Type 2 DM An Independent Risk Factor For Poor Outcome In Moderate To Severe COVID-19

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Abstract: Background: Diabetes Mellitus has been shown to be a risk factor for severe COVID-19 disease. Few studies assessed effect of diabetes on the outcome exclusively in moderate to severe COVID 19 disease. Objective: To compare the clinical characteristics and outcome of hospitalized moderate and severe COVID-19 disease among patients with and without diabetes. Material And Methods: This retrospective study was conducted at Parul Sevashram Hospital from 1st April 2021- 30th April 2021. Data on demographic profile, clinical symptoms, laboratory findings, complications and clinical outcome was collected and compared between patients with and without diabetes. Result: Total 319 patients were included with mean age 54.81±11.72 years. 28.5% had diabetes. The most common symptoms were fever, cough and shortness of breath. As compared to patients without diabetes, these patients had significantly higher levels of leucocyte count, CRP, Ferritin, LDH and D-Dimer. They also had more complications like ARDS, secondary infection and stroke and higher need of respiratory support (92.3% vs. 69.7%, P < 0.001). We also observed significantly greater mortality in patients with diabetes compared to those without diabetes (29.7% vs. 13.6%; P = 0.0014). These findings held true even on comparing patients with only diabetes as comorbidity to those without any comorbidity. Conclusion: The study confirms that diabetes is an independent risk factor for higher inflammatory markers, risk of complications and in hospital mortality during hospitalization with moderate to severe COVID 19. New strategies are needed for more aggressive management of COVID 19 cases with diabetes to improve prognosis in these cases. [Mitra S Natl J Integr Res Med, 2022; 13(2): 11-19, Published on Dated: 10/02/2022]

Key Words: COVID-19, Diabetes Mellitus, Severity, Mortality

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Introduction: In December 2019, clusters of pneumonia cases of unknown etiology emerged in Wuhan, Hubei Province, China. Deep sequencing analysis from lower respiratory tract samples of these patients indicated a novel coronavirus as the causative agent, which was named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), and the disease it caused was called COVID-19[1-3].

On 30th January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern, and on March 11, the epidemic was upgraded to a pandemic[4]. As of November 25, 2021, a total of 3, 45, 55,431 laboratory confirmed cases and over 467468 deaths have been documented in India[5].

It has been observed that most severe and fatal cases with COVID-19 have occurred in the elderly or in patients with underlying comorbidities, particularly cardiovascular diseases, diabetes mellitus, chronic lung and renal disease, hypertension, and cancer[6-9]. In a meta nalysis conducted by Li et al.[10], patients with diabetes or hypertension had a 2-fold increase in risk of severe disease or requiring intensive care unit (ICU) admission, while those with cardio-cerebro vascular disease had a 3-fold increase in the same. Therefore, careful attention should be paid to the treatment of underlying comorbidities, especially in older patients with COVID-19. It has also been reported that COVID-19 patients with diabetes might be at a higher risk of death[6].

These observations created a need to study demography, clinical characteristics and evolution of disease in COVID 19 patients with diabetes as comorbidity. Hence, in this study we aimed to evaluate and compare demographic and clinical characteristics, laboratory findings and outcomes of COVID-19 in patients with and without diabetes.

Material & Methods: This was a retrospective observational study conducted at a tertiary care hospital in Gujarat from 1st April 2021 to 30th April 2021 on patients with moderate and severe COVID-19 disease.

All laboratory (RTPCR) confirmed cases of COVID-19 with moderate to severe disease were included in the study. It was conducted after getting approval from the Institutional ethics committee. Patients with age ≥ 18 years, with Type 1 or Gestational diabetes or whose clinical or laboratory data was incomplete in records were excluded.

The clinical records were accessed for collecting the demographic and laboratory data. Data abstracted included age, gender, exposure history, history of diabetes, history of other underlying comorbidities (hypertension, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease etc), symptoms and vital signs at admission, as well as the laboratory parameters at admission (CBC, blood glucose level, C- Reactive protein (CRP), D-DIMER, renal function test, serum electrolytes, chest X ray, chest computed tomographic (CT) scans (when indicated) etc.

