Outcome of Acute Kidney Injury in COVID-19 Patients – A Prospective Cohort at a Single Centre in Pakistan

F. Saeed, A. Alam, S. Memon, J. Chughtai, S. Ahmed, S. Tariq, B. Salman, and S. Imtiaz

ABSTRACT

**Introduction:** There is continuous experience that AKI is very common in COVID-19 patients and that SARS-CoV-2 specifically invades the kidneys with poor outcome. In-hospital AKI is associated with multiple risk factors including DM, CCF, drugs etc. Also, there is difference in the mortality rate all over the world for various reasons. To date no data has been found from Pakistan on outcome of AKI with COVID-19 infection. Therefore, this study was conducted to help determine the outcome and associated risk factors in this part of the world.

**Material and Method:** This is a prospective cohort of COVID-19 adult patients with AKI admitted in Indus Hospital COVID ICU from March 2020 to September 2020. History, clinical examination, laboratory investigations, and ultrasound imaging of the kidneys was acquired from the Health Management Information System (HMIS) record of the patients. The data was analyzed in SPSS version 21. Association between outcomes of AKI with different variables was assessed by applying Chi square test. P value of less than 0.05 was considered significant.

**Results:** There were total 208 patients with AKI in our study, in which 146 (70.2%) were male while 62 (29.8%) were female. The mean age was 60.3±12.7 years and the most prevalent comorbid was HTN 147 (70.7%) in our patients, while the most common cause of AKI was sepsis 188 (90.4%) and on the same way, oliguria was the most common symptoms of AKI 76 (36.5%). Death was the most frequent outcome of our patients 147 (70.7%) as compared to recovery 47 (22.6%). There was male predominance in patients, who died with AKI as compared to female 112 (76.2%) and 35 (23.8%) respectively. Also, treatment didn’t show any benefit on worst outcome. Similarly, 124 (59.6%) patients needed ventilatory support in which 118 (95.2%) died while only 5 (4%) recovered (p ≤ 0.001)

**Conclusion:** Renal involvement in SARS-COV-2 infection is more common than initially thought and has been associated with increased morbidity and mortality. We have found significant association of AKI in covid-19 with outcome variables.

**Keywords:** COVID-19, Acute kidney Injury, Sepsis.

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I. INTRODUCTION

Critically ill patients frequently come across with acute kidney injury (AKI), especially those with serious infections, and has been associated with substantial morbidity and mortality [1]. A certain portion of COVID-19 patients required admission in high dependency and intensive care area due to respiratory compromise or other issues. The AKI is well-known to occur in patients being admitted in such special care areas, as around 19%, in the earlier days of epidemic [2]. Although, at the time of emergence of disease few of the studies reported a very low incidence of AKI [3]. However, there is continuous experience that AKI is very common in COVID-19 patients and that SARS-CoV-2 specifically invades the kidneys with poor outcome. In different studies, estimated incidence of AKI and the need for renal replacement therapy (RRT) among hospitalized COVID-19 patients varies and reportedly ranging from 0.5% to as high as 40% [4], [7]. Two of the largest studies epitomized this wide variation, for example from China Guan et al reported an AKI incidence of only 0.5% in an analysis of 1099 hospitalized patients, while a recent analysis from New York reported an AKI incidence of 26.9% among 5700 hospitalized COVID-19 patients [4], [7]. There is gross variation,
variation in the incidence of COVID-19 infection globally, it is highest in American region (now more than 20 million confirmed cases) while it is lowest in Western Pacific region (around 800000 confirmed cases) [8].

Risk stratification is essential to modify monitoring and initiate prevention and/or early treatment strategies for patients who will benefit the most from intervention. Data from China and the USA propose that male sex, older age, Black race, diabetes mellitus, chronic kidney disease (CKD), hypertension, cardiovascular disease (CVD), congestive heart failure (CHF), higher body mass index, use of angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatories, acute respiratory distress syndrome, and admission elevated ferritin, creatinine kinase, brain natriuretic peptide, and troponin I were identified as the risk factors for in-hospital AKI [9]-[12]. Also, those with AKI are more likely to need vasopressors as well as mechanical ventilation [11], [12].

There is difference in the mortality rate all over the world for various reasons which we will discuss later. A retrospective cohort study from a tertiary teaching hospital in Wuhan, China, strikingly showed that 72% of patients with COVID-19 with AKI died during hospitalization, and AKI was an independent risk factor of in hospital mortality [13].

