Characteristics and Outcomes of Hospitalized COVID-19 patients with Acute Kidney Injury: The Makati Medical Center Experience

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Abstract

Introduction. Since the breakout of COVID-19 in December 2019, the virus has already affected and taken millions of lives over the past year. There is still much to learn about this disease. It has been postulated that the human kidney is a potential pathway for COVID-19 due to the presence of the ACE2 receptors found in the surfaces of kidney cells. Some studies that demonstrated acute tubular necrosis and lymphocyte infiltration among post mortem COVID-19 patients, concluding that the virus could directly damage the kidney, increasing the risk of the development of Acute Kidney Injury (AKI) among patients with COVID-19. This study investigated the incidence and severity of AKI among hospitalized COVID-19 patients and the association of the degree of AKI with regards to the severity and outcomes of COVID-19 patients.

Methods. This was a single-center cross-sectional study retrospective chart review of COVID-19 patients who developed AKI. Descriptive statistics were used to summarize the general and clinical characteristics of the patients. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption was described using mean and standard deviation, while those that did not were described using median and range. Continuous variables which are normally distributed were compared using the One-way ANOVA, while those variables that are not normally distributed were compared using the Kruskal-Wallis H test. For categorical variables, the Chi-square test was used to compare the outcomes. If the expected percentages in the cells are less than 5%, Fisher's Exact Test was used instead.

Results. A total of 1441 COVID-19 in-patients from March 1, 2020 to March 1, 2021 were reviewed, 59 of whom were excluded. Among the adults with COVID-19 who developed AKI, 60% were in stage I, 10% in stage II, and 30% in stage III. The incidence of AKI among COVID-19 in-patients at Makati Medical Center was 13.10% (95% CI 11.36% - 14.99%). Among the 181 patients, 79 (43.65%, 95% CI 36.30 - 51.20) had died. The mortality rate is 22.02% for Stage I, 50% for Stage II, and 85.19% for Stage III. The median length of hospital stay was 12 days, ranging from 1 day up to 181 days. Full renal recovery on discharge was observed only in one-third of the patients. It was observed in 44.95% of those in Stage I, 27.78% of those in Stage II, and 5.56% of those in Stage III.

Conclusion. The study demonstrated that the incidence of AKI in hospitalized COVID-19 patients was 13.1% (95% CI 11.36% - 14.99%), which was lower than previously reported. This could be attributed to the longer study period wherein, to date, we have a better understanding of the disease and had already established a standard of care for treatment for the disease attributing to the decreased incidence of AKI among COVID-19 patients than what was initially reported. The development of AKI has a direct correlation with the degree of infection. Among patients who developed AKI, 20% required renal replacement therapy. Overall development of AKI increases the risk of mortality among hospitalized COVID-19 patients. The stage of AKI has a direct correlation with regards to mortality and has an indirect relationship with regards to renal recovery.

Keywords: Acute Kidney Injury, AKI, COVID-19, Renal Replacement Therapy, Mortality

Introduction

In December 2019, in Wuhan, Hubei province of China, COVID 19, was first identified, and since then, it has spread globally, affecting almost 2.9 million people worldwide and has been declared by the World Health

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Organization as a global pandemic.[1] The first confirmed case of COVID-19 in the Philippines was reported on January 30, 2020. As of April 27, 2020 there are about 7,777 reported cases locally.[2]

In a study by Zhang et al. (2020), they reported that COVID 19 enters the host via the human ACE-II (Angiotensin-converting enzyme II) receptors in the lungs and can serve as a reservoir for viral invasion. Its expression is also found in extrapulmonary tissues, including the heart, kidney, endothelium, and intestine.[3] According to Diao et al. (2020), the human kidney is a potential target as well of COVID 19. They were able to demonstrate kidney tissues from post-mortem patients having severe acute tubular necrosis and lymphocyte infiltration, concluding that the virus can directly target the kidneys, specifically the kidney tubules causing acute tubular damage.[4]

