

The Effect of Diabetes Mellitus on Outcomes of Patients Admitted with COVID-19: A Single – Center Experience from a Tertiary Hospital in India

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Abstract

Background and Objectives: Diabetes mellitus is associated with poor clinical outcomes in patients with coronavirus disease 2019 (COVID-19). This study aimed to explore the clinical characteristics of patients with type 2 diabetes with COVID-19, and to determine the impact of type 2 diabetes on clinical outcome of patients with COVID-19. **Material and Methods:** This single-center, retrospective, observational study enrolled patients admitted from March 2020 to June 2021 with COVID-19. The clinical and biochemical characteristics of patients with known type 2 diabetes, newly diagnosed diabetes, type 2 diabetes with comorbidities and those who succumbed to illness were analyzed. **Results:** Of 4,559 patients with COVID-19, 2,090 (45.8%) had type 2 diabetes. Patients with COVID-19 with diabetes were older, more likely to receive mechanical ventilation, had higher odds of mortality from COVID-19 as compared with patients without diabetes. In addition, patients with diabetes had significantly higher levels of serum creatinine, C-reactive protein, ferritin, lactate dehydrogenase, and D-dimer. Compared with previously diagnosed patients with diabetes, newly diagnosed patients had higher mortality (33% vs. 27%, $P = 0.049$). Among patients with COVID-19 and diabetes, nonsurvivors had significantly higher levels of inflammatory markers and had severe impairment of cardiac, renal, and coagulation parameters as opposed to survivors. **Conclusion:** Patients with COVID-19 with diabetes were more likely to have severe disease and had higher mortality. Presence of chronic kidney disease and coronary artery disease in patients with diabetes with COVID-19 was associated with adverse outcome. Patients with newly diagnosed diabetes had higher odds of severe disease at presentation and had higher mortality.

Keywords: Chronic kidney disease, coronary artery disease, COVID-19, mechanical ventilation

INTRODUCTION

The COVID-19 pandemic caused by the SARS-CoV2 virus has spread quickly from Wuhan China to the whole world posing unprecedented challenges and threats to patients and healthcare systems.^[1] Elderly individuals along with those with pre-existing comorbidities, such as diabetes mellitus, hypertension, malignancy, cardiovascular diseases have demonstrated increased risk for developing more severe COVID-19 disease as well as higher risk of mortality.^[2-4] Observational studies have revealed that diabetes increases the risk of hospitalization, admission to intensive care unit, and mortality from SARS-CoV2.^[5,6] An analytical cross-sectional study from India demonstrated increased susceptibility to SARS-CoV2 infection in patient with diabetes.^[7] A multicenter

study in Wuhan reported that the risk of fatal outcome was 1.49 times higher in patients with diabetes while a report from the UK suggested that the risk of mortality could be even up to two to three times higher.^[8] Another study from India demonstrated that random plasma glucose value at time of admission in patients hospitalized for COVID-19 is a strong predictor for

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disease severity and mortality. This study reported a three times higher mortality in patients with diabetes as compared with those without diabetes.^[9] A systematic review conducted by Almeida-Pititto *et al.*^[10] demonstrated increased severity and higher mortality in patients with diabetes as compared with patients without diabetes. Multiple pathophysiological mechanisms like compromised innate immune system due to chronic hyperglycemia, proinflammatory state characterized by inappropriate cytokine response, and underlying prothrombotic state have been implicated in the association between diabetes and COVID-19 severity.^[9,11]

Considering this scenario, it is critical to define the precise strength of association between diabetes and the prognosis of COVID-19 which might help to create more effective prevention strategies in the population. The aim of this study is to evaluate the association between type 2 diabetes and clinical outcomes in COVID-19 patients.

MATERIAL AND METHODS

The medical records of 4,559 patients with laboratory investigations of confirmed COVID-19 patients admitted to Dayanand Medical College and Hospital, Ludhiana, Punjab between March 2020 and June 2021, were retrospectively examined. Our center serves as the tertiary care referral hospital providing in-patient care to COVID-19 patients from North India. All the patients included in the study tested positive for SARS-CoV-2 in quantitative reverse transcriptase polymerase chain reaction of samples obtained from the nasopharynx. All the patients were classified into three clinical categories: mild, moderate, and severe depending upon their clinical presentation according to guidelines published by the Ministry of Health and Family Welfare (MoHFW), Government of India.^[12] The study was approved by the Institutional Ethical Committee.