Duration from the onset of symptoms to admission, total length of stay in hospital, development of any other complications and mortality were also recorded.

Two study investigators independently checked the collected data. The cases were divided into diabetic and non diabetic groups.

The diabetic and non diabetic groups in both moderate and severe classes were compared for demographic and clinical characteristics, laboratory markers, and length of hospital stay, complications and survival.

The diagnosis of COVID-19 was made according to the World Health Organization interim guidance[11].

The method of detection of SARS-CoV-2 using throat swabs and RT-PCR was as reported previously[12].

Diagnostic criteria for moderate disease and severe disease were:

Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have oxygen saturation (SpO2) ≥94% on room air at sea level.

Severe Illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%[13].

The patient was labelled diabetic in presence of self-reported medical history of diabetes with evidence of use of antidiabetic drugs or in presence of ADA criteria for diagnosis of diabetes mellitus II (HbA1C ≥ 6.5% or Fasting Blood Glucose ≥126 mg/Dl or Random Blood Glucose ≥ 200 mg/dL)[14].

The outcome measures were increase in inflammatory markers, ICU admissions, length of hospital stay, development of new complications and in hospital mortality.

Statistical Analysis: All the collected data was entered in Microsoft excel sheet. The data was analyzed using SPSS software (version 22.0).

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are expressed as frequencies and percentages (%).

Chi square test was applied to compare categorical variables and independent t-test was applied to compare continuous variables, as appropriate.

For all the statistical analyses, p-value < 0.05 was considered statistically significant

Results: A total of 319 hospitalized patients with COVID-19 confirmed by RT-PCR were included in this study. Among these, 91(28.5%) were diabetic while 228(71.5%) were non-diabetic.

The mean age of the patients was 54.81±11.72 years (mean age of 56.84±10.27 years in the diabetes group vs. 54.03±12.16 years in the non diabetes group).

185(58%) of the total patients were men and 134(42%) were females.

There was no significant difference between the patients with and without diabetes in terms age

and gender. The most common symptoms at presentation were fever (75.9%), cough (72.4%), and shortness of breath (65.2%), headache (46.4%), fatigue (45.8%) and myalgia (44.2%).

Less common symptoms were sore throat (39.8%), loss of taste (27.9%), loss of smell (26.9%), rhinorrhoea (21%), diarrhoea (13.8%), nausea (9.4%) and abdominal pain (9.4%).

A total of 243 (76.2%) patients had moderate disease and 76 (23.8%) patients had severe disease. 180 (56.4%) patients presented with at least one comorbid condition; the most common of which was hypertension (35.4%), followed by diabetes (28.5%), COPD (23.5%), obesity (16.3%), cardiovascular disease (6.9%), chronic liver disease (5.9%), chronic kidney disease (4.1%), thyroid disease (3.8%) and stroke (3.4%).

Comorbidities like hypertension, cardiovascular disease and cerebrovascular disease were significantly more common in diabetics as compared to non diabetics. ($P < 0.001$, 0.0106 and 0.022 respectively)(Table1).

Table 1: Baseline Demographics And Clinical Characteristics Of Patients With Covid-19 Infection

