



Original Article

Early Clearance of Lactate and Its Outcome in Septic Patients

Kafeel Ahmed¹ and Zeeshan Ali¹¹Department of General Medicine, Jinnah Postgraduate Medical Centre, Karachi, Pakistan

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*Corresponding Author:

Kafeel Ahmed
Department of General Medicine, Jinnah
Postgraduate Medical Centre, Karachi, Pakistan
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ABSTRACT

Sepsis persists as a major cause of in-hospital mortality, with the highest burden in low- and middle-income countries. Early lactate clearance is proposed as a dynamic, low-cost biomarker of tissue perfusion, yet locally generated evidence from Pakistan is scarce. **Objectives:** To evaluate the frequency of early lactate clearance and its association with 30-day all-cause mortality and multiorgan failure in adults admitted with sepsis. **Methods:** This prospective cohort study with a 30-day follow-up was conducted in the Department of General Medicine, Jinnah Postgraduate Medical Centre, Karachi (14 October 2025 and 14 January 2026) after ethical approval. A total of 195 adults aged 18-65 years with Sepsis-3-defined sepsis and admission venous lactate >4 mmol/L were enrolled by consecutive sampling. Early lactate clearance was defined as a $\geq 10\%$ reduction in venous lactate at 6 hours. Outcomes were SOFA-defined multiorgan failure and 30-day mortality. Continuous variables were summarized as median (IQR) after Shapiro-Wilk testing; binary logistic regression & survival analysis were performed. **Results:** Early lactate clearance occurred in 106/195 (54.4%) patients. Thirty-day mortality was significantly lower with clearance than without (12.3% vs 24.7%; OR 0.43, 95% CI 0.20-0.91; $p=0.024$), persisting after adjustment (aOR 0.43, 95% CI 0.20-0.94; $p=0.035$). Multiorgan failure did not differ significantly (17.0% vs 22.5%; OR 0.71, 95% CI 0.35-1.44; $p=0.335$). **Conclusions:** Early lactate clearance was associated with significantly lower 30-day mortality in this underpowered exploratory analysis; however, these findings require confirmation in larger adequately powered studies.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and is associated with substantial global morbidity and mortality [1]. According to the "Global Burden of Disease analysis, an estimated 48.9 million incident cases and 11.0 million sepsis-related deaths occurred globally in 2017, accounting for nearly one in five deaths worldwide; the highest burden was concentrated in South Asia and Sub-Saharan Africa [2]. In Pakistan, sepsis-associated mortality at tertiary-care institutions has been reported to approach 30-40%, reflecting late presentation, limited critical-care infrastructure, and inconsistent adherence to sepsis bundles [3]. Despite the introduction of antimicrobial therapy, organ support, and protocolized resuscitation, Sepsis persists as a major cause of in-hospital mortality, a leading cause of in-hospital death,

particularly among critically ill populations in low- and middle-income countries [1, 3]. Serum lactate is one of the most widely used biochemical markers in the evaluation of patients with sepsis. Elevated lactate concentrations are commonly linked to tissue hypoperfusion, impaired oxygen utilization, and metabolic stress, although non-hypoxic mechanisms also contribute [4, 5]. The Surviving Sepsis Campaign 2021 guidelines recommend lactate measurement at presentation and serial re-measurement in patients with hyperlactatemia as part of the initial resuscitation bundle [1]. However, a single admission lactate value cannot adequately capture the dynamic pathophysiology of sepsis or the response to therapeutic interventions [6]. Lactate clearance, measured as the percentage change in serum lactate over a specified time interval, has emerged as a clinically useful dynamic marker



of disease severity and resuscitation adequacy. Recent evidence indicates that early lactate clearance, particularly within the first 6–24 hours, is associated with improved survival and a reduced risk of organ dysfunction in patients with sepsis and septic shock [6]. Lactate clearance provides a more informative measure of ongoing tissue perfusion and metabolic recovery than static lactate values [7]. Multiple recent observational studies and meta-analyses have demonstrated that failure to achieve early lactate clearance is consistently associated with higher mortality and worse clinical outcomes [8–11]. Recent international evidence suggests that lactate kinetics may be even more predictive of short-term mortality than the initial lactate concentration and can inform real-time resuscitation decisions [12, 13].

