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Immunosuppression and *Clostridioides difficile* Infection Risk in Metabolic and Bariatric Surgery Patients

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Abstract

Background: Immunosuppressant use increases the risk of *Clostridioides difficile* infection. To date no studies have analyzed the relationship between immunosuppressant use and *Clostridioides difficile* infections after metabolic and bariatric surgery.

Methods: A retrospective analysis of the 2015–2018 Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) data was conducted. The MBSAQIP data includes information from 854 affiliated practices in the United States and Canada. Initial sample size was 760,076 MBS patients. After excluding participants due to missing variables (n= 188,106) and the use of surgical procedures other than Roux-en-Y gastric bypass and sleeve gastroplasty (n=129,712), final analyses were performed on 442,258 participants. Logistic regression models generated the odds of post-MBS *Clostridioides difficile* infection by immunosuppressant status (+/−).

Results: Unadjusted logistic regression analysis showed that patients using immunosuppressants were 95% more likely to have post-operative *Clostridioides difficile* infection (OR=1.945, 95% CI= 1.230 to 3.075; p <0.001) versus MBS patients not taking immunosuppressants. After adjusting for age, gender, ethnicity, pre-operative BMI, diabetes status, and surgery procedure

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Author Contributions:

EMM conceived the research idea, wrote the first draft of the manuscript, and worked on authors' feedback. MU and LX analyzed the data, created the tables, and completed the statistical analysis. SEM obtained the database and reviewed and edited the manuscript and oversaw the analysis. JM and NDLCM reviewed and edited the manuscript. All authors approved of the final version of the manuscript.

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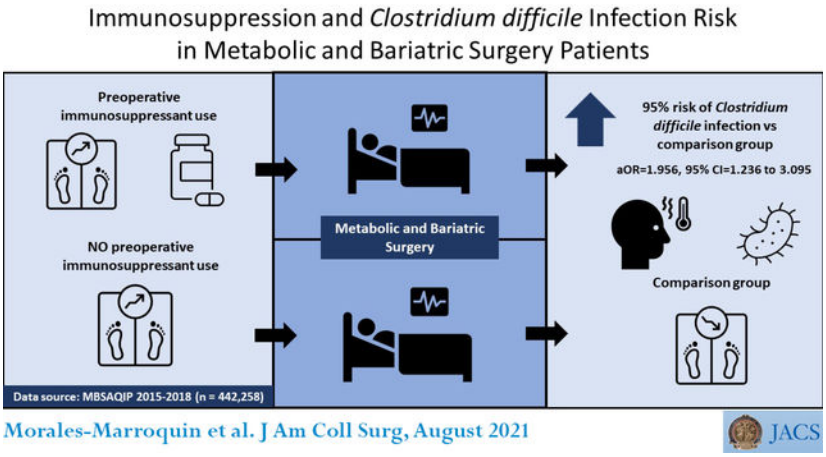
type, the association remained unaffected (aOR=1.956, 95% CI=1.236 to 3.095; p <0.01). Patients who completed the laparoscopic Roux-en-Y gastric bypass procedure had more than double the odds of developing *Clostridioides difficile* infection compared to those who completed the laparoscopic sleeve gastrectomy procedure (OR=2.183, 95% CI=1.842 to 2.587; p < 0.0001).

Conclusions: Our results using a population-based sample of MBS patients show that those taking immunosuppressants have significantly higher risk of developing *Clostridioides difficile* infection post-operatively. These findings suggest that patients using immunosuppressants should be closely monitored both pre- and post-procedure.

Graphical Abstract



Precis

This study showed for the first time that immunosuppressant increased postmetabolic and bariatric surgery *Clostridioides difficile* infection risk by 95% in comparison with patients who also underwent operation but were not consuming immunosuppressant. Increased attention to metabolic and bariatric surgery patients taking immunosuppressant is needed.