The severity of COVID 19 varies from no symptoms while some develop Severe Acute Respiratory Distress Syndrome which could be potentially fatal resulting in multiorgan failure.[1] Patients with COVID 19 are at high risk of developing AKI. As defined by KDIGO, AKI is an increase in the serum creatinine by 0.3mg/dl within 48 hours or an increase in serum creatinine by 1.5 times baseline which is known or presumed to have occurred within the prior seven days or a urine volume < 0.5 ml/kg/h for six hours as observed by the clinical course of the disease.[5]

The study described the clinical profile and outcomes among hospitalized COVID-19 patients with AKI. The study determined the clinical characteristics of those at risk for developing AKI and their clinical outcomes. Other information included the number of patients who required Renal Replacement Therapy (RRT), the length of hospital stay, and mortality.

Methods

The study is a cross-sectional chart review of COVID-19 patients admitted from March 1, 2020 to March 1, 2021, at the Makati Medical Center, aged > 18 years old and developed AKI during their confinement.

A list of all admitted COVID-19 patients, confirmed by RT-PCR was provided by the Medical Records Section. The Medical Records numbers of the patients were used to identify the medical charts to be reviewed (*Figure 1*)

Charts of patients included in the study were reviewed from the time of admission through hospital discharge or death. The following data were collected, which included age, sex, and weight. Other data included comorbidities (hypertension, diabetes, cardiovascular disease, chronic kidney disease, chronic lung disease, and/or cancer). Admitting blood tests including complete blood count, ferritin (ng/ml), CRP or hs-CRP (mg/L), LDH (U/L), d-dimer (mg/L), procalcitonin (ng/mL), sodium (mmol/L), potassium (mmol/L), ionized calcium (mg/dl), total calcium (mg/dl), magnesium (mg/dl), and arterial blood gas (ABG) were also recorded. Medications during the admission (lopinavir/ritonavir, remdesivir, tocilizumab),

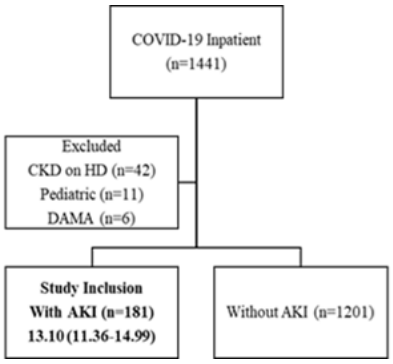

Figure 1. Flow diagram of included COVID-19 in-patients for analysis

use of anti-coagulants or inotropes, as well as need for RRT were also captured.

Excluded were patients < 18 years, chronic kidney disease patients on maintenance hemodialysis, incomplete medical records, patients who were transferred or discharged against medical advice. Adverse outcomes (in-hospital mortality) occurring during hospitalization and the length of hospitalization were recorded.

Definition of Terms

1) Acute Kidney Injury (AKI)—will be based on KDIGO 2012, using either serum creatinine or urine output upon referral.
   a) AKI Stage 1 – Maximum creatinine exceeds baseline creatinine by 1.5 to 1.9x; and/or urine output <0.5 mL/kg/hr for 6-12 hours
   b) AKI Stage 2 – Maximum creatinine exceeds baseline creatinine by 2.0 to 2.9x; and/or urine output <0.5 mL/kg/hr for >=12 hours
   c) AKI Stage 3 – Maximum creatinine exceeds baseline creatinine by at least 3.0x, or creatinine exceeded 4.0 mg/dL, or need for renal replacement therapy
2) Baseline creatinine - the result on admission or the lowest creatinine during the admission
3) Maximum creatinine—the highest recorded creatinine during the admission
4) Intermittent Hemodialysis – renal replacement therapy occurring over 3-4 hours per session at least two to three times a week
5) Slow/Prolonged intermittent renal replacement therapy – renal replacement therapy lasting for at least 6-12 hours
6) CRRT – renal replacement therapy continuously 24 hours a day
7) Renal Recovery
   a) Full - serum creatinine concentration returns to baseline
   b) Partial - serum creatinine remained >1.5x or >= 0.3 mg/dL above the baseline but was

