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# Prevalence, clinical manifestations, and biochemical data of type 2 diabetes mellitus versus nondiabetic symptomatic patients with COVID-19: A comparative study

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**Summary.** *Background:* There is a scarcity of data regarding the effect of Type 2 diabetes mellitus (T2DM) and associated comorbidities on the clinical presentation and outcome of symptomatic patients with COVID-19 infection in comparison with non-diabetic patients. *Aim of the study:* We described and compared the clinical presentation and radiological and hematological data of a cohort of symptomatic COVID19 positive T2DM diabetic patients (n = 59) versus another cohort of non-diabetic symptomatic COVID19 positive patients (n =244) diagnosed at the same time from January 2020 to May 2020. Associated comorbidities were assessed, and the Charlson Comorbidity Index was calculated. The outcomes including duration of hospitalization, duration of Intensive Care Unit (ICU) stay, duration of mechanical ventilation, and duration of O2 supplementation were assessed. *Results:* Prevalence of T2DM in symptomatic COVID19 positive patients was 59/303 (=19.5%). Diabetic patients had higher prevalence of hypertension, chronic kidney disease (CKD) and cardiac dysfunction [coronary heart disease (CHD)], and congestive heart failure (CHF). Charlson Comorbidity score was significantly higher in the T2DM patients (2.4± 1.6) versus the non-diabetic patients (0.28 ± 0.8; p: < 0.001). Clinically and radiologically, T2DM patients had significantly higher percentage of pneumonia, severe pneumonia and ARDS versus the non-diabetic patients. Hematologically, diabetic patients had significantly higher C-reactive protein (CRP), higher absolute neutrophilic count (ANC) and lower counts of lymphocytes and eosinophils compared to non-diabetic patients. They had significantly higher systolic and diastolic blood pressures, longer duration of hospitalization, ICU stay, mechanical ventilation

and oxygen therapy. CRP was correlated significantly with the duration of stay in the ICU and the duration for oxygen supplementation (r = 0.37 and 0.42 respectively; p: <0.01). *Conclusions:* T2DM patients showed higher inflammatory response to COVID 19 with higher absolute neutrophilic count (ANC) and CRP with lower lymphocytic and eosinophilic counts. Diabetic patients had more comorbidities and more aggressive course of the disease with higher rate of ICU admission and longer need for hospitalization and oxygen use.

**Key words:** COVID 19, diabetes mellitus, clinical manifestations, radiological findings, comorbidities, severity, complications.

## Introduction

Diabetes mellitus (DM) is challenging in the context of the COVID-19 pandemic. The prevalence of diabetes in patients with COVID-19 (Coronavirus Disease 2019), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has varied across countries, ranging from 5–20% in China, 17% in Lombardy in Italy and 33% in the USA (1-4).

DM can interfere with host–viral interactions and host–immune responses via several mechanisms that could also lead to poorer outcomes. Individuals with DM, hypertension, and severe obesity (BMI ≥ 40 kg/m$^2$) appear to be more likely to be at a higher risk for complications and death from COVID-19. In some studies, the prevalence of diabetes patients hospitalized in intensive care units (ICUs) for COVID-19 was two- to threefold higher, and the mortality rate at least double, than that of non-diabetes patients. As the population with diabetes is highly heterogeneous, it is of major interest to determine the effect of Type 2 diabetes mellitus (T2DM) on the progression to a more severe SARS-CoV-2 infection (5-9). However, there is some overlap of these comorbidities because of the high prevalence of cardiovascular disease (CVD), obesity, and hypertension in patients with DM. It is unknown whether DM independently contributes to this increased risk. On the other hand, plasma glucose levels and DM were independent predictors for mortality and morbidity in patients with SARS infection (10).

There is a paucity of data regarding the effect of T2DM and associated comorbidities on the clinical presentation and outcome of symptomatic patients with SARS-CoV-2 infection in comparison with non-diabetic patients.

The main purpose of this study was to describe the clinical presentation and radiological and hematological data of symptomatic COVID19 positive T2DM patients versus non-diabetic symptomatic COVID19 positive patients, and to compare their outcomes including duration of hospitalization, duration of ICU stay, duration of mechanical ventilation, and duration of O2 supplementation.

## Patients and Methods

A retrospective study was conducted on COVID 19 positive adult patients (n = 303) who presented with symptoms (fever, cough, dyspnea and respiratory distress ) and admitted in one of the COVID-19 designated facilities hospitals, including : Al- Hazm Mebaireek General Hospital (HMGH), Communicable

Disease Center (CDC), Mesaieed Hospital (MGH), and Ras Laffan Hospital (RLH), between January 2, 2020, and May 17, 2020.

