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Impact of *Clostridiodes difficile* Infection on Outcomes of Acute Cholecystitis in Hospitalized Patients

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Abstract

Approximately 200,000 individuals are affected by acute cholecystitis (AC) annually. Mainstay treatment options for acute cholecystitis involve antibiotics and laparoscopic cholecystectomy. This may predispose patients to diarrhea from Clostridioides Difficile infection (CDI), a leading healthcare-associated infection. With this study, we aim to assess the influence of CDI on outcomes of hospitalized AC patients in the United States using the National Inpatient Sample (NIS) database. The NIS database was surveyed to account for all AC admissions in the US from 2016 to 2020. This data was later stratified into patients with CDI and without CDI. Outcomes included mortality, LOS, critical care needs, gallbladder complications, and procedural timing. Multivariate regression was performed to identify the association between AC and CDI, as well as risk factors for mortality in the AC and CDI cohort. We found that CDI was associated with significant increase in mortality (8.45% vs 0.90%, p<0.0001), LOS (16.32 vs 4.61days, p<0.0001), increased critical care needs - ICU admission (14.66% vs 2.32%, p<0.0001), mechanical ventilation (11.74% vs 1.94%, p<0.0001), central venous catheter insertion (5.39% vs 0.52%, p<0.0001), and vasopressor support (3.74% vs 0.75%, p<0.0001). CDI was also associated with reduced same-admission cholecystectomy (45.85% vs 78.53%, p < 0.0001). Moreover, the CDI cohort was noted to have higher rates of cholecystostomy (20.49% vs 5.98%, p < 0.0001). Our study demonstrates that CDI is associated with significantly worse outcomes in hospitalized AC patients. Emphasis should be placed on early recognition of risk factors and antibiotic stewardship to mitigate the co-infection with CDI.

Keywords: acute cholecystitis; clostridioides difficile infection; gall bladder disease; cholecystectomy; antibiotic stewardship; mortality

1. Introduction

Globally acute cholecystitis impacts over 6,300 per 100,000 individuals under 50 years, escalating markedly to approximately 20,900 per 100,000 in those aged 50 and above [1]. This acute inflammation of the gallbladder can be triggered by multiple causes, including but not limited to cholelithiasis, motility disorders, chemical injury, ischemia, etc. [2] As per published literature, gallbladder disease affects nearly 20-25 million Americans, with almost 20% individuals suffering from symptomatic illness requiring medical or surgical intervention. [3] Although AC is primarily an

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inflammatory illness, it can be complicated by secondary bacterial infections due to cystic duct obstruction and bile stasis. [4,5]. Additionally, complications such as gangrene, gallbladder perforation, and emphysematous cholecystitis are seen in nearly 7.2% to 26% of cases, and certain cases can advance to sepsis and multiorgan dysfunction. [6-8]

Clostridioides difficile has come to light as a major contributor to healthcare-associated diarrhea. [9] Colonization by C. difficile, characterized by the organism's presence without clinical manifestations, is quite prevalent and affects up to 15% of healthy individuals, 21% of hospitalized patients, and nearly 30% of individuals in long-term care institutions. The likelihood of acquiring an active infection is markedly increased by factors such as recent antibiotic exposure, advanced age, gut dysbiosis, and frequent exposure to healthcare environments. [10] Over the past 2 decades, the burden of C. difficile infection (CDI) has increased. While the annual incidence of CDI increased by 43% from 2001 to 2012, the cases of recurrent CDI surged by 188%. [11] As per Lessa et al, CDI was responsible for an estimated 453,000 infections and approximately 14,000 deaths in the USA, focusing on its impact on public health and healthcare systems. [12]

The Tokyo Guidelines 2018 proposed early laparoscopic cholecystectomy as the standard of care for the majority of patients. [13] However, in critically ill or high-risk patients, percutaneous or endoscopic gallbladder drainage may be necessary. [14,15] Regardless of the severity, almost all patients are provided therapy with antibiotics and analgesics. [4,5, 16-18] Although essential, the widespread use of antibiotics may unintentionally raise the incidence of healthcare-associated infections, notably CDI. [19, 20] Patients with AC may be more susceptible to CDI due to similar risk factors between AC and CDI, including advanced age, hospitalization, and broad-spectrum antibiotic use.

