Original Article

Acute Kidney Injury Is A Predictor Of Mortality In Patients Hospitalized With Covid-19

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Abstract

Background: *Common biomarkers used to determine the disease severity and prognosis of corona virus disease -19 (Covid-19) are well determined. Among these biomarkers only few can reliably predict disease outcome but they are not easily available and costly. So organ-specific functional status especially acute kidney injury (AKI) can be use as predictor of prognosis.*

Objective: *To determine the kidney disease indicator as a marker in predicting the severe disease in COVID-19 patients.*

Material & Methods: *We studied the health records for all purposively selected hospitalized Covid-19 patients for three months from 1st May to 31st July, 2020, at combined military hospital Dhaka, Bangladesh. Those who were more than 18 years old and hospitalized RT-PCR positive for COVID-19 patients were enrolled. Those having history of renal replacement therapy (RRT) and unwilling to participate were excluded from the study. Kidney disease significance between survivors and deceased were examined using Cox proportional hazard regression analysis. In-hospital death was ascertained by using the Kaplan-Meier method.*

Results: *Total 470 patients were enrolled in this study. Mean age of study population was 54.7 (± 14.3) years and male to female ratio was about 2:1. Hypertension (51.91%) and diabetes mellitus (43.19%) were the most common co morbidity. During hospital stay 106 (22.55%) patients developed AKI. Total 23 (4.89%) patients were died of the total study population. Among them 19 (82.60%) had AKI. Mortality rate was significantly (P value<.001) higher among patients who developed AKI than those who did not (82.60 % vs 17.40%).*

Conclusion: *Monitoring functional status of kidney should be given due importance to all Covid-19 patients even with mild disease. Early diagnosis and appropriate treatment of kidney injury and avoidance of nephrotoxic medications may help to reduce mortality and improve prognosis of COVID-19.*

Key words: *Acute kidney injury (AKI); Corona virus disease-19; Predictor of mortality.*

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Introduction

The pandemic of corona virus disease (COVID-19) has started 2019. It is the deadliest pandemic after the Spanish flu in 1919 1. Causative organism of the disease is a virus, known as severe acute respiratory syndrome corona virus (SARS-CoV-2).[2] As of 27 May 2022, there have been 1,953,328 confirmed cases of COVID-19 with 29,130 deaths in Bangladesh .[3] Presentation of the disease is versatile. Most of these COVID-19 patients are either asymptomatic or mildly symptomatic and usually recover with or without supportive treatment. Nearly 20% of patients develop severe respiratory symptom and require immediate oxygen supplementation. A few of these patients become critically ill and develop organ or life threatening condition which need intensive care support.[4] Considering this wide variety of clinical presentation of COVID-19, it is extremely important to identify the patients who are at risk. Pathophysiology involving a cytokine storm, endothelitis are well established mechanism of severe covid-19 infection now a day.[5,6] Common biomarkers used to determine the disease severity and prognosis are lactate dehydrogenase (LDH), transaminases, C-reactive protein (CRP), activated partial thromboplastin time (aPTT), prothrombin time (PT), D-dimer, interleukin (IL)-6, procalcitonin (PCT). Among these biomarkers only few can reliably predict disease outcome and even fewer can predict treatment responses.[7] But considering the Bangladesh perspective these biomarkers are costly and not easily available in most of the

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government and private hospital. Severe COVID-19 infection often complicated to heart, liver, and kidney dysfunction. So considering the co morbidity and organ-specific functional status can be use as markers or predictor of disease severity and assessment of treatment response during evaluation of these patients. Acute Kidney injury (AKI) is a major complication of COVID-19 and a significant risk factor of death.[8] This aim of this study was to determine the acute kidney injury as a marker that is clinically helpful in predicting a severe disease in COVID-19 patients.

