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The relationship between obesity, hemoglobin A1c and the severity of COVID-19 at an urban tertiary care center in New York City: a retrospective cohort study

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ABSTRACT

Objectives To determine if obesity and diabetes are risk factors for severe outcomes in COVID-19 and to compare patient outcomes in those two conditions.

Design Retrospective cohort study.

Setting Urban tertiary care center in New York City.

Participants 302 patients admitted in an inpatient setting, ≥18 years old, with a laboratory-confirmed diagnosis of COVID-19 via nasal PCR swab were randomly selected. Patients were separated into two cohorts based on their body mass index and hemoglobin A1c. 150 patients were placed in the non-obese, non-diabetic cohort and 152 patients were placed in the corresponding cohort (obesity alone, obesity and diabetes, and diabetes alone).

Measurements Primary outcomes were development of acute kidney injury, commencement of renal replacement therapy, aminotransferase elevation, troponin elevation, lactic acidosis, development of septic shock, use of vasopressors, presence of acute respiratory distress syndrome (ARDS) and intubation. The secondary outcomes were length of stay in days and mortality.

Results Patients with obesity and/or diabetes were more likely to develop ARDS (79 patients vs 57 patients, p<0.0001) and to be intubated (71 patients vs 45 patients, p=0.0031). Patients with obesity and/or diabetes were more likely to require vasopressors (60 patients vs 41 patients, p=0.0284) and to develop lactic acidosis (median 3.15 mmol/L, IQR 1.8 to 5.2 mmol/L, p=0.0432). When comparing patients with diabetes with and without obesity against patients with obesity alone, they were more likely to develop ARDS (87.5%, p=0.0305). Despite these findings, there was no difference in mortality.

Conclusions In patients hospitalised with COVID-19, those with obesity and/or diabetes were more likely to suffer severe complications, but had negligible differences in mortality. This highlights the importance of close monitoring of patients with these conditions and additional areas of research needed to explain the mortality findings.

Strengths and limitations of this study

- This article offers a detailed analysis of two commonly encountered comorbidities; it also provides novel findings by comparing and contrasting them, while offering new avenues of research to explain the mortality results.
- This study's designation of acute respiratory distress syndrome is limited, because not every patient had a recorded arterial blood gas.
- Patients who received sedation after being intubated often required the use of vasopressors, which confounds the use of this metric as a proxy for the development of septic shock.
- The use of body mass index in elderly patients is limited, as it underestimates the presence of excess body fat, due to changes in fat distribution that take place with the ageing process.
- Our study is limited by the presence of confounders such as age and other comorbidities, due to the large proportion of elderly patients hospitalised for the treatment of COVID-19 at our institution.

INTRODUCTION

COVID-19 was initially described in Wuhan, China, in December 2019.[1] The disease spread worldwide and the first documented case in the USA was reported on 31 January 2020, in Washington state.[1] New York City later became the epicenter of the pandemic and at the time of writing, it had over 226 280 confirmed cases with over 23 556 deaths.[2] As a region, New York City currently ranks seventh overall, globally, in terms of total deaths.[2] According to viral sequencing, the majority of cases in New York City originated from community spread within the USA as well as overseas, from Europe.[3]

Initial research studies identified diabetes and obesity as some of the most predominant comorbidities found in COVID-19 patients.[4] In a study of 5700 COVID-19 patients in the greater New York City metropolitan area, 41.7% had obesity and 33.8% had diabetes.[5] At the time this study was initiated, there was limited, preliminary data suggesting worse outcomes for COVID-19 patients with these comorbidities; however, despite their prevalence, data comparing and contrasting both of these conditions is lacking, and our study aimed to address these gaps in the literature.

