Pancreatology 19 (2019) 136–142

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Increase in serum chloride and chloride exposure are associated with acute kidney injury in moderately severe and severe acute pancreatitis patients

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ARTICLE INFO

Article history:
Received 25 May 2018
Received in revised form
12 November 2018
Accepted 16 November 2018
Available online 17 November 2018

Keywords:
Chloride
Hyperchloremia
Acute kidney injury
Severe acute pancreatitis

ABSTRACT

Objective: We aimed to evaluate whether early (first 48 h) hyperchloremia and/or the change of serum chloride concentration are associated with acute kidney injury (AKI) in patients with moderately severe and severe acute pancreatitis (MSAP and SAP).
Methods: We retrospectively collected the data of patients with a primary diagnosis of MSAP or SAP from a tertiary center between January 2014 and June 2017. Consecutive chloride levels within the first 48 h after admission were retrieved for further calculation. Logistic regression analysis and receiving operating characteristic (ROC) curve were used to assess the relationship between hyperchloremia and AKI.
Results: 145 patients were enrolled for analysis, of whom 33.5% (47/145) developed hyperchloremia during the observation period. The incidence of AKI was significantly higher in the hyperchloremia group (40.4% vs 7.1%; $p < 0.001$). On multivariate analysis, the increase in serum chloride (Δ[Cl-]) was independently associated with AKI [OR = 1.32 (1.00–1.74)], as was chloride exposure [OR = 1.01 (1.00–1.02)], and these associations were found to be stronger in patients identified as predicted SAP (PSAP). Moreover, even in patients without hyperchloremia, increase in serum chloride (Δ[Cl-]) was still associated with AKI [OR = 1.65 (1.18–2.32)]. Area under the curve of the ROC curve (AUCROC) analysis found that Δ[Cl-] is a good predictor of AKI with an optimal cutoff point at 3.5 mmol/L, showing an AUCROC of 0.81.
Conclusion: Hyperchloremia is common in patients with AP and $\Delta[Cl^-]$ and chloride exposure during the first 48 h were independent risk factors for AKI in MSAP and SAP patients.

Introduction

Both moderately severe and severe acute pancreatitis (MSAP and SAP) are characterized by the presence of organ failure during the disease course [1]. Acute kidney injury (AKI) is one of the most common systemic complications, especially in critically ill patients. AKI in the setting of SAP has been shown to have a dramatic impact on clinical outcome [2–4]. A series of risk factors have been shown to be associated with the incidence of AKI including intra-abdominal hypertension, septic shock and volume depletion [5].

Recently, accumulating evidence had shown a correlation

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https://doi.org/10.1016/j.pan.2018.11.006
1424-3903/

between hyperchloremia and AKI in critically ill in general and in other clinical situations [6–9]. Increased plasma chloride is a common consequence of short-time rapid fluid resuscitation with chloride rich crystalloids (e.g. saline), which is a recommended therapeutic measure for patients in shock or with dehydration in the early phases of acute pancreatitis (AP) [10–12]. The frequent use of saline in patients with AP, however, could lead to a considerable chloride load, which may be clinically relevant [13].

Studies have demonstrated that hyperchloremia, a side-effect of saline administration, has negative effects on blood pressure, renal blood flow, and fluid retention in animals and human subjects [14–17]. In patients, the association between hyperchloremia and AKI has been seen in different patients populations, but it has not been assessed in patients with AP. In this study, we aimed to test the hypothesis that hyperchloremia and/or the change of serum chloride concentration would be associated with greater risk of developing AKI in patients with MSAP and SAP.

Methods

Study design and participants

This study was a retrospective cohort study of patients with MSAP or SAP admitted to Jinling Hospital in Nanjing, a tertiary pancreatitis referral center, from January 2014 to June 2017. We included adults patients meeting with the following criteria: (1) 18 years or older; (2) diagnosis of MSAP or SAP (defined by The Revised Atlanta Classification), based on international consensus, which stratifies AP into 3 categories: mild [no organ failure (OF) and no local complications], moderate (transient OF resolving in less than 48 h and/or local complications), and severe (persistent OF lasting at least 48 h with/without local complications) [18]; (3) within 7 days after onset of acute pancreatitis; and (4) in whom initial serum chloride and daily serum chloride concentration for the first 48 h were repeatedly measured at least on a daily basis. We excluded patients with pre-existing chronic renal failure or underwent renal replacement therapy (RRT) before admission or within the first 48 h after admission, as the use of RRT would greatly impact serum chloride level. Moreover, patients with pre-existing AKI or new onset AKI within 48 h were also excluded.

