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Characteristics and Determinants of COVID-19-Associated AKI Among Patients of COVID-19 in Rivers State, Nigeria

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Abstract: *Background:* Severe acute respiratory coronavirus-2 (SARS-CoV-2)-induced coronavirus disease 2019 (COVID-19) is reportedly associated with acute renal injuries (AKI). However, this has been characterized majorly among Caucasians who have pre-existing confounding comorbidities that may also induce AKI, and hence, limit the conclusions of these previous studies. Consequently, the current study evaluated AKI incidence and associated factors among Nigerian COVID-19 patients of Negroid race who are without any pre-existing comorbid conditions. *Methods:* This was a retrospectively-designed observational study conducted among COVID-19 patients who presented at a COVID-19-designated treatment facility in Port Harcourt, Nigeria. Demographic, medical, and laboratory data obtained upon presentation were acquired and analyzed by AKI status using descriptive and inferential statistics. *Results:* Upon presentation, AKI occurred among 46.4% (n=181) of the entire studied population (n=390) which were majorly of stage 1, etiologically pre-renal, community-acquired, and of transient clinical course. Most of the AKI occurred among males, those with severe COVID-19 variants, and those who are unvaccinated against the disease. Those with COVID-19-associated AKI also had higher levels of peak plasma creatinine, plasma C-reactive protein, serum D-dimer, plasma osmolality, proteinuria, and hematuria but lower levels of within 24-hour urine volume, urine specific gravity, and urine osmolality compared to the non-AKI sub-group upon presentation. However, AKI patients with concurrent severe COVID-19 had a higher preponderance of stage 3, intra-renal and persistent AKI compared to patients with non-severe COVID-19 disease. In multivariate models, severe COVID-19 variant (OR: 6.017; CI: 5.880–6.422; p<0.001), the need for ICU transfer/treatment (OR: 3.210; CI: 3.119–3.341; p<0.001), serum D-dimer levels (OR: 3.967; CI: 3.688-4.297; p<0.001), and proteinuria (OR: 2.008; CI: 1.971–2.174; p=0.002) were independent risk factors for AKI among the studied population. *Conclusion:* AKI is common among COVID-19 patients independent of pre-existing comorbidities. The various COVID-19-associated AKI risk factors identified in the current study are valuable parameters that may guide clinical management among COVID-19 patients.

Keywords: COVID-19, COVID-19 Severity, COVID-19-Induced AKI

1. Introduction

As the coronavirus disease 2019 (COVID-19) induced by severe acute respiratory syndrome-2 (SARS-CoV-2) continues to spread unabated around the globe, various research findings continue to emerge on the consequences of the virus [1]. The initial notion, since the inception of the

SARS-CoV-2-induced COVID-19 pandemic, was that the disease was majorly a respiratory one [1, 2]. However, due to the ubiquitous presence of the virus biologic receptor (angiotensin converting enzyme-2) in humans, COVID-19 has been found to affect several other extra-respiratory systems including the renal systems [2-7].

It has been widely documented that SARS-CoV-2-induced COVID-19 adversely influences the renal systems inducing various degrees of acute kidney injuries (AKI) [3, 4]. Consequently, COVID-19-induced AKI has been adjudged the most frequently observed severe complication in association with disease severity, morbidity, and mortality among those infected.[3-7] Different incidence rates of COVID-19-associated AKI of 10.5%, 36.6%, 56%, and 14.6% have been reported in various studies in recent times from China, the United States, Brazil, and Nigeria, respectively [4-7].

However, most of the previous studies on this subject were conducted on patients with several pre-existing confounding comorbid conditions (e.g. advanced age, hypertension, diabetes, renal disorders, etc) before SARS-CoV-2 infection and COVID-19 diagnosis [4-7]. These pre-existing conditions are known risk factors for AKI that may have influenced the conclusions of these previous studies [4-7]. Moreover, little research evidence has been provided on the characteristics and determinants of AKI among Nigerian patients of COVID-19 to date [7].

The current study characterized AKI and its associated determinants among young adults and middle-aged COVID-19 patients, who are devoid of any pre-existing comorbid conditions, presenting in a COVID-19-dedicated treatment facility in Rivers State, Nigeria.

