10-25-2021

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Recommended Citation
Amjad W, Qureshi W, Malik A, Singh R, and Jafri SM. The outcomes of Clostridioides difficile infection in inpatient liver transplant population. Transpl Infect Dis 2021.

Received: 17 July 2021 | Revised: 22 September 2021 | Accepted: 8 October 2021

DOI: 10.1111/tid.13750

ORIGINAL ARTICLE

WILEY

The outcomes of *Clostridioides difficile* infection in inpatient liver transplant population

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Abstract

Background: Chronic immunosuppression is a known cause of *Clostridioides difficile*, which presents with colon infection. It is associated with increased mortality and morbidity. Our aim is to determine the inpatient outcomes of liver transplant patients with *Clostridioides difficile* infection (CDI) and trends in the last few years.

Methods: We utilized the national re-admission data (2010–2017) to study the outcomes of CDI in liver transplant patients. Association of *C. difficile* with re-admission was computed in a multivariable model adjusted for age, sex, gastrointestinal bleeding, hypertension, diabetes, hyperlipidemia, congestive heart failure, cerebrovascular disease, obesity, cancer, insurance, chronic kidney disease, chronic obstructive pulmonary disease, dementia, peripheral vascular disease, smoking, hospital location, and teaching status.

Results: During 2010–2017, there were 310 222 liver transplant patients hospitalized. Out of these, 9826 had CDI. CDI infection in liver transplant patients was associated with higher 30-day re-admission (14.3% vs. 11.21%, hazard ratio [HR]: 1.14, 95% confidence interval [CI]: 1.01–1.28, $p = .02$) and in-hospital mortality (odds ratio [OR]: 1.36, 95% CI: 1.14–1.61, $p < .001$). The most common causes of re-admission in the CDI group were recurrent CDI (41.1%), liver transplant complications (16.5%), and sepsis (11.6%). The median cost for liver transplant patients with *C. difficile* was significantly higher, $53 064 (IQR $24 970–$134 830) compared to patients that did not have *C. difficile*, $35 703 ($18 793–$73 871) ($p < .001$). The median length of stay was also longer for patients with CDI, 6 days (4–14) vs. 4 days (2–7) ($p < .001$).

Conclusion: CDI in post-liver transplant patients was associated with higher mortality, re-admission, health care cost, and longer length of stay. The most common cause of re-admission was recurrent CDI, which raises the question of the efficacy of standard first-line therapy.

KEYWORDS
Clostridioides difficile infection, immunosuppression, liver transplant

1 | INTRODUCTION

Clostridioides (formerly *Clostridium*) *difficile* is a gram-positive, spore-forming bacteria that is one of the most common causes of nosocomial infection. It infects the colon and typically presents with diarrhea.[1,2] The incidences of *C. difficile* infection (CDI) have increased in the last two decades and is reported as 147 cases per 10 000 people in the United States.[2,3] The traditional risk factors for CDI are antibiotics use, advanced age, health care exposure, chemotherapy, and immunocompromised state.[1,4] Other risk factors include hypoalbuminemia, long hospital stay, gastric acid suppression, obesity, tube feeding, and gastrointestinal surgeries.[2,5–7]

The immune system is compromised by medications in solid organ transplant (SOT) patients and potentially contributes to a higher risk of CDI. Studies have suggested increased incidences of CDI post liver transplant, which can be explained due to change in gastrointestinal anatomy, prolonged hospital stay, frequent use of antibiotics, and immunosuppressant use.[8,9] The published data suggest that the incidence of CDI in SOT patients is 7.4%–11.8%.[10,11] The studies had reported up to 9% CDI cases in liver transplant recipients, and one single-center study had shown the incidence of 18.9%.[10,12,13] The CDI is seen in the immediate post-transplant period. The peak time of onset of infection is ranged from 6 to 31.5 days. The late-onset CDI is either due to repeated antibiotic exposure or an increased dose of immunosuppression in the setting of rejection.[12,14] The reported complications of the CDI in SOT population are fulminant colitis, renal failure, colectomy, graft loss, and mortality.[8,15–17] Surprisingly, a few studies had shown no major difference in mortality between CDI patients with and without SOT.[18–21] Although the comparative study by Gellad and colleagues[20] had shown that corticosteroid use was associated with CDI irrespective of transplantation.

The prior studies on the CDI with liver transplants have variations in study methodology, making it difficult to draw firm conclusions. A better understanding is required for clinicians to improve management and outcomes. Our aim is to determine the burden of CDI in the liver transplant population using large national data. We also seek to estimate the in-hospital outcomes, including mortality, resource utilization, and hospital re-admission.

