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Hyperchloremia and acute kidney injury: a retrospective observational cohort study on a general mixed medical-surgical not ICU-hospitalized population

Gianmarco Lombardi[1,2,3] · Pietro Manuel Ferraro[2,3] · Matteo Bargagli[2,3] · Alessandro Naticchia[2,3] · Silvia D'Alonzo[2,3] · Giovanni Gambaro[1,2,3]

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Abstract

The aim of this observational retrospective cohort study was to analyze the association between hyperchloremia and serum chloride variation with in-hospital acute kidney injury (AKI) and mortality in a general, no-ICU hospitalized population. We performed a retrospective study on inpatient population admitted to Fondazione Policlinico Universitario A. Gemelli IRCCS between January 2010 and December 2014 with inclusion of adult patients with at least two values available for chloride, sodium and creatinine. Hyperchloremia was defined as serum chloride concentration ≥ 108 mmol/L (moderate hyperchloremia: chloremia between 108–110 mmol/L, severe hyperchloremia: chloremia > 110 mmol/L). According to the time of onset of the electrolyte disturbance, hyperchloremia was then classified as hospital acquired (HA) and community acquired (CA). In patients with HA-hyperchloremia, chloride variation (ΔCl) was calculated. In-hospital AKI was defined according to creatinine kinetics criteria occurring 48 h after hospital admission. Logistic regression analysis was used to evaluate the association between the exposures of interest and in-hospital AKI and mortality. A total of 24,912 hospital admissions met the inclusion criteria. Regression analyses showed that only severe HA-hyperchloremia was associated with increased risk of in-hospital AKI [odds ratio (OR) 2.60, 95% confidence interval (CI) 1.58, 4.30, p value < 0.001] and death (OR 3.89, 95% CI 2.11, 7.18, p value < 0.001). With increasing ΔCl, the OR of in-hospital AKI increased progressively (p value for trend = 0.005). In conclusion, severe hyperchloremia is an independent predictor for in-hospital AKI and mortality; HA-hyperchloremia is more detrimental for patient outcome; higher ΔCl from hospital admission is associated with increased risk of AKI.

Keywords Hyperchloremia · Acute kidney injury · Mortality · Retrospective study · Electrolyte disturbance

Introduction

Chloride is the most abundant anion in extracellular fluid compartment [1]. It plays a key role in different physiological processes such as acid–base balance, muscular activity, osmosis, and immunomodulation [2].

Hyperchloremia is a common electrolyte disturbance frequently observed in critical patients in intensive care units (ICU) and it is defined as a serum chloride concentration ≥ 108 mmol/L.

Several published studies analyzed the association between hyperchloremia and poor outcomes in the hospital setting. Hyperchloremia, as well as the infusion of chloride-rich solutions and chloride load, have been associated with higher in-hospital mortality [3–6] and acute kidney injury (AKI) development [7–11]. Therefore, the harm

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✉ Pietro Manuel Ferraro
pietromanuel.ferraro@unicatt.it

[1] Nefrologia, Dipartimento di Medicina, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italia

[2] U.O.C Nefrologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Via G. Moscati 31, 00168 Roma, Italia

[3] Università Cattolica del Sacro Cuore, Roma, Italia

from chloride has recently garnered medical and scientific interest.

Experimental models demonstrated the detrimental effect of chloride on renal function. Renal vasoconstriction leading to reduction in renal cortical tissue perfusion and renal interstitial edema causing renal intracapsular hypertension provide biological plausibility to the link between hyperchloremia and AKI [7–9].

However, most of the scientific evidence on hyperchloremia and AKI comes from studies on critical patients (with sepsis or septic shock) in ICU. To date, no study has directly analyzed the association between hyperchloremia and in-hospital clinical outcomes in a general (non-ICU) hospitalized population and its association with development of AKI and mortality.

The aim of our study is to analyze the association between hyperchloremia and serum chloride variation with in-hospital AKI and mortality.

Methods

Study population

We performed a retrospective observational study on patients admitted to Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome between January 1, 2010 and December 31, 2014.

