Low blood sodium increases risk and severity of COVID-19：a systematic review, meta-analysis and retrospective cohort study

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Abstract

Background

Novel coronavirus (SARS-CoV-2) infects human lung tissue cells through angiotensin-converting enzyme-2 (ACE2), and the body sodium is an important factor for regulating the expression of ACE2. Through a systematic review, meta-analysis and retrospective cohort study, we found that the low blood sodium population may significantly increase the risk and severity of SARS-CoV-2 infection.

Methods

We extracted the data of serum sodium concentrations of patients with COVID-19 on admission from the articles published between Jan 1 and April 28, 2020, and analyzed the relationship between the serum sodium concentrations and the illness severity of patients. Then we used a cohort of 244 patients with COVID-19 for a retrospective analysis.

Results

We identified 36 studies, one of which comprised 2736 patients.The mean serum sodium concentration in patients with COVID-19 was 138.6 mmol/L, which was much lower than the median level in population (142.0). The mean serum sodium concentration in severe/critical patients (137.0) was significantly lower than those in mild and moderate patients (140.8 and 138.7, respectively). Such findings were confirmed in a retrospective cohort study, of which the mean serum sodium concentration in all patients was 137.5 mmol/L, and the significant differences were found between the mild (139.2) and moderate (137.2) patients, and the mild and severe/critical (136.6) patients. Interestingly, such changes were not obvious in the serum chlorine and potassium concentrations.

Conclusions

The low sodium state of patients with COVID-19 may not be the consequence of virus infection, but could be a physiological state possibly caused by living habits such as low salt diet and during aging process, which may result in ACE2 overexpression, and increase the risk and severity of COVID-19. These findings may provide a new idea for the prevention and treatment of COVID-19.

Introduction

A global pandemic of the novel coronavirus (2019-nCoV) -infected pneumonia (NCIP) or coronavirus disease 2019 (COVID-19) has caused great impact on the world economy and human health and life. Clinical research findings have demonstrated that the infection and transmission of this virus has a wide range of susceptibility in populations, but also highlights some of the following characteristic:[1-7] the elderly and people with basic diseases and underlying conditions such as cardiovascular diseases, diabetes, chronic kidney diseases and obesity, etc., are prone to develop to be severe/critical situations after infection; the young and middle-aged people after infection usually have mild symptoms and less chance of forwarding to the severe/critical conditions; the minors are less likely to be infected and onset; there are asymptomatic virus carriers; the mortality rate is related to countries, regions and races.[8] Up to now, the exact reasons and mechanisms that cause such epidemic characteristic have not been clear, and no specific therapeutic drugs and reliable vaccines have been developed and used. Therefore, it is very important to find the key susceptible factors for the prevention and control of this deadly epidemic disease.

The gene sequence of SARS-CoV-2 is highly homologous with that of SARS-CoV.[9, 10] Previous studies have found that such types of viruses mainly enter host cells through the receptor angiotensin-converting enzyme 2 (ACE2), [11, 12] and then replicates and releases new viruses from the host cells, resulting in virus overload in the body, and finally leading to different degree of damage to tissues and organs, especially in lung, through a series of complex pathophysiological mechanisms.

A large number of epidemiological studies have demonstrated that low salt diet plays a role in the prevention and reduction of cardiovascular and cerebrovascular diseases.[13-19] Therefore; it is widely promoted as a healthy diet habit in developed countries and some developing countries. In animal studies, it was found that the decrease of salt intake can upregulate the expression of ACE2 through the activation of the renin-angiotensin-aldosterone system (RAAS).[20, 21] Therefore, we could speculate that the long-term low salt diet or the condition of sodium insufficiency may result in the low body sodium and the overexpression of ACE2 in lower respiratory tract cells, which could increase the susceptibility and pathogenicity of SARS-CoV-2 infection. In this study, we aimed to find a key risk factor for SARS-CoV-2 epidemic by investigating the relationship between the blood sodium concentration and the severity of patients with COVID-19 through a systematic reviews, meta-analysis and retrospective cohort study.

Methods

Systematic review and meta-analysis

Search strategy and selection criteria

We did a systematic review and meta-analysis from the observational and retrospective cohort studies to compare the serum sodium concentrations of confirmed patients with COVID-19 in relation to the severity of disease according to PRISMA guidelines.[22] MedRxiv and BioRxiv databases, PubMed and the Web of Science Core Collection (Clarivate Analytics) were used for searching articles published between Jan 1 and April 28, 2020 using the keyword “sodium” in combination with other keywords “SARS-CoV-2”, “COVID-19”, “Coronavirus”, “nCoV”, “HCoV” or “NCIP”. Detailed search strategies were presented in Figure 1. After removing duplicates, two researchers were assigned to independently screen the titles and abstracts, and then examine the full text. Any questions with conflict were resolved by discussion. Inclusion criteria were as follows: (1) any study must contain the information about serum biochemical test of electrolytes on admission, (2) restriction language to English only, and (3) studies that presented the severity of disease in relation to the serum sodium concentrations or allowed us to evaluate the severity of disease by using the clinical information, experimental tests and imaging data, etc., presented in the reports according to the criteria as mentioned below in the retrospective cohort study. Exclusion criteria were (1) data that could not be reliably extracted, (2) reviews, editorials, comments, expert opinions, case reports or articles with small number of cases (≤ 10).

Retrospective cohort study

Study design and participants

The retrospective cohort study included a cohort of 244 COVID-19 inpatients aged from 7 to 96 years old and 59 non-COVID-19 inpatients (control) aged from 10-90 years old from Zhongnan Hospital of Wuhan University (Wuhan, China). All patients who were diagnosed with COVID-19 according to WHO interim guidance were screened from Dec 31, 2019 to Feb 27, 2020 (control patients from Dec 1, 2019 to Jan 25, 2020). This case series was approved by the Zhongnan Hospital of Wuhan University for Ethics Committee (No. 2019125).

Definition of severity

The severity of patients with COVID-19 was defined at admission based on the criteria established by China's National Health Commission.[23] Mild (I): Minor symptoms only, without evidence for pneumonia by chest X-ray; Moderate (II): Fever and respiratory symptoms are present, and there is evidence for pneumonia by chest X-ray; Severe (III): Defined by any of the following conditions: (1) Dyspnoea, respiratory rate 30 /min, (2) resting hypoxia $SaO_2 \leq 93\%$, and (3) $PaO_2/FiO_2 \leq 300$ mmHg; Critical (IV): The presence of any of the following conditions: (1) Respiratory failure, require mechanical ventilation, (2) shock, and (3) other acute organ failure.

