Study of Acute Kidney Injury in Patients Hospitalized with COVID-19: A Single Center Study in Bangladesh

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Abstract:

Introduction: The incidence of acute kidney injury (AKI) associated with hospitalized corona virus disease -19(Covid-19) patients and associated outcomes are not well determined. This study describes the presentation, risk factors and outcomes of AKI in patients hospitalized with Covid-19.

Material & Methods: In this cross sectional study, we reviewed the health records for all conveniently selected patients hospitalized with Covid-19 irrespective of co morbidity from 1st May to 31st July, 2020, at combined military hospital Dhaka, Bangladesh. Patients younger than 18 years, end stage kidney disease or with a kidney transplant recipient were excluded from the study. AKI was deûned according to kidney disease improving global outcome (KDIGO) criteria.

Results: A total of 470 Covid-19 patients were recruited in this current study, out of them 67.02% were male and 32.98% of were female; with male to female ratio was 2:1. The mean age of the study population was 54.71(±14.31) years. AKI developed among 106 (22.55%) patients of whom 50 patients had CKD. The peak stages of AKI were stage 3 in 58(12.34%), followed by stage 1 in 37(7.87%), and stage 2 in 11(2.34%) patients. Renal replacement therapy was required (RRT) for 37(7.87%) patients. Risk factors included older age, hypertension, diabetes mellitus, cardiovascular disease, and chronic kidney disease and those who presented with prolong fever and breathlessness.AKI was commonly seen in patients with severe disease. Considerable number of patient had proteinuria 222(47.23%) and haematuria in 63 (13.40%) and were significantly associated with AKI. Elevated level of ferritin, D-dimer and procalcitonin were observed among 249(52.98%), 179(38.08%) and 138(35, 88%) patients respectively which were substantially correlated with AKI. COVID-19 patients complicated to acute kidney injury were strongly associated with higher mortality19 of 23 (82.60%).

Conclusion: Renal involvement in COVID-19 (Corona virus-nephropathy) has a complex etiology. It is closely associated with severity of disease and indicating poor prognosis. Further study will be needed for better understanding the causes of AKI and patient outcomes.

Key words: Acute kidney injury (AKI); Corona virus disease-19(COVID-19); Severe disease.

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Introduction:

A highly contagious infectious disease presented as unexplained pneumonia was first detected in Wuhan City of China in December 2019[1]. Later on the disease was named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) which is caused by severe acute respiratory syndrome corona virus (SARS-CoV-2)[2]. Immediately after the outbreak, the virus has rapidly spread throughout the globe. As of June 10, 2020, the cumulative number of confirmed cases had reached 7145539 including 408025 deaths (mortality rate of 3.0%), in the world[3]. COVID-19 is presenting as mild self-limiting respiratory tract illness to severe acute respiratory distress syndrome (ARDS), multiple organ failure and death. Though respiratory system is the main organ system involved in the manifestation of disease, it also involves other organ system like cardiovascular, gastrointestinal, renal and nervous systems. The cause of kidney involvement in COVID-19 is likely to be multifactorial such as sepsis, hypovolaemia, nephrotoxins, cytokine release syndrome (CRS) etc. Preexisting co morbidity like diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD) and

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chronic kidney disease (CKD) are important contributory factor for developing Acute Kidney Injury (AKI)[4]. Pathophysiology though not yet fully established, autopsy findings indicated that the endothelium is affected in the lung and kidney. Virus particles were reported to be present in renal endothelial cells, indicating viraemia as a possible cause of endothelial damage in the kidney and a probable contributor to AKI [5,6]. Additionally, SARS-CoV-2 can directly infect the renal tubular epithelium and podocytes through an angiotensin converting enzyme 2 (ACE2)-dependent pathway and cause mitochondrial dysfunction, acute tubular necrosis. Other contributors to AKI might include rhabdomyolysis, macrophage activation syndrome, and the development of microemboli and microthrombi in the context of hypercoagulability and endotheliitis.[7]

Methods:

This cross sectional study was conducted among 470 conveniently selected COVID-19 patients admitted at Combined Military Hospital (CMH) Dhaka, one of the major tertiary care teaching hospital in Bangladesh from May 2020 to July 2020 (three month). Only adult (age more than 18 years) patients of both sex irrespective of co-morbidity who fulfill the diagnostic criteria of COVID-19 provided by the World Health Organization (WHO) and admitted were included in the study. Patients with a history of maintenance dialysis, renal transplant recipient and unwilling to participate were excluded from the study. The investigation method includes questionnaire, clinical evaluation and laboratory methods. The demographic, clinical and laboratory data, were gathered from medical records up to 31st July, 2020.

