SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 9
Issue: 5
Page N. 43-49
Year: 2025

Original Article www.wjahr.com

HYPERCHLOREMIA AND ITS ASSOCIATION WITH HOSPITAL MORTALITY IN SEVERE SEPSIS AND SEPTIC SHOCK PATIENTS

Ghaith Jabbar Waheed*[1] and Ibrahim Khalil Al Shemari[2]

[1]Al-Hussein Military Hospital, Ministry of Defense, Baghdad, Iraq.
[2]Baghdad- Al-Karkh Health Directorate, Baghdad, Iraq.

Article Received date: 24 February 2025 **Article Revised date:** 17 March 2025 **Article Accepted date:** 05 April 2025

***Corresponding Author: Ghaith Jabbar Waheed**
Al-Hussein Military Hospital, Ministry of Defense, Baghdad, Iraq.

ABSTRACT

Background: Electrolyte disturbances, including hyperchloremia, are frequently observed in critically ill patients with severe sepsis and septic shock. However, the association between hyperchloremia and hospital mortality remains unclear. **Aim:** This study aimed to evaluate the relationship between hyperchloremia and hospital mortality in patients with severe sepsis and septic shock. **Patients and Method:** In this prospective cohort study, 100 patients diagnosed with severe sepsis and septic shock were included. Serum chloride levels were measured at admission and after 72 hours. Based on the chloride level at 72 hours, patients were divided into two groups: hyperchloremic (Cl72 ≥110 mEq/L, N=50) and non-hyperchloremic (Cl72 <110 mEq/L, N=50). Baseline clinical and laboratory data were also recorded. **Results:** The mean age of the patients was 57.5±20.51 years. After 72 hours of admission, 50% of patients developed hyperchloremia. Compared to the non-hyperchloremic group, patients with Cl72 ≥110 mEq/L showed a significantly higher prevalence of acute kidney injury (72% vs. 20%), need for dialysis (24% vs. 4%), respiratory failure (80% vs. 40%), mechanical ventilation (72% vs. 24%), shock (76% vs. 36%), and use of vasopressors/inotropes (76% vs. 36%). Notably, the hospital mortality rate was markedly higher in the hyperchloremic group (84% vs. 28%). **Conclusion:** Hyperchloremia at 72 hours is associated with increased mortality and worse clinical outcomes in septic patients. Reducing the use of high-chloride intravenous fluids may improve outcomes in this population.

KEYWORDS: Hyperchloremia, sepsis, Septic shock, Hospital mortality, Electrolyte disturbances, Chloride.

INTRODUCTION

Hyperchloremia, defined as elevated levels of chloride ions in the blood, is a significant electrolyte disturbance commonly observed in critically ill patients, especially those with severe sepsis and septic shock. Sepsis is a life-threatening condition caused by a dysregulated immune response to infection, leading to systemic inflammation, organ dysfunction, and potentially death. Septic shock represents its most severe form, characterized by profound hypotension and multiple organ failure. In this context, hyperchloremia has garnered increasing attention due to its potential association with worse clinical outcomes, particularly hospital mortality.[1] Chloride plays an essential role in acid-base balance, blood pressure regulation, and neuromuscular function. However, excess chloride can disturb these balances, contributing to metabolic acidosis and impaired cardiovascular and immune responses.[2] One major contributor to hyperchloremia is the frequent use of 0.9% sodium chloride (normal saline) for resuscitation, which has a high chloride content. This can result in hyperchloremic metabolic acidosis, potentially exacerbating inflammation and leading to adverse outcomes in sepsis patients.[2] Evidence suggests that hyperchloremia may independently predict increased hospital mortality, acute kidney injury (AKI), and multiple organ dysfunction syndrome (MODS) in septic patients.[3] It is associated with impaired hemodynamics and a higher incidence of dialysis, respiratory failure, mechanical ventilation, and vasopressor use. These findings emphasize the need for cautious fluid management. Balanced crystalloids, which contain lower chloride concentrations, may offer safer alternatives to normal saline.[4] To evaluate sepsis severity, clinical tools such as the quick Sequential Organ Failure Assessment (qSOFA), Systemic Inflammatory Response Syndrome (SIRS) criteria, and the SOFA score are employed.[5-7] Sepsis incidence is high globally, especially in low- and middle-income countries, accounting for 11 million deaths annually.[8] In the U.S.,

over 1.7 million cases occur yearly, with high mortality rates in severe sepsis and septic shock.[9] Hyperchloremia in sepsis results from fluid resuscitation with saline, renal dysfunction, inflammatory responses, medications, and prolonged illness.[10] Diagnosis involves clinical evaluation, electrolyte panels, ABG analysis, and renal function tests.[11] Management includes using balanced fluids, correcting electrolyte and acid-base disturbances, and providing organ support, including renal replacement therapy when needed.[12,13] The aim of study to evaluate the association between hyperchloremia and hospital mortality in severe sepsis and septic shock patients.

