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The prognostic effects of hyponatremia and hyperchloremia on postoperative NSCLC patients

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ABSTRACT

Electrolytic disorders are common in lung cancer patients. But the association between serum electrolytes levels and survival in patients undergoing lung cancer resections for non–small-cell lung cancer (NSCLC) has been poorly investigated. A retrospective study was conducted on consecutive postoperative NSCLC patients. Pearson's test was used to determine the association between serum sodium and chlorine levels and clinical characteristics, and cox regression and Kaplan-Meier model were applied to analyze risk factors on overall survival. We found that hyponatremia was an independent prognostic factor associated with poor prognosis in NSCLC patients undergoing complete resection (log-rank test, $P = 0.004$). In addition, we found that hyperchloremia predicted a poor clinical outcome in patients with non-anion-gap (log-rank test, $P = 0.011$), whereas it predicted a favorable clinical outcome in patients with high-anion-gap (log-rank test, $P = 0.002$). The serum electrolytes levels may reflect the prognosis of NSCLC patients who receive complete resection. Early detection, monitoring, and management of hyperchloremia and hyponatremia might improve patients' prognosis.

ARTICLE INFO

Keywords: Hyponatremia; Hypochloremia; NSCLC; Prognosis; Anion gap

☆ Conflict of interest: The authors declare that they have no competing interests.

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Introduction

Lung cancer is one of the most common causes of death from cancer in men and women.[1] Electrolytic disorders are common in lung cancer patients, especially those patients undergoing lung resection. Many factors can lead to electrolytic disorders in lung cancer patients, such as side effects of chemotherapy or radiotherapy, concurrent diseases, and the cancer itself.[2] Among different types of electrolytic disorders, both hyponatremia and hyperchloremia are one of the most common disorders in cancer patients. Out of various types of cancer, hyponatremia is most frequently associated with lung cancer.[3]

The serum anion gap (AG) is defined as the sum of serum chloride and bicarbonate concentrations subtracted from the serum sodium concentration. The sum of circulating cations must equal the sum of circulating anions. Serum circulating cations include sodium, potassium, calcium, magnesium, and cationic proteins; serum circulating anions include chloride, bicarbonate, anionic proteins, inorganic phosphate, sulfate, and organic anions. However, routinely, only sodium ions, potassium ions, chloride ions, and bicarbonate are measured. The remaining cations and anions can be designated as unmeasured cations and anions, respectively. Unmeasured anions subtracting unmeasured cations, AG is obtained. The concentration of potassium in the blood usually is relatively small compared with that of sodium, chloride, and bicarbonate; therefore, many clinicians omit this variable when calculating the AG, which generally is given as $Na^+–(Cl^- + HCO_3^-)$.

AG could be classified into 3 categories, high-AG, low-AG, and non-AG. Serum AG is often elevated, especially for patients suffering from acidosis. The most common cause of an elevated serum AG is metabolic acidosis,[4,5] and the most common type of metabolic acidosis is hyperchloremic metabolic acidosis. For patients with metabolic acidosis, it is very important to correct acidosis prior to surgery. On the other hand, a nongap metabolic acidosis is characterized by a serum AG that is unchanged from baseline, or a decrease in serum [HCO3$^-$] that exceeds the rise in the AG.[6,7] Nongap metabolic acidosis is defined as a metabolic acidosis in which the fall in serum [HCO_3^-] is matched by an equivalent increment in serum Cl^-.[6,8] Hyperchloremia refers a metabolic acidosis in patients with or without elevation of AG. So it stands to reason that hyperchloremia should associate with the poor outcome of patients with non–small-cell lung cancer (NSCLC). That, however, was not the case in our study.

The associations between serum electrolytes levels and survival of lung cancer patients are rarely investigated, and potential prognostic biomarkers of serum electrolytes level are not well identified. In this study, we performed an analysis to determine the relationship between serum electrolyte level and survival in NSCLC patients, and to investigate the potential prognostic implication of serum electrolyte level, including serum sodium and chlorine.

