



ORIGINAL ARTICLE

Epidemiology/Genetics

The association between obesity and peak antibody titer response in COVID-19 infection

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Abstract

Objective: Obesity is associated with severe coronavirus disease 2019 (COVID-19) infection. Disease severity is associated with a higher COVID-19 antibody titer. The COVID-19 antibody titer response of patients with obesity versus patients without obesity was compared.

Methods: The data of individuals tested for COVID-19 serology at the Mount Sinai Health System in New York City between March 1, 2020, and December 14, 2021, were retrospectively retrieved. The primary outcome was peak antibody titer, assessed as a binary variable (1:2,880, which was the highest detected titer, versus lower than 1:2,880). In patients with a positive serology test, peak titer rates were compared between BMI groups (<18.5, 18.5 to 25, 25 to 30, 30 to 40, and ≥ 40 kg/m²). A multivariable logistic regression model was used to analyze the independent association between different BMI groups and peak titer.

Results: Overall, 39,342 individuals underwent serology testing and had BMI measurements. A positive serology test was present in 12,314 patients. Peak titer rates were associated with obesity (BMI < 18.5 [34.5%], 18.5 to 25 [29.2%], 25 to 30 [37.7%], 30 to 40 [44.7%], ≥ 40 [52.0%]; $p < 0.001$). In a multivariable analysis, severe obesity had the highest adjusted odds ratio for peak titer (95% CI: 2.1-3.0).

Conclusion: COVID-19 neutralizing antibody titer is associated with obesity. This has implications on the understanding of the role of obesity in COVID-19 severity.

INTRODUCTION

Obesity is an independent risk factor for severe illness, hospitalization, and mortality from coronavirus disease 2019 (COVID-19) (1-4). Several mechanisms have been proposed to explain the link between obesity and COVID-19 severity. Specifically, the impact of obesity on the immune response to COVID-19 has been a focus of

interest. Prior knowledge of other viruses has shown that obesity is associated with an impaired immune response following infection or vaccination (5-10).

Antibody tests, also known as serology tests, can be used to assess the adaptive immune response following COVID-19 infection (11). Studies have demonstrated that COVID-19 patients develop antibodies within 1 to 2 weeks after the onset of symptoms. These

antibodies remain elevated for at least several months (12). Several studies have shown that a higher neutralizing antibody titer is associated with disease severity (13,14).

The COVID-19 antibody profile in patients with obesity is poorly understood. This study aimed to compare the COVID-19 antibody titer response of patients with obesity versus patients without obesity.

METHODS

Study setting

We retrospectively retrieved data of adult patients (age ≥ 18) who underwent COVID-19 serology testing and had available BMI measurements from the electronic health record (EHR) of a large, diverse academic health system, the Mount Sinai Health System (MSHS) in New York City. The MSHS encompasses the Icahn School of Medicine at Mount Sinai and eight hospital campuses in the New York metropolitan area, and it has a large, regional ambulatory footprint. The study time frame was between March 1, 2020, and December 14, 2020. We chose this study end date to ensure there were no vaccinated patients included in the cohort, as the COVID-19 vaccinations were first introduced to New York on December 14, 2020. Structured patient data were retrieved from the EHR system (Epic, Epic Systems Corp., Verona, Wisconsin). The Mount Sinai Institutional Review Board approved this study prior to data collection.

Serology testing

Serology testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was performed at the MSHS beginning in March 2020 (12). The test uses enzyme-linked immunosorbent assay (ELISA), which has been extensively used in research (15-18). The test was established in Mount Sinai's center for clinical laboratories, where it received the New York State Department of Health and FDA emergency use authorization (19,20). The MSHS started to screen individuals for antibodies to SARS-CoV-2 to recruit volunteers as donors for convalescent plasma therapy (21). In addition, the MSHS also offered the antibody test to MSHS employees and it was available for clinical use. The ELISA setup results in a discrete titer at either $<1:80$, $1:80$, $1:160$, $1:320$, $1:960$, or $1:2,880$, which was the highest detected titer. A positive test was defined as a titer of $1:80$ and above.

