EGYPTIAN JOURNAL OF ANAESTHESIA
2022, VOL. 38, NO. 01, 665–671
https://doi.org/10.1080/11101849.2022.2143181

Implications of hyperchloremia in critically ill patients

Fawzy Abbas Badawy, Ahmed Elsaeed, Nehal Samir and Abdelhady Ahmed Helmy

Department of Anesthesiology, ICU and Pain Management, Faculty of Medicine, Sohag University, Sohag, Egypt

ABSTRACT

Hyperchloremia is a repeated insult in critically ill subjects, leading to more morbidity and mortality. There is a strong relation between hyperchloremia with mortality and morbidity, as renal injury, more extended ICU stay, more mechanical ventilation (MV) period, and other electrolyte disturbances. Our aim is to evaluate the association of hyperchloremia in critically ill subjects with the incidence of mortality and also to study the development of morbidities such as renal injury and electrolyte disturbances and development of metabolic acidosis and its relationship to the period of MV and ICU stay time. A total number of 400 patients subjected to hyperchloremia estimation and laboratory tests were divided into two groups: hyperchloremic group (HG) and non-hyperchloremic group (NHG). The whole incidence of hyperchloremia for the total cohort has been estimated, as well as the whole incidence of mortality, duration of MV, ICU stay time, development of renal injury, and its association with occurrence of metabolic acidosis and electrolyte disturbances among the HG and NHG. The study included 400 patients, 180 of them (45%) were HG, and 220 (55%) were NHG. Mortality was more in 128 HG patients (71.1%), while 48 patients died (21.8%) in NHG (p-value = 0.005). The incidence of morbidities was more in HG than NHG as more; period of MV, ICU stay, renal injury, acidosis and more electrolyte disturbances (p-value < 0.05). Hyperchloremic patients had an increased incidence of mortality. Moreover, they were susceptible to longer mechanical ventilation, ICU stay, renal injury, metabolic acidosis, and electrolytes disorders.

ARTICLE HISTORY
Received 01 October 2022
Revised 25 October 2022
Accepted 30 October 2022

KEYWORDS
Hyperchloremia; renal injury; mechanical ventilation; acidosis

1. Introduction

Chloride is the primary anion of the extracellular fluid and is essential for serum electroneutrality, acid–base balance, muscular contraction, neutrophils activity, and osmolarity [1]. Hyperchloremia is defined as plasma chloride concentrations of more than 111 mmol/l, according to local laboratory variations [2]. Increased chloride levels in critically ill subjects in the ICU may result from infusion with fluids with a low bicarbonate level or by giving Cl-rich fluids excessively [3]. Also, increased Cl- levels probably may affect the end outcome of critically ill subjects, leading to renal injury, longer hospitalization, or death [4].

2. Our study aimed to

The aim is to evaluate the association of hyperchloremia in critically ill subjects with the incidence of mortality as the primary outcome and also to study the development of morbidities such as renal injury and electrolyte disturbances and development of metabolic acidosis and its relationship to the period of MV and ICU stay time, as secondary outcomes.

3. Patients and methods

This analytic prospective cohort study included a total number of 400 eligible adult patients of both sexes, their age range was from 18 to 60 years old, as a total coverage for all critically ill patients admitted to Sohag University Hospital ICU (from April 2019 to March 2021), after a signed informed consent from all patients or their relatives and after medical research ethics committee approval of Faculty of Medicine, Sohag University, under (IRB) Registration number: Soh-Med-22-07-32. All included patients were within normal renal function (Creatinine level less 1.3 mg/dL) at the time of admission and were hospitalized for more than 48 hours in ICU. Renal injury is calculated using the RIFLE score [5], based in our study on serum creatinine elevation (Table 1).

4. Exclusion criteria

Patients with diabetes mellitus, on dialysis, for plasmapheresis, with creatinine more than 1.3 mg/dl before ICU admission, and who admitted to the ICU for less than 48 hours were excluded. We considered 106–111 mEq/L as the normal chloride value. If, after 48 hours of ICU admission, the chloride level was at

CONTACT Fawzy Abbas Badawy fabadawy@gmail.com Department of Anesthesiology, ICU and Pain Management, Faculty of Medicine, Sohag University, Sohag, Egypt

Table 1. RIFLE score for AKI.