Study variables

Serum chloride concentration was measured by indirect potentiometry in the central laboratory of Jinling Hospital. $[Cl^-]_0$ was the initial serum chloride concentration measured at admission. The maximal serum chloride concentration during the first 48 h was designated as $[Cl^-]_{max}$. The increase in serum chloride, $\Delta[Cl^-]$, was the difference between maximal serum chloride level and initial serum chloride level ($\Delta[Cl^-] = [Cl^-]_{max} - [Cl^-]_0$). Hyperchloremia was defined as $[Cl^-]_{max} \geq 110$ mmol/L according to previous reports [19]. Hypernatremia was defined as a serum sodium concentration (Na_{max}, maximal serum chloride concentration during the first 48 h) of greater than 145 mmol/L [20].

Since changes in chloride should always be interpreted with changes in free water, we additionally used $[Cl]_{corrected}$ to appreciate and quantitate the Cl^- levels [21,22]. The following formulae was used to calculate the corrected chloride:

$$[Cl^-]_{Corrected} = ([Na^+]_{Normal}/[Na^+]_{Measured}) * [Cl^-]_{Measured}$$

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was determined by using clinical and laboratory data at admission. AKI was diagnosed and classified by the Kidney Disease Improving Global Outcomes (KDIGO) consensus criteria [23], which stratifies AKI into 3 stages: stage 1 [1.5 to 1.9 times baseline or ≥0.3 mg/dl increase in serum creatinine, or urine output <0.5 ml/kg/hour for 6–12 h], stage 2 [2.0 to 2.9 times baseline of serum creatinine or urine output <0.5 ml/kg/hour for ≥12 h] and stage 3 [≥3 times baseline or increase in serum creatinine to ≥4.0 mg/dl or RRT, or urine output <0.3 ml/kg/hour for ≥24 h or anuria for ≥12 h]. To evaluate the influence of chloride in patients with different severity of disease, the study subjects were additionally divided to predicted severe acute pancreatitis (PSAP) group and non-PSAP group. PSAP was identified as those at risk for local and systemic complications (APACHEII score of ≥8, C-reactive protein of >150 mg/L, or modified Glasgow score of ≥3 at the first 24 h of admission) at the first 24 h assessment of admission [24]. Analyses were performed and compared in patients with PSAP and non-PSAP, respectively.

Study outcomes

The primary outcome was the development of AKI. The secondary outcomes were the requirement of RRT, length of hospital stay, length of intensive care unit (ICU) stay, in-hospital cost and 28-day mortality.

Statistical analysis

Demographic and clinical data were compared for patients with hyperchloremia and without hyperchloremia and with AKI and without AKI. Continuous data were reported using mean ± standard deviation (SD) or median (interquartile range) as appropriate and categorical data as percentage depending on the distribution. We used t tests to compare normally distributed continuous data

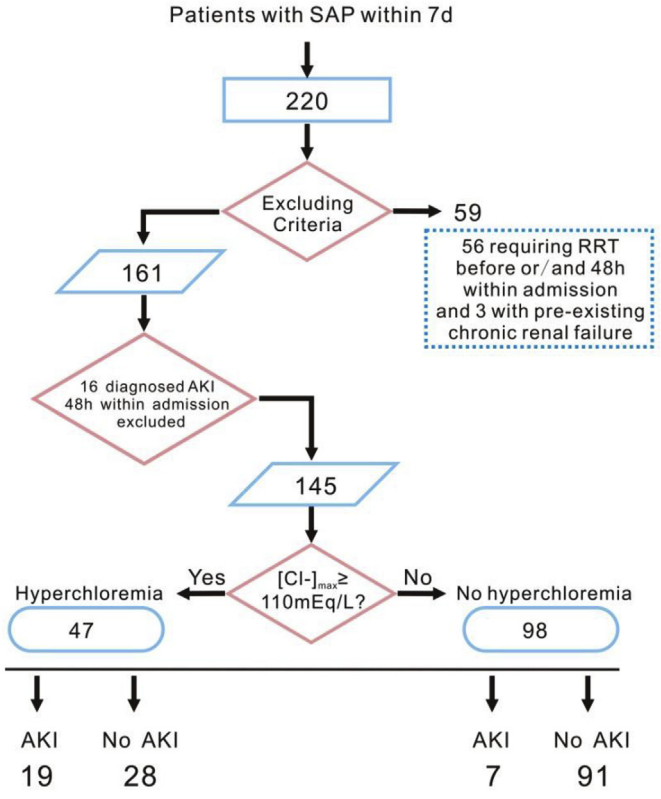

Fig. 1. Flow chart of the patients with SAP in the study. $[Cl-]_{max}$ maximal chloride concentration during the first 48 h, SAP severe acute pancreatitis, AKI acute kidney injury, RRT renal replacement therapy.

