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Research Article

Serum Creatinine as a Predictive Tool of Adverse Outcomes in Covid-19 Patients

Créatinine Sérique comme Outil Prédictif des Résultats Défavorables chez les Patients Atteints de Covid-19

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ABSTRACT

Introduction. Renal impairment is frequent in hospitalized patients with COVID-19 and is associated with poor outcomes. The aim of our study was to assess the prevalence of elevated serum creatinine in COVID-19 patients at the Douala General and Laquintinie Hospitals in Douala. **Methods.** This was a hospital-based retrospective cohort study from March 2020 to March 2022. We included all files of patients admitted and diagnosed of Covid-19 using the RDT, RT-PCR, chest CT Scan and/or clinical symptoms. We noted the highest serum creatinine values during admission. Elevated serum creatinine was defined as >13mg/l for males, and >12mg/l for females. **Results.** A total of 543 files were included. The prevalence of elevated serum creatinine was 50%. Hypertension and type 2 diabetes mellitus were significantly more prevalent in patients with elevated creatinine (p=0.001 and p=0.014) respectively. The most common biological abnormalities associated with elevated creatinine were: elevated C-reactive protein and D-dimer, neutrophilia, and lymphopenia. Patients with elevated creatinine received more oxygen therapy (p=0.046). The mortality rates were 45.8% and 14.1% in patients with elevated and normal Creatinine respectively (p<0.001). On multivariate analysis, age>60 years, and low oxygen saturation <95 % (aOR 3.116, 95% CI 1.368-7.099) were independent predictors of mortality in COVID-19 patients with kidney impairment. **Conclusion.** Half of hospitalized patients with COVID-19 had elevated Serum creatinine, and about one out of two of them died.

RESUME

Introduction. Les troubles rénaux sont fréquents chez les patients hospitalisés atteints de la COVID-19 et sont associés à de mauvais résultats. L'objectif de notre étude était d'évaluer la prévalence de l'élévation de la créatinine sérique chez les patients atteints de la COVID-19 à l'hôpital général de Douala et Laquintinie à Douala. **Méthodes.** Il s'agissait d'une étude de cohorte rétrospective basée sur des données hospitalières de mars 2020 à mars 2022. Nous avons inclus tous les dossiers des patients hospitalisés et diagnostiqués avec la Covid-19 à l'aide du test RDT, de la RT-PCR, de la tomodensitométrie thoracique et/ou des symptômes cliniques. Nous avons noté les valeurs les plus élevées de créatinine sérique lors de l'admission. Une élévation de la créatinine sérique était définie comme >13mg/l pour les hommes et >12mg/l pour les femmes. **Résultats.** Un total de 543 dossiers ont été inclus. La prévalence de l'élévation de la créatinine sérique était de 50 %. L'hypertension et le diabète de type 2 étaient significativement plus fréquents chez les patients présentant une créatinine élevée (p=0,001 et p=0,014) respectivement. Les anomalies biologiques les plus courantes associées à une créatinine élevée étaient : une augmentation de la protéine C-réactive et du D-dimère, une neutrophilie et une lymphopénie. Les patients avec une créatinine élevée ont reçu plus de thérapie à l'oxygène (p=0,046). Les taux de mortalité étaient de 45,8 % et 14,1 % chez les patients avec une créatinine élevée et normale respectivement (p<0,001). Dans l'analyse multivariée, l'âge>60 ans et une saturation en oxygène faible <95 % (aOR 3,116, IC à 95 % 1,368-7,099) étaient des prédicteurs indépendants de la mortalité chez les patients atteints de la COVID-19 avec des troubles rénaux. **Conclusion.** La moitié des patients hospitalisés atteints de la COVID-19 présentaient une élévation de la créatinine sérique, et environ sur sur deux d'entre eux est décédé.

HIGHLIGHTS

What is known of the subject

Mortality rates in Covid-19 patients with kidney failures have been reported to range from 30% to 50%.