Data regarding demographic profile, symptoms, comorbidities, new onset diabetes, glycosylated hemoglobin, inflammatory markers, treatment received, requirement for ventilatory support, and outcome was extracted from the medical records. The outcomes of patients with and without diabetes were compared for the proportion of severe cases, the proportion of cases requiring oxygen therapy, admission to intensive care units (ICU) and inotropic support. The number of deaths in each group and markers of inflammation (C reactive protein, interleukin -6, D-dimer, ferritin, lactate Dehydrogenase) were also compared. According to American diabetes association, newly diagnosed diabetes was defined as fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) and glycosylated hemoglobin $\geq 6.5\%$ (47.5 mmol/mol) with no past history of diabetes.^[13] Patients with steroid-induced/stress-induced hyperglycemia were not included in the diabetes group for analysis. Prediabetes was defined by any of three measures^[13] — fasting plasma glucose (FPG), 100–125 mg/dL (5.6–6.9 mmol/L), 2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L), or glycosylated hemoglobin 5.7–6.4% (39–46 mmol/mol).

Glycosylated hemoglobin levels were measured by ion exchange high performance liquid chromatography using Bio-Rad D-10 analyzer. Plasma D-dimer levels were detected by immunoturbidimetry using ACL TOP CS 300 system. Serum levels of ferritin and interleukin-6 (IL-6) were measured by electrochemiluminescence immunoassay. Serum levels of C-reactive protein (CRP) were measured by using immunoturbidimetric method. Lactate dehydrogenase (LDH) levels were estimated by enzymatic photometric UV assay. Serum creatinine and glucose levels were measured photometrically by Jaffe's method and hexokinase enzymatic assay, respectively. Ferritin, IL-6, CRP, LDH, creatinine, and glucose were measured on Cobas 8000 autoanalyzer.

Statistical methods

Statistical analysis was done using IBM SPSS statistics software version 22.0 (IBM Corp, Armonk NY). Categorical variables were presented as frequency and percentages, whereas continuous variables were described either as mean and standard deviation (SD) or median and inter quartile range IQR. Chi-square test was used to compare differences between categorical variables and the student's *t* test was used to compare continuous variables. A *P* value of <0.05 was considered statistically significant. Mann–Whitney *U* test was used for the comparison of nonnormally distributed quantitative variables. Multivariate analysis was done using binomial logistic regression using the forward LR method to identify factors independently predicting severe disease and mortality.

RESULTS

The current study included 4,559 hospitalized patients with COVID-19. The mean age was 53.4 ± 16.3 years, and 3,005 (65.9%) were men. Among them, 1,149 (25.2%) had severe disease and 947 (20.8%) patients required admission in intensive care unit. During hospitalization, 621 (13.6%) patients received mechanical ventilation. The baseline characteristics of patients admitted with COVID-19 is shown in Table 1.

Of all patients, 2,090 (45.8%) had type 2 diabetes and 2,469 (54.2%) did not have diabetes [Table 2]. Patients with diabetes were older as compared with patients without diabetes (unadjusted odds ratio = 1.05, 95% CI: 1.04 – 1.05; $P < 0.001$). Compared with patient without diabetes, patients with diabetes were more likely to have hypertension (52% vs. 19%, $P < 0.001$), coronary artery disease (13% vs. 4%, $P < 0.001$) and chronic kidney disease (10% vs. 3%, $P < 0.001$). Patients with diabetes had significantly higher prevalence of fever, cough and shortness of breath than patients without diabetes ($P < 0.01$). During hospitalization, use of inotropes, intravenous steroids and tocilizumab was significantly higher in patients with diabetes ($P < 0.01$). During hospital stay, more number of patients with diabetes needed admission to intensive care unit as opposed to those without diabetes (unadjusted odds

