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Longitudinal Changes in Cerebrospinal Fluid Lactate Predict Clinical Outcomes in Critically Ill Adults with Bacterial Meningitis: A Prospective Cohort Study

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Abstract

Aim: Despite advances in intensive care, bacterial meningitis remains associated with high mortality among critically ill adults. Although cerebrospinal fluid (CSF) lactate is well established as a diagnostic biomarker, its longitudinal prognostic value remains uncertain.

Study Design: This prospective, single-center cohort study enrolled 45 adults with confirmed bacterial meningitis admitted to a tertiary ICU between June and December 2024. CSF lactate was measured at admission and again on day 14. The primary outcome was in-hospital mortality. Prognostic performance was evaluated using receiver operating characteristic (ROC) analysis with bootstrap-derived 95% confidence intervals (Cis) and Kaplan–Meier survival analysis.

Results: Ten patients (22.2%) died during hospitalization. Compared with survivors, non-survivors were older and had lower Glasgow Coma Scale (GCS) scores and higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Among survivors, CSF lactate declined significantly from admission to day 14 (median Δ, –1.4 mmol/L, $p<0.001$), whereas non-survivors demonstrated a significant increase (median Δ, +1.3 mmol/L, $p<0.001$). Day-14 CSF lactate strongly predicted mortality (optimism-adjusted area under the curve=0.93, 95% CI: 0.84–0.99; $p<0.001$). Patients with a CSF lactate >4.3 mmol/L had significantly lower survival than those with lower levels (log-rank $p<0.001$).

Conclusions: Persistent elevation of CSF lactate after two weeks of treatment identifies critically ill adults with bacterial meningitis who are at high risk of death, likely reflecting ongoing cerebral metabolic dysfunction. Serial CSF lactate monitoring may serve as a simple, inexpensive adjunct for prognostic assessment in ICU patients.

Keywords: Bacterial meningitis, cerebrospinal fluid, critically ill adults, lactate, prognosis.

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Introduction

Acute bacterial meningitis remains a devastating disease associated with substantial mortality and long-term neurological sequelae despite advances in antimicrobial therapy and critical care [1]. Mortality among adults admitted to intensive care units (ICUs) may reach 20%–30%, and many survivors experience persistent cognitive impairment or neurological deficits [2]. Early identification of patients at greatest risk of poor outcomes is therefore essential, as it may guide the intensity of therapeutic interventions, monitoring strategies, and prognostic counseling for patients and their families.

Traditional prognostic assessment relies primarily on neurological status at presentation, particularly the Glasgow Coma Scale (GCS), and systemic severity scores such as the Acute Physiology and Chronic Health Evaluation II (APACHE II). Although these tools are clinically useful, they are nonspecific and may be influenced by sedation, systemic illness, or underlying comorbidities [3,4]. Conventional cerebrospinal fluid (CSF) parameters, including pleocytosis, protein concentration, and glucose level, remain the cornerstone of diagnosis, however, their ability to predict clinical outcomes is inconsistent [5]. Consequently, there remains a need for objective, reliable, and readily available biomarkers that complement clinical assessment in patients with bacterial meningitis.

Cerebrospinal fluid lactate, a byproduct of anaerobic glycolysis, increases in response to cerebral hypoxia, inflammation, and impaired oxidative metabolism [6]. Its diagnostic utility in differentiating bacterial from viral meningitis is well established, and it is widely used as a rapid, inexpensive biomarker, particularly in resource-limited settings [7]. However, its prognostic value remains uncertain. Most available evidence originates from neurosurgical or post-traumatic populations [8,9], while studies in bacterial meningitis have generally evaluated only admission lactate concentrations and have reported conflicting findings [10].

We hypothesized that serial measurement of CSF lactate, rather than a single admission value, would provide more robust prognostic information independent of initial disease severity in critically ill adults with bacterial meningitis. Persistent elevation of CSF lactate may reflect ongoing cerebral metabolic dysfunction despite appropriate treatment, whereas declining concentrations may indicate recovery. To our knowledge, few prospective studies have evaluated the prognostic significance of serial CSF lactate measurements in ICU patients with bacterial meningitis, particularly in low- and middle-income countries where diagnostic resources are limited.

Accordingly, this prospective cohort study was designed to evaluate the temporal kinetics of CSF lactate as a prognostic marker in adult ICU patients with bacterial meningitis and to compare its predictive performance with that of conventional CSF indices, systemic inflammatory biomarkers, and established clinical severity scores. By emphasizing serial rather than single admission measurements, this study addresses an important gap in the literature and represents one of the first prospective evaluations of serial CSF lactate kinetics in adults with bacterial meningitis admitted to a medical ICU. Furthermore, because serial CSF lactate measurement is simple, inexpensive, and widely available, it may represent a practical prognostic tool in resource-limited ICUs where advanced neuroimaging and specialized biomarker assays are not routinely accessible.

