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Prevalence And Impact of Hyponatremia in Chronic Kidney Disease Patients with Coronavirus Disease 2019

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is frequently associated with hyponatremia. Individuals with history of chronic kidney disease (CKD) are more likely to experience critical complications related to COVID-19.

Objective: This study aimed to identify the prevalence and outcomes of admittance of hyponatremia in COVID-19 patients with history of CKD.

Patients and Methods: The study involved admitted CKD patients with COVID-19 between January 2021 and April 2021. It was performed at Zagazig University hospital. Subjects were divided according to admittance serum sodium into group 1 with hyponatremia (80 subjects) and group 2 with normonatremia (68 subjects). Hypernatremic patients were excluded. Clinical and laboratory data were collected from all subjects. Patients were observed for the occurrence of acute respiratory failure, and acute renal failure. Additionally, mortality rates were recorded.

Results: Patients in group 1 stayed longer in the hospital than in group 2 ($p = 0.034$). Additionally, they had higher systolic blood pressure records ($p < 0.001$). Group 1 had significantly shorter survival and higher incidence rates of acute kidney injury (AKI) than group 2. Finally, multivariate analysis revealed that the significant risk factors for in-hospital mortality in group 1 were older age, longer hospital stay, higher serum potassium, and higher LDH.

Conclusion: In our study, hyponatremia affected 54% of CKD patients with COVID-19 and was attributed to higher rates of AKI and in-hospital mortality.

Keywords: Chronic kidney diseases, COVID-19, Hyponatremia, In-Hospital mortality, Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

INTRODUCTION

About 26% of patients with community-acquired pneumonia suffer from low levels of serum sodium (< 135 mmol/l) [(1)]. The associated hyponatremia increases the rates of admission to the critical care units, total admission days, and rates of death [(2)].

The severity of hyponatremia appears to differ according to the causative organism with up to 45% of patients with Legionnaires' disease have hyponatremia [(3)]. Additionally, recent studies have demonstrated a frequent occurrence of low serum sodium in Coronavirus disease 2019 (COVID-19) [(4, 5)]. Furthermore, hyponatremia has been identified in 30% of cases having COVID-19 in recent research in New York [(6)].

Chronic kidney disease (CKD) patients are more prone to serious complications of COVID-19 [(7)]. The pathophysiology of hyponatremia has not been entirely clarified. The main explanation is that viral particles directly invade renal tubular cells causing cellular dysfunction and tissue necrosis, which results in excessive sodium loss in urine as part of Fanconi syndrome [(8, 9)].

Additionally, SIADH often develops in COVID-19 pneumonia and causes dilutional hyponatremia [(10)]. Another explanation is the non-osmotic secretion of antidiuretic hormone induced by high interleukin-6 (IL-6) levels and inflammation [(11)]. This concept is of considerable concern because cytokine storming has been frequently detected in severe COVID-19 [(12, 13)]. Thus, we planned to identify the frequency and outcomes of hyponatremia in CKD patients having COVID-19.

PATIENTS AND METHODS

This retrospective cohort study was performed at Zagazig University hospital between January 2021 and April 2021. We recruited cases who were admitted with COVID-19 and had chronic kidney disease (CKD). Infection was verified by virus testing using reverse transcription polymerase chain reaction.

Values of plasma sodium were adjusted according to the Katz formula when serum glucose is ≥ 100 mg/dL. Katz formula is as follows (actual sodium + 0.016 x (serum glucose − 100)) [(14)]. We did not include patients who developed hyponatremia 24 hours after admission as it would be a result of the ongoing intravenous fluid, not the primary disease COVID-19. Additionally, we excluded cases who had hypernatremia as it would result in increased mortality by itself, not by the primary disease.

The participants were divided into :

- **Group 1** that included 80 subjects having confirmed COVID-19, CKD, and low plasma sodium levels (<135 mmol/L). Mean age of cases in this group was 64.6 ± 14.1 years.
- **Group 2** included 68 subjects having confirmed COVID-19, CKD, and normal plasma sodium levels (135-145 mmol/L). Mean age of cases in this group was 67.15 ± 15.3 years.

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We collected demographic data of all subjects including the history of comorbidities, presenting symptoms including cough, fever, sore throat, confusion, and gastrointestinal symptoms, and presenting examination records including vital signs and oxygen saturation. Additionally, complications of COVID-19 during the hospitalization period were recorded including respiratory failure, acute renal failure, and mortality.

