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REVIEW PAPER

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COVID-19 and diabetes: Is there enough evidence?

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Abstract

The pandemic of COVID-19, a disease caused by a novel coronavirus SARS-CoV-2, is associated with significant morbidity and mortality. Recent data showed that hypertension, diabetes mellitus, cardiovascular diseases, and chronic obstructive pulmonary disease were the most prevalent comorbidities in COVID-19 patients. Additionally, data indicate that hypertension, diabetes, and cardiovascular diseases are important risk factors for progression and unfavorable outcome in COVID-19 patients. There is only limited amount of data regarding follow-up of these patients, and they provided conflicting results. The main limitation is a small number of participants and particularly those who experienced primary composite outcome (admission in intensive care unit, use of mechanical ventilation, or death). Additionally, the limited number of patients was essential obstacle for performing analysis that would include many confounding factors such as advanced age, smoking status, and obesity and potentially change conclusion. So far, there is no study that demonstrated independent predictive value of diabetes on mortality in COVID-19 patients, but there are many speculations about the association between diabetes and susceptibility to novel coronavirus, as well as its impact on progression and prognosis of COVID-19. The aim of this review article was to summarize the current knowledge about the relationship between diabetes and COVID-19 and its role in outcome in these patients.

1 | INTRODUCTION

Pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first time reported on December 31, 2019.[1] Since then, the COVID-19 pandemic, disease caused by this virus, had spread around the world. Until April 10, over 1.6 million confirmed cases in total and almost 100 000 deaths were identified worldwide. Everything started from Wuhan, Hubei Province, in China more than 4 months ago, and therefore practically, all relevant clinical data are coming from China. These findings are showing that arterial hypertension, diabetes, cardiovascular diseases, and chronic obstructive pulmonary disease are common comorbidities in patients with COVID-19[2-22] (Tables 1 and 2). Even though the number of studies with follow-up is rather limited, these data are suggesting that hypertension, diabetes, and cardiovascular disease are underlying conditions associated with adverse outcome—admission in intensive care unit, mechanic ventilation, and death[6-9,13,18] (Table 3). However, findings are inconsistent and data are more epidemiological than analytical. Majority of studies did not analyze effect of many confounding factors, such as age, sex, and obesity, which could significantly change interaction between comorbidities and outcome. It is clear that sudden outbreak of COVID-19 raised a great attention and forced rapid publication in order to explain epidemiology, therapeutic approach, and outcome. Many parameters were not available, and inclusion of some risk factors, such as obesity, that would probably interfere with final results was not possible so far. Therefore, one should be careful in interpretation of available data and indicating hypertension and diabetes as one of the most responsible risk factors, at least not in global population.

The aim of this review was to summarize currently available data regarding the prevalence of diabetes in patients with COVID-19 and its role in outcome in these patients. Hence, a comprehensive systematic search was performed on PubMed, Scopus, Web

of Science, and Google scholar, to find articles published until April 10, 2020.

2 | EPIDEMIOLOGICAL STUDIES

It is still unknown whether patients with diabetes have a higher susceptibility to COVID-19, but there is an observation that the risk is higher for both infection and disease severity. However, the percentage of patients with diabetes varies from 3% to 21%.[16,17] In two largest meta-analyses that included 46 248 and 76 993 COVID-19 patients, respectively, diabetes was detected in 8.6% and 7.9%.[19,20] However, it should be noted that large level of heterogeneity exists between published studies that differ in sample size, age of patients, severity of COVID-19, hospital facilities, investigated comorbidities, therapeutic approach, and finally outcome.

In one of the largest study published (n = 1099) so far, diabetes was present in 7.4% of COVID-19 patients and it was significantly more prevalent in patients with severe form of disease and those who experienced primary outcome end point (admission to an intensive care unit, the use of mechanical ventilation, or death).[2] The same group of authors in a larger group of COVID-19 patients (n = 1590) reported diabetes in 8.2%, and it was significantly more prevalent among COVID-19 patients with severe form than in patients with non-severe form of disease (34.6% vs 14.3%).[11] The most recent study which included 1012 non-critically ill COVID-19 patients reported diabetes in only 3% of patients.[17] Even though the prevalence of diabetes was low, COVID-19 patients with aggravation of illness during follow-up were more frequently diabetic in comparison with those who did not have complication during COVID-19.

Lian et al[3] included 788 patients with COVID-19 and divided patients into two groups: younger than 60 years and older than 60 years, thereby contributing to explain why diabetes is related to susceptibility and severity of COVID-19. The authors showed that many comorbidities (hypertension, cardiovascular disease, and chronic obstructive pulmonary disease), including diabetes, were more prevalent in patients older than 60 years than in patients younger than 60 years.[3] Difference in age is probably one of the main reasons for risk that is ascribed to diabetes in patients with COVID-19.

