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ORIGINAL ARTICLE

Prevalence and associated factors for kidney dysfunction in hospitalized patients with COVID-19 pneumonia in Zambia

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ABSTRACT

Background: A significant link has been reported between COVID-19 pneumonia, disease severity and development of kidney dysfunction. This study assessed the prevalence and correlated factors for kidney impairment in hospitalized patients with COVID-19 infection

Methods: This nested retrospective study examined medical files of patients with confirmed COVID-19 pneumonia. The outcome variable was kidney dysfunction (defined as functional renal indexes beyond the normal range) and associated factors. Multivariate logistic regression was employed to establish factors associated with renal dysfunction.

Results: 179 patients were included in this nested study and the mean age was 58.3 years (SD 16.5) and 49.0% were female. The prevalence of renal dysfunction was 51.9% and 39.3% these patients renal had eGFR<60 mL/min/1.73m^2. The proportion of kidney impairment was higher in males than females (59.3% vs.44.3 %), patients with underlying hypertension than normotensive (60.5% vs. 39.5 %) and those with chronic kidney disease (CKD) than those without (90% vs. 10%). After adjusting for age, male gender, critical COVID-19 disease, and raised white cell count, hypertension was an independent predictor of kidney impairment with a AOR 1.54 (95% CI [1.06-2.23], p=0.022). Presence of HIV or diabetes mellitus showed a non statistical significance with renal dysfunction.

Conclusion: The study demonstrated a high prevalence of kidney dysfunction in hospitalized patients with COVID-19 pneumonia and presence of hypertension predicted nearly 2-fold development renal impairment.

INTRODUCTION

The corona virus disease (COVID-19) was first identified in December 2019 and since then; published studies have reported a significant link between COVID-19 disease and kidney dysfunction [1] with the kidney being shown as prevalent organ that is affected by severe acute respiratory syndrome corona virus-2 (SARS-Cov-2).

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The rates of kidney dysfunction in hospitalized patients with COVID-19 pneumonia has been estimated to range from as low as 2% to as high as 80% depending on the study definition for kidney impairment employed, patient population and geographical area. [2-4]. A USA study in hospitalized patients with COVID-19 pneumonia, reported high incident rates of 50% and 80% of acute kidney injury (AKI) in none intensive care units (ICU) and ICU settings respectively. [3] In contrast, a single center retrospective cohort study in Italy reported a slight lower rate of AKI at 22.4%. [5] In China, Yang *et al.* reported a respective 57.2% and 15.5% rates of kidney impairment based on proteinuria and elevated baseline serum creatinine in China.[6]

Co-morbid conditions in COVID-19 patients have been shown to be positively associated with kidney dysfunction. [2, 7] Diabetes mellitus patients with COVID-19 pneumonia have a risk of developing AKI than their non-diabetic counterparts. [2] In a study by Khalili *et al,* the incidence of AKI among diabetic patients was 28.3% compared to 17.3% among the non-diabetics.[2] Apart from diabetes mellitus, hypertension has also been cited as a risk for kidney dysfunction in COVID-19 patients. In a retrospective review of patients with COVID-19 pneumonia in Paris, the rate of acute kidney impairment was twice higher in hypertensive patients than the normotensive.[7]

Africa has a dearth of data on COVID-19 associated renal impairment.[8] Furthermore, comorbidities such as hypertension and diabetes mellitus are prevalent in Sub-Saharan countries like Zambia. [9, 10] These comorbidities are also associated with severe disease and poor outcomes in COVID-19 pneumonia patients. [9] Therefore, it is important to characterize the potential risk factors linked with kidney dysfunction in patients with SARS-Cov-2 because kidney impairment in these patients worsens outcomes.[11]

METHODS

Study design, setting and population

This retrospective cohort analysis was performed on a subset of COVID-19 patients who were admitted acutely to Ndola Teaching Hospital and Kitwe Teaching Hospital from December 1, 2020, to February 28, 2021. Consecutive COVID-19 patients who had available serum creatinine were enrolled in the study. [12] 171 medical files were censored due to missing laboratory valuables.

Study procedure

From the medical files, demographic information, and comorbidities data (hypertension, diabetes mellitus, chronic kidney disease, HIV/AIDs) and also laboratory information such as complete blood count, creatinine, urea, inflammatory markers C reactive protein (CRP) and D-Dimers) were extracted non- electronically. Information on COVID-19 disease severity was also obtained. Both laboratories at the two facilities employed the Jaffes' method to analyze for serum creatinine levels.[13] The primary outcome of the study was to determine the prevalence of kidney dysfunction and associated factors.