Laboratory parameters of all subjects at the time of admission were collected including kidney function tests, serum electrolytes, complete blood picture, liver function tests, acute inflammatory markers, and the ratio of partial pressure of arterial oxygen to fractional inspired oxygen (P/F Ratio) were done.

Ethical approval:

This observational cohort study was authorized by the Ethics Board of Zagazig University (ZU-IRB #9411) and each participant signed an informed written consent form. This work followed the regulations of Declaration of Helsinki.

Statistical analysis

We examined the assembled data by the application of SPSS 26.0 statistics. The Shapiro-Wilk test was employed to assess the normality of continuous variables. Means and standard deviations were calculated for normally dispersed continuous variables, whereas medians and interquartile ranges were calculated for non-normally dispersed continuous variables. Nominal data were shown as numbers and percentages (%) and were assessed using Chi-square test.

Continuous variables were tested with the Student's T-Test and Mann-Whitney U test according to normal or non-normal dispersion, respectively. The development of acute respiratory failure, acute kidney injury (AKI), and mortality in our observational study were graphically represented using Kaplan–Meier survival curves. We estimated the difference between hyponatremic and normonatremic subjects using the log-rank test. Predictors of in-hospital mortality were examined using univariate tests, and factors were examined using a multivariate logistic regression model. $P \leq 0.05$ was identified as significant.

RESULTS

On the basis of admittance serum sodium levels, two groups of patients were defined: hyponatremic (n = 80, 54% of the cohort) and normonatremic (n = 68, 46% of the cohort). Hyponatremic cases stayed longer duration in the hospital than normonatremic cases with a median of 7.5 days (p = 0.034). Additionally, higher systolic blood pressure records were detected in hyponatremic cases compared to normonatremic cases (p < 0.001) (Table 1).

Table (1): Comparison of the demographic data between the studied cases

Variable	Group 1 (n=80)	Group 2 (n=68)	Test	p-value
Age (years), Mean ± SD	64.6 ± 14.1	67.15 ± 15.3	-1.062	0.290
Male sex, No (%)	46 (57.5%)	44 (64.7%)	0.801	0.371
History of diabetes, No (%)	36 (45%)	32 (47.1%)	0.063	0.802
History of hypertension, No (%)	50 (62.5%)	36 (52.9%)	1.380	0.240
Confusion, No (%)	14 (17.9%)	12 (17.6%)	0.002	0.96
Vomiting and diarrhea, No (%)	10 (12.5%)	12 (17.6%)	0.769	0.380
SBP (mm Hg), Median (IQR)	133.5 (125-152)	124 (105-136)	-3.834	< 0.001**
DBP (mm Hg), Median (IQR)	73 (64-83)	69 (62-78)	-1.572	0.116
Temperature (C°), Median (IQR)	37 (36.4-38.8)	37 (36-39)	-0.302	0.763
Pulse (beat/m) , Median (IQR)	92±13	90.74±16.8	0.531	0.597
O2 saturation (%), Mean ± SD	93.6±3.5	94.5±3.37	-1.508	0.134
Mechanical ventilation, No (%)	22 (27.5%)	20 (29.4%)	0.344	0.842
Admission duration (days), Median (IQR)	7.5 (4-15)	6 (3-10)	-2.126	0.034*

(*): Significant, (**): Highly significant, (IQR): Interquartile range, (SD): Standard deviation, (BMI): Body mass index, (SBP): Systolic blood pressure, and (DBP): Diastolic blood pressure.

Analysis of laboratory parameters of the patient at the time of admission showed that serum alanine transaminase (ALT) and D-dimer levels were higher in hyponatremic cases than normonatremic cases, while serum urea and hemoglobin levels were lower in hyponatremic cases than in normonatremic cases (Table 2).

