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# Is Increased BMI a Risk Factor for Developing Severe Clostridioides Difficile Infection? A Retrospective Study

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## Abstract

*Background*: **Obesity is associated with a relative increase in bacterial phyla like firmicutes, which helps in the colonization of Clostridioides Difficile.**

*Hypothesis*: **Individuals with increased BMI (greater than 25) are more susceptible to severe Clostridioides Difficile infection (CDI).**

*Methods*: **Data was collected by retrospective chart query. Severe CDI was defined as a white blood cell count of more than 15,000 (x 109 cells/L) or serum creatinine levels greater than 1.5 mg/dL. To examine the association between the primary outcome (severe CDI) and BMI, the factors of age, gender, albumin level, ICU admission, antibiotic use within 3 months of admission, diabetes, and hypertension were also considered. Patients with chronic kidney disease, end-stage liver disease, pregnancy, inflammatory bowel disease, previous gastrointestinal surgeries, active malignancy, and immunosuppressed were excluded.**

*Results*: **219 patients were included in the final study. Of these 52.8% of patients had severe CDI, and 47.2% had non-severe CDI. Compared to normal-weight patients, risk of severe CDI was not influenced by being obese (OR = 1.26, p = 0.5119), overweight (OR = 1.65, p = 0.21), or underweight (OR = 1.05, p = 0.9383). Males had higher odds of having severe CDI when compared with females (OR = 1.76, 95% CI = 1.03 to 3.01, p = 0.0395). Albumin levels greater than 3.0 mg/dL were associated with lower odds of having severe CDI (OR = 0.41, 95% CI = 0.27 to 0.62, p< 0.0001).**

*Conclusion*: **BMI of an individual does not appear to be associated with the severity of CDI.**

***Keywords:*** Clostridium difficile, Clostridioides difficile, *Clostridium difficile* diarrhea, Clostridioides difficile diarrhea, *Clostridium difficile* infection, Host-pathogen interactions, Obesity, Dysbiosis, Retrospective studies

## 1. Introduction

Clostridioides difficile, previously known as *Clostridium difficile* is the most common cause of antibiotic-associated diarrhea, as well as healthcare-associated diarrhea.[1] In the early 2000s, a rise in Clostridioides difficile infections (CDI) was observed due to the emergence of the highly virulent ribotype 007 along with the use of more sensitive assays for diagnosis.[2,3] During the period from 2011 through 2017, the estimated national burden of CDI and associated hospitalizations decreased owing to an overall decline in healthcare-associated infections attributable to improved hospital hygiene practices.[3] Despite an observed decline in the total number of cases, the magnitude of mortality and morbidity by CDI remains high. In the year 2017 CDC reported 223,900 new cases of Clostridioides difficile along with 12,800 deaths due to CDI.[4] Recent evidence suggests that there is a rising number of community-acquired CDI as compared

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to hospital-acquired CDI.[5] Traditionally, antibiotic use, advanced age, hospitalization, and gastrointestinal surgery are associated with increased risk for CDI.[1] But recently it has been observed that the patients with community-acquired CDI are comparatively younger with fewer comorbidities, lesser antibiotics exposure, and a lower number of conventional risk factors for CDI.[5]

With this changing landscape of CDI, researchers are pursuing the presence of additional novice risk factors. Researchers across the world have identified obesity, chronic opioid use, statins, and antidepressant use are variables of interest for possible risk factors for CDI.[6] A retrospective cohort study by Mora et al. showed a statistically significant increase in CDI cases among hospitalized patients with a moderate to a high dose of opioid use, likely secondary to the slowing of peristalsis.[7] A greater incidence of severe CDI and CDI-associated morbidity has been observed in patients of inflammatory bowel disease (IBD). The derangement of intestinal microbiota in IBD patients has been attributed to be the cause of their greater susceptibility to severe CDI.[8] A similar dysbiosis of intestinal microbiota is seen in patients with antibiotic use. In recent times, it has become more evident that obese individuals display paucity in the diversity of intestinal micro-organisms.[9] Therefore, it has been hypothesized that obesity might be an independent risk factor for severe CDI. Obesity remains one of the most common comorbidities among our patients, both inpatient and outpatient practice. Thus, we investigated the association of obesity with severe CDI, in this study.

