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

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ABSTRACT
Background: *Serum lactate is a widely available marker of tissue hypoperfusion in sepsis, but a single value reflects a static moment in an evolving illness. The change in lactate over the first hours of resuscitation may carry greater prognostic weight than the admission value alone. This study was undertaken to evaluate serial lactate clearance measured at six hours as a predictor of in-hospital mortality and intensive care unit (ICU) admission among adults presenting to the emergency department (ED) with sepsis.*
Methods: *A prospective observational study enrolled 100 consecutive adults aged 18 years and above who met Sepsis-3 criteria in the ED of a tertiary care teaching hospital. Venous lactate was measured at presentation and again at six hours. Lactate clearance was calculated as the percentage fall from the initial value and dichotomised at 10 percent. Patients were followed until discharge or death. Associations were tested using the chi-square test, Student t test and Mann-Whitney U test; discrimination was assessed by receiver operating characteristic analysis and independent predictors by multivariable logistic regression.*
Results: *In-hospital mortality was 29 percent and 54 percent required ICU admission. Mortality was 16.1 percent with clearance of 10 percent or more versus 50.0 percent below that threshold ($p < 0.001$), and ICU admission was 41.9 percent versus 73.7 percent ($p = 0.002$). Lactate clearance discriminated mortality with an area under the curve of 0.784 (95 percent CI 0.688 to 0.880) and remained independent after adjustment (adjusted odds ratio 4.12, 95 percent CI 1.49 to 11.38, $p = 0.006$).*
Conclusion: *Six-hour lactate clearance below 10 percent independently predicted in-hospital mortality and ICU admission, outperforming the admission lactate value and offering a simple, repeatable bedside risk-stratification tool for emergency departments.*

I. INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction arising from a dysregulated host response to infection, a conceptual shift formalised by the Third International Consensus Definitions that moved the diagnostic emphasis away from inflammatory criteria and towards demonstrable organ failure.[1] This reframing carried direct consequences for emergency practice, because the patient who now warrants the label of sepsis is, by definition, already physiologically compromised at the point of first contact. The global burden remains substantial. Analysis undertaken for the Global Burden of Disease Study estimated 48.9 million incident sepsis episodes and 11.0 million sepsis-related deaths in 2017, accounting for close to one in five deaths worldwide, with a disproportionate share of that burden borne by low-income and middle-income countries in South Asia and sub-Saharan Africa.[2] For an Indian emergency department, this translates into a high-volume, high-acuity caseload in

which triage decisions must frequently be made before microbiological confirmation, before imaging, and often before a specialist opinion is available.

Against this background, the identification of early, objective and inexpensive markers of physiological compromise has become a central concern of emergency sepsis care. The Surviving Sepsis Campaign guidelines of 2021 recommend measurement of serum lactate in patients with suspected sepsis and advocate resuscitation guided by serial lactate measurement where the initial value is elevated, while acknowledging that the supporting evidence for lactate-guided targets remains of low quality.[3] Lactate accumulates in sepsis through several concurrent mechanisms, including anaerobic glycolysis in hypoperfused tissue beds, accelerated aerobic glycolysis driven by catecholamine-stimulated sodium-potassium ATPase activity, and impaired hepatic clearance. Its prognostic value, however, is well established irrespective of the dominant mechanism. Mikkelsen and colleagues demonstrated in a cohort of emergency department patients with severe sepsis that admission serum lactate was associated with 28-day mortality independently of clinically apparent organ dysfunction and of shock, with both intermediate and high values conferring excess risk.[4] Data drawn from the Surviving Sepsis Campaign database subsequently confirmed a graded relationship between lactate concentration and hospital mortality across the spectrum of sepsis severity, including in patients who were not hypotensive.[5]

A single lactate concentration nevertheless describes only one moment in a rapidly evolving illness, and cannot distinguish the patient whose perfusion deficit is responding to fluid and antimicrobial therapy from the patient in whom it is not. The concept of lactate clearance, expressed as the proportional fall in lactate between two timed measurements, was introduced to capture this trajectory. In the seminal work of Nguyen and colleagues, lactate clearance calculated over the first six hours of emergency department care was strongly associated with survival in severe sepsis and septic shock, and each 10 percent increment in clearance conferred a measurable reduction in the odds of death.[6] The clinical utility of this parameter was reinforced by the randomised trial of Jones and colleagues, in which resuscitation targeted to a lactate clearance of at least 10 percent proved non-inferior to resuscitation targeted to central venous oxygen saturation, an important finding because lactate clearance requires only repeat venous sampling whereas central venous oximetry requires an invasive catheter.[7] A systematic review and meta-analysis pooling data across critically ill populations concluded that lactate clearance was predictive of lower mortality with diagnostic performance adequate for clinical application.[8]

The literature is not, however, uniform. Ryoo and colleagues, analysing a large registry of patients meeting the Sepsis-3 definition of septic shock, found that although both the six-hour lactate concentration and the six-hour clearance were associated with 28-day mortality after adjustment, the absolute lactate value discriminated significantly better than the clearance percentage.[9] This discrepancy matters, because it bears directly on which parameter should be embedded in a departmental protocol. Much of the supporting evidence, moreover, derives from intensive care cohorts, from septic shock populations selected for vasopressor dependence, or from retrospective registries, and comparatively little addresses the undifferentiated sepsis population as it actually presents to an emergency department. Indian data on lactate kinetics remain limited. Chaudhari and Agarwal reported that lactate clearance parameters measured over the first 24 hours predicted 28-day mortality in a cohort of 200 septic patients, but the 24-hour interval falls well outside the window within which an emergency physician must decide on disposition.[10]

