RESEARCH ARTICLE

Diabetes Mellitus as a Bad Prognostic Marker in COVID-19 Patients and Its Relationship with Inflammatory Markers (CRP, D-dimer, LDH, and Ferritin)

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a newly recognized illness that is spreading rapidly around the world, causing many disabilities and deaths. Some diseases, for instance, diabetes, are continuously suggested as a risk factor, which contribute to the severity and mortality of COVID-19. However, to date, there are no comprehensive studies done that are aimed at explaining the exact relationship between diabetes mellitus and COVID-19. Thus, this study aims to evaluate the relationship between diabetes and COVID-19 and its relationship with inflammatory markers.

Materials and methods: This single-center retrospective observational study was conducted on 187 patients diagnosed with COVID-19. The data were collected on admission or during hospitalization by the attending physicians and was documented in the form of electronic medical records. The need for informed consent from patients was waived due to the time constraints during the COVID-19 emergency.

Results: Of the 187 hospitalized patients with COVID-19, 50 patients had diabetes. The median age was 59 years and 35 (70.00%) were male. Common symptoms among all patients included fever (57.21%) and cough (48.13%). Patients with diabetes had a non-significantly higher LDH, ferritin, CRP, and D-dimer when compared with those without diabetes. Coronavirus disease 2019 patients with diabetes were significantly more likely to develop severe disease or suffer mortality, indicating a poorer prognosis among COVID-19 patients.

Conclusion: We concluded that diabetes mellitus is associated with greater disease severity and poor outcome (mortality) in COVID-19, and a higher but statistically non-significant inflammatory burden.

Keywords: Coronavirus disease 2019, Diabetes mellitus, Outcome.

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Introduction

In early December of 2019, the first few pneumonia cases of an unknown origin were found in China. The pathogen had been identified as a novel enveloped RNA beta-coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated pneumonia quickly became a newly recognized deadly illness, that was seen spreading rapidly throughout Wuhan (Hubei province), and to the other provinces in China, and it still continues to spread around the world.[1] The World Health Organization (WHO) pronounced the official name of SARS-CoV-2-induced disease as the coronavirus disease 2019 (COVID-19).[2] Fever, dry cough, dyspnea, fatigue, and lymphopenia are identified as the symptoms of patients with COVID-19,[3] with the asymptomatic disease also being common.[4] The clinical manifestations were very similar to those of SARS-CoV and the Middle East respiratory syndrome (MERS). It is mainly transmitted by droplets or direct contact, and infected through the respiratory tract, with some reports suggesting a fecal route of transmission.[5] Due to the novelty of the disease, the factors affecting the severity of disease and death remain unknown. Nevertheless, it is assumed that patients with underlying health conditions, people of older age, and delayed referral to a hospital, all contribute to the severity of the symptoms.[6] Patients with underlying health conditions such as diabetes are considered as the high-risk group for catching the novel coronavirus.[7] Furthermore, it is considered that such patients are likely to suffer further complications and are at higher risk of death from COVID-19.[8] Coronavirus disease 2019 also has an indirect effect on people with various underlying health conditions.

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Materials and Methods

Study Design and Participants

This single-center retrospective observational study was conducted on 187 patients diagnosed with COVID-19 by RT-PCR. Data were collected on admission or during hospitalization by attending physicians and documented in the form of electronic medical records. The need for informed consent from patients was waived due to the time constraints during the COVID-19 emergency.

Data Collection

We collected data of 187 patients from their medical records. These data included age, sex, comorbidities, the severity of illness (asymptomatic, mild, moderate, and severe), signs and symptoms, treatment given, laboratory findings, and computed tomography (CT) images. All the data were reviewed and analyzed by senior physicians.

Statistical Analysis

Normally distributed continuous variables are expressed as means ± standard deviations, and non-normally distributed continuous variables as medians and interquartile ranges. The categorical variables are described as frequencies and percentages. The independent *t*-test or Mann–Whitney *U* test was conducted to compare the continuous variables between the group of patients with diabetes and that of the patients without diabetes. Meanwhile, the χ^2-test or Fisher's exact test was used to analyze the associations between categorical variables. Two-sided $p < 0.05$ was considered as statistically significant, and all statistical analyses were performed using Epi-info software.

