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Observational Study

A Comparative Study of Clinical Manifestation and Severity of Coronavirus Disease Infection in Patients with and without Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus is one of the well-known chronic illness characterized by inflammatory overdrive and vascular complication. Secondary infection is abundant in diabetes mellitus but the impact of coronavirus disease (COVID-19) on diabetes mellitus not well established. The present study was designed to comparatively assess the clinical presentation, laboratory parameters and radiological findings for COVID-19 manifestation in patients of diabetes mellitus (DM) as compared to that of COVID-19 non-diabetic patients. Beside diabetes mellitus, the influence of other antecedent comorbid conditions on COVID-19 manifestation was also comparatively analysed in both groups.

Aim: To assess whether diabetes mellitus influences the clinical manifestation, progression and severity of COVID-19 disease.

Methods: A total of 1,680 admitted patients were enrolled and categorized into four groups namely, group 1 of all diabetic patients, group 2 of all non-diabetic patients, group 3 had patients with isolated DM after exclusion of other comorbidities and group 4 included non-diabetic patients without other comorbidities. The epidemiological data, medical history, symptoms and signs, laboratory findings, digital radiographic of chest, ultrasonography chest and high-resolution computed tomography scans of chest were extracted for evaluation, interpretation and comparison among groups.

Results: In the present study, COVID-19 patients with isolated diabetes mellitus without other comorbidities exhibited a higher prevalence of symptomatic presentation with an exaggerated inflammatory response and hypercoagulable state. Serum levels of IL-6, C-reactive protein, ferritin, FDP and D-dimer were significantly raised ($p < 0.01$) in DM patients compared to those without DM, suggesting higher susceptibility to an inflammatory storm in COVID-19. Radiological findings available from chest radiograph, USG chest and HRCT chest suggested severe lung involvement in diabetes group as compared to non-diabetics ($p<0.05$).

Conclusion: The severity of COVID-19 in diabetics could be attributable to the dysfunctional immune system which further aggravated by inflammatory factors, hypercoagulability, organ damage and leads to an increased symptomatic presentation, laboratory parameters, and radiological pulmonary involvement which precipitate severe and fatal COVID-19 infection in these patients compared to non-diabetic patients. Hence, diabetic patients with COVID-19 required extra preventive care.

Keywords: Clinical manifestation, COVID-19, diabetes mellitus, severity of disease

Introduction

A novel coronavirus, known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been identified as the COVID-19 pathogen, that triggered clinical manifestation ranging from asymptomatic to severe pneumonia and acute lung failure.[1] Coronavirus belongs to coronaviridae family that possesses an envelope with a positive-sense, extraordinarily large RNA genome and a nucleocapsid of helical symmetry.[2] The average incubation period of SARS-CoV-2 is 5-6 days ranging from 2 to 14 days. The usual clinical presentation of COVID-19 is fever followed by cough, fatigue, shortness of breath, muscle and joint pains. Less common symptoms include headache, haemoptysis, diarrhoea, decreased sense of smell or disturbances in taste.[3,4] Moreover, some COVID-19 positive patients do not exhibit noticeable symptoms along the course of the disease. The associated complications of COVID-19 include pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, disseminated intravascular coagulation and death.[5,6] COVID-19 patients have also been reported to have cardiovascular complications viz. myocardial infarction, heart failure, arrhythmias, myocarditis and neurologic manifestations in some cases that include seizure, stroke, encephalitis and Guillain–Barré syndrome.[5,6]

Angiotensin-converting enzyme 2 (ACE2) is the identified surface receptor utilized by SARS coronavirus (SARS-CoV), with direct interaction with the spike glycoprotein (S protein).[7] A recent study suggested 10-20 folds higher affinity between ACE2 and the receptor-binding domain (RBD) of SARS-CoV-2 as compared to that of SARS-CoV, indicating a plausible role of ACE2 as a receptor facilitating SARS-CoV-2 invasion.[8] Diabetes mellitus (DM) is one of the major causes of morbidity and mortality worldwide that is capable of affecting almost every bodily system. [(9)] Consequently, a deregulated immune system in diabetics may increase the susceptibility to infectious diseases like COVID-19.[10] Moreover, due to glycosylation in DM, ACE2 expression is reduced, with subsequent inhibition of anti-inflammatory action of ACE2. This exaggerated immune response could explain the occurrence of severe lung injury and ARDS in COVID-19 patients. Hence, diabetics either with or without other comorbidities might be at higher risk of COVID-19 infection and a severe outcome. The present study in the above context was designed to find out whether DM was associated with the occurrence, progression and prognosis of COVID-19 patients or not. Clinical presentation and severity of disease in diabetes mellitus and non-diabetic patients were also compared.

Method

The present descriptive, observational study was conducted on 1,680 COVID-19 patients admitted to S.M.S. Medical College and attached hospitals, Jaipur, Rajasthan, India as of 30th June 2020. All the patients with a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 were categorized into four groups. Data for analysis regarding epidemiology, medical history, symptoms and signs, laboratory findings, digital chest radiograph findings, ultrasonography (USG) chest and high-resolution computed tomography (HRCT) scans of the chest was extracted and tabulated accordingly.

Data Collection

The diagnosis of COVID-19 was based on the World Health Organization (WHO) interim guidance of RT-PCR response to nasal and pharyngeal swab specimen for SARS-CoV-2.[1] In the first part, all the RT-PCR COVID-19 positive patients for SARS-CoV-2 were divided into two groups based on whether they had diabetes (I) Group 1 had all patients of DM and (II) Group 2 had all patients without DM. To avoid the influence of other comorbidities, sample population excluded from other comorbidities and divided into two more groups which include (I) Group 3 of diabetic patients after exclusion of other comorbidities and (II) Group 4 of non-diabetic patients after exclusion of other comorbid diseases. Patients included in non-diabetic groups had similar age group as that of diabetic groups to avoid age-related confounding factors. Data concerned with epidemiology, medical history, clinical presentation, laboratory investigation, radiological imaging of every group were collected, evaluated and compared.