We included all adult (≥ 18 years old) patients with at least two serum chloride and consensual (in the same day) sodium values and at least two creatinine values recorded during the hospitalization period.

From analysis and data calculation, we excluded all patients who were admitted to an intensive care unit (ICU) during their hospital stay and patients with end-stage renal disease (ESRD).

Data collection

Demographic data including age and sex, main diagnosis based on the ICD-9 (International Classification of Diseases, 9th Revision) codes, laboratory data including serum chloride, sodium and creatinine values were extracted from the institutional electronic database.

Definitions

Hyperchloremia was defined as serum chloride (Cl) ≥ 108 mmol/L.

According to severity of the electrolyte disturbance, hyperchloremia was classified as moderate (Cl between 108 and 110 mmol/L) and severe (Cl > 110 mmol/L) [12, 13].

According to the time of onset of the electrolyte disturbance, hyperchloremia was then classified in hospital acquired (HA) and community acquired (CA). CA-hyperchloremia was defined when hyperchloremia was present at admission. HA-hyperchloremia was when hyperchloremia occurred after > 24 h of hospitalization.

In patients with HA-hyperchloremia, chloride variation (ΔCl) between the highest peak Cl value (before AKI) and the Cl baseline value (read at hospital admission) was calculated.

AKI definition followed the creatinine kinetics (CrK) criteria [14]. The presence of AKI was assessed using absolute increase of creatinine (Cr) concentration during hospitalization. To do this, we calculated the difference between each Cr and the previous measured value during hospitalization. According to CrK criteria, we defined AKI as an absolute increase in Cr of 0.3-mg/dL over 24 h or a 0.5-mg/dL increase over 48 h.

Estimated glomerular filtration rate (eGFR) was estimated for all patients at hospital admission by applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI equation) [15].

In-hospital AKI was defined as AKI occurring ≥ 48 h after hospital admission.

ESRD was identified according to ICD-9 CM codes using chronic ESRD criteria: procedure codes for arteriovenous fistula creation or revision (39.27, 39.42, 39.43, and 39.93); history of ESRD requiring either kidney transplant (identified through discharge diagnosis ICD-9 V42.0) or maintenance dialysis (ICD-9 V45.1, V45.11, V45.12, V56, V56.0, V56.8). Dialysis criteria were: any of the following procedure codes: 39.95 (hemodialysis), V45.1 (renal dialysis status), V56.0 (extracorporeal dialysis), or V56.1 (fitting and adjustment of extracorporeal dialysis catheter); the initiation of dialysis in a patient with no known history of prior dialysis (ICD-9p 39.95, 54.98).

Hyperchloremia condition was identified for each hospital admission according to the highest Cl value recorded during hospital stay. Only Cl values preceding AKI development where considered in analysis and data calculation.

Na indifference and SID was calculated for each hospital admission. The first one was calculated between the first Na value at hospital admission and the last one before AKI development. The difference between Na and Cl was used as surrogate for strong ionic difference (SID) and was assessed for each patient.

Outcomes, exposures and covariates

The outcome of interest of this study was in-hospital AKI. Second, we evaluated in-hospital mortality.

The exposures of interest were the severity of hyperchloremia (moderate and severe, as categorical variable) and the quartiles of ΔCl (as categorical and continuous variable).

Covariates assessed to control for confounding were age, sex, main diagnosis, Na peak value (both the highest and the lowest Na value read during hospital stay), Na indifference, eGFR, and Charlson/Deyo comorbidity index score [16].

Hyperchloremia was considered as an indirect parameter for acidemia (according to Stewart's SID [17], hyperchloremia associates to low serum bicarbonate for electrical neutrality). However, through sodium correction in all regression models, we indirectly test hyperchloremia or chloride variation independence from SID.

Statistical analysis

Statistical analysis was performed using R version 3.4.4 (Free software Foundation, California).

Continuous variables are reported as mean (SD) for normal distribution and median (interquartile range) for skewed distribution. Categorical variables are presented as the number (percent). Normality of data distribution was assessed by visual inspecting of histogram and Q–Q plot.