Laboratory procedures

Methods for laboratory confirmation of COVID-19 infection have been described elsewhere.[6] COVID-19 detection was done in respiratory specimens by next-generation sequencing or real-time RT-PCR methods. Serum biochemical test of electrolytes at admission was carried out with other tests including renal and liver function, creatine kinase, lactate dehydrogenase, myocardial enzymes, interleukin-6 (IL-6), serum ferritin, and procalcitonin, etc.

Data collection

For the systematic review and meta-analysis, the data for laboratory test of serum sodium, chloride and potassium concentrations, and the clinical severity of patients on admission were collected, and the concentration is represented as median (IQR, interquartile range) or mean (SD, standard deviation) depending on the reports. For the retrospective cohort study, epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records, and only basic information such as age, gender, clinical severity of patients and serum sodium, potassium and chloride concentrations on admission were selected for data analysis. All data were checked independently by two researchers.

Data analysis

For the systematic review and meta-analysis, median or mean values of serum sodium, chloride and potassium concentrations from each report were considered as an independent variable for statistical analysis, and an unpaired *t*-test was used to compare the differences between the groups related to the severity of disease. For the retrospective cohort study, one-way ANOV, followed by Tukey's multiple comparisons test, was used to compare the differences among groups or an unpaired t-test was used if necessary. To assess the association between sodium, chloride or potassium concentration, and the severity of patients with COVID-19, Spearmann's rank correlation coefficient was used. $P<0.05$ was defined as showing statistical significance of differences. All analyses were performed by using GraphPad Prism 7 software.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors (JD and YL) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For the systematic review and meta-analysis, we identified 682 papers published between Jan 1 and April 28, 2020. After removing unsuitable studies (duplicates, not relevant, inappropriate reviews, inadequate information and case reports), 36 studies had adequate data that were represented in the dataset (Table S1) for further analysis. These studies included 32 observational (or cohort) reports from different regions in China, 3 from the United States (US), and 1 from Iran. The smallest sample size included 12 patients and the largest one comprised 2736 patients. 15 of 36 studies (44.4%) provided the normal range of serum sodium concentration, which mostly were 137-147 mmol/L (Table S1).

We found that the serum sodium concentrations in patients with COVID-19 on admission presented the characteristic as follows (Table 1, Figure 2): regardless of the disease severity, the mean serum sodium concentration was 138.6 mmol/L (138.6±2.5, n=31), which was significantly lower than the median level (142.0) of normal reference range (137.0-147.0); the mean serum sodium concentration in severe/critical patients was 137.0 mmol/L (137.0±2.02, n=25), close to the lower level of normal range, and was significantly lower than those in mild (140.8±4.0, n=7) and moderate (138.7±2.35, n=23) patients (P=0.0019 and P=0.0141, respectively), but there was no significant difference between the mild and moderate patients (P=0.0927) (Table 1, Figure 2A); some studies showed that the serum sodium concentrations in patients who died after admission were even lower than that in recovered patients (Table S1, refs 30); the serum sodium concentrations in severe/critical patients with tuberculosis (Table S1, ref 16) were very low (131.67±3.08); Three studies from the United States demonstrated that the median level of serum sodium concentrations in patients with COVID-19 was approximately 136.0 mmol/L (135.5-137.0), close to the lower level of normal range (Table S1, refs 23, 31 and 35); The median serum sodium concentration from 34 paediatric patients aged from 1 to 144 months (median 33) with COVID-19 was 139.0 mmol/L (137.88-141.13), which is lower than the median level of normal range (Table S1, ref 17). The serum sodium concentrations were significantly correlated to the illness severity of patients (Table 1, Figure 2B, r=-0.4558, p=0.0005).

In addition, we analyzed the serum chloride and potassium concentrations related to the disease severity. The mean serum chlorine concentrations in all, mild, moderate and severe/critical patients were 101.8 mmol/L (101.8±2.25, n= 10), 103.15 mmol/L (102.9 and 103.4, respectively, n=2), 102.1 mmol/L (102.1±2.39, n=9) and 101.3 mmol/L (101.3±2.06, n=10), respectively, and no statistical differences were found between the comparable groups (Table 1, Figure 2C) , while the mean serum potassium concentrations in all, mild, moderate and severe/critical patients were 4.01 mmol/L (4.01±0.20, n=28), 3.99 mmol/L (3.99±0.18, n=7), 3.99 mmol/L (3.99±0.19, n=21) and 3.90 mmol/L (3.90±0.28, n = 23), respectively, and there were no statistical differences between the groups (Table 1, Figure 2E). The serum chloride and potassium concentrations were not correlated to the severity of patients (Table 1, Figure 2D, F).

For the retrospective cohort analysis, we collected data of 244 laboratory-confirmed COVID-19 patients and 59 non-Covid-19 patients as control from a single center (Zhongnan Hospital of Wuhan University) between Dec 30, 2019 and Feb 27, 2020 (from Dec 1, 2019 to Jan 9, 2020 for control). The data of age, gender and severity of patients with and without COVID-19 were summarized in Table 2. The average age was 57.49 years (57.49±19.13) from 7-96 years in the patients with COVID-19, and 51.07 years (51.07±19.21) from 10-90 years in the control group. 127 of 244 (52.05%) were male, 117 (47.95 %) were female, and 7 were minors (2.87 %) in the COVID-19 group. The numbers of mild, moderate, severe and critical patients were 65, 61, 77, and 41, respectively. We have obtained very similar results as those in the systematic review and meta-analysis (Table 2, Figure 3): the mean serum sodium concentration in all patients was 137.5 mmol/L (137.5±4.12, n=244, Table 2, Figure 3A, D), which was much lower than the median value of normal reference range (142.0 mmol/L, 137.0 -147.0, Table 2) and significant lower than the mean level of control patients (138.9±2.77, n=59, p=0.0443, Table 2, Figure 3D); the mean serum sodium concentration in 60 years and older patients was 136.6 mmol/L (136.6±4.62, n=120), which was significant lower than that in patients under 60 years (138.3±3.411, n=124, P=0.0019, Table 2, Figure 3B); there was significant difference between male and female in the mean serum sodium concentrations (136.7±4.25 and 138.3±3.82, P=0.0021, Table 2, Figure 3C), however, there were no difference in gender and age (<60 years and ≥60 years) in control patients (Table 2) ; the mean serum sodium concentrations in the mild, moderate and severe/critical patients were 139.2 mmol/L (139.2±2.72, n=65), 137.2 mmol/L (137.2±3.72, n=61), and 136.6 mmol/L (136.6±4.66, n=118), respectively, and the differences between the mild and moderate groups as well as the mild and severe/critical groups were significant (p=0.0330 and p=0.0003, respectively) , but there was no significant difference between the moderate and severe/ critical groups (p=0.7886) (Table 2, Figure 3D); The serum sodium concentrations were significantly correlated to the illness severity of patients (Table 2, Figure 3E, r=-0.2462, p=0.0001).