All patients were diagnosed based on the WHO recommendations for cases who have a positive PCR test for SARS-CoV-2 (11). WHO guidelines for clinical management were utilized to categorize the severity of COVID-19 patients accordingly (12).

The diabetic group included all patients with Type 2 DM on insulin and/or oral hypoglycemic agents (n = 59). The non-diabetic group included all the other patients with no history of taking antidiabetic medication and who had normal random blood glucose and HbA1c on admission. Patients with Type 1 DM and pregnant females were excluded from the study.

The clinical, radiological (chest X ray and/or CT chest) and lab data including complete blood count (CBC), differential white blood cells (WBC) count, C-reactive protein (CRP) level at presentation were recorded for all patients on admission and on discharge. The durations of hospitalization, ICU admission, mechanical ventilation, O2 supplementation were calculated. The duration that was required for PCR to turn negative was also assessed. In addition, the Charlson Comorbidity Index was calculated for each patient.

The Charlson Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use (13,14).

The study was approved by the Institutional Review Board in HMC [MRC-05-104].

**Statistical analysis**

Data for diabetic and non-diabetic patients are presented as mean ± SD. Non-paired student "t" test was used to compare variables between the two groups when the data were normally distributed and Wilcoxon rank sum test when the data were not normally distributed. Linear regression equation was used to find possible correlation between clinical and lab variables. Significance was accepted when p value was <0.05.

**Results**

Prevalence of T2DM in symptomatic COVID19 positive patients was 59/303 (=19.5%). 4/59 diabetic patients had chronic kidney disease (CKD) versus 1/244 in the non-diabetic group. 31/59 diabetic patients had hypertension versus 15/244 in the non-diabetic group. 4/59 diabetics had history of myocardial infarction versus 1/244 in the non-diabetic group. 3/59 diabetic patients had previous cerebrovascular accidents (CVA, TIA) versus 1/244 in the non-diabetic group, and 2/59 of diabetic patients had congestive heart failure (CHF). Charlson Comorbidity score was significantly higher in the T2DM in symptomatic COVID19 positive patients (2.4± 1.6) versus the non-diabetic patients (0.28 ± 0.8; p: < 0.001).

T2DM patients had significantly higher percentage of pneumonia, severe pneumonia and acute respiratory distress syndrome (ARDS) versus the non-diabetic patients. Moreover, they had higher admission rate to ICU, requiring more mechanical ventilation and had a higher mortality rate compared to non-diabetic patients. Hematologically, diabetic patients had significantly higher percentage of elevated CRP and lower percentage of eosinophilia compared to non-diabetic patients **(table 1)**.

Diabetic patients were significantly older and heavier versus non-diabetic patients. Diabetic patients had significantly higher systolic and diastolic blood pressures, longer duration of hospitalization, ICU stay, mechanical ventilation and oxygen therapy. The duration time for the normalization of CRP levels was the same in both groups **(table 2)**.

Hematological data of showed significantly higher ANC count and lower lymphocyte and eosinophil counts in the diabetic group compared to the non-diabetic group. CRP was significantly higher in the diabetic group **(table 3)**.

**Table 1.** Comparison of clinical, radiological and laboratory data between T2DM patients and non-diabetic patients with COVID-19