Logistic regression analysis was used to evaluate the association between the exposures of interest and in-hospital AKI and mortality by calculating odds ratio (OR) and 95% confidence interval (CI) adjusting for age, sex, Na indifference, Na peak value, eGFR, main diagnosis, and Charlson/Deyo comorbidity index score. As sensitivity analysis, we included AKI as categorical variable (yes/no) in all regression model testing the association between hyperchloremia and death. Restricted cubic spline was used to reveal the association between ΔCl as a continuous variable and the log-OR for kidney event.

In all regression analyses, we included all hospital admissions using standard errors clustered by hospital admission to account for repeated hospitalizations for the same patient.

A p value < 0.05 was considered statistically significant.

Ethical

The ethics committee of Fondazione Policlinico Universitario A. Gemelli IRCCS approved the research protocol (Prot. number 34327/18 ID 2210).

Results

Population characteristics

A total of 24,912 hospital admissions from 21,196 unique patients during the study period matched inclusion criteria (Table 1). There were 5538 (22.2%) admissions from 4708 unique patients with hyperchloremia during their hospital stay (16.7% with moderate hyperchloremia, 5.5% with severe hyperchloremia). Among patients with hyperchloremia, 3312 (13.3% of the whole study population, 59.8% of the hyperchloremic group) were already hyperchloremic at hospital admission (CA), while 2226 (8.9% of the whole study population, 40.2% of the hyperchloremic group) developed hyperchloremia during hospital stay (HA).

Descriptive measurements of the entire cohort are reported in Table 1. As compared with the non-hyperchloremic group, patients with hyperchloremia had lower eGFR at hospital admission. With increasing hyperchloremia severity, eGFR declined from 75.6 (± 25.9) mL/min/1.73 m^2 in patients with moderate hyperchloremia to 65.7 (± 29.8) mL/min/1.73 m^2 in patients with severe hyperchloremia.

Patients with hyperchloremia had higher sodium peak value [140 (IQR 4), no hyperchloremia; 142 (IQR 3), moderate hyperchloremia; 144 (IQR 4), severe hyperchloremia] and lower SID (strong ionic difference) peak value [37 (IQR 4), no hyperchloremia; 33 (IQR 3), moderate hyperchloremia; 31 (IQR 4), severe hyperchloremia] during hospitalization.

Clinical outcomes

Hyperchloremia and AKI

Overall, 547 hospital admissions from 459 patients matched creatinine kinetics criteria for AKI diagnosis. 65 (4.7%), 76 (1.8%) and 406 (2.1%) hospital admissions reported AKI in severe hyperchloremic, moderate hyperchloremic and non-hyperchloremic groups, respectively (Table 2).

Severe hyperchloremia was independently associated with in-hospital AKI with an OR of 1.69 (95% CI 1.24, 2.32, p value = 0.001) compared with non-hyperchloremic state (Table 2). Adjustment for the number of measurements did not change the magnitude of the association (OR 1.69).

In analyses stratified by onset time, only the HA-hyperchloremic condition was significantly associated with in-hospital AKI (OR 2.60, 95% CI 1.58, 4.30, p value < 0.001 [Table 3]).

Consequently, we described the dose–response relationship between chloride variation (ΔCl) and in-hospital AKI in the HA-hyperchloremic subgroup. With increasing ΔCl, the odds of in-hospital AKI increased progressively (p value for trend = 0.005; Supplemental Fig. 1). Only the highest quartile of ΔCl was significantly associated with in-hospital AKI in unadjusted (OR 3.80, 95% CI 1.86, 7.77, p value < 0.001) as well as in fully adjusted (OR 2.53, 95% CI 1.02, 6.32, p value = 0.046) models (Table 4).