## 2. Methods

### 2.1. Definitions used in the study

A case of CDI was defined as a positive *C. difficile* toxin assay or a positive *C. difficile* molecular assay (PCR) of a stool specimen at the time of symptoms as per standard nomenclature. Severe CDI was defined as WBC count >15,000 cells/ml or serum creatinine >1.5 mg/dl as per Infectious Diseases Society of America guidelines.[10]

We categorized patients as underweight who had BMI <18.5, normal weight with BMI 18.5 to <25, overweight with BMI 25.0 to <30, and obese with BMI >30.0.[11]

### 2.2. Inclusion and exclusion criteria

Inclusion criteria included 1) age above 18 years and b) Clostridioides difficile diarrhea: the presence of diarrhea with stool positive for Clostridioides difficile toxin.

Our exclusion criteria were 1) diagnosis of active malignancy 3) ongoing chemotherapy 4) ongoing cause of immunosuppression (HIV, transplant, on chronic steroids, immunodeficiency syndromes) 5) diagnosis of chronic kidney disease (CKD) or end-stage kidney disease, 6) pregnancy 7) history of inflammatory bowel disease and 8) history of previous gastrointestinal surgeries. CKD was specifically chosen to be one of the exclusion criteria, as the definition of severe CDI included creatinine of more than 1.5 mg/dL. Any patients with baseline creatinine more than or equal to 1.5 mg/dL due to CKD would have been falsely classified in the category of severe CDI.

### 2.3. Data collection

We requested records of 1000 patients admitted to OSF hospitals, with a diagnosis of CDI going back from 31st May 2020 by placing a query in the electronic health data system. After applying exclusion criteria, 219 patients met the criteria for inclusion in the study.

The other variables collected from the electronic medical record were age at the time of admission, gender, weight in kilograms, height in meters, hypertension status, diabetes mellitus status, white blood cell count (WBC) on admission, neutrophil count on admission, albumin levels on admission, creatinine level on admission, current use of proton pump inhibitors, antibiotic use in last 3 months, ICU admission in 3 months before current diagnosis, required ICU care during current admission or not. The variable BMI was computed using the weight in kilograms (kg) and the height in meters (m) using the formula BMI = weight in kg/(height in meters)$^2$. Since creatinine and WBC formed part of the outcome, these two were not included as covariates in the logistic regression model.

### 2.4. Statistical analysis

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). In this study, means and standard deviations were reported for continuous variables, and percentage values were reported for categorical variables. Chi-square tests or exact Chi-square tests were used to check on the associations with categorical variables. Wilcoxon rank-sum tests were used to compare continuous variables. Other appropriate descriptive statistics, such as frequency, median, lower quartile (q25), upper quartile (q75),

minimum, and maximum were used to summarize the data results.

To examine the association between the primary outcome severe *C. difficile* infection and BMI, the factors of age, gender, albumin level, requiring ICU admission, current use of proton pump in, antibiotic use within previous 3 months of admission, diabetes mellitus type 2 and hypertension were all considered.

The univariate analysis and the univariate logistic regression models were first performed, and covariates whose p-value $\leq 0.25$ were included in the multiple logistic regression model. The stepwise model selection was performed, and the final model was constructed. Analysis giving $p< 0.05$ value is considered a statistically significant test. All values are expressed as median (IQR).

## 3. Results

Of 219 individuals who met the inclusion criteria, 106 (48.4%) were males and 113 (51.6%) were females, the median age was 69.0 (59.0–81.0) years, mean weight in kg was 79.8 ± 24.6, mean height in meters 1.7 ± 0.1 and mean BMI in Kg/m2 27.9 ± 8.1.24 (7.9%) patients were under-weight and nearly one-third (107,35.4%) met the criteria for obesity, and nearly half (115, 52.8%) met criteria for severe CDI. Approximately one-third of the patients, 61 (27.9%) needed ICU admission. Of these, 17 patients with CDI had a history of ICU admission in the past 3 months. Table 1 depicts the patient characteristics when comparing severe CDI with non-severe infection.

