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Hypokalemia and Its Correlates Among Nigerian SARS-CoV-2 Infected Patients

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Abstract: *Background*: Disorders of electrolytes balance, especially that of potassium, have frequently been documented among patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, most of these reports have been documented among the western populations. Hence, this current study was aimed to evaluate the pattern of derangement in potassium balance and its correlation to other clinical and laboratory variables among Nigerians. *Methods*: Archived data of all eligible adult patients, who were managed at the Eleme treatment center in Port Harcourt, Nigeria following a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 infection, were enrolled for this study. All relevant data of enrolled subjects were retrieved from the archived case notes, medical review charts, nurses' charts, and laboratory-related records at initial presentation before any form of medical treatment by trained research assistants using well-structured data extraction forms. The collected data was analyzed using descriptive and comparative statistics. *Results*: Hypokalemia was recorded in 323 (62.8%) subjects out of a total of 515 eligible subjects. Mild, moderate, and severe hypokalemia was recorded among 32 (9.9%), 219 (67.9%), and 72 (22.2%) subjects, respectively. The subjects with severe hypokalemic status were mostly males and also of older age and had significantly higher systolic blood pressure, CRP, D-dimer, neutrophil count, and higher proportions of those with severe SARS-CoV-2 infection but lower albumin levels, lymphocyte and platelet counts compared to those with mild and moderate hypokalemic status ($p<0.05$). Inverse relationships were established between plasma potassium status and systolic blood pressure, sodium, C-reactive protein, D-dimer, and neutrophil count. While a significant positive relationship was observed between plasma potassium status and plasma albumin, lymphocyte counts, platelet counts, and oxygen saturation among the hypokalemic subjects ($p<0.05$). Compare to mild and moderate hypokalemic status, severe hypokalemic status was associated with severe SARS-CoV-2 infection (OR: 5.671; (95%CI: 4.467-7.365); $p<0.001$) and unfavorable clinical outcomes (OR: 7.863; (95%CI: 6.502-9.342); $p<0.001$) among the hypokalemic subjects. *Conclusion*: The present study findings suggest a high frequency of hypokalemia among subjects with the SARS-CoV-2 infection who are mostly males and of older age. The observed hypokalemia, especially the severe variant, was found in association with the severe infection and unfavorable clinical outcome. These findings should be considered during the management of SARS-CoV-2 infection. However, further studies are recommended to verify the conclusions of the present study.

Keywords: SARS-CoV-2, SARS-CoV-2 Infection, COVID-19, Hypokalemia

1. Introduction

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the widely known etiologic agent for the novel coronavirus disease 2019 (COVID-19) pandemic, continues on its rising trend throughout the world, several countries continue to bear the brunt of the novel viral pandemic on their respective health system, social, and economic activities since its evolution from Wuhan City, Hubei Province, China by the end of 2019 [1-3]. To date, the exact pathophysiology of the SARS-CoV-2 infection is still poorly characterized in medical parlance as experts around the globe continue to study and report daily on its unique features [4, 5].

However, a large number of epidemiological evidence now exist to suggest that the SARS-CoV-2 infection has multi-systemic and multi-organ effects on those infected [6, 7]. These multiple effects culminate in derangements of several hematological, coagulation, and biochemical parameters as vastly observed and reported. Biochemical derangements, especially the electrolyte imbalance involving the electrolyte potassium, is one of the most common disorders observed among SARS-CoV-2 infected patients during the early phase of the infection in China [8, 9]. As widely reported, the imbalance of the potassium electrolyte among the SARS-CoV-2 patients is significantly associated with several adverse consequences of the infection [10].

However, most of these reports [8-10] have been documented mostly among Caucasians with a dearth of data among SARS-CoV-2 infected patients in Nigeria. Therefore, this present study was aimed to evaluate the pattern of derangement in potassium balance and its correlation to other clinical and laboratory variables among Nigerians.

