Stephen Smith ORCID iD: 0000-0002-9158-6136

Adam Brufsky ORCID iD: 0000-0001-8080-7960

Impaired glucose metabolism in patients with diabetes, prediabetes and obesity is associated with severe Covid-19

Running title: Association of severe Covid-19 with diabetes & obesity

Stephen M. Smith, MD[1], Avinash Boppana[1], Julie A. Traupman[1], Enrique Unson[1], Daniel A. Maddock[1], Kathy Chao[1], David P. Dobesh, MD[2], Adam Brufsky, MD, PhD[3], Ruth I. Connor, PhD[4]

[1]The Smith Center for Infectious Diseases and Urban Health, East Orange, New Jersey

[2]Saint Barnabas Medical Center, RWJBarnabas Health, Livingston, New Jersey

[3]UPMC Hillman Cancer Center, Magee-Women's Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania

[4]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Corresponding Author:

Stephen M. Smith, M.D.

The Smith Center for Infectious Diseases and Urban Health

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jmv.26227.

310 Central Avenue, Suite 307

East Orange, NJ 07018

USA

Phone: 973-809-5566

Email: ssmith1824@gmail.com

Keywords: COVID-19, SARS-CoV-2, diabetes mellitus, obesity, hyperglycemia, glucose metabolism disorder

Conflicts of Interest: All authors report no potential conflicts of interest.

Authors' contributions: S.M.S., A.B. and R.I.C. designed the study. S.M.S. and A.B. performed the statistical analyses and interpretations. J.A.T., A.B., E.U., D.A.M., K.C. and D.P.D. collected, organized, and contributed to interpretion of the data. S.M.S. and R.I.C. were in charge of overall direction and planning.

ABSTRACT

Background: Identification of risk factors of severe Covid-19 is critical for improving therapies and understanding SARS-CoV-2 pathogenesis.

Methods: We analyzed 184 patients hospitalized for Covid-19 in Livingston, New Jersey for clinical characteristics associated with severe disease.

Results: The majority of Covid-19 patients had diabetes mellitus (DM) (62.0%), Pre-DM (23.9%) with elevated FBG, or a BMI > 30 with normal HbA1C (4.3%). SARS-CoV-2

infection was associated with new and persistent hyperglycemia in 29 patients, including several with normal HbA1C levels. Forty-four patients required intubation, which occurred significantly more often in patients with DM as compared to non-diabetics.

Conclusions: Severe Covid-19 occurs in the presence of impaired glucose metabolism in patients, including those with DM, PreDM and obesity. Covid-19 is asociated with elevated FBG and several patients presented with new onset DM or in DKA. The association of dysregulated glucose metabolism and severe Covid-19 suggests that SARS-CoV-2 pathogenesis involves a novel interplay with glucose metabolism. Exploration of pathways by which SARS-CoV-2 interacts glucose metabolism is critical for understanding disease pathogenesis and developing therapies.

INTRODUCTION

SARS-CoV-2, the causative agent of coronavirus disease 2019 (Covid-19) was first detected in late December 2019 in Wuhan province in China and rapidly spread across the globe [1]. To date over 8.1 million cases of Covid-19 have been reported worldwide with approximately 2.1 million cases in the United States and 116,862 deaths [2,3].

Early reports from China and later Italy examined risk factors for severe Covid-19 and identified advanced age as a major indicator for increased mortality [4,5]. A recent study of over 4,000 patients with confirmed Covid-19 in the United States found older age (>65 years), obesity (BMI >40), chronic kidney disease and a history of heart failure were most associated with hospitalization, while critical illness was linked to low oxygen saturation (<88%) at admission, first d-dimer (>2500), first ferritin (>2500) and first C-reactive

protein (>200) indicating hypoxia and inflammation in patients with clinically progressive disease [6].

