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ORIGINAL ARTICL

Risk Factors of Acute Kidney Injury among COVID-19 Patients

Omaima Mohamed Ali [1] , Hosny Abdelwahab Gafaar [1*] , Ragaa Ramadan Mohamed [2] ,Ehab Saleh Mahmoud [1] , Ahmed Gaber Kenawy [1]

[1]Department of Internal Medicine, Faculty of Medicine, Aswan University

[2]Department of Internal Medicine, Faculty of Medicine,Al Azhar University

ABSTRACT

Keyword: Acute Kidney Injury, COVID-19 infection, Renal Replacement Therapy.

*__Corresponding author__: Hosny Abdelwahab
Email: hosnyabdelwahab85@gmail.com

Phone: 01029814381

Background: COVID-19 was declared by the WHO as pandemic around the world. The impact of COVID-19 on different body systems was established. The link between kidney injury and COVID-19 is still controversial. **Aim:** This work aimed to assess acute kidney injury in COVID-19 cases. **Patient and methods:** A total of 200 confirmed COVID-19 infection patients with acute kidney injury were included. Medical files were reviewed and analyzed to explore the correlation between acute kidney injury and COVID-19 along with the outcome of the studied patients. **Results:** Patients' age ranged between 28 and 93 years with a mean of 68.1 years. Out of those patients; about half of cases males. Elevated inflammatory markers, hypovolemia and severe COVID-19 infection were the most frequently reported risk factors for acute kidney injury. About one-fifth of patients required renal replacement therapy. Also, about 60% of them were admitted to intensive care unit and about two-thirds of them deteriorated and died. Median length of hospital stay was 10 days (4-75 days). **Conclusion:** One of the most frequent complications in hospitalized COVID-19 patients was acute renal injury. Strict follow up of patients with possible risk factors of AKI should be performed.

INTRODUCTION:

Although lungs are the main organ affected by COVID-19 infection, it is recognized recently in other organs such as kidney, GIT, heart, and coagulation system. There are few clinical data on the prevalence of AKI in COVID-19 infection, despite the growing body of scientific evidence connecting COVID-19 infection to kidney disease. AKI has been found to occur in COVID-19 hospitalized patients at rates ranging from 0.5% to 27% (1).

A cluster of pneumonia episodes brought on by an unidentified virus were first noted in Wuhan, Hubei province, China, in 2019. The main complaints were fever, exhaustion, dry cough, myalgia, and dyspnea. Following the isolation and identification of the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) designation has been given by the WHO to this unique coronavirus. (1).

It was reported that kidney dysfunction was reported in great percentage of COVID-19 infection (2). Also, it was found that acute kidney injury (AKI) was associated with COVID-19 in-hospital mortality (3). Contrarily, Wang et al. could not detect direct link between SARS-CoV-2 and obviously kidney damage (4). Thus, the link between AKI and COVID-19 infection is still unclear.

According to recent research, there are three potential mechanisms—cytokine-induced injury, systemic effects, and organ crosstalk—through which the kidney may be affected by COVID-19 illness. These factors interact with one another and have significant effects on extracorporeal therapy (1, 2). Currently, it is thought that SARS-CoV-2 directly targets intrinsic renal cells as the cause of kidney damage in COVID-19 patients. A potential kidney damage target may be proximal tubular epithelial cells with high ACE2 expression (3).

It was reported that swelling, vacuolar degeneration, shedding of renal tubular epithelial cells, and the presence of visible protein casts and pigmented casts in the lumen are the predominant pathological abnormalities in the kidneys of COVID-19 patients. Additionally, renal tubular epithelial cells have been discovered to contain SARS-CoV-2 inclusion bodies (4). According to these results, SARS-CoV-2 may specifically target renal tubular epithelial cells and result in AKI. Furthermore, SARS-CoV-2 has the ability to directly afflicted renal tubules, podocytes, and glomerular endothelia, leading to acute tubular damage and, on rare occasions, collapsed localized segmental glomerulopathy in the kidney tissue (5).

In severe cases, several risk factors, such as the increase in patients' age may play a role in the development of AKI. Additionally, comorbid conditions including DM and HTN, are known to increase kidney susceptibility. One of the common disorders that could result in the development of AKI is ARDS, which is also one of the main justifications for hospital admission in those with severe COVID-19 (1).

