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Research article

Changes in Selected Renal Function Parameters of Newly Admitted COVID-19 Patients from One Infectious Diseases Center in Ibadan, Nigeria: Indication for Immunopathology

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Summary: COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) enters the host cells through attachment to the Angiotensin Converting Enzyme-2 receptors (ACE-2) on the host cells. Angiotensin Converting Enzyme-2 is known to affect renal functions, vasoconstriction and fluid homeostasis. Thus, the impact of SARS-CoV-2 infection on renal function parameters is worth investigating. Plasma obtained from whole blood samples collected from consecutive and newly diagnosed two hundred and two COVID-19 patients admitted for management at the Infectious Disease Center, Olodo in Ibadan the capital of Oyo State, South Western Nigeria were analysed for albumin, urea, creatinine, Na, K, Cl and HCO_3 using auto analysers. The results obtained were used to determine the frequency of COVID-19 patients with abnornal renal function parameters. It was observed that 57.1%, 37.8%, 32.7%, 28.1%, 18.7%, 17.8% and 3.4% of newly diagnosed COVID-19 patients had values of Cl, creatinine, albumin, Na, K, HCO_3 and urea respectively outside the reference ranges. While 43.3%, 4.7%, 2.5%, 2.5%, 2.0%, 1.7% and 1.0% of COVID-19 patients had values of Cl, creatinine, Na, K, albumin, Urea and HCO_3 respectively above the reference ranges. Of all admitted patients, 33.1%, 30.7%, 25.6%, 16.8%, 16.3%, 13.8% and 1.7% had creatinine, albumin, Na, HCO_3, K, Cl and urea values respectively below reference ranges. The changes in some renal function parameters of newly diagnosed COVID-19 patients portend that renal failure is possible in poorly managed COVID-19 patients and this has immunopathologic implications.
Keywords: *COVID-19, Reference Ranges, Creatinine, Electrolytes, Urea, Immunopathology*

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes the disease named by World Health Organisation (W.H.O) as coronavirus disease 2019 (COVID-19)is still spreading worldwide (Center for Systems Science and Engineering 2020; Chan et al., 2020). The prevalence of asymptomatic infected carriers is unknown (Flaxman et al., 2020) but symptomatic patients presents with upper and lower respiratory tract illnesses, multiple organ failure and in some cases, death (Zhou et al., 2020). A significant number of SARS-COV-2 infected patients have acute renal dysfunction which may progress to renal failure requiring dialysis (Chu et al., 2005; Nehme et al., 2015; Rodrigues et al., 2017). In previous reports of SARS and MERS-CoV infections, acute kidney injury (AKI) developed in 5–15% cases with60–90% mortality (Chu et al., 2005). Nevertheless, the incidence of acute kidney failure in SARS-CoV-2 patients is unknown and information about the clinical impact remains sparse (Chu et al., 2005; Nehme et al., 2015; Rodrigues et al., 2017). In this sense, early estimation of renal functional changes in COVID-19 patients should be taken as a priority.

Angiotensin Converting Enzyme-2 (ACE-2) receptors are found in high concentrations in the kidney, small intestine, testis, heart, and the thyroid gland and are known to bind and facilitate SARS-CoV-2 entry into the cells in patients with COVID-19 (Nehme et al., 2015; Rodrigues et al., 2017). Binding of SARS-COV-2 Spike (S) protein with ACE-2 cause reduction of membrane-bound ACE-2 and subsequently an imbalance of therenin–angiotensin system (RAS). ACE-2 is also largely expressed in the nasal and oropharyngeal epithelium (Nehme et al., 2015), where SARS-CoV-2 entrance intothe hosts also occurs. Activation of the ACE 2/Angiotensin II/Angiotensin-II Type-1 receptor axis aggravates inflammation, fibrosis, oxidative stress, cellular growth and migration while Angiotensin II is known for its cardiovascular and renal functions, vasoconstriction and fluid homeostasis (Rodrigues et al., 2017). It was thus suggested that up-regulation of this classical renin-angiotensin system might partially be responsible for the deleterious pathophysiological derangements observed in COVID-19 (Imai et al., 2005) especially renal functions which is the rationale for this study.

