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Original article

Association of prior metabolic and bariatric surgery with severity of coronavirus disease 2019 (COVID-19) in patients with obesity

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Abstract

Background: Obesity is a risk factor for poor clinical outcomes in patients with coronavirus disease 2019 (COVID-19).

Objectives: To investigate the relationship between prior metabolic surgery and the severity of COVID-19 in patients with severe obesity.

Setting: Cleveland Clinic Health System in the United States.

Methods: Among 4365 patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between March 8, 2020 and July 22, 2020 in the Cleveland Clinic Health System, 33 patients were identified who had a prior history of metabolic surgery. The surgical patients were propensity matched 1:10 to nonsurgical patients to assemble a cohort of control patients (n = 330) with a body mass index (BMI) $\geq$ 40 kg/m^2 at the time of SARS-CoV-2 testing. The primary endpoint was the rate of hospital admission. The exploratory endpoints included admission to the intensive care unit (ICU), need for mechanical ventilation and dialysis during index hospitalization, and mortality. After propensity score matching, outcomes were compared in univariate and multivariate regression models.

Results: The average BMI of the surgical group was 49.1 ± 8.8 kg/m^2 before metabolic surgery and was down to 37.2 ± 7.1 at the time of SARS-CoV-2 testing, compared with the control group's BMI of 46.7 ± 6.4 kg/m^2. In the univariate analysis, 6 (18.2%) patients in the metabolic surgery group and 139 (42.1%) patients in the control group were admitted to the hospital (*P* = .013). In the multivariate analysis, a prior history of metabolic surgery was associated with a lower hospital admission rate compared with control patients with obesity (odds ratio, 0.31; 95% confidence interval, 0.11−0.88; *P* = .028). While none of the 4 exploratory outcomes occurred in the metabolic surgery group, 43 (13.0%) patients in the control group required ICU admission (*P* = .021), 22 (6.7%) required mechanical ventilation, 5 (1.5%) required dialysis, and 8 (2.4%) patients died.

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Conclusion: Prior metabolic surgery with subsequent weight loss and improvement of metabolic abnormalities was associated with lower rates of hospital and ICU admission in patients with obesity who became infected with SARS-CoV-2. Confirmation of these findings will require larger studies. (Surg Obes Relat Dis 2021;17:208–214.)

Key words: Coronavirus; COVID-19; SARS-CoV-2; Metabolic surgery; Bariatric surgery; Obesity; Diabetes; Weight loss

A unique feature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is that its clinical presentation can vary from asymptomatic or mild infection to serious illness leading to death [1,2]. A growing body of evidence indicates that patients with obesity are disproportionately affected with a severe form of SARS-CoV-2 infection and may experience resultant higher mortality. The association between obesity and coronavirus disease 2019 (COVID-19) outcomes has biological and physiologic plausibility. The presence of obesity-related co-morbidities, including cardiometabolic, thromboembolic, and pulmonary diseases; coexistence of a proinflammatory state with high levels of cytokines and oxidative stress; changes in the innate and adaptive immune response; restrictive changes to the mechanics of the lungs and chest wall; and limited response to mechanical ventilation, may contribute to poor prognoses of COVID-19 in patients with obesity [2−10].

Metabolic surgery (defined as procedures that influence metabolism by inducing weight loss and altering gastrointestinal physiology) leads to substantial and sustained weight loss; improvement in cardiometabolic risk factors, including diabetes and blood pressure control; reduction in the risk of major adverse cardiovascular events; improvement of cardiopulmonary and renal functions; amelioration of the obesity-associated proinflammatory state; and survival benefits in patients with severe obesity [11−18].

Generally, patients are healthier following metabolic surgery, which may result in a less severe form of SARS-CoV-2 infection and a better prognosis after contracting this disease. To test this hypothesis, the present study was designed to determine the association of prior metabolic surgery with severity of SARS-CoV-2 infection in patients with severe obesity.

Methods

This is a retrospective, matched-cohort analysis of a prospective, observational, institutional review board–approved clinical registry of all patients tested for SARS-CoV-2 infection within the Cleveland Clinic Health System. A waiver of informed consent from study participants in the registry was granted by the institutional review board. The cohort included all patients who were tested for SARS-CoV-2.