Table 1: Baseline characteristics of 4559 patients with COVID-19

Variable	n (%)
Age (years, means±SD)	53.4±16.3
Male: female	1.93:1
Presenting symptoms	
Fever	2985 (65.5)
Dyspnea	2025 (44.4)
Cough	1626 (35.7)
Severity of disease	
Mild COVID-19	2377 (52.1)
Moderate COVID-19	1033 (22.6)
Severe COVID-19	1149 (25.2)
Diabetes	2090 (45.8)
Hypertension	1542 (33.8)
Coronary artery disease	365 (8.0)
Chronic kidney disease	284 (6.2)
Chronic liver disease	140 (3.1)
Intensive care unit admission	947 (20.8%)
Mechanical ventilation	621 (13.6%)
Hospital stay (days, median, IQR)	7.00 (4.00-11.00)
C- reactive protein (mg/L, median, IQR)	56.60 (14.72-136.69)
Ferritin (ng/mL, median, IQR)	428.00 (176.00-906.00)
Lactate dehydrogenase (U/L, median, IQR)	333.00 (228.50-478.50)
D dimer (ng/mL, median, IQR)	466.00 (250.00-998.50)
Interleukin - 6 (pg/mL, median, IQR)	47.39 (13.50-127.95)
International normalized ratio	1.10 (1.05-1.23)

SD, standard deviation; IQR interquartile range

ratio = 2.06, 95% CI: 1.78–2.38; $P < 0.001$). The requirement for mechanical ventilation was seen in significantly higher number of patients with diabetes as compared with those without diabetes (unadjusted odds ratio = 3.34, 95% CI: 2.48–4.50; $P < 0.001$). Patients with diabetes had longer hospital stay in comparison to patients without diabetes (8.0 vs. 7.0 days, $P < 0.001$). The inflammatory markers including C reactive protein, D-dimer, ferritin, interleukin 6 and lactate dehydrogenase were significantly raised in patients with diabetes as opposed to patients without diabetes ($P < 0.05$). The mortality was significantly higher in patients with diabetes as compared with those without diabetes (unadjusted odds ratio = 1.77, 95% CI: 1.53–2.04; $P < 0.001$). Multivariate logistic regression analysis showed that patients with diabetes were significantly older (adjusted odds ratio = 1.041, 95% CI: 1.036–1.047), had severe disease (adjusted odds ratio = 2.42, 95% CI: 1.71–3.40), higher levels of C reactive protein (adjusted odds ratio = 1.001, 95% CI: 1.001–1.002) and were more likely to die from COVID-19 as opposed to patients without diabetes (adjusted odds ratio = 1.42, 95% CI: 1.25–1.62).

Patients with diabetes were further categorized into two groups: those with previously diagnosed diabetes ($n = 1822$, 40%) and those with newly diagnosed diabetes ($n = 268$, 5.8%). As expected, the presence of other comorbidities like hypertension, coronary artery disease, and chronic kidney disease was more frequently encountered in patients with

known diabetes as compared with patients with newly diagnosed diabetes [Table 3]. It was seen that newly diagnosed patients had severe disease at presentation ($P = 0.016$) and had significantly longer duration of hospital stay (9.0 days vs. 8.0 days, $P = 0.013$). Patients with newly diagnosed diabetes had significantly higher glycosylated hemoglobin as compared with previously diagnosed diabetes patients. The requirement for admission to intensive care unit was significantly higher in patients with newly diagnosed diabetes in comparison to previously diagnosed diabetes (36% vs. 26%, $P < 0.001$), whereas need for mechanical ventilation did not differ significantly between the two groups. The patients with newly diagnosed diabetes were more likely to die from COVID-19 as compared with patients with previously diagnosed diabetes (33% vs. 27%, $P = 0.049$). The level of inflammatory markers did not differ significantly between the two groups.

Out of all patients with diabetes, 268 (12.8%) patients had coronary artery disease. In contrast to patients with diabetes without coronary artery disease, patients with diabetes and coronary artery disease had significantly higher mortality (38% vs. 26%, $P < 0.001$) and need for admission to intensive care unit (34% vs. 26%, $P = 0.005$). The requirement for mechanical ventilation, steroids and tocilizumab was higher in patients with diabetes and coronary artery disease but could not reach statistical significance. The level of inflammatory markers was not significantly different between the two groups but showed a higher trend in patients with diabetes and coronary artery disease. Chronic kidney disease was evident in 10.3% ($n = 215$) of patients with diabetes. Patients with diabetes and chronic kidney disease had significantly higher rate of severe disease, admission to intensive care unit, and need for hospitalization as opposed to patients with diabetes and no chronic kidney disease ($P < 0.05$). The level of inflammatory markers was significantly higher in patients with diabetes and chronic kidney disease ($P < 0.05$) and these patients were more likely to die from COVID-19 as compared with patients with diabetes and no chronic kidney disease (44% vs. 26%, $P < 0.001$).

