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The incidence, risk factors, and outcome of new-onset diabetes among post-COVID-19 patients: A single-center study

Siddaganga[1], Archana Dambal[2], Akhila Nekkanti[3], Yashika C[4]

[1]Assistant Professor, [2]Professor, [3,4]Post Graduate, Department of General Medicine, SDM College of Medical Sciences and Hospital, SDM University, Dharwad, Karnataka, India

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) infection may elevate the risk of hyperglycemia and other complications in patients with and without prior diabetes history. It is not clear whether the virus induces type 1 or type 2 diabetes or instead causes a novel form of diabetes. Precise mechanism of diabetes onset in COVID-19 patients remains unresolved. **Aims and Objectives:** The aims of this study were to know the incidence, risk factors, and outcome of new-onset diabetes among post-COVID-19 patients and association of disease severity and occurrence of new-onset diabetes in post-COVID-19 Patients. **Materials and Methods:** Patients age more than 18 years, not known diabetic, tested positive with rapid antigen test or reverse transcription polymerase chain reaction admitted to a tertiary care hospital were included in the present prospective observational study. The patients who developed new-onset diabetes during the 3 months follow-up and, the risk factors associated with new-onset diabetes are assessed. Patients with hemoglobin (HbA1c) >6.5% were diagnosed with new-onset diabetes. **Results:** Total 246 patients were non-diabetics at admission, at 1 week 188 were non-diabetics and 49 were diabetics, and nine were prediabetics. Patients were within the age range of 21–95 years with mean age of 49.46 ± 17.02 years and male predominance (59.76%). Out of 188 non-diabetics, 19 (10.10%) developed new-onset diabetes, and 2 (1.06%) developed new-onset prediabetes after 3 months. Out of 49 diabetics, 19 (38.77%) became non-diabetic, 30 (61.22%) remained diabetic, and out of nine prediabetes 2 (22.22%) developed new-onset diabetes, 5 (55.55%) reversed to non-diabetic, and 2 (22.22%) remained prediabetic after 3 months. In total, from HbA1c at admission and 3 months, 51 subjects had new-onset diabetes (20.73%). Most common risk factors found with occurrence of new-onset diabetes were those on high dose of steroid (P = 0.0001), family history of diabetes mellitus (DM) (P = 0.001), over weight and obesity (P = 0.0001), fungal infection (P = 0.0001), and need of oxygen and intensive care unit requirement (P = 0.0001). The patient with increased laboratory markers of inflammation such as ferritin, neutrophil leukocyte ratio, lactate dehydrogenase, and C-reactive protein D-dimer had strong association with occurrence of new-onset diabetes (P = 0.0001). **Conclusion:** COVID-19 infection confers an increased risk for type 2 diabetes. Patients of all ages and genders had an elevated incidence and risk for occurrence of new-onset diabetes. Moreover, it was strongly associated with overweight and obesity, steroid dosage, and its duration, disease severity, positive family history of DM, and increased laboratory markers of inflammation. Hence, particular attention should be paid during the first 3 months after COVID-19 infection and patients need to be under follow-up for blood glucose monitoring.

Key words: Coronavirus disease 2019; Hemoglobin; Inflammatory markers; New-onset diabetes mellitus; Obesity; Severity

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Address for Correspondence:
Dr. Siddaganga, Assistant Professor, Department of General Medicine, SDM College of Medical Sciences and Hospital, SDM University, Dharwad, Karnataka, India. **Mobile:** +91-9449364445. **E-mail:** drsiddaganga@gmail.com

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic responsible for approximately 216 million confirmed cases and 4.49 million deaths that continue to spread rapidly.[1] The virus responsible for COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, in 2019 and spreads through droplet transmissions, leading to variable symptoms that can range from asymptomatic or mild respiratory illness to severe multiorgan failure and death in infected individuals.

