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Journal Pre-proof

Efficacy of Bariatric Surgery in COVID-19 Patients: An Updated Systematic Review and Meta-Analysis.

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PII: S2666-2620(22)00081-X
DOI: <https://doi.org/10.1016/j.sipas.2022.100140>
Reference: SIPAS 100140



To appear in: *Surgery in Practice and Science*

Received date: 30 June 2022
Revised date: 17 October 2022
Accepted date: 20 October 2022

Please cite this article as: Nimra Hasnain , Abdul Moeed , Eisha Waqar , Syed Ali Farhan , Fnu Amreek , Efficacy of Bariatric Surgery in COVID-19 Patients: An Updated Systematic Review and Meta-Analysis., *Surgery in Practice and Science* (2022), doi: <https://doi.org/10.1016/j.sipas.2022.100140>

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Key points:

- Protective effects of bariatric surgery on COVID-19 patients are not well understood.
- Prior bariatric surgery was linked with decreased hospitalizations.
- Low overall mortality in the surgery group.
- Bariatric surgery was associated with less severe COVID-19 infection.

Journal Pre-proof

Efficacy of Bariatric Surgery in COVID-19 Patients: An Updated Systematic Review and Meta-Analysis.

Short Title: A comparison of bariatric surgery and non-bariatric surgery COVID-19 patients on in-hospital mortality, hospitalization, and severe infection.

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1. Nimra Hasnain: conception and design of work, analysis, and interpretation of results.
2. Abdul Moeed: design of work, analysis and interpretation of results.
3. Eisha Waqar: drafting the work
4. Syed Ali Farhan: design of the work, critical review of the work
5. Fnu Amreek: revising critically for intellectual content, final revisions

Abstract

Introduction: Obesity is linked with poor prognostic outcomes in patients with SARS-CoV-2 infection. In patients with BMI > 35 kg/m², increased rates of hospital and subsequently ICU admissions have been noted. Bariatric surgery resulting in sustained weight loss is hypothesized to decrease the morbid outcomes associated with COVID. In this review, we planned to update the evidence on the topic presented by Aminian et al.

Methods: An extensive literature search was conducted of the electronic databases. Screening of the articles based on the eligibility criteria was followed by relevant data extraction. Other than the articles used in the previous meta-analysis, relevant databases were searched to filter for any new articles. Initially, two independent reviewers screened Pubmed and Cochrane database followed by a thorough search of additional databases such as Google scholar and Medrxiv. The articles were first screened using title and abstract, followed by a full text read. Duplicates, meta-analysis, letter to the editors, and commentaries were excluded. No language restrictions were placed.

Results: A total of nine articles with a population of 1,130,341 were entered into the RevMan. Patients with bariatric surgery were significantly associated with decreased hospitalizations (OR: 0.52, 95% CI [0.45, 0.61]), less likely to be admitted to the ICU (OR: 0.44, 95% CI [0.29, 0.67]), and reported reduced overall mortality (OR: 0.42, 95% CI [0.25, 0.70]).

Conclusion: Surgically induced weight loss is more beneficial in reducing the morbidity and mortality burden of COVID-19. More studies are needed to stratify the effect of demographics and metabolic profiles on disease progression.

Keywords:

Bariatric surgery; COVID-19; Weight loss

INTRODUCTION:

Obesity, previously associated with increased morbidity and mortality in respiratory viral infections (1), leads to worse clinical outcomes in patients with COVID-19. In a recent meta-analysis of patients infected with COVID-19, the risk of disease severity was 2.31 times higher in obese patients than non-obese patients (2). Obesity has been further identified as a modifiable risk factor in COVID-19 patients for increased intensive care unit (ICU) admissions and invasive mechanical ventilation (3). The pro-inflammatory effects of obesity can often supplement the pro-thrombotic effects of COVID-19, leading to detrimental disease processes such as deep vein thrombosis, myocardial infarction, stroke, and pulmonary embolism in COVID-19 infected patients (1).

