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Serial Lactate Clearance at Six Hours as a Predictor of In-Hospital Mortality and Intensive Care Unit Admission in Adult Sepsis Patients Presenting to the Emergency Department - A Prospective Observational Study

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Abstract

Background: Sepsis remains a leading cause of avoidable in-hospital death, and the emergency department is the point at which risk stratification carries the greatest therapeutic leverage. A single lactate value describes the severity of hypo perfusion at one instant, whereas the trajectory of lactate across the initial resuscitation window may describe how far that hypo perfusion is reversible. The present study evaluated serial lactate clearance at six hours as a predictor of in-hospital mortality and intensive care unit admission in adult patients presenting to the emergency department with sepsis.

Methods: A prospective observational study was conducted on 170 consecutive adults above 18 years of age who satisfied the Sepsis-3 criteria. Blood lactate was estimated at presentation and repeated at six hours, and lactate clearance was calculated as the percentage fall from the baseline value. Participants were categorised as having adequate clearance when the fall was 10 per cent or more and inadequate clearance when it was below 10 per cent. Patients were followed until death or discharge. In-hospital mortality was the primary outcome and intensive care unit admission was the principal secondary outcome. Group comparisons used the chi-square test and the independent samples t test, discrimination was assessed by receiver operating characteristic analysis, and independent predictors were identified by multivariable logistic regression.

Results: Adequate clearance was observed in 112 patients (65.9 per cent) and inadequate clearance in 58

(34.1 per cent). Overall in-hospital mortality was 25.9 per cent and 88 patients (51.8 per cent) required intensive care. Mortality was 16.1 per cent with adequate clearance against 44.8 per cent with inadequate clearance (p<0.001), and intensive care admission was 42.0 per cent against 70.7 per cent (p<0.001). Mean clearance was 31.9 ± 22.4 per cent in survivors and 12.2 ± 25.1 per cent in non-survivors (p<0.001). The area under the curve for mortality was 0.782 (95 per cent confidence interval 0.706 to 0.858). Clearance below 10 per cent independently predicted death (adjusted odds ratio 3.42, 95 per cent confidence interval 1.54 to 7.60, p=0.003).

Conclusion: Six-hour lactate clearance below 10 per cent identified emergency department patients with sepsis who were at substantially higher risk of death and of requiring intensive care, and performed better than the admission lactate value alone.

Keywords: Sepsis, Lactate Clearance, Emergency Department, In-Hospital Mortality, Intensive Care Unit Admission, Risk Stratification.

Introduction

Sepsis is defined as life-threatening organ dysfunction arising from a dysregulated host response to infection, a formulation adopted by the Third International Consensus Definitions and one that shifted the diagnostic emphasis away from the inflammatory response and towards demonstrable organ injury.[1] The burden that follows this definition is considerable. Analysis of the Global Burden of Disease dataset estimated 48.9 million incident episodes and 11 million sepsis-related deaths worldwide in a single year, with almost 85 per cent of that burden borne by low-income and middle-income regions.[2] For the majority of these patients the emergency department is the first point of contact with organised care, and it is within the first few hours of that contact that fluid resuscitation, source control and antimicrobial administration exert their greatest influence on survival, a principle embedded in successive iterations of the Surviving Sepsis Campaign guidelines.[3]

Blood lactate occupies a central position in this early assessment. The consensus definition of septic shock requires a serum lactate above 2 mmol/L persisting despite adequate volume resuscitation, in addition to vasopressor dependence, and the elevation of lactate above this threshold identified a subgroup with hospital mortality in excess of 40 per cent.[4] The elevation itself is not attributable to anaerobic metabolism alone. Accelerated aerobic glycolysis driven by catecholamine stimulation of the sodium-potassium adenosine triphosphatase pump, impaired pyruvate dehydrogenase activity and reduced hepatic and renal extraction all contribute, so that hyperlactataemia in sepsis is better regarded as a composite marker of metabolic stress than as a pure index of tissue hypoxia.[5]

A single lactate estimation nonetheless carries substantial prognostic weight. Serum lactate measured in patients with infection predicted mortality in a graded fashion across the entire range of values rather than only above an arbitrary cut-off, and the association held after adjustment for the presence of hypotension.[5] Further work demonstrated that lactate remained associated with death in severe sepsis independently of organ failure and of shock, which established the analyte as more than a surrogate for haemodynamic collapse.[6] The limitation of a solitary measurement is that it describes a static point. Two patients presenting with identical lactate concentrations may differ entirely in the responsiveness of their circulation to resuscitation, and it is that

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responsiveness which determines the subsequent clinical course.