2. Materials and Methods

2.1. Study Design and Site

This was a retrospectively-designed study of upon presentation/admittance data of patients managed at a COVID-19-designated treatment facility located at Eleme town in Rivers State, Southern Nigeria, which was established in response to the COVID-19 pandemic. The facility has a side laboratory that is well-equipped with automated laboratory analyzers for investigative studies during COVID-19 treatment. Investigative results are properly archived at the treatment facility. Patients in the facility are referred from the COVID-19 Holding Area for suspected SARS-CoV-2 infected patients at the Rivers State University Teaching Hospital (RSUTH) who are waiting for confirmatory real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test using a nasopharyngeal and/or oropharyngeal swab. The RT-PCR tests are done at the COVID-19 Molecular Laboratory in RSUTH. Suspected SAR-CoV-2 infected patients are eventually referred to the Eleme COVID-19 treatment facility following a positive RT-PCR test.

2.2. Ethical Considerations

Approval for the study was granted by the Research Ethics Committee of Rivers State Hospital Management Board (RSHMB) with Reference RSHREC/11.21/VOL.1/097. The study was conducted with strict adherence to the RSHMB-recommended guidelines and the principles embodied and laid down in the Helsinki Declarations of 1964, and as revised in 2013.

2.3. Study Tools and Population

The study utilized properly archived data of patients with RT-PCR-confirmed COVID-19 disease who had presented and/or were admitted at the treatment facility from 2020 to 2022.

2.4. Sample Size Determination

The minimum sample population required was approximately 390. This was calculated using the sample size formula for evaluating variables in a population of ≥10,000, at a 95% confidence interval and 5% margin of error, using a recently reported prevalence rate of 22.4% [8, 9]. Though the calculated sample size yielded 268 sample populations, 390 were eventually recruited due to the availability/accessibility of relevant data.

2.5. Eligibility Criteria

Criteria for inclusion included complete relevant data, adult (aged ≥18 but ≤64 years), normal health status before SARS-CoV-2 infection/COVID-19 diagnosis, and RT-PCR-confirmed status. Criteria for exclusion included incomplete data, age <18/> 64 years, pregnancy, unconsciousness, COVID-19 re-infection, recent intravenous fluid/diuretic therapy, referred from other healthcare facilities besides RSUTH, previous/pre-existing comorbidities (aged ≥65 years, cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, HIV/AIDS, diabetes, cancer, obesity, AKI, acute kidney disease, chronic kidney disease, chronic liver disease, previous/current cigarette smoker, organ transplant recipient, and receiving immunosuppressive therapy) before current SARS-CoV-2 infection/COVID-19 diagnosis, and on current medications known to modify renal tubular function, such as diuretics, proton pump inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists.

2.6. Data Collection

Data were obtained from each patient's medical case notes, medical chart reviews, nurses' charts, and laboratory records by trained research assistants. Extraction of data was done using pre-tested data extraction templates. The various acquired data included the demographics, social, and clinical including vaccination status, type of vaccination, duration of symptom onset after vaccination, and doses of vaccines obtained.

Other relevant data included anthropometric and laboratory data which included results of nasopharyngeal and/or oropharyngeal swab RT-PCR test, identified SARS-

CoV-2 variants (n=16), plasma sodium, potassium, chloride, bicarbonate, urea, creatinine, glucose, calculated plasma osmolality, albumin, total plasma proteins, pro-calcitonin (PCT), C-reactive protein (CRP), D-dimer levels, white cell count (WBC)/differentials, and platelet count. The urinary data included specific gravity, calculated urine osmolality, proteinuria, and hematuria.

2.7. Specimen Acquisition, Processing, and Laboratory Analysis

Whole blood/spot urine specimens were collected within minutes upon presentation and analyzed following standard protocols. Heparinized plasma was analyzed for plasma sodium, potassium, bicarbonate, and chloride on an ion-selective electrode (ISE) chemistry analyzer (SFRI 6000, SFRI Diagnostics, Berganton, France) including the analyses for urea, creatinine, albumin, total protein, and CRP done on an automated chemistry analyzer (BS200, Mindray, Shenzhen, China). EDTA tube-acquired whole blood was analyzed for FBC/differentials, RBC, and platelet counts on an automated hematology analyzer (BC10, Mindray, Shenzhen, China). Plain-tube processed serum was analyzed for pro-calcitonin, and D-dimer on an automated immunoassay analyzer (Mini Vidas, Biomerieux, France). Urine protein/blood levels were determined on an automated urine biochemistry analyzer (Combilizer-13, Human Diagnostics, Germany) while the specific gravity of urine was determined using the urine dipstick method.

