Clinics of Oncology

Research Article ISSN: 2640-1037 | Volume 6

Abnormal Sodium and Chlorine Level Is Associated With Prognosis of Lung Cancer Patients

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Received: 29 Jun 2022
Accepted: 07 Jul 2022
Published: 13 Jul 2022
J Short Name: COO

Citation:

Wang W. Abnormal Sodium and Chlorine Level Is Associated With Prognosis of Lung Cancer Patients. Clin Onco. 2022; 6(9): 1-9

Keywords:

Chlorine; Hematologic Tests; Lung Neoplasms; Prognostic Factor; Serum ions; Sodium

1. Abstract

1.1. Objective: The imbalance of sodium and chloride ions occurs frequently in patients with lung cancer. However, the correlation between ion concentration change and patients prognosis have not been studied thoroughly. Our research will fill the gap, especially for high ion concentration.

1.2. Methods: We retrospectively studied inpatients diagnosed with primary NSCLC and treated between May 2015 and July 2017. The basic clinical information and blood test data before and after treatment were collected. According to the clinical reference range of normal ion concentration, the patients were divided into three groups: low, normal and high level. Kaplan-Meier curve was used to analyze the difference of overall survival (OS) prognosis among each group. The correlation between ion concentration and other clinical parameters was further analyzed. Finally, a prognostic nomogram model was established by LASSO-COX method.

1.3. Results: In the 1237 patients cohort, the median follow-up period was 861 days (range 3-2128 days). Firstly, 6 serum ions were included in the study, and only sodium (Na) and chloride (cl) ions were significantly associated with OS. Low level patients were found nearly just in III-IV stage patients, in contrast, high level patients distribute evenly in all stages. Then, correlation analysis showed that increased Na and cl concentrations were associated with decreased neutrophil number and elevated lymphocyte proportion. Finally, prognostic model analysis showed that cl is a crucial parameter.

1.4. Conclusion: Serum Na and cl ion concentrations are closely related to the OS of lung cancer patients, and should be considered as clinical prognostic factors.

2. Introduction

Sodium (Na) and chlorine (cl) ion homeostasis plays an important role in maintaining the balance of human immune system. Salt is the main source of blood sodium and chlorine.

Recent study have shown that high salt diet is a protective factor for lung cancer bearing mice for some possible reasons by immune triggering effect. Firstly, high salt can directly prime macrophages and CD4+ T cells to induce effective tumor specific anti-cancer responses [1]. Secondly, high salt diet can increase the local concentration of sodium chloride in tumor tissue, thus inhibit myeloid-derived suppressor cells (MDSCs) expansion and its accumulation in the blood [2]. Thirdly, high salt induces natural killer (NK) cell–mediated tumor immunity by inhibiting PD-1 expression while enhancing IFN-γ production in blood [3].

A study focused on NSCLC patients staged IIIb/IV, and found

that normal serum Na (NNa) group had significantly longer median progression-free survival (PFS) (7 months vs. 6 months) and overall survival (OS) (16 months vs. 11 months) compared to low serum Na (LNa) group [4]. Similar results were found in a Danish population-based cohort study. Patients with low sodium non-small cell lung cancer have a significantly worse prognosis than those with small cell lung cancer (<135 mM: median OS 0.46 years vs. ≥135 mM: median OS 1.05 years) [5]. Although LNa has been shown to be associated with poor prognosis in patients with lung cancer, high serum Na (HNa) and serum chlorine have rarely been studied. For patients with esophageal cancer treated with radiotherapy or chemoradiotherapy, serum sodium >140.0 mmol/L showed better 5-year progression-free survival (PFS) and overall survival (OS) [6].

According to our hospital laboratory standards, serum sodium concentration is defined as normal between 135-145 mM, and the chlorine is 96-108 mM. We divided the NSCLC patients into three groups (high, normal and low level) according to the reference range, and studied the differences between the groups.