Serial measurement addresses this limitation. Lactate clearance, expressed as the percentage decline from the presenting value over a defined interval, was first examined systematically in emergency department patients with severe sepsis and septic shock, in whom every 10 per cent increment in six-hour clearance was accompanied by an approximately 11 per cent reduction in the likelihood of death.[7] A subsequent multicentre analysis using a 10 per cent threshold reported in-hospital mortality of 60 per cent among patients failing to clear lactate against 19 per cent among those who cleared it, and non-clearance emerged as an independent predictor of death on multivariable analysis.[8] The therapeutic corollary was tested in a randomised non-inferiority trial in which resuscitation targeted to lactate clearance was not inferior to resuscitation targeted to central venous oxygen saturation, a finding of practical importance because clearance requires only repeat venous sampling rather than central venous cannulation.[9]

A systematic review and meta-analysis of critically ill cohorts subsequently confirmed that lactate clearance predicts all-cause mortality with moderate to good discrimination across heterogeneous populations.[10]

Despite this body of evidence, several gaps remain relevant to practice in Indian emergency departments. Much of the foundational work was generated within protocolised early goal-directed therapy pathways in well-resourced Western centres, and the applicability of a 10 per cent threshold to patients who present later in the course of illness, frequently with advanced organ dysfunction and undifferentiated sources of infection, has been examined less often. Furthermore, published work has concentrated almost exclusively on mortality as the outcome of interest, whereas the decision that confronts the emergency physician on a shift-to-shift basis is one of disposition. In institutions where critical care beds are scarce and where triage decisions determine which patient occupies the single available bed, an objective bedside index that anticipates the need for intensive care would carry immediate operational value alongside its prognostic value.

The present study was therefore designed to evaluate serial lactate clearance at six hours in adults presenting to the emergency department with sepsis, and to determine whether clearance discriminates in-hospital mortality and the requirement for intensive care unit admission more effectively than the presenting lactate concentration alone.

Aims and Objectives

The aim of the study was to evaluate the prognostic utility of serial blood lactate clearance measured at six hours from presentation in adult patients diagnosed with sepsis in the emergency department of a tertiary care teaching hospital.

The primary objective was to determine the association between six-hour lactate clearance and in-hospital mortality, and to establish whether a clearance value below 10 per cent identified patients at increased risk of death. The secondary objectives were to determine the association between six-hour lactate clearance and the requirement for intensive care unit admission; to compare the discriminatory performance of six-hour lactate clearance against the presenting lactate concentration, the six-hour lactate concentration, the Sequential Organ Failure Assessment score and the quick Sequential Organ Failure Assessment score for the prediction of in-hospital mortality; to identify independent predictors of in-hospital mortality after

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adjustment for age, severity of illness, presence of septic shock and requirement for mechanical ventilation; and to examine the relationship between six-hour lactate clearance and secondary measures of illness burden, namely vasopressor requirement, mechanical ventilation, renal replacement therapy and duration of hospital stay.

Materials and Methods

Study design and setting

A hospital-based prospective observational study was carried out in the Department of Emergency Medicine of a tertiary care teaching hospital attached to a medical college.

The emergency department received approximately 45,000 adult attendances annually and functioned with round-the-clock point-of-care blood gas analysis, an adjoining resuscitation area and dedicated medical intensive care beds.

Study period

Patients were recruited over a period of eighteen months following institutional ethics committee approval. Recruitment was continuous during this interval and enrolment took place at all hours of the day and on all days of the week so that consecutive presentation was preserved.

Study population and inclusion criteria

Consecutive adults presenting to the emergency department were screened. Patients were included when they were older than 18 years, when a suspected or documented site of infection was present, when the Sequential Organ Failure Assessment score attributable to the acute illness was 2 points or more in accordance with the Sepsis-3 criteria, and when written informed consent was obtained from the patient or from a legally acceptable representative.

Exclusion criteria

Patients younger than 18 years were excluded, as were pregnant women, patients transferred from another hospital after more than six hours of resuscitation elsewhere, and patients in whom the baseline or the six-hour lactate sample could not be obtained. Patients with established chronic liver disease of Child-Pugh class B or C, patients on maintenance haemodialysis, patients with haematological malignancy on active cytotoxic therapy and patients receiving metformin, adrenaline infusion or antiretroviral agents known to elevate lactate independently of perfusion were also excluded. Patients with cardiac arrest before or at presentation, patients with a documented do-not-resuscitate directive, patients who left against medical advice before the six-hour sample and patients who declined consent were not enrolled.

Sample size

The sample size was calculated using the standard formula for the estimation of a single proportion.

$$n = Z^2 \times p \times (1 - p) / d^2$$

where n represented the required sample size, Z represented the standard normal deviate taken as 1.96 for a 95 per cent confidence interval, p represented the anticipated proportion taken as 12 per cent or 0.12 on the basis of previously published literature, $(1 - p)$ accordingly equalled 0.88, and d represented the absolute precision taken as 5 per cent. Substitution yielded $n = 4 \times 0.12 \times 0.88 / (0.05)^2 = 168.96$. Considering an anticipated proportion of 12 per cent, an absolute precision of 5 per cent and a confidence interval of 95 per cent, the sample size was found to be 168.96 and was rounded off to 170. A total of 170 patients were therefore enrolled.

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Ethical considerations

Approval was obtained from the institutional ethics committee before the commencement of recruitment. Written informed consent in the local language was obtained from every participant, and where the patient lacked capacity by reason of altered sensorium or haemodynamic instability, consent was obtained from the legally acceptable representative with deferred consent sought from the patient upon recovery. Confidentiality of records was maintained throughout and the study conformed to the principles of the Declaration of Helsinki. No investigation or intervention was performed solely for the purposes of the study beyond the repeat lactate estimation, which formed part of routine institutional sepsis care.