Material and Methods

This cross sectional study was carried out among 470 purposely selected COVID-19 patients admitted at Combined Military Hospital (CMH) Dhaka, Bangladesh from May 1, 2020 to July 31, 2020, (three months). Those who were more than 18 years old and hospitalized RT-PCR positive for COVID-19 patients were enrolled. Those having history of renal replacement therapy (RRT) in the form of maintenance dialysis or renal transplant recipient and unwilling to participate were excluded from the study. The investigation method includes questionnaire, clinical examination and laboratory investigation. The clinical and laboratory data were collected from medical records. The first day of symptom onset was considered as first day of disease. Definition of AKI was adopted from Kidney Disease Improving Global Outcomes (KDIGO) criteria as increase in S.Cr (Serum creatinine) by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or increase in S.Cr to ≥ 1.5 times from baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume less than 0.5ml/kg/hour within 6 hours.[9] The stage of AKI was determined using serum creatinine level with increase 1.5-1.9 as stage I, 2.0-2.9 as stage II and ≥ 3 times from baseline as stage III. The endpoint was the in-hospital death. Data analysis was performed by Statistical Package for Social Science-20 (SPSS-20). Numerical variables are summarized as mean with standard deviation (SD). Categorical variables are presented as number with percentage. Level of significance was measured by using appropriate procedures like chi-square test (X2), t-test, or Fisher's exact for categorical variables and nonparametric Kruskal-Wallis test for continuous variables. The cumulative rates of in-hospital death were ascertained by using the Kaplan-Meier method. The associations of kidney disease significance between survivors and deceased were examined using Cox proportional hazard regression analysis. Level of significance (p value) was set at 0.05.Ethical clearance was obtained from ethical clearance committee of CMH Dhaka.

Table I: Demographic and clinical characteristics of the study cohort (n=470)

Character	Variable	Total (N= 470)	Deceased (N=23)	Survivors (N=447)	P value
Demographic	Age (Years)	54.7 (± 14.3)	64.9 (±11.2)	54.2 (±14.3)	<.001
	Male	315 (67.02%)	15 (65.22%)	300 (67.11%)	0.824
	Female	155 (32.98%)	8 (34.78%)	147 (32.89%)	0.824
Presentation	Fever	336(71.49%)	19 (82.61%)	317 (70.92%)	0.343
	Fever duration	5.75 (± 4.2)	7.17 (±2.72)	5.68 (±4.25)	0.016
	SOB	202 (42.98%)	22 (95.65%)	180 (40.27%)	< .001
	Cough	263 (55.96%)	15 (65.22%)	248 (55.48%)	0.397
	Loose Motion	61 (12.98%)	3 (13.04%)	58 (12.98%)	1.000
	Fatigue	134 (28.51%)	6 (26.09%)	128 (28.64%)	1.000
Co morbidity	DM	203 (43.19%)	15 (65.22%)	188 (42.06%)	0.032
	HTN	244 (51.91%)	17 (73.91%)	227 (50.78%)	0.033
	IHD	69 (14.68%)	9 (39.13%)	60 (13.42%)	0.002
	CVD	10 (2.13%)	1 (4.35%)	9 (2.01%)	0.398
	COPD/Asthma	41 (8.72%)	2 (8.7%)	39 (8.72%)	1.000
	CKD	61 (12.98%)	12 (52.17%)	49 (10.96%)	<.001
	Pregnant	10 (2.13%)	0 (0%)	10 (2.24%)	1.000
Clinical	Systolic BP	123 (± 18)	118 (± 27.8)	124 (± 17.3)	0.463
	Diastolic BP	77.2 (± 10.3)	69.1 (± 20.0)	77.6 (± 9.38)	0.054
	RR	22.3 (± 5.16)	29.3 (± 4.58)	21.9 (± 4.93)	<.001
	Temp (F)	99.6 (± 1.43)	100 (± 1.39)	99.6 (± 1.43)	0.023
	BMI	25.2 (±2.77)	24.5 (±2.78)	25.3 (±2.76)	0.134
	24hr U/O/ L	1.17 (± 0.543)	0.677 (± 0.582)	1.2 (± 0.529)	<.001
	SpO2 %	92.1 (± 7.79)	83.3 (± 7.91)	92.5 (± 7.52)	<.001
	ICU needed	118 (25.11%)	17 (73.91%)	101 (22.6%)	<.001
	O2 Support	310 (65.96%)	23 (100%)	287 (64.21%)	<.001
	Inotrope needed	41 (8.72%)	19 (82.61%)	22 (4.92%)	<.001
	Dialytic support	37 (7.87%)	23 (100%)	14 (03.13 %)	<.001
	Hospital days	8.77 (± 5.81)	11.4 (± 5.88)	8.64 (± 5.81)	0.018

Comparisons are made between Deceased and Survivors using Fisher exact test for qualitative data and nonparametric Kruskal-Wallis test for quantitative data.

