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ACUTE KIDNEY INJURY IN PATIENTS WITH CORONAVIRUS DISEASE 2019 (COVID 19): PERSPECTIVES FROM PAKISTAN

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ABSTRACT

Kidney involvement in patients with Coronavirus Disease 2019 (COVID-19) can have variable presentations and clinical courses. Consequently, COVID 19 related Acute Kidney Injury (AKI) can increase the morbidity and mortality of these patients who are at increased risk of death consequent to non-renal organ involvement. **Objectives:** The present study aims to describe the clinical and epidemiological profile of patients with COVID-19 who have AKI during the course of their illness. **Study Design:** This was a retrospective review of data collected at four hospitals in Lahore, Pakistan from May 1, 2020, to June 30, 2020. A total of 445 patients were reviewed and analyzed. Patients designated as having AKI at admission, those who received Renal Replacement Therapy (RRT), and those patients with a history of chronic kidney disease (CKD) with superimposed AKI were included in the retrospective review.

Results: Out of 445 patients, 57 (12.8%) patients developed AKI. The presence of AKI correlated significantly with history of diabetes, CKD, septic shock and need for invasive positive pressure ventilation. RRT showed a moderate correlation with death. D-dimers levels at presentation, presence of diabetes and septic shock also predicted death.

Conclusion: The incidence of AKI in COVID-19 patients reported from Pakistan aligns with global figures, with the need for renal replacement therapy serving as a prognostic marker for mortality in AKI cases.

Keywords: Coronavirus Disease 2019, COVID 19, Acute Kidney Injury, AKI, Renal replacement therapy.

INTRODUCTION

The Coronavirus Disease 2019 has been the pandemic of a lifetime. Since the first cased reported from Wuhan, China in December 2019, World Health Organization puts the total number of confirmed cases at more than 776 million. The death toll is also huge (> 7 million) [2]. Being true to the nature of any viral pandemic, the disease has shown myriad presentations and is now considered to be a multi-system disorder. Usual clinical manifestations include fatigue, aches, fever, dyspnea,

cough, loss of sense of smell and taste, normal or low leucocyte count, and radiological evidence of pneumonia. The progression of the disease varies, from symptom-free infection to widespread organ failure and fatality.

The outcomes of COVID-19 pneumonia have been shown to be dependent upon organ dysfunction, especially lung, and the kidney. The risk factors of progression of severe disease are generally the same as those described for a lot of other infectious diseases, namely diabetes, hypertension and cardiovascular disease.

Pakistan has borne the brunt of this pandemic as well as any other country in the region. Till date there have been around 1.58 million confirmed cases along with around 30000 deaths [3]. The two years of pandemic were characterized by lockdowns, media campaigns, economic restructuring and healthcare infrastructure upgradation.

In spite of several studies from Pakistan already published in local and international journals regarding the epidemiology and treatment of COVID-19, there is paucity of data from renal perspective. We undertook the present retrospective analysis of the data to elucidate the patterns of acute kidney injury and its effect on outcomes in patients with COVID-19.

Objectives:

1. To explore the incidence of Acute Kidney Injury and the implementation of Renal Replacement Therapy among patients with SARS-CoV-2 Pneumonia.
2. To study the impact of Acute Kidney Injury on the mortality of patients with SARS-CoV-2 Pneumonia.

MATERIALS AND METHODS

This was a retrospective review and re-analysis of cross-sectional data (IRB#: FMH-20/02/2023-IRB-1183) collected (later on published) [1] four leading public and trust run hospitals of Lahore, the second largest city of Pakistan. That study did not deep-dive into the question of AKI in COVID 19 as intended by us. We were well aware of the differing patient demographics presenting to the private and public hospitals, however we surmised that because of burden of disease the demographics would not differ much between the private and public hospitals, hence it seemed unlikely that there would be a selection bias in our approach. The original dataset was collected from May 1, 2020 to June 30, 2020 during the first wave of COVID-19. This dataset was reviewed and analyzed for patients with AKI by all six authors. We based our case definitions of AKI, on the basis of following four points keeping in mind the criteria for diagnosis of AKI as given by KDIGO:

1. The patients were not categorized as having chronic kidney disease at admission. This was checked from patients' history. Also, previous medical records were checked for confirmation where available. The diagnosis of CKD was based on the KDIGO criteria.
2. For patients with no previous history of CKD, if they had serum creatinine level of $\geq$ 0.3 mg/dL above the upper limit of normal for the reporting lab on admission, were designated as AKI and were included in analysis. We understand that different labs report ranges slightly differently however the difference is quite small and as is the usual clinical practice, was not felt to be of much consequence.
3. Those who received Renal Replacement Therapy during the course of their illness, provided they were not on renal replacement therapy previously.
4. Patients were also included if they were marked as having Acute Kidney Injury superimposed on chronic kidney disease. The diagnosis of CKD was extracted from patients' history / records (as given in point 1, above) and AKI was designated according to KDIGO criteria of an increase in S/Creatinine of $\geq$ 0.3 mg/dL within 48 hours of presentation above their previous stable serum creatinine values.