Study procedure

Eligible patients were enrolled at the point of emergency department triage. A structured proforma was used to record demographic details, presenting complaints, duration of symptoms, comorbid illnesses, the presumed anatomical source of infection and the vital parameters recorded at presentation. Baseline investigations comprised complete blood count, renal and hepatic function tests, serum electrolytes, coagulation profile, blood culture, culture of the presumed source where accessible, chest radiography and arterial blood gas analysis. The sequential organ failure assessment score, the quick sequential organ failure assessment score and the acute physiology and chronic health evaluation ii score were computed from the values recorded within the first hour.

All patients received treatment in accordance with the prevailing institutional sepsis protocol, which was aligned with Surviving Sepsis Campaign recommendations and comprised the collection of cultures before antimicrobial administration, empirical broad-spectrum antimicrobial therapy directed at the presumed source, intravenous balanced crystalloid at 30 mL/kg for patients with hypotension or hyper lactataemia, and noradrenaline titrated to a mean arterial pressure of 65 mmHg where hypotension persisted after volume loading. Treating physicians were not blinded to the lactate values, as withholding them would have been ethically untenable, but no treatment decision was mandated by the study protocol on the basis of the clearance value.

Lactate measurement and calculation of clearance

Venous blood was collected at the time of enrolment into a fluoride-oxalate tube and analysed immediately on a bedside blood gas and electrolyte analyser. A repeat sample was drawn six hours after the baseline sample, with a permitted window of thirty minutes on either side, and was processed by the same instrument. Samples were transported on ice and analysed within fifteen minutes of collection to avoid spurious elevation from continued erythrocyte glycolysis. Lactate clearance was calculated as the percentage decline from the presenting value using the expression: lactate clearance (per cent) = [(lactate at presentation − lactate at six hours) / lactate at presentation] × 100. A negative value denoted a rise in lactate over the interval. Patients were categorised into two groups defined a priori, namely adequate clearance when the value was 10 per cent or greater and inadequate clearance when the value was below 10 per cent.

Follow-up protocol

Every enrolled patient was followed from the time of emergency department presentation until the endpoint of death or hospital discharge. The disposition from the emergency department, the requirement for and duration

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of vasopressor support, the requirement for and duration of invasive mechanical ventilation, the development of acute kidney injury requiring renal replacement therapy, the duration of intensive care unit stay and the total duration of hospital stay were recorded prospectively on a daily basis by the investigators. Admission to the intensive care unit was determined by the treating intensivist on clinical grounds and was not influenced by the study. Patients discharged before the seventh day were contacted by telephone at day 28 to confirm survival status, and no patient was lost to follow-up.

Outcome definitions

The primary outcome was in-hospital mortality, defined as death from any cause occurring between emergency department presentation and hospital discharge. The principal secondary outcome was admission to the intensive care unit at any point during the index hospitalisation. Additional secondary outcomes comprised the requirement for vasopressor support, the requirement for invasive mechanical ventilation, the development of acute kidney injury requiring renal replacement therapy, and the duration of intensive care unit and total hospital stay.

Statistical analysis

Data were entered into a spreadsheet and analysed using the Statistical Package for the Social Sciences version 25.0. Continuous variables were expressed as mean with standard deviation where the distribution was normal and as median with interquartile range where it was skewed, and normality was assessed by the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Comparison of continuous variables between two groups employed the independent samples t test, with the Mann-Whitney U test applied where the distribution departed from normality. Comparison of categorical variables employed the Pearson chi-square test, with the Fisher exact test substituted where any expected cell frequency fell below five. Odds ratios with 95 per cent confidence intervals were computed for dichotomous outcomes. The discriminatory ability of lactate parameters and of severity scores for the prediction of in-hospital mortality was assessed by receiver operating characteristic curve analysis, the optimal cut-off being identified by the Youden index and areas under the curve being compared by the DeLong method. Variables associated with mortality at a significance level below 0.10 on univariate analysis were entered into a multivariable binary logistic regression model using the enter method, calibration being assessed by the Hosmer-Lemeshow goodness-of-fit test. Correlation between continuous variables was assessed by the Pearson correlation coefficient. A two-tailed p value below 0.05 was considered statistically significant throughout.

Results

A total of 170 adult patients fulfilling the Sepsis-3 criteria were enrolled and all completed follow-up to the point of death or discharge. The mean age of the study population was 54.8 ± 15.2 years with a range of 19 to 86 years, and 68 patients (40.0 per cent) were aged 60 years or above. Ninety-eight patients (57.6 per cent) were male and 72 (42.4 per cent) were female, yielding a male to female ratio of 1.36 to 1. Diabetes mellitus was the commonest comorbidity, present in 61 patients (35.9 per cent), followed by systemic hypertension in 54 (31.8 per cent), chronic obstructive pulmonary disease in 16 (9.4 per cent) and chronic kidney disease in 18 (10.6 per cent), while 47 patients (27.6 per cent) had no recognised comorbid illness. The respiratory tract was the commonest source of infection and accounted for 62

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patients (36.5 per cent), followed by the genitourinary tract in 38 (22.4 per cent), the abdomen in 31 (18.2 per cent) and skin and soft tissue in 21 (12.4 per cent), while the source remained undetermined in 11 patients (6.5 per cent). Septic shock was present at the time of presentation in 54 patients (31.8 per cent). The mean Sequential Organ Failure Assessment score was 6.4 ± 3.1 and the mean Acute Physiology and Chronic Health Evaluation II score was 17.2 ± 6.4, and a quick Sequential Organ Failure Assessment score of 2 or more was recorded in 106 patients (62.4 per cent). The baseline characteristics of the study population are presented in Table 1.