Results

Total 470 patients were enrolled in this study. Mean age of study population was 54.7 (± 14.3) years and male to female ratio was about 2:1. Most common symptom was fever followed by cough, breathlessness. Hypertension (51.91%) and diabetes mellitus (43.19%) were the most common co morbidity. Chronic kidney disease (CKD) was the fourth common co morbidity (12.98%). Mean (±SD) duration of illness among survivors and deceased was 8.64 (± 5.81) and 11.4 (± 5.88) days respectively.

During hospital stay 106 (22.55%) patients developed Acute KidneyInjury (AKI). Among them 50 (11%) had AKI on CKD, among the total 61(12.98%) CKD patients. Dialysis was needed for 37 patients (overall 7.87% of all patients), representing 34.90% of those with AKI. In-hospital death occurred in 23(4.89 %) of total admitted patients. The mean (±SD) time to death was 11.4 (± 5.88) days. Elevated 48 hours serum creatinine among the deceased was 2.11 (± 1.71) which was comparatively higher than those of the survivors (1.20 (± 1.70)(Table-I , Table-II).

Table II: Laboratory characteristics of the study cohort (n=470)

Variable	**Total** (N = 470)	**Deceased** N= 23 (4.89%)	**Survivors** N=447 (95.11 %)	**P value**
Hb (gm/dl)	12.1 (± 1.76)	11.2 (± 2.00)	12.2 (± 1.74)	0.042
TLC(1x109)	10.4 (± 6.21)	15.5 (± 8.08)	10.1 (± 5.99)	<.001
Lymph%	19.7 (± 13.1)	8.90 (±3.38)	20.3 (± 13.2)	<.001
Proteinuria	162 (34 %)	20 (86 .12 %)	142 (31.76%)	<.001
Haematuria	63 (13.4%)	12 (52.17%)	51 (11.41%)	<.001
u/PCR(mg/mmol)	76.85 (± 135.8)	110 (±71.6)	73.9 (±140)	0.009
Urea(mg/dl)	53.5 (± 34.5)	103 (± 59.6)	50.9 (± 30.7)	<.001
Admission/Cr (mg/dl)	1.04 (± 0.611)	1.38 (± 1.06)	1.02 (± 0.575)	0.009
48 hrs Cr (mg/dl)	1.25 (± 1.71)	2.11 (± 1.71)	1.20 (± 1.70)	0.003
LDH (U/L)	832 (± 430)	1105 (± 350)	818 (± 429)	<.001
CPK	295 (± 409)	433 (± 456)	288 (± 406)	0.056
ALT (U/L)	58 (± 53.8)	78.5 (± 93)	56.9 (± 51)	0.985
Procalcitonin (ng/ml)	0.998 (± 3.22)	1.58 (± 2.29)	0.931 (± 3.31)	0.003
CRP (mg/L)	10.2 (± 7.60)	14.4 (± 8.40)	9.97 (± 7.50)	0.006
Ferritin (ng/ml)	969 (± 1492)	1415 (± 1329)	946 (± 1497)	0.017
D - dimer (mcg/ml)	1.09 (± 1.04)	2.24 (± 1.22)	1.03 (± 0.994)	<.001
CT Involvement (%)	41.5 (± 25.3)	64.9 (± 17.4)	39.6 (± 25)	<.001

Comparisons are made between deceased and survivors using Fisher exact test for qualitative data and nonparametric Kruskal-Wallis test for quantitative data.