Therefore, the current research aimed to explore the link between COVID-19 infection and kidney affection and whether cases with kidney impairment affected by COVID-19 are more prone for AKI and to investigate the pattern of AKI among COVID-19 cases.

SUBJECTS AND METHODS

This cross-sectional analytical study was conducted at the Aswan Governorate Isolation Hospitals during the period from March 2020 to December 2021. Cases with kidney impairment and confirmed as positive COVID-19 infection via polymerase chain reaction (PCR) was enrolled in the study while patients on regular hemodialysis and/or aged < 18 years were excluded.

G-Power 3.1.9.7 software was used for sample calculation. A minimum sample of 180 participants was sufficient to demonstrate relevant 20% prevalence of AKI in Covid-19 patients with type I error of 5% and type II error of 80%. A total of 200 patients were included.

i. Procedure

All patients were subjected to thorough history taking and clinical evaluation. Baseline demographic and clinical data (Age, sex, body mass index (BMI), any comorbidities as diabetes mellitus (DM), hypertension (HTN), cardiac disease and chronic kidney disease (CKD) were recorded.

ii. Operational Definition

SARS-CoV-2 was defined according to the Ministry of health and population (MOH) as any COVID-19 case confirmed laboratory, regardless of clinical symptoms and signs).

AKI Definition: AKI severity classification is helped by the RIFLE criteria (5);

- AKI Risk is defined when there is 1.5-fold rise in s. creatinine/or glomerular filtration rate (GFR) drop by one-quarter/or urine output (UOP) < 0.5ml/kg/hour for 6 hours.
- AKI injury stage is defined when there is 2-fold rise in s. creatinine/or GFR drop by half, or UOP < 0.5ml/kg/ hour for 12 hours.
- Kidney failure is defined when there 3-fold rise in s. creatinine/rise in s. creatinine to 4 mg/dl/GFR drop by three-quarters/UOP < 0.3ml/kg/ hour for 24 hours/anuria for 12 hours.
- Loss is defined as kidney function is lost completely for > 4 weeks.

- End Stage defined as kidney function is lost completely for > 3 months.

iii. *Statistical analysis*

IBM-SPSS ver.-23 was used for data processing. Data was expressed as mean ± SD, median and interquartile range (IQR). Qualitative variables were expressed as frequency and percentages. Significance test: independent sample t-test was used to test the difference in means for continuous data. Chi-square test/Fischer exact test is used to test the difference in frequency for qualitative data as appropriate. Significance was considered when $p<0.05$.

iv. *Ethical Consideration*

Medical Ethic Committee, Faculty of Medicine, Aswan University provided approval of this study (IRB no 511/2/21). This work abided with the guidelines of the Helsinki Declaration guidelines and STROBE checklist for research ethics. The study aims, methodology, cons and pros were detailed in the information sheet provided for each participant. Upon accepting to participate, every participant signed a written informed consent. Confidentiality and anonymity were approved. Every participant was assured of the freedom to withdraw at any time and this won't affect any medical service provided.

RESULTS

This cross-sectional study included 200 COVID-19 cases with a mean age of 68.1 ± 10.3 years and ranged between 28 and 93 years with the majority (81.5%) were in the old age group (≥ 60). About half (n=104) of them was males. Additionally, the mean body mass index (BMI) was 25.04 kg/m2 with 58.5% had normal weight, 28.5% overweight and 13% obese. The most frequent stages of AKI were risk stage (54.5%), injury stage (24.5%) and failure stage (24%) **(Table 1 and Fig. 1)**

Table (1): Baseline Characteristics of the studied Cohort

Parameter	n=200	%
Age: (years)		
< 60	37	18.5%
60 - < 70	67	33.5%
70 - < 80	70	35.0%
≥ 80	26	13.0%
Mean ± SD (Range)	68.11 ± 10.30 (28.0-93.0)	
Sex:		
Male	104	52.0%
Female	96	48.0%
Weight:		
Mean ± SD (Range)	75.29 ± 11.98 (50.0-110.0)	
Height:		
Mean ± SD (Range)	173.22 ± 4.40 (154.0-182.0)	
BMI:		
Normal	117	58.5%
Overweight	57	28.5%
Obese	26	13.0%
Mean ± SD (Range)	25.04 ± 3.54 (18.6-35.5)	