Materials and Methods

Study Design and Setting

This prospective, observational cohort study was conducted in the ICU of a tertiary referral fever hospital in Egypt between June and December 2024. The study protocol was approved by the institutional Research Ethics Committee (Approval No. 10/2024ANET39). Written informed consent was obtained from all participants or their legally authorized representatives before enrollment. The study was conducted in accordance with the Declaration of Helsinki and is reported in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies.

Participants

Eligible participants were adults aged ≥18 years with a confirmed diagnosis of bacterial meningitis. Diagnosis required a compatible clinical presentation (including fever, headache, neck stiffness, or altered mental status) together with CSF pleocytosis, defined as a white blood cell count >5/μL. In addition, at least one of the following criteria was required: a positive CSF culture, a positive CSF Gram stain, or a positive blood culture yielding a recognized meningeal pathogen. For patients with negative cultures, the diagnosis was established based on compatible clinical features together with CSF findings

consistent with bacterial meningitis, specifically pleocytosis combined with either a CSF protein concentration >100 mg/dL or a CSF-to-serum glucose ratio <0.4. These diagnostic criteria were consistent with the Infectious Diseases Society of America guidelines [11]. Patients were excluded if they were pregnant, had a known coagulopathy, active malignancy, immunosuppression, recent traumatic brain injury, advanced liver disease, or known metabolic disorders that could affect lactate metabolism. Patients were also excluded if informed consent could not be obtained.

Data Collection

All patients underwent a comprehensive clinical assessment on admission, including neurological evaluation using the GCS and systemic severity assessment using the APACHE II score. In intubated or sedated patients, the verbal component of the GCS was assigned a score of 1 (intubated), and the total GCS score was calculated using the eye and motor components, consistent with standard practice in critically ill patients. Empirical intravenous antibiotic therapy was initiated immediately and consisted of ceftriaxone (2 g every 12 hours) plus vancomycin (15–20 mg/kg every 8–12 hours). Antibiotic therapy was subsequently adjusted according to culture results and sensitivity results, antimicrobial susceptibility testing, and local resistance patterns. Adjunctive dexamethasone (0.15 mg/kg every six hours for 2–4 days) was administered before or with the first dose of antibiotics. All patients received supportive care according to international ICU guidelines, including fluid resuscitation, vasopressor support for septic shock, and mechanical ventilation when indicated.

Cerebrospinal fluid was obtained by lumbar puncture under aseptic conditions within two hours of ICU admission. Samples were analyzed for cell count and differential, glucose, protein, microbiological culture, and lactate concentration. CSF lactate was measured by amperometry using the ABL800 FLEX analyzer (Radiometer Medical, Denmark). Repeat CSF sampling was performed on day 14 in all 45 enrolled patients because each met the institutional clinical criteria for follow-up lumbar puncture owing to persistent neurological impairment and/or ongoing systemic febrile manifestations. Daily laboratory investigations included complete blood count, renal and liver function tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, procalcitonin (PCT), coagulation profile, and serum lactate. Although ESR was measured routinely, it was not included in the primary analyses because of its limited specificity and relatively slow response in acute bacterial meningitis.

Neurological status was assessed using the GCS, and systemic disease severity was evaluated using the APACHE II score by ICU physicians who were blinded to the study analysis. Laboratory personnel measuring CSF and serum biomarkers were blinded to clinical outcomes. CSF lactate results were not disclosed to the treating clinicians during the study period, and patient management was based exclusively on standard clinical and laboratory findings.

Outcome Definition

The primary outcome was all-cause in-hospital mortality. Secondary outcomes included associations between CSF lactate concentrations and other CSF indices, neurological status as assessed by the GCS, and disease severity as measured by the APACHE II score.

Statistical Analysis

Sample size was determined prospectively based on the primary objective of evaluating the prognostic performance of CSF lactate for predicting in-hospital mortality. A sample size of 45 patients was estimated to provide 80% power to detect an area under the receiver operating characteristic curve (AUC) of at least 0.75 for predicting in-hospital mortality at a significance level of α=0.05, assuming an event rate of approximately 22%. Given the single-center design and modest sample size, AUC estimates are presented with bootstrap-derived 95% confidence intervals (CIs) to better reflect statistical uncertainty.