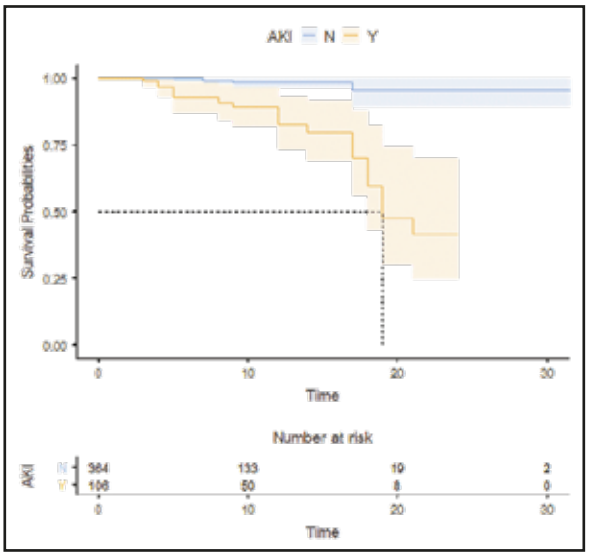

Figure 1: Kaplan-Meier curve showing the incidence of hospital death of covid-19 patients with AKI (n=470).

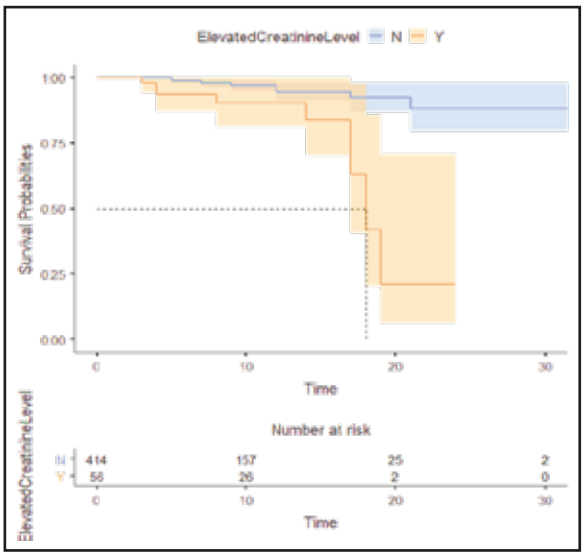

Figure 2: Kaplan-Meier curve showing the incidence of hospital death of covid-19 patients with elevated creatinine (n=470).

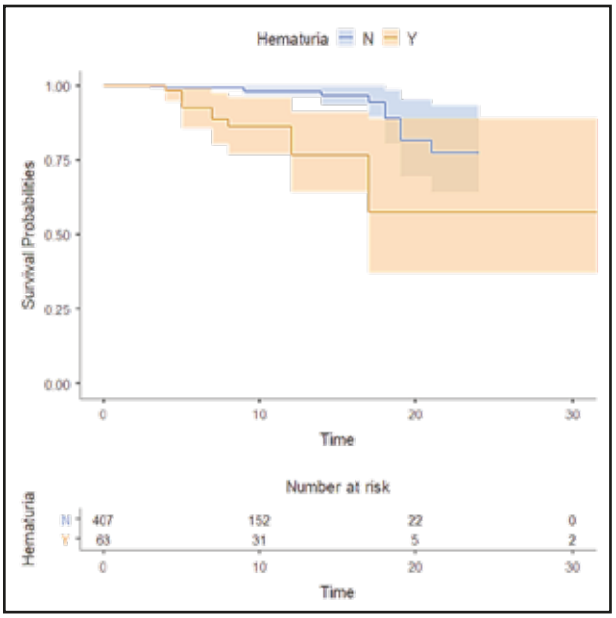

Figure 3: Kaplan-Meier curve showing the incidence of hospital death of covid-19 patients with haematuria (n=470).