Keywords

Bariatric surgery; LRYGB; Clostridioides difficile; C. difficile; weight loss surgery

INTRODUCTION

C. difficile is a spore-forming, gram-positive bacteria that causes pseudomembranous enterocolitis, which can lead to fulminant colitis (1), and as such is considered a significant public health threat (2). According to the Centers for Disease Control and Prevention there are approximately half a million *C. difficile* infections each year in the United States (US) (3, 4). Additionally, it is estimated that 15,000 deaths are directly attributed to *C. difficile* infection in the US annually, with a higher mortality risk among those aged 65 years or older (3). Focused efforts to prevent *C. difficile* infections resulted in a 36% decrease in health care-associated *C. difficile* infections from 2011 to 2017 but community-associated *C. difficile* infections and in-hospital death rates have not changed despite these efforts (5).

Immunosuppressants are commonly prescribed for autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, systemic vasculitis, and post-organ transplantation (6). However, immunosuppressants have been associated with long-term adverse effects including increased risk of infection, malignancy, cardiovascular disease, marrow suppression, and cytopenia, even after treatment has ceased (6). Research shows that the use of a single immunosuppressant increases the risk for opportunistic infections such as *C. difficile* more than 3.2 times, whereas the combination of two or more immunosuppressants increases infection risk by 6.5 times (7). The proposed mechanism of action through which immunosuppressants lead to increased *C. difficile* infections is by immune system response inhibition, leading to increased *C. difficile* toxins (8). In addition to immunosuppressants, other proposed risk factors for *C. difficile* infection include gastrointestinal surgeries, antibiotic use, and obesity, especially if a patient was already an asymptomatic *C. difficile* carrier (9–12).

Metabolic and bariatric surgery (MBS) is a safe and effective long-term treatment option for obesity (13, 14). Incidence of *C. difficile* infection in MBS patients is low (0.13%); however, the presence of *C. difficile* is associated with increased length of stay and 30-day post-operative surgical complications including anastomotic leaks, deep surgical site infection, re-operations, and re-admissions as well as increased risk of pneumonia, acute kidney injury, venous thromboembolism, sepsis, intubation, and mortality in these patients (15–17). While fecal microbial transplantation, a new innovative treatment, has shown to be effective against *C. difficile* infection, it is not effective in all patients (18). Therefore, the best strategy to prevent *C. difficile* infection is to minimize its occurrence in the first place (18).

Due to the lack of evidence evaluating the relationship between immunosuppressants use and *C. difficile* infection rates in MBS patients, this analysis examined this relationship in a population-based, national sample of US MBS patients.

METHODS

Design

A retrospective analysis was conducted using data from the 2015–2018 MBS Accreditation and Quality Improvement Program (MBSAQIP). The University of Texas Health Science Center institutional review board considers a retrospective analysis of public, anonymized data, such as the MBSAQIP dataset, exempt from review.

Data source

In 2012 the American College of Surgeons (ACS) and the American Society for MBS (ASMBS) merged their programs to form the MBS Accreditation and Quality Improvement Program (MBSAQIP)(19). The MBSAQIP collects prospective, risk-adjusted data, based on preoperative, intra-operative, and post-operative standardized definitions of variables that are specific for MBS. Perioperative care is standardized across centers ensuring reliable data (20). The merged 2015–2018 MBSAQIP Participant Use Data File (PUF) were used for this analysis and includes MBS patients who received their clinical care at one of the accredited centers in the USA and Canada (16). The PUF contains 173 HIPAA-compliant variables on

204,837 cases submitted from 854 centers in 2018; 200,374 from 832 centers in 2017; 186,772 from 791 centers in 2016; and 168,903 from 742 centers in 2015.