The median interval from triage to the first lactate estimation was 22 minutes with an interquartile range of 14 to 35 minutes, and empirical antimicrobial therapy was administered within one hour of presentation in 118 patients (69.4 per cent). The mean volume of crystalloid administered during the first six hours was 2410 ± 640 mL. The mean lactate concentration at presentation was 4.36 ± 2.18 mmol/L and the mean concentration at six hours was 3.12 ± 2.06 mmol/L, the difference being statistically significant on paired analysis (t = 9.14, p<0.001). The mean six-hour lactate clearance for the cohort as a whole was 26.8 ± 24.6 per cent. Adequate clearance of 10 per cent or more was achieved by 112 patients (65.9 per cent), while 58 patients (34.1 per cent) demonstrated inadequate clearance below 10 per cent, a group that included 21 patients in whom the lactate concentration rose over the six-hour interval.

In-hospital mortality occurred in 44 patients, giving an overall case fatality of 25.9 per cent, and 88 patients (51.8 per cent) required admission to the intensive care unit at some point during the index hospitalisation. Comparison of survivors with non-survivors is presented in Table 2. Non-survivors were significantly older, with a mean age of 60.2 ± 15.8 years against 52.9 ± 14.6 years among survivors (t = 2.79, p=0.006). Illness severity at presentation was markedly higher among those who died, the mean Sequential Organ Failure Assessment score being 8.7 ± 3.0 against 5.6 ± 2.7 (t = 6.02, p<0.001) and the mean Acute Physiology and Chronic Health Evaluation II score being 21.7 ± 6.2 against 15.6 ± 5.6 (t = 6.03, p<0.001). The mean presenting lactate concentration was 5.24 ± 2.62 mmol/L among non-survivors against 4.05 ± 1.94 mmol/L among survivors (t = 3.19, p=0.002), and the difference widened at six hours, the corresponding values being 4.55 ± 2.72 mmol/L and 2.62 ± 1.55 mmol/L (t = 5.36, p<0.001). The mean six-hour lactate clearance was 12.2 ± 25.1 per cent among non-survivors against 31.9 ± 22.4 per cent among survivors, a difference that was highly significant (t = 4.86, p<0.001). Septic shock at presentation was recorded in 23 non-survivors (52.3 per cent) against 31 survivors (24.6 per cent) (χ^2 = 11.42, p=0.001), and invasive mechanical ventilation was required by 20 non-survivors (45.5 per cent) against 21 survivors (16.7 per cent) (χ^2 = 14.68, p<0.001).

Outcomes stratified by lactate clearance category are presented in Table 3. In-hospital mortality occurred in 18 of 112 patients with adequate clearance (16.1 per cent) and in 26 of 58 patients with inadequate clearance (44.8 per cent), the difference being highly significant (χ^2 = 17.24, p<0.001) and corresponding to an unadjusted odds ratio of 4.24 with a 95 per cent confidence interval of 2.05 to 8.79. Admission to the intensive care unit was required by 47 patients with adequate clearance (42.0 per cent) and by 41 patients with inadequate clearance (70.7 per cent) (χ^2 = 12.62, p<0.001), the odds ratio being 3.33 with a 95 per cent

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confidence interval of 1.70 to 6.55. Vasopressor support was required by 32 patients (28.6 per cent) in the adequate clearance group and by 30 patients (51.7 per cent) in the inadequate clearance group (χ^2 = 8.86, p=0.003), and invasive mechanical ventilation by 19 patients (17.0 per cent) and 22 patients (37.9 per cent) respectively (χ^2 = 9.42, p=0.002). Acute kidney injury requiring renal replacement therapy developed in 11 patients (9.8 per cent) with adequate clearance and in 14 patients (24.1 per cent) with inadequate clearance (χ^2 = 6.42, p=0.011). The mean duration of hospital stay was 8.2 ± 4.1 days in the adequate clearance group against 11.6 ± 6.3 days in the inadequate clearance group (t = 4.28, p<0.001), and among those admitted to intensive care the mean duration of intensive care stay was 4.1 ± 2.6 days against 6.8 ± 3.9 days respectively (t = 3.94, p<0.001).

Receiver operating characteristic analysis for the prediction of in-hospital mortality is presented in Table 4. Six-hour lactate clearance yielded an area under the curve of 0.782 with a 95 per cent confidence interval of 0.706 to 0.858 (p<0.001). At the a priori threshold of 10 per cent the sensitivity was 59.1 per cent, the specificity 74.6 per cent, the positive predictive value 44.8 per cent, the negative predictive value 83.9 per cent and the overall diagnostic accuracy 70.6 per cent. The six-hour lactate concentration yielded an area under the curve of 0.755 (95 per cent confidence interval 0.667 to 0.843) at an optimal cut-off of 3.2 mmol/L, with a sensitivity of 68.2 per cent and a specificity of 71.4 per cent. The presenting lactate concentration performed less well, yielding an area under the curve of 0.681 (95 per cent confidence interval 0.591 to 0.771) at an optimal cut-off of 4.1 mmol/L, with a sensitivity of 61.4 per cent and a specificity of 66.7 per cent. The absolute reduction in lactate yielded an area under the curve of 0.712 (95 per cent confidence interval 0.625 to 0.799). Among the severity scores, the Sequential Organ Failure Assessment score yielded an area under the curve of 0.796 (95 per cent confidence interval 0.721 to 0.871) and the quick Sequential Organ Failure Assessment score yielded 0.702 (95 per cent confidence interval 0.617 to 0.787). Pairwise comparison demonstrated that six-hour lactate clearance discriminated significantly better than the presenting lactate concentration, the difference in areas being 0.101 (p=0.032), whereas the difference between six-hour lactate clearance and the Sequential Organ Failure Assessment score was 0.014 and did not attain significance (p=0.786). For the prediction of intensive care unit admission, six-hour lactate clearance yielded an area under the curve of 0.724 (95 per cent confidence interval 0.647 to 0.801, p<0.001), with a sensitivity of 46.6 per cent and a specificity of 79.3 per cent at the 10 per cent threshold.