The aim of our study

Serum creatinine as a predictive tool of adverse outcomes in COVID-19 patients in Douala

Key Results

1. The prevalence of elevated serum creatinine was 50%.
2. Hypertension and type 2 diabetes mellitus were significantly more prevalent in patients with elevated creatinine (p=0.001 and p=0.014) respectively
3. The mortality rates were 45.8% and 14.1% in patients with elevated and normal Creatinine respectively (p<0.001).
4. On multivariate analysis, age>60 years, and low oxygen saturation <95 % (aOR 3.116, 95% CI 1.368-7.099) were independent predictors of mortality in COVID-19 patients with kidney impairment.

Implications for future practices and policies

Healthcare providers should routinely screen and closely monitor kidney function in COVID-19 patients, particularly those with pre-existing conditions such as hypertension and diabetes mellitus.

INTRODUCTION

Even though the primary affected organs by SARS-CoV-2 are the lungs, numerous studies have shown that the virus affects many other organs**[1,2].** The kidneys are the second most commonly affected organ after the lungs and a large proportion of patients with COVID-19 develop some type of kidney damage**[2].** This can be explained by the fact that the virus enters the body by directly binding to the Angiotensin Converting Enzyme 2 receptors which are highly expressed on podocytes and the epithelial cells of the renal proximal tubule, causing tubular damage **[1-3].** The most commonly reported lesions are tubular injury, acute interstitial nephritis, and collapsing glomerulonephropathy**[4].** Renal damage during hospital stay is considered a marker of severity and poor prognostic factor in COVID-19 patients. Some frequently reported adverse outcomes are prolonged hospital stay, need for kidney replacement therapy and higher odds of mortality **[5,6].** According to silver et al., It has been reported thatAccording to Silver et *al*., 1 in 3 hospitalised COVID-19 patients develop acute kidney failure, which is related to the severity of the coronavirus disease and is more common in the elderly[7]. Many other studies have demonstrated high mortality rates in COVID-19 patients with kidney failure, compared to those without **[3,8,9].** Mortality rates in these patients have been reported to range from 30% to 50% **[10].** With these high rates of mortality and other poor outcomes in COVID-19 patients with kidney failure, we therefore sought to determine the place of serum creatinine, as a predictive tool for adverse outcomes in COVID-19 patients**[11].** Knowing if serum creatinine is an independent predictive tool for adverse outcomes would help identify patients who are likely to have a poorer prognosis early enough and implement early preventive strategies and prompt treatment, which will subsequently improve the overall prognosis of these patients. Numerous markers like D-dimers, neutrophils/lymphocytes ratio, lactate dehydrogenase and C-reactive protein [**12]** have been proven to be markers of disease severity and predictors of poor outcomes in COVID-19, but the place of creatinine (which is a rapid and inexpensive way to assess for renal function) is still to be studied as an independent prognostic tool in our setting **[13].**

PATIENTS AND METHODS

Study design and population

This was a hospital-based, retrospective cohort study conducted in the COVID-19 units of the Douala General and Laquintinie Hospitals where files of patients admitted from March 2020 to March 2022 were reviewed.

Study area and population

These two hospitals were chosen because they served as reference centres for the management of COVID-19 patients for the Littoral region of Cameroon and both hospitals have a unit which was specifically for the management of COVID-19 patients. The COVID-19 units of both hospitals were created in 2020 and equipped with beds and oxygen concentrators and run 24 hours daily, from Monday to Sunday. Treatment was free of charge but patients had to pay for laboraotory and other complementary examinations. Patients were treated following the National protocol for the management of COVID-19. . The medical staff consists of general practitioners, specialists of different domains such as pneumologists, nephrologists, anesthesiologists and neurologists, radiologists and intensivists, always available according to the patient's needs.

Data collection tools

Patient data was collected from the records into an Excel spreadsheet. The highest serum creatinine level recorded during the hospital stay and before the occurrence of our outcome of interest was noted. Other laboratory parameters and radiologic findings on chest computed tomography scan was also recorded. Elevated serum Creatinine was defined as a level >13mg/l for males, and >12mg/l for females. Serum creatinine levels were measured using the Jaffe method, a chemical method based on the reaction between creatinine and picrate ion in an alkaline medium to yield an orange-red complex, and the enzymatic method (creatinine deaminase). COVID-19 was diagnosed using the RDT, RT-PCR, chest CT Scan and/or clinical symptoms.