We also analyzed the serum chloride and potassium concentrations in all patients and there were no significant differences in gender (male vs female) and age (≥ 60 vs <60 years) in the non-COVID patients (Table 2). The mean serum chlorine concentrations in all, mild, moderate and severe/critical patients were 102.1 mmol/L (102.1±4.20, n=244), 103.2 mmol/L (103.2±3.05, n=65), 102.2 mmol/L (102.2±4.34, n = 61), and 101.4 mmol/L (101.4±4.55, n=118), respectively. There were no significant differences between the groups with the exception of the mild and severe/critical groups (p=0.0306) (Table 2, Figure 3F). The serum chloride concentrations were significantly correlated to the severity of patients (Table 2, Figure 3G, r=-0.1753, p<0.0060). The mean serum potassium concentrations in all, mild, moderate and severe/critical patients were 4.00 mmol/L (4.00±0.56, n=244), 4.10 mmol/L (4.10±0.41, n=65), 3.96 mmol/L (3.96±0.65, n=61) and 3.97 mmol/L (3.97±0.65, n =118), respectively, and there were no statistical differences between the groups (Table 2, Figure 3H). The serum potassium concentrations were slightly correlated to the severity of patients (Table 2, Figure 3I, r=-0.1394, p=0.0419). There was no differences in serum potassium and chlorine concentrations between the 60 years and older patients (3.99±0.59 and 101.6±4.7 mmol/L, respectively, n=120) and the patients under 60 years old (4.02±0.53 and 102.5±3.57 mmol/L, respectively, n=124) (Table 2, Figure 3B).

Discussion

In this study, we found that the patients infected by SARS-CoV-2 on admission have presented the low blood sodium levels (hyponatremia) that were related to the disease severity. The occurrence of such a condition may not be the consequence of virus infection, but should be a physiological state being existed in the body before virus infection. There were no clear reasons that could cause such a significant reduction of blood sodium concentration because diarrhea and vomiting occurred only in a small number of patients. The fever, a main symptom of patients with CIVID-19, may lead to dehydration and then should increase, but not reduce the blood sodium concentration. Therefore, we could boldly speculate that the low blood sodium population, especially the elderly and people with underlying diseases, may increase the risk and illness severity to SARS-CoV-2 infection, and one possible explanation is that the people companied with long-term hyponatremia may increase the expression of ACE2 in tissue cells, especially in lung cells, through the RAAS.[20, 21]

Hyponatremia is closely related to the incidence and severity of community-acquired pneumonia and perforated acute appendicitis in children.[24-26] Clinical studies have showed that the elderly are more susceptible to SARS-CoV-2 infection and become more severe than the young and middle aged people, which may be due to the lower blood sodium levels in the elderly population. One of the reasons may be the decrease of the regulation mechanism of sodium ion in the elderly, including the decrease of renal reabsorption function for sodium ion during aging process; however, another key reason may be the result of long-term low sodium diet. For a long time, especially in the developed countries, the strategy of low sodium diet being actively implemented by physicians, medical organizations and public health agencies has played an important role in preventing and controlling hypertension and related diseases,[27,28] however, some recent evidence suggests that very low sodium intake may actually have adverse effects on human health, which may also preset a very unfavorable state in certain population against SARS-CoV-2 infection. In this study, we found that some young severe patients with CODIV-19 had serious hyponatremia, reinforcing our interpretations. In addition, the low susceptibility of SARS-CoV-2 infection to the minors suggests that the relative high levels of blood sodium may play a role in fighting against the virus infection. Whether an age-dependent change in blood sodium levels is related to increasing expression of ACE2 in human tissue cells, in particular in alveolar cells, remains to be experimentally confirmed.

The presence of high concentration of extracellular sodium ions in lower aquatic organisms, even reaching to 440 mmol/L in squid, may be a natural means for them to fight against various microbial infections besides the realization of physiological functions such as nerve action potential. The blood sodium concentration with an average level of 146.0 mmol/L in bats that can coexist with multiple coronaviruses in vivo is indeed much higher than that in human beings.[29] In addition, it was found that

North American bat populations, if its blood sodium level was significantly reduced during hibernation, would increase their infection to fungal and develop white nose syndrome causing widespread death of bats.[30] Such a finding may provide a physiological mechanism for an explanation of coexisting with various coronaviruses in bats, and also indicate a possibility that many asymptomatic SARS-CoV-2 carriers may hold higher blood sodium levels and have lower expression of ACE2 in lower respiratory tract cells.

Three studies from the United States have showed that the median levels of serum sodium in COVID-19 patients were approximately 136.0 mmol/L, which was much lower than an average level of approximately 138.0 mmol/L as reported in most studies from China. It remains to be clarified whether such a difference could provide an explanation for the higher mortality rate after SARS-CoV-2 infection in US as compared to that in China.

There exist two limitations in this study. The data from the systematic review and meta-analysis were mainly extracted from the observational studies in a preprint form due to an unexpected, fast and short-period SARS-CoV-2 pandemic, which would not allow the research works to be published immediately through a traditional review way. However, it could be recognized that the standardization and automatic detection methods for serum electrolytes used in the modern hospitals could ensure the reliability of extracted data from the identified studies. In addition, for the retrospective cohort analysis, although a small cohort of 59 non-COVID-19 inpatients as control have provided very useful control data, however, it would be benefit to our conclusion if a normal control population matched with age and sex, etc.; during the SARS-CoV-2 epidemic period.