A minority of the cases had more than one serology test. For those individuals, we chose the first positive test or, in cases with only negative tests, the first negative test.

BMI data

We queried the EHR for BMI measurements for all patients with serology testing. Only patients with a documented BMI measurement

Study Importance

What is already known?

- ▶ Obesity is an independent risk factor for developing severe coronavirus disease 2019 (COVID-19).
- ▶ A higher severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralizing antibody titer is associated with COVID-19 severity.

What does this study add?

- ▶ This multisite study shows that the neutralizing antibody peak titer following SARS-CoV-2 infection is associated with obesity and severe obesity.
- ▶ The difference in peak titer levels between patients with obesity versus patients without obesity is especially prominent in patients younger than 50.

How might these results change the direction of research or the focus of clinical practice?

- ▶ Future research should clarify the kinetics and activity of the immune response developed in individuals with obesity, as they are relevant to understanding the pathophysiology of COVID-19 severity in patients with obesity.

(weight in kilograms divided by height in meters squared) were included in the study. Patients with missing BMI were excluded. The time stamp of the BMI recording was obtained and compared with the serology test time stamp.

Patients were clustered into five groups based on BMI measurements: <18.5 , 18.5 to 25 , 25 to 30 , 30 to 40 , and ≥ 40 kg/m^2 . The obesity group was defined as BMI 30 to 40 kg/m^2 , and the severe obesity group was defined as BMI ≥ 40 kg/m^2 (22).

Covariates

We further obtained data of COVID-19 nasopharyngeal swab polymerase chain reaction (PCR) testing. When available, for each patient, we included the date of the first positive PCR test performed before the serology test. For all positive PCR cases, we obtained records pertaining to COVID-19-related hospital admission.

Other variables obtained for each patient included demographics (age, sex, race), comorbidities, and smoking status. Comorbidities were coded as International Classification of Diseases records. The International Classification of Diseases codes were grouped using the diagnostic clinical classification software (23). Smoking was defined as past or present smoking.

Statistical analysis

Categorical variables were compared using the chi-square test. Continuous variables were compared using either the unpaired *t* test to compare two groups or one-way ANOVA to compare more than two groups.

We compared titer levels between different BMI groups (<18.5, 18.5 to 25, 25 to 30, 30 to 40, and ≥ 40 kg/m²). In order to segregate the group of patients with prior COVID-19 laboratory diagnosis, we performed sub-analyses for patients with and without a prior positive PCR. We also performed sub-analyses for individuals below and above 50 years of age (24) and patients with and without prior COVID-19-related hospital admission.

In patients with a positive titer, we used a multivariable logistic regression model to analyze the independent association between different BMI groups and peak titer (1:2,880). Similarly to a previous study, peak titer was defined as the maximal serum dilution observed in our laboratory (1:2,880) (Nilles EJ et al. medRxiv, doi:10.1101/2020.11.11.20229724, unpublished data). A BMI of 18.5 to 25 kg/m² was used as the reference group. The model was adjusted for demographics, comorbidities, and prior admission. A correlation matrix was constructed to assess the possible collinearity between covariates in the model, demonstrating that all correlations were below 0.52 (Supporting Information Figure S1). Prior positive PCR was not included as a covariate as it had high collinearity (0.70) with prior admission. Adjusted odds ratios (aOR), 95% CI, and *p* values were calculated for the models' variables. All analyses were performed using Python version 3.6.5 (Python Software Foundation, Wilmington, Delaware).

RESULTS

Overall, 63,988 individuals who underwent serology testing were identified. BMI recordings were available for 39,342 of those patients. Positive titer levels ($\geq 1:80$) were present in 12,314 patients (Figure 1). The median time between BMI recordings and serology tests was 127 days (interquartile range 33 to 245 days).

Table 1 presents the characteristics of the study cohort. A total of 24.8% of individuals were categorized as having obesity, and 4.2% of individuals were categorized as having severe obesity. Compared with patients with BMI < 30, patients with obesity and severe obesity had more comorbidities.