A number of studies have identified an increased risk of severe disease in Covid-19 patients with underlying health conditions. Data compiled by the COVID-19 Associated Hospitalization Surveillance Network (COVID-NET) identified hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (DM) (28.3%) and cardiovascular disease (27.8%) as the most commonly found co-morbidities among hospitalized Covid-19 patients in the United States [3]. A recent study of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19 found 13% of patients had DM, reinforcing early observations that diabetes is a risk factor for more severe disease [7]. This is supported by data from a study of 24 patients hospitalized for Covid-19 in nine Seattle-area hospitals in which 58% of critically ill patients had DM and an average BMI of 33 [8]. Interestingly, in the 2003 SARS-CoV outbreak in China, hyperglycemia and DM were also noted as risk factors for mortality and morbidity [9]. These observations and several in-depth reviews [10–12] have raised concerns that diabetics with elevated fasting blood glucose are at increased risk of developing severe Covid-19.

We report here our experience of 184 patients admitted for Covid-19 to a teaching hospital in Livingston, New Jersey within the epicenter of the SARS-Cov-2 pandemic in the United States. Extending early observations, we find the vast majority of our Covid-19 patients are diabetic, prediabetic or obese. Moreover, we identify Covid-19 patients with PreDM and others with normal HbA1C levels who developed new onset DM, similar in presentation to Type 1 DM, coincident with recent acquisition of SARS-CoV-2 infection.

Our data establish that impaired glucose metabolism, due to either DM or obesity, is significantly associated with severe Covid-19 in this high-risk population.

METHODS

Study Population

Patients with Covid-19 were referred to our practice by the Emergency Medicine department or admitting physician at a large suburban hospital (Saint Barnabas Medical Center, Livingston, New Jersey). Consecutive admission of 184 Covid-19 patients occurred over a period of seven weeks (March 16, 2020 to May 2, 2020) and all patients received care through our practice. A diagnosis of Covid-19 was made on the basis of a confirmed positive laboratory test for SARS-CoV-2 in 177 patients. The remaining patients were diagnosed based on clinical presentation including new onset hypoxia, increased LDH, increased D-dimer, increased ferritin and elevated blood glucose. All patients were included in the analysis for this study. Ethical approval for the study was granted by the Institutional Review Board of St. Barnabas Medical Center.

Diabetes Status

A high percentage of patients testing positive for SARS-CoV-2 and referred to our practice were already known diabetics and receiving treatment for DM at the time of admission. We used the ADA definitions to diagnose DM, New Onset DM and PreDM [13]. A new diagnosis of DM was made in patients previously unaware of their condition based on an HbA1C >6.4%. New onset DM was defined by persistently elevated fasting blood glucose (FBG) > 125 mg/dL and requiring insulin therapy. Prediabetes (PreDM) was

defined by an HbA1C of 5.7 - 6.4%. Non-diabetic patients were defined as having an HbA1C < 5.7% and FBG ≤ 125 mg/dL. Fever was defined as Tmax ≥100°F during the first 6 hrs after admission. Hypoxia was defined as room oxygen saturation <94%.

Outcomes

The primary indicator of severe Covid-19 was intubation. The need for intubation was determined on the basis of clinical presentation in patients receiving full care throughout their hospitalization. Death during hospitalization included patients put on comfort care at any time during or after admission. Comfort care measures were determined by the primary attending physician and included but were not limited to morphine drips or intensive care without further escalation of care. We developed a simple, scoring system for outcomes, based up a patient's diabetes status, BMI, A1C, Age and initial blood glucose level. For details, please see Supplemental Information.

Statistical Analyses

A one-sample proportion Z-test was used to determine the prevalence of DM, PreDM, and NonDM in Covid-19 patients as compared to the US population. The sample size used for this analysis was 184 with at least 10 patients in each DM status. One-sided hypothesis tests were used to determine if the proportions of Covid-19 patients with DM and PreDM were larger than the U.S. population proportions, and if the proportion of NonDM patients was smaller than the U.S. population proportion. A chi-squared test was used to determine significance between intubation and diabetes status within each patient group. 95% confidence intervals were calculated using standard errors. Statistical

significance was defined as a P-value < 0.05. All statistical analyses were performed using R version 3.4.4.