In a Systematic review and Meta-analysis, 30 studies including 21,591 patients from hospitals in Asia, Europe and US were analyzed among which 20 Cohorts had, Kidney related information. Prevalence of AKI was found to be 17%. The median age was 56 years (range, 43-72 years) with 55% male patients. Among these 77% patient either required ICU admission or were reported to have severe infection, and mortality rate was reported to be 52% [14].

To date no data has been found from Pakistan on outcome of AKI with Covid-19 infection. Therefore, this study was conducted to help determine the outcome and its associated risk factors in our part of the world.

II. MATERIAL AND METHOD

This is a prospective cohort of COVID-19 patients with AKI admitted in Indus Hospital COVID ICU from March 2020 to September 2020. We included all patients of more than 16 years of age and the diagnosis was made by RT-PCR by nasopharyngeal swab. Patients with a history of maintenance dialysis, chronic kidney disease, or renal transplantation were excluded. Permission from the institutional ethical review committee was taken prior to conduction of study. History, clinical examination, laboratory investigations, and ultrasound imaging of the kidneys was acquired from the Health Management Information System (HMIS) record of the patients. Data was collected on a structured proforma which included variables like age, gender, residence, socioeconomic status, profession, comorbid conditions, drug history, clinical presentation, hemodynamic status and lab parameters and cause of AKI on admission. Outcome variables were recovery from AKI, developing chronic kidney disease and death. All the patients who got discharged with deranged creatinine were followed as a routine in the clinic for three months from the time of admission to label them as CKD. Therefore, serum creatinine for these patients were rechecked at discharge, then at 2nd and 3rd months at nephrology clinic of Indus hospital. All the patients received standard treatment of COVID according to hospital protocol along with hemodialysis and CRRT when needed.

III. STATISTICAL ANALYSIS

The data was entered and analyzed in SPSS version 21. Cleaning and coding of data was done prior to analysis. Mean ± STD and median with IQR were computed for continuous data while for categorical variables frequency with percentages were measured. We made categories of some continuous variables like age and laboratory parameters for the purpose of analysis. Association between outcomes of AKI with different variables was assessed by applying Chi square test. P value of less than 0.05 was considered significant.

IV. RESULTS

There were total 208 patients with AKI in our study, in which 146 (70.2%) were male while 62 (29.8%) were female. The mean age was 60.3 ± 12.7 years with minimum of 17 year and maximum of 90 years. The most prevalent comorbid was HTN 147(70.7%) in our patients, while the most common cause of AKI was sepsis 188(90.4%) and in the same way, oliguria was the most common symptoms of AKI 76(36.5%) (Table I).

![Table I: Demographic and Clinical Parameters of COVID Patients with AKI](http://dx.doi.org/10.24018/ejclinicmed.2021.2.3.61)

All lab parameters with their mean ± std, median with IQR and minimum and maximum are shown in (Table II).

Death was the most frequent outcome of our patients 147(70.7%) as compared to recovery 47(22.6%). We analyzed the association of outcome with patient’s parameters and found that the majority of patients, who died were in the age group of 51 -65 years 72(49%) as compared to other age groups, but within each age groups the death and recovery
were almost the same, therefore, p value is not significant (p=0.467). Gender was significantly associated with outcome of COVID-19 (p=0.012), there was male predominance in patients, who died with AKI as compared to female 112(76.2%) and 35(23.8%) respectively. Comorbid conditions like DM, HTN and IHD did not have any significant association with outcome of COVID-19, neither the outcome had any association with complication of the disease like thromboembolism. The reason might be a very low number of patients who suffered these events.

The patients who developed AKI in hospital succumbed to death 94(63.9%) as compared to the patients who came with AKI 53 (36.1%). Similarly, hospital acquired AKI had less recovery 18(38.3%) than AKI on arrival 29(61.7%) (p<0.001) (Table III).

To detect any association between severity markers and outcome of disease we categorized our laboratory parameters by their cutoff values. Our majority of patients had higher levels of LDH 197(94.7%), in which 143(72.6%) died, 43 (21.8%) recovered while only 11 (5.6%) developed CKD (P=0.01). Similarly, the patients with higher level of CRP, Ferritin, D-Dimer and Procalcitonin encountered death more than recovery, although the association is statistically insignificant.