The laboratory investigation included data of hemogram, C-reactive protein (CRP), ferritin, erythrocyte sedimentation rate (ESR) at 1st hour, fibrin degradation product (FDP), D-dimer and interleukin-6 (IL-6). Radiological findings were inferred using chest radiograph (CXR), ultrasonography (USG) and high-resolution computed tomography (HRCT) scans of the chest. Digital chest radiographs (CXR) was evaluated using the average visual score (rated 0 to 4 according to visual assessment of involved lung area) and proportional classic for COVID images (basal and peripheral predominant, multiple, bilateral & ground glass haziness).[11] USG chest was evaluated using average severity score (sliding scoring scale of severity

on basis of 14 zone severity scores ranging from 0 to 42).[12] HRCT chest was evaluated for CT severity score (CT Severity Score was assigned out of 25 based on the percentage area involved in each of the 5 lobes) and proportion of patients who had CT severity score >10/25.[13] The aforementioned data was compiled, tabulated, compared and interpreted among groups to establish differences of COVID-19 manifestation in DM.

Statistical Analysis

The descriptive statistics for quantitative data were expressed as mean and standard deviation and qualitative data was expressed as proportions. The parameters were compared among different groups using chi-square test and z-score for significant differences.[14, 15] The level of significance was assigned at a p-value less than 0.05.[16]

Results

In the present study, a total of 1,680 patients of confirmed RT-PCR for COVID-19 were assessed and required data collected, evaluated, interpreted and correlated in all four groups **(Figure 1)**.

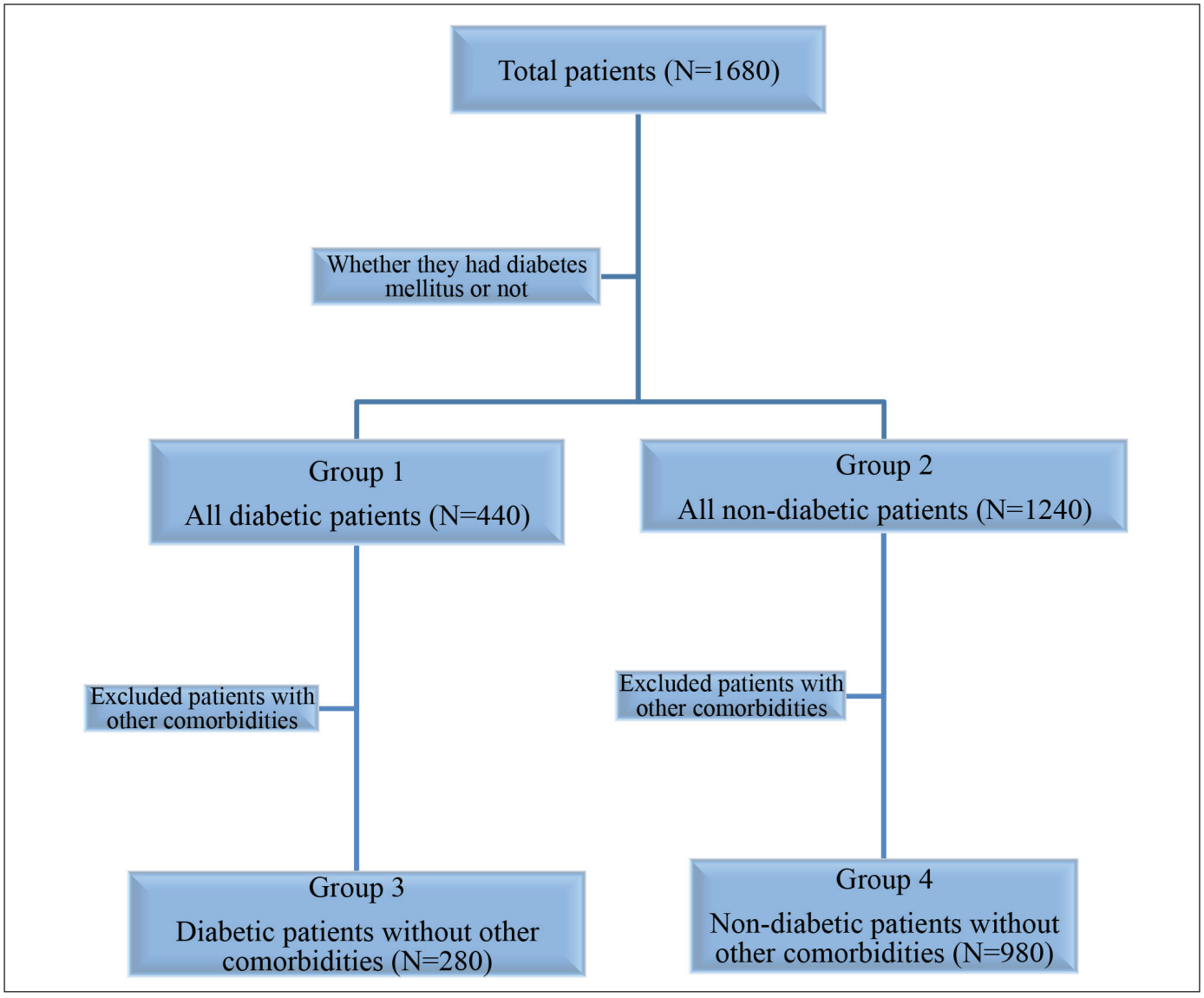

Figure 1. Flow diagram showing categorization of diabetic and non-diabetic COVID-19 patients in four groups

Clinical Presentation, Laboratory Parameters and Radiological Findings Among Group 1 and 2

The overall mean age of SARS-CoV-2 infected patients was 55.98 year (55.98±11.64 year). Mean age in the diabetes group (56.73±9.57 year) was slightly higher (p=0.0512) as compared to that of the non-diabetes group (55.48±12.17 year) **(Table 1)**. The gender distribution in terms of sex ratio (M: F) among both groups did not differ significantly, where sex ratio (F: M) was 0.49 in the diabetes group, 0.47 in the non-diabetes group and 0.48 in the sample population.