Methods

Patients

A retrospective study was conducted on consecutive patients with NSCLC undergoing complete resection between January 2007 and May 2014 at Shandong Provincial Hospital affiliated to Shandong University. Clinical data were collected from individual cases. And patients were excluded if they had small-cell lung cancer, or died within 1 month after surgery or pathologically diagnosed with positive surgical margins. Patients with kidney failure, gastrointestinal diseases, and other diseases causing electrolyte disturbances were excluded. Patients with preoperative chemotherapy or radiotherapy were excluded. This study was approved by the Ethical Committee of Shandong Provincial Hospital affiliated to Shandong University.

The eighth edition TNM classification was applied to determine tumor staging.[9] The clinical characters including gender, age, smoking status, pathologic TNM stage, tumor differentiation grade, AG, and electrolyte parameters were collected.

Serum electrolyte

Serum electrolyte values, including Na^+, Cl^-, and HCO_3^-, were detected in 48 hours before surgery. Blood sample was collected from venous blood and detected in 1 hour after collection.

Follow-up

Follow-up information was obtained from all patients through office visits or telephone interviews with the patient, or with a relative, or with their primary physicians. Patients were followed up every 3 months for 1 year after operation, every 6 months for 3 years, and every year thereafter, with a mean follow-up period of 40.84 months (range from 1 to 92 months). A total of 1304 patients were followed up until death or the last day of follow-up (May 2014). The overall survival (OS) in each patient was defined as the interval between the date of the definitive resection and the date of the last follow-up or death, and disease-free survival was defined as the time interval between the date of the definitive resection and detection of first disease recurrence, metastasis, or the date of the last follow-up.

Statistical analysis

All the statistical analyses were performed by SPSS software (version 24.0; SPSS Inc, Chicago, IL). Pearson's test and Fisher's χ^2 exact test were used to conduct the correlation analysis. OS and PFS analyses were performed using the Kaplan-Meier method, and the heterogeneity between groups was analyzed by the log-rank test. The correlations between multiple variables and OS were measured by multivariate Cox regression model. Variables accepted into the multivariate Cox regression model were obtained from the variables that were statistically significant in univariate analysis. R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) with the survival and RMS package was used to perform all analyses via RStudio software (version 1.1.463). Details of the R code used to generate the Kaplan-Meier curve can be assessed in the additional information (Supplementary File 3). The Kaplan-Meier curve was created by use of survival and RMS packages of R 3.5.1.

The optimal cut-off points of electrolyte parameters were identified by using receiver operating characteristic curves (Supplementary File 1).[10,11] For serum sodium level, the cutoff was 141.9 mmol/L. For serum chlorine level, the cutoff was 106.9 mmol/L. A running log-rank test was performed to avoid bias at intervals between the fifth percentile and the 95th percentile of the percentage composition of serum electrolyte parameters. The cutoff value was defined when the log-rank statistical value was maximum.

All the P values were 2-sided, and a P value less than 0.05 was considered to have a significant statistical difference.

Results

Hyponatremia predicted a poor clinical outcome in patients with non-AG

We found that hyponatremia predicted a poor clinical outcome in patients with non-AG (log-rank test, $P = 0.0037$; Fig 1A). To determine the independent predictors of OS, the Cox proportional hazards regression models were used. In univariate Cox analysis, gender ($P = 0.009$), age ($P < 0.001$), smoking status ($P = 0.007$), TNM classification ($P < 0.001$), tumor differentiation ($P < 0.001$), serum sodium ($P = 0.004$) and chlorine ($P = 0.012$) levels were all statistically significant predictors for OS (Table 2). And in multivariate Cox Regression analysis, age was identified as a significantly and independently unfavorable prognostic factor ($P = 0.001$) as well as TNM classification ($P < 0.001$), and tumor differentiation ($P < 0.001$; Table 2). However, there was