Bariatric surgery is an established treatment modality for severe obesity and is associated with favorable long-term outcomes. It not only helps in achieving sustained weight loss but has also been shown to reduce co-morbidities associated with obesity such as hyperlipidemia, obstructive sleep apnea, hypertension, type-2 diabetes mellitus (4,5). In light of the evidence in favor of the detrimental effects of obesity on COVID-19 infections, bariatric surgery has been researched as a

mitigating factor and a treatment tool to enhance the quality of life in patients suffering from COVID-19.

Extensive evidence is now being generated indicating the protective effects of bariatric surgery on clinical outcomes related to severe COVID-19. A recent meta-analysis published by Aminian et al. validated this rationale by concluding that prior bariatric surgery was associated with a lower rate of mortality and hospital admission in obese patients infected with COVID-19 (6). However, since COVID-19 is an ongoing pandemic, an increasing level of research is continuously being published on the subject. We aim to conduct an updated systematic review and literature search on the association between prior bariatric surgery and the clinical outcomes of COVID-19 infection. This will further help to promote the narrative of an ongoing double pandemic, i.e., COVID-19 and obesity, and subsequently alert public health authorities to resume and enhance access to bariatric surgery during the current pandemic.

METHODS

This meta-analysis is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for updated meta-analysis (7) and follows the structure laid out by the Cochrane Collaboration (8).

Data Sources and Search Strategy

A detailed literature search of PubMed and Cochrane Central was conducted from its inception up until January 2022. Google scholar and Medrxiv.org were utilized as an additional search engines to screen any non-peer reviewed articles. The search strategy used in the electronic databases included keywords (“COVID-19 OR “coronavirus” OR “SARS-Cov-2”) and

("bariatric" OR "RYGB" OR "gastric bypass" OR "sleeve"). The complete search strategy is available in the supplementary material (S1). No restrictions on time, language, study design, and sample size were applied. Editorials and bibliographies of relevant review articles and unpublished databases were manually reviewed, ensuring none of the studies from white and grey literature were omitted.

Study Selection

Articles retrieved from the literature search were transferred to the Endnote Reference Library (Version X7.5; Clarivate Analytics, Philadelphia, Pennsylvania), where the duplicates were identified and removed. Two independent reviewers (N.H and A.M) used a two-phase blinded selection process. Articles were separately assessed according to their title and abstract details followed by a thorough full-text read. Selected articles were verified against the predefined inclusion criteria which were later matched and the duplicates were removed. In case of any conflict, a third reviewer (E.W) was consulted. Studies irrespective of language, containing full-text, and those dating to January 2022 were included. Meta-analyses and/or systematic reviews, letters to the editors (LTEs), and perspectives were excluded. Studies with patients with the following characteristics were included in the study: a) COVID-19 positive and b) with or without bariatric surgery. The primary end-points of the study were: mortality, hospital admission, and severe COVID-19 infection (ICU admission and mechanical ventilation combined).

Data Extraction and Quality Assessment

Following variables of interest were extracted from each study on a standard excel sheet: study population, study design, sample size, number of patients in each group (bariatric and non-

bariatric), general patient characteristics of each group (age, gender, and race), comorbidities present amongst patients at baseline (hypertension, diabetes mellitus, hyperlipidemia, renal disease, and respiratory illness) and primary end-points including mortality, hospital admission, ICU admission, and mechanical ventilation. Two independent reviewers (E.W and A.M) conducted Quality Assessment to determine the risk of bias in each study. Newcastle-Ottawa scale (9) was employed for the pooled retrospective cohort studies. Studies were gauged on the selection, comparability, and outcomes of the representative cohorts. Those displaying most representativeness of the community, had least attrition loss, longer follow-up duration, and a standardized method to assess the outcome were attributed as having lower risk of bias. Any discrepancies found were resolved by consensus and discussion. (Table S1) Additionally, GRADE (10), an assessment tool to gauge the quality of systematic reviews/meta-analyses was employed. Studies included in the analysis are evaluated on the basis of risk of bias, inconsistency, indirectness, imprecision, and probability of a bias in publication. A detailed summary is provided in Table 2.

