Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Association between serum chloride levels and 28-day mortality in geriatric septic ICU patients: A retrospective cohort study

Irem Durmus[a,*], Kubra Taskin[a], Merve Bulun Yediyildiz[a], Reyhan Fidan[b]

[a]University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, Department of Anesthesiology and Reanimation, Istanbul, Türkiye
[b]Tuzla State Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Türkiye
*Corresponding author: irem.durmus89@gmail.com (Irem Durmus)

MAIN POINTS

- Hyperchloremia in elderly septic ICU patients was found to be an independent predictor of 28-day all-cause mortality.
- The frequency of hyperchloremia was significantly higher in non-survivors than in survivors.
- In multivariate regression analysis, hyperchloremia and the APACHE II score were independently associated with mortality risk.
- Routine chloride monitoring during sepsis management may help identify high-risk patients earlier and guide individualized fluid therapy.
- Optimizing chloride balance could improve prognosis and reduce mortality in geriatric intensive care patients with sepsis.

Cite this article as: Durmus I, Taskin K, Bulun Yediyildiz M, Fidan R. Association between serum chloride levels and 28-day mortality in geriatric septic ICU patients: A retrospective cohort study. *Ann Med Res*. 2026;33(6):277–283. doi: 10.5455/annalsmedres.2025.11.344.

ABSTRACT

Aim: This study aimed to examine whether serum chloride concentrations obtained within the first 24 hours after intensive care unit (ICU) admission are associated with 28-day all-cause mortality in elderly patients with sepsis, which was defined according to Sepsis-3 criteria (suspected infection plus ≥2-point increase in SOFA score) and to explore their potential prognostic value.

Materials and Methods: This retrospective cohort study was conducted at a single center and involved 221 patients aged 65 years and older who were hospitalized in the ICU with sepsis between December 1, 2023 and May 31, 2024. Patient categorisation was based on serum chloride levels measured within the first 24 hours. Patients were categorised as hypochloremic (<95 mEq/L), normochloremic (95–110 mEq/L), or hyperchloremic (>110 mEq/L). Information on demographics, laboratory results, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores was collected. Data analysis involved the Mann-Whitney U test, the Chi-square test, and logistic regression.

Results: A total of 221 patients were evaluated, with a mean age of 80.87 ± 8.04 years. The 28-day all-cause mortality rate was found to be 67.4%. The prevalence of hyperchloremia (62.4%) was significantly higher than that of normochloremia (25.8%) and hypochloremia (11.8%). Multivariate logistic regression analysis showed that hyperchloremia was an independent predictor of 28-day mortality (OR=4.95; 95% CI, 1.51–16.21; p=0.008). A rise in the APACHE II score was found to be a highly significant predictor of mortality (p<0.001).

Conclusion: An independent association between elevated chloride levels and 28-day mortality was observed in elderly septic patients requiring intensive care. Routine monitoring of serum chloride levels and careful management of chloride load may contribute to an improved prognosis in this vulnerable patient population.

Keywords: Sepsis, Chlorides, Mortality, Critical care, Intensive care units, Aged

Received: Nov 25, 2025 **Accepted:** Jan 05, 2026 **Available Online:** Jun 25, 2026

INTRODUCTION

Sepsis represents a condition in which an infection triggers a dysregulated and maladaptive host immune response, leading to widespread inflammation [1]. This aberrant response can disrupt microcirculatory function, impair tissue perfusion and ultimately progress to multi-organ dysfunction. Clinically, a substantial proportion of affected individuals require management in the intensive care unit, and sepsis continues to be recognised as one of the primary contributors to mortality among intensive care unit (ICU) patients [2]. In this study, sepsis was defined according to the Sepsis-3 criteria, requiring suspected infection and a ≥2-point increase in the SOFA score. Geriatric patients were defined as individuals aged ≥65 years [3].

Serum chloride represents the predominant extracellular anion and is essential for multiple physiological processes, including the regulation of acid–base homeostasis, osmotic equilibrium, neuromuscular signalling and various enzyme functions [4,5]. In addition, chloride channels have been implicated in intracellular inflammatory pathways, which are known to contribute substantially to the underlying mech-

anisms of sepsis [6]. Notwithstanding chloride's vital functions, it is frequently not evaluated with the same rigour as sodium or potassium in ICU practice, resulting in its clinical importance being somewhat overlooked.

