Hyperchloremia is associated with acute kidney injury in critical ill patients: an analysis of the MIMIC-III database

Jie Gu  
The first affiliated hospital of Soochow University

Tingting Zuo  
The first affiliated hospital of Soochow University

Qingqing Zhu  
The first affiliated hospital of Soochow University

Hui Chen  
The first affiliated hospital of Soochow University

Yanbin Chen  
The first affiliated hospital of Soochow University

Cuiping Fu (✉ fucuipingjy@163.com)  
The first affiliated hospital of Soochow University  https://orcid.org/0000-0002-8805-0998

Research

Keywords: Hyperchloremia, Acute kidney injury, Intensive care unit, chloride

DOI: https://doi.org/10.21203/rs.3.rs-133533/v1

License: ☺️ ☛️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Objective: Balanced fluid with no critical increase of chloride in serum was recommended in clinic. Whether hyperchloremia could make a difference for intensive care unit (ICU) patients with a higher acute kidney injury (AKI) occurrence remains controversial.

Methods: The Medical Information Mart for Intensive Care III (MIMIC-III) database was searched to identify patients hyperchloremia or non-hyperchloremia, and relationship between level of chloride and AKI incidence was analyzed using the univariate and multivariate logistic regression. Patients were divided into four disease subgroups based on the diagnosis at admission: cardiac, cerebral, gastrointestinal, respiratory. The association between maximum chloride (chloride_max) and incidence of AKI in each subgroup was evaluated using the Lowess Smoothing technique. Receiver operating characteristic curves were applied to analyze the diagnostic value of hyperchloremia (chloride_max>110mmol/L) in these four subgroup patients.

Results: A total of 34,617 patients were included in our study, of which 12667 patients (36.6%) was diagnosed with hyperchloremia. The risk of incidence of AKI was increased in the hyperchloremia group. As the higher level of hyperchlorimia, the bigger adjusted odds ratio (OR) presented in terms of AKI, with the OR increasing from 1.13 (95%CI 1.06-1.21; P<0.001) to 4.09 (95%CI 3.04-5.52; P<0.001). Normal level of chloride (95-110mmol/L) was associated with the lower incidence of AKI rate compared to the hypochloremia (<95mmol/L) or the hyperchloremia (>110mmol/L) in any subgroup of cerebral, cardiac, respiratory and gastrointestinal disease. The diagnostic performance was good for cerebral disease (AUC=0.617), cardiac disease (AUC=0.636), respiratory disease (AUC=0.623) and gastrointestinal disease (AUC=0.633). The optimal cut-off value in terms of chloride_max for diagnosing AKI was 116mmol/L for the subgroup of cerebral, respiratory and gastrointestinal diseases, and 115 mmol/L for cardiac patients.

Conclusion: Hyperchloremia was associated with increased risk adjusted AKI incidence among critical ill patients. For ICU patients with cerebral, gastrointestinal and respiratory admission diagnose, the predictive threshold was at 116mmoL/L, and cardiac diagnose was at 115 mmol/L.

Background

Acute kidney injury (AKI) is a major challenge in intensive care unit (ICU) settings, which is characterized by elevated serum creatinine and/or decreased urine output due to a sudden loss of renal function [1]. Critically ill patients are particularly at risk, accounting for 57% of AKI cases [2–4]. Numerous studies showed that changes in serum chloride concentration, independent of serum sodium and bicarbonate, are associated with increased risk of AKI, morbidity, and mortality [5–6]. Hyperchloremia occurred in 57.4% of the study patients within 48 h to ICU admission [7]. The chloride-restrictive intravenous strategy intervention period was associated with a 50% decrease in the incidence of AKI and a decrease in renal replacement therapy (RRT) use [8–10]. Thus balanced fluid with no critical increase of chloride in serum
was recommended in clinic. However, whether hyperchloremia could make a difference for ICU patients with a higher AKI occurrence remains controversial.