The statistical analysis was carried out on IBM SPSS v.26. We calculated means $\pm$ SD for quantitative variables and frequencies (%age) for qualitative variables. Logistic regression analysis was carried out to elucidate the effect of variables on the outcomes. Kaplan Meier survival analysis, keeping in

view the outcomes of patients with AKI, was also carried out. The outcomes of interest were death and the requirement of renal replacement therapy. For inferential statistics a p value of < 0.05 was considered significant wherever applicable.

RESULTS

We carried out a post hoc power analysis for the significant findings in our analysis. The overall sample size (N = 445) provided sufficient power for detecting moderate-to-large effects, hence significant findings were expected to be robust and clinically meaningful. However, we were well aware that small subgroup size (n = 57 for AKI patients) may limit power for detecting weaker effects or interactions.

Out of 445 patients, 57 (12.8%) patients developed AKI. All patients were positive for COVID by PCR analysis. The demographics for the sub-cohort of AKI is given in table 1a and 1b.

Table 1a: Demographics and clinical characteristics of the AKI subset.

Demographics	N/%	Clinical characteristics	N/%
Cohort (N)	445	ICU admission	15 (26.3)
Cohort AKI	57	Need for IPPV	11 (9.3)
Gender	**M:** 35(61.4), **F:** 22(38.6)	Need for RRT	21 (36.8)
Diabetes	23 (40.4)	Septic Shock	11 (19.3)
Hypertension	20 (35.1)	Obesity	5 (8.8)
Coronary Artery Disease	9 (15.8)	Smokers	7 (12.3)
Chronic Kidney Disease	3 (5.3)	ICU admission	15 (26.3)

AKI: Acute kidney injury; ICU: Intensive Care Unit; IPPV: Invasive positive pressure ventilation; RRT: Renal replacement therapy.

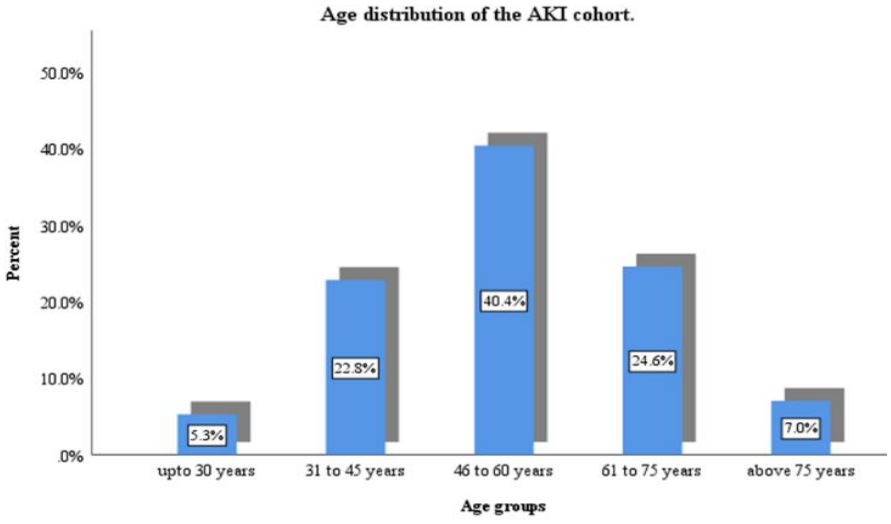
Table 1b: Demographics and clinical characteristics of the AKI subset.

Clinical parameter	Mean $\pm$ SD	Clinical parameter	Mean $\pm$ SD
O_2 requirement at presentation (L)	9.38 $\pm$ 4.71	CRP	135 $\pm$ 201.8
O_2 saturations at presentation (%)	88.14 $\pm$ 6.62	D Dimers (ng/mL)	574.22 $\pm$ 514.03
LDH (IU/L)	502.9 $\pm$ 980.4	Serum creatinine (mg/dL)	2.22 $\pm$ 1.56
		Hospital stay (days)	8.24 $\pm$ 3.60

CRP: C Reactive Protein, LDH: Lactate Dehydrogenase.

Age distribution is given in Fig 1. No effect of age or gender was noted, however, the presence of AKI correlated

Fig.1: Age distribution of AKI Cohort.