For the purpose of this study, the study population included all 4365 patients between March 8, 2020 and July 22, 2020 who tested positive by the reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 using nasopharyngeal or oropharyngeal swab specimens. Patients with a history of organ transplant, active cancer, and current pregnancy at the time of positive testing were excluded. Among the remaining patients, 482 had a body mass index (BMI) $\geq$ 40 kg/m^2 and 1003 had a BMI $\geq$ 35 kg/m^2.

The exposure of interest was a history of prior metabolic surgery. In total, 33 patients with a positive test for SARS-CoV-2 were identified who had a prior history of metabolic surgery. The surgical patients were matched 1:10 to nonsurgical patients to assemble a cohort of control patients with a BMI $\geq$ 40 kg/m^2 at the time of a positive test for the virus.

Baseline characteristics, co-morbidities, medications, and clinical outcomes of patients were extracted from the SARS-CoV-2 registry. Perioperative data of metabolic surgical patients were obtained from the Cleveland Clinic Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program database.

The prespecified primary endpoint was the rate of hospitalization for SARS-CoV-2 infection. The prespecified exploratory endpoints included admission to the intensive care unit (ICU), need for mechanical ventilation and dialysis during the index hospitalization, and mortality.

Statistical analysis

Baseline data are presented as mean ± standard deviation, median (interquartile range [IQR]), and number (%). Time zero for analysis was the date of a positive viral test. Propensity scores were used to match 33 SARS-CoV-2 positive patients who had a history of prior metabolic surgery to 330 patients with a BMI $\geq$ 40 kg/m^2 (for the primary analysis) and with a BMI $\geq$ 35 kg/m^2 (for the sensitivity analysis), to balance the distributions between the 2 groups at the time of a positive viral test for age, sex, race, ethnicity, location (Ohio versus Florida), smoking status, and history of chronic obstructive pulmonary disease (COPD), asthma, or cancer. Patients were not intentionally matched based on the BMI and cardiometabolic risk factors (e.g., hypertension and diabetes) or medications at the time of viral test, since favorable changes on those factors could be the potential derivers for improvement of outcomes after metabolic surgery. The propensity scores were estimated using a logistic regression model involving these predictors, resulting in a score on the scale of the linear predictor. Using these scores, matching of metabolic surgical cases to comparable nonsurgical control patients with obesity was performed using

Table 1
Characteristics of metabolic surgery patients and matched control patients at the time of SARS-CoV-2 test

Baseline variable	Metabolic surgery, n = 33	Primary analysis		Sensitivity analysis	
		Matched control, n = 330	Standardized difference*	Matched control, n = 330	Standardized difference*
Sex			.007		.044
Female	26 (78.8)	239 (78.5)		254 (77.0)	
Male	7 (21.2)	71 (21.5)		76 (23.0)	
Age, years	46.1 ± 12.7	49.8 ± 14.3	.267	48.8 ± 14.7	.190
BMI, kg/m^2	37.2 ± 7.1†	46.7 ± 6.4	1.409	42.3 ± 7.0	.720
Race			.276		.317
White	16 (48.5)	154 (46.7)		154 (46.7)	
Black	13 (39.4)	159 (48.2)		162 (49.1)	
Other	4 (12.1)	17 (5.2)		14 (4.2)	
Ethnicity			.017		<.001
Non-Hispanic	32 (97.0)	319 (96.7)		320 (97.0)	
Hispanic	1 (3.0)	11 (3.3)		10 (3.0)	
Smoking status			.078		.020
Current	0	1 (.3)		0	
Former	10 (30.3)	100 (30.3)		97 (29.4)	
Never	21 (63.6)	209 (63.6)		213 (64.5)	
Unknown	2 (6.1)	20 (6.1)		20 (6.1)	
Testing location			<.001		.026
Ohio	31 (93.9)	310 (93.9)		312 (94.5)	
Florida	2 (6.1)	20 (6.1)		18 (5.5)	
Hypertension	12 (36.0)‡	205 (62.1)	.533	201 (60.9)	.533
Diabetes	2 (6.1)§	113 (34.2)	.750	95 (28.8)	.628
Coronary artery disease	4 (12.0)	22 (6.7)	.188	33 (10.0)	.068
Heart failure	2 (6.1)	28 (8.5)	.093	35 (10.6)	.165
Asthma	12 (36.4)	114 (34.5)	.038	116 (35.2)	.025
COPD	1 (3.0)	10 (3.0)	<.001	10 (3.0)	<.001
Cancer	1 (3.0)	10 (3.0)	<.001	10 (3.0)	<.001
Steroid use	5 (15.0)	56 (17.0)	.050	54 (16.4)	.033
Angiotensin converting enzyme inhibitor use	2 (6.1)	52 (15.8)	.315	47 (14.3)	.273
Angiotensin receptor blocker use	4 (12.0)	35 (10.6)	.048	37 (11.2)	.028

