Diabetes in COVID-19 pandemic-prevalence, patient characteristics and adverse outcomes.

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Abstract

Abstract Background: Current literature on COVID-19 pandemic has identified diabetes as a common comorbidity in patients affected. However, the evidence that diabetes increases the risk of infection, effect of diabetes on outcomes and characteristics of patients at risk is not clear. Objectives: To explore the prevalence of diabetes in COVID-19 pandemic, effect of diabetes on clinical outcomes and to characterise the patients with diabetes affected by COVID-19. Methods: A literature review of articles published in English language and reported outcomes on prevalence and effect of diabetes on outcomes and patients characteristics. Results: The prevalence of diabetes in COVID-19 patients appears similar to that in the general population. The evidence of diabetes increasing the risk of severe infection and adverse outcomes is substantial. The progression of the disease into acute respiratory distress syndrome, the requirement for intensive care admission or mechanical ventilation and mortality all have been increased by the presence of diabetes. Patients with diabetes at risk of COVID-19 appear to be obese, of older age, have uncontrolled glycaemia and have coexisting comorbidities especially cardiovascular disease and hypertension. Tight glycaemic control on admission to hospital using insulin infusion has shown some beneficial effects however, the role of hypoglycaemic medications in the management of these patients is not yet clear. Conclusion: High risk group should be identified and prioritised in future vaccination programmes. Future research is required to optimise management of patients with diabetes and develop new ways to manage them via technological developments such as telecare.

Introduction

In December 2019, a new coronavirus - the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) - has emerged in Wuhan, China and was named COVID-19 by the WHO. The virus spread rapidly across continents to cause a global pandemic. [1] Although the virus affected all age groups, the incidence was particularly shifted towards older age groups especially in those with underlying chronic health conditions. Among these chronic health conditions, diabetes mellitus in particular, appeared to be a major risk factor for both COVID-19 infection and worse outcomes. Diabetes is already known to be associated with increased mortality from any acute and chronic illness including infection. [2] However, with this new pandemic, the characteristics of patients with diabetes infected with the COVID-19 virus have not been clearly defined. Therefore, it is not yet known whether particular subgroups with diabetes are at increased risk of COVID-19 infection. This manuscript aims to explore the prevalence of diabetes in COVID-19 pandemic, characteristics of patients with diabetes affected by COVID-19 and the effect of diabetes on clinical outcomes.

Methods

We undertook a detailed literature search with full assessment of relevant articles by searching the following databases: Google Scholar, Medline and Embase. We used Medical Subject Heading (MeSH) terms: diabetes mellitus, COVID-19, infection, comorbidity, patients' characteristics, risk factors, adverse outcomes,

prevalence, mortality, predictors, disease progression, disease severity and glycaemic control. We searched articles for three categories of data:

1. Articles that reported diabetes as comorbidity in patients with COVID-19.

2. Articles that reported diabetes as a contributing factor to clinical outcomes.

3. Articles that specifically reported the characteristics of patients with diabetes affected by COVID-19.

Articles were reviewed for relevance by abstract. A manual search of citations in retrieved articles was performed in addition to the electronic literature search. We limited our selection to studies published in English language and reported clear outcomes. For data extractions, all articles derived from the search enquiry were independently examined by the authors and data was extracted in a standardised format, which included study design, population studied and main findings.

Prevalence

Diabetes is commonly reported as a premorbid condition for people infected with COVID-19 although whether diabetes is a risk factor for this infection is still unclear. In a Chinese nationwide analysis of 1,590 hospitalised patients with COVID-19, at least one comorbidity was present in 25.1% of patients. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). [3]In a data analysis of 12 studies that included 2,108 Chinese patients with confirmed SARS- Cov-2 infection, the prevalence of diabetes was 10.3%. [4] In another meta-analysis of six studies including 1,527 Chinese patients, the proportions of hypertension, cardio-cerebrovascular disease and diabetes in patients with COVID-19 were 17.1%, 16.4% and 9.7%, respectively. [5] A systematic review of 8 studies including 46,248 Chinese patients, found that diabetes was the second (8%) most prevalent co-morbidity, after hypertension (17%), in people hospitalised with COVID-19.[6] In a quantitative meta-analysis of 19 studies (18 from China and one from Australia), 36.8% of CODID-19 cases had underlying comorbidities (95% CI 24.7 to 48.9%), the most significant being hypertension (18.6%, 8.1 to 29.0%), cardiovascular disease (14.4%, 5.7 to 23.1%), and diabetes (11.9%, 9.1 to 14.6%).[7] Data from a British report of 20,133 patients with severe COVID-19 who were hospitalised, showed a median age of 73 years (IQR 58, 82) and 77% had a documented comorbidity. The prevalence of diabetes was 21%, only second to chronic cardiac disease (31%).[8] In a US long-term care facility report of 101 residents with COVID-19, the median age was 83 years (range, 51 to 100), the hospitalization rate was 54.5% and the case fatality rate was 33.7%. Most (94.1% of 101) of the residents had chronic underlying health conditions, with hypertension (67.3%), cardiac disease (60.4%), renal disease (40.6%), diabetes mellitus (31.7%), pulmonary disease (31.7%), obesity (30.7%) and cancer (14.9%) being most common.[9] The main international data reporting diabetes as a common comorbidity in patients with COVID-19 are summarised in Table 1[10-13].