Fig. 1: Stages of AKI (RIFLE Staging)

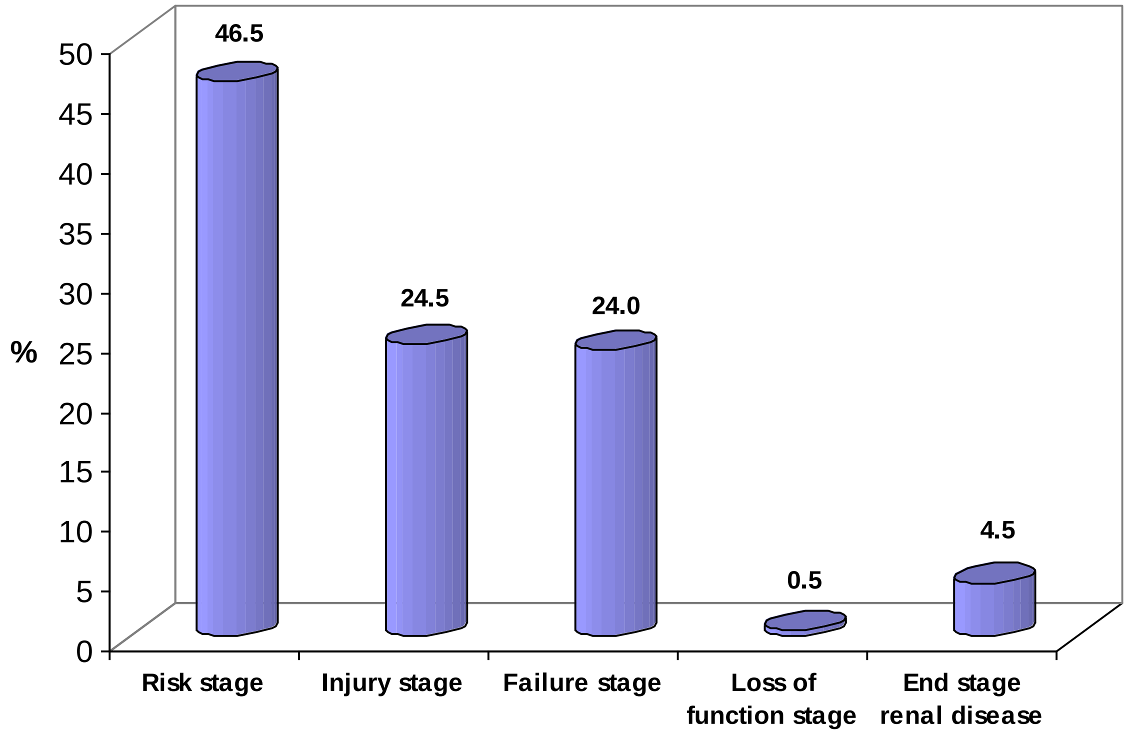


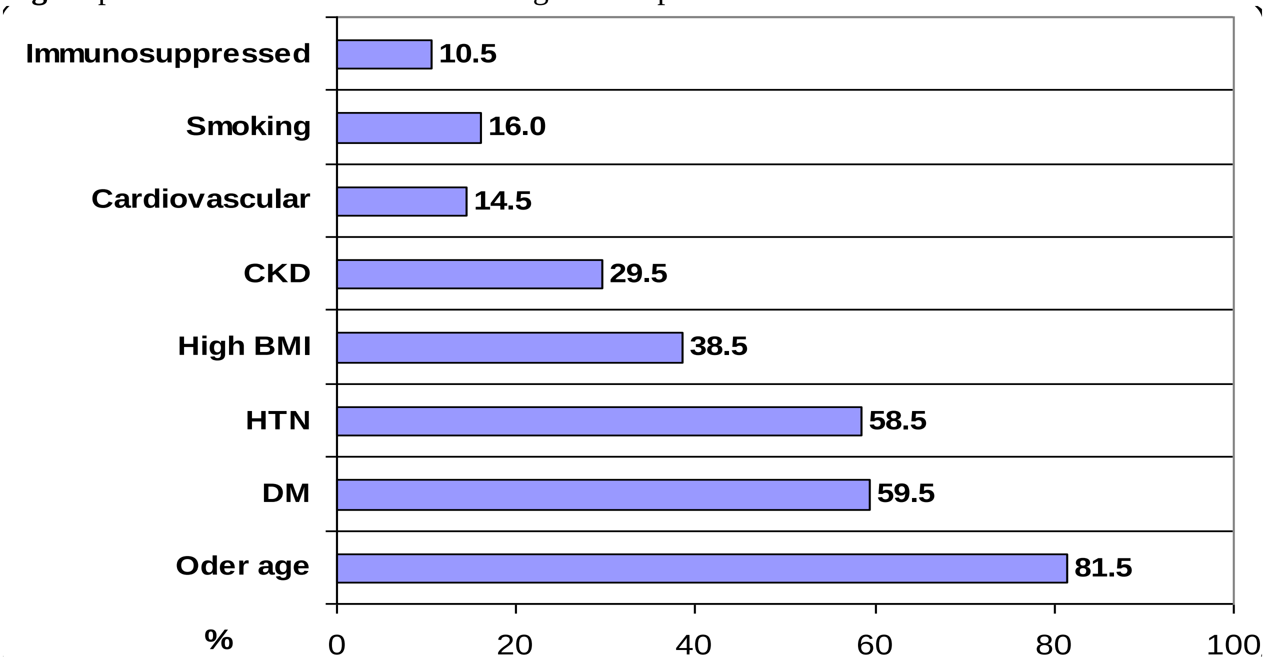
Table 2 and Fig. 2 showed the frequency of the possible risk factors for AKI among studied patients. The most frequent possible risk factors for AKI in the current study were elevated inflammatory markers i.e. c-reactive protein (CRP) and D-dimer (81.5%), leukocytosis (52.5%), hypovolemia (50.5%), severe covid-19 infection (48.5%) and high BMI (38.5%).

Table (2): Risk factors among the studied Cohort

Risk factors	No. (200)	%
At Admission		
Severity of Covid-19:		
Mild	14	7.0%
Moderate	48	24.0%
Severe	97	48.5%
Critically ill cases	41	20.5%
Leukocytosis	105	52.5%
Elevated markers of inflammation	163	81.5%
Hypovolemia	101	50.5%
Nephrotoxins	33	16.5%
On Hospitalization		
Nephrotoxins	22	11.0%
Ventilation	71	35.5%
Vasopressors	60	30.0%

Aswan University Medical Journal, volume 4 / No.3/ December 2024 (1-11) Online ISSN: **2735-3117**

Fig. 2: possible risk factors of AKI among studied patients



