A retrospective study on the incidence of CKD Diagnosis Post COVID-19 infection with variations in glycemic control

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Introduction

Even though primarily a respiratory illness, patients with COVID-19, especially those with more severe presentations, are predisposed to developing multi-organ complications. The frequency of these complications is greater in patients with preexisting conditions such as type-2 diabetes mellitus (T2DM). Not only is pre-existing diabetes a risk factor for poor outcomes after SARS-CoV-2 infection, more recently, studies have highlighted the development of T2DM post-infection via ACE2 receptor-mediated endocytosis of SARS-CoV-2 virions in the pancreatic islets, leading to disruptions in insulin secretion and blood glucose regulation.[1] Therefore, diabetes is both a risk factor and a post-infection sequelae of COVID-19. Furthermore, one of the more common post-infection sequelae of COVID-19 is acute kidney injury (AKI), owing to immune system excessive inflammatory response and more direct injury via ACE2 receptor is highly expressed in renal tubular cells.[2]

Glycated hemoglobin (HbA1c) provides an average measure of blood glucose over a three month period. HbA1c is divided into three categories based on proportion of glycated hemoglobin: normal (<5.7%), pre-diabetes (5.7-6.4%), and diabetes (>6.5%). The level of HbA1c is correlated with disease severity and poor health outcomes. One of the complications of long standing elevated blood glucose in diabetes is the development of diabetic nephropathy (DN), which proceeds through a mechanism of advanced glycation end-product (AGE) formation in the glomerular basement membrane. Formation of AGE in the glomerulus leads to hyperfiltration and albuminuria. Sustained elevated blood glucose can lead to chronic DN which is characterized by interstitial fibrosis, nodular glomerulosclerosis, and basement membrane thickening. These permanent changes lead to further decreases in eGFR and more severe albuminuria. DN represents just one mechanism of kidney injury that can lead to chronic kidney disease (CKD), which is divided into five categories based on eGFR and presence or absence of microalbuminuria. Most available studies that correlate HbA1c to the development or progression of CKD or reduced kidney function show increased risk with higher or more labile levels of HbA1c.[3,4] Given the localization of SARS-CoV-2 virions to the renal tubules, and the increased risk for renal damage from elevated blood sugar levels, T2DM has been shown to be a risk factor for AKI in COVID-19 patients.[5] However, patients often developed CKD after years of uncontrolled levels of HbA1c.

In this study, we investigate the development of CKD in patients with different levels of HbA1c after their initial SARS-CoV-2 infection and hypothesize that COVID-19 may accelerate the development of CKD in these already at-risk patients with higher levels of HbA1c.

Aims and Objectives

Aim 1: Characterize the population of COVID-19 patients in terms of demographics, comorbidities and COVID severity.

Aim 2: Compare the incidence of CKD after mild or severe (hospitalized) COVID19, up to a 8 month follow up period.

Aim 3: Examine the association of prior hemoglobin A1c levels, comorbidities, demographic characteristics, and COVID-19 severity with post COVID-19 incidence of CKD/ESRD.

Aim 4. Develop a model to predict risk of developing CKD after COVID-19.

Methods

This study is a retrospective analysis of electronic medical records of adult patients (>18 y) that were diagnosed with COVID-19 by PCR between 1/1/2020 - 9/15/2021. Records were extracted for a follow up period of 8 month period after COVID-19 diagnosis. The variables of interest included patient demographics (age, sex, race, ethnicity), HbA1c values, COVID-9 severity, and other comorbidities (Table 1). COVID-19 severity was determined based on whether the patient was hospitalized within 14 days of diagnosis.[6] To determine if the observed differences in post COVID-19 development of CKD were statistically significant, the following tests were performed: two sample t-test (unequal variance) for continuous variables, as well as Chi-square test and Fisher's Exact Test for categorical variables.

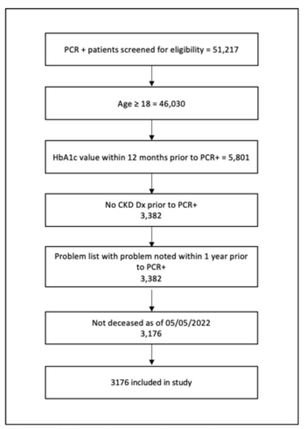

Figure 1 Flow diagram showing the inclusion criteria and changes in numbers when PCR+ patients are filtered HbA1c value, No CKD prior, problem list, and non deceased as of 05/05/2022.

Results

Table 1 Characteristics of Patients who did or did not develop CKD post COVID-19.