2. Materials and Methods

2.1. Study Design

This was a sub-study of a large retrospective, observational, and cross-sectional study performed at the Eleme COVID-19 treatment center, a Rivers State Government-owned center dedicated to the management of both inpatients/outpatients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Port Harcourt, Nigeria. The center was established and is currently under the management of the Government of Rivers State through two major agencies [the Rivers State Ministry of Health and the Rivers State Hospital Management Board (RSHMB)].

The center receives and admits hundreds of SARS-CoV-2 infected cases per year and has a side laboratory that is well-equipped with automated chemistry/hematology analyzers dedicated for laboratory investigations following COVID-19 diagnosis and subsequent management. The results of these investigations are properly archived at the treatment center. The SARS-CoV-2 infected patients are usually referred to the treatment center following a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test result from a nasal and/or throat swab at the Rivers State University Teaching Hospital (RSUTH) SARS-CoV-2 testing laboratory.

The study protocol was approved by the RSHMB Ethics Committee and complied with the principles embodied in the World Medical Association's Helsinki Declaration. The minimum sample size for the study was obtained with the sample size formula for studying features in a population of > 10,000, at a 95% confidence interval and 5% margin of error, using an assumed SARS-CoV-2 prevalence rate of 50% [11]. The obtained minimum sample size was approximately 480 including an anticipated 10% attrition rate, but 515 were eventually recruited to magnify the power of the study. All properly archived data of the eligible patients with RT-PCR-confirmed SARS-CoV-2 infection who were admitted/managed at the treatment center between 2020 and 2021 were utilized as study tools.

The criteria for inclusion were data of adults, with relatively stable health/normal renal status before the COVID-19 diagnosis, who are of age ≥18 at the time of diagnosis/admission in the treatment center. Those excluded were data of the pregnant patients, those on recent/current medications known to influence potassium balance (potassium-sparing/non-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, etc) at the time of diagnosis. Also excluded were patients with any clinical features or known comorbid conditions notorious for influencing potassium balance such as diarrhea, vomiting, oliguria, polyuria, anorexia, poor oral intake, malabsorption syndromes, and acute/chronic renal diseases.

2.2. Data Collection

All baseline/clinical data including those of the laboratory were obtained upon presentation before any form of medical treatment. These data were acquired from each patients' case notes, medical review charts, nurses' charts, and laboratory result sheets by well-trained research assistants (nurses/laboratory scientists/doctors) mandated to work at each treatment center. The extraction of data was carried out using standardized data extraction forms.

The basic variables of which data was acquired included the socio-demographic, clinical, anthropometric, pre-existing comorbidities, and laboratory data. The laboratory data included plasma/serum sodium, potassium, chloride, bicarbonate, urea, creatinine, albumin, total plasma protein, pro-calcitonin, C-reactive protein (CRP), and ferritin, plasma fibrinogen, D-Dimer levels, full blood count (FBC)/FBC differentials, red blood cell count (RBC), hemoglobin concentrations, and platelet count. The urine biochemistry parameters included microalbuminuria, proteinuria, hematuria, and urine albumin-creatinine ratio (UACR).

2.3. Laboratory Protocols

During the study period, all specimens were acquired following standard protocols in the treatment center

including the laboratory analyses by experienced analysts.

Heparinized plasma was analyzed for plasma sodium, potassium, bicarbonate, chloride on an ion-selective electrode chemistry analyzer (SFRI 6000, SFRI Diagnostics, Berganton, France). The heparinized plasma was also analyzed for urea, creatinine, albumin, and total protein on an automated chemistry analyzer (BS200, Mindray, Shenzhen, China). EDTA whole blood was analyzed for Hb concentration, FBC, RBC, and Platelet counts on an automated hematology analyzer (BC10, Mindray, Shenzhen, China).

Plain-tube processed serum was analyzed for pro-calcitonin, D-dimer, ferritin on an automated immunoassay analyzer (Mini Vidas, Biomerieux, France). The plain tube-derived serum was analyzed for CRP using a CRP analyzer (HEALES, Shenzhen, China). Citrated plasma fibrinogen level was determined using a coagulation analyzer (COA04, Biobase, China). Urine biochemistry was investigated using a standard urine automated analyzer (Combilyzer-13, Human Diagnostics, Germany).

