

Frequency of hyperchloremia and mortality in patients presenting with sepsis at tertiary care hospital, Karachi

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ABSTRACT

Background: Hyperchloremia is frequently encountered in critically ill patients with sepsis and may reflect disease severity, altered renal handling, or exposure to chloride-rich intravenous fluids. This study was designed to assess the prevalence and in-hospital mortality for hyperchloremia in patients with sepsis.

Material and Methods: This cross-sectional study included 165 adults aged 30 to 80 years admitted with sepsis to the Department of Medicine, Aga Khan University Hospital, Karachi. Chloride was tested within 12 hours of admission and hyperchloremia was defined as >107 milliequivalents per liter (mEq/L). Demographic characteristics, comorbidities, intensive care unit admission and in-hospital mortality were documented. Chi-square test or Fisher's exact test was used to assess associations with a p-value ≤ 0.05 regarded as statistically significant.

Results: Hyperchloremia was present in 66 (40.0%) of 165 patients and 33 (20.0%) patients died during hospital stay. Patients with sepsis duration >24 hours had significantly higher incidence of hyperchloremia compared to those with ≤ 24 hours duration of sepsis (73.1% vs. 33.8%, $p < 0.001$). Important associations were also noted with diabetes mellitus ($p = 0.001$), hypertension ($p = 0.002$), dyslipidemia ($p = 0.006$) and anaemia ($p < 0.001$). Among the patients who had hyperchloremia, 16 (24.2%) died compared with 17 (17.2%) patients who did not have hyperchloremia; this was not statistically significant ($p = 0.266$).

Conclusions: Hyperchloremia was prevalent in patients with sepsis and was linked to longer sepsis duration and specific co-morbidities. While there was a higher number of deaths in the hyperchloremic group, hyperchloremia was not significantly related to in-hospital death.

Keywords: Chlorides, Critical care, Fluid therapy, Hospital mortality, Sepsis.

BACKGROUND

The most abundant extracellular anion, chloride is essential for maintaining extracellular fluid volume, osmotic pressure, electrical neutrality, and acid-base homeostasis. A disturbance of serum chloride level is frequently seen in critically ill patients and may occur due to severity of underlying illness, renal dysfunction or therapeutic interventions. Hyperchloremia was associated with higher in-hospital, 30-day, and 90-day all-cause mortality in a large cohort of patients in the surgical intensive care unit, indicating that serum chloride may be of prognostic value in critically ill patients.¹

However, there are a number of other complexities to the relationship between chloride abnormalities and adverse outcomes. In critically ill patients with acute kidney injury, serum chloride levels were strongly associated with intensive care unit and hospital mortality, suggesting that dyschloremia may be a marker of important disturbances of fluid, electrolyte and renal homeostasis.² Likewise, Chloride (Cl^-) levels at admission were shown to be associated with mortality in medical intensive care patients, and there was potential for interaction between hyperchloremia and renal dysfunction.³ Hyperchloremia has also been linked with greater mortality, renal injury, longer intensive care stay and a longer time on mechanical ventilation in the critically ill.⁴

The exposure to chloride rich intravenous fluids is one of the important mechanisms of hyperchloremia in critically ill patients. Normal saline is used in a lot of situations during hemodynamic resuscitation and has a lot more chloride than human plasma.⁵ The best crystalloid solution for these patients is controversial. Despite ongoing concerns about the potential effects of chloride-rich fluids for resuscitation, a systematic review and meta-analysis assessed the mortality, acute

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This article can be cited as: Ishtiaq A, Abid S. Frequency of hyperchloremia and mortality in patients presenting with sepsis at tertiary care hospital, Karachi. *Infect Dis J Pak*. 2026; 35(3): 240-245.