| | DM with COVID 19 | | Non-DM with COVID 19 | | Chi Square test |
|---|---|---|---|---|---|
| **Clinical Data** | **Number =56** | **%** | **Number=243** | **%** | **Significance** |
| Pneumonia | 25.00 | 44.64 | 50.00 | 20.58 | 0.0002 |
| Severe Pneumonia | 6.00 | 10.71 | 6.00 | 2.47 | 0.0091 |
| ARDS | 12.00 | 21.43 | 15.00 | 6.17 | 0.0004 |
| Sepsis picture | 0.00 | 0.00 | 6.00 | 2.47 | 0.2327 |
| Admission ICU | 17.00 | 30.36 | 17.00 | 7.00 | < 0.0001 |
| Mechanical Ventillation | 14.00 | 25.00 | 10.00 | 4.12 | < 0.0001 |
| Mortality | 2.00 | 3.57 | 0.00 | 0.00 | 0.0032 |
| **Blood picture** | | | | | |
| Eosinophilia | 15.00 | 26.79 | 146.00 | 60.08 | < 0.0001 |
| Mild > 500 <1500 per uL | 12.00 | 21.43 | 135.00 | 55.56 | < 0.0001 |
| Moderate > 1500 per uL | 3.00 | 5.36 | 11.00 | 4.53 | 0.7739 |
| Lymphocytosis > 4000 per uL | 3.00 | 5.36 | 11.00 | 4.53 | 0.7739 |
| Lymphopenia <1000 per ul | 8.00 | 14.29 | 18.00 | 7.41 | 0.0990 |
| ANC < 1500/ul | 1.00 | 1.79 | 5.00 | 2.06 | 0.9226 |
| ANC >8000/ul | 9.00 | 16.07 | 26.00 | 10.70 | 0.2666 |
| Platelets > 450 /ul | 2.00 | 3.57 | 13.00 | 5.35 | 0.5767 |
| Platelets <150 / ul | 1.00 | 1.79 | 8.00 | 3.29 | 0.5549 |
| High CRP > 10mg/L | 32.00 | 57.14 | 55.00 | 22.63 | < 0.0001 |
| **Radiological findings** | | 0.00 | | | |
| Increased Bronchovascular markings | 14.00 | 25.00 | 101.00 | 41.56 | 0.0264 |
| GGO (ground glass opacity) pneumonitis | 12.00 | 21.43 | 42.00 | 17.28 | 0.4808 |
| Lobar Consolidation | 5.00 | 8.93 | 10.00 | 4.12 | 0.1380 |
| Bronchopneumnonia | 12.00 | 21.43 | 14.00 | 5.76 | 0.0002 |
| ARDS | 12.00 | 21.43 | 10.00 | 4.12 | < 0.0001 |
| Pleural Effusion | 6.00 | 10.71 | 14.00 | 5.76 | 0.1761 |

**Table 2.** Clinical data and management requirement in T2DM patients versus non-diabetic patients with COVID-19

| | | Age | Weight | Systolic BP | Diastolic BP | Days of Hospitalisation | Days of ICU admission | Days on Mech Vent | days on O2 supplen | Days PCR to turn negative |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Kg | mmHg | mmHg | | | | | |
| DM | Mean | 52.1* | 76.4* | 142* | 83.4* | 14.84* | 3.89* | 2.48* | 5.69* | 20.67 |
| | SD | 12.67 | 18.85 | 25.13 | 14.73 | 9.46 | 6.12 | 5.03 | 8.66 | 4.48 |
| No DM | Mean | 36.22 | 71.6* | 123.60 | 77.47 | 7.33 | 1.12 | 0.50 | 1.60 | 19.00 |
| | SD | 11.43 | 13.46 | 14.43 | 9.63 | 12.08 | 4.94 | 3.07 | 6.51 | 11.54 |

* p, 0.05

Correlation analysis showed that the diabetes status had the higher correlation with Charlson comorbidity score compared to other comorbidities [hypertension, CKD, and coronary heart disease (CHD)]. CRP correlated significantly with the duration of stay in the ICU and the duration for oxygen supplementation **(table 4)**.

## Discussion

A relationship between diabetes and infection has long been clinically recognized. Infections, particularly influenza and pneumonia, are often common and more serious in older people with T2DM. Nevertheless, the evidence remains controversial regarding whether

**Table 3.** Hematological and laboratory data in T2DM patients versus non-diabetic patients with COVID-19

| | | WBC2 | HB2 | PLT2 | ANC2 | LYMP | ESINO | CRP |
|---|---|---|---|---|---|---|---|---|
| | | 1000/mm3 | g/dl | 1000/mm3 | 1000/mm3 | 1000/mm3 | 1000/mm3 | <10 mg/L |
| DM | Mean | 8.43 | 14.04* | 256.63 | 5.32* | 1.98 | 0.38 | 67.9* |
| n=59 | SD | 1.65 | 0.96 | 107.08 | 1.72 | 1.00 | 0.56 | 86.89 |
| No DM | Mean | 8.73 | 13.37 | 267.13 | 4.84 | 2.36* | 0.63* | 24.60 |
| n = 244 | SD | 4.53 | 1.69 | 92.86 | 1.67 | 1.03 | 0.55 | 55.37 |