Statistical analyses were performed using IBM SPSS version 27.0. (Armonk, NY, USA: IBM Corp., released 2020). Normality was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation (SD) or (interquartile range [IQR]), and were compared using the t test or the Mann–Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was used to assess discriminatory performance, with AUCs reported together with 95% CIs. Optimism correction of the AUC was performed using 2,000 bootstrap resamples. Correlations were assessed using Spearman's rank correlation coefficient (ρ), with adjustment for multiple comparisons using the Benjamini–Hochberg false discovery rate procedure. Changes in paired CSF lactate concentrations between admission and day 14 were evaluated using the Wilcoxon signed-

rank test. Because only 10 deaths occurred, multivariable logistic regression was considered exploratory. A sample size of 45 patients provided 80% power to detect an AUC of at least 0.75 at a significance level of α=0.05. All analyses were verified using R version 4.3.

Results

Forty-five adults with confirmed bacterial meningitis were enrolled, of whom 35 (77.8%) survived and 10 (22.2%) died during hospitalization (Fig. 1). All deaths occurred after day 14 (mean survival, 26.5 days), allowing complete day-14 follow-up for all participants. The remaining in-hospital deaths occurred after day 14. Non-survivors were significantly older (59.7±5.9 vs. 39.0±19.5 years, p=0.006) and presented later after symptom onset (p=0.014). Sex distribution and comorbidities did not differ between groups. Classical meningeal signs were less frequent among non-survivors, with neck stiffness present in 60% compared with 100% of survivors (p=0.001), suggesting a more atypical presentation in severe disease (Table 1).

At admission, non-survivors had significantly lower GCS scores (8.70±0.67 vs. 11.86±1.52, p<0.001) and higher APACHE II scores (median, 22.0 [19.0–24.0] vs. 13.0 [9.0–18.0], p<0.001), indicating greater systemic illness severity. They also had significantly higher respiratory and heart rates than survivors (p<0.01) (Table 1).

By day 14, non-survivors demonstrated persistent systemic inflammation and multiorgan dysfunction. Compared with survivors, they had markedly higher CRP (145.5 [139–146] vs. 12 [12–26.5] mg/L), procalcitonin (68.03 [68.01–76.02] vs. 0.4 [0.12–0.72] ng/mL), ferritin (614 [544–776] vs. 310 [276–384] μg/L), and International Normalized Ratio (INR) (1.21 [1.2–1.58] vs. 1.02 [1.01–1.1]) (all p<0.001). Non-survivors also exhibited anemia, thrombocytopenia, and renal dysfunction, with serum creatinine levels of 3.9 [3.83–5.78] vs. 0.6 [0.5–0.7] mg/dL (p<0.001). Serum lactate followed a similar trajectory: although admission concentrations were only modestly higher in non-survivors (3.3 [3.1–3.4] vs. 3.0 [2.4–3.2] mmol/L; p=0.014), by day 14 they had increased markedly (4.4 [4.3–5.1] mmol/L), whereas survivors had declined to near-normal levels (1.9 [1.6–2.1] mmol/L; p<0.001). Collectively, these findings indicate persistent inflammation, progressive multiorgan dysfunction, and sustained metabolic derangement consistent with severe sepsis (Tables 2 and 3).

Admission CSF lactate concentrations did not differ significantly between survivors and non-survivors (median, 3.56 vs. 3.5 mmol/L, p=0.381). By day 14, however, survivors showed a decline in CSF lactate (median, 1.8 mmol/L), whereas non-survivors exhibited a substantial increase (median, 6.8 mmol/L; p<0.001). Longitudinal analysis demonstrated a significant reduction in CSF lactate among survivors (median change, −1.41 mmol/L; p<0.001) and an increase among non-survivors (median change, +1.33 mmol/L; p<0.001). The between-group difference in lactate change was substantial (median Δ difference, −2.74 mmol/L; p<0.001), indicating that persistent elevation, rather than baseline concentration, was associated with mortality. Consistent with these findings, admission CSF lactate showed poor prognostic performance (AUC=0.41, 95% CI: 0.25–0.57; p=0.32). In contrast, day-14 CSF lactate strongly predicted mor-