The date of disease onset was defined as the day when the symptom was noticed. The severity of the disease was staged according to the guidelines published by World Health Organization WHO on June 4, 2020 [2]. Severe case was defined as either: (i) respiratory rate > 30/min, or (ii) oxygen saturation d" 93%, or (iii) PaO2/FiO2 ratio d" 300mmHg. Critical case was defined as one of the following: shock; respiratory failure requiring mechanical ventilation; combined with the other organ failure or admission to intensive care unit (ICU). AKI was defined as an increase in serum creatinine (S Cr) by 0.3 mg/dl within 48 hours or a 50% increase in serum creatinine from the baseline within 7 days according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria [8]. The stage of AKI was determined using serum creatinine level with increase 1.5-1.9, 2.0-2.9 and e" 3 times from baseline being defined as stage 1, 2 and 3, respectively. Data analysis was performed by latest version of Statistical Package for Social Science (SPSS).Categorical variables were summarized as percentages, and continuous variables were expressed as the mean ± standard deviation. Level of significance was measured by using appropriate procedures like chi-square test (X^2), t-test,F test (ANOVA) for categorical variables and nonparametric Kruskal-Wallis test for continuous variables. Spearman's rank correlation coefficient and others test were done where applicable. Level of significance (p value) was set at 0.05.Ethical clearance was obtained from ethical clearance committee of CMH Dhaka.

Results:

A total of 470 patients were recruited in this current study, after qualifying the selection criteria. Out of total participants, 67.02% were male and 32.98% of were female; with male to female ratio was 2:1. The mean age and BMI of the study population was 54.71(±14.31) years and 25.24 (± 2.77) respectively. Most common presenting feature was fever (71.49%). Albeit distinguished number of patients were suffering from multiple co morbidity, HTN ((51.91%) was most common.

We compare baseline demographic characteristics between patients without AKI and among the three stages AKI [table I] and found significant difference (P< .001) in age.

Table-I

Demographic characteristics of study cohort by AKI status (n=470)

Variable	No AKI (n 364)	AKI (n 106)	Stages of AKI			P value (No AKI vs. all AKI)
			Stage 1 (n37)	Stage 2 (n 11)	Stage 3 (n58)	
Age (years)	53.4 (± 14.4)	59.2 (± 13.2)	61.4 (± 9.06)	55.7 (± 11)	58.5 (± 15.6)	< .001
Male	236(50.21%)	79 (16.81%)	25 (5.32%)	10 (2.13%)	44 (9.36%)	0.078
Female	128(27.23%)	27 (5.74%)	12 (2.55%)	1 (0.21%)	14 (2.98%)	0.078

Comparisons are made between no AKI and all AKI using Fisher exact test for categorical variables.

The peak stages of AKI were stage 3 in 58(12.34%), followed by stage1 in 37(7.87%), and stage 2 in 11(2.34%).AKI was more common among male patients (M: F=2.92:1). (Fig: 1)

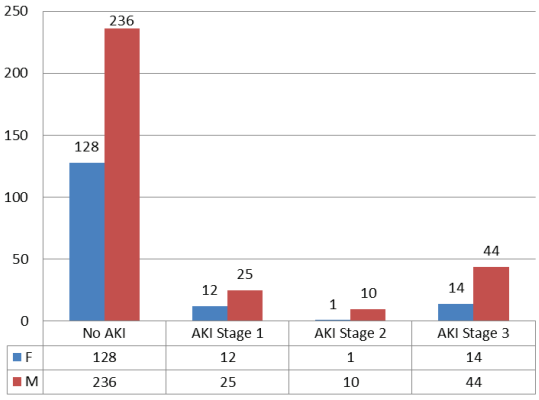


Fig.-1: *Distribution different stages of AKI on the basis of gender (n=470)*

Comparisons are made between no AKI and all AKI using Fisher exact test for categorical variables and or nonparametric Kruskal-Wallis test for continuous variables.

