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Associations between hypochloremia with in-hospital mortality and vasopressor dependence in patients with septic shock requiring vasopressors

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ABSTRACT:

Background: Hypochloremia is common and has been linked to increased mortality among critically ill patients. However, the pathophysiological role of hypochloremia is insufficiently explored. This study aimed to assess the associations between hypochloremia with in-hospital mortality and vasopressor dependence among patients with septic shock.

Method: A retrospective cohort study was conducted at Khon Kaen Hospital. Patients with septic shock requiring vasopressors were included from July to December 2022 and categorized into three groups based on serum chloride levels prior to vasopressor initiation (up to 72 hours before septic shock diagnosis): hypochloremia (<96 mEq/L), normochloremia (96-105 mEq/L), and hyperchloremia (>105 mEq/L). The primary outcome was a comparison of in-hospital mortality between patients with hypochloremia and normochloremia. Secondary outcomes include vasopressor duration and vasopressor dependence or death at 24, 48, and 72 hours.

Result: Of the 420 patients included, 35.7% were hypochloremic and 52.4% were normochloremic based on baseline serum chloride status. In-hospital mortality was higher in patients with hypochloremia compared with normochloremia (48.7% vs 37.3%; $P=0.044$). In multivariable analysis ($N=373$), after adjustment for age, sex, infection source, bacteremia, fluid balance, and baseline bicarbonate status, hypochloremia remained associated with increased mortality (adjusted RR 1.48, 95% CI 1.13-1.96; $P=0.005$). No significant differences were found in vasopressor duration or vasopressor dependence or death at 24, 48, and 72 hours among the 3 groups.

Conclusion: Hypochloremia was associated with increased in-hospital mortality after multivariable adjustment in patients with septic shock. However, an association between hypochloremia and vasopressor dependence or duration was not demonstrated. Other adverse outcomes of hypochloremia leading to excess mortality should be further explored.

Keywords: Hypochloremia; Sepsis; Septic shock; Vasopressor

INTRODUCTION

Once considered the “neglected electrolyte,” [1] serum chloride has garnered increasing attention for its essential physiological roles, particularly in critically ill patients [2]. Chloride plays an important part in maintaining serum electroneutrality, acid-base balance, fluid homeostasis, osmotic pressure, gastric acid secretion, renal function, vascular tone, and arterial blood pressure [2, 3].

While the adverse effects of hyperchloremia have been studied extensively, particularly in relation to the use of chloride-rich intravenous fluids and its impact on renal function [4–10], hypochloremia has received comparatively less attention. In recent years, observational studies have suggested an association between hypochloremia and increased mortality in critically ill patients [11], including patients with heart failure [12, 13], cirrhosis [14, 15], and septic shock [16]. Despite this, the mechanistic underpinnings and clinical implications of low serum chloride levels remain inadequately understood, particularly among patients with septic shock. Several physiological pathways may explain these associations, including the role of chloride in vascular smooth muscle cell regulation and plasma tonicity [17, 18], whereby hypochloremia could theoretically lead to vasoplegia, decreased response to catecholamines, and reduced effective intravascular volume.

Given these potential hemodynamic effects, it is important to explore whether hypochloremia correlates with vasopressor requirements—a surrogate marker for circulatory failure. Understanding such associations could provide new insights into the prognostic significance of chloride levels in patients with septic shock.

To our knowledge, no previous study in a cohort from Thailand has evaluated the association between hypochloremia and mortality in septic shock, nor has the association between hypochloremia and vasopressor dependence been examined. This study aimed to evaluate the association between hypochloremia, defined by serum chloride measured within 72 hours before septic shock diagnosis, and clinical outcomes with particular focus on in-hospital mortality and vasopressor dependence as markers of overall prognosis and circulatory failure.