RESULTS

Demographic and clinical characteristics of the patients

During a seven-week period, 184 patients were admitted to the hospital for Covid-19 and referred to our practice. The average age of study patients was 64.4 years (range: 21-100 yrs.) with 86 (46.7%) females and 98 (53.3%) males (Table 1). The racial and ethnic composition of the study population was black (53.8%), white (25.5%), Latino (6.5%) and Asian (6.0%). Clinical presentation at the time of admission included hypoxia (83.7%) and fever (62.5%) (Table 1). Hypoxia and fever occurred together often (48.9%); only a small percentage (7.6%) of patients presented without fever or hypoxia. In addition to DM, as described herein, the most common preexisting conditions included hypertension (60.3%), hyperlipidemia (33.7%), dementia (13.0%),chronic kidney disease (13.0%) coronary artery disease (12.0%), and congestive heart failure (10.9%) (Table 1).

Increased prevalence of diabetes, pre-diabetes and obesity

The majority of Covid-19 patients had DM (62.0%), PreDM (23.9%) or BMI > 30 with normal HbA1C (4.3%). The prevalence of DM was 4.7-fold higher in this patient group as compared to the general US population, while the prevalence of PreDM was 1.3-fold higher [14]. A significant number of patients were clinically obese. The mean BMI of the study patients was 29.8 (17.5- 61.4), including 20 patients with BMIs > 40. HbA1C

levels measured at admission in 171 patients also showed significant elevation with 64 patients (37.4%) having values between 5.7-6.4% and 82 (48.0%) having values ≥ 6.5%.

Age relationship to BMI, HbA1C and initial blood glucose level

To determine whether patient age was associated with differences in clinical presentation, data on BMI, HbA1C and initial FBG were stratified by age at admission. The rates of DM and PreDM were similar in patients ≤60 yrs as compared to those > 60 yrs (Table 2) as were mean initial FBG levels (200.5 vs 165.4 mg/dL). However, patients ≤60 years of age were significantly more likely to be clinically obese. As compared to patients >60 yrs, the frequency of obesity and the mean BMI in those ≤60 yrs were significantly higher (26.6% vs 65.3% and 27.2 vs 33.4, respectively; $p < 0.0001$) (Table 3). Patients ≤ 60 yrs were also significantly more likely to be severely obsese with a BMI>40 (20.0% vs 3.7%, p = 0.0013). Similarly, patients ≤ 60 yrs had a significantly higher mean HbA1C level than older patients (8.0 vs 6.9%; $p = 0.003$) suggesting more pronounced metabolic dysregulation in younger patients. Taken together, these data indicate that younger patients may be more likely to present with abnormalities in glucose metabolism due to obesity, which may put them at increased risk of developing severe Covid-19. These findings are consistent with a recent report of 265 Covid-19 patients demonstrating a significant inverse correlation of age and BMI in which younger patients hospitalized for Covid-19 were more often obese [15].

Association of obesity and uncontrolled glycemia with intubation

Intubation was evaluated as an indicator of Covid-19 progression and severity in hospitalized patients. To determine whether higher rates of intubation were associated

with uncontrolled glycemia, data on BMI, HbA1C and FBS were evaluated for intubated patients and compared to their non-intubated counterparts. Among 184 hospitalized patients receiving full care for Covid-19, 44 (23.9%) required intubation. The mean BMI of patients requiring intubation was significantly higher than that of non-intubated patients (32.3 vs 29.3; *p = 0.030*; 95% C.I. = 0.3-5.8). More strikingly, patients with a BMI > 40 were intubated at a significantly higher rate than patients with BMIs < 25 (47.4 vs 15.6%; *p = 0.0078*).

HbA1C levels were available for 41 intubated patients and revealed only four (9.8%) had normal values. Of these, three were known to be diabetic and receiving treatment for DM. In total, 40 of 41 (97.6%) intubated patients had either elevated HbA1C or were receiving therapy for DM. As compared to patients not requiring intubation, the mean HbA1C of intubated patients was significantly higher (8.0 vs 7.2%; *p = 0.034*; C.I. = 0.07-1.67). Accordingly, the rate of intubation among patients with poorly-controlled DM (HbA1C ≥7.5%) was significantly higher than that of patients with HbA1C < 7.5% (31.5 vs 17.8%; *p = 0.045*). The mean FBG at admission for intubated patients was also significantly increased when compared to that of patients not requiring intubation (238.0 vs 163.7 mg/dL; *p = 0.013*; C.I. = 9.02-135.9) suggesting that uncontrolled glycemia, due to obesity or DM, is a significant risk factor for severe Covid-19.