* p, 0.05

**Table 4.** Correlation of comorbidities with disease severity

| | A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|
| CHARLSON CO-MORBIDITY INDEX | 1.00 | | | | | | |
| ESINO2 | 0.00 | 1.00 | | | | | |
| BASO2 | 0.22 | 0.18 | 1.00 | | | | |
| CRP2 | 0.10 | -0.16 | 0.10 | 1.00 | | | |
| Days of ICU admission | -0.16 | -0.17 | -0.03 | 0.37 | 1.00 | | |
| Days on Mechanical Ventilation | -0.15 | -0.16 | -0.03 | 0.16 | 0.84 | 1.00 | |
| Number of days on oxygen supplementation | -0.15 | -0.18 | -0.05 | 0.41 | 0.98 | 0.84 | 1.00 |
| DM | 0.65 | 0.04 | 0.08 | 0.11 | -0.08 | -0.08 | -0.07 |
| CKD | 0.56 | -0.04 | 0.00 | 0.02 | -0.02 | -0.02 | -0.03 |
| MI | 0.40 | 0.15 | 0.03 | 0.14 | -0.02 | -0.02 | -0.03 |
| HTN | 0.55 | 0.01 | 0.08 | 0.11 | -0.08 | -0.07 | -0.08 |
| CHF | 0.16 | -0.01 | 0.10 | -0.03 | -0.02 | -0.01 | -0.02 |

***Legend*** **= A:** Charlson Comorbidity Index; **B:** eosinophils 2; **C:** basophils 2; **D:** C-reactive protein (CRP) 2; **E:** days of ICU admission; **F:** days of mechanical ventilation; **G:** number of days on oxygen supplementation

diabetes itself indeed increases susceptibility and impacts outcomes from infections, or the cardiovascular and renal comorbidities that are frequently associated with diabetes are the main factors involved (15-17).

Diabetes is among the most frequently reported comorbidities in patients infected with COVID-19. The prevalence of COVID positive patients in our symptomatic cohort of T2DM patients was 19.5%. According to the World Health Organization, the prevalence of DM in Qatari adult population is approximately 17% (18). These data support the previous notion that diabetic patients have similar risk to get the infection compared to the non-diabetic population and confirm the previously reported data that diabetic patients do not appear to be at increased risk of contracting SARS-CoV-2 infection compared to the general population (19).

However, DM remains a risk factor for developing severe and critical forms of COVID-19, requiring admission to an ICU and / or use of invasive mechanical ventilation, with high mortality rates.

The characteristics of diabetic patients at risk for developing severe and critical forms of COVID-19, as well as the prognostic impact of diabetes on the course of COVID-19, are under current investigation (20, 21). Our study on symptomatic patients with COVID 19, confirmed that diabetic patients had significantly higher percentage of pneumonia, severe pneumonia and ARDS versus the non-diabetic patients. Their radiological findings showed significantly more occurrence of bronchopneumonia, ARSD and increased bronchovascular changes compared to non-diabetic patients. In addition, they had higher admission rate to ICU, requiring more mechanical ventilation and had higher mortality rate compared to non-diabetic patients.

In the current SARS-CoV-2 pandemic, some studies supported our findings that older patients with chronic diseases, including diabetes, were at higher risk for developing severe COVID-19 and higher mortality (20, 22). However, other studies did not find a clear association between diabetes and severe disease (21,23,24).

Two studies indicated that elevated fasting blood glucose (FBG) at admission could be an important risk factor for critical illness and poor outcomes in patients with COVID-19.

Our data of poorer outcome of COVID- 19 in diabetic patients are supported by Zhang et al. (25). In another study, researchers examined the medical records of 123 laboratory-confirmed COVID-19 patients from three designated hospitals of Wuhan and Guangzhou, China. They confirmed that patients with higher fasting blood glucose had poorer prognosis and found that FBG was positively correlated with inflammatory biomarkers such as white blood cells and neutrophils, and negatively correlated with lymphocyte count. FBG was an independent risk factor for developing critical illness of COVID-19 patients, and glucose control helped to improve the outcome of patients with COVID-19 (26).

Potential mechanisms that may increase the severity and complications for COVID-19 in patients with DM include: (a) higher affinity cellular binding and efficient virus entry, (b) decreased viral clearance, (c) diminished T cell function, (d) increased susceptibility to hyperinflammation and cytokine storm syndrome, and (e) presence of CVD (27).

In animal models, structural lung changes have been related to diabetes, such as augmented vasculature permeability and collapsed alveolar epithelium (28). In rodents with DM an increased expression of angiotensin-converting enzyme 2 (ACE2) has been demonstrated in the lung, kidney, heart, and pancreas. Augmented ACE2 expression in alveolar type 2 progenitor cells (AT2), myocardium, kidney, and pancreas may favor increased cellular binding of SARS-CoV-2 (29,30). In vitro studies have shown that pulmonary epithelial cells exposure to high glucose concentrations significantly increases influenza virus infection and replication, indicating that hyperglycemia may enhance viral replication in vivo (31).

