RESEARCH ARTICLE

Int J Life Sci Pharma Res., Vol: 16, Issue: 3, 2026; 46-51

International Journal of Life science and Pharma Research

Content Available at www.ijlpr.com ISSN: 2250-0480

PREDICTION OF OUTCOME BY MEASURING SERUM LACTATE CONCENTRATION-TIME DATA IN PATIENT WITH ACUTE PARAQUAT POISONING

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DOI: https://doi.org/10.22376/ijlpr.v16i3.2055

ARTICLE HISTORY: Received: 19.07.2026 Revised: 26.09.2026 Accepted: 11.10.2026

Abstract

The standard prognostic assay for acute paraquat poisoning—plasma paraquat concentration-is frequently unavailable in resource-limited settings. Although serum lactate and time-lagged composite models have been proposed as accessible alternatives, they lack robust external validation. This study aimed to externally validate an established arterial lactate-time prognostic model using venous serum lactate and evaluate its utility for predicting in-hospital mortality.

Methods: We conducted a hospital-based observational study involving 46 adults presenting with acute paraquat poisoning at a single center in Central India. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC), with bootstrap-derived 95% confidence intervals (CIs).

The cohort experienced an in-hospital mortality rate of 78.26%. Admission serum lactate alone demonstrated excellent discrimination (AUC = 0.963; 95% CI: 0.896–1.000). The externally validated lactate–time model yielded a lower point estimate (AUC = 0.861; 95% CI: 0.718–0.966). An optimal serum lactate cutoff of 3.0 mmol/L, derived from the study cohort, predicted mortality with a sensitivity of 0.944. Time lag was not independently associated with mortality in an exploratory multivariable model (p = 0.153). In this setting, the complex composite model did not demonstrate a statistically significant discriminative advantage over serum lactate alone. Although a serum lactate threshold of 3.0 mmol/L shows promise for triage, its derivation from the study cohort necessitates further validation in larger, multicenter studies.

Keywords: *Clinicaltoxicology, lactate, paraquat, prognosis, risk stratification.*

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INTRODUCTION

Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) is a widely used contact herbicide that carries a severe mortality rate following intentional self-poisoning. Currently, no specific antidote exists. The established gold standard for prognosticating patient outcomes relies on plasma paraquat concentrations, traditionally assessed via Proudfoot's or Jones' nomograms [1], [2]. However, the specific assays required for these measurements are rarely available in resource-limited or rural hospital settings where agricultural poisonings are most prevalent.

Consequently, clinicians have sought accessible prognostic alternatives. Serum lactate is a ubiquitous marker; in paraquat toxicity, its elevation is driven by redox cycling and reactive oxygen species generation [3] in addition to systemic hypop-erfusion. Sun *et al.* [4] proposed a multivariable prognostic model that combines arterial lactate with the time lag from ingestion to hospital presentation. While theoretically compelling, this composite lactate-time algorithm has seen limited external validation.

This study aims to externally validate the Sun *et al.* lactate-time prognostic model using admission venous serum lactate in a real-world, resource-limited setting. The primary contributions of this paper are:

- Providing an external validation of the Sun *et al.* model in a Central Indian cohort.
- Demonstrating that deploying complex composite scoring algorithms may not yield a discriminative advantage over raw biomarker analysis in this population.

- Evaluating a venous serum lactate cut-off for immediate bedside triage and comparing it to previously proposed arterial thresholds in the literature.

Related Work

A. Plasma Paraquat Prognostics

Early efforts in risk stratification focused heavily on measuring plasma concentrations. Proudfoot *et al.* [1] and later Jones *et al.* [2] developed widely cited nomograms. While robust, their clinical utility is severely limited by the requirement for specialized testing, creating a persistent informatics gap in triage capabilities for low-resource settings.

B. Lactate

Elevated blood lactate is a well-established predictor of mortality in critical illness [5]. In paraquat poisoning, multiple cohorts have identified initial lactate as a strong independent prognostic factor [6], [7]. However, these studies rely primarily on arterial samples. Previous studies have proposed arterial lactate cut-offs ranging from 2.5 mmol/L [6] to 4.4 mmol/L [7]. Our study evaluates venous serum lactate, offering a potentially more accessible threshold for standardized triage.