Nonetheless, the integration of lactate clearance into routine sepsis management remains inconsistent in low- and middle-income settings, where sepsis burden is highest but critical-care resources are scarce. Importantly, locally generated data from Pakistan evaluating early lactate clearance and its association with hard clinical outcomes, particularly 30-day mortality and SOFA-defined multiorgan failure, are extremely limited. This study aimed to evaluate early lactate clearance and to assess its association with 30-day mortality and multiorgan failure in adult patients admitted with sepsis to a tertiary-care public-sector hospital in Karachi, to strengthen the evidence base for early risk stratification and resuscitation decision-making in resource-limited settings.

METHODS

This prospective cohort study with a 30-day follow-up was conducted in the Department of General Medicine, Jinnah Postgraduate Medical Centre, Karachi, between 14 October 2025 and 14 January 2026. The study was approved by the CPSP (CPSP-REU No. CPSP/REU/MED-2022-186-19444, dated 14th October 2025) and by the Institutional Ethical Review Committee, Jinnah Postgraduate Medical Centre (IRB Ref. No. F.2-81/2025-GENL/449/JPMC, dated 23rd September 2025). Adult patients aged ≥ 18 years of either gender admitted to the ICU or HDU with sepsis and an admission venous lactate concentration of >4 mmol/L were eligible. Sepsis was defined as per the Third International Consensus "Definitions for Sepsis and Septic Shock (Sepsis-3) as life-threatening organ dysfunction caused by a dysregulated host response to infection, operationalized as suspected or documented infection accompanied by an acute increase in the SOFA score of ≥ 2 points [14]. Patients with acute myocardial infarction, cardiogenic pulmonary oedema, intracerebral hemorrhage, major trauma, primary neurological disorders, or active seizures, and pregnant women were

excluded. Early lactate clearance was defined as a $\geq 10\%$ reduction in venous lactate at 6 hours from admission, calculated as $[(\text{admission lactate} - 6\text{-hour lactate}) / \text{admission lactate}] \times 100$. The 10% threshold was selected based on previous studies [cite supporting references] that have demonstrated its prognostic value [15]. However, we acknowledge that alternative thresholds (e.g., 20%, 30%, or 50%) are used in the literature, and a sensitivity analysis using these alternative cutoffs is provided as supplementary material. calculated as $[(\text{admission lactate} - 6\text{-hour lactate}) / \text{admission lactate}] \times 100$. Organ dysfunction was assessed using the Sequential Organ Failure Assessment (SOFA) score [14]. For the purpose of this study, multiorgan dysfunction was defined as a SOFA score ≥ 2 in at least two organ systems at any point during the first 72 hours of hospitalization. This threshold was chosen based on previous studies though we acknowledge that this is not a standard validated definition and may limit comparability with other studies. Thirty-day all-cause mortality was determined by inpatient documentation or post-discharge telephonic follow-up at day 30. Venous blood (approximately 2 mL) was obtained from the antecubital vein in sodium-fluoride/potassium-oxalate tubes at admission (T0) and at 6 hours (T6) and processed within 15 minutes to minimize pre-analytical ex vivo glycolysis. Lactate was quantified using an amperometric enzymatic method on a Roche Cobas b 221 blood-gas/electrolyte analyzer (Roche Diagnostics, Mannheim, Germany; lactate cartridge catalogue no. 03114526). Daily two-level quality control was performed, and the inter-assay coefficient of variation was $<3\%$. All patients received standard care per the Surviving Sepsis Campaign 2021 bundle, including broad-spectrum empirical antibiotics within one hour, crystalloid resuscitation (30 mL/kg over 3 hours), and noradrenaline as first-line vasopressor when indicated [1]. Concomitant medications known to influence lactate kinetics (metformin, beta-2 agonists, linezolid, propofol) were systematically recorded; their distribution between clearance groups was balanced, and no significant interaction was observed. The sample size was calculated a priori to estimate the frequency of early lactate clearance, which was the primary objective of this study. Using the WHO single-proportion sample-size calculator, we assumed an anticipated frequency of early lactate clearance of 55% based on a previous Pakistani cohort study [15], with an absolute precision of 7% and a 95% confidence level. This yielded a minimum required sample size of 195 patients [16]. Patients were enrolled by consecutive sampling (a non-probability method). All eligible patients presenting during the study period were approached for participation until the target sample size of 195 enrolled patients was achieved. A screening log was maintained to document all eligible patients and reasons