Recent evidence suggests that disturbances in serum chloride concentrations can contribute to unfavourable clinical outcomes. In septic patients, reduced chloride levels may lead to metabolic alkalosis and may be associated with increased mortality risk. Conversely, hyperchloremia has been shown to induce hyperchloremic metabolic acidosis and renal vasoconstriction, consequently impairing organ function and contributing to mortality [7, 8].

We hypothesized that serum chloride levels measured during the first 24 hours of ICU admission would be independently associated with 28-day mortality in geriatric septic patients.

This study aimed to examine how serum chloride levels, obtained during the first 24 hours of ICU admission, relate to 28-day mortality in patients with sepsis. A secondary aim was to explore whether different chloride categories (hypochloremia, normochloremia, hyperchloremia) might be useful as prognostic indicators in this population.

MATERIALS AND METHODS

Study design and ethical approval

Ethical approval for the study was obtained from the Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (Date: 20/05/2025, Approval No: 2025/08/1128). The research was conducted in accordance with the Declaration of Helsinki. This retrospective cohort investigation was performed at a single centre, the Intensive Care Unit of Tuzla State Hospital, and covered the period from 1 December 2023 to 31 May 2024.

Study population

A total of 221 individuals aged 65 years or older who were admitted to the intensive care unit with a diagnosis of sepsis were included in the study population. Patient information was retrospectively extracted from the electronic medical records. Demographic variables included age and sex. Laboratory parameters included white blood cell (WBC) count, haemoglobin level, platelet count (PLT), red cell distribution width (RDW), albumin, calcium, sodium, potassium, creatinine, lactate, C-reactive protein (CRP), and procalcitonin. In addition, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and serum chloride values obtained during the first 24 hours after ICU admission were recorded.

Inclusion and exclusion criteria

Patients were eligible for inclusion if they were 65 years of age or older, had a documented diagnosis of sepsis, and had serum chloride levels measured during the initial 24 hours of their ICU stay. Individuals without chloride measurements within this timeframe, those discharged or deceased within the first 24 hours, and those presenting with acute kidney injury prior to ICU admission were excluded from the analysis. To ensure a homogeneous cohort of elderly patients admitted for medical reasons, postoperative and trauma-related admissions were excluded.

Data collection and variables

Serum chloride levels were measured within the first 24 hours after ICU admission and recorded for all patients. The classification of patients was based on the following values: hypochloremia(<95 mEq/L),normochloremia(95–110 mEq/L), and hyperchloremia (>110 mEq/L). Each patient was categorised according to the earliest measured chloride value within the first 24 hours following admission to the ICU.

At the conclusion of the ICU stay, patients were evaluated according to two clinical outcomes: survivors and non-survivors. The principal outcome of interest was overall mortality within 28 days of ICU admission. In addition, comorbidities such as diabetes mellitus, hypertension, coronary artery disease, heart failure, chronic obstructive pulmonary disease, cerebrovascular disorders, and chronic kidney disease were documented and evaluated to determine their relationship with mortality.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test indicated that the numerical variables were not normally distributed. Accordingly, comparisons of continuous variables between groups were performed with the Mann–Whitney U test. The Kruskal–Wallis test was used for comparisons of parameters among the chloride groups, with Dunn's test applied for post hoc analyses. Categorical variables were analysed using the Chi-square test, Fisher's exact test, the Fisher–Freeman–Halton exact test, or Yates' continuity correction, when appropriate. Variables that were significant in univariate analyses were further assessed using a multivariable logistic regression model. The multivariable logistic regression model was adjusted for hyperchloremia, albumin, calcium, creatinine, lactate, C-reactive protein, procalcitonin, and APACHE II score. A p-value below 0.05 was accepted as the threshold for statistical significance. Additionally, a post-hoc power analysis for the observed association between hyperchloremia and 28-day mortality ($\alpha = 0.05$, two-tailed, confidence level 0.95) demonstrated an achieved power ($1-\beta$) of 0.99.

