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Incidence, Clinical Characteristics and Outcomes Associated with Acute Kidney Injury in Patients Hospitalized with COVID-19

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ABSTRACT

Background: Acute kidney Injury associated with Coronavirus disease COVID-19 appeared to negatively influence clinical outcomes and is found to be associated with significant risk of death. This retrospective study aimed to describe the incidence of Acute Kidney Injury, its associations with clinical characteristics and outcomes among COVID-19 patients in Sukraraj Tropical and Infectious Disease Hospital, a tertiary infectious disease hospital in Nepal.

Methods: A cross-sectional study was done where. Medical and lab records of reverse transcriptase Polymerase chain reaction positive COVID-19 inpatients, admitted between April 2021 to July 2021 were reviewed. It represented the second wave of wave of coronavirus pandemic caused by the delta strain. Patients aged less than 18 years, pregnant females and patients with known chronic kidney disease were excluded

Results: Of 393 admissions, 83 (21.1%) patients developed Acute Kidney Injury. Characteristics found to have significant association with development of AKI was age ($p < 0.001$), multiple co morbidities (2 or more) ($p < 0.001$), use of mechanical ventilation ($p < 0.001$), lymphopenia ($p<0.001$), Neutrophil to Lymphocyte Ratio ($p = 0.001$) and d-dimer levels ($p < 0.001$). Mortality was found to be significantly higher in COVID-19 patients with AKI compared to COVID-19 patients without AKI ((36.14% vs 15.8%, p value <0.01)). The median duration of hospital stay for patients with AKI was higher than for patients without AKI (10 days vs 6 days,p <0.01).

Conclusions: AKI develops in a sizeable percentage of patients with COVID-19 and is significantly associated with increasing age, multiple comorbidities, increased biomarkers, use of mechanical ventilation and is associated with poor outcome in terms of mortality and morbidity.

Keywords: AKI; COVID-19; Nepal; outcomes.

INTRODUCTION

Corona Virus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed a serious public health threat worldwide. [1, 2]

The second wave in Nepal wreaked havoc in the health system with an exponential increase in severe COVID 19 cases everyday.. sampling sequencing and analysis revealed that about 97% of the new cases were attributed to delta-variant.[3]

COVID-19 may directly and/or indirectly affect the kidneys. Directly by binding ACE2 in the kidney and indirect pathway is mediated by cytokine storm, sepsis,

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circulatory disturbances, and use of nephrotoxic drugs. [4, 5]

AKI is found to develop in a considerable percentage of patients with COVID-19 and is significantly associated with mortality.[6-18]

Despite increased recognition of this phenomenon there is still inadequacy of data regarding the incidence and clinical characteristics of AKI associated with COVID-19 in Nepalese context. This retrospective study aims to shed light in these matters

METHODS

This was an investigator-initiated, single centered hospital based, retrospective cross-sectional study, based on COVID-19 patients admitted to Sukraraj Tropical and Infectious Disease hospital in Kathmandu, Nepal, between April 2021 and July 2021.

In this study, a total of 393 patients who were positive for COVID 19 by real-time reverse transcription polymerase chain reaction (RT-PCR) assay and admitted for COVID-19 to Sukraraj Tropical and Infectious Disease hospital in Kathmandu, Nepal, between April 2021 and July 2021, were included. Individuals with diabetes mellitus type 1, Patients aged less than 18 years, pregnant female, patients with history of end-stage renal disease, kidney transplant and those on renal replacement therapy were excluded from the study.

The study was conducted after approval from the Ethical Review Board of Nepal Health Research Council (Reference number 1130, date of approval—22 November 2021) and permission was taken from the hospital director to include medical records of the inpatients of Sukraraj Tropical and Infectious Disease Hospital. The requirement for taking consent was waived off by the ethical review board, this study being a retrospective study and data analysis done anonymously. The study was conducted according to the principles expressed in the Declaration of Helsinki, and the results are reported according to the strengthening the reporting of observational studies in epidemiology (STROBE) guideline

Medical and lab records of reverse transcriptase Polymerase chain reaction (RT-PCR) positive COVID-19 inpatients, admitted between April 2021 to July 2021, representing second wave of COVID -19 in Nepal caused by the Delta strain were explored. Data regarding occurrence of AKI, clinical, epidemiological and laboratory parameters, Length of Hospital stay and Outcome were extracted into Data Collection Sheet.