Clinical presentation (Table 1):

Overall, 468 patients (27.86%) were symptomatic and percent symptomatic diabetic patients (36.36%) was significantly more than that compared to non-diabetes group (24.84%) with p<0.001. The percent clinical presentation of COVID-19 positive patients was fever (18.10%), cough (16.43%), sore throat (15.48%), shortness of breath (14.76%), headache (8.57%), chest pain (2.14%) and other non-respiratory symptoms like pain abdomen, vomiting, diarrhoea, altered sensorium made up 2.38%. Clinical presentation with fever (21.36% in Group 1 and 16.94% in Group 2), cough (19.77% in Group 1 and 15.24% in Group 2) and shortness of breath (27.27% in Group 1 and 10.32% in Group 2) were significantly high (p<0.05) in diabetes group as compared to that observed in the non-diabetes group.

Table 1. Epidemiological, clinical manifestation, comorbid disease of SARS-CoV-2 infected patients. #The p-values indicate differences between diabetes and non-diabetes patients. A p<0.05 was considered statistically significant; z-value is a standardized score which measures the distance between the mean and an observation; $_{\chi}2$ = chi-square test.

	Patients Infected With SARS-CoV-2			
Characteristics	**Total no./mean value (N=1680)**	**Group 1 (diabetes) (N= 132)**	**Group 2 (non-diabetes) (N=916)**	**p-value#**
Age	55.98 year±11.64	60.24 year (95% CI: 60.24±4.15, SD=12.17)	33.06 year (95% CI: 33.06±2.03, SD=15.71)	<0.00001
Gender				
Male	1135 (67.56%)	84 (63.64%)	624 (68.12%)	$_{\chi}2$ = 0.264, p=0.606
Female	545 (32.44%)	48(36.36%)	292 (31.88%)	
Clinical features				
Symptomatic presentation	468 (27.86%)	42 (31.81%)	184 (20.08%)	z=0.063, p=0.0022
Fever	304 (18.10%)	26 (19.69%)	130 (14.16%)	z=1.661, p=.0969
Cough	276 (16.43%)	30 (22.72%)	136 (14.84%)	z=2.318, p=.0203
Shortness of breath	248 (14.76)	40 (30.30%)	100 (10.91%)	z=6.128, p=<0.001
Sore throat	260 (15.48%)	20 (15.15%)	104 (11.35%)	z=1.263, p=0.207
Headache	144 (8.57%)	13 (9.84%)	60 (6.55%)	z=1.391, p=0.164
Chest pain	36 (2.14%)	4 (3.03%)	20 (2.18%)	z=0.608, p=0.541
Other	40 (2.38%)	4 (3.03%)	16 (1.74%)	z=1.007, p=0.312
Comorbidities				
Hypertension	252 (15.00%)	68 (51.51%)	64 (6.98%)	z=14.41, p<0.001
Cardiovascular disease	136 (8.10%)	24 (18.18%)	36 (3.93%)	z=65.89, p<0.001
Pulmonary disease	212 (12.62%)	18 (13.63%)	90 (9.82%)	z=1.346, p=0.1770
Malignancy	60 (3.57%)	7 (5.30%)	25 (2.72%)	z=1.606, p=0.1074
Cerebrovascular disease	32 (1.90%)	4 (3.03%)	12 (1.31%)	z=1.507, p=0.1307
Chronic kidney disease	76 (4.52%)	18 (13.63%)	22 (2.40%)	z=6.298, p<0.001
Chronic liver disease	24 (1.43%)	3 (2.27%)	9 (0.98%)	z=1.302, p=0.1936
Other	32 (1.90%)	6 (4.54%)	10 (1.09%)	z=2.266, p=0.0232

The observed underlying comorbidities were hypertension (15.00%), pulmonary diseases (12.62%), cardiovascular diseases (8.10%), malignancy (3.57%), chronic kidney disease (4.52%), cerebrovascular disease (1.90%), chronic liver diseases, (1.43%) and other chronic diseases (1.90%) like hypothyroidism, immunodeficiency disease, nutritional deficiency diseases, etc. Hypertension (27.27% in Group 1 and 10.65% in Group 2, p<0.001), cardiovascular diseases (14.55% in Group 1 and 5.81% in Group 2, p<0.001), chronic kidney disease (8.18% in Group 1 and 3.23% in Group 2, p<0.001) and malignancy (5.45% in Group 1 and 2.90% in Group 2, p=0.0131) were found significantly high in diabetes group as compared to that observed in the non-diabetes group.

Laboratory parameters (Table 2):

The following parameters were observed in the present study: mean haemoglobin 12.12 g/dL (95% CI: 12.12±0.30, SD=1.61), total leukocyte count 7.24 x 10^9/L (95% CI: 7.24±1.32, SD=3.62), platelet count 2.20 Lac/µl (95% CI: 2.20±0.20, SD=0.87), neutrophil/lymphocyte (N/L) ratio 2.96 (95% CI: 2.96±0.54, SD=1.24), C-reactive protein 5.59 mg/L (95% CI: 5.59±1.05, SD=3.14), ferritin 275.54 ng/mL (95% CI: 275.54±42.44, SD=317.26), ESR 41.08 mm at 1st hour (95% CI: 41.08±1.82, SD=19.62), fibrin degradation product 20.08 µg/L (95% CI: 20.08±4.09, SD=27.52), D-dimer 3.45 µg/L (95% CI: 3.45±0.74, SD=5.80) and interleukin-6, 52.04 pg/mL (95% CI: 52.04±29.42, SD=98.84).

The mean value of different laboratory parameters in Group 1 and Group 2 were observed as follows: haemoglobin 11.98 vs. 12.18 (p=0.0239), N/L ratio 3.16 vs. 2.84 (p<0.001), ferritin level 318.74 ng/mL vs. 262.60 ng/mL (p=0.0022), D-dimer 4.10 µg/L vs. 3.01 µg/L (p<0.001), IL-6 level 63.90 pm/mL v/s 48.54 pg/mL (p =0.0061). The aforementioned parameters were significantly high in diabetes group as compared to that observed in the non-diabetes group that suggests that COVID-19 patients with diabetes could presumably be prone to develop excessive uncontrolled inflammation responses and hypercoagulable states that in effect could contribute to a guarded prognosis for COVID-19.