Characteristics	Total (N=319)	Diabetes (N=91)	No Diabetes (N=228)	P Value[a]
Age	54.81±11.72	56.84±10.27	54.03±12.16	0.0591
Gender				
Male	185 (58%)	50 (54.9%)	135 (59.2%)	0.5678
Female	134 (42%)	41 (45.1%)	93 (40.8%)	
Smoker	28 (8.8%)	9 (9.9%)	19 (8.3%)	0.8223
Symptoms				
Fever	242 (75.9%)	65 (71.4%)	177 (77.6%)	0.3058
Cough	231 (72.4%)	61 (67.03%)	170 (74.6%)	0.2226
Dyspnea	208 (65.2%)	60 (65.9%)	148 (64.9%)	0.9658
Headache	148 (46.4%)	43 (47.3%)	105 (46.1%)	0.9444
Fatigue	146 (45.8%)	51 (56.04%)	95 (41.7)	0.028±
Myalgia	141 (44.2%)	40 (43.9%)	101 (44.3%)	0.9557
Sore Throat	127 (39.8%)	39 (42.9%)	88 (38.6%)	0.5651
Loss Of Taste	89 (27.9%)	28 (30.8%)	61 (26.8%)	0.5594
Loss Of Smell	86 (26.9%)	29 (31.9%)	57 (25%)	0.2676
Rhinorrhoea	67 (21%)	21 (23.1%)	46 (20.2%)	0.6728
Diarrhoea	44 (13.8%)	13 (14.3%)	31 (13.6%)	0.8719
Nausea/Vomiting	30 (9.4%)	11 (12.1%)	19 (8.3%)	0.4094
Abdominal Pain	30 (9.4%)	9(9.9%)	21 (9.2%)	0.8511
Comorbidity				
Hypertension	113 (35.4%)	54 (59.3%)	59 (25.9%)	<0.001±
Cardiovascular Diseases	22 (6.9%)	12 (13.2%)	10 (4.3%)	0.0106±
Cerebrovascular Disease	11 (3.4%)	7 (7.7%)	4 (1.8%)	0.0223±
COPD	75 (23.5%)	23 (25.3%)	52 (22.8%)	0.7466
Chronic Liver Disease	19 (5.9%)	5 (5.5%)	14 (6.1%)	0.8258
Chronic Kidney Disease	13 (4.1%)	5 (5.5%)	8 (3.5%)	0.6196
Thyroid Disease	12 (38%)	4 (4.4%)	8 (3.5%)	0.9601
Obesity	52 (16.3%)	15 (16.5%)	37 (16.2%)	0.9555
Disease Onset To Hospitalization	6.25±1.95	6.18±1.96	6.29±1.95	0.6522
ICU Admission	76 (23.8%)	30 (32.9%)	46 (20.2%)	0.0164±
Duration Of Hospitalisation	14.66±5.71	16.28±5.44	13.16±5.59	0.0011±

COPD- Chronic Obstructive Pulmonary Disease, ICU- Intensive care unit. [a]p value indicates difference between patients with diabetes and without diabetes. $P \leq 0.05$ was considered to be statistically significant. Mean duration from symptom onset to hospitalisation was 6.25±1.95 days and was not significantly different in diabetics as compared to nondiabetics (6.18±1.96

days vs 6.29±1.95 days; p=0.6522). ICU admission was significantly greater in diabetic patients as compared to non diabetic patients; 30(32.9%) vs.

46(20.2%); p=0.0228. Mean duration of hospitalisation was 14.66±5.71 days which was significantly higher in patients with diabetes than with patients without diabetes (16.28±5.44 vs. 13.16±5.59; p=0.0011). (Table1).

In terms of laboratory investigations, diabetic patients showed significantly higher white blood cell count (11.92±4.5 $\times 10^3$ cells/µL vs. 9.94±5.4 $\times 10^3$ cells/µL; p = 0.009), CRP (79.45±42.5 mg/L vs. 66.99±37.96 mg/L; p=0.039), LDH (966.9±463 U/L vs. 812.2±325.9 U/L; p=0.0357), Ferritin (519.6±380.9 U/L vs. 358.3±200.1 U/L; p= 0.0332 and D-Dimer levels (1687.6±797.8 vs. 1395.1±810.8; p-0.0454) as compared to non diabetic patients.

PaO2 level in ABG at admission was also significantly lower in diabetic patients when compared to non diabetic patients (73.28±10.4 vs. 81.23±11.9 mmHg; p-0.002). However, no significant difference was noted in other laboratory parameters like AST, ALT, serum albumin and creatinine levels between the two groups (Table 2).