2.8. Variable Definitions/Stratifications

2.8.1. AKI Definition Guidelines/Staging

According to the Kidney Disease Improving Global Outcome (KDIGO) guidelines, AKI was defined as any of the following [10]:

(1) An increase in plasma creatinine (PCr) by 0.3 mg/dL (26.5 μmol/L) within 48 hours; or
(2) An increase in PCr 1.5 times of baseline within the prior 7 days; or
(3) Urine output volume (UOV) <0.5 mL/kg/hour for 6 hours

AKI can be also staged for severity according to KDIGO [10]:

Stage 1: Increased in PCr to 1.5–1.9 times baseline or by 0.3 mg/dL (26.5 μmol/L) or UOV <0.5 mL/kg/h for 6–12 hours;

Stage 2: Increased PCr to 2.0–2.9 times baseline or UOV <0.5 mL/kg/hour for 12 hours;

Stage 3: Increased PCr to 3.0 times baseline or increase in serum creatinine to 4.0 mg/dL (353.6 μmol/L) or the initiation of renal replacement therapy or UOV <0.3 mL/kg/hour for 24 hours or anuria for 12 hours.

2.8.2. Baseline Creatinine Values

Baseline PCr values were taken as those values obtained within 24 hours while at the RSUTH COVID-19 Holding Area before the RT-PCR test and any medical intervention. For patients with previous PCr values in the 7–365 days before presenting at the RSUTH COVID-19 Holding Area, the most recent PCr value was considered the baseline creatinine [10]. For patients without a baseline creatinine in the 7–365 days before/during presentation at the RSUTH COVID-19 Holding Area, the baseline PCr was imputed based on the Modification of Diet in Renal Disease estimated glomerular filtration rate of 75 ml/min per 1.73 m as per the KDIGO AKI guidelines [10].

2.8.3. Categorization of AKI by Timing of Its Onset Relative to Presentation

This was categorized as either community-acquired or hospital-acquired as previously described [11]. Community-acquired AKI was defined as AKI that occurred before or within 48 hours of presentation and hospital-acquired AKI was defined as AKI that occurred after 48 hours upon presentation.

2.8.4. Categorization of AKI by Etiologic Origins

This was categorized as either pre-renal, intra-renal (intrinsic), or post-renal AKI [12, 13]. The distinction between pre-renal and renal AKI was established using the obligatory (response to fluid challenge) and other optional criteria proposed by Heller and colleagues in addition to using other well-established single and composite urinary/plasma biochemical indices proposed by Makris and colleagues [12, 13].

2.8.5. Categorization of AKI by Clinical Course / Recovery Status

By clinical course, AKI was categorized as transient AKI or sustained AKI. Transient AKI are reversed AKI (a return to baseline PCr within 72 hours post-AKI) in less than 72 hours following fluid administration or using other medical interventions while persistent AKI are those AKI cases that continue to manifest beyond 72 hours despite fluid administration or using other medical interventions [13].

2.8.6. Calculated Plasma and Urine Osmolality

Plasma osmolality (mOsmol/kg) was calculated with the formula: 2 (Na^+ + K^+) + glucose + urea concentration (mmol/l) measured at the same time [14]. The urine osmolality was calculated by multiplying the last two digits of the measured urine specific gravity value by a factor of thirty-five [15].

2.8.7. Characterization of COVID-19 Severity

COVID-19 severity was classified based on the Nigerian Centre for Disease Control National (NCDC) case management guidelines as non-severe and severe [16]. The disease severity was defined as the presence of fever >38˚C or suspected respiratory infection, plus one of respiratory rate >30 breaths/min; severe respiratory distress; oxygen saturation (SpO2) of ≤93% on room air and the presence of co-morbid conditions such as diabetes, asthma, hypertension in adults and cough or difficulty in breathing and at least one of the following central cyanosis or SpO2 <92%; severe respiratory distress e.g. grunting breathing, very severe chest in-drawing and signs of pneumonia in children.