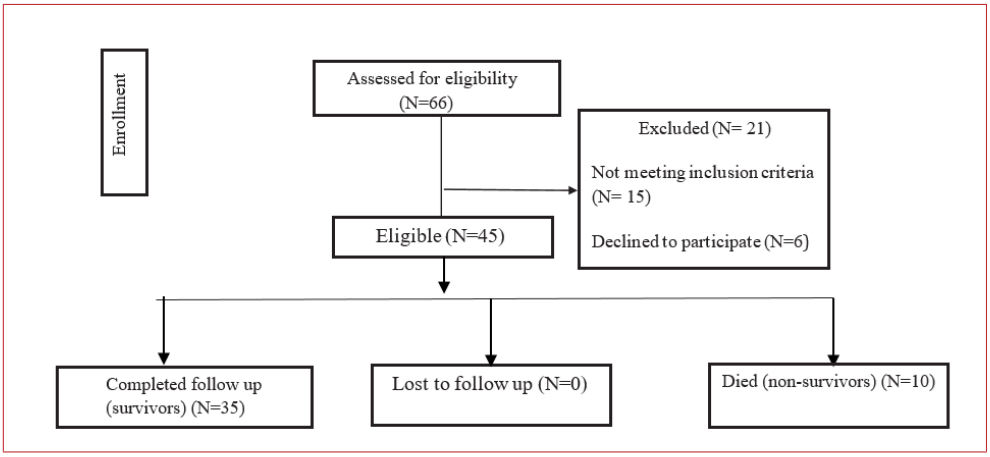

Figure 1. Study flow diagram.

Table 1. Demographic and clinical characteristics according to in-hospital outcome

Characteristic	Total (n=45)	Survivors (n=35)	Non-survivors (n=10)	p
Sex				
Male	21 (46.7%)	18 (51.4%)	3 (30.0%)	
Female	24 (53.3%)	17 (48.6%)	7 (70.0%)	0.296
Age (years)	43.58±9.42	38.97±19.51	59.70±5.93	0.006
Comorbidities				
DM	10 (22.2%)	6 (17.1%)	4 (40.0%)	0.194
HTN	12 (26.7%)	7 (20.0%)	5 (50.0%)	0.101
Asthma	6 (13.3%)	5 (14.3%)	1 (10.0%)	1.000
IHD	4 (8.9%)	3 (8.6%)	1 (10.0%)	1.000
Time from symptom onset to admission				
<1 day	25 (55.6%)	23 (65.7%)	2 (20.0%)	
≥2 days	20 (44.4%)	12 (34.3%)	8 (80.0%)	0.014
Antibiotic therapy before admission				
No	38 (84.4%)	29 (82.9%)	9 (90.0%)	
Yes	7 (15.6%)	6 (17.1%)	1 (10.0%)	1.000
Clinical presentation				
Headache	39 (86.7%)	29 (82.9%)	10 (100.0%)	0.312
Fever	37 (82.2%)	27 (77.1%)	10 (100.0%)	0.168
Vomiting	29 (64.4%)	21 (60.0%)	8 (80.0%)	0.292
Blurred vision	24 (53.3%)	20 (57.1%)	4 (40.0%)	0.476
Kernig's sign	21 (46.7%)	17 (48.6%)	4 (40.0%)	0.729
Brudzinski's sign	11 (24.4%)	7 (20.0%)	4 (40.0%)	0.228
Neck stiffness	41 (91.1%)	35 (100.0%)	6 (60.0%)	0.001
APACHE II score at admission				
Min–Max	6.0–28.0	6.0–25.0	10.0–28.0	<0.001
Median (IQR)	15.0 (10.0–21.0)	13.0 (9.0–18.0)	22.0 (19.0–24.0)	

DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischemic heart disease; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 2. Neurological status and vital signs

Characteristic	Total (n=45)	Survivors (n=35) Mean±SD	Non-survivors (n=10) Mean±SD	p
Neurological status				
GCS at admission	11.16±1.91	11.86±1.52	8.70±0.67	<0.001
GCS score on day 14	12.0±4.32	14.26±0.70	4.10±0.57	<0.001
Vital signs				
Temperature (°C)	39.40±0.62	39.33±0.66	39.62±0.41	0.202
Respiratory rate (breaths/min)	22.51±2.85	21.51±2.12	26.0±2.31	<0.001
Heart rate (beats/min)	108.8±13.66	105.7±11.53	119.5±15.62	0.004
Systolic blood pressure (mmHg)	117.6±25.60	114.6±21.47	128.0±36.15	0.287
Diastolic blood pressure (mmHg)	74.0±12.68	72.86±11.78	78.0±15.49	0.350

GCS: Glasgow Coma Scale.