In spite of this, there is a relative scarcity of information on how concurrent CDI affects the clinical outcomes of individuals with AC. Our study aims to address that knowledge gap by assessing outcomes such as mortality, duration of stay, utilization of healthcare resources, need for critical care treatments, and complications.

2. Methods

2.1. Data Source

We conducted a retrospective cohort analysis using the data from the National Inpatient Sample (NIS) spanning the years 2016-2020. The NIS, created as part of the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ), is the largest publicly available all-payer inpatient database in the United States. It provides national representative estimates of hospitalizations, encompassing roughly 35 million discharges each year through weighted sampling. As NIS is a publicly available de-identified database, IRB approval is not required under the Health Insurance Portability and Accountability Act (HIPAA). [21]

2.2. Study Design

ICD-10-CM codes were used to identify adult patients over the age of 18 who had AC as their diagnosis. Based on whether or not a concomitant active Clostridium difficile infection (CDI) was present, the study sample was divided into 2 cohorts. In this retrospective study design, we used propensity score matching to minimize confounding. ICD codes have been mentioned in the Supplementary Table.

2.3. Study Outcomes

In-hospital mortality, duration of hospital stay, and healthcare resource use (as determined by total hospitalization costs converted to 2020 USD) were the primary outcomes. Additionally, we also investigated the use of critical care interventions such as vasopressor support, mechanical ventilation, and admission to an intensive care unit. Major complications such as Acute Kidney Injury (AKI), sepsis, septic shock, peritonitis, gallbladder gangrene, and gallbladder perforation were also evaluated.

2.4. Statistical Analysis

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t-test and Wilcoxon rank-sum test were used for comparing continuous variables, and the chi-square test was used for comparing categorical variables. For determining association, we used a multivariate logistic regression model. A p-value less than 0.05 was deemed statistically significant. SAS software version 9.4 was used for all analyses.

2.5. Procedural Timing Classification

ICD-10 PCS codes were utilized to identify all procedure entries (PR1-PR15) with their corresponding timing information from the dataset. The time to cholecystectomy was determined for each patient based on the first occurrence of these codes. The number of days from admission to the procedure (PRDAY) was then converted to hours by multiplying it by 24. Patients were categorized into 4 groups after this: < 24 hours, 24-48 hours, 48-72 hours, and > 72 hours. Procedure performed during the first 72 hours of admission was labeled as an early laparoscopic cholecystectomy (ELC).

3. Results

3.1. Patient Demographics and Characteristics

From 2016-2020, 1,061,355 patients were admitted with AC, and 6865 patients had a concurrent diagnosis of Clostridioides difficile infection (CDI). Following propensity score matching, 6685 Patients with and without active CDI were chosen for further analysis.

The median age of CDI patients was 71 years (IQR: 60-81), while the median age of non-CDI patients was 59 years (IQR: 42-72). In the CDI group, 71.95%were identified as White, 11.44% as Hispanic, 9.80% as Black, and 52.43% as female. In contrast, among patients without CDI, 52.26% were White, 18.55% Black, 15.71% Hispanic, and 57.74% were females. Table 1 provides specific baseline characteristics.

Table 1. Baseline Characteristics of hospitalizations of AC with and Without CDI, NIS 2016 - 2020.

Characteristics	With CDI (n = 6685)	Without CDI (n=6685)	p-value
Age Group			
18-34 years	265	950	<0.0001
35-60 years	1410	2500	
60-84 years	3945	2855	
> 85 years	1065	379	
Gender			
Male	3180	2825	<0.0001
Female	3505	3860	
Ethnicity			
White	4810	3895	<0.0001
Black	655	1240	
Hispanic	764	1050	
Asian and Pacific Islander	240	140	
Native American	35	15	
Other	180	345	
Hospital Type			
Rural	474	340	<0.0001

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Urban non-teaching	1595	1645	
Urban Teaching	4615	4700	
Primary Insurance			
Medicare	4625	2750	<0.0001
Medicaid	675	820	
Private Insurance	1140	2120	
Self Pay	245	995	

3.2. Primary Outcomes

1. Inpatient mortality: Patients with AC and active CDI had a significantly higher inpatient mortality rate than those without CDI (8.45% vs 0.90%, p<0.0001)
2. Hospital length of stay (LOS): Hospital stays for patients with AC and concurrent CDI were noticeably longer (16.32 vs 4.61days) than those without CDI. Table 2 includes all the outcomes in detail.