These laboratory data indicated that the COVID-19 patients with diabetes were more prone to severe inflammatory response and respiratory complications leading to poorer prognosis compared to patients without diabetes.

Table 2: Laboratory Findings Among Hospitalised Covid-19 Patients With And Without Diabetes

Parameter	Normal Range	Diabetes (N=91)	No Diabetes (N=228)	P Value[a]
Hemoglobin (gm/dl)	12-15	12.18±1.93	12.03±2.11	0.6203
Luecocyte count $\times 10^3$ (cells/µL)	4-11	11.92±4.5	9.94±5.4	0.009
Platelet count ($\times 10^5$/cu mm)	1.5-4	2.01±1.13	2.19±1.13	0.2809
HbA1C (%)	<6.4%	8.16±1.44	5.62±0.34	0.0001±
CRP	< 3 mg/L	79.45±42.5	66.99±37.96	0.0396±
LDH	132-248 U/L	966.9±463.4	812.2±325.9	0.0357±
Ferritin	20-250 U/L	519.6±380.9	358.3±200.1	0.0332±
D-Dimer	<500ng/mlç	1687.6±797.8	1395.1±810.8	0.0454±
ALT	7-50 U/L	44.3±51.02	41.9±38.3	0.7542
AST	5-40 U/L	37.9±18.25	39.39±18.67	0.5969
Creatinine	0.5-1.2mg/dL	1.81±1.62	1.07±0.56	0.1427
Albumin	3.4-5.4g/dl	3.03±0.52	2.95±0.47	0.3095
PaO2	80-100mmHg	73.28±10.4	81.23±11.9	0.002

HbA1c- Glycosylated hemoglobin, CRP- C reactive protein, LDH- Lactate dehydrogenase, ALT- Alanine aminotransferase, AST- Aspartate aminotransferase, PaO2- Partial pressure of oxygen.

[a]p value indicates difference between patients with diabetes and without diabetes. P ≤0.05 was considered to be statistically significant.

During hospitalization, a total of 243 patients (76.2%) received oxygen therapy.

Among these oxygen inhalation (O2 mask or nasal prongs), non-invasive ventilation and invasive mechanical ventilation were needed in 59 (18.5%), 147 (46.1%) and 37 (11.6%) patients respectively. Significantly more patients with diabetes as compared to those without diabetes required oxygen (19.9% vs. 17.5%; p< 0.003), noninvasive ventilation (51.6% vs. 43.9%; p=0.014) and invasive mechanical ventilation (21.1% vs. 7.9%; p=0.002).

All patients received treatment based on ICMR guidelines.

Antivirals Remdesivir or Favipiravir were given to 283 (88.7%) and steroids were given to 273 (85.6%) patients.

Most common complications were ARDS (Acute respiratory distress syndrome) and sepsis seen in 85 (26.6%) and 57 (17.8%) patients respectively.

Other complications observed were acute hepatitis seen in 15(4.7%), stroke in 7(2.2%), myocardial infarction in 6(1.8%) and acute

pancreatitis in 5(1.6%) patients. These complications were also significantly more common in diabetics as compared to nondiabetics (ARDS in 35.2% vs. 23.2%, p=0.0419, sepsis in 27.5% vs. 14.04%, p=0.007, pancreatitis in 4.4% vs. 0.4%, p=0.0384 and stroke in 5.5% vs. 0.9%, p=0.0341). 58 patients (18.2%) died while 261 patients (81.8%) were discharged. Mortality was significantly greater in patients with diabetes as compared to that in patients without diabetes. (29.7% vs 13.6%; p = 0.0014)(Table 3).