Patient characteristics

A case series to describe the characteristics of 28 Chinese patients, mean (SD) age was 68.6 (9.0) years, 75% were males and 50% were admitted to Intensive care unit (ICU). The HbA1c level was similar between ICU (7.3%) and non-ICU (7.5%) patients but random blood glucose concentrations were significantly higher in ICU patients (13.7 mmol/L vs 9.8 mmol/L, p=0.03 respectively). Seventeen (60.7%) patients had coexisting chronic diseases, including hypertension, heart disease, cerebrovascular disease, and chronic respiratory disease.[14] In another study of 193 Chinese patients with severe covid-19, 48 of them (24.9%) had diabetes. Compared with patients without diabetes, those with diabetes were older (70 years vs 60 years, p<0.001), had more comorbidities (60.4% vs 44.8%, p=0.06), were more likely to receive mechanical ventilation (81.3% vs 49.0%, p<0.001) and had a higher mortality rate (81.3% vs 47.6%, p<0.001). [15] In a Chinese study of 904 patients, 136 (15%) had diabetes, insulin usage was associated with poor prognosis while the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) was not associated with adverse clinical outcomes. [16] Data from the UK of a total of 3,154,300 patients with diabetes showed that uncontrolled diabetes (HbA1c >86 mmol/mol vs 48-53 mmol/mol) and obesity (BMI >40 kg/m^2 vs 25-29.9 kg/m^2) were independently associated with increased COVID-19 mortality in both

type 1 and type 2 diabetes.[17] In the univariate analysis of the French study that included 1,317 patients with diabetes hospitalised for COVID-19, characteristics significantly associated with the primary outcome (mechanical ventilation and/or death within 7 days of admission) were sex, BMI and previous treatment with renin angiotensin aldosterone system (RAAS) blockers, but not with age, type of diabetes, HbA1c, diabetic complications or glucose-lowering therapies. However, in multivariable analyses, only BMI remained positively associated with the primary outcome. [18] Data from the US showed that mortality rate was 28.8% in patients with diabetes or uncontrolled hyperglycaemia compared to only 6.2% for patients without diabetes or hyperglycaemia. Also, hyperglycaemia related mortality was 41.7% compared to 14.8% for patients with diabetes but no hyperglycaemia suggesting that hyperglycaemia played a crucial role in adverse outcome.[19] Characteristics of patients with diabetes and COVID-19 infection are summarised in Table 2.

Outcomes

Diabetes was a common comorbidity in COVID-19 patients who were either admitted to ICU or died. [20-22] In a meta-analysis that included 1382 patients hospitalised for COVID-19, diabetes was identified as a risk factor for both ICU admission (OR 2.79, 95 % CI 1.85 to 4.22, $p < 0.0001$) and mortality (3.21, 1.82 to 5.64, $p < 0.0001$). [23] In another meta-analysis of 1936 COVID-19 patients, diabetes significantly correlated with COVID-19 severity (OR 2.67, 95% CI 1.91 to 3.74, $P<0.01$).[24] Prevalence of diabetes was also double in patients with COVID-19 who required ICU admission compared to those who did not.[25] Diabetes was the second most common morbidity in patients who reached a composite outcome of mechanical ventilation or death (26.9%) only second to hypertension (35.8%).[26] An outcome study has shown that in patients with COVID-19 who developed acute respiratory distress syndrome (ARDS), more patients had diabetes (19.0%) compared with those who did not (5.1%), respectively (difference, 13.9%, 95% CI 3.6% to 24.2%).[27] It has also been reported that diabetes was the most common morbidity (22% in one study and 60% in another) of patients who died in hospital. [28, 29] Compared with patients with non-severe COVID-19, diabetes was more common in severe cases although it did not reach statistical significance (OR 2.07, 95% CI 0.89 to 4.82). [30] In a US retrospective chart review of all patients enrolled in a follow up telemedicine outpatient clinic, the rate of hospitalisation for patients with diabetes was double (10.2%) the rate of hospitalisation for all other patients (5.1%) suggesting that the risk of severe COVID-19 is increased in individuals with diabetes. [31] Retrospective Chinese report has shown that compared with non-diabetes subjects, patients with diabetes were more likely to develop severe COVID-19 disease (P=0.028) with more complications including acute respiratory distress (38.1% vs 19.5%, P=0.001), acute cardiac injury (14.5% vs 5.1%, P=0.016) and non-invasive and invasive mechanical ventilation (P=0.037).[32] Diabetes as well as fasting blood glucose were independent risk factors for COVID-19 mortality (HR 3.641, 95% CI 1.086 to 12.214, P=0.036 and 1.187, 1.078 to 1.306, P<0.001, respectively) after adjustment for age, cardiovascular disease, chronic kidney disease and laboratory markers. [32] The recently reported British database analysis of 17,425,445 NHS registered adults showed that 5,683 deaths were attributed to COVID-19 and uncontrolled diabetes (HbA1c >=7.5%) was independent risk factor for mortality (HR 2.36, 95% CI 2.18 to 2.56). [33] Main studies reporting outcomes of patients with diabetes and COVID-19 are summarised in Table 3.