We compare various clinical and l characteristics between patients without AKI and among the three stages AKI [table II] and found significant difference (P< .001) in duration of fever, symptom of breathlessness (SOB). Patients with coexisting conditions [DM, HTN, IHD CKD] were more susceptible to develop AKI (P< .001).

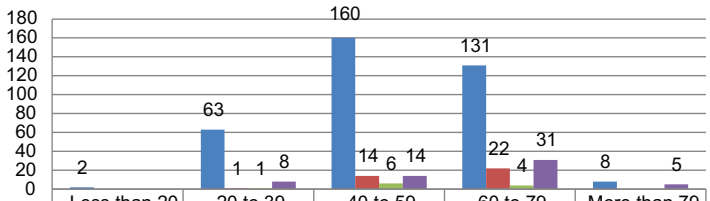
Those who develop AKI total 57(53.77%) patients were in sixty to seventy nine years age group followed by 34(32.07%) in fourty to fifty-nine years group. (Fig: 2)

Among thetotalparticipant (n-470) 61 patients had CKD before suffering from Covid-19 and 50(11%) of them develop AKI on CKD. (Fig: 3) The number of patients requiring dialytic support at some point was 37 (overall

Table-II

Clinical characteristics of study cohort by AKI status (n=470)

Variable	No AKI(n 364)	AKI(n 106)	Stages of AKI Stage 1 (n37)	Stage 2 (n 11)	Stage 3 (n58)	P value (No AKI vs. all AKI)
BMI	25.3 (± 2.74)	25 (± 2.85)	24.9 (± 3.35)	25.8 (± 2.34)	24.9 (± 2.6)	0.45
RR	21.4 (± 4.52)	25.2 (± 6.11)	24.9 (± 5.53)	22.5 (± 6.39)	25.8 (± 6.35)	< .001
Temperature	99.6 (± 1.41)	99.9 (± 1.48)	99.6 (± 1.79)	100 (± 0.79)	100 (± 1.36)	0.052
F/duration	5.46 (± 4.35)	6.76 (± 3.42)	5.78 (± 3.27)	6.36 (± 3.17)	7.47 (± 3.45)	< 0.001
SOB	135(28.72%)	67 (14.26%)	22 (4.68%)	6 (1.28%)	39 (8.3%)	<0.001
Cough	196 (41.7%)	67 (14.26%)	20 (4.26%)	8 (1.7%)	39 (8.3%)	0.096
Loose Motion	43 (9.15%)	18 (3.83%)	2 (0.43%)	1 (0.21%)	15 (3.19%)	0.188
Fatigue	106(22.55%)	28 (5.96%)	6 (1.28%)	2 (0.43%)	20 (4.26%)	0.627
Pregnant	7 (1.49%)	3 (0.64%)	0 (0%)	0 (0%)	3 (0.64%)	0.701
DM	140(29.79%)	63 (13.4%)	25 (5.32%)	4 (0.85%)	34 (7.23%)	<0.001
HTN	175(37.23%)	69 (14.68%)	30 (6.38%)	8 (1.7%)	31 (6.6%)	0.003
IHD	43 (9.15%)	26 (5.53%)	11 (2.34%)	2 (0.43%)	13 (2.77%)	0.002
CVD	8 (1.7%)	2 (0.43%)	0 (0%)	0 (0%)	2 (0.43%)	1
COPD/asthma	34 (7.23%)	7 (1.49%)	4 (0.85%)	1 (0.21%)	2 (0.43%)	0.44
CKD	11 (2.34%)	50 (10.64%)	16 (3.4%)	3 (0.64%)	31 (6.6%)	<0.001
Systolic BP	125 (± 14.8)	117 (± 25.2)	129 (± 21)	120 (± 14.8)	110 (± 26.5)	0.024
Diastolic BP	78.5 (± 7.72)	72.9 (± 15.6)	78.2 (± 8.15)	80 (± 11.6)	68.2 (± 18.2)	0.057
24hr U/O ml	1318 (± 443)	678 (± 562)	1287 (± 489)	632 (± 78.3)	299 (± 204)	< .001
SpO_2 (%)	92.8 (± 7.5)	89.7 (± 8.32)	92.2 (± 6.55)	92.8 (± 8.35)	87.6 (± 8.82)	< .001
ICU needed	72 (15.32%)	46 (9.79%)	14 (2.98%)	2 (0.43%)	30 (6.38%)	<0.001
O_2 Support	231(49.15%)	79 (16.81%)	28 (5.96%)	7 (1.49%)	44 (9.36%)	0.036
Inotropeuse	14 (2.98%)	25 (5.32%)	7 (1.49%)	0 (0%)	18 (3.83%)	<0.001
Hosp (days)	8.61 (± 5.71)	9.33 (± 6.14)	8.57 (± 6.53)	5.64 (± 3.26)	10.5 (± 6.01)	0.407
Expired	4 (0.85%)	19 (4.04%)	5 (1.06%)	0 (0%)	14 (2.98%)	<0.001
Discharged	109(23.19%)	28 (5.96%)	11 (2.34%)	1 (0.21%)	16 (3.4%)	0.544
Hospitalized	251 (53.4%)	59 (12.55%)	21 (4.47%)	10 (2.13%)	28 (5.96%)	0.014