Intubation rate increases in Non-DM, PreDM and DM patients

To determine whether Covid-19 severity was associated with diabetes status, patients requiring intubation were stratified as Non-DM, PreDM or DM. Determination of diabetic status was made on the basis of clinical presentation, HbA1C values and FBG

levels for all patients. The majority (35 of 44; 79.5%) of intubated patients had DM, including seven newly diagnosed and five with new onset DM. Another seven (15.9%) were PreDM with high FBG levels. Only one patient requiring intubation was non-DM with normal HbA1C and FBG levels at admission, but was clinically obese with a BMI > 30.

Within the entire Covid-19 patient cohort, diabetes status was also associated with increasing rates of intubation. Among 25 patients with no diabetes and normal HbA1C levels, only one (4.0%) required intubation. Of patients with preDM, 18.5% (10 of 54) were intubated, while 28.85% (30 of 104) of patients with DM required intubation. Comparison of intubation rates demonstrated a significant difference between non-DM patients (4.0%) and those with DM (difference = 24.85%; $p = 0.0093$: C.I. = 7.4-34.8%). These findings again suggest that changes in glycemia occurring with the onset and progression of diabetes are associated with a corresponding increase in the likelihood of severe Covid-19 requiring intubation.

Twenty-four patients died without intubation. The average age of these patients was 80.5 yrs (range 45-100 yrs) and the majority were put on comfort care with DNR orders in place. Among these patients 17 (70.8%) had DM, four (16.7%) were PreDM and three (12.5%) were nonDM.

We developed a simple scoring system, the Smith Center Covid-19 Severity Score, based upon age, diabetes status, BMI, A1C level and initial blood glucose level. 169 of the 184 patients had all needed measurements. For details see the supplemental data. 111 of the 169 lived and were never intubated; 58 patients were intubated and/or expired; 44

patients expired (with or without prior intubation). The minimum and maximum total scores are 0 and 25. The mean scores for the alive, never intubated, intubated and/or expired and expired groups were 10.2, 13.1, and 13.4 respectively. The differences between the alive/never intubated group and the other two groups were statisticially significant with p-values < 0.0001. More importantly, 31 patients had a SCCSS <=7, 30 had a good outcome; the other patient, who has end-stage renal disease, was intubated and lived; none died. A screening system, such as the SCCSS, might be useful in triaging patients, especially in resource limited areas.

Covid-19 associated hyperglycemia

Obesity, PreDM and DM are typically associated with elevated blood glucose levels. We found blood glucose was increased in the majority of Covid-19 patients at admission with a mean of 179.9 mg/dL. For most patients, these values were obtained after fasting. The presenting FBGs were markedly elevated in many Covid-19 patients and 15 (10.2%) had FBG levels > 350 mg/dL on admission; four were in diabetic ketoacidosis.

While transient increases in blood glucose may be due to stress and more prolonged elevations can occur during treatment with corticosteroids, we found 23 of 54 (45.6%) Covid-19 patients with PreDM had persistently and markedly elevated FBG in the absence of corticosteroid therapy. Similarly, six patients without DM and with normal HbA1C levels also had repeatedly elevated FBG. Together, these 29 patients had FBG levels consistent with new onset DM and temporally associated with recent acquisition of SARS-CoV-2 infection. These findings support the possibility of direct dysregulation of

glucose metabolism due to a newly acquired viral infection and point to an increased likelihood of developing severe Covid-19 in these high-risk patients.

DISCUSSION

Identifying risk factors for development of severe Covid-19 in patients hospitalized with SARS-2-CoV is imperative for informing clinical decisions around patient care. Initial reports of Covid-19 from countries impacted early in the pandemic showed a strong association between older age and risk of Covid-19 mortality [4,5]. Data now emerging from the United States, which has the highest number of Covid-19 cases globally to date, has demonstrated increased incidence of severe Covid-19 in patients with co-morbid conditions including hypertension, obesity and diabetes. These findings have important implications for managing the clinical course of Covid-19 in severely ill patients and further understanding the pathophysiology of this disease.