Table 2. Comparison of laboratory and radiological parameters between diabetic and non-diabetic COVID-19 patients. Abbreviations: COVID-19- Coronavirus disease 2019; ESR- Erythrocyte sedimentation rate; FDP- Fibrinogen; IL-6- Interleukin-6; CI- Confidence interval; USG- Ultrasonography, HRCT- High-resolution computed tomography. #The p- values indicate differences between diabetes and non-diabetes patients. A p<0.05 was considered statistically significant; z-value is a standardized score which measures the distance between the mean and an observation.

Laboratory investigation	Normal range	Total no./mean value (N=1680)	Group 1 (diabetes) (N=440)	Group 2 (non-diabetes) (N=1240)	p-value#
Haemoglobin (g/dL)	11.5 to15.0 g/dL	12.12 g/dL (95% CI: 12.12±0.30, SD=1.61)	11.98 g/dL (95% CI: 11.98±0.22, SD=1.32)	12.18 g/dL (95% CI: 12.18±0.34, SD=1.68)	p=0.0239
Total leukocyte count (x10^9/L)	4.0 to 10.0x10^9/L	7.24x10^9/L (95% CI: 7.24±1.32, SD=3.62)	7.34x10^9/L (95% CI: 7.34±1.66, SD=4.18)	7.20x10^9/L (95% CI: 7.20±1.24, SD=3.34)	p=0.4809
Platelet (Lac/µL)	1.5 to 4.0 Lac/µl	2.20 Lac/µl (95% CI: 2.20±0.20, SD=0.87)	2.22 Lac/µl (95% CI: 2.22±0.40, SD=1.01)	2.19 Lac/µl (95% CI: 2.19±0.23, SD=0.84)	p=0.5426
Neutrophil/lymphocyte ratio	1.1 to 3.2	2.96 (95% CI: 2.96 ±0.54, SD=1.24)	3.16 (95% CI: 3.16±0.80, SD=1.72)	2.84 (95% CI: 2.84±0.51, SD=1.08)	p<0.001
C-reactive protein (mg/L)	1.0 to 3.0 mg/L	5.59 mg/L (95% CI: 5.59±1.05, SD=3.14)	5.84 mg/L (95% CI: 5.84±0.59, SD=3.24)	5.51 mg/L (95% CI: 5.51±0.50, SD=3.11)	p=0.0588
Ferritin (ng/mL)	21.8 to 275 ng/mL	275.54 ng/mL (95% CI: 275.54±42.44, SD=317.26)	318.74 ng/mL (95% CI: 318.74±78.82, SD=416.44)	262.60 ng/mL (95% CI: 262.60±34.02, SD=292.64)	p=0.0022
ESR (mm/h)	0 to 20 mm/h	41.08 mm/h (95% CI: 41.08±1.82, SD=19.62)	42.27 mm/h (95% CI: 42.27±3.30, SD=21.04)	40.46 mm/h (95% CI: 40.46±1.69, SD=18.52)	p=0.0897
FDP (µg/L)	0 to 5 µg/L	20.08 µg/L (95% CI: 20.08±4.09, SD=27.52)	21.56 µg/L (95% CI: 21.56±5.61, SD=30.16)	19.12 µg/L (95% CI: 19.12±3.24, SD=23.38)	p=0.0828

Laboratory investigation	Normal range	Total no./mean value (N=1680)	Group 1 (diabetes) (N=440)	Group 2 (non-diabetes) (N=1240)	p-value[#]
D-dimer (µg/L)	0 to 0.5 µg/L	3.45 µg/L (95% CI: 3.45±0.74, SD=5.80)	4.10 µg/L (95% CI: 4.10±0.94, SD=5.88)	3.01 µg/L (95% CI: 3.01±0.57, SD=5.75)	p<0.001
IL-6 (pg/mL)	0 to 5.9 pg/mL	52.04 pg/mL (95% CI: 52.04±29.42, SD=98.84)	63.90 pg/mL (95% CI: 63.90±42.80, SD= 120.77)	48.54 pg/mL (95% CI: 48.54±26.51, SD=92.74)	p=0.0061
Chest radiograph					
Average visual score	0 to 4	0.69 (95% CI: 0.69 ±0.45, SD=0.83)	0.88 (95% CI: 0.88±0.63, SD=0.90)	0.61 (95% CI: 0.61±0.39, SD=0.80)	p<0.001
Classic for COVID-19 images		244 (14.52%)	96 (21.82%)	148 (11.94%)	z=5.054, p<0.001
USG chest		248 (14.76%)	72 (16.36%)	176 (14.19%)	z=1.102, p=0.2713
Average severity score	0 to 42	14.96 (95% CI: 14.96±4.62, SD=8.98)	16.04 (95% CI: 16.04±5.18, SD=10.7)	14.17 (95% CI: 14.17±4.04, SD=8.4)	p=0.1442
HRCT chest		512 (30.48%)	144 (32.73%)	368 (29.68%)	z=1.194 p=0.2340
CT severity score	0 to 25	6.04 (95% CI: 6.04±1.33, SD=5.75)	7.24 (95% CI: 7.24±2.51, SD=6.68)	5.67 (95% CI: 5.67±1.44, SD=5.30)	p=0.0054
CT severity score >10/25		100 (19.53%)	44 (30.56%)	56 (15.22%)	z=3.936, p<0.001

Radiological findings (Table 2):

