

RESEARCH PAPER

Incidence and predictors of acute kidney injury among hospitalized patients with COVID-19 infection

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Abstract

Background and objectives: Acute kidney injury (AKI) may occur in the setting of COVID-19 infection and associated with worse outcome. We aimed to estimate the incidence of AKI among hospitalized patients with COVID-19 infection.

Methods: We conducted an observational study on 339 hospitalized patients with COVID-19 infection at Basra teaching hospital for two months. We studied the rate of AKI, requirement for renal replacement therapy (RRT) and in-hospital mortality.

Results: Among 339 hospitalized patients, AKI was reported in 54 (16%). The peak stages of AKI were stage 1 in 42.6%, stage 2 in 22.2% and stage 3 in 35.2%. AKI was primarily seen in patients with shock on vasopressors in 64.8% and in patients on mechanical ventilation in 25.9%. Increased age, obesity, hypertension, vasopressors and mechanical ventilation were independent risk factors for development of AKI. Among the 54 patients with AKI, 20 patients (37%) required renal replacement therapy (RRT). Sixteen out of 20 patients (80%) of those who required RRT died and only 5 out of 34 patients (15%) of those not required RRT died with a totally mortality in AKI patients of 21 patients (39%).

Conclusions: AKI occurs in patients with COVID-19 disease especially in ICU in association with vasopressors use and mechanical ventilation and is associated with poor prognosis.

Keywords: COVID-19, acute kidney injury, intensive care unit, mechanical ventilation, vasopressors

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Introduction

COVID-19 pandemic affect over 2.5 million individuals in less than 5 months. COVID-19 infection may cause multiple

organ dysfunction and AKI is a marker of disease severity and bad outcome in critically ill patients (1). The predisposing factors for AKI include hypovolemia, sepsis, nephrotoxins, direct viral infection of the renal tubular epithelial cells, endothelial cells and podocytes, macrophage activation syndrome, rhabdomyolysis, microthrombi development and acute cardiorenal syndrome (1). The incidence of AKI was differ in different countries and different studies; the

incidence of AKI was reported as follows: 3% in all hospitalized patients and 19% in the ICU by systematic review (2), 22.2% of hospitalized patients in New York City between March 1 and April 4, 2020 (3), 3.6% in cohort study of 138 hospitalized adults admitted to Zhongnan Hospital in Wuhan, China in January 2020 (4), 3% in 99 adults admitted to Jinyintan Hospital in Wuhan, China in January 2020 (5), 5.1% in a cohort study of 701 patients hospitalized in China in 2020 (6) and 0% in a cohort study of 116 patients admitted to Renmin Hospital in Wuhan, China between January 14 and February 13, 2020 (7). AKI was associated with increased mortality (8-10).

The purpose of the study was to estimate the incidence of AKI in hospitalized patients with COVID-19 infection in Basra, Iraq.

Methods

Data source, study design and cohort

This was a single center observational study conducted on patients hospitalized at Basra Teaching Hospital (Basra, Iraq) from March 1, 2020, to May 10, 2020 with clinical diagnosis of COVID-19 infection which was confirmed by positive polymerase chain reaction in specimens obtained from nasopharyngeal swabs. The study was approved by the Institutional Review Board of the University of Basra and Basra Health Directorate of Ministry of Health. Data were obtained from the medical records of patients in the medical wards and in the intensive care units (ICU). Patients in the ICU were either transferred from the medical wards or admitted primarily at the ICU. The patients with baseline chronic kidney disease were excluded from the study.

Definitions and measurements

AKI was defined according to kidney disease improving global outcomes (KDIGO) criteria as follows: stage 1- increase in serum creatinine by 0.3 mg/dL within 48 hours or a 1.5 to 1.9 times increase in serum creatinine from baseline within 7 days; stage 2- increase in serum creatinine 2 to 2.9 within 7 days; stage 3- increase in serum creatinine 3 times or more or serum creatinine > 4 mg/dL within 7 days or renal replacement therapy (RRT) requirement (11). Baseline serum creatinine was defined as a median serum creatinine within 8 to 365 days prior to hospital admission. In patients with no prior baseline serum creatinine, the admission serum creatinine was used as the baseline. The requirement for RRT was defined as per KDIGO AKI criteria for those with stage 3 AKI.