3. Materials and Methods

3.1. Study Population

This is a single-center retrospective study, inpatients who diagnosed with NSCLC at Sichuan Cancer Hospital (SCCH) from May 2015 to July 2017 were enrolled in the study. The exclusion criteria were as follows: (1) no hematologic test before surgery, (2) with kidney disease complications, (3) received any anti-tumor treatment in other hospitals previously, (4) not primary NSCLC or with other primary carcinomas.

The pathological type (Pathotype) was confirmed by histopathology, which includes squamous carcinoma (Squa), adenocarcinoma (Aden), and adenosquamous carcinoma (Adsq). Staging (I, II, III, IV) was performed according to the AJCC eighth edition staging system [7].

3.2. Data source

After approval, all clinical and hematologic test data were provided by the hospital information center and big data center. The patient-sensitive information were removed, data from different sources were matched with encrypted patient ID. A total of 55 hematologic test parameters were included in the analysis, in which 29 parameters were complete blood cell count and 26 parameters were biochemical test. Six serum chemical ions, sodium (Na), chlorine (cl), Calcium (Cal), Phosphorus (P), Potassium (K), Magnesium (Mg), were studied in the analysis, and the reference normal ranges were shown in Supplementary (Table S1).

3.3. Follow-up Investigation

The OS time was defined as the time from diagnosis to death from any cause or to the time of censoring on the date of the last follow-up. The final follow-up evaluation was conducted in May 2021.

3.4. Statistical Analysis

Statistical processing and analysis were performed with R version 4.0.2 (2020-06-22). The study obtained important continuous variables with LASSO regression analysis firstly, and then added categorical variables for multivariate cox analysis, finally constructed a prognostic model. Differences between groups in tables were assessed by the Mann-Whitney U test for continuous variables, Chi square test, and Fisher's exact test for categorical variables. For Kaplan-Meier (K-M) analysis, the log-rank test was used to evaluate the differences between groups. For nomogram, the concordance index (c-index) values were used to evaluate the distinction between the prediction nad true value. The correlation coefficient between ion level and survival outcome was calculated with the Spearman method. For all the statistical analysis, $P < 0.05$ was considered significant.

4. Results

4.1. Patients Screening

A total of 2216 NSCLC inpatients were included in the study and followed by two necessary steps to screen qualified patients (Figure 1). Medical record screening step eliminated 599 patients. Data integrity check step removed another 380 patients. Only 1237 NSCLC patients were included in the analysis.

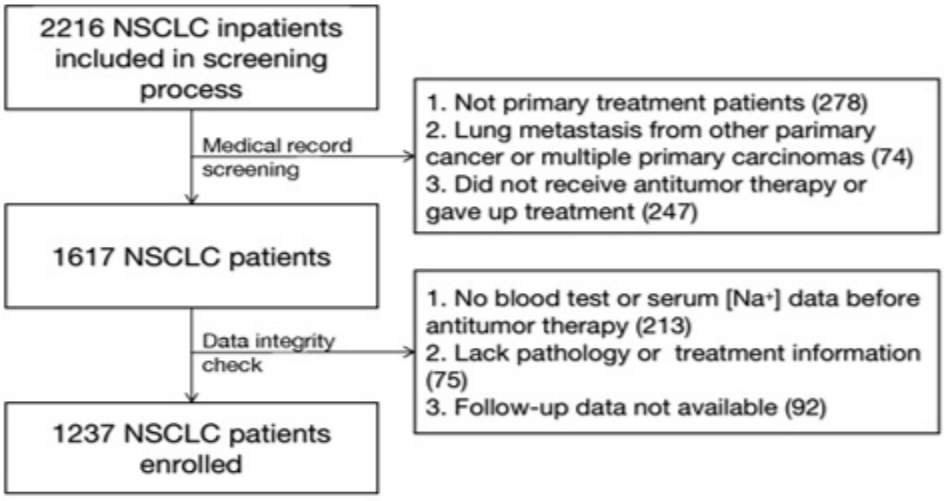


Figure 1: Flow chart of inclusion and exclusion of NSCLC patients included.