In conclusion, we found that people with low serum sodium (hyponatremia) may be related to the susceptibility of SARS-CoV-2 infection and the development of severity of disease. This finding may provide an important idea to prevent the widespread prevalence of this virus or even other types of coronavirus, and to treat the patients. In the epidemic stage, it may be of great significance to properly provide enough sodium intake or maintain blood sodium at a reasonable level for the susceptible population in order to reduce the virus infection, and treat patients through therapeutic sodium supplementation (such as infusion) to prevent from the development of severe condition of disease.

Contributors

JD had the idea for and designed the study. JD collected the data for systematic review and meta-analysis. YL (first author) and YL collected the data for retrospective cohort study. JD and both of YL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JD drafted the paper, and JD and both of YL agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

We declare no competing interests.

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Table 1 The results of systematic review and meta-analysis

	Severity	**Mean ± SD**	**Number of**	**Comparison**	***P* value**
Sodium (Na)	All	138.6±2.5	31	All vs. Mild	0.0774
	Mild	140.8±4.0	7	All vs. Moderate	0.9531
	Moderate	138.7±2.35	23	All vs. Severe/Critical	0.0139
	Severe/Critical	137.0±2.02	25	Mild vs. Moderate	0.0927
	Correlation	r= -0.4558		Na concentration vs Severity	0.0005
Chlorine (Cl)	All	101.8±2.25	10	All vs. Moderate	0.7769
	Mild	102.9-103.4	2	All vs. Severe/Critical	0.5839
	Moderate	102.1±2.39	9	Moderate vs. Severe/Critical	0.419
	Severe/Critical	101.3±2.06	10		
	Correlation	r= -0.2817		Cl concentration vs Severity	0.216
Potassium (K)	All	4.01±0.20	28	All vs. Mild	0.7673
	Mild	3.99±0.18	7	All vs. Moderate	0.5866
	Moderate	3.99±0.19	21	All vs. Severe/Critical	0.1199
	Severe/Critical	3.90±0.28	23	Mild vs. Moderate	0.942
	Correlation	r= -0.1523		K concentration vs Severity	0.2861
	SD: Standard deviation				

Table 2 The results of retrospective cohort study

			Mean ± SD (mmol/L)				Comparsion	*p* value
			Control	N	COVID-19	N		
Sodium (Na)		Average	51.07±19.21	59	57.49±19.13	244		
	Age	<60 years	138.9±2.78	40	138.3±3.41	124	Control	>0.05
		≥60 years	139.4±2.27	19	136.6±4.62	120	COVID-19	0.0019
	Gender	Male	139.2±2.51	29	136.7±4.25	127	Control	>0.05
		Female	138.9±2.77	30	138.3±3.82	117	COVID-19	0.0021
		All	138.9±2.77	59	137.5±4.12	244	Control vs. All	0.0443
	Severity	Mild			139.2±2.72	65	Control vs. Severe/Critical	0.0012
		Moderate			137.2±3.72	61	All vs. Mild	0.0140
		Severe/Critical			136.6±4.66	118	Mild vs. Moderate Mild vs. Severe/Critical The others	0.0397 0.0003 >0.05
		Correlation	r= -0.2462				Na concentration vs Severity	0.0001
Chloride (Cl)	Age	<60 years	104.2±2.70	40	102.5±3.57	124	Control	>0.05
		≥60 years	102.7±3.56	19	101.6±4.70	120	COVID-19	>0.05
	Gender	Male	103.6±2.85	29	101.4±4.26	127	Control	>0.05
		Female	103.8±3.27	30	102.7±4.03	117	COVID-19	0.016
		All	103.8±3.27	59	102.1±4.20	244	Control vs. All	0.0390
	Severity	Mild			103.2±3.05	65	Control vs. Severe/Critical	0.0032
		Moderate			102.2±4.34	61	Mild vs. Severe/Critical	0.0386
		Severe/Critical			101.4±4.55	118	The others	>0.05
		Correlation	r= -0.1753				Cl concentration vs Severity	0.0060
Potassium (K)	Age	<60 years	4.15±0.45	40	4.02±0.53	124	Control	>0.05
		≥60 years	4.27±0.49	19	3.99±0.59	120	COVID-19	>0.05
	Gender	Male	4.22±0.51	29	3.97±0.56	127	Control	>0.05
		Female	4.15±0.41	30	3.97±0.57	117	COVID-19	
		All	4.15±0.41	59	4.00±0.56	244	All	>0.05
	Severity	Mild			4.10±0.41	65		
		Moderate			3.96±0.65	61		
		Severe/Critical			3.97±0.65	118		
		Correlation	r= -0.1394				K concentration vs Severity	0.0419

SD: Standard deviation; Normal range: 137-147, 99-110 and 3.5-5.3 mmol/L for Na, Cl and K, respectively.

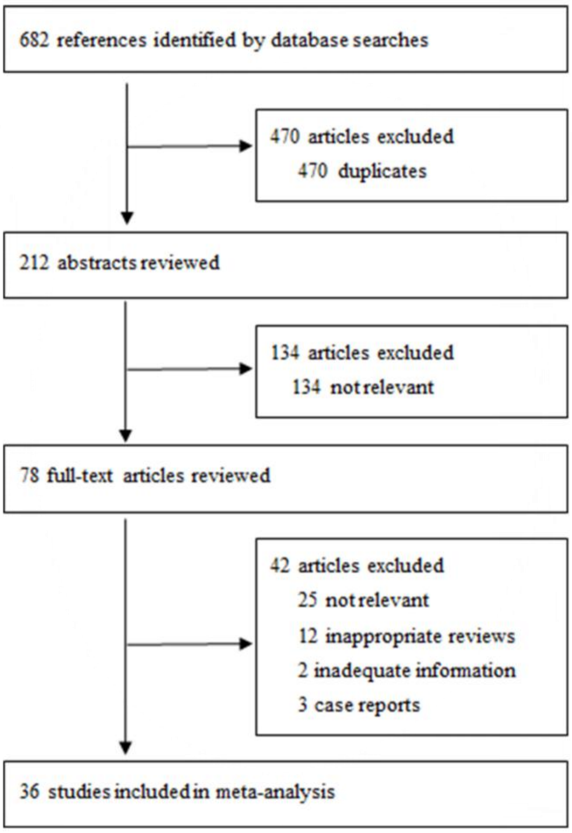

Figure 1. Study selection in systematic review and meta-analysis. Serum sodium in patients with COVID-19.