Table 1
Demographic and clinical outcomes of patients classified by serum chloride status.

Variable	Hyperchloremia N = 47	No hyperchloremia N = 98	p
Demographics			
Age, yr, mean ± SD	49.3 ± 13.8	43.3 ± 11.0	0.01*
Male, n (%)	24 (51.1)	58 (59.2)	0.38
BMI, mean ± SD	26.2 ± 3.7	25.7 ± 4.0	0.43
Underlying diseases			
Hypertension, n (%)	12 (25.5)	21 (21.4)	0.67
DM, n (%)	11 (23.4)	15 (15.3)	0.25
Etiology of SAP			
Biliary, n (%)	21 (44.7)	39 (39.8)	0.59
Hyperlipidemia, n (%)	22 (46.8)	49 (50.0)	0.73
Alcoholic, n (%)	2 (4.3)	1 (1.0)	0.25
Traumatic, n (%)	0	2 (2.0)	1.00
Idiopathic, n (%)	2 (4.3)	7 (7.1)	0.72
Clinical parameters at presentation			
Creatinine, mg/dL, mean ± SD	0.7 ± 0.2	0.6 ± 0.2	0.02*
APACHE II score, mean ± SD	7.8 ± 3.9	6.5 ± 3.7	0.04*
HCT, %, mean ± SD	35.2 ± 6.5	35.5 ± 6.8	0.82
HCO3, mmol/L, mean ± SD	21.8 ± 2.1	22.3 ± 2.3	0.14
Clinical parameters at 48 hr			
Fluid intake, L, mean ± SD	7.6 ± 1.8	7.1 ± 1.7	0.06
Urine output, L, mean ± SD	4.2 ± 1.7	4.1 ± 1.6	0.79
Chloride exposure, mEq, mean ± SD	1009.5 ± 137.7	865.2 ± 132.5	<0.001*
BD, mmol/L, mean ± SD	0.3 ± 2.0	0.3 ± 2.0	0.54
Decreased Hct>10%, n (%)	22 (46.8)	42 (42.9)	0.72
Ranson score, median (IQR)	3.0 (3.0–4.0)	3.0 (2.0–4.0)	0.31
Chloride parameters, mmol/L, mean ± SD			
Initial chloride ($[Cl^-]_0$)	108.3 ± 3.9	102.4 ± 3.7	<0.001*
Maximal Cl in 48 h ($[Cl^-]_{max}$)	113.8 ± 3.4	105.2 ± 2.9	<0.001*
Increase in serum Cl ($\Delta[Cl^-]$)	5.6 ± 3.2	2.8 ± 2.7	<0.001*
Clinical outcome			
AKI, n (%)	19 (40.4)	7 (7.1)	<0.001*
RRT, n (%)	6 (12.8)	2 (2.0)	0.01*
28-day mortality, n (%)	4 (8.5)	1 (1.0)	0.04*
Length of stay, d, median (IQR)	11.0 (7.0–23.0)	7.0 (4.0–11.0)	0.02*
Length of ICU stay, d, median (IQR)	6.0 (3.0–15.0)	3.0 (2.8–5.0)	0.03*
Cost, 10000¥, median (IQR)	6.2 (4.2–17.2)	4.0 (2.8–6.2)	0.03*

BMI body mass index, SD standard deviation, DM diabetes mellitus, SAP severe acute panceatitis, IQR interquartile rate, APACHE **II** Acute Physiology and Chronic Health Evaluation **II**, HCT hematocrit, BD base deficit, $[Cl^-]_0$ initial chloride concentration, $[Cl^-]_{max}$ maximal chloride concentration in the first 48 h, Hyperchloremia: $[Cl^-]_{max} \geq 110$ mmol/L, $\Delta[Cl^-]$ increase in serum chloride, AKI acute kidney injury, RRT renal replacement therapy.
*Indicates statistical significance, $p < 0.05$.

and Wilcoxon signed-rank tests for non-normally distributed data. For categorical variables, a chi-square test was used.