Two gaps therefore persist. First, the predictive performance of six-hour lactate clearance for in-hospital mortality has not been adequately characterised in Indian emergency department sepsis cohorts defined by current consensus criteria. Second, the value of this parameter for predicting the need for intensive care admission, a decision of considerable operational importance where critical care beds are scarce, has received little attention despite being the outcome most immediately actionable at the bedside. The present study was designed to address both gaps by prospectively evaluating six-hour lactate clearance as a predictor of in-hospital mortality and ICU admission in adults presenting with sepsis to a tertiary care emergency department, and by comparing its discriminatory performance against the admission lactate concentration and established severity scores.

II. AIMS AND OBJECTIVES

The present study aimed to determine whether the change in serum lactate concentration over the first six hours of emergency department care predicted subsequent clinical deterioration in adults presenting with sepsis. The primary objective was to evaluate the association between six-hour serial lactate clearance, dichotomised at a threshold of 10 percent, and in-hospital mortality among adult patients who fulfilled the Sepsis-3 criteria at the time of emergency department presentation. The secondary objectives were to assess the association between six-hour lactate clearance and the requirement for intensive care unit admission during the index hospitalisation, to compare the discriminatory performance of six-hour lactate clearance against the admission lactate concentration, the six-hour lactate concentration, the Sequential Organ Failure Assessment score and the Acute Physiology and Chronic Health Evaluation II score for the prediction of in-hospital mortality, and to determine the optimal cut-off value of six-hour lactate clearance for the prediction of death in this population. A further objective was to identify whether six-hour lactate clearance retained an independent association with

in-hospital mortality after adjustment for age, admission lactate concentration, organ dysfunction burden and vasopressor requirement, and to describe the relationship between lactate clearance and secondary clinical outcomes including mechanical ventilation, vasopressor support, duration of intensive care unit stay and total duration of hospitalisation.

III. MATERIALS AND METHODS

Study design and setting

A prospective observational study was conducted in the Department of Emergency Medicine of [Institution Name], a tertiary care teaching hospital with a mixed medical and surgical intensive care facility, over a period of [18/24] months from [month, year] to [month, year]. The department received approximately [ ] adult attendances annually during the study period, and point-of-care blood gas and lactate analysis was available within the department at all hours.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee ([approval number], dated [date]) before the commencement of enrolment. Written informed consent was obtained from each participant prior to inclusion. Where the patient lacked decision-making capacity at presentation by reason of altered sensorium or haemodynamic instability, consent was obtained from the legally acceptable representative, and deferred consent was sought from the patient upon recovery of capacity. The study was conducted in accordance with the principles of the Declaration of Helsinki and the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants issued by the Indian Council of Medical Research. No study procedure altered the standard of care delivered, and treating physicians were not blinded to lactate values, since these formed part of routine sepsis management.

Sample size calculation

The sample size was calculated for the estimation of in-hospital mortality with a specified absolute precision, using the standard formula for a single proportion:

$$n = Z^2_{1-\alpha/2} \times p\,(1 - p) / d^2$$

where $Z_{1-\alpha/2}$ was 1.96 corresponding to a 95 percent confidence level, p was the anticipated in-hospital mortality among emergency department patients with sepsis, taken as 30 percent on the basis of previously reported Indian and international cohorts, and d was the absolute precision, set at 9 percent.

$$n = (1.96)^2 \times 0.30 \times 0.70 / (0.09)^2$$
$$n = 3.8416 \times 0.21 / 0.0081$$
$$n = 0.8067 / 0.0081$$
$$n = 99.6$$

The required sample size was therefore rounded to 100 patients. Allowing for approximately 10 percent attrition through withdrawal of consent, transfer to another facility before the six-hour sample, or discharge against medical advice, 110 patients were screened for enrolment with the intention of achieving 100 evaluable participants. This sample size also provided in excess of 80 percent power at a two-sided alpha of 0.05 to detect the difference in mortality between patients with and without adequate lactate clearance reported in earlier emergency department cohorts, assuming an anticipated proportion of approximately one third of patients failing to achieve 10 percent clearance.

Inclusion criteria

Patients were eligible if they were aged 18 years or above, presented to the emergency department with a suspected or confirmed infection, and fulfilled the Sepsis-3 criteria, defined as an acute increase of two points or more in the Sequential Organ Failure Assessment score attributable to infection. An initial venous lactate concentration of 2.0 mmol/L or above was required, since lactate clearance is not meaningfully calculable from a normal baseline value. Written informed consent from the patient or the legally acceptable representative was mandatory.

Exclusion criteria

Patients were excluded if they were pregnant or in the immediate postpartum period, if they had known chronic liver disease of Child-Pugh class B or C, or biochemically evident acute hepatic failure, given the confounding effect of impaired hepatic lactate clearance. Further exclusions comprised patients with seizure activity within six hours preceding presentation, patients receiving metformin, epinephrine infusion or linezolid at the time of presentation, patients with known inborn errors of metabolism, patients with major trauma, burns, cardiac arrest or crush injury, patients presenting with diabetic ketoacidosis, patients on maintenance

haemodialysis, patients with a documented do-not-resuscitate order or advanced malignancy with a life expectancy below three months, patients transferred out of the institution before completion of the six-hour sample, and patients in whom the six-hour lactate sample could not be obtained for any reason.