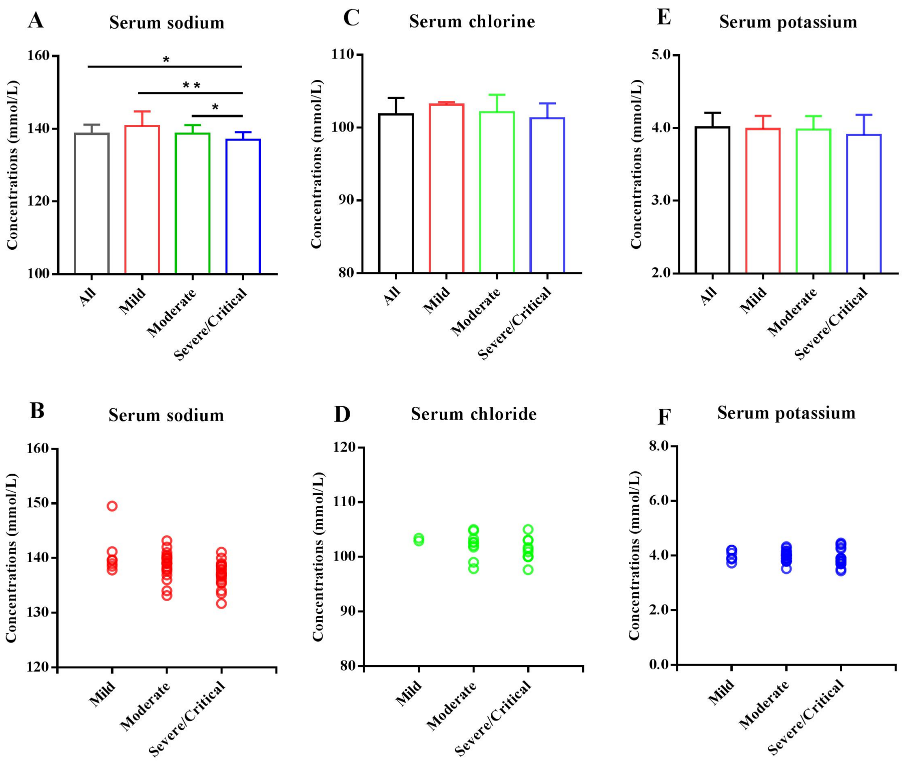

Figure 2. Comparisons in serum sodium, chloride and potassium concentrations related to the severity of patients with COVID-19 based on the data of systematic review and meta-analysis. The mean serum sodium concentrations in all (n=31), mild (n=7), moderate (n=23) and severe/critical (n=25) patients with COVID-19, and the significant differences were found between the groups as indicated by bar lines and asterisks (A). The concentrations of serum sodium were significantly correlated to the illness severity of patients (B). The mean serum chloride concentrations in all (n=10), mild (n=2), moderate (n=9) and severe/critical (n=10) patients with COVID-19 (C). The concentrations of serum chloride were not correlated to the illness severity of patients (D). The mean serum potassium concentrations in all (n=28), mild (n=7), moderate (n=21) and severe/critical (n=23) patients with COVID-19 (E). There were no differences in serum chloride and potassium concentrations among the different groups. The serum potassium concentrations were also not correlated to the illness severity of patients (F). Data are shown as the mean ± SD. n=the number of studies. Asterisks indicate a significant difference in different groups. *P<0.05, **P<0.01.