Digital chest radiograph (CXR) of all patients, USG chest of 248 patients (14.76%) and HRCT chest of 512 patients (30.48%) were available for analysis. In the study population, CXR represented a classic picture for COVID images in 244 patients (14.52%) with an average visual score of 0.69 (95% CI: 0.69±0.45, SD=0.83) out of 4. USG severity score was 14.96 (95% CI: 14.96±4.62, SD=8.92) out of 14 and an average CT severity score of 6.04 (95% CI: 6.04±1.33, SD=5.75) out of 25. The CT severity scores were >10/25 in 100 patients (19.53%). Results of radiological findings in diabetes and non-diabetes group were as follows: CXR average visual score was 0.88 and 0.61 (p<0.001) while classic for COVID images in 21.82% and 11.94% patients (p<0.001) among Group 1 and 2 respectively. The CT severity score was significantly high in the diabetes group (7.25) as compared to the non-diabetes group (5.67) (p=0.0054) **(Figure 2 and 3).** The CT severity score was >10/25 in 30.56% and 15.22% patients in respective groups (p<0.001)

Clinical Presentation, Laboratory Parameters and Radiological Findings Among Group 3 and 4

To avoid the influence of comorbidities, other than diabetes mellitus on COVID-19 manifestations, in this part we excluded patients with other comorbidities. In this part study population (1260 patients) were classified into two groups: patients with isolated diabetes without other comorbidities belongs to Group 3 while patients without diabetes and other comorbidities belong to Group 4.

The mean age of SARS-CoV-2 infected patients without other comorbidities was 53.19±9.1 year. The mean age of the diabetes group (54.08 years) was not significantly higher as compared to that observed in the non-diabetes group (52.95 years) **(Table 3)**. The gender distribution did not differ significantly among the groups, where the sex ratio (F: M) was 0.68 in the diabetes group and 0.49 in the non-diabetes group without co-morbidities.

Clinical presentation (Table 3):

Among patients devoid of pre-existing comorbidities, 352 patients (27.94%) were symptomatic for COVID-19, though only 22.86% non-diabetic patient were symptomatic as compared to 45.71% symptomatic diabetic patients, a statistically

significant difference (p<0.001). COVID-19 infected patients without other comorbidities predominantly presented with fever (21.90%), cough (24.13%), sore throat (18.10%), shortness of breath (14.60%), headache (10.16%), chest pain (4.13%) and other symptoms (3.81%) like pain abdomen, vomiting, diarrhoea, altered sensorium. Clinical presentation with fever (28.57% in Group 3 vs. 20.00% in Group 4), cough (30.36% in Group 3 vs. 22.35% in Group 4), shortness of breath (27.14% in Group 3 vs. 11.02% in Group 4) and headache (13.57% in Group 3 vs. 9.18% in Group 4) was observed significantly higher in the diabetes group compared to the non-diabetes group.

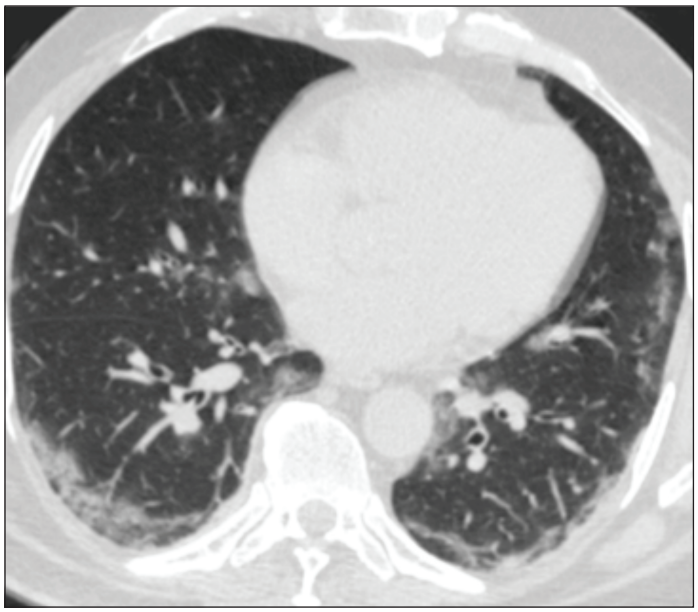

Figure 2. Axial view of HRCT chest of a 62-year-old patient of type 2 diabetes mellitus presented with COVID-19 infection suggestive CT severity score of 12/25

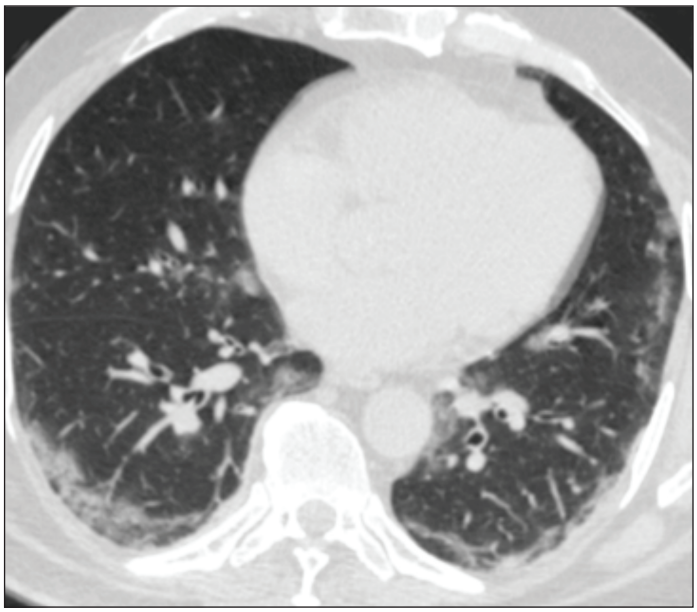

Figure 3. Axial view of HRCT chest of COVID-19 positive patient suggestive of GGOs with CT severity score 4/25 in non-diabetic patients

Table 3. Correlation of demographic and clinical manifestation of COVID-19 disease in patients with isolated diabetes and non-diabetes group after exclusion of other comorbidities. #The p-values indicate differences between diabetes and non-diabetes patients. A p<0.05 was considered statistically significant; z-value is a standardized score which measures the distance between the mean and an observation; $_{\chi}2$ = chi-square test.