Of 2,090 patients with COVID-19 with diabetes, 581 (27.8%) patients succumbed to the illness [Table 4]. Compared with survivors, non-survivors with diabetes reported more cough, fever, and shortness of breath. The requirement of inotropes and tocilizumab was higher in nonsurvivor group as opposed to survivor group. More nonsurvivors were admitted to intensive care unit (65% vs. 12%, $P < 0.001$) and required mechanical ventilation (56% vs. 3%, $P < 0.001$). The prevalence of coronary artery disease and chronic kidney disease was significantly higher in nonsurvivor group as compared with survivor group. Age, gender, presence of hypertension, and need for glucocorticoids between survivors and nonsurvivors with diabetes showed no significant differences. Nonsurvivor had significantly higher glycosylated hemoglobin as opposed to survivors (9.7% vs. 8.4%, $P < 0.0001$). Compared with survivors with diabetes, nonsurvivors had higher levels of CRP, D-dimer, ferritin, lactate dehydrogenase and interleukin 6

Table 2: Comparison of patients with COVID-19 with or without diabetes

	Diabetes (n=2090) Number (%)	Non diabetes (n=2469) Number (%)	P
Age (years, mean±SD)	59.26±12.84	48.44±17.37	< 0.001
Male to female ratio	2.08	1.82	0.187
Symptoms			
Fever	1441 (68.9)	1544 (62.5)	< 0.001
Dyspnea	806 (38.6)	820 (33.2)	< 0.001
Cough	1150 (55.0)	875 (35.4)	< 0.001
Severity			
Mild	874 (41.8)	1503 (60.9)	< 0.001
Moderate	505 (24.2)	528 (21.4)	
Severe	711 (34.0)	438 (17.7)	
Hypertension	1079 (51.6)	463 (18.7)	< 0.001
Coronary artery disease	268 (12.8)	97 (3.9)	< 0.001
Chronic kidney disease	215 (10.3)	69 (2.7)	< 0.001
Chronic liver disease	71 (3.4)	69 (2.7)	0.403
Chronic pulmonary disease	29 (1.4)	20 (0.8)	0.803
Intensive care unit admission	568 (27.2)	379 (15.3)	< 0.001
Mechanical ventilation	377 (18.0)	244 (9.9)	< 0.001
Duration of symptoms prior to admission (days, median, IQR)	4.0 (2-7)	4.0 (2-8)	< 0.001
C- reactive protein (mg/l, median, IQR)	81.5 (9.8-159.9)	37.10(7.2-102.2)	< 0.001
Ferritin (ng/mL, median, IQR)	508.0 (227-1023)	362.3 (141-806.2)	< 0.001
Lactate dehydrogenase (U/L, median, IQR)	359.0 (258.2-512.7)	305.0 (209-447.5)	< 0.001
D dimer (ng/mL, median, IQR)	562.0 (308-1,000)	374.0 (211.2-838.5)	< 0.001
Interleukin 6 (pg/mL, median, IQR)	56.0 (16.6-156)	38.9 (10.2-107)	0.001
Creatinine (mg/dL, median, IQR)	0.92 (0.7-1.5)	0.80 (0.62-1.03)	< 0.001
Length of hospital stay (days, median, IQR)	8.00 (5-13)	7.00 (4-11)	< 0.001
Mortality	581 (27.8)	386 (15.6)	< 0.001

SD, standard deviation; IQR, interquartile range

which indicates toward more severe inflammatory response in such patients. Nonsurvivors with diabetes also had significantly higher levels of serum creatinine, international normalized ratio, and troponin T than survivors reflecting severe renal, cardiac, and coagulation impairment.

Out of 2,469 patients without diabetes, 257 (10.4%) patients had prediabetes. Among patients diagnosed with prediabetes, 133 (51.7%) had mild disease, whereas 70 (27.2%) had severe disease at presentation. Compared with patients without diabetes, prediabetic patients had higher odds of developing severe disease ($P = 0.0001$). Mortality was higher in patients with prediabetes as compared with patients with normal glucose level (17.8% vs 15.4%, $P = 0.291$) but it was statistically insignificant.

DISCUSSION

The aim of this current retrospective study was to ascertain the clinical characteristics of patients with COVID-19 and diabetes and assess the impact of diabetes on the outcome. We mainly demonstrated that patients with COVID-19 and diabetes were older, had more severe inflammatory response and higher mortality as compared with patients with COVID-19 without diabetes. Furthermore, our study showed that patients with newly diagnosed diabetes had poor outcome compared with patients with known diabetes.

