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COVID-19 and acute kidney injury presentation; stages and prognosis

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) can present with acute kidney injury (AKI). Although the rate of AKI among these patients is not high, their outcome could be much worse than the other patients. Serum creatinine rise along with other laboratory findings may help as a clinical predictor of COVID-19 disease prognosis.
Objectives: We aimed to evaluate the incidence and possible predictors of AKI occurrence and its outcome during the COVID-19 pandemic.
Patients and Methods: In a retrospective observational study of 946 hospital-admitted patients with confirmed COVID-19 between March 20, 2020 and May 9, 2020, we described AKI incidence and its stages along with their association with demographic data, comorbidities, habitual and past-medical history, and laboratory findings using STATA version 14.
Results: The mean age of participants was 55.6 (±18.7) years of which 60.4% were male. The most and least frequent underlying diseases were hypertension and chronic liver disease, 20.1% and 1.5%, respectively. Among patients with AKI, 45.9% had a higher age mean and female sex was more prevalent. In addition, hypertension, ischemic heart disease, diabetes, and chronic renal disease were more common in patients with AKI compared to patients without AKI. Moreover, AKI patients had lower oxygen saturation and mean levels of lymphocytes and higher mean levels of LDH and CKMB in comparison with no AKI group on admission. Overall, 80% of the patients were discharged (i.e. alive), of which 63.7% were non-severe patients and 19.4% of the patients expired during hospitalization.
Conclusion: Comorbidities were more prevalent among AKI groups. Female and older patients were more prone to AKI during COVID-19 progression. The level of CK-MB was also higher in AKI group, suggesting probable cardiac injury. Lymphopenia and leukocytosis may be poor-prognostic factors for both AKI and COVID-19.

Introduction

In December 2019, abundant cases of pneumonia with unidentified origin presented with acute respiratory distress syndrome (ARDS) in Hubei Province of China. It did not take long for the cause to be discovered and labeled as "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" that resulted in a rapidly progressive pandemic. Soon, "coronavirus disease 2019 (COVID-19)" became a global challenge (1,2) with 105 137 224 confirmed cases and more than 2 284 340 deaths by February first (3).

COVID-19 manifests by various signs and symptoms including fever, cough, fatigue, and hyposmia (4), albeit, ARDS and

Key point

In a retrospective observational study on 946 hospital-admitted patients with confirmed COVID-19, we found that comorbidities were more prevalent among AKI patients and female and older patients were more susceptible to acute kidney injury during the COVID-19 pandemic.

diffuse alveolar destruction are the major complications (5). The virus could also enter the bloodstream and cause multi-organ failure, particularly kidney damage (6).

Along with chronic kidney disease (CKD) as an underlying disease and poor prognostic factor (7), acute kidney injury (AKI) is also a serious complication of COVID-19.

Although it is an uncommon manifestation reported in only 0.5-7% of all cases and 2.9%-23% of ICU patients (8), it carries a high mortality rate (91.7%) and can cause severe forms of the disease (9,10), like previous epidemics of SARS and MERS (6).

Plasma creatinine level was elevated in 4.3% of severe cases and 18.6% of patients by Guan et al (4) and Li et al (10), respectively.

Furthermore, in a study by Cheng et al (11) elevated blood urea nitrogen (BUN) (13.1%), proteinuria (43.9%), and hematuria (26.7%) were reported among patients emphasizing the vital role of understanding how the kidney is involved during this illness. SARS-CoV-2 has already been detected in urine samples and kidney tissues of several patients (12,13) suggesting the direct viral tropism of the kidney. Binding agents of virus, including Angiotensin converting enzyme and dipeptidyl peptidase-4 are highly expressed on renal tubular cells (14,15) which is in accordance with the potential direct cytopathic effects theory for SARS-CoV-2 (8) and the potential drug mechanisms under investigation for the disease (16).

The second postulated mechanism could be the cytokine storm syndrome leading to hypo-perfusion and then pre-renal AKI (6,14,15). Therefore, it is of importance to pay more attention to the kidney and its related diagnostic parameters, especially during the early stages of the disease course to prevent AKI or rationally schedule renal replacement therapy (RRT).

Objectives
In this study, we aimed to study patients presenting with AKI and discuss their clinical manifestations, laboratory findings, including kidney biomarkers, and final outcome with a focus on their electrolyte imbalances. Moreover, it is noteworthy to find factors anticipating a negative prognosis.