MATERIALS AND METHODS

Study design and participants

We conducted a single-center, retrospective cohort study of patients diagnosed with septic shock, identified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code R57.2 from inpatient records, Khon Kaen Hospital, Thailand. Exclusion criteria included: age <15 years, receipt of <1,000 mL isotonic crystalloid resuscitation within 24 hours before or after septic shock diagnosis, absence of vasopressor therapy, terminal illness, incomplete medical records, unavailable baseline serum chloride levels, and cases adjudicated as non-septic shock. Patients discharged or referred alive within 72 hours after vasopressor initiation were also excluded to ensure adequate assessment of outcomes during the acute phase of septic shock. For patients diag-

KEY MESSAGES:

- Hypochloremia has been increasingly recognized as a mortality risk factor among critically ill patients, including those with heart failure and septic shock.
- The mechanisms linking hypochloremia to adverse outcomes in septic shock remain poorly understood, particularly whether these effects are mediated through hemodynamic pathways, given the physiological roles of chloride in plasma tonicity and vascular tone.
- In our study, we found that hypochloremia was associated with mortality among patients with septic shock requiring vasopressors after multivariable adjustment. However, the associations between hypochloremia and vasopressor duration or vasopressor dependence were not demonstrated.
- These findings suggest that excess mortality associated with hypochloremia may be mediated through non-hemodynamic mechanisms and warrant further investigation.

nosed with septic shock multiple times during a single admission, only the first episode was analyzed. The time of vasopressor initiation was defined as the time of septic shock diagnosis.

Exposure

Patients were stratified into three groups based on baseline serum chloride levels as follows: hypochloremia (serum chloride <96 mEq/L), normochloremia (serum chloride 96–105 mEq/L), and hyperchloremia (>105 mEq/L). Baseline serum chloride levels were defined as the level of serum chloride within 72 hours before vasopressor initiation, reflecting pre-resuscitation status. Baseline serum bicarbonate was categorized as low (<24 mEq/L), normal (24–26 mEq/L), or high (>26 mEq/L). The type and volume of isotonic crystalloid administered within 72 hours after septic shock diagnosis was recorded. Daily fluid balance was also recorded for up to 72 hours.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included vasopressor dependence or death at 24, 48, and 72 hours and vasopressor duration. The composite outcome of vasopressor dependence or death was used to avoid misclassification of patients who died before the assessment timepoint as not vasopressor dependent and to reflect failure of hemodynamic recovery. Vasopressor duration was analyzed among patients who survived to vasopressor discontinuation; patients who died before vasopressor discontinuation were excluded from this analysis. We hypothesized that both hypochloremia and hyperchloremia would be associated with increased mortality compared to normochloremia

and that hypochloremia would be associated with greater vasopressor dependence. Therefore, in-hospital mortality was compared between the 2 groups of hypochloremia and normochloremia, hyperchloremia and normochloremia, and hypochloremia and hyperchloremia. Other potential factors were also analyzed to define the predictors of in-hospital mortality. The differences in vasopressor duration and vasopressor dependence or death at different time points were compared among the 3 groups.

Statistical analysis

Categorical variables were reported as frequencies (percentages), and continuous variables were reported as means with standard deviations or medians with interquartile ranges, as appropriate. Group differences were assessed using the chi-square or Fisher's exact test for categorical variables and the ANOVA or Kruskal-Wallis test for continuous variables, based on data distribution. Normality was assessed using the Shapiro-Wilk test. Given the relatively high incidence of the primary outcome, modified Poisson regression with robust variance was used to estimate adjusted risk ratios (RRs) and 95% confidence intervals (CIs) for in-hospital mortality. Covariates were selected based on clinical relevance and prior literature, with consideration of data availability. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC). All analyses were performed using STATA version 14.1. A two-sided P-value <0.05 was considered statistically significant.

Sample size calculation

Sample size estimation was based on a previous cohort study by Beck et al. [19] that reported an in-hospital mortality of approximately 53% among septic shock patients requiring vasopressors, while Oh HJ et al. [16] reported that hypochloremia was associated with increased in-hospital mortality, with an adjusted hazard ratio of 1.48. In the absence of directly reported absolute risks by chloride category, an approximate effect size was used, recognizing that hazard ratios do not directly translate into risk differences. Using these estimated mortality proportions (53%

vs. 70%), a two-sided alpha error of 0.05, and a beta error of 0.20 (power of 80%), a minimum of 128 patients per group was required to detect a statistically significant difference between the two subgroups.

