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ACUTE KIDNEY INJURY IN HOSPITALIZED COVID-19 PATIENTS: ETIOLOGY, RISK FACTORS AND OUTCOME

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ABSTRACT

Acute Kidney Injury (AKI) is now recognized as a common complication of COVID-19. As with AKI from other causes, COVID-19-associated AKI (COVID-19 AKI) is associated with adverse outcomes, including the development or worsening of comorbid disease as well as greater use of health-care resources. The aim of the present study is to assess the risk factors and outcome of hospitalized Covid 19 patients who developed AKI, thus reduce the morbidity and mortality of these patients. This is a Cross Sectional Descriptive type of Observational study on patients of AKI admitted to Covid Unit (CU) of AKMMCH. Duration of the study was 6 months. Inclusion criteria- Adult population 18-95 years, both male and female, patients of ICU (Intensive Care Unit), suffering from AKI who fulfills the RIFLE criteria, patients with sign symptoms of COVID-19, both RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) for COVID-19 positive and negative cases with raised inflammatory markers and HRCT (High Resolution Computed Tomography) chest shows peripheral ground glass shadows suggestive of COVID. Age below 18 years, patients with Chronic Kidney Disease (CKD) on maintenance hemodialysis (MHD), or on peritoneal dialysis (PD) or with renal transplant were excluded from the study. A total number of 212 patients were included in the study. Among them 113 (53.3%) were male and 99 (46.7%) were female, M:F was 1.14:1. Mean age (Mean ±SD) of the patients was 63.06±13.14 (Age Range 18-95 years). Most of the patients, 33.78% (68) from age group 61-70 years. Next to which were age group 51-60 years, 54 (25.47%) and 71-80 years, 47 (22.27%). Most of the patients were suffering from Hypertension (HTN) 79.25% (168). Next to which was Diabetes mellitus (DM) 59.43% (126). 56.13% (119) patients were of both HTN and DM. 161 (75.94%) patients were of RT PCR for Covid-19 positive and 24.06% (51) were negative whereas all of the patients were symptomatic with HRCT chest showed Covid pneumonia. HRCT chest showed 32.55% (69) patients had 26-50% lung involvement and 63(29.72%) were of 51-75%. Mean values of important biochemical markers were Serum Creatinine 3.56±2.75 mg/dl, Blood Urea 108.81±72.89 mg/dl, HbA1C (Glycated hemoglobin) 7.9±2.32%, C Reactive Protein (CRP) 80.67±86.20 mg/L, D-Dimer 1.77±2.21mg/L, LDH (Lactate dehydrogenase) 397.73±227.59 U/L, IL-6(Interleukin-6) 211.48±950.78 pg/ml and Serum Ferritin 1092.14±1622.98 ng/ml. 74.06% (157) patients were admitted to cabin and 3.77% (8) and 22.17% (47) admitted to HDU and ICU respectively. Mortality rate was 27.03% in cabin, 13.51% in HDU and 59.46% in ICU. The distribution of patients according to the Stages of AKI, 37.26% (79) patients were of Stage 1, 31.13% (66) Stage 2 and 31.60% (67) patients were of Stage 3 AKI. 7.08% (15) of Stage 3 AKI (22.79% of all patients) needed Hemodialysis (Sustained low efficacy dialysis-SLED). All of the patients received Antiviral and Anticoagulant drugs. 87.26% (185) patients were treated with Monoclonal antibodies and 15 (7.08%) patients needed Hemodialysis. 174 (82.08%) patients recovered and 37 (17.45%) patients died and 1 patient took DORB and shifted to other hospital. We came to know that, most of the patients who developed AKI after COVID-19, were of older age group, mostly males with co morbidities (Hypertension and DM) with lung involvement 50%. So older age, male patients, co morbidities were the risk factors of developing AKI in COVID-19. All of them had high inflammatory markers. One fourth of the patients of Stage 3 AKI needed hemodialysis and mortality rate was high in ICU. These data provide robust evidence to support the patients with COVID-19 who should be closely monitored for the development of AKI and measures taken to prevent this, though further studies are required to determine the most effective clinical approach.

KEYWORDS: Acute Kidney Injury, COVID-19, Intensive care unit, Inflammatory Markers.

INTRODUCTION

An unexplained acute respiratory disease was detected in Wuhan, Hubei Province, China in December of 2019. On 12 February 2020, the International Committee on Taxonomy of Viruses announced that this new coronavirus was officially classified as SARS-CoV-2.