RIFLE criteria	Creatinine criteria	Urine output criteria	Score
Risk of injury to the kidney	Increased serum creatinine×1.5 Above the baseline	UO < 0.5 ml/kg/h for 6 hours	1
Injury of renal function	Increased serum creatinine ×2 Above baseline	UO < 0.5 ml/kg/h for 12 hours	2
Failure of renal function	Increased serum creatinine×3 Above baseline	UO < 0.3 ml/kg/h for 24 hours Or anuria for 12 hours	3
Loss	Persistent ARF, complete loss of renal function > 4 weeks		4
End stage	End-stage renal disease (ESRD), complete loss of renal function > 3 months		5

AKI: acute kidney injury, ARF: acute renal failure, UO: urine output

≥111 mEq/L, the patient was considered in the exposed cohort group (HG), and if <111 mEq/L, the patient was considered NHG. The whole incidence of hyperchloremia for the total cohort has been estimated, and the whole incidence of mortality among HG and NHG and also the incidence of mortality among the HG itself were calculated; MV duration, ICU stay time, development of renal injury in patients admitted with normal renal function, and its association with development of metabolic acidosis and electrolyte disturbances among HG and NHG were calculated.

5. Data collection

Age, sex, height (BMI), cause of ICU admission, the period of MV, and ICU stay time were recorded. In addition to laboratory tests; (including serum electrolytes (Na, Cl, K), ABG, and serum creatinine level, every 24 hours), and a daily clinical follow-up throughout the ICU stay. ICU physician informed by all values, including hyperchloremia, which managed according to the policy of the department.

5.1. Primary outcome

Incidence of mortality between HG and NHG and among HG itself is the primary outcome.

5.2. Secondary outcomes

Incidence of renal injury, acidosis, and electrolyte disturbances, period of MV, and ICU stay time between HG and NHG are secondary outcomes.

5.3. Statistical analysis

Data analysis was performed using a statistical package for social science IBM SPSS 26.0 software. Categorical variables were described by the number and percent and were compared by the chi-square test and Fisher's exact test. Continuous variables are described by the mean and standard deviation and compared by independent samples student's *t*-test. For prediction, we used the Cox regression model, Kaplan–Meier survival curves, and binary logistic regression. A two-tailed p-value < 0.05 was considered statistically significant. No sample size calculation was performed because it was a total coverage study.

6. Results

The study included 400 patients who were admitted to ICU after 24 months, 180 of them (45%) were hyperchloremic considered as HG and 220 patients (55%) were considered NHG. One hundred seventy-six patients (44%) out of 400 patients included in the study died, whereas 224 (56%) were discharged from ICU with improvement; mortality was more in HG in which 128 patients died (71.1%), while 48 patients died (21.8%) in NHG, with the p-value < 0.001, which is clinically significant. There is a statistically significant difference with death as the outcome and hyperchloremia, and the number of deaths was 128 patients (72.73%), while the number of discharged improved was 52 patients (23.21%) with the p-value > 0.001 (Figure 1). In relation to sex out of 400 participants, 252 were males (63%) and 148 were females (37%), and in HG, 100 patients were males (55.6%) and 80 were females (44.4%), while in NHG, 152 (69.1%) were males and 68 (30.9%) were females in NHG, with the p-value of 0.005 (statistically significant) (Table 2).

The causes of admission were confined to all types of critically ill patients, mostly combined causes and the most common causes were neurocritical (78%), dysnatremic (56%), and septic (30%) (Table 3).