Acute kidney injury (AKI) was hypothesised to contribute to COVID mortality (Cheng et al., 2020) and a previous report showed a strong association between acute elevation of creatinine and mortality in COVID-19 patients (Wang et al., 2020). Another study indicated that 3% of hospitalized patients with COVID-19 had AKI but the incidence was higher (19%) in COVID-19 patients admitted into the Intensive Care Unit (Ng et al., 2020). These observations suggested an association between COVID-19 severity and renal injury. A multicentre cohort study on hospitalized COVID-19 patients found a markedly high rate of AKI (36.6%) in COVID-19 patients. These authors also found that diabetes, hypertension, and cardiovascular disease were the co-morbid conditions closely associated with therisk of AKI (Hirsch et al., 2020). Therefore, both pre-existing conditions in a given patient population must be considered carefully when evaluating the prevalence of AKI and or its use as a predictor of clinical outcome in COVID-19. The same multi-centered study pointed out that AKI rates peaked on the first day after admission, suggesting that monitoring for AKI early in hospital admissions could greatly aid decision making.

Another study (Cheng et al., 2020) recorded baseline serum creatinine levels of patients with COVID-19 on admission and found that patients with elevated creatinine had a significantly higher rate of AKI. The authors also found that elevated creatinine at baseline correlated with a 2.5-fold higher risk of death in this patient population (13.2% vs 33.7%), suggesting it as a significant risk factor for mortality in the presence of COVID-19 infection. Apart from creatinine, several other markers of kidney injury were also associated with significantly increased risk of mortality of COVID-19 patients. Both elevated serum creatinine and serum urea nitrogen on admission were associated with significantly increased risk of mortality, but elevated serum urea nitrogen (Cheng et al., 2020) had more than twice the level of associated risk compared with AKI. Therefore, both serum creatinine and serum urea nitrogen concentrations on admission were concluded to serve as useful guidelines for assessment of disease severity and level of care for patients with COVID-19.

Previous study reported that kidney failure affects general immunity by causing intestinal barrier dysfunction, systemic inflammation and immunodeficiency (Kurts et al., 2013, Betjes, 2013; Yatim and Lakkis, 2015). It is therefore essential to manage renal dysfunctions as indirect measures to sustain immunity during SARS-COV-2 infection.

MATERIALS AND METHODS

Study site*:* The COVID-19 patients were enrolled from the Infectious Diseases Centre, Olodo, Oyo State, Nigeria.

Study Population: Ethical approval (reference number: UI/EC/20/0283) was obtained from UI/UCH Ethic Committee. A total of 202 COVID-19 patients (not in severe or critical stage) were consecutively enrolled into this study. The study participants were COVID-19 cases certified by real-time reverse-transcriptase polymerase-chain reaction (RT-PCR) assay using nasal and pharyngeal swab specimens following W.H.O guideline (W.H.O, 2020). The participants also exhibited signs and symptoms of COVID-19 such as fever, cough, anosmia, agenuia and headache. All subjects with co-morbidities (sickle cell anaemia, peptic ulcer, hypertension and diabetes mellitus) or on compulsory medication were excluded from this study.

Sample collection: Two millilitres of 10 ml venous blood obtained from the SARS-CoV-2 infected patients at the point of admission to the center was used for this study. The blood samples were dispensed into lithium heparin containing sample bottles.

Plasma analyses: Plasma obtained from whole blood sample was analysed for albumin, urea, creatinine, Na, K, Cl and HCO_3 using auto-analysers (Erba Mannheim XL-200, Germany). The auto-analyser was calibrated daily and the standard samples were included during all analyses. Reference values for clinical chemistry were used to classify the results as within or outside the normal reference range (Bugdayci et al., 2015).

Result presentation: The results obtained from these analyses were used to determine the frequency of COVID-19 patients having values of blood parameters below, within and above reference ranges. Data were represented as frequencies and percentages.