COVID-19 cases were grouped into the following severity of illness categories.[19]

Asymptomatic or pre-symptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms that are consistent with COVID-19.

Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnoea, or abnormal chest imaging.

Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have peripheral capillary saturation of oxygen (SpO_2) ≥ 94% on room air at sea level.

Severe illness: Individuals who have SpO_2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

Critical illness: Individuals who have respiratory failure, septic shock and/or multiple organ dysfunctions.

AKI, the primary end point, was defined as per Kidney Disease Improving Global Outcomes (KDIGO) criteria: a change in the serum creatinine of 0.3 mg/dl over a 48-hour period or 50% increase in baseline creatinine.[20]

All RT-PCR positive COVID-19 patients, admitted for COVID-19 to Sukraraj Tropical and Infectious Disease hospital in Kathmandu during the study period, without exclusion criteria were taken into study. So, there were no selection bias. All the medical records were explored to extract all data of patients. However missing data could have caused information bias.

The purpose of this study was to compare patients with AKI to patients without AKI. All variables were grouped accordingly.

Reporting of baseline characteristics was done as Medians and interquartile ranges (IQRs) for continuous variables and as counts and percentages for Categorical variables. Kruskal-Wallis test was used for continuous variable and Chi squared tests for comparison across groups. p-values were tabulated with a level of significance set at <0.05.

All data were analysed using IBM Statistical Packages for Social Sciences (SPSS), version 24.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

RESULTS

Over the period of 4 months from April 2021 to July 2021, 393 patients COVID-19 positive by RT-PCRwere included in the study. Out of 393 admissions, 248(63.1%) were male patients and 145(36.9%) were female.

Of the total patients, majority, 306 (77.9%) patients presented as severe disease, 62(15.8%) presented as moderate disease, 14 (3.6%) presented as critical disease while 11(2.8%) presented as mild. 83 (21.1%) patients developed AKI during hospital stay. Age and severity were found to have significant association with development of AKI. However, AKI was not found to have significant association with sex of the patient. Presence of Diabetes mellitus, Hypertension, Heart Disease, Chronic Pulmonary Disease, Thyroid Disorders and Cerebrovascular disease didn't have significant association with development of AKI. But Presence of multiple comorbidity (2 or more) and use of mechanical ventilation was significantly associated with development of AKI (Table 1).

Table 1. Characteristics of Patients with and without AKI.

Characteristics	AKI		Total N=393	P value
	YES (n=83)	NO (n=310)		
Age in years, median (IQRs)	59(46-69)	51(40-63)	52(41-65)	<0.001
Age Group in years, n (%)				
<40	7(8.43)	77(24.84)	84(21.37)	0.005
40-59	35(42.17)	126((40.64)	161(40.97)	
60-79	33(39.76)	92(29.68)	125(31.81)	
≥80	8(9.64)	15(4.84)	23(5.85)	
Gender				
Male, n (%)	49(59.03)	199(64.19)	248(63.1)	0.387
Severity				
Mild	0(0)	11(3.55)	11(2.8)	<0.001
Moderate	4(4.82)	58(18.71)	62(15.78)	
Severe	71(85.54)	235(75.81)	306(77.86)	
Critical	8(9.64)	6(1.93)	14(3.56)	
Comorbidities, n (%)				
Diabetes Mellitus	19(22.89)	57(18.39)	76(19.33)	0.29
Hypertension	28(33.73)	84(27.09)	112(28.5)	0.28
Heart Disease	6(7.23)	12(3.87)	18(4.58)	0.19
Chronic Pulmonary Disease	8(9.64)	20(6.45)	28(7.12)	0.316
Hypothyroidism	7(8.43)	15(4.84)	22(5.6)	0.206
Presence of multiple Comorbidities	23(27.71)	35(11.29)	58(14.76)	<0.001
Use of mechanical ventilation	47(56.66)	54(17.41)	101(25.7)	<0.001

Amongst patients who developed AKI and required mechanical ventilation, 38 patients developed AKI after initiation of mechanical ventilation, while 9 patients developed AKI prior to mechanical ventilation. The median duration after mechanical ventilation after patient developed AKI was 7 days (Range 1-23 days). Most (27/38, 71.05%) developed AKI within the first 10 days of mechanical ventilation, while other developed AKI after 10 days.