There is an increase in hyperglycemic conditions and complications in COVID-19 patients both with and without diabetes. Specifically, new-onset diabetes has been observed following COVID-19 infection,[2] including acute hyperglycemia in COVID-19 patients without diabetes, diabetic ketoacidosis in COVID-19 patients with pre-existing diabetes, and new-onset diabetes in COVID-19 patients.[3,4] There is increasing evidence that patients recovering after a SARS-CoV-2 infection may have a variety of acute sequelae including newly diagnosed diabetes. However, the risk of diabetes in the post-acute phase is unclear. COVID-19-associated diabetes mellitus (DM) and hyperglycemia were found in 19.70% and 25.23% of patients, respectively,[5] but the incidence of complications, such as need for intensive care unit (ICU) and mechanical intubation, varies between studies, with some showing an increase and others no difference when compared to normoglycemic patients.[6] However, the exact mechanisms causing new-onset diabetes in COVID-19 patients are unknown.[7] Several complex interrelated processes, such as previously undetected diabetes, stress hyperglycemia, steroid-induced hyperglycemia, and direct or indirect effects of SARS-CoV-2 on the β-cell are likely to be implicated.[7] DM and reactive hyperglycemia have been identified as predictors of severity in SARS-CoV-2 infected patients.[7]

To overcome this question, we aimed to determine if there was any association between status post-COVID-19 infection, risk factors, and incidence of new-onset diabetes.

Aims and objectives

The objectives of this study were to know the incidence, risk factors, and outcome of new-onset diabetes among post-COVID-19 patients and association of disease severity and occurrence of new-onset diabetes in post-COVID-19 patients.

MATERIALS AND METHODS

A prospective observational study carried out for a period of 6 months from July 2021 to December 2021 at a tertiary care hospital. Informed consent of all participants was taken and the Institutional Ethical Committee permission was sought before the start of study (Institutional Ethical Committee approval no SDMIEC/2021/110). All patients who were admitted with COVID-19 were screened for comorbidities including DM. Four hundred patients were screened with glycosylated hemoglobin (HbA1c) and fasting glucose, out of which 246 not known diabetic and age >18 years, who tested positive with rapid antigen test or reverse transcription polymerase chain reaction (RT-PCR) and treated in our hospital were included others excluded due to pre-existing DM. The treatment of all patients was done as per ICMR protocol. All patients were followed up at regular intervals 1 week for steroid dosage tapering and compliance, and after 3 months for HbA1c sampling. Data collection demographic data, clinical severity (according to ICMR grading), number of days of hospital stay, systemic corticosteroid dose during hospitalization, oxygen requirement, need for ICU admission, and need for ventilator support was noted. Laboratory parameters – fasting blood glucose (FBS), post-prandial blood sugar, and glycosylated HbA1c at admission and at follow-up using immunoturbidimetry method were done. Furthermore, the treatment category and inflammatory markers were documented.

Definitions: Non-diabetic patients were defined as having an HbA1c<6.4% and diabetic if HbA1c≥6.5%.[8] Follow-up patients were followed up telephonically for at 1 week for steroid dosage tapering, compliance, persisting symptoms, and HbA1c after 3 months.

Inclusion criteria

The following criteria were included in the study:

- Patients diagnosed with COVID-19 positive status
- Diagnosis of COVID-19 confirmed by RT-PCR
- Newly diagnosed DM as per the American Diabetes Association criteria
- Age above 18 years.

Exclusion criteria

The following criteria were excluded from the study:

- Past history of DM
- Pregnant women.

Statistical analysis

Continuous variables were expressed as mean±SD and categorical variables were expressed as numbers and percentages Chi-square test was used to check the association between attributes. P≤0.05 indicates statistical significance. Logistic regression analysis was applied to know relative risk factors.

RESULTS

Total 400 patients were screened with HbA1c and fasting glucose, out of which 246 not known diabetic at admission, at 1 week 188 were non-diabetics and 49 were diabetics and nine were prediabetics. Patients were within the age range of 21–95 years with mean age of 49.46±17.02 years and male predominance (59.76%) (Table 1). Out of 188 non-diabetics, 19 (10.10%) developed new-onset diabetes, and 2 (1.06%) developed new-onset prediabetes after 3 months. Out of 49 diabetics, 19 (38.77%) became non-diabetic, 30 (61.22%) remained diabetic, and out of nine prediabetes 2 (22.22%) developed new-onset diabetes, 5 (55.55%) reversed to non-diabetic, and 2 (22.22%) remained prediabetic after 3 months. In total, from HBA1c at admission and 3 months, 51 subjects had new-onset DM (20.73%) (Table 2).