Conclusions

People with diabetes are at risk for greater susceptibility to COVID-19 infection and worse outcomes. This review aimed to explore the prevalence of diabetes in COVID-19 affected patients, whether it increases the risk of such infection, characteristics of patients at risk and their outcomes. (Figure 1)

Does diabetes increase the risk of COVID-19?

Diabetes appears to be a common comorbidity in patients with COVID-19 although a causal relationship is not clear. For example, a prevalence of diabetes among Chinese cohort, mean age 49.6 years, was reported to be 10.3% which is comparable to the prevalence of diabetes in the general population of China at 10.9% overall and 12.3% among people aged 40-59. [4, 34] Similarly, the prevalence of diabetes among British COVID-19 patients, median age 73 years, of 21% was similar to the reported prevalence of 23.8% among those above the age of 75 years. [35] The US data showed slightly higher prevalence of 33.8% in COVID-19 patients while the

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prevalence in the general population of a similar age is around 26.8%.[36] Therefore, the variable prevalence of diabetes reported in COVID-19 studies may simply reflect the local demographics across different countries. Diabetes may increase the risk of infection due to immunologic defects, such as decreased neutrophilic migration, phagocytosis, intracellular killing, and chemotaxis, however, the evidence remains controversial whether diabetes itself or the associated comorbidities is the main factor involved. [37]

Who is at risk?

The most common characteristics of patients with diabetes who are affected by COVID-19 in addition to older age and multiple morbidities are uncontrolled glycaemia and obesity. [17-19] Diabetes and uncontrolled glycaemia have been previously reported as significant predictors of severity and mortality in patients with viral pneumonias.[38-40] Infection with COVID-19 in people with diabetes may increase stress that leads to increased secretion of hyperglycaemic hormones such as glucocorticoids and adrenaline causing hyperglycaemia and fluctuating blood glucose levels. [41] The occurrence of hypoglycaemia due to variability of blood glucose levels may stimulate pro-inflammatory monocytes and increase platelet reactivity, contributing to a higher cardiovascular mortality in patients with diabetes. [42, 43] A recent study has shown that insulin infusion to tighten blood glucose control in patients with hyperglycaemia and hospitalised with COVID-19 has a protective effect. The study demonstrated that optimal glucose control in the immediate post-admission period for almost 18 days was associated with a significant reduction of inflammatory cytokines and pro-coagulant state which may reduce the risk of disease progression. [44]Obesity is a common feature of patients with diabetes affected by COVID-19. In a small study of 49 outpatients with diabetes and COVID-19 the reported median BMI was 33.9 with a range that reaches as high as 63.9 Kg/m^2. [31] Obesity is known to be associated with the severity and the longer duration of viral infections.[45] Central obesity, which is the predominant type in individuals with diabetes, is particularly associated with higher risk due to the increased secretion of cytokines and chronic low-grade inflammation that may induce an impaired immune response.[46] Other factors may be related to the fact that obesity may mechanically impair ventilation with reduced aeration of the lung bases therefore leading to accumulation of secretions and increased risk of infection. [47]

What causes worse outcomes?

The evidence for the increased adverse outcomes of COVID-19 due to pre-existing diabetes is consistent. For example, diabetes prevalence among COVID-19-deceased Italian cohort was 35.5% and only 20.3% in the general Italian citizens with the same age and gender distribution.[4] One explanation is the fact that diabetes usually coexists with other cardiovascular disease especially hypertension which has been shown to be associated with worse outcomes in COVID-19.[5-8]Poorly controlled diabetes is also associated with increased oxidative stress and increased inflammatory cytokines such as tumour necrosis factor and interleukin-6, due to increased insulin resistance, which may increase the risk of progression to severe disease. [37] In addition, endothelial dysfunction and enhanced platelet aggregation lead to the development of a hypercoagulable, pro-thrombotic state that may contribute to poor control of the virus replication, prolonged pro-inflammatory response and eventually poor outcome. [22] Diabetes may also be associated with decreased forced expiratory volume and forced vital capacity compromising optimal pulmonary function. [48]Diabetes -related complications may also be a factor. Microangiopathic changes that occur in the respiratory tract may impair gas exchange and lung compliance increasing susceptibility to lower respiratory tract infections by atypical microorganisms and severe pneumonias.[37]

Other mechanisms may be related to the fact that the COVID-19 virus gains entry to pulmonary cells through binding to the membrane ACE2 receptor. The ACE inhibitors, ARBs and non-steroidal anti-inflammatory drugs appear to increase ACE2 receptors expression and therefore their use in people with diabetes may increase COVID-19 infectivity and illness severity. [49] On the contrary to this, these medications may reduce the pulmonary and systemic inflammatory response by decreasing cytokines and therefore may be beneficial.[50] Therefore, it is still unclear what is the balance between the benefits and the risks might be in continuing or stopping RAAS inhibitors. Other drugs used in the treatment of COVID-19 may have a deleterious effect on blood glucose level regulation such as the hyperglycaemic effect of glucocorticoids and the hypoglycaemic effect of hydroxychloroquine although this has not been clearly reported in the literature.

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Any role of frailty?

