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Prognostic Impact of Dysnatremia in COVID-19 Pneumonia: Risk Stratification of Hospitalized Patients

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Abstract

Background and Objectives: Severe dysnatremia is associated with poor prognosis and worse outcome and therefore needs more attention to unravel its relation with poor prognosis in patients admitted with coronavirus disease 2019 (COVID-19). The aim of our study was to determine varying degree of dysnatremia among hospitalized COVID-19 patients and identify the clinical outcome associated with it.

Methods: This retrospective record analysis study was conducted on the hospitalized COVID-19 patients in Guwahati Neurological Research Centre Medical, North Guwahati and for every included patient, medical records were scrutinised anonymously.

Results: COVID-19 positive participants were divided into four categories like, dysnatremic (serum sodium > 146 or < 134 mmol/L), hypernatremic (> 146 mmol/L), hyponatremic (< 134 mmol/L) and eunatremic (134 – 146 mmol/L). Total 37.9% of the participants exhibited dysnatremia compared to only 20% from the control group demonstrating a significant difference ($p = 0.02$). Hypernatremia was significantly high ($p = 0.01$) compared to hyponatremia (27.7% vs 12.3%) and also turned out to be relatively severe with significantly high ICU admittance ($p<0.0001$) and mortality rate ($p = 0.01$). Magnitude of dysnatremic patients showing aberration in the other laboratory parameters was significantly high to that of eunatremic group with high fatality rate among hypernatremic. Dysnatremic group demonstrated significantly high SOFA score but mortality risk, based on CURB 65 score and probability of death, was increased in hypernatremic group.

Interpretation and Conclusion: Dysnatremia, mainly hypernatremia, is associated with increased mortality and morbidity which highlights the significance of considering it as a predictive marker.

Keywords: Corona Virus; COVID-19; Dysnatremia; Pneumonia; SARS-CoV-2.

Introduction

The enduring widespread outbreak of coronavirus disease 2019 (COVID-19) has wobbled the entire health care system fostering with both pulmonary and extra-pulmonary complications. With limited knowledge about this novel virus, there is still miles to know all the hitches arising from COVID-19 infection. [1-3] But substantial evidence revealed that COVID-19 is also accompanied by electrolyte imbalance. [1,4-6]

Almost 50% of the hospitalized COVID-19 patients were witnessed to

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develop hyponatremia [7,8] with reports of inverse correlation between serum sodium and interleukin-6 (IL-6). [7,9] On the contrary, almost 6% to 26% of COVID-19 patients admitted in intensive care units (ICUs) were reported to acquire hypernatremia. [7,10] Incidents of treatment resistant hypernatremia resulted from scrupulous use of steroids and diuretics were also reported. [7,11] Severe dysnatremia is associated with poor prognosis and worse outcome [4,6,7,12-15] and therefore, this association of dysnatremia with viral infection and sepsis needs more attention to unravel its relation with poor prognosis in patients admitted with COVID-19.

The mechanisms of development of dysnatremia in COVID-19 pneumonia patients may be due to syndrome of inappropriate antidiuresis (SIAD) and decreased water clearance. [4,16-19] There is surplus release of interleukin-1β and IL-6 due to COVID-19 infection, resulted in non-osmotic release of arginine, vasopressin and SIAD causing hyponatremia. [20-22] Hence, serum sodium level can be used as a marker to measure the degree of inflammatory response and severity of infection. [20,23] It is used as a tool for pneumonia severity index (PSI) scoring because of its severity assessment role in pneumonia. [4,19] Therefore risk stratification at the time of admission is essential to identify the high risk patients [20,24-27].

Most of the studies on electrolyte imbalances in COVID-19 patients reported hyponatremia, while few stated hypernatremia to be more common. [4,28,29] However, there is no conclusive data stating the prevalence and outcome of dysnatremia in patients tested positive for COVID-19.

The primary objective of this study was to investigate the prevalence of dysnatremia whether hypo or hyper and its association with age and gender along with its impact on patient-outcome. We also analysed the role of serum sodium as a predictive marker for COVID-19 immune response. For this purpose, we used total leucocyte cell (TLC) count, differential leucocyte count (DLC), high sensitivity C reactive protein (hs-CRP), ferritin, prothrombin time (PT), lactate dehydrogenase (LDH), fibrinogen (FIB), procalcitonin (PCT), IL-6, D-Dimer, and serum sodium correlations.