The connection between obesity and diabetes with COVID-19 is related to the proinflammatory state caused by metabolic syndrome, as well as the dysregulated host response to the virus itself.[4] Adipose tissue is metabolically active and produces proinflammatory molecules, such as adipokines, which contribute to the chronic, low-grade inflammation found in patients with obesity.[6] Studies demonstrated that patients with obesity have higher levels of C reactive protein (CRP) and increased levels of proinflammatory cytokines, leading to additional recruitment of macrophages and further continuation of this proinflammatory process.[7] Diabetes, in addition to obesity, is also characterised by a proinflammatory state.[8] Patients with diabetes also have higher levels of CRP and levels of proinflammatory cytokines, such as interleukin 6 (IL-6), when compared to patients without diabetes.[8 9] IL-6, in particular, is one of the central cytokines implicated in COVID-19's 'cytokine storm,' which causes significant morbidity and mortality.[10]

SARS-CoV-2 avoids the host's initial innate immune response from interferon-I and interferon-III.[4 11] This causes the host to overproduce inflammatory chemokines in order to recruit cells such as monocytes, macrophages, dendritic cells and neutrophils to control viral replication.[4 11–16] This inappropriate immune response causes monocytes and macrophages to enter the lungs and produce proinflammatory cytokines such as IL-1β, 6, 8, tumour necrosis factor-α and additional chemokines to recruit more effector inflammatory cells.[4 11–16] This proinflammatory mechanism creates a positive feedback process causing a 'cytokine storm,' resulting in increasing levels of fluid, diminished gas exchange at the alveolar level, and subsequent acute respiratory distress syndrome (ARDS).[4 11–17] This process, in tandem with the already proinflammatory state caused by metabolic syndrome, allows SARS CoV-2 to cause severe morbidity and mortality in patients with diabetes and obesity.[4]

METHODS

This retrospective, single-institution cohort study used 302 patients that were selected at random out of an eligible pool of 643 patients, between 1 March and 1 June 2020. At the time the study was initiated, there were limited data available from similar studies, and the rate of severe hospitalisations in New York City was higher than the rest of the world (as it became the epicenter of the pandemic). Thus, there was not an adequate estimate of effect size for the study to be prior powered. However, the difference in disease severity was large enough that including all 643 patients would result in an overpowered study. Therefore, we estimated that a sample size of 150 patients per cohort would reflect the difference in disease severity with 80% power and alpha=0.05 using a Fisher's exact test. As a result, there were more patients to choose from, and a random sample of available patients was chosen to reach our powered sample size.

Randomization was conducted using SAS V.9.4. Eligible patients included in the study were aged ≥18 years old, had a confirmed COVID-19 diagnosis by a nasal PCR swab, and only included hospitalised patients. They were divided into two cohorts. Those with an hemoglobin A1c (HgbA1c) ≥6.5% and/or a body mass index (BMI) ≥30 kg/m^2 comprised one group (n=152 patients). Those with an HgbA1c <6.5% and a BMI <30 kg/m^2 were placed in the other group (n=150 patients). Diabetes was defined as having an HgbA1c ≥6.5% and obesity was defined as having a BMI ≥30 kg/m^2. One of the hypotheses of the study was that poor glycemic control is associated with worse outcomes for COVID-19 patients; therefore, we decided to group patients according to their HgbA1c and not their diabetic medical history. This simplified grouping of patients and allowed for a greater understanding of long-term glycemic control as a marker for the prognosis and degree of complications of COVID-19. In addition, it provided a laboratory value that confirmed the diagnosis of diabetes mellitus, instead of relying on documentation, which may not always be available—considering the challenges of healthcare literacy in the patient population served by our institution.

The primary outcomes measured were the sequelae of COVID-19, including the development of acute kidney injury (AKI), commencement of renal replacement therapy, aminotransferase elevation, elevation in levels of troponin, lactic acidosis, presence of septic shock, use of vasopressors, development of ARDS and the presence of intubation. The secondary outcomes were length of stay (LOS) in days and mortality.

AKI was defined by the by the Kidney Disease Improving Global Outcomes definition.[18] AKI was defined as a rise in serum creatinine by at least 0.3 mg/dL that occurred within 48 hours, or by an increase of at least 50% compared with baseline within the past 1 week, or a urine volume that is less than 0.5 mL/kg/hour for at least 6 hours.[18]

Baseline creatinine levels were recorded when available. Similar to AKI, levels of troponin were compared with a patient's baseline. A rise of ≥0.04 ng/mL was considered to be an elevation and was defined as an acute cardiac injury.