C. Composite and Severity Scores

To improve upon single-biomarker approaches, researchers have evaluated complex severity scores, such as the Sequential Organ Failure Assessment (SOFA) score [8]. Sun *et al.* [4] developed a specific logistic regression model incorporating both lactate and presentation time lag. The significant gap in this literature is the lack of rigorous external validation. Prediction models frequently suffer from optimism bias when evaluated on their derivation cohorts [9], [10], necessitating independent validation to confirm their generalizability.

METHODS

A. Study Design and Setting

We conducted a hospital-based observational study at a single center, the Department of Medicine at Pt. J.N.M. Medical College and Dr. B.R. Ambedkar Memorial Hospital in Raipur, India. Patient enrolment occurred between March 2024 and February 2026. This study adhered to the TRIPOD (prediction-model validation) [9] and STROBE [11] guidelines.

B. Participants

Participants were recruited using universal sampling. Eligibility required patients to be adults (≥ 18 years of age) presenting to the hospital within three days of acute oral paraquat ingestion. We excluded patients with non-oral paraquat exposure, chronic kidney disease, chronic liver disease, malignancy, HIV infection, or chronic pancreatitis. Patients receiving concurrent medications known to substantially alter lactate metabolism—specifically metformin (> 2 g/day), valproic acid, amiodarone, or tetracycline-were excluded. There was no missing data for the primary variables in the final cohort. Notably, while the Sun *et al.* [4] model was originally derived for patients presenting within 19 hours of ingestion, our inclusion criteria permitted presentations up to 72 hours. Eight patients (17.4%) in our cohort presented beyond the 19-hour window, providing an opportunity to assess model robustness in delayed presentations common to our setting.

C. Ethics and Consent

The study protocol received approval from the Institutional Ethics Committee. Written informed consent was obtained from all patients or their legally authorized representatives prior to enrolment. All patient data were anonymized for analysis.

D. Predictor Variables and External Model

The primary predictor was initial venous serum lactate (L), measured immediately upon hospital admission using a Roche cobas c311 analyzer. The time lag (t) was defined as the elapsed time in hours from paraquat ingestion to hospital presentation. The composite lactate-time product (LT) was calculated as:

$$LT = L \times t \quad (1)$$

In addition to the primary predictors, we recorded baseline clinical and laboratory parameters, including oxygen saturation (SpO2), respiratory rate, and markers of hepatic (AST, ALT, bilirubin) and renal (creatinine, urea) function. These were measured at admission using standard automated hospital assays. The estimated ingested amount of paraquat was determined via detailed history taking from the patient, relatives, or referring primary care records. We evaluated the external prognostic model developed by Sun *et al.* [4], which outputs the predicted probability of survival (p) via the logistic equation:

$$Logit(p) = 3.066 - 0.139 \times t - 0.177 \times L \quad (2)$$

The predicted probability of mortality was defined as $1 - p$.

E. Outcome Definition

The primary outcome was defined as in-hospital mortality. Patients who survived to hospital discharge were classified as the discharged group.

F. Statistical Analysis

Normally distributed data were expressed as mean ± standard deviation (SD), while skewed continuous variables were expressed as median and interquartile range (IQR). Group comparisons utilized the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Exact p-values were reported, with $p < 0.001$ utilized as a floor. Discrimination was assessed by plotting Receiver Operating Characteristic (ROC) curves and calculating the Area Under the Curve (AUC). We computed 95% confidence intervals (CIs) for all AUC values utilizing a 10,000-iteration bootstrap method with a fixed seed to account for small sample variance. A paired bootstrap comparison was utilized to formally extract exact p-values and AUC differences between models. Sensitivity, specificity, and corresponding Wilson 95% CIs were calculated. The optimal cut-off for serum lactate was derived using the maximal Youden index within the sample. Calibration was assessed using a calibration plot (Fig. 5). Formal statistical calibration testing (e.g., Hosmer-Lemeshow) was omitted, as the extremely

limited sample size of survivors precludes reliable assessment. Given the constrained events per variable, multivariable logistic regression with Odds Ratios (OR) and 95% CIs to assess the independent contribution of time lag was strictly exploratory. Statistical significance was defined as a two-tailed $p < 0.05$.

RESULTS

A. Cohort Characteristics

The cohort consisted of 46 patients, of whom 10 (21.74%) were discharged and 36 (78.26%) experienced in-hospital mortality (see Figure 01).