Methods

For this retrospective record analysis study, we used patients' data collected from all hospitalized COVID-19 patients in Guwahati Neurological Research Centre (GNRC) Medical, North Guwahati including patients admitted to the intensive care unit (ICU), during the period June, 2020 to September, 2021 with approval of the Institutional Ethical Committee. Informed consent was obtained from all participants at the time of admission mentioning that their clinical data may be used for research purpose. For every included patient, his or her medical records were extracted from a standardized electronic medical record collection system and scrutinized anonymously. Hypernatremia was considered as a serum sodium concentration above 146 mmol/L, and hyponatremia as a serum sodium concentration below 134 mmol/L. Total, 383 hospitalized patients with positive polymerase chain reaction (PCR) processed in ICMR approved Truenat machine of Molbio Diagnostics/ rapid antigen test (RAT) using Standard Q Covid-19 Ag test kit of SD Biosensor for SARS-CoV-2 were included in our study. Another 90 patients who tested negative for COVID-19, but admitted for other reasons were used as a control group to compare the occurrence of dysnatremia in patients with COVID-19 and those with other illness. Association between dysnatremia and mortality in COVID-19 was analyzed by comparing the incidences of dysnatremia in deceased patients and patients who stayed alive. Then the patient's results (dysnatremia) were evaluated with age, gender, results of liver function tests (LFT), results of renal function tests (RFT), inflammatory biomarkers etc. The instruments used for processing the biochemical, haematological, and inflammatory markers were respectively, Dimension EXL 200/ADVIA Centaur (Siemens Healthineers India), DxH 900 (Beckman Coulter) and Hemostar 4CA (Tulip Diagnostic Private limited). Patients were included in our study if they met the inclusion criteria's for the study.

Inclusion Criteria:

1. A positive test result of PCR/RAT test for SARS-CoV-2.
2. At least one serum sodium concentration measurement was obtained (at any time during admission).

Exclusion Criteria:

1. A negative test result of PCR/RAT test for SARS-CoV-2.
2. COVID-19 positive patients without a single serum sodium concentration measurement during his/her hospital stay.

Statistical analysis:

For standard statistical analysis, Microsoft Office Excel Worksheet and Graph Pad Prism 5 software were used. Fisher's exact test, Chi-square ($\chi 2$) statistical test, Student's t test and Survival test were used for the statistical analysis where, statistical significance was expressed by '*' ($p < 0.05$), '**' ($p < 0.005$), and '***' ($p < 0.001$) and '****' ($p < 0.0001$). The results were expressed as mean ± SD.

Results

Medical records of a total of 383 COVID-19 positive patients were scrutinized. It was observed that most common clinical presentation was cough (47.5%) followed by fever (38.4%). Almost 12.8% were asymptomatic, hospitalized for some other ailment and diagnosed accidentally to be SARS-CoV-2 positive. Though 23% of the patients were admitted with respiratory distress, only 15.4% of them showed positive radiological findings. Total 110 (28.7%) Covid-19 participants presented with co-morbidities such as diabetes (19.1%) and

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hypertension (18.2%). Though other co-morbidities were less frequent, multi-organ involvement was found in 30.9% of the studied participants. Common treatment protocol followed was antibiotic (94.8%), steroid (50%), antiviral (28.2%), and oxygen support (23%). In 29.5% patients, oxygen saturation was found to be < 95%. Pulse rate (> 100), respiratory rate (> 24) and blood pressure (> 140/90) were recorded high in respectively, 19.3%, 5.2% and 15.4% of the studied COVID-19 patients (Table SI, Supplementary file).

For convenience of data analysis, the COVID-19 positive participants were divided into four categories like, dysnatremic (serum sodium > 146 mmol/L or < 134 mmol/L), hypernatremic (serum sodium > 146 mmol/L), hyponatremic (serum sodium < 134 mmol/L) and eunatremic (serum sodium in between 134 to 146 mmol/L). Along with the COVID-19 positive patients (test group), serum sodium status of 90 (age and sex matched) hospitalized patients (control group) who demonstrated a negative test result of PCR/RAT test for SARS-CoV-2 were also observed. Though the mean age of both the groups was almost same, there observed a male predominance (68.4% in test and 56.7% in control group) in both the groups. There was no significant difference (p = 0.9) in the mean serum sodium level between the test (141 ± 5.9 mmol/L) and the control group (142 ± 6.5 mmol/L). The age and gender distribution of the studied groups did not display any significant variation. Significant numbers (p = 0.02) of COVID-19 participants exhibited hypernatremia (27.7%) compared to only 13.3% (12/90) of the control group. Whereas hyponatremia was observed only in 12.3% and 6.7% in test and control group, respectively (p=0.1). Altogether, 145 out of 383 (37.9%) of the included COVID-19 participants exhibited dysnatremia compared to only 18 out of 90 (20%) of the patients from the control group, demonstrating a significant difference with a p value of 0.02 (Figure 1).