In our patient with AKI, treatment did not show any benefit on worst outcome, for example Methylprednisolone was given to 159(76.4%) patients in which 121 (76.1%) died while only 32(20.1%) recovered (p=0.001). Similarly, Remdesivir and Tocilizumab were given to 42(20.2%) and 60(28.8%) patients, respectively in which 38(90.5%) patients died who received Remdesivir (p=0.005) while 54(90%) died who were treated with Tocilizumab (p<0.001). Likewise, the hemodialysis modality also did not contribute to patients’ survival, as we diaryzed 66(31.7%) patients in which 50(75.8%) died, 7(10.6%) recovered while 9(13.6%) patients developed CKD (p=0.001). In the same way 124(59.6%) patients needed ventilatory support in which 118(95.2%) died while only 32(20.1%) recovered (p<0.001) (Table IV).

### Table II: Lab Parameters of COVID Patients

| Variables | Mean± std & Median, IQR | Minimum | Maximum |
|-----------|------------------------|---------|---------|
| Hb (gm/dl) | 1.6 ± 2.7 & 11.3, 6.6 | 3.5     | 18.5    |
| TLC (+10/L) | 17.4 & 15.7, 11.2 | 1.9     | 79      |
| Lymphocyte count (%) | 8.7 & 6.5 | 749     | 18      |
| Platelet (+10^9/L) | 251.8 153.9 238, 747 | 18      | 767     |
| Albumin (g/dl) | 3.0 6 3.1, 0.8 | 1.4     | 4.3     |
| Urea (mg/dl) | 135.7 81.1 108, 15 | 15      | 426     |
| Creatinine (mg/dl) | 4.2 3.7 3.1, 2.9 | 0.3     | 26      |
| Sodium (meq/l) | 139.8 9.9 140.1, 101 | 23      | 701     |
| Potassium (meq/l) | 4.8 1.2 4.6, 1.4 | 2       | 8.9     |
| Chloride (meq/l) | 105.13 86.3 105, 11 | 72      | 125     |
| Bicarb (meq/l) | 17.3 6 17.8 | 5       | 41      |
| Calcium (mg/dl) | 7.8 1.8 1.3 | 4.8     | 14.8    |
| LDH (U/L) | 940.9 994 656, 1454 | 190     | 92289   |
| Ferritin (ng/ml) | 1887.4 2928.1 | 47.2    | 33511   |
| CRP (mg/L) | 165.5 122.3 149.5, 178.8 | 1       | 562     |
| Procalcitonin (ng/ml) | 17.3 49.2 2.2, 12.5 | 0.04    | 612     |

Hb Hemoglobin, TLC Total leucocyte count, LDH Lactate dehydrogenase, CRP C reactive protein.

### Table III: Association of Demographic and Clinical Parameters with Outcome of AKI

| Variables | Outcome of AKI n=208 (Column %) |
|-----------|---------------------------------|
|            | Recovered 47(22.6) | CKD 14(6.7) | Death 147(70.7) | Total | p-value |
| Age        | ≤ 50 years 9(19.1) | 3(55.7) | 3(55.7) | 15(17.2) | 0.46 |
|            | ≥ 65 years 13(27.7) | 4(28.6) | 5(38.5) | 23(21.4) | 0.09 |
| Gender     | Male 27(57.4) | 7(50) | 11(76.2) | 14(68.7) | 0.01 |
|            | Female 20(42.6) | 7(50) | 3(28.6) | 26(12.5) | 0.05 |
| Type of AKI| Hospital acquired 18(38.3) | 3(21.4) | 9(46.9) | 11(55.3) | <0.001 |
|            | AKI at arrival 29(61.7) | 11(78.6) | 5(36.1) | 39(18.8) | <0.001 |
| Comorbid conditions |          |            |            |          | |
| DM         | Yes 26(55.3) | 7(50) | 78(53.1) | 111(53.4) | 0.932 |
|            | No 21(44.7) | 8(50) | 69(46.9) | 97(46.6) | 0.995 |
| HTN        | Yes 33(70.2) | 10(71.4) | 104(70.7) | 147(70.7) | 0.995 |
|            | No 14(29.8) | 4(28.6) | 43(29.3) | 61(29.3) | 0.869 |
| IHD        | Yes 12(25.5) | 4(28.6) | 34(23.1) | 50(24) | 0.869 |
|            | No 35(74.5) | 10(71.4) | 113(76.9) | 158(76) | 0.869 |
| Complications of covid 19 |          |            |            |          | |
| ACS        | Yes 1(2.1) | 2(14.3) | 8(54) | 11(53) | 0.2 |
|            | No 46(97.9) | 12(85.7) | 139(94.6) | 197(94.7) | 0.054 |
| CCF        | Yes 4(8.5) | 4(28.6) | 117(51) | 19(9) | 0.999 |
|            | No 46(97.9) | 12(85.7) | 139(94.6) | 189(90.9) | 0.999 |
| PVD        | Yes 2(4.3) | 0(0) | 6(41) | 8(38) | 0.869 |
|            | No 45(95.7) | 14(100) | 141(95.9) | 200(96.2) | 0.869 |
| CVA        | Yes 2(4.3) | 17(71) | 13(88) | 16(77) | 0.672 |
|            | No 45(95.7) | 13(92.9) | 134(91.2) | 192(92.3) | 0.672 |