Sepsis was defined using Sepsis-2 criteria, which is mandated by the New York State Department of Health, for all New York hospitals.[19] Sepsis was, therefore, defined as having a source of infection and meeting ≥2 systemic inflammatory response syndrome criteria (temperature >38°C or <36°C; heart rate >90 beats per minute;

respiratory rate >20 breaths/min or alveolar carbon dioxide tension <32 mm Hg; white cell count >12× 10^9/L, <4 x 10^9/L or >10% neutrophil band count).[20]

Septic shock was defined by the Surviving Sepsis Guidelines.[21 22] This is sepsis with a lactate level >2 mmol/L, systolic blood pressure (SBP) less than 90 mm Hg or a SBP drop ≥40 mm Hg from baseline, which persists after adequate fluid resuscitation.

Elevated aminotransferase levels were defined as a rise in the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to five times the upper limit of normal, corresponding to an AST of 200 IU/L, and an ALT of 300 IU/L.

ARDS was diagnosed based on the following: acute onset, non-cardiac generated bilateral lung infiltrates noted with chest radiography, and a PF ratio (arterial oxygen tension/fractional inspired oxygen) less than 300 mm Hg. Patients without arterial blood gases (ABGs) were excluded because their PF ratios could not be calculated.

All categorical variables were summarised with frequency and percent, and groups were compared with Fisher's exact test. All continuous variables were checked for symmetry. Symmetry was not upheld; therefore, medians and IQRs were used to summarise the data. A Wilcoxon test was then used to determine group differences. Multivariate models that controlled for age, race and gender were performed and these factors did not affect the results of the study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Table 1 describes the results of the study. There were statistically significant findings with lactic acid levels, elevations in troponin, the presence

Table 1 Data summary

Variable	Value	Low BMI/HgbA1c n=150	High BMI/HgbA1c n=152	P value
Age (years)		73.5 (62–85)	67 (59–74.5)	0.0011
Gender	Male	96 (64%)	99 (65.13%)	0.9043
	Female	54 (36%)	53 (34.87%)	
Race	Asian	15 (10%)	19 (12.5%)	0.0405
	Black	16 (10.67%)	14 (9.21%)	
	White	96 (64%)	77 (50.66%)	
	Other/unk/Hisp	23 (15.33%)	42 (27.63%)	
Baseline creatinine (mg/dL)		0.9 (0.6–1.1)	0.8 (0.6–1.1)	0.2916
Baseline troponin (ng/mL)		0.02 (0.01–0.045)	0.03 (0.01–0.05)	0.2723
Max ALT (IU/L)		39 (21–105)	43 (27–86)	0.7753
Max AST (IU/L)		74 (39–141)	68 (38–120)	0.1991
Max creatinine (mg/dL)		1.9 (1–4.3)	1.6 (1–3.15)	0.7899
Max lactic acid (mmol/L)		2.4 (1.8–3.8)	3.15 (1.8–5.2)	0.0432
Max troponin (ng/mL)		0.08 (0.03–0.3)	0.04 (0.01–0.13)	0.0062
AKI	Yes	96 (64%)	99 (65.13%)	0.904
ARDS	Yes	57/103 (55.34%)	79/96 (82.29%)	<0.0001
Intubation	Yes	45 (30%)	71 (46.71%)	0.0031
Septic shock	Yes	44 (29.33%)	60 (39.47%)	0.07
Vasopressors	Yes	41 (27.33%)	60 (39.47%)	0.0284
Hemodialysis	Yes	27 (18%)	22 (14.47%)	0.4379
Aminotransferase Elevation	Yes	25 (16.67%)	6 (3.97%)	0.0003
Acute cardiac Injury	Yes	88 (64.71%)	72 (48%)	0.006
LOS (days)		9 (5–14)	9.5 (6–18)	0.1936
Expired	Yes	67 (44.67%)	70 (46.05%)	0.8182

Table 1: all categorical variables are summarised with n (%) and compared using the Fisher's exact test. All continuous variables were checked for symmetry and summarised with median and IQR range (25th–75th) then compared using the Wilcoxon rank sum test.
AKI, acute kidney injury; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BMI, body mass index; HgbA1c, hemoglobin A1c; LOS, length of stay.