As regard hyperchloremia and renal injury, more renal injury is observed in HG than NHG, and as there is a statistically significant difference by RIFLE score (p-value = 2.8×10^{-1}), the RIFLE score ranged from 0–3. Relating the hyperchloremic state to acid–base balance, there are more metabolic acidosis, less PH, and less HCO_3 in HG than NHG with the p-value of 0.045 and 0.005, respectively, and they are significant. Serum electrolytes (Na and K) were more in HG than NHG as p-values are 3.9×10^{-1} and 4.7×10^{-7}, respectively, so there is a significant difference between the two groups. The duration of ICU stay ranged from 3–27 days, with longer ICU stay in HG than NHG as the p-value is 0.000006, which is significant. A longer period of mechanical ventilation is 0–26 days, as the p-value is 1.7×10^{-9}, which is also significant among HG and NHG (Tables 4 and 5).

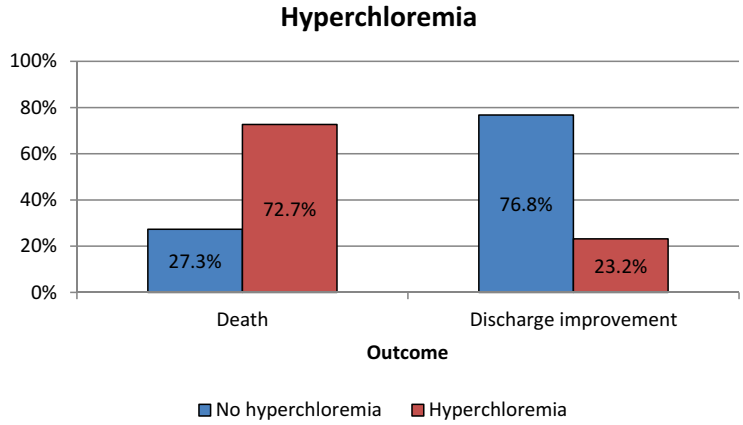

Figure 1. Outcome of hyperchloremic and nonhyperchloremic patients.

Table 2. Outcome of hyperchloremia and relation between hyperchloremia with sex.

		NHG (n = 220)	HG (n = 180)	Total	p-value
Outcome	Death	48 (27.2%)	128 (72.8%)	176 (44%)	<0.001*
	Discharge improvement	172 (76.8%)	52 (23.2%)	224 (56%)	
Sex	Male	152 (69.1%)	100 (55.6%)	252 (63%)	0.005*
	Female	68 (30.9%)	80 (44.4%)	148 (37%)	

Data are represented by n (%) ; * Significant p-value

Table 3. Relation between hyperchloremia and the cause of admission.

		NHG (n = 220)	HG (n = 180)	Total
Neurocritical		188 (85.5%)	124 (68.9%)	312 (78%)
Sepsis		4 (420.0%)	76 (42.2%)	120 (30%)
Dysnatremia		92 (41.8%)	132 (73.3%)	224 (56%)
Operative and surgical	Abdominal exploration	44 (20.0%)	68 (37.8%)	112 (28%)
	Extradural	80 (36.4%)	96 (53.3%)	176 (44%)
	Subdural	8 (3.6%)	8 (4.4%)	16 (4%)
	Depressed fracture\fracture base	48 (21.8%)	24 (13.3%)	72 (18%)
	Brain tumour	64 (29.1%)	0 (0.0%)	64 (16%)
	SAH	12 (5.5%)	12 (6.7%)	24 (6%)
	IVH	16 (7.3%)	12 (6.7%)	28 (7%)
	Posticteal convulsions	0 (0.0%)	12 (6.7%)	12 (3%)
	Brain contusion	16 (7.3%)	32 (17.8%)	48 (12%)
	Pneumocephaly	4 (1.8%)	12 (6.7%)	16 (4%)
Medical comorbidities	HTN	8 (3.6%)	24 (13.3%)	32 (8%)
	Epilepsy\status epilepticus	20 (9.1%)	0 (0.0%)	20 (5%)
	Cerebral infarction	8 (3.6%)	0 (0.0%)	8 (2%)
	Heat stroke	8 (3.6%)	0 (0.0%)	8 (2%)
	Paraplegia	8 (3.6%)	0 (0.0%)	8 (2%)
	Hypoxic encephalopathy	0 (0.0%)	4 (2.2%)	4 (1%)
	Burn	4 (1.8%)	0 (0.0%)	4 (1%)
	Pulmonary oedema	4 (1.8%)	4 (2.2%)	8 (2%)
	SLE	0 (0.0%)	4 (2.2%)	4 (1%)

Data are represented by n (%), SAH: subarachnoid haemorrhage, IVH: intraventricular haemorrhage, HTN: hypertension, SLE: Systemic lupus erythematosus.