The 0.9% Saline vs Plasma-Lyte 148 (PL-148) for ICU fluid Therapy (SPLIT) trial did not demonstrate reduced risk of AKI, rates of RRT, or in-hospital mortality with chloride-restrictive fluid compared with normal saline [11]. Besides, recent meta-analysis showed that there was no clear recommendation to support the choice of chloride-restrictive fluid versus unbalanced fluid [12]. Furthermore, Oh et al. pointed out that increase in chloride levels and perioperative hyperchloremia were not significantly related to the development of postoperative AKI [13]. Lower urinary chloride concentration was associated with increased mortality and incidence of AKI in the ICU [14]. This statement discounts the physiological value of balanced chloride fluid in clinical. With proper insights, the proper chloride concentration can be a significant clinical marker, and the optimal level of chloride for ICU patients to reduce AKI occurrence remains uncertain.

The relationship between hyperchloremia and AKI could make difference in different disease. Hyperchloremia was reported to be a known risk factor for subsequent development of AKI in patients with aneurysmal subarachnoid hemorrhage [15] or septic shock [16], but make no difference in postoperative patients [17]. The effect of chloride level on ICU patients admitted for different systematic diseases was not clear.

In the present study, we aimed to examine the association between hyperchloremia and AKI in ICU patients, further to characterize the optimal scope of chloride concentration with better clinical outcomes, as well as to find out the higher incidence of AKI in distinguished disease, in order to better understand the significance of controlling chloride level in ICU.

**Methods**

**Study design**

We conducted a retrospective single-center study based on a large US-based database called the Medical Information Mart for Intensive Care III (MIMIC-III) [18], which containing data associated with over 50,000 distinct ICU hospital patients between 2001 and 2012. The MIMIC-III (v1.4) database contains comprehensive and high-quality data of well-defined and characterized patients admitted to ICUs at the Beth Israel Deaconess Medical Center. The institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) approved the establishment of the database. The database is accessible to researchers who have completed a ‘protecting human subjects’ training. Data presented in this study were extracted by author Gu, who completed the online training course of the National Institutes of Health (certification number: 34397689).

**Study population and stratification**
Patients who were younger than 18 years old were excluded from this analysis. The following information was extracted: age, gender, comorbidity, sequential organ failure assessment score (SOFA), simplified acute physiology score (SAPS), renal replacement therapy (RRT), glomerular filtration rate (eGFR), initial level of creatinine after ICU admission (creatinine\textsubscript{initial}), maximum level of creatinine during ICU (creatinine\textsubscript{max}), initial level of sodium after ICU admission (sodium\textsubscript{initial}), maximum sodium (sodium\textsubscript{max}), change of sodium during ICU (ΔSodium), initial level of chloride after ICU admission (chloride\textsubscript{initial}), maximum chloride (chloride\textsubscript{max}), change of chloride (ΔChloride), hospital mortality.

We firstly used 95–110 mmol/L as the normal range and reference group in the present study. To further examine the effect of hyperchloremia, chloride\textsubscript{max} was further categorized into five levels for analysis with logistic regression models: level 1 (< 95 mmol/L), level 2 (95–109 mmol/L), level 3 (110–114 mmol/L), level 4 (115–119 mmol/L), level 5 (120–124 mmol/L) and level 6 (≥ 125 mmol/L) to find out the optimal level of chloride for ICU patients. The data were also analyzed in terms of subgroups based on diagnosis at admission: cerebral, cardiac, respiratory and gastrointestinal disease.

Definitions and outcomes

The primary endpoint was incidence of AKI. An increase in serum creatinine level of more than 1.5 times above baseline was considered to be acute kidney injury according to the Kidney Disease Improving Global Outcome criteria [19]. Secondary endpoints included number of patients underwent renal replacement therapy (RRT), hospital mortality, ICU mortality, hospital length of stay (LOS), ICU LOS, score of simplified acute physiology score (SAPS II) and maximum SOFA during ICU stay. For patients with more than one ICU stay, only the first ICU stay was considered.

