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ORIGINAL ARTICLE

Serum Chloride Fluctuation and its Association to Mortality in Critically Ill Patients

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ABSTRACT

Background: Previous research found that serum chloride is an independent predictor of hospital mortality; its increase within 48 hours of admission was linked to a higher percentage of 0.9% saline administration. Furthermore, the number of days that a patient survived was negatively connected with the extent of the serum chloride elevation. So we aimed to predict the outcome among critically ill patients admitted to the surgical intensive care unit in Zagazig University Hospitals and its association with serum chloride fluctuations on admission and within 5 days of intensive care unit stay.

Methods: This prospective cohort study was conducted on 300 critically ill patients with an age over 18 years old in the Surgical Intensive Care Unit (SICU), Faculty of Medicine, Zagazig University hospitals. Serum chloride level was measured on admission, 3rd day, and 5th day. According to chloride level on admission, the patients were classified into 3 groups: Group 1 included patients with chloride levels <95 mEq/L, Group 2 included patients with chloride levels 95-105 mEq/L, and Group 3 included patients with chloride levels > 105 mEq/L.

Results: Longer periods of stay in the intensive care unit were correlated with higher serum chloride levels at admission (24.33 ± 26.87 days). On ICU admission, patients with hypochloremia had a high death rate (19.3%). Positive fluctuation of serum chloride after admission was linked to a high mortality rate (11.4%).

Conclusion: Changes in the serum chloride level endanger the clinical outcome of critically ill patients in the form of longer periods of ICU stay and higher rates of mortality.

Keywords: Chloride Fluctuation, Mortality, Critically ill, Hyperchloremia, Hypochloremia.

INTRODUCTION

Changes in serum electrolytes have a significant impact on health and are considered a serious challenge in therapeutic practices. These substances support the preservation of homeostasis in the human body **[1].**

Chloride ions are the most common anions in the extracellular fluid. The stomach's production of hydrochloric acid, the preservation of the acid-base equilibrium, and the control of cellular electrolytes are all major physiological processes in which chloride ions play a major part **[2].**

Dyschloremia means chloride levels outside the normal range (96-106 mmol/L). Serum chloride levels below 96 mmol/L are typically considered hypochloremia, while values beyond 106 mmol/L are typically considered hyperchloremia; however, the exact description of each condition differs based on the laboratory in question. Chloride concentrations are quite sensitive to dilution or plasma contraction and do interact strongly with the body's water content **[3].**

Doctors frequently undervalue the impact of dyschloremia on clinical practice, despite the fact that chloride is one of the primary electrolytes included in the basic chemistry panel. One of the frequent electrolyte disorders, hospital-acquired

dyschloremia, accounts for 30% and 40% of hospital stays **[4].**

Most cases of hypochloremia are commonly obtained from the community. Hyperchloremia is frequently developed in hospitals. During their hospital stay, patients who initially have normochloremia may eventually acquire dyschloremia **[4].**

Chloride homeostasis changes that are developed in the hospital may be a consequence of medical treatments or illnesses. The administration of chloride-rich crystalloids is one of the most common causes of iatrogenic hospital-acquired hyperchloremia, particularly in severely ill patients. **[5].**

The most often used crystalloid fluid is normal saline because it is inexpensive and easily accessible, yet it contains 154 mEq/L of supraphysiologic amounts of chloride. On the other hand, more balanced crystalloids, such as Ringer's lactate, Hartmann's solution, and Ringer's acetate, have greater physiologic chloride concentrations (98–112 mEq/L). A growing quantity of clinical trials have been carried out to examine the impact of different types of crystalloids on the results obtained **[6, 7].**

While the concentration of sodium in 0.9% sodium chloride (0.9% NaCl) is near to that of sodium plasma (154 vs. 135–145 mmol/L, respectively), the concentration of chloride in 0.9% NaCl is more than that of chloride in plasma (154 vs. 95–105 mmol/L, respectively). Therefore, a significant load of chloride is infused when large doses of 0.9% NaCl are given to patients in septic shock; this can lead to hyperchloremia and, in turn, metabolic acidosis. Also, this effect has been observed in animal models, healthy individuals, and postoperative patients **[8, 9].**

METHODS

This prospective cohort study was carried out at Zagazig University Hospitals' Faculty of Medicine's Surgical Intensive Care Unit (SICU) during the period from 1st of August 2023 to 31st. In January 2024, 300 patients aged between 18 and 70 years old attended SICU and were expected to stay 5 days or more. The study was approved by the ethical committee of the faculty of medicine at Zagazig University (IRB number 9705-24-8-2022).