A total of 2,755/39,342 (7.0%) of the patients had a previous positive PCR test. The majority of the PCR-positive participants had a positive serology test (89.5%). The time difference between positive PCR test and serology test was highest in the group with severe obesity (BMI < 18.5: 30.4 ± 41.1 days; BMI 18.5 to 25: 31.5 ± 45.8 days; BMI 25 to 30: 32.7 ± 45.8 days; BMI 30 to 40: 38.1 ± 52.0 days; BMI ≥ 40 : 39.9 ± 54.6 days, *p* = 0.002). BMI distributions in the sub-analyses groups are presented in Supporting Information Figure S2. A total of 1,387 patients with a positive serology test had a prior hospital admission with positive PCR. Supporting Information Table S1 demonstrates the ten most common primary diagnoses in this group.

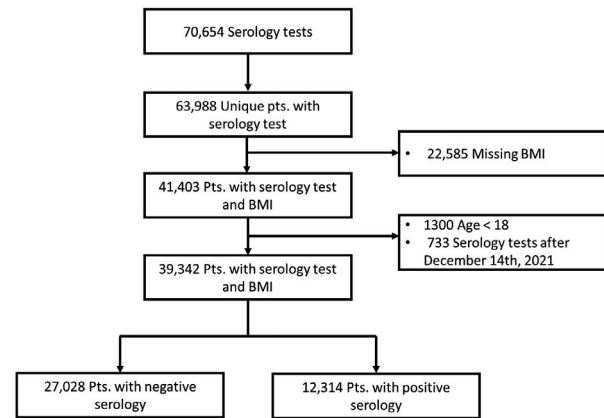


FIGURE 1 Study flowchart

Univariable analysis

Peak titer levels were associated with obesity and severe obesity in the entire cohort (BMI <18.5: 34.5%; BMI 18.5 to 25: 29.2%; BMI 25 to 30: 37.7%; BMI 30 to 40: 44.7%; BMI ≥ 40 : 52.0%, *p* < 0.001) (Figure 2).

The association between obesity and peak titer rates was also observed after stratifying by positive PCR status (BMI < 18.5: 58.7%; BMI 18.5 to 25: 49.2%; BMI 25 to 30: 53.3%; BMI 30 to 40: 57.1%; BMI ≥ 40 : 61.8%, *p* = 0.007), and negative PCR status (BMI < 18.5: 25.2%; BMI 18.5 to 25: 24.6%; BMI 25 to 30: 34.0%; BMI 30 to 40: 41.5%; BMI ≥ 40 : 48.6%, *p* < 0.001).

The association was also preserved after stratifying for age less than 50 (BMI < 18.5: 23.8%; BMI 18.5 to 25: 18.6%; BMI 25 to 30: 27.3%; BMI 30 to 40: 34.2%; BMI ≥ 40 : 47.3%, *p* < 0.001), and age over 50 (BMI < 18.5: 47.1%; BMI 18.5 to 25: 44.3%; BMI 25 to 30: 48.4%; BMI 30 to 40: 54.1%; BMI ≥ 40 : 58.0%, *p* < 0.001).

In patients with prior COVID-19-related admission, no statistical difference was observed between different BMI groups (BMI < 18.5: 61.9%; BMI 18.5 to 25: 56.1%; BMI 25 to 30: 54.8%; BMI 30 to 40: 55.5%, BMI ≥ 40 : 59.6%, *p* = 0.839). In patients without prior COVID-19 related admission, obesity and severe obesity were associated with higher peak titer rates (BMI < 18.5: 28.3%; BMI 18.5 to 25: 26.2%, BMI 25 to 30: 35.7%; BMI 30 to 40: 43.3%, BMI ≥ 40 : 50.6%, *p* < 0.001). Antibody titer frequencies stratified by BMI groups are presented in Supporting Information Figure S3A-S3F).

Multivariable analysis

Multivariable analysis (Figure 3) revealed that severe obesity had the highest aOR for peak titers (aOR 2.5, 95% CI: 2.1-3.0, *p* < 0.001). This was followed by BMI levels of 30 to 40 kg/m² (aOR 1.8, 95% CI: 1.6-2.0, *p* < 0.001). Other features positively associated with peak titer included BMI 25 to 30 kg/m², previous COVID-19-related admission, age decile, chronic kidney disease, congestive heart failure, and diabetes mellitus. White race was negatively associated with peak titers (aOR 0.7, 95% CI: 0.7-0.8, *p* < 0.001).

