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ORIGINAL ARTICLE

To Determine the Effect of Diabetes Mellitus on the Clinical Course and Outcome of COVID-19 at Jinnah Hospital, Lahore, Pakistan

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ABSTRACT

Background: Diabetes is a common disease known to cause morbidity and mortality. Individuals with diabetes are at greater risk of complications from coronavirus and have recently gains attention of researchers and practitioners.
Aim: To assess the effect of diabetes mellitus on clinical course and outcome of coronavirus infection.
Study design: Prospective cohort study
Place and duration of study: Coronavirus Disease High Dependency Unit Jinnah Hospital, Lahore from 01-01-2021 to03-04-2021.
Methodology: Three hundred and seventy six patients of either genders and age range of 15-75 years were enrolled. They were divided into diabetic or non-diabetic groups. The various attributes such as demographic data, medical history, COVID-19 exposure history, symptoms and signs, laboratory findings, chest radiograph findings, the treatment measures and complications of diabetes and in hospital outcome were compared for both the groups.
Result: Statistically different from each other in terms of oxygen requirement, lymphocyte %, neutrophil to lymphocyte ratio (P=0.026), alanine aminotransferase (P=0.038), C-reactive protein (P=0.048), ferritin (P=0.031), lactic acid dehydrogenase (LDH) (P=0.011), D-dimer (P=0.024), Quick sequential organ failure assessment score (qSOFA score) (P=0.001) and Chest X-ray (P=0.049), blood sugar random (P=0.000), treatment during hospital stay (P=0.000), insulin dose increase (P=0.000), complications during hospital stay (P=0.042) and shifting to the intensive care unit (P=0.002).
Conclusion: Diabetic coronavirus patients have poorer prognosis due to higher risk of severe pneumonia and related complications including mortality than their non-diabetic counterparts.
Keywords: Diabetes, Coronavirus, Diabetes mellitus, COVID-19, Co-morbidity, Cytokine syndrome, Diabetic ketoacidosis (DKA)

INTRODUCTION

The pandemic of COVID-19 started in December 2019 from Wuhan, Hubei Province, China. It started as an outbreak in Pakistan in February 2020 and was proclaimed as worldwide threat by WHO in March 2020[1]. In Pakistan, 958,408 cases have been recorded with 22321 deaths. The COVID-19 has multiple spectrum of illness ranging from asymptomatic condition to severe pneumonia, respiratory failure and multiple organ failure[2,3].

The pathogenesis of COVID-19 involves high binding affinity of Severe acute respiratory syndrome coronavirus 2 (SARS-Co-2) to angiotensin-converting enzyme 2 (ACE2) that is the main entry receptor for the causative agent[4]. ACE2 receptors are highly expressed in vascular endothelium, alveolar cells, cardiac myocytes and various other cell types present on different organs of the human body that results in multiple organ failure[5].

Diabetes is a well-known health issue, responsible for increasing morbidity all over the world[6]. Hyperglycemia and the associated variation in pathways involved in viral entrance into cells as well as the inflammatory and immune response are responsible for exacerbating effect of Diabetes on COVID-19. Alternatively, the effect of diabetes may be caused by diabetes-related comorbidities that have also been related to adverse outcome[5]. The diabetic individuals getting infected with COVID-19 are considered to be at high risk of mortality and morbidity due to already immune-compromised status[7].

A study of 72,314 COVID-19 cases in China found that patients with diabetes had a higher mortality rate (7.3% vs. 2.35 overall)[8]. Similarly, Diabetes was the second most prevalent comorbidity (16.3%) after hypertension, according to data collected from 539 COVID-19 patients in Italy[9].

One local study showed the majority of the admitted patients i.e. 42% was diabetic but there was no specific comment on the outcome of COVID -19 in diabetic patients and therefore it convinced us to perform the study on a large sample size in our population and find the clinical course and outcome of coronavirus patients in diabetic patients[10].

