# Epidemiology of Acute Kidney Injury in Diabetic Patients Infected with COVID-19 in Assiut University Hospital

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#### Abstract

### ABSTRACT

**Background:** Across numerous investigations, diabetes has emerged as a prominently reported comorbidity associated with unfavorable prognosis in patients with COVID-19. Furthermore, a substantial proportion of critically ill patients are prone to the development of acute kidney injury (AKI) at some point during their intensive care unit (ICU) admission.

**Objectives:** To study the epidemiology of AKI in diabetic patients infected with COVID-19 infection compared to non-diabetic cases admitted to ICU.

**Patients and Methods:** This study is a retrospective cross-sectional study performed at the ICU in quarantine at Assiut University Hospital from the first of March 2021 to the end of March 2022. This study includes two groups of patients: non-diabetic COVID patients with AKI and diabetic COVID patients with AKI.

**Results:** The study included 90 COVID-19-infected patients (38 were non-diabetic (42.2%), and 52 cases (57.8%) were diabetic. There was a statistically significant reduction among the studied groups regarding comparing kidney function tests among non-diabetic individuals with COVID-19 over time. ROC curve for AKI prediction by APACHE II score with the area under the curve = 0.638 (0.52 to 0.75), the best cut-off point 15.5, Sensitivity 66.7%, Specificity 62.7%, and P value = 0.026.

**Conclusion:** AKI is one of the main complications among COVID-19-infected individuals, regardless of the presence of other risk factors such as diabetes and/or hypertension.

Keywords: Diabetes, COVID-19, Acute Kidney Injury.

# Introduction:

The symptoms and morbidity caused by a COVID-19 infection fluctuate from person to person based on ethnicity, genetics, age, and geographical region. The destruction of lung epithelial cells, hypercoagulation, thrombosis, and vascular leakage that lead to sepsis are all part of the pathophysiology of severe instances of COVID-19 (1,2).

The occurrence of diseases with poor prognosis among individuals with severe COVID-19 includes diabetes as well as the use of renin-angiotensin-aldosterone system antagonists, diminished expression of proinflammatory cytokines, and reduced expression of ACE2. This is because of the pro-inflammatory cytokine production, patients' compromised innate immunity, and the usage of corticosteroids (**3,4**).

Acute kidney injury (AKI) occurs in nearly half of individuals with serious illnesses admitted to the Intensive Care Unit (ICU) (5).

After ARDS, AKI is the second most common consequence found in those who

ultimately pass away. Persons who died from COVID-19 were found to have varying degrees of AKI. Kidney damage in COVID-19-infected people has a complex etiology: (1) Prerenal azotemia, or ATN, may develop for a variety of reasons, among them: cytokine storm, shock, hypoxia, volume depletion, rhabdomyolysis. or (2)glomerulopathy, (3) thrombotic microangiopathy, (4) tubular proximal and (5) difficulties from the injury, treatment of COVID-19.

The purpose of this research was to study the occurrence of AKI among hospitalized diabetic individuals with COVID-19 infections in comparison to nondiabetic cases.

## Patients and Methods

This retrospective cross-sectional study was conducted at the ICU in quarantine of Internal Medicine and Chest Department in Assiut University Hospital.

### **Patients:**

Adult patients over 18 years old hospitalized in the Intensive Care Unit with COVID-19 from March 2021 to March 2022 have been recruited, and we compared two groups of patients: non-diabetic COVID patients with AKI and and diabetic COVID patients with AKI.

### **Ethical Considerations**

All patients signed informed consent. Assiut Faculty of Medicine, Institutional Review Board approved the study with **IRB No. 17101554**.

### Inclusion Criteria:

Adult patients (18 years old) who were infected with COVID-19 and required hospitalization.

### Exclusion

Criteria: People on maintenance dialysis for end-stage renal disease; those with stage four or five ESRD who are not on dialysis but whose condition has progressed despite treatment.

### **Study Definitions:**

 <u>AKI</u>: By the KDIGO definition, AKI is diagnosed by an absolute increase in sCr, at least 0.3 mg/dL (26.5 μmol/L) within 48 hours or by a 50% increase in sCr from baseline within 7 days, or a urine volume of less than 0.5 mL/kg/h for at least 6 hours. (6)

- 2. <u>CORADS</u>: Classification for the level of suspicion of COVID-19 infection created on the CT results. (7)
- 3. <u>APACHE II score</u>: The severity of the disease in adults admitted to intensive care units was intended to be measured using the APACHE II score.