2.8.8. Definition of Vaccination Status

The unvaccinated patients refer to those patients who have never received any of the approved COVID-19 vaccines. The partially vaccinated, fully vaccinated, or boosted vaccinees were defined as those who have received one, two, or three doses of AstraZeneca, Moderna, Pfizer BioNTech COVID-19 vaccines, respectively, at least 14 days before SARS-CoV-2 infection.

The fully vaccinated vaccinees were also referred to as those who received two Johnson & Johnson COVID-19 vaccine (Ad26.COV2. S by Johnson & Johnson) doses at least 14 days before SARS-CoV-2 infection.

The boosted vaccinees also included those who received one or two doses of the Johnson & Johnson vaccine and a booster vaccine dose using any of the bivalent mRNA vaccines (Moderna vaccine/Pfizer BioNTech) at least 14 days before SARS-CoV-2 infection.

All the patients who have RT-PCR-confirmed SARS-CoV-2 infection in less than 14 days after receiving either the first or the second dose of any of these vaccines were also labeled as partially vaccinated.

2.8.9. Study Outcome

The primary outcome is to determine AKI incidence while the secondary outcome included the AKI-associated risk factors.

2.9. Data Management / Statistical Analyses

Continuous variables were initially evaluated for conformity to a normal distribution pattern using Shapiro-Wilk tests. Continuous data found to have violated normal distribution patterns were log-transformed before analysis, then reported using means ± standard deviations and finally compared by independent student t-test or analysis of variance, as appropriate. Categorical data were reported as counts/percentages and compared by Chi-square or Fisher's exact probability tests, as appropriate. Univariate and multivariate logistic regression models (variables presenting $p<0.05$ in univariate analysis were included in multivariate logistic regression) were used to identify/test associations between exposure variables. A p-value <0.05 was deemed statistically significant. The data management, including statistical analyses, was done using a statistical package for social sciences software for Windows (version 25; IBM Co., Armonk, NY, USA).

3. Results

During the study span period (2020-2022), 947 positive COVID-19 patient attendees presented in the treatment center, however, 390 met the eligibility criteria to be considered eligible for the study.

As depicted in Table 1, AKI occurred among 46.4% (n=181) studied population (n=390) upon presentation with the majority of AKI of stage 1 (n=88; 48.6%), pre-renal by etiologic origin (n=123; 68.0%), community-acquired (n=115; 63.5%), and of transient clinical course (n=128; 70.7%). Based on the COVID-19 clinical course (non-severe/severe), most cases of AKI occurred among those with severe COVID-19 variant (n=62; 96.9%) ($p<0.05$) (Table 1). Those with severe COVID-19 also presented with a higher preponderance of stage 3 (n=35; 56.5%), intra-renal (n=51; 82.2%), community-acquired (n=56; 90.3%), and sustained (n=43; 69.4%) AKI compared to those with the non-severe COVID-19 variants ($p<0.05$) (Table 1).

In Table 2, patients with AKI were mostly males (males: 120 versus females: 60), had lower oxygen saturation levels but higher severe disease clinical course, need for ICU transfer/treatment, and fatigue/lethargy upon presentation compared to those with no AKI ($P<0.05$). AKI also occurred mostly among those who are unvaccinated compared to those who are vaccinated against COVID-19 ($p<0.05$) (Table 2).

In Table 3, patients with AKI had higher levels of peak plasma/serum creatinine, C-reactive protein, D-dimer, osmolality, and proteinuria, hematuria but lower within 24-hour urine volume, urine specific gravity, and urine osmolality upon presentation compared to those with no AKI ($p<0.05$).

As shown in Table 4, following univariate and multivariate logistic models, COVID-19 severity (OR: 6.017; CI: 5.880–6.422; $p<0.001$), need for ICU transfer/treatment (OR: 3.210; CI; 3.119–3.341$p<0.001$), serum D-dimer levels (OR: 3.967; CI: 3.688-4.297; $p<0.001$), and proteinuria (OR: 2.008; CI: 1.971–2.174; $p=0.002$) were independent predictors of AKI incidence among the studied population.