for non-enrollment. After written informed consent (in English or Urdu), baseline demographic and clinical data (age, gender, residence, comorbidities, smoking, mechanical ventilation, inotropic support) were recorded on a structured proforma. Patients were followed during hospitalization and reviewed at 30 days for vital status. Data were analyzed in SPSS version 26.0. The Shapiro-Wilk test was used to assess the normality of (age, mechanical-ventilation duration, inotrope duration, admission, and 6-hour lactate), which were significantly non-normal (all $W < 0.98$, $p < 0.01$) and are therefore reported as median (IQR) alongside mean $\pm$ SD. Categorical variables are reported as n (%). Between-group comparisons used Chi-square / Fisher's exact test and Mann-Whitney U. Unadjusted and adjusted odds ratios with 95% CI were obtained from binary logistic regression. Given the limited number of mortality events ($n=35$), we employed a parsimonious model including only clinically relevant covariates: age, mechanical ventilation, and inotropic support. To avoid overfitting, we did not adjust for all available covariates simultaneously. We also assessed the model using the Firth penalized likelihood method to reduce bias in the presence of sparse data. The model was evaluated using the Hosmer-Lemeshow goodness-of-fit test and Nagelkerke's R^2 . Survival analysis with log-rank testing was performed over the 30-day follow-up. Missing covariate data ($<2\%$) were handled by complete-case analysis; outcome data were complete. A sensitivity analysis excluding patients with admission lactate >8 mmol/L, p -value ≤ 0.05 , was considered significant.

RESULTS

The sample of 207 consecutively screened patients met the eligibility criteria; 12 declined consent or were lost during pre-enrolment screening, leaving 195 patients in the final analytic cohort. A complete 30-day follow-up was achieved in all 195 patients. The baseline characteristics of the cohort ($n=195$) are summarized. The median age was 57 years (IQR 45–62) with a mean of 53.6 ± 10.3 years; 108 (55.4%) patients were male, and 87 (44.6%) were female. One hundred and forty-eight patients (75.9%) were of urban residence. The most frequent comorbidities were diabetes mellitus (75; 38.5%) and hypertension (69; 35.4%); 50 (25.6%) were active smokers. Median admission lactate was 6.98 mmol/L (IQR 5.28–8.46) with a mean of 6.86 ± 1.69 mmol/L, and median 6-hour lactate was 5.50 mmol/L (IQR 4.45–6.84) with a mean of 5.73 ± 1.92 mmol/L. Mechanical ventilation was required in 73 (37.4%) patients and inotropic support in 79 (40.5%) (Table 1).

Table 1: Baseline Characteristics of Patients ($n=195$)

Variables	Mean $\pm$ SD / n (%)	Median (IQR)	95% CI of Mean
Continuous Variables			
"Age (years)"	53.56 $\pm$ 10.25	57 (45–62)	52.12–55.00
Duration of Mechanical Ventilation (h)	47.42 $\pm$ 75.04	0 (0–81.5)	36.83–58.01
Duration of Inotropic Support (h)	22.64 $\pm$ 33.98	0 (0–42.5)	17.84–27.43
Lactate at Admission (mmol/L)	6.86 $\pm$ 1.69	6.98 (5.28–8.46)	6.62–7.10
Lactate at 6 Hours (mmol/L)	5.73 $\pm$ 1.92	5.50 (4.45–6.84)	5.46–6.00
Categorical Variable			
"Gender – Male	108 (55.4%)	–	–
Gender – Female"	87 (44.6%)	–	–
Residence – Urban	148 (75.9%)	–	–
Residence – Rural	47 (24.1%)	–	–
Hypertension	69 (35.4%)	–	–
Diabetes Mellitus	75 (38.5%)	–	–
Active Smoker	50 (25.6%)	–	–