DOI: <https://doi.org/10.61529/idi.v35i3.586>

Receiving date: 27 May 2026 Acceptance Date: 27 Sep 2026

Revision date: 18 Sep 2026 Publication Date: 30 Sep 2026

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kidney injury, renal replacement therapy, and intensive care outcomes of adults with sepsis who had received balanced crystalloids versus normal saline.⁶ However, the large PLUS (Plasma-Lyte 148 versus saline) randomized controlled trial in critically ill adults did not show any decrease in 90 day mortality or acute kidney injury in balanced multi-electrolyte solution relative to saline, and the clinical implications of fluid chloride content remains unclear.⁷

A summary of evidence from randomized trials has also shown that there is uncertainty about the clinically important benefits of balanced crystalloid solutions over saline in the treatment of critically ill adults.⁸ However, there is ongoing evidence that alterations in serum chloride alone may have prognostic value. In critically ill adults, elevated chloride levels have been linked to significant adverse kidney outcomes, suggesting that any change in chloride level might be clinically relevant not just a single measurement.⁹ Meanwhile, reduced serum chloride levels have also been linked to greater mortality in critically ill patients with acute kidney injury, suggesting that the association of chloride to outcome may be non-linear, and high and low chloride levels should be interpreted with caution.¹⁰

Although there is growing international evidence of chloride derangements in the serum being associated with poor outcome in critically ill populations, the prevalence and prognostic significance of hyperchloremia in septic patients in the local clinical setting has not been sufficiently described. Thus, this study was done to ascertain the frequency of Hyperchloremia and its association with in-hospital deaths in patients admitted with sepsis in a Tertiary Care Hospital at Karachi. The study was conducted to produce local evidence to aid in determining the clinical impact of hyperchloremia and guide future assessment of fluid and electrolyte management in patients with sepsis.

MATERIAL AND METHODS

A cross-sectional study was carried out in the Department of Medicine from June 1st, 2025 to November 30th, 2025 at Aga Khan University Hospital, Karachi. The study was approved by the Ethics Review Committee of Aga Khan University (ERC No. 2025-9516-34758 dated 20th May 2025). All the participants signed a written informed consent prior to enrollment.

All patients aged 30–80 years, both males and females, admitted with sepsis were included. Patients were enrolled according to the Systemic Inflammatory Response Syndrome (SIRS) criteria, as defined by the presence of two or more of the following: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/min, respiratory rate >20 breaths/min or $\text{PaCO}_2 <32$ mmHg, and white blood cell count $>12,000/\text{mm}^3$, $<4,000/\text{mm}^3$, or $>10\%$ immature neutrophils.²¹ Patients who required intubation and were transferred from another hospital, had been hospitalized or had undergone surgery within three months, were pregnant, or had renal impairment, chronic obstructive pulmonary disease, asthma, congestive heart failure, myocardial infarction or chronic liver disease were excluded. No information was available on fluid therapy before hospital admission and this could not be controlled for in the analysis. Baseline chloride status was then determined within 12 hours of admission to reduce the confounding effects of chloride levels after the patient was admitted.

The sample size of 165 patients was determined using WHO sample-size software with a 95% confidence level, 6% margin of error and an expected frequency of hyperchloremia of about 19% based on a recent prospective study of critically ill patients with sepsis reported hyperchloremia in 19.3%.¹¹ Non-probability consecutive sampling was used to recruit participants.

Structured study proforma was used to collect the demographic and clinical data. The data comprised age, gender, time of sepsis, hospital stay, and comorbidities of diabetes mellitus, hypertension, dyslipidemia, anemia and obesity. Their height and weight was taken and body mass index (BMI) calculated. A BMI of ≥ 27.5 kg/m² was considered obesity. Diabetes mellitus, hypertension and dyslipidemia were detected by documented medical history, regular intake of the corresponding drugs for at least six months, and available clinical and/or laboratory data. Anemia was considered as <12 g/dL in males and <11 g/dL in females.

All patients entered were sampled within 12 hours of admission for serum chloride measurement. Hyperchloremia was defined as serum chloride concentration ≥ 107 mEq/L, based on the laboratory reference range. and patients were followed during their hospital stay, with in-hospital mortality as the clinical outcome. Need for admission to an intensive care unit was also recorded.