Univariate logistic regression was used to test for unadjusted association between chloride parameters and AKI. Area Under the Curve of the Receiving Operating Characteristic Curve (AUCROC) analysis was used to define the optimal cutoff point for some significant factors to predict the development of AKI. We then introduced potential confounders ($P < 0.1$ in the univariate analysis) as well as several priori variables (age, gender) into logistic regression models to define the relationship between chloride parameters and the clinical outcome of AKI. All analyses were performed using SPSS, version 20 (SPSS, Chicago, IL, USA). A two-sided p value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

During the study period, 220 consecutive patients with MSAP and SAP were screened for potential inclusion. Fifty-six patients were excluded because they received RRT pre-admission or during the first 48 h within admission. Three patients with pre-existing chronic renal disease were also excluded. Another sixteen patients with pre-existing AKI or new onset AKI during the first 48 h were also excluded. The remaining 145 patients were eligible for further evaluation (Fig. 1). Of these, 47 patients (32.4%) showed hyperchloremia during the 48 h study period and 98 patients (67.6%) did not. Demographics, baseline characteristics, clinical parameters and outcome of patients with and without hyperchloremia are shown in Table 1. Patients with hyperchloremia, who had a higher APACHE II score and higher admission serum creatinine, were older than patients without hyperchloremia (49.3 ± 13.8 versus 43.3 ± 11.0, $p = 0.01$). Notably, chloride exposure was higher in patients with hyperchloremia (1009.5 ± 137.7 versus 865.2 ± 132.5, $p < 0.001$), while fluid intake and urine output were similar between the two groups. Worse outcome could also be seen in hyperchloremic patients evidenced by higher incidence of AKI, higher requirement of RRT, and higher 28-day mortality (Table 1).

Among the study patients, 26 patients (17.9%) developed new-onset AKI. Clinical variables and outcome of patients with AKI and without AKI are shown in Table 2. During the first 48 h of admission, AKI patients received more fluid but urine output was similar. For the outcomes, patients with AKI suffered longer ICU and hospital stay, greater requirement for RRT and a higher mortality. Although the initial serum chloride concentration measured at admission ($[Cl\text{-}]_0$) did not differ between AKI and non-AKI patients, the maximal serum chloride concentration during the first 48 h ($[Cl\text{-}]_{max}$) and the increase in serum chloride ($\Delta[Cl\text{-}]$) were both significantly higher in the AKI group (Table 2).

Table 2
Clinical variables and outcomes of patients classified by the complication of AKI.

Clinical Variable	AKI (N = 26)	Non-AKI (N = 119)	p
Demographics			
Age, yr, median (IQR)	49.5 (34.7–62.5)	43.4 (36.4–50.3)	0.049*
Male, n (%)	16 (61.5)	66 (55.5)	0.67
BMI, mean ± SD	26.4 ± 3.5	25.7 ± 4.0	0.40
RAC of SAP			
SAP, n (%)	22 (84.6)	10 (8.4)	<0.001*
Clinical parameters at presentation			
Creatinine, mg/dL, mean ± SD	0.7 ± 0.2	0.6 ± 0.2	0.01*
Hct (%), mean ± SD	34.7 ± 4.8	35.5 ± 7.0	0.49
HCO3, mmol/L, median (IQR)	21.3 (18.7–23.7)	22.7 (20.7–23.3)	0.28
Chloride parameters, mmol/L, mean ± SD			
Initial chloride ($[Cl^-]_0$)	105.7 ± 4.2	104.0 ± 4.7	0.10
Maximal Cl in 48 h ($[Cl^-]_{max}$)	112.3 ± 4.3	107.1 ± 4.7	<0.001*
Increase in serum Cl ($\Delta[Cl^-]$)	6.7 ± 2.4	3.1 ± 2.9	<0.001*
Sodium parameters, mmol/L, mean ± SD			
Initial sodium (Na_0)	138.1 ± 4.6	137.2 ± 4.7	0.36
Maximal Na in 48 h (Na_{max})	144.0 ± 4.1	140.4 ± 4.5	0.02*
Increase in serum Na (ΔNa)	4.7 ± 2.5	3.2 ± 3.3	0.04*
Clinical parameters at 48 hr			
Fluid intake, L, mean ± SD	7.9 ± 2.1	7.1 ± 1.6	0.04*
Urine output, L, mean ± SD	4.3 ± 1.9	4.1 ± 1.5	0.60
Chloride exposure, mEq, mean ± SD	1028.9 ± 125.3	886.5 ± 143.0	<0.001*
Sodium exposure, mEq, mean ± SD	1002.2 ± 163.7	922.5 ± 145.3	0.01*
BD, mmol/L, mean ± SD	0.2 ± 3.2	−0.1 ± 1.8	0.69
Decreased Hct>10%, n (%)	10 (38.5)	54 (45.4)	0.66
Ranson score, median (IQR)	3.0 (2.8–4.0)	3.0 (2.0–4.0)	0.31
Clinical outcome			
RRT, n (%)	8 (30.8)	0	<0.001*
28-day mortality, n (%)	5 (19.2)	0	<0.001*
Length of stay, d, median (IQR)	22.0 (10.8–38.0)	7.0 (5.0–11.0)	0.002*
Length of ICU stay, d, median (IQR)	15.5 (6.0–21.0)	3.0 (2.0–5.0)	0.003*
Cost, 10000¥, median (IQR)	15.8 (7.0–25.7)	4.0 (2.9–6.0)	0.01*