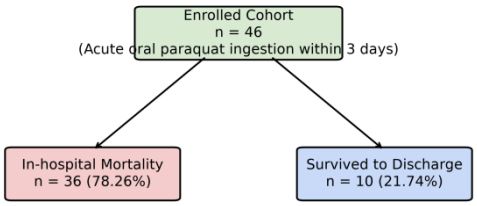


Figure 01: Study Flow Diagram depicting patient outcomes.

The mean age was 33.28 ± 9.51 years, with 29 males and 17 females. Age and sex were not significantly associated with outcome (p = 0.305 and p = 1.000, respectively). Intentional self-poisoning was the dominant mode of exposure, accounting for 41 cases, while 5 cases were accidental. Mode of poisoning was significantly associated with mortality (p = 0.006). During the hospital stay, ICU admission was most common among those who died (29 of 36) but rare among survivors (1 of 10). Baseline demographics are detailed in Table 0I.

Table 0I: Baseline Characteristics by Outcome

Characteristic	Discharged (n=10)	Mortality (n=36)	p-value
Age (years)	35.0 (30.5–40.2)	31.0 (24.0–41.2)	0.305
Sex (Male/Female)	6 / 4	23 / 13	1.000
Mode (Intentional/Accidental)	6 / 4	35 / 1	0.006

B. Distribution of Predictors and Clinical Markers

The median time lag from ingestion to presentation did not differ significantly between groups (9.00 hours vs 10.00 hours; p = 0.245). However, admission serum lactate was substantially higher in the mortality group (6.80 mmol/L vs 2.00 mmol/L; $p < 0.001$). Figure 02 demonstrates the significant elevation and wider variance of lactate in non-survivors (box whiskers extend to standard 1.5×IQR limits). Figure 02 illustrates that severe hyperlactatemia was concentrated entirely within the mortality cohort regardless of time lag. Core predictor distributions are summarized in Table II.

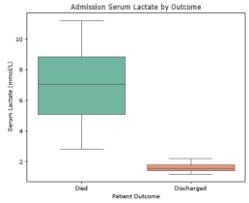


Figure 02: Distribution of admission serum lactate across outcome groups.

Table 02: Predictor Variables By Outcome

Predictor	Discharged (n=10)	Mortality (n=36)	p-value
Time lag (hours)	9.0 (6.5–10.7)	10.0 (6.0–17.2)	0.245
Serum lactate (mmol/L)	2.00 (1.52–2.00)	6.80 (5.00–9.77)	< 0.001
Lactate-time (mmol/L·h)	15.5 (12.3–19.8)	60.0 (33.6–134.3)	< 0.001
Sun model prob. death	0.19 (0.14–0.23)	0.38 (0.25–0.71)	0.001

Note: Continuous data presented as median (IQR).

Beyond the core prognostic model variables, mortality was associated with deranged laboratory values at admission. The median estimated ingested amount was significantly higher in non-survivors (30.0 mL vs 10.0 mL, p = 0.007). Furthermore, non-survivors had significantly elevated markers of acute kidney injury (creatinine and urea) and hepatic injury (total bilirubin) compared to survivors (all $p \leq 0.003$). These parameters are detailed comprehensively in Table III.

Table 03: Additional Clinical and Laboratory Parameters

Parameter	Discharged (n=10)	Mortality (n=36)	p-value
Amount Ingested (mL)	10.0 (10.0–22.5)	30.0 (18.8–41.2)	0.007
Creatinine (mg/dL)	1.25 (1.04–1.94)	3.54 (2.87–4.67)	0.003
Urea (mg/dL)	50.5 (35.8–93.8)	155.0 (85.2–182.2)	< 0.001
Total Bilirubin (mg/dL)	1.22 (1.11–1.47)	4.29 (3.43–5.13)	< 0.001
Note: Continuous data presented as median (IQR).			