TABLE 1 Characteristics of the study cohort, stratified by BMI groups (<18.5, 18.5 to 25, 25 to 30, 30 to 40, and ≥40 kg/m²)

	All patients (n = 39,342)	<18.5 kg/m ² (n = 848, 2.2%)	18.5 to 25 kg/m ² (n = 14,071, 35.8%)	25 to 30 kg/m ² (n = 12,978, 33.0%)	30 to 40 kg/m ² (n = 9,788, 24.9%)	≥40 kg/m ² (n = 1,657, 4.2%)	p value
Demographics							
Age, median (IQR), y	48.0 (34.0-61.0)	42.0 (30.0-64.0)	42.0 (31.0-59.0)	50.0 (37.0-62.0)	52.0 (39.0-62.0)	49.0 (38.0-59.0)	<0.001
Female, N (%)	23,209 (59.0)	582 (68.6)	8,776 (62.4)	6,709 (51.7)	5,953 (60.8)	1,189 (71.8)	<0.001
Black, N (%)	5,736 (14.6)	126 (14.9)	1,386 (9.9)	1,836 (14.1)	1,895 (19.4)	493 (29.8)	<0.001
White, N (%)	15,464 (39.3)	358 (42.2)	6,280 (44.6)	5,075 (39.1)	3,266 (33.4)	485 (29.3)	<0.001
COVID-19							
POS serology, N (%)	12,314 (31.3)	226 (26.7)	3,770 (26.8)	4,130 (31.8)	3,552 (36.3)	636 (38.4)	<0.001
Previous POS PCR, N (%)	2,755 (7.0)	75 (8.8)	796 (5.7)	891 (6.9)	812 (8.3)	181 (10.9)	<0.001
Ab-PCR time difference, median (IQR), d	21.0 (4.0-50.0)	9.0 (3.0-30.0)	22.0 (4.0-48.0)	20.0 (4.0-48.0)	21.0 (4.0-56.0)	23.0 (4.0-59.0)	0.002
Previous COVID-19 admission, N (%)	1,593 (4.0)	52 (6.1)	434 (3.1)	500 (3.9)	489 (5.0)	118 (7.1)	<0.001
Comorbidities							
CAD, N (%)	4,453 (11.3)	98 (11.6)	1,218 (8.7)	1,557 (12.0)	1,311 (13.4)	269 (16.2)	<0.001
CHF, N (%)	2,605 (6.6)	83 (9.8)	752 (5.3)	807 (6.2)	765 (7.8)	198 (11.9)	<0.001
DM, N (%)	13,602 (34.6)	212 (25.0)	3,468 (24.6)	4,560 (35.1)	4,462 (45.6)	900 (54.3)	<0.001
HTN, N (%)	13,501 (34.3)	214 (25.2)	3,071 (21.8)	4,674 (36.0)	4,635 (47.4)	907 (54.7)	<0.001
CKD, N (%)	2,706 (6.9)	92 (10.8)	793 (5.6)	896 (6.9)	766 (7.8)	159 (9.6)	<0.001
COPD, N (%)	2,887 (7.3)	96 (11.3)	839 (6.0)	913 (7.0)	852 (8.7)	187 (11.3)	<0.001
Past or present smoking, N (%)	10,557 (26.8)	219 (25.8)	3,156 (22.4)	3,631 (28.0)	3,038 (31.0)	513 (31.0)	<0.001

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; PCR, polymerase chain reaction; POS, positive.