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; BMI = body mass index; COPD = chronic obstructive pulmonary disease.
Values are n (%) or mean ± standard deviation.
* Standardized differences are the absolute value of the difference in means or proportions between groups divided by pooled standard deviation.
† BMI was not considered in the propensity matching. BMIs of surgical patients decreased from 49.1 ± 8.8 kg/m^2 at the time of metabolic surgery to 37.2 ± 7.1 kg/m^2 at the time of SARS-CoV-2 test.
‡ Hypertension was not considered in the propensity matching. There were 21 (63.6%) patients who had hypertension before metabolic surgery.
§ Diabetes was not considered in the propensity matching. There were 9 (27.3%) patients who had type 2 diabetes before metabolic surgery.

functionality in the Matching package in R [19]. After propensity score matching, outcomes were compared in univariate and multivariate regression models. Sampling weights as observation weights were used in the outcome models.

A significance level of .05 for 2-sided comparisons was considered statistically significant, and 95% confidence intervals (CIs) were reported where applicable. All analyses were done in the R statistical programming language (version 4.0.0).

The sensitivity of the odds ratio estimates for independent predictors of primary outcome obtained from the multivariate regression model were tested in a separate matched control group (n = 330) who had BMIs ≥35 kg/m^2.

Results

A total of 363 patients, including 33 individuals who had metabolic surgery and 330 matched patients with a positive RT-PCR test and severe obesity, were included in the primary analysis. The mean BMIs of the surgical and the control groups at the time of a positive test were 37.2 ± 7.1 and 46.7 ± 6.4 kg/m^2, respectively.

The distribution of baseline covariates was balanced after matching between the surgical and control groups (Table 1), including sex (female sex, 79% versus 78%, respectively), age (46.1 versus 49.8 years old, respectively), race (White, 48% versus 47%, respectively), ethnicity (non-Hispanic, 97% versus 97%, respectively), testing location (Ohio, 94% versus 94%, respectively), current smoking (0 versus 0, respectively), history of asthma (36% versus 34%, respectively), COPD (3% versus 3%, respectively), and cancer (3% versus 3%, respectively).

Metabolic surgical procedures included sleeve gastrectomy (SG; n = 20) and Roux-en-Y gastric bypass (RYGB; n = 13). In the early postoperative period, 2 minor