The WHO also announced that the disease caused by SARS-CoV-2 had been officially named COVID-19.[1] As of 19 December 2021, more than 273 million COVID-19 cases and over 5.3 million deaths have been reported globally.[2] Covid 19 cases in Bangladesh are approaching 1,949,725 while death has surpassed 29,112 on February 28, 2022. Total patient recovered during this period is 1,862,808.[3] COVID-19 has become a major infectious disease that seriously endangers human health.

COVID-19 is primarily transmitted through respiratory droplets and direct contact.[4,5] Most patients with COVID-19 have dyspnea as the main clinical manifestation, and some cases may be complicated by heart, kidney, circulatory, liver, nerve and other multisystem injuries.[6-10] These patients may eventually die of diffuse alveolar injury and progressive respiratory failure. The cytokine storm syndrome involved in the pathogenesis of acute respiratory distress syndrome and organ failure during SARS-Co V infection seems to be related to a massive inflammatory reaction. Viral replication in targeted organs, including the kidneys, induces systemic viral sepsis and systemic inflammatory responses, as well as subsequent cell damage in multiple organs. In addition, renal failure in patients with COVID-19 may occur due to rhabdomyolysis, hypoxemia, dehydration, presence of underlying diseases and improper administration of nonsteroidal anti-inflammatory drugs.[11]

In 2003, 6.7% of SARS cases were complicated by acute renal impairment, and 91.7% of patients who died from SARS suffered from acute kidney injury (AKI) as a complication.[12] Studies also have shown that patients infected with SARS-CoV-2 had significantly increased serum creatinine (S. Cr) and hospital mortality after AKI.[13–15]

Initial reports also indicated that rates of acute kidney injury (AKI) were negligible.[16-21] However, growing evidence has demonstrated that AKI is in fact prevalent among patients with COVID-19, particularly among patients in the intensive care unit (ICU).[22-33] The reported rates of AKI are extremely variable; however, available evidence suggests that it likely affects >20% of hospitalized patients and >50% of patients in the ICU.[22-33] Similar to the association of AKI with other forms of community-acquired pneumonia, AKI is now recognized as a common complication of COVID-19.[34] As with AKI from other causes, COVID-19-associated AKI (COVID-19 AKI) is associated with adverse outcomes, including the development or worsening of comorbid disease as well as greater use of health-care resources. However, despite considerable advances in our understanding and management of other forms of AKI, relatively little is known about the pathogenesis or optimal management of COVID-19 AKI.

The aim of the present study is to assess the risk factors and outcome of hospitalized Covid 19 patients who developed Acute Kidney Injury (AKI), thus reduce the morbidity and mortality of these patients.

MATERIALS AND METHODS

This study was conducted by the Covid Unit (Department of Nephrology), Anwer Khan Modern Medical College Hospital (AKMMCH), a tertiary level center of Dhaka, during the period of July 1, 2021 to December 31 2021. This is a Cross Sectional Descriptive type of Observational study on patients of Acute Kidney Injury (AKI) admitted to Covid Unit (CU) of AKMMCH. Duration of the study was 6 months. Intending sample size depending upon the coverage of the patients during the study period. Our Inclusion criteria were as follows- Adult population 18-95 years, both male and female, patients of ICU, suffering from Acute Kidney Injury (AKI) who fulfills the RIFLE criteria, patients with sign symptoms of Covid with or without RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) for COVID-19 positive with raised inflammatory markers and HRCT chest shows peripheral ground glass shadows suggestive of COVID. Age below 18 years, patients with Chronic Kidney Disease (CKD) on maintenance hemodialysis (MHD), or on peritoneal dialysis or with renal transplant were excluded from the study.

The study protocol and the waiver of written informed consent were approved by the Ethical committee of AKMMCH. All the patients admitted to Intensive Care Units who fulfills the RIFLE criteria of Acute Kidney Injury were included in the study. Intending sample was depending upon the coverage of patients during study period. To maintain patient confidentiality and to ensure privacy, no personally identifying information was collected. However, clinical and laboratory data required for the study were gathered, which were sourced from the electronic health record system. The clinical data included age, sex, nationality, clinical presentation, contact and travel history, whether comorbidities were present, PaO2 /FiO2 (partial pressure of arterial oxygen/percentage of inspired oxygen) ratio, disease severity, whether mechanical ventilation or ICU was required at admission, whether death occurred in hospital, whether AKI was present and its outcome, and the need for renal replacement therapy (RRT). Laboratory data were also collected at admission (complete blood count, renal function, electrolytes, disease-related inflammatory markers, and the estimated glomerular filtration rate [eGFR] and during hospitalization, which included peak levels of creatinine and urea. All COVID-19 pneumonia treatments were recorded and noted on Data collection sheet. Blood samples were drawn in the morning, all the subject had rested for at least 10 minutes before blood sampling. Venous blood was collected from the cubital vein of the hand of the patients with minimal stasis without frothing using standard equipment. Serum was collected and was send for biochemical test.