Statistical analysis

Values are presented as the means (standard deviations) or medians [interquartile ranges (IQRs)] for continuous variables, and categorical variables are presented as total numbers and percentages. Comparisons between groups were made using the Student’s t-test, Wilcoxon rank-sum test as appropriate. Categorical variables were presented as a percentage and were analyzed using the $X^2$ test. The Lowess Smoothing technique was used to explore the crude relationship between chloride and AKI. A logistic regression model was built for each subgroup, applying the normal range of chloride level (95–110 mmol/L) as the reference group. A stepwise backward elimination method with a significance level of 0.1 was used to build the final model. Potential multicollinearity was tested using a variance inflation factor, with a value of ≥ 5 indicating multicollinearity. Receiver operating characteristic curves were depicted to show the diagnostic performance. All statistical analyses were performed using the software Stata V.15. All tests were two sided, and a significance level of $P < 0.05$ was used.

Results

The MIMIC III database contains records for 61567 admissions, of which 15091 were excluded for duplications. Of the remaining 46476 admissions, 7938 were excluded because of age less than 18 years
old, and 3921 were excluded because of data shortage. Finally, 34617 patients were included in this analysis. Among them, 7364 admissions were AKI patients and 27253 admissions were non-AKI patients. The flow diagram of patient selections was presented in Fig. 1.

Demographic characteristics of the AKI and non-AKI were presented in Table 1. The number of patients of each disease subgroup was as follows: cerebral group (8883, 25.7%), cardiac group (28887, 83.4%), respiratory group (16833, 55.0%) and gastrointestinal group (13424, 38.8%). Group of AKI owed more complication of chronic kidney disease (CKD) or sepsis or septic shock but less history of diabetes, hypertension, heart failure, and chronic obstructive pulmonary disease. AKI patients presented higher level of glomerular filtration rate (eGFR), creatinine\textsubscript{initial}, and creatinine\textsubscript{max} than non-AKI patients, and more patients in the AKI group underwent RRT. For the level of chloride, higher level of chloride\textsubscript{max} and \Delta\text{chloride} but not chloride\textsubscript{initial} was shown in the group of AKI patients.
Table 1
Comparisons of demographics between AKI and non-AKI

| Variable                              | AKI      | Non-AKI   | P value |
|---------------------------------------|----------|-----------|---------|
| N                                     | 7364     | 27253     | 0.401   |
| Male sex                              | 4236     | 15528     |         |
| Age (year)                            | 84.8 ± 64.9 | 71.8 ± 50.7 | < 0.000 |
| Cerebral disease (N)                  | 2116     | 6767      | < 0.000 |
| Cardiac disease (N)                   | 6529     | 22358     | < 0.000 |
| Respiratory disease (N)               | 4826     | 12007     | < 0.000 |
| Gastrointestinal disease (N)          | 3929     | 9495      | < 0.000 |
| History of                            |          |           |         |
| CKD (N)                               | 1576     | 1158      | < 0.000 |
| DM (N)                                | 2548     | 6483      | < 0.000 |
| Hypertension (N)                      | 2619     | 12671     | < 0.000 |
| Heart failure (N)                     | 2993     | 5501      | < 0.000 |
| COPD (N)                              | 231      | 468       | < 0.000 |
| Sepsis or septic shock (N)            | 1951     | 1387      | < 0.000 |
| eGFR (ml/min/1.73 m²)                 | 37.4 ± 49.6 | 85.5 ± 70.3 | < 0.000 |
| Creatinineinitial (mg/L)             | 2.1 ± 1.8 | 1.1 ± 1.1 | < 0.000 |
| Creatininenax (mg/L)                 | 2.4 ± 2.0 | 1.2 ± 1.2 | < 0.000 |
| RRT (N)                               | 538      | 100       | < 0.000 |
| Chlorideinitial (mmol/L)             | 105.4 ± 7.4 | 105.9 ± 5.7 | 0.005   |
| Chloridemax (mmol/L)                 | 110.6 ± 6.8 | 108.6 ± 5.2 | < 0.000 |
| ΔChloride (mmol/L)                   | 11.1 ± 6.9 | 8.2 ± 5.7 | < 0.000 |

AKI: acute Kidney Injury; CKD: chronic kidney disease; DM: diabetes; COPD: chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment score; SAPS: simplified acute physiology score; RRT: renal replacement therapy; eGFR: glomerular filtration rate. The standard deviation (SD) was shown in brackets.