Ethical considerations

This study was approved by the Institutional Review Board of Khon Kaen Hospital, Khon Kaen, Thailand (KEXP66018). Informed consents were omitted due to the retrospective design of the study. All clinical investigations were conducted in accordance with the guidelines of the 2013 Declaration of Helsinki [20].

RESULTS

Baseline characteristics

A total of 420 patients with septic shock requiring vasopressors were included. Of these, 115 (27.4%) had hypochloremia, 220 (52.4%) had normochloremia, and 85 (20.2%) had hyperchloremia. (Figure 1) The median age was 64 years, and 60.5% were male. Common comorbidities included diabetes mellitus (24.8%) and hypertension (18.1%). The most frequent sources of infection were respiratory (39.5%), urinary (17.1%), and skin/soft tissue (10.2%). Among patients with available data, the mean SOFA score was 11.3 ± 2.2 and was similar across chloride groups. The median cumulative fluid balance over the first 72 hours was 3,700 (1,700-5,700) ml. Baseline acid-base parameters differed across groups, with significant differences in bicarbonate and base excess, while arterial pH was similar; other clinical characteristics and laboratory parameters are presented in Table 1.

In-hospital mortality

The overall in-hospital mortality was 42.4%. Mortality rates by chloride group were hypochloremia: 48.7% (95% CI 39.7%-57.8%), normochloremia: 37.3% (95% CI 31.1%-43.9%), and hyperchloremia: 47.1% (95% CI 36.7%-57.7%). Mortality was significantly higher in the hypochloremia group compared to normochloremia ($P=0.044$), but not significantly different between hyperchloremia and nor-

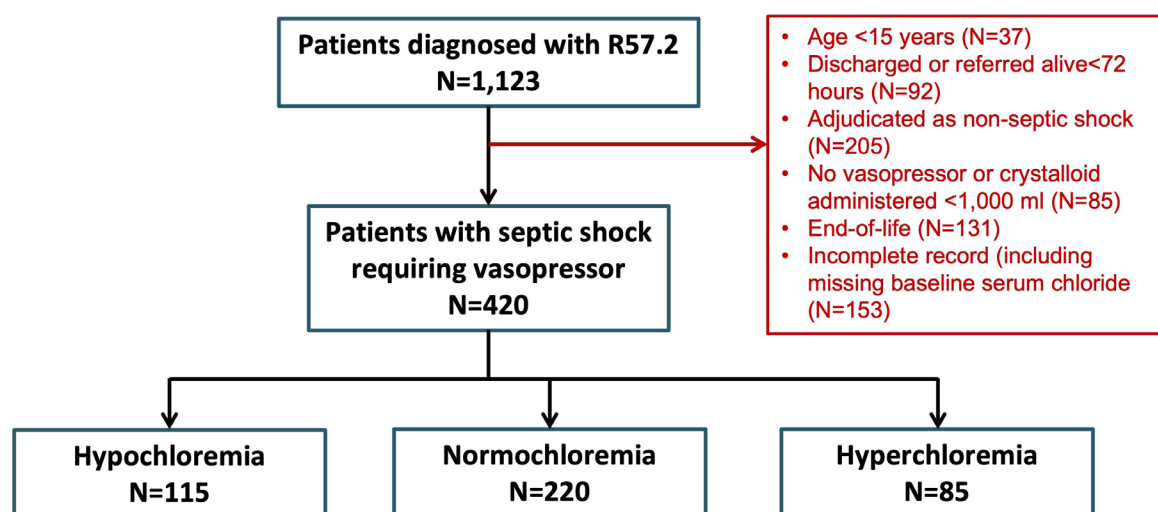


Figure 1. Study flow diagram.

Table 1. Baseline characteristics.

