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ORIGINAL ARTICLE

COVID-19 among Hospitalized Patients with Diabetes in Karachi: A Single Centre Study

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ABSTRACT

Aim: To evaluate the clinical characteristics, severity, and outcomes of local COVID-19 patients with diabetes.
Study Design: Case series
Place and duration of study: Orthopedic Medical Institute Hospital, Karachi from 1st September 2020 to 28th February 2021.
Methods: One hundred and forty seven COVID-19 positive patients with diabetes and pre-diabetes were enrolled. The patients' demographic and clinical information specific to COVID-19 and diabetes was collected and analyzed.
Results: The mean age of 64.03±11.56 years. The ischemic heart disease (39.9%) and hypertension (74.3%) were the two most prevalent comorbid conditions. The overall mortality rate of 20.3%. Between patients with diabetes receiving steroids and those receiving no steroids, the mean fasting (FBG) and random blood glucose (RBG) were relatively elevated. Glycemic control had no discernible impact on the severity, results, or length of the COVID-19 hospital stay (p>0.05).
Conclusion: No significant effect of diabetes millitus control on COVID severity and outcomes, but the altered blood glucose levels suggest a need to define specific targeted intervention for COVID-19 patients with comorbidities, specifically diabetes mellitus.
Keywords: COVID-19, Diabetes mellitus, Diabetes control, Outcome

INTRODUCTION

As of December 15th, 2021, the World Health Organization (WHO) has documented that SARS-CoV-2 has infected more than 270 million people worldwide and contributed to over five million deaths.[1] The increased COVID severity and worst outcomes linked to multiple comorbidities. As per data presented in a systematic review and meta-analysis of 46248 confirmed COVID-19 cases, hypertension and diabetes are the most frequently reported comorbid conditions[2]. Additionally, increasing age, obesity, cardiovascular, and chronic obstructive pulmonary disease are the other common observations reported among deceased patients with severe COVID-19[3,4]. Additionally, the complexity of illness is increased in patients with diabetes due to the presence of concomitant cardiovascular disease. Studies from China and United States report one-third of the COVID deaths in relation to DM[5,6] suggesting a two-fold increase in the disease fatality rate among those with DM than those without DM[7].

In addition, patients with DM required ICU care, mechanical ventilation and developed acute kidney injury more frequently than those without DM[6]. This disease progression and high severity is possibly because DM attenuates immunity, increasing infection susceptibility, dysregulation of an innate immune response, and defective cell-mediated immunity among patients with COVID-19[8].

The best treatment strategy for managing DM in the setting of COVID-19 is not entirely clear. In this study we relied mainly on insulin for escalating treatment for blood glucose control, as both hypoglycemia and hyperglycemia lead to adverse outcomes in hospitalized COVID patients. Glycemic control must be optimized to avoid hyperglycemic peaks and hypoglycemic events, leading to mitigation of the inflammatory state and subsequent complications. The preferred therapeutic options for glucose control with low glucose variability among non-critically ill COVID-19 patients include subcutaneous insulin and GLP-1 receptor agonists (GLP-1RAs)[9].

To date, the local literature on the COVID-19 clinical characteristics and outcomes in diabetics is scarce. The current study aimed to document experience in this area and fills some of the gaps in understanding.