Table 3: Treatments, Complications And Outcomes Of Hospitalised Covid-19 Patients With And Without Diabetes

Treatment	Total (N=319)	Diabetes (N=91)	No Diabetes (N=228)	P Value[a]
Respiratory Support	243 (76.2%)	84 (92.3%)	159 (69.7%)	<0.001
Oxygen mask	59 (18.5%)	18 (19.9%)	41 (17.5%)	0.003±
Non invasive ventilation (NIV)	147 (46.1%)	47 (51.6%)	100 (43.9%)	0.014±
Invasive ventilation	37 (11.6%)	19 (21.1%)	18 (7.9%)	0.002±
Medication				
Antiviral	283 (88.7%)	85 (93.4%)	198 (86.8%)	0.1396
Antibiotics	319 (100%)	91 (100%)	228 (100%)	NA
Steroid therapy	273 (85.6%)	80 (87.9%)	193 (84.6%)	0.5669
Antifungal	4 (1.3%)	3 (3.3%)	1 (0.4%)	0.130
Complications				
ARDS	85 (26.6%)	32 (35.2%)	53 (23.2%)	0.0419±
MI	6 (1.8%)	4 (4.4%)	2 (0.9%)	0.1026
Stroke	7 (2.2%)	5 (5.5%)	2 (0.9%)	0.0341±
Acute Hepatitis	15 (4.7%)	3 (3.3%)	12 (5.3%)	0.6482
Acute Pancraetitis	5 (1.6%)	4 (4.4%)	1 (0.4%)	0.0384±
Sepsis	57 (17.8%)	25 (27.5%)	32 (14.04%)	0.007±
Outcome				0.0014±
Discharge	261(81.8)	64 (70.3%)	197 (86.4%)	
Death	58 (18.2%)	27 (29.7%)	31 (13.6%)	

ARDS- Acute Respiratory Distress Syndrome, MI- Myocardial Infarction, O2- Oxygen.

[a]p value indicates difference between patients with diabetes and without diabetes. P ≤0.05 was considered to be statistically significant.

A similar analysis was carried out to compare patients with only diabetes as comorbidity and those without any comorbidity to investigate whether diabetes increases the disease severity and death per se.

We found that patients with only diabetes as comorbidity also had significantly higher levels of white blood cell count (12.95±5.74×10^3cells/µL vs. 9.80±5.22×10^3 cells/µL; p-0.0178), HbA1C (8.2±0.932 vs. 5.6±0.37, p=0.0001), CRP (77.4±41.7 vs. 60.7±32 mg/L; p=0.0401), LDH (1072±334U/L vs. 871±372.5U/L; p=0.0425), Ferritin (564.6±466.7U/L vs. 303.6±192.9 U/L; p= 0.0375 and D-Dimer levels (1622.65±737.9 vs. 1228.5±517.9; p=0.0187).

Similarly PaO2 levels were also significantly lower in those with only diabetes as comorbidity as compared to those without any comorbidity (70.9±10.6 vs. 82.5±9.9, p=0.003).

Patients with diabetes were more likely to have suffered ARDS (56.3% vs. 16.5%; P < 0.0001) and sepsis (62.5% vs. 20.14%); p <0.0001) as compared to patients without diabetes.

(Table 4) Comparison of the mortality between COVID-19 patients with diabetes and those without diabetes in absence of other comorbidities also showed statistically significant differences (28.1% vs. 10.8%; p=0.0236).

Table 4: Clinical Characteristics, Laboratory Findings And Outcomes Of Hospitalized COVID-19 Patients With Only Diabetes As Comorbidity And In Absence Of Any Comorbidity