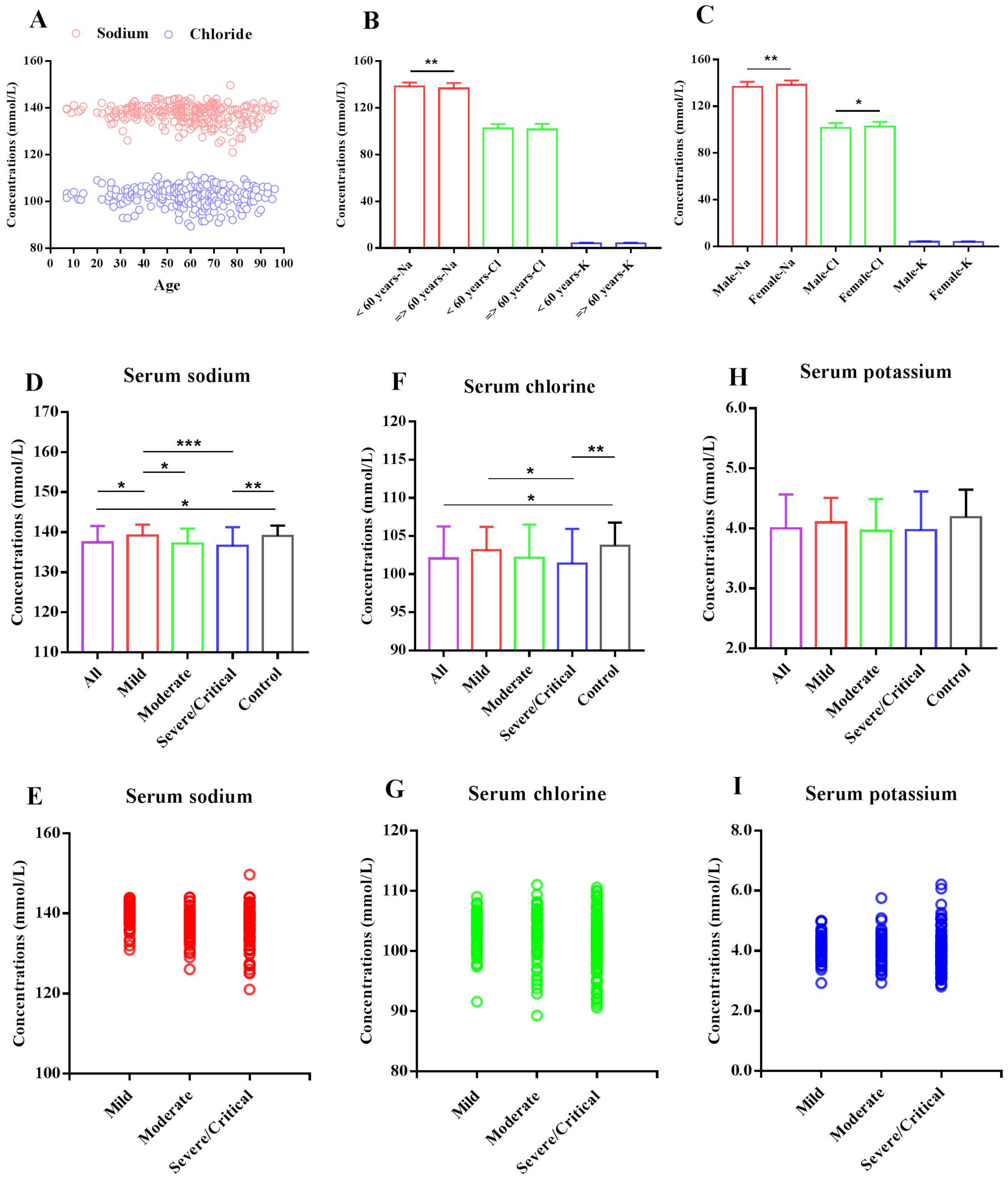

Figure 3. Comparisons in serum sodium, chloride and potassium concentrations related to the severity of patients with COVID-19 based on the data of retrospective cohort study. The age-dependent distribution of serum sodium and chloride concentrations in 244 patients with COVID-19 (A). The serum sodium, chloride and potassium concentrations in patients with COVID-19 related to age (<60 vs ≥60 years). A significant difference was found in the serum sodium concentrations, but not in serum chloride and potassium concentrations (B). The serum sodium, chloride and potassium concentrations in patients with COVID-19 related to gender. The significant differences were found in the serum sodium and chloride concentrations, but not in serum potassium concentrations (C). The mean serum sodium (D), chloride (F) and potassium (H) concentrations in control patients (n=49), and all (n=244), mild (n=65), moderate (n=61) and severe/critical (n=118) patients with COVID-19. The significant differences were found between the groups as indicated by bar lines and asterisks. The correlations between the serum sodium, chloride and potassium concentrations and the illness severity of patients with COVID-19 were shown in F, G and I, respectively. The concentrations of serum sodium and chloride, but not serum potassium were significantly correlated to the illness severity of patients. Data are shown as the mean ± SD. n=the number of patients. *P<0.05, **P<0.01, ***P<0.001.

Supplementary materials

Table S1 The data of systematic review and meta-analysis

No	Ions	Normal range	All cases	N	Mild	N	Moderate	N	Severe /Critical	N	Brief description	Refs
A1	Na	np	138.2 (136.1–140.3)	1099	nd		138.4 (136.6–140.4)	926	138.0 (136.0–140.0)	173	1,099 severe or and non-severe patients with laboratory-confirmed 2019-nCoV ARD from 552 hospitals in 31 provinces/provincial municipalities in China, from Dec, 2019 to Jan 29, 2020.	Guan et al., (ref 1)
	K	np	3.8 (3.5– 4.2)	1099	nd		3.9 (3.6–4.2)	926	3.8 (3.5–4.1)	173		
	Cl	np	102.9 (99.7–105.6)	1099	nd		102.7 (99.7–105.3)	926	103.1 (99.8–106.0)	173		
A2	Na	136-145	138.4 (136-140.5)	193	nd		138.6 (136.5-140.6)	128	136.8 (133.9-140.5)	65	193 adult patients with laboratory-confirmed COVID-19 from 4 hospitals in China.	Li et al., (ref 2)
	K	3.50-5.10	3.96 (3.63-4.28)	193	nd		4.01 (3.75-4.28)	128	3.82 (3.49-4.28)	65		
	Cl	np	nd		nd		nd		nd			
A3	Na	np	139.0 (137.0-140.0)	61	nd		140.0 (137.9-141.0)	44	137.0 (136.0-138.5)	17	61 patients with 2019-nCoV infection treated at Beijing Ditan Hospital, China, from Jan 13 to Jan 31, 2020.	Liu et al., (ref 3)
	K	np	3.8 (3.5-4.1)	61	nd		3.8 (3.5-4.1)	44	3.7 (3.5-4.1)	17		
	Cl	np	102.0 (100.0-104.0)	61	nd		103.3 (101.0-105.0)	44	100.0 (98.5-103.5)	17		
A4	Na	np	145.9±43.4	40	149.5±52.5	27	nd		138.6±6.2	13	40 confirmed COVID-19 patients at Wuhan Union Hospital, China, from Jan 5 to Jan 24, 2020.	Liu et al., (ref 4)
	K	np	3.8±0.5	40	3.9±0.5	27	nd		3.7±0.4	13		
	Cl	np	nd		nd		nd		nd			
A5	Na	np	139±5	710	nd		nd		nd		710 COVID-19 patients admitted in a tertiary teaching hospital with 3 branches in Wuhan, China, from Jan 28 to Feb 11, 2020.	Cheng et al., (ref 5)
	K	np	4.2±0.8	710	nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A6	Na	np	nd		139.67±2.46	9	139.14±3.058	71	136.53±2.19	8	88 confirmed COVID-19 patients from the Second Hospital of Nanjing, China, and 22 Non-COVID-19 pneumonia patients (mean sodium concentration: 140.509±2.732).	Zheng et al., (ref 6)
	K	np	nd		3.88±0.44	9	3.88±0.39	71	3.86±0.36	8		
	Cl	np	nd		nd		nd		nd			
A7	Na	np	139 (137-141)	265	nd		139 (138-141)	243	136 (131-139)	22	265 confirmed COVID-19 patients admitted to Shanghai Public Health Center, China. Only 5 cases are mild type.	Lu et al., (ref 7)
	K	np	3.80 (3.60-4.00)	265	nd		3.8 (3.5-4.0)	243	3.9 (3.6-4.1)	22		
	Cl	np	nd		nd		nd		nd			
A8	Na	137-147	139 (137.25-141)	91	139.6 (137.6-142)	82	nd		137.85 (135.3-139.38)	9	88 cases of laboratory-confirmed and 3 cases of clinical-confirmed COVID-19 were admitted to five hospitals in Zhejiang province, China, from Jan 20 to Feb 11, 2020.	Qian et al., (ref 8)
	K	3.5-5.3	4.04 (3.72-4.23)	91	4.09 (3.72-4.27)	82	nd		3.82 (3.76-3.89)	9		
	Cl	99-110	103 (100.55-105)	91	103.4 (101.28-105.23)	82	nd		101.4 (99.28-104.5)	9		
A9	Na	136-145	nd		nd		nd		138·8 (137·1-140·8)	35	35 adult female severe patients with laboratory-confirmed COVID-19 from Tongji Hospital in Wuhan, China, from Jan 28 to Feb 18, 2020.	Cui et al., (ref 9)
	K	3·5-5·1	nd		nd		nd		3·9 (3·7-4·3)	35		
	Cl	np	nd		nd		nd		nd			