RESULTS

A total of 221 elderly patients diagnosed with sepsis and admitted to the ICU were included in the study, with ages ranging from 66 to 97 years. Among them, 117 (52.9%) were women and 104 (47.1%) were men. The overall mean age

https://doi.org/10.5455/annalsmedres.2025.11.344

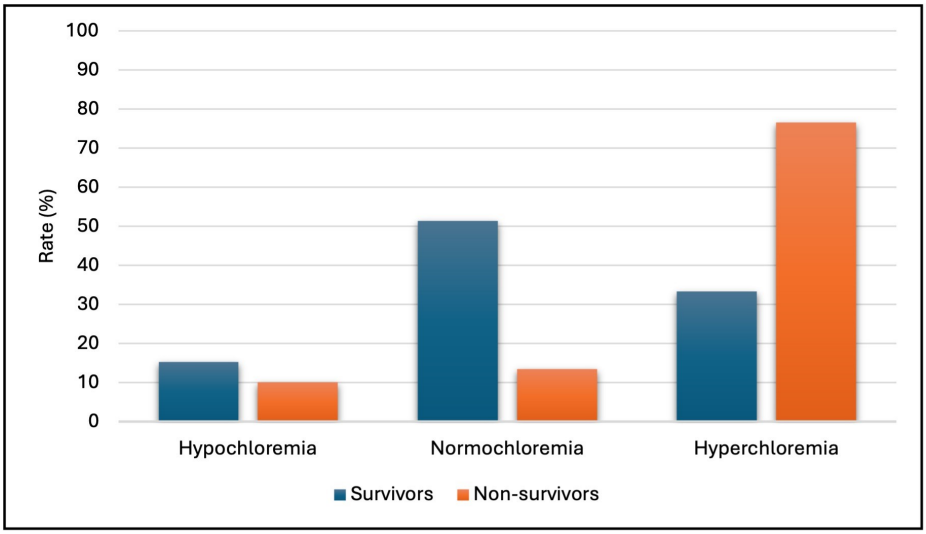

Figure 1. Distribution of survival and non-survival rates according to serum chloride levels.

Table 1. Distribution of serum chloride levels.

Chloride Level	n	%
Hypochloremia	26	11.8
Normochloremia	57	25.8
Hyperchloremia	138	62.4
Total	221	100

n = number.

of the study population was 80.87 ± 8.04 years. In total, 149 patients (67.4%) were non-survivors, while 72 (32.6%) were survivors. As shown in Table 1, hypochloremia, normochloremia, and hyperchloremia were identified in 11.8%, 25.8%, and 62.4% of patients, respectively.

No significant differences were detected between the surviving and non-surviving groups with respect to age or sex (p>0.05).

Non-survivors exhibited significantly lower albumin (p=0.001) and calcium levels (p=0.005), whereas creatinine (p=0.011), lactate (p=0.002), CRP (p=0.033), procalcitonin (p=0.009), and APACHE II scores (p=0.001) were significantly higher compared with survivors.

Serum chloride concentrations were strongly and significantly associated with mortality (p=0.001).

Chronic obstructive pulmonary disease was observed more frequently among survivors (35.4%) than non-survivors (18.4%), a difference that reached statistical significance (p=0.039).

Other comorbidities showed no significant relationship with mortality (p>0.05) (Table 2).

Hyperchloremia was more common in patients who died (76.5%) than in those who survived (33.3%) (Figure 1).

When patients were stratified according to serum chloride levels, no significant difference in age was observed among the chloride groups (p>0.05). Albumin (p=0.004) and calcium levels (p=0.006) differed significantly among the groups; both parameters were lower in the hyperchloremia group than in the hypochloremia and normochloremia groups (p<0.05). Sodium levels also varied significantly among the chloride groups (p=0.001) and were highest in patients with hyperchloremia. Similarly, APACHE II scores differed significantly between groups (p=0.001), with higher scores observed in the hyperchloremia group. No statistically significant differences were detected among the chloride groups in terms of WBC, hemoglobin, platelet count, RDW, potassium, creatinine, lactate, CRP, or procalcitonin levels (p>0.05) (Table 4).

The prevalence of comorbidities differed significantly between chloride groups (p=0.048), with a higher prevalence in the hypochloremia group than the hyperchloremia group. Chronic kidney disease was not observed in the normochloremia group, but it was significantly more frequent in patients with hypochloremia and hyperchloremia (p=0.042). Mortality rates differed significantly among the chloride groups (p=0.001), with the highest mortality observed in the hyperchloremia group; no significant difference in mortality was found between the hypochloremia and normochloremia groups (p>0.05).