	Patients Without Other Comorbidities			
Characteristics	**Total no./mean value (N=1260)**	**Group 3 (diabetes) (N=73)**	**Group 4 (non-diabetes) (N=711)**	**p-value#**
Age	53.19 year±9.1	61.00 year (95% CI: 61 ±4.912, SD=11.48)	31.43 year (95% CI: 31.43 ±2.03, SD=14.89)	<0.00001
Gender				
Male	830 (65.87%)	45 (61.90%)	480 (67.51%)	$_{\chi}2$ = 1.069, p=0.301.
Female	430 (34.13%)	28 (38.10%)	231 (32.49%)	
Clinical features				
Symptomatic presentation	352 (27.94%)	25 (34.24%)	130 (18.28%)	z=3.2611, p=0.0011
Fever	276 (21.90%)	18 (24.66%)	103 (14.49%)	z=2.290, p=.0220
Cough	304 (24.13%)	21 (28.77%)	112 (15.75%)	z=2.821, p=.0048
Shortness of breath	184 (14.60%)	24 (32.88%)	66 (9.28%)	z=6.022, p=<0.001

	Patients Without Other Comorbidities			
Characteristics	**Total no./mean value (N=1260)**	**Group 3 (diabetes) (N=73)**	**Group 4 (non-diabetes) (N=711)**	**p-value[#]**
Sore throat	228 (18.10%)	14 (19.18%)	86 (12.10%)	z=1.727, p=.0836
Headache	128 (10.16%)	7 (9.59%)	49 (6.89%)	z=0.852, p=.3953
Chest pain	52 (4.13%)	3 (4.11%)	17 (2.39%)	z=0.886, p=.3734
Other	48 (3.81%)	4 (5.48%)	16 (2.25%)	z=1.666, p=.0949

Laboratory parameters (Table 4):

The mean value of laboratory parameters observed was as follows: haemoglobin 12.80±1.64 g/dL, total leukocyte count (TLC) 6.74x10^9±3.12/L, platelet count 2.28±0.85 Lac/µL, neutrophil/lymphocyte (N/L) ratio 2.85±1.18, C-reactive protein 5.55±4.06 mg/L, ferritin 302.27±294.58 ng/mL, ESR 37.08±19.88 mm/h, fibrin degradation product 17.20±23.19 µg/L, D-dimer 3.14±3.98 µg/L and interleukin-6 (IL-6) 39.45±67.75 pg/mL. The mean value of different laboratory parameters in Group 3 and Group 4 were observed as follows: Haemoglobin 12.56g/dL vs. 12.98 g/dL (p=0.0005), TLC 7.52x10^9/L vs. 6.48x10^9/L (p<0.001), N/L ratio 3.1 vs. 2.78 (p<0.001), CRP 6.24 mg/L vs. 5.26 mg/L with (p=0.0004), ferritin level 364.58 ng/mL vs. 284.46 ng/mL (p<0.001), FDP 20.84 µg/L vs. 16.18 µg/L (p=0.0026), D-dimer 3.98 µg/L vs. 2.76 µg/L (p<0.001), IL-6 level 58.60 pm/mL vs. 34.44 pg/mL (p<0.001). The aforementioned parameters were significantly higher in diabetes group as compared to non-diabetes group without comorbidities.

Table 4. Comparison of laboratory and radiological parameters between diabetic and non-diabetic COVID-19 patients after exclusion of other comorbidities. Abbreviations: COVID-19- Coronavirus disease 2019; ESR- Erythrocyte sedimentation rate; FDP- Fibrinogen; IL-6- Interleukin-6; CI- Confidence interval; USG- Ultrasonography, HRCT- High-resolution computed tomography; [#]The p-values indicate differences between diabetes and non-diabetes patients. A p<0.05 was considered statistically significant; z-value is a standardized score which measures the distance between the mean and an observation.

Laboratory investigation	**Normal range**	**Total no./mean value (N=1260)**	**Group 3 (diabetes) (N=280)**	**Group 4 (non-diabetes) (N=980)**	**p-value[#]**
Haemoglobin (g/dL)	11.5 to 15.0	12.80±1.64	12.56±1.43	12.98±1.85	p=0.0005
Total leukocyte count (x10^9/L)	4.0 to 10.0	6.74±3.12	7.52±4.14	6.48±2.84	p<0.001
Platelet (Lac/µL)	1.5 to 4.0	2.28±0.85	2.20±0.66	2.30±0.92	p=0.0897
Neutrophil/lymphocyte ratio	1.1 to 3.2	2.85±1.18	3.1±1.84	2.78±0.98	p<0.001
C-reactive protein (mg/L)	1.0 to 3.0	5.55±4.06	6.24±3.89	5.26±4.15	p=0.0004
Ferritin (ng/mL)	21.8 to 275	302.27±294.58	364.58±415.9	284.46±245.74	p<0.001
ESR (mm/h)	0 to 20	37.08±19.88	38.76±22.78	36.45±18.33	p=0.0792
FDP (µg/L)	0 to 5	17.20±23.19	20.84±27.92	16.18±21.15	p=0.0026
D-dimer (µg/L)	0 to 0.5	3.14±3.98	3.98±4.24	2.76±3.76	p<0.001
IL-6 (pg/mL)	0 to 5.9	39.45±67.75	58.60±72.45	34.44±64.45	p<0.001

Laboratory investigation	Normal range	Total no./mean value (N=1260)	Group 3 (diabetes) (N=280)	Group 4 (non-diabetes) (N=980)	p-value#
Chest radiograph					
Average visual score	0 to 4	0.63±0.81	0.74±0.9	0.58±0.78	p=0.0035
Classic for COVID-19 images		208 (16.51%)	80 (28.57%)	128 (13.06%)	z=6.165, p<0.001
USG chest		200 (15.87%)	54 (19.29%)	146 (14.90%)	z=1.772, p=0.0767
Average severity score	0 to 42	14.88±9.18	17.86±11.84	13.48±8.45	p=0.0041
HRCT chest		424 (33.65%)	102 (36.43%)	322 (32.86%)	z=1.115, p=0.2627
CT severity score	0 to 25	5.81±5.44	7.24±6.4	5.32±5.08	p=0.0020
CT severity score >10/25		80 (18.87%)	30 (29.41%)	50 (15.53%)	z=3.123, p=0.0018