RAC revised Atlanta classification, SAP severe acute panceatitis, SD standard deviation, IQR interquartile rate, HCT hematocrit, BD base deficit, $[Cl^-]_0$ initial chloride concentration, $[Cl^-]_{max}$ maximal chloride concentration in the first 48 h, $\Delta[Cl^-]$ increase in serum chloride, Na_0 initial sodium concentration, Na_{max} maximal sodium concentration in the first 48 h, AKI acute kidney injury, RRT renal replacement therapy.
*Indicates statistical significance, $p < 0.05$.

Univariate analysis

On univariate analysis, we observed an association between Δ[Cl-] and the development of AKI with an odds ratio of 1.52 (95% CI, 1.27–1.81, $p < 0.001$). In addition, Δ[Cl-] remained strongly correlated with AKI even in those patients who never reached the criteria of hyperchloremia with an odds ratio of 1.65 (95% CI 1.18–2.32; $p = 0.003$) (Table 3). Moreover, a dose-dependent relationship of Δ[Cl-] and severity of AKI was observed: the greater the Δ[Cl-], the more severe the AKI stage. The mean Δ[Cl-] in patients without AKI was 3.08 mmol/L, but 5.61 mmol/L and 9.00 mmol/L for AKI stage1 and AKI stage 2 and 3, respectively (Fig. 2).

Multivariate analysis

To adjust for baseline differences we incorporated age, gender and other potentially confounding variables ($P < 0.1$ in the univariate analysis) such as APACHE II score, Δ[Cl-], ΔNa, hyperchloremia, hypernatremia, serum creatinine, chloride exposure, sodium exposure, fluid intake into a multivariate model and found that Δ[Cl-] remained independently associated with AKI with an odds ratio of 1.32 (95% CI, 1.00–1.74; $p = 0.04$) (Table 4). Similar findings were present for chloride exposure, which was found to be associated with the development of AKI with an odds ratio of 1.01 (95% CI, 1.00–1.02; $p = 0.04$). In contrast, none of the other related variables were independent risk factors for AKI (Table 4).

To account for changes in sodium status, we calculated corrected chloride and took $[Cl^-]_{Corrected}$ into the multivariate analysis. The results showed that $\Delta[Cl^-]_{Corrected}$ remained independently associated with AKI with an odds ratio of 1.29 (95% CI, 1.01–1.66; $p = 0.04$).

Among the 145 patients, 104 were identified as PSAP. On the multivariate analysis of PSAP patients, the association between Δ[Cl-] and the development of AKI was much stronger with an odds ratio of 1.74 (95% CI, 1.03–2.96; $p = 0.04$), while it was found insignificant even in univariate analysis in the other 41 patients. Besides, chloride exposure was also found to be one of the independent risk factors of AKI in PSAP patients with an odds ratio of 1.02 (95% CI, 1.00–1.03; $p = 0.03$) (Table .5).

Receiver operating characteristic curve analysis

AUCROC analysis demonstrated that a Δ[Cl-] cutoff point of 3.5 mmol/L had optimal predictive value (Fig. 3) for the development of AKI with a sensitivity of 96%, a specificity of 61% and an AUCROC of 0.81, which was greater than other potential risk factors such as admission APACHE II score (0.67) and the increase in serum sodium (ΔNa) (0.68).