Urine was examined for electrolytes and urinalysis using automated microscopy with the onset of AKI. Significant proteinuria was defined as > 2+ protein on urine dipstick or > 0.5 g/g on urine protein-to-creatinine ratio. Nephrotic-range proteinuria was defined as > 3+ protein on urine dipstick or > 3 g/g on urine protein-to-creatinine ratio. Significant hematuria was defined as > 5 rbcs/hpf and significant leukocyturia was defined as > 6 wbcs/hpf.

Covariates

Data were collected on patient demographics, history of chronic diseases, bed location, home medications. Chronic kidney disease was not included in this study. Blood workups for inflammatory markers were done and the peak levels for the positive acute phase reactants and the lower levels for the negative acute phase reactants were documented. Plasma electrolytes (monovalent and divalent) were measured by arterial blood gas and basic metabolic panel and the values during the AKI was utilized. Patients

required vasopressors were those with mean arterial pressure (MAP) < 60 mm Hg. Patients required mechanical ventilation were assessed by the intensivist who decided to intubate the patients with severe respiratory distress that is not responding to high flow oxygen therapy and prone position. Adult respiratory distress syndrome was defined as acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen [PaO₂/FiO₂] ≤ 200 mmHg with bilateral infiltrates on chest radiograph (12).

Outcomes

The primary outcome of the study was the development of AKI. Secondary outcome was need for RRT and in-hospital mortality. The mode of RRT was either intermittent hemodialysis or continuous renal replacement therapy. Patients who required mechanical ventilation were documented.

Statistical analysis

Descriptive statistics were performed including means and standard deviations for normally distributed continuous variables, medians and interquartile ranges for skewed continuous variables and proportions for categorical variables. Baseline clinical and laboratory characteristics between patients with and without acute kidney injury (AKI) and across the stages of AKI were compared statistically; Fisher exact test was used for categorical variables and nonparametric Kruskal-Wallis test was used for continuous variables. Laboratory characteristics of patients with AKI were described as medians and interquartile ranges for baseline and admission serum creatinine and as number and percentages for the other variables and also were compared statistically across the stages of AKI

using Chi square test. The identifications of risk factors for the development of AKI, binary logistic regression analyses were performed with adjustment of risk factors that differed between patients who developed AKI from those who did not. All statistical tests were 2-sided, and a P value <0.05 was considered statistically significant. Statistical analysis was done by SPSS version 25.

Results

From March 1, 2020, to May 10, 2020, 351 patients were admitted to Basra teaching hospital with a diagnosis of COVID-19 infection that was confirmed by polymerase chain reaction. Of these, 339 were used in the analysis cohort after exclusion of 12 patients with CKD. Overall, 54 of 339 patients (16%) developed AKI during their hospitalization (Figure 1). Of total of 54 AKI patients, 20 patients (37%) required RRT during their hospitalization (19 patients were in the ICU and 1 patient was in the medical ward) and 34 patients (63%) were not required RRT. Twenty patients required renal replacement therapy (RRT). Sixteen out of 20 patients (80%) of those who required RRT died and only 5 out of 34 patients (15%) of those not required RRT died with a totally mortality in AKI patients of 21 patients (39%).

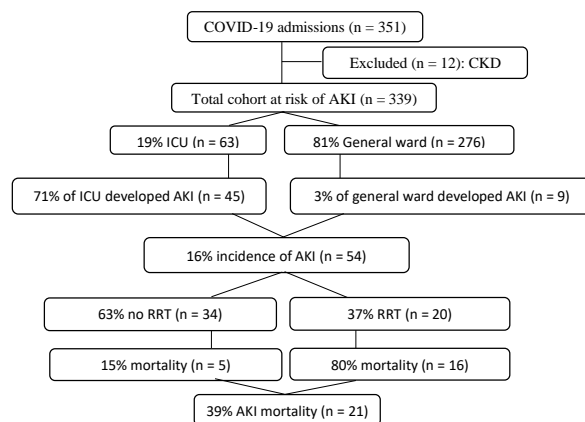


Figure 1. Flow chart illustrating the incidence and mortality of acute kidney injury (AKI) with renal replacement therapy (RRT) requirement.

