

Mortality in patients with diabetes by COVID 19 a systematic review.

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Abstract

Background: Diabetes mellitus might be associated with severity and death in patients with COVID-19; but its mechanisms are still unknown.

Objective: to carry out a systematic review of what has been published so far on mortality in patients with COVID-19 associated with diabetes comorbidity.

Methods: A search was carried out in PubMed, Ovid MEDLINE, EMBASE and EMBASE Classic and Google Scholar databases; up to April 2020 using the search medical subheadings (MeSH) terms : "mortality from Coronavirus", "mortality from COVID-19" and "mortality in patients with diabetes by COVID-19". Enrolled studies were assessed independently by two blinded researchers. Studies quality was assessed using the Jadad scale. The articles score equal or greater than two points were considered highly methodological quality.

Results: Initially, 65 articles were found and 46 were excluded for not meeting the eligibility criteria. Among the 10 remaining, 3 were excluded because had Jadad score lower than two points. Among the remaining seven, two were excluded because they were meta-analysis. Eventually, five articles remained for final analysis. For all, mortality among patients with diabetes was higher than without diabetes. The risk of global mortality among diabetes patients was 8.9 times higher ($p < 0.0001$) than without diabetes. The time of diagnosis could be more determining for mortality, meanwhile HB1Ac level was not determining.

Conclusion: Mortality risk observed by COVID-19 is higher among diabetes patients than healthy age matched peers. This result can be partially explained by hormonal signaling changes, such as blood clotting and abnormal pancreas functioning.

Introduction

Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease (COVID-19) and, in severe cases, developing into the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality in patients with prior diabetes mellitus comorbidity and a detailed clinical illness course, including viral shedding, have not been well described^{1,2}.

On April 7, 2020, the World Health Organization (WHO) reported 2,287,836 confirmed cases of COVID-19 worldwide. Also 160,323 deaths were reported, 7% death rate worldwide. The United States of America has most of cases with 733,921 and 39,019 deaths (0.053 death rate), followed by Spain with 191,726 cases and 20,043 deaths (0.101 death rate). Surprisingly, Italy does not have as much number of cases as reported in other countries (175,925 confirmed cases and 23,227 deaths), however, it presents the higher mortality rate (0.132) seen up to this date³.

A retrospective cohort study investigated several risk factors for death in adults with COVID-19⁴. In particular, older age, d-dimer levels greater than 1 µg/mL and higher SOFA score prior to hospital admission were associated with higher odds of in-hospital death. Additionally, elevated levels of blood IL-6, high-sensitivity cardiac troponin I, lactate dehydrogenase and lymphopenia were more commonly seen in severe COVID-19 illness⁴. Similar results have already been shown by other studies^{5,6,7}.

Although the clinical manifestations of COVID-19 are surrogates of respiratory symptoms^{8,9} some patients with diabetes commonly develop severe illness¹⁰. In addition, these patients might have increased death risk¹¹. The coronavirus 2019 disease (COVID-19) currently represents a serious public health issue worldwide. As well known, diabetic patients are at higher risk of infection especially during period of poor glycaemic control¹¹. Recent investigations have reported that diabetes mellitus (DM) is one of the most common comorbidity accompanied the COVID-19 infection,^{12,13}. Additionally, some studies have suggested that these subjects seem to have a higher mortality risk during the infection^{14,15}.

Therefore, understanding the damage caused by SARS-CoV-2 to the diabetes patients, as well as its underlying mechanisms, is of great importance, so that the treatment of these patients can be promptly and effectively towards mortality reduction. According to this, our study aimed to carry out a systematic review of what has been published so far on mortality from COVID-19 in diabetes patients.

Method

Search strategy and selection criteria

Studies search was carried out in the PubMed, Ovid MEDLINE, EMBASE and EMBASE Classic and Google Scholar databases up to April 2020 using the search medical subheading (MeSH) terms : "mortality from coronavirus", "mortality from COVID-19" and "mortality in patients with

diabetes by COVID-19". The search was limited to written English manuscripts. At first studies analysis, general characteristics of the study sample and COVID-19 mortality in diabetes patients was necessary to be reported. Manuscripts published as review articles, letters, case studies, editorials, conference abstracts, family-based studies and articles without abstracts were excluded.