Out of the 200 enrolled patients; 41 (20.5%) patients required renal replacement therapy (RRT), 60.5% of them were admitted to intensive care unit (ICU) and about two-thirds (67%) of them were deteriorated and died. Hospital stays ranged between 4 and 75 days with median 10 days. Patients who received RRT had shorter hospital stay and about 66% of them had < 10 days hospital stay **(Table 3)**

Table (3): Clinical Data of the studied Cases

	No. (200)	**%**
RRT:		
Yes	41	20.5%
No	159	79.5%
HCV & HBV & HIV:		
HCV	21	10.5%
HBV	1	0.5%
Negative	178	89.0%
Isolation hospital:		
Aswan University Hospital	42	21.0%
Aswan General Hospital	158	79.0%
Place of admission:		
ICU	121	60.5%
Ward	79	39.5%
Prognosis:		
Death	134	67.0%
Recovery	60	30.0%
Discharge on demand	6	3.0%
Hospital stay: (days)		
< 10	98	49.0
10 - 15	53	26.5
> 15	49	24.5
Median (Range)	10.0 (4.0-75.0)	

The outcome of studied patients based on severity of Covid-19 was illustrated in **table 4**. The different grades of COVID-19 severity showed no significant differences (p>0.05) as regard RRT, and hospital stay while frequency of death was significantly (p<0.001) increasing with advancing in the severity. All critically ill patients and about 86% of those with severe diseased were deteriorated and died.