Statistical Analysis

This analysis was performed using Review Manager (RevMan) Version 5.4 Cochrane Collaboration. Generic invariance and the random-effects model were employed to derive odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for the pooled outcomes. Forest plots were used to represent each outcome. Higgins I^2 statistics were utilized to assess the heterogeneity across the pooled studies. The value of $I^2=25\%-50\%$ was considered mild, $50\%-75\%$ moderate, and $>75\%$ severe heterogeneity. A p-value <0.05 was considered significant. Since there were less than 10 studies, the funnel plot could not be used to evaluate the publication bias.

RESULTS

Study selection and characteristics

Our search of electronic databases yielded a total of 275 articles. After an initial screening of abstracts, 93 studies were assessed for detailed evaluation. Of these studies, a total of 9 studies (5,10–17) satisfied our eligibility criteria and were included in the quantitative synthesis, as shown in Figure 1. The remaining studies shortlisted for full-length assessment were excluded on being either single-arm (n=38) or having incomplete data (n=34). All nine studies included in the meta-analysis were retrospective cohorts with a total patient population of n=1,130,341. Most studies were peer reviewed except for Bramante et al. (12), were propensity matched cohorts, conducted analysis between 2020-2021, and contained patients tested positive for COVID through PCR. However, a few didn't specify the screening method and included COVID susceptible cases as well (10-11). Most were conducted in the US, however, a few were based on the Iranian (10) and French (11) databases. Except for Purdy and Bramante et.al (5, 13), studies specified the nature of the surgical technique, with majority including Roux-en-Y gastric bypass (11-12, 14-18), sleeve gastrectomy (11-12, 14-18), and gastric banding (12, 14, 17). Among the included studies, females were the predominant sex in both bariatric and non-bariatric groups, with diabetes and hypertension being the common comorbidities. Characteristics of all included studies are present in Table. 1.

Mortality (Figure 2)

A random-effect analysis of eight studies reporting mortality was performed by pooling odds ratios (ORs) from dichotomous data. Compared with non-bariatric, the bariatric surgery group

was significantly associated with an overall lower mortality (OR: 0.42, 95% CI [0.25, 0.70]; $p < 0.0009$; $I^2 = 73\%$).

Severe COVID-19 Infection (Figure 3)

Eight studies assessing COVID-19 severity (mechanical ventilation and/or ICU admission) were pooled to derive ORs using a random-effects model. Patients undergone bariatric surgery in the past were significantly associated with developing a less severe COVID-19 infection (OR: 0.44, 95% CI [0.29, 0.67]; $p < 0.0001$; $I^2 = 83\%$).

Hospital Admission (Figure 4)

Pooling of six studies evaluating hospital admission in COVID-19 positive patients with or without bariatric surgery showed patients with bariatric surgery were less likely to be hospitalized (OR: 0.52, 95% CI [0.45, 0.61]; $p < 0.00001$; $I^2 = 0\%$).

Sensitivity Analysis

A leave-one-out sensitivity analysis was carried out to measure the degree of disproportionate effects produced by one single study. Purdy et al. (5) was identified as the study heavily influencing mortality and severe COVID-19 infection outcomes due to differences in the number and demographics of BMS and non-BMS groups. Despite the large population size, the methodology remains substandard due to the lack of individual patient data and multivariate analysis. Removal of Purdy et al. resulted in a decrease in heterogeneity from 73% to 0% in

mortality and from 83% to 0% in severe COVID-19 infection. Both forest plots are present in [supplementary figures 2 and 3](#).