Table 1 Baseline characteristics of the study population

	All	No hyperchloremia	Moderate hyperchloremia	Severe hyperchloremia
N admissions	24,912	19,374	4162	1376
N patients	21,196	16,488	3565	1143
Age [years, mean (SD)]	63.0 (16.9)	63.3 (16.7)	61.0 (17.2)	64.8 (17.6)
Male sex (*n*, %)	9737 (45.9)	7911 (48.0)	1383 (38.8)	443 (38.8)
Charlson/Deyo score [mean (SD)]	0.38 (0.87)	0.39 (0.87)	0.33 (0.81)	0.49 (1.00)
Charlson/Deyo score category (*n*, %)				
0	16,172 (76.3)	12,490 (75.8)	2851 (80.0)	831 (72.7)
1	3263 (15.4)	2642 (16.0)	460 (12.9)	161 (14.1)
2	993 (4.7)	756 (4.6)	142 (4.0)	95 (8.3)
> 2	768 (3.6)	600 (3.6)	112 (3.1)	56 (4.9)
Main diagnosis (*n*, %)				
Cardiovascular	2745 (13.0)	2223 (13.5)	393 (11.0)	129 (11.3)
Endocrine/metabolic	603 (2.8)	494 (3.0)	85 (2.4)	24 (2.1)
Gastrointestinal	2550 (12.0)	2011 (12.2)	424 (11.9)	115 (10.1)
Hematology	213 (1.0)	147 (0.9)	40 (1.1)	26 (2.3)
Oncology	6579 (31.0)	5025 (30.5)	1184 (33.2)	370 (32.4)
Infectious disease	454 (2.1)	358 (2.2)	56 (1.6)	40 (3.5)
Respiratory disease	1091 (5.1)	938 (5.7)	99 (2.8)	54 (4.7)
Injury/poisoning	1301 (6.1)	988 (6.0)	228 (6.4)	85 (7.4)
Sepsis/SIRS	111 (0.5)	85 (0.5)	14 (0.4)	12 (1.0)
Other	1198 (5.7)	906 (5.5)	215 (6.0)	77 (6.7)
eGFR [mL/min/1.73 m^2, mean(SD)]	76.9 (26.4)	77.9 (26.1)	75.6 (25.9)	65.7 (29.8)
Sodium_max (mmol/L, median, IQR)[a]	141 (4)	140 (4)	142 (3)	144 (4)
SID_max (mmol/L, median, IQR)[a]	36 (4)	37 (4)	33 (3)	31 (4)
Chloride_baseline (mmol/L, median, IQR)	103 (5)	103 (5)	108 (4)	111 (5)
Chloride_max (mmol/L, median, IQR)[a]	105 (5)	104 (4)	109 (1)	112 (2)

[a]The highest value before AKI

Table 2 Association between the severity of hyperchloremia and in-hospital AKI

	No hyperchloremia	Moderate hyperchloremia	Severe hyperchloremia
N admissions	19,374	4162	1376
N patients	16,488	3565	1143
AKI (*n*, %)	406 (2.1)	76 (1.8)	65 (4.7)
Univariate model			
OR (95% CI)	1.00 (Reference)	0.87 (0.68, 1.11)	2.32 (1.76, 3.04)
p value		0.266	< 0.001
Multivariate model[a]			
OR (95% CI)	1.00 (Reference)	1.00 (0.78, 1.30)	1.69 (1.24, 2.32)
p value		0.971	0.001

[a]Adjusted for age, sex, main diagnosis, Charlson/Deyo score, eGFR, Na indifference, Na peak value

Hyperchloremia and death

Overall, 258 (1.2%) patients died during hospital stay. Severe hyperchloremia was associated with increased risk of death during hospital stay with an in-hospital mortality of 2.4% in severe hyperchloremic sample compared with 1.2% in the non-hyperchloremic group and 1.0% in the moderate hyperchloremic group (Table 5).