4.2. Clinic Pathological Characteristics

Of the 1237 NSCLC patients, more than 98% are Han, and 806 (65.2%) were male, and 431 (34.8%) were female. The median age of all patients was 61 years (interquartile range (IQR): 52-67 years). The majority of patients were diagnosed in III-IV stages (66.9%). The proportion of patients diagnosed with adenocarcinoma, squamous cell carcinoma and adenosquamous cell carcinoma were 67.7%, 28.1% and 1.9%, respectively. About 46% patients were current or former smokers. Patients with abnormal blood sodium and chlorine were 7.1% and 12.5%, respectively.

4.3. Survival Analysis

The median follow-up period was 798 days (range 3-2128 days). The 1-year, 3-year, and 5-year OS for the entire cohort were 69.8%, 39.7% and 10.8% respectively. The median OS was 800 days (IQR: 279-1349 days), and female patients had a significantly better prognosis than men. The median OS for men and women were 664 days (IQR: 242-1198 days) and 1048 days (IQR: 414-1478 days), respectively.

4.4. Occurrence Characteristics of Ion Imbalance

In this cohort, 3.2% and 3.9% of patients were identified as LNa or HNa, respectively (Table 2). Women and non-smokers are more likely to develop HNa. The incidence of high serum chlorine (Hcl) and low serum chlorine (Lcl) were 11.0% and 1.5%, respectively (Table 3). It is important to note that HNa and Hcl were evenly distributed across all stages, while LNa and Lcl were found nearly only in stage III-IV patients.

We also studied the characteristics of patients with abnormal serum potassium, phosphorus, magnesium and calcium ions (Tables not show). No patient had magnesium ions below normal concentrations. No significant correlation was found between abnormal potassium and magnesium and other clinical characteristics. Due to the small number of abnormal cases, it was not possible to confirm the correlation of phosphorus and calcium with sex and stage, respectively.

Table 1: Patient characteristics of the NSCLC patients included (N = 1237).

Characteristics	Level	Overall
Age (median [IQR])		61.0 [52.0,67.0]
Race (%)	Han	1215 (98.2)
	Non-Han	22 (1.8)
Status (%)	Censored	693 (56.0)
	Died	544 (44.0)
Sex (%)	Female	431 (34.8)
	Male	806 (65.2)
Smoking (%)	No	664 (53.7)
	Yes	573 (46.3)
Stage (%)	I	206 (16.7)
	II	132 (10.7)
	III	398 (32.2)
	IV	431 (34.8)
	Undefined	70 (5.7)
Pathotype (%)	Aden	817 (67.7)
	AdSq	23 (1.9)
	Squa	348 (28.1)
	Undefined	29 (2.3)
Na (%)	Abnormal	88 (7.1)
	Normal	1149 (92.9)
Cl (%)	Abnormal	157 (12.5)
	Normal	1082 (87.5)

Table 2: Characteristics of NSCLC patients stratified by sodium level at time of diagnosis (N = 1237)

Characteristics	Level	LNa (<135 mM)	NNa (135-145 mM)	HNa (>145 mM)	P-value
Patients (%)		40 (3.2)	1149 (92.9)	48 (3.9)	
Age (median [IQR])		64.5 [52.0,66.0]	61.0 [52.0,66.0]	65.0 [58.5,71.0]	0.023
Sex (%)	Female	8 (20.0)	395 (34.4)	28 (58.3)	<0.001
	Male	32 (80.0)	754 (65.6)	20 (41.7)	
Smoking (%)	No	19 (47.5)	609 (53.0)	36 (75.0)	0.008
	Yes	21 (52.5)	540 (47.0)	12 (25.0)	
Stage (%)	I	0 (0.0)	189 (16.4)	17 (35.4)	<0.001
	II	1 (2.5)	122 (10.6)	9 (18.8)	
	III	17 (42.5)	371 (32.3)	10 (20.8)	
	IV	22 (55.0)	400 (34.8)	9 (18.8)	
	UN	0 (0.0)	67 (5.8)	3 (6.2)	
Pathotype (%)	Aden	28 (70.0)	771 (67.1)	38 (79.2)	0.296
	AdSq	0 (0.0)	22 (1.9)	1 (2.1)	
	Squa	10 (25.0)	331 (28.8)	7 (14.6)	
	UN	2 (5.0)	25 (2.2)	2 (4.2)	