Studies supplied by the database search strategy were assessed independently by two blinded researchers. Study quality was assessed using the Jadad scale¹⁶. The Jadad scale has a maximum score of five points, it is subdivided into three topics: randomization, blind and an account of all patients. The score of the articles is, thus, distributed as explained below.

- Randomization : 1 point if randomization is mentioned; 1 additional point if the method of the randomization was accomplished using a computer-based randomization software, generated appropriately by random number list, coin toss or well-shuffled envelopes. Deduct 1 point if the method of randomization is inappropriate (minimum 0).
- Blind : 1 point if blinding is mentioned; 1 additional point if the method blinding is appropriate. Deduct 1 point if the method of blinding is inappropriate (minimum 0).
- An account of all patients: 1 point if all patients in the trial is known. If there are no data the reason is stated.

Initially, the researchers were trained to standardize the methodological application, which consisted of discussing the Jadad scale items and summarizing the articles; two researchers applied the scale independently and any disagreements between them were solved by discussing and reaching a consensus. The articles that obtained a score equal or greater than two points on the scale were considered as having high methodological quality.

Results

Initially 53 articles were found with the mesh terms "mortality from Coronavirus", "mortality from COVID-19" and "mortality in patients with diabetes by COVID-19". Then a second search round was performed based on the references of the first studies found; 12 additional articles were found, 3 were duplicated. Among the 62 full text found, 46 were excluded for not meeting the eligibility criteria (none of those included the mortality rate for diabetes patients). Among the 10 articles that met the criteria, 3 were excluded because both evaluators rated a Jadad score lower than two points. Among the remaining seven, two were excluded because they were meta-analysis. Final analysis comprised five full text studies (Figure 1).

The table 1 shows studies general characteristics such as authors names, studies' objectives, place of recruitment, study type and conclusion.

Table 2 shows COVID-19 mortality for patients with and without diabetes according to each study. The lowest mortality rate in patients with and without diabetes was found by W. Guan et. al. 2020 (22.3 and 6.4%, respectively). No other author found similar mortality rate among groups; for all, the mortality rate in patients with diabetes was higher as compared to non-diabetic patients. o HB1Ac level and diagnosis time of diabetes was reported only by a study.

Death risk among diabetic patients was compared to individuals without diabetes in each of the studies. In Fei Zhou et. al. study, the risk was 3.9 (CI 95% of 2.1 to 7.9, $p < 0.0001$); for Chaomin Wu et. al, study, it was 3.3 (CI 95% of 1.8 to 5.9, $p < 0.0001$); In Mingli Yuan et. al. study, 5.9 (CI 95% from 4.5. to 29, $p < 0.0001$); in Xiaobo Yang et. al. study, 6.4 (CI 95% from 3.1 to 13.4, $p < 0.0001$); and, finally, in W. Guan et. al., 3.7 (CI 95% from 1.5 to 8.0, $p < 0.002$) (Figure 2).

Based on the final studies analysis, a global average mortality risk from COVID-19 in patients with diabetes was assessed. It was seen that the mortality risk was 8.9 times higher for patients with diabetes than individuals without diabetes (Figure 2).

Discussion

The aim of this systematic review was to identify COVID-19 mortality rate and risk among patients with diabetes. Our review showed that mortality rate due to COVID-19 varied widely according to each study, however, in all the mortality rate was higher among patients with diabetes. Nevertheless, while evaluating the average mortality risk for patients with diabetes in relation to non-diabetics patients, OR was 8.9 times higher. The new finding that o HB1Ac level and diagnosis time can contribute to higher mortality.

In one of the first published studies evaluating the mortality risk of COVID-19, the authors showed that older age, high SOFA score and d-dimer greater than 1 $\mu\text{g} / \text{mL}$ could help clinicians to identify patients with poor prognosis at an early stage¹⁷. Also is known that the age-

dependent defects in T-cell and B-cell functioning and the excess production of type 2 cytokines could lead to a deficiency in viral control replication and more prolonged proinflammatory responses, potentially leading to poor outcome¹⁸. It is known that the sofa severity scale is also a good marker of mortality in patients with sepsis¹⁹; it has been shown that sepsis occurs in about 40% of patients with COVID-19 due to pneumonia²⁰.