The baseline clinical characteristics of the patients were provided in Table 1. The median age was 51, median BMI was 29, 39% were males, 36% were hypertensive, 26.5% were diabetic. Of these, 63 (18.6%) were admitted to the ICU, 37 (10.9%) had shock, 15 (4.4%) were on mechanical ventilation and 21 (6.2%) died. The frequency of stages of AKI were as follows: stage 1 in 42.6%, stage 2 in 22.2% and stage 3 in 35.2%. Patients with AKI in comparison to those who did not developed AKI were older with a median age of 70, more males (51.9%), obese with median BMI of 32, had more comorbidity (hypertension in 90.7% and diabetes in 64.8%), were more in the ICU (83.3%), more on ventilation (25.9%), more on vasopressors (64.8%) and more likely to die (38.9%). The inflammatory markers were higher in AKI patients. The use of vasopressors, ventilation and death were more in stage 3 AKI (Table 2).

Variables	Overall cohort (n = 339)
Age (years)	51 (41, 60)
Male	132 (39)
BMI (kg/m ²)	29 (28, 30)
BMI > 30	117 (34.5)
Hypertension	122 (36)
Diabetes Mellitus	90 (26.5)
Coronary artery disease	29 (8.6)
Heart failure	17 (5%)
Admission serum creatinine (mg/dL)	0.9 (0.6, 1.0)
ICU	63 (18.6)
Shock/vasopressors*	37 (10.9)
Mechanical ventilation	15 (4.4)
Death	21 (6.2)

Values are expressed as median (interquartile range) or n (%). BMI, body mass index; ICU, intensive care unit; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

*Vasopressors include dopamine and noradrenaline.

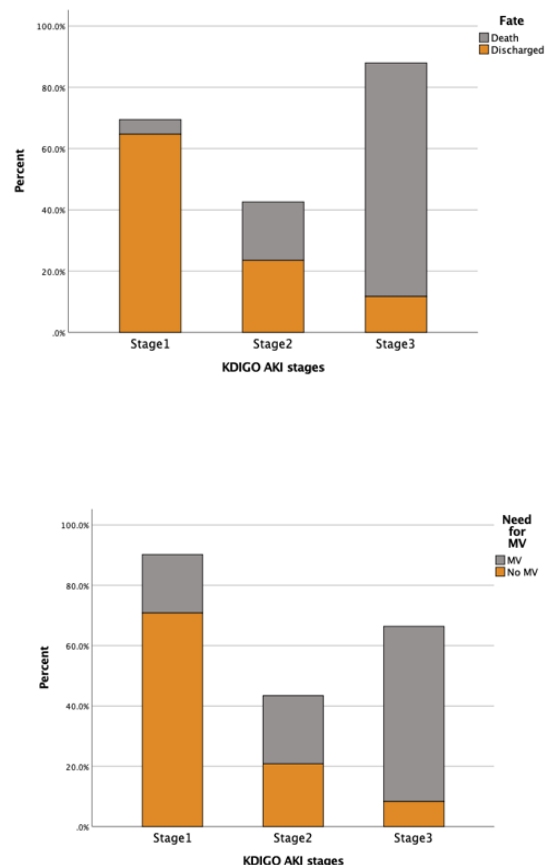


Figure 2. Fate and need for mechanical ventilation according to KDIGO AKI stages status.

In AKI patients, hypernatremia occurred in 48%, hypocalcemia in 76%, hyperkalemia in 19%, hyperphosphatemia in 22%, metabolic acidosis in 30% but lactic acidosis was not reported. Urinary abnormalities showed urine fractional excretion of sodium (FENa) > 40 in 64.8%, sub-nephrotic proteinuria in 32%, hematuria in 22% and leukocyturia in 9% (Table 3).

Independent risk factors for AKI include increased age, obesity, hypertension,

vasopressors use and mechanical ventilation (Table 5).

Mechanical ventilation was more common in stage 3 AKI (58.1%) (Figure 2). Death was more in stage 3 AKI (76.2%) (Figure 3) and death was more in patients required RRT (Figure 4).

Discussions

AKI is a common complication among hospitalized patients for a variety of conditions. In the present study, among patients hospitalized with COVID-19 infection, 16% of patients (3% in the medical ward and 13% in the ICU) developed AKI during their hospitalization. This incidence was similar to systematic review of 9 observational study recruited 2775 patients hospitalized with COVID-19 in China and United State where the incidence of AKI was 3% among all hospitalized patients and 19% among ICU patients (2). A study by Safiya Richardson et al. done on 5700 hospitalized patients with a median age of 63 years and 60.3% were males, reported that the incidence of AKI was 22.2%. The higher incidence compared to the present study may be due inclusion of patients with chronic kidney disease (4.7%) and end-stage kidney disease (3.2%) (3). The incidence of AKI was lower in these studies from China; 3.6% (4), 3% (5), 7% (13), 5.1% (6), 0% (7). Higher incidence of AKI was reported in a study by Hirsch et al. where the rate of AKI was 36.6% which can be explained by large sample size, high rate of comorbidities, more severe cases with use of vasopressors and more mechanical ventilation. The rate of mechanical ventilation in the present study is 25.9% compared to 53.6% in Hirsch study (14). The rate of AKI by Velez et al. was 28% and this higher rate can be explained by severe disease where mechanical ventilation was used in 63% (15). The requirement for RRT is higher in our study compared to this study (5% vs 2%) (2). In-