Inclusion Criteria:

- Critically ill patients (any patient who has a life-threatening multisystem process that can result in significant morbidity or mortality).
- Patients aged more than 18 years old.
- Both sexes.
- Duration of stay in ICU: 5 days or more continuously.

Exclusion Criteria:

- Referral from other hospitals or other ICU units.
- If a patient was discharged and then readmitted to the ICU two or more times during the study period.

Serum chloride level was measured on admission, 3rd day, and 5th day after admission. The patients were divided into 3 groups according to serum chloride level on admission: Group 1 included patients with serum chloride levels less than 95 mEq/L; Group 2 included patients with serum chloride levels 95-105 mEq/L; and Group 3 included patients with serum chloride levels more than 105 mEq/L.

Other data collection included age, sex, causes of ICU admission, comorbidities, length of stay in the ICU, and 30-day mortality rates.

Laboratory investigations included measurements of blood gases, anion gap, strong ion difference, serum potassium, and serum sodium levels.

Sample Size:

Assuming the total number of cases admitted and stayed 5 days in one month were 50 patients in the surgical intensive care unit at the Zagazig University Hospital's Faculty of Medicine, so total patients in the study's six-month duration will be 300 patients.

Patients were divided according to serum chloride level at admission into three groups:

Patients hospitalized in the intensive care unit (ICU) with serum chloride levels less than 95 mEq/L were included in Group 1, as were those with levels between 95 and 105 mEq/L, who were allocated to the second group, and patients with levels greater than 105 mEq/L were allocated to the third group.

Fluctuations in chloride during the 5 days after ICU admission (main independent variable):

The initial serum chloride level measured was chosen for this investigation's baseline chloride to be within 24 hours of ICU admission. The differences between the highest and minimum values of serum chloride and the baseline level of serum chloride, respectively, were measured in the third and fifth days following ICU admission **[10].** Positive fluctuation is considered when the serum chloride level on the 5th day is more than its level on the 1st day of admission, while negative fluctuation is considered when the chloride level on the 5th day is less than its level on the 1st day.

Outcome:

- Primary outcome: 30-day mortality.
- Secondary outcome: ICU stay length in days.

STATISTICAL ANALYSIS

All of the data were collected, tabulated, and statistically analyzed using SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA). The Cox regression models, the Mann-Whitney U test, the Student t-test, the Spearman's correlation analysis, the Chi-square test, the one-way ANOVA test, and the Kruskall-Wallis test were among the tests that were employed.

RESULTS

A total of 300 participants (147 male (49%), and 153 female (51%), were included in the study (Table S1), with a mean age of 51.29 ± 10.77 years. As regarding comorbidities, nearly half of the cases 144 (48%) were hypertensive, about 108 (36%) were diabetic, 109 oncology patients represented 36.3%, about 55 (18.3%) had central nervous system diseases (CNS), 42 (14%) had ischemic heart disease (IHD), 57 (19%) complained of chronic kidney disease (CKD), chronic pulmonary diseases were found in 42 patients (14%) of cases, and 75 (25%) of them need surgical intervention (Table S2S3). In terms of clinical diagnosis, 69 cases were diagnosed by respiratory disorders, accounting for almost 23% of cases, 45 cases by sepsis for 15% of cases, and 43 cases by acute renal injury for 14.3% of cases (Table S3).

The length of stay in ICU was 15.46 ± 14.05 days and the mortality rate was 11%. The serum chloride level for all patients on admission was 97.35 ± 6.49 mEq/L, and on the 3rd day and 5th days, the serum chloride level was 97.41 ± 6.35 and 97.82 ± 6.13, respectively, with no significant difference between these levels. (Table 1).