Significantly with presence of diabetes (r: 0.208, p=0.000, N=445), the presence of CKD (r: 0.147, p=0.002, N=445), need for invasive positive pressure ventilation (r: 0.128, p=0.007, N=442) and presence of septic shock (r: 0.101, p=0.033, N=445).
Out of all the lab parameters of interest, only presentation D dimers showed an acceptable prediction potential for death with area under the receiver operating characteristic curve (AUROC curve) of 0.645 (Fig. 2, 3). A cut off of 281 ng/ml.

Fig 2: The predictive potential of presentation D-Dimers on the outcomes.

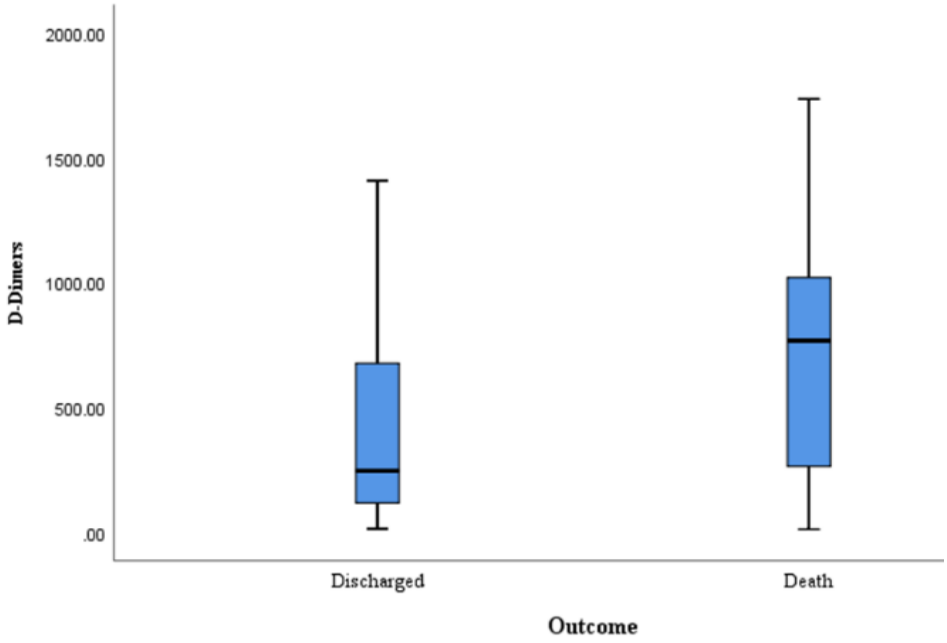
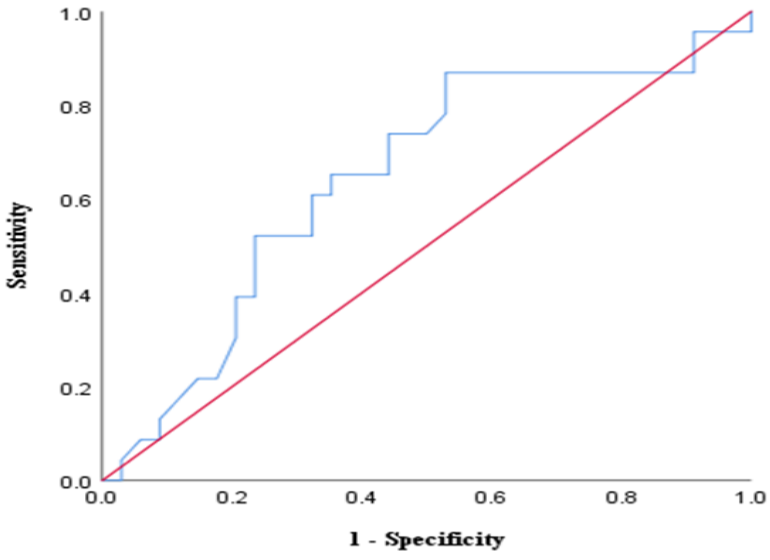


Fig. 3: ROC Curves for D-Dimers (AUROC: 0.645)