hospital mortality was 38.9% in our study which is higher than study by Cheng et al. where the in-hospital mortality was 16.1% (8). The development of AKI was associated with increased in-hospital mortality (3, 9). Mortality

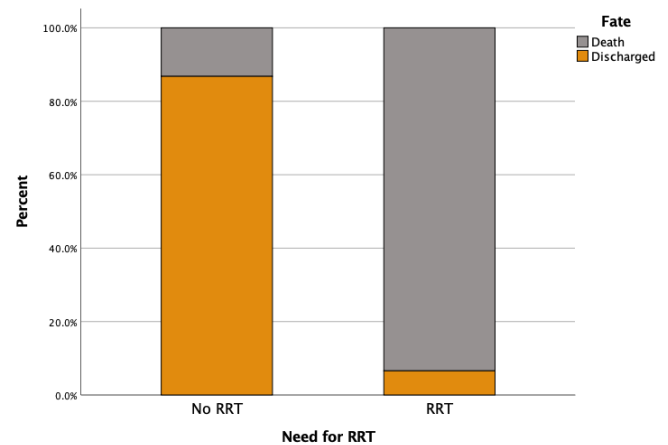


Figure 3. Fate of AKI patients per renal replacement therapy status.

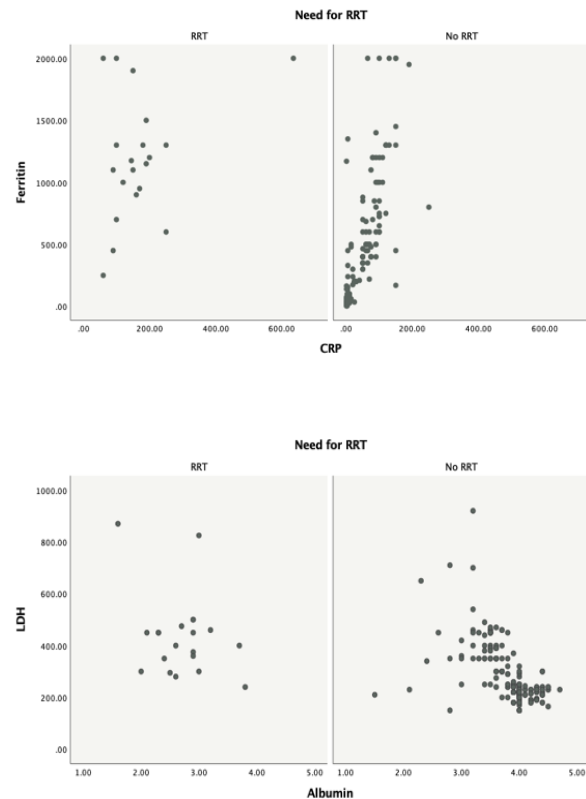


Figure 4. Correlation of laboratory parameters with requirement for RRT.

Table 2. Baseline and laboratory characteristics of the study cohort by AKI and KDIGO AKI stages' status (n = 339)