Quality Assessment

From the nine retrospective cohort studies included in this meta-analysis, one study, Ianelli et al. (11), was classified as of “Fair” quality, whereas the rest were of “Good” quality. Detailed quality assessment is included in the supplementary material ([Table S2](#)). GRADE rated all three outcomes as having moderate to critical importance and attributed the evidence as highly certain. (Table 2)

DISCUSSION:

This study is an updated meta-analysis that further confirms the protective function of bariatric surgery in patients infected with SARS-COV2, as stated by Aminian et al. (6). However, our meta-analysis consists of a larger population (n= 1,130,341 vs. 9022) and additionally evaluates the severity of infection. Patients admitted to the ICU and/or those who underwent mechanical ventilation were labeled with severe COVID-19 infection. Bariatric surgery was found to be unanimously beneficial; linked with decreased rates of hospitalization, less severe infection, and a more significant mortality benefit.

In patients infected with SARS-COV2, obesity has been attributed as the single most prognosis determining factor. According to a meta-analysis, individuals with obesity have an almost 50% higher risk of contracting SARS-COV2, with every patient getting hospitalized and every 3 in 4 at risk for ICU admission. Consequently, dismal outcomes such as the need for mechanical

ventilation and ultimately death were observed in every 4 and 3 out of 6 individuals, respectively (19). Moreover, intensive care patients, those having a BMI of $>35 \text{ kg/m}^2$ are reported to be at a greater risk for disease progression (3). Hypothetically, weight loss measures in general may ameliorate the severity of the disease and fasten recovery though surgical measures supersede pharmacological treatment.

Patients with bariatric surgery are 44% less likely to witness a severe event such as a mechanical event and/or ICU admission. The mortality rate in the surgical group is 42% less than in the nonsurgical group, which is higher (22 %) than that reported by the previous meta-analysis (6). Similarly, the rate of inpatient admissions in the surgical group was lower as compared to the previous meta-analysis [OR= 0.52, 95% CI (0.45-0.61) vs. 0.28, CI (0.12–0.65)]. The larger sample population in ours makes the protective benefit of bariatric surgery more explicit and lends validity to the hypothesized therapeutic effect of bariatric surgery.

The morbidity and mortality outcomes in COVID-19 patients seem to be dependent on two factors: 1) severity of the inflammatory response 2) primary lung function. Literature suggests that surgical weight loss measures assist in mitigating the damage posed by hyper-inflammatory states, such as that in COVID-19, as they help ‘calm’ the cytokine storm. (20,21) Additionally, in females, surgically induced weight loss is associated with a greater decrease in CD4 and CD3 T cells leading to a reduced inflammatory response. (22) However, these benefits are only witnessed following a significant period of sustained weight loss.(23) Additionally, morbidly obese patients have deranged pulmonary function tests, increased V/Q mismatch, lower ventilatory reserve, and are at a greater risk of developing right heart failure in cases of

obstructive sleep apnea. Furthermore, prolonged ICU stay, acute lung events such as pneumonia and embolism, and intensive mechanical ventilation have been reported in such patients. (24–27) This was similarly witnessed in patients with Middle eastern respiratory syndrome (MERS-COV) and influenza. The former reported lower mortality rates in the surgical group, with the latter documenting lesser emergency admissions and shorter sick leaves. (28–30) Matos et al. found significant improvement in the pulmonary function tests following bariatric surgery, with respiratory efficiency becoming similar to that of controls after 6 months. (31)

An improvement in the pre-existing co-morbidities indirectly impacts the progression of COVID-19. Other than sustained and prompt weight loss benefits of bariatric surgery, various obesity-related comorbidities are better controlled following surgical intervention. Bariatric surgery has been documented to benefit patients with increased HbA1C, hence, decreasing the morbidity and incidence of complication, followed by a substantial improvement in survival rates. (32–36) A meta-analysis by Buchwald et al. found that surgical measures reduced weight up to 60% and helped reduce metabolic parameters such as blood glucose total cholesterol, followed by improvement in hypertension and sleep apnea. (37) Therefore, current recommendations emphasize the protective role of bariatric/metabolic surgery and classify it as an emergency surgery in patients with ≥ 2 underlying chronic metabolic conditions. (38) These findings recommend the medical community to continue exploring safe surgical practices during the pandemics and establish better algorithms to prioritize those needing emergent care. Furthermore, additional studies stratifying the outcomes of bariatric surgery on the basis of demographics and metabolic profile must be conducted to get a more holistic view.