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MATERIALS AND METHODS

The clinical records of 147 patients with DM or pre-DM, confirmed COVID-19 cases admitted to OMI hospital in Karachi, Pakistan during 1st September 2020 to 28th February 2021 were included in this case series. Ethical approval was obtained from the Independent Ethical Review Committee of Medicell Institute of Diabetes, Endocrinology & Metabolism (MIDEM) (IRB-007/MHS/20; July 1st, 2020). Those who tested negative for SARS-CoV2 were excluded from the analysis. COVID-19 diagnosis was based on the RT-PCR analysis. The patient's data from the time of admission to death or discharge was studied. Baseline information regarding demographic characteristics, medical history, comorbidities, laboratory findings, COVID-19 symptomatology, and diabetes-related characteristics were recorded. Furthermore, the inpatient treatment against COVID-19, disease progression, duration of hospital stays, complications, and outcomes (death or discharge) were also recorded. COVID-19 severity, i.e., mild, moderate, and severe, was determined on the basis of NIH, Pakistan criteria, which included clinical and biochemical parameters and oxygen requirement at the time of hospital admission. Recently diagnosed diabetes was defined as DM duration of < 6 months, while those with >6 months duration were considered having pre-existing diabetes. The haemoglobin A1c (HbA1c) levels ≤7.0 and >7.0 were considered as controlled and uncontrolled diabetes, respectively. Baseline HbA1c was missing for 16 patients (10.8%) known to have DM.

All patients had the following tests on admission and periodically thereafter; complete blood count, arterial blood gases, urea, creatinine and electrolytes, liver function tests, international normalized ratio (INR), D-dimer, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin and HbA1c. The treatment approach included supportive care with oxygen therapy, and the COVID-specific therapy, while diabetes-specific treatment included Metformin, Empagliflozin, Dapagliflozin, Vildagliptin, Sitagliptin, Glimepiride, Gliclazide, and Insulin. No patient received any GLP-1 agonist or pioglitazone. The management and treatment strategy, other than that specified for diabetes, was based on the same protocol that was used for our previously published study[10].

The statistical analysis was performed on SPSS version 25.0. The Chi-square test and Independent T-test was used for evaluating the differences in the qualitative and quantitative

variables, respectively, considering a p-value less than 0.05 significant. Pearson correlation was also applied to assess the correlation of DM control with COVID severity and outcome.

RESULTS

Two-thirds of the patients also had hypertension [74.3%] (Table 1). Among COVID associated treatment modalities, enoxaparin sodium (61.9%), ivermectin (59.86%) and doxycycline (54.42%) were most commonly administered. While insulin, metformin and sitagliptin were common diabetes specific treatment given to the patients (Table 2).

The clinical profiles, symptomatology, and outcomes among the studied population are elaborated in table 3. Around 83.6% had T2DM, 15.6% had Pre-DM and 0.7% had GDM. There was no case of T1DM in this cohort (Table 3).

Although the mean FBG and RBG levels were relatively low among the patients who did not receive steroid than those receiving it, but the difference was insignificant (Table 4). The mean HbA1c of uncontrolled group was 8.77±2.31 and controlled group was 6.36±0.96 and even then, it did not affect the outcome. There was no significant difference in the baseline demographic and clinical characteristics among the patients with controlled and uncontrolled DM. The majority of patients with uncontrolled DM had moderate COVID 19 severity (38.8%), while the disease was in severe category in 28.6% of them; whereas 39% of those with well controlled DM had severe COVID-19, 36.4% had mild, and 24.7% were moderate in severity. Diabetes mellitus control was not significantly correlated with COVID severity and outcome. However, a significant positive correlation was noted between COVID severity and outcomes (r=0.518; p<0.01).

Table 1: Baseline demographic characteristics of the study population (N=147)

Variable		Mean±SD
Age (years)		64.03±11.56
BMI; kg/m^2 (n=4)		30.63±7.87
Gender	Male	88 (59.5%)
	Female	59 (39.9%)
Comorbidities	Hypertension	110(74.3%)
	Ischemic Heart Disease	59(39.9%)
	Cerebrovascular Disease	9(6.1%)
	Asthma	7(4.7%)
	Other	65(43.9%)
Duration of hospital stay		19.24±55.35