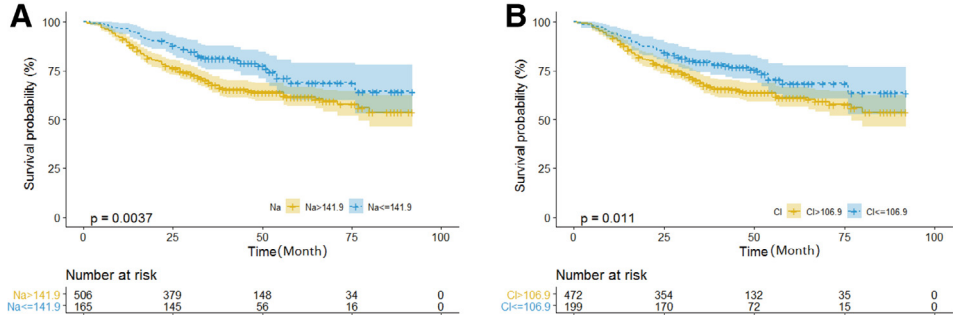

Fig. 1. Hyponatremia and hyperchloremia both predicted a poor clinical outcome in patients with non-anion-gap. (A) The Kaplan-Meier curve of hyponatremia and nonhyponatremia NSCLC patients undergoing complete resection for OS in non-anion-gap group ($P = 0.0037$). (B) The Kaplan-Meier curve of hyperchloremia and nonhyperchloremia NSCLC patients undergoing complete resection for OS in non-anion-gap group ($P = 0.011$). NSCLC, non–small-cell lung cancer; OS, overall survival.

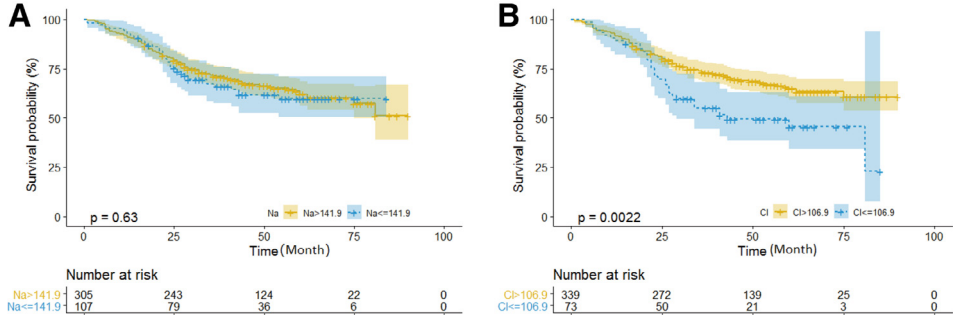

Fig. 2. Hyperchloremia predicted a favorable clinical outcome in patients with high-anion-gap. (A) The Kaplan-Meier curve of hyponatremia and nonhyponatremia NSCLC patients undergoing complete resection for OS in high-anion-gap group ($P = 0.63$). (B) The Kaplan-Meier curve of hyperchloremia and nonhyperchloremia NSCLC patients undergoing complete resection for OS in high-anion-gap group ($P = 0.0022$). NSCLC, non–small-cell lung cancer; OS, overall survival.

no significant association between serum sodium levels and survival with high-AG (data not shown).

Hyperchloremia predicted a poor clinical outcome in patients with non-AG but a favorable one in high-AG group

A total of 1304 patients were enrolled in the study, including 926 males and 378 females. Mean age was 58.77(range from 20 to 84 years old). Of all eligible 1304 patients, 412 were with high-AG, and 671 were with non-AG, and the others are with low-AG. Patients' characteristics, grouped by AG levels, were shown in Table 1. And chi-square tests were used to evaluate the relations between AG levels and clinicopathologic characteristics of NSCLC patients. There were no significant differences observed in gender ($P = 0.998$), age ($P = 0.151$), smoking index ($P = 0.533$), histology ($P = 0.263$), T stage ($P = 0.266$), N stage ($P = 0.057$), TNM stage ($P = 0.610$) and tumor differentiation ($P = 0.134$; Table 1). What interested us most was that hyperchloremia predicted a poor clinical outcome in patients with non-AG (log-rank test, $P = 0.011$; Fig 1B), whereas it predicted a favorable clinical outcome in patients with high-AG (log-rank test, $P = 0.0022$; Fig 2B).

