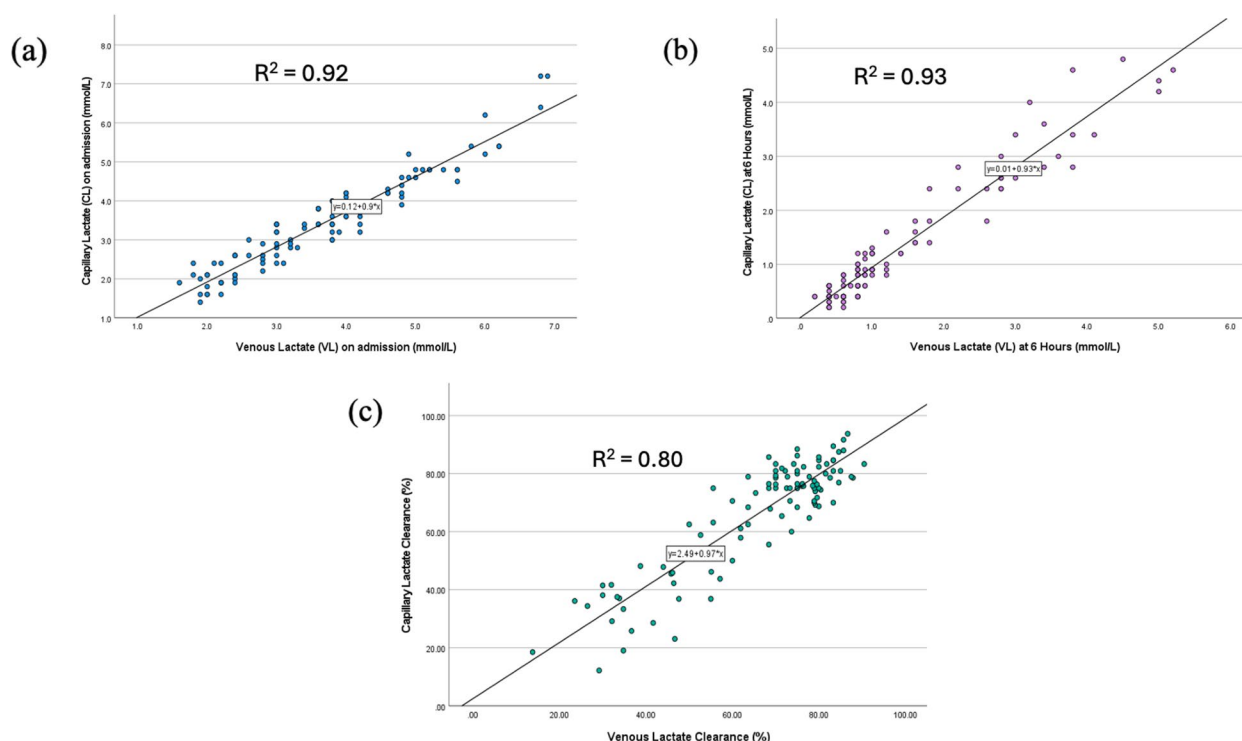


Fig. 1 Correlation between venous lactate (VL) and capillary lactate (CL) in the study population. The scatter diagrams demonstrate the correlation between VL and CL values obtained from a hand-held lactate meter; (a) VL and CL on admission (t_0), (b) VL and CL at 6 h (t_6), (c) VL clearance and CL clearance at 6 h (t_6). Correlation was assessed by Spearman correlation. R^2 denotes the correlation coefficient