In the backward stepwise logistic regression model constructed using variables that were significant in the univariate analyses (hyperchloremia, albumin, calcium, creatinine, lactate, CRP, procalcitonin, and APACHE II) the overall model reached statistical significance (p=0.001; p<0.05) and explained 83.2% of the variance (Nagelkerke R^2). The explanatory accuracy of the model was 92.8%. Hyperchloremia and APACHE II score remained independent predictors of mortality (p<0.05), with hyperchloremia increasing the odds of mortality by approximately 4.952-fold and each unit rise in APACHE II score being associated with a 1.335-fold higher mortality risk. Although lactate was not statistically significant (p>0.05), it remained in the model and was associated with a 1.329-fold increase in mortality risk (Table 3).

https://doi.org/10.5455/annalsmedres.2025.11.344

Table 2. Comparisons according to mortality.

	Survivors (n=72) Median (IQR)	Non-survivors(n=149) Median (IQR)	Total (n=221) Median (IQR)	p
Age (years)	81.5 (73-88)	81 (75-87)	81 (74-88)	0.712[1]
Sex n (%)				0.543[2]
Female	36 (50%)	81 (54.4%)	117 (52.9%)	
Male	36 (50%)	68 (45.6%)	104 (47.1%)	
WBC (×10^9/L)	11.87 (9.04-16.05)	13.2 (9.72-18.44)	12.9 (9.55-18.07)	0.109[1]
HGB (g/dL)	10.6 (8.53-11.98)	9.7 (8.3-11)	9.9 (8.4-11.55)	0.066[1]
PLT (×10^9/L)	240 (148.75-297)	211 (128.5-300)	217 (135-299)	0.232[1]
RDW (%)	51.15 (46.9-55.15)	52.3 (48.35-59.25)	52 (47.75-57.7)	0.058[1]
Albumin (g/L)	29 (24.25-31)	25 (21-29.5)	27 (22-30)	0.001*[1]
Calcium (mmol/L)	8.19 (7.81-8.51)	7.9 (7.3-8.4)	8 (7.48-8.42)	0.005*[1]
Sodium (mEq/L)	140.5 (137-145)	141 (136.5-147)	141 (137-146)	0.839[1]
Potassium (mEq/L)	3.88 (3.54-4.47)	3.96 (3.52-4.6)	3.92 (3.53-4.54)	0.476[1]
Creatinine (mg/dL)	1.01 (0.82-1.32)	1.3 (0.82-2.07)	1.19 (0.82-1.81)	0.011*[1]
Lactate (mmol/L)	1.95 (1.3-2.88)	2.5 (1.6-4.2)	2.3 (1.45-3.6)	0,002*[1]
CRP (mg/L)	131.25 (65.33-182)	152.8 (89.1-219.5)	140.3 (80.9-215.01)	0.033*[1]
Procalcitonin (ng/mL)	1.12 (0.28-4.76)	2.71 (0.71-10.15)	1.82 (0.57-9.2)	0.009*[1]
APACHE II	26 (23-32.75)	52 (44.5-56.5)	45 (32-55)	0.001*[1]
Chloride level n (%)				0.001*[2]
Hypochloremia	11 (15.3%)	15 (10.1%)	26 (11.8%)	
Normochloremia	37 (51.4%)	20 (13.4%)	57 (25.8%)	
Hyperchloremia	24 (33.3%)	114 (76.5%)	138 (62.4%)	
Comorbidities n (%)	48 (66.7%)	98 (65.8%)	146 (66.1%)	0.895[1]
Diabetes mellitus n (%)	13 (27.1%)	31 (31.6%)	44 (30.1%)	0.711[3]
Hypertension n (%)	25 (52.1%)	55 (56.1%)	80 (54.8%)	0.645[2]
Coronary artery disease n (%)	8 (16.7%)	10 (10.2%)	18 (12.3%)	0.397[3]
Conjestive heart failure n (%)	8 (16.7%)	27 (27.6%)	35 (24.0%)	0.215[3]
Chronic obstrructive pulmonary disease n (%)	17 (35.4%)	18 (18.4%)	35 (24%)	0.039*[3]
Cerebrovascular disease n (%)	9 (18.8%)	29 (29.6%)	38 (26.0%)	30.229[3]
Chronic kidney disease n (%)	3 (6.3%)	9 (9.2%)	12 (8.2%)	0.751[4]

[1]Mann Whitney U Test, [2]Chi-square test, [3]Continuity (yates) correction, [4]Fisher's Exact test *p<0.05. Continuous variables are expressed as median (IQR); categorical variables as n(%). WBC: white blood cells HGB: hemoglobin, PLT: platelet RDW:red cell distribution width CRP: C-reactive protein APACHE II: Acute Physiologic and Chronic Health Evaluation II.

Table 3. Logistic regression analysis of factors associated with mortality.