Only severe hyperchloremic condition was significantly associated with in-hospital death with an adjusted OR of 2.20 (95% CI 1.40, 3.45, *p* value < 0.001) compared with the non-hyperchloremic group (Table 5). Even after adjustment

Table 3 Association between the onset time of hyperchloremia and in-hospital AKI

	Community-acquired hyperchloremia			Hospital-acquired hyperchloremia		
	No hyperchloremia	Moderate hyperchloremia	Severe hyperchloremia	No hyperchloremia	Moderate hyperchloremia	Severe hyperchloremia
N admissions	19,374	2,338	974	19,374	1,824	402
N patients	16,488	2,017	816	16,488	1,548	327
AKI (*n*, %)	406 (2.1)	42 (1.8)	41 (4.2)	406 (2.1)	34 (1.9)	24 (6.0)
Univariate model						
OR (95% CI)	1.00 (Reference)	0.85 (0.62, 1.18)	2.05 (1.46, 2.88)	1.00 (Reference)	0.89 (0.62, 1.26)	2.97 (1.95, 4.52)
p value		0.337	< 0.001		0.508	< 0.001
Multivariate model[a]						
OR (95% CI)	1.00 (Reference)	0.99 (0.71, 1.39)	1.47 (0.99, 2.16)	1.00 (Reference)	1.08 (0.76, 1.54)	2.60 (1.58, 4.30)
p value		0.975	0.051		0.666	< 0.001

[a]Adjusted for age, sex, main diagnosis, Charlson/Deyo score, eGFR, Na indifference, Na peak value

Table 4 Association between ΔCl and in-hospital AKI in HA-hyperchloremia

	1st quartile, < 3 mmol/L	2nd quartile, 3–4 mmol/L	3rd quartile, 4–6 mmol/L	4th quartile, > 6 mmol/L	*p* value for trend
N admissions	843	339	501	543	
N patients	724	284	428	439	
AKI (*n*, %)	11 (1.3)	11 (3.2)	10 (2.0)	26 (4.8)	
Univariate model					
OR (95% CI)	1.00 (Reference)	2.54 (1.09, 5.91)	1.54 (0.65, 3.66)	3.80 (1.86, 7.77)	0.001
p value		0.031	0.327	< 0.001	
Multivariate model[a]					
OR (95% CI)	1.00 (Reference)	2.06 (0.84, 5.04)	1.17 (0.45, 3.00)	2.53 (1.02, 6.32)	0.005
p value		0.113	0.748	0.046	

[a]Adjusted for age, sex, main diagnosis, Charlson/Deyo score, eGFR, Na indifference, Na peak value

Table 5 Association between the severity of hyperchloremia and in-hospital death

	No hyperchloremia	Moderate hyperchloremia	Severe hyperchloremia
N admissions	19,374	4162	1376
N patients	16,488	3565	1143
Death (*n*, %)	195 (1.2)	35 (1.0)	28 (2.4)
Univariate model			
OR (95% CI)	1.00 (Reference)	0.81 (0.57, 1.14)	2.17 (1.50, 3.12)
p value		0.224	< 0.001
Multivariate model[a]			
OR (95% CI)	1.00 (Reference)	1.21 (0.85, 1.74)	2.20 (1.40, 3.45)
p value		0.290	< 0.001

[a]Adjusted for age, sex, main diagnosis, Charlson/Deyo score, eGFR, Na indifference, Na peak value

for the number of measurements, the magnitude of the association did not change (OR 2.23).

The stratified analysis between CA-hyperchloremia and HA-hyperchloremia (Table 6) demonstrated that only the HA-hyperchloremic condition was independently associated with in-hospital death (OR 3.89, 95% CI 2.11, 7.18, p value < 0.001), however the number of events in the CA-hyperchloremia group was quite small.

These associations were even confirmed after including AKI development as categorical variable (yes/no) for risk adjustment (OR 2.07, 95% CI 1.31, 3.28, $p = 0.002$, in severe hyperchloremia sample compared with no hyperchloremia;

Table 6 Association between the onset time of hyperchloremia and in-hospital death