Studies that investigated cardiac injury in COVID-19 patients, defined by increased cardio-specific enzymes, showed that diabetes was significantly more frequent among patients with cardiac injury than in patients without it.[4,5] Nevertheless, prevalence of hypertension, cardiovascular diseases, and chronic renal disease was significantly higher in patients who experienced cardiac injury, and it would be difficult to separate the effect of diabetes from other underlying diseases. Moreover, there was a large difference in age between COVID-19 patients with detected cardiac injury and those who did not have cardiac injury, which also could contribute to worse outcome and cardiac injury.[4,5] The authors concluded that cardiac injury is common in COVID-19 patients (20%-28%) and it is associated with significantly higher mortality in this population.[4,5]

Guo et al[16] investigated the effect of diabetes on the progression and prognosis of patients with COVID-19. In limited sample, it was found that serum levels of inflammation-related biomarkers such as IL-6, C-reactive protein, serum ferritin and coagulation index, and D-dimer were significantly higher in patients with diabetes compared with those without,[16] which indicates that diabetic patients are predisposed to an hyper-inflammatory state that ultimately leads to prompt deterioration of COVID-19. There was no significant difference in age between diabetics and non-diabetics, but diabetics had more frequently cardiovascular disease than their non-diabetic counterparts.[16] However, even when diabetic patients without other comorbidities were analyzed, the results remained the same—inflammatory and pro-coagulant factors were significantly higher in diabetic patients. Among patients with diabetes, 29.2% were on insulin therapy and increased the dose of insulin after admission, whereas 37.5% were on oral antidiabetic therapy before admission and started insulin therapy after admission.[16] This means that patients had poor glycemic control during hospitalization.

Diabetes is hyper-inflammatory condition and seems that it may increase susceptibility for COVID-19 independently of other underlying diseases. There are several possible mechanisms: (a) inflammation, (b) hyper-coagulable state, and (c) activation of renin-angiotensin-aldosterone system (RAAS) and dysregulation of sympathetic nervous system. There is evidence that SARS-CoV, the novel coronavirus responsible for COVID-19, uses ACE2 on the surfaces of epithelial cells to bind and enter to infected cells.[24] ACE2 is located in cardiac, kidney, lung, and intestinal tissues and converts angiotensin II to angiotensin 1-7, which promotes vasodilation. The function of RAAS in diabetic patients is already significantly modified,[25] and acute change in activity of ACE2 may be the final trigger for hyper-inflammatory and hyper-coagulable storm in COVID-19. However, these are only hypotheses without reliable clinical evidence. Some observations from the COVID-19 pandemic indicated that RAAS inhibitors were more frequently taken by COVID-19 patients with unfavorable outcome.[5] These raised large concerns about use of RAAS inhibitors, which are often prescribed to diabetic patients with or without concomitant hypertension, another frequent comorbidity in COVID-19 patients. Recent findings from COVID-19 patients showed that RAAS inhibitors improve outcome in these patients,[26] and confirmed recent position statements from several societies who strongly recommended continuation of regular treatment with RAAS inhibitors.

3 | OUTCOME STUDIES

Data regarding influence of diabetes on outcome in diabetic patients are still limited (Table 3). Guo et al[5] in the large study of COVID-19 patients showed that diabetes was not a prevalent comorbidity in total population (7.4%), but it was significantly more prevalent in patients who experienced the primary composite end point (intensive

TABLE 1 Summary of studies that provided data on prevalence of diabetes in COVID-19 patients