After these findings, other studies began to evaluate other prognostic factors, such as heart disease, arterial hypertension, chronic obstructive lung disease, chronic kidney disease and carcinoma^{21,22,23}. Diabetes and uncontrolled glycaemia were reported as significant predictors of severity and deaths in patients infected with different viruses - including the 2009 pandemic influenza A (H1N1)²⁴, SARS-CoV²⁵ and MERS-CoV²⁶. Previous studies had shown the risk of complications of COVID-19 in patients with diabetes, with increased rates in ICU admission ICU and mechanical ventilation need^{7,9}.

Most recently a meta-analysis showed that diabetic patients with COVID-19 infection have an higher risk of ICU admission and higher mortality risk²⁷. A relationship between diabetes and infection has long been clinically recognized²⁸. Infections - particularly influenza and pneumonia - are common and more serious in older people with type 2 diabetes mellitus²⁸. However, there is no evidence whether diabetes itself increases susceptibility of infections developing in these patients. Still, remains uncertain how exactly the inflammatory and immune response occurs in patients COVID-19, as well as whether hyper or hypoglycemia may alter the SARS-CoV-2 virulence or the virus itself interferes with insulin secretion or glycemic control.

There are several hypotheses for which the patient with diabetes has complications due to COVID-19. Chronic inflammation, increased coagulation activity, immune response impairment and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying pathophysiological mechanisms contributing to the increased morbidity and mortality of COVID-19 in people with diabetes²⁹.

Another possibility is that diabetes is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities that can affect its response to pathogens³⁰. Hyperglycemia and insulin resistance promote increased synthesis of the end of glycosylation oxidative stress products (AGEs), and proinflammatory cytokines; in addition, it stimulates the production of adhesion molecules that mediate tissue inflammation^{14,15}. This inflammatory process may be part of the underlying mechanism that leads to a greater propensity to infections - worse results in patients with diabetes³¹.

Insulin resistance and T2DM are associated with endothelial dysfunction and increased platelet aggregation and activation. These abnormalities predispose the hypercoagulable prothrombotic state development³². It is possible that coagulation disorders are one of the main mechanisms that increase mortality from COVID-19 among patients with diabetes. Coronavirus inoculation has already been found in pancreatic islets. Therefore, although more evidence is needed, pancreatic damage may also be present in patients with COVID-19, possibly contributing to a higher risk of mortality in diabetic patients³³.

Although diabetes is associated with worse prognosis for COVID-19 patients, the susceptibility to COVID-19 infection does not appear to be greater than non-diabetic individuals. According to several studies, the prevalence of diabetes in people infected with the virus is about the same as overall population, even slightly lower³⁴.

The limitations of this study are related to the fact that we did not carry out risk analysis corrected by age and sex; as it is already known that age, as well as, male gender can influence higher mortality rates. Nevertheless, this study has important clinical applications related to the fact that the increase in mortality in diabetic patients may be related to coagulation disorders and pancreatic changes.

Conclusion

According to the presented analyzes, we can conclude that mortality risk and mortality observed in COVID-19 disease is higher among patients with diabetes than individuals without diabetes. This can be partially explained by changes in its disease mechanism, such as blood clotting and abnormal pancreas functioning.

Declarations

COI (Conflict of Interest statement)

"The authors declared that they have no conflict of interest"

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:




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Tables

Table 1. General characteristics of studies considered for the outcome mortality in diabetes patients.