Data were processed and analyzed using computer software SPSS (Statistical Package for Social Science) version 20. The test statistics were used to analyze the data by descriptive statistics and Chi-square Test. The descriptive statistics are frequency, mean and standard deviation of mean. The data measured on continuous scale were presented as mean and standard deviation from the mean (SDM) were compared using Chi-square Test Categorical data were expressed as percentages and were evaluated using Chi-square Test. The level of significance is 0.05. P-value < 0.05 were considered significant. The summarized information were than presented in the from of tables and charts.

Operational Definition

Acute Kidney Injury (AKI) and RIFLE's Criteria

Acute Kidney Injury was defined as patients whose serum creatinine and/or urine output fulfilled the **RIFLE** criteria. **Risk** class was defined as increase in serum creatinine ≥ 1.5 x baseline or urine output < 0.5 ml/kg/hour for the duration of ≥ 6 hours. **Injury** class was defined as increase in serum creatinine ≥2 x baseline or urine output < 0.5 ml/kg/hour for the duration of > 12hours. **Failure** class was defined as increase in serum creatinine >3 x baseline or an absolute serum creatinine 4mg/dl or urine output ≤ 0.3 ml/kg/hour for the duration of ≥ 24hours or anuria > 12 hours. **Loss** was defined as complete loss of kidney function > 4 weeks, requiring dialysis. **ESRD** was defined as complete loss of kidney function, requiring dialysis for > 3 months. Oliguria was defined as urine output below 500ml/day. Patients who fulfilled RIFLE criteria within 48 hours of admission were classified as community acquired AKI (CAAKI) and patients who fulfilled RIFLE criteria 48 hours after admission were classified as hospital acquired AKI (HAAKI). Complete renal recovery was defined as estimated glomerular filtration rate (eGFR) returning to a value of >60ml/min/1.73m^2 within 3 months. Chronic kidney disease (CKD) was defined as persistent reduction in eGFR after 3 months with a value <60ml/min/1.73m^2. Mortality was defined as patients expiring during the hospital stay.[35,36,37]

RESULT

A total number of 212 patients were included in the study. Among them 113 (53.3%) were male and 99 (46.7%) were female, M:F was 1.14:1. Mean age (Mean ±SD) of the patients was 63.06±13.14 (Age Range 18-95 years). Most of the patients, 33.78% (68) from age group 61-70 years. Next to which were age group 51-60 years 54 (25.47%) and 71-80 years 47 (22.27%) (Table 1). Most of the patients were suffering from Hypertension (HTN) 79.25% (168). Next to which was Diabetes mellitus (DM) 59.43% (126). 56.13% (119) patients were of both HTN and DM (Table 2).

161 (75.94%) patients were of RT PCR for Covid 19 positive and 24.06% (51) were negative whereas all of the patients were symptomatic with HRCT chest showed Covid pneumonia (Table 3). Table 4 described the lung involvement of the patients. 32.55% (69) patients had 26-50% lung involvement and 63(29.72%) were of 51-75%. Mean values of important biochemical markers were Serum Creatinine 3.56±2.75 mg/dl, Blood Urea 108.81±72.89 mg/dl, HbA1C (Glycated hemoglobin) 7.9±2.32%, C Reactive Protein (CRP) 80.67±86.20 mg/L, D Dimer 1.77±2.21mg/L, LDH (Lactate dehydrogenase) 397.73±227.59 U/L, IL-6(Interleukin-6) 211.48±950.78 pg/ml, Serum Ferritin 1092.14±1622.98 ng/ml (Table 5). 74.06% (157) patients were admitted to cabin and 3.77% (8) and 22.17%(47) admitted to HDU and ICU respectively. Mortality rate was 27.03% in cabin, 13.51% in HDU and 59.46% in ICU (Table 6).

Table 7 describes the distribution of patients according to the Stages of AKI, 37.26% (79) patients were of Stage 1, 31.13% (66) Stage 2 and 31.60% (67) patients were of Stage 3 AKI. 7.08% (15) of Stage 3 AKI (22.79% of all patients) needed Hemodialysis (Sustained low efficacy dialysis-SLED) (Table 7). All of the patients received Antiviral and Anticoagulant drugs. 87.26% (185) patients were treated with Monoclonal antibodies and 15 (7.08%) patients needed Hemodialysis (Table 8) 174 (82.08%) patients recovered and 37 (17.45%) patients died and 1 patient took DORB and shifted to other hospital (Table 9).