Table 1
The analysis of clinical characteristics of NSCLC patients in high-anion-gap and non-anion-gap group, respectively.

	NSCLC ($N = 1083$)				
	High-anion-gap ($n = 412$)		Non-anion-gap ($n = 671$)		
	No.	%	No.	%	*P*
Gender					0.998
Male	288	69.9	469	69.9	
Female	124	30.1	202	30.1	
Age					0.151
≤65	310	75.2	478	71.2	
>65	102	24.8	193	28.8	
Smoking index					0.533
Never	156	37.9	271	40.4	
<400	33	8.0	60	8.9	
≥400	223	54.1	340	50.7	
Histology					0.263
Adenocarcinoma	209	50.7	366	54.6	
Squamous	167	40.5	239	35.6	
others	36	8.7	66	9.8	
T stage					0.266
1	154	37.4	323	48.1	
2	110	26.7	156	23.3	
3	129	31.3	178	26.5	
4	19	4.6	14	2.1	
N stage					0.057
0	210	51.0	393	58.6	
1	88	21.4	127	18.9	
2	109	26.5	148	22.1	
3	5	1.2	3	0.5	
TNM stage					0.610
I	154	37.4	323	48.1	
II	110	26.7	156	23.3	
III,IV	148	35.9	192	28.6	
Tumor differentiation					0.134
well	54	13.1	118	17.6	
moderate	278	67.5	436	65.0	
poor	80	19.4	117	17.4	

NSCLC, non–small-cell lung cancer.

Hyponatremia and hyperchloremia were both not significant predictors of survival in low-AG group

In low-AG group, clinical outcome in patients with hyponatremia showed no significant difference (log-rank test, $P = 0.23$; Fig 3A), and hyperchloremia was also not a significant predictor of survival in patients with low-AG (log-rank test, $P = 0.61$; Fig 3B).

Metabolic acidosis was not a significant predictor of survival in non-AG group

To explore the causes of the dichotomy predictive effect of serum chlorine levels between non-AG and high-AG, we made a subgroup analysis for non-AG. We classified serum chlorine levels of non-AG into metabolic acidosis, normal, and metabolic alkalosis. And metabolic alkalosis was not included, because it was rare and not enough for statistics analysis. Metabolic acidosis was not a significant predictor of in non-AG group (log-rank test, $P = 0.410$; Fig 4).

Table 2
The univariate and multivariate Cox regression analysis of clinical characteristics of NSCLC patients undergoing lung cancer resection.

	Non-anion-gap($n=671$)		Univariate		Multivariate	
	No.	%	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				0.009		
Male	469	69.9	1			
Female	202	30.1	0.658 (0.481-0.901)			
Age				<0.001		0.001
≤65	478	71.2	1		1	
>65	193	28.8	1.025 (1.012-1.037)		1.616 (1.208-2.161)	
Smoking index				0.007		
<400	331	49.3	1			
≥400	340	50.7	1.450 (1.108-1.897)			
T stage				0.001		
1	323	48.1	1			
2,3,4	348	51.9	1.662 (1.224-2.257)			
N stage				<0.001		
0	393	58.6	1			
1,2,3	278	41.4	3.162 (2.397-4.172)			
TNM stage				<0.001		<0.001
I	323	48.1	1		1	
II,III,IV	348	51.9	3.812 (2.793-5.203)		2.590 (1.597-4.199)	
Tumor differentiation				<0.001		<0.001
well	118	17.6	1		1	
moderate and poor	553	82.4	5.749 (2.950-11.206)		3.373 (1.702-6.684)	
Serum sodium level				0.004		
>141.9	506	75.4	1			
≤141.9	165	24.6	0.606 (0.430-0.854)			
Serum chlorine level				0.012		
>106.9	472	70.3	1			
≤106.9	199	29.7	0.668 (0.488-0.914)			

CI, confidence interval; HR, hazard ratio; NSCLC, non–small-cell lung cancer.