	Variables in the Equation	OR	95% CI		p
			Lower	Upper	
Step 6a	Hyperchloremia	4.952	1.512	16.219	0.008*
	Lactate	1.329	0.939	1.88	0.109
	APACHE II	1.335	1.224	1.456	0.001*

OR = Odds Ratio, CI = Confidence Interval *p<0.05. Variable(s)entered on step 1: Hyperchloramia, Albumin, Calcium, Creatinine, Lactate, CRP, Procalcitonin, APACHE II. APACHE II = Acute Physiology and Chronic Health Evaluation II CRP: C-reactive protein.

DISCUSSION

This study analyzed the association between serum chloride levels and 28-day mortality in elderly intensive care patients with sepsis. This study demonstrated that hyperchloremia was prevalent in the study population and significantly associated with mortality. Multivariate analysis demonstrated that hyperchloremia was an independent risk factor for 28-day mortality. This observation highlights the potential of hyperchloremia as an indicator of adverse outcomes in critically ill septic individuals. The notably high 28-day mortality rate observed in this study may be explained by the advanced age of the cohort and the markedly elevated APACHE II scores at ICU admission. Unlike previous studies that primarily included mixed adult ICU populations, our study focuses exclusively on geriatric (≥65 years) septic ICU patients and evaluates serum chloride concentrations obtained within the first 24 hours after ICU admission, thereby providing incremental evidence on the prognostic significance of chloride disturbances in this high-risk group. This higher mortality rate differs from that reported in several previous studies and may be partially explained by differences in patient characteristics. Our study population consisted exclusively of elderly patients admitted for medical conditions; postoperative and trauma-related cases were excluded and therefore were not represented in the cohort.

In 2011, a prospective cohort study was the first to demon-

https://doi.org/10.5455/annalsmedres.2025.11.344

Table 4. Comparison of study parameters by chloride levels.

	Hypochloremia (n=26) Median (IQR)	Normochloramia (n=57) Median (IQR)	Hyperchloremia (n=138) Median (IQR)	p
Age (years)	81 (70-86.5)	82 (73-88.5)	80.5 (75-88)	0.517[1]
Sex n (%)				0.042*[2]
Female	15 (57.7%)	22 (38.6%)	80 (58%)	
Male	11 (2.3%4)	35 (61.4%)	58 (42%)	
WBC(×10^9/L)	12,55 (9.4-15.8)	12.4 (8.8-15.4)	13.15 (9.8-18.8)	0.287[1]
HGB (g/dL)	9.15 (8.4-10.9)	10.4 (8.9-11.7)	9.85 (8.3-11.5)	0.292[1]
PLT(×10^9/L)	269 (155.5-325.8)	221 (136-298.5)	207.5 (133.8-299)	0.4021
RDW(%)	52.3 (48.4-58.9)	50.5 (46.3-54.6)	52.3 (48.4-59.2)	0.105[1]
Albumin (g/L)	29 (23.8-32.5)	28 (24-31)	25 (21-30)	0.004*[1]
Calcium (mmol/L)	8.225 (7.8-8.7)	8.12 (7.8-8.6)	7.9 (7.3-8.3)	0.006*[1]
Sodium (mEq/L)	136 (128.8-140.5)	139 (136-143)	143.5 (138-150)	0.001*[1]
Potassium (mEq/L)	4.015 (3.5-4.7)	3.91 (3.5-4.5)	3.905 (3.5-4.5)	0.782[1]
Creatinine (mg/dL)	1.235 (0.9-1.8)	1.11 (0.9-1.5)	1.25 (0.8-2.1)	0.473[1]
Lactate (mmol/L)	2.35 (1.3-3.7)	2 (1.3-3.3)	2.4 (1.6-3.8)	0.385[1]
CRP (mg/L)	149.5 (115.2-197)	119 (52.1-208.7)	146.35 (87.2-217)	0.189[1]
Procalcitonin (ng/mL)	2.355 (0.6-9.4)	1.09 (0.3-5)	2.3 (0.7-9.6)	0.108[1]
APACHE II	42 (25-52)	33 (24-44)	48 (39.8-56)	0.001*[1]
Comorbidities n (%)	22 (84.6%)	40 (70.2%)	84 (60.9%)	0.048*[2]
Diabetes mellitus n (%)	7 (31.8%)	11 (27.5%)	26 (31%)	0.910[2]
Hypertension n (%)	12 (54.5%)	24 (60%)	44 (52.4%)	0.728[2]
Coronary artery disease n (%)	0 (0%)	7 (17.5%)	11 (13.1%)	0.112[3]
Conjestive heart failure n (%)	8 (36.4%)	7 (17.5%)	20 (23.8%)	0.250[2]
Chronic obstrructive pulmonary disease n (%)	7 (31.8%)	16 (40%)	12 (14.3%)	0.005*[2]
Cerebrovascular disease n (%)	3 (13.6%)	8 (20%)	27 (32.1%)	0.126[2]
Chronic kidney disease n (%)	3 (13.6%)	0 (0%)	9 (10.7%)	0.042*[3]
Mortality n (%)	15 (57.7%)	20 (35.1%)	114 (82.6%)	0.001*[2]