Within the studied groups, there was a statistically significant difference in terms of age and sex; group 3's mean age was much lower than group 2's. Additionally, group 3 participants' mean number of ICU stay days was statistically significantly longer than group 2 members (Table 1).

Regarding Spearman's correlation analysis, as shown in Table (2), the anion gap, sodium level, and strong ion difference all showed a positive, substantial connection with ICU stay. Additionally, there was a substantial inverse relationship between potassium level and ICU stay. There was an inverse relationship between ICU stay and chloride level but not significant (Table 2).

Between the studied groups, there was only a statistically significant difference in the CO2 level, but there was a statistically highly significant difference in the sodium level, HCO3, and strong ion difference among the studied groups. (Table 3).

There was a statistically significant difference regarding the 30-day mortality rate in the studied groups. There was a significant increase in mortality rate in group 1 when compared to group 2 (P< 0.019) (Table 4). Regarding chloride fluctuation, cases were classified into the positive fluctuation group 158 cases (52.7%), and the negative fluctuation group 142 cases (47.3%) (Table 5).

When comparing the mean amount of fluctuating chloride between the two groups, there was a statistically significant difference. Additionally, there was a statistically significant difference in the values of the anion gap and a strong ion difference between the two groups mean values on admission and SID mean value on the 5th day, but there was only a significant difference regarding the anion gap between the two groups on the 3rd day (Table 6). Mortality rate increased in group 1 (positive fluctuation), but this increase was not significant (Table 7).

Table 1: Demographic data and ICU stay of the studied groups

Variable		Serum chloride level (mE/L)					Post hoc
		Group 1 (<95)(n=78)	Group 2 (95-105) (n=198)	group 3 (>105) (n=24)	Tests		
					Test	*P* value	
Age (years) Mean±SD		55.8 ± 5.6	51.2 ± 9.9	36.8 ± 16.4	34.9	**<0.001***	**P1=0.001*** **P2<0.001*** **P3<0.001***
Sex	Female	N 30	111	12	18.9	**<0.001***	-----
		% 38.5	56.1%	50%			
	Male	N 48	87	12			
		% 61.5%	43.9%	50.0%			
ICU stay (Days) Mean ± SD Median (IQR)		**16.78 ± 13.87 10 (8-25)**	**13.86 ± 11.27 9 (7-15)**	**24.33 ± 26.87 14 (8-28)**	6.401 (k)	**0.041**	P1=0.083 P2=0.392 **P3=0.032**

ANOVA Test (f), Chi-Square Tests, Kruskal-Wallis Test (k), P1 = group 1 vs group 2, P2 = group 1 vs group 3, and P3 = group 2 vs group 3. Data were represented in the form of mean ± SD and median. P value considered significant when < 0.05 and highly significant when < 0.001

Table 2: Correlation between ICU stay and on-admission different parameters

Variables		**ICU stay (days)**
Serum chloride	r	-0.054
	p	0.348
K	r	**-.191**
	p	**0.001****
Na	r	**.140**
	p	**0.015**
PH	r	-0.021
	p	0.712
Anion gap	r	**0.142**
	p	**0.014**
Strong ion difference	r	**0.117**
	p	**0.043**

The correlation coefficient ***r*** is a unit-free value between -1 and 1. Statistical significance is indicated with a p-value. The closer ***r*** is to zero, the weaker the linear relationship. Positive ***r*** values indicate a positive correlation, where the values of both variables tend to increase together. Negative ***r*** values indicate a negative correlation, where the values of one variable tend to increase when the values of the other variable decrease. P value was considered to be significant when < 0.05 and highly significant when < 0.001

