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Original Article

Abnormal Renal Function Tests at Presentation in Severe COVID-19 Pneumonia and its Effect on Clinical Outcomes

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Abstract

Objective: To determine the incidence of abnormal renal function tests at presentation in patients from Karachi admitted with severe COVID-19 pneumonia and determine its effect on disease severity and clinical outcomes.
Study type, settings & duration: This was a cross-sectional study conducted at the COVID Intensive care unit of a large tertiary care government hospital in Karachi from February 2021 to June 2021.
Methodology: A total of 190 patients admitted over five months were included in the study. Patient demographic characteristics, comorbidities, and clinical manifestations of COVID-19 infection were recorded. Laboratory values at the time of presentation, including hemoglobin, neutrophil lymphocyte ratio, platelets, blood urea nitrogen, estimated glomerular filtration rate (eGFR), inflammatory markers, liver function tests, and electrolytes were recorded. Patient outcomes and need for mechanical ventilation were assessed 28 days after admission and compared with the incidence of abnormal renal functions at presentation.
Results: Mean eGFR and BUN at presentation were 69.7 and 28.4 respectively. Of the total, 109 (57.4%) patients had abnormal renal function tests at the time of presentation. Among them, 76 (40%) patients had low eGFR and 33 (17.4%) had only raised BUN with normal eGFR. Mean eGFR was lower in non-survivors vs survivors (*p*-value 0.000) and in patients who required mechanical ventilation (*p*-value 0.008). Patients who had low eGFR showed greater mortality than those with normal eGFR (*p*-value 0.04) and were more likely to require mechanical ventilation (*p*-value 0.04).
Conclusion: Low eGFR at presentation is common in patients with severe COVID-19 pneumonia and is associated with a higher in-hospital mortality rate and need for mechanical ventilation.
Key words: Glomerular filtration rate (eGFR), blood urea nitrogen (BUN), creatinine clearance (CrCl), COVID-19, mortality rate, mechanical ventilation.

Introduction

The spectrum of SARS CoV 2 infection ranges from asymptomatic infections to symptomatic disease with mild-severe symptoms.[1] Severe illness is characterized by SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50% on imaging.[2] Among hospitalized patients, the proportion of critical or fatal diseases is higher.[3] Among those who are critically ill, respiratory failure from acute respiratory distress syndrome (ARDS) is the dominant finding.[4]

Studies have shown that patients with COVID-19 can have abnormal kidney function tests and evidence of acute kidney injury during hospitalization.[5] The ability of the virus to target angiotensin-converting enzyme (ACE2) receptors, allows it to target several organs, including the lungs and the kidneys.[6] The pathophysiology and mechanisms of acute kidney in COVID-19 patients are not fully understood. Kidney involvement can range from the presence of hematuria and proteinuria to acute kidney injury requiring renal replacement therapy.[7] Renal complications are

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Authors Contribution

MH & KKS conceptualized the project, did the data collection and performed the statistical analysis along with the literature search. Drafting, revision & writing of manuscript were done by MH, KKS, VM, ZS & SH.

associated with higher mortality in COVID-19 patients.[8]

Previous studies were done in China report an incidence of acute kidney injury from 0-15% in hospitalized patients. However, studies from the US report a higher incidence of acute kidney injury from 14-69% amongst hospitalized patients.[9] We carried out our study in the Intensive care unit of one of Pakistan's largest tertiary care public hospitals, Jinnah postgraduate medical center. We aimed to determine the incidence of abnormal renal function tests in patients with severe SARS Cov2 pneumonia and determine its effect in predicting disease severity and clinical outcomes. The study was designed to determine the frequency of abnormal renal function tests at presentation in patients admitted with severe COVID-19 pneumonia in a tertiary care hospital and determine its effect in predicting disease severity and clinical outcomes.

Methodology

This was a cross-sectional study conducted at the COVID isolation ward of Jinnah Postgraduate Medical Center, one of the largest tertiary care government hospitals in Karachi, Pakistan. Patients admitted over a period of five months from February 2021 till June 2021 were included in the study. Inclusion criteria included adult patients aged >18 years and positive PCR test for SARS CoV2. Exclusion criteria included previous respiratory pathologies including interstitial lung disease, chronic pulmonary disease and pulmonary tuberculosis; heart failure; chronic liver disease or chronic kidney disease; history of malignancy; use of immunosuppressive drugs including long term steroids; sepsis; recent major surgical procedures; active urinary tract infection or urinary tract obstruction; suspicion of drug-induced renal injury and hypertensive crisis.