LNa: low serum Na, NNa: normal serum Na, HNa: high serum Na, mM: mmol/L, Aden: Adenocarcinoma, AdSq: adenosquamous carcinoma, Squa: squamous cell carcinoma, UN: Unknown.

Table 3: Characteristics of NSCLC patients stratified by chlorine level at time of diagnosis (N = 1237)

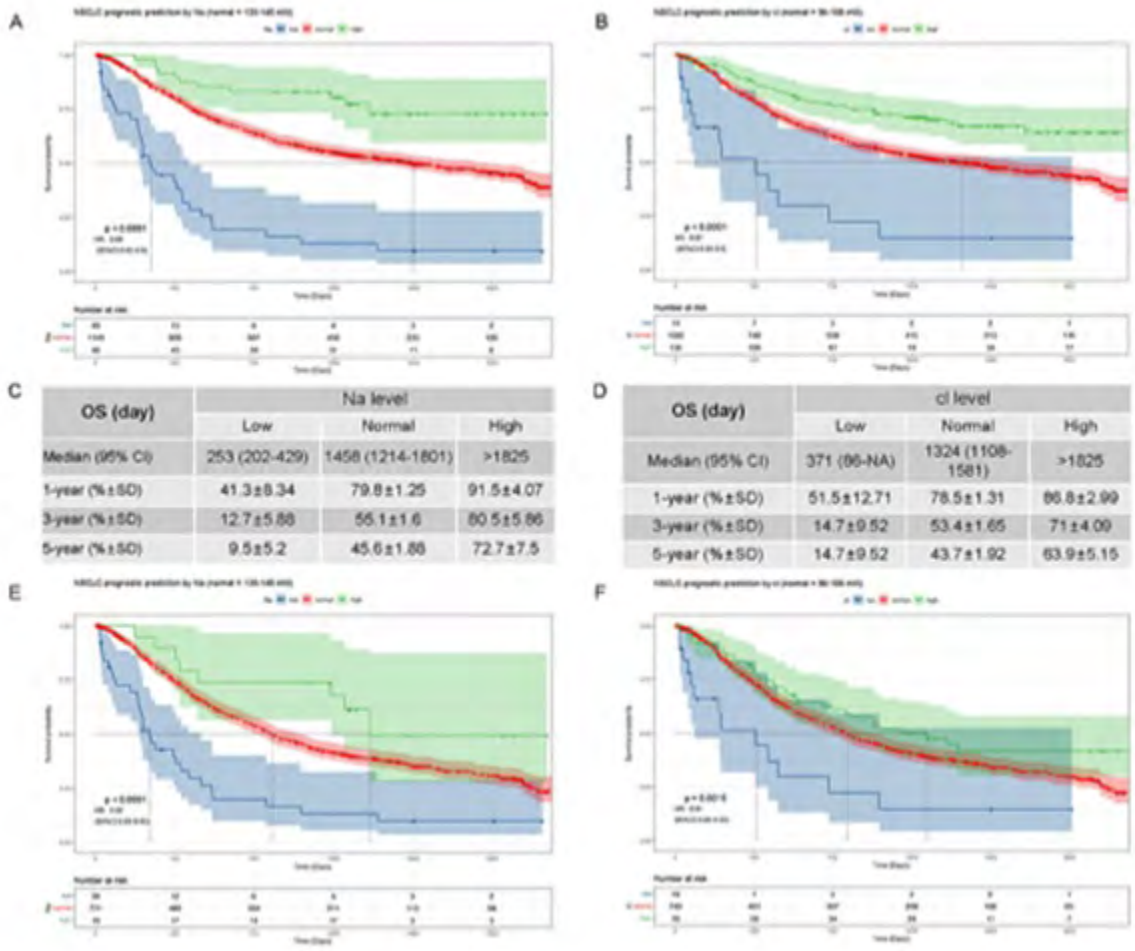
Characteristics	Level	Lcl (<96 mM)	Ncl (96-108 mM)	Hcl (>108 mM)	P-value
Patients (%)		19 (1.5)	1082 (87.5)	136 (11.0)	
Age (median [IQR])		63.0 [53.0, 68.0]	61.0 [52.0, 66.0]	62.0 [52.0, 68.0]	0.655
Sex (%)	Female	3 (15.8)	379 (35.0)	49 (36.0)	0.208
	Male	16 (84.2)	703 (65.0)	87 (64.0)	
Smoking (%)	No	12 (63.2)	575 (53.1)	77 (56.6)	0.526
	Yes	7 (36.8)	507 (46.9)	59 (43.4)	
Stage (%)	I	0 (0.0)	167 (15.4)	39 (28.7)	<0.001
	II	0 (0.0)	112 (10.4)	20 (14.7)	
	III	5 (26.3)	360 (33.3)	33 (24.3)	
	IV	14 (73.7)	380 (35.1)	37 (27.2)	
	UN	0 (0.0)	63 (5.8)	7 (5.1)	
Pathotype (%)	Aden	13 (68.4)	728 (67.3)	96 (70.6)	0.813
	AdSq	0 (0.0)	22 (2.0)	1 (0.7)	
	Squa	5 (26.3)	308 (28.5)	35 (25.7)	
	UN	1 (5.3)	24 (2.2)	4 (2.9)	