Ninety (36.59%) non-diabetics did not require steroids; yet, 4 (7.84%) developed new-onset diabetes most of the diabetic patients required moderate to high dose of steroid compared to non-diabetics (Table 1). Almost 92.15% of the patients who developed new-onset diabetes were on steroids during COVID-19 treatment (P<0.0001). Patients on moderate dose steroid have 35 times risk of having diabetes (Table 3). Family history of DM was present in 20 (39.22%) patients who developed new onset of diabetes (P<0.0001), they are 7.22 times risk of having new-onset diabetes in comparison to non-diabetes (Table 3). There was a significant difference between BMI (24.69±2.38 vs. 21.23±1.33; P<0.0001) (Table 1). Twenty-two (43.14%) of the newly diagnosed DM patients were overweight or obese. Out of 51 patients who developed new-onset diabetes, 28 patients (54.90%) had severe CT severity score at the time of admission and they were 5.75 times high-risk having diabetes (Table 3). Nearly, 43 (84.31%) and 23 (45.10%) diabetic patients needed oxygen and ICU admission, respectively (P=0.0001*), also 6 and 10 times of risk of having diabetic, respectively (Table 1). Thirty-three (64.71%) diabetic patients stayed more than 7 days in hospital compared to non-diabetic (Table 1). Hypertension 19 (37.25%) was the common comorbidity found in patients with new-onset diabetes (Table 1). Around seven patients (13.73%) of new-onset diabetic presented with fungal infection during follow-up (P=0.0001*). Patients with increased laboratory markers of inflammation such as ferritin, neutrophil leukocyte ratio (N/L Ratio), lactate dehydrogenase (LDH), C-reactive protein (CRP), and D-dimer had strong association with occurrence of new-onset diabetes (P=0.0001) (Table 1). Patients with high CRP more than 26 had risk of 134.7 times higher than CRP of <6 having incidence of new-onset diabetes analyzed und logistic regression analyzer (Table 3).

Fasting blood glucose (207.2±108.8) and glycated hemoglobin (6.5–8.5%) were found to be significantly higher in the newly diagnosed diabetic patients (P<0.0001). Forty (78.4%) patients were on oral hypoglycemic drugs. Six (11.7%) patients were on insulin and 5 (9.8%) patients both on insulin and oral hypoglycemic drugs.

DISCUSSION

Insulin resistance and impaired insulin secretion have been described in individuals without diabetes history who recovered from SARS-CoV-2 infections.[9] Cytokines and TNF-α remain up regulated after remission of COVID-19, which may induce beta-cell dysfunction and insulin resistance.[9]

SARS-CoV-2, the virus that causes COVID-19, binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta-cells, adipose tissue, the small intestine, and the kidneys.[10] Thus, it is acceptable that SARS-CoV-2 may cause alterations of glucose metabolism that could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of disease. In the present study, 51 subjects had new-onset DM (20.73%) among the 246 patients admitted with COVID-19 infection. This agreed with several studies. Wang et al., reported that 29.1% (176/605) of COVID-19 patients with no previous diagnosis of DM had fasting glucose ≥126 mg/dL.[11] Smith et al., reported that COVID-19 is associated with increased fasting glucose and 15.8% of patients developed new-onset diabetes.[12]

In another study, COVID-19 associated DM and hyperglycemia were found in 19.70% and 25.23% of patients, respectively.[5] In retrospective analysis, 2 (5.7%) of 35 COVID-19 patients had recently been diagnosed diabetes.[13] In a systematic review of 3711 COVID-19 patients from eight studies (492 patients with new-onset diabetes), the pooled prevalence of new-onset diabetes was 14.4% (95% CI 5.9–25.8%) from a random-effect meta-analysis.