#### Score items include:

- A. Acute Physiology Score (measured within 24 hours of AaDO2 or PaO2 (for admission): FiO2 at least 0.5 or under 0.5, respectively), mean arterial pressure, white blood cell count. body temperature (rectal), blood pH. respiratory rate, heart rate, creatinine (double point score for acute renal failure), serum potassium, serum sodium, hematocrit as well as Glasgow Coma Scale (15 minus actual GCS)
- B. Age:  $\leq 44$  (0), 45-54 (2), 55-64 (3), 65-74 (5),  $\geq 75$  (6)
- C. Chronic health points. (8)
- D. Study outcome:
  - B. Good **outcome:** This was defined as a patient who improved and whose kidney function returned to normal at discharge.
  - C. **Poor outcome:** This was defined as a patient who didn't improve at the time of discharge regarding kidney function test.

### Sample Size

Based on patients' inclusion and exclusion criteria, the sample size was estimated to be 90 COVID-19 patients, Sample Size for Frequency in a Population (from Open Epi, Version 3, open-source calculator-SSPropor). Sample Size for Frequency in a Population Hypothesized % frequency of outcome factor in the population (p): 50% + -5 Confidence limits as % of 100 (absolute +/- %) (d): 5% Design effect (for cluster surveys-DEFF). We compared three groups of patients: nondiabetic COVID patients with AKI, diabetic COVID patients with AKI, and diabetic COVID patients without AKI.

## **Statistical Methods**

All of the statistical computations were performed with version 22 of SPSS, which is a statistical tool for social science that was developed by SPSS Inc. in Chicago, Illinois, USA. The student t-test and the Mann-Whitney U test were used to compare the quantitative variables. The student t-test was used on data normally distributed, and the Mann-Whitney U test was used on data not normally distributed. The Paired Sample Test or the Friedman Test was utilized to compare paired continuous data. Tests like the Chi-square test, the Fisher exact test, the Spearman rho correlation test, and the Receiver Operating Characteristic Curve (ROC) analysis can be utilized when comparing categorical data.

### Results

**Table (1)** summarizes the study population's demographic data. The mean age of the studied cases was  $60.00 \pm 15.44$ , with a male-to-female ratio of 1:1. The median GCS score was 15 (range 10 – 15). Out of 90 COVID-19-infected patients, 38 patients (42.2%) were non-diabetic, and 52 patients (57.8%) had diabetes.

No significant difference was observed between diabetic and non-diabetic patients for all baseline laboratory data except for the baseline random blood glucose level that was significantly higher among diabetic patients (215.63  $\pm$  84.17 vs. 138.54  $\pm$  43.91, P<0.001) in diabetic versus non-diabetic patients respectively as shown in **Table (2)**.

No significant difference was observed between diabetic and non-diabetic patients for kidney function tests, as shown in **Table** (1) supplementary.

Kidney function tests (serum urea and creatinine) show a significant reduction over time from admission time to discharge among non-diabetic patients with COVID-19 infection (P=0.001 and <0.001), respectively, as shown in **Table (3).** Other associated comorbidities were summarized in **Table 2-4** supplementary tables.

The mean APACHE II score was significantly higher among patients whose AKI was complicated than those who didn't develop AKI (13.51  $\pm$  6.50 vs. 16.10  $\pm$  5.19, P=0.044), respectively, as shown in **Table** (4).

**Among diabetic patients**, no significant difference was observed in mean APACHE II score between patients who were complicated by AKI compared to those who didn't develop AKI ( $14.48 \pm 6.64$  vs.  $15.78 \pm 5.94$ , P=0.461) respectively, as shown in **Table(4) supplementary**.

ROC curve for AKI prediction in patients with COVID-19 infection, as shown in **Figure (1)**.

Demographic data	Total (n=90)	Non-diabetic(n=38)	Diabetic(n=52)	P value
Age (years)				0.493
$Mean \pm SD$	15.44±60.00	17.13±58.68	14.17±60.96	
Sex				0.200
Male	45 (50.00)	22 (57.9)	23 (44.2)	
Female	45 (50.00)	16 (42.1)	29 (55.8)	
GCS				0.406
Median (range)	(15-10) 15	(15-10) 15	(15-10) 15	