Data management and analysis

We used the Statistical Package for Social Sciences version 26 for analysis. Categorical variables were summarized using counts and percentages and presented using bar and pie charts. Continuous variables were summarized using means, standard deviations, medians, and interquartile ranges where necessary. Bivariate analyses by Chi-square tests for the categorical variables and t-tests for continuous variables as appropriate. Stepwise binary logistic regression was used to select

and estimate the association between elevated serum creatinine and mortality. A p value < 0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Institutional Review Board of the Faculty of Health Sciences, University of Buea (2022/1281-01/UB/SG/1RB/FHS), and given the retrospective nature of the study, the patient consent was waved.

RESULTS

During the period of study, 601 patients were admitted to the COVID-19 units, 58 files were excluded for incomplete data (absence of creatinine values, history of chronic kidney disease). Out of a total of 543 participants who had at least one serum creatinine done, 273 had elevated serum creatinine, thus an estimated prevalence of 50%.

Sociodemographic characteristics

Of the 273 COVID-19 patients with elevated serum creatinine, 148 were males (54.2%). As shown in Table 1, patients with elevated serum creatinine were older (60.2 vs. 57.0 p=0.001). Hypertension and Type 2 Diabetes Mellitus were significantly more prevalent in patients with elevated Scr. (p=0.001 and 0.014 respectively) **(Table I).** Patients with elevated serum creatinine were more likely to present with dyspnea (28.7% vs 27.3, p=0.018) and lower oxygen saturation (87.2% and 89.9%, p=0.019) **(Table II).**

Comparison of biological parameters of patients with elevated and normal serum creatinine values

Leucocytosis, lymphopenia, elevated CRP, elevated D-dimer and positve procalcitonin levels were significantly associated with raised creatinine(p=.0.007, p= 0.03, p=0.021, p=0.006, p=0.004) **(Table III).**

Serum creatinine and mortality in COVID-19 patients

The mortality rate was significantly higher in patients with raised serum creatinine (45.8% vs 14.1%, p<0.001) **(Figure 1).**

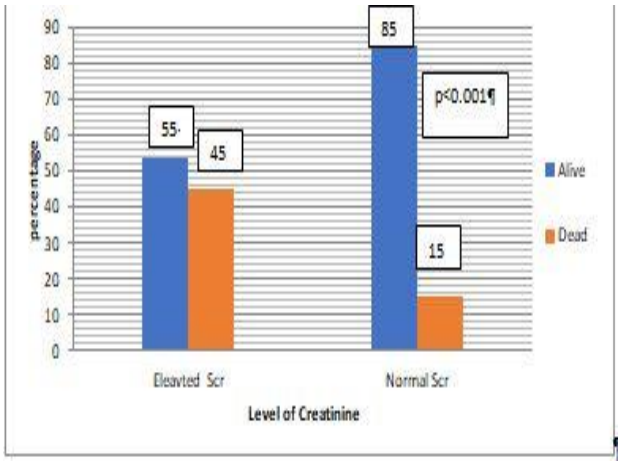

Figure 1. Mortality rates in patients with normal and elevated serum creatinine.

Predictors of death in patients with elevated serum creatinine

On unvariate analysis, age>60, dyspnea, cardiovascular diseases, oxygen saturation <80%, CRP>6 mg/l, lymphopenia, elevated d-dimer and procalcitonin were associated with mortality in COVID-19 patients with elevated scr. On multivariate logistic regression analysis, low oxygen saturation <95 % (aOR 3.116, 95% CI 1.368-7.099, p =), and age > 60 years (aOR: 2.498. CI: 1.278-3.891) were predictors of mortality in COVID-19 patients with kidney damage **(Table IV).**