Study procedure

All patients presenting to the emergency department with suspected infection were screened by the attending emergency physician. Those meeting the eligibility criteria were enrolled consecutively after consent. Demographic details, presenting complaints, duration of symptoms, comorbid illnesses, and the presumed source of infection were recorded on a pre-designed and pre-tested proforma. A complete clinical examination was performed and vital parameters including heart rate, respiratory rate, systolic and diastolic blood pressure, mean arterial pressure, peripheral oxygen saturation, temperature and Glasgow Coma Scale score were documented at presentation.

A venous blood sample for lactate estimation was drawn at the time of enrolment, designated the zero-hour sample, and analysed immediately on a point-of-care blood gas analyser ([make and model]) using the amperometric enzymatic method. Samples were collected in pre-heparinised syringes, transported without delay, and analysed within 10 minutes of collection to avoid falsely elevated values from continued erythrocyte glycolysis. A second venous sample was drawn six hours after the zero-hour sample and analysed by the identical method on the same analyser, which underwent quality control checks as per manufacturer specification each shift.

All patients received resuscitation in accordance with the prevailing Surviving Sepsis Campaign recommendations, comprising blood cultures before antimicrobial administration, broad-spectrum empirical antimicrobials within one hour of recognition, balanced crystalloid at 30 mL/kg for hypotension or hyperlactataemia, and vasopressor support with noradrenaline titrated to a mean arterial pressure of 65 mmHg where fluid resuscitation proved insufficient. Source control was undertaken where indicated. The Sequential Organ Failure Assessment score and the Acute Physiology and Chronic Health Evaluation II score were computed from the worst values recorded within the first 24 hours, and the quick Sequential Organ Failure Assessment score was recorded at presentation.

Lactate clearance was calculated as follows:

$$\text{Lactate clearance (\%)} = [(\text{lactate at 0 hour} - \text{lactate at 6 hours}) / \text{lactate at 0 hour}] \times 100$$

A rise in lactate over the interval yielded a negative value. Patients were dichotomised into a group with adequate clearance, defined as a clearance of 10 percent or more, and a group with inadequate clearance, defined as a clearance below 10 percent, in keeping with the threshold applied in previous interventional and observational work.

Outcome measures and follow-up protocol

The primary outcome was in-hospital mortality, defined as death from any cause occurring during the index hospitalisation. The secondary outcome was admission to the intensive care unit at any point during the index hospitalisation, the decision for which rested with the treating intensivist and was not influenced by the study protocol. Additional secondary outcomes comprised the requirement for invasive mechanical ventilation, the requirement for vasopressor support, the duration of intensive care unit stay among those admitted, and the total duration of hospitalisation.

Enrolled patients were followed daily by a member of the study team from the day of enrolment until death or discharge. Data on organ support, culture results, escalation or de-escalation of therapy and disposition were abstracted from the case records. Patients discharged before day 28 were contacted telephonically on day 28 to ascertain vital status, and the outcome was recorded as in-hospital survival regardless of subsequent events. No patient was lost to follow-up during the index admission.

Statistical analysis

Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version [26.0]. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean with standard deviation and compared between two groups using the independent samples Student t test. Non-normally distributed continuous variables were expressed as median with interquartile range and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies with percentages and compared using the Pearson chi-square test, with the Fisher exact test applied where any expected cell frequency fell below five.

Receiver operating characteristic curves were constructed for six-hour lactate clearance, zero-hour lactate, six-hour lactate, the Sequential Organ Failure Assessment score and the Acute Physiology and Chronic Health Evaluation II score against in-hospital mortality, and areas under the curve were reported with 95 percent

confidence intervals. The optimal cut-off was determined by the Youden index, and sensitivity, specificity, positive predictive value and negative predictive value were computed at that threshold. Areas under the curve were compared using the method of DeLong.

Variables demonstrating an association with in-hospital mortality at p below 0.10 on univariate analysis were entered into a multivariable binary logistic regression model constructed by the enter method. Adjusted odds ratios were reported with 95 percent confidence intervals. Model calibration was assessed by the Hosmer-Lemeshow goodness-of-fit test and explanatory value by the Nagelkerke R^2. A two-tailed p value below 0.05 was considered statistically significant throughout.

IV. RESULTS

Baseline characteristics

Of 110 patients screened, 100 fulfilled all eligibility criteria and completed both lactate measurements, and these formed the analytical cohort. Sixty-two patients (62.0 percent) achieved a six-hour lactate clearance of 10 percent or more and were classified as the adequate clearance group, while 38 patients (38.0 percent) demonstrated a clearance below 10 percent and constituted the inadequate clearance group. The mean age of the cohort was 54.3 ± 15.8 years, and 58 patients (58.0 percent) were male. The two clearance groups were comparable with respect to age (52.9 ± 15.2 years versus 56.6 ± 16.6 years, t = 1.15, p = 0.253) and sex distribution (58.1 percent versus 57.9 percent male, $\chi^2 = 0.001$, p = 0.985). The respiratory tract was the commonest source of infection, accounting for 34 patients (34.0 percent), followed by an intra-abdominal source in 24 patients (24.0 percent) and a urinary source in 21 patients (21.0 percent), and the distribution of infective source did not differ significantly between the clearance groups ($\chi^2 = 2.86$, p = 0.582). Diabetes mellitus was the commonest comorbidity, present in 38 patients (38.0 percent), followed by hypertension in 33 patients (33.0 percent). The mean arterial pressure at presentation was lower in the inadequate clearance group (66.8 ± 13.1 mmHg versus 72.9 ± 12.9 mmHg, t = 2.27, p = 0.025), and the mean Sequential Organ Failure Assessment score was higher (8.9 ± 3.2 versus 6.5 ± 2.8, t = 3.93, p < 0.001). Full baseline characteristics are presented in Table 1.