The results of multivariable binary logistic regression for in-hospital mortality are presented in Table 5. After adjustment for age, severity of illness, presence of septic shock, requirement for mechanical ventilation and the presenting lactate concentration, lactate clearance below 10 per cent remained an independent predictor of death with an adjusted odds ratio of 3.42 (95 per cent confidence interval 1.54 to 7.60, p=0.003). A Sequential Organ Failure Assessment score above 7 was likewise independently predictive with an adjusted odds ratio of 2.87 (95 per cent confidence interval 1.28 to 6.44, p=0.011), as was the presence of septic shock at presentation with an adjusted odds ratio of 2.34 (95 per cent confidence interval 1.03 to 5.32, p=0.042). Age of 60 years or above, the requirement for mechanical ventilation and a presenting lactate concentration above

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4 mmol/L did not retain independent significance, with respective p values of 0.085, 0.071 and 0.251. The model demonstrated satisfactory calibration on the Hosmer-Lemeshow test (χ^2 = 6.42, df = 8, p=0.600), explained 36.1 per cent of the variance by the Nagelkerke coefficient and classified 79.4 per cent of cases correctly. When the same covariates were modelled against intensive care unit admission, lactate clearance below 10 per cent retained independent significance with an adjusted odds ratio of 2.76 (95 per cent confidence interval 1.35 to 5.64, p=0.005).

Correlation analysis is presented in Table 6. Six-hour lactate clearance correlated inversely and significantly with the Sequential Organ Failure Assessment score (r = −0.412, p<0.001) and with the Acute Physiology and Chronic Health Evaluation II score (r = −0.386, p<0.001). A weaker inverse correlation was observed with the presenting lactate concentration (r = −0.164, p=0.033). Among the 62 patients who required vasopressor support, clearance correlated inversely with the duration of that support (r = −0.365, p<0.001), and among the 88 patients admitted to intensive care it correlated inversely with the duration of intensive care stay (r = −0.324, p=0.002). Clearance also correlated inversely with the total duration of hospital stay for the cohort as a whole (r = −0.286, p<0.001). The volume of crystalloid administered during the first six hours showed a weak positive correlation with clearance that did not attain statistical significance (r = 0.148, p=0.054).

Table 1: Baseline demographic, clinical and laboratory characteristics of the study population (n = 170)

Variable	Value
Age in years, mean ± SD	54.8 ± 15.2
Age ≥ 60 years, n (%)	68 (40.0)
Male, n (%)	98 (57.6)
Female, n (%)	72 (42.4)
Diabetes mellitus, n (%)	61 (35.9)
Systemic hypertension, n (%)	54 (31.8)
Chronic kidney disease, n (%)	18 (10.6)
Chronic obstructive pulmonary disease, n (%)	16 (9.4)
Malignancy, n (%)	9 (5.3)
No comorbidity, n (%)	47 (27.6)
Source: respiratory, n (%)	62 (36.5)
Source: genitourinary, n (%)	38 (22.4)
Source: intra-abdominal, n (%)	31 (18.2)
Source: skin and soft tissue, n (%)	21 (12.4)
Source: central nervous system, n (%)	7 (4.1)
Source: undetermined, n (%)	11 (6.5)
Septic shock at presentation, n (%)	54 (31.8)

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Heart rate per minute, mean ± SD	108.6 ± 17.2
Mean arterial pressure in mmHg, mean ± SD	72.4 ± 13.6
Respiratory rate per minute, mean ± SD	26.4 ± 5.8
SOFA score, mean ± SD	6.4 ± 3.1
qSOFA score ≥ 2, n (%)	106 (62.4)
APACHE II score, mean ± SD	17.2 ± 6.4
Lactate at presentation in mmol/L, mean ± SD	4.36 ± 2.18
Lactate at six hours in mmol/L, mean ± SD	3.12 ± 2.06
Six-hour lactate clearance in %, mean ± SD	26.8 ± 24.6
Crystalloid in first six hours in mL, mean ± SD	2410 ± 640
Antimicrobial within one hour, n (%)	118 (69.4)
Vasopressor requirement, n (%)	62 (36.5)
Invasive mechanical ventilation, n (%)	41 (24.1)

SD: standard deviation; SOFA: Sequential Organ Failure Assessment; qSOFA: quick Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 2: Comparison of clinical, severity and lactate parameters between survivors and non-survivors