Table 2: Laboratory investigations at admission & discharge

Variable		Mean±SD
GCS; mean±SD		14.47±1.98
Inflammatory/ Biochemical Markers; Median(IQR)	Ferritin	
	Admission (n=129)	509.1(1649.1)
	Discharge (n=3)	758.0(1137.0)
	D-Dimer	
	Admission (n=120)	0.59(1.77)
	Discharge (n=3)	257.50(635.04)
	LDH	
	Admission (n=123)	347.0(272.00)
	Discharge (n=8)	589.0(738.0)
	CRP	
	Admission (n=132)	2.80(3.70)
	Discharge (n=8)	1.90(4.70)
	Procalcitonin	
	Admission (n=117)	0.08(9.94)
	Discharge (n=5)	0.05(0.14)
	CPK	
	Admission (n=17)	465.11±950.99
	Discharge (n=1)	11490.0±0.00
	Il-6 (On admission)	103.00(137.34)
	Pro-BNP (On admission)	633.90(2262.50)
	Troponin-1 (On admission)	0.10(0.11)
Liver Function Tests; Median(IQR)	ALT	35.65±23.38
	AST	38.88±25.59
	T. Bilirubin	0.50(0.40)
Coagulation function; Median(IQR)	PT	11.50(2.00)
	APTT	28.50(6.10)
	INR	1.00(0.20)
HbA1c; mean±SD		7.33±2.01

Table 3: Clinical profiles, symptomatology, and outcomes among the studied population

Variable		N(%)
Duration of diabetes	Recently Diagnosed (<6 Months)	36(24.3)
	Pre-Existing Diabetes (>6 Months)	8(5.4)
	Not reported	103(70.06)
Glycemic control at admission*	Uncontrolled	52(35.3)
	Controlled	79(53.7)
	Not recorded	16(10.8)
Symptomatology	Fever	126(85.1)
	Cough	99(66.9)
	Sputum	2(1.4)
	Runny Nose	2(1.4)
	Breathlessness	
	Grade 1	10(6.8)
	Grade 2	35(23.6)
	Grade 3	20(13.5)
	Grade 4	10(6.8)
	Abdominal Pain	6(4.1)
	Nausea/Vomiting	16(10.8)
	Diarrhea	12(8.1)
	Anosmia/Hyposmia	3(2.0)
	Skin Rash	1(0.7)
	Drowsiness	2(1.4)
COVID Progression/ Complications	ARDS	17(11.5)
	Bronchiectasis	2(1.4)
	Respiratory Failure	30(20.3)
	ILD	3(2.0)
	Sepsis/Septic Shock	19(12.8)
	Coagulopathy	5(3.4)
	Heart Failure/MI	9(6.1)
	Acute Kidney Injury	10(6.8)
Diabetes Complications		15(10.1)
Disease Severity	Mild	54(6.7)
	Moderate	46(31.1)
	Severe	47(31.9)
Average Daily Insulin Dose (U/kg)	Baseline	0.28±0.22
	Midpoint	0.16±0.14
	Final Outcome	0.13±0.06
Outcomes	Discharged	117(79.1)
	Death	30(20.3)

Table 4: Mean Blood glucose levels among patients receiving and not receiving steroids

Variable	Steroid therapy	No steroid therapy	p-value
	Mean±SD		
FBG			
Baseline	197.22±96.39	161.67±68.28	0.106
Midpoint	200.33±61.44	169.19±65.09	0.286
Final outcome	207.50±26.16	136.25±54.61	0.094
RBG			
Baseline	205.25±89.33	187.88±83.64	0.410
Midpoint	260.0±74.39	206.64±66.91	0.085
Final outcome	267.50±61.51	197.29±86.98	0.295

DISCUSSION

There is a scarcity of literature addressing the comorbidities and their impact amongst hospitalized COVID-19 patients, specifically in Pakistan. To the best of our knowledge, this case series is one of the few studies presenting the clinical characteristics, severity, and outcomes of COVID-19 among DM patients who presented at a tertiary care private hospital in Karachi-Pakistan.

Although the precise mechanisms behind new-onset diabetes due to COVID-19 are not completely known, but evidently, several complex interconnected processes are involved. Undiagnosed diabetes, stress, corticosteroid therapy, and direct or indirect effects of SARS-CoV-2 on the β-cell are among the few known contributors of hyperglycemia among COVID-19 patients.[11] Management of COVID 19 with corticosteroids remains controversial, and it should be carefully instituted for patients with diabetes to avoid major fluctuations in the blood glucose levels leading to exacerbation of the disease process. As was to be expected, the mean FBG and RBG were relatively high among the patients' receiving steroids than their counterparts.