A meta-analysis of 13 studies showed, that overall, 32.3% of people developed glucocorticoid-induced hyperglycemia and 18.6% developed diabetes.[14] In our study, almost 92.15% of the patients who developed new-onset diabetes were on steroids during COVID-19 treatment. This indicates that use of steroids, particularly following the publication of the RECOVERY trial with the use of dexamethasone in patients admitted to the hospital with COVID-19, may therefore be associated with an increased

Table 1: Demographic, clinical, and laboratory characteristics of patients by incidence of new-onset diabetes mellitus in post-COVID-19 infections

Variables	New-onset DM				Total	%	Chi-square	P-value
	No	%	Yes	%				
Age groups								
20–39 h years	69	35.38	8	15.69	77	31.30	7.4660	0.0240*
40–59 years	69	35.38	25	49.02	94	38.21		
≥60 years	57	29.23	18	35.29	75	30.49		
Mean age	48.50		53.12		49.46			
SD age	17.81		13.11		17.02			
Gender								
Male	115	58.97	32	62.75	147	59.76	0.2390	0.6250
Female	80	41.03	19	37.25	99	40.24		
BMI								
<18.5	8	4.10	0	0.00	8	3.25	87.515	0.0001*
18.5–24.9	186	95.38	29	56.86	215	87.40		
≥25.0	1	0.51	22	43.14	23	9.35		
Mean	21.23		24.69		21.94			
SD	1.33		2.38		2.13			
Family history								
No	179	91.79	31	60.78	210	85.37	31.120	0.0001*
Yes	16	8.21	20	39.22	36	14.63		
CT severity								
Mild	69	35.38	6	11.76	75	30.49	15.629	0.0010*
Moderate	70	35.90	17	33.33	87	35.37		
Severe	56	28.72	28	54.90	84	34.15		
Duration of stay								
<7	127	65.13	18	35.29	145	58.94	14.869	0.0001*
>7	68	34.87	33	64.71	101	41.06		
HTN								
No	153	78.46	32	62.75	185	75.20	5.3550	0.0210*
Yes	42	21.54	19	37.25	61	24.80		
IHD								
No	183	93.85	46	90.20	229	93.09	0.8370	0.3600
Yes	12	6.15	5	9.80	17	6.91		
Oxygen requirement								
No	105	53.85	8	15.69	113	45.93	23.704	0.0001*
Yes	90	46.15	43	84.31	133	54.07		
Steroids								
No	86	44.10	4	7.84	90	36.59	87.051	0.0001*
40–60	84	43.08	8	15.69	92	37.40		
60–80	23	11.79	38	74.51	61	24.80		
Pulse T	2	1.03	1	1.96	3	1.22		
Complications fungal infection								
No	195	100.00	44	86.27	239	97.15	27.549	0.0001*
Yes	0	0.00	7	13.73	7	2.85		
Fever								
No	67	34.36	16	31.37	83	33.74	0.1610	0.6880
Yes	128	65.64	35	68.63	163	66.26		
Treatment								
A	94	48.21	4	7.84	98	39.84	29.750	0.0001*
B	100	51.28	45	88.24	145	58.94		
C	1	0.51	2	3.92	3	1.22		
ICU requirement								
No	181	92.82	28	54.90	209	84.96	45.488	0.0001*
Yes	14	7.18	23	45.10	37	15.04		
Ventilator								
No	192	98.46	49	96.08	241	97.97	1.1530	0.2830
Yes	3	1.54	2	3.92	5	2.03		
N/L ratio								
<3	124	63.59	8	15.69	132	53.66	37.307	0.0001*
>3	71	36.41	43	84.31	114	46.34		
RFT								
Normal	155	79.49	31	60.78	186	75.61	7.6680	0.0060*
Deranged	40	20.51	20	39.22	60	24.39		

(Contd...)