Study definition

In this study, kidney dysfunction was defined as elevated baseline serum creatinine at admission [14, 15] above the upper limit of normal reference range with an associated decreased estimated glomerular filtration rate (eGFR) <60 **mL/min**/1.73m^2. Chronic kidney was defined according to the kidney disease improving global outcomes criteria [10]

COVID-19 pneumonia was confirmed by positive reverse transcription polymerase chain reaction (RT–PCR) and patients were classified as mild, moderate, severe or critical COVID-19 in line with the World Health (WHO)[16] and Ministry of Health of Zambia case management guidelines. Patients with confirmed SARS-Cov-2 and clinical signs of pneumonia with either oxygen desaturating <90% on room air, respiratory rate >30 breaths per minute or signs of severe respiratory distress were classified as severe COVID-19 pneumonia[16]. Clinical signs of pneumonia with no signs of severe pneumonia plus SPO2 >90% on room air was considered moderate COVID-19. Critical were COVID-19 patients with acute respiratory distress syndrome, sepsis, sepsis

shock or presence of conditions that normally required provision of life sustaining interventions such as mechanical ventilation or use of vasopressors[16]. Diagnosis of cardiovascular disease was based on presence of heart failure, ischemic heart disease or hypertensive heart disease.

Statistical analysis

IBM SPSS Statistics Version 20, Release 20.0.0 was used to analyze the data. The probability plot (P-P) was used to check for normality of the data. Normally distributed data was summarized using Means (Standard deviation), while for skewed data; the Median (IQR Q_1, Q_3) was used. Whilst the independent student-test was used to compare means, the Mann-Whitney U test was used to compare medians. The Pearsons Chi-squared test and fishers 'exact test was used to establish associations depending on data distribution, whilst the unadjusted Odds Ratio (95% Confidence interval) was used to estimate magnitudes of associations. Multivariate logistic regression using Deviations as Contrast, backward: LR as Method, Probability for Stepwise: Entry (0.05) and Removal (0.051) was run to identify independent factors associated with renal dysfunction. The level of statistical significance was set at 5%.

RESULTS

After censoring 171 medical files (without serum creatinine), a total of 179 patients' files were included in the study with a mean age of 58.3 years (SD16.5) and their characteristics are shown in Table 1. Of the 179 patients, 50.8% were male; nearly 30.0% were diabetic, and 50.0% hypertensive. Compared to males, the females were more likely to be hypertensive (59.1% vs. 40.7%, p=0.015). The median levels of sodium, hemoglobin and serum creatinine were significantly lower in females than males. Among the indexed patients, the COVID-19 disease severity was classified as mild, moderate, severe and critical in 2.7%, 4.7%, 70.5% and 22.1% respectively.

Table 1: Clinical and laboratory characteristics of the COVID-19 patients

Characteristics	Total n=179	Female n=88	Male n= 91	P value
Age, mean±SD	58.3±16.5	60.1 ±17.4)	56.7±15.4	0.089
Age > 55 years, n (%)	108 (60.7)	60(55.6)	48(44.4)	**0.030**
Diabetes Mellitus, n (%)	49(28.6)	24(48.9)	25(51.0)	0.538
Hypertension, n (%)	86(49.7)	51(59.3)	35(40.7)	**0.015**
HIV, n (%)	28(21.5)	17(60.7)	11(39.3)	0.273
Cardiac disease, n (%)	13(7.9)	6(46.1)	7(53.9)	1.000
CKD, n (%)	10(7.6)	2(20.0)	8(80.0)	0.106
COVID-19 severity				
Mild, n (%)	4 (2.7)	4(100.0)	0(0.0)	**0.036**
Moderate, n (%)	7(4.7)	1(14.3)	6 (85.7)	
Severe, n (%)	105(70.5)	50(47.6)	55 (52.4)	
Critical, n (%)	33(18.6)	19(57.6)	14(42.2)	
Duration, median (IQR)	6(3-10)	6(3-10)	5(2.9)	0.236
SPO2%, median (IQR)	88(75,94)	87(68,94)	88(81,94)	0.303
WCC (10^3/uL), median (IQR)	8.6(5.5,11.7)	8.4(5.4,11.2)	8.8(5.6,12.4)	0.443
DBP mmHg) mean (SD)	79.3(14.7)	77(73,80)	81(74,84)	0.985
SBP mmHg, mean (SD)	129.5(20.90	127(122,131)	132(128,137)	0.956
HB g/dl, median (IQR)	13.2(12.0,14.5)	12.7(11.7-14.0)	13.8(12.7,15.0)	**<0.001**
Platelet (10^3/uL), median (IQR)	244(165,328)	228(168,351	251(165,312)	0.893
RBS (mmol/l), median (IQR)	7.8(5.8,11.6)	7.7(5.9,9.7)	8.2(5.6,12.4)	0.716
D-Dimer, (ug/mL), median (IQR)	1.6(0.89,7.4)	1.9(1.05,7.1)	1.1(0.72,8.8)	0.463
CRP, (mg/L), median (IQR)	102(36.6,215.0)	106(40,218.1)	96.5(30.6,212	0.774
Na (mmol/L), median (IQR)	141(137,144)	136(135,143)	142(139-,145)	**0.019**
K+ (mmol/L), median (IQR)	4.2(3.6,4.7)	3.9(3.5,4.5)	4.2(3.7,5.0)	0.185
Urea (mmol/L), median (IQR)	6.7(4.3,9.3)	6.6(3.7,8.3)	7.0(5.0,9.9)	**0.035**
SCr (mmol/L), median (IQR)	113.2(91.2,146)	106.1(85.2,140.6)	122.8(102.,147.9	**0.018**
eGFR (mL/min/1.73 m^2), median (IQR)	65.2(46.9,86.1)	59.6(44.4-80.6)	68.7(50.2-88.3)	**0.043**