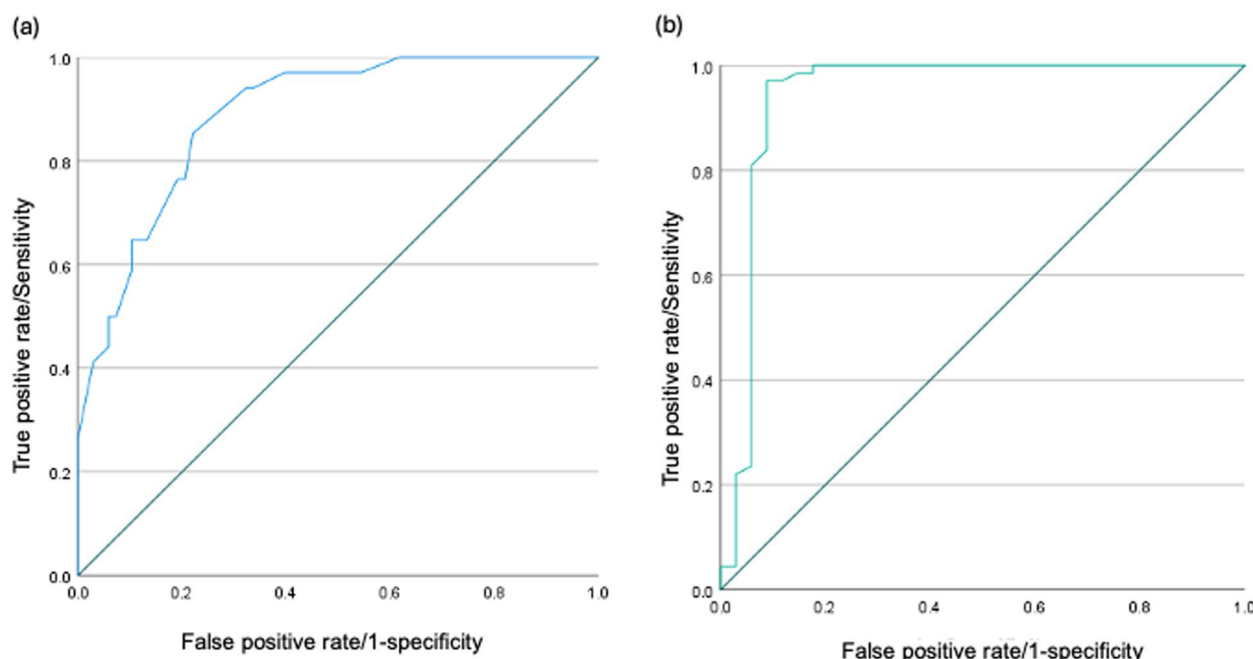


Fig. 2 Receiver operating characteristic (ROC) curves showing the ability of capillary lactate (CL) and CL clearance in predicting 28-day mortality in patients with sepsis. Sepsis was defined by a qSOFA ≥ 2 in the presence of clinical evidence of infection. Figures demonstrate ROC curves for; (a) 28-day mortality for CL on admission (t_0) (AUC = 0.89, $p < 0.001$); (b) 28-day mortality for CL clearance at 6 h after admission (t_6) (AUC = 0.94, $p < 0.001$). AUC; area under the curve

data on the reliability of CL remain inconclusive. The findings of this study underscore the clinical utility of CL as a prognostic biomarker in sepsis.

Our results show that CL strongly correlates with VL levels, both at t_0 and t_6 , offering a quicker and more patient-friendly option for monitoring lactate levels in patients with sepsis. These findings are in concordance with those of previous studies [14, 16]; however, the strength of this correlation varies. Contenti et al. reported a strong correlation ($r = 0.82$) between CL and AL similar to our findings after studying 103 patients fulfilling the systemic inflammatory response criteria, whereas Guarino et al. reported a moderate correlation ($r = 0.5$) between CL and AL from their 203 patients with suspected sepsis [14, 16]. Several studies on critically ill patients in the ICU have also reported strong correlations between the same parameters [13, 17, 18, 20]. A few other