2.4. Data Definitions/Categorizations

COVID-19 severity was classified based on the Nigerian Centre for Disease Control National (NCDC) case management recommendations as non-severe and severe [12]. The disease severity was defined as the presence of fever >38˚C or suspected respiratory infection, plus one of respiratory rate >30 breaths/minute; severe respiratory distress; oxygen saturation (SpO_2) of ≤ 93% on room air and the presence of comorbid conditions such as diabetes, asthma, hypertension in adults and cough or difficulty in breathing and at least one of the following central cyanosis or SpO_2 < 92%; severe respiratory distress e.g. grunting breathing, very severe chest in-drawing and signs of pneumonia in children.

Confirmed COVID-19 infection was defined as positive RT-PCR from a nasal and/or throat swab together with signs, symptoms, and/or radiological findings suggestive of COVID-19 infection.

Plasma potassium status was defined as normokalemia (3.5-5.0 mmol/L), hypokalemia (<3.5 mmol/L), and hyperkalemia (>5.0 mmol/L) [13].

The hypokalemic status was further categorized as mild (3.0-3.4 mmol/L), moderate (2.5-3.0 mmol/L), and severe (<2.5mmol/L) hypokalemia as previously described [9]. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation [14]. Normal renal status was defined eGFR of ≥ 90 mls/minute with nil evidence of proteinuria/hematuria. The patients' clinical outcome was categorized as satisfactory (discharged in a good clinical condition) and unsatisfactory (intensive care unit referral/treatment care and mortality) outcomes.

2.5. Statistical Analysis

Data management and analyses were executed using the Statistical Package for Social Sciences software version 23.0 (IBM Co., Armonk, NY, USA). The continuous variables were first tested for departure from normal distribution using both visual (histogram) and statistical protocols (Kolmogorov-Smirnov test).

The continuous data found to have deviated from a normal distribution were subsequently log-transformed before analysis and summarized using means±standard deviations (SD) following analyses; comparison made with analysis of variance.

The categorical data were summarized and presented as proportions in counts/percentages; comparison made with the chi-square test or Fisher's exact test as appropriate. The relationships and associations between outcome variables and predictors were respectively evaluated using the linear and logistic regression models at 95% confidence intervals. A p-value of less than 0.05 (5%) was deemed statistically significant.

3. Results

During the period under study, a total of 678 RT-PCR positive COVID-19 patients was managed both as inpatients/outpatients in the treatment center. However, 515 met the eligibility criteria for the current study and were recruited for the study. Among the 515 subjects who met the inclusion criteria, 182 (35.3%), 10 (1.6%), and 323 (62.8%) had normal plasma potassium status (that is, normokalemia), hyperkalemia, and hypokalemia, respectively (Table 1).

Table 1 depicts the basic characteristics of the study cohorts including the comparative analysis of these basics among the normokalemic, the hyperkalemic, and the hypokalemic subgroups. The entire study cohorts were mostly males (Table 1). Moreover, the subjects in the hypokalemic group were predominantly males and of older age compared to the normokalemic and hyperkalemic subjects ($p<0.05$) (Table 1). The hypokalemic subjects also had significantly higher mean values of body temperature, systolic blood pressure, respiratory rate, sodium, bicarbonate, CRP, D-dimer, white cell count, neutrophil count, and higher proportions than those with pre-existing comorbid conditions, severe SARS-CoV-2 infection, and unfavorable clinical outcomes but lower plasma albumin levels, lymphocyte count, platelet count, and the measured oxygen saturation at presentation when compared to the normokalemic and the hyperkalemic subjects ($p<0.05$) (Table 1).

Among the 323 hypokalemic subjects, 32 (9.9%), 219 (67.9%), and 72 (22.2%) were of mild, moderate, and severe grades, respectively (Table 2). The subjects with severe hypokalemic status (n=72; 22.2%) were mostly males and also of older age compared to those with mild and moderate hypokalemic status ($p<0.05$) (Table 2).