A10	Na	np	140.8±1.9	41	141.2±1.8	17	140.5±1.9	24	nd		41 mild or moderate consecutive hospitalized health staff with confirmed COVID-19 at the Central Hospital of Wuhan in Wuhan, China, from Jan 15 to Jan 24, 2020.	Liu et al., (ref 10)
	K	np	4.19±0.31	41	4.20±0.35	17	4.17±0.29	24	nd			
	Cl	np	nd		nd		nd		nd			
A11	Na	133-149	136.7 (134.8, 138.7)	291	137.8 (135.9, 139.3)	29	136.9 (134.9, 139.0)	212	135.5 (133.5, 137.0)	50	291 laboratory-confirmed COVID-19 peitients from Jan 23 to Feb 14, 2020 in two designated hospitals in Hunan province, China.	Chen et al., (ref 11)
	K	3.50-5.50	3.98 (3.64, 4.29)	291	3.73 (3.53, 4.30)	29	4.04 (3.69, 4.33)	212	3.79 (3.50, 4.09)	50		
	Cl	95.0-101.0	102.0 (99.3, 104.1)	291	102.9 (98.5, 105.3)	29	102.1 (99.9, 104.2)	212	100.9 (98.3, 103.0)	50		
A12	Na	np	nd		nd		nd		137.2±4.0	45	45 critically ill patients with confirmed SARS-CoV-2 pneumonia in 7 ICUs in Guangdong Province, China	Xu et al., (ref 12)
	K	np	nd		nd		nd		3.9±0.7	45		
	Cl	np	nd		nd		nd		nd			
A13	Na	np	139.89±5.45	103	nd		nd		nd		104 laboratory-confirmed COVID-19 peitients in Hunan Province, China, from Jan 22 to Feb 12, 2020.	Qiu et al., (ref 13)
	K	np	3.87±0.47	103	nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A14	Na	137-147	139 (137.0-141.0)	190	nd		139.0 (137.0-141.0)	171	137.0 (133.0-139.0)	19	198 laboratory-confirmed COVID-19 peitients who admitted the ICU (severe type) or not-ICU (moderate type) in shanghai, China, from Jan 22 to Feb 12, 2020.	Cao et al., (ref 14)
	K	3.5-5.3	3.8 (3.5-4.0)	191	nd		3.8 (3.5-4.00)	172	3.8 (3.5-4.1)	19		
	Cl	np	nd		nd		nd		nd			
A15	Na	137-147	136±3.11	12	138.5	2	136±3.12	8	133.50	2	12 patients diagnosed with COVID-19 in a tertiary hospital in Guangdong province, China, from Jan 20 to Feb 20, 2020.	Hong et al., (ref 15)
	K	3.5-5.3	3.61±0.44	12	4.2	2	3.52±0.38	8	3.44	2		
	Cl	np	nd				nd		nd			
A16	Na	137-147	132.77±22.37	36	nd		133.15±25.37	27	131.67±3.08	9	36 confirmed COVID-19 patients with latent or active tuberculosis from Shenyang, China, from Feb 1 to Feb 29, 2020.	Chen et al., (ref 16)
	K	3.5-5.3	4.31±1.46	36	nd		4.33±0.97	27	4.25±2.15	9		
	Cl	99-110	97.8±16.85	36	nd		97.85±18.78	27	97.66±6.60	9		
A17	Na	137-155	139.00 (137.88-141.13)	34	nd		nd		nd		34 paediatric patients with COVID-19 were included from 4 hospitals in the west of China, from Jan 1 to Feb 25, 2020.	Zhang et al., (ref 17)
	K	3.50 - 5.50	4.45 (4.28-4.73)	34	nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A18	Na	np	139.90 (138.20-141.10)	39	nd		139.90 (138.40 - 141.20)	30	137.30 (132.75-142.65)	9	52 laboratory-confirmed linked peitients with COVID-19 in three separate hospitals in Wuhan, China.	Hu et al., (ref 18)
	K	np	3.87 (3.63-4.18)	38	nd		3.93 (3.67 – 4.19)	30	3.50 (3.10– 4.13)	8		
	Cl	np	nd		nd		nd		nd			
A19	Na	137-147	142.9 (138.8-144.2)	403	nd		143.2 (139.6-144.3)	303	141.1 (136.6-144.2)	100	403 laboratory-confirmed patients with COVID-19 from Eastern Campus of Renmin Hospital, Wuhan University, China, from Jan 30 to Feb 25, 2020.	Luo et al., (ref 19)
	K	np	nd		nd		nd		nd			
	Cl	np	nd		nd		nd		nd			