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(*N*):	1000000
Hypothesized % frequency of outcome factor in the population (*p*):	5%+/-7
Confidence limits as % of 100(absolute +/- %)(*d*):	7%
Design effect (for cluster surveys-*DEFF*):	1

Sample Size(*n*) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	38
80%	16
90%	27
97%	46
99%	65
99.9%	105
99.99%	147

Equation

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

Results from OpenEpi, Version 3, open source calculator--SSPropor
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

discharged without the need for renal replacement therapy

c) Failure - patient requiring intermittent dialysis upon discharge

The minimum computed sample required for this study was 42. This was computed using online software, OpenEpi, Version 3. Based on the study of Cheng, Y. et al. (2020), 5% of the patients exhibited acute kidney injury.[8] The margin of error used is 7%. At 95% confidence level, the result showed that the sample size is 38.

To account for the missing data, there should be an additional 10%. The computation is as follows:

$$N_{final} = 38 + .10N_{final}$$
$$0.90N_{final} = 38$$
$$N_{final} = 42.22$$

Descriptive statistics were used to summarize the general and clinical characteristics of the patients. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption was described using mean and standard deviation, while those that did not were described using median and range.

Continuous variables which are normally distributed were compared using one-way ANOVA, while those variables that are not normally distributed were compared using the Kruskal-Wallis H test. For categorical variables, the Chi-square test was used to compare the outcomes. If the expected percentages in the cells are less than 5%, Fisher's Exact Test was used instead.

All valid data were included in the analysis. Missing values were neither imputed nor estimated. The null hypothesis was rejected at 0.05 α-level of significance. *STATA 15.0* was used for data analysis.

The study adhered to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, Data Privacy Act of 2012, and the National Ethics Guidelines for Health Research and was approved by Institutional Review Board of Makati Medical Center.

Results

We reviewed a total of 1441 charts, 59 of whom were excluded. Of these 42 were patients were on maintenance hemodialysis, 11 were pediatric patients, and six were discharged against medical advice. We

Table I. Demographic and clinical characteristics of COVID-19 patients who developed acute kidney injury (n = 181)

	Mean ± SD; Frequency (%); Median (Range)				*p*
	Overall (n=181)	Stage I (n=109)	Stage II (n=18)	Stage III (n=54)	
Age (Mean ± SD)	66.69 ± 14.08	66.25 ± 15.28	67.39 ± 11.08	67.36 ± 12.53	0.873*
Sex (n, %)					0.738†
Male	131 (72.38)	81 (74.31)	13 (72.22)	37 (68.52)	
Female	50 (27.62)	28 (25.69)	5 (27.78)	17 (31.48)	
Weight, kg	70 (41 – 155)	70 (42.8 – 155)	70 (41 – 101)	70 (43 – 150)	0.959‡
Comorbidities (n, %)					
COPD	12 (6.63)	8 (7.34)	1 (5.56)	3 (5.56)	0.999§
Chronic renal disease	41 (22.65)	26 (23.85)	6 (33.33)	9 (16.67)	0.290§
Cardiovascular disease	40 (22.1)	23 (21.1)	6 (33.33)	11 (20.37)	0.458§
Hypertension	132 (72.93)	75 (68.81)	12 (66.67)	45 (83.33)	0.113§
Diabetes mellitus	86 (47.51)	52 (47.71)	8 (44.44)	26 (48.15)	0.962†
Cerebrovascular Disease	18 (9.94)	9 (8.26)	1 (5.56)	8 (14.81)	0.395§
Chronic liver disease	4 (2.21)	2 (1.83)	0 (0)	2 (3.7)	0.738§
Cancer	10 (5.52)	5 (4.59)	1 (5.56)	4 (7.41)	0.701§
Others	16 (8.84)	8 (7.34)	0 (0)	8 (14.81)	0.139§

Statistical tests used: * - One-way ANOVA; † - Chi-square test; ‡ - Kruskal-Wallis H test; § - Fisher's Exact test

Table II. Laboratory values of COVID-19 patients who developed acute kidney injury (n = 181)