Table 1: *(Continued)*

Variables	New-onset DM				Total	%	Chi-square	P-value
	No	%	Yes	%				
Ferritin								
<500	148	75.90	14	27.45	162	65.85	49.208	0.0001*
>500	40	20.51	24	47.06	64	26.02		
>1000	7	3.59	13	25.49	20	8.13		
LDH								
Normal	100	51.28	8	15.69	108	43.90	20.799	0.0001*
Increased	95	48.72	43	84.31	138	56.10		
D-dimers								
0–500	134	68.72	11	21.57	145	58.94	49.332	0.0001*
500–1000	57	29.23	29	56.86	86	34.96		
>1000	4	2.05	11	21.57	15	6.10		
CRP								
<6	57	29.23	1	1.96	58	23.58	70.154	0.0001*
7–26	127	65.13	24	47.06	151	61.38		
>26	11	5.64	26	50.98	37	15.04		
HBA1c								
<5.7	195	100.00	0	0.00	195	79.27	246.00	0.0001*
5.7–6.5	0	0.00	3	5.88	3	1.22		
6.5–8.5	0	0.00	46	90.20	46	18.70		
>8.5	0	0.00	2	3.92	2	0.81		
Total	195	100.00	51	100.00	246	100.00		

*P<0.05. RFT: Renal function tests, CRP: C-reactive protein, N/L ratio: Neutrophil-leukocyte ratio, LDH: Lactate dehydrogenase, ICU: Intensive care unit

Table 2: Distribution of patient's status of new-onset diabetes after 3 months of COVID-19 infection

At 3 month	Number of patients	% of patients
Non-DM	195	79.27
DM	51	20.73
Total	246	100.00

DM: Diabetes mellitus

risk of developing diabetes, which could be attributed to delayed recovery of β-cell function.[15]

In the present study, as compared to non-diabetic patients, the newly diagnosed diabetic patients had significantly older age (53.12±13.11 vs. 48.50±17.81, P<0.0240*), over weight and obese (24.69±2.38 vs. 21.23±1.33, P<0.0001), and positive family history of diabetes (39.22% vs. 8.21%, P<0.0001). This was in comparison with Li et al., who reported that COVID-19 patients with newly diagnosed DM and hyperglycemia were slightly older and obese.[16]

Our study also revealed that patients with new-onset diabetes had more severe infection, required oxygen supplementation and ICU admission, as well as elevated levels of inflammatory markers such as CRP, LDH, D-dimer, and ferritin level than non-diabetic patients. Our results were in concordance with Li et al., who stated that patients with newly diagnosed diabetes and hyperglycemia often had more severe symptoms as well as higher levels of inflammatory markers.[16] Infection with COVID-19 decreases ACE2 expression, resulting in hyper inflammation, cellular damage, and respiratory failure.[17] Furthermore, study conducted by Fadini et al.,[4] after adjusting for age and sex, diabetes (pre-existing and newly diagnosed altogether) and COVID-19 severity remained significant (RR 1.49; 95% C.I. 1.07–2.09; P=0.019).

The results of the present study revealed that severe chest CT findings (54.90% vs. 28.72% P<0.0010) and D-dimer (21.57% vs. 2.05% P<0.001) were higher in diabetic group as compared to non-diabetic group. Anti-diabetic treatment persisted in 30 (61.22%) patients, while 19 (38.77%) patients became euglycemic and did not need anti-diabetic treatment after recovery from the acute illness, indicating that they had stress-induced hyperglycemia, an adaptive immune-neurohormonal response to physiological stress.

Our logistic regression analysis showed that older age, higher BMI, family history, severity of infection, oxygen requirement and need of ICU, elevated CRP, elevated ferritin D dimer, LDH, and N/L ratio were the significant predictors of newly diagnosed DM among COVID-19 patients (P<0.001).

Non-COVID patients were not taken as controls because during the COVID Pandemic period non-COVID admission was very few.