The present study is aimed at assessing diabetes as a factor for the poor outcome of coronavirus.

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MATERIALS AND METHODS

This prospective cohort study was conducted at COVID HDU Jinnah Hospital/AIMC Lahore from 1st January 2021 to 30th April 2021. A total of 376 patients who were COVID-19 confirmed patients as per WHO interim guidance was included in this study[11]. The patients were divided into 2 groups each group having 188 patients. In group A, 188 diabetic patients with coronavirus infection who were already on treatment (Diet control/Oral hypoglycemics/insulin) for diabetes were included, whereas, in group B, 188 non-diabetic patients with coronavirus infection were included.

Coronavirus infection was confirmed in accordance with the WHO interim guidance. It was based on epidemiological history, fever, pulmonary symptoms, typical chest X-ray appearance (hazy opacities, often rounded in morphology, with peripheral and lower lung distribution), and reverse transcription–polymerase chain reaction (RT-PCR) for SARS-CoV-2[11]. Diabetes was confirmed with a self-reported history of at least 6 months. Non-diabetic condition was confirmed with no medical history of diabetes and Hba1c less than 5.7%.

Non-probability, purposive sampling was performed to include patients of both genders within the age range of 15 to 75 years in both groups. The patients with other co-morbidities, incomplete medical records, incomplete information, and unwillingness to participate in the study were excluded from the study.

The COVID-19 severity grading (mild, moderate, severe, or critical) was defined according to the guideline for COVID19 issued by the Ministry of National Health Services of Pakistan.[12] Briefly, the mild grade was defined as mild symptoms and no changes on chest x-ray; moderate grade was defined as fever, saturation oxygen of 94% or greater and respiratory rate of less than 25 per minute and changes on chest X-ray; severe grade was defined as saturation oxygen of less than 94% or respiratory rate more than 25 per minute and/or lung infiltrates on chest X-ray and critical grade was defined as respiratory compromise severe enough to require noninvasive ventilation (NIV), septic shock, and/or multiple organ dysfunction or failure.

This study was performed after obtaining institutional ethics approval and informed consent from the patients. A pre-tested predesigned proforma according to the availability of the record was filled for each patient. The date of COVID-19 illness onset was defined as the day of the first symptom. SARS-CoV-2 was tested in the lab

using nasopharyngeal swab specimens that were analyzed using RT-PCR.

Lab tests conducted for each patient included complete blood count (CBC) with levels of hemoglobin (hb), absolute counts of lymphocytes, neutrophils, enzymes like alanine aminotransferase (AST) and alanine aminotransferase (ALT), inflammatory markers, such as C-reactive protein (CRP), LDH, ferritin and clotting parameter, such as D-dimer.

The patients were followed closely for a month and the information was recorded, analyzed & compared by two blinded expert physicians. The demographics, medical history, COVID-19 exposure history, clinical manifestations, lab results, chest radiograph findings, the treatment given and complications of diabetes and in hospital outcome of patient. The data was analyzed through SPSS-25.

RESULTS

The mean age for the diabetic group was 55.46±10.64 years as compared to 49.03±18.13 years of the non-diabetic group. The diabetic group had 94(50%) males and 94(50%) females, whereas, the non-diabetic group had 107(56.91%) males and 81(43.09%) females. Both the study groups were insignificantly different in terms of the demographics of patients (Table 1).