studies however, revealed a poor correlation between CL and AL but the study population included ICU patients and emergency department admissions not necessarily related to sepsis, suggesting limited clinical utility for CL in these settings. [21, 22]. Critically ill patients tend to be more haemodynamically unstable, which could cause fluctuations in capillary lactate levels due to rapid production of lactic acid and increased clearance due to aggressive fluid resuscitation. The capillary microcirculation is the initial site of tissue hypoxia due to circulatory compromise and the last site of recovery following resuscitation. Therefore, CL levels are expected to be greater in ICU patients than in those with initial presentation of sepsis. On the other hand, CL readings may be falsely low due to peripheral vasoconstriction. This variability suggests that while the CL is a promising marker for early risk stratification and prognostication in sepsis, the VL or AL may be more reliable for monitoring ICU patients. The CL levels obtained from the POC lactate analyser were calibrated with the AL levels from the general biochemistry analyser prior to conducting the study and correlated well, reassuring the validity of using the analyser for the study. This would have eliminated any potential instrument bias, which may have confounded the above results.

Blood lactate levels serve as significant predictors of mortality and adverse outcomes in patients with sepsis [9]. Compared to other biomarkers such as procalcitonin,

Table 3 Association between the optimal cut-off capillary lactate level of 3.5 mmol/L at t_0 and the outcomes of sepsis

Outcome	Capillary lactate level at t_0		P Value
	< 3.5 (n = 58)	≥ 3.5 (n = 44)	
ICU/HDU admission	3 (5.2)	12 (27.3)	0.002
Vasopressor requirement	7 (12.1)	25 (56.8)	< 0.001
Mortality during hospital stay	2 (3.4)	27 (61.4)	< 0.001
Mortality at 28-days	5 (8.6)	29 (65.9)	< 0.001

lactate reflects haemodynamic status important in the early resuscitation of patients. Our findings showed that a high CL at both t_0 and t_6 was significantly associated with increased 28-day mortality ($p < 0.05$), which is in line with previous literature [14, 16]. CL is known to overestimate classical blood lactate levels; therefore, using traditional blood lactate cut-offs for CL carries the risk of over-triage and unwarranted treatment unless a higher threshold is set. Patients with sepsis are prone to more severe microcirculatory compromise in relation to systemic circulatory dysfunction, resulting in higher CL levels. The ROC curve analysis revealed that CL at t_0 predicted 28-day mortality with an AUC of 0.8 (0.72–0.91) and a cut-off value of $CL \geq 3.5$ mmol/L had 85% sensitivity, 78% specificity. This cut-off was also associated with increased vasopressor requirements and ICU admissions. Patients with a $CL \geq 3.5$ mmol/L at admission were 9-times more likely to succumb at 28-days even after correcting for other confounding factors such as age and laboratory values. Similar cut-offs have been derived in past studies but for different outcomes. A $CL > 16.8$ mmol/L was found to be predictive of 48-h mortality, with 72.22% sensitivity and 94.02% specificity in one study [16]. A lactate level of such a high degree compared with our level could be expected for the prediction of short-term mortality, in contrast to 28-day mortality as in this study. Purcarea et al. obtained a cut-off closer to ours (2.6 mmol/L) for predicting poor outcomes in patients with sepsis admitted to the ward. This cut-off was derived for the follow-up lactate level (within 12–36 h of admission) and incorporated a broader definition of poor outcomes, which included 30-day mortality as well as the need for higher care, which could explain the relatively lower level compared with our findings [23]. The high performance of the derived cut-off of 3.5 in our study could be due to selection of patients with one clinical entity (sepsis) rather than multiple medical presentations and also due to the selection of patients with organ dysfunction (high qSOFA) in sepsis. Therefore, we observed that CL on admission is reliable in predicting poor outcome and it is a valuable tool for risk stratification in sepsis.

Studies have reported that serum lactate clearance rates ranging from 10 to 36% at 6 h can predict poor outcomes and mortality. Our study yielded a significant cut-off of 64% (sensitivity 97%, specificity 91%, AUC 0.94, $p < 0.05$). While this value is admittedly higher than those previously reported, it is worth noting the high degree of variation that exists for such cut-off values. Moreover, this is the first study assessing lactate clearance from capillary samples. These findings, combined with the increased proportion of poor outcomes with high CL levels at t_6 , suggest that serial blood lactate levels and the presence of persistent hyperlactatemia is predictive of poor outcomes

which is in concordance with the findings of previous studies [23–25].