Table (2): Comparison of the laboratory data between the studied cases

Variable	Group 1	Group 2	Test	p-value
Alanine transaminase (IU/L), Mean ± SD	78 ± 12	23.2 ± 1.4	3.663	< 0.001**
Albumin (g/dL), Mean ± SD	3.62 ± 0.58	3.42 ± 0.61	2.04	0.052
Urea (mg/dL), Mean ± SD	72 ± 7.8	97 ± 8.6	-1.78	0.004**
eGFR (ml/min/1.73 m²), Mean ± SD	48.93 ± 2.49	43.65 ± 2.5	1.282	0.202
Potassium (mmol/L), Mean ± SD	4.5 ± 0.6	4.59 ± 0.56	-0.896	0.372
Hemoglobin (g/dL) , Mean ± SD	11.83 ± 2.3	12.7 ± 2.36	-2.402	0.018*
WBC ($x10^3/mm^3$), Mean ± SD	7.8 ± 0.39	7.92 ± 0.37	-0.182	0.856
Platelets ($x10^3/mm^3$), Mean ± SD	226 ± 7.6	213 ± 8.3	0.988	0.325
NLR (%),Mean ± SD	8.23 ± 1	7.93 ± 0.6	0.208	0.835
PLR (%),Mean ± SD	269 ± 20	271 ± 18	-0.05	0.96
C-Reactive protein (mg/L), Mean ± SD	113 ± 9.5	114 ± 10	-0.075	0.94
D-dimer (ng/ml), Mean ± SD	4500 ± 600	2890 ± 700	0.369	< 0.001**
Ferritin (ng/mL), Mean ± SD	1493 ± 166	1939 ± 188	-1.504	0.135
LDH (IU/L), Mean ± SD	439 ± 25.6	469 ± 24.6	-0.707	0.481
P/F Ratio, Mean ± SD	220 ± 13	218 ± 14	0.099	0.921

(eGFR): Estimated glomerular filtration rate, (WBC): White blood cells, (NLR): Neutrophil-to-lymphocyte ratio, (PLR): Platelet-to-lymphocyte ratio, and (LDH): Lactate dehydrogenase.

The Kaplan-Meier survival curve showed that hyponatremic cases had significantly shorter survival than normonatremic cases (p = 0.031) (Figure 1). Additionally, it showed that there was no significant difference in the occurrence of acute respiratory failure between the hyponatremic and normonatremic cases (p = 0.548) (Figure 2). However, hyponatremic CKD patients had higher incidence rates of AKI on top of CKD than normonatremic CKD patients as shown by the Kaplan-Meier survival analysis (p = 0.039) (Figure 3).