Our study shows that among hospitalized patients with COVID-19 nearly 45.8% had diabetes. In contrast to our observation, earlier studies and systematic reviews from the initial four months of the pandemic (December 2019 through March 2020) reported a pooled prevalence ranging from 11% to 14.5%.^[14,15] High prevalence in Indian population could be attributed to the delayed peak stage of COVID-19 in India and sensitization by then of the general public and physicians through media, and scientific reports highlighting the possible role of diabetes as a major risk factor for severe COVID-19. However, higher grades of severity at admission also points toward the likelihood of more symptomatic and severe disease in patients with diabetes necessitating hospitalization rather than admission bias. Another study from India conducted by Mithal *et al.*,^[14] reported similar findings with 47.1% prevalence of diabetes among hospitalized patients. Bradley *et al.*^[15] conducted a systematic review and meta-analysis including 10,648 patients and found 31% pooled prevalence of diabetes in hospitalized patients.

According to our study, patients with COVID-19 with diabetes had significantly higher proportion of symptoms of cough, fever, and dyspnea as compared with patients with COVID-19 without diabetes. The laboratory abnormalities observed in our study were high CRP, interleukin 6, ferritin, and lactate dehydrogenase in patients with COVID-19 with diabetes as opposed to COVID-19 patients without diabetes. In addition,

Table 3: Comparison of baseline characteristics of newly diagnosed diabetes patients and previously diagnosed diabetes patients infected with COVID-19

	Newly diagnosed diabetes (n=268) Number (%)	Previously diagnosed diabetes (n=1822) Number (%)	P
Age	55.25±14.56	59.85±12.46	< 0.001
Symptoms			
Fever	183 (68.3)	1258 (69.0)	0.852
Dyspnea	148 (55.2)	1002 (54.9)	0.783
Cough	109 (40.7)	679 (37.3)	0.314
Severity			
Mild	89 (33.2)	785 (43.1)	< 0.001
Moderate	62 (23.1)	443 (24.3)	
Severe	117 (43.6)	594 (32.6)	
Hypertension	67 (25.0)	1012 (55.5)	< 0.001
Coronary artery disease	11 (4.1)	251 (13.7%)	< 0.001
Chronic kidney disease	17 (6.3)	198 (10.9%)	0.023
Chronic liver disease	10 (3.7)	59 (3.2)	0.713
Chronic pulmonary disease	1 (0.3)	18 (0.9)	0.498
Intensive care unit admission	96 (35.8)	472 (25.9)	< 0.001
Mechanical ventilation	58 (21.6)	319 (17.5)	0.100
C- reactive protein (mg/l, median, IQR)	86.445 (25.7-157.7)	81.11 (30.35-160.44)	0.609
Ferritin (ng/ml, median, IQR)	581.5 (312.32-1169)	484.2 (220.7-987.50)	0.375
Lactate dehydrogenase (U/l, median, IQR)	429 (298.5-616.25)	347.5 (253-491.25)	0.041
D dimer (ng/ml, median, IQR)	644.5 (290.75-1,000)	557.5 (310-1,000)	0.220
Interleukin 6 (pg/ml, median, IQR)	58.38 (13.72-168.6)	54.35 (17.73-152.12)	0.380
Glycosylated hemoglobin % (mmol/mol), mean±SD	10.1±3.3 (87±13)	8.3±3.2 (67±11)	< 0.001
Creatinine (mg/dl, median, IQR)	0.88 (0.7-1.20)	0.95 (0.7-1.5)	0.025
INR (mean±SD)	1.19±0.24	1.21±0.56	0.686
Length of hospital stay (days, median, IQR)	9 (5-14.5)	8 (5-12)	0.013
Mortality	88 (32.8)	493 (27.1%)	0.049

SD, standard deviation; IQR, interquartile range; INR, international normalized ratio

Table 4: Comparison of baseline characteristics of survivor and non-survivor in patients with COVID-19 with diabetes