Using portable analysers for capillary blood lactate testing offers significant benefits over traditional arterial and venous lactate measurements. This technique can be carried out with the same fingerpick used for capillary glucose measurement, which results in minimal risk, pain and inconvenience for the patient, and requires minimal training of the personnel. Additionally, the limited availability of blood gas analysers in resource constraint settings makes CL measurement by a hand-held analyser, an invaluable tool.

The surviving sepsis guidelines highlight the importance of early identification of sepsis to commence prompt resuscitation [11]. Compared with serum lactate, measuring CL significantly hastens the time taken for blood lactate estimation. According to two studies, the mean time differences between CL estimation and traditional AL or VL lactate estimation were 35 min [26] and 65 min [15], respectively. This translates to shortened clinical decision-making duration, which can have a major impact on time-sensitive conditions such as sepsis. Lactate testing via portable analysers can also be implemented in a prehospital setting, further accelerating subsequent care. Another advantage of using CL for prognostication is that it may be more sensitive than VL or AL measurements for detecting early changes in sepsis [23]. This early rise in CL can be attributed to peripheral microcirculatory dysfunction in early or compensated sepsis, when the systemic haemodynamic status is still unaltered. Therefore, stagnant tissue perfusion in peripheral areas, such as the fingertips, where capillary samples are often collected, results in localized anaerobic metabolism and lactate production. Consequently, capillary hyperlactatemia may not be reflected in venous or arterial samples in early sepsis.

Limitations

We acknowledge several limitations of our study. As a monocentric study with a limited sample size, our findings may lack generalizability and statistical power. Second, we utilized the qSOFA for initial sepsis screening. While proven to be useful, its sensitivity in early sepsis detection is debated, which might impact the study's predictive accuracy. The tourniquet time for venous sampling was not standardized, which could lead to artificially elevated venous lactate levels due to transient local hypoxia. However, prior studies indicate that this phenomenon has a minimal effect on lactate levels [27]. Notably, the accuracy of handheld lactate analysers may also be influenced by external factors, temperature and sweat and may lead to operational or technical errors during sampling or testing, which could affect reliability.

Conclusions

This study highlights the utility of CL measurement as a valuable prognostic tool in patients with suspected sepsis. Our findings demonstrate a strong correlation between CL and VL levels at admission and at 6 h, supporting the utility of CL as a more practical, cost-effective and patient-friendly option for lactate monitoring in sepsis, especially in resource limited settings. The optimal admission CL cut-off of ≥ 3.5 mmol/L was associated with significantly higher 28-day mortality, increased need for vasopressors, and higher ICU admissions, suggesting that CL can effectively aid in early risk stratification.

Moreover, CL clearance emerged as an important indicator of survival, with a 64% clearance threshold predicting improved outcomes, aligning with the role of lactate clearance in assessing response to treatment. While our findings support CL as a reliable measurement in general ward settings, further research is warranted to validate its accuracy in critically ill patients, particularly those in ICU settings where microcirculatory changes may impact capillary measurements.

Abbreviations

AL	Arterial Lactate
AUC	Area Under the Curve
CI	Confidence Interval
CL	Capillary Lactate
HDU	High-Dependency Unit
ICU	Intensive Care Unit
IQR	Interquartile Range
POC	Point-of-Care
qSOFA	Quick Sepsis-related Organ Failure Assessment
ROC	Receiver Operating Characteristic
VL	Venous Lactate

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

P.J. was responsible for conceptualization, methodology, data collection, analysis, writing the original draft and editing of the manuscript. D.D., A.C., B.B. and V.A. contributed data collection, analysis and manuscript preparation. S.H. and R.R. assisted in data analysis and interpretation. K.W. revised the manuscript. J.I., N.P. contributed to conceptualization, supervision and reviewed the final manuscript. All authors have contributed and approved the final manuscript.

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None.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Review Committee of Colombo South Teaching (Reference Number: PL/MO/2020). Informed written consent was obtained from all participants prior to recruitment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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