Table 4. Distribution of studied patients according to BMI and other parameters including ICU stay, period of mechanical ventilation, RIFLE score, ABG, and serum electrolytes

	Range	Mean ± SD
BMI (kg/m^2)	21–36	27.5 ± 3.65
Period of MV (days)	0–26	3.56 ± 4.83
ICU stay (days)	3–27	6.14 ± 4.38
RIFLE score	0–3	0.38 ± 0.73
PH	7.11–7.56	7.4 ± 0.06
PCO_2 (mmHg)	10.8–63	38.45 ± 7.06
HCO_3 (meq/L)	12–38.7	24.07 ± 4.05
CL (mmol/L)	87–154	110.63 ± 6.71
Na (mmol/L)	113.2–176	140.33 ± 9.45
K (mmol/L)	2.3–6.3	3.78 ± 0.52

BMI, Body Mass Index; SD, Standard Deviation; MV, Mechanical Ventilation

Table 5. Distribution of hyperchloremic patients according to demographic data and laboratory findings.

	NHG (n = 220) Mean ± SD Range	HG (n = 180) Mean ± SD Range	p-value
Age (years)	39.33 ± 13.92 18–60	38.27 ± 15.98 18–60	0.479
BMI (kg/m^2)	27.45 ± 3.9 21–36	27.56 ± 3.33 22–34	0.784
Period of MV (days)	2.27 ± 4.71 0–26	5.13 ± 4.5 0–23	1.7×10^{-9}*
ICU stay (days)	5.25 ± 3.86 3–26	7.22 ± 4.73 3–27	0.000006*
RIFLE score	0.15 ± 0.48 0–2	0.67 ± 0.87 0–3	2.8×10^{-1}*
PH	7.41 ± 0.05 7.28–7.56	7.4 ± 0.07 7.11–7.56	0.045*
PCO_2 (mmHg)	38.22 ± 6.53 22–63	38.65 ± 7.5 10.8–60.1	0.125
HCO_3 (meq/L)	24.31 ± 3.31 14–37 87–111	23.85 ± 4.59 12–38.7 87–154	0.005*
Na (mmol/L)	135.65 ± 6.84 113.2–176	144.5 ± 9.5 115–170	3.9×10^{-1}*
K (mmol/L)	3.72 ± 0.43 2.7–5.9	3.83 ± 0.58 2.3–6.3	4.7×10^{-7}*

Data are represented as mean and standard deviation (SD), BMI: body mass index, MV: mechanical ventilation, *: significant p-value,

Table 6. Cox regression model for time to death outcome.

		95% CI		
	Hazard ratio	Lower	Upper	p-value
Age (years)	1.014	1.003	1.024	0.010*
Sex	1.391	0.947	2.042	0.092
Neurocritical	0.671	0.382	1.178	0.164
Sepsis	1.858	1.121	3.079	0.016*
Dysnatremia	0.300	0.170	0.530	0.000**
Hyperchloremia	1.450	1.015	2.072	0.041*

CI: Confidence Interval, *: significant p-value.

Age, sepsis, dysnatremia, and hyperchloremia are risk factors for death as there is a significant difference between death as an outcome and these have p-values of 0.010, 0.016, 0.000, and 0.041, respectively (Table 6).

In Figure (2), the curve is an estimation of the survival function, and the X-axis represents the period of ICU admission in days, while the Y-axis represents the percentage of survived patients. Horizontal line lengths along the X-axis represent the duration of survival of the subject. The occurrence of an event terminates the interval; the vertical lines are events of interest happening (death). Vertical distances between horizontals are important because they illustrate a change in the cumulative probability of surviving at a given time seen on the Y-axis. The probability of surviving five days, for example, was about 70% for HG, while it was 85% for NHG. The probability of surviving 15 days, for example, was about 10% for HG, while it was 30% for NHG (Figure 2).