Our study showed that the mortality rate among the enrolled COVID-19 DM patients was 20.3% patients[12]. Guo et al[13] reported that 16% of the COVID-19 patients with DM died due to significant disease progression. Similarly, Zhu et al[14] reported a death rate of 7.8% among COVID-19 patients with pre-existing diabetes, while other studies report a mortality rate ranging between 17% to 20%[15-18]. Many published studies report increased severity and

worsening outcomes among COVID patients with diabetes than those without diabetes[19-21]. A Chinese cohort study including 1561 COVID-19 patients reported an increased severity associated with DM and ICU requirement among such patients. Moreover, they also reported a high death rate among the COVID-19 patients with DM than those without DM.[18] Furthermore, data of 10926 dead COVID-19 patients from a British hospital indicated increased mortality risk among patients with uncontrolled diabetes.[19] Another recent study, including COVID-19 patients with diabetes and uncontrolled hyperglycemia, also reported longer hospitalization and higher mortality among these patients[20]. In contrast, there was no significant difference in the disease severity, outcomes, and duration of hospital stay among the enrolled COVID patients with uncontrolled and controlled diabetes. This may be due to the insufficient records of HbA1c; DM control was not determined for a few COVID-19 cases with DM. However, the in-hospital glucose levels in both groups (with and without steroid) were well within acceptable levels of care.

Among the many complications of COVID-19 in DM patients, Diabetic ketoacidosis (DKA) remains the most lethal. As the condition potentiates from insulin deficiency, hence it requires appropriate scheduling of insulin doses to avoid associated complications.[21] Considering the risk and complication rate, the patients were provided with effective COVID and diabetes-associated treatment. None of the patients developed DKA and severe hypoglycemia during the hospital stay. Furthermore, increasing age, comorbid conditions (hypertension and DM), increased levels of NLR, LDH, and CRP are recognized as significant mortality predictors among COVID-19 patients, both locally and globally[10,22]. Although there was no significant difference in the mean NLR, ferritin, D-dimer, and LDH levels among the DM patients with uncontrolled DM as compared to those with controlled DM, but the mean difference is apparent between the two groups in terms of these biochemical markers.

All patients who needed treatment escalation for DM were either started on basal bolus Insulin (0.5 units/kg per day) or if already on insulin, their treatment protocol was intensified in accordance with a protocol for added correctional doses of insulin. Recent studies have reported the benefits of pioglitazone and the rationale of using it to tackle the insulin resistance[23], which appears to be a dominant pathogenic factor. Additionally, it has been discovered to prevent the release of IL-6[24] and other pro-inflammatory cytokines. It is believed that COVID-19 has a worse prognosis in pro-inflammatory states. As a result, this kind of medication is regarded as supportive therapy for COVID-19[25]. However, none of our patients received pioglitazone or GLP-1 agonist.

Despite the present study findings and associated limitations, glucose monitoring and glycemic control must be included in the treatment protocol of all the COVID-19 patients, even without pre-existing diabetes. These patients are prone to dysglycemia and uncontrolled DM has the potential for adverse COVID 19 outcomes. The authors acknowledge the present study's limitations, including selection bias and data accuracy (ascertained by record keeping omissions). The present study adds value to the existing data on COVID-19 within this region, as this study has comprehensively described the clinical profile of COVID diabetic patients.

CONCLUSION

It is concluded from the study results that there is no significant effect of DM control on COVID severity and outcomes, though the altered blood glucose levels suggest a need for appropriate diagnosis and management of hyperglycemia among the COVID-19 patients to optimize the disease severity and outcomes associated with the treatment approach. Further large-scale follow-up studies are required to establish COVID-19 associated new-onset diabetes.

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