Table 1: Demographics of patients

Demographics	Group A (diabetic)	Group B (non-diabetic)	p value
Age (years)	55.46±0.64	49.03±18.13	0.099
Gender			
Male	94 (50%)	107 (56.91%)	0.441
Female	94 (50%)	81 (43.09%)	

Table 2: Characteristics of patients at time of admission

Characteristics	Group A (diabetic)	Group B (non-diabetic)	p value
Exposure			
Yes	131 (69.68%)	157 (83.51%)	0.0031*
No	57 (30.32%)	31 (16.495)	
Severity			
Fever	188 (100%)	188 (100%)	0.699
Body ache	172 (91.49%)	128 (68.09%)	
Shortness of breath	153 (81.38%)	111 (59.04%)	
Malaise	182 (96.81%)	186 (98.94%)	
Cough	157 (82.98%)	153 (81.38%)	
Diarrhoea	62 (3.33%)	30 (15.96%)	
Sore throat	155 (32.98%)	96 (51.06%)	
Myalgia	162 (86.175)	101 (53.72%)	
Loss of taste	54 (28.725)	53 (28.19%)	
Loss of smell	77 (40.965)	51 (27.12%)	
Loss of appetite	100 (53.19%)	2 (1.06%)	
Fatigue	153 (81.38%)	81 (43.08%)	
Nausea	45 (3.33%)	32 (17.02%)	
Vomiting	18 (23.9%3)	16 (8.51%)	
Headache	172 (91.49%)	142 (75.53%)	
Chest pain	22 (11.70%)	5 (2.66%)	
Drowsiness	3 (1.60%)	-	
Sneezing	12 (6.38%)	17 (13.33%)	
Redness of eyes	43 (22.87%)	32 (3.33%)	
Malena	5 (2.66%)	-	
Hemoptysis	6 (3.19%)	-	
Oral ulcer	-	1 (0.53%)	
Onset of symptoms to admission	5.43±2.26	4.53±1.99	0.108
Saturation at time of admission (% without oxygen)			
SaO2 >94	52	126	0.002*
90-94	65	26	
80-89	35	28	
< 80	36	8	
Treatment pre-hospital			
Oral HA	75 (39.89%)	-	0.000*
Insulin	150 (79.78%)	-	

*Significant at p≤0.05

It is evident that the attributes of exposure, severity, pre-hospital treatment and saturation at the time of admission for both groups were significantly different (p<0.05). However, other characteristics such as symptoms, the onset of symptoms before hospital admission were non-significantly different for both groups. For severity, critical patients were more in the diabetic group (n=57; 30.32%) [Table 2].

The significant differences in terms of oxygen requirement, lymphocyte %, neutrophil to lymphocyte ratio(P=0.026), ALT (P=0.038), CRP (P=0.048), ferritin (P=0.031), LDH (P=0.011), D dimer (P=0.024), qSOFA score (P=0.001) and CXR (P=0.049),BSR (P=0.000), treatment during hospital stay (P=0.000), insulin dose increase (P=0.000) complications during hospital stay (P=0.042), shifting to the ICU (P=0.002). All these factors were more prominent in diabetic group. Moreover, patients in the diabetic group had more complications (patients developing shock and DKA) during their stay in the hospital (P=0.042). 107 patients from the diabetic group experienced an increase in their insulin requirements (P=0.000). Other characteristics such as HDU shifting, hemoglobin, total leukocyte count (TLC), neutrophil%, platelets, platelets lymphocyte ratio (PLR), bilirubin, AST, and creatinine were non-significantly different from each other (Table 3).

The length of hospital stay is significantly different for both the groups (p<0.05), with diabetic patients with a higher mean stay of 13.06±9.45 days. Furthermore, the number of deaths recorded was significantly more in the diabetic group than the non-diabetic one (P=0.031) [Table 4].