The probability of surviving five days, for example, during MV was about 62% for HG, while it was 70% for NHG (Figure 3).

There is a significant difference in cumulative survival probability between HG and NHG in relation to ICU stay, as the p-value is less than 0.001 (Table 7).

There is a statistically significant difference in cumulative survival probability between HG and NHG in relation to MV, as the p-value is equal to 0.007 (Table 8).

Variables of Na and K with odds ratios of 1.102 and 1.599, respectively, dysnatremia, and serum K disorders are considered risk factors for mortality and bad prognosis in hyperchloremic patients, (Table 9).

7. Discussion

The appearance of hyperchloremia is a repeated insult in hospitalized critically ill subjects, leading to more morbidity and more mortality than subjects without hyperchloremia [6]. In our research, mortality was more in HG than NHG as the p-value is 5.6×10^{-23}, so there is a significant difference. There is a significant difference regarding death as outcome and hyperchloremia, with the p-value > 0.001. Age, sepsis, dysnatremia, and hyperchloremia are risk factors for death as there is a significant difference between death as an outcome and these have p-values of 0.010, 0.016, 0.000, and 0.041, respectively. The probability of survival according to the duration of MV and hospital stay time was

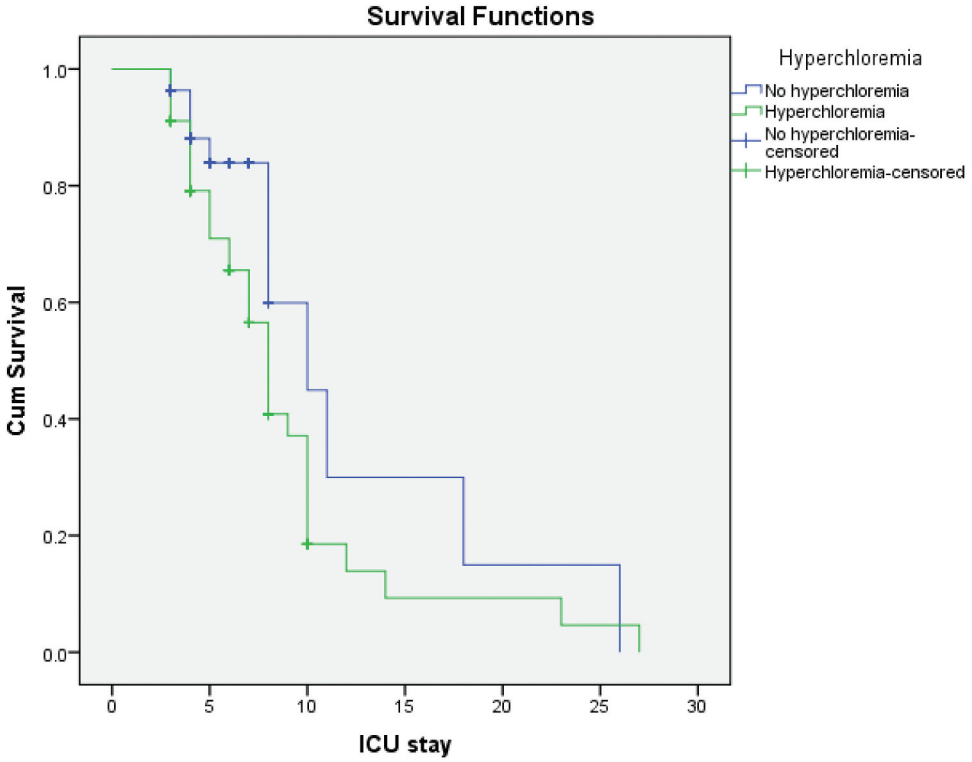

Figure 2. Expected mortality and morbidity in HG and NHG during ICU stay.