AKI was found to have significant association with Lymphopenia, increased neutrophil to lymphocyte ratio, increased d-dimer levels and increased C-Reactive Protein as shown in Table 2. Values for ferritin and CRP were missing for 107 and 96 patients respectively and were excluded during analysis.

Table 2. Laboratory parameter in COVID-19 patients with and without AKI.

Laboratory Values (IQRs)	AKI		Total	P value
	YES	NO		
Hemoglobin (g/dL)	12.2 (11.4-13.3)	12.8(11.7-13.9)	12.6(11.7-13.8)	0.017
Leucocyte (×10³/μL)	7800(5100-10900)	6900(5375-9500)	7000(5350-9500)	0.125
Neutrophil (%)	83(76-91)	80(69-88)	81(70.5-88)	0.004
Lymphocyte (%)	11(7-20)	15.0(9-25)	14(9-23)	0.002
Neutrophil to Lymphocyte Ratio	7.82(3.8-13.2)	5.33(2.9-8.9)	5.79(3.11-10)	0.001
Platelet (×10³/μL)	195(155-286)	188(143-257)	190(143-262.5)	0.247
ALT (U/L)	44(24-71)	40(26-66)	40.5(25-40.5)	0.607
AST (U/L)	49.5(28.2-75.7)	46(32-69)	47(31-71)	0.796
ALP (U/L)	101(69-128)	87.5(69-115)	89(69-115)	0.358
Baseline Cr (mg/dL)	0.7(0.5-1.0)	0.7(0.6-0.9)	0.7(0.6-0.9)	0.092
Sodium(mEq/L)	136(133-139)	137(135-139)	137(134-139)	0.380
Potassium (mEq/L)	4.0(3.6-4.3)	3.9(3.7-4.2)	3.9(3.7-4.2)	0.257
RBS (mg/dL)	166(133-250)	150(116-208)	157.5(118-215)	0.126
D-dimer (ng/mL)	0.85(0.61-1.2)	0.56(0.28-1.14)	0.53(0.21-0.98)	<0.001
Ferritin (μg/L)	468.33(215.4-754)	496(260-725.03)	491.5(250-729.63)	0.679
C-Reactive Protein (mg/L)	80(45.2-126.5)	48.30(20.66-93.69)	56(24.7-105.9)	0.001

AST, aspartate transaminase; ALT, alanine transaminase; ALP, Alkaline Phosphatase

Among 393 patients, 305 (77.6%) were discharged, 68 (17.8%) patients expired, 20 (5.1%) had to be referred to super specialist hospital. Among 83 patients with AKI, 49 patients were discharged, 30 of them expired and 4 were referred. P value of <0.01 shows that there is significant statistical association between development of AKI and outcome amongst patients with AKI (Figure 1).

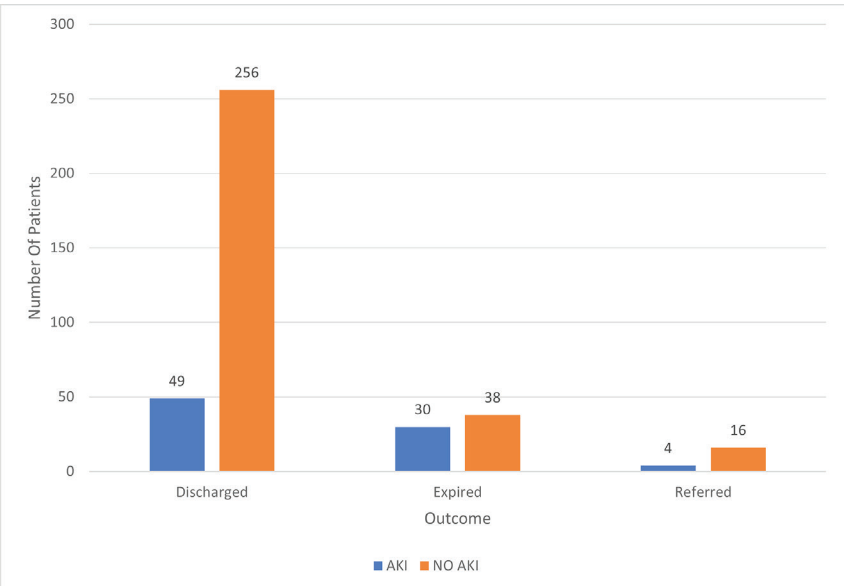

Figure 1. Distribution of outcome among patients with and without AKI.