Patients and Methods
Study design and population
In this single-center, retrospective study, we enrolled 946 patients with COVID-19 admitted to the Emergency Department of Shohadaye Tajrish hospital from March 20, 2020, to May 9, 2020. Shohadaye Tajrish hospital of Shahid Beheshti University of Medical Sciences is located in Tehran City, Iran. This tertiary teaching hospital is one of the major designated COVID-19 treatment hospital in Tehran. All cases aged more than 14 and were screened due to the presence of clinical presentations attributable to COVID-19 including cough, fever, fatigue, myalgia, hyposmia, pharyngodynia and other upper respiratory tracts infection's symptoms. Based on the WHO's interim guidelines (3), a confirmed COVID-19 patient is defined as an individual with a positive reverse transcription-polymerase chain reaction (RT-PCR) result or a patient with common COVID-19 symptoms and a CT-scan compatible to COVID-19 pattern confirmed by experts.

Based on the disease severity, patients were classified into two groups (17);

Patients presenting with ARDS criteria including dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤92%, PaO2/FiO2 ratio 50% of the lung field during 1-2 days were classified as severe cases. The critically ill cases admitted to respiratory care unit (RCU) due to respiratory failure, sepsis or multiple organs dysfunction were also in this group. As the study population were all inpatients, mild cases (outpatients) were not included in this study and other patients were classified as moderate cases if not severe based on the definition mentioned above.

Laboratory confirmation
For all patients, the throat swabs were used to collect samples and then were put into 150-μL viral preservation solution. After total RNA extraction, SARS-CoV-2 nucleic acid was detected using RT-PCR method. The result was positive if at least one of the following gene sites were amplified: (a) Open reading frame (ORF) 1ab gene, (b) Nucleocapsid protein (NP) gene. The threshold of the RT-PCR cycle was recorded.

Data collection
An expert medical team collected and revised demographic, clinical, laboratory and imaging data from hospital medical records. The missing data were clarified through a phone call or via attending clinician's consultation. The demographic data included age, gender, comorbidities, body mass index (BMI). A thorough medical history had been taken from each patient consisting of clinical symptoms, past-medical and habitual history and final outcome. The recorded laboratory tests included complete blood count (CBC), blood biochemistry, creatine kinase, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), liver enzymes, arterial blood gas, and BUN. In addition, vital signs including O2-SAT at admission, systolic and diastolic blood pressure, heart rate, and respiratory rate were recorded to assess disease severity. All recorded data were transferred to the data-analyzing center and were entered into a computerized database for further statistical analysis.

Definition
AKI was defined based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) definition (18): A rise in serum creatinine (SCr) more than 0.3 mg/dL in 48 hours, or more than 50% rise in SCr, or less than 0.5 mL/kg/h urine volume for more than 6 hours were defined as stage 1. Stage 2 includes patients with a more than 100% rise in SCr two folds times above the baseline. Patients with more than 200% rise in SCr three folds times above the baseline or SCr more than 4 mg/dL were in stage 3

of AKI. Additionally, any patients requiring RRT were in stage 3.

If the baseline SCr was not available, it was calculated based on the Modification of Diet in Renal Disease (MDRD) equation for a normal GFR of 75 mL/min per 1.73 m² (19).

Ethical issues

The research was in accordance with the Declaration of Helsinki. The Ethics Committee of Shahid Beheshti University of Medical Sciences has approved this study (IR.SBMU.MSP.REC.1396.900). Written informed consent was also obtained from all patients.

Statistical analysis

Descriptive statistics were presented using mean (SD) or frequency (percentage). Bivariate comparisons were made using independent-samples t test for continuous variables and chi-square test for categorized variables. Post hoc comparisons were applied whenever necessary. All the analyses were performed using STATA statistical software version 14. Probability level of less than 5% was considered statistically significant.

Results

Overall, data on kidney function tests were available for 946 patients with COVID-19 in two referral hospitals in Tehran city. The Mean age of the patients was 55.6 (±18.7) years and more than half of them (n=572, 60.4%) were male. The most and least frequent underlying diseases reported from the patients were hypertension (HTN) (n=191, 20.1%) and chronic liver disease (n=15, 1.5%), respectively. In terms of hospitalization outcomes, 80% of the patients were discharged (i.e. alive), amongst them the highest proportion belonged to non-severe patients (n=603, 63.7%). 19.4% (n=184) of the patients expired during hospitalization (Table 1).