	Less than 20	20 to 39	40 to 59	60 to 79	More than 79
No AKI	2	63	160	131	8
AKI Stage 1		1	14	22	
AKI Stage 2		1	6	4	
AKI Stage 3		8	14	31	5

Fig.-2: *Distribution of stages of AKI on the basis of age group (n=470)*

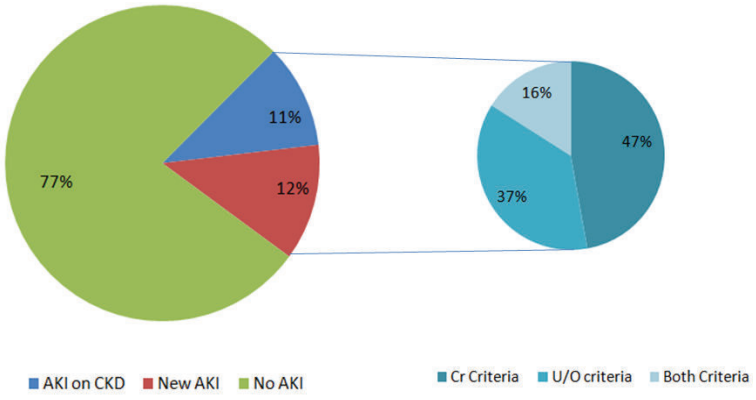
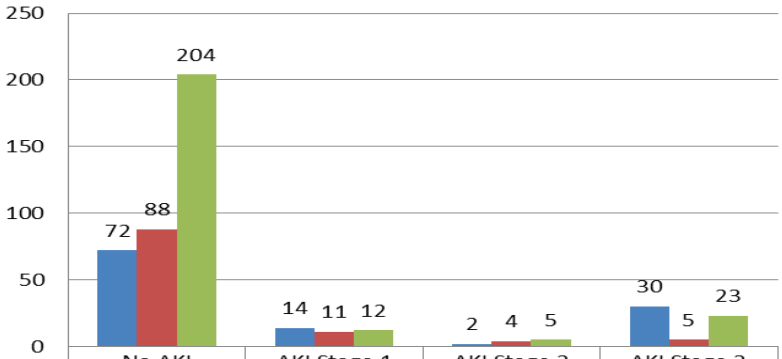


Fig: 3: *AKI on the basis of different defining criteria*

7.87% of all patients), representing 34.90% of those with AKI. The modality utilized was intermittent hemodialysis.