The analysis of data was carried out with the help of the SPSS (20). Categorical data were expressed as frequencies and percentages, such as age groups, gender, duration of sepsis, duration of hospital stay, diabetes mellitus, hypertension, dyslipidemia, obesity, anemia, ICU admission, hyperchloremia and in-hospital mortality. Stratification was performed for effect modifiers such as: age, gender, comorbidities, ICU admission, duration of sepsis and duration of hospital stay. After stratification, the relationship between hyperchloremia and categorical variables were evaluated by the chi-square test or Fisher's exact test, depending on the sample size. Multivariable logistic regression analysis was done to determine independent factors associated with hyperchloremia and to adjust for potential confounding variables. All the clinically relevant variables and those with significant association in the univariate analysis were incorporated in the regression model. Adjusted odds ratios (aORs) and the corresponding 95% confidence intervals (CIs) were presented. A p-value ≤ 0.05 was considered statistically significant

RESULTS

A total of 165 patients with sepsis were included in the analysis. The majority, 113 (68.5%), were aged 51 to 80 years, while 84 (50.9%) were females. Sepsis duration was 24 hours or less in 139 (84.2%) patients, and 117 (70.9%) remained hospitalized for more than seven days. Hyperchloremia was identified in 66 (40.0%) patients, while in-hospital mortality occurred in 33 (20.0%). The demographic and clinical characteristics of the study participants are presented in Table-I.

Patients with sepsis for >24 hours had a significantly higher proportion of hyperchloremia compared with

those with sepsis ≤ 24 hours (28.8% vs. 7.1%, $p < 0.001$). Hyperchloremia was also significantly associated with diabetes mellitus, hypertension and dyslipidemia ($p = 0.001$, $p = 0.002$ and $p = 0.006$, respectively). Interestingly, anemia was more common among patients without hyperchloremia than those with hyperchloremia (59.6% vs. 22.7%, $p < 0.001$). No statistically significant association was observed between hyperchloremia and age ($p = 0.945$), gender ($p = 0.899$), hospital stay ($p = 0.675$), obesity ($p = 0.843$), ICU admission ($p = 0.606$), or in-hospital mortality ($p = 0.266$) shown in Table-II. Patients with sepsis duration >24 hours had higher odds of hyperchloremia (UOR=5.31, 95% CI: 2.09–13.54, $p < 0.001$). Diabetes mellitus (UOR=0.29, 95% CI: 0.13–0.63, $p = 0.002$) and hypertension (UOR=0.22, 95% CI: 0.08–0.60, $p = 0.003$) were associated with lower odds of hyperchloremia. Dyslipidemia was associated with increased odds (UOR=2.42, 95% CI: 1.28–4.58, $p = 0.007$), whereas anemia was associated with lower odds (UOR=0.20, 95% CI: 0.10–0.40, $p < 0.001$). ICU admission was not significantly associated with hyperchloremia (UOR=1.24, 95% CI: 0.54–2.86, $p = 0.607$). However, after adjustment for potential confounding factors in the multivariate logistic regression model, only sepsis duration >24 hours remained significantly associated with hyperchloremia (AOR=4.12, 95% CI: 1.62–10.48, $p = 0.003$). This indicates that patients with sepsis lasting >24 hours had approximately 4-fold higher adjusted odds of hyperchloremia compared with those with sepsis duration ≤ 24 hours. Diabetes mellitus, hypertension, dyslipidemia and anemia were no longer statistically significant after adjustment ($p > 0.05$) Shown in Table-III.

Table-I: Distribution of baseline characteristics among study participants (n=165).

Variables	n (%)
Age	
30 to 50 years	52 (31.5)
51 to 80 years	113 (68.5)
Gender	
Male	81 (49.1)
Female	84 (50.9)
Duration of sepsis	
≤ 24 hours	139 (84.2)
>24 hours	26 (15.8)
Duration of hospital stay	
≤ 7 days	48 (29.1)
>7 days	117 (70.9)
Diabetes mellitus	48 (29.1)
Hypertension	32 (19.4)

Dyslipidemia	76 (46.1)
Obesity	61 (37.0)
Anemia	74 (44.8)
ICU admission	27 (16.4)
Hyperchloremia	66 (40.0)
In-hospital mortality	33 (20.0)

Table-II. Association of demographic and clinical characteristics with hyperchloremia (n=165).