	Non survivors (n=581) Number (%)	Survivors (n=1439) Number (%)	P
Age (years, mean±SD)	61.01±13.05	58.59±12.7	< 0.001
Hypertension	306 (52.7)	773 (51.2)	0.555
Coronary artery disease	102 (17.6)	166 (11.5)	< 0.001
Chronic kidney disease	95 (16.4)	120 (8)	< 0.001
Chronic liver disease	21 (3.6)	48 (3.2)	0.619
Chronic pulmonary disease	8 (1.4)	11 (0.7)	0.162
Intensive care unit admission	380 (65.4)	188 (12.5)	< 0.001
Mechanical ventilation	327 (56.3)	50 (3.3)	< 0.001
Glycosylated hemoglobin mmol/mol, mean±SD	9.7±3.1 (83±10)	8.4±3.0 (68±9.0)	< 0.001
Blood glucose at admission (mmol/L, mean±SD)	14.5±7.1	12.5±5.7	< 0.001
C- reactive protein (mg/L, median, IQR)	120.3 (54.7-216)	69.03(23.9-142)	< 0.001
Ferritin (ng/mL, median, IQR)	745.70(365.6-1330)	427 (196.8-847.2)	< 0.001
Lactate dehydrogenase (U/L, median, IQR)	501.5 (360-719.2)	321 (238-430)	< 0.001
D dimer (ng/mL, median, IQR)	994 (507.7-1000)	453.5 (269.7-894.7)	< 0.001
Interleukin 6 (pg/mL, median, IQR)	92.9 (30.2-288.5)	43.3 (12.6-103.2)	< 0.001
Creatinine (mg/dL, median, IQR)	1.20 (0.8-2.3)	0.90 (0.7-1.2)	< 0.001
INR (mean±SD)	1.29±0.46	1.19±0.41	0.001
Length of hospital stay (days, median, IQR)	7.00 (3-14)	9.00 (6-12)	0.003

SD, standard deviation; IQR, interquartile range; INR, international normalized ratio

patients with COVID-19 and diabetes had significantly higher level of serum creatinine, international normalized ratio and

d-dimer. This observation may suggest that patients with COVID-19 with diabetes had severe inflammatory response

and renal and coagulation impairment at presentation. These findings are similar to data from numerous pathway studies that suggest increased levels of inflammatory cytokines in individuals with diabetes in comparison to those without diabetes.^[16,17] Patients with diabetes were more likely to have severe disease at presentation with odds ratio of 2.42 (95% CI: 1.71 to 3.40, $P=0.001$). Our findings are in line with the results of meta-analysis conducted by Bradley *et al.*^[15] and Barrera *et al.*^[18] that showed increased severity and mortality in patients with diabetes as compared with patients without diabetes. Another meta-analysis reported relative risk of 2.11 (95% CI: 1.40–3.51) for severe COVID-19 and 1.83 (95% CI: 0.89–3.73) for mortality due to COVID-19 in patients with diabetes.^[19] The comparison of our results and findings of various meta-analysis in relation to severity and mortality of COVID-19 is shown in Table 5.

The prevalence of newly diagnosed patients with diabetes was 5.8% in the current study. Another study from India conducted by Mithal *et al.*^[14] reported 5.2% prevalence of newly diagnosed diabetes that is in line with our observation. However, a meta-analysis conducted by Sathish *et al.*^[20] reported 14.4% prevalence of newly diagnosed diabetes in patients with COVID-19. In this meta-analysis, six out of eight studies did not measure glycosylated hemoglobin in all patients, and it is likely that patients with stress-induced or glucocorticoid-induced hyperglycemia were included in the category of newly diagnosed diabetes. Our study did not include patients with stress-induced or glucocorticoid-induced hyperglycemia in category of newly diagnosed diabetes. The comparison of various clinical and laboratory parameters among patients with newly diagnosed diabetes and previously diagnosed diabetes revealed severe disease at presentation and significantly higher blood glucose level at admission in the former group. In addition, more patients with newly diagnosed diabetes required admission to the intensive care unit and higher mortality was observed in them. Increased severity and high mortality in patients with newly diagnosed diabetes could be attributed to the masked presence of end organ dysfunction due to ongoing hyperglycemia, which cannot be accounted for during statistical analysis in comparison to cases of known diabetes in where clinically manifest organ dysfunction can be accounted for statistically.^[21] Likewise, chronic low grade inflammation caused by hyperglycemia affects the body's capability of mounting an adequate immune response and healing process thereby delaying recovery.^[22]