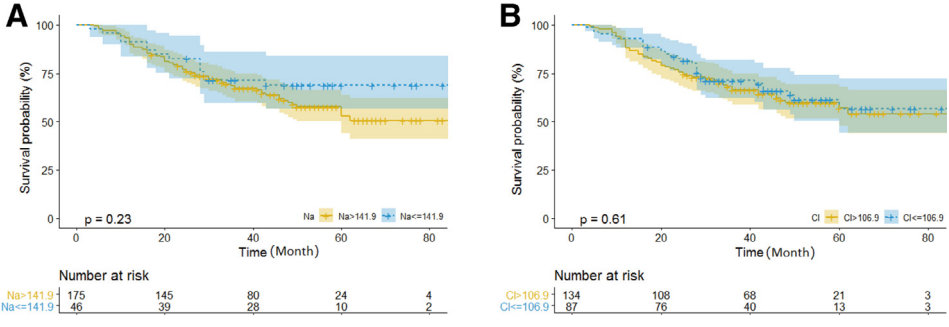

Fig. 3. Hyponatremia and hyperchloremia had no significant effect on prognosis of NSCLC patients with low-anion-gap. (A) The Kaplan-Meier curve of hyponatremia and nonhyponatremia NSCLC patients undergoing complete resection for OS in low-anion-gap group ($P=0.23$). (B) The Kaplan-Meier curve of hyperchloremia and nonhyperchloremia NSCLC patients undergoing complete resection for OS in low-anion-gap group ($P=0.61$). NSCLC, non–small-cell lung cancer; OS, overall survival.

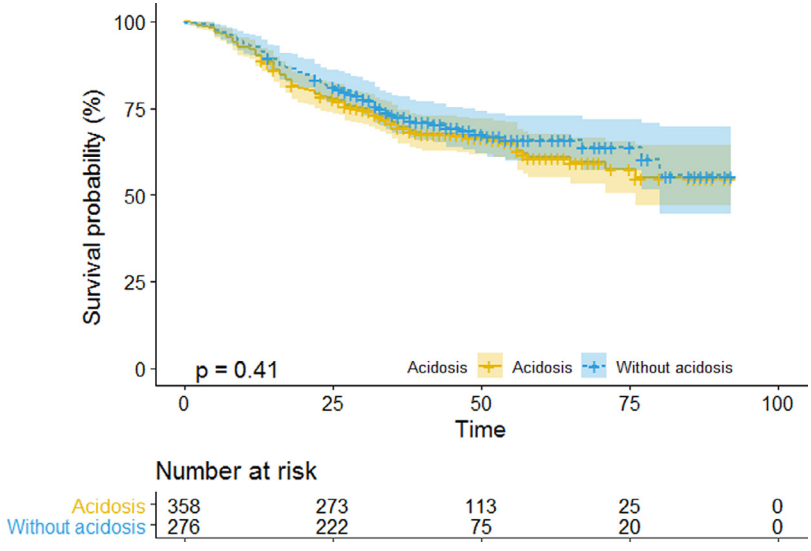

Fig. 4. Metabolic acidosis was not a significant predictor of survival in non-anion-gap group. The Kaplan-Meier curve of acidosis and nonacidosis NSCLC patients undergoing complete resection in non-anion-gap group ($P = 0.41$). NSCLC, non–small-cell lung cancer.

Discussion

Serum AG is often elevated, especially when patients suffer acidosis. In our study, there are 412 cases (31.60%) of elevated serum AG (Table 1). And we found that in high-AG group, hyperchloremia predicts a poor clinical outcome of patients with NSCLC. The most common cause of an elevated serum AG is metabolic acidosis.[4,5] Other probable causes of elevation of serum AG include laboratory error,[12] accumulation of anionic paraproteins (mainly hyperalbuminemia),[13] and so on.