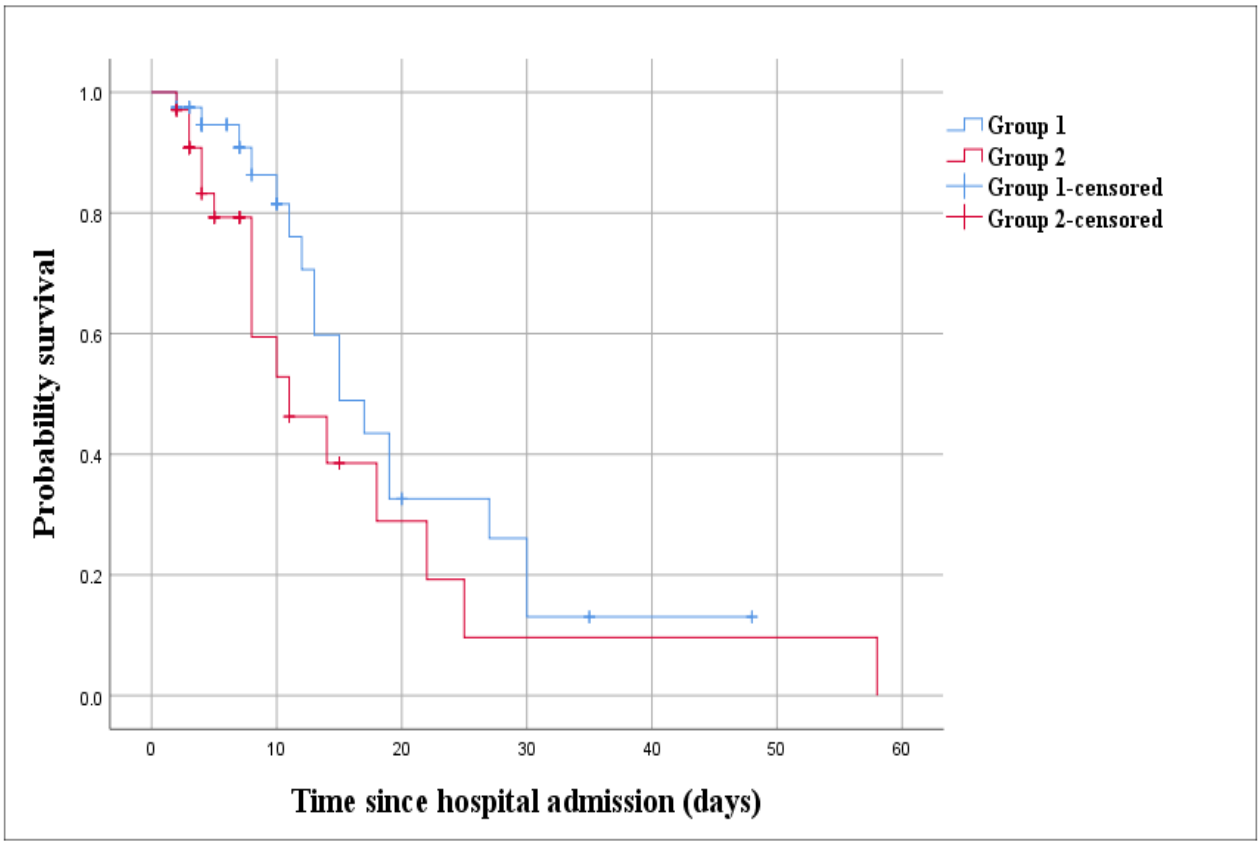

Figure (1): Kaplan-Meier curve of in-hospital mortality in the studied cases.

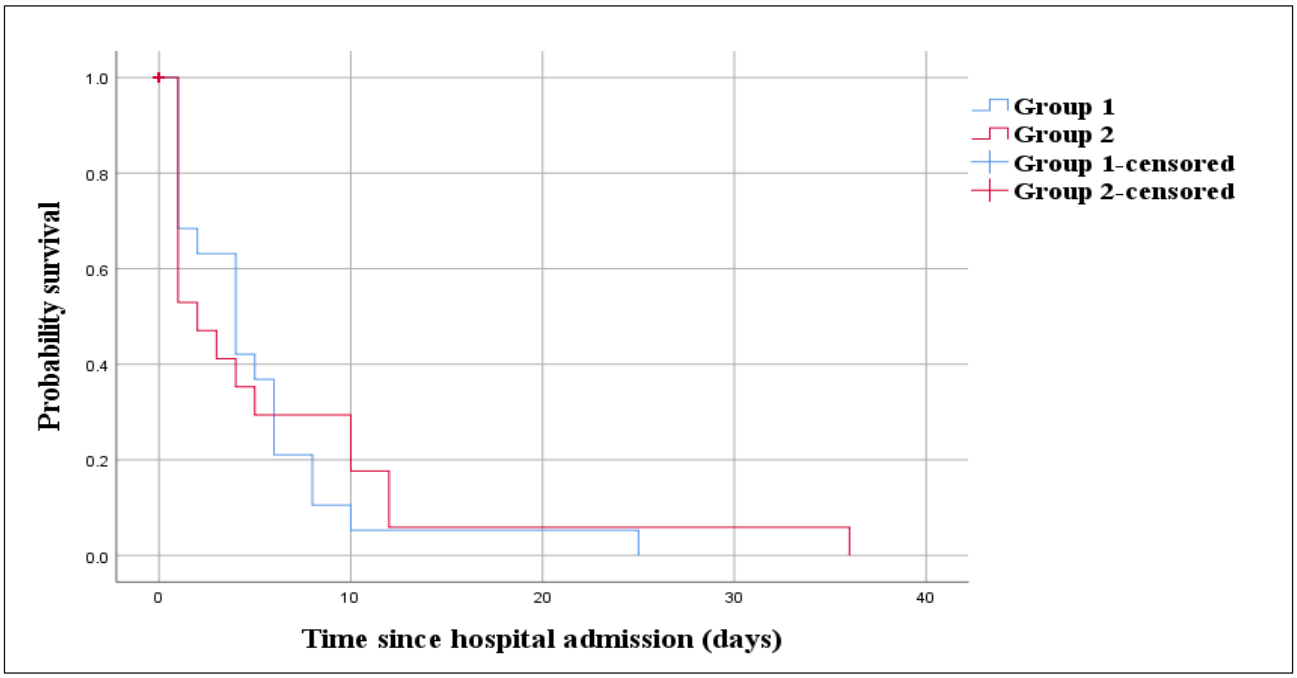

Figure (2): Kaplan-Meier curve of the occurrence of acute respiratory failure in the studied cases.