Radiological findings (Table 4):

Digital chest radiograph (CXR) of all patients, USG chest of 200 patients (15.87%) and HRCT chest of 424 patients (33.65%) was available for analysis. CXR depicted a classic for COVID images in 208 patients (16.51%) with an average visual score of 0.63±0.81 out of 4. USG severity score was 14.88±9.18 out of 14 and average CT severity score was observed to be 5.81±5.44 out of 25 with CT severity score >10/25 in 80 patients (18.87%) **(Figure 4 and 5)**. Radiological findings observed among diabetes group and non-diabetes group without comorbidities were as follow: The CXR average visual score was 0.74 and 0.58 (p=0.0035) while classic for COVID images was observed in 28.57% and 13.06% patients (p<0.001) in Group 3 and Group 4 respectively. USG chest severity score was significantly higher in diabetes group (17.86) as compared to the non-diabetes group (13.48) (p=0.0041) **(Figure 6 and 7)**. CT severity score was 7.24 in the diabetes group and 5.32 in the non-diabetes group (p=0.0020) with a CT severity score >10/25 in 29.41% and 15.53% patients in the respective groups (p=0.0018).

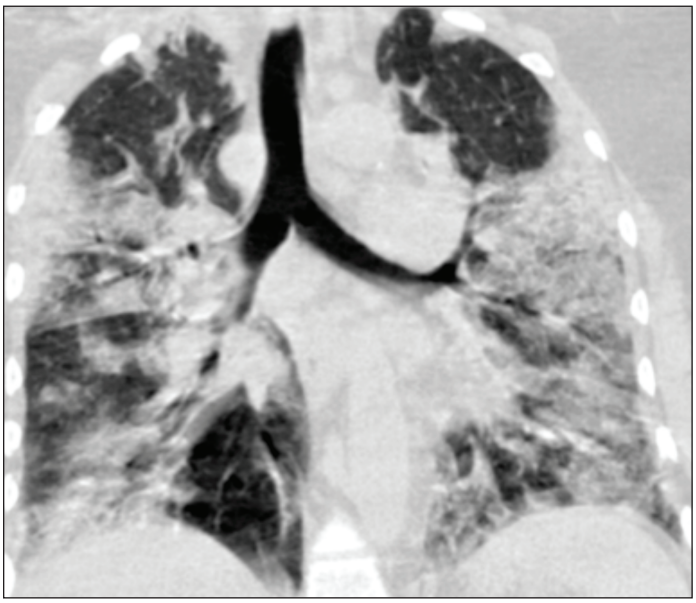

Figure 4. Coronal section of HRCT chest of a 68-year-old male of T2DM presented with chief complain of fever, cough, shortness of breath and diagnosed as COVID-19, CT severity score found to be 20/25

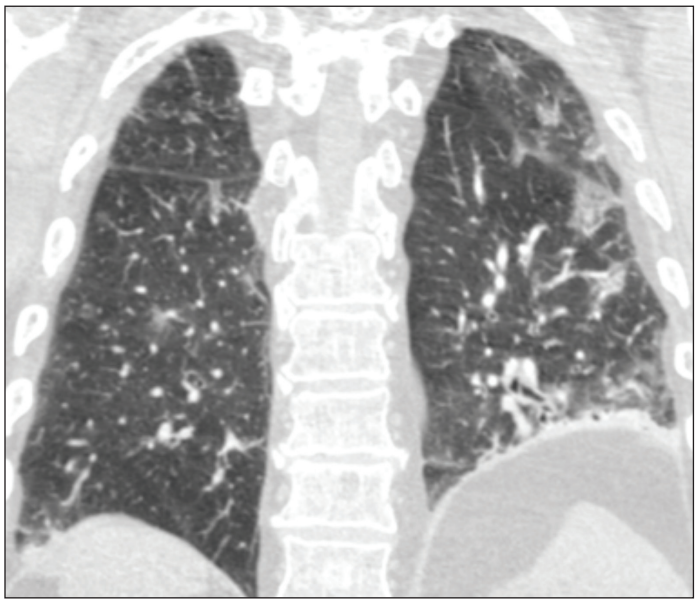

Figure 5. Coronal section of HRCT chest of non-diabetic COVID-19 positive patient presented with cough, fever and shortness of breath had CT severity score 9/25

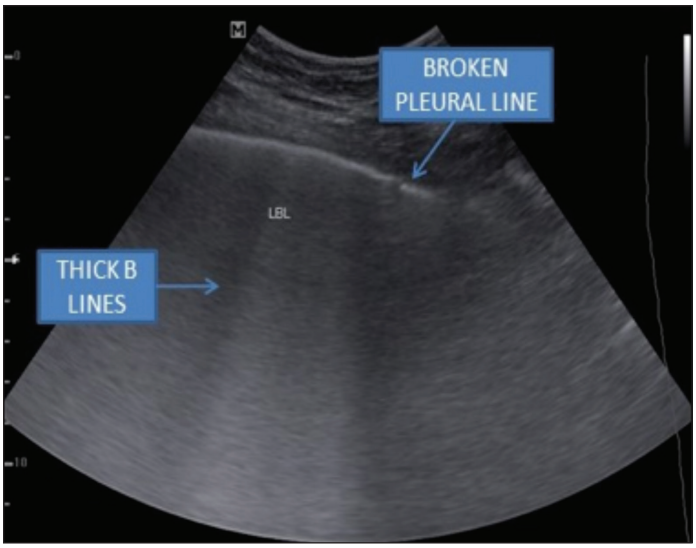

Figure 6. USG chest of a 52year old patient of T2DM with COVID-19 infection show broken pleural line with thick B line with an average severity score of 30/42