Table 2. Impact of CDI on outcomes of Hospitalized AC patients, NIS 2016 - 2020.

Column 1	**With C. Difficile (n = 6685)**	**Without C. Difficile (n=6685)**	**P-value**
Inpatient Mortality	565 (8.45%)	60 (0.90%)	<0.0001
Length of Hospital Stay (days)	16.32 (± 20.19)	4.61 (± 5.79)	
Septicemia	3285 (49.14%)	825 (12.34%)	<0.0001
Septic Shock	1395 (20.87%)	140 (2.09%)	<0.0001
Intubation	785 (11.74%)	130 (1.94%)	<0.0001
ICU admission	980 (14.66%)	155 (2.32%)	<0.0001
CVC	360 (2.69%)	35 (0.52%)	<0.0001
Vasopressors	250 (3.74%)	50 (0.75%)	<0.0001
Gallbladder Gangrene	215 (3.22%)	100 (1.50%)	<0.0001
Gallbladder Perforation	75 (1.12%)	15 (0.22%)	<0.0001
Peritonitis	535 (8.00%)	80 (1.20%)	<0.0001
Gallbladder drainage	1370 (20.49%)	400 (5.98%)	<0.0001
Toxic Megacolon	35 (0.52%)	25 (0.37%)	0.1957
AKI	2150 (32.16%)	805 (12.04%)	<0.0001

3.3. Critical Care Requirements

Critical care interventions such as ICU admission (14.66% vs 2.32%), mechanical ventilation (11.74% vs 1.94%), central venous catheter insertion (5.39% vs 0.52%), and vasopressor support (3.74% vs 0.75%), were required more often for patients with acute cholecystitis and active CDI than for those without CDI.

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3.4. Gallbladder Complications and Interventions

Gallbladder-related complications, such as gallbladder perforation (1.125 vs 0.22%) and gangrene (3.22% vs 1.5%), were more common in patients with concurrent CDI and AC than in those without CDI. Compared to the non-CDI group, the CDI group was significantly less likely to undergo same-admission cholecystectomy (45.85% vs 78.53%, $p < 0.0001$). Additionally, among those who had the same admission surgery, a larger proportion in the CDI cohort experienced delayed intervention beyond 72 hours (38.76% vs 11.83%, $p < 0.0001$). Active CDI patients had a higher likelihood of undergoing gallbladder drainage (20.49% vs 5.98%, $p < 0.0001$)

The CDI cohort also revealed significantly higher rates of additional complications, including septicemia (49.14% vs 12.34%, $p < 0.05$), septic shock (20.87% vs 2.09%, $p < 0.05$), acute kidney injury (32.16% vs 12.04%, $p < 0.05$), and peritonitis (8% vs 1.20%, $p < 0.05$).

3.5. Predictors of CDI in AC Patients

Among patients with acute cholecystitis (AC), certain characteristics were associated with a higher likelihood of concurrent CDI. These included age higher than 35 years, female gender (OR: 1.16, 95% CI: 1.103-1.219), and other comorbid conditions such as diabetes (OR: 1.101, 95% CI: 1.044-1.161), hypertension (OR: 1.097, 95% CI: 1.032-1.166), and congestive heart failure (CHF) (OR: 1.720, 95% CI: 1.623-1.823). The odds of CDI were lower for patients from non-White ethnic origins than for White patients. In terms of hospital attributes, there was no significant difference between urban non-teaching hospitals and urban teaching hospitals (table); however, the former were linked to a marginally lower chance of CDI (OR: 0.934, 95% CI: 0.881-0.990). Regionally, compared to patients in the Northeast, those treated in Midwest hospitals had a greater risk of CDI (OR: 1.15, 95% CI: 1.068-1.244), whereas hospitals in the West and South did not show a statistically significant difference (Table 3)

Table 3. Predictors of CDI among Hospitalized AC patients in the United States, NIS 2016 - 2020.