	Community acquired hyperchloremia			Hospital acquired hyperchloremia		
	No hyperchloremia	Moderate hyperchloremia	Severe hyperchloremia	No hyperchloremia	Moderate hyperchloremia	Severe hyperchloremia
N admissions	19,374	2338	974	19,374	1824	402
N patients	16,488	2017	816	16,488	1548	327
Death (*n*, %)	195 (1.2)	11 (0.5)	16 (2.0)	195 (1.2)	24 (1.6)	12 (3.7)
Univariate model						
OR (95% CI)	1.00 (Reference)	0.44 (0.25, 0.79)	1.61 (0.99, 2.62)	1.00 (Reference)	1.28 (0.86, 1.92)	3.54 (2.12, 5.93)
p value		0.006	0.055		0.223	< 0.001
Multivariate model[a]						
OR (95% CI)	1.00 (Reference)	0.70 (0.38, 1.31)	1.68 (0.94, 3.00)	1.00 (Reference)	1.87 (1.24, 2.84)	3.89 (2.11, 7.18)
p value		0.266	0.082		0.003	< 0.001

[a]Adjusted for age, sex, main diagnosis, Charlson/Deyo score, eGFR, Na indifference, Na peak value

OR 3.23 95% CI 1.70, 6.15, $p < 0.001$, in HA severe hyperchloremia sample compared with no hyperchloremia).

Discussion

In this retrospective observational study, we show an association between hyperchloremia and AKI in a general, non-ICU medical-surgical mixed hospitalized population. That severe hyperchloremia increases the risk of in-hospital AKI during hospital stay and associates with poor prognosis was already known; ours, is the first demonstration that this is a phenomenon occurring also in non-critically ill patients.

Hyperchloremia is probably one of the most underestimated electrolyte disturbances. The reported incidence of hyperchloremia during hospitalization is extremely variable. According to scientific literature, it spans from near 20% up to 90% [13, 18, 19]. In one of the most recent and largest retrospective observational study on heterogeneous critically ill patients, hyperchloremia occurred in 57% of the study population within 48 h to ICU admission [18]. Different study populations, hyperchloremia management and fluid administration justify such variability. However, most studies on this topic evaluated critical hospitalized population, septic and post-operative patients, a few of them considered not critical ill patients. To date, the largest study on chloride abnormalities in a general mixed hospitalized population discovered an incidence of hyperchloremia (Cl ≥ 108 mmol/L) of 14.9% ($n = 11,395$ of 76,719) on admission [20].

In the present study on a general hospitalized population, the overall prevalence of in-hospital hyperchloremia was 22.2% (13.3% on hospital admission, 8.9% developed during hospital stay).

The association between hyperchloremia with poor hospital outcomes, documented in recent observational and interventional studies, garnered medical and clinical interest on this topic.

Shaw et al. in a retrospective study on 109,836 patients with systemic inflammatory response showed an increased in-hospital mortality rate for higher total chloride load [6]. These results were subsequently supported by Raghunathan et al. on 6730 critically ill patients with sepsis; they reported an association between Cl-rich solutions and increased in-hospital mortality [5]. In a heterogeneous hospitalized population, considering ICU and non-ICU patients, Thongprayoon et al. observed a significant increase in all-cause mortality rate (OR 1.12, 95% CI 1.10, 1.14) for sCl ≥ 108 mmol/L [20].

Confirming previous reports, we described an increase in-hospital mortality in patients with hyperchloremia. However, only severe hyperchloremic conditions were independently associated with in-hospital mortality (Table 5).

Acute kidney injury is an important complication of hospitalized population. A large body of evidence suggest the relevant role that even mild increase in serum creatinine plays on patient survival [21]. The association of AKI and hyperchloremia is currently giving rise to much debate within medical community. Yunos et al. evidenced a lower AKI-rate when Cl-rich solutions restriction was applied in ICU patients [10]. A recent observational study concluded that hyperchloremia within 48 h of ICU admission was significantly associated with AKI (OR 6.44, 95% CI 2.95, 14.10) and mortality in a heterogeneous cohort of 250 critically ill patients [18]. On the other hand, Yessayan et al. retrospectively reviewing 1045 patients with sepsis or septic shock, did not find an association of AKI either with chloride on admission in ICU or with chloride changes within the first 72 h [22]. Unfortunately, most of the available scientific evidences are observational. Recently, a recent large randomized trial failed to demonstrate an effect of buffered crystalloids compared with 0.9% saline on AKI

or mortality [23]. On the other hand, the SMART ED trial comparing the balanced crystalloid versus saline in patients in the emergency department showed a lower incidence of major adverse kidney events in the first group. In particular, balanced crystalloid group documented a significant lower incidence of hyperchloremia (> 110 mmol/L) [24].