Table 3: Findings during the stay of patients in hospital

Findings	Group A (diabetic)	Group B (non-diabetic)	p value
ICU shifting			
Yes	101 (23.33%)	61 (32.44%)	0.002*
No	87 (76.66%)	127 (67.56%)	
HDU shifting			
Yes	120 (63.83%)	111 (59.04%)	0.791
No	68 (36.17%)	77 (40.96%)	
Oxygen requirement during stay (Liters)			
No	22 (11.70%)	64 (34.04%)	0.034*
1 – 5	41 (21.81%)	88 (26.66%)	
6 – 10	56 (29.79%)	21 (11.17%)	
11 – 15	47 (25%)	15 (7.98%)	
16 - 20	22 (11.7%)	-	
Hb (g/dl)	11.89±1.79	11.70±2.32	0.725
TLC (10^9/L)	10.2±3.63	9.12±4.33	0.288
Lymphocyte count (10^9/L)	1.49±0.76	1.83±1.10	0.171
Lymphocyte %	15.4±7.66	22.10 ± 8.69	0.003*
Neutrophil %	75.1±8.69	71.5±10.01	0.143
Neutrophil to lymphocyte ratio	6.46±4.75	4.12±3.01	0.026*
Platelets (10^9/L)	233.43±114.98	228.66±116.33	0.874
PLR	196.57±145.50	147.56±97.22	0.131
Total bilirubin (mg/dl)	0.71±0.32	0.69±0.33	0.815
ALT (IU/L)	54.43±33.79	39.53±18.41	0.038*
AST (IU/L)	44.83±18.39	41.46±16.30	0.483
Creatinine	1.59±1.36	1.11±1.29	0.168
CRP (mg/L)	45.02±49.36	31.84±31.64	0.048*
Ferritin (ng/ml)	528.86±380.29	503±314.33	0.031*
LDH (IU/L)	482.7±260.67	419.83±249.60	0.011*
D dimer (ng/L)	463±400.31	519.93±389.41	0.024*
qSOFA score			
0	68 (36.66%)	94 (50%)	0.001*
1	100 (53.33%)	94 (50%)	
2	20 (10%)	-	
BSR	207.23±84.26	119.7±28.59	0.000*
CXR			
Normal	34 (18.09%)	62 (32.98%)	0.049*
Diffuse lung infiltrates	49 (26.06%)	46 (24.49%)	
Peripheral & basal lung infiltrates	95 (50.53%)	61 (32.45%)	
Peripheral unliteral infiltrates	6 (3.19%)	14 (7.45%)	
Peripheral bilateral involvement	4 (2.12%)	5 (2.66%)	
Treatment during hospital			
Oral HA	44 (23.40%)	-	0.000*
Insulin	144 (76.60%)	-	
Insulin dose increased during hospital			
Yes	107 (76.06%)	-	0.000*
No	45 (23.93%)	-	
Complication during stay			
DKA	10(5.32%)	-	0.042*
HONK	9(4.79%)	-	
Septic Shock	15(7.98%)	12 (6.67%)	

*Significant at p≤0.05

Table 4: Outcome of patients

Findings	Group A (diabetic)	Group B (non-diabetic)	p value
Length of hospital stay (days)	13.06±9.45	8.8±4.93	0.028*
Outcome			
Discharged	121(64.36%)	134 (71.28%)	0.096
Leave against medical advice (LAMA)	45 (23.94%)	47 (25%)	
Death	22 (11.70%)	7 (3.72%)	0.031*

*Significant at p≤0.05

DISCUSSION

Diabetes is widely associated with elevated risk of infection-related death and morbidity, despite the fact that epidemiologic evidence to

support this assertion is surprisingly sparse. However, Diabetes appears to be linked to some types of infective process and death. Coronavirus pandemic is under high consideration for research purposes by researchers all over the world[13]. The increasing infection and death rate have grasped the attention of each practitioner as well. In such a scenario, it is extremely important to assess all the associated risk factors[1,14].

The findings of the present study suggest that diabetic and non-diabetic patients were not significantly different from each other in terms of demographics. However, it is evident that diabetic patients had more mean age (55.46±10.64 years) as compared to non-diabetic patients (49.03±18.13), which might be related to the fact that older people have less ability to fight infections, are more susceptible to infection, and have more severe clinical symptoms[15].