Compared to normal weight patients, risk of severe CDI was not influenced by being obese (OR = 1.26, p = 0.5119), overweight (OR = 1.65, p = 0.21), or underweight (OR = 1.05, p = 0.9383, Table 2). Males had higher odds of having severe CDI when compared with females (OR = 1.76, 95% CI = 1.03 to 3.01, p = 0.0395). We also observed that with every unit (1 mg/dL) increase in albumin the odds of having severe *C. difficile* infection decreased. Albumin levels greater than 3.0 mg/dL were associated with lower odds of having severe CDI (OR = 0.41, 95% CI = 0.27 to 0.62, p< 0.0001). Patients who required ICU level care were associated with higher odds of having severe *C. difficile* infection when compared with non-ICU patients (OR = 2.30, 95% CI = 1.24 to 4.27, p = 0.0085), which is an expected association.

In the final model (Table 3), after multivariate logistic regression and adjusting for all other factors,

*Table 1. Patient characteristics.*

| *Variables* | *Severe C. difficile infection* | | | *P Value* |
|---|---|---|---|---|
| | *Total N = 218(%)* | *No N = 103(%)* | *Yes N = 115(%)* | |
| **Gender** | | | | *0.039* |
| Female | 113 (100) | 61 (54.0) | 52 (46.0) | |
| Male | 105 (100) | 42 (40.0) | 63 (60.0) | |
| Missing | 0 | 0 | 0 | |
| **Age** | | | | *0.656* |
| N | 218 | 103 | 115 | |
| Median (min - max) | 69.0 (23.0–99.0) | 68.0 (23.0–98.0) | 70.0 (23.0–99.0) | |
| Median (q25 - q75) | 69.0 (59.0–81.0) | 68.0 (59.0–78.0) | 70.0 (59.0–81.0) | |
| Mean ± SD | 66.6 ± 18.0 | 66.2 ± 17.3 | 67.0 ± 18.7 | |
| Missing | 0 | 0 | 0 | |
| **Diabetes** | | | | *0.879* |
| No | 164 (100) | 77 (47.0) | 87 (53.0) | |
| Yes | 54 (100) | 26 (48.1) | 28 (51.9) | |
| Missing | 0 | 0 | 0 | |
| **Hypertension** | | | | *0.543* |
| No | 78 (100) | 39 (50.0) | 39 (50.0) | |
| Yes | 140 (100) | 64 (45.7) | 76 (54.3) | |
| Missing | 0 | 0 | 0 | |
| **Proton Pump Inhibitor use** | | | | *0.077* |
| No | 132 (100) | 56 (42.4) | 76 (57.6) | |
| Yes | 86 (100) | 47 (54.7) | 39 (45.3) | |
| Missing | 0 | 0 | 0 | |
| **Antibiotic use in last 3 months** | | | | *0.982* |
| No | 106 (100) | 50 (47.2) | 56 (52.8) | |
| Yes | 112 (100) | 53 (47.3) | 59 (52.7) | |
| Missing | 0 | 0 | 0 | |
| **ICU admission in last 3 months** | | | | *0.987* |
| No | 201 (100) | 95 (47.3) | 106 (52.7) | |

(*continued on next page*)