In this study, we demonstrate an independent association between severe hyperchloremia and AKI (Table 2). Severe hyperchloremia was a significant predictor for in-hospital AKI with an OR of 1.69 ($p = 0.001$) in multivariate logistic regression (Table 2). However, only HA-hyperchloremia showed an independent association with AKI (OR 2.60, $p < 0.001$) (Table 3). Even admissions with CA-hyperchloremia documented an increased risk of in-hospital AKI (OR 1.47), nevertheless this did not reach the statistically significance maybe due to small sample size considered. As reported in Table 4, the magnitude of chloride fluctuations during hospital stay increases the risk for developing AKI. Namely, it was the greatest quartile of ΔCl to independently associate with AKI (OR 2.53, $p = 0.046$) after adjustment for possible confounders.

The effects of hyperchloremia or fluid resuscitation containing sodium–chloride on the human body are still debated. We may speculate that given the relationship only between severe hyperchloremia and AKI, it could be conceivably associated with chloride-rich solution treatment. Hyperchloremia metabolic acidosis with SID reduction is a common consequence of saline solution. This phenomenon was also confirmed in humans with the administration of 0.9% saline fluids vs. other electrolyte solutions [7, 24, 25]. SID acidosis could also be related to CKD condition, especially with tubulo-interstitial involvement, or to an important volume depletion (such as in severe diarrhea condition) that could justify our findings. However, our results suggest the independence of hyperchloremia-induced AKI from Na (and SID). It was demonstrated that hyperchloremia causes metabolic acidosis, but other clinical effects of this electrolyte imbalance are possible and have to be considered. Recent findings suggest that high chloride induces renal vasoconstriction in animal models. Fluid overload causing renal interstitial edema, intracapsular hypertension or vasomotor renal disease could also explain kidney injury [7, 9, 25].

Several important limitations in our study should be addressed. Since this study was a retrospective, single-center observational study, we cannot generalize our results. We used ICD-9 CM codes to identify comorbid conditions and adjusted multivariate analysis to control confounding factors, but we could not adjust for acid–base state and treatments due to database limitations. Furthermore, although we could not control our analysis for acid–base state, we adjusted all regression models for serum sodium (Na indifference and Na peak values) that together with chloride defines SID, an accepted marker of metabolic acidosis.

Although a cause–effect relationship could not be determined from our analysis, our study is one of the largest on the association between hyperchloremia and hospital outcomes and, to the best of our knowledge, the first analyzing the association between hyperchloremia and ΔCl with kidney injury in a general hospitalized non-critical ill population. Furthermore, at odds of other studies, we did not use administrative codes but a validated creatinine-based method to identify in-hospital AKI.

In conclusion, this study clearly demonstrates that hyperchloremia may play an important role even in non-ICU patients and may significantly impact on their prognosis; in fact (1) severe hyperchloremia is an independent predictor for in-hospital AKI and mortality; (2) in-hospital-acquired hyperchloremia is more detrimental for patient outcome; (3) higher ΔCl from hospital admission is associated with increased risk of in-hospital AKI.

Whether the deleterious effects of high chloride are the consequence of high chloride per se, or to some other conditions associated with high chloride that we did not capture is not known. Only, interventional trial could probably answer this question. This has also been advocated in the largest, but negative trial ever performed until now.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The study protocol and the waiver of consent were approved by the ethics committee of Fondazione Policlinico Universitario A. Gemelli IRCCS (Approval No. 34327/18 ID 2210). The study was conducted in accordance with Declaration of Helsinki.

Informed consent This study waived the requirement for written informed consent due to the retrospective nature of this study.

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