Those with the severe hypokalemic status also had significantly higher systolic blood pressure, CRP, MD-dimer, neutrophil count, and higher proportions of those with severe SARS-CoV-2 infection but lower albumin levels, lymphocyte and platelet counts compared to those with mild and moderate hypokalemic status ($p<0.05$) (Table 2).

Table 3 depicts the results of the adjusted linear regression model to explore the relationship between plasma potassium status and the significant continuous variables from Table 2.

The results show that the systolic blood pressure, plasma sodium, CRP, D-dimer, and neutrophil count all had significant inverse relationship with plasma potassium status ($p<0.05$) (Table 3). While a significant positive relationship was established between the plasma albumin, lymphocyte counts, platelet counts, oxygen saturation, and plasma potassium status ($p<0.05$) (Table 3).

Table 4 shows the results of logistic regression analysis used to evaluate the association between the severity and clinical outcome of SARS-CoV-2 infection and plasma potassium status among the hypokalemic subjects. On the crude unadjusted model, both moderate and severe hypokalemia was observed in association with plasma potassium status when compared to the mild hypokalemic subjects ($p<0.05$) (Table 4). However, following adjustment of all the observed confounders, only the severe hypokalemic status maintained a significant association with the severe variant of SARS-CoV-2 infection (OR: 5.671; (95%CI: 4.467-7.365); $p<0.001$) and unfavorable outcome (OR: 7.863; (95%CI: 6.502-9.342); $p<0.001$) while the moderate hypokalemic status lost their statistical significance of association (Table 4).