Table (4): Severity of Covid-19 with Prognosis, RRT and Hospital stay

	Severity of COVID-19								**P-value**
	Mild		**Moderate**		**Severe**		**Critically ill Cases**		
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Prognosis:									
Death	2	14.3	8	16.7	83	85.6	41	100.0	<0.001*
Recovery/ discharge	12	85.7	40	83.3	14	14.4	0	0.0	
RRT:									
Yes	4	28.6	9	18.8	17	17.5	11	26.8	= 0.535
No	10	71.4	39	81.3	80	82.5	30	73.2	
Hospital stay: (days)									
< 10	9	64.3	20	41.7	51	52.6	18	43.9	
10 - 15	5	35.7	10	20.8	25	25.8	13	31.7	= 0.117
> 15	0	0.0	18	37.5	21	21.6	10	24.4	

Moreover, the relationship between renal replacement therapy, hospital stay, and place of admission and disease outcome was presented in **table 5**. It was found that died patients were older (71.6 ± 12.1 years) compared with those alive (42.2 ± 6.1 years). Likewise, died patients had shorter hospital stay and about three-quarters (n=101) of them were admitted to ICU while about two-thirds (n=46) of alive patients were admitted to the Ward.

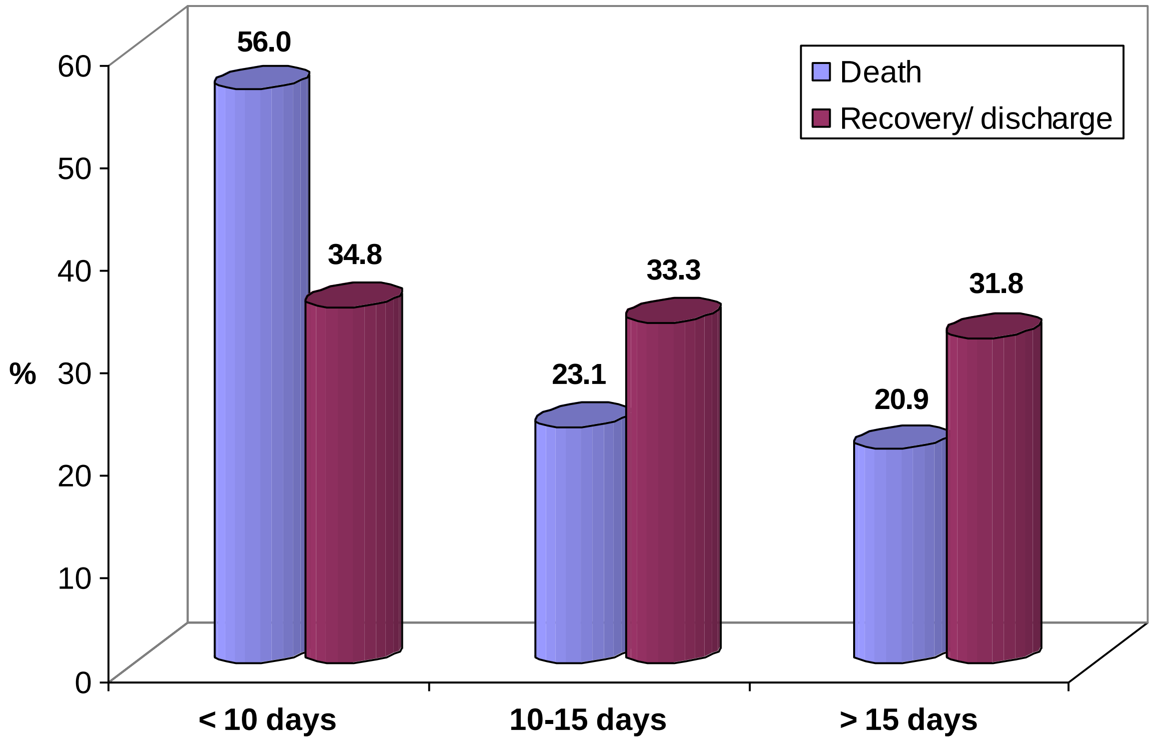
Table (5): Prognosis with RRT, **Hospital stay, Isolation hospital, Place of admission**

	Prognosis				**P-value**
	Death		**Recovery/ discharge**		
	No.	**%**	**No.**	**%**	
Age/years (mean ± SD)	71.62 ± 12.1		42.21 ± 6.1		0.000*
RRT:					
Yes	30	22.4	11	16.7	0.346
No	104	77.6	55	83.3	
Hospital stay: (days)					
< 10	75	56.0	23	34.8	
10 - 15	31	23.1	22	33.3	0.019*
> 15	28	20.9	21	31.8	
Isolation hospital:					
Aswan University Hospital	27	20.1	15	22.7	0.674
Aswan General Hospital	107	79.9	51	77.3	
Place of admission:					
ICU	101	75.4	20	30.3	0.000*
Ward	33	24.6	46	69.7	

Aswan University Medical Journal, volume 4 / No.3/ December 2024 (1-11) Online ISSN: **2735-3117**

Fig. 3 showed the relationship between RRT, and hospital stay. About 90% of those with RRT treatment had <15 days length of stay while 28% of those untreated with RRT had > 15 days hospital stay and this was statistically significant (p=0.022).