	Overall (n=181)	Stage I (n=109)	Stage II (n=18)	Stage III (n=54)	*p*
	Median (Range); Mean ± SD				
CBC‡					
Hemoglobin, g/dL	13.5 (2.3–18.3)	13.4 (8.2–17.8)	14.05 (9.8–17.7)	13.2 (2.3–18.3)	0.333
Hematocrit, %	38.9 (7.2–54.6)	39.2 (23.7–54.6)	39.15 (28.1–48.7)	36.8 (7.2–52.1)	0.164
WBC, x10^9/L	8 (0.68–51.2)	7 (0.68–24.3)	8.75 (5.8–16)	9.70 (2.1–51.2)	**0.006**
Neutrophils, %	79 (30– 95)	77 (30–95)	84.5 (48–94)	83 (59–94)	**0.006**
Lymphocytes, %	12 (2–45)	13 (2–44)	9 (2–45)	10.5 (3–33)	0.059
Monocytes, %	7 (2–28)	8 (2–28)	6.5 (3–14)	6 (2–24)	**0.004**
Eosinophils, %	0 (0–12)	0 (0–12)	0 (0–2)	0 (0–3)	0.188
Platelets, x10^9/L	211 (33–619)	212 (33–576)	213 (38–381)	209.5 (114–619)	0.418
ABG					
ABG FiO2	0.52 (0.21–100)	0.28 (0.21–40)	0.8 (0.21–100)	0.74 (0.21–100)	**0.003‡**
pH	7.43 (7–7.63)	7.43 (7.27–7.54)	7.43 (7.3–7.6)	7.44 (7–7.63)	0.923‡
PCO2, mmHg	32 (18–64)	32 (19–47)	31 (25–36)	31 (18–64)	0.148‡
PaO2, mmHg	83 (45–415)	83 (50–415)	82.5 (51–182)	87.5 (45–317)	0.959‡
>80	102 (58.29)	61 (59.22)	10 (55.56)	31 (57.41)	0.868§
60-79	56 (32)	33 (32.04)	7 (38.89)	16 (29.63)	
40-59	17 (9.71)	9 (8.74)	1 (5.56)	7 (12.96)	
<40	0 (0)	0 (0)	0 (0)	0 (0)	
HCO3, mEq/L	21.6 (6.4–40.2)	21.7 (10.6–35)	19.6 (7.47–26.9)	21.2 (6.4–40.2)	0.170‡
O2 sats, %	87.6 (73.5–100.3)	97.6 (86.2–100)	97.45 (89.5–100)	97.9 (73.5–100.3)	0.958‡
PF ratio	249.25 (0.5–850)	281 (2.5–571.4)	119.25 (0.7–519)	177.35 (0.5–850)	**0.002‡**
>300	63 (36)	45 (43.69)	5 (27.78)	13 (24.07)	0.104§
Mild (201-300)	35 (20)	22 (21.36)	2 (11.11)	11 (20.37)	
Moderate (100-199)	35 (20)	15 (14.56)	5 (27.78)	15 (27.78)	
Severe (<100)	42 (24)	21 (20.39)	6 (33.33)	15 (27.78)	
Electrolytes					
Baseline creatinine, mg/dL	1.04 (0.53–8.88)	1.01 (0.57–2.98)	1.10 (0.53–3.57)	1.14 (0.64–8.88)	0.094‡
Maximum creatinine. mg/dL	1.84 (0.96–20.98)	1.47 (0.96–4)	2.56 (1.05–5.89)	4.17 (1.12–20.98)	**<0.001‡**
Sodium	133.1 (108.4–147.7)	133.5 (113.4–147.7)	135 (124.1–143.3)	131.15 (108.4–142.4)	**0.047‡**
<136	134 (74.03)	82 (75.23)	11 (61.11)	41 (75.93)	0.553§
136-145	45 (24.86)	25 (22.94)	7 (38.89)	13 (24.07)	
>145	2 (1.1)	2 (1.83)	0 (0)	0 (0)	
Potassium	3.88 ± 0.62	3.86 ± 0.59	3.93 ± 0.66	3.92 ± 0.67	0.811‡
<3.5	44 (24.31)	26 (23.85)	4 (22.22)	14 (25.93)	0.400
3.5-5.1	130 (71.82)	81 (74.31)	13 (72.22)	36 (66.67)	
>5.1	7 (3.87)	2 (1.83)	1 (5.56)	4 (7.41)	
Ionized calcium	1.17 (0.77–1.46)	1.16 (0.96–1.35)	1.18 (1.01–1.39)	1.15 (0.77–1.46)	0.055‡
<1.12	46 (26.44)	28 (27.18)	1 (5.88)	17 (31.48)	0.151§
1.12-1.32	120 (68.97)	71 (68.93)	14 (82.35)	35 (64.81)	
>1.32	8 (4.6)	4 (3.88)	2 (11.76)	2 (3.7)	
Corrected calcium, mg/dL	8.43 (7.46–9.9)	8.4 (7.7–9.9)	9.03 (8.83–9.22)	8.22 (7.46–9.38)	0.612‡
<8.42	10 (50)	5 (55.56)	0 (0)	5 (55.56)	0.656§
8.42-10.23	10 (50)	4 (44.44)	2 (100)	4 (44.44)	
Magnesium	2.15 ± 0.35	2.11 ± 0.33	2.26 ± 0.35	2.21 ± 0.39	0.267‡
<1.60	8 (5.71)	6 (7.32)	1 (7.14)	1 (2.27)	0.188§
1.6-2.6	122 (87.14)	73 (89.02)	11 (78.57)	38 (86.36)	
>2.60	10 (7.14)	3 (3.66)	2 (14.29)	5 (11.36)	
BUN	21.84 (9.33–147.86)	21.42 (9.33–74.23)	33.47 (9.64–84.87)	20.96 (9.33–147.86)	**0.017‡**
Inflammatory markers					
Serum ferritin, ng/mL	1530.41 (30.79–14018.15)	1383.11 (60.26–14018.15)	2115.99 (205.73–9380.03)	2150.63 (30.79–13109.39)	0.180‡