Table 1. Characteristics of the study population

Variable		Total n (%)	Elevated Scr (%)	Normal Scr n(%)	p-value
Gender	Male	289(53.2)	148(54.2)	141(52.2)	**NA**
	Female	254(46.8)	125(45.8)	129(47.8)	
Mean age +/-SD		60.6+/-14.7	60.2+/-11.5	57.0+/-14.3	**0.001**
Hypertension		268 (49.4)	160 (29.5)	108 (19.9)	**0.001**
T2DM*		142 (26.2)	82 (15.1)	60 (11.1)	**0.014**
Cardiovascular Diseases		59 (10.9)	26 (44.1)	33 (55.9)	0.892
HIV/AIDS**		38 (6.9)	18 (3.3)	20 (3.6)	0.561
Obesity		32 (5.9)	15 (2.8)	17 (3.1)	0.522
Malignancy		23 (4.2)	12 (2.2)	11 (2.0)	0.826
CLD****		10 (1.8)	02 (0.3)	08 (1.5)	0.289

*T2DM= Type 2 diabetes mellitus, ** HIV/AIDS= Human Immune Virus/Acquired Immunodeficiency Syndrome, ****CLD= Chronic lung conditions

Table 2. Clinical presentation on admission

Symptom	Total n (%)	Elevated Scr n (%)	Normal Scr n (%)	p-value
Fever	343 (63.2)	164 (30.2)	179 (33.0)	0.356
Cough	327 (60.2)	165 (30.4)	162 (29.8)	0.573
Dyspnea	304 (56.0)	156 (28.7)	148 (27.3)	0.018
Asthenia	300 (55.2)	146 (26.9)	154 (28.3)	0.416
Anorexia	180 (33.1)	90 (16.6)	90 (16.6)	0.898
Headache	119 (21.9)	59 (10.9)	60 (11.0)	0.837
Chest pain	95 (17.5)	42 (7.7)	53 (9.8)	0.366
Abdominal pain	24 (4.4)	16 (2.9)	8 (1.5)	0.414
Diarrhoea	72(13.3)	44 (8.1)	28 (5.2)	0.416
Vomiting	34 (6.3)	19 (3.5)	15 (2.8)	0.593
Loss of taste	35 (6.4)	12 (2.2)	23 (4.2)	0.708
Loss of smell	33 (6.1)	12 (2.2)	21 (3.9)	0.722
Rhinitis	37 (6.8)	17 (3.1)	20 (3.7)	0.132
Sore throat	9 (1.7)	6 (1.1)	3 (0.6)	0.183
Coma	5 (0.9)	2 (0.3)	3 (0.6)	0.954
Mean +/- SD oxygen saturation	88.4 +/-11.04	87.2 +/-13.1	89.9 +/-9.8	0.019

Table 3. Biological parameters of patients with elevated and normal serum creatinine