Fig. 3: Relation between RRT with hospital stay



DISCUSSION

Preliminary studies speculated that the occurrence of AKI in cases with COVID-19 was low (6). Guan et al. included 1,099 confirmed COVID-19 cases; the majority were hospitalized, but only 8.5% either admitted to the ICU or developed ARDS, while only 0.5% developed AKI (7). Despite this, AKI is most common in critically ill COVID-19 patients, affecting 20–40% of patients admitted to ICU. It is thought to be a marker of disease severity and a poor prognostic factor for survival (8). A multicenter retrospective study from Wuhan looked at 239 critically ill COVID-19 patients and found that the most common complications were ARDS, acute cardiac injury, and AKI (68.6 %, 43.1 %, and 49.8 %, respectively) (9).

The current study was conducted on 200 patients with AKI and COVID-19 infection. The mean age of those patients was 68.11 ± 10.30 years. Fifty-two percent were males and 41.5% was overweight/obese. In line with the current study, Nimkar et al. found that the median age of COVID-19 patients with AKI was 75 years, 56% of them was males and 35% of them was obese (10).

In this study, the most frequently reported risk factors for AKI were old age (≥60 years) (81.5%), DM (59.5%), HTN (58.5%), high BMI (38.5%), history of CKD (29.5%) and cardiovascular diseases (14.5%). This agreed with previous studies which stated that older age wasn't only a risk for AKI among patents with COVID-19 infection but also, according to previous data, it raises the likelihood of adverse outcomes like mortality and AKI (10-12). Also, previous study found that patients with AKI were significantly older, and more affected by the major comorbidities (HTN, DM, and CKD) than those without AKI (10).

Furthermore, Nadim et al. proposed that old age (≥60 years), CKD, hypertension, DM, obesity, and heart failure are all correlated with poor results and considered as determinants for AKI in COVID-

19 cases (13). With odds ratios of 3.53 (95% CI (2.92- 4.25), p0.001) and 6.07 (95% CI (2.53-14.58), p0.001), respectively, Lin et al. (2020) demonstrated that age 60 years and severe infection were independent risk factors for AKI during COVID-19 infection (14).

Other risk factors for AKI that were reported among those patients included severe COVID-19 infection (48.5%), leukocytosis (52.5%), elevated markers of inflammation as CRP and D-dimer (81.5%), hypovolemia (50.5%) and nephrotoxins (16.5%). According to a recent study, individuals with severe COVID-19 had higher incidence of AKI than those with milder COVID-19 (OR=11.1) (15). Casas-Aparicio et al. (2021) found that D-dimer increase was more prevalent in AKI cases at admission. This molecule, which is produced when cross-linked fibrin degrades, is a sensitive indicator of thrombosis and activation of the coagulation process. Also, the authors stated that in patients with AKI, increased C-reactive protein levels were more prevalent at admission. Unfavorable characteristics of COVID-19 disease have been connected to higher C-reactive protein levels (16). Additionally, COVID-19 can cause AKI when associated with shock, high temperature, dehydration, hypoxia, and NSAIDs/ antivirals/ antibiotics/ potentially nephrotoxics are used to treat the condition.

Further to that, COVID-19, when combined with a high fever, shock, dehydration, and hypoxemia, and treated with nonsteroidal anti-inflammatory drugs, antiviral drugs, antibiotics, and other potentially nephrotoxic drugs, can result in AKI. Furthermore, advanced age, diabetes, and hypertension all contribute to or exacerbate the occurrence and progression of AKI (2). The viral clearance ability of male patients with COVID-19 is significantly lower than that of female patients with COVID-19, which may represent one potential reason for the increased severity of symptoms and incidence of complications observed in male patients with COVID-19 (17).