CHARACTERISTICS	NO AKI (N = 285)	AKI (N = 54)	KDIGO AKI STAGE			P VALUE ^A (AKI VS NO AKI)	P VALUE ^B (AKI KDIGO)
			Stage 1 (n = 23)	Stage 2 (n = 12)	Stage 3 (n = 19)		
Age	48 (39, 57)	70 (65, 75)	69 (65, 73)	69 (61, 77)	70 (65, 76)	< 0.001	0.521
Male	104 (36.5%)	28 (51.9%)	12 (52.2%)	7 (58.3%)	9 (47.4%)	0.047	0.837
BMI (kg/m ²)	29 (28, 29))	32 (30, 35)	30 (30, 31)	31 (30, 33)	35 (34, 36)	< 0.001	<0.001
Hypertension	73 (25.6%)	49 (90.7)	20 (87%)	11 (91.7%)	18 (94.7%)	< 0.001	0.682
Diabetes mellitus	65 (19.3%)	35 (64.8%)	12 (52.2%)	7 (58.3)	16 (84.2)	0.001	0.083
Coronary artery disease	8 (2.8%)	21 (38.9%)	9 (39.1%)	5 (41.7%)	7 (36.8%)	<0.001	0.964
Heart failure	5 (1.8%)	12 (22.2%)	(30.4%)	(41.7%)	0 (0.0%)	< 0.001	0.011
ICU	18 (6.3%)	45 (83.3%)	17 (73.9%)	12 (100%)	16 (84.2%)	< 0.001	0.144
Mechanical ventilation	1 (0.4%)	14 (25.9%)	1 (4.3%)	3 (25%)	10 (52.6%)	< 0.001	0.002
Vasopressors ^c	2 (0.7%)	35 (64.8%)	12 (52.2%)	10 (83.3%)	13 (68.4%)	< 0.001	0.172
Death	0 (0.0%)	21 (38.9%)	1 (4.8%)	4 (19%)	16 (76.2%)	< 0.001	< 0.001
Admission serum creatinine mg/dL	0.6 (0.6, 0.8)	1.7 (1.4, 3)	1.4 (1.3, 1.5)	1.7 (1.4, 1.9)	3.2 (3, 4)	<0.001	< 0.001
Random plasma glucose mg/dL	130 (130, 140)	150 (130, 300)	150 (140, 300)	165 (130, 350)	150 (100, 300)	< 0.001	0.471
CRP (mg/L)	5 (5, 5)	100 (15 – 635)	75 (65, 110)	105 (91, 120)	150 (90, 190)	< 0.001	0.023
Ferritin (ng/mL)	50 (50, 73)	1000 (575, 1300)	750 (400, 1200)	1100 (962, 1300)	1175 (685, 1500)	< 0.001	0.038
LDH (U/L)	200 (200, 230)	400 (350, 460)	400 (350, 450)	400 (350, 457)	450 (350, 500)	<0.001	0.511
Albumin (g/dL)	4 (4, 4)	3.2 (2.7, 3.5)	3.4 (3.2, 3.5)	3.4 (2.6, 3.5)	2.7 (2.3, 2.9)	< 0.001	0.001

Values are expressed as median (interquartile range) or n (%).

AKI, acute kidney injury; KDIGO, kidney disease improving global outcomes; ICU, intensive care unit; CRP, C-reactive protein; LDH, lactate dehydrogenase.

^aComparisons are made between no AKI and AKI using Fisher exact test for categorical variables and nonparametric Kruskal-Wallis test for continuous variables.

^bComparisons are made across the stages of AKI using Kruskal-Wallis rank sum test.

^cVasopressors include dopamine and noradrenaline.

Table 3. Laboratory characteristics of patients by KDIGO AKI stages (n = 54)

CHARACTERISTICS	VALUES	AKI STAGE 1 (N = 23)	AKI STAGE 2 (N = 12)	AKI STAGE 3 (N = 19)	P VALUE*
Baseline serum creatinine (mg/dL)	0.7 (0.6, 0.9)	0.85 (0.7, 0.9)	0.7 (0.5, 0.9)	0.6 (0.5, 1.0)	0.015
Admission serum creatinine (mg/dL)	1.7 (1.4, 3)	1.4 (1.3, 1.5)	1.7 (1.4, 1.9)	3.2 (3, 4)	< 0.001
Hyperglycemia > 200 mg/dL	22 (41%)	9 (39.1%)	5 (41.7%)	8 (42.1%)	0.978
Hypernatremia > 145 mmol/L	26 (48%)	14 (60.9%)	7 (58.3%)	5 (26.3%)	0.054
Hyponatremia < 135 mmol/L	3 (6%)	0 (0.0%)	0 (0.0%)	3 (15.8%)	ND
Hyperkalemia > 5.5 mmol/L	10 (19%)	0 (0.0%)	1 (8.3%)	9 (47.4%)	0.001
Hypokalemia < 3.5 mmol/L	4 (7%)	1 (4.3%)	1 (8.3%)	2 (10.5%)	0.248
Hypocalcemia < 8.8 mg/dL	41 (76%)	16 (69.6%)	10 (83.3%)	15 (78.9%)	0.617
Hyperphosphatemia > 4.5 mg/dL	12 (22%)	1 (4.3%)	1 (8.3%)	10 (52.6%)	0.001
Metabolic acidosis < 24 mmol/L	26 (30%)	2 (8.7%)	7 (68.3)	17 (89.6%)	< 0.001
Hyperlactatemia 2-4 mmol/L	4 (6%)	0 (0.0%)	1 (8.2%)	3 (15.7%)	0.045
Lactic acidosis	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	ND
Urine Na <20 mmol/L	19 (35.2)	16 (69.6)	2 (16.7)	1 (5.3)	0.725
>40 mmol/L	35 (64.8)	7 (30.4)	10 (83.3)	18 (94.7)	0.0001
Proteinuria 2+ dipstick or UPCR 0.5 – 3 g/g	17 (32%)	4 (17.4%)	8 (66.7%)	5 (26.3%)	0.012
3+ dipstick or > 3 g/g	2 (4%)	0 (0.0%)	0 (0.0%)	2 (10.5%)	ND
Hematuria > 5 rbc/hpf	12 (22%)	2 (8.7%)	4 (33.3%)	6 (31.6%)	0.01
Leukocyturia > 6 wbc/hpf	5 (9%)	1 (4.3%)	2 (16.7%)	2 (10.5%)	0.136