METHOD

This prospective cohort study was conducted at Al-Imamian Al-Kadhimain Medical City in Baghdad, within the medical wards, from April 1, 2023, to March 31, 2024. It aimed to assess the impact of hyperchloremia on hospital prognosis and mortality among patients diagnosed with severe sepsis and septic shock. A total of 100 adult patients were enrolled based on the inclusion criteria: age ≥18 years, diagnosis of severe sepsis or septic shock, availability of serum chloride measurements at baseline and 72 hours, and completion of comprehensive clinical and laboratory evaluations. Patients were excluded if they had chronic kidney disease, baseline metabolic acidosis, conditions affecting chloride balance (e.g., chronic diarrhea, long-term diuretic use), initial chloride levels outside 96–110 mEq/L, incomplete records, or died within 72 hours of admission. Patients were categorized into two groups based on their 72-hour serum chloride levels: hyperchloremic (Cl72 ≥110 mEq/L) and non-hyperchloremic (Cl72 <110 mEq/L). Data were collected from patient files and included demographics, comorbidities, baseline clinical and laboratory parameters, fluid intake, use of diuretics, and hospital course. Outcomes such as acute kidney injury, dialysis need, respiratory failure, mechanical ventilation, shock, vasopressor use, and mortality were recorded. Laboratory tests included serial arterial blood gas analyses to assess acid-base status and the presence of hyperchloremic non-anion gap metabolic acidosis. The primary outcome was hospital mortality. Secondary outcomes included hospital stay duration and clinical associations with chloride levels. Statistical analysis was performed using SPSS version 26.0. Continuous variables were presented as mean ± SD or median (IQR), while categorical variables were expressed as frequencies and percentages. Logistic regression was used to assess associations, and Kaplan-Meier survival curves with log-rank tests were applied to compare survival across groups. Ethical approval was obtained from the Iraqi Scientific Council for Internal Medicine. All data were anonymized to ensure confidentiality.

RESULTS

The study included 100 participants, divided into two groups based on chloride levels: ≥110 mEq/L (n = 50) and <110 mEq/L (n = 50). Across all participants, the mean age was 57.90 years (±20.512). Gender distribution showed a ratio of 60% males to 40% females. The initial septic status revealed that 74% of participants presented with severe sepsis, while 26% presented with septic shock.

Table 1: age, baseline biomarkers and initial septic status.

Variable		Mean	Std. Deviation
Age		57.9	± 20.512
Blood urea		41.06	± 6.325
S.Creatinine		0.86	± 0.157
eGFR		90.84	± 14.586
Hemoglobin		14.14	± 1.595
WBCs count		16.03	± 5.950
Platelets		130.82	± 55.486
Serum albumin level		3.22	± 0.302
S.Chloride level on admission(Cl0) S.Chloride level after 72 hours (Cl72)		102.65 112.25	± 3.721 ±11.829
Gender	Frequency	Percent%	
Female	40	40	
Male	60	60	
Total	100	100	
Initial Septic Status	Frequency	Percent%	
Septic shock	26	26	
Severe sepsis	74	74	
Total	100	100	

Table 2 reveals a statistically significant difference in age between the two groups, with patients in the Cl72 ≥110 mEq/L group being older on average (p = 0.04). In contrast, there was no significant difference in gender distribution (p = 0.541), indicating that age, but not gender, may influence the development of hyperchloremia in septic patients. The study also examined the prevalence of various co-morbidities in