Estimated Glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation[10] and Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation.[11] Abnormal renal function tests were defined as eGFR<60 ml/min, based on the normal values suggested by National Kidney Foundation and Kidney Disease Improving Global Outcome (KDIGO) or blood urea nitrogen (BUN) more than 24mg/dl, which was the normal limit of the laboratory of our hospital.[12,13]

Blood samples of all patients were drawn for routine laboratory tests within 24 hours of admission. The routine tests include arterial blood gas analysis, complete blood count, liver function tests, renal function tests, coagulation profile and inflammatory markers (C reactive protein, Lactate dehydrogenase, D Dimers and Ferritin). Chest X-rays for all patients was done within 24 hours of admission to determine the degree of lung involvement.

Other demographic characteristics of patients; including age, gender and comorbidities were also recorded. The variables of outcome were recorded by documenting the total duration of hospital stay, need for mechanical ventilation and clinical status of the patient at 28 days post admission.

Data was analyzed using SPSS version 26. Mean and Standard deviation was calculated for quantitative variables like Hemoglobin, Total leukocyte count, Neutrophil lymphocyte ratio, Platelets, Urea, Creatinine, eGFR, CrCl, CRP, LDH, and D-Dimers. Frequencies and percentages were used for qualitative data, including gender and comorbidities. The rest of the data was organized into categorical variables, including PiO2/FiO2 ratio, oxygen requirement and duration of hospital stay. The Chi-Square test was used for the analysis of categorical data. An Independent Sample t-test was used to check inter-categorical differences of mean values. *p*-values of less than 0.05 were considered statistically significant.

The ethical approval was obtained from Institutional Review Board Committee of Jinnah Postgraduate Medical Centre, Karachi vide reference 2-81/2021-GENL/Conf-10/JPMC.

Results

Total number of SARS CoV2 positive patients admitted during the period of study was 372. After application of inclusion and exclusion criteria, we were able to obtain the data of 190 patients. Amongst those studied, 118 (62.1%) were males and 72 (37.9%) were females. The mean age of the patients was 57 years. Of the total, 95 (50.0%) of patients had diabetes mellitus, 84 (44.2%) of patients had hypertension and 18 (9.5%) had ischemic heart disease. Most patients, 98 (51.6%) had PO_2/FiO_2 ratio less than 100 at presentation. Most patients 107 (56.3%) had oxygen requirement of more than 15 litres at presentation. Patient demographics, comorbidities and clinical manifestations are summarized in Table-1.

Mean BUN at presentation was 29.1.4 mg/dl, CrCl 75.9 ml/min and eGFR 69.7 ml/min. One hundred nine (57.4%) patients had abnormal renal function tests at the time of presentation. From them, 76 (40.0%) patients had low eGFR and 33 (17.4%) had only raised BUN with normal eGFR. The laboratory characteristics of patients at presentation are summarized in Table-2.

Table 1: Patient demographics, comorbidities and clinical characteristics.

Demographic/ Comorbidity		*Number of Cases/ (Percentages)*
Age	20-40	15 (7.9)
	40-60	79 (41.6)
	60 and above	96 (50.5)
Gender	Male	118 (62.1)
	Female	72 (37.9)
Co-morbidity	Diabetes mellitus	95 (50.0)
	Hypertension	84 (44.2)
	Ischemic heart disease	18 (9.5)
	Others	12 (6.3%)
Oxygen saturation at room air	90-93%	4 (2.1%)
	70-89%	103 (54.2%)
	<70%	83 (43.7%)
Need for oxygen in liters at presentation	1-5L/min	21 (11.1%)
	6-15L/min	62 (32.6%)
	>15L/min	107 (56.3%)
PO2/FiO2 ratio	<100	98 (51.6%)
	100-300	91 (47.9%)
	>300	1 (0.5%)

Table 2: Laboratory characteristics at presentation.