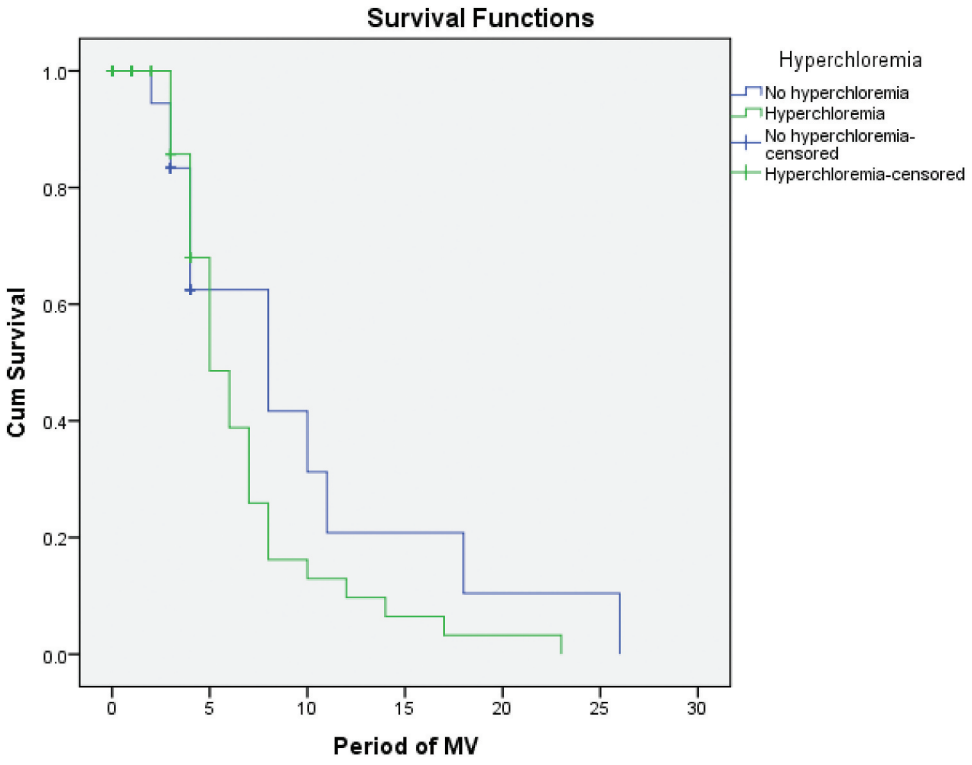

Figure 3. Expected mortality and morbidity in HG and NHG during the period of MV.

less in HG than NHG. Renal injury by RIFLE score was more in HG than NHG, with the *p*-value =of 2.8×10^{-1}, which is statistically significant. More metabolic acidosis as lower PH less HCO_3 in HG than NHG, *p*-value = 0.045 and 0.005 respectively. Electrolyte disturbances (Na and K) were more in HG than NHG as *p*-values are 3.9×10^{-1} and 4.7×10^{-7}, respectively, and considered as risk factors for mortality and bad prognosis in hyperchloremic patients. ICU stay time in HG was higher than that in NHG as the *p*-value is 0.000006, the period of MV is higher in HG than in NHG as *p*-value is 1.7×10^{-9}, and both are statistically significant. *Neyra et al.* [7] studied 1,940 ICU subjects with sepsis, included hyperchloremia patients only in the

Table 7. Kaplan–Meier survival curves for time to death as an outcome according to ICU stay related to hyperchloremia.

		95% CI		
	Mean ± SE	Lower Bound	Upper Bound	*p* value
NHG	12.307 ± 1.182	9.989	14.624	<0.001*
HG	9.083 ± 0.538	8.028	10.137	

SE: Standard Error, CI: confidence Interval, *: significant *p*-value

Table 8. Kaplan–Meier survival curves for time to death as an outcome according to the period of MV related to hyperchloremia.