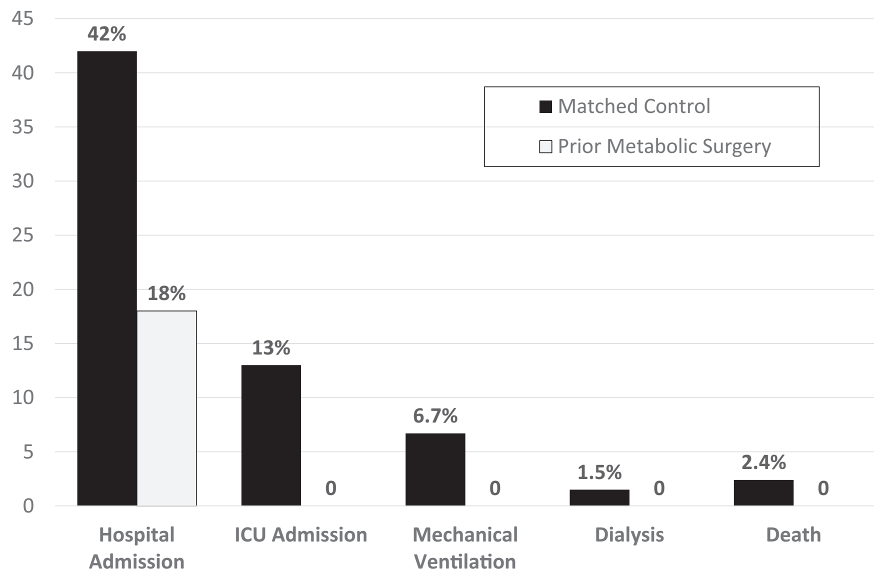

Fig. 1. Primary analysis: univariate comparison of study outcomes for COVID-19 patients with history of metabolic surgery (n = 33) versus a matched control group with BMI ≥ 40 kg/m^2 (n = 330). Chi-square test *P* value of .013 for hospital admission and Fisher's exact test *P* value of .021 for ICU admission. COVID-19 = coronavirus disease 2019; BMI = body mass index; ICU = intensive care unit.

complications (superficial surgical site infection and urinary tract infection) and 1 major complication (deep vein thrombosis) occurred. There were 3 patients with intractable gastroesophageal reflux disease who underwent conversion of their SG to RYGB.

The median interval between the metabolic surgery and the positive viral test was 46 months (IQR, 29−85). The BMIs of patients decreased from 49.1 ± 8.8 kg/m^2 at the time of metabolic surgery to 37.2 ± 7.1 kg/m^2 at the time of SARS-CoV-2 test (paired difference of 12.6 kg/m^2; $P < .001$). There were 9 (27.3%) patients who had type 2 diabetes before metabolic surgery, including 4 patients on insulin therapy. At the time of the SARS-CoV-2 positive test, diabetes was in remission (glycated hemoglobin < 6.5% off diabetes medications) in 7 of these surgical patients. Similarly, of the 21 (63.6%) patients who had hypertension at the time of metabolic surgery, 9 patients were not on antihypertensive medications at the time of a positive viral test. In patients with a history of hypertension, the median numbers of antihypertensive medications at the time of metabolic surgery and a positive viral test were 2 (IQR, 1−2.5) and 1 (IQR, 0−2), respectively ($P = .001$). Other frequent co-morbidities at the time of metabolic surgery included obstructive sleep apnea (n = 27; 81.8%) and hyperlipidemia (n = 9; 27.3%).

In the univariate analysis, 6 (18.2%) patients in the metabolic surgery group and 139 (42.1%) patients in the control group were admitted to the hospital ($P = .013$). While none of 4 exploratory outcomes occurred in the metabolic surgery group, 43 (13.0%) patients in the control group required ICU admission ($P = .021$), 22 (6.7%) required mechanical ventilation ($P = .24$), 5 (1.5%) required dialysis ($P > .99$), and 8 (2.4%) died ($P > .99$; Fig. 1).

In the multivariate analysis controlling for BMI and all covariates listed in Table 1 at the time of viral test, a prior history of metabolic surgery was associated with lower hospital admission rates compared with control patients with obesity (odds ratio [OR], 0.31; 95% CI, 0.11−0.88; $P = .028$). Other independent predictors of hospital admission were race (with higher OR for Blacks; OR, 1.76; 95% CI, 1.04−2.99) and age (OR, 1.05; 95% CI, 1.03−1.07).

Results of the sensitivity analysis are detailed in Tables 1 and 2 and in Fig. 2. The mean BMI of the control cohort for the sensitivity analysis was 42.3 ± 7.0 kg/m^2. In the univariate analysis, 6 (18.2%) patients in the metabolic surgery group and 148 (44.8%) patients in the control group were admitted to the hospital ($P = .006$; Fig. 2). In the multivariate analysis, a prior history of metabolic surgery was associated with a lower rate of hospital admission compared with control patients with obesity (OR, 0.28; 95% CI, 0.11−0.74; $P = .010$; Table 2).