Clinical outcome was explored between the hyperchloremia and non-hyperchlomeria patients. Crude outcomes were observed in Table 2 for patients with hyperchloremia and non-hyperchloremia. Without adjusting for other factors, higher incidence rate of AKI and RRT were observed in the hyperchloremia...
group. Hyperchloremia patients presented increased mortality during ICU, as well as higher hospital mortality rate compared to the non-hyperchloremia group. Besides, the hyperchloremia group was associated with longer LOS and ICU length. In addition, patients with hyperchloremia owed higher score of SOFA and SAPS II than the non-hyperchloremia group.

Table 2
Unadjusted outcomes by max serum chloride categories in all patients

| Outcomes             | Total (n = 34617) | Hyperchloremia (n = 12667) | Non-hyperchloremia (n = 21950) | p    |
|----------------------|-------------------|-----------------------------|--------------------------------|------|
| AKI (n(%))           | 7364(21.8)        | 3656(28.9)                  | 3691(16.8)                     | < 0.000 |
| RRT (n(%))           | 638(1.8)          | 306(2.4)                    | 332(1.5)                       | < 0.000 |
| Hospital mortality [n(%)] | 3952(11.4)       | 1980(15.6)                  | 1972(9.0)                      | < 0.000 |
| ICU mortality [n(%)]  | 2971(8.4)         | 1463(11.5)                  | 1508(6.9)                      | < 0.000 |
| Hospital LOS (days) [median(IQR)] | 7.0(4.2–12.1)    | 8.8(5.2–16.2)              | 6.3(3.8–10.3)                  | < 0.000 |
| ICU LOS (days) [median(IQR)] | 2.2(1.3–4.4)    | 3.1(1.7–7.1)               | 2.0(1.1–3.5)                   | < 0.000 |
| SOFA [median(IQR)]   | 4(2–6)            | 4(3–7)                      | 3(1–5)                         | < 0.000 |
| SAPS II [median(IQR)]| 33(25–43)         | 37(29–47)                   | 31(23–40)                      | < 0.000 |

ICU: intensive care unit; LOS: length of stay; AKI: acute Kidney Injury; RRT: renal replacement therapy; SOFA: SOFA, sequential organ failure assessment; SAPS II: Simplified Acute Physiology Score.

Relationship between level of chloride and AKI incidence was analyzed using the univariate and multivariate logistic regression (Table 3). As insignificant chloride_initial was noticed in terms of AKI, chloride_max was categorized into six groups, which were used as design variables in six regression models. The normal level of serum chloride (95–110 mmol/L) was served as the reference group. Results showed that both hypochlorimia ((chloride_max < 95) and hyperchlorimia (chloride_max > 110) were significantly associated with increased AKI. As the higher level of hyperchlorimia, the bigger adjusted odds ratio (OR) presented in terms of AKI, with the OR increasing from 1.13 (95%CI 1.06–1.21) to 4.09 (95%CI 3.04–5.52). Besides, the multivariate logistic regression analyses showed a significant positive effect of diabetes, chronic kidney disease, heart failure, COPD, and sepsis in terms of AKI.
Table 3
Cox proportional hazard models exploring the association of chloride_max with AKI