Discussion

Key findings

We performed a retrospective study of patients with MSAP and SAP to test the hypothesis that changes in serum chloride and the presence of hyperchloremia might be independent risk factors for the development of AKI. We found that hyperchloremia was common and strongly associated with the development of AKI in SAP. The increase in serum chloride ($\Delta[Cl^-]$) and chloride exposure rather than the initial serum chloride concentration ($[Cl^-]_0$) were independent risk factors for AKI. In addition, we also found that the

Table 3
Univariate logistic regression model to test association of AKI and increase in serum chloride ($\Delta[Cl\text{-}] = [Cl-]_{max}$ - $[Cl-]_0$) in all patients and patients without hyperchloremia.

Variable	AKI stage 1–3 Odds ratio (95% CI)	p
All patients		
$\Delta[Cl^-]$	1.52 (1.27,1.81)	<0.001*
Patients without hyperchloremia		
$\Delta[Cl^-]$	1.65 (1.18–2.32)	0.003*

AKI acute kidney injury, $\Delta[Cl^-]$ increase in serum chloride, $[Cl^-]_{max}$ maximal chloride concentration in the first 48 h, $[Cl^-]_0$ initial chloride concentration, CI confidence interval.
*Indicates statistical significance, $p < 0.05$.

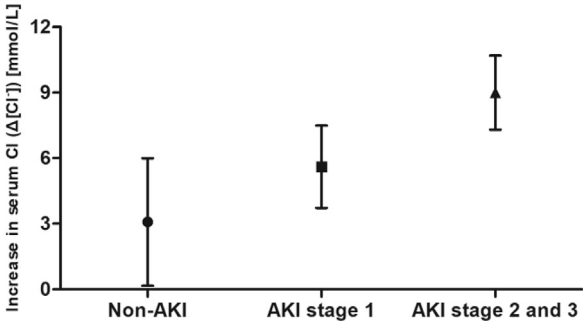

Fig. 2. Increase in serum chloride and AKI severity. The mean increase in serum chloride (Δ[Cl-]) in AKI stage 1, 2 and 3 is significantly higher than in patients without AKI ($p < 0.05$).Δ[Cl-] increase in serum chloride, AKI acute kidney injury.

more $[Cl^-]$ increased, the more severe AKI was likely to develop. Even in the patients who never reached the criteria of hyperchloremia, $\Delta[Cl^-]$ was still associated with the occurrence of AKI. Last but not least, the association between the increase in serum chloride ($\Delta[Cl^-]$) and the occurrence of AKI was found to be stronger in patients identified as PSAP with substantial risk for local and systemic complications.

Relationship of findings to previous relevant studies

Recent studies have found that hyperchloremia resulting merely from fluid therapy was associated with a significant increase in the incidence of AKI in different patient settings and restriction of chloride intake could decrease the incidence of AKI and need for RRT [6–8,25]. AP is a systemic disease in which local inflammatory pathological changes of the pancreas could involve multiple remote organs [26]. The combination of renal impairment and AP can result in an unfavorable clinical outcome, which was repeatedly shown in the literature [5,27,28]. In this study, we found that MSAP and SAP patients with AKI had longer ICU and hospital stay and higher in-hospital cost. Moreover, these patients accounted for all the deaths in the study subjects with a mortality of 19.2%, while no death occurred in patients without AKI.

A study conducted by Bandarn Suetrong et al. [6] in adults with severe sepsis and septic shock found that hyperchloremia and a moderate increase in serum chloride ($\Delta[Cl^-] \geq 5$ mmol/L) were associated with a significant increase in the incidence of AKI. A similar phenomenon can also be seen in other studies [7,8] conducted in patients with subarachnoid hemorrhage and cerebral hemorrhage. However, a systematic review and meta-analysis [29] of randomized controlled trials comparing fluid resuscitation with balanced solution versus isotonic saline in adult patients in operating rooms and ICUs showed that in-hospital mortality, as well as the occurrence of AKI and need for RRT, were not different. In this study, we also found that chloride exposure was significantly associated with AKI in the multivariate logistic model, suggesting a potential role that infusion of chloride may played during the development of renal impairment.

Changes in serum chloride can alter renal blood flow significantly [15], which may partly explain the association between hyperchloremia and increased morbidity of AKI. Recent animal and human studies [14–17] have demonstrated that infusion of saline could result in decreased renal blood flow, reduced glomerular filtration rate, and delayed time to micturition, which could certainly aggravate renal injury. In addition, the tubuloglomerular feedback mechanism initiated by detection of chloride at the macula densa can result in afferent arteriolar vasoconstriction, mesangial contraction and decreased glomerular filtration rate [30]. Similar changes can also be seen in healthy human volunteers treated by saline infusion [17,31,32]. Therefore, it is plausible that hyperchloremia could contribute to the development of AKI.