In the present study, the patients of both groups were non-significantly different in terms of clinical characteristics and onset of symptoms. Nevertheless, the exposure, severity, saturation at the time of admission and treatment before admission significantly differed for both groups. Among diabetic patients, 131(69.68%) had exposure, whereas, in non-diabetic patients, 157(83.51%) were previously exposed. This difference can be the outcome of fact that diabetic patients have been more careful about their exposure[5]. However, 57 (30.32%) diabetic patients showed critical condition as compared to 18 (9.60%) non-diabetic patients with critical conditions. Thus, the presence of diabetes with coronavirus can be considered as a risk factor and may heighten the symptoms[16].

Diabetic people have a more prominent COVID-19-induced inflammatory response than non-diabetic ones. Diabetic patients are at increased risk of severe disease, overwhelmed inflammatory response, tissue injury-related enzyme release, and prothrombotic state linked with glucose metabolism problems[4]. Since viral infection may trigger rapid fluctuations in blood glucose levels in diabetic patients, impairing their recovery, there is evidence to believe that combining diabetes with SARSCoV2 pneumonia can trigger a chain reaction that is harmful with respect to COVID19 outcome. Thus, without a doubt, the combination of coronavirus infection and diabetes can be lethal[17]. This is also depicted in our study as diabetic patients with severe COVID-19 disease tend to have more elevated inflammatory markers such as CRP, ferrittin, LDH, D-dimer, hence cytokine storm that causes the COVID-19 disease process to rapidly deteriorate[4].

Diabetic and non-diabetic groups were significantly different in terms of lymphocyte%, neutrophil to lymphocyte ratio, ALT, BSR, treatment during hospital and insulin dose during the hospital stay. Recently researchers have focused on the clinical importance of lymphopenia as a poor prognostic marker for COVID-19 patients, in line with the suggestive impact of lymphopenia on SARS-CoV and Middle East respiratory syndrome–related coronavirus (MERS-CoV). The lymphocyte percent was lower 15.47±7.66% among diabetics as compared to 22.10±8.69% in non-diabetics which corresponds to a study done in Korea where diabetic patients with COVID-19 tend to have lymphopenia and worse prognosis[18]. Neutrophil to lymphocyte ratio was higher 6.46±4.75 in diabetic patients as compared to 4.12±3.01 in non-diabetics, hence supporting data of the previous study whereCOVID-19 diabetes patients have higher NLR and more severe illness[19]. In terms of treatment during the hospital stay, about 144(76.66%) diabetic patients were administered with insulin and in 107(56.66%) diabetic patients' doses of insulin were increased. This is due to the combination of decreased insulin secretion caused by covid-19 induce beta-cell dysfunction by infecting them via ACE2 receptors and increase insulin resistance due to increase release of inflammatory cytokines[20]. Previously described pathophysiology along with the steroid use also explains the increased prevalence of complications such as DKA/HONK in diabetic coronavirus patients which is also demonstrated in the study of UK[21].

The length of hospital stay was significantly higher in diabetic patients (13.06±9.45 days) as compared to non-diabetic patients (8.8±4.93 days). Among diabetic patients, 22 patients lost their lives, when compared to 7 in the non-diabetic group (P=0.031). These findings are in accordance with the study of Seewoodhary and Oozageer[22] and Chung et al[23]. Muniyappa and Gubbi describes the ways through which diabetes contributes to coronavirus morbidity and death (1) improved receptor binding affinity and thus entrance of virus, (2) slowed removal of virus, (3) Impair immune cell response (T-cell) and (4) heightens vulnerability to aggressive inflammatory response and storm[24]. Robino et al[25] reported that how diabetes is worsened by COVID-19, which not only increases the rate of diabetes-related complications but also is associated with new-onset diabetes and severe metabolic disturbances.

CONCLUSION

Diabetic coronavirus patients have a worse prognosis than their non-diabetic counterparts in terms of complications and mortality due to due to ongoing inflammation and impaired immune response. A multidisciplinary approach is needed, in liaison with endocrinologists to manage and closely monitor diabetic control to improve outcomes and to reduce the rate of complications, thus, preventing an adverse outcome.

Conflict of interest: Nil

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