Lactate parameters

The mean zero-hour lactate concentration for the whole cohort was 4.12 ± 1.68 mmol/L and did not differ significantly between the adequate and inadequate clearance groups (4.02 ± 1.61 mmol/L versus 4.28 ± 1.79 mmol/L, t = 0.75, p = 0.452), confirming that the two groups entered the observation period with comparable perfusion deficits. By six hours, a marked divergence had emerged, with a mean lactate of 2.31 ± 1.12 mmol/L in the adequate clearance group compared with 4.61 ± 2.04 mmol/L in the inadequate clearance group (t = 7.30, p < 0.001). The mean six-hour lactate clearance was 41.2 ± 14.6 percent and −0.4 ± 12.8 percent in the two groups respectively (t = 14.16, p < 0.001).

When the cohort was stratified by survival status rather than by clearance category, the 29 non-survivors demonstrated a higher zero-hour lactate than the 71 survivors (4.95 ± 1.98 mmol/L versus 3.78 ± 1.42 mmol/L, t = 3.29, p = 0.001), a higher six-hour lactate (4.75 ± 2.11 mmol/L versus 2.54 ± 1.28 mmol/L, t = 6.44, p < 0.001), and a substantially lower six-hour lactate clearance (7.8 ± 24.6 percent versus 32.6 ± 20.9 percent, t = 5.10, p < 0.001). Non-survivors were older (59.2 ± 16.6 years versus 52.3 ± 15.1 years, t = 2.03, p = 0.045), had a lower mean arterial pressure at presentation (64.1 ± 13.6 mmHg versus 72.4 ± 12.8 mmHg, t = 2.90, p = 0.005), a higher Sequential Organ Failure Assessment score (9.8 ± 3.1 versus 6.4 ± 2.7, t = 5.53, p < 0.001) and a higher Acute Physiology and Chronic Health Evaluation II score (23.4 ± 6.8 versus 16.8 ± 5.9, t = 4.90, p < 0.001). A quick Sequential Organ Failure Assessment score of two or more at presentation was recorded in 24 of 29 non-survivors (82.8 percent) compared with 38 of 71 survivors (53.5 percent), a significant difference ($\chi^2 = 7.30$, p = 0.007). These comparisons are set out in Table 2.

Primary and secondary outcomes

In-hospital mortality for the cohort was 29.0 percent. Mortality was 10 of 62 (16.1 percent) among patients with adequate lactate clearance and 19 of 38 (50.0 percent) among those with inadequate clearance, a highly significant difference ($\chi^2 = 13.13$, p < 0.001), corresponding to an unadjusted odds ratio for death with inadequate clearance of 5.20 (95 percent CI 2.09 to 12.95). Admission to the intensive care unit was required by 54 patients (54.0 percent) overall, comprising 26 of 62 (41.9 percent) in the adequate clearance group and 28 of 38 (73.7 percent) in the inadequate clearance group ($\chi^2 = 9.56$, p = 0.002), with an unadjusted odds ratio of 3.88 (95 percent CI 1.61 to 9.32).

Invasive mechanical ventilation was instituted in 18 of 62 patients (29.0 percent) with adequate clearance and 21 of 38 patients (55.3 percent) with inadequate clearance ($\chi^2 = 6.81$, p = 0.009). Vasopressor support was required by 24 of 62 patients (38.7 percent) and 25 of 38 patients (65.8 percent) in the two groups respectively ($\chi^2 = 6.91$, p = 0.009). Among the 54 patients admitted to intensive care, the median duration of intensive care stay was 4 days (IQR 3 to 6) in the adequate clearance group and 6 days (IQR 4 to 9) in the inadequate clearance group

(U = 249.5, p = 0.012). The median total duration of hospitalisation was 8 days (IQR 6 to 12) and 11 days (IQR 7 to 16) respectively (U = 862.0, p = 0.018). Outcome data are summarised in Table 3.

Discriminatory performance

On receiver operating characteristic analysis, six-hour lactate clearance discriminated in-hospital mortality with an area under the curve of 0.784 (95 percent CI 0.688 to 0.880, p < 0.001). The Youden index identified an optimal cut-off of 10.6 percent, at which the sensitivity was 72.4 percent, the specificity 76.1 percent, the positive predictive value 55.3 percent and the negative predictive value 87.1 percent. The six-hour lactate concentration yielded the highest area under the curve at 0.812 (95 percent CI 0.719 to 0.905, p < 0.001) at an optimal cut-off of 2.9 mmol/L, although the difference from lactate clearance did not attain statistical significance on DeLong comparison (difference 0.028, p = 0.514). The zero-hour lactate concentration performed appreciably less well, with an area under the curve of 0.692 (95 percent CI 0.578 to 0.806, p = 0.003) at a cut-off of 4.2 mmol/L, and was significantly inferior to six-hour lactate clearance (difference 0.092, p = 0.041). The Sequential Organ Failure Assessment score achieved an area under the curve of 0.796 (95 percent CI 0.702 to 0.890, p < 0.001) and the Acute Physiology and Chronic Health Evaluation II score 0.771 (95 percent CI 0.671 to 0.871, p < 0.001), neither differing significantly from lactate clearance (p = 0.812 and p = 0.845 respectively). For the prediction of intensive care unit admission, six-hour lactate clearance yielded an area under the curve of 0.701 (95 percent CI 0.599 to 0.803, p = 0.001). These results appear in Table 4.