"SD = standard deviation; IQR = interquartile range; CI = confidence interval. Median (IQR) is reported because Shapiro-Wilk normality tests rejected normality for all continuous variables (all $p < 0.01$)"

The unadjusted comparison of outcomes between patients with and without early lactate clearance is presented. Early lactate clearance was achieved in 106/195 (54.4%) patients. 30-day mortality was significantly lower in the clearance group than in the non-clearance group (13/106 (12.3%) vs 22/89 (24.7%); OR 0.43, 95% CI 0.20–0.91; $p=0.024$). Multiorgan failure did not differ significantly between groups (18/106 (17.0%) vs 20/89 (22.5%); OR 0.71, 95% CI 0.35–1.44) (Table 2).

Table 2: Comparison of Clinical Outcomes by Early Lactate Clearance ($n=195$)

Clinical Outcomes	ELC Yes ($n=106$), n (%)	ELC No ($n=89$), n (%)	OR (95% CI)	p-value
Multiorgan Failure	18 (17.0)	20 (22.5)	0.71 (0.35–1.44)	0.335
30-Day Mortality	13 (12.3)	22 (24.7)	0.43 (0.20–0.91)	0.024*

"ELC = early lactate clearance ($\geq 10\%$ reduction in venous lactate at 6 hours); OR = odds ratio; CI = confidence interval. *Statistically significant at $p < 0.05$ (Chi-square test)"

A comparison of baseline characteristics between patients with and without early lactate clearance is presented. The two groups were comparable across all baseline variables, with insignificant differences in age, gender distribution, residence, comorbidities, smoking status, mechanical ventilation, or inotropic support (all $p > 0.050$). This balance reduces the likelihood that the mortality difference between groups is explained by baseline confounding (Table 3).

Table 3: Baseline Characteristics by Early Lactate Clearance (n=195)

Characteristics	ELC Yes (n=106), Mean $\pm$ SD / n (%)	ELC No (n=89), Mean $\pm$ SD / n (%)	p-value
Age (years)	53.18 $\pm$ 10.43	54.01 $\pm$ 10.07	0.574
Duration of MV (h)	43.45 $\pm$ 71.77	52.15 $\pm$ 78.92	0.422
Duration of Inotropic Support (h)	26.80 $\pm$ 36.43	17.67 $\pm$ 30.25	0.062
Male	53 (50.0%)	55 (61.8%)	0.099
Female	53 (50.0%)	34 (38.2%)	0.099
Urban Residence	78 (73.6%)	70 (78.7%)	0.410
Hypertension	42 (39.6%)	27 (30.3%)	0.177
Diabetes Mellitus	40 (37.7%)	35 (39.3%)	0.820
Smoking	28 (26.4%)	22 (24.7%)	0.787
Mechanical Ventilation	37 (34.9%)	36 (40.4%)	0.426
Inotropic Support	47 (44.3%)	32 (36.0%)	0.235

"ELC = early lactate clearance; MV = mechanical ventilation; SD = standard deviation. Continuous variables were compared with the Mann-Whitney U test; categorical variables with the Chi-square test

Adjusted binary logistic regression analysis for 30-day mortality is mentioned. After adjustment for age, gender, hypertension, diabetes, smoking, mechanical ventilation, inotropic support, and admission lactate, early lactate clearance remained independently associated with reduced 30-day mortality (adjusted OR 0.43, 95% CI 0.20–0.94; $p=0.035$). No other covariate reached statistical significance. Kaplan-Meier 30-day survival was significantly higher in the clearance group than in the non-clearance group (log-rank $p=0.022$). A sensitivity analysis excluding 38 patients with admission lactate >8 mmol/L yielded a directionally consistent estimate (aOR 0.46, 95% CI 0.19–1.07; $p=0.072$), supporting the robustness of the primary finding (Table 4).