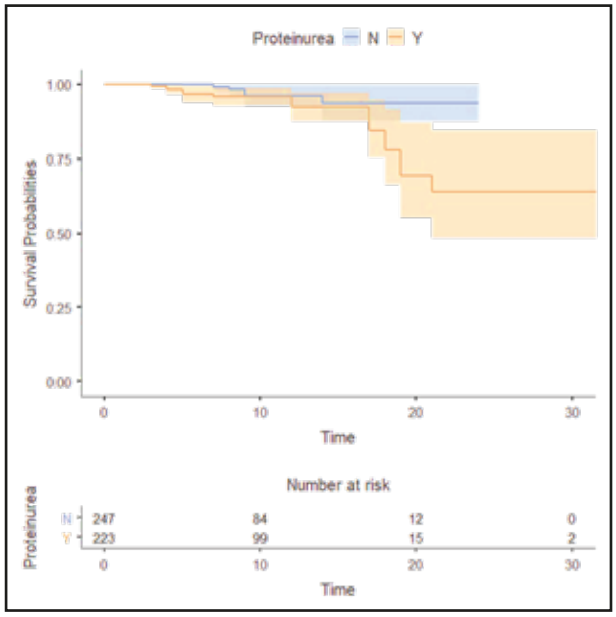

Figure 4: Kaplan-Meier curve showing the incidence of hospital death of covid-19 patients with proteinuria (n=470).

Kaplan-Meier test demonstrated that higher in-hospital death for patients with abnormalities in kidney function, including elevated 48 hours serum creatinine, hematuria, proteinuria, and AKI (Fig 1, Fig 2, Fig 3 and Fig 4) .

Cox regression analysis also demonstrated that the kidney disease exponents as mentioned above were also strongly related with in hospital death (Fig 5).

Hazard ratio for all form of AKI, elevated serum creatinine, hematuria, proteinuria were strongly associated with hospital death in patients with Covid-19 (Table-III)

Table III: Association between kidney disease and hospital death in patients with Covid-19

Variables	Hazard Ratios	95% Confidence Interval	P value
Age > 65 years	0.65	0.36 -1.17	0.149
Sex	0.44	0.18 -1.06	0.068
Any Comorbidity	0.15	0.02 -1.12	0.065
Proteinuria	2.08	1.03 -4.20	0.042
Hematuria	5.39	2.37 -12.24	<0.001
Elevated Serum Creatinine	6.45	2.84 -14.69	<0.001
AKI	13.23	4.48 -39.05	<0.001

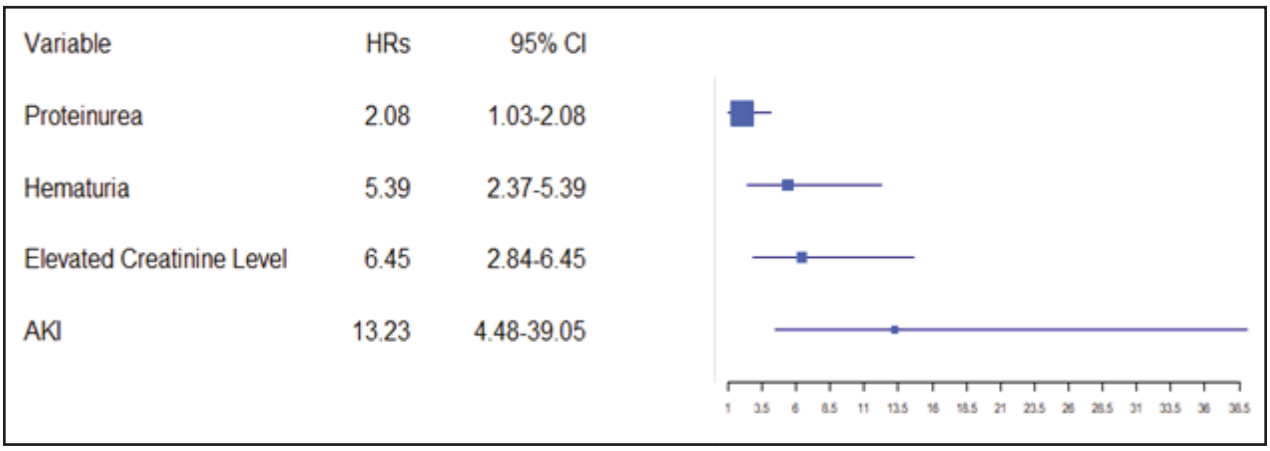

Figure 5: Cox regression analyses showing the effect of proteinuria, hematuria, elevated serum creatinine and AKI on the survival of covid-19 cohort.