*Table 1. (continued)*

| *Variables* | *Severe C. difficile infection* | | | *P Value* |
|---|---|---|---|---|
| | *Total* *N = 218(%)* | *No* *N = 103(%)* | *Yes* *N = 115(%)* | |
| Yes | 17 (100) | 8 (47.1) | 9 (52.9) | |
| Missing | 0 | 0 | 0 | |
| **WBC** | | | | *< 0.001* |
| N | 187 | 83 | 104 | |
| Median (min - max) | 10.0 (1.5−47.0) | 7.8 (1.5−14.9) | 13.6 (3.0−47.0) | |
| Median (q25 - q75) | 10.0 (6.9−14.2) | 7.8 (5.6−9.9) | 13.6 (9.6−17.6) | |
| Mean ± SD | 11.8 ± 7.1 | 7.8 ± 2.8 | 15.0 ± 7.9 | |
| Missing | 31 | 20 | 11 | |
| **Neutrophil** | | | | *< 0.001* |
| N | 211 | 99 | 112 | |
| Median (min - max) | 10.5 (1.4−45.2) | 6.7 (1.4−12.3) | 15.8 (4.0−45.2) | |
| Median (q25 - q75) | 10.5 (6.3−15.9) | 6.7 (4.9−9.5) | 15.8 (12.3−21.8) | |
| Mean ± SD | 12.4 ± 7.6 | 7.0 ± 2.6 | 17.1 ± 7.5 | |
| Missing | 7 | 4 | 3 | |
| **Albumin** | | | | *< 0.001* |
| N | 210 | 98 | 112 | |
| Median (min - max) | 3.0 (1.3−4.7) | 3.3 (1.9−4.5) | 2.7 (1.3−4.7) | |
| Median (q25 - q75) | 3.0 (2.4−3.6) | 3.3 (2.8−3.7) | 2.7 (2.3−3.3) | |
| Mean ± SD | 3.0 ± 0.7 | 3.2 ± 0.6 | 2.8 ± 0.7 | |
| Missing | 8 | 5 | 3 | |
| **Required ICU** | | | | *0.008* |
| No | 157 (100) | 83 (52.9) | 74 (47.1) | |
| Yes | 61 (100) | 20 (32.8) | 41 (67.2) | |
| Missing | 0 | 0 | 0 | |
| **Calculated BMI** | | | | *0.978* |
| N | 217 | 103 | 114 | |
| Median (min - max) | 26.0 (12.8−56.7) | 25.7 (15.2−56.7) | 26.5 (12.8−51.9) | |
| Median (q25 - q75) | 26.0 (21.9−32.7) | 25.7 (21.8−33.2) | 26.5 (22.4−32.3) | |
| Mean ± SD | 27.9 ± 8.1 | 28.1 ± 8.5 | 27.7 ± 7.9 | |
| Missing | 1 | 0 | 1 | |
| **Weight status** | | | | *0.415* |
| Underweight | 20 (100) | 8 (40.0) | 12 (60.0) | |
| Normal | 70 (100) | 37 (52.9) | 33 (47.1) | |
| Overweight | 51 (100) | 20 (39.2) | 31 (60.8) | |
| Obese | 76 (100) | 38 (50.0) | 38 (50.0) | |
| Missing | 1 | 0 | 1 | |

*Table 2. Univariate analysis.*

| *Variables* | *Severe Cdiff* | | | *P Value* |
|---|---|---|---|---|
| | *Total* *N = 218 (%)* | *No* *N = 103 (%)* | *Yes* *N = 115 (%)* | |
| **Gender** | | | | *0.039* [C] |
| Female | 113 (100) | 61 (54.0) | 52 (46.0) | |
| Male | 105 (100) | 42 (40.0) | 63 (60.0) | |
| Missing | 0 | 0 | 0 | |
| **Required ICU** | | | | *0.008* [C] |
| No | 157 (100) | 83 (52.9) | 74 (47.1) | |
| Yes | 61 (100) | 20 (32.8) | 41 (67.2) | |
| Missing | 0 | 0 | 0 | |
| **Protonic** | | | | *0.077* [C] |
| No | 132 (100) | 56 (42.4) | 76 (57.6) | |
| Yes | 86 (100) | 47 (54.7) | 39 (45.3) | |
| Missing | 0 | 0 | 0 | |
| **Antibiotic within 3 months** | | | | *0.982* [C] |
| No | 106 (100) | 50 (47.2) | 56 (52.8) | |
| Yes | 112 (100) | 53 (47.3) | 59 (52.7) | |
| Missing | 0 | 0 | 0 | |
| **Diabetes** | | | | *0.879* [C] |
| No | 164 (100) | 77 (47.0) | 87 (53.0) | |

(*continued on next page*)