Reference	Sample size	Age	Women (%)	Diabetes (%)	Other important findings
Guan et al[2]	1099	47 (35-58)	459 (42)	81 (7)	Epidemiological study that concerned only prevalence of diabetes.
Lian et al[3]	788	46	381 (48)	57 (7)	Older COVID-19 patients showed significantly higher female sex, rate of comorbidities, and rate of severe/critical disease.
Shi et al[4]	416	64 (21-95)	211 (50)	60 (14)	Cardiac injury is common (19.7%) in patients with COVID-19.
Guo et al[5]	187	58.5 ± 14.7	96 (51)	28 (15)	Myocardial injury is significantly associated with fatal outcome of COVID-19. The prognosis of patients with underlying CVD without myocardial injury is significantly better.
Chen et al[6]	274	62 (44-70)	103 (38)	47 (17)	Acute respiratory distress syndrome and respiratory failure, sepsis, acute cardiac injury, and heart failure were the most common critical complications during exacerbation of COVID-19.
Yang et al[7]	52	59.7 ± 13.3	17 (33)	9 (17)	Patients older than 65 years with comorbidities and ARDS had higher mortality risk.
Zhou et al[8]	191	56 (46-67)	72 (38)	36 (19)	Older age, higher sequential organ failure assessment, and D-dimer were predictors of mortality in COVID-19 patients.
Huang et al[10]	41	49 (41-58)	11 (27)	8 (20)	Epidemiological study, which did not investigate the effect of diabetes or CVD.
Guan et al[11]	1590	48.9 ± 16.3	674 (43)	130 (8)	Diabetes and hypertension were risk factors for admission to intensive care unit, invasive ventilation, and mortality. The risk increased with higher number of comorbidities.
Wang et al[12]	138	56 (22-92)	63 (46)	14 (10)	Study did not investigate the individual effect of diabetes.
Liu et al[14]	137	57 (20-83)	76 (56)	14 (10)	Epidemiological study, which did not investigate the effect of diabetes on outcome.
Wu et al[15]	201	51 (43-60)	73 (36)	22 (11)	Older age was associated with increased risk of ARDS and lethal outcome.
Guo et al[16]	174	59 (49-67)	98 (56)	37 (21)	Serum levels of inflammation-related biomarkers (IL-6, C-reactive protein, serum ferritin and coagulation index, and D-dimer), were significantly higher in DM patients compared with those without DM.
Wang et al[17]	1012	50 (39-58)	488 (48)	27 (3)	Male, elder age, diabetes, and cardiovascular diseases were all risk factors for aggravation of illness.

care admission, mechanical ventilation, and death) than in patients who did not have these complications (26.9% vs 6.1%). Nevertheless, only 67 out of 1099 patients experienced primary end point and it should be cautious in interpretation of these results.

Other studies that investigated outcome were significantly smaller, and results about impact of diabetes are different. In most of the studies exists the trend toward higher prevalence of diabetes among non-survivors, but in majority of studies, it did not reach

TABLE 2 Summary of the meta-analyses that provided findings on diabetes in COVID-19 patients

Reference	Sample size	Age	Women (%)	Diabetes (%)	Other important findings
Li et al[19]	1527	—	—	148 (10)	Hypertension, CVD, and diabetes are the most prevalent comorbidities in COVID-19 patients.
Yang et al[20]	46 248	—	—	8 ± 6%	The most prevalent comorbidities were hypertension, diabetes, cardiovascular disease, and respiratory disease.
Emami et al[22]	76 993	—	—	7.9%	The most prevalent comorbidities were hypertension, cardiovascular disease, smoking, and diabetes.
Rodriguez-Morales et al[22]	656	52	289 (44)	94 (14.4)	36.8% of patients had 1 or more comorbidities. The most significant were hypertension, cardiovascular disease, and diabetes.
Wang et al[23]	1558	—	667 (43)	—	Diabetes is associated with severity of clinical symptoms, but not with admission in intensive care unit.

TABLE 3 Prevalence of diabetes in COVID-19 patients in outcome studies

Reference	Non-survivors/ survivors	Number of patients	Age	Women (%)	Diabetes (%)
Chen et al[6]	Non-survivors	113	68 (62-77)	30 (27)	24 (21)
	Survivors	161	51 (37-66)	73 (45)	23 (14)
Yang et al[7]	Non-survivors	32	64.6 ± 11.2	11 (34)	7 (22)
	Survivors	20	51.9 ± 12.9	6 (30)	2 (10)
Zhou et al[8]	Non-survivors	54	69 (63-76)	16 (30)	17 (31)
	Survivors	137	52 (45-58)	56 (41)	19 (14)
Du et al[9]	Non-survivors	85	65.8 ± 14.2	23 (27)	19 (22)
Deng et al[13]	Non-survivors	109	69 (62-74)	36 (33)	17 (16)
	Survivors	116	40 (33-57)	65 (56)	9 (8)
Li et al[18]	Non-survivors with ARDS	44	68.5 (59-75)	15 (34)	11 (25)
	Survivors with ARDS	40	50 (40-57)	9 (23)	5 (13)

statistical significance due to the small sample size[6,7,13,18] (Table 3). Zhou et al[8] reported significantly higher prevalence of diabetes among non-survivors, and they proved that diabetes was associated with mortality from COVID-19, but after adjustment for age and smoking status, this predictive value vanished. The same was reported for other comorbidities such as hypertension, coronary heart disease, and chronic obstructive pulmonary disease,[8] which raised the question about actual importance of diabetes and emphasized the unfavorable significance of patients' age. The same study showed that pro-inflammatory biomarkers were not independent

predictors of mortality, whereas d-dimer >1 μg/mL was the only independent predictor from coagulable parameters. These findings are challenging the hypothesis that hyper-inflammation state in diabetic patients may be responsible for mortality of these patients in COVID-19. Nevertheless, the number of patients in this study is very limited (n = 51) and drawing conclusion is not an easy task.