[1]Kruskal Wallis Test, [2]Chi-square test, [3]Fisher Freeman Halton Exact test *p<0.05. Continuous variables are expressed as median (IQR); categorical variables as n(%).

strate an association between hyperchloremia and poorer outcomes in critically ill patients.The study reported a significant relationship between increased serum chloride levels and mortality among ICU patients [9]. Previous evidence also indicates that increased serum chloride levels predict mortality in both early and late phases. Supporting those observations, the present results show a clear relationship between high chloride levels and 28-day mortality among geriatric septic patients [10].

Aggressive fluid therapy in sepsis management frequently involves chloride-rich crystalloid solutions. However, beyond achieving hemodynamic stabilization, this approach may lead to metabolic disturbances associated with increased chloride load. Recent observational data suggest that differences in the content of resuscitation fluids may play a determining role in patient outcomes.The administration of resuscitation fluids containing low chloride or balanced crystalloids has been documented to result in a reduction in mortality [11,12]. Overall, the evidence indicates that fluid composition is an important factor shaping prognosis in critical illness, while limiting chloride excess may positively affect patient outcomes. Although we were unable to analyze specific fluid administration patterns, the observed association suggests that minimizing chloride load may benefit geriatric septic patients, aligning aligns with emerging evidence in fluid resuscitation research.

Multiple studies suggest that patients with low chloride levels experience higher mortality during sepsis. Evidence from one report further indicates that a moderate increase in chloride within 24 hours may be associated with better outcomes in those initially presenting with hypochloremia. In addition, other studies have described an L-shaped relationship between serum chloride levels and mortality, suggesting that particularly low chloride levels may be linked to worse outcomes [4]. A further study was conducted to compare the mortality rates of patients with septic shock according to their chloride status (hypochloremia, normochloremia, and hyperchloremia). Prior work has shown hypochloremia to be an independent determinant of elevated in hospital mortality [13]. In contrast, other investigators have linked early hyperchloremia with poorer outcomes, independent of metabolic or renal variables [14]. Our current findings similarly demonstrate a significant association between elevated chloride levels and mortality among older patients with sepsis.This finding suggests that both low and high chloride levels can disrupt physiological balance; however, in elderly septic patients, elevated chloride levels appear to represent a more prominent prognostic risk. The observed variations across studies may be attributed to heterogeneity in patient populations and variability in fluid therapy practices.

The relationship between hyperchloremia and mortality can be explained by several pathophysiological mechanisms. It has been demonstrated that an elevation in chloride concentra-

https://doi.org/10.5455/annalsmedres.2025.11.344

tion induces vasoconstriction at the macula densa, thereby reducing renal blood flow. Additionally, elevated chloride levels have been observed to induce vasoconstriction in renal arterioles, thereby exerting a deleterious effect on renal perfusion [15]. These mechanisms have been demonstrated to contribute to renal hypoperfusion and acidosis. Hyperchloremic metabolic acidosis resulting from chloride overload has been demonstrated to decrease myocardial contractility and impair vasopressor responsiveness [16]. As demonstrated by experimental sepsis models, elevated chloride levels have been shown to trigger proinflammatory responses [17]. Collectively, these mechanisms provide plausible physiological explanations for the negative impact of hyperchloremia on mortality.

Multivariate analysis in our study further suggested that the detrimental effect of hyperchloremia on mortality might be more pronounced in patients with higher APACHE II scores. Concomitant hyperchloremia and elevated APACHE II scores are hypothesised to result in deleterious clinical outcomes through mechanisms including an enhanced inflammatory response, renal hypoperfusion, and metabolic acidosis. This finding suggests that the prognostic impact of chloride imbalance may also be associated with disease severity.