Table 1. *Baseline characteristics of studied cohorts.*

Variables	Entire Subjects n=515 (100%)	$NormoK^+$ Subjects n=182 (35.3%)	$HyperK^+$ subjects n=10 (1.9%)	$HypoK^+$ subjects n=323 (62.8%)	p-value***
	M±SD/n	M±SD/n (%)	M±SD/n (%)	M±SD/n (%)	
Age, years	42.62±6.78	41.07±6.19	43.22±6.09	48.11±6.42	<0.001*
Males/Females	316/199	60/122	7/3	199/124	0.033*
BMI, kg/m^2	28.66±5.05	28.24±4.94	28.87±4.32	28.54±4.88	0.314
Body temperature, °C	36.71±3.07	36.95±3.08	36.74±3.11	37.89±3.17	0.020*
SBP, mmHg	135.07±6.43	134.82±6.08	136.32±5.97	139.71±6.13	0.042*
DBP, mmHg	87.58±4.42	87.34±4.61	87.84±4.43	88.04±4.90	0.064
HR/minute	81.18±4.24	80.95±4.19	81.65±4.07	81.08±4.23	0.088
RR/minute	23.65±2.98	23.41±2.76	23.55±2.82	28.86±2.44	0.010*
Plasma sodium, mmol/L	136.89±7.09	136.41±7.33	136.78±7.43	146.71±7.66	<0.001*
Plasma chloride, mmol/L	98.27±6.91	97.63±6.84	98.42±6.99	98.03±6.64	0.083
Plasma bicarbonate, mmo/L	22.67±4.71	23.03±4.09	23.11±4.53	29.97±5.08	0.017*
Plasma urea, mmol/L	7.17±1.24	6.81±1.32	6.55±1.22	6.22±1.08	0.116
Plasma creatinine, µmol/L	97.16±7.73	95.82±7.17	96.94±7.92	94.96±7.69	0.096
Plasma albumin, g/L	35.62±4.41	35.89±4.03	34.99±4.57	32.77±4.69	0.014*
Plasma total protein, g/L	63.74±6.41	62.47±6.55	62.32±6.62	62.01±6.53	0.122
Hemoglobin concentration, g/L	110.94±7.69	109.68±7.70	109.71±7.88	108.96±7.95	0.234
Serum pro-calcitonin, µg/L	3.16±1.41	2.88±1.76	2.93±1.65	2.91±1.66	0.340
Serum C-reactive protein, nmol/L	133.64±9.77	135.83±9.79	136.21±9.43	151.11±9.93	<0.001*
Serum ferritin, pmol/L	967.74±22.88	955.11±21.98	957.72±21.04	968.02±20.64	0.063
Plasma fibrinogen, g/L	7.17±1.44	6.18±1.52	6.27±1.63	6.84±1.70	0.075
D-Dimer, (≤500 µg/L FEU)	998.76±95.74	974.43±94.93	1,.164±95.06	1,412.71±95.85	<0.001*
Total WBC x 10^9/L	16.84±3.41	15.93±3.06	16.20±3.01	18.22±3.10	<0.001*
WBC Differentials,					
Neutrophil count x 10^9/L	14.17±2.17	13.78±1.97	14.76±2.91	16.65±2.23	<0.001*
Lymphocyte count x 10^9/L	1.48±0.14	1.41±0.13	1.43±0.10	1.31±0.09	0.022*
Monocyte count x 10^9/L	0.91±0.19	0.87±0.17	0.87±0.17	0.89±0.18	0.135
Eosinophil count x 10^9/L	0.34±0.02	0.32±0.03	0.39±0.06	0.27±0.11	0.210
Basophil count x 10^9/L	0.19±0.23	0.17±0.22	0.18±0.21	0.16±0.19	0.311
Platelet count x 10^9/L	143.64±9.22	142.96±9.88	139.94±8.77	128.64±8.98	<0.001*
Red cell count x 10^{12}/L	4.37±1.29	4.08±1.14	4.11±1.12	3.97±1.16	0.431
UACR, mg/mmol	1.87±0.23	1.72±0.23	1.72±0.24	1.73±0.33	0.087
eGFR, mls/minute	93.72±6.63	92.87±6.49	92.91±6.19	93.12±6.30	0.417
Oxygen saturation,%	93.44±6.45	94.08±6.31	93.71±6.07	90.78±6.32	<0.001*
Comorbid conditions:**Yes/No	170/345	20 (11.7)/162 (46.9)	5 (2.9)/5 (1.5)	145 (85.4)/178 (51.6)	<0.001*
Severity: Severe/non-severe	50/465	4 (8.0)/178 (38.3)	1 (2.0)/9 (0.9)	45 (90.0)/278 (59.8)	<0.001*
Outcome: unfavorable/favorable	65/450	9 (13.8)/ 173 (38.4)	1 (1.5)/9 (2.0)	55 (84.7)/268 (59.6)	<0.001*

*Statistically significant; M±SD: mean±standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; $NormoK^+$: normokalemia; $HyperK^+$: hyperkalemia; $HypooK^+$: hypokalemia;

**comorbidities included being aged ≥65 years; having cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, HIV/AIDS, diabetes, cancer, obesity, or chronic kidney disease, chronic liver disease; being a cigarette smoker; being a transplant recipient, and receiving immunosuppressive therapy;

*** ANOVA p-values for $NormoK^+$ versus $HyperK^+$ versus $HypoK^+$.

Table 2. *Comparison of significant variables from Table 1 by different degrees of hypokalemia.*