Discussion

As more evidence unfolds, patients with obesity are found to be disproportionately affected by SARS-CoV-2 infection. This matched-cohort study suggests that a history of metabolic surgery is associated with lower severity of SARS-CoV-2 infection in patients with severe obesity, as manifested by lower risks of hospital and ICU admission. The findings of the primary analysis were consistently observed in a sensitivity analysis. Surgical patients had higher BMIs

Table 2
Independent predictors of hospital admission in patients with SARS-CoV-2 infection in the primary and the sensitivity analyses

Independent predictor	Primary analysis		Sensitivity analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Metabolic surgery versus control	.31 (.11−.88)	.028	.28 (.11−.74)	.010
Black versus White race	1.76 (1.04−2.99)	.035	2.06 (1.22−3.45)	.006
Age	1.05 (1.03−1.07)	<.001	1.05 (1.03−1.07)	<.001

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; OR = odds ratio; CI = confidence interval; COPD = chronic obstructive pulmonary disease.

Multivariate analyses were adjusted for all variables listed in Table 1, including BMI, sex, age, race, ethnicity, smoking status, history of hypertension, diabetes, coronary artery disease, heart failure, asthma, COPD, cancer, and use of a steroid, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker.

before metabolic surgery compared with the control group. Without undergoing surgery, they could have had COVID-19 outcomes similar to the control group. After surgery, their BMI decreased on average by 12.6 kg/m^2, their metabolic abnormalities improved, and they experienced less severe forms of SARS-CoV-2 infection. As noted in the current literature [20−23], advanced age and Black race were also found to be significant independent predictors of hospitalization after SARS-CoV-2 infection when controlling for other confounders. However, the association between the metabolic surgery and the study outcome was greater than the observed effects of age and race. As a disease process that has been demonstrated to target older and disenfranchised communities, the benefits of metabolic surgery may counteract the detrimental effects of age and race on patients testing positive for SARS-CoV-2 infection.

Multiple studies from the United States, Europe, and China have consistently reported adverse clinical outcomes, including higher rates of hospitalization, severe pneumonia, ICU admission, need for invasive mechanical ventilation, and mortality in patients with obesity who develop COVID-19 [2−9]. The findings of the present study suggest that metabolic surgery provides substantial and durable weight loss and an overall improved health profile that may lead to better outcomes in patients with SARS-CoV-2 infection. Metabolic abnormalities, including type 2 diabetes and hypertension, were significantly improved after metabolic surgery in most surgical patients. Although the sample size was small, none of the surgical patients experienced ICU admission, mechanical ventilation, dialysis, or death after contracting SARS-CoV-2 infection. As a proinflammatory and prothrombotic disease process, the effects

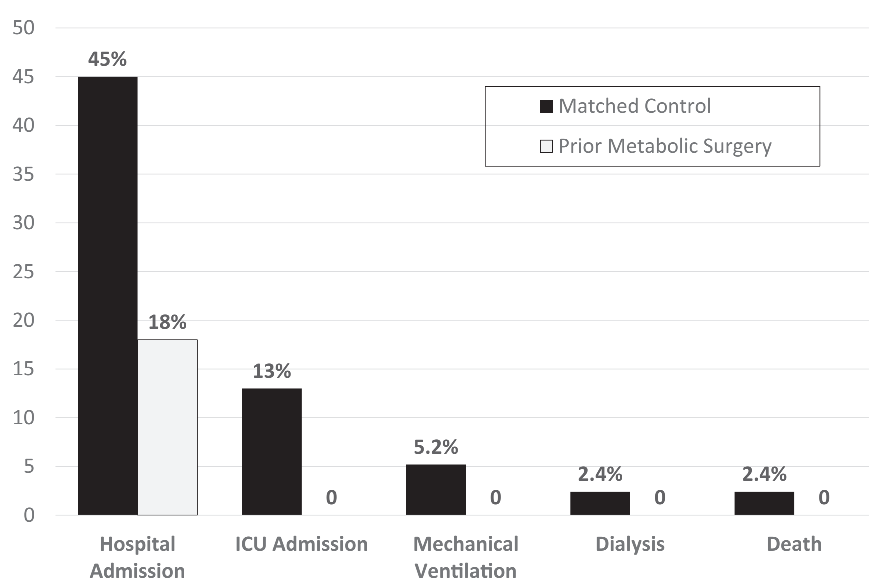

Fig. 2. Sensitivity analysis: univariate comparison of study outcomes for COVID-19 patients with history of metabolic surgery (n = 33) versus a matched control group with BMI ≥ 35 kg/m^2 (n = 330). Chi-square test *P* value of .006 for hospital admission and Fisher's exact test *P* value of .022 for ICU admission. COVID-19 = coronavirus disease 2019; BMI = body mass index; ICU = intensive care unit.