Values are expressed as median (interquartile range) or n (%).

AKI, acute kidney injury; KDIGO, kidney disease improving global outcomes; CRP, C-reactive protein; LDH, lactate dehydrogenase; UPCR, urine protein-to-creatinine ratio; ND, statistic can't be done.

*Comparisons are made across all stages of AKI using Kruskal-Wallis rank sum test.

Table 4. Univariate and multivariate logistic regression analyses of risk factors associated with development of AKI

VARIABLE	UNADJUSTED OR	95% CI	P VALUE	ADJUSTED OR	95% CI	P VALUE
Age (year)	20.2	9.5-42.8	<0.001	4.60	1.2-18.4	0.031 ^a
Male	2	1.14-3.68	0.022	3.46	0.85-13.9	0.082
Obesity	25	10.2-61	<0.001	9.77	2.2-42.6	0.002 ^a
HTN	28.5	10.9-74.2	<0.001	8.49	1.6-44.2	0.011 ^a
DM	7.7	4-14.5	0.001	1.58	0.39-6.4	0.519
CAD	22.03	9.04-53.7	<0.001	2.94	0.59-14.5	0.187
HF	16.00	5.37-47.7	<0.001	3.42	0.52-22.6	0.202
Vasopressors ^b	260.7	58-1166	<0.001	27.2	3.8-195.3	0.001 ^a
MV	355	46-2717	<0.001	38.5	3.0-490.8	0.005 ^a

AKI, acute kidney injury; CI, confidence interval; OR, odds ratio; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; MV, mechanical ventilation.

^aindependent risk factors include increased age, obesity, hypertension, vasopressors use and mechanical ventilation. ^bVasopressors include noradrenaline and dopamine.

was 57% in a study by Pei et al. which may be due to more severe disease and large sample size (10). Mortality in our study according to AKI stages was 4.8% in stage 1, 19% in stage 2 and 76.2% in stage 3 which is lower than study by Pei where the mortality was 25% in stage 1, 75% in stage 2 and 91% in stage 3 (10). In our analysis, the greater predictors for development of AKI were increased age and vasopressors use which was in agreement with study by Hirsch et al. in which the need for ventilator support and vasopressors use were the major predictors for the development of AKI (14). Proteinuria in the present study was reported in 32% which is lower to a study by Cheng et al, where the reported rate was 43.9% and 69% in a study by Velez et al. (8, 15). Proteinuria was reported in 82% in a study by Pei et al (10). Hematuria in the present study was 22% which is similar to a study by Cheng et al. where hematuria was reported in 26.7% (8).

Significant hematuria was reported in 19% in a study by Velez et al. (15). Hematuria was reported in a study by Pei et al. (10).

The present study has limitations. First, the association does not mean causality and because this is an observational study, we can't make causality of association between exposure and AKI. Second, there may be some confounding unmeasured variables that may affect the results of the study. Third, this is a study of AKI in hospitalized patients, so we lack the community cases of AKI.

Conclusions

AKI was a relatively common complication among hospitalized patients with COVID-19. It is linked to severe disease mainly in the ICU in those who required vasopressors and mechanical ventilation. The development of AKI was associated with poor prognosis.

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