Variables	Entire HypoK$^+$ subjects n=323	Mild HypoK$^+$ subjects, n=32 (9.9%)	Moderate HypoK$^+$ subjects, n=219 (67.9)	Severe HypoK$^+$ subjects, n=72 (22.2)	p-value***
	M±SD/n	M±SD/n (%)	M±SD/n (%)	M±SD/n (%)	
Sex: Males/Females	199/124	17/15	119/100	63/9	0.021*
Age, years	48.11±6.42	46.07±5.94	47.84±6.08	49.91±6.41	<0.001*
Body temperature, °C	37.89±3.17	36.74±3.12	36.95±3.14	37.04±3.16	0.281
SBP, mmHg	139.71±6.13	138.51±5.78	140.89±6.22	144.64±6.13	<0.001*
RR/minute	28.86±2.44	27.94±2.07	28.30±2.15	28.11±2.36	0.117
Plasma sodium, mmol/L	146.71±7.66	144.55±7.41	146.44±7.32	149.54±7.53	<0.001*
Plasma bicarbonate, mmo/L	29.97±5.08	28.64±5.63	29.04±5.76	28.96±5.82	0.241
Plasma albumin, g/L	32.77±4.69	34.60±4.54	30.42±4.33	28.43±3.94	<0.001*
Serum C-reactive protein, nmol/L	151.11±9.93	148.67±8.77	157.51±8.87	163.24±9.04	<0.001*
D-Dimer, (≤500 µg/L FEU)	1,412.71±95.85	955.62±93.64	1,212.71±95.85	1,633.24±97.09	<0.001*
Total WBC x 10^9/L	18.22±3.10	17.63±2.96	18.84±3.61	19.75±3.73	0.069
WBC Differentials,					
Neutrophil count x 10^9/L	16.65±2.23	14.77±2.76	16.04±2.80	18.11±2.94	<0.001*
Lymphocyte count x 10^9/L	1.31±0.09	1.38±0.05	1.28±0.06	1.15±0.08	0.014*
Platelet count x 10^9/L	128.64±8.98	134.35±7.84	122.07±7.62	110.±6.77	<0.001*
Oxygen saturation,%	90.78±6.32	92.66±7.17	91.03±6.44	89.41±6.02	<0.001*
Comorbid conditions:**Yes/No	145/178	10 (6.9)/22 (12.4)	68 (46.9)/151 (84.8)	67 (46.2)/5 (2.8)	0.314
Severity: Severe/non-severe	45/278	4 (8.9)/28 (10.1)	11 (24.4) /208 (74.8)	30 (66.7)/42 (15.1)	<0.001*
Outcome: unfavorable/favorable	55/268	3 (5.5) /29 (10.8)	12 (21.8)/207 (77.2)	40 (72.7)/32 (11.9)	<0.001*

*Statistically significant; M±SD: mean±standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; NormoK$^+$: normokalemia; HyperK$^+$: hyperkalemia; HypooK$^+$: hypokalemia;
**comorbidities included being aged ≥65 years; having cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, HIV/AIDS, diabetes, cancer, obesity, or chronic kidney disease, chronic liver disease; being a cigarette smoker; being a transplant recipient, and receiving immunosuppressive therapy;
*** ANOVA p-values for Mild NormoK$^+$ versus Moderate HyperK$^+$ versus Severe HypoK$^+$.

Table 3. *Adjusted linear regression analysis between plasma potassium status and the significant continuous variables from Table 2 among the hypokalemic subjects (n=323).*

Variables	β** Coefficient	Standard Error of Regression	95% Confidence Interval	p-value
SBP, mmHg	-0.740	0.191	-0.860 to -0.601	<0.001*
Plasma sodium, mmol/L	-0.419	0.322	-0.487 to -0.357	<0.001*
Plasma albumin, g/L	0.315	0.143	0.233 to 0.467	<0.001*
Serum C-reactive protein, nmol/L	-0.403	0.098	-0.477 to -0.341	0.006*
D-dimer, (≤500 µg/L FEU)	-0.334	0.047	-0.456 to -0.280	0.010*
WBC Differentials,				
Neutrophil count x 10^9/L	-0.224	0.413	-0.293 to -0.144	<0.001*
Lymphocyte count x 10^9/L	0.560	0.108	0.416 to 0.687	<0.001*
Platelet count x 10^9/L	0.433	0.134	0.320 to 0.582	<0.001*
Oxygen saturation,%	0.672	0.216	0.511 to 0.762	<0.001*

*Statistically significant; M±SD: mean±standard deviation; SBP: systolic blood pressure; β: coefficient of regression; **Adjusted for age and sex.