Lcl: low serum chlorine, Ncl: normal serum chlorine, Hcl: high serum chlorine, mM: mmol/L, Aden: Adenocarcinoma, AdSq: adenosquamous carcinoma, Squa: squamous cell carcinoma, UN: Unknown

4.5. Correlation Analysis between Ion Levels and Survival Outcome

Analysis showed that patients can be stratified into 3 groups by Na or cl (figure 2A and B), while other ions (Mg, K, P, Cal) can not (figures not show). The OS of patients with HNa and Hcl were significantly better than that of patients with LNa and Lcl (figure 2 C and D). The median OS time of HNa and Hcl patients were more than 1825 days , which is significantly higher than the normal (1458 days, 95% CI: 1214-1801 days) and LNa 253 days, 95% CI: 202-429 days) patients. The 1-year, 3-year and 5-year OS rates of HNa group were 91.5%, 80.5% and 72.7, while the LNa group were 41.3%, 12.7% and 9.5%, respectively. The similar results were obtained in chlorine (figure 2D).

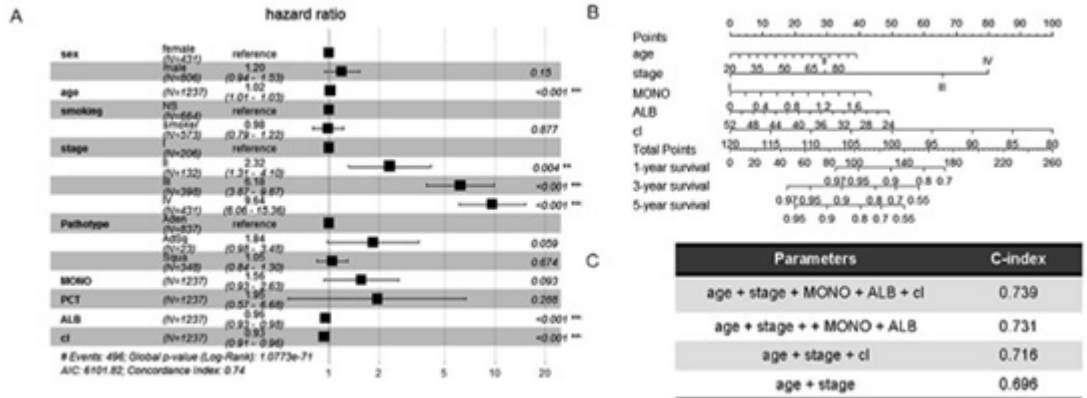
Since high sodium and chlorine patients only exist in stage III-IV, we further analyzed the K-M curve for these patients. The results were basically consistent with the all cohort, but the benefits of patients with high chlorine levels were reduced (figure 2E and F).