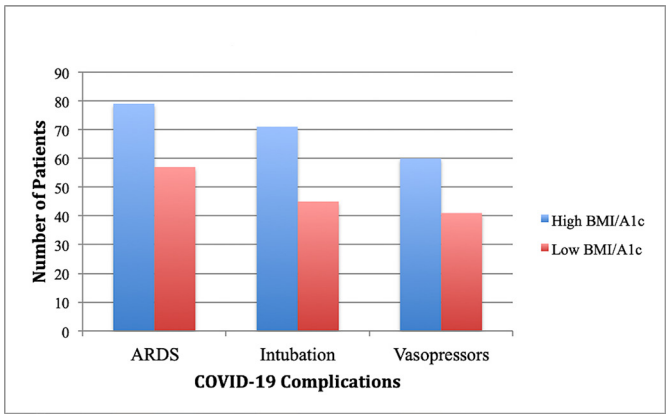

Figure 1 Describes statistically significant differences for the high BMI/HgbA1c group versus the low BMI/HgbA1c group in terms of the number of patients per COVID-19 complication. ARDS, acute respiratory distress syndrome; BMI, body mass index; HgbA1c, hemoglobin A1c.

of intubation, the use of vasopressors and elevations in aminotransferase levels.

Figure 1 describes statistically significant differences for the high BMI/HgbA1c group vs the low BMI/HgbA1c group in terms of the number of patients per COVID-19 complication.

Tables 2 and 3 describe subgroup analysis of the higher BMI/HgbA1c cohort in terms of severe respiratory complications of COVID-19 (intubation and ARDS). Statistically significant findings include a higher rate of ARDS in patients with diabetes with and without obesity compared with patients with obesity alone.

DISCUSSION

COVID-19 was associated with significant morbidity and mortality in hospitalised patients, according to the results of our study (table 1). Approximately 65% of patients in both cohorts developed AKI and 16% required renal replacement therapy. Approximately 34% of all the patients developed septic shock. Both cohorts had an LOS that averaged approximately 9–10 days. Mortality was also significant, as 67 patients in the low BMI/HgbA1c cohort expired (44.67%) and 70 patients in the high BMI/HgbA1c cohort expired (46.05%). Of note, males constituted 65% of the patients enrolled in the study.

Statistically significant differences for the low BMI/HgbA1c group included higher elevated levels of troponin (median 0.08 ng/mL, IQR 0.03 to 0.3 ng/mL, p=0.0062) and subsequent acute cardiac injury (64.71% vs. 48%, p=0.006). The low BMI/HgbA1c cohort also had a statistically significant, more frequent development of aminotransferase elevation (16.67% vs. 3.97%, p=0.0003). However, these results are limited, given the small number of total cases (31 patients) combined for both cohorts. In addition, the development of fulminant hepatic failure was rare; therefore, this finding was not clinically significant.

While the cohorts did not have statistically significant differences in terms of the development of septic shock, the higher BMI/HgbA1c group did have statistically significant differences in the development of lactic acidosis (median 3.15 mmol/L, IQR 1.8 to 5.2 mmol/L, p=0.0432) and the use of vasopressors (39.47% vs. 27.33%, p=0.0284). These findings correspond to the higher rates of hypoxia and respiratory distress encountered by this cohort, as hypoxia triggers the production of lactic acidosis, and vasopressors are often required after patients receive sedation while being intubated. As a result, there were statistically significant differences in the development of ARDS (79 patients vs. 57 patients, p<0.0001) and of intubation (71 patients vs 45 patients, p=0.0031) for the higher BMI/HgbA1c cohort (figure 1). These findings mirrored those of other studies, with the caveat that our study differed in that it demonstrated no statistically significant difference in mortality.[23–25] We hypothesise that the lower BMI/HgbA1c cohort's statistically significant differences in age (median 73.5 years old, IQR 62 to 85 years old, p=0.0011) and acute cardiac injury (64.71% vs 48%, p=0.006) were the reasons for this finding. Several recent studies demonstrated that older patients with COVID-19, when compared to younger patients with COVID-19, had increased mortality, an increased incidence of acute cardiac injury, and acute cardiac injury itself was a predictor for an increased risk of mortality.[26 27] However, additional research is needed to further explain this lack of discrepancy for mortality.