**Table (1)** Demographic characteristics and vital signs of cases with COVID-19 in relation to diabetic status.

Demographic data	Total (n=90) Non-	diabetic(n=38)	Diabetic(n=52)	P value
SBP (mm/Hg)			X	0.006
Mean ± SD	$119.78\pm15.93$	$114.74 \pm 14.28$	$123.16\pm16.19$	
DBP (mm/Hg)				0.015
Mean $\pm$ SD	$77.22\pm7.19$	$75.26 \pm 7.26$	$78.65\pm6.87$	
Mean BP (mm/Hg)				0.002
Mean $\pm$ SD	$91.32\pm9.67$	$88.21 \pm 9.29$	$93.60\pm9.38$	
Temperature (°C)				0.812
Mean $\pm$ SD	$38.44 \pm 0.50$	$38.47 \pm 0.44$	$38.42\pm0.55$	
Oxygen saturation (%)				0.709
Mean $\pm$ SD	$87.29\pm6.05$	$87.29 \pm 5.73$	$87.29 \pm 6.33$	
PaO2				0.902
Mean $\pm$ SD	$75.86 \pm 8.52$	$76.16\pm8.12$	$75.63\pm8.87$	
Respiratory rate (breaths/min	n)			0.580
Mean $\pm$ SD	$30.70\pm8.19$	$31.32\pm8.52$	$30.25\pm7.99$	
Heart rate (beats/min)				0.519
Mean $\pm$ SD	$110.33\pm18.39$	$111.97\pm18.84$	$109.13\pm18.14$	

Table (1) Demographic characteristics and vital signs of cases with COVID-19 in relation to diabetic status. (*Cont.*)

**Table (2)** baseline laboratory data, swap, and CT chest of cases with COVID-19 in relation to diabetic status:

<b>Baseline laboratory</b>	Total (n=90)	Non-diabetic		P value
data	× ,	( <b>n=38</b> )	Diabetic (n=52)	
RBG(mg/dL)				< 0.001
Mean $\pm$ SD	$183.22\pm79.58$	$138.54\pm43.91$	$215.63\pm84.17$	
WBCs(*10 <sup>3</sup> /ul)				0.285
Mean ± SD	$11.34\pm5.55$	$10.60\pm5.75$	$11.87 \pm 5.40$	
Lymphocyte(*10 <sup>3</sup> /ul)				0.085
Mean ± SD	$0.77\pm0.85$	$0.75 \pm 1.12$	$0.78\pm0.59$	
Neutrophils(*10 <sup>3</sup> /ul)				0.347
Mean ± SD	$11.00\pm7.02$	$12.20\pm8.32$	$10.13\pm5.82$	
Hemoglobin (g/dl)				0.193
Mean ± SD	$10.67\pm2.10$	$11.01\pm2.30$	$10.42 \pm 1.92$	
Platelets (*10 <sup>3</sup> /ul)				0.330
Mean ± SD	$302.34 \pm 136.08$	$285.89\pm128.21$	$314.37 \pm 141.56$	
HCT (%)				0.172
Mean ± SD	$36.83 \pm 7.22$	$38.05\pm6.46$	$35.94 \pm 7.66$	
Sodium (mEq/L)				0.786
Mean ± SD	$139.21\pm5.32$	$138.66\pm4.34$	$139.62\pm5.94$	
Potassium (mmol/L)				0.588
Mean ± SD	$4.07\pm0.46$	$4.07\pm0.39$	$4.07\pm0.51$	
Calcium (mg/dL)				0.150
Mean $\pm$ SD	$7.79\pm0.71$	$7.84 \pm 0.91$	$7.74\pm0.51$	
Crp (mg/dl)				0.621
Mean $\pm$ SD	$75.26\pm65.22$	$66.32 \pm 49.67$	$81.79\pm74.36$	

	Total	( <b>n=90</b> )	Non-diabetic		P value
Baseline laboratory data			( <b>n=38</b> )	Diabetic (n=52	)
Swap					
Negative	9	(10.0)	3(7.9)	6(11.5)	
Positive	81	(90.0)	35(92.1)	46(88.5)	
CT chest					0.315
Corad 2 "low"	4	(4.4)	3(7.9)	1(1.9)	
Corad 3 "indeterminate"	28	(31.1)	10(26.3)	18(34.6)	
Corad 4 "high"	57	(63.3)	24(63.2)	33(63.5)	
Corad 5 "very high"	1	(1.1)	1(2.6)	0(0.0)	
Mechanical ventilation					0.836
No ventilation	22	(24.4)	10(26.3)	12(23.1)	
Need ventilation	48	(53.3)	19(50.0)	29(55.8)	
Intubated	20	(22.2)	9(23.7)	11(21.2)	

 Table (2) baseline laboratory data, swap, and CT chest of cases with COVID-19 in relation to diabetic status: (Cont)

Table (3)	<b>Kidney function tests</b>	"urea and creatinine"	of patients with	COVID-19 in
relation t	o diabetic status at diff	erent studied points:		