The proportion of patients with AKI was estimated as 45.9% (n=434), which were categorized into first (n=419, 44.3%), second (n=7, 0.7%), and third stages (n=8, 0.8%).

Compared to patients free of AKI, those with AKI had significantly higher mean age (62 versus 50.2 years, $P<0.001$), and higher proportion of females (44.9% versus 34.9%, $P=0.002$). Patients with AKI reported significantly higher proportions of HTN (26.9%), ischemic heart disease (25.1%), diabetes (19.5%), and chronic renal diseases (9.9%) compared to their non-AKI counterparts (P value for all comparisons <0.001).

Compared to the second and third stages of AKI, patients in the first stage had significantly higher proportion of HTN (n=111, 25.5%), ischemic heart disease (n=105, 24.1%), diabetes (n=81, 18.6%) and chronic renal disease (n=40, 9.2%) (P for all comparisons <0.001). While the prevalence of substance abuse did not show any significant difference between AKI and no AKI patients, its prevalence was significantly higher among patients in the first stage of

Table 1. Baseline clinical characteristics of hospitalized COVID-19 patients

Variable	Overall (n= 946)
Age	55.66 (±18.73)
Gender	
Male	572 (60.47%)
Female	374 (39.53%)
Comorbid conditions	
Asthma	19 (2.01%)
COPD and other respiratory conditions	63 (6.66%)
HTN	191 (20.19%)
IHD	171 (18.08%)
Diabetes	145 (15.33%)
Chronic liver disease	15 (1.59%)
Chronic renal disease	60 (6.34%)
Cancer	42 (4.44%)
BMI (n=381)	
Underweight	15 (3.94%)
Normal	129 (33.86%)
Overweight	175 (45.93%)
Mild obese	47 (12.34%)
Severe obese	15 (3.94%)
Smoking habit	
Non-smoker	884 (93.45%)
Smoker	62 (6.55%)
Medications	
ACEI	26 (2.75%)
ARBs	103 (10.89%)
Hydroxychloroquine	392 (41.44%)
Naproxen	77 (8.14%)
Vancomycin	195 (20.61%)
Intubated	83 (8.77%)
Hospitalization duration (day)	2.83 (±6.40)
Alive	762 (80.55%)
Alive severe	343 (36.26%)
Alive non-severe	603 (63.74%)
Expired	184 (19.45%)

COPD: chronic obstructive pulmonary disease; HTN: hypertension; IHD: ischemic heart disease; BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers;

AKI (n=11, 2.5%, $P<0.001$).

Compared to non-AKI patients, lower mean level of O2 saturation was recorded in AKI patients (88.7 versus 91.1 in non-AKI patients, $P<0.001$). Mean level of O2 saturation was also significantly higher in first stage AKI patients ($P<0.001$). First stage AKI patients also showed significantly higher mean heart rate compared to the other stages ($P<0.001$). Regarding disease outcome, more than half of the expired patients had AKI symptoms (69.9%, $P<0.001$), amongst whom 62% had first stage of AKI. More specifically, AKI symptoms were diagnosed from 57% of alive patients with severe COVID-19, which was significantly higher than severe patients without AKI (42.3%, $P<0.001$; Table 2).

Patients with AKI also showed a higher mean value for LDH (671 versus 587, $P=0.006$), CKMB (41.30 versus 24.5, $P=0.001$), and BUN (30.41 versus 14.91, $P<0.001$).

Table 2. Comorbidities, clinical findings, medications, outcome and laboratory findings of patients