Table 3. Laboratory findings at admission and day 14

Variable	Total (n=45)	Survivors (n=35)	Non-survivors (n=10)	p
Hematological parameters, median (IQR)				
HB (g/dL), admission	12.6 (11.5-12.9)	12.6 (11.6-13.2)	11.85 (10.83-12.9)	0.250
HB (g/dL), day 14	11.5 (10.5-12.4)	11.8 (11.3-12.85)	7 (6.93-7.08)	<0.001
TLC (×10³/μL), admission	17 (15.7-23)	17 (15.85-24)	15.85 (15.7-22.7)	0.366
TLC (×10³/μL), day 14	13 (8.3-18.6)	11.1 (8-14)	27 (26.25-32.75)	<0.001
PLT (×10³/μL), admission	287 (256-345)	310 (273-357)	260.5 (256-277)	0.007
PLT (×10³/μL), day 14	306 (191-365)	316 (268.5-378)	75 (48.5-82.5)	<0.001
Inflammatory markers, median (IQR)				
CRP (mg/L), admission	103 (86-126)	118 (96-127.5)	62 (61-94)	<0.001
CRP (mg/L), day 14	24 (12-49)	12 (12-26.5)	145.5 (139-146)	<0.001
PCT, admission	6.8 (2.9-9.2)	5.8 (2.85-9)	6.9 (6.8-9.2)	0.396
PCT, day 14	0.7 (0.2-1.6)	0.4 (0.12-0.72)	68.03 (68.01-76.02)	<0.001
Coagulation, median (IQR)				
INR, admission	1.2 (1.05-1.49)	1.1 (1.04-1.27)	1.77 (1.74-2.04)	<0.001
INR, day 14	1.04 (1.01-1.12)	1.02 (1.01-1.1)	1.21 (1.2-1.58)	<0.001
Iron studies, median (IQR)				
Ferritin, admission	794 (569-873)	690 (559.5-860.5)	1319 (863.75-1324.25)	<0.001
Ferritin, day 14	325 (298-417)	310 (276-384)	614 (544-776)	<0.001
Renal function, median (IQR)				
Creatinine (mg/dL), admission	0.9 (0.7-1.2)	0.8 (0.7-1.1)	1.05 (1-1.2)	0.083
Creatinine, day 14	0.6 (0.5-1.35)	0.6 (0.5-0.7)	3.9 (3.83-5.78)	<0.001
Urea (mg/dL), admission	38 (34-60)	37 (32-59.5)	45.5 (45-60)	0.208
Urea, day 14	28 (25-136)	27 (23-31)	180 (178.5-224.5)	<0.001
Metabolic markers, median (IQR)				
RBG (mg/dL), admission	146 (116-176)	136 (108.5-149)	177 (176-266)	<0.001
RBG (mg/dL), day 14	116 (100-124)	110 (94-122.5)	132.5 (124-180.75)	<0.001
Serum lactate (mmol/L), admission	3.1 (2.5-3.4)	3.0 (2.4-3.2)	3.3 (3.1-3.4)	0.014
Serum lactate (mmol/L), day 14	2.1 (1.7-2.4)	1.9 (1.6-2.1)	4.4 (4.3-5.1)	<0.001
Microbiology, n (%)				
No growth	15 (33.3%)	11 (31.4%)	4 (40.0%)	1.000
Staphylococcus aureus	2 (4.4%)	2 (5.7%)	0 (0.0%)	–
Streptococcus pneumoniae	27 (60.0%)	21 (60.0%)	6 (60.0%)	–
Neisseria meningitidis	1 (2.2%)	1 (2.9%)	0 (0.0%)	–

HB: Hemoglobin; TLC: Total leukocyte count; PLT: Platelet count; CRP: C-reactive protein; PCT: Procalcitonin; INR: International Normalized Ratio; RBG: Random blood glucose.

tality (optimism-adjusted AUC=0.93, 95% CI: 0.84–0.99; p<0.001). A threshold of >4.3 mmol/L yielded 92% sensitivity, 91% specificity, a positive predictive value of 79%, and a negative predictive value of 96% (Table 4).

A strong positive correlation was observed between day-14 CSF lactate and concurrent serum lactate concentrations (Spearman's ϱ=+0.78, p<0.001), suggesting a close association between cerebral and systemic metabolic dysfunction during the second week of illness. Higher day-14 CSF lactate was associated with lower GCS scores at admission (ϱ=−0.65, p<0.001) and day 14 (ϱ=−0.57, p<0.001), higher APACHE II scores (ϱ=+0.57, p<0.001), higher CSF protein concentrations (ϱ=+0.53, p<0.001), and lower CSF

Table 4. Comparison of cerebrospinal fluid biochemical and cytological parameters between survivors and non-survivors