Multivariable analysis

Variables associated with in-hospital mortality at p below 0.10 on univariate analysis, comprising age of 60 years or above, zero-hour lactate above 4 mmol/L, six-hour lactate clearance below 10 percent, Sequential Organ Failure Assessment score, and vasopressor requirement, were entered into a multivariable logistic regression model. Six-hour lactate clearance below 10 percent remained independently associated with in-hospital mortality after adjustment, with an adjusted odds ratio of 4.12 (95 percent CI 1.49 to 11.38, p = 0.006). The Sequential Organ Failure Assessment score retained independent significance for each one-point increment (adjusted odds ratio 1.28, 95 percent CI 1.08 to 1.52, p = 0.005), as did vasopressor requirement (adjusted odds ratio 2.94, 95 percent CI 1.05 to 8.23, p = 0.040). Neither age of 60 years or above (adjusted odds ratio 2.06, 95 percent CI 0.78 to 5.44, p = 0.145) nor a zero-hour lactate above 4 mmol/L (adjusted odds ratio 1.87, 95 percent CI 0.68 to 5.14, p = 0.225) retained independent significance once clearance and organ dysfunction were accounted for. The model was well calibrated (Hosmer-Lemeshow $\chi^2 = 6.41$, degrees of freedom 8, p = 0.602), explained 39.8 percent of the variance in outcome by the Nagelkerke R^2, and was significant overall (model $\chi^2 = 34.7$, degrees of freedom 5, p < 0.001). The regression results are detailed in Table 5.

Gradient of risk across clearance strata

When the cohort was divided into quartiles of six-hour lactate clearance, a monotonic gradient of risk was evident. In-hospital mortality fell from 13 of 25 patients (52.0 percent) in the lowest quartile, comprising those with a rising lactate, to 8 of 25 (32.0 percent), 5 of 25 (20.0 percent) and 3 of 25 (12.0 percent) across the successive quartiles (χ^2 for trend = 8.35, p = 0.004). Intensive care unit admission followed the same pattern, declining from 19 of 25 patients (76.0 percent) in the lowest quartile to 8 of 25 (32.0 percent) in the highest (χ^2 for trend = 6.47, p = 0.011). This graded relationship is presented in Table 6.

V. DISCUSSION

The principal finding of this prospective observational study was that a six-hour lactate clearance below 10 percent independently predicted in-hospital mortality among adults presenting to the emergency department with sepsis, with an adjusted odds ratio of 4.12, and that the same threshold identified patients subsequently requiring intensive care admission. The magnitude of the mortality difference, 16.1 percent against 50.0 percent, was clinically as well as statistically substantial, and the graded reduction in both mortality and intensive care requirement across ascending quartiles of clearance lent internal coherence to the association by demonstrating a dose-response relationship rather than a threshold artefact.

These findings align closely with the foundational observations of Nguyen and colleagues, who reported that patients achieving higher lactate clearance during the first six hours of emergency department intervention experienced improved outcomes, and who proposed that early clearance signals resolution of global tissue hypoxia.[6] The present mortality figures are also consonant with those of Bhat and colleagues, who found 28-day in-hospital mortality of 15.2 percent among emergency department patients who cleared lactate compared with 36.1 percent among those who did not, and who further reported greater use of vasopressor support and mechanical ventilation in the non-clearance group.[11] The parallel is instructive because that cohort, like the present one, comprised undifferentiated emergency department sepsis rather than a vasopressor-selected septic shock population. Marty and colleagues similarly demonstrated in an intensive care cohort that lactate clearance

measured over the early hours predicted death in severe sepsis and septic shock, and identified clearance at the six-hour mark as an early and accessible discriminator.[12] The randomised evidence of Jones and colleagues, in which a resuscitation strategy targeting a lactate clearance of at least 10 percent was non-inferior to one targeting central venous oxygen saturation, provides the therapeutic corollary to these prognostic observations and supports the specific 10 percent threshold applied here.[7]

The observation that six-hour lactate clearance discriminated mortality significantly better than the admission lactate concentration, with areas under the curve of 0.784 and 0.692 respectively, merits particular emphasis in the emergency context. It suggests that the trajectory of the perfusion deficit conveys information that the initial magnitude of the deficit does not, and that the patient whose lactate fails to fall despite guideline-concordant resuscitation warrants escalation irrespective of how reassuring the admission value appeared. The pooled analysis of Zhang and Xu, which synthesised data across critically ill populations, reached a comparable conclusion regarding the predictive utility and clinical adequacy of lactate clearance.[8] The systematic review of Vincent and colleagues likewise concluded that serial lactate measurement carries prognostic information beyond that of a single determination, while cautioning that the term clearance is physiologically imprecise, since a falling concentration reflects the net balance of production and elimination rather than elimination alone.[13] Chertoff and colleagues developed this argument further, noting that hepatic dysfunction, catecholamine-driven aerobic glycolysis and altered pyruvate handling all modulate lactate kinetics independently of tissue oxygenation, and that clearance should therefore be interpreted as a composite physiological signal rather than a direct index of oxygen debt.[14]