Our single-center, consecutive series study of 184 patients with Covid-19 demonstrates several important findings. The majority of patients who developed moderate or severe Covid-19 had DM or preDM based on their HbA1C levels. Severe Covid-19, defined by the need for intubation, did not occur in the absence of DM, whether pre-existing or newly diagnosed, PreDM or obesity. Our data also establish that SARS-CoV-2 infection significantly worsens hyperglycemia in patients with glucose metabolism problems.

Our data in patients with severe Covid-19 and DM are consistent with a recent report by Bhatraju and colleagues [8]. In both studies, 58-62% of patients severely ill with Covid-19 were diabetic with mean BMIs >30 and the majority had elevated blood glucose.

Additionally, we found 24% of patients with moderate-severe Covid-19 in our study were prediabetic. Taken together these data suggest that insulin resistance and uncontrolled glycemia play a significant role in worsening Covid-19. In all critically ill Covid-19 patients, blood glucose levels were elevated and tight glycemic control may therefore be an important consideration for improving clinical outcomes.

Several studies on Covid-19 patients have reported on diabetes as a pre-existing diagnosis. In two recent observational studies, ~36% of Covid-19 patients were diabetic [16,17]. These studies relied on passive surveillance at the time of admission. Similarly, 42.9% of our patients were known diabetics at the time of admission. However, we specifically reviewed prior medical records to ascertain each patient's diabetes status. Further, we diagnosed an additional 17.1% during this admission. Most studies have not reported on prediabetes, a recognized syndrome with impaired glucose metabolism. By measuring HbA1C levels in every patient, we diagnosed 20.4% with prediabetes. Because of active surveillance, our data diabetes and prediabetes are replete and accurate. We have seen several non-diabetic Covid-19 patients with persistently high FBG levels.

Binding of ACE2 by SARS-CoV-2 in COVID 19 also suggests that prolonged uncontrolled hyperglycemia, and not just a history of diabetes mellitus, may be important in the pathogenesis of the disease [18]. A known history of diabetes (DM) and ambient hyperglycemia were found to be independent risk factors for morbidity and mortality in SARS [9]. In a follow-up analysis of 135 patients, high fasting plasma glucose was an independent predictor of SARS mortality [19]. Diabetes was found in 7.4% of a cohort of hospitalized COVID 19 patients and appeared to be a risk factor for severity of disease [20].

Mortality of COVID 19 in patients with diabetes was found to be 7.6% versus 0.9% in patients with no co-morbidities [4].

A possible explanation for a link between hyperglycemia and ACE2 levels in the severity of COVID 19 disease could be explained by several clinical observations in SARS and preclinical observations in the NOD diabetic mouse. Potential changes in glycosylation of the ACE2, as well as glycosylation of the viral spike protein, both possibly induced by uncontrolled hyperglycemia, may alter both the binding of the viral spike protein to ACE2 and the degree of the immune response to the virus.

In a subset of 39 patients who had no prior diabetes, received no steroid treatment during hospitalization, and who survived SARS, fasting plasma glucose (FPG) levels during hospitalization were found to decrease before discharge [19]. Twenty of these 39 (51%) patients had diabetes during hospitalization [19], and at three years of follow-up only 2/39 (5%) did. This suggests a mechanism of transient hyperglycemia induced by a transient inflammation of the islet cells of the pancreas by SARS-CoV through binding of SARS-CoV to the ACE2 present on islet cells, resulting in a transient insulin dependent diabetes mellitus, which resolved with resolution of disease [19].

ACE2 protein levels in the lung of NOD diabetic mouse were elevated when compared to control mice and returned to the control level when insulin was administered [21]. Glycemic control could reduce levels of glycosylated ACE2 in the lung, possibly reducing the number of viral binding sites, and possibly ameliorate some of the inflammation and symptoms of COVID 19 disease. A possible paracrine loop hypothesis for COVID 19 infection is suggested, where the virus infects the pancreas and lung,

leading to hyperglycemia and upregulation of ACE2 in the lung, and further virus binding and inflammation. Poor glycemic control could therefore make the disease more severe. In a case series of 138 COVID 19 patients, glucocorticoid therapy was used in 44.9% of non-ICU patients and 72.2% of ICU patients [22], and presumably this glucocorticoid use made hyperglycemia, and possibly clinical symptoms, more severe.