Marker	Time point	Total (n=45)	Survivors (n=35)	Non-survivors (n=10)	p
Lactate (mmol/L)	Admission	3.50 (3.37-3.80)	3.56 (3.14-3.90)	3.5 (3.4-3.5)	0.381
	Day 14	2.1 (1.7-2.3)	1.8 (1.5-2.1)	6.8 (5.7-7.1)	<0.001
Neutrophils (×10⁶/L)	Admission	16.37 (14.92-22.61)	16.66 (14.97-21.73)	15.533 (14.95-22.7)	0.883
	Day 14	0.28 (0-6.12)	0.147 (0-0.38)	15.93 (11.81-17.59)	<0.001
Lymphocytes (×10⁶/L)	Admission	0.56 (0.31-0.91)	0.785 (0.36-1.26)	0.195 (0-0.32)	<0.001
	Day 14	9.6 (7.3-13.72)	8.4 (7.02-13.51)	11.07 (9.23-15.1)	0.338
Protein (mg/dL)	Admission	177 (100-200)	180 (98-197.5)	176.5 (160.25-207.25)	0.545
	Day 14	37 (32-52)	35 (29.5-37)	112.5 (94.25-127.5)	<0.001
Glucose (mg/dL)	Admission	20 (14-25)	23 (12.5-25)	18 (15.5-19.75)	0.840
	Day 14	59 (45-65)	63 (56.5-65)	33 (30.25-34.75)	0.006

All values are presented as median (interquartile range [IQR]).

glucose concentrations (ϱ=−0.30, p=0.047). These associations remained significant after adjustment for age and APACHE II score using partial correlation analysis.

Kaplan–Meier analysis demonstrated a mean survival time of 26.5 days, with 77.8% of patients surviving to hospital discharge. Patients with day-14 CSF lactate concentrations >4.3 mmol/L had significantly lower survival than those with lower concentrations (log-rank p<0.001) (Fig. 2).

In an exploratory logistic regression model including age, APACHE II score, and day-14 CSF lactate concentration, only lactate remained associated with mortality (odds ratio=3.81 per 1 mmol/L increase; 95% CI: 1.5–9.4; p=0.004). These findings should be interpreted cautiously because of the limited number of deaths (n=10) (Table 5).

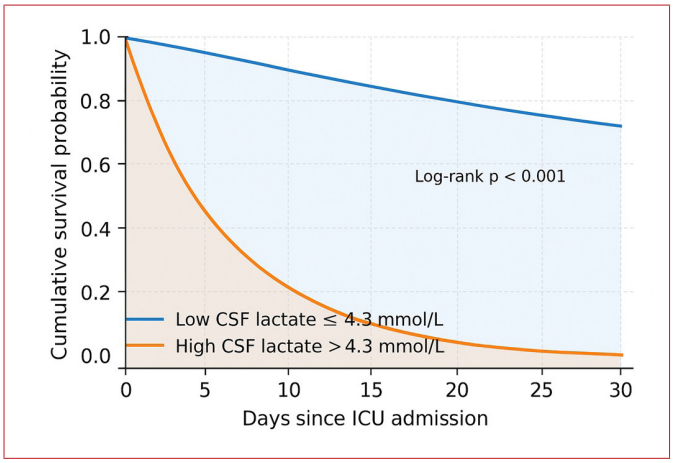

Figure 2. Kaplan–Meier survival curves stratified according to day-14 cerebrospinal fluid (CSF) lactate concentration.

Table 5. Exploratory multivariable logistic regression analysis of predictors of in-hospital mortality

Variable	Odds ratio (95% CI)	p
Age (per 1-year increase)	1.08 (0.98-1.20)	0.112
APACHE II score at admission (per 1-point increase)	1.13 (0.93-1.38)	0.228
Day-14 CSF lactate (per 1 mmol/L increase)	3.81 (1.55-9.38)	0.004

Discussion

The principal finding of this study is that the temporal kinetics of CSF lactate, rather than its admission concentration, provide meaningful prognostic information in critically ill adults with bacterial meningitis. Although admission CSF lactate levels were comparable between survivors and non-survivors, longitudinal analysis demonstrated a significant decline from admission to day 14 among survivors and a significant increase among non-survivors. The difference in these trajectories was substantial (median Δ difference, −2.74 mmol/L; p<0.001). This pattern suggests that although patients may initially present with comparable cerebral metabolic disturbances, recovery of cerebral metabolism, as reflected by declining CSF lactate concentrations, is closely associated with survival.

Normalization of CSF lactate in survivors likely reflects effective antimicrobial therapy, resolution of inflammation, and recovery of aerobic cerebral metabolism. In contrast, persistently elevated CSF lactate probably indicates

ongoing cerebral hypoxia, microcirculatory dysfunction, or mitochondrial impairment despite microbiological control of infection. Consequently, a follow-up CSF lactate measurement obtained two weeks after admission appears to provide a more informative assessment of cerebral metabolic recovery than admission values alone, which may be influenced by delays in presentation or prehospital treatment.