In diabetic patients, circulating levels of furin, a cellular protease involved in facilitating viral entry by cleaving the S1 and S2 domain of the spike protein, are elevated. In addition, a recent study reported that clearance of SARS-CoV-2 was delayed in patients with DM, a finding that needs to be confirmed in larger studies (32-34). These findings may explain in part the higher rate of pneumonia, severe pneumonia and ARDS in our patients with diabetes compared to non-diabetic patients.

Our diabetic patients had higher inflammatory response compared to non-diabetic patients as shown by significantly higher CRP level and higher ANC count with lower lymphocyte count compared to non-diabetic patients. CRP was correlated significantly with the duration of stay in the ICU and the duration for oxygen supplementation. In fact, poorly controlled diabetes has been linked to inhibited lymphocyte proliferative response to different kinds of stimuli. This may explain the lower lymphocyte count in some of our diabetic patients. In addition, poor control of diabetes lead to impaired monocyte/macrophage and neutrophil functions (35, 36).

DM inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes. Impairments in adaptive immunity characterized by an initial delay in the activation of Th1 cell-mediated immunity and a late hyperinflammatory response is often observed in patients with diabetes (34). In patients with COVID-19, peripheral counts of CD4+ and CD8+ T cells are low, but with a higher proportion of highly proinflammatory Th17 CD4+ T cells, as well as elevated cytokine levels (35-38). Thus, it is likely that patients with DM may have blunted anti-viral IFN responses, and the delayed activation of Th1/Th17 may contribute to accentuated inflammatory responses.

Our COVID-19 positive non-diabetic patients had significant eosinophilia that was significantly higher compared to diabetic patients. Several studies have evaluated the role of eosinophils against respiratory viruses. Eosinophils contain and produce molecules with antiviral activity, including RNases and reactive nitrogen species. They can also participate in adaptive immunity, serving as antigen-presenting cells. Eosinophil antiviral response has been demonstrated against some respiratory viruses *in vitro* and *in vivo*, including respiratory syncytial virus and influenza. In COVID-19, the eosinophil antiviral role might be an important factor to consider in modifying the lung pathology (39-44).

The significantly lower eosinophilic count in our diabetic patients may negatively affect the local resistance to and increase the pulmonary inflammatory response.

In addition, infection of SARS-CoV-2 in diabetic patients possibly triggers higher stress conditions, with greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability.

Hyperglycemia and insulin resistance promote increased synthesis of glycosylation end products (AGEs) and pro-inflammatory cytokines, oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation (45,46). On the other hand, a retrospective study from Wuhan reported that around 10% of the patients with T2DM and COVID-19 suffered at least one episode of hypoglycemia (<3.9 mmol/L) (47). Hypoglycemia has been shown to mobilize pro-inflammatory monocytes and increase platelet reactivity, contributing to a higher cardiovascular mortality in patients with diabetes (48).

Our T2DM patients were significantly older, heavier and had more comorbidity including CKD, hypertension, CVDs, higher Charlson comorbidity index and higher inflammatory markers compared to the non-diabetic group. Atherosclerosis, vascular inflammation and endothelial dysfunction are also part of the pathogenesis of DM and its associated chronic conditions including hypertension and CVDs (49). It has been reported that older people (those aged over 60 years) and people with co-morbidities were more likely to develop severe disease compared to young children and adolescents. Across all age groups younger than 18 years, more than 50% of children experienced mild symptoms or were asymptomatic, with less than 6% of children developing severe symptoms. This may be due to ageing lung microenvironment and defective T cell activation (9, 50-52). Animal studies involving SARS-CoV reported that older age was related to defects in T-cell and B-cell function and excess inflammation markers (27). Therefore, T2DM alone, or in association with older age, hypertension and/or CVDs, might have deficient control of SARS-CoV-2 replication and more prolonged proinflammatory response, potentially leading to poor outcomes.

## Conclusions

Our symptomatic Diabetic COVID19 positive patients had higher Charlson Comorbidity score, inflammatory markers, and lower lymphocyte and eosinophil counts compared to non-diabetic COVID19 positive patients. They had higher prevalence of complications including pneumonia and required more ICU admissions and longer requirement of hospitalization and days of oxygen supplementation. Future research is needed to provide a better understanding regarding the underlying pathophysiological mechanisms that increase the aggression of COVID-19 in patients with diabetes and their early management.

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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