*Table 2. (continued)*

| *Variables* | *Severe Cdiff* | | | |
|---|---|---|---|---|
| | *Total* $N = 218$ (%) | *No* $N = 103$ (%) | *Yes* $N = 115$ (%) | *P Value* |
| Yes | 54 (100) | 26 (48.1) | 28 (51.9) | |
| Missing | 0 | 0 | 0 | |
| **Hypertension** | | | | *0.543* [C] |
| No | 78 (100) | 39 (50.0) | 39 (50.0) | |
| Yes | 140 (100) | 64 (45.7) | 76 (54.3) | |
| Missing | 0 | 0 | 0 | |
| **ICU admission within 3 months** | | | | *0.987* [C] |
| No | 201 (100) | 95 (47.3) | 106 (52.7) | |
| Yes | 17 (100) | 8 (47.1) | 9 (52.9) | |
| Missing | 0 | 0 | 0 | |
| **Age** | | | | *0.656* [W] |
| N | 218 | 103 | 115 | |
| Median (min - max) | 69.0 (23.0–99.0) | 68.0 (23.0–98.0) | 70.0 (23.0–99.0) | |
| Median (q25 - q75) | 69.0 (59.0–81.0) | 68.0 (59.0–78.0) | 70.0 (59.0–81.0) | |
| Mean ± SD | 66.6 ± 18.0 | 66.2 ± 17.3 | 67.0 ± 18.7 | |
| Missing | 0 | 0 | 0 | |
| **WBC on admission** | | | | *< 0.001* [W] |
| N | 187 | 83 | 104 | |
| Median (min - max) | 10.0 (1.5–47.0) | 7.8 (1.5–14.9) | 13.6 (3.0–47.0) | |
| Median (q25 - q75) | 10.0 (6.9–14.2) | 7.8 (5.6–9.9) | 13.6 (9.6–17.6) | |
| Mean ± SD | 11.8 ± 7.1 | 7.8 ± 2.8 | 15.0 ± 7.9 | |
| Missing | 31 | 20 | 11 | |
| **Neutrophil** | | | | *< 0.001* [W] |
| N | 211 | 99 | 112 | |
| Median (min - max) | 10.5 (1.4–45.2) | 6.7 (1.4–12.3) | 15.8 (4.0–45.2) | |
| Median (q25 - q75) | 10.5 (6.3–15.9) | 6.7 (4.9–9.5) | 15.8 (12.3–21.8) | |
| Mean ± SD | 12.4 ± 7.6 | 7.0 ± 2.6 | 17.1 ± 7.5 | |
| Missing | 7 | 4 | 3 | |
| **Albumin** | | | | *< 0.001* [W] |
| N | 210 | 98 | 112 | |
| Median (min - max) | 3.0 (1.3–4.7) | 3.3 (1.9–4.5) | 2.7 (1.3–4.7) | |
| Median (q25 - q75) | 3.0 (2.4–3.6) | 3.3 (2.8–3.7) | 2.7 (2.3–3.3) | |
| Mean ± SD | 3.0 ± 0.7 | 3.2 ± 0.6 | 2.8 ± 0.7 | |
| Missing | 8 | 5 | 3 | |
| **Calculated BMI** | | | | *0.978* [W] |
| N | 217 | 103 | 114 | |
| Median (min - max) | 26.0 (12.8–56.7) | 25.7 (15.2–56.7) | 26.5 (12.8–51.9) | |
| Median (q25 - q75) | 26.0 (21.9–32.7) | 25.7 (21.8–33.2) | 26.5 (22.4–32.3) | |
| Mean ± SD | 27.9 ± 8.1 | 28.1 ± 8.5 | 27.7 ± 7.9 | |
| Missing | 1 | 0 | 1 | |
| **Weight status** | | | | *0.415* [C] |
| Underweight | 20 (100) | 8 (40.0) | 12 (60.0) | |
| Normal | 70 (100) | 37 (52.9) | 33 (47.1) | |
| Overweight | 51 (100) | 20 (39.2) | 31 (60.8) | |
| Obese | 76 (100) | 38 (50.0) | 38 (50.0) | |
| Missing | 1 | 0 | 1 | |