Characteristics		Total (N=171)	Diabetes (N=32)	No Comorbidity (N=139)	P-Value[a]
Age		52.2±12.21	55.38±11.38	51.50±12.37	0.1055
Gender					
Male		108 (63.2%)	17 (53.1%)	91 (65.5%)	0.2706
Female		63 (36.8%)	15(46.9%)	48 (34.5%)	
Symptoms					
Fever		124 (72.5%)	25 (78.1%)	99 (71.2%)	0.5694
Cough		134(78.4%)	22 (68.8%)	112(80.6%)	0.2200
Dyspnea		114 (66.7%)	22 (68.8%)	92 (66.1%)	0.9447
Headache		90 (52.6%)	13 (40.6%)	77 (55.4%)	0.1894
Fatigue		79 (46.2%)	15 (46.9%)	64 (46%)	0.9322
Myalgia		95 (55.6%)	16 (50%)	79 (56.8%)	0.6141
Sore throat		61 (35.7%)	12 (37.5%)	49 (35.3%)	0.9723
Loss of taste		41 (23.97%)	9 (28.1%)	32 (23%)	0.7039
Loss of smell		45 (26.3%)	10 (31.3%)	35 (25.2%)	0.6309
Rhinorrhoea		39 (22.8%)	12 (37.5%)	27(19.4%)	0.0496±
Diarrhoea		28 (16.4%)	3 (9.4%)	25 (17.9%)	0.3566
Nausea/Vomiting		11 (6.4%)	3 (9.4%)	8 (5.8%)	0.7242
Abdominal Pain		14 (8.2%)	3 (9.4%)	11 (7.9%)	0.7857
Lab Parameters	**Normal Range**				
Hemoglobin (gm/dl)			12.23±1.71	12.32±1.88	0.8662
Leucocyte count $\times 10^3$ (cells/µL)	4-11		12.95±5.74	9.80±5.22	0.0178±
Platelet count ($\times 10^5$/cu mm)	1.5-4		2.16±1.20	2.35±1.18	0.553
HbA1C (%)	> 6.4%		8.2±0.932	5.6±0.37	0.0001±
CRP	< 3 mg/L		77.4±41.7	60.7±32	0.0401±
LDH	132-248 U/L		1072±334	871±372.5	0.0425±
Ferritin	20-250 U/L		564.6±466.7	303.6±192.9	0.0375±
D-Dimer	<500ng/mL		1622.65±737.9	1228.5±517.9	0.0187
ALT	7-50 U/L		41.06±15.93	43.29±20.95	0.6785
AST	5-40 U/L		39.7±23.98	39.8±20.04	0.9834
Creatinine	0.5-1.2mg/dL		0.98±0.3	0.92±0.3	0.3721
Albumin	3.4-5.4g/dl		3.07±0.35	2.89±0.45	0.1032
PaO2	80-100mmHg		70.9±10.6	82.5±9.9	0.003±
Complications					
ARDS		41 (23.97%)	18 (56.3%)	23 (16.5%)	<0.0001±
MI		3 (1.8%)	2 (6.3%)	1 (0.7%)	0.1610
Stroke		5(2.9%)	4 (12.5%)	1 (0.7%)	0.0028±
Acute Hepatitis		13(7.6%)	3 (9.4%)	10 (7.2%)	0.9603
Acute Pancreatitis		5(2.9%)	4 (12.5%)	1 (0.7%)	0.0028±
Sepsis		48 (28.1%)	20 (62.5%)	28 (20.14%)	<0.0001±
Mortality		24 (14.04%)	9 (28.1%)	15 (10.8%)	0.0236±

HbA1c- Glycosylated hemoglobin, CRP- C reactive protein, LDH- Lactate dehydrogenase, ALT- Alanine aminotransferase, AST- Aspartate aminotransferase, PaO2- Partial pressure of oxygen. [a]p value indicates difference between patients with diabetes and without diabetes. P ≤0.05 was considered to bestatistically significant.

Discussion: The purpose of this study was to evaluate the clinical characteristics of patients with moderate and severe COVID-19 disease with and without diabetes and to assess the role of diabetes in the final outcome of these patients. It has previously been shown that SARS- CoV-2 has a high transmission rate in humans, especially in those with comorbidities[6-9,15].