		95% CI		
	Mean ± SE	Lower Bound	Upper Bound	*p*-value
NHGHT	9.715 ± 1.048	7.660	11.770	0.007*
HG	6.835 ± 0.389	6.074	7.597	

MV; Mechanical Ventilation, SE: Standard Error, CI: confidence Interval, *: significant *p*-value

Table 9. Binary logistic regression.

	p-value	ODDR (CI)
Hyperchloremia		
PH	0.012*	0.04 (0.003–0.492)
PCO_2 (mmHg)	0.000*	0.958 (0.936–0.98)
HCO_3 (mmol/L)	0.010*	0.946 (0.907–0.987)
CL (mmol/ L)	0.000*	1.548 (1.483–1.616)
Na (mmol/ L)	0.000*	1.102 (1.082–1.122)
K (mmol/ L)	0.000*	1.599 (1.255–2.038)

ODDR: Odd's Ratio, CI: Confidence Interval (upper and lower bound), *: significant *p*-value

study, and concluded a chloride elevation at 72 hours, which was a risk element for death in agreement with our study. Contrary to our study, *Neyra* [7] research was restricted to septic persons, and no data about MV duration or hospital stay time were found. *Lee et al*. [8] included 266 polytraumatized persons, by retrospective chart review and concluded that the frequency of chloride disorders was around 25% (45% in our study) and hyperchloremia is an independent risk factor for death (agreed with our study). Contrary to our study cohort, that was a prospective cohort, including all patients in general ICU, but no data about hospital stay duration, MV period, or risk of acidosis were found. *Megahed et al*. [9] studied 375 general ICU subjects for the effects of hypochloremia (<99meq/l) and hyperchloremia (>110meq/l) on mortality and length of stay (LOS) in ICU and hospital with normochromic subjects. They concluded that the rate of mortality was significantly increased in patients with high Cl- levels of 67.3% (45% in our study) and low Cl- levels (72.1%) than in patients with normal levels (36.3%) ($P < 0.001$). It was also concluded that patients with low Cl- levels had significant LOS in the ICU and hospital ($P < 0.0001$). Contrary to our study, *Megahed* [9] allowed the inclusion of dyschloremic (hypo, hyper, and normochloremic) patients in a study; he did not study the duration of MV, the incidence of renal injury, electrolyte disturbances, or metabolic acidosis. *Thongprayoon et al*. [6] studied 76,719 hospitalized subjects, retrospectively to know the spread and the effect of Cl- disorders on the death rate. They concluded that Cl- disorders (outside 100–108 mEq/L) were an independent factor for mortality in hospitalized persons, and this partially agrees with our study. Compared to our findings, this research was retrospective, included a large number of patients in a generalized ICU, and did not study the ICU stay time, MV duration, the incidence of renal failure, electrolyte disorders, or metabolic acidosis. *Tani et al*. [6] study, on 844 adults in ICU retrospectively, aimed to search for the incidence of death and time of hospitalization in dyschloremic patients, concluded that only hypochloremia had significant death rates; 14% ($P < 0.0001$), longer hospital stay and more alkalemia than other groups in disagreement to our study, it was the only study that did not conclude a relation between hyperchloremia and death, and he did not study the MV period, the prevalence of renal failure, electrolyte disturbances or metabolic acidosis in relation to dyschloremia. *Bonatti et al*. [10], on a retrospective cohort study on 175 persons in ICU, concluded that hyperchloremia had not been considered a single risk element to death, but hyperchloremia with hypoalbuminemia had a high significant relation to mortality. Contrary to our study, the *Boniatti* [10] study disagreed with our study, as it was retrospective research, on a small number of patients, with no data about hospital stay time, MV duration, or incidence of renal impairement. *Van Regenmortel et al*. [11] studied a big retrospective cohort including 6480

subjects (general ICU), in agreement with our study, and concluded that severe hyperchloremia is associated with a high death rate, and so considered it as a risk element of mortality in ICU. *Van Regenmortel* [11] disagreed with our study in some points, as he considered serum CL 107−110 mmol/L as moderate hyperchloremia; his study was retrospective in nature, and no data about the hospital stay duration or MV duration were found. Moreover, *Zahid et al*. [12] performed retrospective research on 205 adults who died in ICU in 1 year with any disease after at least three days in the ICU. They considered chloride levels ≥107 meq/l as hyperchloremia. In agreement with our study, they concluded that patients with hyperchloremia had a - higher percent of mortality (50.5%) after three days of admission. They concluded that solutions with a less amount of chloride, like lactated ringer, might be given in a big amount without causing hyperchloremia. *Zahid* [12,13] disagreed with our study, as it has a low number of participants and was retrospective in nature; they did not study the length of hospital stay, MV duration, the prevalence of renal injury, electrolyte disturbances, or metabolic acidosis in relation to hyperchloremia.