In the COVID-19 participants, incidence of hypernatremia was significantly high (p = 0.01) compared to hyponatremia (27.7% vs 12.3%) and turned out to be relatively severe with significantly high (p = 0.01) mortality i.e. 41.5% among hypernatremic compared to only 21.3% among hyponatremic. However, 2.1% (08/383) of the included COVID-19 participants developed both hyper and hyponatremia during their hospital stay without any history of intravenous administration. The length of hospitalisation of the participants from the control group (2 ± 1.1 days) was significantly less (p = 0.03) compared to that of the test group (9 ± 6.2 days). The difference in the occurrence of dysnatremia between deceased and surviving test and control group did not reach statistical significance. On several occasions, i.e. 11.7% in test group and 5.5% of control group, sodium concentration reached critical values on either side of the normal. Because of the brief hospital stay and inadequate laboratory data, statistical comparison of the other clinical characteristics between the test and the control group was not feasible (Table I).

Number of COVID -19 participants presenting aberration in their serum sodium at the time of admission was more compared to the number of participants that had developed later and the difference was statistically significant in case of hyponatremic patients (p = 0.005), but it did not affect the mortality rate (p> 0.05). However, there was a significantly high mortality among the COVID-19 positive participants when admitted with a critically high sodium value (p<0.0001). The occurrence of dysnatremia (p = <0.0001) including both hyper and hyponatremia was observed to be significantly high among male patients than the female patients. Furthermore, the condition was proved to be more critical with significantly high mortality rate, among male than the female COVID-19 participants but did not show any significant correlation with age (Table II).

The association of sodium levels with adverse outcome was analyzed by the number of the non-surviving COVID-19 participants and their length of average hospital stay. As depicted in Figure 2 and Table III, mortality among the dysnatremic group including both hyper and hyponatremia was significantly high compared to that of the eunatremic COVID-19 participants. Though the rate of casualty among both the hyper and hyponatremic group of participants were

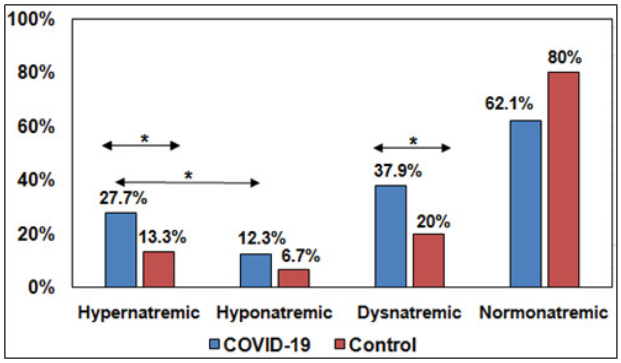

Figure 1: Serum sodium status of the COVID-19 positive participants and the control group.

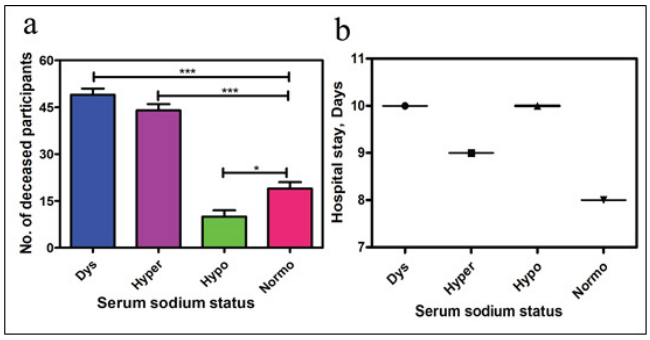

Figure 2: Graphical depiction showing the relation of serum sodium status of the COVID-19 positive participants with the (a) casualty rate and (b) their average hospital stay.

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Table I: Statistical comparison (Fisher's exact test) between COVID-19 positive participants and control group.