Table 4. *Association between severity/clinical outcome of SARS-CoV-2 infection and plasma potassium status among the hypokalemic subjects (n=323).*

Variables	Mild HypoK$^+$	Moderate HypoK$^+$	Severe HypoK$^+$
1. Crude Logistic Regression	OR	OR; (95% CI); p-value	OR; (95% CI); p-value
Severe SARS-Cov-2 infection	1.0 (Reference)	1.762; (1.466 - 2.878); 0.022*	5.450; (4.361 - 7.033); <0.001*
Unfavorable clinical outcome	1.0	1.881; (1.501 - 2.061); 0.034*	7.621; (6.344 - 9.110); <0.001*
2. Adjusted** Logistic Regression			
Severe SARS-Cov-2 infection	1.0 (Reference)	1.213; (1.042 - 1.453); 0.067	5.671; (4.467 - 7.365); <0.001*
Unfavorable clinical outcome	1.0	1.239; (1.134 - 1.322); 0.084	7.863; (6.502 - 9.342); <0.001*

*Statistically significant; M±SD: mean±standard deviation; OR: odds ratio; CI: confidence interval; SARS-CoV-2: severe acute respiratory distress coronavirus 2; **Adjusted for age, sex, SBP, sodium, albumin, CRP, D-dimer, neutrophil counts, lymphocyte count, and platelet count.

4. Discussion

4.1. Major Findings

Disorders of potassium balance have frequently been documented among patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, most of these reports have been documented among the western populations. Hence, the current evaluated derangements in potassium balance and its correlation to

other clinical/laboratory variables among Nigerians. We had excluded all subjects with any clinical features (diarrhea, vomiting, poor oral intake) and medical conditions known to influence plasma potassium status to have an objective assessment of balance among the studied population. Hypokalemic status was documented among 62.8% of those evaluated with the mild, moderate, and severe hypokalemia recorded in 32 (9.9%), 219 (67.9%), and 72 (22.2%) subjects, respectively. The subjects with severe hypokalemic status were mostly males and also of older age and had significantly higher systolic blood pressure, CRP, D-dimer, neutrophil count, and higher proportions of those with severe SARS-CoV-2 infection but lower albumin levels, lymphocyte and platelet counts compared to those with mild and moderate hypokalemic status. Inverse relationships were established between plasma potassium status and systolic blood pressure, sodium, C-reactive protein, D-dimer, and neutrophil count while a significant positive relationship was observed between plasma potassium status and plasma albumin, lymphocyte counts, platelet counts, and oxygen saturation among the hypokalemic subjects. In addition, compare to mild and moderate hypokalemic status, severe hypokalemic status was associated with the severe SARS-CoV-2 infection and the unfavorable clinical outcome.

4.2. Relationship with Pre-existing Literature

The current study demonstrated a high frequency of hypokalemia among the studied Nigerians with SARS-CoV-2 infection.

Chen and colleagues had reported a 55% of rate of hypokalemia among their Chinese populations with SARS-CoV-2 infection during the early days of the pandemic. Though Chen and colleagues had used different cut-off plasma potassium values to defined hypokalemic status, they had also observed higher rate (84%) of hypokalemia among the severely/critically ill SARS-CoV-2 infected patients in their study [15]. In a recent study reported from Italy by Alfano and colleagues [9], the authors had reported a 41% prevalence of hypokalemia among their studied Italian population. The current study recorded a 62.8% rate of hypokalemia, which is higher than the rates reported among the Chinese and the Italians.

In contrast to the current findings, Alfano and colleagues found no association between hypokalemia and unfavorable outcome (intensive care unit transfer, in-hospital mortality, and composite intensive care unit transfer and in-hospital mortality) among their studied cohorts [9]. These discordant findings by Alfano and colleagues could be related to the methodological differences in both studies. Alfano and colleagues had assessed potassium in serum while the current study assessed potassium status in plasma. The assessment of potassium in either blood serum or plasma has been documented to significantly differ in laboratory practice [16].

The higher frequency of severe hypokalemia among the males and the older age group including the significantly higher systolic blood pressure, plasma sodium, CRP, D-dimer, neutrophil count, but lower albumin levels, lymphocyte counts, and platelet counts observed among the severe hypokalemic subjects compared to those with mild and moderate hypokalemic status are all related to the unique pathophysiologic features and the severity of the SARS-CoV-2 infection as previously documented [8-10, 17].