Participants

All participants from the dataset were included unless they had missing data from variables used for this analysis. The MBSAQIP database PUF contains a total sample size of 760,076 participants from years 2015–2018. After excluding participants due to missing variables (n= 188,106) and the use of other surgical procedures (n=129,712), final analyses were performed on 442,258 participants

Variables

The primary dependent (outcome) variable for this analysis was *C. difficile* infection and the primary independent (predictor) variable was immunosuppressant use for a chronic condition. The *C. difficile* infection variable included patients who developed *C. difficile* colitis within 30 days post-MBS. Both independent and dependent variables are dichotomous variables with yes/no categories. Covariates included age, ethnicity, pre-operative body mass index (BMI), pre-surgery diabetes status, and MBS procedure type. Three age groups were created as follows: < 30 years; 31–60 years; and > 60 years. Ethnic groups were classified as Non-Hispanic White; Non-Hispanic Black; Hispanic, and Other based on patient self-report. Pre-operative BMI was classified into four groups using the following cut points: < 35; 35 to 39; 40 to 49; and ≥ 50 kg/m^2. Diabetes status was analyzed as a dichotomous variable (Yes/No) depending on pre-surgery diagnosis. Finally, surgical procedure type was classified into two groups with 1) CPT code 43775 as Laparoscopic Sleeve Gastrectomy (LSG), and 2) CPT code 43644 as Laparoscopic Roux-en-Y Gastric Bypass (LRYGB).

Statistical analysis

Descriptive analysis was performed for baseline characteristics including age, gender, ethnicity, pre-operative BMI, pre-surgery diabetes status, and surgical procedure type. Next, a comparison of patient characteristics between *C. difficile* positive and negative diagnosis was performed using chi-square tests. Additionally, a comparison of patient characteristics in relation to immunosuppressant use for chronic condition was also performed using chi-square tests. Finally, via logistic regression analysis, the crude odds ratio (model 1) was calculated for *C. difficile* infection among patients with immunosuppressant use for chronic condition (control, immunosuppressant use). A 10% rule was applied to identify any potential confounders from the list of covariates including age, gender, ethnicity, pre-operative BMI, diabetes status, and surgery type; none of these covariates were shown to be confounders. Backward selection was performed with the variables age, gender, ethnicity, pre-operative BMI (controlled for due to the conflicting findings with regards to the effect it has on *C. difficile* infection risk) (21–25), diabetes status, and surgical procedure type as they were all significantly associated with *C. difficile* infection and/or immunosuppressant use in bivariate analysis. To produce the final model (model 2), an adjusted logistic regression model controlling for the covariates from the backward selection process to determine the effect these covariates had on the potential relationship between *C. difficile*

infection and immunosuppressant use was run. All statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC). Type one error was maintained at 5%.

RESULTS

A total of 760,076 individuals who completed MBS between 2015–2018 were identified. After excluding participants due to missing variables (n= 188,106) and the use of surgical procedures other than LRYGB and LSG (n=129,712), final analyses were performed on 442,258 participants. Seventy-eight percent of the population were between 31 and 60 years old and 80% of the participants were female. The ethnic distribution was 58.33% non-Hispanic White, 16.90% non-Hispanic Black, 9.74% Hispanic, and 15.04% other ethnicities. A total of 5.34% had a BMI < 35 kg/m^2, 18.73% a BMI between 35–39 kg/m^2, 52.24% between 40–49 kg/m^2, and 23.69% had a BMI ≥ 50 kg/m^2. Almost three quarters of the participants (74.41%) reported not having diabetes diagnosis at the time of the surgery whereas 25.59% reported having the diagnosis. Likewise, nearly three quarters of the surgeries were LSG (72.84%) and 27.16% were LRYGB.

Table 1 illustrates baseline demographics based on *C. difficile* infection diagnosis. After excluding missing data, the total number of *C. difficile* cases in patients undergoing either LRYGB or LSG was 551 with an overall incidence of 0.12% within 30 days of MBS. Gender, ethnicity, and surgery type were significant. It is interesting to note that even though the total population distribution of MBS surgeries was 72.84% and 27.16% for LSG and LRYGB respectively, the distribution of participants within the *C. difficile* group were 54.45% and 45.55% for LSG and LRYGB, respectively.

Table 2 shows baseline demographics based on immunosuppressants use. A total of 7,987 participants (1.8%) were taking immunosuppressants. All covariates were significant and, in comparison to people without prior immunosuppressant use, there was a higher percentage of individuals with BMI between 35 and 39 in the group with prior immunosuppressant use (20.26 versus 18.70%).