Implications of study findings

In this retrospective cohort study, we found that the increase in serum chloride ($\Delta[Cl^-]$) during the first 48 h of admission is a key

Table 4
Predictors of AKI in MSAP and SAP.

	Moderately severe acute pancreatitis and severe acute pancreatitis (n = 145)	
	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age	1.05 (1.01,1.08)	1.03 (0.97,1.09)
Male	1.29 (0.54,3.06)	1.57 (0.43,5.7)
BMI	1.05 (0.94,1.19)	1.08 (0.90,1.31)
APACHE II	1.16 (1.04,1.29)	1.05 (0.89,1.24)
Serum creatinine	1.03 (1.01,1.05)	1.02 (0.98,1.06)
$\Delta[Cl^-]$	1.52 (1.27,1.81)	1.32 (1.00,1.74)*
Hyperchloremia($[Cl^-]_{max}$>=110)	8.82 (3.36,23.14)	2.85 (0.77,10.54)
ΔNa	1.14 (1.01,1.30)	0.90 (0.74,1.10)
Hypernatronemia(Na_{max}>145)	4.69 (1.78,12.33)	1.14 (0.31,4.16)
Chloride exposure	1.01 (1.00,1.01)	1.01 (1.00,1.02)*
Sodium exposure	1.00 (1.00,1.01)	0.99 (0.98,1.00)
Fluid intake	1.00 (1.00,1.00)	1.00 (1.00,1.00)

Multivariate logistic regression model was adjusted by incorporating all potentially confounding factors including age, gender, APACHE II score, serum creatinine, chloride and sodium status, chloride exposure, sodium exposure and fluid intake.
BMI body mass index, AKI acute kidney injury, CI confidence interval, APACHE Acute Physiology and Chronic Health Evaluation, $[Cl^-]_0$ initial chloride concentration, $[Cl^-]_{max}$ maximal chloride concentration in the first 48 h, $\Delta[Cl^-]$ increase in serum chloride, Hyperchloremia: [Cl–] max ≥ 110 mmol/L, Na_0 initial sodium concentration, Na_{max} maximal sodium concentration in the first 48 h.
*Indicates statistical significance on the multivariate analysis, $p < 0.05$.

Table 5
Predictors of AKI in PSAP.

	Predicted severe acute pancreatitis (n = 104)	
	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age	1.04 (0.99,1.08)	1.03 (0.96,1.11)
Male	0.99 (0.37,2.67)	1.48 (0.21,10.30)
BMI	1.05 (0.91,1.22)	1.07 (0.83,1.38)
APACHE II	1.16 (1.02,1.32)	1.02 (0.83,1.26)
Serum creatinine	1.02 (0.99,1.05)	0.97 (0.92,1.03)
$\Delta[Cl^-]$	1.85 (1.40,2.44)	1.74 (1.03,2.96)*
Hyperchloremia($[Cl^-]_{max}$>=110)	17.33 (4.58,65.61)	3.73 (0.40,35.18)
ΔNa	1.19 (1.02,1.39)	0.80 (0.60,1.8)
Hypernatronemia(Na_{max}>145)	8.66 (2.72,27.58)	2.91 (0.50,16.80)
Chloride exposure	1.01 (1.01,1.02)	1.02 (1.00,1.03)*
Sodium exposure	1.01 (1.00,1.01)	0.99 (0.97,1.00)
Fluid intake	1.00 (1.00,1.00)	1.00 (1.00,1.00)

Multivariate logistic regression model was adjusted by incorporating all potentially confounding factors including age, gender, APACHE II score, serum creatinine, chloride and sodium status, chloride exposure, sodium exposure and fluid intake.
BMI body mass index, AKI acute kidney injury, CI confidence interval, APACHE Acute Physiology and Chronic Health Evaluation, $[Cl^-]_0$ initial chloride concentration, $[Cl^-]_{max}$ maximal chloride concentration in the first 48 h, $\Delta[Cl^-]$ increase in serum chloride, Na_0 initial sodium concentration, Na_{max} maximal sodium concentration in the first 48 h.
*Indicates statistical significance on the multivariate analysis, $p < 0.05$.

risk factor for AKI, remaining significant even in patients without hyperchloremia and on multivariate analysis. In practice, unlike other more "crucial" electrolytes like sodium and potassium, less attention was usually paid to chloride levels as its clinical significance was not extensively studied. Our results strongly suggest the importance of continuously monitoring and adjusting chloride levels in treatment of MSAP and SAP. Moreover, as the association between chloride and the development of AKI became even stronger in PSAP patients who were supposed to be at substantial risk for local and systemic complications, adjustment of chloride levels should be carefully considered in these patients.