Characteristics	Total (N=420)	Hypochloremia (N=115)	Normochloremia (N=220)	Hyperchloremia (N=85)	P-value
Male (%)	254 (60.5)	72 (62.6)	127 (57.7)	55 (64.7)	0.461
Age (years)	64 (53-74)	62 (51-72)	65 (53-75)	62 (53-73)	0.237
Comorbid conditions (%)					
Diabetes	104 (24.8)	26 (22.6)	57 (25.9)	21 (24.7)	0.802
Hypertension	76 (18.1)	20 (17.4)	43 (19.6)	13 (15.3)	0.670
Heart disease	34 (8.1)	8 (7.0)	17 (7.7)	9 (10.6)	0.622
Chronic kidney disease	34 (8.1)	10 (8.7)	19 (8.6)	5 (5.9)	0.704
COPD/asthma	18 (4.3)	3 (2.6)	10 (4.6)	5 (5.9)	0.475
HIV disease	12 (2.9)	5 (4.4)	5 (2.3)	2 (2.4)	0.537
Malignancy	16 (3.8)	4 (3.5)	9 (4.1)	3 (3.5)	1.000
Sources of infection (%)					
Respiratory tract infection	166 (39.5)	46 (40.0)	82 (37.3)	38 (44.7)	0.489
Skin/soft tissue infection	43 (10.2)	13 (11.3)	21 (9.6)	9 (10.6)	0.874
Urinary tract infection	61 (14.5)	20 (17.4)	33 (15.0)	8 (9.4)	0.274
Gastrointestinal infection	21 (5.0)	4 (3.5)	11 (5.0)	6 (7.1)	0.527
Hepatobiliary infection	29 (6.9)	5 (4.4)	21 (9.6)	3 (3.5)	0.092
Bone and joint infection	2 (0.5)	1 (0.9)	1 (0.5)	0 (0.0)	1.000
CNS infection	5 (1.2)	1 (0.9)	3 (1.4)	1 (1.2)	1.000
Undifferentiated/Unknown source	72 (17.1)	15 (13.0)	39 (17.7)	18 (21.2)	0.303
Bacteremia (%)	74 (17.6)	19 (16.5)	41 (18.6)	14 (16.5)	0.848
Mechanical ventilator (%)	360 (85.7)	100 (87.0)	188 (85.5)	72 (84.7)	0.892
Renal replacement therapy (%)	19 (4.5)	2 (1.7)	12 (5.5)	5 (5.9)	0.250
SOFA score*	11.3±2.2	11.7±2.5	11.2±2.2	11.1±2.0	0.225
Fluid balance in first 72 hours**	3,700 (1,700-5,700)	4,000 (1,900-5,600)	3,500 (1,700-5,700)	4,000 (1,600-7,200)	0.456
Isotonic crystalloid administration in first 72 hour**	5,600 (4,000-7,400)	5,700 (4,400-7,900)	5,500 (3,900-7,200)	5,400 (3,900-7,000)	0.215
0.9% NaCl administration in first 72 hour**	1,400 (0-3,100)	1,600 (0-4,100)	1,400 (0-2,800)	1,000 (0-2,800)	0.144
Balanced crystalloids administration in first 72 hour**	3,600 (1,500-5,800)	3,400 (1,600-5,200)	3,600 (1,500-6,200)	4,200 (1,400-5,700)	0.891
Baseline laboratory parameters (%)					
Creatinine***	1.5 (1.0-2.5)	1.4 (0.9-2.6)	1.8 (1.1-2.5)	1.4 (0.8-2.2)	0.086
Sodium	135 (131-139)	134 (130-140)	135 (131-139)	135 (131-139)	0.944
Hyponatremia	201 (47.9)	58 (50.4)	106 (48.2)	37 (43.5)	0.284
Normonatremia	191 (45.5)	46 (40.0)	100 (45.5)	45 (52.9)	
Hypernatremia	28 (6.7)	11 (9.6)	14 (6.4)	3 (3.5)	
Potassium	3.8 (3.3-4.2)	3.7 (3.3-4.4)	3.8 (3.4-4.2)	3.8 (3.3-4.3)	0.982
Chloride	100 (95-105)	92 (89-94)	101 (98-103)	108 (107-111)	<0.001
Bicarbonate	18.2±5.1	18.9±6.0	18.4±4.8	16.5±4.2	<0.001
Bicarbonate <22 mEq/L	320 (76.2)	80 (69.6)	164 (74.6)	76 (89.4)	<0.001
Bicarbonate 22-26 mEq/L	71 (16.9)	19 (16.5)	47 (21.4)	5 (8.9)	
Bicarbonate >26 mEq/L	29 (6.9)	16 (13.9)	9 (4.1)	4 (4.7)	
pH****	7.36 (7.27-7.43)	7.38 (7.30-7.44)	7.35 (7.26-7.42)	7.38 (7.26-7.46)	0.163
BE****	-8.5 (-14.1 to -4.0)	-6.6 (-12.8 to -2.0)	-9.1 (-14.0 to -5.1)	-9.8 (-14.6 to -6.8)	0.029