Outcome		COVID-19 positive group		Control Group		*p*-value
Mean (SD) sodium		141(5.9) mmol/L		142 (6.5) mmol/L		p = 0.9
Range		114 – 182 mmol/L		123 – 163 mmol/L		-
Mean age (Range)		52 ± 16.1 (10 m- 90 y)		53 ± 15.7 (17-81 y)		p = 1.0
Male; n(%)		262/383 (68.4%)		51/90 (56.7%)		p = 0.3
Female; n(%)		121/383 (31.6%)		39/90 (43.3%)		p = 0.1
Hospital stay (Average)		9 ± 6.2 days		2 ± 1.1 days		p = **0.03**
Hypernatremia; n(%)		106/383 (27.7%)	p_1 = 0.01	12/90 (13.3%)	p_1 = 0.1	p = **0.02**
	Survivors	62/106 (58.5%)		10/12 (83.3%)		p = 0.4
	Non-survivors	44/106 (41.5%)	p_2 = 0.01	02/12 (16.7%)	p_2 =1.0	p = 0.3
Hyponatremia; n(%)		47/383 (12.3%)		06/90 (6.7%)		p = 0.1
	Survivors	37/47 (78.7%)		05/06 (83.3%)		p = 1.0
	Non-survivors	10/47 (21.3%)		01/06 (16.7%)		p = 1.0
Dysnatremia; n(%)		145/383 (37.9%)		18/90 (20%)		p = **0.02**
	Survivors	96/145 (66.2%)		15/18 (83.3%)		p = 0.5
	Non-survivors	49/145 (33.8%)		03/18 (16.7%)		p = 0.4
*Both; n(%)		08/383 (2.1%)		0		-
	Survivors	03/08 (37.5%)		0		-
	Non-survivors	05/08 (62.5%)		0		-
Eunatremia; n(%)		238/383 (62.1%)		72/90 (80%)		p = 0.6
	Survivors	219/238 (92%)		68/72 (94.4%)		p = 0.9
	Non-survivors	19/238 (8%)		04/72 (5.6%)		p = 0.6
**Critical reporting; n(%)		17/145 (11.7%)		01/18 (5.5%)		p = 0.1

*Both: Presenting both Hyper & Hyponatremia;
** Critical reporting: Serum sodium either >160 mmol/L or <120 mmol/L;
p_1 (between hypernatremia & hyponatremia); p_2 (Between non-survivors of hypernatremia & hyponatremia)

Table II: Serum sodium status with statistical analysis (Chi-square test) of the Covid-19 positive participants

Observed criteria	Dysnatremia (*n* = 145)	Hypernatremia (*n* = 106)	Hyponatremia (*n* = 47)	Both (n = 08)
On admission	87 (60%)	54(50.9%)	33(70.2%)	-
Developed later	66 (45.5%)	52(49.1%)	14(29.8%)	-
p value	0.08	0.8	0.005	
Mortality when aberration presented on admission	31	23	06	
Mortality when aberration developed later	23	21	02	
p value	0.2	0.7	0.06	
Mean Age (yrs)	54.8	54.1	55.6	53.1
p value (compared with eunatremic group, mean age = 50.5)	0.6	0.7	0.6	0.7
Male	104(71.7%)	75(70.8%)	36(76.6%)	07(87.5%)
Female	41(28.3%)	31(29.2%)	11(23.4%)	01(12.5%)
p value	<0.0001	<0.0001	0.0002	0.03
Mortality among male	37	32	09	4
Mortality among female	12	12	01	1
p value	0.0003	0.002	0.01	0.1
Observed criteria		***n* (%)**		***p* value**
1. Total critical hypernatremic value		16/106 (15.1%)		p_1= 0.001
2. Total critical hyponatremic value		01/47 (2.1%)		
3. Critical value (hyper) detected on admission a. Non-Survivors		06/54 (11.1%) 06/06 (100%)		p_2 =0.1 p_3 < 0.0001
4. Critical value (hyper) detected later a. Non-Survivors		10/52 (19.2%) 04/10 (40%)		
5. Critical value (hypo) detected on admission a. Non-Survivors		01/33 (3%) 0/01 (0%)		
6. Critical value (hypo) detected later		0/14 (0%)		

*p_1 (1-2); p2 (3-4); p3 (3a-4a)

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Table III: Statistical analysis (Fisher's exact test) showing the association of sodium levels (on admission) with adverse outcome