Table 1: Distribution of Patients According to Age.

Age in Years	No (%)
<20	0(0%)
21-30	1(0.47%)
31-40	13(6.23%)
41-50	16(7.65%)
51-60	54(25.47%)
61-70	68(33.78%)
71-80	47(22.27%)
81-90	8(3.91%)
>90	5(0.22%)
Total	212(100%)

Table 2: Distribution of Patients According to Primary Disease.

Primary Disease	No (%)
Hypertension	168(79.25%)
Diabetes Mellitus	126(59.43%)
Both Hypertension and Diabetes Mellitus	119(56.13%)
Ischemic Heart Disease/NSTEMI/MI/CABG/PCI	23(10.85%)
Left Ventricular Failure/ Chronic Heart Failure	16(7.55%)
Hypothyroid	12(5.66%)
COPD, BA	11(5.19%)
Others (HBsAg positive, Anti HCV positive, Hyper-gammaglobulinemia, UTI/Urosepsis, APN, Ca Breast, Salt losing nephropathy, OA, Bipolar disorder)	18(8.49%)
No Primary Disease	34(16.04%)

NSTEMI-Non-ST elevated MI, MI-Myocardial infarction, CABG- Coronary artery bypass graft, PCI- Percutaneous coronary intervention, HBsAg- Hepatitis B virus surface antigen, HCV- Hepatitis C virus, UTI- Urinary tract infection, APN- Acute pyelonephritis, Ca- Carcinoma, OA- Osteoarthritis.

Table 3: Distribution of Patients According to RT-PCR Reports.

RT-PCR	No (%)
RT-PCR **Positive**, Symptoms and HRCT Chest Positive	161(75.94%)
RT-PCR **Negative** but Symptoms and HRCT Chest Positive	51(24.06%)
Total	212(100%)

RT-PCR- Reverse transcriptase polymerase chain reaction, HRCT- High resolution computed tomography

Table 4: Distribution of Patients According to Lung involvement in HRCT Chest.

Lung involvement in HRCT Chest in percentage	No (%)
0-25%	53(25%)
26-50%	69(32.55%)
51-75%	63(20.72%)
>75%	27(12.73%)
Total	212(100%)

Table 5: Distribution of Patients by baseline Biochemical variables(n-212).

Biochemical parameters	Mean +SD
S. Creatinine	3.56±2.75 mg/dl
B. Urea	108.81±72.89 mg/dl
HbA_1C	7.9±2.32 %
C Reactive Protein	80.67±86.20mg/L
D Dimer	1.77±2.21mg/L
Lactate Dehydrogenase	397.73±227.59U/L
IL-6	211.48±950.78pg/ml
S. Ferritin	1092.14±1622.98ng/ml

IL-6 Interleukin-6, HbA_1C Glycated hemoglobin

Table 6: Distribution of Patients According to Clinical area of Admission and Death.

Clinical Area	Admission: No (%)	Death: No (%)
Cabin/Ward	157(74.06%)	10(27.03%)
HDU	8(3.77%)	5(13.51%)
ICU	47(22.17%)	22(59.46%)

HDU High dependency unit, ICU Intensive care unit

Table 7: Distribution of Patients According to Stages of Acute Kidney Injury (AKI): (N-212).

Stages of AKI	No (%)	HD(SLED) needed
Stage 1	79(37.26%)	0(0%)
Stage 2	66(31.13%)	0(0%)
Stage 3	67(31.60%)	15(7.08% of total patients and 22.39% of Stage 3 AKI patients)
Total	212(100%)	

HD- Hemodialysis, SLED- Sustained low efficacy dialysis

Table 8: Distribution of Patients According to Treatment Protocol.

Treatment Given	Given No (%)	Not Given No (%)
Anti-viral (Remdesivir)	212(100%)	0(0%)
Monoclonal Antibody (Tocilizumab/Adalimumab/Bevacizumab)	185(87.26%)	37(14.74%)
Hemodialysis needed	15(7.08%)	197(92.92%)

Table 9: Distribution of Patients According to Prognosis.

Prognosis	No (%)
Recovered	174(82.08%)
Death	37(17.45%)
DORB	1(0.47%)
Total	212(100%)

DORB Discharged on risk bond.