Yielded sensitivity, specificity, PPV and NPV of 73.9%, 44.1%, 73.9% and 50% for prediction of death. Variables contributing to the death of patients in our cohort were also analyzed by the help of logistic regression analysis. The variables that we evaluated through regression included presence of diabetes, septic shock, need for positive pressure ventilation, need for renal replacement therapy and presentation D-Dimers. The full model containing all predictors was statistically significant, $\chi 2$: 18.373 (df 2, n:57, p=0.0001) indicating that the model was able to distinguish between subjects who died or were discharged. 87 % of all deaths were correctly predicted by this model. Based on odds

ratio or effect sizes, diabetic patients (OR: 9.5, dF:1, CI: 2.26 – 40.24, p<0.02) and patients in septic shock (OR: 9.2, dF:1, CI: 0.98 – 86.1, p=0.05) were much more likely to die than those patients who were non diabetic or did not have septic shock. Although AKI directly did not influence the incidence of death, renal replacement therapy was found to have a significant correlation with death (r=0.632, p<0.001, N=57). 17 of 21 patients requiring RRT expired in contrast to six of 36 patients not requiring RRT. Patients requiring renal replacement therapy had a lower mean survival as well, as depicted by the Kaplan-Meier survival plot (Table 2, Fig. 4).

Table 2: Effect of Renal Replacement Therapy on Survival.

Renal Replacement Therapy	Estimate mean survival ± SD (days)	95% CI	
		Upper	Lower
No	13.9 ± 0.755	12.414	15.374
Yes	8.2 ± 0.691	6.887	9.596

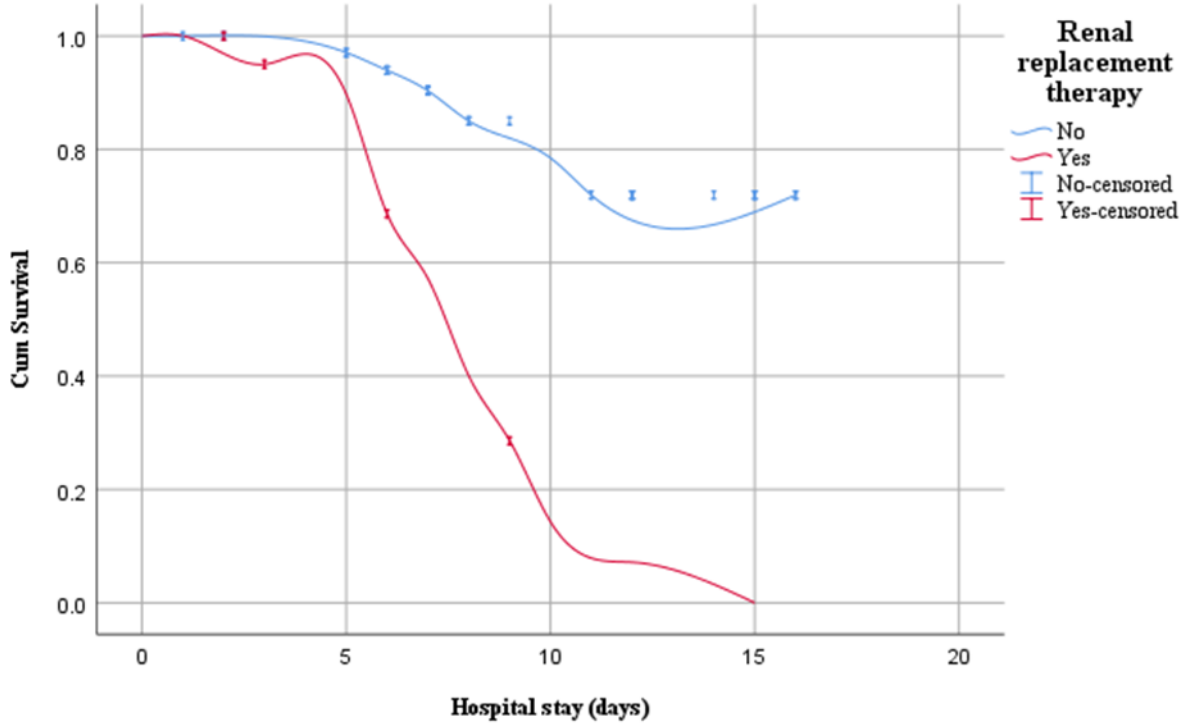


Fig. 4: Kaplan-Meier Survival Plot for patients with AKI requiring Renal Replacement Therapy.

DISCUSSION

The pandemic of COVID-19 infection brought to attention the kidney involvement. The causes of AKI in patients with CKD having COVID-19 can be myriad. Moderate to severe infections accompanied by fever, shock, and dehydration can cause pre-renal azotemia. Treatment commonly entails the use of non-steroidal anti-inflammatory drugs, antibiotics, and other nephrotoxic drugs that may lead to AKI. Moreover, advanced age, diabetes, and hypertension have been suggested as risk factors for developing AKI.