Adverse Outcome	Dysnatremic	Hypernatremic	Hyponatremic	Eunatremic	*p* value
	(*n* = 145)	(*n* = 106)	(*n* = 47)	(*n* = 238)	
Non-surviving: *n*(%)	49 (33.8%)	44 (41.5%)	10 (21.3%)	19 (8%)	p_1<0.0001
OR	0.236	0.1923	0.375		p_2<0.0001
					p_3 = 0.02
					p_4= 0.01
Hospital stay (days)	10	9	10	8	p_1 = 0.6
					p_2 = 0.8
					p_3 = 0.6

*p_1 (Dysnatremic-Eunatremic); p_2 (Hypernatremic-Eunatremic); p_3 (Hyponatremic-Eunatremic); p_4 (Hypernatremic-Hyponatremic).

more compared to the eunatremic participants, hypernatremia was proved to be graver than the hyponatremia as illustrated by the significantly less mortality rate in the hyponatremic group compared to that of hypernatremic group of COVID-19 participants. The average hospital stay of the dysnatremic (10 days) including both hypernatremic (9 days) and hyponatremic (10 days) did not show any significant difference with that of the eunatremic participants (8 days).

To evaluate the clinical impact of dysnatremia and its correlation with other laboratory parameters, we retrospectively evaluated the data from all the included COVID-19 positive patients. While correlating the other laboratory findings with the patients' serum sodium status, it was observed that, all the scrutinized parameters were not analyzed in each and every participant of this study. For example, out of 383 human participants, TLC/TC was done in 377(98.4%) patients, likewise DLC in 376(98.2%), haemoglobin (Hb) in 349(91.1%), platelet in 232(60.6%), random blood sugar (RBS) in 193(50.4%), glycosylated haemoglobin (A1C) in 51(13.3%), urea and creatinine in 382(99.7%), liver enzymes like alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) in 364(95%), total proteins (TP) and fractions in 362(94.5%), hs-CRP in 202(52.7%), ferritin in 97(25.3%), PT in 141(36.8%), LDH in 91(23.8%), FIB in 93(24.3%), PCT in 93(24.3%), IL-6 in 93(24.3%) and D-Dimer in 104(27.2%) participants of the study (Table SII, Supplementary file).

Magnitude of dysnatremic patients showing aberration in the circulatory level of the other laboratory parameters e.g. TC, polymorph (poly), monocyte (mono), urea, creatinine, ferritin, PT, LDH, FIB, PCT, IL-6, D-Dimer were significantly high to that of eunatremic COVID-19 participants. Except for A1C, there was no significant difference in magnitude in the above mentioned observations between hypernatremic and hyponatremic group. Number of hyponatremic COVID-19 patients with high A1C value (92.3%) was significantly high (p=0.04) than the hypernatremic COVID-19 patients with high A1C (66.7%). Out of the total 383 participants, 116 (30.3%) participants required intensive care unit (ICU) facilities of which 36 (31%) succumbed to death. Requirement of ICU facility was significantly high in dysnatremic (46.2%; p = 0.001) and also in hypernatremic group of patients (54.7%; p< 0.0001) than the eunatremic group (20.6%). ICU requirement in hyponatremic group (34%) did not reach significant level (p = 0.06) and the difference between hypernatremic and hyponatremic was significant showing a p value of 0.02. It was observed that, dysnatremia, especially hypernatremia when associated with aberrant circulatory levels of the scrutinized parameters except, mono and A1C ended up with a significantly high (p < 0.05) mortality rate compared to that of the eunatremic group. Almost similar observation was also noticed in hyponatremia except when associated with aberrant TC/poly/creatinine/ TP/ FIB and PCT. Fatality rate was significantly more among hypernatremic with aberrant laboratory parameters than that of hyponatremic except when associated with high ALP, hs-CRP, PT, FIB, PCT, IL-6, and D-Dimer, where it failed to attain the significant level. Similarly, dysnatremic participants demanding ICU facilities demonstrated significantly high mortality rate (p<0.0001) compared to eunatremic group requiring ICU facilities. Though the magnitude of non-survivors among hypernatremic requiring ICU admission (51.7%) was more than that of the hyponatremic (37.5%) but the difference did not reach the significant level (p=0.1). (Table SII, Supplementary file).

The severity parameters which showed statistically significant raised mean values in the dysnatremic group were TC, poly, urea, creatinine, hs-CRP (with an exception in hyponatremic group, where the elevation was not statistically significant), ferritin, PT, LDH, PCT and D-Dimer. Conversely, parameters showing significantly decreased mean values in the dysnatremic group compared to the eunatremic group were lymphocytes (lympho), mono (with an exception in hyponatremic group, where the reduction was not statistically significant), TP and albumin. The mean values of all the scrutinised parameters did not demonstrate significant difference between hypernatremic and hyponatremic group with the exception of urea and IL-6

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where mean urea and mean IL-6 was found to be significantly high in hypernatremic group than that of the hyponatremic group (Table SIII, Supplementary file).