Previous studies have highlighted the prognostic value of CSF biochemical markers in different forms of meningitis. Abassi et al. [12] reported that elevated CSF lactate in cryptococcal meningitis was associated with altered consciousness, seizures, and elevated intracranial pressure, whereas Tubiana et al. [1] identified low leukocyte count, hypoglycorrhachia, and elevated protein concentration as independent predictors of adverse outcomes in bacterial meningitis. Our findings are consistent with these observations, suggesting that persistently elevated CSF lactate concentrations, rather than admission values, are associated with unresolved cerebral metabolic dysfunction. Similarly, De Almeida et al. [5] demonstrated that persistent lactate elevation predicted mortality, while Liu et al. [13] found that elevated CSF lactate within 48 hours predicted poor outcomes in tuberculous meningitis. Abbasi et al. [12] similarly reported higher CSF lactate concentrations in bacterial and cryptococcal meningitis, demonstrating good diagnostic performance.

Not all studies have reached similar conclusions. Makowiecki et al. [10] reported no difference in lactate between survivors and non-survivors with community-acquired bacterial meningitis, suggesting that prognostic performance may depend on patient population and sampling time. Our findings help reconcile these discrepancies by showing that serial measurements capture metabolic recovery, whereas a single admission measurement does not. This finding may help explain the inconsistent results reported in previous studies. To our knowledge, this is among the first prospective studies in an adult medical ICU population to evaluate the prognostic significance of CSF lactate kinetics. Our findings may help reconcile these conflicting reports by demonstrating that serial assessment of CSF lactate, rather than reliance on a single admission measurement, more accurately reflects recovery of cerebral metabolism. By evaluating longitudinal changes in CSF lactate within individual patients and comparing trajectories between survivors and non-survivors, our study provides a longitudinal perspective that has been lacking in many previous cross-sectional studies. This approach may help explain why admission CSF lactate concentrations alone have shown inconsistent prognostic value, whereas serial measurements reveal a clearer association with mortality.

By day 14, non-survivors also demonstrated higher CSF protein concentrations and lower CSF glucose levels, findings consistent with persistent blood–brain barrier disruption and impaired substrate transport, similar to those reported by Makowiecki et al. [10]. Neurological status also remained an important prognostic indicator, as non-survivors had significantly lower GCS scores both at admission and during follow-up, consistent with previous reports by Park et al. [3], Martín-Cerezuela et al. [4], and others. Additionally, delayed hospital presentation was associated with poorer outcomes, in agreement with the findings of Tubiana et al. [1].

Beyond its prognostic performance, CSF lactate demonstrated clinically meaningful associations with several markers of disease severity. Both admission and day-14 CSF lactate concentrations were negatively correlated with GCS scores and CSF glucose concentrations and positively correlated with CSF protein concentrations, APACHE II scores, and systemic inflammatory markers, including CRP, ESR, PCT, and ferritin. The lower admission CRP concentrations observed in non-survivors may reflect variability in the timing or magnitude of the acute-phase response, whereas the marked increase by day 14 is consistent with progressive systemic inflammation and organ dysfunction. A notable finding was the significantly lower admission CRP concentrations in non-survivors. Although admission CRP concentrations were lower in non-survivors, they increased markedly by day 14, indicating progressive systemic inflammation and organ dysfunction rather than immune exhaustion. The initially lower CRP concentration may reflect differences in the timing of presentation or individual variability in the acute-phase response; however, the subsequent marked elevation is consistent with progressive systemic inflammation and organ dysfunction. In this context, a low admission CRP concentration could represent an ominous indicator of an inadequate inflammatory response rather than less severe disease (4). Significant positive correlations were also observed between CSF lactate and renal function indices (urea and creatinine), as well as serum lactate. The strong correlation between day-14 serum and CSF lactate concentrations (ρ=+0.78) suggests that persistent cerebral metabolic dysfunction parallels systemic metabolic failure and shock. This find-

ing is consistent with the presence of multiorgan dysfunction in non-survivors and reinforces the concept that elevated CSF lactate serves as an integrative marker of both cerebral and systemic disease severity. The inverse correlation between CSF lactate and GCS scores suggests that increasing CSF lactate concentrations parallel worsening neurological status, whereas its positive associations with inflammatory markers and renal function indices further support its role as an integrative marker of overall illness severity. This multidimensional pattern of correlations strengthens the biological plausibility and clinical relevance of CSF lactate as a dynamic biomarker of disease severity rather than merely an isolated metabolic byproduct. [1,5,7,10].