These findings are further strengthened by the observed significant inverse relationships were established between plasma potassium status and systolic blood pressure, sodium, C-reactive protein, D-dimer, and neutrophil count, while a significant positive relationship was observed between plasma potassium status and plasma albumin, lymphocyte counts, platelet counts, the oxygen saturation and plasma potassium status among the hypokalemic subjects as previously documented [8-10].

Hyperkalemia was also observed among 9.9% (n=32) of the studied population which has not been widely documented and observed as a characteristic laboratory feature of the SARS-CoV-2 infection in the literature. However, SARS-CoV-2 infection is significantly associated with acute renal involvement as documented recently by Pourfridoni and colleagues which may account for the hyperkalemia in this small subset of patients [18]. Though we excluded those likely to have renal involvement and also utilized the eGFR with urinalysis findings to recruit those with normal renal status, these measures may not be perfect indices of acute renal involvement in clinical practice [19].

4.3. Mechanistic Considerations

Two mechanisms have been described to account for the high incidence of hypokalemia among SARS-Cov-2 infected patients [15, 17, 20, 21]. First, potassium loss through the gastrointestinal tract from diarrhea/vomiting including poor oral intake which is highly prevalent among these patients with SARS-CoV-2 infection [22]. However, in the current analysis, almost all the studied patients had none of these features. Secondly, the effect of the SARS-CoV-2 on the renin-angiotensin-aldosterone system (RAAS) has widely been suggested to be the key initiator of hypokalemia among those infected with SARS-CoV-2 [17, 20, 21]. Angiotensin-converting enzyme 2 (ACE2) is a negative regulator of the RAAS activities which tends to diminish the biochemical generation of angiotensin II and aldosterone through its opposing effect on the activities of the angiotensin-converting enzyme I (ACE1). ACEI stimulates the RAAS activities to generate angiotensin II known to induce raised blood pressure, vascular complications, inflammation, and aldosterone synthesis [15, 20, 21].

SARS-CoV-2 binds to its host receptor, ACE2, and likely reduces ACE2 expression which restricts its opposing effects on the ACE1 activities, thus leading to increased angiotensin II and ultimately aldosterone, which induces increased potassium excretion by the kidneys with the resultant hypokalemia as observed among these patients [15, 17, 20, 21].

4.4. Significance to Current Clinical Practice and Subsequent Research

Hypokalemia in patients infected with SARS-CoV-2 has important clinical implications which should be seriously considered during clinical management. Hypokalemia is a serious complication that exacerbates respiratory distress syndrome which is the cardinal pathophysiologic event in SARS-CoV-2 infection. This may also provide a pathway to understanding the pathophysiologic basis of the SARS-CoV-2 infection which should be an area of aggressive future research.

4.5. Study Limitations

The study was limited by some factors which are crucial areas for improvement in future research. First, it was solely conducted in a single center, so its findings may not necessarily be representative of the entire population within the studied area. Secondly, the study was based on the acquisition of retrospective data, hence, the under-reporting of the actual number of SARS-CoV-2 infected patients cannot certainly be ruled out. Lastly, as with other observational studies, the study conclusions do not infer causality but associations.

5. Conclusion

The present study findings suggest a high frequency of hypokalemia among subjects with the SARS-CoV-2 infection who mostly were males and of older age.

The observed hypokalemia, especially the severe variant, was found in association with the severe infection and unfavorable clinical outcome. Hence, these findings should be considered during the management of SARS-CoV-2 infection. However, further studies are recommended to verify the conclusions of the present study.

Statement of Ethics

The ethical approval of the study was obtained from the Research Ethics Committee of RSHMB following the review of the study protocols and the study was executed in compliance with the principles embodied in the Helsinki Declaration.

Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

All the authors were involved substantially in the concept and design of the study, data acquisition, analysis and interpretation of the data, drafting the article, revising the article critically for its intellectual content, and in the final approval of the version to be published.

Data Availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (CA) upon reasonable request.

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