AKI Acute kidney injury, DM Diabetes mellitus, HTN Hypertension, IHD Ischemic heart disease, ACS Acute coronary syndrome, CCF Congestive cardiac failure, PVD peripheral vascular disease, CVA cerebrovascular event.

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TABLE IV: ASSOCIATION OF SEVERITY MARKER OF DISEASE AND MANAGEMENT WITH OUTCOME OF COVID-19 PATIENTS WITH AKI

| Variables | Disease Severity marker | CKD 14(6.7) | Death 147(70.7) | Total | p-value |
|-----------|-------------------------|-------------|----------------|-------|---------|
|          | Recovered 47(22.6)      |             |                |       |         |
|          | 42(21.8)                | 3(16.7)     | 138(71.5)      | 193(92.8) | 0.522  |
| Lactate dehydrogenase | ≤ 240 U/L              | 4(36.4)     | 3(27.3)        | 11(53) | 0.01   |
|          | > 240 U/L               | 43(21.8)    | 11(53.6)       | 143(72.6) | 0.974  |
|          | < 500                   | 2(20)       | 2(20)          | 6(60)  | 0.048  |
| Ferritin | ≤ 500                   | 45(22.7)    | 12(61.6)       | 141(71.2) | 0.985  |
|          | 0.01 - 0.49             | 14(28)      | 9(45)          | 52(84) | 0.049  |
| Procalcitonin | > 0.49                | 33(20.9)     | 106(53.8)      | 157(84) | 0.028  |
|          | ≤ 10                    | 43(22.1)    | 13(67.6)       | 139(73.1) | 0.528  |
| C reactive protein | ≤ 0.5                   | 5(33.3)     | 16(75)         | 21(72) | 0.051  |
| D Dimer  | >0.5                    | 42(21.8)    | 13(67.6)       | 138(71.5) | 0.985  |
|          | Management              |             |                |       |         |
| Remdesivir | Yes                     | 4(95)       | 0(0)           | 38(95.5) | 0.005  |
|          | No                      | 15(30.6)    | 8(16.3)        | 26(53.1) | 0.004  |
| Methylprednisolone | Yes                    | 32(20.1)     | 6(38)          | 121(76.1) | 0.001  |
|          | No                      | 15(30.6)    | 8(16.3)        | 26(53.1) | 0.003  |
| Tocilizumab | Yes                     | 6(10)       | 0(0)           | 54(90)  | 0.004  |
|          | No                      | 41(27.7)    | 14(9.5)        | 55(65)  | 0.001  |
| HCQ      | Yes                     | 5(14.7)     | 2(5.9)         | 7(14.3) | 0.004  |
|          | No                      | 42(24.1)    | 12(6.9)        | 54(25)  | 0.001  |
| Ventilatory support | Yes                    | 5(9)        | 11(20)         | 115(69) | 0.001  |
|          | No                      | 40(28.2)    | 8(16.3)        | 48(24)  | 0.001  |

LDH Lactate dehydrogenase, PCT Procalcitonin CRP C reactive protein, MPS Methylprednisolone, HCQ Hydroxychloroquine, Ven.S Ventilatory support, HD Hemodialysis.

V. DISCUSSION

To our knowledge this the first publication from Pakistan on AKI and COVID-19. Pakistan was predicted to become one of the vulnerable countries for the spread of coronavirus disease due to poverty, poor health literacy, imbalance and weak healthcare infrastructure, religious travelling and prayer assembly five time a day [15]. But this prediction took a nosedive when lockdown plummeted to very low level. There were many assumptions and supposition like relatively younger population of Pakistan like only 4% of the population is over 65 compared with USA and Italy 16% and 23% respectively. The average age in Pakistan is 22, more than a decade younger than Brazil, and 25 years younger than Italy according to United Nations data [16]. There is hypothesis for theses improved outcome, like differences in social behavior, genetic evolution, hygiene behavior and BCG vaccination [17].