Variables	Total n (%)	Elevated Scr n (%)	Normal Scr n (%)	p-value
Mean Leucocyte +/-SD*	9109.6 +/-955.4	10672+/-1279	7156+/-488	**0.007**
Leucocyte categories(n=527)				
<4,000	56 (10.6)	21 (4.0)	35 (6.6)	<0.001
4-10,000	326(61.9)	152 (28.8)	174 (33.1)	0.001
>10,000	145(27.5)	89 (16.9)	56 (10.6)	<0.001
Mean neutrophil % +/-SD	64.1+/-18.8	64.5+/-19.6	59.2+/-19.3	0.141
Neutrophil categories (%)(n=504)				
<40	61 (12.1)	27 (5.4)	34(6.7)	0.798
40-60	111 (22.0)	45 (8.9)	66(13.1)	0.685
>60	332 (65.9)	177 (33.1)	155 (30.8)	0.549
Mean lymphocyte %+/-SD	26.4+/-17.3	25.5+/-17.6	59.2+/-19.3	**0.031**
Lymphocyte categories (%)(n=504)				
<20	234(46.4)	129 (25.6)	105 (20.8)	0.269
20-40	179 (35.5)	83 (16.5)	96 (19.0)	0.478
>40	91 (18.1)	37 (7.3)	54 (10.8)	0.160
Mean haemoglobin +/-SD	11.8 +/-2.3	10.9 +/-2.0	11.5+/-1.8	**0.021**
Hemoglobin categories((n=536)				
<8	28 (5.2)	20 (3.7)	8 (1.5)	0.008
8-10	76 (14.2)	53 (9.9)	23 (4.3)	0.052
>10	432 (80.6)	190 (35.4)	236(45.2)	0.009
Mean platelets +/-SD	235100+/-8972	231658.3	239362.1	0.599
Platelets categories(n=527)				
<150,000	134 (25.0)	70 (13.1)	64 (11.9)	0.434
150-400,000	343 (64.0)	171(31.9)	172 (32.1)	0.321
>400,000	50 (9.3)	21 (3.9)	29 (5.4)	0.426
Mean CRP** +/-SD	77.2 +/-7.5	86.4+/-8.0	59.9+/-6.5	**0.006**
CRP categories(n=542)				
<6	22 (4.1)	9 (1.7)	13 (2.4)	0.723
6-160	426 (78.6)	208(38.3)	218 (40.3)	0.736
>160	94 (17.3)	51 (9.4)	43 (7.9)	0.549
Mean D-dimer +/-SD	4132+/-619	4697+/-502	2872+/-619	**0.004**
D-dimer categories(n=231)				
<500	16 (6.9)	8 (3.5)	8 (3.4)	0.486
500-2000	81(35.1)	34 (14.7)	47 (20.4)	0.973
>2000	134(58.0)	71(30.7)	63 (27.3)	0.244
Mean procalcitonin +/-SD	3.7 +/-2.2	1.6+/-1.0	1.3+/-0.7	0.621
Procalcitonin categories(n=266)				
<0.1	90 (33.8)	29 (10.9)	61 (22.9)	**0.002**
0.1-0.25	45 (16.9)	18 (6.8)	27 (10.1)	**<0.001**
>0.25	131(49.2)	76 (28.6)	55 (20.6)	0.195
Mean PT*** +/-SD	75.9 +/-17.8	73.7 +/-19.7	78.4+/-15.6	0.213
Mean aPTT**** +/-SD	19.8 +/-2.7	20.9 +/-7.5	18.9+/-8.3	0.476

Table 4. Factors independently associated with mortality

Variables	aOR	95% CI	P-value
Oxygen Saturation (<95%)	3.116	1.368-7.099	**<0.001**
Age >60years	2.498	1.278-3.891	**0.019**
CRP*(>6mg/L)	0.109	0.012-0.969	0.109
Dyspnea	0.907	0.507-1.621	0.904
Lymphopenia	0.025	0.001-0234	1.231
Elevated D-Dimer	0.897	0.456-2.589	0.745
Procalcitonine	1.253	0.896-3.254	0.457