2 | METHODS

2.1 | Study population and design

This retrospective study utilized national re-admission data (NRD), which is a national representative cohort of hospitalized admissions that were admitted from January 1, 2010 to December 31, 2017. The NRD is a subgroup of the Healthcare Cost and Utilization Project (HCUP). It is the nation's largest inpatient database of encounter-level hospital care and all-payer data, which is sponsored by the Agency for Healthcare Research and Quality (AHRQ).[22] It provides approximately 20% of the stratified sample of all hospitals in the United States, which represents more than 95% of the national population. The database provides de-identified information about the patients' demographics and hospital-based information. In addition, it provides information about the re-admission status. As a publicly available database was used, the study was considered exempt from obtaining permission from the institutional review board.

We used the International Classification of Diseases, Ninth Edition (ICD-9) and ICD-10 diagnostic codes to identify patients with liver transplant (ICD-9: 996.82, V42.7 and ICD-10: Z944, T86.40, T8641, T86.42, T86.4, T86.49, T86.42) and CDI (ICD-9: 008.45 and ICD-10: A04.72, A04.7, A04.71). All adult patients ≥18 years were included in the study. Patients were excluded if they were discharged during the month of December to ensure at least a 30-day follow-up. Based on this exclusion, we identified 9826 liver transplant patients with CDI with a national estimate of 0.9%.

2.2 | Patient and hospital characteristics

Baseline patient demographic characteristics (age, sex, race, hospital, and insurance payer) were extracted. The AHRQ Elixhauser and Charlson's comorbidity index was calculated to report the comorbidities.[23,24] Diagnostic codes were used to identify the history of renal transplant, human immunodeficiency virus (HIV), pneumonia, complications of liver transplant hypertension, diabetes mellitus, hyperlipidemia, obesity, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, prior myocardial infarction, and causes of liver diseases (Table S1). The discharge disposition and length of stay were also reported.

2.3 | Outcomes

The primary outcome was 30-day all-cause re-admission and predictors of re-admission. In addition, predictors of mortality were also studied. We also evaluated the trends of 30-day re-admission and mortality. In-hospital complications such as intubation, ICU admission, and use of pressors were captured. We reported length of stay on re-admission and index hospitalization.

2.4 | Statistical analysis

Baseline characteristics were expressed as weighted values based on discharge weights provided in the database. Continuous variables with normal distribution were expressed as weighted mean ± standard deviations and with skewed distribution as weighted median with interquartile range (IQR). Categorical variables were expressed as weighted whole numbers with percentages. These were compared with the Pearson chi-square test and analysis of variance where appropriate for patients with and without CDI. We computed the hazard ratio (HR) with 95% confidence intervals (CI) for the association of 30-day re-admission in multivariable Cox regression models adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, obesity, chronic obstructive pulmonary disease, acute kidney injury, chronic kidney disease, primary causes of liver disease, history of renal

TABLE 1 Baseline characteristics

Variables	Total cases N = (310 151)	*Clostridioides difficile* infection		p-Value
		Present (n = 9826)	Absent (n = 300 325)	
Age		50.6 ± 21.5	52.0 ± 20.2	.02
Female	125 306 (40.4%)	4634 (47.2%)	120 672 (40.2%)	<.001
Hypertension	113 890 (36.7%)	3190 (32.5%)	110 700 (36.9%)	<.001
Hyperlipidemia	45 808 (14.8%)	1265 (12.9%)	44 543 (14.8%)	.003
Diabetes mellitus	130 454 (42.1%)	4118 (41.9%)	126 337 (42.1%)	.87
Smoker	68 067 (21.9%)	1833 (18.7%)	66 233 (22.1%)	<.001
Obesity	26 532 (8.55%)	713 (7.25%)	25 819 (8.6%)	.02
Chronic obstructive pulmonary disease	68 423 (22.1%)	2310 (23.5%)	66 113 (22.0%)	.10
Congestive heart failure	50 353 (16.2%)	1864 (19%)	48 489 (16.1%)	<.001
Acute kidney injury	86 074 (27.8%)	4063 (41.4%)	82 011 (27.3%)	<.001
Chronic kidney disease	154 091 (49.7%)	5505 (56%)	148 586 (49.5%)	<.001
Prior myocardial infarction	22 436 (7.23%)	703 (7.15%)	21 733 (7.24%)	.86
Cancer	39 648 (12.8%)	1416 (14.4%)	38 232 (12.7%)	.02
History of renal transplant	28 324 (9.13%)	951 (9.68%)	27 372 (9.11%)	.312
Complications of liver transplant	75 802 (24.4%)	2517 (25.6%)	73 285 (24.4%)	.22
Pneumonia	29 020 (9.36%)	1161 (11.8%)	27 858 (9.28%)	<.001
HIV	1171 (0.38%)	23 (0.24%)	1148 (0.38%)	.11
Any GI bleed	23 914 (7.71%)	1056 (10.7%)	22 857 (7.61%)	<.001
Teaching hospital	255 285 (82.3%)	8666 (88.2%)	246 620 (82.1%)	<.001
Urban hospital	266 520 (85.9%)	8897 (90.6%)	257 622 (85.8%)	<.001
ICU admission	17 916 (5.8%)	1072 (10.9%)	16 844 (5.6%)	<.001
Insurance				.10
Medicare	151 983 (49.1%)	4655 (47.5%)	147 328 (49.2%)	
Medicaid	50 739 (16.4%)	1608 (16.4%)	49 130 (16.4%)	
Private	95 880 (31.0%)	3247 (31.1%)	92 632 (30.9%)	
Self-pay	3034 (0.98%)	59 (0.61%)	2975 (0.99%)	