Laboratory Value at Presentation	*Mean ± SD*
Hemoglobin (mg/dl)	12.4± 1.9
Total leukocyte count x 10^9L	11.9 ± 5.0
Neutrophil lymphocyte ratio	11.1 ± 8.2
Platelets x 10^9L	238.5±99.9
Blood urea nitrogen mg/dl	29.1±19.8
Creatinine mg/dl	1.4±1.5
Estimated glomerular filtration rate ml/min	69.7±30.6
Creatinine clearance ml/min	75.9±38.4
C reactive protein mg/L	126.6±148.7
D dimers mg/L	4.4±5.9
Lactate dehydrogenase U/L	825.3±486.8
Ferritin mcg/L	903.1±573.9
International normalized ratio	1.1±0.8
Serum sodium mmol/L	137.4±6.0
Serum potassium mmol/L	3.9±0.7
Total bilirubin mg/dl	0.6±0.4
Alkaline phosphatase U/L	150.5±110.4
Alanine aminotransferase U/L	65.9±138.4

All patients received IV methylprednisolone or dexamethasone. About 74.6% of patients received remdesivir. Only 4.2% of patients received Tocilizumab due to non-availability. Of the total, 188 (98.9%) received anticoagulation (enoxaparin/ heparin). Two patients didn't receive anticoagulation because of contraindications.

The outcome variables of patients included in the study are summarized in Table-3. Most patients, 117 (61.6%), stayed in the hospital for more than 7 days. One hundred twenty eight (67.4%) of patients required non-invasive ventilation and 76 (40.0%) of patients required invasive ventilation. 23 (12.1%) patients required dialysis.

By 28 days post-admission, most patients (61.6%) died, 28.4% were discharged on room air, 4.2% remained admitted with oxygen support, 3.7% remained admitted with non-invasive ventilation and 2.1% were discharged on home oxygen (Table-3).

Table 3: Outcome of cases.

	Outcome	*Number of Cases/ (Percentages)*
Outcome after 28 days	Death	117 (61.6%)
	Discharged on room air	54 (28.4%)
	Discharged on home oxygen	4 (2.1%)
	Admitted with oxygen support via mask/nasal cannula	186 (97.9%)
	Admitted with non-invasive ventilation	7 (3.7%)
	Admitted with invasive ventilation	1 (0.5%)
Duration of hospital stay	0-7 days	73(38.4%)
	More than 7 days	117 (61.6%)
Need for mechanical ventilation	Non-invasive ventilation	128 (67.4%)
	Invasive ventilation	76 (40.0%)
Need for dialysis	Yes	23 (12.1%)
	No	167 (87.9%)

Table 4: Chi-square test – comparison of the incidence of low eGFR in different groups of patients.

Grouping Variable		*No. of Cases*	*Z score*	*p-value*
Need for mechanical ventilation	Yes	61	4.200	0.040
	No	16		
Outcome at 28 days	Survivor	20	8.478	0.004
	Non-Survivor	57		
Duration of hospital stay	0-7 days	33	1.077	0.299
	More than 7 days	44		

Tables 4 & 5 compare the incidence of low eGFR and mean eGFR in different groups of patients respectively. Abnormal renal function tests did not show any significant association with patient comorbidities. We did not find any significant difference in lab parameters including neutrophil-lymphocyte ratio, platelets, alanine aminotransferase, and C-reactive protein in patients with low eGFR vs those with normal eGFR. Patients who were more than 60 years old were more likely to present with low eGFR than younger patients (*p*-value 0.001). Mean eGFR was significantly lower in non-survivors vs survivors (*p*-value 0.001) and in patients who required mechanical ventilation (*p*-value 0.008). Patients who had low eGFR showed greater mortality than those with normal eGFR (*p*-value 0.04) and were more likely to require mechanical ventilation (*p*-value 0.04). However; when compared with patients with normal eGFR,

patients with low eGFR did not show any significant variance with the duration of hospital stay.

Table 5: Independent sample test – comparison of mean eGFR in different groups of patients.

Grouping Variable		*Mean eGFR +/- STD*	*T score*	*p-value*
Need for mechanical ventilation	Yes	65.9±30.7	-2.694	0.008
	No	78.9±28.7		
Outcome at 28 days	Survivor	81.1±28.4	-4.211	0.001
	Non-survivor	62.6±30.0		
Duration of hospital stay	0-7 days	66.7±33.3	-1.070	0.286
	More than 7 days	71.6±28.86		

Discussion

We studied the incidence of abnormal renal function tests in patients with severe COVID-19 pneumonia and determined its effect on clinical outcomes and disease progression. Many studies, to date, have recorded the incidence of abnormal renal function tests in mild and severe COVID-19 cases. Some studies have also compared the predictive effect of eGFR on mortality. However, there is a lack of large cohort studies in the South Asian population. Our study was carried in one of the largest, yet resource-limited, public sector tertiary care hospital in Pakistan.