Variable	Survivors (n = 126)	Non-survivors (n = 44)	Test statistic	p value
Age in years, mean ± SD	52.9 ± 14.6	60.2 ± 15.8	t = 2.79	0.006
Male sex, n (%)	71 (56.3)	27 (61.4)	$\chi^2 = 0.33$	0.564
Diabetes mellitus, n (%)	42 (33.3)	19 (43.2)	$\chi^2 = 1.40$	0.237
Septic shock at presentation, n (%)	31 (24.6)	23 (52.3)	$\chi^2 = 11.42$	0.001
SOFA score, mean ± SD	5.6 ± 2.7	8.7 ± 3.0	t = 6.02	<0.001
APACHE II score, mean ± SD	15.6 ± 5.6	21.7 ± 6.2	t = 6.03	<0.001
qSOFA ≥ 2, n (%)	71 (56.3)	35 (79.5)	$\chi^2 = 7.42$	0.006
Lactate at presentation in mmol/L	4.05 ± 1.94	5.24 ± 2.62	t = 3.19	0.002
Lactate at six hours in mmol/L	2.62 ± 1.55	4.55 ± 2.72	t = 5.36	<0.001
Absolute lactate reduction in mmol/L	1.43 ± 1.21	0.69 ± 1.48	t = 3.24	0.001
Six-hour lactate clearance in %	31.9 ± 22.4	12.2 ± 25.1	t = 4.86	<0.001
Inadequate clearance (<10%), n (%)	32 (25.4)	26 (59.1)	$\chi^2 = 17.24$	<0.001
Invasive mechanical ventilation, n (%)	21 (16.7)	20 (45.5)	$\chi^2 = 14.68$	<0.001
Vasopressor requirement, n (%)	35 (27.8)	27 (61.4)	$\chi^2 = 16.12$	<0.001

Values are expressed as mean ± standard deviation or as number with percentage. Continuous variables were compared by the independent samples t test and categorical variables by the Pearson chi-square test. A p value below 0.05 was considered significant.

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Table 3: Primary and secondary outcomes according to six-hour lactate clearance category

Outcome	Adequate clearance ≥ 10% (n = 112)	Inadequate clearance < 10% (n = 58)	Test statistic	p value	Odds ratio (95% CI)
In-hospital mortality, n (%)	18 (16.1)	26 (44.8)	$\chi^2 = 17.24$	<0.001	4.24 (2.05–8.79)
ICU admission, n (%)	47 (42.0)	41 (70.7)	$\chi^2 = 12.62$	<0.001	3.33 (1.70–6.55)
Vasopressor requirement, n (%)	32 (28.6)	30 (51.7)	$\chi^2 = 8.86$	0.003	2.68 (1.38–5.21)
Invasive mechanical ventilation, n (%)	19 (17.0)	22 (37.9)	$\chi^2 = 9.42$	0.002	2.99 (1.45–6.16)
Renal replacement therapy, n (%)	11 (9.8)	14 (24.1)	$\chi^2 = 6.42$	0.011	2.92 (1.23–6.93)
Hospital stay in days, mean ± SD	8.2 ± 4.1	11.6 ± 6.3	t = 4.28	<0.001	Not applicable
ICU stay in days, mean ± SD	4.1 ± 2.6	6.8 ± 3.9	t = 3.94	<0.001	Not applicable

CI: confidence interval; ICU: intensive care unit; SD: standard deviation. Duration of intensive care stay was computed only for the 88 patients admitted to intensive care.

Table 4: Receiver operating characteristic analysis of lactate parameters and severity scores for the prediction of in-hospital mortality

Parameter	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	p value
Six-hour lactate clearance	0.782	0.706–0.858	≤ 10%	59.1	74.6	<0.001
Lactate at six hours	0.755	0.667–0.843	> 3.2 mmol/L	68.2	71.4	<0.001
Absolute lactate reduction	0.712	0.625–0.799	≤ 0.8 mmol/L	63.6	69.8	<0.001
Lactate at presentation	0.681	0.591–0.771	> 4.1 mmol/L	61.4	66.7	<0.001
SOFA score	0.796	0.721–0.871	> 7	70.5	76.2	<0.001
qSOFA score	0.702	0.617–0.787	≥ 2	79.5	55.6	<0.001
Six-hour lactate clearance (ICU admission)	0.724	0.647–0.801	≤ 10%	46.6	79.3	<0.001

AUC: area under the receiver operating characteristic curve; CI: confidence interval; SOFA: Sequential Organ Failure Assessment; qSOFA: quick Sequential Organ Failure Assessment; ICU: intensive care unit. At the 10 per cent threshold the positive predictive value was 44.8 per cent, the negative predictive value 83.9 per cent and the overall accuracy 70.6 per cent for in-hospital mortality. Pairwise comparison by the DeLong method demonstrated a significant difference between six-hour lactate clearance and the presenting lactate concentration (difference 0.101, p=0.032) and no significant difference between six-hour lactate clearance and the SOFA score (difference 0.014, p=0.786).