RESULTS

The prevalence of newly-diagnosed COVID-19 patients with abnormal renal function parameters is shown in Table 1. 57.1%, 37.8%, 32.7%, 28.1%, 18.7%, 17.8% and 3.4% COVID-19 patients had Cl, creatinine, albumin, Na, K, HCO_3 and urea respectively outside the reference ranges. As also shown in Table 1, 43.3%, 4.7%, 2.5%, 2.5%, 2.0%, 1.7% and 1.0% of COVID-19 patients had Cl, creatinine, Na, K, albumin, Urea and HCO_3 respectively above the reference ranges while 33.1%, 30.7%, 25.6%, 16.8%, 16.3%, 13.8% and 1.7% of the patients had creatinine, albumin, Na, HCO_3, K, Cl and urea respectively below reference ranges.

DISCUSSION

Reference values provide a basis for interpretation of laboratory data. In clinical practice, it is a usual practice to compare patient's result with the corresponding reference interval, which is bounded by a pair of reference limits (Bugdayciet al., 2015).

Between 3.4% to 51.7% newly diagnosed COVID-19 patients recruited for this study had one or more deranged values of renal function parameters on admission. Previous reasons for the involvement of COVID-19 in renal abnormalities were based on high ACE-2 expression in the kidneys (Li et al., 2020), direct cytopathic effects on kidney tissue by SARS-CoV-2 especially the podocytes and proximal straight tubule cells (Pan et al., 2020), cytokine storm-mediated kidney damage (Jin et al., 2020) and formation of immune complexes (Tisoncik et al., 2012).

Table 1:
Plasma electrolyte and urea levels of newly-diagnosed COVID-19 patients with abnormal renal function parameters

Variables (Reference Ranges)	Within Reference Ranges	Abnormal Reference Ranges		
		Below	Above	Total
Albumin (3.5-5g/dL)	136 (67.3)	62(30.7)	4 (2.0)	66 (32.7)
Urea (15-45mg/dL)	169 (96.6)	3(1.7)	3 (1.7)	6 (3.4)
Creatinine (0.5-1.5mg/dL)	107 (62.2)	57(33.1)	8 (4.7)	65 (37.8)
Na^+ (0.5-1.5mg/dL)	146 (71.9)	52(25.6)	5 (2.5)	57 (28.1)
K^+ (3.5 -5mmmol/L)	165 (81.3)	33(16.2)	5 (2.5)	38 (18.7)
Cl^- (95-100MEq/L)	87 (42.9)	28(13.8)	88(43.3)	116(57.1)
HCO_3(20-30mmol/L)	166 (82.2)	34(16.8)	2 (1.0)	36 (17.8)

Percentages in parentheses

Understanding renal functions during COVID-19 may give part of pathophysiologic clue to SARS-CoV-2 infection. SARS-CoV-2 ribonucleic acid (RNA) was shown to bind ACE-2 of proximal tubule of COVID-19 infected patient (Rodrigues et al., 2017). After binding and endocytosis, surface ACE-2 is down-regulated resulting in angiotensin-2 accumulation (Kai and Kai, 2020). Angiotensin-2 facilitates sodium reabsorption by stimulating sodium-hydrogen exchange in the proximal convoluted tubule of the kidney (Imai et al., 2005). Increased renal sodium re-absorption is accompanied by increased renal chloride reabsorption and increased potassium excretion, potentially resulting in hyperchloremia (as recorded in 13.8% of the present COVID-19 patients) and hypokalemia (as recorded in 16.2% of present COVID-19 patients). Chen et al. (2020) reported a high prevalence of hypokalaemia in individuals with COVID-19. Increased plasma angiotensin-2 concentration has been described in patients with COVID-19, possibly acting as mediator of acute lung injury in SARS-CoV animal models (Liu et al., 2020). Another contributor to hypokalemia and other electrolyte imbalance in some COVID-19 patients might be gastrointestinal losses, with diarrhea and nausea (Pan et al., 2020). Hypomagnesaemia which is common during COVID-19 is known to affect the performance of the sodium–potassium ATPase pump, the intracellular potassium concentration decreases following hypomagnesaemia (Imai *et al.,* 2005). As a result of hypomagnesemia, the renal outer medullary potassium channel causes a decrease in potassium by increasing the distal secretion of potassium and increasing distal sodium delivery (Huang et al., 2020).