Severity of failed organs can be numerically quantified by the SOFA score (a method for risk stratification and prognosis of patients with severe sepsis) based on PaO2/FiO2, the Glasgow Coma Scale, mechanical ventilation (yes/no), platelets, bilirubin, mean arterial pressure or administration of vasoactive agents, and creatinine.[24,30] As PaO2 was not captured for most of patients, the peripheral arterial oxygen saturation (SpO2) to FiO2 ratio (SaO2/ FIO2) was used. This alternative option has been previously validated with high correlation. [30,31] The CURB-65 score is another mortality risk score for community acquired pneumonia (CAP), based on confusion, blood urea nitrogen, respiratory rate, blood pressure, and age, attributing 1 point for each item. It has been extensively validated to predict 30-day mortality in CAP.[32]

We employed both the severity scores but due to non-availability of all the required parameters we could calculate the SOFA score of only 28.7% (110/383) and CURB 65 score of only 32.4% (124/383) of the COVID-19 participants. It was observed that dysnatremic group ($p < 0.0001$) of participants, including both hyper ($p<0.0001$) and hyponatremia ($p = 0.0005$) demonstrated significantly high SOFA score compared to eunatremic group of participants. But the difference between hypernatremic and hyponatremic was not significant ($p = 0.7$). Mortality risk based on CURB 65 score was found to be significantly high in hypernatremic group ($p=0.001$) but failed to reach the statistical significance in hyponatremic ($p=0.1$) compared to eunatremic group. However, the difference in the occurrence of both the high SOFA scores and high CURB 65 scores between deceased and surviving dysnatremic (including both hyper and hyponatremia) participants did not reach statistical significance (Table IV).

Probability of death based on serum sodium values 24hrs after admission was assessed with the help of Kaplan-Meier curve. It was observed that probability of death was 2.35-fold increased in hypernatremic patients compared to eunatremic patients demonstrating a significant (Bonferroni corrected) p value of 0.002 (Figure 3). On the contrary, the probability of death in the hyponatremic group of patients failed to attain the statistical significance ($p= 0.3$) with a 0.7-fold increase.

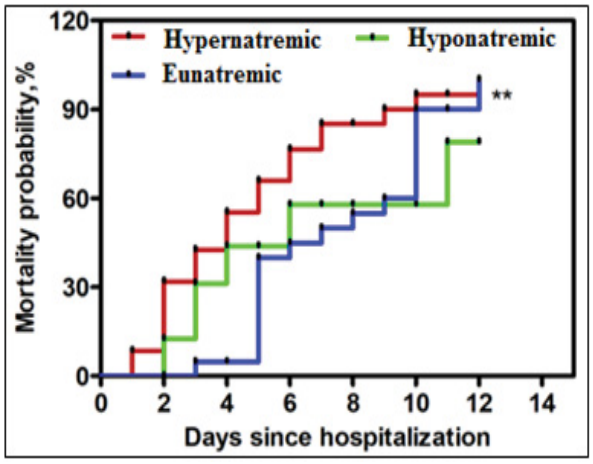

Figure 3: Kaplan-Meier curve showing the probability of death based on serum sodium values 24hrs after admission.

Table IV: Calculated SOFA score and CURB 65 score with statistical comparison (Student's t test) among different study groups.

Sodium Status	SOFA Score							
	Survivors		Non Survivors		*p* value	Total		*p* value
	n	Mean ± SD	*n*	Mean ± SD		*n*	Mean ± SD	
Dysnatremic	36	4.5 ± 2.2	20	5.1 ± 2.1	0.3	56	4.71 ± 2.16	p_1<0.0001
Hypernatremic	18	4.1 ± 2.22	18	5.2 ± 2.15	0.1	36	4.6 ± 2.22	p_2<0.0001
Hyponatremic	18	4.9 ± 2.17	02	4.5 ± 2.12	0.8	20	4.9 ± 2.11	p_3=0.0005
Eunatremic	46	2.7 ± 1.09	08	3.6 ± 1.3	0.09	54	2.9 ± 1.16	p_4= 0.7
	CURB 65 Score							
Dysnatremic	72	1.44 ± 0.63	52	1.6 ± 0.77	0.2	124	1.51 ± 0.69	p_1=0.001
Hypernatremic	44	1.5 ± 0.59	42	1.57 ± 0.74	0.6	86	1.53 ± 0.66	p_2=0.001
Hyponatremic	28	1.36 ± 0.68	10	1.7 ± 0.95	0.3	38	1.45 ± 0.76	p_3=0.1
Eunatremic	90	1.26 ± 0.49	13	1.31 ± 0.48	0.7	103	1.26 ± 0.48	p_4= 0.5