Strengths and limitations

This study has several strengths. It is the first to explore the impact of hyperchloremia on the development of AKI in MSAP and SAP patients. Our data show that the change in serum chloride is an independent risk factor for AKI in this specific entity. In addition, the data also show that chloride exposure is an independent risk factor even after adjustment for key confounders such as illness severity and fluid intake. Finally, by showing an association with the change in chloride even in the setting of normochloremia and by showing a dose-dependent gradient of association, our study carries a degree of biologically and clinically logical credibility.

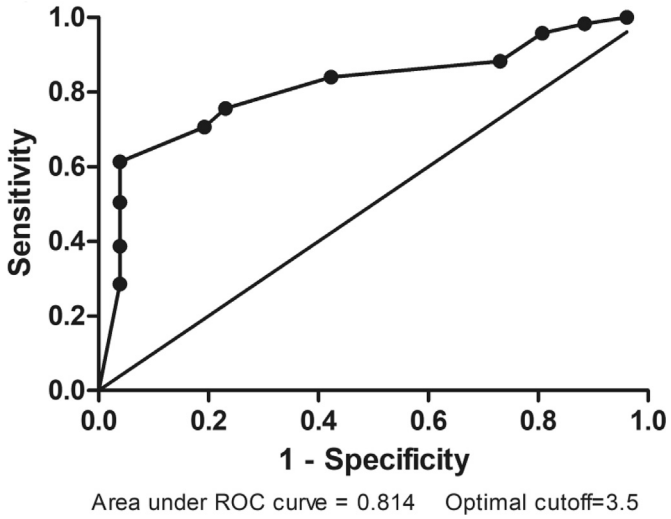

Fig. 3. a, b Receiver operator characteristic analysis for increase in serum chloride in the first 48 h and the development of AKI.

There are several limitations of this study. First, it is a retrospective observational study with limited sample size so that the association between hyperchloremia and AKI does not necessarily imply causality. Thus, a prospective study is needed to address whether restriction of chloride intake is beneficial in the study population. Secondly, in this study, we excluded 59 patients who underwent RRT before admission or within the first 48 h after admission, which may cause a bias toward the low rate of RRT requirement. We did this because the use of RRT would greatly impact serum chloride level, which would confound the study findings. Though RRT is not the standard treatment of pancreatitis in the latest guidelines, it is still widely used in the acute stage of pancreatitis not only to maintain renal function but also to scavenge inflammatory mediators. Most of the excluded 59 patients using RRT had oliguria or anuria and were much more severely ill, which may have contributed to the relatively lower overall morbidity of AKI in this study. Finally, the degree of intra-abdominal hypertension could not be added to the analysis due to missing values.

Conclusion

In conclusion, hyperchloremia is a common finding in MSAP and SAP patients. The increase in serum chloride ($\Delta[Cl^-]$) and chloride exposure rather than initial serum chloride concentration are independent risk factors of AKI and a dose-dependent relationship between Δ[Cl-] and severity of AKI was observed. A moderate increase in serum chloride ($\Delta[Cl^-]$>3.5) was a reasonably accurate predictor of AKI in this population. Further RCTs of intravenous fluid comparing saline vs. balanced solutions with AKI as the primary outcome would be helpful to clarify the possible causal relationship between chloride administration and AKI in the study population.

Availability of data and material

The datasets are available from the corresponding author on reasonable request.

Acknowledgements

Source of funding: The National Natural Science Foundation of China No. 81770641 and Wu Jieping Medical Foundation No.HRJJ20171014.

Disclosures: All authors declare they have nothing to disclose.

Author's contributions: Mao Wenjian had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Lu Ke, Zhihui Tong,Weiqin Li,and Jieshou Li substantially contributed to the study design, Wenjian Mao,Jingyi Wu, He Zhang, Jing Zhou, Bo Ye,and Gang Li contributed to data interpretation and drafting of the manuscript.Wenjian Mao,Lin Gao, and Xiaoyao Li analyzed the data.

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