| Variable                | Univariate model | Multivariate model |
|-------------------------|------------------|--------------------|
|                         | Odds ratio       | 95%CI              | P      | Odds ratio       | 95%CI              | P      |
| Chloride_max (< 95)     | 2.88             | 1.98–2.84          | < 0.000 | 1.84             | 1.51–2.24          | < 0.000 |
| Chloride_max (95–109)   | Ref.             | -                  | -      | Ref.             | -                  | -      |
| Chloride_max (110–114)  | 1.15             | 1.08–1.21          | < 0.000 | 1.13             | 1.06–1.21          | < 0.000 |
| Chloride_max (115–119)  | 2.04             | 1.85–2.26          | < 0.000 | 1.78             | 1.60–2.00          | < 0.000 |
| Chloride_max (120–124)  | 3.02             | 2.46–3.71          | < 0.000 | 2.67             | 2.12–3.36          | < 0.000 |
| Chloride_max (≥ 125)    | 4.43             | 3.40–5.78          | < 0.000 | 4.09             | 3.04–5.52          | < 0.000 |
| Age                     | 1.00             | 1.00–1.00          | < 0.000 | 1.00             | 1.00–1.00          | < 0.000 |
| DM                      | 1.70             | 1.61–1.80          | < 0.000 | 1.36             | 1.28–1.45          | < 0.000 |
| CKD                     | 6.13             | 5.65–6.65          | < 0.000 | 4.60             | 4.20–5.05          | < 0.000 |
| Heart failure           | 2.71             | 2.56–2.86          | < 0.000 | 2.17             | 2.03–2.31          | < 0.000 |
| Hypertension            | 0.64             | 0.60–0.67          | < 0.000 | 0.83             | 0.78–0.88          | < 0.000 |
| COPD                    | 6.13             | 5.65–6.65          | < 0.000 | 1.57             | 1.32–1.88          | < 0.000 |
| Sepsis                  | 6.72             | 6.23–7.24          | < 0.000 | 6.52             | 6.03–7.06          | < 0.000 |

AKI: acute Kidney Injury; DM: diabetes; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease

The specific relationship between chloride_max and incidence rate of AKI for patients in terms of cerebral, cardiac, respiratory and gastrointestinal disease subgroups was analyzed using the Lowess Smoothing technique (Fig. 2). We observed that the normal level of chloride (95–110 mmol/L) was associated with the lower incidence of AKI rate compared to the hypochloremia (< 95 mmol/L) or the hyperchloremia (> 110 mmol/L) in patients with any of the four systematic diseases. Observed lowest AKI rate was shown in the chloride level of 105–110 mmol/L. Thus, it suggests that chloride level of 105–110 mmol/L might be the optimal chlorimia in cerebral, cardiac, respiratory or gastrointestinal patients. Meanwhile, another four logistic regression models were built for analysis of the cerebral, cardiac, respiratory and gastrointestinal disease subgroups. Figure 2 shows the OR and 95%CI for the four subgroups. A similar trend showed that OR was increased either in group of hyperchloremia or the group of hypochlormia, which indicated the normal chlormia contributed to less AKI in ICU.
Receiver operating characteristic curves were applied to analyze the diagnostic value of hyperchloremia (chloride_max > 110 mmol/L) in these four subgroup patients (Fig. 3). The results showed the diagnostic performance was good for cerebral disease (AUC = 0.617), cardiac disease (AUC = 0.636), respiratory disease (AUC = 0.623) and gastrointestinal disease (AUC = 0.633). The optimal cut-off value in terms of chloride_max for diagnosing AKI was 116 for the subgroup of cerebral, respiratory and gastrointestinal diseases. It indicated that hyperchloremia (chloride_max > 116 mmol/L) could be used to predictive diagnostic of AKI in ICU patients with cerebral, respiratory, or gastrointestinal diseases. For the subgroup of cardiac patients, the cut-off value was shown in 115, which suggested that hyperchloremia (chloride_max > 115 mmol/L) could be applied to predictive diagnostic of AKI in ICU.