Kidney function tests	Inction tests On admission to		On discharge	
of non-diabetic (n=38)	ICU			P value
Urea(mmol/l)				
Mean ± SD	$23.23 \pm 13.78$	$20.75 \pm 12.76$	$17.08 \pm 11.35$	0.001
Createnine(umol/l				
Mean $\pm$ SD	$309.32 \pm 287.03$	$272.83 \pm 288.52$	$180.00 \pm 254.04$	< 0.001
Urea(mmol/l)				
Mean $\pm$ SD	$27.76\pm20.34$	$24.83 \pm 16.34$	$20.29 \pm 13.05$	< 0.001
Createnine(umol/l)				
Mean ± SD	$276.58 \pm 241.94$	$261.56 \pm 218.06$	$219.16\pm208.82$	< 0.001

Table (4) Relation between APACHE II score and acute kidney injury among patients with COVID-19 (n=90).

APACHE II score No AKI (n=51)		<b>AKI (n=39)</b>	P value
Mean $\pm$ SD	$13.51 \pm 6.50$	$16.10\pm5.19$	0.044



#### Figure (1) ROC curve for AKI prediction in cases with COVID-19 infection.

AUC: Area under the curve; CI: confidence interval. \*Significance defined by p < 0.05APACHE II score (blue) and Reference line (green). Area under the curve = 0.638 (0.52 to 0.75), the cut-off point 15.5, Sensitivity 66.7%, Specificity 62.7%, and P value = 0.026.

Kidney function tests	Total (n=90)	Non-diabetic (n=38)	Diabetic (n=52)	P value
On admission				
Urea(mmol/l)				0.459
Mean $\pm$ SD	$25.85 \pm 17.92$	$23.23 \pm 13.78$	$27.76 \pm 20.34$	
Createnine(umol/l)				0.938
Mean $\pm$ SD	$290.40 \pm 260.88$	$309.32 \pm 287.03$	$276.58 \pm 241.94$	
On ICU admission				0.236
Urea(mmol/l)				
Mean $\pm$ SD	$23.16 \pm 15.04$	$20.75 \pm 12.76$	$24.83 \pm 16.34$	
Createnine(umol/l)				0.331
Mean $\pm$ SD	$266.17 \pm 247.78$	$272.83 \pm 288.52$	$261.56 \pm 218.06$	
On discharge				
Urea(mmol/l)				0.209
Mean ± SD	$18.97 \pm 12.41$	$17.08 \pm 11.35$	$20.29 \pm 13.05$	
Createnine(umol/l)				0.226
Mean ± SD	$217.85 \pm 227.20$	$216.00 \pm 254.04$	$219.16 \pm 208.82$	

**Table (5)** supplementary Kidney function tests "urea and creatinine" of patients with COVID-19 in relation to diabetic status at different studied points:

**Table (6)** supplementary Comorbidities of patients with COVID-19 in relation to diabetic status.

Comorbidities	Total (n=90)	Non-diabetic (n=38)	Diabetic (n=52)	P value
Hypertension	30 (33.3)	4(10.5)	26 (50)	< 0.001
Ischemic heart disease	14 (15.6)	4(10.5)	10 (19.2)	0.260
Chronic kidney disease	7 (7.8)	0(0.0)	7 (13.5)	0.020
Cerebrovascular stroke	9 (10.0)	4(10.5)	5 (9.6)	1
COPD	5(5.6)	3 (7.9)	2 (3.8)	(0.646)

able (6) supplementary Comorbidities of patients with COVID-19 in relation to diabeti	ic
atus. <u>(Cont).</u>	

Comorbidities	Total (n=90)	Non-diabetic (n=38)	Diabetic (n=52)	P value
Others				
SLE	1(1.1)	1(2.6)	0 (0.0)	
HCV	2	2 (5.3)	0 (0.0)	
Liver cirrhosis	1 (1.1)	0 (0.0)	1 (1.9)	
Scleroderma	1 (1.1)	1 (2.6)	0 (0.0)	
Asthmatic	2(2.2)	0 (0.0)	2 (3.8)	

**Table (7)** Supplementary clinical outcome of patients with COVID-19 in relation to diabetic status:

Clinical outcome	<b>Total (n=90)</b>	Non-diabetic (n=38)	Diabetic (n=52)	P value
Final outcome				0.267
Good	32 (35.6)	16 (42.1)	16 (30.8)	
Poor	58 (64.4)	22 (57.9)	36 (69.2)	
Complication				
AKI	39 (43.3)	12 (31.6)	27 (51.9)	0.054
CKD	6 (6.7)	4 (10.5)	2 (3.8)	0.236
ESRD	5 (5.6)	3 (7.9)	2 (3.8)	0.646
Died	10 (11.1)	3 (7.9)	7 (13.5)	0.509

**Table (8)** Supplementary relation between APACHE II score and acute kidney injury among diabetic and non-diabetic patients with COVID-19.