Table 3 displays the association between immunosuppressant use and *C. difficile* infection among MBS patients. Model 1 and Model 2 represent unadjusted and adjusted odds ratios, respectively. It was observed in all models that immunosuppressant use is associated with an increased risk of *C. difficile* infection. Unadjusted logistic regression models showed that patients using immunosuppressants were 95% more likely to have post-operative *C. difficile* infection (OR=1.945, 95% CI= 1.230 to 3.075; p <0.01) versus MBS patients not taking immunosuppressants (Table 3). After adjusting for age, gender, ethnicity, pre-operative BMI, diabetes status, and surgery procedure type, the association between immunosuppressant use and *C. difficile* infection remained significant with a 96% (OR= 1.956, 95% CI= 1.236 to 3.095; p <0.01) increased risk of *C. difficile* infection among those who used immunosuppressants prior to MBS. Patients between 31 and 60 years of age had a 17% (OR=0.826, 95% CI=0.639 to 1.067; p < 0.05) lower risk of *C. difficile* infection in comparison to those younger than 30 years. No significant differences in *C. difficile* infection risk were noted in NHB and Hispanics in comparison to NHW. Women had a 41% increased risk of *C. difficile* infection (OR=1.407, 95% CI=1.112 to 1.780; p < 0.01) in

comparison to their male counterparts. No significant differences between BMI categories were noted. Patients who completed LRYGB had more than double the odds of developing *C. difficile* infection (OR=2.183, 95% CI=1.842 to 2.587; $p < 0.0001$) in comparison to patients who had LSG. Lastly, no differences in C. difficile risk were noted between patients previously diagnosed with diabetes versus their non-diagnosed counterparts.

DISCUSSION

This is the first nationally representative study evaluating the relationship between immunosuppressant therapy and the risk of *C. difficile* infection in patients following MBS. Analysis showed a remarkable 95% higher odds of *C. difficile* infection post-MBS among those patients taking immunosuppressants for chronic medical conditions versus MBS patients not taking immunosuppressants. This finding suggests it may be crucial for health care providers to increase *C. difficile* awareness post-MBS, particularly in patients taking immunosuppressants. This is relevant as *C. difficile* infections are associated with longer hospital stay (26), and those on immunosuppression are at a greater risk for recurrent *C. difficile* infection (27) and increased mortality (17). The observed overall incidence of *C. difficile* infection post-MBS in the present study is lower than the reported incidence of *C. difficile* in other surgery populations (0.13% versus 0.47%)(28).

Two previous studies have examined *C. difficile* infections in patients undergoing MBS. One study focused on the differences in the infection rates between surgery types whereas the other identified specific risk factors, however, none of them evaluated immunosuppressant use. The first study evaluated the impact of open or LRYGB and open or LSG on *C. difficile* infection (29). The authors found an 87% higher infection rate in patients that underwent open or LRYGB versus open or LSG, however, the potential explanation for this difference was not studied. The second study evaluated the MBSAQIP dataset 2015–2017 to search for risk factors for *C. difficile* infection in patients following MBS (16). Despite not analyzing immunosuppressants use and including a year less of data compared to the present analysis, they also found a higher risk of *C. difficile* infection in females. Other identified risk factors from this study included chronic kidney disease, a history of venous thromboembolism, and obstructive sleep apnea. Likewise, patients who underwent LRYGB had more than twice the risk of *C. difficile* infection versus patients who underwent LSG (16). These outcomes are in agreement to the results obtained in the present study as we observed a more than double increased risk of *C. difficile* infection rate in patients who had LRYGB versus those who had LSG. It is possible that the observed disparities are caused by the different anatomical location of the surgical incisions. LSG utilizes a gastric resection whereas LRYGB involves a gastric resection alongside two anastomoses involving the intestine: a gastrojejunostomy and a jejunojejunostomy (30). The concentration of bacteria capable of surviving the acidic environment in the stomach (pH 1–2) is quite low, whereas the concentration of bacteria normally present in the duodenum and jejunum is higher, likely due to the less acidic environment (pH 5.7–6.4) (30). Therefore, it is possible that creating a resection within the stomach where there is a lower concentration of bacteria might lead to a lower risk of infection compared to creating two anastomoses at the intestinal level, where bacterial concentrations are higher. It is also possible that the differential C. difficile risk by MBS

procedure type is caused by the distinct microbial composition caused by LRYGB versus LSG (16, 31).