It has been suggested that diagnosis and treatment of post-COVID syndrome require integrated rather than disease-specific approaches.[18] If confirmed, the results of the present study indicate that diabetes screening in

Table 3: Logistic regression analysis of incidence of new-onset diabetes mellitus after 3 months by demographic, clinical, and laboratory characteristics of patients

Variables	OR	95% CI for OR		P-value
		Lower	Upper	
Age groups				
20–39 h years	Ref.			
40–59 years	3.13	1.32	7.41	0.0100*
≥60 years	2.72	1.10	6.72	0.0300*
Gender				
Male	Ref.			
Female	0.85	0.45	1.61	0.6250
Family history				
No	Ref.			
Yes	7.22	3.38	15.43	0.0001*
CT severity				
Mild	Ref.			
Moderate	2.79	1.04	7.50	0.0420*
Severe	5.75	2.23	14.86	0.0001*
Duration of stay				
<7	Ref.			
>7	3.42	1.80	6.53	0.0001*
HTN				
No	Ref.			
Yes	2.16	1.12	4.20	0.0220*
IHD				
No	Ref.			
Yes	1.66	0.56	4.94	0.3640
Oxygen requirement				
No	Ref.			
Yes	6.27	2.80	14.03	0.0001*
Steroids				
No	Ref.			
40–60	2.05	0.59	7.06	0.2560
60–0	35.52	11.49	109.78	0.0001*
Pulse T	10.75	0.80	144.94	0.0740
Fever				
No	Ref.			
Yes	1.15	0.59	2.22	0.6880
Treatment				
A	Ref.			
B	10.58	3.66	30.54	0.0001*
C	47.00	3.49	633.21	0.0040*
ICU requirement				
No	Ref.			
Yes	10.62	4.90	23.04	0.0001*
Ventilator				
No	Ref.			
Yes	2.61	0.43	16.07	0.3000
N/L ratio				
<3	Ref.			
>3	9.39	4.18	21.08	0.0001*
RFT				
Normal	Ref.			
Deranged	2.50	1.29	4.84	0.0070*
Ferritin				
<500	Ref.			
>500	6.34	3.01	13.37	0.0001*
>1000	19.63	6.74	57.23	0.0001*
LDH				
Normal	Ref.			
Increased	5.66	2.53	12.66	0.0001*
D-Dimers				
0–500	Ref.			
500–1000	6.20	2.90	13.25	0.0001*
>1000	33.50	9.14	122.80	0.0001*
CRP				
<6	Ref.			
7–26	10.77	1.42	81.58	0.0210*
>26	134.73	16.52	1099.11	0.0001*

*P<0.05. RFT: Renal function tests, CRP: C-reactive protein, N/L ratio: Neutrophil-leukocyte ratio, LDH: Lactate dehydrogenase, ICU: Intensive care unit

individuals who have recovered from COVID-19 should be recommended.

Limitations of the study

1. Small sample size – This was a single institution study and convenient sampling was done from patients admitted to our hospital which makes generalization difficult
2. Needs long-term follow-up.

CONCLUSION

COVID-19 infection confers an increased risk for type 2 diabetes. Patients of all ages and genders had an elevated incidence and risk for occurrence of new-onset diabetes. Moreover, it was strongly associated with overweight and obesity, steroid dosage, and its duration, disease severity, positive family history of DM, and increased laboratory markers of inflammation. Hence, particular attention should be paid during the first 3 months after COVID-19 infection and patients need to be under follow-up for blood glucose monitoring.

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Authors' Contributions:
SG- Literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, editing, and manuscript revision and submission of article; **AD-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **AN-** Design of study, data collection, statistical Analysis and Interpretation; **YC-** Data collection. Coordination and Manuscript revision.

Work attributed to:
Department of General Medicine, SDM College of Medical Sciences and Hospital, SDM University, Dharwad, Karnataka, India.

Orcid ID:
Dr. Siddaganga - https://orcid.org/0000-0003-1614-6912
Dr. Archana Dambal - https://orcid.org/0000-0002-7447-6795
Dr. Akhila Nekkanti - https://orcid.org/0000-0001-8242-9414
Dr. Yashika C - https://orcid.org/0000-0002-1311-9209

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