Diabetic Patients(n=52)	No AKI (n=25)	AKI (n=27)	P value
APACHE II score			
Mean $\pm$ SD	$14.48\pm6.64$	$15.78\pm5.9$	4 0.461
Non-diabetic Patients(n=38)	No AKI (n=26)	AKI (n=1	2)
APACHE II score			
Mean ± SD	$12.58\pm 6.35$	$16.83 \pm 2.9$	95 0.034

#### Discussion

In the present retrospective case comparison study, we aimed to study the epidemiology of AKI in diabetic patients admitted by COVID-19 infection and whether AKI affects those patients more or not, in addition to identifying the general characteristics and associated risk factors of diabetic patients infected with COVID-19 who developed AKI, and outcome of diabetic patients admitted by COVID-19 infection.

The mean age of the studied cases was  $60.00 \pm 15.44$ , fluctuating from 20 to 90 years

old. A similar mean age was reported by many previous studies (9-12). Similar to the current study, a Chinese study indicated that men and women had identical COVID-19 prevalence but were 2.4 times more likely to die (13). A recent meta-analysis of 3 111 714 documented global cases indicated no disparity among the proportion of male and female COVID-19 cases. This was discovered, although there is no variation in the number of cases caused by COVID-19 (14).

Individuals with COVID-19 may have a better prognosis if their renal abnormalities

are identified and treated early on. Thus, more frequent serum creatinine monitoring is warranted for enhanced early diagnosis of renal damage (**15,16**). In the current study, we measured the kidney function tests (at baseline, during ICU, and on discharge), and we observed a significant reduction over time from admission time to discharge among diabetics and non-diabetic COVID-19-infected individuals.

Serum C-reactive protein (CRP) is a key measure that fluctuates considerably in people with severe COVID-19. CRP concentration decreases when inflammation or tissue damage heals, making it a helpful marker for tracking disease progression (17).In the current research, we detected a rise in CRP from baseline to after follow-up for both diabetic and non-diabetic patients, with borderline significance.

In the current study, no significant variance was observed among diabetic and non-diabetic individuals for their outcome and/or development of complications. This finding could be explained by the fact that the studied diabetic patients may have good glycemic control, and it is well known that glycemic less control is related to unfavorable results in diabetic COVID-19 persons. Also, previous studies stated that it is not clear if diabetes alone increases the risk of death or morbidity due to COVID-19 (18).

In our study, Kidney failure was reported to be a prevalent consequence of COVID-19, with 43.3 percent of those treated developing acute kidney injury. Our investigation found a greater incidence of AKI than prior reports. Based on three previously published meta-analyses, the estimated prevalence of acute kidney injury was 4.5 percent (19). Twenty-four percent of coronavirus disease cases in 2019 had AKI, according to a distinct Iranian meta-analysis (20). Many previous studies were consistent with such findings (21-23).

Interestingly, we observed that mean APACHE II was significantly higher in COVID-19 patients whose AKI was more complicated than their counterparts. This finding was supported by the recent study of Dereli et al., who observed that patients with AKI have a highly significant APACHE II compared to patients without AKI (24).

Higher mortality was observed in patients who had higher point scores (OR 1.08, CI 95%, 1.02–1.98;) as well as in patients who developed stage 3 AKI (OR 1.11, CI 95%, 1.05–2.57;) in the setting of COVID-19, where the APACHE II score was similarly related to acute kidney injury in a Latin American cohort (OR 1.97, CI 95%, 1.08–2.64;). These findings provide credence to the hypothesis that acute kidney injury is a significant factor in the prognosis of COVID-19 patients. Higher APACHE II scores have been linked, across a variety of studies on COVID-19 patients, to a worse prognosis as well as more severe AKI (25).

Based on the available information, the case fatality rate in Egypt was calculated to be 5.65 percent. Based on studies that were carried out on a very small number of individuals, the estimated mortality rate while in the hospital ranged from 18.9% (28/148) (23) to 24.4% (39/160) (26). The present indicated mortality rate was below the mortality rate described by Kandil et al., who reported that 26.5% of the examined cases were fatal (12) as well as the recent Egyptian study by Shaban et al., who reported that seventeen out of fifty-three COVID-19 infected patients (32.1%) died (27).

# Conclusion

We could conclude that AKI is a common difficulty among COVID-19infected individuals, regardless of the presence of other risk factors such as diabetes and/or hypertension.

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