Variable Mean (SD)/Number (%)	No AKI (n=512, 54.1%)	AKI (n=434, 45.9%)	Stages of AKI			P value (no AKI vs. all AKI)	P value (trend)
			1 (n=419, 44.3%)	2 (n=7, 0.7%)	3 (n=8, 0.8%)		
Age (range)	50.2	62.0	61.6 (15-102)	78.8 (40-89)	66.8 (47-81)	<0.001	<0.001
Male	333 (65.04%)	239 (55.07%)	227 (52.3%)	5 (1.15%)	7 (1.61%)	0.002	0.003
Comorbid condition							
Asthma	13 (2.54%)	6 (1.38%)	6 (1.38%)	0	0	0.206	0.626
COPD and other respiratory diseases	28 (5.47%)	35 (8.06%)	32 (7.37%)	1 (0.23%)	2 (0.46%)	0.11	0.079
HTN	74 (14.45%)	117 (26.96%)	111 (25.57%)	2 (0.46%)	4 (0.92%)	<0.001	<0.001
IHD	62 (12.11%)	109 (25.12%)	105 (24.19%)	3 (0.69%)	1 (0.23%)	<0.001	<0.001
Diabetes	60 (11.72%)	85 (19.59%)	81 (18.66%)	2 (0.46%)	2 (0.46%)	0.001	0.008
Chronic liver disease	7 (1.37%)	8 (1.84%)	8 (1.84%)	0	0	0.559	0.878
Chronic renal disease	17 (3.32%)	43 (9.91%)	40 (9.21%)	1 (0.23%)	2 (0.46%)	<0.001	<0.001
Cancer	18 (3.52%)	24 (5.53%)	24 (5.53%)	0	0	0.134	0.339
Obesity (BMI ≥30 kg/m²)	23 (11.17%)	39 (22.29%)	37 (21.14%)	1 (0.57%)	1 (0.57%)	0.003	0.018
Signs and symptoms							
Fever	219 (42.77%)	192 (44.24%)	182 (41.93%)	4 (0.92%)	6 (1.38%)	0.650	0.276
Chills	175 (34.18%)	123 (28.34%)	115 (26.49%)	3 (0.69%)	5 (1.15%)	0.054	0.031
Myalgia	157 (30.66%)	110 (25.35%)	106 (24.42%)	2 (0.46%)	2 (0.46%)	0.070	0.345
Rhinorrhoea	24 (4.69%)	19 (4.38%)	19 (4.38%)	0	0	0.820	0.864
Cough	211 (41.21%)	170 (39.17%)	160 (36.86%)	4 (0.92%)	6 (1.38%)	0.524	0.123
Respiratory distress	208 (40.63%)	202 (46.54%)	189 (43.54%)	7 (1.61%)	6 (1.38%)	0.067	0.002
Sore throat	62 (12.11%)	37 (8.53%)	35 (8.06%)	0	2 (0.46%)	0.073	0.107
Pleuritic chest pain	66 (12.89%)	44 (10.14%)	43 (9.90%)	1 (0.23%)	0	0.188	0.448
Nausea and vomiting	106 (20.70%)	74 (17.05%)	70 (16.12%)	1 (0.23%)	3 (0.69%)	0.154	0.234
Abdominal pain	49 (9.57%)	46 (10.60%)	46 (10.60%)	0	0	0.600	0.531
Diarrhea	72 (14.06%)	41 (9.54%)	41 (9.54%)	0	0	0.029	0.108
Headache	114 (22.27%)	64 (14.75%)	61 (14.05%)	2 (0.46%)	1 (0.23%)	0.003	0.022
Consciousness alterations	40 (7.81%)	87 (20.05%)	82 (18.89%)	3 (0.69%)	2 (0.46%)	<0.001	<0.001
Loss of appetite	52 (10.16%)	36 (8.29%)	35 (8.06%)	0	1 (0.23%)	0.326	0.636
Habitual history							
Current smoker	41 (8.01%)	21 (4.84%)	20 (4.6%)	1 (0.23%)	0	0.050	0.159
Past smoker	26 (5.08%)	17 (3.92%)	15 (3.45%)	1 (0.23%)	1 (0.23%)	0.393	0.269
Substance abuse	13 (2.54%)	13 (3%)	11 (2.53%)	2 (0.46%)	0	0.669	<0.001
Vital signs (admission)							
BP	$\frac{119 \pm 17}{75 \pm 11}$	$\frac{119 \pm 21}{75 \pm 12}$	$\frac{119 \pm 21}{74 \pm 12}$	$\frac{121 \pm 14}{72 \pm 9}$	$\frac{140 \pm 31}{83 \pm 16}$		
HR	88.65743 ± 14.74	89.5711 ±17.18	89.5628 ±17.01	84.42857 ±16.53	94.5 ±26.20	0.191	0.519
RR	18.89212 ±5.85	19.33498 ±4.94	19.11224 ±4.41	23.57143 ±9.25	27.57143 ±13.86	0.114	<0.001
O2Sat	91.14345 ±6.63	88.77966 ±9.07	88.85176 ±9.12	87.28571 ±7.22	86.5 ±8.15	<0.001	<0.001
Medications							
ACEI	11 (2.15)	15 (3.46)	14 (3.22)	1 (0.23)	0 (0.00)	0.220	0.175
ARBs	57 (11.13)	46 (10.60)	42 (9.67)	3 (0.69)	1 (0.23)	0.793	0.051
Hydroxychloroquine	210 (41.02)	182 (41.94)	176 (40.55)	3 (0.69)	3 (0.69)	0.775	0.985
Naproxen	40 (7.81)	37 (8.53)	33 (7.60)	3 (0.69)	1 (0.23)	0.689	0.009