*Note: p_1 (dysnatremic–eunatremic); p_2 (hypernatremic–eunatremic); p_3 (hyponatremic–eunatremic); p_4 (hypernatremic–hyponatremic).

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Discussion

In this study, we have put forward the findings of the retrospective record analysis study in which we have investigated the incidence of dysnatremia among SARS-CoV-2-positive participants (n = 383) compared to SARS-CoV-2- negative participants (n = 90). Contradicting some of the earlier findings, [4-9,13,20,33] we have observed that a significant (p = 0.02) number of aforementioned participants demonstrated hypernatremia (27.7%) compared to only 13.3% age and gender matched participants from the control group. Comparable to our findings, few studies have also been reported testifying hypernatremia to be a common extra-pulmonary impediment in COVID-19 patients associated with adverse outcome. [1,10,34] Angiotensin-converting enzyme 2 (ACE2), a counter regulator of renin-angiotensin-aldosterone system (RAAS), is considered as the specific functional receptor for invasion of the SARS-CoV-2 into the human body leading to suboptimal level of this enzyme in infected individuals. [35-38] It has been reported that SARS-CoV-2 can also down-regulate the ACE2 expression on cells. [38,39] ACE2 plays a protective role against pathogenesis of many diseases and decrease in ACE2 levels through the above mentioned mechanisms harmonized with the systemic manifestations of the COVID-19 patients as well as the significant (p = 0.03) increase of hospital stay among them. [35,40] ACE2 expression is reported to decrease with increasing age and higher in females than in males which explains the increased incidence of COVID-19 in elderly people (mean age 52 yrs) as well as more prevalence among males than females (68.4% vs 31.6%). [36] Besides, manipulation of the RAAS, which is a set of intricate systems involved mainly in fluid and electrolyte homeostasis and thus affects the function of many organs, has been implicated in the pathogenesis of COVID-19-related dysnatremia. [1,35,38] This also explains the highest incidents (30.9%) of multi-organ injuries among COVID-19 participants observed in our study. As our data analysis illustrated fever as one of the prominent symptoms, therefore, it could also contribute to the development of hypernatremia due to insensible water loss because of increased respiratory rate. [4] Concurrently, hyponatremia was also witnessed in 12.3% of COVID-19 participants (though significantly less with p = 0.01 compared to hypernatremia) possibly due to the syndrome of inappropriate anti-diuretic hormone release (SIADH). [1,4,5] Another hypothesis is that the dysregulation of the immune system may lead to the development of hyponatremia in patients with COVID-19 pneumonia. [4,13]

Comparable to some previous studies, [4,20,41] the proportion of dysnatremia on admission (60%) was relatively higher (to hyponatremia= 70.2% and hypernatremia= 50.9%) than developed later. The use of steroid (used in 50% cases in our study) to restrain the hyper-inflammatory symptoms of COVID-19 might have added to the frequent occurrence of hypernatremia among the hospitalised COVID-19 participants (49.1%). [1,2] Besides, limited use of intravenous fluid due to the risk of developing bradykinin-mediated pulmonary oedema (hallmark of COVID-19 infection) may be considered as another contributing factor. [1,42] The relative disinclination of the healthcare workers to enter the isolation rooms of COVID-19 patients due to the stringent personal protective measures seems to be an additional predisposing factor. [1,33] Incidence of dysnatremia whether hyper or hypo, as well as the mortality rate was more among males compared to females which might be due to high proportion of COVID-19 affected male patients (68.4% vs 31.6%). It was observed that the critical hypernatremia when detected on admission was fatal with 100% mortality compared to 40% fatality when developed later. Activation of RAAS leading to physiological alterations causing permanent damage of the organs may be an explanation of the increased mortality rate among critical reporting during admission. Whereas, the possibility of iatrogenic critical hypernatremia reported later, which could be corrected as soon as developed leading to less mortality.