We found that the demography of our patients regarding age is different as reported in other part of the world. Majority of patients in our cohort who suffered and died from COVID-19 were from middle age group (51 years to 65 years) as compared to older age population of more than 65 years [18]. The reason of this discrepancy might be due to relatively low population of elderly people (majority reached to that age when they do not have the comorbid) in our country. Gender distribution of the disease is similar to other part of the world, but surprisingly, it is different from the neighboring countries of similar population in respect of demography and socioeconomic status. The male predominance in fatality was not observed in India, Nepal, Vietnam, and Slovenia where fatality rate is higher in female [19].

There has been large variations observed in the prevalence of comorbidities in patients with COVID-19 and AKI for example, we found out that hypertension was present in 70.7% of our population which is higher as compared to other studies [20], [21] on the other hand diabetes was present in 53.4% of our patients which is somewhat consistent with studies from the US as 41% to 47% but not from China which reported 14% diabetics [21]. But we did not identify hypertension and diabetes as risk factor for mortality in COVID-19 patients with AKI, in contrast to a study from the US [22]. On the contrary, the cardiac and thromboembolic complications like CCF, ACS, PVD and CVA were sparse and did not show any association with the three outcomes of the disease in contrast to the study by Kolhe and Fluck [23].

Majority of our patients developed AKI after hospitalization. The development of AKI in hospital and in community has an impact on the outcome as shown in meta-analysis that community acquired AKI has better prognosis with lesser stay in the ICU [24]. Similarly, patients who developed AKI in hospital after COVID-19 showed grave prognosis [10]. We also found the same trend of mortality in our patients as death was highly associated with hospital acquired AKI.

We found the inflammatory markers, which determine the severity of COVID infection were very high in all of our patients. The reason might be due to presence of AKI in all of our patients, which itself a bad prognostic marker and determinant of the severity of underlying infection. Lactate dehydrogenase (LDH) is a reliable predictor associated with COVID19 severity and mortality in patients with different medical conditions [25]. Although all markers were high, but we found LDH is significantly associated with the death of COVID patients.

Effect of treatment on COVID patients with severe disease is frustrating. Methylprednisolone was given to 159(76.4%) patients in which 121 (76.1%) died while only 32(20.1%) recovered. Similar observation was made by other, in a retrospective analysis of COVID patients with severe disease Zu and Li also concluded that it does not improve prognosis in this population [26]. Similar observation was made with Inj Remdesivir there was significantly high mortality (38/42) in those who received Remdesivir in patients with AKI.
Remdesivir was found superior to placebo in low-risk patients in large placebo trial [27]. But in another randomized, double-blind, placebo-controlled, multicenter trial at ten hospitals in Hubei, China. Remdesivir use was not associated with a difference in time to clinical improvement, rather adverse events were reported in 102 (66%) of 155 Remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early [28]. Similarly, Tocilizumab was given to 60 patients out of which 54 died in this group of patients in our cohort of COVID with AKI. Although not in patients with AKI this disenched result was observed by others, for example in a randomized, double-blind, placebo-controlled trial involving patients with confirmed severe COVID-19 infection, tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients. While patients who received tocilizumab had fewer serious infections than patients who received placebo [29]. Although it showed some improvement in retrospective trials [30]. Patients who required renal replacement therapy in the form of hemodialysis or hemofiltration also showed worst outcome in our population as observed by other [10].

There have been certain limitations in our study as relatively low number of patients can transfuridge a lack of statistical power. In addition, the monocenter design may have limited external validity of our findings. We could not have the urinalysis as a baseline to find out if COVID-19 affects kidneys earlier than the biochemical changes. Further studies, assessing levels of proteinuria and hematuria, pathologial findings and translational research are needed to further explore different mechanisms that may participate to AKI during severe SARS-CoV-2 infection.

VI. CONCLUSION
Renal involvement in SARS-COV-2 infection is more common than initially thought and has been associated with increased morbidity and mortality. We have found significant association of AKI in COVID-19 with outcome variables as 70.7% patients died, while among those who survived 22.6% experience recovery of AKI before discharge. Treatment including medications, hemodialysis and ventilatory support do not change the outcome. Further studies are needed on kidney involvement in COVID-19 so that effective strategies for prevention and early management of AKI can be established.

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