Frailty has not been formally assessed as a risk factor for COVID-19 infection in people with diabetes. However, due to old age and multiple comorbidities being associated with worse outcome in a proportional fashion, it is likely that frailty is a confounding unmeasured factor.[51] Diabetes is known to increase the risk of frailty.[52] Frailty is a syndrome that is characterised by multisystem, including immune system, dysregulation which leads to reduced physiologic reserve and increased risk of adverse health outcomes including increased susceptibility to severe infections. Frailty has been shown to be associated with poor post-vaccination immune response, increased rates of influenza like illness and laboratory-confirmed influenza infection. [53] In a prospective cohort study in a tertiary hospital investigating older patients (aged [?]65 years) admitted with community acquired pneumonia, nursing home residency (a proxy for frailty) was an independent predictor of viral pneumonia (relative risk {RR} 3.06, P = 0.01) which highlights the role of frailty in institutionalised populations for the increased risk of viral illness. [54] In the British cohort study of patients with diabetes mellitus and COVID-19, the relationship of BMI association with the risk of COVID-19 related-mortality was U-shaped. The risk was greatest for those with very high BMI and the nadir of risk being in those with a BMI 25-29·9 kg/m^2. The authors suggested that the higher risks in people with lower BMI could be linked to the effect of confounding by factors that are associated with weight loss which have either not been considered in their analysis. [17] Therefore, frailty may be an unmeasured factor for adverse outcome in people with diabetes and COVID-19.

Future perspectives

The appropriate management of patients with diabetes and COVID-19 is not yet clear. Patients with diabetes should be declared as risk group for severe disease and worse outcomes. Future research may help develop a scoring system to identify vulnerable patients who may benefit from aggressive treatment or intensive support from outset to limit deterioration. Although a specific anti-viral drug is urgently required, a multi-target agent is also required to help regulate the dysregulated neuro-endocrine-immune system that is common in metabolic disease, including diabetes, cardiovascular disease, atherosclerosis, insulin resistance, hypertension, dyslipidaemia and obesity. The role of hypoglycaemic medications such as dipeptidyl peptidase-4 (DPP-4) inhibitors, which may act as receptor for COVID-19 and the glucagon-like peptide-1 receptor agonist (GLP-1 RA), that may reduce inflammation, will need further investigation. [55, 56] Similarly, the role of RAAS inhibitors with COVID-19 infection need exploration. It is not yet clear why insulin users had worse prognosis compared with other hypoglycaemic medications. [16] Whilst insulin users tend to have advanced disease with long duration of diabetes, prevalent complications and co-existing comorbidities to explain their worse outcome, further clarification is required. The role of hyperglycaemia, hyperinsulinaemia and hypoglycaemic agents in the pathogenesis of COVID-19 and how diabetes affects the efficacy of future vaccines and antiviral agents currently in trials are warranted. COVID-19 related mortality was reported to be higher in the Black and Asian ethnic groups with diabetes compared with the White population. [17]Therefore, future research is needed to provide a better understanding of the potential differences in genetic predispositions across populations and the underlying pathophysiological mechanisms. Finally, novel ways to deliver care to patients with diabetes using telehealth, remote patient monitoring and wearable technologies are required.

Conclusion

Diabetes appears to be a common morbidity in patients affected by COVID-19 however, the evidence that it increases the risk of infection is not yet clear. On the other hand, the evidence that diabetes increases the risk of severe disease and risk of adverse outcomes is substantial. Patients with diabetes who are at risk of COVID-19 tend to be obese, of older age, have uncontrolled diabetes and comorbidities, in particular cardiovascular disease and hypertension. Further research is still required to investigate appropriate management of people with diabetes and COVID-19 and develop novel ways of management including telecare.

Key points

- Diabetes is a common comorbidity in patients with COVID-19.
- Diabetes is associated with severe illness and worse outcomes.

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- Uncontrolled diabetes and obesity appear to be the major characteristics of patients at risk.
- Frailty may be a confounding factor that increases the risk of adverse outcomes.
- Future research is required to optimise the management of patients with diabetes and COVID-19.

References

1. Hui DS, AZHAR EI, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020; 91: 264-6.

2. Zoppini G, Fedeli U, Schievano E, et al. Mortality from infectious diseases in diabetes. Nutr Metab Cardiovasc Dis 2018; 28: 444-50.

3. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. European respiratory Journal 2020; DOI:10.1183/13993003.00547-2020.

4. Fadini GP, Morieri ML, Longato E, et al. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest 2020; 43: 867-9.

5. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020; 109: 531-8.

6. Yang J, Zhen Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020; 94: 91-5.

7. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020; 34: 101623. doi:10.1016/j.tmaid.2020.101623.

8. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020; 369:m1985.

9. McMichael TM, Currie DW, Clark S, et al. Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington. NEJM 2020; DOI: 10.1056/NEJMoa2005412.

10. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. European respiratory Journal 2020; DOI:10.1183/13993003.00547-2020.

11. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*. Published online March 23, 2020. doi:10.1001/jama.2020.4683

12. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020; 369:m1985.

13. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; doi:10.1001/jama.2020.6775.

14. Wang F, Yang Y, Dong K, et al. CLINICAL CHARACTERISTICS OF 28 PATIENTS WITH DIABETES AND COVID-19 IN WUHAN, CHINA Endocr Pract 2020; 10.4158/EP-2020-0108. doi:10.4158/EP-2020-0108.

15. Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with

severe covid-19 with diabetes. BMJ Open Diab Res Care 2020; 8: e001343. doi:10.1136/

bmjdrc-2020-001343.

16. Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients With

Diabetes and COVID-19 in Association With Glucose-Lowering Medication. Diabetes Care 2020; dc200660.https://doi.org/10.2337/dc20-0660.

17. Holman N, Knighton P, Kar P, et al. Type 1 and Type 2 diabetes and COVID-19 related mortality in England: a cohort study in people with diabetes. WWW.england.nhs.uk/publication/type-1-and-type-1diabetes-and-covid-19-related-mortality-in-england.

18. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. DIABETOLOGIA IN PRESS (DOI 10.1007/s00125-020-05180-x).

19. Bode B, Garrett V, Messler J, et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. J Diabetes Sci Technol 2020; doi: 10.1177/1932296820924469.

20. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; doi:org/10.1001/jama. 2020; 1585.

21. Epidemiological analysis of new coronavirus pneumonia. Epidemiology group of new coronavirus pneumonia emergency response mechanism of Chinese centre for disease control and prevention. Chinese Journal of Epidemiology, 2020; 41: 145-51.

22. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult

inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; doi.org/10.1016/S0140-6736(20)30566-3.

23. Roncon L, Zuin M, Rigatelli G, et al. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol 2020; 127:104354.

doi: 10.1016/j.jcv.2020.104354.

24. Chen Y, Gong X, Wang l, et al. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. doi:https://doi.org/10.1101/2020.03.25.20043133.

25. Bo L, Yang j, Zaho F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020; 109: 531-8.

26. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-20.

27. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020; doi:10.1001/jamainternmed.2020.0994.

28. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet 2020; 8: 475-81.

29. Yuan M, Yin W, Tao Z, et al. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PLoS ONE 2020; 15: e0230548. https://doi.org/10.1371/journal.pone.0230548.

30. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020; 94: 91-5.

31. Shabto JM, Loerinc L, O'Keefe GA, et al. Characteristics and Outcomes of COVID-19 Positive Patients with Diabetes Managed as Outpatients. Diabetes Res Clin Pract 2020; 22 : 108229.

32. Zhang Y, Cui Y, Shen M, et al. Comorbid Diabetes Mellitus was Associated with Poorer Prognosis in Patients with COVID-19: A Retrospective Cohort Study. Medrxiv 2020;

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doi:https://doi.org/10.1101/2020.03.24.20042358.

33. Williamson E, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv. doi: https://doi.org/10.1101/2020.05.06.20092999.

34. Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, Li Y, Zhao Z, Qin X, Jin D, Zhou M, Tang X, Hu Y (2017) Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA 317:2515–2523

35. 3.8 million people in England now have diabetes-Gov.uk. Accessed 28th May 2020.

36. Statistics about diabetes-American diabetes association. Accessed 29th May 2020.

37. Knapp S. Diabetes and infection: is there a link? - a mini-review.*Gerontology* . 2013; 59: 99-104.

38. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis. 2019;19(1):964.

39. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 2006;23(6):623-8.

40. Banik GR, Alqahtani AS, Booy R, Rashid H. Risk factors for severity and mortality in patients with MERS-CoV: Analysis of publicly available data from Saudi Arabia. Virol Sin. 2016;31(1):81-4.

41. Wang A, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res Clin Pract 2020: 108118.

42. Zhou J, Tan J. Diabetes patients with COVID-19 need better care. Metabolism 2020: 154216.

43. Iqbal A, Prince LR, Novodvorsky P, Bernjak A, Thomas MR, Birch L, et al. Effect of Hypoglycemia on Inflammatory Responses and the Response to Low-Dose Endotoxemia in Humans. J Clin Endocrinol Metab. 2019; 104(4):1187-99.

44. Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in Patients With Hyperglycemia Affected by Covid-19: Can We Do More on Glycemic Control? Diabetes care 2020; https://doi.org/10.2337/dc20-0723

45. Honce R, Schultz-Cherry S. Impact of obesity on influenza a virus pathogenesis, immune response, and evolution. *Front Immunol* 2019; 10: 1071.

46. Huttunen R, Syrjanen J. Obesity and the risk and outcome of infection. *Int J Obes (Lond)* 2013; 37: 333-40.

47. Dixon AE, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med* 2018; 12: 755-67.

48. Klein OL, Aviles-Santa L, Cai J, et al. Hispanics/Latinos with type 2 diabetes have functional and symptomatic pulmonary impairment Mirroring kidney microangiopathy: findings from the Hispanic community health Study/Study of Latinos (HCHS/SOL). Diabetes Care 2016; 39: 2051-7.

49. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertension 2020; doi: 10.1097/HJH.0000000000002450.

50. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020. doi: 10.1002/ddr.21656.

51. Sinclair AJ, Abdelhafiz AH. Age, frailty and diabetes – triple jeopardy for vulnerability to COVID-19 infection. EClinicalMedicine 2020; doi.org/10.1016/j.eclinm.2020.100343.

52. Sinclair AJ, Abdelhafiz AH, Rodriguez-Manas. Frailty and sarcopenia - newly emerging and high impact complications of diabetes. J Diabetes Complication 2017; 31: 1465-73.