The only additional studies that have analyzed the effect of immunosuppressants on *C. difficile* infection rates in surgical patients are those involving solid organ transplants. Research in this area aligns with our findings as results show that the prevalence of *C. difficile* infection is higher in transplant patients consuming corticosteroids at the time of the infection (32) and during the early post-transplant period when patients are taking the highest doses of immunosuppressants (33).

Recent evidence suggests that C. difficile infection might be associated with alterations to the gut microbial composition (34). However, the specific taxa associated with a higher risk have not been fully elucidated. A systematic review published by our team (35), showed that MBS leads to changes to the gut microbiota that are different depending on the MBS procedure type. Although no studies have analyzed the gut microbial changes associated with a higher risk of C. difficile infection after MBS, it is possible that these changes could increase the risk of colonization and posterior invasion of pathogenic bacteria. For example, after RYGB surgery there is a pronounced decrease of the genera Bifidobacterium and Lactobacillus, both recognized probiotics; and a decrease in the butyrate-producing bacterial specie Faecalibacterium prausnitzii, which is the most abundant specie in the colon of healthy humans (36). It is possible that MBS, peri-surgery medication, various dietetic composition and how it interacts with environmental factors all affect gut microbial composition and affect C. difficile infection risk."

The focus of this study was the effect of chronic immunosuppressant use on C. *difficile* risk; however, it is possible that short-term use of these medications might also increase the risk of *C. difficile* infection. During the current COVID-19 pandemic, high-dose glucocorticoids, a type of immunosuppressant, have been recommended to decrease COVID-19 severity (37, 38). Studies have shown that taking immunosuppressants <15 days before the diagnosis of *C. difficile* infection is associated with a two-fold increase in mortality (17). Therefore, it is possible that even short-term (2–3 weeks) treatments with glucocorticoids, such as those recommended for COVID-19, may significantly increase the risk of *C. difficile* infection and severity. Avoiding glucocorticoids may not be an option when treating those acutely ill with COVID-19 during the pandemic, so it is important for all healthcare providers, including MBS surgeons, to be aware of the potentially increased risk of *C. difficile* infection in patients who have recently been treated with glucocorticoids due to COVID-19 (8–10, 37–40). It is also important to note that the symptoms of COVID-19 and *C. difficile* infection overlap, with both presenting with diarrhea, nausea, vomiting, and abdominal pain, but with almost opposite responses to glucocorticoid treatment (8–10, 40–43). While immunosuppressants have been shown to decrease mortality in COVID-19 patients, they increase mortality in *C. difficile* infection (44). Previous studies have shown that glucocorticoid exposure triples the risk of *C. difficile* infection in comparison to other immunosuppressant agents such as infliximab, azathioprine, mercaptopurine, and methotrexate (7, 9, 45).

There are some limitations of the current analysis that need to be noted. First, it was not possible to differentiate between the specific immunosuppressant sub-categories, the duration of immunosuppression, the underlying conditions for which these medications were prescribed, and the previous history of *C. difficile* infection. Second, there was no available information regarding relevant medication such as antibiotics and proton pump inhibitors which increase *C. difficile* risk (10, 46), or metformin, which is related to a lower risk of *C. difficile* infection (47). Third, information regarding probiotic consumption was not collected and therefore we could not evaluate the effect of probiotics on *C. difficile* infection risk in patients taking immunosuppressants. This information is relevant as probiotics have shown to be protective in non-immunosuppressed patients but their effect on immunosuppressed patients is more debatable (48, 49). Lastly, the short follow up period of 30 days post-surgery limits any findings to within a relatively short post-MBS period. Therefore, *C. difficile* infections that developed beyond this time are not represented in our study. However, one of the strengths of the present study is the utilization of the MBSAQIP database, which is the largest MBS dataset in the country representing hundreds of MBS practices and hundreds of thousands of patients. The observed striking increased risk of *C. difficile* infection in patients taking immunosuppressive medications may lead to the development of a pre-MBS *C. difficile* prediction model for high-risk patients. Specifically, this pre-operative tool could help surgeons to easily identify the post-operative risk of *C. difficile* infection in patients who are prescribed immunosuppressants or have other factors that increase their risk of infection and disease severity. Similar models have been developed to predict the occurrence of *C. difficile* infection in hospitalized patients who receive antibiotics.