DISCUSSION

Currently, a number of published studies describe hospitalized patients with COVID-19 and AKI.[38] The incidence of AKI in these studies varies widely likely due to differences in criteria for hospital admission, definition of AKI, ethnicities, and other variables. The studies also have considerable heterogeneity among demographic characteristics, severity, risk factors, morbidities, and mortalities. In this issue of the American Journal of Nephrology, Zahid and colleagues performed a detailed retrospective analysis of AKI in 469 COVID-19 patients admitted to Brookdale University Hospital in Brooklyn, NY, of whom 27.1% developed this complication during hospitalization.[39]

In our study mean age of the patients was 63.06±13.14years (Mean ±SD) and range was 18-95 years. In the study of Lin L et al it is shown that 60.7% patients were of ≥ 60 years of age and a higher proportion of patients with Covid 19 from North America were aged ≥ 65 years.[40] Whereas in our study most of the patients 33.78% (68) were of 61-70 years age range which is similar to their study. In another study of VK Nitin et al it was found that Covid-19 patients with AKI were older, mean age 72.1±16.1 years (Mean ±SD) which is near to our study.[41] So AKI mostly developed in older age group with Covid-19. In the study of T Abdulraqeeb et al mean age was 54.3±13.5 years (Mean ±SD) which was different from our study.[42] In the study of P Guangchang et al mean age of the patients was 56.3±13.4 years (Mean ±SD) and 54.7% (142 of 333) patients were male.[43]

53.3% (113 of 212) patients were male and 46.7%(99 of 212) were female in our study and M:F ratio was 1.14:1 which is similar to P Guangchang et al study. In the study of T Abdulraqeeb et al 60.3% (44) were male and 39.7% (29) were female.[42] Both the study were similar to our study, male predominant.

The prevalence of hypertension and diabetes mellitus was 32.2% (107 of 333) and 22.9% (76 of 333) respectively in the study of P Guangchang et al.[43] In our study, 168 (79.25%) patients were hypertensive and 128 (59.43%) patients suffering from diabetes mellitus. 56.13% (119) had both diabetes mellitus and hypertension which were much more than their study. So diabetes mellitus and hypertension are the risk factors of developing AKI in Covid-19.

In our study mean values of important investigations were, S Creatinine 3.56±2.75 mg/dl, CRP 80.67±86.20 mg/L, D Dimer 1.77±2.2 mg/L and S Ferritin 1092.14±1622.98 ng/ml. But in the study of T Abdulraqeeb et al S Creatinine 1.53±1.56 mg/dl, CRP 89.33±73.01 mg/L, D Dimer 2.78±4.31 mg/L and S Ferritin was 946.01±647.12.[42] Which were near to our study.

In the study of T Abdulraqeeb 11.0% reached Stage 1 AKI, 15.1% Stage 2 and 13.7% reached Stage 3 AKI. Of all patients, 7 (9.6%) required hemodialysis.[42] In the study of C Lili et al the proportions with Stages 1, 2, 3 AKI were 39%, 19% and 42% respectively and 19% required hemodialysis.[44] Another concerning observation, of the study of Rudnick MR and Hilburg R was that 50.8% of the patients who developed AKI during hospitalization had Stage 3 AKI and rest 49.2% was Stage1 and 2.[45] In our study 37.26% (79) patients were of Stage 1, 31.13% (66) Stage 2 and 31.60% (67) patients were of Stage 3 AKI. 7.08% (15) of Stage 3 AKI

(22.79% of all patients) needed hemodialysis (Sustained low efficacy dialysis-SLED). Our study was similar to other studies.

In the study of VK Nitin mortality rate was higher in COVID-19 AKI (60.1%).[41] In our study 17.45% (37) patient died among which 59.46% (22) were from ICU, 13.51% (5) from HDU and 10 (27.03%) from cabin. Mortality rate was higher in ICU (59.46%). 82.08% (174) patients were recovered. So overall mortality rate of our study was much lower than other study.

From above discussion we came to know that, most of the patients who developed AKI after COVID-19, were of older age group, mostly males with co morbidities (Hypertension and DM) with lung involvement 50%. They had high inflammatory markers. One fourth of the patients of Stage 3 AKI needed hemodialysis and mortality rate was high in ICU.

CONCLUSION

In conclusion, we found high incidence of AKI in patients with COVID-19 that was independently associated with greater age and comorbidities. These data provide robust evidence to support the patients with COVID-19 who should be closely monitored for the development of AKI and measures taken to prevent this, though further studies are required to determine the most effective clinical approach. AKI was a common and serious complication of COVID-19. Older age and having severe COVID-19 were independent risk factors for AKI. The risk of in hospital death was significantly increased in patients with COVID-19 complicated by AKI.

LIMITATION

This study has some limitations. The causal relationships between different variables and AKI cannot be confirmed given the observational nature of the study. These results cannot be generalized to the entire population with COVID-19 pneumonia in Bangladesh because of the relatively small sample size and single-centered nature of the study. Multi-center studies could confirm the rate of AKI in COVID-19.

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