relation to chloride levels. No significant associations were observed between chloride levels and the following conditions: diabetes (p = 0.311), hypertension (p = 0.840), heart failure (p = 0.774), anemia (p = 0.269), ischemic heart disease (p = 0.454), or malignancy (p = 1.000). However, a statistically significant association was found between respiratory illness and chloride levels (p = 0.017), with a higher prevalence of respiratory disease in the Cl72 <110 mEq/L group. This suggests that respiratory comorbidity may be more common in patients with lower chloride concentrations. During the first 72 hours of hospitalization, fluid type and volume were significantly associated with chloride levels. Patients with Cl72 <110 mEq/L received more lactated Ringer's solution and oral fluids, while those with Cl72 ≥110 mEq/L received more normal saline. This pattern indicates that fluid composition plays a role in influencing serum chloride levels. In terms of initial septic status, a higher proportion of patients with Cl72 ≥110 mEq/L presented with septic shock (36%) compared to those with Cl72 <110 mEq/L (16%), implying a relationship between elevated chloride levels and more severe septic presentations. These findings collectively highlight the importance of fluid management and its potential impact on electrolyte balance and clinical outcomes in sepsis care. The analysis showed a strong association between q-SOFA scores and septic status (p < 0.001), affirming q-SOFA's value in severity stratification. Despite similar median scores, septic shock was more prevalent in the hyperchloremic group. No significant difference in hospital stay duration was found between groups (p = 0.871). This suggests chloride levels impact outcomes but not hospitalization length.

Table 2: Distribution of the two groups patients according to demographic data, Co-morbidities and some clinical parameters.

		Cl72h >= 110 mEq/L (N = 50)		Cl72h < 110mEq/L (N = 50)		p-value
Demographics			No.		No.	
Age, years, mean ± SD		60.16 ± 21.197		55.65 ± 19.757		0.04
Gender	**Female%**	36%	18	44%	22	0.541
	Male%	64%	32	56%	28	
Co-morbidities						
Diabetes % (yes/no)		(Yes: 64%)	32	(Yes: 52%)	26	0.311
		(No: 36%)	18	(No: 48%)	24	
Hypertension% (yes/no)		(Yes: 60 %)	30	(Yes: 56%)	28	0.840
		(No: 40%)	20	(No: 44%)	22	
Heart failure % (yes/no)		(Yes: 12%)	6	(Yes: 16%)	8	0.774
		(No: 88%)	44	(No: 84 %)	42	
Anemia % (yes/no)		(Yes: 4%)	2	(Yes: 12%)	6	0.269
		(No: 96%)	48	(No: 88%)	44	
Ischemic heart disease% (yes/no)		(Yes: 16%)	8	(Yes: 24%)	12	0.454
		(No: 84%)	42	(No: 76%)	38	
Malignancy % (yes/no)		(Yes: 8%)	4	(Yes: 8%)	4	1.000
		(No: 92%)	46	(No: 92%)	46	
Respiratory disease% (yes/no)		(Yes: 8%)	4	(Yes: 28%)		140.01736
		(No: 92%)	46	(No: 72%)		
q-SOFA score, median(IQR)		2(1)		2(0)		<.001
Initial septic status (severe sepsis or septic shock)		Severe sepsis (64%)	32	Severe sepsis (84%)	42	0.039
		Septic shock (36%)	18	Septic shock (16%)	8	
Diuretic, % (yes/no)		(Yes: 12.0%)	6	(Yes: 8.0%)	4	0.741
		(No: 88.0%)	44	(No: 92.0%)	46	
Fluids taken within 72hrs, median(IQR):						
Oral fluid intake(L)		1.5(3)		2.5(2)		<.001
Normal saline (L)s		8(3)		1(2)		<.001
Glucose saline		1(3)		2(4)		0.051
Lactated ringer		0.0(0)		1.0(2.5)		<.001
Dextrose water		0.0(0)		0.0(1)		0.147
Length of hospital stay days, median (IQR)		7 (14)		7 (7)		0.871

Table 3 presents an overview of the progression and outcomes associated with chloride levels (<110 mEq/L vs. ≥110 mEq/L) in patients, highlighting significant differences in various parameters. Notably, patients with chloride levels ≥110 mEq/L exhibit a higher prevalence of acute kidney injury (72% vs. 20%), leading to a substantially higher requirement for dialysis (24% vs. 4%). This observation underscores the association between elevated chloride levels and renal dysfunction, necessitating dialysis for management. Additionally, patients with chloride levels ≥110 mEq/L are more prone to respiratory failure (80% vs. 40%), requiring

mechanical ventilation (72% vs. 24%), and experiencing shock (76% vs. 36%) and the need for vasopressors/inotropes (76% vs. 36%) compared to those with lower chloride levels. Importantly, the mortality rate is markedly higher among patients with chloride levels ≥110 mEq/L (84% vs. 28%).

Table 3: Progression and outcomes in relation to chloride levels.