Like any other meta-analysis, this too has its inherent limitations. Firstly, as very few studies have reported their metabolic profile, subgroup analysis could not be performed. Secondly, although the majority of the data being propensity-matched eliminates the risk of heterogeneity I², findings by Purdy et al. (5) render the data inhomogeneous (severe COVID-19 infection I² =83%, mortality= 73%). Other than that, the implicit bias of selective outcomes and data reporting cannot be gauged and eliminated as such. One example is the study by the University of Minnesota (13), which did not contribute to any heterogeneity, is not peer-reviewed, and hence, the findings may introduce bias. As seen in our analysis, females were more likely to undergo surgery than their male counterparts. However, multivariate regression revealed that the male gender presents with more severe disease, leading to increased morbid outcomes (39). Due to the lack of individual outcomes in both genders, subgroup analysis could not be performed. Hence, the surgical benefit in COVID-19 patients could not be stratified based on gender. Although a few propensity-matched studies did not match BMI, race, and age, this did not affect the results as these factors were not included in our subgroup analysis. However, future meta-analyses may need to be wary of these confounders. Furthermore, the temporal relationship between surgery and contracting SARSCOV2 could not be evaluated due to the lack of data. In addition, assessment made by GRADE is rendered subjective, and recommendations made on the evidence provided should be dealt with caution. Although the findings of this meta-analysis lend credibility to the previous, future meta-analyses must evaluate for the missing endpoints.

Conclusion:

Bariatric surgery assists in alleviating the disease progression in patients with SARS-COV2. Decreased hospitalization, reduced ICU admissions, and lower mortality rates are positive outcomes in moderate to severe obesity patients. Future studies are needed to evaluate the endpoints points, highlight the confounders, and devise strategies for continual surgical access during pandemics.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Acknowledgements: No acknowledgements to disclose.

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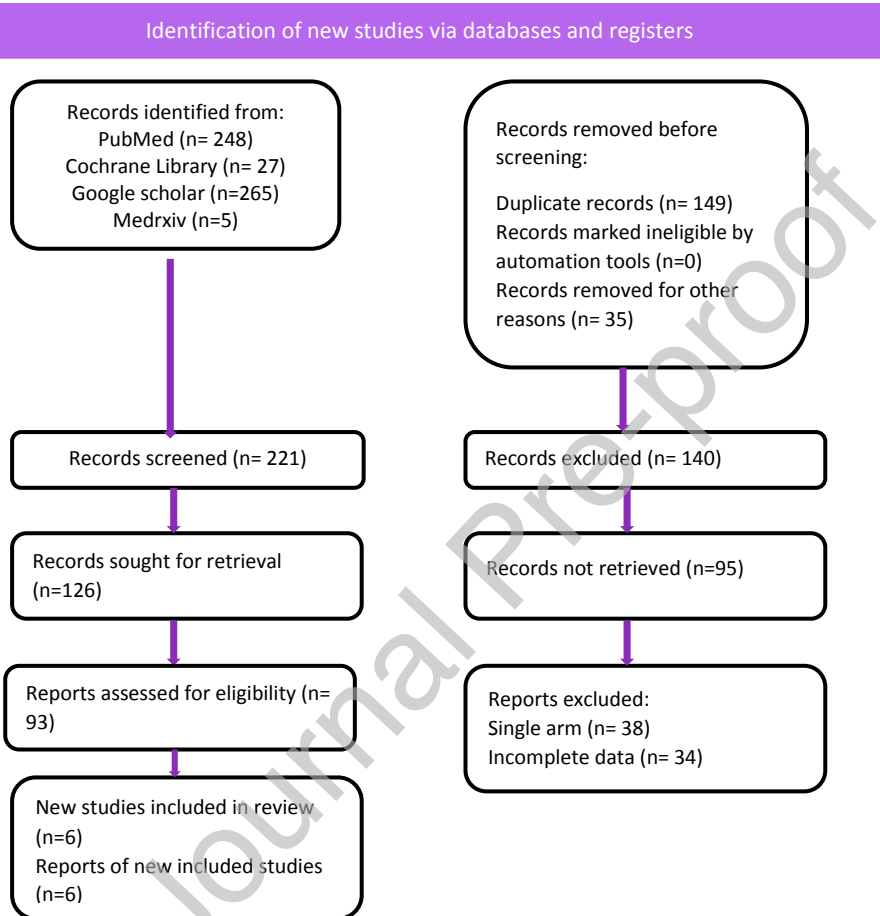
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**Fig 1: PRISMA model**