In our study, greater number of hospitalized patients was males (58%), in accordance with the previous studies reporting that men have a higher risk of COVID-19 infection. This has been attributed to the fact that men commute more

than females thus increasing chances of exposure to the infected and also because of higher prevalence of smoking in men[16,17]. In our study 28 (8.8%) patients (all males) gave history of smoking. This was similar to observations made by Akbariqomi et al.[15] and Shi et al.[18] who showed prevalence of smoking to be 6.7% and 5.2% respectively. The most common symptom of COVID-19 disease was fever (75.9%), cough (72.4%) and breathlessness (65.2%), which were consistent with recent publications[1,15,18,19]. One of the important factors observed in increasing the transmission of the virus is the time lapse from the disease onset to hospital admission. In present study, the time from symptom onset to hospital admission was 6.25±1.95 days, which indicates need for raising awareness to reduce the spread of this infection.

Connections between diabetes and increased susceptibility to infections, including respiratory tract, urinary tract and soft tissue infections have long been accepted[20].The available evidence demonstrates that diabetes predisposes people to developing infectious diseases and patients with diabetes are at greater risk of infection-related mortality[21,22].Diabetes is now known to be one of the most important underlying comorbidities in patients with COVID-19 infection[6,18] We also found high prevalence of diabetes (28.5%) in patients with Covid-19 disease.

In this study, laboratory findings at admission showed significantly higher increase in leukocyte counts and inflammatory markers like CRP, LDH, Ferritin and D-Dimer in diabetics as compared to patients without diabetes, indicating a more severe inflammatory response and tissue damage in diabetics. Similar observations were made by Akbariqomi et al.[15] and Shi et al.[18] The suggested mechanisms responsible for greater inflammatory response and increased complications in diabetics especially in COVID-19 disease is hyperglycemia induced synthesis of glycosylation end products and cytokines, leading to oxidative stress and tissue inflammation.

It also causes blunting of the immune response as it affects lymphocyte, macrophage, neutrophil, and complement functions adversely[23]. Studies have shown that the SARS-CoV-2 enters endothelial cells through the angiotensin-converting enzyme 2 (ACE2) receptor protein.

ACE2 receptors are expressed abundantly in endothelial tissue. Its expression leads to a local increase of angiotensin-II, causing vasoconstriction and cytokine release through endothelial activation.

Furthermore, endothelial cell dysfunction and microthrombi formation caused by COVID-19 is further worsened from pre-existing microangiopathy associated with poorly controlled diabetes[24].

Lastly, ACE2 pathway imbalances can also lead to β-cell dysfunction in the pancreas, further worsening hyperglycemia, accelerating vasculopathy and coagulopathy[25]. On the other hand, diabetes can cause microvascular injury in the lung, leading to decreased diffusion capacity for carbon monoxide (DLCO).

The injury is directly related to the levels of glycated hemoglobin (HbA1C) and the presence of other microvascular complications such as diabetic neuropathy, retinopathy, and nephropathy.

This entity has been described as a "diabetic lung" and can predispose to increased COVID-19 severity[24].

In our study we found that patients with diabetes had significantly higher mortality and greater number of severe cases as was verified by the need for more ICU admissions, greater need for NIV(Non-invasive ventilation) and invasive mechanical ventilation and higher incidences of complications like ARDS and secondary infections. These findings could also be because of co-existence of other co morbidities like hypertension, obesity, chronic kidney disease,

cardiovascular diseases etc. Many recent studies have shown an association of hypertension and obesity with severe covid 19 disease[6,26,28].

However, on further analysis we also found that COVID-19 patients with only diabetes as comorbidity also had similarly significantly more complications and mortality as compared to those without any comorbidities.

This may suggest that diabetes is an independent comorbidity that can increase complications and mortality in patients with COVID- 19 disease irrespective of presence of other comorbidities.

Thus, COVID-19 patients with diabetes need more aggressive treatment.

Conclusion: The study confirms that diabetes is an independent risk factor for higher inflammatory markers, risk of complications and in hospital mortality during hospitalization with moderate to severe COVID 19. New strategies are needed for more aggressive management of COVID 19 cases with diabetes to improve prognosis in these cases.

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