Abbreviation: BE: base excess; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; HIV: Human immunodeficiency virus; SOFA: sequential organ failure assessment. *SOFA score was available in 59 patients with hypochloremia, 82 with normochloremia, and 38 with hyperchloremia. **Fluid data was available in 109 patients with hypochloremia, 200 with normochloremia, and 79 with hyperchloremia. ***Serum creatinine was available in 112 patients with hypochloremia, 210 with normochloremia, and 82 with hyperchloremia. ****Arterial pH and base excess were available in 76 patients with hypochloremia, 122 with normochloremia, and 46 with hyperchloremia.

mochloremia ($P=0.118$) or between hypochloremia and hyperchloremia ($P=0.819$) (Figure 2). Modified Poisson regression analysis with robust variance was performed in 373 patients with complete data. After adjustment for age, sex, respiratory infection as the source of sepsis, bacteremia, fluid balance at day 3, and baseline bicarbonate status, hypochloremia remained associated with increased mortality (adjusted RR 1.48, 95% CI 1.13-1.96, $P=0.005$) (Table 2). Model discrimination was moderate, with an AUC of 0.71.

Secondary outcomes

Among the three groups based on baseline serum chloride levels, the median (interquartile range) of vasopressor duration was 34 (16–68) hours in the hypochloremia group, 31 (14–57) hours in the normochloremia group, and 28 (13–64) hours in the hyperchloremia group, with no statistically significant difference observed ($P=0.79$). Vasopressor dependence or death rates at the 24, 48, and 72 hours, were also comparable across the three groups (Table 3).

DISCUSSION

Our study demonstrated that hypochloremia was significantly associated with increased in-hospital mortality compared to normochloremia, while patients with hyperchloremia also exhibited a higher mortality rate, though the difference did not reach statistical significance. These findings support the growing body of evidence suggesting a U-shaped relationship between serum chloride levels and mortality among hospitalized patients [21]. This pattern has been consistently observed across various populations, including those with heart failure [22, 23] and surgical ICU admissions [24]. Our results further underscore the prognostic relevance of serum chloride levels in septic shock.

Hypochloremia may represent a potentially modifiable risk factor of mortality, as evidenced by previous studies where correction of hypochloremia was associated with improved outcomes. Oh HJ et al. reported that an increase in serum chloride levels among patients with

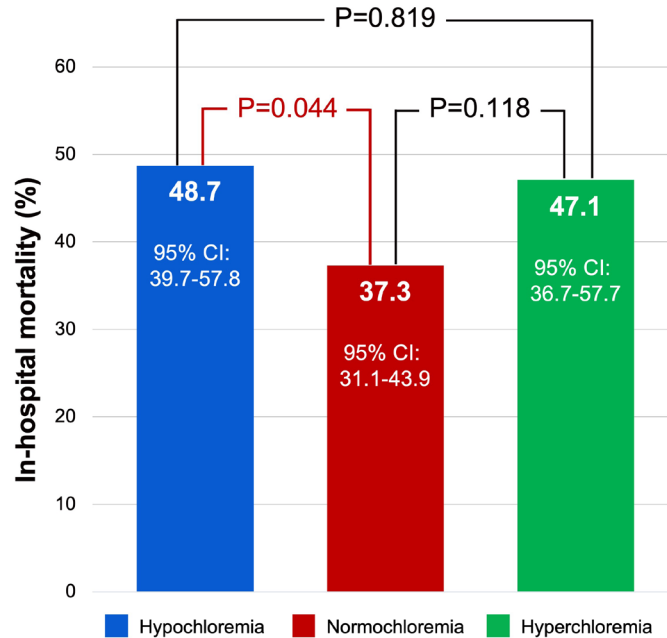


Figure 2. Primary outcome. Abbreviation: CI: confidence interval.