Discussion

Our results revealed that hyperchloremia was associated with increased AKI patients who were critically ill. A ‘U’-shaped relationship between maximal chloride and AKI was found in our study. Hyperchloremia was related to increased risk of AKI for patients with cardiac, cerebral, respiratory, or gastrointestinal admission disease. To the best of our knowledge, this is the largest study with comprehensive analysis to establish a link between level of chloride imbalance and AKI using MIMIC database.

Chloride plays essential roles in maintaining water balance, muscular activity, acid-base equilibrium, and osmotic balance [20]. Hyperchloraemia induced renal vasoconstriction and reduced glomerular filtration rate in an animal model; Subsequently, associations between hyperchloraemia and mortality have repeatedly been shown in critically ill patients [21–22]. However, the results have been inconsistent and the underlying mechanisms remain unknown. A large observational study conducted by Neyra et al. recently showed that serum chloride concentration at 72 hours from ICU admission—but not at the time of ICU admission—was independently associated with hospital mortality [23]. This is the reason we choose chloride_max as the inference. A potential cause of hyperchloraemia in the ICU may be inappropriate chloride load in fluid therapy, given that the superiority of chloride-restrictive fluid strategy, compared to chloride-liberal fluid strategy, for preventing hyperchloraemia, adverse kidney events.

We found that chloride level of 95–110 was the most optimal serum chloremia for the all-cause critical ill patients, which presented the lowest incidence of AKI. Limited studies regarding the optimal serum chloride level in ICU patients are available. Previous studies showed different opinions about relationship between chloride level and incidence of AKI. Our findings are consistent with several negative retrospective cohorts assessing the role of hyperchloremia in ICU patients. Mao et al. reported that chloride exposure during the first 48 hours were independent risk factors for AKI in moderately severe and severe acute pancreatitis patients [24]. Strong associations between high chloride levels and worse outcome, AKI or death, have been reported [9, 11, 25]; however, in various cohort studies discrepant results exist [26, 27]. None of them found a significant difference in AKI and mortality. Our result was different from previous studies in perioperative hyperchloraemia. Tak et al. showed that increase in chloride levels and perioperative hyperchloraemia were not significantly related to the development of postoperative AKI [13]. The perioperative study included hundreds of participants and pointed out that perioperative
hyperchloremic metabolic acidosis but not chloride level was independently related to an increased incidence of AKI.

Our study showed the positive relationship between hyperchloremia and incidence of AKI. Although some study reported that there was no significant relationship between postoperative chloride concentration and AKI, those study lack high evidence RCT or large enough prospective population [28–29]. Among patients with cerebral disease, previous study reported similar results with our study. Tak et al. pointed out that perioperative hyperchloremia was associated with an increased risk of postoperative AKI after craniotomy for primary brain tumor resection [30]. For patients with respiratory and gastrointestinal disease, few study reported findings in these aspects. The present study innovatively reported relatively higher incidence of AKI in respiratory or gastrointestinal disease admission ICU patients.

The advantage of the present study is the large sample size, which allowed for subgroup analysis and adjustment for confounding factors, but it also has limitations. Firstly, the level of chloride was calculated in the present study rather than being measured directly, which could cause deviation from actual chloride values despite careful consideration of the optimal equation [31]. Secondly, the grouping method was based on diagnosis at admission, and thus overlap within subgroups was unavoidable. Finally, our study provided the association between hyperchloremia and AKI, and pointed out the significant link between hyperchloremia and mortality, owing to the nature of retrospective research, a definitive causal link for further investigation was needed. It also provided compelling evidence to explore that whether correction of the hyperchloremia could reduce AKI or mortality among these patients.

**Conclusion**

Hyperchloremia was associated with increased AKI patients who were critically ill. A ‘U’-shaped relationship between maximal chloride and AKI was found in our study. Hyperchloremia was related to increased risk of AKI for patients with cardiac, cerebral, respiratory, or gastrointestinal admission diseases.