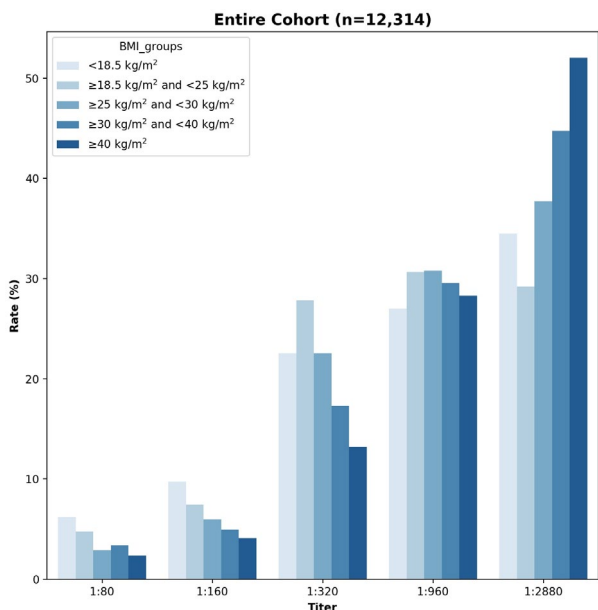


FIGURE 2 Antibody titer frequencies stratified by BMI groups for the entire cohort [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

This retrospective study of a large urban cohort demonstrated that the magnitude of the neutralizing antibody response following COVID-19 infection is associated with obesity and severe obesity.

Previous research has shown that antibody titer level against COVID-19 is associated with disease severity (13,14,25). Additionally, it was found that patients with obesity have an increased risk for severe COVID-19 illness (1,24). Thus, our observation of a high titer among patients with obesity could be explained by their more severe illness. These results are particularly intriguing as it has been shown that patients with obesity develop poor seroconversion response after other disease infections such as influenza (26).

The higher titer values among COVID-19 patients with severe obesity may be an indication of a strong immune response. This could be a result of a severe infection that is more evident in patients with severe obesity (1,2). Alternatively, an activated immune system with high antibody formation may be the cause of severe symptoms. The latter explanation could be more applicable as the adipose abnormal cytokine production has been proposed as a key mediator of COVID-19 severity in patients with obesity (27-29).

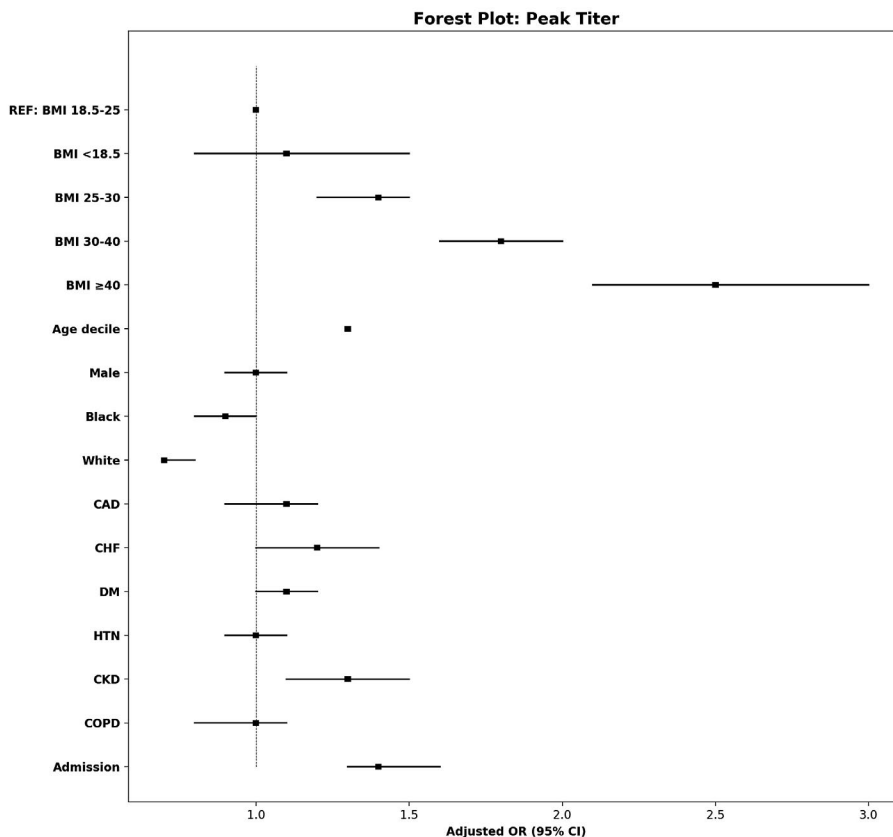


FIGURE 3 Forest plot presenting multivariable analysis evaluating variables independently associated with peak titer (1:2,880). The model was adjusted for BMI levels of <18.5, 25 to 30, 30 to 40, and ≥40 kg/m²; age decile; male sex; race; CAD; CHF; HTN; DM; CKD; COPD; smoking (past or present); and previous positive PCR. Patients with BMI of 18.5 to 25 kg/m² served as the reference group. CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension

We have also shown that the difference between the BMI groups for high peak titer was most prominent in the young population (age less than 50). This strengthens our earlier finding that obesity is a stronger predictor for severe disease and mortality among young COVID-19 patients (24). The current results reinforce the significant role of severe obesity in COVID-19 pathogenesis in young patients.

When analyzing patients hospitalized because of COVID-19, there was no significant difference between BMI groups for high peak titer. This could be explained by the fact that inpatients due to COVID-19 experience severe disease requiring hospitalization. Of note, it was previously demonstrated that elevation of neutralizing antibodies among all hospitalized patients reaches 80% of maximal levels rapidly after symptom onset (25).

It was recently shown by Nilles et al. that the humoral response against COVID-19 is not adversely affected in patients with obesity (medRxiv, doi:10.1101/2020.11.11.20229724, unpublished data). In contrast to our results, they did not detect a difference in the antibody titers between the BMI groups. The difference in the studies populations could explain this. Their study included a limited number of individuals with seropositive tests, and among them, only five patients with severe obesity. Our study included more than 650 individuals with severe obesity and a positive antibody test.

Interestingly, a recent study evaluated the antibody titer response following two doses of the BNT162b2 mRNA COVID-19 vaccine according to different BMI groups (Pellini R, et al. medRxiv, doi: 10.1101/2021.02.24.21251664, unpublished data). The researchers found that individuals with obesity had a less efficient humoral response compared with the normal-weight group. The immune response to COVID-19 infection in patients with obesity is attributed to the adipose tissue responsible for inflammation and the cytokine storm that results in severe symptoms (30,31). This may lead to the high titer observed following infection but not the vaccine. Another factor that may contribute to the elevated titer after an infection is the increased percentage of proinflammatory memory B cells among patients with obesity (32).

The protective role of antibody titer following infection or vaccination of COVID-19 is not fully understood (33). It has been shown that the presence of antibodies could reduce the risk for reinfection (34). Moreover, from the experience of different viral infections, the antibody titer is correlated with plasma viral neutralizing activity. Our research sheds light on the humoral immunological response of COVID-19 patients with obesity. Future research should evaluate the longevity and efficacy of the antibody reaction in patients with obesity to further elucidate the link between obesity and COVID-19.

Our study has several limitations. This was an observational retrospective analysis. The time of disease onset is not available for all participants, and it has been shown that the antibody titer declines over time (11). In our study, in cases in which the PCR was available, the average time lapse between the PCR and the antibody test was greater among patients with obesity. Nevertheless, they presented with a higher antibody titer. Additionally, although we adjusted and performed sub-analyses for previous COVID-19 admission

and previous positive PCR, our study may have a selection bias. Furthermore, we excluded patients without available BMI records, which could also lead to a selection bias. Moreover, the indication for serology testing was not available. There may also be a selective survival bias, whereby patients with a more severe disease died and did not have a titer antibody test. Although information related to medications used by the study participants would be informative, considering that certain drugs may alter COVID-19 infection rates, these data were not available. Lastly, data regarding disease severity were also not available.

In conclusion, COVID-19 neutralizing antibody titer is associated with BMI, with the highest titer in patients with severe obesity. This has implications on the understanding of the role of obesity in COVID-19 severity. Future studies should clarify the kinetics and activity of the antibody developed in individuals with obesity, as they are relevant to the protection against reinfection and vaccine response. **O**

CONFLICT OF INTEREST

The authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the author EK on reasonable request. The data are not publicly available because of information that could compromise the privacy of research participants.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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