OS (day)	Na level		
	Low	Normal	High
Median (95% CI)	253 (202-429)	1458 (1214-1801)	>1825
1-year (%±SD)	41.3±8.34	79.8±1.25	91.5±4.07
3-year (%±SD)	12.7±5.88	56.1±1.6	80.5±5.86
5-year (%±SD)	9.5±5.2	45.6±1.88	72.7±7.5

OS (day)	cl level		
	Low	Normal	High
Median (95% CI)	371 (86-NA)	1324 (1108-1581)	>1825
1-year (%±SD)	51.5±12.71	78.5±1.31	86.8±2.99
3-year (%±SD)	14.7±9.52	53.4±1.65	71±4.09
5-year (%±SD)	14.7±9.52	43.7±1.92	63.9±5.15

Figure 2: Kaplan-Meier survival curves for OS according to pretreatment serum ion concentrations divided into high, normal and low risks by normal ranges. A and B are for all cohort, and E and F are for stage III-IV population. The median and 1-, 3-, 5- year OS of different Na (C) and cl (D) groups.



Parameters	C-index
age + stage + MONO + ALB + cl	0.739
age + stage + + MONO + ALB	0.731
age + stage + cl	0.716
age + stage	0.696

Figure 3: The forest plot of predictive factors (A) by multivariate analysis with important factors. The final prognostic model by nomogram with five selected parameters (B). The c-index list of the prognostic model constructed with different parameters (C). Pathotype: pathological type, ALB: albumin, MONO: monocyte number, PCT: Thrombocytocrit, C-index: concordance index. C-index were calculated by "rms" package.

4.6. Clinical Parameter Correlation Analysis

We analyzed the correlation between serum Na and cl ion concentration and other clinical parameters, including pathology type, therapeutic method, EGFR and ROS mutation features, ki-67 expression levels and blood test parameters. As the number of patients with abnormal sodium and chloride ions were too small, and the treatment plan of patients was too diversified, we could not get important correlation between abnormal ions and clinical effects, gene features and treatment response.

However, in the correlation analysis of blood test parameters, we found that both chloride and sodium ions associate positively with lymphocyte ratio and negatively with neutrophils number. Additionally, sodium was directly proportional to albumin, ALB/GLB ratio and , but inversely proportional to white blood cell number and monocyte number (Table 4). While the chlorine was negatively correlated with neutrophils ratio and platelet number. Since neutrophils, monocytes and lymphocytes have been proved to play an important role in the development and progression of tumors, these results suggest that these two ions play an important role in regulating immune surveillance of tumor cells.

4.7. Dynamic Change Analysis

Of the 82 patients with sodium abnormalities, 10 had only been tested for sodium once during hospitalization. The remaining 72 patients were performed a dynamic ion change analysis. Sodium levels returned to normal in all HNa patients during treatment. Seven LNa patients failed to return to normal levels during hospitalization. The median survival of unrecovered patients was 211 days, remarkably lower than that of other patients' 1020 days.

Among the 134 patients with multiple chloride assays, 6 patients with abnormal chlorine did not return to normal, four of whom were Hcl and two Lcl. Similar to the sodium imbalance condition, the median survival was 250 and 1133 days in the chloride recovery groups and the unrecovered groups, respectively.