If the accumulating acid contains an anion other than chloride, such as lactate in lactic acidosis or hydroxybutyrate in ketoacidosis, then the decrement in serum bicarbonate will be accompanied by an elevation in the unmeasured anion concentration.[4,5,14,15] This type of metabolic acidosis, therefore, is termed high AG acidosis. High AG acidosis generally is due to overproduction of organic acids or the concomitant and proportionate reduction in the excretion of anions and net acid noted with various types of renal failure.[4,16] AG could be classified into 3 categories—high-AG, non-AG, and low-AG. And similarly, non-AG could be classified into nongap metabolic acidosis, normal, and nongap metabolic alkalosis. In our study, we found that there was no correlation between hyperchloremia and survival in non-AG categories, which is not in accordance with the previous study.[17]

Patients with hyperalbuminemia could be expected to be associated with elevation of AG.[18] Whenever possible, the AG should be corrected for the effect of a change in serum albumin concentration.[19] The serum AG might actually decrease slightly, because the negative charges on albumin are titrated by accumulating protons.[6,20]

There are at least 6 types of chloride channels, including volume-activated (or swelling-activated) chloride channels, the CLC chloride channel family, cystic fibrosis transmembrane conductance regulator, calcium-activated chloride channels, intracellular chloride channels, and ligand-gated chloride channels.[21] In many cells, volume-activated chloride channels are involved in the regulatory volume decrease process induced by hypotonic challenge.[22,23] When cells are swollen under hypotonic conditions, the volume-activated chloride channels, as well as potassium channels, are activated. For instance, hypotonic condition significantly reduced intracellu-

lar Cl^- concentration and simultaneously activated an outward rectifying $I_{Cl,vol}$ in A10 cells.[24] However, in isotonic conditions, the activities and the activation mechanisms of the swelling-activated chloride channels are far from clarified. Mao et al reported that CLC-3 enhanced the migration capabilities of nasopharyngeal carcinoma via regulatory volume decrease.[25] The activation of chloride channels may be involved in the progression of tumor.

Hyponatremia is one of the most common tumor-related electrolyte disturbance and is associated with adverse outcomes of cancer patients. Previous studies have reported that hyponatremia was a poor prognostic factor in several cancers, including hepatocellular cancer,[26] gastric cancer,[27] renal cell cancer,[28] and SCLC.[3,29,30] There were also research papers about the effect of hyponatremia on survival of NSCLC.[31,32] A study of 386 patients with NSCLC showed that serum sodium concentration is a negative prognosis factor in resected NSCLC; however, the *P* value is marginal ($P = 0.047$).[31]

Besides, hyponatremia in patients with cancer is associated with longer hospital stay and higher mortality.[33] The causes of hyponatremia are various, such as syndrome of inappropriate secretion of antidiuretic hormone, excessive water intake, hypotonic infusion, gastrointestinal sodium losses, diuretic use, renal failure, congestive heart failure, liver cirrhosis, nephrotic syndrome, hypothyroidism, adrenal insufficiency, diabetic decompensation, and so on.[34] The most common cause of hyponatremia in cancer patients is secretion of antidiuretic hormone.[35]

In conclusion, hypernatremia predicts a poor clinical outcome of NSCLC patients with non-AG. And the serum chlorine level is reversely associated with survival of NSCLC patients with non-AG. The opposite results are interesting and indicate different significance and prognostic implication of serum chlorine.

The AG is an artificial index, calculated with several electrolyte parameters. However, the elevation of serum AG might not always be parallel to organic acidosis in all patients, which indicate that the serum AG is an insensitive screen for mild to moderate organic acidosis.[36] And the mechanisms that produce normal AG or hyperchloremic acidosis have not been well delineated, it is possible that changes in the reabsorption of chloride independent of sodium or bicarbonate may contribute to the development of hyperchloremic acidosis.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.12.006.

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