Apart from the presence of occult end organ damage, higher blood glucose level at the time of admission in newly diagnosed diabetes group in our study could have contributed to increased mortality. Our observations were in line with the previous findings that patients with newly diagnosed diabetes with COVID-19 had higher mortality and intensive care unit admission compared with pre-existing diabetes.^[21,22] A direct attack by SARS-CoV-2 virus on pancreatic beta cells causing hyperglycemia is a real possibility, given the presence of ACE 2 receptors on the pancreatic beta cells.^[23] In addition, our study demonstrated increased risk of developing severe disease in patients with prediabetes as compared with patients with normal glycemic status. However, there was no statistically significant difference in terms of mortality between the two groups. A meta-analysis including 3,027 patients reported increased risk of severe disease in prediabetic patients with odds ratio of 2.58.^[24]

The current study also assessed the impact of comorbidities on the presentation and outcome of COVID-19 in patients with diabetes. The breakdown of mortality data suggested significantly higher mortality in patients with coronary artery disease and chronic kidney disease as opposed to diabetes patients without coronary artery disease and chronic kidney disease. A Brazilian study including 1170 patients hospitalized with COVID-19 showed significantly higher mortality in patients with diabetes and associated chronic kidney disease.^[25] Another study conducted by Leon-Abarca *et al.*^[26] reported more severe clinical course of COVID-19 illness in patients with diabetic nephropathy. It is well-known that chronic kidney disease especially diabetic nephropathy is associated with a pro-inflammatory state and functional deficits in both the innate and adaptive immune systems which could account for increased severity of COVID-19 in this subgroup.^[27,28]

Among patients with COVID-19 with diabetes, more nonsurvivors were symptomatic and required mechanical ventilation. Nonsurvivors had poor glycemic control as compared with survivors which is in line with the previous finding that higher glycosylated hemoglobin level is associated with increased mortality.^[29] Uncontrolled glycemic status has been linked to excessive glycosylation leading to augmented production of advanced glycation end products.^[30] Increased level of advanced glycation end products was shown to be associated with dysfunction of immunoglobulins and could impair the clearance of infectious agents including bacteria

Table 5: Comparison of present study findings with results of various meta-analysis

Study	Estimated RR/OR of suffering severe COVID-19 in patients with DM as compared with those without DM	Estimated RR/OR of mortality from COVID-19 in patients with DM as compared with those without DM
Present study	OR 2.42 (1.71-3.40)	OR 1.42 (1.25-1.62)
Almeida-Pititto <i>et al.</i> ^[10]	OR 2.35 (1.80-3.06)	OR 2.50 (1.74-3.59)
Bradley <i>et al.</i> ^[15]	OR 3.39 (2.14-5.37)	OR 2.44 (1.93-3.09)
Barrera <i>et al.</i> ^[18]	RR 1.50 (0.90-2.50)	RR 2.78 (1.54-3.73)
Singh <i>et al.</i> ^[19]	RR 2.11 (1.40-3.51)	RR 1.83 (0.89-3.73)

OR, odds ratio; RR, relative risk; DM, diabetes mellitus

and viruses.^[31,32] In addition, nonsurvivors with diabetes had marked inflammatory response, and hepatic, renal and coagulation dysfunction which is consistent with previously reported data.^[2]

The strengths of the study are discussed as follows. First, the clinical data of patients with COVID-19 was collected from Dayanand Medical College and Hospital, which is a designated hospital responsible for the management of patients with COVID-19 in North India. Second, our study included a large number of patients from a single center, having uniform admission and treatment policy. Some shortcomings of our study must be recognized. First, this was a retrospective observational study and therefore causal relationship could not be established. Second, the possibility of selection bias cannot be ruled in view of the retrospective design of the study. Third, the impact of obesity on COVID-19 outcomes could not be determined as the data regarding body mass index was not available in the records. Fourth, a subgroup analysis to delineate differences in outcome variables between first wave and second wave was not performed.

CONCLUSION

Our study demonstrated that patients with COVID-19 with diabetes were more likely to have severe disease and had higher mortality. Patients with newly diagnosed diabetes had higher odds of severe disease at presentation as compared with previously diagnosed diabetes. Presence of chronic kidney disease and coronary artery disease in patients with diabetes with COVID-19 adversely affects the outcome. Poor glycemic control was also associated with increased mortality. Our findings suggest that the presence of diabetes can be considered as a significant risk factor for mortality in patients with COVID-19. Lastly, to conclude aggressive treatment for diabetes mellitus must be considered in the management of hospitalized COVID-19 patients.

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Conflicts of interest

There are no conflicts of interest.

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