	Post Covid CKD		
	No CKD (%)	CKD (%)	p-value
Days to CKD dx post PCR, *Mean ± SD*	.	117.9 ± 180.9	
Demographics			
Age, *median (IQR)*	51 (25)	61 (21)	p<0.0001
Female, *n (%)*	1619 (65.1)	332 (48.9)	p<0.0001
Race, *n (%)*			p<0.0001
White or Caucasian	1566 (62.9)	370 (54.5)	
Black or African American	619 (24.9)	244 (35.9)	
Other	297 (11.9)	65 (9.6)	
Clinical			
Severe COVID, *n (%)*	748 (30.1)	510 (75.1)	p<0.0001
BMI, *mean ± SD*	33.5 ± 9.6	34.0 ± 9.4	p=0.3655
HBA1C, m*ean ± SD*	5.7 ± 1.3	7.0 ± 2.3	p<0.0001
HbA1c categories			p<0.0001
Normal HbA1c, *n (%)*	1567 (63.0)	194 (28.6)	
Pre-Diabetes HbA1c, *n (%)*	669 (26.9)	217 (32.0)	
Diabetes HbA1c, *n (%)*	252 (10.1)	268 (39.5)	
Chronic Conditions, *n (%)*			
Hypertension	1339 (53.8)	510 (75.1)	p<0.0001
Hyperlipidemia	1358 (54.6)	469 (69.1)	p<0.0001
Previous Stroke or TIA	208 (8.4)	77 (11.3)	p<0.0162
Heart Failure	138 (5.5)	81 (11.9)	p<0.0001
T2DM	707 (28.4)	371 (54.6)	p<0.0001
Acute MI	105 (4.2)	44 (6.5)	p<0.0137
AFIB	134 (5.4)	76 (11.2)	p<0.0001
Glaucoma	92 (3.7)	40 (5.9)	p=0.0113

IQR= Interquartile range, ND: Native Indian, COVID (Coronavirus Disease), CKD (chronic kidney disease, SD (standard deviation, HbA1c (Hemoglobin A1c), TIA (Transient ischemic attack), MI (myocardial infarction), AFIB (atrial fibrillation).

Table 2 Adjusted odds ratios for developing CKD after SARS COV2 infection based on multivariable logistic regression.

Variable	Adj Odds Ratio	Lower 95% CI	CI Upper 95% CI	Wald p-value
Severe Covid	4.48	3.63	5.52	<.0001
HbA1c [per unit]	1.57	1.46	1.69	<.0001
Gender [Male]	1.51	1.23	1.85	<.0001
AFIB	1.47	1.05	2.07	.0284
Hypertension	1.46	1.14	1.85	.0023
Hypothyroidism	1.31	1.04	1.66	.0223
Age [per unit year]	1.02	1.02	1.03	<.0001
Race: Caucasian & other vs. AA	.75	.68	.84	<.0001

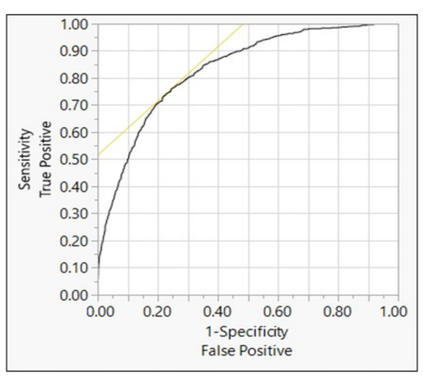

Figure 2 ROC curve for HbA1c, severe COVID, gender, atrial fibrillation, hypertension, hypothyroidism, age and race associated with the diagnosis of CKD within 8 months of PCR+. ROC curve area: 0.83.

Conclusions

- Severe COVID (any COVID-19 course in which a patient was hospitalized within 14 days of their initial diagnosis[6]) was most significant risk factor for CKD onset with OR 4.48 (95% CI, 3.36-5.52). Our results are consistent with previously published research that shows that COVID-19 is associated with kidney damage and AKI.
- The second most significant risk factor for developing CKD is HbA1c with an OR 1.57 (95% CI, 1.46 to 1.69). These results are consistent with the current medical understanding that diabetes and longstanding hyperglycemia are risk factors for CKD.
- Our results suggest that severe COVID-19 illness exacerbates the rate at which uncontrolled blood sugars can lead to CKD.
- Other variables found to be associated with increased risk of developing CKD post COVID were, male gender, atrial fibrillation, hypertension, hypothyroidism, age, and non-white race. These should be further explored in future studies. However modifiable factors such as hypertension and hypothyroidism should receive appropriate medical management to decrease risk of CKD development after COVID-19.

References

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Study Limitations

Limitations of this study include: 1) possible incomplete post-discharge medical records; 2) possible misclassification of AKI for CKD; 3) Lack of confirmation of CKD using glomerular filtration rates, or other kidney function lab results.