Clinical presentation also differed between outcome groups. Although fever and headache were common in both survivors and non-survivors, neck stiffness was observed in all survivors but in only 60% of patients who died. This lower frequency among non-survivors likely reflects a more severe disease course, in which profound impairment of consciousness, as evidenced by significantly lower GCS scores, may obscure or reduce the elicitation of classical meningeal signs. In these patients, the clinical presentation is often dominated by the systemic manifestations of sepsis and multiorgan dysfunction rather than by focal neurological signs. Our findings are consistent with previous reports showing that the classic triad of bacterial meningitis is frequently incomplete, particularly in critically ill adults and those with fatal disease, potentially contributing to delays in diagnosis and treatment initiation [14,15]. Accordingly, the absence of neck stiffness in a patient with suspected central nervous system (CNS) infection should not reduce clinical suspicion for bacterial meningitis; rather, it may indicate more severe disease requiring prompt, aggressive management. These findings underscore the importance of integrating clinical assessment with laboratory and biomarker data, rather than relying on any single clinical sign, for early risk stratification in the ICU.

Several systemic abnormalities were also associated with mortality in our cohort. Non-survivors exhibited tachycardia, tachypnea, anemia, thrombocytopenia, and marked leukocytosis, consistent with previous reports by Yang et al. [16], Wall et al. [17], and Matulyte et al. [18]. Inflammatory and coagulation markers, including procalcitonin, C-reactive protein, ferritin, and INR, were also significantly elevated, in agreement with previous studies [4,7,10,19,20]. Renal dysfunction was strongly associated with mortality, consistent with the findings of Makowiecki et al. [10] and Iwata et al. [21] Collectively, these findings suggest that persistent elevation of CSF lactate reflects both cerebral and systemic organ dysfunction, supporting its potential role as an integrated marker of disease severity.

This study has several strengths. Blinded measurement of CSF lactate and blinded outcome assessment minimized observer bias. Serial CSF sampling enabled assessment of metabolic trajectories rather than isolated measurements, complemented by comprehensive clinical and laboratory evaluation. Finally, the focus on critically ill adults treated in a resource-limited ICU enhances the clinical applicability of serial CSF lactate monitoring in similar healthcare settings.

This study also has several limitations. First, the relatively small sample size limited statistical power and restricted adjustment for potential confounders. Because only 10 deaths occurred, we were unable to determine whether serial CSF lactate independently predicted mortality beyond established risk factors such as age and illness severity. Although the observed association was strong, confirmation in larger studies is required.

Second, we excluded patients with immunocompromising conditions, recent trauma, liver disease, or septic shock to reduce potential confounding. Although these exclusion criteria improved cohort homogeneity, they may limit the generalizability of our findings. Furthermore, the prognostic performance of CSF lactate may be overestimated compared with that observed in broader, more heterogeneous ICU populations. To minimize overfitting, bootstrap-adjusted estimates and conservative statistical methods were used throughout the analyses.

Third, the limited sample size precluded analyses stratified by the causative bacterial pathogen. Fourth, although elevated CSF protein concentrations and reduced CSF glucose concentrations at day 14 suggested ongoing blood–brain barrier dysfunction, we were unable to determine whether these abnormalities reflected persistent inflammation or residual infection. Although follow-up cultures were negative, more sensitive molecular diagnostic techniques, such as polymerase chain reaction (PCR), were not performed and therefore residual bacterial DNA could not be assessed. Consequently, the underlying mechanism responsible for the persistent CSF abnormalities observed in non-survivors remains uncertain.

Furthermore, because all patients in our medical ICU cohort met the institutional criteria for follow-up lumbar puncture on day 14 owing to persistent neurological impairment and/or ongoing systemic manifestations, complete serial CSF data were obtained without selection bias. However, this also indicates that our cohort represents the more severe end of the bacterial meningitis spectrum, and the findings may not be generalizable to patients with milder disease who do not require repeat lumbar puncture.

These limitations highlight the need for larger, multicenter studies to validate our findings and further characterize CSF lactate kinetics. Future studies should also evaluate earlier serial measurements, such as on days 3–5, to determine whether changes in CSF lactate can identify high-risk patients sufficiently early to guide clinical management. Incorporation of molecular microbiological testing into serial CSF assessment may also help distinguish persistent inflammation from residual infection in patients with poor clinical recovery.

Overall, this study provides preliminary prospective evidence supporting the prognostic value of serial CSF lactate monitoring in adults with bacterial meningitis and establishes a foundation for larger studies.

Conclusion

In this prospective ICU cohort of adults with bacterial meningitis, serial CSF lactate measurements provided robust prognostic information. Admission CSF lactate concentrations did not distinguish survivors from non-survivors, whereas persistently elevated concentrations after two weeks were strongly associated with mortality, likely reflecting sustained cerebral metabolic dysfunction. Given its simplicity, low cost, and wide availability, serial CSF lactate monitoring may represent a practical adjunct for risk stratification. Larger multicenter studies are warranted to confirm these findings and to determine the optimal integration of CSF lactate kinetics into prognostic models alongside established clinical and laboratory predictors .

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