Abbreviations: SCr; serum creatinine, SBP; systolic blood pressure, DBP; diastolic blood pressure, WCC; white cell count, RBS; random blood sugar, CRP; C-reactive protein, eGFR; estimated Glomerular filtration rate, Na; sodium, K+; Potassium, IQR; interquatile range

Renal dysfunction in hospitalized COVID-19 patients

Table 2 shows the characteristics of the patients with and without kidney dysfunction. The prevalence of kidney dysfunction was 51.9% and 39.3% of these patients had an eGFR<60 **mL/min**/1.73m$^{2.}$ The kidney dysfunction was significantly higher in males than females (59.3% versus. 44.3%, p =0.044) and in patients with underlying hypertension than those without (60.5% versus. 39.5%, p =0.039). Patients with kidney disease were also likely to have a low coma scale and low oxygen saturation, the later being markers of severe COVID-19 pneumonia. In unadjusted analysis, male gender, hypertension, critical COVID-19 disease and were associated with development of renal impairment in patients with COVID-19 pneumonia. Variables significant in bivariate analysis were included in multivariate analysis. However, in adjusted analysis, only hypertension independently predicted renal impairment in patients with COVID-19 pneumonia, (AOR 1.53, 95% CI 1.06-2.23).

Table 2: Characteristics of COVID-19 patients with and without renal disease

Characteristics	Kidney dysfunction N=93	No Kidney dysfunction n=86	P value
Age ≥55, n (%)	62(57.4)	46 (42.6)	0.058
Gender			
Male, n (%)	54(59.3)	37(40.7)	**0.044**
Female, n (%)	39(44.3)	49(55.7)	
Co morbidities			
DM, n (%)	29(59.2)	20(40.8)	0.277
HTN, n (%)	52(60.5)	34(39.5)	**0.039**
HIV, n (%)	11(39.3)	17(60.7)	0.235
CKD, n (%)	57(46.7)	65(53.3)	**0.043**
Cardiac disease, n (%)	7(53.8)	6(46.2)	0.933
Duration(days), median (IQR)	6 (2,9)	6(3,10)	0.252
COVID-19 pneumonia severity			
Critical, n (%)	23(69.7)	10(30.3)	**0.038**
Mild, n (%)	0(0.0)	4(100.0)	
Moderate, n (%)	4(66.7)	3(33.3)	
Severe, n (%)	52(49.5)	53(50.5)	
In hospital mortality, n (%)	41(45.6)	49(54.4)	**0.042**
Vitals			
SBP (mmHg), mean (SD)	130.6(20.4)	128.2(21.4)	0.779
DBP (mmHG), mean, SD	81.7(15.3)	76.6(13.7)	0.987
RR (beats/min), median (IQR)	22(20,26)	21(20,26)	0.162
Pulse (beats/min), median (IQR)	96(82,114)	100(87,115)	0.340
GCS, , median,(IQR)	15(14,15)	15(15,15)	0.017
Q –SOFA score, median (IQR)	1(0,2)	1(1,0)	0.180
SPO2, median (IQR)	85(70,92)	90(78,95)	**0.023**
Laboratory			
WCC, median (IQR)	9.3(5.5,13.1)	8.2(5.5,11.0)	0.307
HB (g/dL), median (IQR)	13.6(12.0,14.9)	13(12.2,14.2)	0.385
Platelet 103, median (IQR)	238(158,320)	249(175,334)	0.446
RBS (mmol/L), median (IQR)	8.2(6.3,12.3)	7.4(5.2,11.6)	0.164
D-Dimer, median (IQR)	2.4(0.9,10.0)	1.5(0.7,7.1)	0.514
CRP, median (IQR)	101(33,222)	104(38,218)	0.971
Sodium (mmol/L), median (IQR)	141(137,145)	141(139,143)	0.671
Potassium (mmol/L), median (IQR)	4.2(3.6,5.2)	4.1(3.7,4.5)	0.373
Chloride (mmol/L), median (IQR)	101(96,106)	104(95,108)	0.692
Urea (mmol/L), median (IQR)	8.3(6.7,11.1)	4.3(3.0,6.3)	<0.001