4.8. Prognostic Model

The data collected in this study are mainly divided into two types: continuous variable blood test data and categorical variable basic clinical data. Firstly, Lasso regression was performed to reduce the dimension of continuous variables, only ALB, cl, and PCT had absolute values greater than 0.03. Then, these 3 retention parameters were combined with the basic clinical parameters and used to construct the COX regression model. Four factors, sex, pathotype, smoking, and PCT, were further removed for P-value > 0.5 (Figure 3A). Finally, we constructed the nomogram with five selected parameters, age, stage, MONO, ALB and cl (Figure 3B). The concordance index (c-index) of this model 0.74 (Figure 3C). The c-index values for the different parameter combinations are shown in (Figure 3C), cl is an important parameter.

Table 4: The correlation coefficient with sodium and chloride ions

Factor	Coef with Na	Coef with cl
Na	1	0.57
cl	0.57	1
ALB	0.33	
A_G_ratio	0.32	
Lymph_ratio	0.32	0.31
WBC	-0.31	
Neu	-0.33	-0.33
MONO	-0.34	
PLT		-0.31
Neu-ratio		-0.31

Coef: correlation coefficient, ALB: albumin, A_G_ratio: ALB/globulin ratio, Lymph_ratio: lymphocyte ratio, WBC: white blood cell number, Neu: neutrophils number, MONO: Monocyte number, PLT: platelet number, Neu-ratio: neutrophils ratio.

Table S1: The reference ranges and units of collated hematologic test parameters.

Features	Blood_test_item	Refenrence_Range	Units
ALT	Alanine aminotransferase	0.00-50.00	U/L
ALB	Albumin	35.00-55.00	g/L
A_G_ratio	Albumin/globin	1.30-2.50	
ALK_phoase	Alkaline phosphatase	40-150	U/L
GLU	Amylaceum	3.90-6.10	mmol/L
BASO	Basopils number	0.0-0.1	10^9/L
BASO_ratio	Basopils ratio	0-1	%
DBIL	Bilirubin direct	0.00-7.50	umol/L
Cal	Calcium	2.10-2.80	mmol/L
cl	Chlorine	96.00-108.00	mmol/L
CHOL	Cholesterol	2.33-5.20	mmol/L
CREA	Creatinine	36.00-106.00	umol/L
CysC	Cystatin C	0.00-1.16	mg/L
EO	Eosinophil number	0.02-0.5	10^9/L
EO_ratio	Eosinophil ratio	0.5-5.0	%
retic_mfd	Reticulocyte with medium fluorescence intensity	2.4-12.5	%
GLB	Globin	20.00-32.00	g/L
HCT	Hematocrit	33.5-45.0	%
HGB	Hemoglobin	110-150	g/L
imretic_ratio	Imretic reticulocytes	2.1-13.8	%
IBIL	Indirect bilirubin	1.70-17.00	umol/L
Lymph	Lymphocytes number	0.80-4.00	10^9/L
lymph_ratio	Lymphocytes ratio	20-40	%
Mg	Magnesium	0.60-1.20	mmol/L
MPV	Mean platelet volume	7.0-11.0	fL
MCHC	Mean RBC hemoglobin concentration	320-360	g/L
AST	Menpartate aminotransferase	0.00-50.00	U/L
MCH	Meverage RBC hemoglobin	27-31	pg
MCV	Meverage RBC volume	80-100	fL
MONO	Monocytes number	0.12-0.8	10^9/L
MONO_ratio	Monocytes ratio	3.0-8.0	%
Neu	Neutrophil number	2.00-7.00	10^9/L
Neu_ratio	Neutrophil ratio	50-70	%
retic_ratio	Percentage of reticulocycytes	0.50-1.5	%
P	Phosphate	0.80-1.80	mmol/L
PDW	Platelet distribution width	15-17	
PLT	Platelets number	100-300	10^9/L
K	Potassium	3.50-5.50	mmol/L
UA	Purine trione	142.00-440.00	umol/L
RBC_SD	RBC distribution width standard deviation	35-56	fL
RBC	Red blood cell number	3.5-5.0	10^12/L
retic_hfd	Reticulocyte with high fluorescence intensity	0.0-2.0	%
retic_lfd	Reticulocyte with low fluorescence intensity	87.8-98.6	%
retic_count	Reticulocyte count	0.024-0.084	10^12/L
Na	Sodium	135.00-145.00	mmol/L
PCT	Thrombocytocrit	0.108-0.282	%