Discussion

This study was conducted in a tertiary care hospital. We observed a high prevalence of kidney disease in hospitalized COVID-19 patients. We had 106 (22.55%) AKI patients as evidence by either creatinine criteria or urine output criteria in our study population. Jamie S. H et al also found 1993 (36.6%) AKI cases, in their study.[10] In our study we found substantially good number of patients developing haematuria and proteinuria during their hospital stay which were indicator of kidney disease. Proteinuria and haematuria was found among 162(34%) and 63 (13.4%) participant respectively. Yichun C, at al. in their study also got higher frequency of proteinuria 194 (43.89%) and haematuria 118(26.69 %).[11] One probable cause of this high frequency of acute kidney injury and other depicter of kidney involvement at hospitalized COVID-19 patient was that, many of them had past history of DM (43.19%), HTN (51.91%), CKD (12.97%) and IHD (14.68%). Such patients had a pro-inflammatory state with functional defects in immune system. On the other hand many of them develop multi organ failure and septicemia during their course of illness. Average procalcitonin, CRP, D-dimer were 1.09 (± 1.04) ng/ml , 10.2 (± 7.60) mg/L, 0.998 (± 3.22) mcg/ml respectively in our study population. Hadith R et al. also depict similar findings of high level of Procalcitonin, CRP, D-dimer in their study.[12] In addition to above mention possibilities, factors like use of anti-platelet, anticoagulant, immunosuppressive medication and drug interaction may played a role in this situation.

Among the study population presence of acute kidney injury and other evidence of kidney damage as indicated by presence of proteinuria and haematuria was significantly associated with in-hospital death. We found mean (±SD) elevated 48 hours serum creatinine was 2.11 (± 1.71 mg/dl and urinary protein-creatinine ratio (u/PCR) was 110 (±71.6 mg/mmol) among the deceased which were significantly higher (P value<0.001) in comparison with the survivor. Similarly haematuria also significantly (P value<0.001) associated with in hospital death. Rong H D et al. also found higher mortality among the Covid-19 patient who had evidence of kidney injury.[13] Total 23 (4.89%) patients were died among the total study population, of them 19 (82.60%) had AKI. Mortality rate was significantly higher among patients who developed AKI than those who did not (82.60 % vs 17.40%). The Cox regression analysis for mortality demonstrated that AKI, elevated 48 hours serum creatinine after admission, haematuria and proteinuria were independently associated with risk of death. (HR 13.23, 6.45, 5.39 and 2.08 respectively) [Fig: 5] This increased mortality associated with AKI has also illustrated in the Kaplan-Meier curve (Fig: 1, 2,3 and 4). Star RA et al. also demonstrate the association of AKI with poor prognosis in their study of covid-19 cohort.[14] Total 37 patients required renal replacement therapy and among them 23 died of total 106 AKI populations. .Ronco C et al. also demonstrated that patient who required renal replacement therapy had poor prognosis.[15] In our study, we found AKI was an independent risk factor irrespective of age, sex and co-morbidities. Because of the observational nature and small sample size of the study, we could only determine an association, but not the definitive cause. However, we presume as the COVID-19 patients developed hyper inflammatory state complicated to capillary leakage may link to excess fluid loss and volume depletion that evolved during the course of the disease. Other factor like presence of preexisting kidney disease, development of septicaemia during the course of illness, non -judicial use of diuretics and nephrotoxic drug may contribute this grave condition. A long term follow-up is needed to determine the condition of those patients who survive AKI.

Conclusion

Monitoring functional status of kidney should be given due importance to all Covid-19 patients even with mild disease. Any alteration of kidney function, particularly reduce urine output and raised serum creatinine have paramount significance in clinical practice. Early diagnosis and treatment of renal injury, including appropriate hemodynamic support and avoidance of nephrotoxic medications where possible, may help to reduce mortality and improve prognosis of COVID-19.

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