Progression and Outcome		Cl_{72}< 110 n(%)	Cl_{72} >=110 n(%)	Total	P-Value
Acute kidney injury	Yes	10(20%)	36 (72%)	46%	
	No	40(80%)	14(28%)	54%	
Dialysis	Yes	2(4%)	12(24%)	14%	
	No	48(96%)	38(76%)	86%	
Respirator y failure	Yes	20(40%)	40(80%)	60%	
	No	30(60%)	10(20%)	40%	
Need for mechanical Ventilation	Yes	12(24%)	36(72%)	48%	
	No	38(76%)	14(28%)	52%	<0.01
Shock	Yes	18(36%)	38(76%)	56%	
	No	32(64%)	12(24%)	44%	<0.01
Need for vasopressors/in otropes	Yes	18(36%)	38(76%)	56%	<0.01
	No	32(64%)	12(24%)	44%	
Need for blood	Yes	8(16%)	12(24%)	20%	0.454
	No	42(84%)	38(76%)	80%	
Fate (Recovery/ Mortality)	Mortality	14(28%)	42(84%)	56%	
	Recovery	36(72%)	8(16%)	44%	<0.01

As demonstrated below in *Table 4*, reflecting the adverse impact of elevated chloride levels on patient outcomes. Overall, the findings underscore the critical role of chloride levels in predicting adverse outcomes.

Table 4: Logistic Regression Analysis of Mortality/Recovery in the two groups.

Variable	p- value	Odds Ratio	95% C.I. Lower	95% C.I. Upper
Hyperchloremia	**<0.001**	0.037	0.010	0.135
Gender	**0.072**	3.311	0.897	12.227
Age	**<0.001**	0.932	0.900	0.965
Initial Septic Status (Severe Sepsis orSeptic Shock)	**0.715**	0.786	0.217	2.852

The analysis revealed that hyperchloremia (Cl ≥110 mEq/L) was strongly associated with increased mortality, with an odds ratio of 0.037 ($p < 0.001$) and a 95% CI of 0.010–0.135. Although female participants showed a higher likelihood of recovery (OR = 3.311), this was not statistically significant ($p = 0.072$). Older age was significantly linked to higher mortality ($p < 0.001$). Additionally, septic shock was associated with worse outcomes compared to severe sepsis. Overall, lower chloride levels and potentially female gender may contribute to reduced mortality risk. As in fig 1, 2.

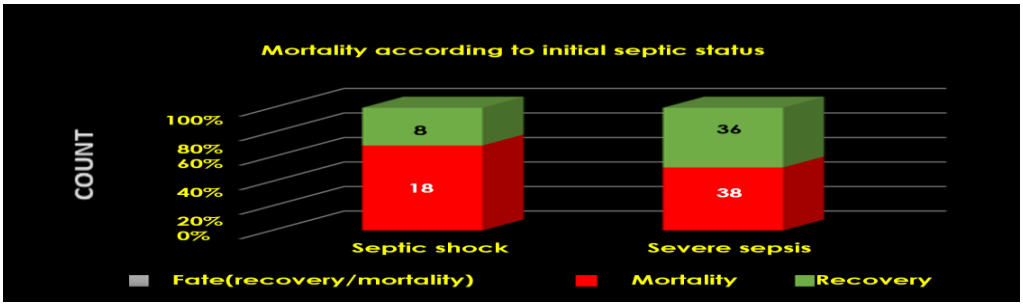

Figure 1: Mortality according to initial septic status.