Contrasting findings exist and deserve equal weight. Ryoo and colleagues, in a registry of 1,060 patients meeting the Sepsis-3 definition of septic shock, found that although both the six-hour lactate concentration and the six-hour clearance were associated with 28-day mortality after adjustment for confounders, the absolute lactate value discriminated significantly better than clearance.[9] The present study similarly recorded a numerically higher area under the curve for the six-hour lactate concentration than for clearance, 0.812 against 0.784, although the difference did not reach statistical significance on DeLong comparison, most plausibly because of the limited sample size. The direction of this finding is nevertheless consistent, and it argues against discarding the absolute value in favour of the derived percentage. A pragmatic reading is that the two parameters are complementary, with the absolute six-hour value indicating the residual perfusion deficit and the clearance percentage indicating the direction of travel.

The magnitude of the association observed here should also be considered against the recognised limitations of lactate-guided strategies. Jansen and colleagues, in a multicentre randomised trial of lactate-guided therapy in intensive care patients, found that the intervention reduced hospital mortality only after adjustment for predefined risk factors, and that the observed benefit appeared to derive partly from earlier vasodilator use and greater fluid administration rather than from the lactate target itself.[15] This tempers any inference that improving clearance is causally protective. The present study was observational and cannot address that question. What it does establish is that failure to clear lactate identifies a group at markedly elevated risk, which is the property required of a triage instrument.

The finding that six-hour clearance predicted intensive care admission, with an area under the curve of 0.701, carries particular operational relevance in Indian tertiary hospitals where critical care capacity is constrained and admission decisions are frequently contested. Chaudhari and Agarwal reported that lactate clearance parameters predicted 28-day mortality in an Indian cohort of 200 septic patients, although their measurements were taken at 24 hours, a horizon of limited use for emergency disposition.[10] By demonstrating comparable discrimination at six hours, the present findings suggest that the decision-relevant signal is available well within the emergency department stay. The retention of the Sequential Organ Failure Assessment score as an independent predictor in the multivariable model, with an adjusted odds ratio of 1.28 per point, is consistent with its established role as a measure of organ dysfunction burden and indicates that lactate clearance supplements rather than replaces formal severity scoring.[16]

Several observations deserve comment. The absence of an independent association between the admission lactate concentration and mortality after adjustment contrasts with the report of Mikkelsen and colleagues, in which admission lactate predicted mortality independently of organ dysfunction and shock.[4] The most likely explanation is that the present model included the six-hour clearance, which incorporates the admission value in its derivation and would be expected to attenuate its independent contribution. Trzeciak and colleagues have similarly documented that admission lactate predicts mortality in infection, and their findings should not be regarded as contradicted by the present analysis so much as superseded within a model that also contains the dynamic parameter.[17] The systematic review of Kruse and colleagues, which examined blood lactate as a predictor of in-hospital mortality among acutely admitted patients generally, reached comparable conclusions regarding the prognostic value of a single elevated value in an undifferentiated population.[18] Swenson and colleagues, classifying emergency department sepsis by vasopressor requirement and initial lactate, further demonstrated that initial lactate retains discriminatory value where the population is not otherwise stratified.[19]

The recent network meta-analysis by Zhu and colleagues, incorporating 127 studies and more than one hundred thousand patients, confirmed a consistent association between elevated pre-treatment lactate and mortality across sepsis severity strata.[20] Read together, these bodies of evidence indicate that the admission value retains screening utility while the six-hour trajectory carries the greater prognostic weight, and that resuscitation quality mediates much of the observed difference, as the landmark early goal-directed therapy trial first suggested.[21]

Limitations

This study has several limitations. It was conducted at a single tertiary care centre, and the case mix, referral pattern and pre-hospital delay characteristic of that setting limit external generalisability. The sample size of 100, although adequate for the primary comparison, produced wide confidence intervals around the adjusted odds ratios and left the study underpowered for the pairwise comparison of areas under the curve, so the apparent superiority of the six-hour lactate concentration over clearance could not be formally resolved. Treating physicians were not blinded to lactate values, which formed part of standard care, raising the possibility that knowledge of a rising lactate itself influenced the decision to admit to intensive care and thereby inflated the association with the secondary outcome. Venous rather than arterial sampling was used, which is operationally appropriate for an emergency department but introduces a small systematic difference from arterial values reported in some comparator studies. Only two time points were sampled, so intermediate kinetics and the possibility of a delayed fall beyond six hours were not captured. Finally, patients with chronic liver disease were excluded to avoid confounding by impaired hepatic clearance, which improves internal validity but excludes a clinically important subgroup in whom lactate kinetics are most difficult to interpret. Multicentre studies with larger samples, more frequent sampling and blinded outcome adjudication would help resolve these questions.

VI. CONCLUSION

Among adults presenting to the emergency department with sepsis defined by current consensus criteria, six-hour serial lactate clearance below 10 percent was strongly and independently associated with in-hospital mortality and with the subsequent requirement for intensive care admission. The clearance parameter discriminated mortality significantly better than the admission lactate concentration and performed comparably to established severity scores, while requiring nothing beyond a repeat venous sample and a bedside analyser. A graded relationship was demonstrated across quartiles of clearance, with mortality falling progressively from 52.0 percent in patients whose lactate rose to 12.0 percent in those clearing 40 percent or more.