Table 1. *AKI descriptions by COVID-19 severity upon presentation among the studied cohorts.*

Description of variables	Non-severe COVID-19, n=326	Severe COVID-19, n=64	p-value	Entire Patients, n=390
	n (%)	n (%)		n (%)
AKI status by KDIGO guidelines			<0.001*	
AKI	119 (36.5)	62 (96.9)		181 (46.4)
No AKI	207 (63.5)	2 (3.1)		209 (53.6)
AKI stage, n=181			0.011*	
KDIGO Stage 1	83 (69.7)	5 (8.0)		88 (48.6)
KDIGO Stage 2	31 (26.1)	22 (35.5)		53 (29.3)
KDIGO Stage 3	5 (4.2)	35 (56.5)		40 (22.1)
AKI etiologic origin, n=181			<0.001*	
Pre-renal AKI	112 (94.1)	11 (7.8)		123 (68.0)
Intrinsic (Intra-renal) AKI	7 (5.9)	51 (82.2)		58 (32.0)
Post-renal AKI	0 (0.0)	0 (0.0)		0 (0.0)

Description of variables	Non-severe COVID-19, n=326	Severe COVID-19, n=64	p-value	Entire Patients, n=390
Timing of AKI onset relative to presentation, n=181			0.024*	
Community-acquired AKI (upon admission)	59 (49.6)	56 (90.3)		115 (63.5)
Hospital-acquired AKI (during admission stay)	60 (50.4)	6 (9.7)		66 (36.5)
AKI clinical course			0.026*	
Transient AKI	109 (91.6)	19 (30.6)		128 (70.7)
Sustained/persistent AKI	10 (8.4)	43 (69.4)		53 (29.3)

*Statistically significant; AKI: acute kidney injury; KDIGO: kidney disease improving global outcome

Table 2. *Baseline characteristics of study population upon presentation.*

	No AKI	AKI	p-value	Entire Patients
	n = 209	n = 181		n = 390
Variables	Mean ± SD/n	Mean ± SD/n		Mean ± SD/n
Demographics/social//clinical				
Age, mean, years	42.22 ± 6.07	43.01 ± 6.15	0.114	42.61 ± 6.79
Gender: Male/female	100/109	120/61	<0.001*	220/170
Religion, christian/moslem	200/9	177/4	0.154	377/13
Alcohol consumption, never/former/current	199/10/0	177/4/0	0.144	376/14/0
Residency, urban/rural	201/8	178/2	0.200	380/10
Marital status, married/single/divorced	169/40/0	145/36/0	0.173	314/76/0
Highest educational level, secondary/tertiary	10/199	6/175	0.241	16/374
Occupation, healthcare worker/others	66/143	45/136	0.079	111/279
Mean body mass index, kg/m^2	27.87 ± 4.27	28.79 ± 5.11	0.222	27.66 ± 4.56
Body temperature, ^oC	37.76 ± 2.46	38.34 ± 2.74	0.058	37.33 ± 2.51
Systolic blood pressure, mmHg	133.55 ± 7.46	134.87 ± 7.78	0.113	136.58 ± 7.46
Diastolic blood pressure, mmHg	86.71 ± 6.17	87.64 ± 6.04	0.170	87.23 ± 6.50
Pulse rate/minute	78.64 ± 5.24	81.34 ± 5.84	0.055	79.21 ± 5.70
Respiratory rate/minute	27.07 ± 3.16	29.45 ± 3.42	0.068	25.82 ± 3.33
Oxygen saturation (SpO_2), %	93.07 ± 6.26	89.67 ± 6.10	0.015*	92.73 ± 6.20
COVID-19 clinical course, non-severe/severe	207/2	119/62	<0.001*	236/64
Outcome within 72 hours upon presentation				
General ward admission/treatment	85	93	0.160	178
Need for ICU transfer/treatment	4	80	<0.001*	84
Pre-existing comorbidities, yes/no	209/0	181	NA	390/0
Presenting symptoms/signs				
Fever	202	180	0.204	282
Cough	208	181	0.161	389
Breathlessness	182	179	0.127	361
Loss of taste	102	94	0.255	196
Loss of smell	106	92	0.210	198
Fatigue/Lethargy	156	180	<0.001*	336
Runny nose	98	86	0.074	184
Sore throat	100	92	0.132	192
Myalgia/arthralgia	71	93	0.151	164
Abdominal discomfort	55	47	0.339	102
Nausea/vomiting	89	71	0.188	160
Diarrhea	47	41	0.350	88
Headache	60	51	0.330	111
Confusion/disorientation	43	37	0.216	80
Malaise	79	61	0.141	140
SARS-CoV-2 variants, n=16			0.184	
Alpha (B.1.1.7)	4	3		7
Eta (B.1.525)	3	2		5
Delta (B. 617.2)	2	2		4
COVID-19 vaccination status			<0.001*	
Unvaccinated	175	180		355
Partially vaccinated	0	1**		1
Fully vaccinated but un-boosted	10	0		10
Vaccinated and boosted	24	0		24