Other possible risk factors during hospitalizations for AKI in the current study were nephrotoxins (11%), ventilation (35.5%) and vasopressors (30%). In agreement with the current study, Casas-Aparicio et al. (2021) stated that the need for mechanical ventilation and vasoactive drugs were risk factor for AKI (16). It is well-established that nephrotoxicity, hypoxia, and ischemia are the major causes of AKI. Ischemia and toxins can easily harm the kidney, which causes vasoconstriction, endothelial damage, and the onset of inflammatory processes. In hospitalized patients with severe COVID-19, the important relationship between AKI and respiratory failure was previously reported It has been established that AKI and respiratory failure have a significant association with severe COVID-19 infection (18, 19).

In the current study, stages of AKI were as follows; risk stage (46.5%), injury stage (24.5%), failure stage (24%), loss of function stage (0.50%) and end stage renal disease (4.5%). Out of the studied patients, 41 (20.5%) patients required RRT, 121 (60.5%) patients were admitted to ICU while 134 (67%) patients were deteriorated and died. Also, we found that patients who received RRT had significantly shorter hospital stay where 65.9% of those received RRT had < 10 days' hospital stay. This could be explained that 30/41(73.2%) from those received RRT were died early during admission.

Nimkar et al. (2020) stated that AKI significantly influenced the likelihood of death among COVID-19-infected hospital patients. When compared to patients without AKI, those with AKI had a significantly higher mortality rate (58.1% [104 of 179] vs. 19.6% [29 of 148]; P.001) (10). Yang et al. (2020) concluded when ICU/severe patients were compared to non-ICU/non-severe cases, the findings showed that AKI occurred 30 times more frequently in critical condition (20). Likewise, Bo Li's study found that the likelihood of acute cardiac damage was almost 13 times higher in patients with severe illness (21). Cheng et al. (2020) also, showed that kidney damage was related to COVID-19' in-hospital mortality (22).

The finding of the current work was in line with that of Xu et al., who found that 50% of the 239 critically ill COVID-19 patients evaluated went on to develop AKI (9). Also, previous studies found that patients with high incidence of AKI on top of severe COVID-19 infection had significantly higher mortality rate (23, 24). These results were in line with earlier studies that found that individuals with COVID-19 who had severe AKI had a higher mortality rate (25).

As regard need for RRT, study by Chand et al. who recruited only ICU admitted cases and reported a higher incidence of AKI (77%) and need for RRT (44%) were reported (24). Previous systematic review and meta-analysis reported that 6% of patients COVID-19 patients with AKI required RRT (26). A previous meta-analysis was conducted by Lin et al (2020), and included 49692 COVID-19 cases,10.6% of COVID-19 cases had AKI. Incidence of AKI were 5.4%, 22.1%, and 22.1%, respectively, in mild/moderate, severe, and died COVID-19 cases. Additionally, 2.4% underwent ongoing renal replacement treatment (14). Based on severity of COVID-19 in the current study, it was found that four (28.6%), nine (18.8%), 17 (17.5%) and 11 (26.8%) patients with mild, moderate, severe, and critically ill disease, respectively required RRT. Lin et al. (2020) concluded that individuals with severe COVID-19 had a considerably higher incidence of RRT than those with mild COVID-19 (14).

Also, the current study revealed that mortality rate was increasing with advancing in the severity of COVID-19. Older cases and all critically ill patients and 85.6% older patients and those with severe disease were died while 85.7% and 83.3% of those with mild and moderate disease, respectively were alive. This was consistent with previous study that found that frequency of mortality was significantly higher among critically ill patients (24). Lin et al (2020) suggested that kidney injury was prevalent in COVID-19 patients and was closely correlated with age, sex, and disease type. Higher mortality rates existed in those with AKI on top of COVID-19. Thus, through proper diagnosis and treatment methods, AKI-related controllable factors must be avoided. (14).

Study limitation: The current study has encountered some limitations including the cross-sectional nature of the study that limits the generalizability of the study findings. Lack of study of some confounders affecting both morbidities.

CONCLUSION

This study concluded that AKI was a frequent and dangerous COVID-19 complication. Two independent risk variables for AKI were identified, old age (≥60 years) and having a severe COVID-19 infection. Patients with COVID-19 complicated by AKI had a considerably higher in-hospital mortality rate.

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