Table 2. Continued

Variable Mean (SD)/Number (%)	No AKI (n=512, 54.1%)	AKI (n=434, 45.9%)	Stages of AKI			P value (no AKI vs. all AKI)	P value (trend)
			1 (n=419, 44.3%)	2 (n=7, 0.7%)	3 (n=8, 0.8%)		
Vancomycin	77 (15.04)	118 (27.19)	109 (25.11)	4 (0.92)	5 (1.15)	<0.001	<0.001
Length of hospitalization (days)	4.89 (8.89)	5.02 (7.71)	4.79 (7.70)	8.33 (7.55)	11.16 (5.56)	0.427	0.216
Patient outcome							
Expired	49 (30.1%)	114 (69.9%)	102 (62.6%)	6 (3.6%)	6 (3.6%)	<0.001	<0.001
Discharged	463 (59.1%)	320 (40.8%)	317 (40.5%)	1 (0.1%)	2 (0.2%)	<0.001	<0.001
Alive severe	140 (27.34)	191 (44.01)	177 (40.78%)	7 (1.61%)	7 (1.61%)	<0.001	0.734
Alive non-severe	372 (72.66)	243 (55.99)	242 (57.76%)	0 (0%)	1 (12.50%)	<0.001	<0.001
Intubated	19 (3.71)	57 (13.13)	46 (10.59%)	6 (1.38%)	5 (1.15%)	<0.001	<0.001
Laboratory Findings							
Troponin levels (ng/mL)							
Normal	155 (49.21)	160 (50.79)	155 (96.87)	2 (1.25)	3 (1.87)	0.118	<0.001
Borderline	5 (45.45)	6 (54.55)	6 (100)	0 (0)	0 (0)	0.945	0.76
High	78 (41.94)	108 (58.06)	102 (94.44)	4 (3.70)	2 (1.85)	0.119	<0.001
CPK (n=595) (IU/L)	183.38 (n=292)	706.15 (n=303)	677.57	1209.167	1772	0.02	<0.001
LDH (n=473) (IU/L)	587.68 (n=252)	671.77 (n=221)	660.55	635.4	1181.6	0.006	<0.001
CK-MB (n=557) (IU/L)	24.51 (n=266)	41.30 (n=291)	40.44	54.66	73.6	0.0014	<0.001
BUN (n=942) (mg/dL)	14.91 (n=508)	30.41 (n=434)	30.52	29.71	25.75	<0.001	<0.001
WBC Count (n=933) (per microliter of blood)	7.72 (n=502)	8.41 (n=431)	8.45	8.35	6.67	0.052	<0.001
Neutrophil (n=891) (%)	72.29 (n=482)	75.77 (n=409)	75.52	84.42	80.41	<0.001	<0.001
Lymphocyte (n=899) (%)	23.00 (n=486)	20.18 (n=413)	20.37	13.57	16.08	<0.001	<0.001
RBC count (n=932) (per microliter of blood)	4.75 (n=502)	4.30 (n=430)	4.30	4.42	4.43	0.018	<0.001
Hemoglobin (n=931) (g/dL)	14.35 (n=501)	12.87 (n=430)	12.87	13.11	12.5	0.057	<0.001
Hematocrit (n=933) (%)	37.83 (n=502)	36.87 (n=431)	36.81	38.90	38.31	0.013	0.004
Platelets (n=932) (per microliter of blood)	190.26 (n=501)	190.15 (n=431)	191.34	163.42	151.5	0.50	<0.001
ESR (n=753) (mm/h)	31.06 (n=414)	37.54 (n=339)	37.67	26.71	42.71	<0.001	<0.001
CRP (n=807) (mg/L)	35.23 (n=435)	42.09 (n=372)	42.17	26.26	51.77	0.004	<0.001
D-dimer (n=52) (ng/mL)	3016.5 (n=22)	2792.6 (n=30)	2741.8	3268	2687	0.42	0.001
Ferritin (n=40) (ng/mL)	364.29 (n=19)	572.53 (n=21)	578.35	456		0.018	<0.001
AST (n=543) (IU/L)	49.53 (n=291)	66.48 (n=252)	62.28	231.36	69.83	0.018	<0.001
ALT (n=541) (IU/L)	42.01 (n=290)	54.30 (n=251)	52.84	128.15	38.81	0.064	<0.001
ALKP (n=515) (IU/L)	210.37 (n=272)	249.15 (n=243)	250.12	140.86	312.33	0.016	<0.001
pH (n=794)	7.32 (n=413) (SD=0.02)	7.34 (n=381) (SD=0.04)	7.34 (0.45)	7.33 (0.02)	7.33 (0.02)	0.319	<0.001
pCO2 (n=796)	45.27 (n=414)	45.44 (n=382)	45.58	43.81	40.66	0.43	<0.001
HCO3 (n=794) (mEq/L)	25.02 (n=413) (0.22)	23.34 (n=381) (0.61)	23.41 (0.63)	22.07 (1.68)	21.2 (1.83)	0.004	<0.001