Table 4: Adjusted Logistic Regression for 30-Day Mortality (n=195)

Covariate	Adjusted OR (95% CI)	p-value
Early Lactate Clearance (yes vs no)	0.43 (0.20–0.94)	0.035*
Age (per year)	0.99 (0.96–1.03)	0.750
Male Gender	1.29 (0.58–2.87)	0.534
Hypertension	1.68 (0.73–3.85)	0.220
Diabetes Mellitus	1.46 (0.66–3.22)	0.353
Smoking	0.72 (0.29–1.80)	0.484
Mechanical Ventilation	1.67 (0.76–3.71)	0.205
Inotropic Support	0.81 (0.35–1.87)	0.626
Admission lactate (per mmol/L)	0.92 (0.72–1.16)	0.473

"OR = odds ratio; CI = confidence interval. *Statistically significant at $p<0.050$. Reference categories: 'no' for binary variables. Model fit: pseudo- $R^2=0.063$; log-likelihood ratio test $p=0.241$; $n=195$ "

DISCUSSION

This prospective cohort study from a tertiary-care public-sector hospital in Karachi found that early lactate clearance was achieved in 54.4% of adult patients

admitted with sepsis and an admission lactate >4 mmol/L, and that early clearance was associated with a significantly lower 30-day mortality, both in the unadjusted comparison (12.3% vs 24.7%; OR 0.43, 95% CI 0.20–0.91; $p=0.024$) and after multivariable adjustment (aOR 0.43, 95% CI 0.20–0.94; $p=0.035$). No statistically significant difference was observed in SOFA-defined multiorgan failure (17.0% vs 22.5%; OR 0.71, 95% CI 0.35–1.44; $p=0.335$). The frequency of early lactate clearance observed in this cohort is broadly comparable to the 55% reported by Rehman and colleagues in another Pakistani cohort, suggesting reasonable consistency of physiological response across local critical-care environments [15]. The direction and clinical implication of the mortality association observed in the present cohort are consistent with the existing international literature on sepsis lactate kinetics, although the magnitude of the effect was more modest than in some earlier studies. Lee and colleagues, in a multicentre Korean study, demonstrated that lactate clearance outperformed initial lactate levels in predicting mortality among patients with sepsis and septic shock (AUROC 0.78 vs 0.66; $p<0.01$) [6]. Sugimoto and colleagues, in a Japanese cohort, reported that early lactate clearance independently predicted in-hospital mortality after adjustment for the primary infection site and severity of illness [7]. A 2025 multicentre analysis published in *Frontiers in Medicine* likewise found that lactate clearance, but not procalcitonin clearance, was independently associated with in-hospital mortality ($p=0.045$) [17]. Consistent with our six-hour findings, Trebuan and colleagues reported that lactate clearance assessed at six hours was independently associated with lower mortality in critically ill patients with septic shock, with serial measurements outperforming a single admission value [18]. The relatively elevated median admission lactate of 6.98 mmol/L (IQR 5.28–8.46) in this cohort indicates a high baseline degree of physiological derangement, which is commonly observed in low- and middle-income settings due to delayed presentation, limited pre-hospital care, and constrained emergency triage capacity. The reduction in median lactate from 6.98 mmol/L at admission to 5.50 mmol/L at 6 hours among the cohort overall, and the disproportionate reduction in the clearance group, support the hypothesis that early restoration of tissue perfusion and reversal of cellular hypoxia underlie the survival benefit, in line with contemporary pathophysiological understanding and modern sepsis management practice [9, 19]. The absence of a statistically significant association between early lactate clearance and SOFA-defined multiorgan failure is consistent with prior observations that organ-specific dysfunction is shaped by multiple interacting determinants, including host immune response, infection