	Overall (n=181)	Stage I (n=109)	Stage II (n=18)	Stage III (n=54)	*p*
	Median (Range); Mean ± SD				
CRP, mg/dL	83.55 (0.1–453.5)	66.6 (0.1–417.8)	107.9 (4.46–453.5)	107.46 (3.79–422.1)	0.068‡
<5	13 (7.3)	10 (9.17)	1 (5.88)	2 (3.85)	0.510§
≥5	165 (92.7)	99 (90.83)	16 (94.12)	50 (96.15)	
LDH, U/L	422.58 (164.13–7294)	371.91 (164.13–1219.31)	517.24 (217.04–2077.89)	483.78 (189.32–7294)	**<0.001‡**
125 – 220	8 (4.47)	5 (4.63)	1 (5.56)	2 (3.77)	0.999§
>220	171 (95.53)	103 (95.37)	17 (94.44)	51 (96.23)	
D-dimer, mg/mL	2029 (100–35200)	1315 (100–8600)	2370 (610–35200)	3095 (250–27000)	**0.018‡**
≤500	21 (14.89)	19 (22.09)	0 (0)	2 (5)	0.008§
>500	120 (85.11)	67 (77.91)	15 (100)	38 (95)	
Procalcitonin, ng/mL	0.31 (0.02–170.64)	0.24 (0.02–61.68)	0.36 (0.05–170.64)	0.44 (0.06–18.16)	**0.003‡**
<.10	35 (21.21)	28 (28.87)	3 (17.65)	4 (7.84)	0.062§
0.10-0.24	36 (21.82)	22 (22.68)	4 (23.53)	10 (19.61)	
0.25-0.49	35 (21.21)	19 (19.59)	3 (17.65)	13 (25.49)	
≥0.50	59 (35.76)	28 (28.87)	7 (41.18)	24 (47.06)	

Statistical tests used: ‡ - Kruskal-Wallis H test; § - Fisher's Exact test.

analyzed 181 adults with COVID-19 who developed stage I (60%), stage II (10%), or stage III (30%) AKI (*Table I*). The incidence of AKI among COVID-19 in-patients at Makati Medical Center was 13.10% (95% CI 11.36% to 14.99%, *Figure 1*). The patients who developed AKI were 67 ± 14 years, with a median weight of 70 kg (Range = 41-155), and were comprised mostly of males (72%). The most common comorbidities were hypertension (73%), diabetes mellitus (48%), chronic renal disease (23%), and cardiovascular disease (22%).