The mechanism of renal injury in patients with COVID-19 is complex and multifactorial. Firstly, SARS CoV 2 PCR fragments have been discovered in the blood and urine of COVID-19 patients and it has been hypothesized that the virus exerts direct cytopathic effects on the kidneys.[6] SARS Cov 2 uses angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor and expression of the receptor in the kidney is very high.[14] Thirdly, virus-induced cytokine release might cause direct renal injury, or indirectly affect the kidney because of hypoxia, shock, or rhabdomyolysis.[15,16]

In our study, 17.4% of patients had an isolated increase in BUN, with normal eGFR. The most common cause of raised BUN is a renal disease leading to reduced clearance of urea from the blood. However, the limitation of urea as a test of renal function is that plasma urea is not a sufficiently accurate reflection of reduced eGFR. Urea may be raised despite a normal eGFR, so BUN is not a specific test for renal function.[17] Extra renal causes of raised urea in hospitalized or critically ill patients include dehydration, heart failure, trauma, severe infection, delayed initiation of enteral feeds, and use of corticosteroids, which could have accounted for the raised BUN and normal eGFR in our patients.[18]

Multiorgan involvement has been seen in patients with COVID-19 [19] and studies have shown lower platelet and lymphocyte counts, higher leukocyte count, and a higher rate of comorbidities in COVID-19 patients who developed acute kidney injury.[6] However, our study did not show any significant difference in comorbidities or lab parameters in patients with abnormal renal function tests vs those with normal tests.

In our study, we excluded patients who had known chronic kidney disease, so that we could have an estimate of the incidence of acute kidney injury in patients with COVID-19. The incidence of abnormal renal functions at presentation was 57.4%, out of which 40.4% of patients had low eGFR and 17.4% had high BUN with normal eGFR.12.1% of patients required dialysis. Many other studies have also shown that COVID-19 is associated with Acute Kidney injury or abnormal renal functions at presentation. A study done on a smaller cohort of patients in Pakistan, earlier in the course of the epidemic, showed that 39.4% of patients had raised creatinine levels at the time of presentation.[20] Another study done on 193 patients in China, early in the course of the epidemic showed that 31% of patients had an elevated level of blood urea nitrogen (BUN) and 22% had increased serum creatinine.[21] In one observational study, carried out at the same time, on 5,449 hospitalized patients in New York City, the incidence of AKI was 36.6% with 14.3% of patients requiring dialysis (30%).[22]

Our study showed a higher incidence of abnormal renal function tests than these studies. Firstly, this could be because our study was done at a public hospital in Pakistan. Pakistan is a country that struggles with low literacy and health awareness and patients usually present later in the course of the disease.[23] Secondly, our study included only cases with severe COVID-19 pneumonia and not mild cases. Thirdly, our study was done later in the course of the epidemic, when more aggressive strains of COVID-19 had emerged.[24]

Our study revealed that patients with low eGFR at the time of presentation had higher mortality and need for mechanical ventilation than those with normal eGFR. However, there were no significant differences in duration of hospital stay. Several studies have shown that low eGFR at the time of presentation is associated with a greater number of complications and in-hospital mortality in COVID-19 patients.[25] Our study showed that the mean eGFR in survivors was significantly lower than

non survivors. However there was a significant overlap in the distribution of GFR between survivors and non survivors, making the value of eGFR a less useful prognostic indicator.

The main limitations of our study were the wide clinical heterogeneity at presentation. Due to social taboos and lack of awareness, patients seek help at local inexperienced centers and present late in the course of the disease at tertiary care government hospitals in Pakistan. Additionally, IL-6 inhibitors were not easily available at the hospital. Poor infection control practices were practiced at the hospital because of a lack of logistics and staff awareness. There was a lack of experienced anesthetists at the center. All of these could have had an impact on the clinical course and outcome of patients. Additionally, baseline creatinine of the patients was not available, because of which we could not make an accurate estimation of acute kidney injury in our patients. Our study was an observational study and provided only information on the association of low eGFR with severe COVID-19 pneumonia. A causal relationship could not be established.

In summary, we concluded that abnormal renal function tests at presentation are very common in patients with severe COVID-19 pneumonia, and are associated with a higher in-hospital mortality rate and need for mechanical ventilation. However, larger multi-centered trials are needed to further validate the results of our study.

Abnormal renal function tests at presentation are common in patients with severe COVID-19 pneumonia and are associated with a higher in-hospital mortality rate and need for mechanical ventilation. However the value of eGFR at admission is less useful as a prognostic indicator in COVID-19 patients.

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Conflict of interest: None declared.

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