Multiple studies involving heterogeneous ICU populations have reached similar conclusions. Hyperchloremia consistently emerged as a predictor of higher mortality in surgical and medical intensive care units and among patients with cerebral bleeding [18-20]. Our data echo these observations, adding further support to the growing recognition of serum chloride as a prognostic indicator in critical illness.

Recent research on artificial-intelligence-based clinical decision support systems has also highlighted the potential of serum chloride as a prognostic parameter. In one study, the incorporation of baseline serum chloride levels into predictive models resulted in enhanced prognostic accuracy [21]. This finding underscores that chloride is not merely a biochemical parameterbut also a clinically meaningful variable that should be considered in decision-making processes.

A notable strength of this study is its focus on geriatric patients with sepsis. Given that electrolyte imbalances may have distinct clinical consequences in elderly patients, this analysis constitutes an original contribution to the literature. Moreover, incorporating multivariate analysis and the APACHE II score into the model enhanced the reliability of evaluating independent effects on mortality.

Limitations

There are a few notable limitations to this research. Because the analysis was conducted retrospectively, some degree of observational bias or the effects of variables not captured in the dataset may persist. The absence of detailed data regarding the type, duration, and amount of fluid therapy makes it challenging to ascertain whether hyperchloremia was a cause or a consequence. This limitation impairs the ability to determine the extent to which hyperchloremia reflects underlying disease severity rather than iatrogenic factors. However, incorporation of clinical variables such as the APACHE II score, lactate, and creatinine into the model was intended to minimise this effect.

Secondly, because this investigation was conducted at a single institution, the external validity of the results may be limited. The limited sample size and relatively short data collection period may reduce the generalisability and statistical reliability of the findings; therefore, the results should be interpreted with appropriate caution. Moreover, disease severity was evaluated solely through the APACHE II scoring system; the omission of additional indices such as SOFA or SAPS II might have limited a more multidimensional assessment of disease severity.

Third, serum chloride concentrations were recorded only during the initial 24 hours after ICU admission, which prevented the analysis of temporal variations and their potential prognostic implications.

Additionally, the wide confidence interval around the adjusted odds ratio for hyperchloremia indicates imprecision in the effect estimate and therefore warrants cautious interpretation.

Lastly, because of the retrospective design, therapeutic decisions regarding fluid administration and electrolyte correction were not entirely uniform across patients.This may represent a significant confounding factor influencing chloride variability.

The absence of pathogen-specific data, detailed information regarding antibiotic modification, and subgroup comparisons across chloride categories constitutes a methodological limitation and should be considered when interpreting the study's findings.

CONCLUSION

Our findings indicate that elevated serum chloride levels correlate strongly with 28-day mortality among elderly septic patients in the ICU. Multivariate analysis revealed hyperchloremia as an independent predictor of death, with its adverse impact becoming more evident as disease severity increased. These findings suggest that routine monitoring of serum chloride levels and careful management of chloride load during fluid therapy may play an important role in improving prognosis among elderly patients with sepsis.

Ethics Committee Approval: Ethical approval for this study was obtained from the Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (Date: 20/05/2025, Approval No: 2025/08/1128).

Informed Consent: Not applicable due to the retrospective design.

https://doi.org/10.5455/annalsmedres.2025.11.344

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declared no conflicts of interest.

Author Contributions: Conceptualization: İD; Data curation: İD, KT; Formal analysis: İD; Investigation: İD, MBY; Methodology: İD; Project administration: RF; Resources: İD, MBY; Software: KT; Supervision: MBY; Validation: İD, RF; Visualization: İD; Roles/Writing - original draft: İD, KT; and Writing - review & editing: İD, MBY.

Financial Disclosure: The authors received no financial support for the research, authorship, or publication of this article.

Artificial Intelligence Disclosure: The authors declare that an artificial intelligence–based tool (ChatGPT, OpenAI, GPT-4.0) was used solely for language editing and improving the clarity and readability of the manuscript. The AI tool did not contribute to the study design, data analysis, interpretation of results, or the development of scientific conclusions. All AI-assisted content was critically reviewed and approved by the authors to ensure its accuracy, originality, and scientific integrity. The authors take full responsibility for the content of the manuscript and confirm that its use complies with the journal's ethical guidelines.