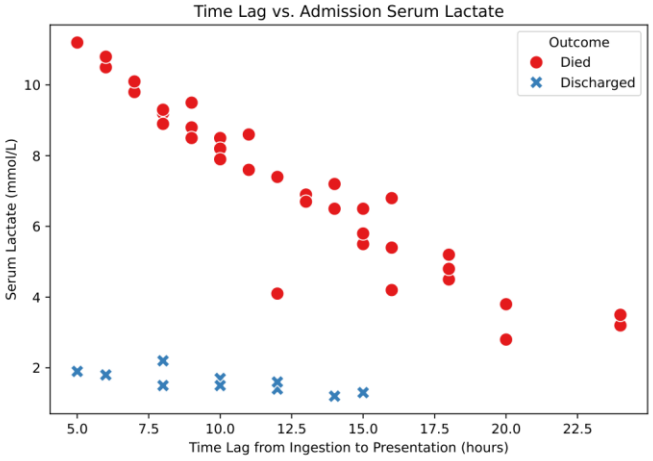


Figure 03: Scatter plot of time lag from ingestion vs. admission serum lactate, categorized by outcome.

C. *Model Validation and ROC Analysis*

Admission serum lactate demonstrated outstanding discrimination for in-hospital mortality, yielding an AUC of 0.963 (95% CI: 0.896–1.000). The composite lactate-time product yielded an AUC of 0.942 (95% CI: 0.829–1.000). The externally validated Sun *et al.* model produced an AUC of 0.861 (95% CI: 0.718–0.966) (see Figure 04).

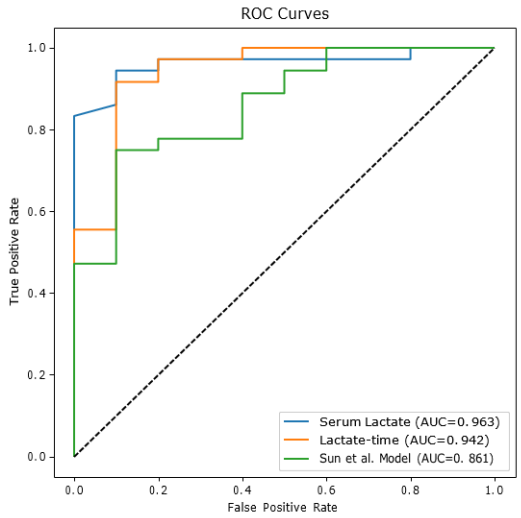


Figure 04: Receiver Operating Characteristic (ROC) curves for serum lactate, lactate-time product, and the Sun *et al.* model in predicting in-hospital mortality.

A paired bootstrap comparison (10,000 iterations) testing the discriminative difference between raw serum lactate and the Sun *et al.* model yielded an AUC difference of 0.101 (95% CI: −0.009 to 0.233), indicating no statistically significant advantage (p = 0.075). Calibration assessment (Fig. 5) revealed that the Sun *et al.* model underestimated mortality risk in our cohort; the overall mean predicted probability of mortality was 42.0%, whereas the observed mortality was 78.3%.

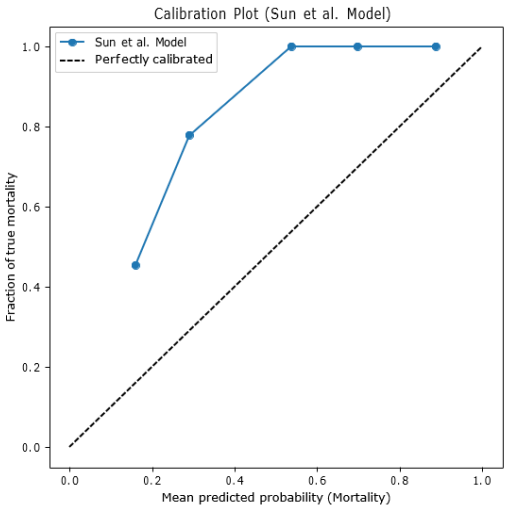


Figure 05: Calibration Plot for the Sun *et al.* model predicting mortality.

Predicted probabilities were notably lower across all quintiles. Using the Youden index, the optimal cut-off for serum lactate in this cohort was 3.0 mmol/L. Diagnostic performance metrics for this threshold are shown in Table IV.

TABLE 04: Diagnostic Performance For Mortality

Predictor	Cut-off	Sens (95% CI)	Spec (95% CI)
Serum Lactate	≥ 3.0 mmol/L	0.944 (0.819–0.985)	0.900 (0.596–0.982)
Sun *et al.* *LT* Model [4]	≥ 11.95 mmol/L·h	1.000 (0.904–1.000)	0.200 (0.057–0.510)

Because this cut-off was derived and evaluated within the same 46 patients, performance metrics inherently incorporate optimism bias. At the original 11.95 mmol/L·h cut-off proposed by Sun et al. [4], the lactate-time product correctly identified all non-survivors (sensitivity 1.000) but had poor specificity in our cohort (0.200), falsely classifying 8 of the 10 survivors.