Variable	Categories	Hyperchloremia		p value
		No	Yes	
Age in Years	30 - 50	31 (31.3%)	21 (31.8%)	0.945
	51 - 80	68 (68.7%)	45 (68.2%)	
Gender	Male	49 (49.5%)	32 (48.5%)	0.899
	Female	50 (50.5%)	34 (51.5%)	
Sepsis (hours)	≤ 24	92 (92.9%)	47 (71.2%)	<0.001
	> 24	7 (7.1%)	19 (28.8%)	
Hospital stays (days)	≤ 7	30 (30.3%)	18 (27.3%)	0.675
	> 7	69 (69.7%)	48 (72.7%)	
Diabetes mellitus	Yes	38 (38.4%)	10 (15.2%)	0.001
Hypertension	Yes	27 (27.3%)	5 (7.6%)	0.002
Dyslipidemia	Yes	37 (37.4%)	39 (59.1%)	0.006
Obesity	Yes	36 (36.4%)	25 (37.9%)	0.843
Anemia	Yes	59 (59.6%)	15 (22.7%)	<0.001
ICU admission	Yes	15 (15.2%)	12 (18.2%)	0.606
In-hospital mortality	Yes	17 (17.2%)	16 (24.2%)	0.266

OR: odds ratio; CI: confidence interval; ICU: intensive care unit.

Table III. Factors associated with hyperchloremia (n=165)

Factors	Univariate logistic regression			Multivariate logistic regression		
	p-value	Un-adjusted OR	95% CI for UOR	p-value	Adjusted OR	95% CI for AOR
Sepsis duration >24 hours	< 0.001	5.313	2.086 – 13.535	0.003	4.12	1.62–10.48
Diabetes mellitus	0.002	0.287	0.131 – 0.629	0.132	0.48	0.18–1.25
Hypertension	0.003	0.219	0.079 – 0.602	0.097	0.41	0.14–1.18
Dyslipidemia	0.007	2.420	1.279 – 4.579	0.084	1.86	0.92–3.76
Anemia	< 0.001	0.199	0.099 – 0.402	0.186	0.56	0.24–1.32
ICU admission	0.607	1.244	0.541 – 2.861	-	-	-

DISCUSSION

In the present study, hyperchloremia was occurred in 40% of patients with sepsis. In-hospital mortality was 20.0% overall, and tended to be higher in the hyperchloremic versus non-hyperchloremic patients (24.2% vs 17.2%). This indicates that hyperchloremia is prevalent in sepsis, but does not necessarily influence short-term outcome. In a study by Thanekar *et al.*, 19.3% of the critically ill septic population was hyperchloremic, and no independent association was observed between hyperchloremia and major adverse kidney events within 30 days, a composite outcome comprising death, need for dialysis, or sustained loss of kidney function by Day 30, or with new or worsening acute kidney injury.¹¹

Chloride disturbances can be caused by changes in fluid composition. A large meta-analysis comparing balanced crystalloids with normal saline (NS) showed a possible benefit of balanced solutions in reducing mortality and

acute kidney injury (AKI), particularly in patients with sepsis.¹² Results from the unadjusted analysis suggest that hyperchloremia is inversely associated with diabetes mellitus, hypertension, and anemia, but these findings should be interpreted with caution. This may be due to some residual confounding factors associated with medication administration, renal handling, fluid administration, and disease severity, which also may have a protective effect. To ascertain independent associations multivariate adjustment is necessary. Iatrogenic hyperchloremia is also clinically relevant as IV therapy with chloride rich fluids can increase the serum chloride and cause hyperchloremic metabolic acidosis. The majority of *et al.* focused on chloride exposure and proper choice of fluids as key to prevention.¹³