In our study because of admission criteria, no asymptomatic or mild disease were admitted in the hospital. Among the admitted patients 118 patients were in critical condition and 46(38.98%) of them developed different stages of AKI. (Fig: 4)

The relationship between respiratory failure and development of AKI was substantial and is displayed in Table III. Among patients who required mechanical



	No AKI	AKI Stage 1	AKI Stage 2	AKI Stage 3
Critical	72	14	2	30
Moderate	88	11	4	5
Severe	204	12	5	23

Fig.-4: *Distribution of AKI on the basis of severity of covid-19 (n=470)*

Table III

Proportion of AKI by requirement of O_2 delivery system (n=470)

AKI status	No use of mechanical ventilation (NC, FM, HFNC)	Required mechanical ventilation (IV, NIV)	P value (AKI vs. No AKI)
No AKI	334 (71.06%)	30 (6.38%)	0.006
AKI	87 (18.51%)	19 (4.04%)	
Stage 1	32 (6.81%)	5 (1.06%)	
Stage 2	9 (1.91%)	2 (0.43%)	
Stage 3	46 (9.79%)	12 (2.55%)	

NC: Nasal cannula; FM: Face mask; HFNC: High flow nasal cannula; IV: Invasive ventilation; NIV: Noninvasive ventilation

ventilation, 19 of 49 (38.77%) developed AKI compared with 87 of 421 (20.66%) in non-mechanically ventilated patients (P value 0.006).

Urine routine microscopic examination shows (Table IV) considerable number of patient had proteinuria 222(47.23%) and haematuria in 63 (13.40%) and were significantly associated with AKI (P <0.05.).

Comparisons were made between no AKI and AKI using Fisher exact test for categorical variables and or nonparametric Kruskal-Wallis test for continuous variables.

In table-V laboratory data showed elevated level of ferritin in 249(52.98%), D-dimer in 179(38.08%), procalcitonin in 138(35, 88%) patients. All of these markers of disease severity had significant influence on developing AKI ((P-<0.001)..

Relationships between clinical and laboratory variable with AKI have shown in fig: 5, using the Spearman correlation coefficient. The following variables showed significant positive correlation to the AKI ($p < 0.05$): advanced age, increasing respiratory rate(R/R), long duration of fever, admission and 48 hours serum creatinine count , procalcitonin, D-dimer, ferritin etc. Of these, beside serum creatinine level, D-dimer, and serum ferritin level had a particularly significantly positive correlation. Patients with lower blood pressure, low SpO_2, low lymphocyte count were negatively correlated with severity of AKI ($p < 0.05$)

Table-IV

Urine tests results obtained in patients developed AKI(n=470)

Urine studies	Total N (%)	AKI n (%)	P Value
Hematuria	63 (13.40%)	24 (5.11%)	0.003
Proteinuria	222(47.23%)	68 (14.46%)	<0.001
Nephrotic	03 (0.64%)	02 (0.43%)	
Overt	123 (26.17%)	35 (7.45%)	
Moderate	96 (20.43%)	31 (6.60%)	

Table-V

Baseline laboratory characteristics of study cohort by AKI status (n=470)