Aberrently glycosylated ACE2 in the lung, nasal airways, tongue, and oropharynx in uncontrolled hyperglycemia could increase SARS-CoV-2 viral binding sites, thus leading to a higher propensity to COVID 19 infection and a higher disease severity.

If true, this argues for better glycemic control in patients with pre-diabetes and diabetes as a potential mechanism to slow COVID 19 spread and reduce the severity of symptoms. Additionally, since 3.8% of the American population without a history of diabetes or pre-diabetes has a hemoglobin A1c over 6.1% in random sampling [23], use of high A1c as a risk stratification for COVID 19 could have merit.

Clinically, SARS-CoV-2 appears to cause new or worsening hyperglycemia, which may lead to more severe pneumonia. In our experience, a tipping point is reached in Covid-19 patients who have symptoms lasting anywhere from two days to over three weeks and the disease then “takes off”. Hospitalization before this acceleration can reduce the rate of critical illness.

It is important to note that our study has several limitations. Patients were seen at a single clinical site and cared for by one group of clinicians. While it is possible our study population is disproportionately weighted towards patients with poor underlying health, the Covid-19 patients in this study were consecutive referrals to our service over the

course of seven weeks in a suburban hospital. It is, therefore, unlikely that a selection bias exists, except for the criteria used by the admitting physicians. Diabetes itself was not considered a criterion for referral.

Given the urgency of finding solutions to this present crisis, our findings may assist in prognostication and triage decisions. Our data shed light on the impact of DM, preDM and uncontrolled hyperglycemia in driving severe Covid-19 and will facilitate identification of novel pathogenesis pathways associated with SARS-CoV-2 infection. This, in turn, may lead to new approaches to therapeutic intervention. Our data currently support the use of tight glycemic control in patients with hyperglycemia. Tight glycemic control was associated with a decrease in mortality (HR 0.14 CI 0.06-0.60, p=0.008) as well as a decrease in ARDS (HR 0.47, CI 0.27-0.83, p=0.009) in an observational study of 500 propensity score matched COVID-19 patients [24]. Our observations are also in line with the WHO recommendation that corticosteroids not be used for COVID-19 pneumonia.

Finally, our findings caution that Covid-19 patients with DM, PreDM or obesity should be monitored closely. Those not infected should be particularly careful to avoid exposure to SARS-CoV-2. This information may be useful in healthcare and other settings to reduce the chances of infection in these high-risk individuals and, conversely, to help triage nonDM, normal glycemic Covid-19 patients safely and efficiently.

References:

1. MMWR Morbidity and Mortality Weekly Report. Centers for Disease Control and Prevention. https://www.cdc.gov/mmwr/index2020.html. Published 2020. Accessed

April 20, 2020.

2. Coronavirus Disease (COVID-19) Situation Reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Published 2020. Accessed May 19, 2020.

3. CDC. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Published 2020. Accessed March 31, 2020.

4. 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;395(10229):1054-1062. doi:https://doi.org/10.1016/S0140-6736(20)30566-3

5. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323(16):1574-1581. doi:10.1001/jama.2020.5394

6. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. *medRxiv*. April 2020:2020.04.08.20057794. doi:10.1101/2020.04.08.20057794

7. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. June 2020. doi:10.1056/NEJMoa2001282

8. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region — Case Series. *N Engl J Med*. March 2020.

doi:10.1056/NEJMoa2004500

9. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med*. 2006;23(6):623-628. doi:10.1111/j.1464-5491.2006.01861.x

10. Ma RCW, Holt RIG. COVID-19 and diabetes. *Diabet Med*. 2020;37(5):723-725. doi:10.1111/dme.14300

11. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr Clin Res Rev*. 2020;14(3):211-212. doi:10.1016/j.dsx.2020.03.002

12. Bloomgarden ZT. Diabetes and COVID-19. *J Diabetes*. 2020;12(4):347-348. doi:10.1111/1753-0407.13027

13. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2010;33(Suppl 1):S62 LP-S69. doi:10.2337/dc10-S062

14. CDC. National Diabetes Statistics Report. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html. Published 2020. Accessed March 31, 2020.

15. Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. *Lancet*. 2020;395(10236):1544-1545. doi:10.1016/S0140-6736(20)31024-2

16. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in

Hospitalized Patients with Covid-19. *N Engl J Med*. May 2020. doi:10.1056/NEJMoa2012410

17. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA*. May 2020. doi:10.1001/jama.2020.8630

18. Brufsky A. Hyperglycemia, Hydroxychloroquine, and the COVID-19 Epidemic. *J Med Virol*. April 2020. doi:10.1002/jmv.25887

19. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47(3):193-199. doi:10.1007/s00592-009-0109-4

20. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. February 2020. doi:10.1056/NEJMoa2002032

21. Roca-Ho H, Riera M, Palau V, Pascual J, Soler M. Characterization of ACE and ACE2 Expression within Different Organs of the NOD Mouse. *Int J Mol Sci*. 2017;18(3):563. doi:10.3390/ijms18030563

22. 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;323(11):1061-1069. doi:10.1001/jama.2020.1585

23. Selvin E, Zhu H, Brancati FL. Elevated A1C in Adults Without a History of Diabetes in the U.S. *Diabetes Care*. 2009;32(5):828 LP - 833. doi:10.2337/dc08-1699

24. Zhu L, She Z-G, Cheng X, Guo J, Zhang B-H, Correspondence HL. Clinical and Translational Report Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab*. 2020;31:1068-1077.e3. doi:10.1016/j.cmet.2020.04.021

Table 1: Demographic and clinical characteristics of Covid-19 patients.

Characteristic	**Patients**
Age	N=184
Ave- Years	64.4 (21-100)
Age - No. (%)	
≤60	75 (40.8)
>60	109 (59.2)
Gender - No. (%)	
Female	86 (46.7)
Male	98 (53.3)
Race and Ethnicity-No. (%)	

Black	99 (53.8)
White	47 (25.5)
Latino	12 (6.5)
Asian	11 (6.0)
Other	15 (8.2)
Presentation Values	
BMI - Ave (Range)	29.8 (17.5-61.4)
HbA1C - Ave % (Range)	7.4 (4.1-14.7)
Glucose - Ave mg/dL (Range)	179.9 (11-1129)
T ≥100°F - No. (%)	115 (62.5)
Hypoxia on room air - No. (%)	154 (83.7)
Preexisting Conditions	**No. (%)**
Hypertension	111 (60.3%)

Hyperlipidemia	62 (33.7%)
Dementia	24 (13.0%)
Chronic Kidney Disease	24 (13.0%)
Coronary Artery Disease	22 (12.0%)
Congestive Heart Failure	20 (10.9%)
Asthma	18 (9.8%)
Atrial Fibrillation	14 (7.6%)
Cancer	17 (9.2%)
COPD	12 (6.5%)
Cerebrovascular Accident	10 (5.4%)
Transplant, Renal	5 (2.7%)

Table 2: Diabetes status, obesity rate and HbA1C levels by age.

	Patients ≤60 yrs (N=75)	Patients >60 yrs (N=109)	*p-value*

DM (%)[1]	64.0	60.6	*0.38*
PreDM (%)[1]	24.0	23.9	*0.50*
NonDM (%)[1]	12.0	15.6	*0.32*
Mean FBG (mg/dL)[2]	200.5	165.4	*0.10*
Mean BMI[3]	33.4	27.2	*<0.0001*
BMI>30 (%)	65.3	26.6	*<0.0001*
BMI>40 (%)	20.0	3.7	*0.0004*
HbA1C (%)	8.0	6.9	*0.003*

[1]Percent of patients with DM, Diabetes Mellitus; PreDM, Pre-Diabetes; NonDM, Non-Diabetic

[2]FBG, Fasting Blood Glucose

[3]BMI, Body Mass Index

Table 3: Hyperglycemia and obesity in Covid-19 patients requiring intubation

	Intubated	Not Intubated	*p-value* (95% C.I.)
N (%)	44 (23.9)	144 (76.1)	

Mean BMI[1]	32.2	29.3	*0.030* (0.3-5.8)
Mean HbA1C (%)	8.0	7.2	*0.034* (0.07-1.67)
Mean FBG (mg/dL)[2]	238.0	163.7	*0.013* (9.02-135.9)

[1]BMI, Body Mass Index

[2]FBG, Fasting Blood Glucose