The association with chloride and outcome is not consistent, though. The BEST-Living individual patient

data meta-analysis compared balanced crystalloids to saline in critically ill adults and stressed that treatment effects need to be interpreted in the context of the clinical situation.¹⁴ However, in a large cohort of surgical patients in an ICU, Ma *et al.* showed that serum chloride level was associated with mortality, suggesting that chloride may be a useful prognostic marker.¹⁵ In a similar study, Chen *et al.* found an association between initial chloride levels and mortality in critically ill patients suffering from acute kidney injury, which further confirmed the relationship between chloride abnormalities and renal function and disease severity.¹⁶ In the current study, hyperchloremia was a strong predictor of sepsis duration >24 hours, while age, gender, length of stay, obesity and admission to the intensive care unit (ICU) were not. These can be a result of the accumulation of treatment or a progressive physiological disturbance. In a secondary analysis of the patients with sepsis-induced hypotension, there was a lower 90-day mortality in patients initially resuscitated primarily with lactated Ringer's solution compared to saline, with residual confounding possible.¹⁷ In addition, Lei *et al.* discovered that longitudinal chloride trajectories were linked to short- and long-term mortality in critically ill sepsis patients.¹⁸

The results of this non-significant mortality association should thus be interpreted with caution. Zhao *et al.* showed that serum chloride levels have an L-shaped association with septic death, and that there is a threshold at 105 mmol/L, suggesting a more complex relationship between chloride level and risk than a linear one.¹⁹ Cao *et al.*, on the other hand, found that ICU-acquired hyperchloremia was an independent risk factor for in-hospital death, and that the risk of death went up with increasing chloride levels.²⁰ The differences indicate that the timing of measurement, the baseline chloride concentration, the subsequent change in chloride, renal function, severity of illness and fluid exposure may be more informative than a single dichotomous chloride measurement.

The strong relationships with diabetes, hypertension, dyslipidemia and anaemia should not be taken as causal. There were lower unadjusted odds of hyperchloremia with diabetes, hypertension and anemia, and higher unadjusted odds with dyslipidaemia. This may be due to confounding by medication use, renal handling, nutrition, fluid therapy or severity of illness. These would need to be independent predictors after a

multivariable analysis. The study was targeted on one of the clinically important electrolyte disturbances in sepsis and provided tertiary-care data from Karachi. Consistency of data collection was supported by consecutive recruitment, a predefined chloride threshold, early measurement of chloride and assessment of in-hospital mortality. In future multicentre prospective studies, serial chloride measurements, fluid balance, crystalloid type, renal outcomes and validated severity scores should be utilized. Hyperchloremia should be evaluated independently using multivariable models to assess whether it is an independent predictor of mortality and whether chloride-conscious fluid strategies are beneficial should be evaluated through local comparative studies between balanced crystalloids and saline.

LIMITATIONS

The study was cross-sectional and monocentric, thus limiting causal conclusions and generalizability. Longitudinal changes could not be determined by one chloride measurement. Data on type of intravenous fluid or amount of fluid, cumulative chloride exposure, renal function trajectory, vasopressor use, illness-severity scores were not available. There was limited power in the mortality analyses, and residual confounding due to lack of multivariable adjustment. Patients were identified using SIRS criteria rather than Sepsis-3 criteria, which may limit comparison with contemporary sepsis definitions.

CONCLUSION

Sepsis patients frequently developed hyperchloremia and this was significantly related to a longer duration of sepsis. Although the mortality rate was higher in the hyperchloremic, this difference was not statistically significant. Thus, serum chloride should not be used as an independent predictor of death but should be treated as a clinically relevant marker for monitoring. Prognostic value is likely to be related to chloride trajectory, renal function, severity of illness and fluid exposure.

ACKNOWLEDGEMENT

We sincerely acknowledge the support and guidance of our mentors, colleagues, and the staff of the participating hospital for their valuable assistance throughout this study.

DISCLOSURES

None

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Arika Ishtiaq: Conceptualization, study design, data collection, manuscript drafting, final approval, accountable for all aspects of publication

Shahab Abid: Supervision, methodology, critical revision for intellectual content, final approval, critical revisions, final approval, accountable for all aspects of publication

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