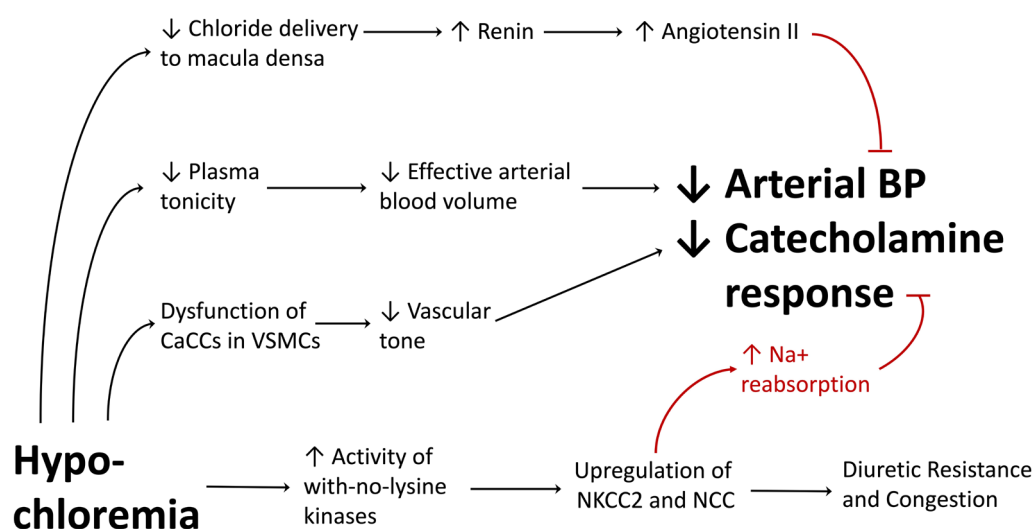
Table 2. Multivariate analysis of factors associated with in-hospital mortality in 373 patients with available data.

Factors	Adjusted RRs (95% CI)	P-value
Age (per 10 year increment)	1.07 (0.98-1.17)	0.141
Male	1.09 (0.85-1.41)	0.500
Respiratory tract infection	1.68 (1.31-2.14)	<0.001
Bacteremia	1.47 (1.13-1.90)	0.004
Positive fluid balance at 72 hours (per 1 L increment)	1.06 (1.03-1.10)	<0.001
Baseline chloride status		
Normochloremia	Reference	
Hypochloremia	1.48 (1.13-1.96)	0.005
Hyperchloremia	1.23 (0.90-1.68)	0.192
Baseline bicarbonate status		
Normal bicarbonate level (22-26 mEq/L)	Reference	
Low bicarbonate level (<22 mEq/L)	1.07 (0.75-1.52)	0.698
High bicarbonate level (>26 mEq/L)	1.02 (0.63-1.65)	0.945

Table 3. Secondary outcomes.

	Hypochloremia	Normochloremia	Hyperchloremia	P-value
Vasopressor du-ration (hours)*	34 (16-68)	31 (14-57)	28 (13-64)	0.79
Death or vasopressor dependence** N (%)				
at 24 hour	75 (65.2)	145 (65.9)	52 (61.2)	0.74
at 48 hour	52 (45.2)	90 (40.9)	38 (44.7)	0.70
at 72 hour	36 (31.3)	68 (30.9)	29 (34.1)	0.86

*Analysis in patients who survived to vasopressor discontinuation: 102 with hypochloremia, 187 with normochloremia, and 72 with hyperchloremia. **Analysis in full cohort.

**Figure 3.** Proposed effects of hypochloremia on blood pressure.

Abbreviation: BP: blood pressure; CaCCs: calcium-activated chloride channels; NCC: sodium-chloride cotransporter; NKCC2: sodium-potassium-2chloride-cotransporter; VSMCs: vascular smooth muscle cells.

septic shock and hypochloremia was associated with decreased 28-day mortality [16]. Similarly, Ramanan et al., in a secondary analysis of the PLUS trial, demonstrated that the mortality benefit favored saline over Plasmalyte-148® in patients with lower baseline chloride levels (<102 mEq/L) [25]. Thus, hypochloremia may represent a potentially modifiable risk factor in the management of critically ill patients [26].