SARS-CoV-2 is considered a direct cytopathic agent, likely utilizing the ACE2 membrane protein to infiltrate host cells[4]. This suggests that proximal tubular cells, which naturally express high levels of ACE2, may serve as pathways for viral entry. Kidney histological findings may include edema, loss and fragmentation of renal tubular epithelial cells, tubular casts, and inclusion bodies [5,6], leading to acute tubular injury, with rare cases of collapsing focal segmental glomerulopathy [7,8]. Additionally, a Cytokine Storm, driven by inflammatory mediators such as IL-6, IL-1β, and TNF-α, may contribute to ischemia and subsequent kidney injury [9 - 11] in COVID-19 patients.

Our study reveals some important aspects. The incidence of AKI occurring in our cohort is comparable to the internationally reported incident rates. Variable AKI rates have been reported from across the world ranging from 0 to 36.6%. AKI rates of 20 to 40 % have been reported in studies from USA and Europe [16]. More subtle signs of renal involvement i.e. proteinuria is seen even more frequently (up to 40%) [13], however urinalysis was not a part of our data collection.

Diabetes and hypertension were the most frequent comorbidities. In our patients, diabetes was found to correlate weakly but significantly with AKI. It was also found to have an OR of 1.9 to predict the development of AKI. In various studies, diabetes has been found to be predictive of poor outcomes in patients with COVID-19 including the development of AKI [17]. The referenced study also gives a higher OR for arterial hypertension which is corroborated by other authors as well, however, our study did not find an association between arterial hypertension and the risk of AKI in patients with COVID-19.

Chronic Kidney Disease (CKD) predisposes patients to AKI [18], though in our cohort, only three AKI cases involved patients with existing CKD. Despite a weak correlation between CKD and AKI, we couldn't conclusively evaluate CKD's impact on mortality. Patients with stable CKD are at risk, as any acute incident can precipitate AKI. Infection, fluid disturbances, and nephrotoxic medications—particularly when not adjusted for creatinine clearance—could all play a role in triggering AKI in patients with CKD.

Both the need for Invasive Positive Pressure Ventilation (IPPV) and septic shock had higher ORs for the development of AKI. This apparent troika of septic shock, need for respiratory support and acute kidney injury may be reflective of severe COVID-19. All three processes are patho-physiologically related as well. Septic shock can cause multi-organ dysfunction including development of ARDS (now being referred to as CADRS: COVID ARDS [19]) and AKI because of hemodynamic disturbances, acute tubular or acute interstitial disease.

In terms of patient outcomes our study revealed that presentation D-dimers was able to predict death with relative certainty. COVID 19 is characterized by abnormal responses of the coagulation cascade thus leading to a prothrombotic state. D-dimers are frequently raised in the settings of deep venous thrombosis/pulmonary thromboembolism, arterial thrombosis, disseminated intravascular coagulation and other conditions. Due to cost considerations in a resource limited country, extensive work up to exclude all of these conditions was not possible. In spite of these limitations, and as suggested by numerous other studies where D-dimers were found to be a reliable predictor of poor outcomes [20 - 22], our study concurs that presentation D-dimers can be utilized as a moderately accurate marker of death in patients with COVID 19 and AKI.

Diabetes and septic shock both came out as having high ORs for death in our cohort. Diabetes is recognized as a risk factor for severe illness and death from COVID-19[23 - 25]. However, one needs to be cautious in the interpretation of these findings in diabetic patients since hyperglycemia due to stress and glucocorticoids may actually be the risk factor for severe illness or death in patients with COVID -19 [26]. Septic Shock in the settings of ICU has been reported to have high ORs for death in numerous studies [27,28]. The incidence of shock in adult COVID-19 patients ranges from 1% to 35%, potentially reflecting variations in study populations and shock definitions. It is notably more common among hospitalized patients [29]. Our study supports global data, confirming septic shock as a risk factor for death

In our cohort, 21 (36.8%) patients required dialysis, however, dialysis requirement was found to correlate weakly but significantly with reduced survival of patients. This finding does not seem surprising since patients requiring renal replacement therapy indicate a subset of critical patients with multiple acute issues compounding each other (septic shock, need for IPPV, possible nephrotoxic medications, etc.). The role of dialysis in COVID-19 associated AKI, especially with regard to its effect on mortality needs to be studied further in prospective studies.

We recognize certain limitations in our retrospective data analysis. The creatinine value at admission may not represent a true baseline, as previous levels may have been unavailable. This was a cross-sectional data collection within the first 48 hours of admission, hence long-term follow-up of

survivors after they returned to community was not documented since it was not the objective of the study. Nonetheless, we believe our study offers important insights from Pakistan.

CONCLUSION

The incidence of AKI in patients with COVID 19 in our community is comparable to the already published data. Diabetes and Septic Shock are risk factors for death in our patients.

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