Authors	Objectives	Place/type	Conclusion
Fei Zhou et al 2020	to explore risk factors of in-hospital death for patients and describe the clinical course of symptoms, viral shedding, and temporal changes of laboratory findings during hospitalization.	Jinyintan Hospital/retrospective, multicentre cohort study	older age, higher SOFA score, and elevated d-dimer at admission were risk factors for death of adult patients with COVID-19. The prolonged viral shedding provides the rationale for testing novel coronavirus antiviral interventions in efforts to improve outcomes.
Chaomin Wu et al 2020	To describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS) or died.	Zhongshan Hospital/retrospective cohort study	Older age was associated with greater risk of developing ARDS and death, likely because of less rigorous immune response. Although fever was associated with the development of ARDS, it was also associated with better outcomes. Several factors related to the development of ARDS were not associated with death, which indicates that different pathophysiological changes from hospital admission to development of ARDS and from development of ARDS to death may exist. Moreover, treatment with methylprednisolone may be beneficial for patients who develop ARDS. Double-blinded randomized clinical trials to determine the most effective treatments for COVID-19 are still needed.
Mingli Yuan et al 2020	To summarize the clinical and radiologic characteristics of 27 confirmed cases and analyze the association of radiologic findings with mortality cases	University of Science and Technology, Wuhan, Hubei, China /retrospective	A simple CT scoring method was capable to predict mortality
Xiaobo Yang et al 2020	We aimed to describe the clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia	Wuhan, China/retrospective, observational study	the mortality of critically ill patients with SARS-CoV-2 pneumonia is high. The survival term of the non-survivors is likely to be within 1-2 weeks after ICU admission. Older patients (>65 years) with comorbidities and ARDS are at increased risk of death. The severity of SARS-CoV-2 pneumonia poses great strain to hospital critical care resources, especially if they are not adequately staffed or resourced.
W. Guan et al 2020	describe the results of our analysis of the clinical characteristics of Covid-19 in a selected cohort of patients throughout China	Hospital of Guangzhou Medical University/retrospective	During the first 2 months of the current outbreak, Covid-19 spread rapidly throughout China and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. (Funded by the National Health Commission of China and others

Table 2. General characteristics of studies as to overall mortality and diabetes mortality rates.

Studies	Sample size, (n)	Overall mortality rate (except diabetics), n(%)	Diabetic patients, n (%)	Alive, n(%)	Death, n(%)
Fei Zhou et. al., 2020 ¹⁷	191	36(18.8)	36(19)	19(52.7)	17(47.3)
Chaomin Wu et. al., 2020 ²	84	33(39.2)	16(19.1)	5(31.7)	11(68.8)
Mingli Yuan et. al., 2020 ²⁵	27	4(14.8)	6 (22.2)	0(0)	6(100)
Xiaobo Yang et. al., 2020 ²²	52	25(48.1)	9 (17.3)	2(12.3)	7(77.7)
W. Guan et. al., 2020 ⁴	1099	71(6.4)	81(7.3)	63(77.7)	18(22.3)