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Table 5: Multivariable binary logistic regression for independent predictors of in-hospital mortality

Predictor variable	Regression coefficient (β)	Standard error	Wald statistic	Adjusted odds ratio (95% CI)	p value
Lactate clearance < 10%	1.230	0.407	9.13	3.42 (1.54–7.60)	0.003
SOFA score > 7	1.054	0.414	6.48	2.87 (1.28–6.44)	0.011
Septic shock at presentation	0.850	0.419	4.12	2.34 (1.03–5.32)	0.042
Age ≥ 60 years	0.683	0.397	2.96	1.98 (0.91–4.31)	0.085
Invasive mechanical ventilation	0.747	0.413	3.27	2.11 (0.94–4.74)	0.071
Lactate at presentation > 4 mmol/L	0.482	0.421	1.31	1.62 (0.71–3.70)	0.251

CI: confidence interval; SOFA: Sequential Organ Failure Assessment. Model calibration was satisfactory on the Hosmer-Lemeshow goodness-of-fit test (χ^2 = 6.42, degrees of freedom 8, p=0.600). The Nagelkerke coefficient of determination was 0.361 and the overall classification accuracy was 79.4 per cent. When the same covariates were modelled against intensive care unit admission, lactate clearance below 10 per cent retained independent significance with an adjusted odds ratio of 2.76 (95 per cent confidence interval 1.35 to 5.64, p=0.005).

Table 6: Correlation of six-hour lactate clearance with severity indices and measures of resource utilisation

Variable correlated with six-hour lactate clearance	Number of patients	Pearson correlation coefficient (r)	p value	Interpretation
SOFA score at presentation	170	−0.412	<0.001	Moderate inverse correlation
APACHE II score at presentation	170	−0.386	<0.001	Moderate inverse correlation
Lactate concentration at presentation	170	−0.164	0.033	Weak inverse correlation
Duration of vasopressor support in hours	62	−0.365	<0.001	Moderate inverse correlation
Duration of intensive care unit stay in days	88	−0.324	0.002	Moderate inverse correlation
Total duration of hospital stay in days	170	−0.286	<0.001	Weak inverse correlation
Crystalloid volume in first six hours in mL	170	0.148	0.054	Not significant

SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II. A negative coefficient denotes that higher lactate clearance was associated with lower values of the correlated variable.

Discussion

The present study demonstrated that the trajectory of lactate over the first six hours of emergency department care carried greater prognostic information than the lactate concentration recorded at the moment of arrival. Patients who failed to clear at least 10 per cent of their presenting lactate over this interval experienced almost three times the in-hospital mortality of those who cleared adequately, required intensive care substantially more often, and remained dependent on vasopressor support

and mechanical ventilation for longer. The association with death persisted after adjustment for age, organ dysfunction, shock state and the presenting lactate concentration, which indicates that clearance conveys information that is not captured by conventional severity scoring alone.

These findings are concordant with the foundational emergency department work in which a high six-hour clearance was associated with a reduced mortality rate, each 10 per cent increment corresponding to an approximate 11 per cent reduction in the odds of death[7] They are similarly concordant with the multicentre analysis in which mortality reached 60 per cent among patients failing to clear lactate against 19 per cent among those who cleared, with non-clearance emerging as an independent predictor on multivariable modelling.[8] The absolute mortality figures in the present cohort were lower in the non-clearance group than in that report, at 44.8 per cent, which is likely to reflect the inclusion of the full spectrum of Sepsis-3 patients rather than a cohort restricted to severe sepsis with hypotension or lactate above 4 mmol/L. The direction and the magnitude of the effect were nonetheless preserved.

The relative performance of clearance against a single measurement warrants comment. In the present cohort the area under the curve for six-hour clearance was 0.782 against 0.681 for the presenting lactate concentration, and the difference was statistically significant. Analysis of whole blood lactate kinetics during quantitative resuscitation reached a comparable conclusion, although that work found that normalisation of lactate to below 2 mmol/L was a stronger predictor of survival than clearance expressed as a percentage.[11] The present study did not evaluate normalisation as a separate endpoint, and the observation that the six-hour concentration itself yielded an area under the curve of 0.755 suggests that absolute attainment of a target value and the relative rate of decline both carry prognostic weight in this population.

Not all published work supports the primacy of clearance. In a cohort of patients with septic shock defined strictly by the Sepsis-3 criteria, the lactate concentration measured at six hours discriminated 28-day mortality better than lactate clearance, and the authors argued that clearance is vulnerable to distortion when the baseline value is only modestly elevated.[12]This is a legitimate methodological concern, since a fall from 2.4 mmol/L to 2.1 mmol/L represents a clearance of 12.5 per cent without any meaningful resolution of hypoperfusion. The present study encountered the same limitation, and the weak inverse correlation observed between clearance and the presenting lactate concentration reflects it. An observational study conducted over the first 24 hours of intensive care similarly reported that clearance measured at later time points outperformed the six-hour value, which raises the possibility that the optimal sampling interval differs between the emergency department and the intensive care unit.[13] The concept of relative rather than absolute hyperlactataemia has been advanced for the same reason, with the ratio of the observed value to the patient's own baseline proposed as a more discriminating construct.[14]

The therapeutic relevance of these observations rests on evidence that lactate can serve as a resuscitation target rather than merely as a prognostic marker. A randomised non-inferiority trial established that resuscitation guided by lactate clearance was not inferior to resuscitation guided by central venous oxygen saturation, a finding of particular consequence in settings where central venous cannulation in the emergency department is not