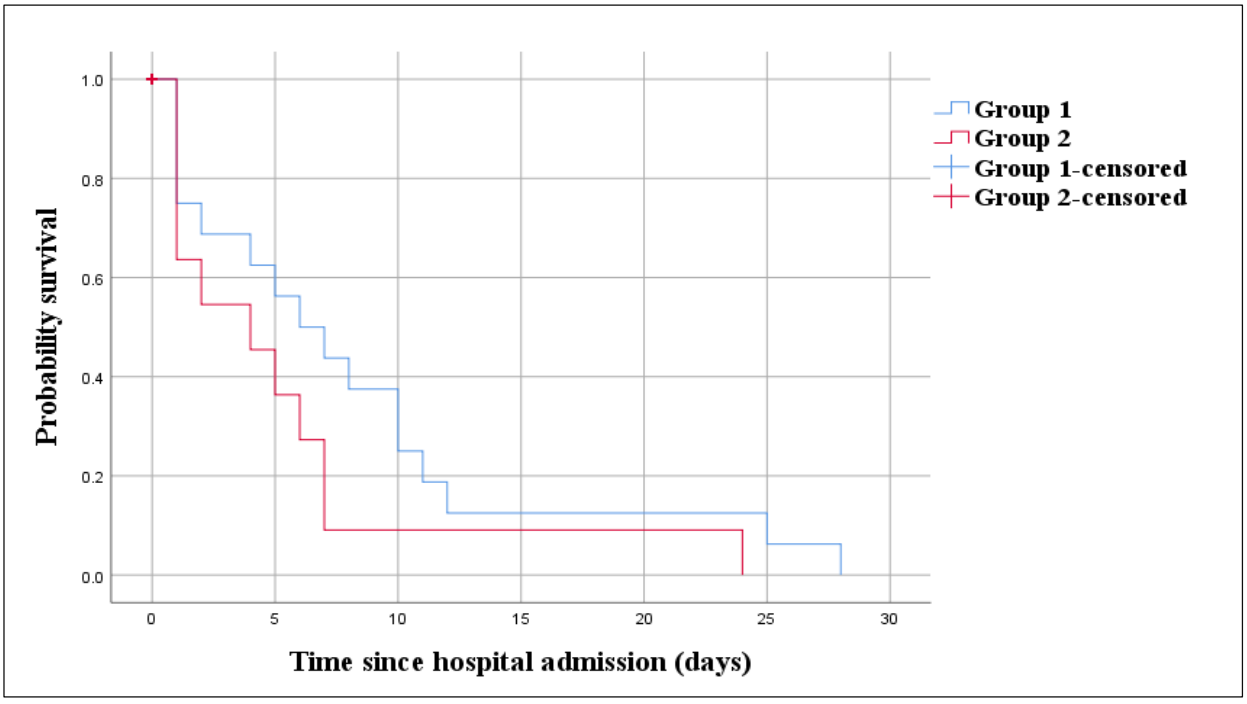

Figure (3): Kaplan-Meier curve of occurrence of acute kidney injury in the studied cases.

On univariate analysis of mortality predictors in hyponatremic CKD cases, the significant risk factors included past history of hypertension, older age, lower diastolic blood pressure, longer hospital stay, higher serum potassium, higher serum urea, lower eGFR, lower hemoglobin, higher D-dimer, higher ALT, lower serum albumin, higher serum lactate dehydrogenase (LDH) and lower P/F Ratio (Table 3).

Table (3): Univariate logistic regression analysis of risk factors predicting in-hospital mortality of the studied participants in group 1

Parameter	β	OR	95% C.I.	p
Male sex	-0.324	0.723	(0.295-1.773)	0.479
History of hypertension	-1.159	0.314	(0.122-0.804)	0.016*
Age	0.09	1.094	(1.046-1.145)	< 0.001**
Length of hospital stay	0.061	1.063	(1.01-1.118)	0.019*
Diastolic blood pressure	-0.053	0.949	(0.912-0.986)	0.008**
Serum potassium	2.726	1.52	(3.8-6.03)	< 0.001**
Serum urea	0.03	1.031	(1.013-1.048)	0.001**
eGFR	-0.03	0.971	(0.951-0.991)	0.004**
Hemoglobin	-0.277	0.758	(0.607-0.947)	0.015*
Neutrophil-to-lymphocyte ratio	-0.008	0.992	(0.949-1.036)	0.707
Platelet-to-lymphocyte ratio	0.001	1.001	(0.999-1.004)	0.236
C-Reactive protein	0.002	1.002	(0.998-1.007)	0.357
D-dimer	0.597	1.817	(1.229-2.687)	0.003**
ALT	0.029	1.029	(1.007-1.051)	0.008**
Serum albumin	-1.256	0.285	(0.112-0.727)	0.009**
Serum lactate dehydrogenase	0.006	1.006	(1.003-1.009)	< 0.001**
P/F Ratio	-0.008	0.992	(0.988-0.996)	< 0.001**