Table 3: Laboratory investigations in the studied groups

Variable	**Serum chloride level (mEq/L)**			**Tests**		**Post hoc**
	Group1 (<95)(n=78)	**Group 2 (95-105) (n=198)**	**Group 3 (>105) (n = 24)**	***Test***	***P* value**	
Potassium level (mEq/L) Mean ± SD Range	4.08 ± 1.38 (1.84-6.9)	4.02 ± 0.91 (2.1-6.4)	3.56 ± 0.42 (3.2-4.5)	2.412	0.091	P1=0.657 **P2=0.033** **P3=0.041**
Sodium level (mEq/L) Mean ± SD Range	130.97 ± 9.24 (110-143)	135.68 ± 5.81 (122-151)	140.5 ± 2.89 (135-145)	22.967	**<0.001***	**P1<0.001*** **P2<0.001*** **P3=0.001***
PH Mean ± SD Range	7.36 ± 0.08 (7.15-7.53)	7.36 ± 0.07 (7.12-7.51)	7.33 ± 0.05 (7.24-7.39)	1.444	0.238	P1=0.704 P2=0.097 P3=0.119
CO_2 (mmHg) Mean ± SD Median (IQR)	47.11 ± 56.62 (23-387)	33.05 ± 5.76 (22-55.7)	33.76 ± 8.12 (23-64)	6.585	**0.002**	**P1<0.001*** P2=0.052 P3=0.910
HCO_3 (mEq/L) Mean ± SD Range	23.14 ± 5.46 (14-36)	20.06 ± 4.44 (9-30.8)	18.4 ± 3.78 (11.6-22.6)	15.394	**<0.001***	**P1<0.001*** **P2<0.001*** P3=0.104

Variable	Serum chloride level (mEq/L)			Tests		Post hoc
	Group1 (<95)(n=78)	Group 2 (95-105) (n=198)	Group 3 (>105) (n = 24)	*Test*	*P* value	
Anion gap (mEq/L) Mean ± SD Range	22.25 ± 6.98 (6.4-37.9)	20.45 ± 8.13 (2.2-37.7)	18.53 ± 2.89 (14.4-27.6)	2.729	0.067	P1=0.076 **P2=0.036** P3=0.241
Strong ion difference (mEq/L) Mean ± SD Range	41.32 ± 5.66 (30-52)	36.49 ± 6.81 (22-49)	33.38 ± 3.02 (29-39)	21.983	**<0.001***	**P1<0.001* P2<0.001* P3=0.023**

ANOVA Test (f), Kruskal-Wallis Test (k), P1 = group 1 vs group 2, P2 = group 1 vs group 3, and P3 = group 2 vs group 3. Data were represented in the form of mean ± SD and median. A P value is considered significant when < 0.05 and highly significant when < 0.001

Table 4: 30 day's mortality rate between the studied groups

Variables	Group 1 (<95) (n = 78)	Group 2 (95-105) (n = 198)	Group 3 (>105) (n = 24)	P value	P between groups	OR (CI)
Died	15 (19.3%)	18 (9.1%)	0	0.011* (X^2)	Ref (cl level 95-105)	
Survived	63 (80.7%)	180 (90.9 %)	24 (100%)		**P1=0.019***	2.38 (1.13-5)
					P2=0.123	1.13 (1.08-1.19)

(X^2) chi-square test, (OR) Odds ratio, (CI) Confidence interval, P1= group 1 vs group 2, P2= group 2 vs group 3.

Table 5: Classification of patients according to serum chloride fluctuation of the studied group (n = 300):

Study group (n=300)			
Category		**No.**	**%**
Chloride fluctuation	Positive fluctuation (0-20) (mE/L)	158	52.7
	Negative fluctuation (-1 to -16) (mEq/L)	142	47.3

Table 6: Age and laboratory investigation in the two groups of serum chloride fluctuation

Variable	Serum chloride fluctuation (mEq/L)		Tests	
	Positive (n=158)	Negative (n=142)	*test*	*P* value
Age (years)	52.04±9.92	50.45±11.63	1.281	0.201
Chloride level difference (mE/L)**	5.55±3.63 5 (4-7)	-5.18±4.42 -3 (-7- -2)	23.051	**<0.001***
Anion gap on admission (mE/L)	22.78±7.51	18.53±7.07	5.209	**<0.001***
Anion gap at 3rd day (mE/L)	16.85±7.19	18.44±5.11	-2.194	**0.029**
Anion gap at 5th day (mE/L)	17.23±6.31	18.45±5.12	-1.819	0.070
Strong ion difference on admission (mE/L)	39.82±6.21	34.92±6.37	6.745	**<0.001***
strong ion difference at 3rd day (mE/L)	36.35±5.05	37.13±5.27	-1.318	0.189
strong ion difference at 5th day (mE/L)	35.09±4.56	37.84±5.7	-4.621	**<0.001***