Study Name, Year	Sample size		Age, yrs		BMI, kg/m ²		Gender, M, F %		Conclusion
	MBS	Non-MBS	MBS	Non-MBS	MBS	Non-MBS	MBS	Non-MBS	
Aminian et al 2020	363		46.1 ± 12.7	49.8 ± 14.3	37.2 ± 7.1	46.7 ± 6.4	21.2, 78.8	21.5, 78.5	Low risk of hospital and ICU admission in patients with obesity and MBS
Bramante et al 2020	373		56.1 IQR-43.5-65.3		35.3±8.2		47.1, 52.9		MBS was associated with a significant reduced risk of admission
Iannelli et al 2020	8285		49.8 ± 12.0	59.8 ± 12.4	N/A	N/A	23.5, 76.5	5.8, 46.2	MBS associated with a lower risk of death and mechanical ventilation in patients with obesity and COVID-19
Hadi et al 2021	981,921		48.13 ± 11.88	48.62 ± 12.44	N/A	N/A	17.37, 82.32	17.37, 82.63	Prior MBS is affiliated with a decreased risk of poor outcomes of COVID-19
Jenkins et al 2021	620		51.7 ± 12.6	52.1 ± 12.9	36.1 ± 8.3	41.4 ± 6.5	31, 69	31, 69	MBS significantly reduces the risk of ER admission, ICU stay, and mortality in patients with COVID-19
Blanchard et al			59.0 ± 10.8	59.8 ± 9.7	33.1 ± 5.4	33.0 ± 5.0	40, 60	41.4, 58.6	MBS in obese patients hospitalized for COVID-19 better prognostic

2021	2398							outcomes than in non-MBS patients
Moradpour et al 2021	236	45.3 ± 11.3	45.1 ± 10.1	29.65 ± 6.2	45.08 ± 5.8	24.1, 75.9	23.5, 76.5	MBS patients with COVID-19 had shorted hospitalization and ICU compared to non-MBS patients
Aminian et al 2021	11809	46.0 (38.0-55.0)	46.0 (34.0-56.0)	45.5 (40.9-51.4)	45.3 (40.8-50.7)	21.4, 78.6	21.5, 78.5	MBS was associated with reduced risk of hospitalization and severe disease in COVID-19 patients
Purdy et al 2022	124,699	N/A	N/A	N/A	N/A	27.6, 72.4	47.6, 52.4	MBS patients with obesity and COVID-19 had better outcomes compared to non-MBS patients

Table 1: Baseline Characteristics of the patient population in each study; T*W= White, B= Black, O= Others, D=Declined, MBS- metabolic and bariatric surgery** Each % within a study corresponds to a different sample size.