(β): Regression coefficient, (OR): Odds ratio, (CI): Confidence interval.

Finally, multivariate analysis revealed that the significant risk factors for in-hospital mortality in hyponatremic CKD patients were older age, longer hospital stay, higher serum potassium, and higher LDH (Table 4).

Table (4): Multivariate logistic regression analysis of risk factors predicting in-hospital mortality of the studied participants in group 1

Parameter	β	OR	95% C.I.	p
Age	0.208	1.231	(1.076-1.409)	0.002**
Length of hospital stay	0.183	1.201	(1.043-1.383)	0.011*
Serum potassium	7.367	1.58	(7.3-14.22)	0.007**
Serum lactate dehydrogenase	0.02	1.02	(1.007-1.034)	0.003**

DISCUSSION

In this observational study, hyponatremia at the time of admission was relatively common and was detected in 80 patients (54%). These observations are consistent with previous reports on dysnatremia and community-acquired pneumonia, which showed that hyponatremia was more prevalent than hypernatremia [15].

In our study, we found that hyponatremic CKD patients stayed in the hospital for a longer duration than normonatremic CKD patients. This agrees with an earlier study by **Tokgöz Akyi *et al*** [16]. Additionally, systolic blood pressure was higher in hyponatremic CKD patients. This is in line with **Wulandari and Nugroho** [17] who reported that hypertension is linked to low serum sodium in COVID-19 cases. Hypertension might develop in COVID-19 because the virus triggers the breakdown of angiotensin-converting enzyme 2 (ACE2) [18]. The low levels of ACE2 cause accumulation of angiotensin II leading to hypertension and hyponatremia [19, 20].

In the comparison of laboratory data between the studied groups, we found that hyponatremic cases had significantly higher ALT levels than normonatremic cases. Our results correspond with **Sadiq *et al.*** [21] who reported that higher ALT levels and lower sodium levels were more common in severe COVID-19. D-dimer levels were higher in hyponatremic cases. Our results agree with **Longhitano *et al*.** [22] who reported that D-dimer levels were higher in hyponatremic and hypernatremic patients than in normonatremic patients. Additionally, **Guan *et al.*** [23] found that D-dimer levels were greater than 0.5 g/ml in 260 of 560 cases and high D-dimer levels have frequently associated with thromboembolic events in severe COVID-19 cases.

In this observational study, we found that hyponatremic cases had shorter survival than normonatremic cases. Additionally, hyponatremic CKD patients had higher incidence rates of AKI on top of CKD than normonatremic CKD patients. Our results agree with a previous study by **De Carvalho *et al*** [24]**.** Poor prognosis in patients with hyponatremia may be due to the interaction of septicemia and hyponatremia. Low serum sodium levels are considered infection risk factor in CKD patients [25]. According to a previous study by **Mandai *et al***. [26], greater plasma sodium levels strengthen pathogen resistance by driving CD4+ cells to develop into T-helper 17 cells.

Additionally, multivariate analysis identified that older age (odds ratio [OR], 1.231; 95% confidence interval [CI], 1.076-1.409; p = 0.002), longer hospital stay (OR, 1.201; 95% CI, 1.043-1.383; p = 0.011), higher serum potassium (OR, 1.58; 95% CI, 7.3-14.22;

p = 0.007) and higher LDH (OR, 1.02; 95% CI, 1.007-1.034; p = 0.003) were the independent risk factors for in-hospital mortality in hyponatremic CKD patients.

CONCLUSION

In CKD patients having COVID-19, hyponatremia was a common laboratory abnormality and independently associated with higher rates of AKI and in-hospital mortality. Detection of this link may assist to distinguish high-risk individuals and encourage health care providers to address hyponatremia as an essential target in the management of COVID-19, especially in CKD.

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