Figures

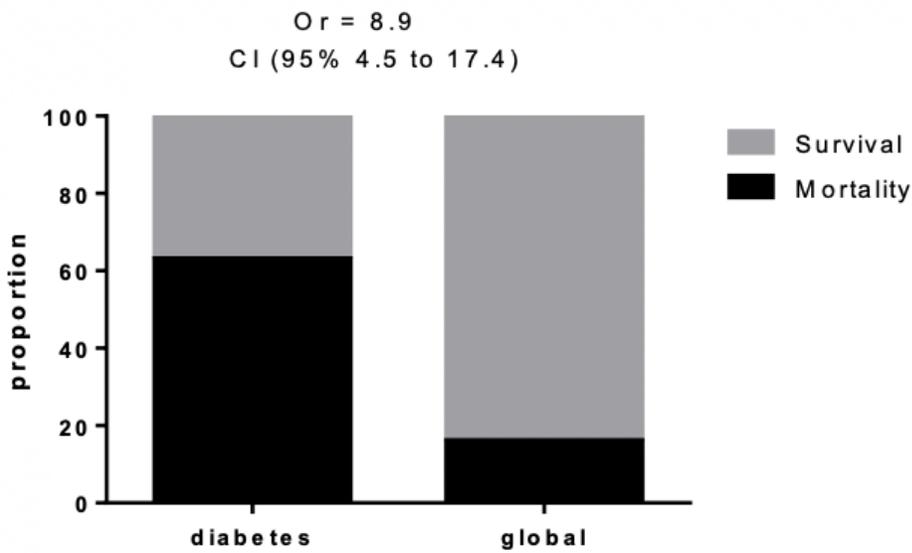


Figure 1

Global mortality risk of from COVID-19 in patients with diabetes

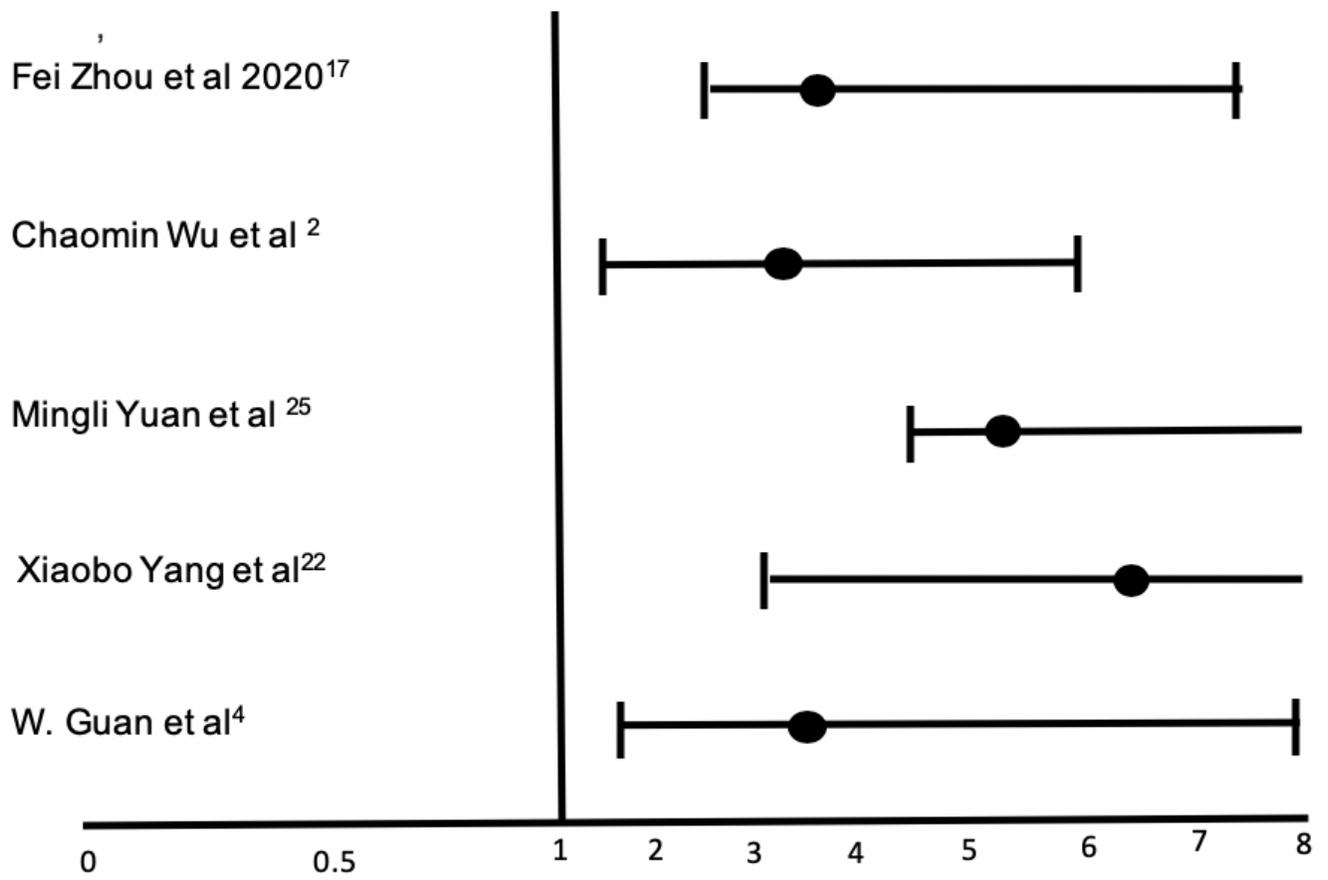


Figure 2

Forest plot of studies investigating mortality risk in patients diabetes mellitus