Results

Discussion

The prevalence of diabetes mellitus is anticipated to increase substantially during the next few decades worldwide and is considered to become the main cause of human deaths. People with diabetes are more susceptible to certain infectious diseases, such as *Staphylococcus aureus* and *Mycobacterium tuberculosis*, possibly because of their dysregulated immune system.[9–12]

Recently, COVID-19 has become a focal topic of various researches, and several investigations have focused on diabetes being a crucial predictor of clinical course and prognosis of COVID-19 cases.[13] Certain studies found that diabetes negatively affected medical complications, including mortality, in COVID-19 cases.[14,15]

In our study, we found that the median age of COVID-19 patients with diabetes mellitus was statistically significantly higher than the median age of non-diabetic patients (59 vs 40 years, *p* value 0001, Table 1). There was no significant difference in the gender distribution of our study population. The mortality rate in diabetes was significantly higher than in non-diabetics (26 vs 6.57%, *p* value 0.001, Table 2) in our study population.

A systematic review by Huang et al. revealed that diabetes was associated with mortality, severity, acute respiratory distress syndrome, and disease progression in patients with COVID-19.[16]

Table 1: Clinical profile of patients

Variable		*Total (n = 187)*	*DM (n = 50)*	*Non-DM (n = 137)*	*p value*
Age in years (median, IQR)		47 (33–62)	59 (38.5–69)	40 (30–82)	0.001
Sex	Male *n* (%)	130 (69.52)	35 (70.00)	95 (73.08)	0.83
	Female *n* (%)	57 (30.48)	15 (30.00)	42 (26.92)	
Fever *n* (%)		107 (57.21)	15 (30.00)	92 (67.15)	0.001
Cough *n* (%)		90 (48.13)	27 (54.00)	63 (45.99)	0.421
Headache *n* (%)		34 (18.18)	8 (16.00)	26 (18.98)	0.800
Malaise *n* (%)		66 (35.29)	28 (56.00)	38 (27.74)	0.001
Shortness of breath *n* (%)		63 (33.69)	26 (52.00)	37 (27.00)	0.001

Table 2: Outcome

Variable	*Total (n = 187)*	*DM (n = 50)*	*Non-DM (n = 137)*	*p value*
Death *n* (%)	22 (11.76)	13 (26.00)	9 (6.57)	0.001
ICU stay (median, IQR) (days)	9.50 (8.0–12.0)	9.50 (8.0–13.0)	9.50 (8.0–12.0)	0.22

Table 3: Severity of disease

Severity	*Total (n = 187)*	*DM (n = 50)*	*Non-DM (n = 137)*	*p value*
Asymptomatic *n* (%)	44 (23.53)	2 (4.00)	42 (30.66)	0.001
Mild *n* (%)	93 (49.73)	25 (50.00)	68 (49.64)	
Moderate *n* (%)	20 (10.70)	10 (20.00)	10 (7.30)	
Severe *n* (%)	30 (16.04)	13 (26.00)	17 (12.41)	

Table 4: Inflammatory markers

Inflammatory marker	*Total (n = 187)*	*DM (n = 50)*	*Non-DM (n = 137)*	*p value*
CRP (median, IQR)	50.90 (16.80–417.0)	68.40 (47.2–417.0)	25.20 (13.70–86.00)	0.27
LDH (median, IQR)	338.20 (261.50–885.0)	360.70 (327.25–885.00)	311 (229.0–448.0)	0.09
D-dimer (median, IQR)	427.00 (322.0–19,500.0)	898.00 (349–19,500.00)	306 (221.0–1,270.0)	0.062
Ferritin (median, IQR)	217.00 (217.0–1,590.0)	277.00 (143–1,420.00)	172 (35.80–1,590.0)	0.43

There was a statistically significant lower proportion of diabetic patients with fever in our study population, when compared with non-diabetics (30 vs 67.15%, *p* value 0.001, Table 1). This may be in part due to immune defects and impairment of body temperature regulation in diabetes.[17] This is clinically important to note, as fever is one of the initial manifestations of COVID-19. Without fever, the patient may not realize he/she has COVID-19 and thus may present to health facilities later in the course of the disease when severity increases, leading to higher morbidity and mortality.