The median hemoglobin, hematocrit, serum sodium, and corrected total calcium were in the low normal ranges (*Table II*). The median neutrophil differential count was elevated, while that of lymphocytes was low. ABG results tended towards respiratory alkalosis. The median Horowitz index for Stage I AKI patients indicated mild ARDS, while the values for patients with more severe renal insult corresponded to moderate ARDS. Maximum recorded creatinine progressively increased from a median of 1.47 mg/dL for Stage I AKI to 4.17 mg/dL in

Table III. Therapies used in COVID-19 patients who developed acute kidney injury (n = 181)

	Frequency (%)				*p*
	Overall (n=181)	Stage I (n=109)	Stage II (n=18)	Stage III (n=54)	
Hydroxychloroquine/Chloroquine	24 (13.26)	15 (13.76)	0 (0)	9 (16.67)	0.193§
Antivirals					
Lopinavir/Ritonavir	15 (8.29)	8 (7.34)	0 (0)	7 (12.96)	0.201§
Remdesivir	87 (48.07)	61 (55.96)	8 (44.44)	18 (33.33)	0.023†
Other antivirals	1 (0.55)	1 (0.92)	0 (0)	0 (0)	0.999§
IL-6 Inhibitor (Tocilizumab)	40 (22.1)	22 (20.18)	3 (16.67)	15 (27.78)	.529§
Anticoagulation					
As prophylaxis for DVT/PE	146 (80.66)	85 (77.98)	13 (72.22)	48 (88.89)	0.135§
For RRT or hemoperfusion	53 (29.28)	14 (12.84)	8 (44.44)	31 (57.41)	**<0.001†**
Inotropes					
Norepinephrine	71 (39.23)	21 (19.27)	9 (50)	41 (75.93)	**<0.001†**
Vasopressin	18 (9.94)	2 (1.83)	4 (22.22)	12 (22.22)	**<0.001§**
Dopamine	18 (9.94)	3 (2.75)	5 (27.78)	10 (18.52)	**<0.001§**
Dobutamine	22 (12.15)	6 (5.5)	6 (33.33)	10 (18.52)	**<0.001§**
Other inotropes	2 (1.1)	0 (0)	0 (0)	2 (3.7)	0.157§
ACEI/ARB	28 (15.47)	17 (15.60)	2 (11.11)	9 (16.67)	0.953§
Convalescent plasma	5 (2.76)	3 (2.75)	0 (0)	2 (3.70)	0.999§
Respiratory Support					**<.001§**
Self-proning	18 (9.94)	16 (14.68)	2 (11.11)	0 (0)	
High flow oxygen	47 (25.97)	35 (32.11)	4 (22.22)	8 (14.81)	
Mechanical ventilation	72 (39.78)	22 (20.18)	7 (38.89)	43 (79.63)	
Proning while on mechanical ventilation	2 (1.1)	1 (0.92)	0 (0)	1 (1.85)	
Nasal Cannula/Face Mask	42 (23.2)	35 (32.11)	5 (27.78)	2 (3.7)	

Statistical tests used: † - Chi-square test; § - Fisher's Exact test.

Table IV. Outcomes in COVID-19 patients who developed acute kidney injury (n = 181)