53. Yao X, Hamilton RG, Weng NP, et al. Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine 2011; 29: 5015-21.

54. Ma HM, Lee KP, Woo J. Predictors of viral pneumonia: The need for viral testing in all patients hospitalized for nursing home-acquired pneumonia. Geriatr Gerontol Int 2013; 13: 949-57.

55. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight 2019;4 131774.

56. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev 2020, http://dx. doi.org/10.1210/endrev/bnaa011.

Table 1: Main international data reporting diabetes as comorbidity risk for COVID-19. 10-13		
Country	**Population**	**Main findings**
China	1,590 patients.	A. Mean (SD) age 48.9 (16.3) years. B. 25.1% have[?]1 comorbidity. C. Diabetes was second common morbidity (8.2%) after hypertension (16.9%).
Italy	1625 died patients	Analysis of subsample of 355 patients: A. Mean (SD) age 79.5 years (8.1). B. Mean (SD) number of comorbidities 2.7 (1.6). C. 99.2% of patients had [?]1 comorbidity. D. Diabetes was the first common comorbidity (35.5%).
UK	20,133 patients.	A. Median age 73 years (IQR 58, 82). B. 77% had documented comorbidity. C. Diabetes was second common comorbidity (21%) after cardiac disease (31%).
USA	5,700 patients	A. Median age, 63 years (IQR 52-75). B. Median (IQR) Charlson Comorbidity Index score was 4 (2-6) points. C. Diabetes was third common comorbidity (33.8%) after hypertension (56.6%) and obesity (41.7%).

SD=Standard deviation, IQR=Inter quartile range.

Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 14-19		
Study	**Population**	**Main findings**

Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]	Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]	Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]
Wang F, et al. Prospective observational, China.	28 patients with COVID-19 and diabetes.	A. Mean (SD) age 68.6 (9.0) years, 75% males. B.17 (60.7%) had comorbidities: hypertension (53.6%), CVD (14.3%), cerebrovascular disease (14.3%), chronic pulmonary disease (14.3%). C. Common symptoms were: fever (92.9%), dry cough (82.1%), fatigue (64.3%), dyspnoea (57.1%), anorexia (57.1%), diarrhoea (42.9%), expectoration (25.0%) and nausea (21.4%). C. 14 patients admitted to ICU, of whom 11 received non-invasive and 7 received mechanical ventilation. D. 12 patients died in ICU, no mortality in non-ICU patients, with ICU mortality rate 86% and overall mortality rate 43%. E. Mean (SD) HbA1c 7.5% (1.2) in non-ICU and 7.3% (0.9) in ICU, p=0.70. F. Mean (SD) RBG 13.7 (5.1) in ICU vs 9.8 (3.4) in ICU patients, P=0.03.
Yan Y, et al. Retrospective observational, China.	193 patients with severe COVID-19, 48 with diabetes mellitus.	Patients with compared to those without diabetes were: A. Significantly older, median (IQR) age 70 (62-77) vs 64 (49-73) years, p<0.001. B. Have more comorbidities (60.4% vs 44.8%, p=0.06), hypertension (50% vs 33.8% < p=0.45), CVD (27.1% vs 12.4, p=0.016, cerebrovascular disease (10.4% vs 2.1%, p=0.036). C. Have significantly more ICU admission (66.7% vs 41.4%, p=0.002). D. Required more mechanical ventilation (81.3% vs 49%, p<0.001). E. Significantly higher mortality (81.3% vs 47.6%, p<0.001). F. Median (IQR) HbA1c 7.2% (6.7-8.3) vs 5.8% (5.5-6.1), p<0.001.

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Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]	Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]	Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]
Chen Y, et al. Retrospective observational, China.	Total 904 patients with COVID-19, 136 with diabetes mellitus.	A. Patients with were significantly older than those without diabetes (66 vs 56 years, p<0.001), had more history of hypertension (61.2% vs 32.5%, p<0.001) and higher HbA1c (7.3% vs 5.9%, p<0.001). B. Risk factors for higher mortality of patients with diabetes were older age (adjusted OR 1.09, 95% CI 1.04 to 1.15) per year increase; P=0.001) and elevated CRP (1.12, 1.0 to 1.24, P=0.043). C. Insulin usage was associated with poor prognosis defined as progression to severe or critical illness (OR 3.58, 95% CI 1.37 to 9.35, P=0.009) but not with mortality. D. ACEI or ARBs use had no impact on outcomes.
Holman N, et al National diabetes and mortality data, England	265,090 people with type 1 and 2,889,210 with type 2 diabetes, all covid-19 positive.	A. Mortality rate 0.16% in type 1 and 0.32% in type 2 diabetes. B. Adjusted mortality HR of HbA1c >86 mmol/mol compared to HbA1c 48-53 mmol/mol 2.19 (95% CI 1.46 to 3.29) for type 1 and 1.62 (1.48 to 1.79) for type 2 diabetes. C. U-shaped relation between BMI and mortality, HRs for BMI >40 kg/m2 compared to 25-29.9 kg/m2 2.15 (95% 1.37 to 3.36) and 1.46 (1.50 to 1.79) for type 1 and type 2 respectively.