Wu et al[18] compared COVID-19 patients with and without acute respiratory distress syndrome (ARDS) and found that diabetes was a significant predictor of ARDS (HR 2.34; 95% CI: 1.35-4.05), but not of mortality (HR 1.58; 95% CI: 0.80-3.13). It should be underlined that multivariate analysis with adjustment for age, sex, and other possible confounding factors was not performed due to small sample size (n = 84).

In meta-analysis that included 1558 patients with COVID-19, it was found that diabetes, as well as hypertension and chronic obstructive pulmonary disease, was associated with exacerbation and admission to intensive care unit.[23]

In the only study that aimed to investigate the effect of diabetes on progression and prognosis of patients with COVID-19 was reported significantly higher mortality among diabetic patients without other comorbidities (16.7% vs 0%).[16] However, diabetic patients were almost twice as old as non-diabetics (61 vs 32 years), which must be taken into consideration. The majority of inflammatory parameters (C-reactive protein, serum ferritin, erythrocyte sedimentation rate, and interleukin-6) and pro-coagulant factors (D-dimer and fibrinogen) were also significantly higher among diabetic patients without other comorbidities.[16] Diabetic complications were more prevalent in patients who died, with borderline statistical significance. Interestingly, ketoacidosis and infectious shock, conditions that would be assumed to be the most responsible for these findings, were not more prevalent among COVID-19 patients with lethal outcome.[16] Initiation of insulin after admission, which speaks in favor of poor glycemic regulation, was also not related to higher mortality. However, only 37 diabetic patients were included in this study and only 24 of them did not have other comorbidities, which is why this study may provide only directions for some future studies, but not conclusions. Coronary artery disease, particularly asymptomatic form, which is frequently present in diabetic patients, could not be excluded as potential confounding factor, which is additional limitation.

There are still many uncertainties whether diabetes interferes with SARS-CoV-2 and facilities the entrance of coronavirus in epithelial cells, as well as development of severe complications resulting in lethal outcome. It is reasonable to hypothesize that preexisting diabetes-induced target organ damage can be responsible for higher susceptibility of diabetic patients to this virus. Furthermore, diabetic patients with increased inflammatory factors and hyper-coagulability are more likely to progress into a worse prognosis. Therefore, patients with diabetes deserve more intensive attention and should be closely monitored due to the risk of rapid deterioration. In order to prevent infection and possible complications, diabetic patients together with hypertensive patients, and particularly those with both comorbidities, should have advantage once the vaccine is available.

4 | LIMITATIONS OF AVAILABLE DATA

There are a number of limitations in available data. The self-reporting of comorbidities on hospital admission, which was used in most of investigation, can cause significant under-reporting of comorbidities due to the lack of awareness and/or the lack of diagnostic testing, which could further interfere with the relationship between comorbidities and clinical outcome. Furthermore, follow-up was short and some patients remained in the hospital when data were analyzed, meaning that actual outcome is unknown, which directly influenced published results. Obesity was not reported in any of these studies and influence of BMI could not be investigated or included in adjustment, which would be of a great importance in diabetic patient. Data about antidiabetic therapy at baseline and during treatment are poor, and the prevalence of patients with uncontrolled diabetes is unknown. Both parameters are potential confounding factors in evaluation of diabetes as independent predictor of susceptibility to virus or outcome of disease. The majority of studies involved only limited number of patients, which can be an important limitation for reaching statistical power. The last, but not the least, important is the fact that all data are coming from China and one should be careful when extrapolating these findings to other countries with current outbreak of COVID-19 because the prevalence of comorbidities varies significantly among countries.

5 | CONCLUSIONS

The influence of diabetes on severity and outcome in COVID-19 patients is not clear because of large gap in evidence. It is not known which antidiabetic therapy was used in diabetic patients, how many patients were untreated, and how many had uncontrolled diabetes. Obesity, as one of the most important comorbidities in diabetic patients, has not been investigated at all. Large studies with comprehensive analysis of all risk factors and longer follow-up are necessary to answer all questions that have been raised, and we should not be surprised if upcoming results from Western countries that are currently affected by COVID-19 will be different from currently available data. Nevertheless, patients with diabetes and hypertension, particularly in advanced age, should have priority once the vaccine becomes available.

CONFLICT OF INTEREST

No conflict of interest.

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