D. Multivariable Analysis

In an exploratory multivariable logistic regression model evaluating both admission serum lactate and time lag, only serum lactate retained a statistically significant independent association with mortality (p = 0.007, OR 5.13 per 1 mmol/L increase; 95% CI 1.56–16.81). The independent contribution of time lag was not statistically significant (p = 0.153).

DISCUSSION

The principal finding of this external validation study is that admission serum lactate is a highly accurate predictor of in-hospital mortality in acute paraquat poisoning. Initial serum lactate alone demonstrated a point estimate for discrimination (AUC 0.963) that exceeded both the composite lactate-time product (AUC 0.942) and the external Sun *et al.* multivariable model (AUC 0.861). Our results suggest that the complexity of incorporating time lag into a regression equation may not yield superior prognostic accuracy in external populations. Furthermore, higher time lags were associated with lower lactate levels among non-survivors (Fig. 3); this collinearity is a plausible reason adding time lag did not independently improve prediction. Prediction models are also acutely sensitive to the baseline characteristics of their derivation cohorts. The Sun *et al.* model was originally derived using arterial lactate measurements [4]. The inherent physiological differences between arterial and venous sampling, combined with cohort-specific variations in transport times to the hospital, may explain the model's calibration drift in our population.

From a clinical informatics perspective, this finding underscores the risk of deploying complex algorithms in resource-limited settings without prior external validation. A single, unadjusted venous serum lactate threshold (3.0 mmol/L) by-

passes the need for mathematical composite score calculations, allowing for immediate, low-barrier triage. This 3.0 mmol/L cut-off aligns reasonably with previously reported arterial thresholds of 2.5 mmol/L [6], 4.2 mmol/L [4], and 4.4 mmol/L [7], though physiological differences between venous and arterial blood prevent direct equivalence. However, the unusually high AUC (0.963) observed in our cohort warrants strict caution. Because the 3.0 mmol/L cut-off was derived and evaluated within the same sample to maximize the Youden index, the reported sensitivity inherently suffers from optimism bias [10].

Limitations

This study has several critical limitations. First, it is a single-center study with a highly constrained sample size (n = 46), including only 10 survivors. This severely limits statistical power; for example, the paired bootstrap testing for AUC superiority was underpowered to detect equivalence, and formal calibration assessment beyond plotting was not feasible. Second, the diagnostic cut-offs were derived in-sample, requiring future validation on an unseen dataset to confirm their true out-of-sample performance. Third, the unavailability of plasma paraquat assays precluded a direct comparison with the clinical gold standard. Fourth, variations in hospital treatment protocols and a lack of post-discharge follow-up for survivors represent unmeasured confounders. Fifth, the estimated ingested amount is a major known confounder in paraquat toxicity. Due to the small sample size, we were unable to formally adjust for the ingested amount alongside serum lactate in a multivariable model. Finally, the external validation represents a partial extrapolation for the 17.4% of patients presenting beyond the original model's 19-hour derivation limit.

Conclusion

Admission serum lactate is a highly accessible prognostic biomarker for in-hospital mortality following acute paraquat poisoning. In this Central Indian cohort, the implementation of an external lactate-time multivariable model did not demonstrate a statistically significant discriminative advantage over raw serum lactate measurements. A preliminary serum lactate cut-off of 3.0 mmol/L yielded excellent sensitivity for triage. Future work must prioritize multicenter external validation of this threshold in larger cohorts and explore serial lactate trajectories.

Acknowledgment

We thank the faculty and staff of the Department of Medicine at Pt. J.N.M. Medical College and Dr. B.R. Ambedkar Memorial Hospital for their clinical support.

Author Contributions

Conceptualization, R.K.P. and R.L.K.; Methodology, R.K.P.; Formal Analysis, R.K.P.; Investigation, R.K.P. and P.D.; Writing - Original Draft, R.K.P.; Writing - Review & Editing, R.L.K. and P.D.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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