REFERENCES

1. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of hospital-treated sepsis—current estimates and limitations. *Am J Respir Crit Care Med.* 2016;193(3):259-272. doi: 10.1164/rccm.201504-0781OC.
2. Font MD, Thyagarajan B, Khanna AK. Sepsis and septic shock: basics of diagnosis, pathophysiology, and clinical decision making. *Med Clin North Am.* 2020;104(4):573-585. doi: 10.1016/j.mcna.2020.02.011.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-810. doi: 10.1001/jama.2016.0287.
4. Zhao Z, Huang F, Shen J, Lv W, Huang Y, Pan J, Shen T. L-shape association between serum chloride and 365-day mortality in critically ill patients with sepsis based on the MIMIC-IV database. Sci Rep. 2025;15(1):20391. doi: 10.1038/s41598-025-08630-x.
5. Marunaka Y. Physiological roles of chloride ions in bodily and cellular functions. *J Physiol Sci.* 2023;73(1):31. doi: 10.1186/s12576-023-00889-x.
6. Lin Z, Deng Z, Liu J, et al. Chloride channel and inflammation-mediated pathogenesis of osteoarthritis. *J Inflamm Res.* 2022;15:953-964. doi: 10.2147/JIR.S350432.
7. Oh HJ, Kim SJ, Kim YC, et al. An increased chloride level in hypochloremia is associated with decreased mortality in patients with severe sepsis or septic shock. *Sci Rep.* 2017;7(1):15883. doi: 10.1038/s41598-017-16238-z.
8. Noritomi DT, Soriano FG, Kellum JA, et al. Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. *Crit Care Med.* 2009;37(10):2733-2739. doi: 10.1097/CCM.0b013e3181a59165.
9. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. *J Crit Care.* 2011;26(2):175-179. doi: 10.1016/j.jcrc.2010.04.013.
10. Huang K, Hu Y, Wu Y, Ji Z, Wang S, Lin Z, et al. Hyperchloremia is associated with worse outcomes in critically ill stroke patients. *Front Neurol.* 2018;9:485. doi: 10.3389/fneur.2018.00485.
11. Shaw AD, Raghunathan K, Peyerl FW, et al. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med.* 2014;40(12):1897-1905. doi: 10.1007/s00134-014-3505-3.
12. Raghunathan K, Shaw A, Nathanson B, et al. Association between choice of IV crystalloid and in-hospital mortality in adults with sepsis. *Crit Care Med.* 2014;42(7):1585-1591. doi: 10.1097/CCM.0000000000000305.
13. Ruan X, Gao Y, Lai X, Wang B, Wu J, Yu X. Trimatch comparison of the prognosis of hypochloremia, normochloremia, and hyperchloremia in patients with septic shock. *J Formos Med Assoc.* 2025;124(5):426-431. doi: 10.1016/j.jfma.2024.05.012.
14. Neyra JA, Canepa-Escaro F, Li X, et al; Acute Kidney Injury in Critical Illness Study Group. Association of hyperchloremia with hospital mortality in critically ill septic patients. *Crit Care Med.* 2015;43(9):1938-1944. doi: 10.1097/CCM.0000000000001161.
15. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg.* 2012;256(1):18-24. doi: 10.1097/sla.0b013e318256be72.
16. Levy B, Collin S, Sennoun N, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. *Intensive Care Med.* 2010;36(12):2019-2029. doi: 10.1007/s00134-010-2045-8.
17. Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. *Chest.* 2006;130(4):962-967. doi: 10.1378/chest.130.4.962.
18. Song K, Yang T, Gao W. Association of hyperchloremia with all-cause mortality in surgical intensive care unit patients: a retrospective cohort study. *BMC Anesthesiol.* 2022;22(1):14. doi: 10.1186/s12871-021-01558-5.
19. Zhou D, Li T, Zhao D, et al. Increase in chloride from baseline is independently associated with mortality in intracerebral hemorrhage patients admitted to intensive care unit: a retrospective study. *J Intensive Med.* 2022;2(4):274-281. doi: 10.1016/j.jointm.2022.04.002.
20. Yılmaz H, Güney BÇ. Evaluation of the effect of hyperchloremia on the prognosis and mortality of medical intensive care patients: a single-center study. *Turk J Med Sci.* 2022;52(5):1689-1696. doi: 10.55730/1300-0144.5510.
21. Wang J, Li Q, Xie C, et al. Predicting in-hospital mortality in intensive care unit patients using Causal SurvivalNet with serum chloride and other causal factors: a cross-country study. *J Med Internet Res.* 2025;27:e70118. doi: 10.2196/70118.