TBIL	Total bilirubin	2.00-24.00	umol/L
T_CO2	Total carbon dioxide	20.00-29.00	mmol/L
TP	Total protein	55.00-80.00	g/L
TG	triglyceride	0.56-1.70	mmol/L
UREA	Urea	2.40-8.20	mmol/L
RBC_cv	Variation coefficient of RBC distribution	11.5-14.5	%
WBC	White blood cell	4.00-10.00	10^9/L
Fuc	α.L.fucosidase	5.00-40.00	U/L
GGTc	γ.Glutamyl-transferase	0.00-45.00	U/L

5. Discussion

In this study, we constructed a single-center cohort of 1237 inpatients with initial diagnosis of NSCLC. Six serum ions were studied for their correlation with patients prognosis. Overall, patients with high sodium and chlorine levels had much better OS than low level groups. Further, we investigated the correlation of sodium and chlorine with other blood test parameters. The high level groups had more anti-tumor benefit features, such as lower neutrophils, monocytes, and platelets [8-10], but higher albumin and lymphocytes ratio [11-12].

It should be noticed that low or high sodium cancer patients will not be diagnosed with hyponatremia or hypernatremia [13], as a result, most research on hyponatremia or hypernatremia are not included as a reference for our study. In addition, there is a lack of research on chlorine and prognosis of cancer patients. To provide more accurate information, we count the survival time down to the day. For example, in a study of patients on palliative care for terminal cancer patients, the hypernatremia group were found to have worse outcomes [14]. These patients had elevated inflammatory markers and impaired liver function. However, the patients in our HNa group had no other significant differences in blood test results.

For the point that LNa is closely associated with poor prognosis in NSCLC patients, our study is consistent with previous reports [4-5]. The incidence of LNa (3.2%) in NSCLC patients of the study is 3.2%, much lower than 16% for the Danish population-based cohort study [5]. Additionally, in their study, LNa was found in all stage patients, while in our study, only in stage III-IV patients. It could be due to diet or population differences, or due to our stricter screening criteria.

In the study of the dynamic change of sodium levels in patients during the treatment, the HNa group all recovered to normal. Further, the recovery group had a better prognosis than the non-recovery group both in sodium and chlorine abnormal patients. Chlorine and sodium are important parameters in the prognostic model, but sodium was removed during LASSO screening because of the close correlation with chlorine, and the abnormal chlorine group have more patients.

The cause of high sodium in lung cancer patients is still unknown. The blood sodium levels are partially affected by salt intake, some studies have reported that lung cancer bearing mice can benefit from a high sodium diet [2]. However, due to the limitations of retrospective study, much data were not available to investigate whether the HNa patients had a high-salt diet. Several studies have shown that tumor cells have higher expression of voltage-gated sodium channels and low expression of salt-inducible kinase 1 (SIK1) to maintain a local high sodium environment [15]. An in vitro study showed that low extracellular sodium promotes proliferation and invasive activity of cancer cells [16]. As the human body has a powerful homeostasis regulation function, the relationship among salt intake, blood sodium and blood chlorine in cancer patients needs further study.

In summary, abnormal blood sodium and chlorine were associated with prognosis in patients with NSCLC. Patients in the high level group and those who returned to normal after treatment had a better prognosis. However, the abnormal patients cohort is relatively small, which requires more clinical validation and mechanism studies.

6. Acknowledgement

This work was supported by Chengdu science and technology bureau key research and development support plan [2021-YF05-01659-SN], National key research and development plan projects [2017YFC0113904], and key research and development projects of science and technology of Sichuan province [2017SZ0004].

7.Funding

The funding information is: Sichuan Key Research and Development Project from Sichuan Provincial Science & Technology Program (Grant No. 2019YFS0405).

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