Variable	No AKI (n 364)	AKI (n 106)	Stages of AKI			P value
			Stage 1 (n 37)	Stage 2 (n 11)	Stage 3 (n 58)	(No AKI vs. all AKI)
Hbgm/dl	12.3(±1.65)	11.5 (± 1.99)	10.8 (± 1.78)	12.7 (± 1.67)	11.7 (± 2.04)	< .001
TLC($1x10^9$)	9.99(±6.22)	11.6 (± 6.02)	13 (± 7.53)	8.02 (± 3.08)	11.4 (± 5.05)	0.002
Lymph (%)	20.6(±13.3)	16.9 (± 12.1)	18.3 (± 13)	21.3 (± 14.6)	15.1 (± 10.8)	0.007
u Pro	75(15.96%)	31 (6.6%)	12 (2.55%)	1 (0.21%)	18 (3.83%)	0.065
uRBC/HPF	39 (8.3%)	24 (5.11%)	5 (1.06%)	2 (0.43%)	17 (3.62%)	0.003
u/PCR mg/mmol	76 (± 155)	78.8 (± 75)	77.3 (± 63)	65.5 (± 65.8)	80.6 (± 84.6)	0.452
Urea mg/dl	44.6(±20.9)	84 (± 50.8)	83.4 (± 39.1)	64.6 (± 36.1)	88.1 (± 58.9)	< .001
Admn Cr mg/dl	0.9 (± 0.24)	1.49 (± 1.09)	1.7 (± 1.09)	1.22 (± 0.68)	1.42 (± 1.15)	< .001
48 hrsCr mg/dl	0.91(±0.25)	2.41 (± 3.33)	2.6 (± 1.22)	1.3 (± 0.83)	2.49 (± 4.37)	< .001
LDH U/L	816 (± 425)	887 (± 443)	864 (± 520)	740 (± 430)	929 (± 389)	0.113
CPK	254 (± 241)	435 (± 722)	329 (± 431)	284 (± 203)	531 (± 903)	0.044
ALT U/L	56.2(±52.6)	64 (± 57.9)	64.3 (± 77.4)	63.4 (± 40.2)	64 (± 45.9)	0.365
Procal (ng/ml)	0.86(±3.63)	1.29 (± 2.13)	1.07 (± 2.32)	0.01 (± 0)	1.49 (± 2.08)	< .001
CRP (mg/L)	9.99 (± 7.7)	10.8 (± 7.24)	8.86 (± 6.35)	12.7 (± 9.43)	11.8 (± 7.17)	0.065
Ferritin (ng/ml)	902(±1585)	1199 (± 1089)	1449 (± 1273)	958 (± 1181)	1086 (± 923)	< .001
D-dimer (mcg/ml)	0.98(±0.99)	1.47 (± 1.13)	1.78 (± 1.24)	0.64 (± 0.39)	1.43 (± 1.08)	< .001
CT	25.1(±28.3)	34.7 (± 28)	33.2 (± 23.6)	22.3 (± 24.7)	37.9 (± 30.7)	< .001

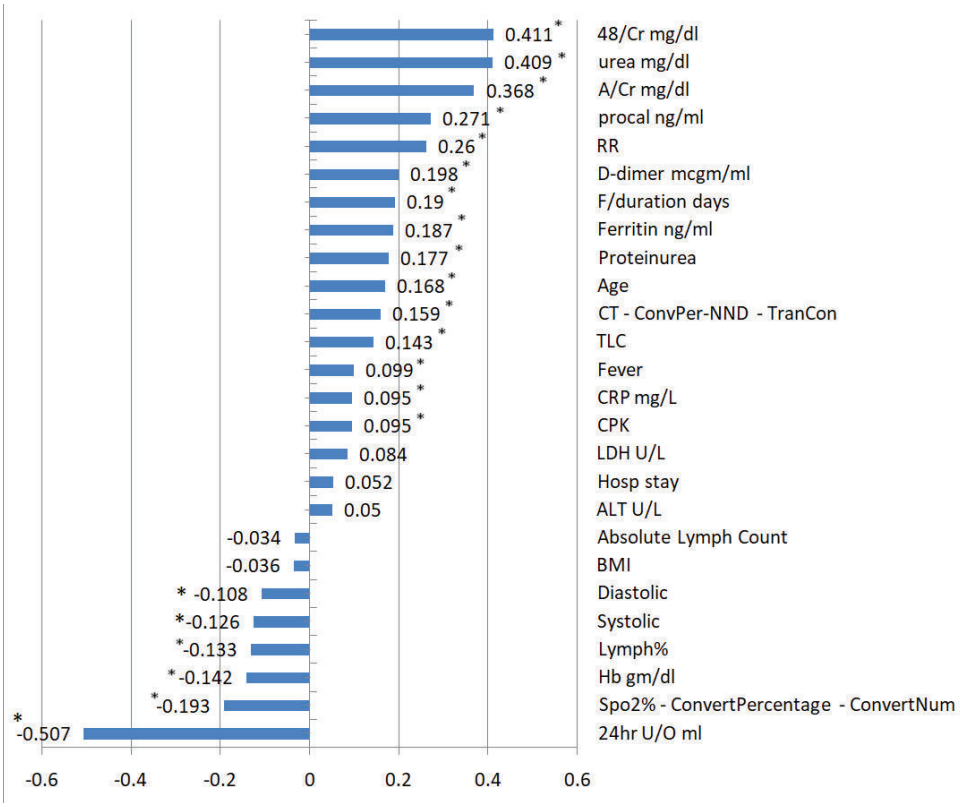


Fig.-V: *Spearman's rank correlation coefficient (*P<0.05)*

Discussion:

AKI is a common complication among patients hospitalized with COVID-19. We found 106 (22.55%) patients developedAKIduring their hospital stay. This is a higher rate than has been reported by Cheng *et al.* where they show only 5.1% of 701 patients[9]. On the other hand Jamie S. H *et al* in there study found 1993 (36.6%) patients had AKI[10]. Though we cannotcompletelyexplainthisdifference but the difference of age and co morbidity may play some role. Increasing age, male sex, and higher BMI were risk factors for poor outcomes of COVID- 19[11].But in this study there were some variation in their relationship to AKI. Older individuals and men were at greater risk ($p< 0.05$), but we found less association with BMI ($P> 0.05$).Among the presenting feature, it is the duration of fever rather than height of temperate have significant impact on severity of kidney injury. Another important thing is the presence co morbidity like DM, HTNetc. which had significant correlation with AKI ($P-<0.001$).There were important relationship between AKI and respiratory condition which are indicated by the following ûndings. First, AKI occurred most commonly in close proximity to the symptom of breathlessness (SOB) and low oxygen saturation (table: III) where mean SpO_2 of all AKI patients was 89.7 ($\pm$ 8.32) in comparison with no AKI which is 92.8 ($\pm$ 7.5) ($p< 0.05$). Second, though trend of mechanical ventilator use is reducing now daysfor treating Covid-19 patients, yet AKI developed among38.77% patientswho were on mechanical ventilator, compared with 20.66% patients who use other oxygen delivery device ($P< 0.05$). Finally, almost all (91.30%) of the expired patients who were on ventilator support had AKI (82%). Taken together, these data the occurrence of kidney dysfunctions might be explained by the kidney-lung crosstalk theory [12,13].Large number (35.85%) of patient had hypotension either due to hypovolaemia or septicemia.Many of them in spite of volume resuscitation need inotropic support and significantly correlated with development AKI (fig: 5).Claudio R also conclude that volume depletion might be a common trigger for AKI[14].Our urinary ûndings were noteworthy as fairly high rates of proteinuria 222(47.23%) and hematuria 63 (13.40%) were associated with AKI (($p< 0.05$). Most of the patients had moderately elevated proteinuria exhibiting the possibility of tubular origin.Rohollah, V. at al also found the similar findings in there study[15]. Su et al., in a study demonstrated that 26 patients had tubular injury in autopsy ûndings.[16]Laboratory data showed elevated level of markers of disease severity like ferritin, D-dimer, procalcitonin and had significant correlation(Fig: 5) on developing AKI (P-<0.05) which may be resulting in small renal vessel thrombosis causing hematuria suggesting renal infarction. Yichun C et al commented that, cytokinestorm often occurs in close temporal proximity to respiratory failure; it is possible that circulating substances or other related factors could contribute to AKI.[17]So the cause of kidney involvement in COVID-19 is likely to be multifactorial. Sepsis, hypovolaemia, immune response dysregulation as indicated by observed lymphopenia and cytokine release syndrome (cytokine storm) all contribute to the development of AKI. There were some limitations in obtaining clinical data due to patient overload during the outbreak, thus we only included patients with complete data on kidney functions. Various drugs and interventions had been applied which could have side effects on kidney functions during the course of treatment.

Conclusion:

In conclusion, we found that AKI was a relatively common ûndings among patients hospitalized with COVID-19. It was strongly linked to the presence of co morbid condition and occurrence of severe disease especially respiratory failure and who need intensive care support. The development of AKI in patients hospitalized for COVID-19 conferred a poor prognosis. Further study will be needed for betterunderstandingthe causes of AKI and patient outcomes.

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