[+]Exact test
[T]t-test; [C]Chi-square test; [W]Wilcoxon rank-sum test

*Table 3. Logistic regression models result.*

| Variable | Unadjusted odds ratio | 95% CI | | P-value |
|---|---|---|---|---|
| Gender *Male vs Female* | 1.76 | 1.03 | 3.01 | 0.0395 |
| Albumin | 0.41 | 0.27 | 0.62 | <0.0001 |
| Required ICU *Yes vs No* | 2.30 | 1.24 | 4.27 | 0.0085 |
| Protonic *Yes vs No* | 0.61 | 0.35 | 1.06 | 0.0780 |
| BMI | 0.99 | 0.96 | 1.03 | 0.6693 |
| Weight status new | | | | 0.4185 |
| *Obese vs Normal* | 1.12 | 0.59 | 2.15 | 0.7301 |
| *Overweight vs Normal* | 1.74 | 0.84 | 3.61 | 0.1391 |
| *Underweight vs Normal* | 1.68 | 0.61 | 4.62 | 0.3132 |

we do not have evidence to conclude that weight status was associated with severe CDI.

## 4. Discussion

CDI is the most common cause of nosocomial diarrhea and is quickly becoming a community-acquired disease.[10] Antibiotic use and proton pump inhibitors are established risk factors for CDI but as the disease is now affecting traditionally low-risk patients, there have been attempts to identify novel risk factors. It is worth looking at risk factors that are not only contributing to the acquisition of the infection but also the severity of the disease.[6]

The causative organism of CDI is Clostridioides difficile which is a spore-forming, gram-positive, obligate anaerobic bacillus of the Firmicutes phylum. It is a part of normal human gut microbiota and its growth is kept under control by other more dominant anaerobes. As there is a disruption in the composition of intestinal microbiota, the commensal relation is lost and C. difficle colonizes the intestines. Human gut microbiota consists of over 1 trillion microorganisms and most of these organisms reside in the colon. Normal gut flora contains 60–80% Firmicutes and 20–40% Bacteroidetes.[12] An unhealthy alteration in the gut microbiome is called dysbiosis. In recent years, intestinal dysbiosis has been associated with multiple disease processes including CDI. Patients with obesity display an increase in the percentage population of firmicutes and a decrease in bacteroidetes population.[13] Ley et al. demonstrated a 50% decrease in the bacteroidetes and a concomitant increase in firmicutes in the gut microbiota of mice with homozygous aberrant leptin gene as compared to wild-type or heterozygous mice with $p< 0.005$.[14] Adipose tissue produces an adipocytokine called leptin which behaves as a cytokine as well as a hormone. Leptin levels are expectedly elevated in obese individuals due to the presence of excess adipose tissue. Via its cytokine-like action, leptin induces a state of chronic low-grade inflammation in the obese, reducing their immunity.[15,16] These pathophysiological milieus in obese individuals may place them at an increased risk of severe CDI.

Voth et al. studied the risk of obesity and severe CDI in populations afflicted with IBD. In that study, it was reported that the risk of severe CDI is 3 and 4 times higher in overweight (BMI >25.0–29.9 kg/m2) individuals as compared to underweight/normal individuals (BMI <24.9 kg/m2), respectively. The association of BMI >30.0 kg/m2 and severe CDI did not reach statistical significance but an odds ratio of 1.99 was strongly suggestive of a possible relationship.[6]

Another case–control study reported a strong association between obesity and CDI. In the study, patients with CDI had higher mean BMI when compared to the ones without CDI (33.6 vs 28.9, respectively; $p< 0.001$). However, the relationship between the severity of CDI and obesity was not assessed.[17]

In a retrospective cohort study of 132 community-acquired *C. difficile* infection (CO- CDI) patients, it was found that patients were twice as likely to be obese when compared to the general population (35% vs 23%), but statistical significance was not reached.[8] However, in the same year, a case–control age and gender-matched study of 189 subjects by Punni et al. assessed the effect of obesity and CDI and did not find an association.[18]