A syndrome of inappropriate secretion of antidiuretic hormone and manifestations of hyponatremia has been reported in COVID-19 patients (Sever et al., 2020, Zhang et al., 2020, Habib et al., 2020). Hypernatremia was observed in 2.5% of COVID-19 patients in the present study. Hypernatremia is usually caused by either decreased total body water or by an inappropriately high sodium input. Hypernatremia in the present COVID-19 patients might be due to dehydration. Creatinine is produced by muscle metabolism and intake of meat diet. Kidneys filter creatinine from blood, thus improper functioning of kidneys may lead an increased level of blood creatinine (Wang et al., 2020). The study by Li et al (2020) in COVID-19 showed that 63% of the patients that exhibited proteinuria had elevated level of plasma creatinine and blood urea nitrogen. In the present study, 33.1% COVID-19 patients with creatinine levels below reference range might be due to reduced protein intake.

Hypoalbuminemia in severe COVID-19 has been reported (Zhang et al., 2020, Xie et al., 2020, Feng et al., 2020 and Guan et al., 2020) and lower albumin levels on admission was shown to predict the outcome of COVID-19. This result is consistent with a previous study associating hypoalbuminemia with severity of Acute Respiratory Disease Syndrome (Hoeboer et al., 2020) or acute kidney injury (Wang et al., 20202). A meta-analysis showed that about 80.4% of patients with abnormal liver function in COVID-19 had hypoalbuminemia, which was associated with prognosis and outcome (Wu et al 2020). In the present study, 30.7% COVID-19 patients had hypoalbuminemia. Albumin is synthesized in the liver with a serum half-life of approximately 21 days (Wu et al., 2020). Hypoalbuminemia was seen predominantly in severe COVID-19 cases (Zhang et al., 2020). compared with mild cases (Arinola et al., 2020b). Hypoalbuminemia observed in 30.7% COVID-19 patients considered for this study might not be as a result of liver dysfunction because the onset of symptoms in COVID-19 is generally 4–5 days after infection, although it can be as late as 14 days (Huang et ala., 2020; Zhang et al., 2020) which is far shorter than the half-life of serum albumin.

Systemic inflammation is common in COVID-19 (Qin et al., 2020., Arinola et al., 2020a., Arinola et al., 2021) and inflammation has been shown to cause the movement of serum albumin into interstitial space due to increased capillary permeability and increased volume distribution of albumin (Soeters et al., 2019). Thus, our study strongly implies that hypoalbuminemia might due to the systemic inflammation in some of the COVID-19 patients. Therapeutic efficacy of albumin in sepsis and cirrhosis demonstrated that it had a modulatory effect on inflammation and oxidative stress in addition to the plasma volume expansion (Bo et al., 2016, He et al., 2019). Also, a meta-analysis reported that albumin treatment improved oxygenation in acute respiratory diseases syndrome (Uhlig et al., 2014). Since there is no specific treatment for the systemic inflammation in COVID-19, an albumin treatment with low side-effect might be a potential approach. However, the efficacy and safety of albumin in COVID-19 requires further studies.

A close association have been established between immunosuppression and abnormal renal functions (Kurt et al., 2013, Tecklenbourg et al., 2018 and Huang et al., 2020), thus taking results of the present study into account, the authors hypothesized the involvement of abnormal renal functions in the immunopathology of severe SARS-COV-2.

In conclusion, our study reports occurrence of abnormal certain renal function parameters in newly diagnosed COVID-19 patients and this may cause deranged immunity in poorly managed COVID-19 patients. Physicians should closely monitor the renal functions (especially chloride and creatinine) of COVID-19 patients during admission, so that appropriate renal replacement therapies can be administered without delay. Determination of renal function parameters in larger number of newly diagnosed COVID-19 patients and COVID-19 patients at discharge is desirable.

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