*Statistically significant; AKI: acute kidney injury; M ± SD: mean ± standard deviation; ICU: Intensive Care Unit; SARS-CoV-2: severe acute respiratory coronavirus virus 2; **KDIGO stage 1

Table 3. *Descriptive depiction of laboratory parameters upon presentation/follow-up.*

	No AKI	AKI	p-value	Entire Patients
	n = 209	n = 181		n=390
Blood parameters	Mean ± SD/n	Mean ± SD/n		
Sodium, mmol/L	135.32 ± 7.54	133.44 ± 7.36	0.124	134.92 ± 7.60
Potassium, mmol/L	3.66 ± 1.11	3.78 ± 1.12	0.080	3.67 ± 1.04
Chloride, mmol/L	96.48 ± 7.43	95.91 ± 7.31	0.267	95.42 ± 7.36
Bicarbonate, mmol/L	23.22 ± 4.26	22.67 ± 4.18	0.326	22.89 ± 4.24
Urea, mmo/L	5.72 ± 1.70	6.12 ± 1.74	0.101	6.14 ± 1.26
Random glucose, mmol/L	5.9.72 ± 1.89	6.54 ± 2.01	0.069	6.06 ± 2.16
Baseline creatinine, µmol/L	76.51 ± 6.99	80.17 ± 7.15	0.064	78.16 ± 7.56
Peak creatinine, µmol/L	78.83 ± 6.91	195.98 ± 12.14	<0.001*	136.19 ± 11.56
Albumin, g/L	34.76 ± 4.61	33.97 ± 4.57	0.081	34.02 ± 4.12
Total protein, g/L	63.02 ± 6.30	62.88 ± 6.05	0.114	64.03 ± 6.06
Pro-calcitonin, µg/L	2.82 ± 0.79	3.07 ± 1.05	0.093	2.44 ± 0.80
C-reactive protein, nmol/L	142.37 ± 9.11	232.06 ± 13.34	<0.001*	157.22 ± 9.67
D-dimer, µg/L	730.61 ± 94.65	1,781 ± 120.09	<0.001*	894.50 ± 97.63
Osmolality, mOsmol/kg	296.40 ± 18.55	367.92 ± 18.41	<0.001*	301.36 ± 17.72
Total white cell count x 10^9/L	14.12 ± 2.60	15.44 ± 3.50	0.112	14.01 ± 2.61
Neutrophil count x 10^9/L	12.55 ± 2.65	13.01 ± 2.80	0.230	12.94 ± 2.70
Lymphocyte count x 10^9/L	1.32 ± 0.28	1.29 ± 0.18	0.161	1.50 ± 0.58
Platelet count x 10^9/L	141.61 ± 6.63	138.11 ± 6.84	0.078	141.03 ± 6.80
Urine parameters				
Within first 24-hour volume, mls	1,966 ± 124.88	1,687 ± 115.65	0.024*	1,774 ± 118.77
Specific gravity	1.026 ± 0.02	1.012 ± 0.01	0.031*	1.016 ± 0.03
Osmolality, mOsmol/kg	710.44 ± 67.88	223.61 ± 15.10	<0.001*	445.23 ± 26.71
Proteinuria, g/L x 10^3	151.66 ± 14.76	220.4 ± 12.33	<0.001*	174.64 ± 16.91
Hematuria, erythrocytes/µl	10.23 ± 1.77	13.31 ± 1.87	<0.001*	11.44 ± 1.89