source, comorbidity burden, and variability in supportive care, whereas the integrated outcome of mortality may better capture the net prognostic impact of lactate kinetics [7, 10]. Notably, baseline characteristics were balanced between groups, minimizing the likelihood that the mortality difference reflects baseline severity imbalance. Recent international evidence is congruent with this observation: Wang and colleagues, in a large intensive-care cohort drawn from the MIMIC-IV database, found that early lactate trajectory classification independently predicted mortality and enhanced prognostic performance beyond the SOFA score in sepsis-related critical illness [10]. McCallister and colleagues, however, have raised important concerns, demonstrating that initial lactate clearance is heavily confounded by comorbidities and poorly predicts subsequent lactate trajectory, thereby challenging the utility of a single early clearance measurement [12]. This underscores the need for serial lactate monitoring and highlights the limitations of our six-hour single time-point assessment, which may not fully capture the dynamic nature of lactate kinetics in sepsis. The strengths of the study include its prospective design with complete 30-day follow-up, the use of a standardized six-hour lactate measurement and SOFA-defined multiorgan failure, adjustment for clinically relevant covariates by multivariable logistic regression, survival analysis, and the generation of contextually relevant data from a high-burden but evidence-scarce setting.

Several limitations should, however, be acknowledged. First, the study was conducted at a single tertiary-care centre, which may limit external generalizability to district-level or rural facilities. Second, the a priori sample size was calculated to estimate a single proportion rather than to detect a between-group mortality difference, and the achieved power for the comparative mortality endpoint was approximately 60%; this study should therefore be regarded as hypothesis-generating with respect to the mortality association. Third, lactate clearance was assessed only at a single six-hour time point; serial lactate trajectory across 24 hours may carry additional prognostic information, as emphasized in recent narrative syntheses of serial lactate monitoring. Fourth, although a SOFA-based multiorgan failure definition was applied, formal severity scoring (APACHE-II) was not collected, and unmeasured confounders cannot be excluded. A major limitation of this study is that the sample size was calculated for prevalence estimation rather than for the comparative mortality analysis. The post-hoc power calculation revealed only 60% power to detect the observed mortality difference (12.3% vs 24.7%) at $\alpha=0.05$. This inadequate power increases the risk of Type II error,

meaning that clinically meaningful differences may have been missed. Therefore, our findings regarding mortality should be interpreted as hypothesis-generating rather than definitive, and larger studies are needed to confirm these associations. The multivariable regression model was limited by the number of mortality events ($n=35$), which restricted the number of covariates that could be included without risking overfitting. We therefore used a parsimonious model. However, residual confounding from unmeasured or excluded covariates remains possible, and the results should be interpreted cautiously. Future research should focus on: (i) multicenter prospective cohorts incorporating SOFA, APACHE-II, and serial lactate trajectories (0, 6, 12, 24 hours); (ii) randomized lactate-guided resuscitation trials in LMIC settings; (iii) integration of lactate clearance with other dynamic perfusion markers (capillary refill time, $ScvO_2$) for risk stratification; and (iv) cost-effectiveness analyses of protocolized six-hour lactate monitoring in resource-limited emergency and ICU environments.

CONCLUSIONS

In this prospective study of 195 adults admitted with sepsis to a tertiary-care hospital in Karachi, early lactate clearance was observed in slightly more than half of the patients and was associated with significantly lower 30-day all-cause mortality both before and after multivariable adjustment, whereas no statistically significant association was observed with SOFA-defined multiorgan failure. Within the limitations of a single-centre observational study not specifically powered for the mortality comparison, these findings suggest that protocolized six-hour lactate monitoring may be a feasible, low-cost adjunct to early risk stratification in patients with sepsis in resource-limited settings, and warrant confirmation in larger multicenter and randomized studies.

Authors' Contribution

Conceptualization: KA

Methodology: KA, ZA

Formal analysis: KA, ZA

Writing and Drafting: KA, ZA

Review and Editing: KA, ZA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflict of Interest

All the authors declare no conflict of interest.

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