Independent t Samples Test (data represented in the form of mean ± SD). **Chloride level difference between the 5th-day mean levels and on-admission mean levels

Table 7: length of stay in ICU and 30-day mortality rates in the two groups of serum chloride fluctuation

Variable			Serum chloride fluctuation (mEq/L)		Tests	
			Positive(n=158)	Negative (n=142)	*Test*	*P* value
ICU stay (Days)			15.09 ± 11.87	15.86 ± 16.16	-1.04	0.297
Survival	**Died**	N	18	15	0.053	0.819
		%	11.4%	10.6%		
	Survived	N	140	127		
		%	88.6%	89.4%		

Chi-Square Tests

DISCUSSION

The demographic characteristics of the studied group included a total of 300 participants (49% male, 51% female) admitted to the surgical intensive care unit and stayed more than 5 days.

On admission, about 23% of cases were diagnosed with respiratory diseases, 15% were diagnosed with sepsis, 14.3% were diagnosed with acute kidney injury, 10.3% of patients showed CNS disorders and head injuries and only 8% had chronic liver diseases.

In the current study, the serum chloride level on admission was 97.35 ± 6.49 mEq/L, and there was no significant difference in chloride level along the days of the study. By contrast, a previous study by **Kim et al., 2019 [10]** reported that the chloride level on admission was 103.7 ± 5.6 mEq/L.

Another study by **Thongprayoon et al., 2020 [4]** reported that the chloride level on admission was 103 ± 5 mEq/L.

Admission serum chloride is affected by disease categories; most cardiovascular admissions had hypochloremia due to frequent diuretics use, and the majority of respiratory disease-related admissions were hypochloremic, which may have been caused by some compensatory metabolic alkalosis in the context of ventilatory insufficiency **[11].**

23% of patients in this study were admitted with respiratory diseases and this is one of the causes of hypochloremia.

On the other hand, hyperchloremia in critically ill patients may occur secondary to regular anion gap acidosis or infusion of fluids containing high amounts of chloride **[12]**

In this study, the acid-base profile was assessed in the hyperchloremic group (group 3), and we found that there was a significant decrease in HCO_3, anion gap, and strong ion difference levels when compared with the other two groups; this result is similar to that found by **Thongprayoon et al., 2017 [11].**

In the current study regarding 30-day mortality, 267 (89%) survived while only 33 (11%) patients died. The mean ICU length of stay was 15.46 ± 14.05 with a median of 9 (7-22) days.

With respect to the length of stay in the intensive care unit, the patients in the hyperchloremic group had the longest duration with a mean of 36.8 ± 16.4 days, while those in the hypochloremic group had a mean of 16.78 ± 13.87 days, and the least ICU stay period was among the normochloremic group with mean days of 13.86 ± 11.27.

This result is similar to that found by **Thongprayoon et al., 2017 [11]**, who stated that there was a noteworthy correlation between the length of stay in the intensive care unit and the level of chloride.

Patients in this study spent 15.46 ± 14.05 days in the intensive care unit; however, in another study, the duration of stay was 3.4 ± 10.6 days as reported by **Kim et al., 2019 [10]** and a median of 5 (3–8) days as found by **Thongprayoon et al., 2020 [4].**

Length of stay in ICU can be affected by multiple variables and chronic illnesses of patients in severe conditions.

In this study, the mortality rate increased significantly in the hypochloremic group (group 1). Thegroups. The mortality rate in the hyperchloremic group (group 3) was 0% as this group included only 24 patients with the youngest mean age when compared with the other two groups This result wasn't in accordance with a previous study by **Thongprayoon et al., 2020 [4],** who, irrespective of the primary disease and coexisting condition, discovered a link between higher serum chlorine levels and hospital death.