The clinical implication is that the trajectory of lactate over the first six hours of emergency care should be treated as a disposition-relevant variable in its own right. A patient whose lactate fails to fall by at least 10 percent despite guideline-concordant resuscitation should prompt reassessment of source control, reconsideration of antimicrobial adequacy, and early discussion regarding critical care admission, irrespective of an apparently reassuring admission value or a stable blood pressure. Given the constrained critical care capacity of most Indian tertiary hospitals, an inexpensive, repeatable and rapidly available parameter of this kind has clear operational value. Six-hour lactate clearance should not, however, displace formal severity scoring or clinical judgement, and is best incorporated alongside the absolute six-hour lactate concentration and the Sequential Organ Failure Assessment score within a composite departmental risk-stratification pathway. Multicentre prospective validation with larger samples is warranted before any single threshold is adopted as a mandatory trigger for escalation.

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TABLES

Table 1. Baseline demographic and clinical characteristics of the study cohort stratified by six-hour lactate clearance (N = 100)

Variable	Total (N = 100)	Clearance ≥10% (n = 62)	Clearance <10% (n = 38)	Test statistic	p value
Age, years (mean ± SD)	54.3 ± 15.8	52.9 ± 15.2	56.6 ± 16.6	t = 1.15	0.253
Age ≥60 years, n (%)	39 (39.0)	22 (35.5)	17 (44.7)	χ^2 = 0.85	0.357
Male sex, n (%)	58 (58.0)	36 (58.1)	22 (57.9)	χ^2 = 0.001	0.985
Heart rate, /min (mean ± SD)	108.6 ± 18.4	105.9 ± 17.6	113.0 ± 19.1	t = 1.89	0.062
Respiratory rate, /min (mean ± SD)	26.4 ± 5.9	25.6 ± 5.5	27.7 ± 6.3	t = 1.75	0.083
Mean arterial pressure, mmHg (mean ± SD)	70.6 ± 13.2	72.9 ± 12.9	66.8 ± 13.1	t = 2.27	0.025
Temperature, °C (mean ± SD)	38.2 ± 1.1	38.3 ± 1.0	38.0 ± 1.2	t = 1.34	0.183
Glasgow Coma Scale (median, IQR)	14 (12–15)	15 (13–15)	13 (11–15)	U = 887.5	0.031
qSOFA ≥2, n (%)	62 (62.0)	33 (53.2)	29 (76.3)	χ^2 = 5.29	0.021
SOFA score (mean ± SD)	7.4 ± 3.2	6.5 ± 2.8	8.9 ± 3.2	t = 3.93	<0.001
APACHE II score (mean ± SD)	18.7 ± 6.7	17.1 ± 6.1	21.3 ± 7.0	t = 3.14	0.002
Source of infection, n (%)				χ^2 = 2.86	0.582
Respiratory	34 (34.0)	21 (33.9)	13 (34.2)		
Intra-abdominal	24 (24.0)	14 (22.6)	10 (26.3)		
Urinary tract	21 (21.0)	15 (24.2)	6 (15.8)		
Skin and soft tissue	12 (12.0)	7 (11.3)	5 (13.2)		
Other or undetermined	9 (9.0)	5 (8.1)	4 (10.5)		
Comorbidities, n (%)					
Diabetes mellitus	38 (38.0)	22 (35.5)	16 (42.1)	χ^2 = 0.43	0.511
Hypertension	33 (33.0)	20 (32.3)	13 (34.2)	χ^2 = 0.04	0.842
Chronic kidney disease	14 (14.0)	7 (11.3)	7 (18.4)	χ^2 = 0.98	0.322

Variable	Total (N = 100)	Clearance ≥10% (n = 62)	Clearance <10% (n = 38)	Test statistic	p value
Chronic obstructive pulmonary disease	11 (11.0)	6 (9.7)	5 (13.2)	$\chi^2 = 0.29$	0.588
Malignancy	7 (7.0)	4 (6.5)	3 (7.9)	$\chi^2 = 0.07$	0.786
Positive blood culture, n (%)	41 (41.0)	23 (37.1)	18 (47.4)	$\chi^2 = 1.02$	0.312

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

Table 2. Comparison of lactate parameters and severity indices between survivors and non-survivors (N = 100)

Variable	Survivors (n = 71)	Non-survivors (n = 29)	Test statistic	p value
Age, years (mean ± SD)	52.3 ± 15.1	59.2 ± 16.6	t = 2.03	0.045
Male sex, n (%)	40 (56.3)	18 (62.1)	$\chi^2 = 0.28$	0.594
Mean arterial pressure, mmHg (mean ± SD)	72.4 ± 12.8	64.1 ± 13.6	t = 2.90	0.005
Zero-hour lactate, mmol/L (mean ± SD)	3.78 ± 1.42	4.95 ± 1.98	t = 3.29	0.001
Six-hour lactate, mmol/L (mean ± SD)	2.54 ± 1.28	4.75 ± 2.11	t = 6.44	<0.001
Absolute lactate fall, mmol/L (mean ± SD)	1.24 ± 1.02	0.20 ± 1.31	t = 4.24	<0.001
Six-hour lactate clearance, % (mean ± SD)	32.6 ± 20.9	7.8 ± 24.6	t = 5.10	<0.001
Lactate clearance <10%, n (%)	19 (26.8)	19 (65.5)	$\chi^2 = 13.13$	<0.001
qSOFA ≥2, n (%)	38 (53.5)	24 (82.8)	$\chi^2 = 7.30$	0.007
SOFA score (mean ± SD)	6.4 ± 2.7	9.8 ± 3.1	t = 5.53	<0.001
APACHE II score (mean ± SD)	16.8 ± 5.9	23.4 ± 6.8	t = 4.90	<0.001
Vasopressor requirement, n (%)	27 (38.0)	22 (75.9)	$\chi^2 = 12.03$	0.001