Variables	Odds Ratio	p-value
Age Group		
18-34 years	Reference	
35-60 years	1.782 (1.558 - 2.039)	<0.0001
60-84 years	2.136 (1.849 - 2.468)	<0.0001
> 85 years	2.074 (1.771 - 2.429)	<0.0001
Gender		
Male	Reference	
Female	1.160 (1.103 - 1.219)	<0.0001
Ethnicity		
White	Reference	
Black	0.936 (0.859 - 1.021)	0.13
Others	0.778 (0.730 - 0.830)	<0.0001
Hospital Type		
Rural	0.909 (0.823 - 1.003)	0.057
Urban non-teaching	0.934 (0.881 - 0.990)	0.021
Urban Teaching	Reference	

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Hospital Region		
Northeast	Reference	
Midwest	1.152 (1.068 - 1.244)	0.0003
South	0.963 (0.895 - 1.036)	0.3
West	1.011 (0.936 - 1.093)	0.77
Hypertension	1.097 (1.032 - 1.166)	0.0028
Diabetes Mellitus	1.101 (1.044 - 1.161)	0.0004
Congestive Heart Failure	1.720 (1.623 - 1.823)	<0.0001

3.6. Predictors of Mortality in AC Patients with CDI

Patients over 35 years old were found to have a considerably increased risk of mortality within the AC and CDI sample (Table). Ethnicity and gender did not significantly affect mortality rates. Among AC patients, hospitals in the Midwest were more commonly linked to CDI; nevertheless, patients treated at Western U.S. hospitals had greater death rates (OR: 1.676, 95% CI: 1.276-2.202). Additionally, diabetes did not significantly correlate with higher mortality, although acute kidney injury (AKI) (OR: 1.726, 95% CI: 1.440-2.069) and congestive heart failure (CHF) (OR: 1.838, 95% CI: 1.523-2.218) showed higher correlation with mortality. (Table 4)

Table 4. Predictors of Mortality among hospitalized AC patients in United States, NIS 2016 - 2020.

Variables	Odds Ratio	p-value
CDI	4.475 (4.094 - 4.890)	<0.0001
Age Group		
18-34 years	Reference	
35-60 years	2.924 (1.493 - 5.728)	0.0018
60-84 years	4.207 (2.162 - 8.186)	<.0001
> 85 years	7.082 (3.541 - 14.163)	<.0001
Gender		
Male	Reference	
Female	0.872 (0.732 - 1.039)	0.12
Ethnicity		
White	Reference	
Black	1.048 (0.761 - 1.445)	0.77
Others	1.087 (0.877 - 1.349)	0.44
Hospital Type		
Rural	0.216 (0.114 - 0.411)	<.0001
Urban non teaching	0.902 (0.733 - 1.112)	0.33
Urban Teaching	Reference	
Hospital Region		

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Northeast	Reference	
Midwest	1.074 (0.810 - 1.424)	0.62
South	0.966 (0.737 - 1.267)	0.8
West	1.558 (1.187 - 2.046)	0.0014
Income Quartile		
Lowest	1.280 (1.218 - 1.345)	<0.0001
Second	1.028 (0.978 - 1.081)	0.28
Third	1.046 (0.995 - 1.099)	0.07
Highest	Reference	
Hypertension	0.794 (0.652 - 0.968)	0.02
Diabetes Mellitus	1.056 (0.877 - 1.272)	0.56

Table 5. Procedural and timing to LC comparison in hospitalized AC patients with and without CDI in the United States, NIS 2016 - 2020.