Author(s): Nimra Hasnain, Abdul Moed, Eisha Waqar, Syed Ali Farhan, Amreek Kataria

Question: Bariatric Surgery compared to Non-Bariatric Surgery in COVID-19 patients

Setting: -

Bibliography: . Bariatric Surgery vs Non-Bariatric Surgery in COVID-19 patients. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

N° of studies	Study design	Certainty assessment					N° of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bariatric Surgery	Non-Bariatric Surgery	Relative (95% CI)	Absolute (95% CI)		

Severe COVID-19 Infection

8	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	609/5496 (11.1%)	30409/133269 (22.8%)	OR 0.44 (0.29 to 0.67)	113 fewer per 1,000 (from 149 fewer to 63 fewer)	⊕⊕⊕⊕ High	CRITICAL
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Hospital Admission

6	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	308/2344 (13.1%)	1123/3731 (30.1%)	OR 0.52 (0.45 to 0.61)	118 fewer per 1,000 (from 139 fewer to 93 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
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Mortality

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bariatric Surgery	Non-Bariatric Surgery	Relative (95% CI)	Absolute (95% CI)		
8	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	248/5487 (4.5%)	14899/133596 (11.2%)	OR 0.42 (0.25 to 0.70)	61 fewer per 1,000 (from 81 fewer to 31 fewer)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; OR: odds ratio

Table 2: GRADE scoring system for the metaanalysis

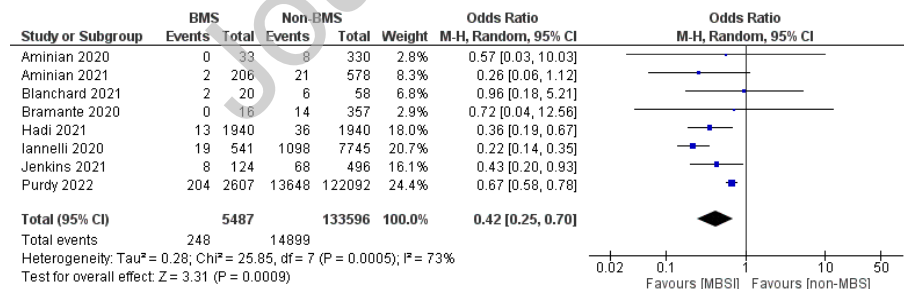


Figure 2: Mortality in COVID-19 patients with bariatric surgery or without bariatric surgery. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals per study. Black diamonds represent the pooled effect estimate.

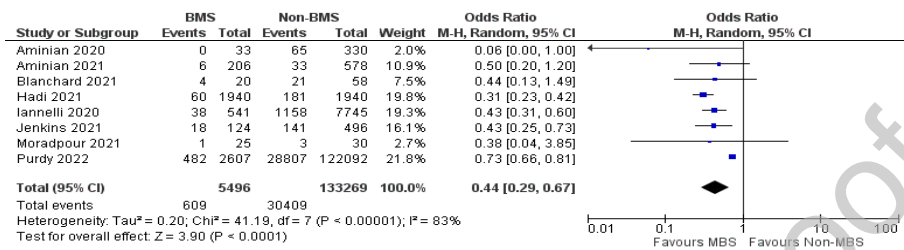


Figure 3: Severe COVID-19 infection in patients with bariatric surgery or without bariatric surgery. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals per study. Black diamonds represent the pooled effect estimate.

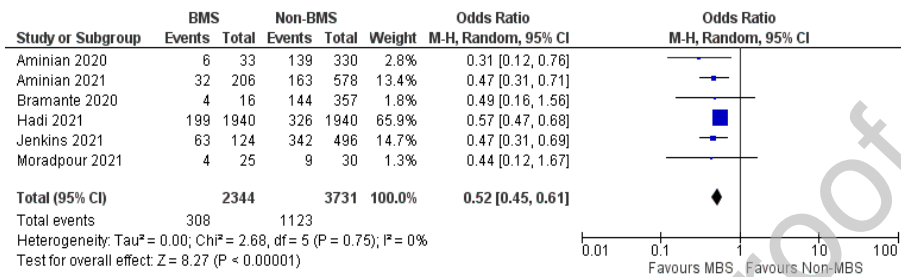


Figure 4: Hospital Admission in COVID-19 patients with bariatric surgery or without bariatric surgery. Blue squares and their corresponding lines are the point estimates and 95% confidence intervals per study. Black diamonds represent the pooled effect estimate.