ng: nanogram; mL: milliliter; IU: international unit; L: liter; mg: milligram; dL: deciliter; g: gram; mm: millimeter; h: hour; mEq: milliequivalent; COPD: chronic obstructive pulmonary disease; HTN: hypertension; IHD: ischemic heart disease; BMI: bodymass index; BP: blood pressure; HR: heart rate; RR: respiratory rate; O2Sat: oxygen saturation ;ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; CK-MB: creatine kinase-MB; BUN: blood urea nitrogen; WBC: white blood cell; RBC: red blood cell; ESR: estimated sedimentation rate; CRP: c-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALKP: alkaline phosphatase; CO2: carbon dioxide; HCO3: bicarbonate; p:-log; H: hydrogene; std: standard deviation

An increasing trend for mean value of LDH, CKMB, and a decreasing trend for BUN was observed according to AKI stages (*P* for trend < 0.0001 for all three trends).

AKI patients also showed significantly higher mean value of neutrophils (75.7 versus 72.2, *P* < 0.001) and lower mean value of lymphocytes (20.18 versus 23, *P* < 0.001). In addition, regarding acute phase reactants, patients with AKI had significantly higher levels of ESR (37.54 versus 31.06, *P* < 0.001) and CRP (42.09 versus 35.23, *P* = 0.004) compared with patients without AKI (Table 2).

Discussion

Herein, we evaluated baseline clinical characteristics of 946 confirmed COVID-19 admitted patients with their disease severity and clinical progress throughout the admission. Overall mean age was 18.73 with male dominance of 60.47%. Among comorbidities, HTN, followed by ischemic heart disease (IHD) and diabetes were the most commons; this was consistent with other major studies (20,21). This finding is probably due to the main shared feature between these diseases; the chronicity and related immune disturbance. In our study we retrospectively evaluated BMI in 381 of a total of 946 patients which more than 45% of our patients were categorized as overweight this may be either due to demographic features of admitted patients or due to more susceptibility to COVID-19 in this group of people but it has been shown that overweight patients have 1.84-fold odds of developing severe COVID-19 compared with normal-weight patients (22). Among different studies various incidence rates of AKI are reported through the globe and in our study group the incidence of AKI was estimated as 45.9%, this was consistent with the global trend toward the increased rate of AKI in COVID-19 patients compared with early reports (23,24). We demonstrated that those with AKI, compared to the non-AKI group, had a significantly higher mean of age (62 versus 50.2 years, *P* < 0.001), and a higher proportion of females (34.9% versus 44.9%, *P* = 0.002); the first one is commonly due to impaired immune system in older patients and probably due to increased baseline inflammation with aging which also may be a contributing factor resulting in AKI (25). Although the consensus view suggests that male sex is among risk factors contributing to COVID-19 AKI (24) and on the other hand the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI classifies female gender susceptible to higher risk for AKI (26), surprisingly we found that the COVID-19 AKI was significantly higher in female gender which may be due to heterogeneity of the patient population. A unique study design that was carried out was the categorization of AKI stages and relation of baseline comorbidities to them which was seen in only a few studies (27,28). We found that HTN, IHD, diabetes, and CKD were significantly higher in the first stage of AKI compared with the second and third stages which was consistent with the study conducted by Hirsch et al except for the comorbidity of CKD which they