In summary, this is the first study evaluating *C. difficile* infection rates in patients who have completed MBS and who are on chronic immunosuppressant therapies. Our analysis showed a 95% higher odds of *C. difficile* infection in immunosuppressed patients after MBS compared with those not taking immunosuppressant medications. Given these results, it is crucial for healthcare providers, especially MBS surgeons, to be aware of the increased risk of *C. difficile* infection among their patients taking immunosuppressants. In light of the current COVID-19 pandemic and its overlapping presentation with *C. difficile* infection, providers may want to consider performing appropriate diagnostic testing, considering the differential effects of glucocorticoid treatment. Type of immunosuppressant, duration of therapy, underlying disease, other medications consumed, and type of MBS are important variables to include to create effective prediction models for post-operative *C. difficile* infection risk. Finally, it is paramount to investigate the role of *C. difficile* infection preventive strategies such as probiotics in this high-risk population.

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Table 1.

Summary of Descriptive Characteristics of Selected Population (MBSAQIP, 2015–2018) by *Clostridioides difficile* Infection Status

Variable	Total (n = 442258)	CDIFF + (n = 551)	CDIFF − (n = 441707)	p Value*
Age				0.064
<30 y	52914 (11.96)	71 (12.89)	52843 (11.96)	
31–60 y	343122 (77.58)	407 (73.87)	342715 (77.59)	
>60 y	46222 (10.45)	73 (13.25)	46149 (10.45)	
Sex				0.0054†
Female	353867 (80.01)	467 (84.75)	353400 (80.01)	
Male	88391 (19.99)	84 (15.25)	88307 (19.99)	
Ethnicity				<0.0001†
Hispanic	43060 (9.74)	41 (7.44)	43019 (9.74)	
NHW	257963 (58.33)	401 (72.78)	257562 (58.31)	
NHB	74730 (16.90)	68 (12.34)	74662 (16.90)	
Other	66505 (15.04)	41 (7.44)	66464 (15.05)	
BMI				0.4625
<35 kg/m^2	23619 (5.34)	35 (6.35)	23584 (5.34)	
35–39 kg/m^2	82838 (18.73)	98 (17.79)	82740 (18.73)	
40–49 kg/m^2	231038 (52.24)	277 (50.27)	230761 (52.24)	
≥50 kg/m^2	104763 (23.69)	141 (25.59)	104622 (23.69)	
Operation type				<0.0001†
LSG	322131 (72.84)	300 (54.45)	321831 (72.86)	
LRYGB	120127 (27.16)	251 (45.55)	119876 (27.14)	
Preoperative diabetes				0.5579
Yes	113174 (25.59)	147 (26.68)	113027 (25.59)	
No	329084 (74.41)	404 (73.31)	328680 (74.41)	

Data presented as n (%)

*Chi-square test

†Statistically significant

CDIFF, *Clostridioides difficile*, LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; NHB, Non-Hispanic black; NHW, Non-Hispanic white.

Table 2.