When examining the data from the subgroup analysis (table 2), there were no statistically significant differences in terms of the rates of ARDS and intubation. However, when comparing diabetic patients with and without obesity compared to patients with obesity alone (table 3), there was a statistically significant difference in the development of ARDS (63 patients vs. 16 patients, p=0.0305). This suggests that diabetes, not just obesity, plays an important role in the development of respiratory distress leading to ARDS. A retrospective study from China indicated that patients with diabetes as their only comorbidity were more likely to develop a more severe form of pneumonia leading to respiratory distress when

Table 2 Subgroup analysis table #1

Variable	Value	Obese+diabetes n=52	Obese only n=40	Diabetes only n=60	P value
Intubated	Yes	24 (46.2%)	15 (37.5%)	32 (53.3%)	0.2972
ARDS	Yes	29/34 (85.3%)	16/24 (66.7%)	34/38 (89.5%)	0.0615

ARDS, acute respiratory distress syndrome.

Table 3 Subgroup analysis table #2

Variable	Value	Diabetes±obesity n=112	Obese only n=40	P value
Intubated	Yes	56 (50.0%)	15 (37.5%)	0.1738
ARDS	Yes	63/72 (87.5%)	16/24 (66.7%)	0.0305

ARDS, acute respiratory distress syndrome.

compared to patients without diabetes.[28] Another study compared patients with an HgbA1c ≥6.5% vs patients with an HgbA1c <6.5%.[29] The study demonstrated that patients with insufficient glycemic control (HgbA1c ≥6.5%) were more likely to be critically ill, develop ARDS, and suffer from secondary respiratory infections, when compared to patients with adequate glycemic control.[29] In addition, HgbA1c itself was independently associated with mortality.[29] With regard to hospitalised patients, additional research demonstrated that patients with strict control of blood glucose levels (glycemic variability between 3.9 and 10.0 mmol/L) had reduced mortality compared to patients with poor blood glucose control (glycemic variability greater than 10.0 mmol/L).[30] These studies demonstrate the importance of having a baseline HgbA1c level and the importance of tight glycemic control for hospitalised COVID-19 patients.

The large number of elderly patients in this study impacted our interpretation of BMI, for several reasons.[31] First, BMI does not account for visceral adipose tissue (VAT), which increases on ageing, and therefore, limits BMI's interpretation of excess body fat.[31 32] Second, an excess amount of VAT is associated with creating a proinflammatory state, causing the release of proinflammatory cytokines, especially IL-6, which demonstrates its clinical relevance with COVID-19.[31 33] Lastly, a recent study demonstrated that excess VAT is associated with worse clinical outcomes in COVID-19 patients.[31] This underscores its importance as a potential limiting factor for the use of BMI, as well as its value as a potential clinical marker.[31] Another study demonstrated that VAT was superior to BMI for predicting the presence of diabetes.[34] The increased amount of VAT in patients with diabetes is a potential factor explaining some of the different clinical outcomes in our study; however, further research is needed to determine the pathophysiologic link between VAT and COVID-19.[31]

Our study was also limited by other factors as well. It analysed a relatively small cohort of patients, thereby limiting statistical significance of the subgroup analyses. ABG results were limited, as only 103 patients in the non-diabetic/non-obese cohort and 96 patients in the obese and/or diabetic cohort had recorded ABGs. Patients who received sedation after being intubated often required the use of vasopressors, which also limits the use of this metric as a proxy for the development of septic shock. Our study is limited by the presence of confounders such as age, due to the large number of elderly patients treated for COVID-19, as well as the presence of other comorbidities excluding diabetes and obesity.

While our study performed a subgroup analysis using some of the most important, severe complications of COVID-19 (ARDS and intubation), further study is warranted comparing other complications as well. Given the prevalence of diabetes and obesity, the low cost of obtaining HgbA1c levels and BMI recordings on patients, our study can be easily replicated. Challenges to external validity and overall generalisability include the aforementioned limitations detailed above.

CONCLUSION

This study suggests that patients with diabetes and obesity are more likely to suffer severe complications from COVID-19, most importantly ARDS and intubation, when compared to patients without these morbidities. Despite these clinical findings, there was no difference in mortality, and further research is needed to explore this discrepancy. However, given the prevalence of these comorbidities, hospitalised patients with diabetes and obesity should have their respiratory statuses closely monitored, and clinicians should consider these comorbidities as risk factors for life-threatening complications of COVID-19.

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