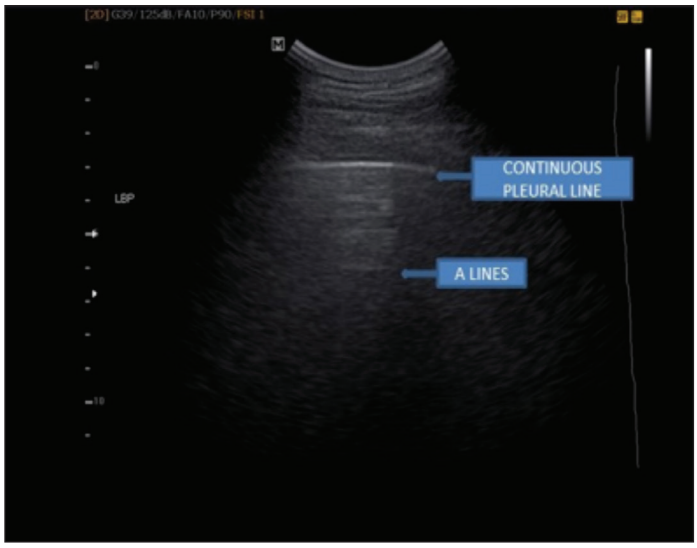

Figure 7. USG chest of a non-diabetic COVID-19 positive patient with continuous pleural line and A-line with an average severity score 4/42

Discussion

Diabetes mellitus predisposes patients for various infectious disease including COVID-19,[17] but how diabetes mellitus influences COVID-19, needs further exploration. A large proportion of the diabetic population can be predisposed for COVID-19 infection as the prevalence of DM in India is 7.3%.[18] Type 2 diabetes mellitus leads to raised inflammatory factors and chemokines as a consequence of the dysfunctional immune system.[19,20] As a consequence of glycosylation, expression of ACE2 receptors reduced in patients of diabetes mellitus which enhances inflammatory storm and invasion of virus leads to severe lung injury and ARDS.[18] In COVID-19 patients, immunostaining of islet tissue for ACE2 has been enhanced, suggesting a plausible role of coronavirus in islet destruction.[21] The present study indicated a more severe clinical picture in the diabetes group as compared to the non-diabetics, especially when other underlying comorbidities were excluded. Clinical presentation among diabetes and non-diabetes group differed significantly in terms of symptoms of fever, cough and shortness of breath. Such a presentation might result due to early and extensive lung involvement of COVID-19 infection in diabetes patients. Neutrophil to lymphocyte ratio in patients of diabetes was also significantly high as compared to that of the non-diabetes group, that could be attributable to neutrophilia or a relative lymphocytopenia as a consequence of SARS-CoV-2 infection. Mean values of total leukocyte count were observed to be significantly high in patients with isolated diabetes as compared to that observed in non-diabetes patients without other comorbidities. Furthermore, higher levels of serum inflammation-related biomarkers such as IL-6, serum ferritin, ESR and CRP were also observed in diabetes group as compared to that observed in patients without diabetes. IL-6 has a prolonged expression time as compared to others cytokines (TNF and IL-1) and can be utilized as a predictor of disease severity and prognosis.[22] Huang *et al*. confirmed the findings of elevated IL-6 levels beside a significantly low lymphocyte count, in patients with SARS-CoV-2 infection, especially those presenting with severe pneumonia.[3] Excessively raised ferritin level is an indicator of activation of the monocyte-macrophage system, that contributes significantly to the inflammatory storm associated with COVID-19.[21] In the present study raised ferritin levels were observed in diabetics, suggesting a higher susceptibility of such patients for an inflammatory storm, responsible for the rapid deterioration of COVID-19. Inflammatory storm in COVID-19 is associated with a significant rise in D-dimer levels. Inflammation associated hypoxia might induce thrombin activation with a consequent unfolding of the exogenous coagulation pathway.[23] In this study, FDP and D-dimer levels were observed to be significantly high in patients with diabetes as compared to that observed in non-diabetes patients that is suggestive of a hypercoagulable state inclusive of disseminated intravascular coagulation in such patients.

Radiological imaging of chest provides an important clue regarding lung involvement in COVID-19 that is a prognostic indicator of disease severity. Digital chest X-ray imaging suggested a higher proportion of sample population exhibiting

lung involvement in diabetics as compared to that observed in non-diabetics. A similar picture was portrayed by CT severity score that was high in diabetic patients as compared to the findings of non-diabetics. However, USG chest severity score was significantly increased in the isolated diabetic group as compared to the non-diabetes group without other comorbidities. The aforementioned findings suggest a severe form of pneumonia in diabetic patients as compared to the non-diabetic patients. Moreover, COVID-19 manifestation and its severity are adversely affected by the associated comorbid disease. In the present study, clinical presentation and laboratory parameters indicated a significant difference among isolated diabetes and the non-diabetes group without comorbidities, compared to groups, with comorbidities.

Limitations of the Study

This study included patients of a single centre, so geographic variation could not be appreciated. This is a retrospective observational study, so definitive postulates could not be formed.

Conclusion

Our study concluded that diabetes mellitus could predispose an individual to a severe clinical and laboratory presentation for COVID-19. The severity of COVID-19 infection in diabetics might be due to exaggerated immune response like cytokine storm which leading to hypercoagulability and organ damage. Diabetic patients more prone to capture the severe form of COVID-19 disease, especially in the form of symptomatic presentation, increased inflammatory markers and radiological pulmonary involvement compared to non-diabetic patients. Diabetes mellitus highly prevalent in India so preventive control measure for COVID-19 in diabetic patients must be initiated.

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Author contributions

Dr. S. Bhandari, Dr. G. Rankawat and Dr. A. Singh formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; Dr. G. Rankawat and Dr. A. Singh collected and analysed data for study. Dr. G. Rankawat wrote the manuscript. Dr. A. Dube and Dr. V. Gupta conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Declaration of Conflicting Interest

All authors report no potential conflicts.

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Ethical approval

This study was approved by the ethical and research committee of S.M.S Medical College and Hospital, Jaipur, India (ethical approval number: MC/EC/2020/417).

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Availability of data and materials

Available from the corresponding author upon reasonable request.

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