8. Conclusion

Hyperchloremia had an increased incidence of mortality as an outcome and may operate as an independent predictor of death in intensive care critically ill patients. Moreover, they are more susceptible to the development of acute renal injury, as well as they are vulnerable more than normochromic critically ill patients to other electrolytes disorders, hyperchloremic metabolic acidosis, longer ICU time, and longer periods of MV.

8.1. Limitations

Limitations of our research are as follows: small sample size, performed for patients with different (heterogeneous) pathological diseases, without a controlled fluid resuscitation protocol prior to admission, serum lactate values were not obtained, RIFLE score depended on serum creatinine only, and the incidence of acute renal injury on the first day was not concluded.

8.2. Recommendations

Further studies on a larger sample size and a multicentric study on a larger geographical scale that emphasizes our conclusion to assess the clinical effect of elevated chloride values on a critically ill patient of specific pathology not only heterogeneous and to assess the relation between hyperchloremia as a risk factor and death as an outcome are recommended.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Vaduganathan M, Pallais JC, Fenves AZ, et al. Serum chloride in heart failure: a salty prognosis. Eur J Heart Fail. 2016 Jun;18(6):669–671.
[2] MUo U. User's Guide, ARUP Laboratories 2018 [cited 2018 01.03.2018]. Available from: https://library.med.utah.edu/WebPath/EXAM/LABREF.html
[3] Marttinen M, Wilkman E, Petaja L, et al. Association of plasma chloride values with acute kidney injury in the critically ill - a prospective observational study. Acta Anaesthesiol Scand. 2016 [2016 Jul];60(6):790–799.
[4] Arzápalo MA, Escalante CA, Góngora MJ, et al. Association of elevated levels of plasma chloride, in severity and mortality, in adult patients in the ICU. Crit Care. 2015;19(Suppl 1):360.
[5] Bellomo R, Ronco C, Kellum JA, et al. Acute dialysis quality initiative workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care. 2004 Aug;8(4):R204–12.PMC522841.
[6] Thongprayoon C, Cheungpasitporn W, Cheng Z, et al. Chloride alterations in hospitalized patients: prevalence and outcome significance. PloS One. 2017;12(3):e0174430.
[7] Neyra J, A., Manllo J, Yessayan L, et al. Association of hyperchloremia with hospital mortality in critically ill septic patients. Crit Care Med. 2015;43(9):1938.
[8] Lee JY, Jung HTH, et al. Hyperchloremia is associated with 30-day mortality in major trauma patients. Scand J Trauma Resusc Emerg Med. 2016;24(Article number):117.
[9] Megahed MM, Zidan DH, Abdelhalim ZM. Effect of chloride level on outcome in critically ill patients, department of critical care medicine, faculty of medicine. Alexandria Egypt Year:Alexandria University;2019. | Volume: 6 | Issue: 3 | Page: 282-286.
[10] Tani M, Morimatsu H, Takatsu F, et al. The incidence and prognostic value of hypochloremia in critically ill patients. Sci World J. 2012;474185.
[11] Boniatti MM, Cardoso PR, Castilho RK, et al. Is hyperchloremia associated with mortality in critically ill patients. J Crit Care. 2011 Apr;26(2):175–179.
[12] Van Regenmortel N, Verbrugghe W, Van den Wyngaert T, et al. Impact of chloride and strong ion difference on ICU and hospital mortality in a mixed intensive care population. Ann Intensive Care. 2016 December;6(1). doi:10.1186/s13613-016-0193-x.
[13] Shad Z, Qureshi M, Qadeer A, et al. Hyperchloremia in intensive care unit mortality: an underestimated fact. Cureus. 2019 May 28;11(5):e4770.