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Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]	Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]	Table 2: Main studies reporting characteristics of patients with diabetes and COVID-19 [14-19]
Cariou B, et al nationwide 53 centres, observational, France	1,317 hospitalised patients with covid-19 and diabetes, primary outcome mechanical ventilation and/or death within 7 days of admission.	A. Mean (SD) age 69.8 (13.0) years, 64.9% men, median BMI 28.4 (25th-75th percentile 25.0-32.7) kg/m^2, type 2 diabetes (88.5%). B. Microvascular and macrovascular diabetic complications 46.8% and 40.8%, respectively. C. Primary outcome encountered in 29.0% (95% CI 26.6 to 31.5), mortality 10.6% (9.0 to 12.4), 18.0% (16.0 to 20.2) discharged on day7. D. In multivariable analyses, only BMI positively associated with primary outcome (OR 1.28, 95% CI 1.10 to 1.47). E. Age (OR 2.48, 95% CI 1.74 to 3.53), treated obstructive sleep apnoea (2.80, 1.46 to 5.38), microvascular (2.14, 1.16 to 3.94) and macrovascular complications (2.54, 1.44 to 4.50) were independently associated with mortality risk on day 7.
Bode B, et al retrospective observational US	Total 1,122 patients in 88 US hospitals, 451 with diabetes or uncontrolled hyperglycaemia.	A. mortality rate 28.8% in 184 diabetes and/or uncontrolled hyperglycemia patients, compared to 6.2% of 386 patients without diabetes or hyperglycemia (*P* <0.001). B. Mortality rate 41.7% in uncontrolled hyperglycaemia and 14.8% in diabetes patients, p<0.001. C. LOS was longer in patients with uncontrolled hyperglycaemia or diabetes compared to those without (5.7 vs 4.3 days, p<0.001).

SD=Standard deviation, CVD=Cardiovascular disease, ICU=Intensive care unit, IQR=Inter quartile range, CRP=C-reactive protein, OR=Odds ratio, CI=Confidence interval, ACEI=Angiotensin converting enzyme inhibitors, ARBs=Angiotensin receptor blockers, HR=Hazard ratio, BMI=Body mass index, LOS=Length of stay.

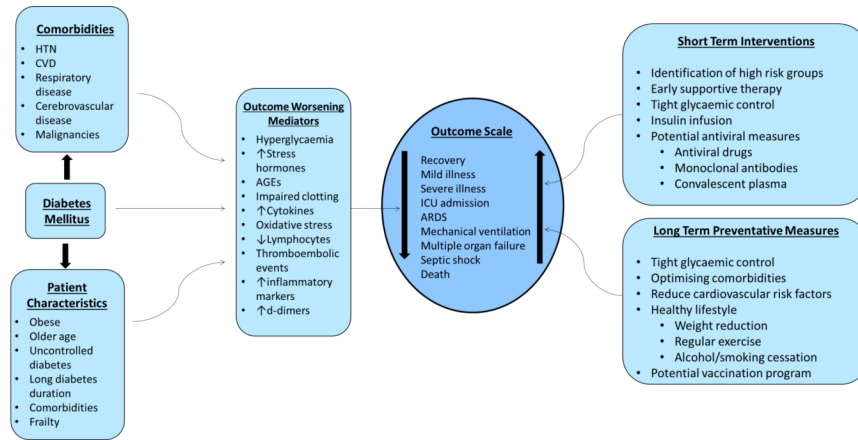| **Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19** 20-33	**Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19** 20-33	**Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19** 20-33
Study	**Population**	**Main findings**

Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 [20-33]	Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 [20-33]	Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 [20-33]
Wang D, et al Retrospective case series China	138 hospitalized patients with COVID-19	A. 102 (73.9%) patients admitted to isolation wards, and 36 (26.1%) admitted to ICU because of organ dysfunction. B. Patients admitted to ICU were significantly older, median (IQR) age 66 (57-78) years vs 51 (37-62) years, P < 0.001), more likely to have hypertension (58.3%) vs (21.6%), diabetes (22.2%) vs (5.9%), CVD (25.0%) vs (10.8%) and cerebrovascular disease (16.7%) vs (1.0%) compared to those who were not in ICU.
Chinese CDC, Cross sectional analysis.	44,672 confirmed cases of COVID-19	A. Total 1,023 deaths occurred, crude fatality rate 2.3%. B. Crude fatality rate of patients with no comorbidities 0.9%. C. Fatality rate of patients with comorbidities 10.5% for CVD, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension and 5.6% for cancer.
Zhou F, et al Retrospective, multicentre, China	191 patients hospitalised with COVID-19	A. 54 (28%) patients died in hospital. B. In univariable analysis, odds of in-hospital death was higher in patients with diabetes (OR 2.85, 95% CI 1.35 to 6.05) or coronary heart disease (21.1, 4.64 to 98.76).
Roncon L, et al, Data base analysis Italy	1,382 patients hospitalised for COVID-19	A. Mean age 51.5 years, 58% men. B. Patients with diabetes had a significantly higher risk for ICU admission (OR 2.79, 95% CI 1.85 to 4.22, p < 0.0001) and mortality (3.21, 1.82 to 5.64, p < 0.000).
Chen Y, et al. Data base analysis China	1,936 patients with COVID-19.	There were significant correlations between COVID-19 severity and hypertension (OR 2.3, 95% CI 1.76 to 3.00, P<0.01), diabetes (67, 1.91 to 3.74, P<0.01), coronary heart disease (2.85, 1.68 to 4.84, P<0.01).