Abbreviations: Diabetes mellitus, HTN, hypertension, SBP; systolic blood pressure, DBP; diastolic blood pressure, RR; respiratory rate, GCS; Glasgow Coma Scale, WCC; white cell count, RBS; random blood sugar, CRP; C-reactive protein, Q-SOFA; Sequential organ failure assessment score, eGFR; estimated Glomerular filtration rate, IQR; inter quartile range, SD: standard deviation. Q –SOFA score parameters; RR≥ 22/min=1, change in mental status=1 and systolic blood pressure ≤100 mmHg=1

DISCUSSION

This study primarily assessed the proportion of COVID-91 patients with renal dysfunction and associated factors in hospitalized patients with COVID-19 disease. The study has revealed a 51.9% prevalence of kidney dysfunction in COVID-19 patients and presence of hypertension predicted development of kidney impairment. Furthermore, kidney impairment occurred at a higher frequency in patients with severe and critical COVID-19 pneumonia.

The finding of an increased rate of kidney dysfunction in patients with COVID-19 pneumonia in our study

Table 3: Predictors of renal dysfunction in COVID-19 pneumonia patients

Factor	OR	UOR (95% CI)	P value	AOR	AOR (95% CI)	P value
Gender Male	1.35	1.01-1.82	0.045	-		
Female	1					
HTN Yes	1.37	1.01-3.86	0.040	1.54	1.06-2.23	**0.022**
No	1			1		
WCC	1.04	0.99-1.11	0.095	-		
Critical COVID - 19 disease	1.56	1.04-2.34	0.032	-		
Not Critical	1					

Abbreviations: HTN, hypertension; CKD; chronic kidney disease, WCC; white cell count

is consonant with previous results. [7, 17] In retrospective and observational studies performed in COVID-19 hospitalized patients, the reported incidences of acute kidney injury (AKI) were 45% in United Arab Emirates, [18] 57% in Mexico [19] and 34% in South Africa. [20] Similar high rates of kidney impairment results were found in studies that were conducted in severe/critical COVID-19 patients that were admitted to intensive care units (ICU) in Brazil and Paris and the reported incidences of AKI were respectively 56% and 52% in studies conducted in Brazil and Paris. [7, 17] In line with our study, a meta-analysis that included 54 articles that consisted of 30, 657 admitted COVID-19 patients, the pooled prevalence of acute renal impairment was nearly 30% and it increased to about 50% in patients with critical COVID-19 disease.[21] Similar to previous studies, the rate of kidney dysfunction in patients with severe COVID-19 disease was higher compared to those with mild disease in our study. Xiang *et al*. reported median serum creatinine levels of 65.0 mmol/L (52.0-77.0) vs. 70.0 mmol/L (54.5-83.5) in patients with mild and severe COVID-19 diseases respectively. [11] In this study, the estimated glomerular filtration rates were also lower in patients with severe disease compared to those with mild disease, [11] a finding observed in our study.