After having assessed the association between diabetes with the severity of COVID-19, Wu et al. found out the proportion of diabetes as comorbidity among severe COVID-19 cases was significantly higher than that among mild cases.[18] Similarly, our data supported that the proportion of severe or critical COVID-19 cases among patients with diabetes was higher than that among those without diabetes (Table 3). This means the clinical course of COVID-19 in patients with diabetes may be more severe than that in those without diabetes. Currently, the mechanisms behind this phenomenon remain unknown; however, high glucose levels may play a certain role in the impairment of antibacterial and phagocyte function of neutrophils, and complications caused by chronic diabetes.[10]

Diabetes results in a proinflammatory homeostatic immune response skewed toward T helper cell 1 (Th_1) and Th_{17} cells, and a decrease in regulatory T cells (Treg).[10] Immune dysfunction of diabetes alone or following infection has been reported for a wide variety of immune cells, not just macrophages, monocytes, and CD4+ T cells. A recent study reported the number of total T cells, CD4+ and CD8+ T cell subsets were substantially reduced and functionally exhausted in COVID-19 patients, especially among geriatric and critically ill patients who required ICU admission.[19] Kulcsar et al. showed that diabetic mice presented a prolonged phase of severe disease and delayed recovery after MERS-CoV infection, which was attributed to a dysregulated immune response, with lower inflammatory monocytes/macrophages and CD4+ T cells.[20]

During the SARS-CoV-1 outbreak, it was also reported that the virus causes damage to the pancreatic islets (possibly via the ACE-2 receptor) and causes acute diabetes.[21] Guo et al. also analyzed the effect of SARS-CoV-2 on the pathology of diabetes, with nearly one-third of diabetics requiring switching to insulin, or an increase in insulin dose after admission for glycemic control.[13] Thus, optimal management of diabetes and intensive daily glycemic control may help prevent the occurrence of life-threatening infections and complications associated with diabetes mellitus, as well as it will help to combat the increased susceptibility of infections due to impaired cellular and humoral immunity, especially in the context of the coronavirus pandemic.

The median values of inflammatory markers in diabetics were higher than non-diabetics in our study, but the difference was statistically non-significant for all the markers (CRP *p* value 0.27, LDH *p* value 0.09, D-dimer *p* value 0.062, and ferritin *p* value 0.43, Table 4). This is in line with the findings reported by Guo et al., who reported significantly higher levels of CRP, ferritin, and D-dimer among diabetics when compared with non-diabetics, indicating these patients are at a higher risk of uncontrolled inflammatory responses and hypercoagulable state.[13]

The study we conducted had several limitations that need to be addressed. First, this study was a retrospective study, so we included a very small proportion of patients with laboratory-confirmed COVID-19 infection since asymptomatic patients and those with mild symptoms were less likely to be enrolled (Berksonian bias). Second, the final survival outcome could not have been determined, as the long-term prognosis was not observed. Third, the other parameters associated with diabetes, including glycated hemoglobin, "peak" or "postprandial" plasma glucose levels could more accurately reflect the association between plasma glucose control and mortality in patients with COVID-19, if that data were available.

Conclusion

In our study, we found that diabetes mellitus is associated with greater disease severity and poor outcomes including death. Stronger personal prophylactic strategies are advised for patients with diabetes, and more intensive surveillance and treatment should be considered when they are infected with COVID-19.
For this reason, our suggestions include:
For prevention:

- Blood glucose must be actively monitored and controlled.
- Reduce unnecessary hospital admissions and visits.
- Attention to nutrition should be taken.
- Follow the guidelines of the country's healthcare system for the prevention of infection.

After infection:

- Monitoring the symptoms and rapid referral.
- Monitoring the blood glucose, switching to insulin if required.
- Monitoring for complications.
- Attention to nutrition (hydration, protein, etc.).
- Long-time follow-up.

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