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Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 20-33	Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 20-33	Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 20-33
Bo L, et al. Data analysis China	1,527 patients with COVID-19.	A. Proportions of hypertension, CCVD and diabetes were 17.1%, 16.4% and 9.7%, respectively. B. Incidences of hypertension, CCVD and diabetes were twofold, threefold and twofold, respectively higher in ICU/severe cases compared to non-ICU/severe counterparts. C. Diabetes accounted for 11.7% of ICU/severe cases and 4.0% of non-ICU/severe cases, RR 2.21, 95% CI 0.88 to 5.57, P = 0.09>
Guan WJ, et al. Retrospective China	1,099 patients with COVID-19.	A. 81 (7.4%) of patients had diabetes. B. Primary composite end point of admission to ICU, mechanical ventilation or death occurred in 26.9% of patients with diabetes, only second to hypertension (35.8%).
WU C, et al Retrospective China	201 patients with COVID-19.	A. 41.8% of patients developed ARDS. B. Patients with compared to those without ARDS, had comorbidities such as hypertension (27.4% vs 13.7%, difference 13.7%, 95% CI 1.3% to 26.1%) and diabetes (19.0% vs 5.1%, difference 13.9%, 95% CI 3.6% to 24.2%).
Yang X, et al Retrospective China	52 critically ill patients with COVID-19.	A. 98% had chronic illness. B. 61.5% died at 28 days. C. Top comorbidities among non-survivors were diabetes (22%) and CVD (22%).
Yuan M, et al Retrospective China	27 patients with COVID-19.	A. 10 patients died in hospital. B. Patients who died were significantly older (median age 68 vs 55 years, p=0.003), had more comorbidities (80% vs 29%, p=0.02), diabetes (60% vs 0%, p=0.001), hypertension (50% vs 0%,p=0.003) and CVD (30% vs 0%, p=0.04).

Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 20-33	Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 20-33	Table 3: Main studies reporting diabetes as adverse outcome risk for COVID-19 20-33
Yang J, et al Data analysis China	1,576 patients with COVID-19.	Significant comorbidity differences between severe and non-severe group were hypertension (OR 2.36, 95% CI 1.46 to 3.83), respiratory disease (2.46, 1.76 to 3.44), CVD (3.42, 1.88 to 6.22) but diabetes was not statistically significant (2.07, 0.89 to 4.82).
Shabto JM, et al Retrospective, US	65 DM and COVID-19 patients	Telemedicine outpatient follow up showed the rate of hospitalisation for patients with diabetes double (10.2%) that of other patients (5.1%).
Zhang Y, et al Retrospective China	258 (63 with diabetes) hospitalised COVID-19 patients.	A. Median age 64 years (range 23-91). B. Patients with diabetes were more likely to develop severe disease, more complications, mechanical ventilation and death (11.1% vs. 4.1%). C. Diabetes (aHR 3.64, 95% CI 1.09 to 12.21) and fasting blood glucose (1.19, 1.08 to 1.31) were associated with the fatality.
Williamson E, et al Data base analysis, UK	17,425,445 NHS registered adults.	A.5683 died of COVID-19. B. Uncontrolled diabetes (HbA1c>+7.5%) increased risk of death (HR 2.36, 95% CI 2.18 to 2.56).

ICU=Intensive care unit, IQR=Inter quartile range, CVD=Cardiovascular disease, CDC=Centre for disease control, OR=Odds ratio, CI=Confidence interval, CCVD=Cardio-cerebrovascular disease, RR=Relative risk, ARDS=Acute respiratory distress syndrome, aHR=Adjusted hazard ratio, NHS=National Health Service.

Comorbidities
- HTN
- CVD
- Respiratory disease
- Cerebrovascular disease
- Malignancies

Diabetes Mellitus

Patient Characteristics
- Obese
- Older age
- Uncontrolled diabetes
- Long diabetes duration
- Comorbidities
- Frailty

Outcome Worsening Mediators
- Hyperglycaemia
- ↑Stress hormones
- AGEs
- Impaired clotting
- ↑Cytokines
- Oxidative stress
- ↓Lymphocytes
- Thromboembolic events
- ↑inflammatory markers
- ↑d-dimers

Outcome Scale
Recovery
Mild illness
Severe illness
ICU admission
ARDS
Mechanical ventilation
Multiple organ failure
Septic shock
Death

Short Term Interventions
- Identification of high risk groups
- Early supportive therapy
- Tight glycaemic control
- Insulin infusion
- Potential antiviral measures
  - Antiviral drugs
  - Monoclonal antibodies
  - Convalescent plasma

Long Term Preventative Measures
- Tight glycaemic control
- Optimising comorbidities
- Reduce cardiovascular risk factors
- Healthy lifestyle
  - Weight reduction
  - Regular exercise
  - Alcohol/smoking cessation
- Potential vaccination program

Figure 1: The effect of diabetes mellitus, patient characteristics, common comorbidities and the potential therapeutic interventions on the outcome of COVID-19. HTN=Hypertension, CVD=Cardiovascular disease.

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