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

Table 3. Primary and secondary outcomes stratified by six-hour lactate clearance (N = 100)

Outcome	Clearance ≥10% (n = 62)	Clearance <10% (n = 38)	Odds ratio (95% CI)	Test statistic	p value
In-hospital mortality, n (%)	10 (16.1)	19 (50.0)	5.20 (2.09–12.95)	$\chi^2 = 13.13$	<0.001
ICU admission, n (%)	26 (41.9)	28 (73.7)	3.88 (1.61–9.32)	$\chi^2 = 9.56$	0.002
Invasive mechanical ventilation, n (%)	18 (29.0)	21 (55.3)	3.02 (1.30–7.03)	$\chi^2 = 6.81$	0.009
Vasopressor support, n (%)	24 (38.7)	25 (65.8)	3.04 (1.31–7.07)	$\chi^2 = 6.91$	0.009
New renal replacement therapy, n (%)	6 (9.7)	9 (23.7)	2.90 (0.94–8.95)	$\chi^2 = 3.67$	0.055
ICU length of stay, days (median, IQR)*	4 (3–6)	6 (4–9)	—	U = 249.5	0.012
Hospital length of stay, days (median, IQR)	8 (6–12)	11 (7–16)	—	U = 862.0	0.018

*CI, confidence interval; ICU, intensive care unit; IQR, interquartile range. *Computed among the 54 patients admitted to intensive care (26 in the adequate clearance group, 28 in the inadequate clearance group).*

Table 4. Receiver operating characteristic analysis for the prediction of in-hospital mortality and ICU admission (N = 100)

Parameter	AUC	95% CI	Optimal cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)	p value
Outcome: in-hospital mortality								
Six-hour lactate clearance	0.784	0.688–0.880	≤10.6%	72.4	76.1	55.3	87.1	<0.001
Six-hour lactate	0.812	0.719–0.905	>2.9 mmol/L	79.3	73.2	54.8	89.7	<0.001
Zero-hour lactate	0.692	0.578–0.806	>4.2 mmol/L	65.5	67.6	45.2	82.8	0.003
SOFA score	0.796	0.702–0.890	>8	75.9	74.6	55.0	88.3	<0.001
APACHE II score	0.771	0.671–0.871	>20	69.0	73.2	51.3	85.2	<0.001
Outcome: ICU admission								
Six-hour lactate clearance	0.701	0.599–0.803	≤14.2%	63.0	71.7	72.3	62.3	0.001
Six-hour lactate	0.724	0.624–0.824	>2.7 mmol/L	66.7	71.7	73.5	64.7	<0.001

AUC, area under the curve; CI, confidence interval; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit. Pairwise DeLong comparisons against six-hour lactate clearance for in-hospital mortality: six-hour lactate p = 0.514; zero-hour lactate p = 0.041; SOFA p = 0.812; APACHE II p = 0.845.

Table 5. Univariate and multivariable logistic regression analysis of predictors of in-hospital mortality (N = 100)

Predictor	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Six-hour lactate clearance <10%	5.20 (2.09–12.95)	<0.001	4.12 (1.49–11.38)	0.006
SOFA score (per 1-point increase)	1.42 (1.21–1.67)	<0.001	1.28 (1.08–1.52)	0.005
Vasopressor requirement	5.14 (1.94–13.62)	0.001	2.94 (1.05–8.23)	0.040
Age ≥60 years	2.51 (1.04–6.06)	0.041	2.06 (0.78–5.44)	0.145
Zero-hour lactate >4 mmol/L	2.63 (1.09–6.35)	0.032	1.87 (0.68–5.14)	0.225
Male sex	1.27 (0.52–3.10)	0.594	Not entered	—
Diabetes mellitus	1.36 (0.57–3.27)	0.492	Not entered	—
Positive blood culture	1.58 (0.66–3.75)	0.302	Not entered	—

OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment. Model summary: overall model $\chi^2 = 34.7$, degrees of freedom 5, $p < 0.001$; Hosmer-Lemeshow $\chi^2 = 6.41$, degrees of freedom 8, $p = 0.602$; Nagelkerke $R^2 = 0.398$; overall classification accuracy 79.0 percent.

Table 6. Distribution of in-hospital mortality and ICU admission across quartiles of six-hour lactate clearance (N = 100)

Quartile of six-hour lactate clearance	Clearance range	n	In-hospital mortality, n (%)	ICU admission, n (%)
Q1 (lowest)	<0.0%	25	13 (52.0)	19 (76.0)
Q2	0.0–19.9%	25	8 (32.0)	15 (60.0)

Quartile of six-hour lactate clearance	Clearance range	n	In-hospital mortality, n (%)	ICU admission, n (%)
Q3	20.0–39.9%	25	5 (20.0)	12 (48.0)
Q4 (highest)	≥40.0%	25	3 (12.0)	8 (32.0)
Total		**100**	**29 (29.0)**	**54 (54.0)**

ICU, intensive care unit. χ^2 for linear trend: in-hospital mortality = 8.35, p = 0.004; ICU admission = 6.47, p = 0.011.