Summary of the Descriptive Characteristics of Selected Population (MBSAQIP, 2015–2018), by Immunosuppressant Use

Variable	Total (n = 442258)	Immunosuppressant use + (n = 7987)	Immunosuppressant use − (n = 434271)	p Value*
Age				<0.0001†
<30 y	52914 (11.96)	445 (5.57)	52469 (12.08)	
31–60 y	343122 (77.58)	6375 (79.82)	4336747 (77.54)	
>60 y	46222 (10.45)	1167 (14.61)	45055 (10.37)	
Sex				<0.0001†
Female	353867 (80.01)	6666 (83.46)	347201 (79.95)	
Male	88391 (19.99)	1321 (16.54)	87070 (20.05)	
Ethnicity				0.0003†
Hispanic	43060 (9.74)	749 (9.38)	42311 (9.74)	
NHW	257963 (58.33)	4667 (58.43)	253296 (58.33)	
NHB	74730 (16.90)	1466 (18.35)	73264 (16.87)	
Other	66505 (15.04)	1105 (13.83)	65400 (15.06)	
BMI				0.0046†
<35 kg/m^2	23619 (5.34)	426 (5.33)	23193 (5.34)	
35–39 kg/m^2	82838 (18.73)	1618 (20.26)	81220 (18.70)	
40–49 kg/m^2	231038 (52.24)	4066 (50.91)	226972 (52.27)	
≥50 kg/m^2	104763 (23.69)	1877 (23.50)	102886 (23.69)	
Operation type				0.0011†
LSG	322131 (72.84)	5946 (74.45)	316185 (72.81)	
LRYGB	120127 (27.16)	2041 (25.55)	118086 (27.16)	
Preoperative diabetes				<0.0001†
Yes	113174 (25.59)	2377 (29.76)	110797 (25.51)	
No	329084 (74.41)	5610 (70.24)	323474 (74.49)	

Data presented as n (%)

*Chi-square test

†Statistically significant

LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; NHB, Non-Hispanic black; NHW, Non-Hispanic white

Table 3.

Crude and Adjusted Logistic Regression Models Showing Association Between *Clostridioides difficile* Infection by Immunosuppressant Use (MBSAQIP, 2015–2018)

Model, variable	Odds ratio	95% CI	p Value
1[*]			
Immunosuppressant use[†]			
Non-immunosuppressant user	1.0 (ref)	1.0 (ref)	-
Immunosuppressant user	1.945	1.230 – 3.075	0.0044[‡]
2[§]			
Immunosuppressant use[†]			
Non-Immunosuppressant user	1.0 (ref)	1.0 (ref)	-
Immunosuppressant user	1.956	1.236 – 3.095	0.0042[‡]
Age group			
<30 y	1.0 (ref)	1.0 (ref)	-
31–60 y	0.826	0.639 – 1.067	0.0375[‡]
>60 y	1.021	0.727 – 1.435	0.3978
Ethnicity			
NHW	1.0 (ref)	1.0 (ref)	-
Hispanic	0.622	0.450 – 0.859	0.9767
NHB	0.609	0.469 – 0.789	0.8189
Other	0.400	0.290 – 0.553	0.0005[‡]
Sex			
Male	1.0 (ref)	1.0 (ref)	-
Female	1.407	1.112 – 1.780	0.0044[‡]
BMI			
35–39 kg/m^2	1.0 (ref)	1.0 (ref)	-
<35 kg/m^2	1.184	0.804 – 1.743	0.4832
40–49 kg/m^2	1.011	0.801 – 1.274	0.3515
≥50 kg/m^2	1.133	0.872 – 1.472	0.5577
Operation type			
LSG	1.0 (ref)	1.0 (ref)	-
LRYGB	2.183	1.842 – 2.587	<0.0001[‡]
Preoperative diabetes			
No	1.0 (ref)	1.0 (ref)	-
Yes	0.985	0.811 – 1.196	0.8789

[*] Crude logistic regression model

[†] Non-immunosuppressant user: Patients who did not use immunosuppressant before the operation (n = 434271); Immunosuppressant user: Patients who used immunosuppressant for chronic health condition before the operation (n = 7987)

[‡] Significant difference in comparison with reference

[§] Adjusted logistic regression model controlling for age, race/ethnicity, sex, preoperative BMI, surgical procedure, and preoperative diabetes

LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; NHB, Non-Hispanic black; NHW, Non-Hispanic white