Procedures	With C Difficile (n = 6685)	Without C. Difficile (n = 6685)	p- Value
Cholecystectomy	3065 (45.84%)	5250 (78.53%)	< 0.0001
Cholecystostomy	1375 (20.56%)	405 (6.05%)	< 0.0001
Timing to Cholecystectomy			
< 24 hours	1070 (18.43%)	1465 (24.6%)	<0.0001
24 - 48 hours	1920 (33.07%)	3170 (53.23%)	<0.0001
48 - 72 hours	565 (9.73%)	615 (10.32%)	0.076
> 72 hours	2250 (38.76%)	705 (11.83%)	<0.0001

4. Discussion

Acute cholecystitis (AC) significantly impacts the healthcare system and remains a major contributor to hospital admissions. It is predominantly thought to affect overweight females in the childbearing age group. Gallstone disease is the major underlying cause, with a global prevalence of 6.1%, and is becoming more common in the 21st century. [22] The pathophysiology of AC is based on the obstruction of the cystic duct by a gallstone, leading to swelling and inflammation of the gall bladder wall. It can progress to ischemia, gangrene, and secondary infection with gas-producing bacteria, all of which are linked to increased mortality rates. [23] The diagnosis of AC has become fairly simple with the help of recent advancements in imaging techniques. The preferred diagnostic method is ultrasound, which often reveals gall bladder wall thickening (>3mm), pericholecystic fluid, gallstones, and a Murphy's sign. In unclear cases, a HIDA scan, considered the most precise technique for the diagnosis of AC, is used. [13,24] Early laparoscopic cholecystectomy (ELC), ideally conducted within 72 hours after admission or within 7-10 days post-symptom onset, continues to be the standard of care. [13,24,25]

Prior to laparoscopic cholecystectomy (LC), preliminary management often includes the administration of intravenous fluids, repletion of electrolytes, providing pain relief, and empiric antibiotics. [13] These empiric antibiotic regimens may consist of piperacillin-tazobactam alone, a combination of fluoroquinolone and metronidazole, or second, third, or fourth-generation

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cephalosporin with metronidazole. For patients who are not eligible for immediate surgical procedure, AC can be managed with an alternative approach like gall bladder drainage (GBD). This can be performed internally using endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography (ERCP)-guided stent placement or externally via percutaneous transhepatic gall bladder drainage (PT-GBD), often serving as a temporary measure until the patient is ready for surgery. [26]

In the United States, Clostridium difficile, formerly known as Clostridium difficile, is the primary cause of healthcare-associated infections and the main cause of deaths from infectious diarrhea, accounting for nearly 500,000 infections and 29,000 associated deaths each year. [12] This organism is a gram-positive, spore-forming anaerobic bacillus. Its spores are remarkably resilient, resistant to many common disinfectants (including alcohol based treatments), and are capable of surviving for extended periods in the environment. The major mechanism of the infection is based on the release of 2 main toxins - TcdA and TcdB from the bacterium, which can disrupt the intestinal epithelial lining and cytoskeleton, ultimately resulting in symptoms like severe diarrhea and complications like acute kidney injury, toxic megacolon, and even death. A diverse and balanced gut microbiome typically prevents germination of spores and expression of toxins. However, disturbance of this microbiota, which is usually caused by the use of antibiotics, can facilitate the expression of toxins and subsequent infection. In addition to these underlying chronic diseases, advanced age, use of gastric acid suppressants are the risk factors for Clostridium difficile infection. [27]

In this retrospective cohort analysis, we analyzed 1,061,355 hospital admissions for acute cholecystitis (AC) from 2016 to 2020, and identified 6,865 cases with Clostridioides difficile infection (CDI). The median age of patients with AC was noted to be 59 years, and 57.74% were females. Conversely, patients with concomitant CDI were older, with a median age of 71 years, and 52.43% of patients were females. The prevalence of CDI in AC patients was significantly related with significantly poor outcomes, including longer hospital stays, higher mortality rates, more complications, and an increased need for critical care.