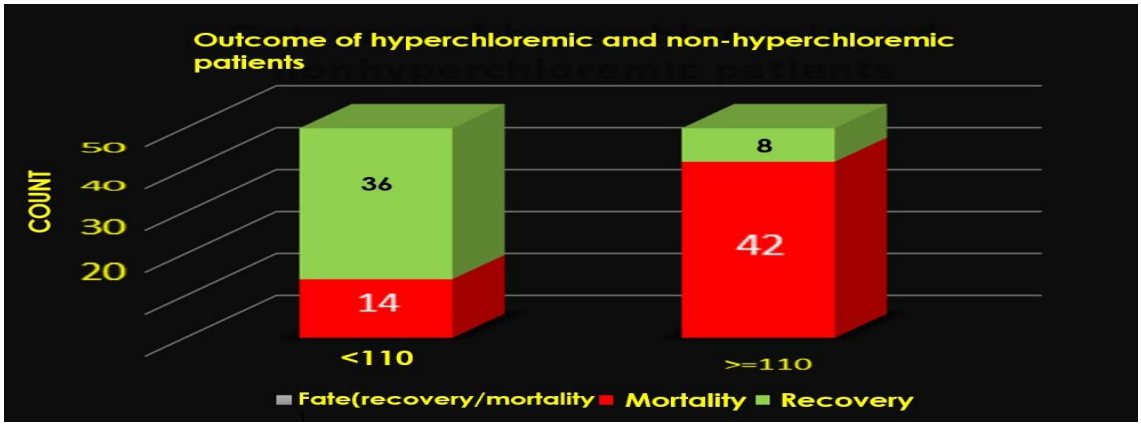

Figure 2: Mortality of hyperchloremic and non-hyperchloremic patients.

Chloride levels measured after 72 hours show a statistically significant association with mortality prediction ($p < 0.01$). While demonstrating relatively high sensitivity and specificity, chloride levels alone may not fully capture mortality risk. Their prognostic value is enhanced when combined with other clinical parameters for more accurate and comprehensive patient assessment. As in table 5.

Table 5: Agreement (sensitivity and specificity) for chloride level to predict mortality.

	p-value	95% C.I.		sensitivity	specificity	PPV	NPV
		Lower	Lower				
Cl level after 72hr	<0.01	0.010	0.135	75%	81.8%	84%	72%

The findings indicate a strong link between NAGMA and increased mortality in the Cl72 ≥110 mEq/L group. Patients who developed NAGMA had a significantly higher mortality rate (89.5%) compared to those who did not (67%), highlighting NAGMA as a potential contributor to worse outcomes in hyperchloremic patients. As in table 6.

Table 6: Association between developing NAGMA (non-anion gap metabolic acidosis) and mortality rates.

	Developed NAGMA: N(%)	Fate : N(%)
Group Cl_{72} >=110 (n=50)	Yes: 38 (76%)	Mortality: 34 (89.5%)
		Recovery: 4 (10.5%)
	No: 12 (24%)	Mortality: 8 (67%)
		Recovery: 4 (33%)

** 1 NAGMA : Non-anion gap metabolic acidosis*

DISCUSSION

This study examined the influence of hyperchloremia on clinical outcomes and hospital mortality in patients with severe sepsis and septic shock. A key finding was the statistically significant association between older age and elevated serum chloride levels at 72 hours (Cl72 ≥110 mEq/L), with a p-value of 0.04. This implies a higher susceptibility among older patients to developing hyperchloremia, which aligns with Shaw et al. (2014), who suggested age-related physiological changes such as diminished renal function and altered fluid balance as contributing factors.[14] Gender distribution showed no significant difference between groups ($p = 0.541$), supporting Raghunathan et al. (2015), who found no gender-based chloride level differences among septic patients.[15] In terms of co-morbidities, no significant associations were observed between chloride levels and diabetes, hypertension, heart failure, anemia, ischemic heart disease, or malignancy. However, a significant relationship was found with respiratory illness ($p = 0.017$), with a higher prevalence in patients with Cl72 <110 mEq/L. This contrasts with Yunos et al. (2012), who found no notable link between respiratory disease and chloride levels, possibly due to differences in patient severity and settings.[16] Initial septic status varied significantly between groups. Those with Cl72 ≥110 mEq/L had a higher incidence of septic shock (36% vs. 16%), while those with Cl72 <110 mEq/L had more cases of severe sepsis (84% vs. 64%), highlighting a link between high chloride levels and sepsis severity. Semler et al. (2018) similarly observed more frequent hyperchloremia in septic shock, suggesting a worsening