Parameter	Frequency (%)				*p*
	Overall (n=181)	Stage I (n=109)	Stage II (n=18)	Stage III (n=54)	
Need for renal replacement therapy or extracorporeal therapy					
None	121 (66.85)	95 (87.16)	12 (66.67)	14 (25.93)	<0.001†
Peritoneal dialysis	0 (0)	0 (0)	0 (0)	0 (0)	-
Intermittent renal replacement therapy	26 (14.36)	0 (0)	0 (0)	26 (48.15)	<0.001§
Periodic intermittent renal replacement therapy	1 (0.55)	0 (0)	1 (5.56)	0 (0)	<0.001§
Continuous renal replacement therapy	10 (5.52)	1 (0.92)	0 (0)	9 (16.67)	<0.001§
Hemoperfusion/Hemadsorption	43 (23.76)	14 (12.84)	5 (27.78)	24 (44.44)	<0.001§
ECMO	0 (0)	0 (0)	0 (0)	0 (0)	-
Length of hospital stay, days (Range)	12 (1 – 181)	11 (2 – 57)	16 (3 – 27)	12 (1 – 181)	0.312‡
Renal recovery					<0.001†
Full	57 (31.49)	49 (44.95)	5 (27.78)	3 (5.56)	
Partial	58 (32.04)	47 (43.12)	6 (33.33)	5 (9.26)	
Failure	66 (36.46)	13 (11.93)	7 (38.89)	46 (85.19)	
Mortality n; % (95% CI)	79; 43.65 (36.30-51.20)	24; 22.02 (14.65-30.97)	9; 50 (26.02-73.98)	46; 85.19 (72.88-93.38)	<0.001†

Statistical tests used: † - Chi-square test; ‡ - Kruskal-Wallis H test; § - Fisher's Exact test.

Stage III patients. The markers ferritin, LDH, D-dimer, PCT, and CRP all showed highly elevated median values (*Table II*)

The investigational therapies for COVID-19 that were given to patients who developed AKI are outlined in *Table III*. Hydroxychloroquine/chloroquine were given to 13.26% of the patients. Remdesivir was given to 48.07%, and lopinavir/ritonavir were given to 8.29%. Tocilizumab was given to 22.1% of the AKI patients. Anticoagulants had been given as prophylaxis in 80.66% of the patients and in 29.28% for RRT or hemoperfusion. The following inotropes were indicated: norepinephrine (39.23%), vasopressin and dopamine at 9.94% each, and dobutamine (12.15%). There were 15.47% who had received ACEI/ARBs. Five patients had received convalescent plasma therapy. Among the COVID-19 patients who developed AKI, there were 72 (39.78%) who had required mechanical ventilation and 47 (25.97%) who had been given high flow oxygen. Other respiratory support were self-proning and nasal cannula or face mask. There was a significantly higher indication or use for anticoagulation for RRT, inotropes, and mechanical ventilation for the higher AKI stages (*Table III*).

Among the 181 patients, 79 (43.65%) died (95% CI 36.30-51.20). The mortality rates were 22.02% for Stage I, 50% for Stage II, and 85.19% for Stage III. The median length of hospital stay is 12 days, ranging from 1 up to 181 days.

Full renal recovery on discharge was observed only in one-third of the patients. It was observed in 44.95% of Stage I AKI patients, 27.78% of Stage II AKI patients, and 5.56% of Stage III patients.

While more than half of the patients did not require any RRT, there were 43 (23.76%) who required hemoperfusion/hemadsorption, 26 (14.36%) who required intermittent RRT, 10 (5.52%) who required continuous RRT and one on prolonged RRT therapy. None of them were on ECMO.

Discussion

The results of the study showed that the incidence of AKI Injury among COVID-19 in-patients was 13.1% (95% CI 11.36% to 14.99%), as shown in *Figure 1*. The incidence of AKI in the general population is noted to be variable considering the differences in the general characteristics of patients. In a study done by Cheng et al., the incidence of AKI among hospitalized patients in the general population prior to COVID-19 pandemic was at 1.6%.[24]

In the study by Diao et al., they have demonstrated that the human kidney is a potential target as well of COVID 19 and was able to observe kidney tissues from post-mortem patients having severe acute tubular necrosis and lymphocyte infiltration, concluding that the virus can directly target the kidneys specifically the kidney tubules causing acute tubular damage.[4] In a study conducted by Ng et al., the possible etiologies of AKI included the following (1) prerenal azotemia, (2) proximal tubular injury, (3) glomerulopathy, (4) thrombotic microangiopathy, and (5) complications from the treatment of COVID-19, of which the most common is acute tubular injury.[32] Several studies have also observed that patients with COVID-19 have a higher risk of developing AKI, ranging from 36.6% to 55.2%.[25-27] The consensus report of the 25th Acute Disease Quality