Uncomplicated AC has a good prognosis and a low fatality rate. In more severe cases, it can cause severe complications such as gangrenous cholecystitis, perforation of the gall bladder, pericholecystic abscess, biliary peritonitis, biliary fistula, emphysematous cholecystitis, empyema, and hemorrhagic cholecystitis, all of which can increase the risk of mortality. [12] In our study, the mortality rate associated with AC (without CDI) was 0.9%, which is comparable to the reported literature. [28,29,30]However, the mortality rate dramatically increased to 8.45% in patients with concomitant CDI. These results align with previously published data on secondary CDI in patients with bacterial infections like pneumonia and urinary tract infections, which have been associated with poorer outcomes and higher mortality rates. [31] As per our knowledge, no prior studies have directly studied the mortality outcomes in AC with concurrent CDI. A study by Marker et al. revealed that individuals with concurrent Clostridioides difficile infection (CDI) and acute diverticulitis had considerably worse outcomes, with a mortality rate of 2% against 0.4% in patients with diverticulitis alone. [32] A study by Drozd EM et al. reported that secondary CDI diagnosis has been associated with worse outcomes than primary CDI. [33] In our study, AC patients with CDI were older and had higher rates of acute kidney injury, sepsis, septic shock, and critical care admission—all of which are known to increase the mortality in patients with AC. [34] Additionally, these patients also experienced more gall bladder-associated complications like gangrene and perforation, classifying them as moderate to severe (Grade 2 or 3) cases using the TG18 criteria [13], which is associated with higher mortality. In our study, CDI was noted to be an independent predictor of mortality in AC with an odds ratio (OR) of 4.475 and a 95% confidence interval (CI) of 4.094 - 4.890.

Acute cholecystitis is one of the most common gastrointestinal disorders necessitating hospitalization and imposes a significant financial strain on the healthcare system, with a projected annual expenditure of $6.3 billion. [35] In our study cohort, patients with isolated acute cholecystitis exhibited an average length of stay (LOS) of 4.61 days. Concurrent presence of Clostridium difficile infection (CDI) increased the LOS to 16.32 days. In a study by Makar et al [32], the average length of stay in CDI and acute diverticulitis group was noted to be much higher (9.40 days vs 4.67 days in non-CDI group) —demonstrating the significant impact of CDI on the clinical burden. The increasing

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need for critical care and the rise in clinical consequences could be the major contributors to this increase. Critical care interventions, including intubation, mechanical ventilation, central venous catheterization, and vasopressor usage, were significantly more common in patients with the AC+CDI group. On top of this, the management of active CDI often involves a multidisciplinary approach, including an infectious disease team, and necessitates increased hospital resources such as isolation protocols and single-use protective equipment. In most cases, prolonged hospital stays are also needed to minimize the risk of community transmission.

Early laparoscopic cholecystectomy (ELC) is largely accepted as the primary therapeutic strategy for acute cholecystitis (AC). Previous data reveal that performing ELC within 72 hours of presentation is associated with fewer perioperative complications, shorter hospital stays, and lower healthcare costs. [36-38] While the overall quality of evidence is considered moderate, the recommendation is endorsed by multiple clinical guidelines. A slightly prolonged time frame, up to 7-10 days after symptom onset, is considered acceptable. In our study, in contrast to 78.53% of patients without concurrent Clostridium difficile infection (CDI), only 45.85% of patients with CDI had cholecystectomy performed during the same hospital stay. Furthermore, patients in the CDI group had higher delays in surgery in nearly 38.76% patients undergoing laparoscopic cholecystectomy after 72 hours of hospitalization, compared to only 11.83% in the non-CDI sample who had LC after 72 hours. This is likely secondary to reduced surgical fitness and increased perioperative risk in CDI patients, which leads to cancelled or delayed procedures.[39] Gall bladder drainage (GBD) is another alternative for patients who are poor surgical candidates. Our analysis revealed that GBD was utilized more frequently in patients with CDI (20.49%) than in those without CDI (5.98%), likely reflecting the higher surgical risk profile in this patient population.