*Statistically significant; AKI: acute kidney injury

Table 4. *Univariate and multivariate logistic regression analyses for AKI-associated predictors.*

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male gender (female as reference)	1.420 (1.044–1.768)	<0.001*	1.110 (0.898–1.403)	0.219
COVID-19 severity	6.226 (6.182–6.339)	<0.001*	6.017 (5.880–6.422)	<0.001*
Need for ICU transfer/treatment	3.229 (3.123–3.355)	<0.001*	3.210 (3.119–3.341)	<0.001*
Oxygen saturation (SpO_2)	1.088 (0.886-1.204)	0.151		
Fatigue/Lethargy	1.531 (1.340-1.763)	0.014*	1.133 (0.933-1.307)	0.226
Within 72-hour peak creatinine value	2.701 (2.411–3.033)	<0.001*	1.121 (1.110–1.223)	0.170
Plasma C-reactive protein	1.224 (1.144-1.356)	0.128		
Serum D-dimer	4.136 (4.031-4.461)	<0.001*	3.967 (3.688-4.297)	<0.001*
Plasma osmolality	1.156 (0.967-1.340)	0.144		
Within first 24-hour urine volume	1.218 (1.007–1.416)	<0.001*	1.109 (1.046–1.578)	0.164
Urine specific gravity	1.045 (0.899-1.178)	0.089		
Urine osmolality	1.719 (1.588–1.861)	0.033*	1.103 (0.890-1.267)	0.310
Proteinuria	2.110 (1.997–2.201)	0.014*	2.008 (1.971–2.174)	0.002*
Hematuria	1.015 (0.901–1.112)	0.610		

*Statistically significant; OR: odd ratio; CI: confidence interval

4. Discussion

4.1. Major Findings

AKI occurred among 46.4% of studied COVID-19 patients who are without any pre-existing comorbid conditions. The majority of AKI were of stage 1, pre-renal, community-acquired, and mostly of transient clinical course. Most of the AKI occurred among males, those with severe COVID-19, and those with unvaccinated status against COVID-19. Patients with COVID-19-associated AKI also had higher levels of peak plasma creatinine, inflammatory indices (plasma C-reactive protein, serum D-dimer), plasma osmolality, proteinuria, hematuria, fatigue/lethargy, need for ICU transfer/treatment but lower oxygen saturation, within 24-hour urine volume, urine specific gravity, and urine osmolality upon presentation compared to those without AKI. However, those with severe COVID-19 presented with a higher preponderance of the KDIGO stage 3, intra-renal (intrinsic AKI), and persistent AKI compared to those with non-severe COVID-19. COVID-19 severity, need for ICU transfer/treatment, serum D-dimer levels, and proteinuria were independent determinants of AKI incidence among

those studied.

4.2. Relationship with Previous Studies

The high COVID-19-associated AKI incidence documented in the current study corroborates recent conclusions of a high burden of AKI among patients with the disease [6, 7]. Though our reported rate may have varied from those reported earlier from China, Nigeria, the United States, and Brazil, it tallies with the rate recently documented by Chan and colleagues [4-7, 17]. It remains unclear why such variations in COVID-associated AKI incidence, it may be related to differences in the burden of comorbid disease, the threshold for hospitalization or respiratory support, racial diversity, and baseline incidences of AKI between countries as documented by Bell and colleagues [11]. The fact that most of the documented AKI were pre-renal by etiologic origin, community-acquired, and of transient clinical course as previously reported, underscores the need for a high index of suspicion among at-risk COVID-19 patients, since incident AKI, no matter how trivial, is significantly associated with short and long-term adverse health consequences [5, 18].

The majority of COVID-19-associated AKI have been previously documented among males, those with severe disease in association with higher staged AKI, mostly etiologically intra-renal, community-acquired, and more persistent AKI [4, 19-29]. These observations are consistent with the findings in the current study. These associations may well be related to all the heightened SARS-CoV-2-driven pathological processes inherent in severe COVID-19 [4, 30-34]. Reports are scarce on the protective effect of SARS-CoV-2 vaccination on the incidence of COVID-19-induced AKI in the general population except among those with comorbidities [4, 35, 36]. However, those who are unvaccinated tend to present with severe disease more likely to induce AKI, as observed in the current study [4, 36]. Consistent with current observations, the preponderance of male gender, lower oxygen saturation levels, need for ICU admission/treatment, higher levels of peak plasma creatinine, plasma C-reactive protein, serum D-dimer, plasma osmolality, proteinuria, and hematuria but lower within 24-hour urine volume, urine specific gravity, and urine osmolality are all cardinal features of severe COVID-19-associated AKI [4, 5, 11, 17-29].