**Declarations**

**Acknowledge**

None

**Authors’ contributions**

B carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.
FCP and CYB conceived of the study, and participated in its design and coordination and helped to draft the manuscript. FCP and GJ conceptualized the research aims, planned the analyses and guided the literature review. GJ extracted the data from the MIMIC-III database. ZTT, CH and ZQQ participated in processing the data and doing the statistical analysis. GJ and FCP wrote the first draft of the paper and the other authors provided comments and approved the final manuscript. The author(s) read and approved the final manuscript.

Funding

The protocol was financially supported by the Suzhou Science, Education and Health Project (KJXW2019003). National Natural Science Foundation of China (Grant No: 81802295).

Availability of data and materials

The datasets presented in the current study are available in the MIMIC III database (https://physionet.org/works/MIMICIIIClinicalDatabase/files/).

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

References

1. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012; 308(15):1566–72.

2. Andrew J P Lewington, Jorge Cerdá, Ravindra L Mehta. Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int. 2013; 84(3):457-67.

3. Rinaldo Bellomo, John A Kellum,Claudio Ronco. RoncoAcute kidney injury. Lancet. 2012; 380(9843):756-66.
4. Kevin Nash, Abdul Hafeez, Susan Hou. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002;39(5):930-6.
5. Marttinen M, Wilkman E, Petäjä L, Suojaranta-Ylinen R, Pettilä V, Vaara ST. Association of plasma chloride values with acute kidney injury in the critically ill a prospective observational study. Acta Anaesthesiol Scand. 2016; 60(6):790–799.
6. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg. 2013; 117(2):412–421
7. Kim de Vasconcellos, David L Skinner. Hyperchloraemia is associated with acute kidney injury and mortality in the critically ill: a retrospective observational study in a multidisciplinary intensive care unit. J Crit Care. 2018; 45:45–51.
8. Brown RM, Wang L, Coston TD, Krishnan Ni, Casey JD, Wanderer JP, Ehrenfeld JM, Byrne DW, Stollings JL, Siew ED, Bernard GR, Self WH, Rice TW, Semler MW. Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial. Am J Respir Crit Care Med. 2019;200(12):1487-1495.
9. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018; 378(9):829–839.
10. Wesley H Self, Matthew W Semler, Jonathan P Wanderer, Li Wang, Daniel W Byrne, Sean P Collins, Corey M Slovis, Christopher J Lindsell, Jesse M Ehrenfeld, Edward D Siew, Andrew D Shaw, Gordon R Bernard, Todd W Rice, SALT-ED Investigators. SALT-ED Investigators: Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med. 2018; 378(9):819–828.
11. Paul Young, Michael Bailey, Richard Beasley, Seton Henderson, Diane Mackle, Colin McArthur, Shay McGuinness, Jan Mehrtens, John Myburgh, Alex Psirides, Sumeet Reddy, Rinaldo Bellomo, SPLIT Investigators. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314(16):1701–10.
12. Anab Rebecca Lehr, Soha Rached-d’Astous, Melissa Parker, Lauralyn McIntyre, Margaret Sampson, Jemila Hamid, Kusum Menon. Impact of balanced versus unbalanced fluid resuscitation on clinical outcomes in critically ill children: protocol for a systematic review and meta-analysis. Syst Rev. 2019;8(1):195.
13. Oh TK, Jeon YT, Sohn H, Chung SH, Do SH. Association of perioperative hyperchloremia and hyperchloremic metabolic acidosis with acute kidney injury after craniotomy for intracranial hemorrhage. World Neurosurg. 2019;125:e1226-e1240.
14. Komaru Y, Doi K, Matsuura R, Yoshida T, Miyamoto Y, Yoshimoto K, Nangaku M. Urinary chloride concentration as a prognostic marker in critically ill patients. Nephrology (Carlton). 2020;25(5):384-389.
15. Ofer Sadan, Owen Samuels, William H Asbury, John J Hanfelt, Kai Singbartl. Low-chloride versus high-chloride hypertonic solution for the treatment of subarachnoid hemorrhage-related complications (The ACETatE trial): study protocol for a pilot randomized controlled trial. Trials. 2018;19(1):628.