The poor outcomes seen in patients with both AC and CDI as opposed to those with AC alone may be explained by a number of hypothesized mechanisms. C. difficile spores rely on the presentence of primary bile acids in the gut, like cholic acid, for germination. Once colonization takes place, CDI triggers a rapid rise in bile acid concentrations in the intestines within the first 24 hours. [40] This disrupts the enterohepatic cycle, potentially increasing the bile secretions and disrupting the homeostasis, which can contribute to gall bladder inflammation and cause ischemia, ultimately aggravating the severity of cholecystitis. Clostridioides difficile toxins, notably TcfA and TcdB, change Rho-family GTPases (including Rho, Rac, and Cdc42) via ADP-ribosylation and glycosylation. This causes disruption of the actin cytoskeleton, breakdown of tight junction,s and induction of apoptosis in the intestinal epithelial cells. These cellular effects trigger a significant immunological response, resulting in a spike in neutrophils and pro-inflammatory cytokines like IL-1, IL-6, IL-8, and TNF-alpha. These cytokines damage the gut linin,g contributing to the systemic inflammation. In patients with AC, especially those with compromised gallbladder tissue from ischemia or necrosis, this systemic inflammatory response can exacerbate local tissue injury, leading to increased chances of local tissue injury, raising the possibilities of gangrenous alterations or perforation along with the higher risk of sepsis. [41]

For a majority of acute cholecystitis cases, the Tokyo guidelines (TG18) strongly advise the use of antibiotics (class A recommendation). Based on the data from various Randomized controlled trials and the guidelines of the Infectious Disease Society of America (IDSA), TG18 encourages the use of cephalosporins, fluoroquinolones, ampicillin, piperacillin-tazobactam, monobactams, and metronidazole selection optimized based on the infection severity. Results from meta-analysis by Slimming et al. [42] discuss a strong link between the use of penicillin-based combinations, cephalosporins, carbapenems, and fluoroquinolones and the risk of CDI. These antibiotic classes are commonly used to target gram-negative and anaerobic bacteria in AC patients, ultimately leading to an elevated risk of CDI in this patient population. Other identified factors include hospitalization, old age, and female gender. In our analysis, female patients had a higher likelihood of developing CDI (OR: 1.16, 95% CI: 1.103-1.219), along with patients over 35 years of age, and with underlying conditions like diabetes mellitus (OR: 1.101, 95% CI:1.044-1.161), congestive heart failure (CHF) (OR: 1.720, 95% CI: 1.623-1.823), Hypertension (OR: 1.097, 95% CI: 1.032-1.166) were at higher risk of developing CDI. When stratified by hospital type, urban non-teaching hospitals had a lower CDI rate

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(OR: 0.934, CI: 0.881- 0.990) in comparison to Urban teaching facilities. Notably, patients in the Midwest had higher incidences of CDI (OR: 1.152, 95% CI:1.068-1.244).

Our study has noteworthy strengths. A major benefit is the use of data from the largest publicly available multi-ethnic database. Generalizability of our data is supported by the fact that NIS represents approximately 97% of the US patient population. To our knowledge, this is one of the first studies evaluating the impact of Clostridioides difficile infection (CDI) on acute cholecystitis (AC), a leading cause of hospital admission in the US. Additionally, the concerns for bias were reduced by the use of propensity score matchin,g which allowed for a clearer assessment of CDI's effect on AC outcomes.

However, this study also has a few limitations. Due to its retrospective nature, it is subject to design-related biases. We could not determine whether patients who developed CDI had received antibiotics, as this database does not include information on drug use. Additionally, due to dependence on ICD codes, we were unable to determine the onset of CDI during hospitalization. The NIS does not include clinical parameters such as vital signs, medication details, lab results, and diagnostic data, which makes it difficult to assess the severity of AC. Furthermore, we noticed longer hospital stays, but the database does not account for underlying causes of increased LOS, which may have been impacted by discharge delays or unmeasured social factors. As with any other dataset, there is a potential for minor coding inaccuracies due to human input.

5. Conclusions

Our study demonstrates that CDI is associated with significantly worse outcomes, including increased mortality and LOS, increased critical care need,s and gallbladder complications in patients admitted with AC. This study establishes a basis for further investigation into the outcomes of AC in this high-risk patient population. It also emphasizes the importance of following institutional antibiotic stewardship to reduce the risk factors associated with CDI, as well as early recognition and timely management to reduce complications.

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