The need for ICU transfer/transfer, D-dimer levels, and proteinuria are all related to the AKI-associated factors that were identified as independent risk factors for AKI in the current study [4, 17, 21, 28]. The need for IUC transfer/treatment may be associated with the high mortality and morbidity inherent in COVID-19-induced AKI [4, 17-24]. Oweiss and colleagues recently observed high mortality among ICU COVID-19 patients with AKI compared to non-AKI patients in Jordan [27]. Among markers of COVID-19 severity, only D-dimer was associated with COVID-19-induced AKI and the odds of recovery of renal function seem to be significantly diminished by d-dimer value as recently documented by Radulescu and colleagues [21].

Hansrivijit and colleagues also recently provided evidence that Increased Di-dimer level was associated with AKI risk (OR: 2.959; 1.280-6.849; P=0.011) among COVID-19 patients [19].

Proteinuria is a significant finding in COVID-19-associated AKI that is also more frequently associated with COVID-19 severity which may be related to the acute renal injuries majorly observed in COVID-19-associated AKI [4, 17, 26].

4.3. Mechanistic Considerations

COVID-19-induced AKI is attributed to the direct and indirect pathomechanisms due to the viral infection. However, the best-understood pathomechanism of kidney damage induced by SARS-CoV-2 is direct cellular infection which is a complex process driven by virus-mediated injury owing to the expression of angiotensin-converting enzyme-2 receptors in proximal tubular cells and podocytes [3, 18]. Other pathomechanisms include fluid balance disorders (nausea, vomiting, and diarrhea leading to hypovolemia), toxic tubular damage due to cytokine release syndrome or following rhabdomyolysis, activation of angiotensin II pathway, thrombotic events, intravascular coagulation, kidney-lung crosstalk theory, and nephrotoxicity from drugs administered during COVID-19 treatment [4, 18, 37-39].

4.4. Relevance to Clinicians, Health Policies, and Future Studies

The findings here highlight the need to screen for AKI as soon as possible among COVID-19 patients seeking treatment. The genetic basis of COVID-19-induced AKI should be an area of intense research.

4.5. Strength and Limitations

The study was strongly strengthened by the recruitment/analysis of only those COVID-19 patients with confirmed positive RT-PCR tests who are without any pre-existing confounding comorbidities. Yet, the study was limited by some factors which are potential areas for improvement in future studies. The study was a single-center study with predominantly black populations, so, its findings may not be representative of the larger population within the studied region. The under-reporting of the number of cases cannot also be ruled with certainty since the data were retrospectively acquired.

5. Conclusion

The current study corroborates a high preponderance of AKI among COVID-19 patients independent of pre-existing confounding comorbidities. The observed AKI were majorly stage 1, etiologically pre-renal, community-acquired, transient clinical course, and occurred predominantly among males, those with severe COVID-19, and those with unvaccinated status against COVID-19. The need for ICU transfer/treatment, Di-dimer levels, and proteinuria were

independent risk factors for AKI which are valuable parameters that may guide clinical management among COVID-19 patients.

Declarations

Author Contributions

Conceptualization, O. C., and C. A.; Methodology, O. C. and C. A.; Software, O. C and B. C. A., and I. J. N.; Validation, O. C., C. A., K. T. W., and E. M. O.; Formal Analysis, O. C., and C. A.; Investigation, K. T. W. and E. M. O; Resources, C. A. and I. J. N.; Data Curation, B. C. A., I. J. N., and K. T. W; Writing – O. C., C. A., and E. M. O.; Writing – Review & Editing, K. T. W., E. M. O., B. C. A., and I. J. N; Visualization, O. C. and C. A.; Supervision, O. C. and C. A.; Project Administration, O. C. and C. A.; Funding Acquisition, O. C. and C. A.

Conflicts of Interest

The authors declare that they have no competing interests.

Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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