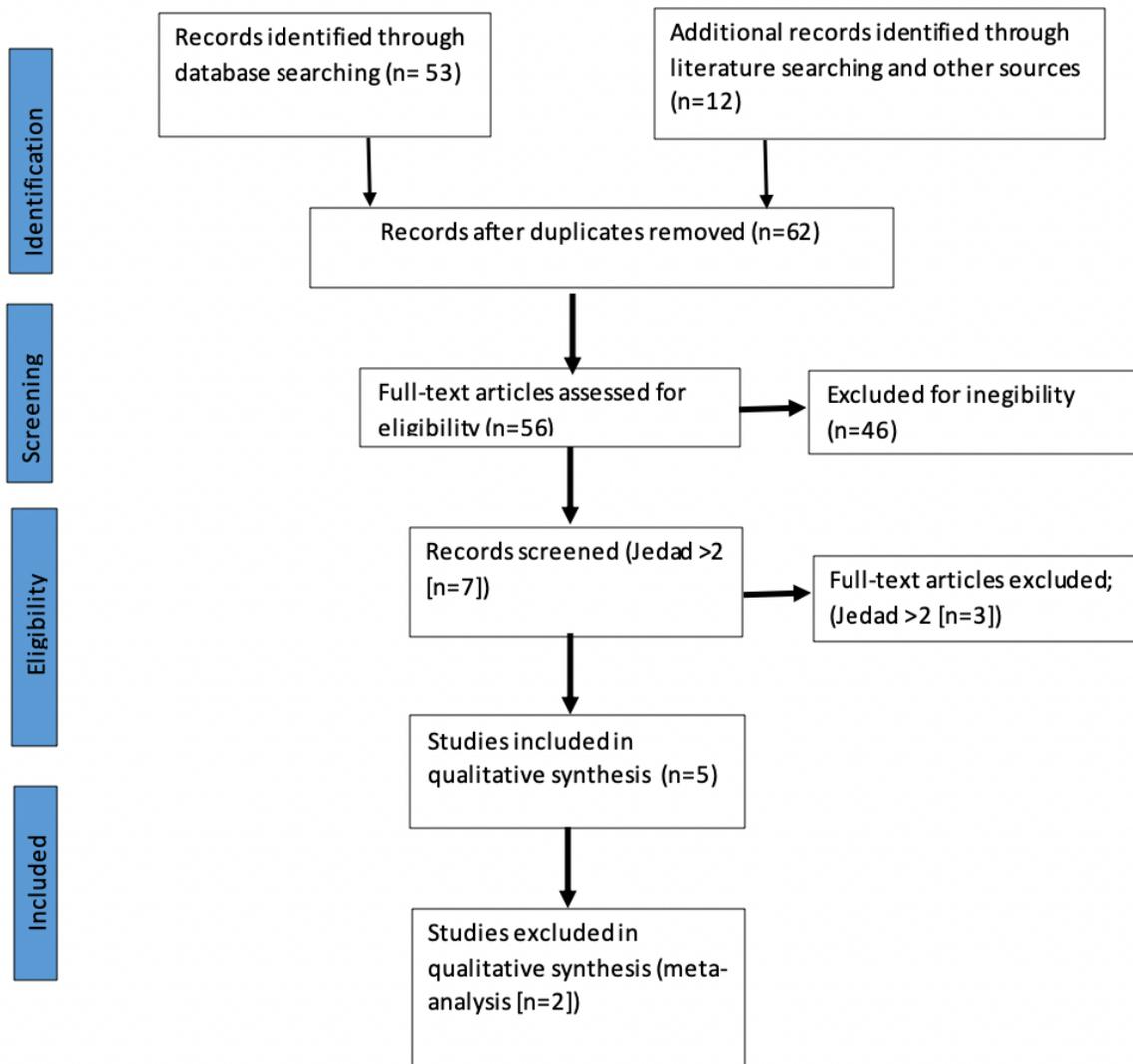


Figure 3

Systematic literature review process. The flow diagram describes the systematic review of the literature for the mortality by COVID-19 in diabetes patients.