16. Suetrong B, Pisitsak C, Boyd JH, Russell JA, Walley KR. Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. Crit Care. 2016;20(1):315.

17. Oh TK, Kim CY, Jeon YT, Hwang JW, Do SH. Perioperative hyperchloremia and its Association With Postoperative Acute Kidney Injury After Craniotomy for Primary Brain Tumor Resection: A Retrospective, Observational Study. J Neurosurg Anesthesiol. 2019;31(3):311-317.

18. Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA, Mark RG. MIMIC-III, a freely accessible critical care database. Scientific Data. 2016;3:160035.

19. Kellum JA, Lameire N, Diagnosis LN. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17(1):204-18.

20. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: chloride in critical illness. Crit Care. 2010;14(4):226-35.

21. Regenmortel NV, Verbrugghe W, Wyngaert TV, Jorens PG. Impact of chloride and strong ion difference on ICU and hospital mortality in a mixed intensive care population. Ann Intensive Care. 2016;6(1):91-99.

22. Masevicius FD, Rubatto Birri PN, Risso Vazquez A, Zechner FE, Motta MF, Valenzuela Espinoza ED, Welsh S, Guerra Arias EF, Furche MA, Berdguer FD, Dubin A. Relationship of at admission lactate, unmeasured anions, and chloride to the outcome of critically ill patients. Crit Care Med. 2017;45(12):e1233–e1239.

23. Neyra JA, Canepa-Escaro F, Li X, Manllo J, Adams-Huet B, Yee J, Yessayan L. Association of hyperchloremia with hospital mortality in critically ill septic patients. Crit Care Med. 2015;43(9):1938-1944.

24. Mao W, Wu J, Zhang H, Zhou J, Ye B, Li G, Gao L, Li X, Ke L, Tong Z, Li W, Li J. Increase in serum chloride and chloride exposure are associated with acute kidney injury in moderately severe and severe acute pancreatitis patients. Pancreatology. 2019;19(1):136-142.

25. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, Wang L, Byrne DW, Shaw AD, Bernard GR, Rice TW; SALT Investigators and the Pragmatic Critical Care Research Group; SALT Investigators. Balanced crystalloids versus saline in the intensive care unit. The SALT randomized trial. Am J Respir Crit Care Med. 2017;195(10):1362–1372.

26. Marttinen M, Wilkman E, Peta-Ja L, Suojaranta-Ylinen R, Pettii L, Vaara ST. Association of plasma chloride values with acute kidney injury in the critically ill - a prospective observational study. Acta Anaesthesiol Scand. 2016;60(6):790–9.

27. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with
SIRS. Intensive Care Med. 2014;40(12):1897-905.

28. Kimura S, Iwasaki T, Shimizu K, Kanazawa T, Kawase H, Shioji N, Kuroe Y, Matsuoka Y, Isoyama S, Morimatsu H. Hyperchloremia is not an independent risk factor for postoperative acute kidney injury in pediatric cardiac patients. J Cardiothorac Vasc Anesth. 2019;33(7):1939-45.

29. McIlroy D, Murphy D, Kasza J, Bhatia D, Wutzlhofer L, Marasco S. Effects of restricting perioperative use of intravenous chloride on kidney injury in patients undergoing cardiac surgery: the LICRA pragmatic controlled clinical trial. Intensive Care Med, 2017, 43(6), 795-806.

30. Oh TK, Kim CY, Jeon YT, Hwang JW, Do SH. Perioperative Hyperchloremia and its Association With Postoperative Acute Kidney Injury After Craniotomy for Primary Brain Tumor Resection: A Retrospective, Observational Study. J Neurosurg Anesthesiol. 2019;31(3):311-317.

31. Heavens KR, Kenefick RW, Caruso EM, Spitz MG, Cheuvront SN. Validation of equations used to predict plasma osmolality in a healthy adult cohort. Am J Clin Nutr. 2014; 100(5):1252-6.