A20	Na	137-147	138.8 (136-142.2)	124	nd		139 (136.5-142.3)	93	137 (132-142)	31	168 confirmed Covid-19 patients in Hainan province, China, from Jan 22 to March 13, 2020	Yan et al., (ref 20)
	K	3.5-5.3	3.8 (3.5-4.1)	124	nd		3.8 (3.5-4.1)	93	3.7 (3.4-4)	31		
	Cl	99-110	104.1 (102-106.4)	123	nd		104.8 (103-106.6)	92	103 (100-106)	31		
A21	Na	np	138.4 (136.0-139.4)	62	nd		nd		nd		163 consecutive adult patients with suspected COVID-19 from three tertiary hospitals in two provinces outside Hubei province from Jan 12 to Feb 13, 2020. 62 confirmed and 101 non-confirmed cases.	Miao et al., (ref 21)
	K	np	4.1 (3.8-4.3)	62	nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A22	Na	136-145	137.7 (135.8-141.1)	102	nd		137.6 (136.0-141.1)	87	138.6 (133.9-142.6)	15	102 laboratory-confirmed patients admitted to a quarantine unit at Tongji Hospital in Wuhan, China, from Jan 31 and March 5, 2020.	Li et al., (ref 22)
	K	3.50-5.10	4.2 (3.8-4.5)	102	nd		4.1 (3.8-4.5)	87	4.4 (3.6-5.1)	15		
	Cl	np	nd		nd		nd		nd			
A23	Na	np	135.5 (135.1, 135.9)	25	nd		nd		nd		54 laboratory-confirmed COVID-19 peitients from Stanford Hospital, USA. Two groups: Female (25) and Male (29).	Rubin et al., (ref 23)
	K	np	4.05 (3.9, 4.2)	25	nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A24	Na	137-147	141 (139-142)	12	nd		nd		nd		12 laboratory-confirmed COVID-19 patients after a flight.	Yang et al., (ref 24)
	K	3.5-5.3	4.17 (3.91-4.2)	12	nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A25	Na	137-147	138 (137-140)	50	nd		nd		nd		59 laboratory-confirmed COVID-19 peitients from Jilin province, China, from Jan 21 to May 5, 2020. Severity not defined	Tian et al., (ref 25)
	K	3.50-5.30	4.05 (3.78-4.37)	50	nd		nd		nd			
	Cl	99-110	100 (97-102)	50	nd		nd		nd			
A26	Na	np	137.6 (135.4-140.1)	564	nd		138.0 (135.9 to	495	135.4 (133.3 to	69	564 consecutively hospitalized patients with confirmed COVID-19 from 9 Hospitals in Hunan province, China, from Jan 17 to Feb 28, 2020.	Feng et al., (ref 26)
	K	np	4.0 (3.6-4.3)	564	nd		4.0 (3.6 to 4.3)		3.9 (3.5 to 4.3)			
	Cl	np	nd		nd		nd					
A27	Na	np	139 (137-142)	69	nd		140 (138-142)	53	137 (135-141)	16	69 laboratory-confirmed COVID-19 adult inpatients admitted to Wuhan Union Hospital (Wuhan, China) from Jan 29 to Mar20, 2020.No mild patients were included.	Yang et al., (ref 27)
	K	np	3.9 (3.5-4.3)	69	nd		3.9 (3.5-4.3)	53	3.9 (3.6-4.3)	16		
	Cl	np	nd		nd		nd		nd			
A28	Na	np	139.4±4.27	208	nd		140.1±3.61	164	136.81±5.47	44	45 moderate and severe type patients with SARS-CoV-2 infections in Jingzhou Central Hospital in hubei province, China, from Jan 23 to Feb 13, 2020.	Wang et al., (ref 28)
	K	np	4.32±0.76	209	nd		4.28±0.61	164	4.46±1.15	45		
	Cl	np	102.42±3.78	208	nd		102.61±3.75	164	101.72±3.83	44		

A29	Na	136-147	142 (140-143)	55	nd		142 (141-143)	47	140 (139-141)	8	55 laboratory confirmed COVID-19 patients (non-severe and severe) in Wuxi city, zhejiang province, China.	Jiang et al., (ref 29)
	K	3.8-5.0	4.0 (3.7-4.4)	55	nd		4.1 (3.8-4.5)	47	3.8 (3.2-4.1)	8		
	Cl	98-106	105 (103-106)	55	nd		105 (103-106)	47	105 (103-106)	8		
A30	Na	np	nd		nd		140.30 (137.25-141.90)	115	138.55 (136.05-142.45)	68	183 COVID-19 patients (115 survivors and 68 nonsurvivors) from the Sino-French New City Branch of Tongji Hospital in Wuhan, China. from Jan 27 to Mar 11, 2020.	Hu et al., (ref 30)
	K	np	nd		nd		4.17 (3.91-4.55)	115	4.42 (4.00-5.06)	68		
	Cl	np	nd		nd		101.80 (99.15,103.55)	115	100.05 (97.70,102.90)	68		
A31	Na	np	137 (134-140)	2015	nd		nd		nd		2,199 confirmed patients from 5 major hospitals: the Mnt Sinai Hospital., located in East Harlem, Manhattan, USA, from Feb 27 to April 2, 2020.	Shi et al., (ref 31)
	K	np	4.2 (3.9-4.6)	2006	nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A32	Na	137-147	139.3 (136.3-141.5)	134	nd		139.5 (137.4-141.8)	88	139.0 (135.0-140.3)	46	134 confirmed COVID-19 cases from 9 Cities outside Wuhan, China.	Lala et al., (ref 32)
	K	3.5-5.3	3.9 (3.7-4.3)		nd		4.0 (3.7-4.4)		3.8 (3.6-4.3)			
	Cl	np	nd		nd		nd		nd			
A33	Na	np	134 (131.8-136)	100	nd		134 (132-136)	85	134 (129.5-135.5)	15	100 hospitalized patients with Covid-19 from Feb 22 to March 5, 2020, admitted to the YAS hospital affiliated to Tehran University of Medical Sciences, Iran.	Ashraf et al., (ref 33)
	K	np	nd		nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A34	Na	np	138.00 (135.00,141.00)	2736	nd		nd		nd		2,736 patients with COVID-19 admitted to one of five Mount Sinai Health System hospitals in NY, USA, from Feb 27 to Apr 12, 2020.	Lala et al., (ref 34)
	K	np	nd		nd		nd		nd			
	Cl	np	nd		nd		nd		nd			
A35	Na	np	136.00 (133.00-139.00)	226	nd		136.00 (133.00-138.00)	226	137.00 (133.00-141.00)		226, 276 and 227 of 5233 patients with COVID-19 fom 13 acute care facilities at Northwell Health, USA, were measured for Na, K and Cl, respectively.	Levy et al., (ref 35)
	K	np	4.10 (3.70-4.50)	276	nd		4.00 (3.70-4.40)	276	4.30 (3.80-4.80)			
	Cl	np	99.00 (96.00-103.00)	227	nd		99.00 (96.00-102.00)	227	100.00 (96.00-106.00)			
A36	Na	137-147	nd		138.99±2.79	72	137.93±3.76	573	nd		645 confirmed patients with SARS-CoV-2 in Zhejing province, China, from Jan 17 to Feb 8, 2020. Normal imaging findings (72); Abnormal imaging findings (573).	Hu et al., (ref 36)
	K	3.5–5.3	nd		3.90±1.13	72	4.04±1.69	573	nd			
	Cl	np	nd		nd		nd		nd			

np: not provided; nd: not detected or determined

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