There are limited studies that have looked at association of kidney dysfunction with COVID-19 pneumonia. Firstly, most of these have come from China, were SARS-Cov-2 was first identified, and they have shown geographical variation in incidences of renal impairment and have reported some lower rates of kidney impairment compared studies in Europe or North America. [6, 22] A meta-analysis that included 21 articles (China 18, USA 2 and 1 from Europe, the overall incidence of AKI was 12.3%, but ranged from 0.5% to about 57% in a few studies that had patients with severe/critical COVID-19 disease. [22] These studies have shown that kidney impairment is a common complication in patients with COVID-19, a finding consistent with our study. Both direct viral induced cytopathic damage and indirect mechanisms such as sepsis, volume depletion, thrombotic micro-pathologies and marked inflammation have been implicated in causing renal impairment in hospitalized COVID-19 patients [4, 23, 24]. The renal proximal tubular cells, the podocytes and glomerular tissue has been shown to significantly express angiotensin converting enzyme 2 (ACE2) receptors and transmembrane protease, serine 2 (TMPSS2), these being the main elements responsible for SARS-Cov2 renal viral entry and associated damage [4, 23]. Inflammatory cytokines such as IL6, 8, TNFα present in patients in patients with severe or critical COVID-19 disease have been shown to cause renal endothelitis, hypo perfusion, thrombotic microangiopathy leading to kidney impairment[24]. The increased rates of kidney impairment in our study might be attributed to fact that 93% of the indexed files had severe/critical COVID-19 disease a finding that has been shown in previous studies. [25] For example, Taher *et al.* in a

single centre study conducted in Bahrain found 40% incidence of AKI. However, in patients with critical disease, the AKI incidence was 61% in this study. [25]

In this present study, hypertension was nearly twice higher in patients with kidney dysfunction compared to those without (60.5% versus. 39.5%) and predicted 1.5-fold odds of developing kidney dysfunction. This finding is consistent with previous studies. Geri *et al.* in a multi center ICU study that was performed among COVID-19 patients in Paris observed nearly 60% vs. 39% rates of hypertension in patients with renal disease compared to those without. [7] Furthermore, in two retrospective studies that were performed among severe critical COVID-19 hospitalized patients in Brazil, found 66.7% vs. 40% and 71.2% vs. 53.9% frequencies of hypertension in the COVID-19 AKI group compared to those without AKI .[17, 26] A meta-analysis of 24 studies respectively revealed 70% and 59% rates of hypertension in COVID-19 patients with critical and non-critical diseases. [27] The mechanism of hypertension induced renal impairment remains unclear. Previous studies have revealed that hypertension likely increased the levels of angiotensin converting enzyme (ACE) causing an imbalance between ACE and angiotensin converting enzyme 2 (ACE2) [28, 29]. The ACE increases angiotensin II/angiotensin II type receptor 1 (Ang II/AT_1R) axis that is proinflammatory, profibrotic and is known to increase reactive oxygen species and decreases nitric oxide, an important renal vasodilator. [28, 29] The ACE2 is further down regulated by the binding of the SARS-Cov 2 post internalization by renal tissue. The ACE2 is an peptide for generation of Angiotensin 1-9/angiotensin II type 2 (Ang II/Ang $_2$R) receptor axis and Angiotensin 1-7/Mas receptor axis (Ang II/MasR) from angiotensin 1 and angiotensin respectively. Both Ang II/MasR and Ang II/Ang $_2$R are potent anti-inflammatory, anti-fibrotic peptides that increase levels of nitric oxide [29]. It appears underlying hypertension is linked to increased severity of COVID-19 disease [27, 30] and that hypertension potentially increases inflammation and endothelial dysfunction [31], that is associated with blunted production of nitric oxide[28, 32] Furthermore, studies in Africa including Zambia, have shown that hypertension was the a prevalent cause of renal dysfunction in patients with kidney failure [10, 33, 34].

To our knowledge, this is the first study in Zambia demonstrating a rate of kidney dysfunction in hospitalized patients with COVID-19 diseases. Our study is not without limitations; it was retrospective in nature, some markers of kidney damage such as proteinuria, hematuria were lacking. Nearly 27% of the patients in this study had unknown cardiac status while the HIV status was unknown in 7.8%.

CONCLUSION

This study revealed a high prevalence of kidney impairment in hospitalized COVID-19 patients and presence of hypertension was an independent predictor of renal impairment and therefore; alertness should be placed in screening for kidney disease in patients with COVID-19 pneumonia and employing various markers of kidney dysfunction.

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Conflict of interest: None

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Authors' contributions

All the listed authors in this study contributed in line with International Committee of Medical Journal Editors (ICMJE).

Ethics Approval

The Tropical Diseases Research Centre Ethics Review Committee and National Health Research Authority (reference #TRC/C4/05/2021) approved the study. Patients lacking serum creatinine were excluded from the study.

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