Acid-base disturbances may also have contributed to the observed association between hypochloremia and mortality. Although most patients in our cohort had metabolic acidosis, the hypochloremia group exhibited significantly higher bicarbonate levels and less negative base excess values than the other groups. This pattern suggests that some patients may have had concomitant chloride-depletion metabolic alkalosis superimposed on metabolic acidosis, potentially related to prior diuretic use, gastrointestinal chloride loss, or respiratory compensation. Therefore, hypochloremia may represent a marker of mixed acid-base disorders associated with adverse outcomes. Notably, the association between hypochloremia and mortality remained significant after adjustment for baseline bicarbonate status, suggesting that differences in acid-base balance alone do not fully explain the observed findings.

Although we hypothesized that hypochloremia might be associated with greater vasopressor dependence due to its role in plasma tonicity and vascular tone regulation [17,

18, 27], we did not observe significant differences in vasopressor duration or vasopressor dependence across chloride groups. These findings suggest that hypochloremia may not substantially influence vasopressor responsiveness in this population and that the observed excess mortality might be mediated through non-hemodynamic pathways.

The underlying mechanisms remain incompletely understood. While chloride contributes to vascular tone [18, 27] and plasma tonicity [17], compensatory neuro-hormonal responses may attenuate its direct effects. In particular, activation of the renin-angiotensin system [28] and chloride-sensitive signaling pathways, including with-no-lysine kinases [29], may enhance distal sodium and chloride reabsorption and partially offset circulatory changes (Figure 3). These mechanisms remain speculative and should be considered hypothesis-generating rather than definitive. Alternatively, hypochloremia may serve as a marker of broader physiological derangements, including disturbances in fluid balance [30] or renal function, rather than a direct mediator of adverse outcomes.

Although previous studies have linked hypochloremia with pneumonia [31], acute kidney injury [32], and other complications, our dataset did not include these outcomes. Future investigations should explore whether these organ dysfunctions mediate the association between hypochloremia and mortality in septic shock.

We acknowledge several limitations. First, the study was a retrospective, single-center study, which may limit the generalizability of our findings and is susceptible to residual confounding. The sample size was relatively modest and might have limited statistical power, particularly for secondary outcomes and analyses involving the hyperchloremia subgroup. Second, severity of illness could not be comprehensively adjusted for. Complete SOFA scores and lactate levels were available in only 179 (42.6%) and 308 (73.3%) of 420 patients, respectively. Although available SOFA scores were broadly similar across chloride groups, the absence of these severity markers from the primary multivariable model may have resulted in residual confounding. Therefore, while hypochloremia remained associated with mortality after adjustment for available covariates, the possibility that this association is partially influenced by unmeasured differences in baseline shock severity cannot be entirely excluded. Third, vasopressor parameters may not fully capture hemodynamic responsiveness. Fourth, baseline chloride was defined using values obtained within 72 hours prior to vasopressor initiation, which may not accurately reflect the physiologic status at shock onset. Fifth, detailed data on fluid composition and volume, as well as use of diuretics or bicarbonate before the measurement of serum chloride, were not consistently available, and hypochloremia may therefore reflect treatment patterns rather than underlying pathophysiology. Lastly, dynamic changes in chloride levels over time were not captured, which may be more prognostically relevant than baseline levels alone.

CONCLUSION

Hypochloremia is associated with increased in-hospital mortality in patients with septic shock after multivariable adjustment. However, it was not associated with differences in vasopressor duration or dependence. Further studies are needed to elucidate the mechanisms by which hypochloremia contributes to adverse outcomes in critically ill patients.

CONFIDENTIALITY

All data were de-identified before analysis and handled in accordance with institutional ethical standards.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Yolardee Khankhonchim and Surasak Faisatjatham; (II) Data curation: Yolardee Khankhonchim; (III) Formal analysis: Surasak Faisatjatham; (IV) Funding acquisition: None; (V) Methodology: Yolardee Khankhonchim and Surasak Faisatjatham; (VI) Project administration: Surasak Faisatjatham; (VII) Visualization: Yolardee Khankhonchim and Surasak Faisatjatham; (VIII) Writing – original draft: Yolardee Khankhonchim and Surasak Faisatjatham; (IX) Writing – review & editing: Surasak Faisatjatham.

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