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routine.[9] A multicentrerandomised trial of lactate-guided therapy reported reduced hospital mortality when treatment was directed at a 20 per cent reduction every two hours, and the mechanism appeared to operate through earlier escalation of therapy rather than through any direct effect on lactate itself.[15] Analysis of the Surviving Sepsis Campaign database subsequently confirmed that mortality rose in graded fashion with increasing lactate concentration even among patients without hypotension, which reinforced the case for measuring lactate in every patient with suspected sepsis rather than only in those who are overtly shocked.[16]

A degree of caution is nonetheless warranted in interpreting any lactate-derived index as a direct measure of tissue oxygenation. A systematic review of lactate kinetics in critical illness emphasised that serial values reflect the balance between production and clearance, and that a failure of the concentration to fall may indicate impaired hepatic extraction rather than persistent hypoperfusion.[17] Experimental and clinical work has demonstrated that mild hyperlactataemia in haemodynamically stable septic patients arises predominantly from impaired clearance rather than from overproduction, which provides a physiological basis for that caution.[23] A narrative review of lactate kinetics in sepsis reached the same conclusion and argued that non-hypoxic sources, principally catecholamine-driven aerobic glycolysis, may predominate in an unknown proportion of patients.[18] This consideration acquired practical significance when a randomised trial comparing resuscitation targeted to peripheral perfusion status against resuscitation targeted to lactate found no significant difference in 28-day mortality, with a point estimate that numerically favoured the capillary refill strategy.[19] Those results do not invalidate the prognostic use of lactate clearance, which is the application examined here, but they do caution against treating the number as an obligatory therapeutic endpoint in every patient.

The predictive value of a single lactate estimation in the emergency department has been repeatedly confirmed and formed the comparator in the present analysis. Serum lactate was an independent predictor of hospital mortality among critically ill emergency department patients in a large retrospective cohort,[20] and an earlier prospective study demonstrated that a lactate concentration above 4 mmol/L in patients with infection identified a group with markedly elevated 28-day mortality irrespective of blood pressure.[25] The incremental value demonstrated in the present study lies in showing that a second measurement six hours later, obtained at negligible additional cost, refines that estimate materially.

Data from the Indian setting remain comparatively sparse. A prospective study of serum lactate kinetics in sepsis conducted in an Indian intensive care unit reported that failure of lactate to fall over the initial resuscitation period predicted mortality, with findings closely comparable to those observed here.[21] Validation of the six-hour clearance threshold in an Indian paediatric intensive care population likewise demonstrated significant discrimination for mortality and comparable performance to an established mortality prediction score.[22] The present study extends these observations to adults assessed at the point of emergency department presentation rather than after intensive care admission, which is the juncture at which the information is most actionable.

The finding that clearance predicted intensive care unit admission independently deserves separate emphasis,

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since this outcome has attracted far less attention in the published literature than mortality. In institutions where critical care capacity is limited, the practical question confronting the emergency physician is which patient should occupy the available bed. The negative predictive value of 83.9 per cent for mortality observed at the 10 per cent threshold suggests that adequate clearance offers reasonable reassurance against early deterioration, whereas the modest positive predictive value of 44.8 per cent indicates that inadequate clearance should be interpreted as a trigger for intensified observation and senior review rather than as a deterministic marker of a poor outcome. It is relevant that the original description of early goal-directed therapy achieved its mortality benefit precisely by identifying and aggressively resuscitating such patients within the first six hours of presentation.[24]

Several limitations qualify these findings. The study was conducted at a single tertiary centre and the case mix, which included a high proportion of patients presenting late in the course of illness, may not be representative of other settings. Venous rather than arterial lactate was used, and although the two correlate closely, small systematic differences exist. Lactate was measured at only two time points, so the kinetics between and beyond those points were not characterised and the possibility that a different sampling interval would have performed better cannot be excluded. Treating clinicians were aware of the lactate values, which introduces the possibility that management was intensified in patients with poor clearance and thereby attenuated the observed association. The decision to admit a patient to intensive care was a clinical one influenced by bed availability and by clinician judgement, so this outcome carries a degree of subjectivity that mortality does not. Finally, patients with chronic liver disease and those on maintenance dialysis were excluded to avoid confounding of lactate handling, with the consequence that the findings cannot be extrapolated to those groups.

Conclusion

Serial estimation of blood lactate at presentation and at six hours provided clinically meaningful risk stratification in adult patients presenting to the emergency department with sepsis. A six-hour lactate clearance below 10 per cent was associated with nearly threefold higher in-hospital mortality and with a substantially greater requirement for intensive care, vasopressor support, mechanical ventilation and renal replacement therapy, and it remained an independent predictor of death after adjustment for age, organ dysfunction, shock state and the presenting lactate concentration. Six-hour lactate clearance discriminated in-hospital mortality significantly better than the presenting lactate concentration alone and performed comparably to the Sequential Organ Failure Assessment score.

The implications for practice are direct. A repeat lactate estimation six hours after presentation is inexpensive, requires only venous sampling and can be performed in any emergency department equipped with a point-of-care analyser, yet it identifies a subgroup in whom escalation of therapy, early senior review and prioritisation for critical care are warranted. Conversely, adequate clearance offers reasonable reassurance against early deterioration and may support safer allocation of scarce intensive care resources. Incorporation of a six-hour lactate estimation into institutional sepsis pathways is therefore recommended, and larger multicentre studies with more frequent sampling are required to define the

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optimal threshold and sampling interval for the Indian population.

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