CRP= C-reactive protein

DISCUSSION

The prevalence of elevated serum creatinine in our study was 50 %. This high prevalence could be explained by the fact that SARS-COV-2 binds to the ACE2 receptors in the renal tubules, whose renal expression was nearly 100 times higher than in pulmonary tissue, thereby causing renal dysfunction which is primarily manifested as raised Scr**[14].** The high prevalence of abnormal kidney function tests in pneumonia is not uncommon. Sloan et al. reported a prevalence of elevated Scr of 41.5% in patients with radiologically confirmed community-acquired pneumonia **[15]**. Our results were similar to the 46.0 % reported by Chan et al. **[9]** in China in 2020, the 44 % reported by Lowe et al. **[10]** in England in 2021, and the 54.9% reported by Nimkar et al **[8]** in the USA in 2020. This was however greater than the 9.6 % and the 7.0%, reported by Yang and Cheng respectively, in China **[16,17].** This heterogeneity is probably due to the differences in the case inclusion criteria and also the varying demographic characteristics and comorbidities of the study population. Cheng excluded all patients with chronic kidney disease, patients on maintenance hemodialysis and those with abnormal urine tests (proteinuria, hematuria). They also excluded patients whose duration of symptoms was >14 days before admission. Most importantly, they included patients with at least 2 serum creatinine values, taken at a 48-hour interval, provided there was at least an increase by 0.3mg/dl. This resulted in an overall reduction in their sample size. Additionally, the nature of his study was prospective; this might have underestimated the overall prevalence of serum creatinine in COVID-19 patients, had it been the kidney event not yet occurred at the time the data was collected. In this study patients with elevated Scr were older (60.2). This was consistent with the means of Pei et al. (57.1) years **[11]** and Azoulay et al. (60.0) years **[18]** in other studies, The age group with the highest reported rate of elevated Scr was 60-80 years, which was similar to that of Chan et al (65-74 years) **[9].** This can be explained by the fact that advanced age is associated with a gradual decline in immune function called immunosenescence, and a chronic increase in systemic inflammation called inflammaging, which are major drivers of disease severity in COVID-19 patients **[19].** We noted that hypertension and T2DM were more prevalent in patients with elevated Scr. This is probably due to the negative effects of high blood pressure and diabetes on the kidney **[17].** These values were in line with the 33.4% and 14.3% reported by Cheng et al, for hypertension and T2DM **[17].** Other co-existing illnesses were considerably similar in both groups. When compared with patients with normal Scr 147(28.2%), those with elevated Scr were more likely to receive oxygen therapy 174(30.9%) (p=0.019). The mean oxygen saturation in both groups of patients was 87.2% and 89.9% respectively. This is probably due to the fact kidney damage mostly occurs in patients with severe illness, and most patients with severe illness present with dyspnea and low oxygen saturation, which warrants the need for oxygen. There were numerous differences in laboratory findings between patients with elevated and those with normal Scr. This may be related to the cytokine storm induced by virus invasion, which causes an increase in neutrophil and leucocyte counts[20] and is more accentuated with severe disease. Since there is an established positive correlation between disease severity and kidney damage, patients with kidney damage would therefore experience a greater destruction of lymphocytes by the virus. Hence, more severe lymphopenia, Elevated CRP, and Abnormalities in the coagulation cascade, including extended activated partial thromboplastin time (aPTT) and higher D-dimer values **[22,23].** The incidence of in-hospital mortality in patients with elevated Scr was higher. These high figures could be explained by the overwhelming deleterious effects of the virus at the kidney level. Also, kidney damage mostly occurs in elderly patients with comorbidities and severe disease, who are more susceptible to worse outcomes. These figures concurred with the mortality rates of 58.1 % and 19.6% reported by Nogueira et al in Italy in 2020 in both groups of patients **[2],** to the 50.0% and 8% reported by Chan et al in China in 2021 **[9].** This was however greater than the 11.2% and 1.2% in both groups of patients reported by Pei et al in China in 2020 **[12].** This difference can be attributed to the fact that we did not exclude patients with CKD, we considered just one value of elevated Scr and we had a larger sample size. This may have increased the capture of deaths in our study, leading to the higher observed mortality rates. There was a statistical difference in the mortality rates of patients with elevated Scr, compared with those with normal Scr. (p<0.001). On multivariate logistic regression analysis, age>60, and low oxygen saturation <95 % were predictors of mortality in COVID-19 patients with kidney damage. This can be explained by the fact that kidney damage in COVID-19 mostly occurs in patients who are severely or critically ill, and most times, these patients are dyspneic and have low oxygen

saturations. There is a positive relationship between disease severity and mortality, hence, the association.

CONCLUSION

About 1 in 2 hospitalized patients with COVID-19 had abnormal kidney function (elevated serum creatinine) at some point during hospitalization. About 1 in 2 patients with elevated serum creatinine died and elevated serum creatinine was associated with a 3-fold increase of mortality. Age>60, and low oxygen saturation are predictors of death in COVID-19 patients with raised creatinine.

Limitations

Only one main short-term outcome (death) was discussed. We did not have detailed information on the subset of patients who required renal replacement therapy. Therefore, the optimal method of kidney replacement therapy remains an important knowledge gap in these patients. Furthermore, given the prominence of elevated Scr in hospitalized patients with COVID-19, further work is needed to better characterize kidney-specific treatment, which was not done in this study.

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Conflict of interest

None

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