The largest retrospective cohort study done to find an association between CDI and obesity included 1,426,807 post-operative patients and surprisingly found that obesity was associated with reduced risk of CDI at 30 days post-surgery in a stepwise manner (1.11%, 0.56%, 0.39%, 0.35%, 0.33% and 0.36% from the lowest to the highest BMI group, respectively; $p< 0.001$ for trend).[19]

In 2017 Mulki et al. performed a retrospective cohort study and demonstrated that BMI >35 kg/m2 was 1.7-fold more likely to be associated with severe CDI compared to a BMI 20–35 kg/m2 ($P< 0.005$) and was an independent predictor of severe CDI ($P = 0.038$). However, unlike our study, they used much broader criteria to define severe CDI. They classified the cases as severe if they met any of the criteria of serum albumin <3 g/dL, severe abdominal tenderness/distention, systolic blood pressure <100 mmHg, temperature >38.5 °C, mental status change, serum lactate levels >2.2 mmol/L or had end-organ failure attributable to CDI.[20]

A retrospective cohort study using the Nationwide Emergency Department Sample (NEDS) from 2017 showed both extremes of BMI, i.e BMI<19 and BMI>40 are associated with increased in-hospital mortality with CDI.[21]

Our study results did not show an association between higher BMI and risk of severe CDI. Current evidence on the association between severe CDI and obesity is somewhat conflicted but leans towards the increased likelihood of CDI in obese individuals (BMI >30kg/m2). A plausible explanation of the lack of expected evidence correlating severe CDI with obesity is the likelihood of under-dosing antibiotics in obese individuals.[22]

Secondarily, we observed in our study that the male gender is associated with the risk of having severe CDI. Traditionally male gender has not been established as a risk factor for CDI or severe CDI.

The existing literature does not have much evidence on gender predilection of CDI. A population-based cross-sectional study in Spain showed no difference in the incidence of CDI between males and females below 45 years but above 45 years.[23]

Our study also showed low albumin level is associated with a greater risk of severe CDI. There are two possible explanations for this association. Low albumin is an indicator of poor nutritional status and lowered immunity making the patient more prone to severe infection. Whilst it is also possible that lower albumin is an inflammatory marker for disease severity.

## 5. Conclusion

There are very few studies dedicated to investigating the association of severe CDI and obesity. The findings of our study do not support an increased risk of severe CDI in patients with obesity, suggesting the possibility of confounding factors influencing previous literature on the subject. The emergence of other factors such as male gender and albumin levels also suggest the possibility of heightened influence of deranged pharmacokinetics in individuals on antibiotics, which may merit exploration by studies designed to assess these factors. The current findings highlight the need for more studies in this area with larger datasets.

### *5.1. Limitations of the study*

We fully acknowledge the limitations arising out of the study design and those inherent to the dataset used. We had strict exclusion criteria but in a retrospective hospital cohort like the current study, it is not possible to eliminate all confounding factors even after using a regression model with multiple factors. Our study also had a relatively small sample size. We could not include CKD patients in our study as elevated baseline creatinine levels would have confounded our definition of severe CDI. So, it is possible that this study could not include quite a few cases of severe CDI. One option was to use absolute rise in creatinine in the patients admitted with CDI, but it was out of the scope of this study.

Moreover, community-acquired and hospital-acquired CDI could not be discerned from our data. The risk factors may be different for the acquisition of these two different modes of infection.

The patients are from multiple hospitals in one catchment area. Virulence of the prevalent C diff strain in the community would impact its infectivity and severity. For eg. *C. difficile* ribotype 027 is a hyper-virulent strain and has been associated with increased morbidity in the community.[24] Besides, determining the strain of *C. difficile* was beyond the scope of our study.

## Disclaimer

This article has not been submitted to other publications. The results are presented at the American College of Physicians (ACP) Southern Illinois Annual Meeting, 2021, and were presented in ACP National 2021 meeting.

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## Conflict of interest

On behalf of all the authors, I, Tulika Chatterjee acknowledge that none of us have any conflict of interest with this research project and this manuscript.

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