did not include it because of data insufficiency (27). These relations may be of value in further patient management and treatment plans with regards to kidney function reservation in response to disease severity namely as the AKI stage. The potential underlying pathophysiology in COVID-19 induced AKI is that it is not only attributable to the hypoxemic and hypotensive state caused by lung and heart injury but also to the direct invasion of the kidney by virus via the angiotensin converting enzyme 2 (ACE2) protein which is highly found in renal tubules and this explains that why AKI patients in our study had lower mean levels of O2 saturation compared with non-AKI group (88.7 versus 91.1, *P* < 0.001) (29, 30). Moreover, it is shown that using ACE inhibitor drugs may alter the outcome of diabetic patients with COVID-19 which necessitates close observation of this group that in our study were among the most common comorbidities in AKI patients of COVID-19 (31). With regards to laboratory data, we found that higher concentrations of serum potassium (i.e. hyperkalemia) were significantly related to higher proportions of AKI symptoms observed in patients. Furthermore, AKI patients showed a higher mean value for LDH (671 versus 87, *P* = 0.006), CKMB (41.30 versus 24.5, *P* = 0.001), and BUN (30.41 versus 14.91, *P* < 0.001) compared to the non-AKI group. Finally, AKI patients also showed significantly higher mean value of neutrophils (75.7 versus 72.2, *P* < 0.001) and a lower mean value of lymphocytes (20.18 versus 23, *P* < 0.001). Concerning these biochemical abnormalities presented in patients, it was shown that high serum LDH (specifically levels higher than 500 U/L which the mean LDH level in our AKI group and non-AKI group was 671.77 and 587.6, respectively), high neutrophil levels and lymphopenia (defined as lymphocyte count lower than 1.0×10^9/L) were associated with severe illness itself or progression to it (32-35). Moreover, another study emphasized on the importance of LDH, lymphocyte and neutrophil counts in combination and the total white blood cell count to be predictive of progression into later stages of AKI (36). The CK-MB, an enzyme frequently elevated during cardiac injury but also rises due to toxins, drug exposure, renal insufficiency, and some cases of cerebral infarction (37), is shown to be elevated in severe COVID-19 patients requiring ICU admission (38). The basis of cardiac injury in COVID-19 patients is thought to be caused by the same ACE2 receptor (which is expressed in renal tubules and discussed earlier) in cardiac muscle cells (39) and thus postulating the idea that maybe increased cardiac injury is concomitantly associated with equally increased kidney injury and the CK-MB levels may not solely serve as the cardiac damage indicator but also as the kidney damage indicator as well. Regarding patients outcome, AKI was diagnosed in 57% of alive patients with severe COVID-19 which was consistent with a previous study (40). Likewise, it was shown that patients deceased from COVID-19 had approximately 20 times higher possibility of having

AKI (41), emphasizing the importance of kidney care in patients with the disease for their further prognosis.

Conclusion

With increasing knowledge regarding the COVID-19 pandemic, different studies have been conducted due to its multi-system involvement. In the current study, 946 patients with COVID-19 were assessed with a primary focus on the kidney and related underlying comorbidities which showed that the comorbidities were more prevalent among AKI patients, since female and older patients were more susceptible to AKI during the COVID-19 pandemic. Besides, the level of CK-MB is higher in the AKI group, suggesting probable cardiac injury which prompts conducting further studies. Lymphopenia and leukocytosis may be poor-prognostic factors for both AKI and COVID-19.

Limitations of the study

This study has some limitations. As staff was involved in the patients' care, there is no long-time follow-up for the patients after discharge. Furthermore, electrolyte imbalance could be a confronting factor that might have been considered in future studies.

Authors' contribution

ET and LJK were the principal investigators of the study. ASo, SK and GS were included in preparing the concept. MSJ and ASh designed the study protocol. DS, SI, MJ, MK and YSK were involved in data collection and further follow-up. SN and LJK were involved in data analysis and statistical methods. ASo, SK, and SM prepared the manuscript and tables. DS, GS, and LJK have evaluated the intellectual contents and revised the manuscript in details. All authors participated in preparing the final draft of the manuscript, revised the manuscript. All authors have read and approved the final manuscript and admitted the accuracy of the article.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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