In accordance with some previous studies, [7,10,11,13] significantly increased number of non-survivors amongst hypernatremic COVID-19 participants compared to that of hyponatremic and eunatremic participants suggested that outcome of hypernatremia is harsher than the hyponatremia. The total physiological alterations resulting from hypernatremia leading to negative inotropic effect, increased hyperventilation, altered glucose metabolism, brain cell shrinkage and vascular rupture may be the contributory factor of high mortality in hypernatremia. [5,10,43] Total hospital stay did not exhibit any significance as average 7 days hospitalization was mandatory for all COVID-19 positive patients.

Dysnatremia, when associated with aberrant circulatory levels of other laboratory parameters (except for few parameters) proved to be more lethal with a significant number of non-survivors among them. Hyponatremia when associated with uncontrolled diabetes with high A1C ended up with significantly high mortality compared to that of eunatremic (p=0.02) and hypernatremic (p=0.003). Increased magnitude of high A1C level among hyponatremic than the eunatremic and hypernatremic might indirectly influence the high mortality among them or might be the result of poor glycemic control as low serum sodium when associated with poor glycemic control resulted in increased mortality. [44] Mean urea and mean IL-6 was found to be significantly high in hypernatremic group than that of the hyponatremic group and the mean IL-6 of the hyponatremic group (10.8 pg/mL) was even less than that of the eunatremic group (12.6 pg/mL) though not significant (p=0.6), contradict the hypothesis that there is an inverse relationship between serum sodium and IL-6. [7,9] Some of the previous studies also have shown that COVID-19 patients with severe illness had numerous

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laboratory abnormalities such as in TC, DLC, D-dimer, CRP, liver function, renal function, LDH, procalcitonin, and electrolytes and thought to be due to multiple organ damage. [26,28,29] But the cause of the organ damage in connection with the serum sodium level and COVID-19 is not yet fully understood. Another study conducted in China, though at odds with some of our findings like incidence of hypernatremia, disease severity, hospital stay and mortality among the hypernatremic group, few of our findings (such as renal insufficiency, hypoproteinemia, mean D-Dimer, albumin, urea, LDH value) were in harmony with our study. [33] As observed, the COVID-19 patients with dysnatremia were mostly of older age group, there might be associated insufficient reserve renal function, consequently resulting renal inabilities to regulate electrolytes. [33] However, further investigations are in demand to establish whether renal insufficiency is the etiology or the consequence of electrolyte imbalance in COVID-19 patients.

Well-known clinical calculators, such as the SOFA or CURB-65 scores were used to measure the severity and mortality risk among the COVID-19 positive participants. However, these scores are limited by their accuracy as the input variables, such as confusion (for CURB-65) and the Glasgow Coma Scale (for SOFA), both of which are ambiguous, difficult to measure, and frequently unavailable. [24] Higher SOFA score was found to be associated with higher odds of in-hospital death [2] but connection of higher SOFA as well as the CURB-65 score with serum sodium status is yet to understand.

Hypernatremia at any time point seems to be a frequent extra-pulmonary complication in our infirmary whereas hyponatremia is more prevalent at the time of admission which highlights the significance of considering dysnatremia as a predictive marker and thus directs a correct path for appropriate management of COVID-19 patients.

Limitations of the study

Our study has limitations beyond its retrospective view of observation. First, due to the non-availability of data all included parameters could not be correlated with the control group.

Second, we have limited information about the etiology of dysnatremia. Few studies have explored the cause and recommended that SIAD, hypovolemia, increased perspiration etc., to be the root causes of dysnatremia. But in our case, due to the limited information in this regard, a consistent deduction of the cause of dysnatremia was not possible.

Third, due to the retrospective study design, not all laboratory parameters were done in all patients, especially CRP, ferritin, PT, LDH, fibrinogen, PCT, IL-6 and D-Dimer. Therefore, their role in predicting mortality might be underestimated. Likewise, risk stratification and mortality risk calculation through SOFA and CURB-65 scores might not be appropriate as both the scores could be applied only on half of the participants due to non-availability of required data.

Fourth, our data often did not allow the analysis of a temporal relationship between the onset of dysnatremia after admission and the clinical course of the disease which might have been helpful in predicting casualty.

Lastly, as this study was observational and retrospective in nature and due to a large number of confounders, such as gender, and different laboratory parameters a causal relationship between dysnatremia and mortality in COVID-19 patients could not be established.

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Conflict of Interest

Authors declare that they have no conflicts of interest

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