The median duration of hospital stay for patients without AKI was 6 days, while the median duration of hospital stay for patients with AKI was 10 days, with p value of <0.01 showing significant association.

The median duration after admission after which AKI developed amongst patients with AKI was 7.5 days (range 1-32 days).

DISCUSSION

This study represents a analysis of AKI among COVID-19 patients admitted at Sukraraj Tropical and Infectious Disease Hospital during the second wave of coronavirus pandemic in Nepal.

In this retrospective study, the incidence of AKI among COVID-19 patients was found to be 21.1%. The incidence of AKI in COVID-19 in our study is like studies from the United States of America, Europe, and Middle east countries (20-40 %).[9-12] Some studies have however reported higher rates of development of AKI (40-60%) [6, 8] while Chinese studies have reported lower incidence . [7, 13-15] The incidence of AKI is shown to vary widely among patients with COVID-19 in different countries and regions. The discrepancies in the incidence of AKI in COVID-19 may be explained in part by differences in patient characteristics and disease severity and variation in the inclusion criteria.

Though different studies have reported Diabetes Mellitus, Hypertension and Heart Disease to be independent risk factors for development of AKI,[9,11,12] development of AKI didn't show significant association with DM, HTN or heart disease in our study. Presence of multiple comorbidities (2 or more than 2) however was found to have significant association with AKI in our study. Association of development of AKI with sex has been found to vary in different studies. Many have shown significant association of development of AKI with male sex.[6, 8, 9] The association might be because of higher proportion of male patients. However, our study didn't show significant association of development of AKI with sex. Old age has been identified to be risk factor for development of AKI among COVID-19 patient in different studies.[8, 9,11,14,16] In line with these studies, our study also showed significant association of AKI with age with significant rise in incidence of AKI with increasing age.

Significant association of lymphopenia and higher neutrophil to lymphocyte ratio with AKI, found in our study is akin to findings form other studies.[8, 16] Increase in D-dimer in COVID-19 is linked with poor prognosis and is also found to have significant development of AKI and other organ dysfunctions.[17,18] In our study, raised D-dimer was also found to be linked more with development of AKI. Measuring the level of D-dimer and coagulation parameters from the early stage of the disease can hence be useful in management of COVID-19 disease.

In our study, AKI was found to have significant association with use of mechanical ventilation, non-invasive or invasive. This is like findings from previous studies which showed significant linkages between mechanical ventilation and AKI development in patients with COVID-19 .[9,11,12,16] Exposure to the inflammatory milieu of Acute Lung Injury and mechanical ventilation-induced injury may precipitate the onset of AKI and is found to have deleterious bidirectional relationship.[21] Hence patients on mechanical ventilation should be carefully monitored for development of AKI.

Mortality among COVID 19 patients was found to have significant association with the development of AKI in our study (36.14% among COVID-19 patients with AKI vs 15.8% among COVID 19 patients without AKI). This finding is in line with other studies showing higher mortality rates in the setting of AKI among COVID-19 patients. [6, 9-15] Besides, AKI was also found to significantly increase hospital stay among COVID-19 patients in our study.

Our study should be interpreted considering following limitations. Since this was a single centered study, the results cannot be generalized. Secondly, data including quantitative CRP measurements, D-dimer and serum ferritin levels were missing for many patients. Additionally, urinalysis reports were missing in majority of the patients. We didn't have data regarding ARDS or ICU severity scores, often associated with AKI. Besides, outcome and follow up of referred patients were not analyzed in this study. Despite these limitations, to the best of our knowledge, this is the first study from Nepal regarding COVID-19–associated AKI incidence, risk factors, and outcomes. Further studies are warranted to predict the risk of AKI, to identify the mechanisms of renal injury and to suggest targeted interventions.

Our study represents the second wave of COVID-19 in Nepal, caused by the delta variant of SARS-CoV-2. It might not be applicable to other variants. There still is scarcity of data regarding implication of variants on AKI or other organ dysfunctions. Further studies are needed to describe and analyse the clinical course of patients with AKI in COVID-19 patients and should include appropriate indices of kidney function and specifications according to SARS-CoV-2 variants

CONCLUSIONS

AKI develops in 21.1% of patients with COVID-19 and is significantly associated with increasing age, multiple comorbidities, increased D-dimer levels and use of mechanical ventilation and development of AKI is associated with poor outcome in terms of mortality and morbidity in COVID -19 patients.

CONFLICT OF INTEREST

There are no conflicts of interest.

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