of SARS-CoV-2 infection may be counteracted by metabolic surgery aimed at ameliorating the obesity-mediated inflammatory response. A reduction in excessive adipose tissue reduces the inflammatory response, enhances immunity, and improves the physiology and mechanics of the lungs and chest wall. Furthermore, improvements in cardiometabolic risk factors after surgically induced weight loss may contribute to improved outcomes of patients with obesity who had prior metabolic surgery.

The COVID-19 pandemic has highlighted the vulnerabilities of patients with obesity and the necessity of creating better strategies for the management of this chronic disease process [24−26]. Efforts to address the obesity epidemic will help improve not only overall individual health, but also the health of a society, by having the greatest impact on improving health outcomes in a vulnerable population. By addressing obesity in our community in an expeditious manner, we can prevent the immediate health effects associated with obesity, in addition to the heightened risks associated with unanticipated local or global health scares [26−28]. As a chronic and progressive disease process, obesity should be managed in a multidisciplinary approach, including lifestyle and behavioral interventions, pharmacotherapy, and metabolic surgery if appropriate. Previous evidence has shown a lower risk of major adverse cardiovascular events, certain cancers, and mortality in patients with obesity who have undergone metabolic surgery [11−18]. An improved prognosis with SARS-CoV-2 infection can be added to the list of potential benefits of metabolic surgery. Metabolic surgery can be a life-saving procedure for many patients with severe obesity and, given its substantial benefits, it should be considered as an essential surgery [27−30].

Limitations

This study has several limitations. First, the small sample size of patients with SARS-CoV-2 infection who had a history of metabolic surgery resulted in wide confidence intervals and could have influenced the statistical comparison of exploratory endpoints such as mortality, which did not reach to the statistical significance level. Furthermore, since only 6 patients in the metabolic surgery group required hospitalization, the laboratory, radiologic, and oxygenation data were not available for a majority of cases and could not be compared with the statistical analyses. As this study reflects findings early in the course of the pandemic, it will be of interest to repeat this study with larger data sets and later in the course of the pandemic. Second, although comprehensive matching between the study groups was performed in the primary and sensitivity analyses and outcomes were subsequently compared with a multivariate regression analysis, residual measured or unmeasured confounders could have influenced findings of this retrospective, observational study. Third, the present study design is not able to determine the main reasons for the observed reduction in adverse outcomes related to SARS-CoV-2 infection in the surgical arm. This observation may be related to weight loss, improvements in cardiometabolic co-morbidities, other metabolic changes afforded by the surgical intervention itself [31−33], or, most likely, a combination of these favorable changes. Fourth, our study lacks a medical weight loss arm, which could give some light on the possible differential effects of medically versus surgically induced weight loss on the study outcomes. Fifth, hospital admission, as the primary endpoint, could be based on nonmedical factors, such as bed availability or subjective criteria for some patients. There may have been a lower threshold to admit patients with more severe obesity in the control group. Sixth, although all patients who tested positive were called daily for 14 days to monitor their disease progression, it is possible that some patients may have been admitted to a hospital outside the Cleveland Clinic Health System and therefore were not captured in our data set.

Conclusion

To our knowledge, this is the first clinical study to demonstrate that prior metabolic surgery with subsequent weight loss and improvement of metabolic abnormalities could potentially reduce morbidity from SARS-CoV-2 infection. The study found that prior metabolic surgery was associated with lower rates of hospital and ICU admission in patients with obesity who became infected with SARS-CoV-2. However, given the nature of the study, these data should be considered hypothesis-generating and not conclusive. Given that the COVID-19 pandemic will not likely disappear soon and that the obesity pandemic is growing, it would be imperative to prioritize research on the clinical and mechanistic role of obesity and intentional weight loss, including metabolic surgery, on the pathophysiology of SARS-CoV-2 infection.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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