role for chloride excess.[17] Fluid type also impacted chloride levels, with the hyperchloremic group receiving more normal saline, whereas those with lower chloride levels received more lactated Ringer's solution, supporting the SPLIT trial by Young et al. (2015), which emphasized the impact of fluid composition on patient outcomes.[18] Clinical outcomes showed that hyperchloremia was significantly associated with higher rates of acute kidney injury (72% vs. 20%), dialysis need (24% vs. 4%), respiratory failure (80% vs. 40%), mechanical ventilation (72% vs. 24%), shock (76% vs. 36%), and vasopressor/inotrope use (76% vs. 36%). These findings are consistent with McCluskey et al. (2013), who linked hyperchloremia with increased risks of renal dysfunction and respiratory complications.[19] Notably, mortality was much higher in the hyperchloremic group (84% vs. 28%), reinforcing Kellum et al.'s (2018) conclusion that elevated chloride levels are linked to increased mortality in septic patients.[20] Although median q-SOFA scores were similar, sepsis severity was significantly different ($p < 0.001$), affirming q-SOFA's value as a prognostic tool, as emphasized by Semler et al. (2018).[17] There was no significant difference in hospital stay duration between groups ($p = 0.871$), suggesting that chloride levels influence outcomes but not hospitalization length. Shaw et al. (2014) suggested that hospital stay is more influenced by underlying conditions and treatment strategies.[14] Logistic regression analysis revealed a strong inverse relationship between hyperchloremia and recovery (OR = 0.037, $p < 0.001$), echoing Yunos et al. (2012) regarding hyperchloremia's negative prognostic value.[16] Septic shock further increased mortality risk compared to severe sepsis, affirming the importance of initial sepsis severity in outcome prediction, as noted by Raghunathan et al. (2015).[15]

CONCLUSION

Our study confirms that elevated chloride levels in septic patients are linked to greater illness severity, complications, and mortality. Consistent with prior research, high-chloride fluids should be avoided in favor of balanced crystalloids like lactated Ringer's. Hyperchloremia developing within 72 hours is especially associated with poor outcomes. Early fluid management adjustments may improve survival rates.

REFERENCES

1. Filis C, Vasileiadis I, Koutsoukou A. Hyperchloraemia in sepsis. Ann Intensive Care, 2018 Mar 27; 8(1): 43.
2. Chatterjee R, Garg AK. Sodium and Chloride Balance in Critically Ill Patients. In: Chatterjee R, editor. Rational Use of Intravenous Fluids in Critically Ill Patients. Cham: Springer International Publishing, 2023; 459–80.
3. Yilmaz 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): 1682–8.
4. Semler MW, Kellum JA. Balanced Crystalloid Solutions. Am J Respir Crit Care Med., 2019 Apr 15; 199(8): 952–60.
5. Guirgis FW, Puskarich MA, Smotherman C, Sterling SA, Gautam S, Moore FA, et al. Development of a simple sequential organ failure assessment score for risk assessment of emergency department patients with sepsis. J Intensive Care Med., 2020 Mar; 35(3): 270–8.
6. Dobson PF, Muller K, Balogh ZJ. Systemic Response to Injury. In: Balogh ZJ, editor. Textbook of Emergency General Surgery: Traumatic and Non-traumatic Surgical Emergencies. Cham: Springer International Publishing, 2023; 91–106.
7. Liang H, Yan J. Infection and Sepsis. In: Liang H, editor. Explosive Blast Injuries: Principles and Practices. Singapore: Springer Nature Singapore, 2023; 227–52.
8. Sepsis. World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/sepsis
9. Yeh P, Pan Y, Sanchez-Pinto LN, Luo Y. Hyperchloremia in critically ill patients: association with outcomes and prediction using electronic health record data. BMC Med Inform Decis Mak., 2020 Dec; 20: 1–10.
10. Pfortmueller CA, Uehlinger D, von Haehling S, Schefold JC. Serum chloride levels in critical illness—the hidden story. Intensive Care Med Exp., 2018 Dec; 6: 1–4.
11. Badawy FA, Ali AA, Esmail NS, HelmyAbdelhady AH. Hyperchloremia in Critically Ill Patients in ICU. Egypt J Hosp Med., 2022 Jan 1; 86(1): 532–7.
12. Hammond DA, Lam SW, Rech MA, Smith MN, Westrick J, Trivedi AP, et al. Balanced crystalloids versus saline in critically ill adults: a systematic review and meta-analysis. Ann Pharmacother, 2020 Jan; 54(1): 5–13.
13. Arzapalo MA. Association of elevated levels of plasma chloride, in severity and mortality, in adult patients in the ICU. Crit Care, 2015 Jan 1; 19(Suppl 1): P360.
14. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization following acute kidney injury in critically ill patients. Kidney Int., 2014; 85(4): 695–702.
15. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med., 2015; 43(7): 1589–97.
16. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA., 2012; 308(15): 1566–72.
17. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med., 2018; 378(9): 829–39.
18. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute

kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA, 2015; 314(16): 1701–10.
19. McCluskey SA, Karkouti K, Wijeysundera DN, et al. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg., 2013; 117(2): 412–21.
20. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl., 2012; 2: 1–138.