On the other hand, **Oh et al. (2017) [13]** found that an increase in chloride levels was linked to a lower

death rate in hypochloremic individuals who had septic shock and sepsis.

According to earlier research, hypochloremia at the time of ICU admission was discovered to be a risk factor for death, which is in line with our findings **[14, 15]**.

Zhu et al., 2022 [16] discovered that among critically sick patients with acute kidney damage, lower serum chloride levels were linked to an increased risk of death in the ICU and hospital.

Zhu et al.'s 2022 [16] study was concerned with patients who had acute kidney injury, unlike our study, which studied variant groups of patients; among them, 14% only had acute kidney injury.

Regarding chloride fluctuation, the mortality rate increased in the positive fluctuation group, but this increase wasn't statistically significant., This result is similar to that demonstrated by **Kim et al., 2019 [10]**, who showed that a rise in 30-day mortality is connected with a positive fluctuation in chloride level during the first 72 hours of an ICU admission.

In contrast, **Oh et al. (2017) [13]** reported that a negative fluctuation of chloride level is possibly a risk factor for 30-day death in patients admitted to the intensive care unit due to hypochloremia.

Post-admission alteration in serum chloride level in an increasing or decreasing pattern may be iatrogenic or secondary to new morbidity. Negative variation of serum chloride may be due to severe fluid loss without adequate replenishment, severe bleeding, or gastrointestinal losses, while positive fluctuation may occur as a result of the administration of large volumes of chloride-rich fluids.

Comparable to this study outcome, regarding the relation between the positive fluctuation and the chloride level after ICU admission and increasing the risk of mortality, **Shaw et al. (2014) [17]** determined that in patients with systemic inflammatory response syndrome, a cut-off value of 10 mmol/L was associated with a higher risk of hospital death, while **Neyra et al. (2015 [18]** found that a 1.37-fold increase in in-hospital mortality was linked to a 5 mmol/L increase in chloride level at 72 hours following ICU admission.

Cardiovascular patients were the only patient category that did not exhibit an elevation in serum chloride, which is consistent with clinical practice as fluid infusion is generally avoided for these patients.

Thongprayoon et al., 2020 [4] revealed that there was a significant correlation between a rise in inpatient mortality and a serum chloride level increase of more than 3 mEq/L. The provision of fluids high in chloride is consistent with the increase in serum chlorine observed after admission **Havel et al.,2011 [19]**

CONCLUSION

Serum chloride alterations outside of normal level are commonly found on ICU admission and may have an impact on the clinical outcome. Longer periods of stay in the intensive care unit are correlated with higher chloride levels at admission. On ICU admission, patients with hypochloremia had a greater death rate. Also, an increase in serum chloride levels after admission is linked to a greater rate of mortality. Therefore, since the majority of patients have access to serum chloride values, which are frequently acquired, consideration should be given to the serum chloride value.

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Table S1: Demographic characteristics of the studied group (n = 300)

Study group (n = 300)			
Age (years) Mean ±SD		51.29±10.77	
		No.	**%**
Sex	Male	147	49
	Female	153	51

Independent t-test (data represented in the form of mean ± SD)

Table S2: History of chronic disease among the studied group (n = 300)

Study group (n = 300)		
Category	**No.**	**%**
HTN	144	48
DM	108	36
Atrial fibrillation	24	8
CNS	55	18.3
IHD	42	14
ICM	12	4
CKD	57	19
Chronic Liver disease	28	9.3
Oncology	109	36.3
Chronic pulmonary diseases	42	14
Surgical intervention	75	25

Table S3: On-admission diagnosis of the studied cases (n = 300)

Study group (n = 300)		
Category	**No.**	**%**
Respiratory disease	69	23
Acute kidney injury	43	14.3
GIT	17	5.7
Sepsis	45	15
Cardiovascular	3	1
Burn	7	2.3
Liver disease	24	8
CNS disorders and head injuries	31	10.3
Cancer	16	5.3
Others	45	15