Initiative (ADQI) Workgroup demonstrated that the incidence of AKI among COVID-19 patients was more than 20% for hospitalized patients and more than 50% for patients in the ICU.[28]

Most of the published studies were done during the early months of the COVID-19 outbreak when the current standard of treatment for COVID-19 patients was not yet utilized, which could account for the higher incidence of AKI. Our study shows a lower incidence of AKI compared to earlier studies. This could be attributed to the more recent study period wherein we have better knowledge of the disease and had already developed a standard of care for treatment attributing to the decreased incidence of AKI among COVID-19 patients than what were initially reported.

Our study analyzed 181 adults with COVID-19 who developed stage I (60%), stage II (10%), or stage III (30%) AKI. The patients who developed AKI had a mean age of 67 years old, median weight of 70 kg, and were comprised mostly of males (72%). The most common comorbidities were hypertension (73%), diabetes mellitus (48%), chronic renal disease (23%), and cardiovascular disease (22%). Considering traditional risk factors of AKI, these were comparable to the general population.

The study has also demonstrated that COVID-19 patients were anemic. This was demonstrated as well in a study done by Cavezzi A. et al., wherein the SARS-CoV-2 can interact with the erythrocyte through ACE2, CD147, and CD26 receptors.[31] This viral-hemoglobin interaction enables the virus to attack the heme on the 1-beta chain of hemoglobin, resulting in hemolysis. Another mechanism demonstrated was that SARS-CoV-2 may mimic the action of hepcidin, which increases circulating and tissue ferritin, that could lead to relative iron deficiency. Hyponatremia was also observed in COVID-19 patients. This was also reported by De La Flor et al. and Gheorghe et al. attributing it to syndrome of inappropriate antidiuretic hormone secretion (SIADH), reduced sodium intake, or use of diuretic therapy which is commonly administered in COVID-19 patients to maintain euvolemia in the setting of ARDS.[29,30] The median neutrophil differential count was noted to be elevated, which could be attributed to a concomitant bacterial infection.

The ABG results on admission tended towards respiratory alkalosis, which could be attributed to the hypoxemia seen among COVID-19 patients where respiratory alkalosis would shift the oxygen-hemoglobin dissociation curve to the left, increasing the affinity of oxygen to hemoglobin. The median Horowitz index for Stage I AKI patients indicated mild ARDS, while the values for patients with more severe renal insult corresponded to moderate ARDS, which indicated that the severity of the infection directly correlates with the degree of AKI.

Among the 181 COVID-19 patients who developed AKI, 79 (43.65%) died, suggesting that the development of AKI increased the risk of mortality among COVID-19 patients. The study also demonstrated that the higher the stage of AKI, the higher the risk of mortality.

Full renal recovery was only observed in one-third of the patients. The higher the stage of AKI, the lesser the chance of renal recovery. Among patients who developed AKI, only 43 (23.76%) underwent hemoperfusion/hemadsorption, and 37 (20.4%) required RRT; therefore, patients who developed AKI should be closely watched during admission and closely followed-up upon discharge.

Limitations of the present study. The study was done in a single center which limits its generalization. Data gathered were solely based on the information indicated in the charts. For further studies, we recommend prospective studies to monitor and follow up the sequelae of hospitalized COVID-19 patients who developed AKI upon discharge

Conclusion

In conclusion, the study demonstrated that the incidence of AKI in hospitalized COVID-19 patients was 13.1% which was lower than previously reported. This could be attributed to the more recent study period when we have a better understanding of the disease and had already established a standard of care for treatment for the disease attributing to the decreased incidence of AKI among COVID-19 patients than what were initially reported.

The development of AKI has a direct correlation with the degree of infection. Among patients who developed AKI, 20% required RRT. Overall, the development of AKI increases the risk of mortality among hospitalized COVID-19 patients. The stage of AKI has a direct correlation with regards to mortality and has an inverse relationship with regards to renal recovery

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