transplant, HIV, complications of the liver transplant, pneumonia, urban versus rural hospital location, teaching hospital status, insurance status, AHRQ mortality risk, all patient-defined DRG mortality risk, and all patient refined severity of illness. For secondary outcomes such as mortality, hospital charges, length of stay, we computed odds ratio (OR) with 95% CI in multivariable-adjusted logistic regression models adjusted for the variables given above after removing the outcome variable. Weighted analyses were used for all statistical calculations. Statistical analysis was performed using STATA version 14.2 (College Station, TX). All *p*-values were two-sided, with a significance threshold of $p < .05$.

3 | RESULTS

Among 310 151 hospitalizations with a history of liver transplant in the NRD database during 2010–2017, there were 9826 (3.2%) patients with a diagnosis of CDI. The baseline characteristics of liver transplant patient admitted to hospital are given in Table 1. The patients with CDI were younger (50.6 ± 21.5 vs. 52.0 ± 20.2, $p = .02$), and had higher percentage of female population (47.2% vs. 40.2%, $p < .001$). The prevalence of acute kidney injury (41.4% vs. 27.3%, $p < .001$), chronic kidney disease (56% vs. 49.5%, $p < .001$), malignancies (14.4% vs. 12.7%, $p = .02$), GI bleed (10.7% vs. 7.61%, $p < .001$), and pneumonia (11.8% vs. 9.28%, $p < .001$) were higher in liver transplant patients with CDI, whereas hypertension (32.5% vs. 36.9%, $p < .001$), hyperlipidemia (12.9% vs. 14.8%, $p = .003$), smoking (18.7% vs. 22.1%, $p < .001$), and obesity (7.25% vs. 8.6%, $p = .02$) prevalence was lower in CDI population. A higher number of *C. difficile* patients were admitted in teaching, urban hospitals, and required ICU admissions (Table 1).

Hepatitis C was the most common etiology in the liver transplant cohort, followed by nonalcoholic fatty liver disease. The patients with *C. difficile* had a higher prevalence of history of alcohol liver disease (8.7% vs. 7.7%, $p = .002$) and primary biliary cholangitis (1.17% vs.

TABLE 2 Primary outcomes and association with *Clostridioides difficile* infection

Outcomes	Hazard ratio	*p*-Value
Inpatient mortality (odds ratio)	1.36 (1.14–1.61)	<.001
Length of stay (beta coefficient)	5.87 (5.09–6.65)	<.001
Length of stay in survivors (beta coefficient)	5.68 (4.90–6.44)	<.001
Hospital charges (beta coefficient)	58 841 (47 827–69 856)	<.001
Hospital charges in survivors (beta coefficient)	52 732 (42 757–62 706)	<.001
30-Day re-admission	1.14 (1.02–1.29)	.02

0.87%, $p = .04$), whereas the patients without *C. difficile* had higher prevalence of history of hepatitis C (15.1% vs. 13%, $p = .001$) and hepatitis B (1.91% vs. 1.45%, $p = .02$) (Table S2). The median length of stay in liver transplant patients with CDI was higher, 6 days (IQR 4–14), as compared to those without CDI, 4 days (IQR 2–7) $p < .001$ (Table 2).

3.1 | Predictors of 30-day re-admission

The liver transplant patients with *C. difficile* had a higher 30-day re-admission rate (14.3% vs. 11.21%, HR: 1.14, 95% CI: 1.01–1.28) as compared to non-*C. difficile* patients. Patients with alcohol liver disease (HR: 1.19, 95% CI: 1.04–1.36), hepatocellular cancer (HR: 1.26, 95% CI: 1.07–1.48), autoimmune liver disease (HR: 1.20, 95% CI: 1.03–1.41), and primary sclerosing cholangitis (HR: 1.15, 95% CI: 1.02–1.3) were associated with a higher likelihood of 30-day re-admission. The other independent factors associated with increased 30-day re-admission were liver transplant-related complications and history of gastrointestinal bleed, acute kidney injury, chronic kidney disease, diabetes mellitus, chronic obstructive pulmonary disease, and coronary artery disease (Figure 1 and Table S4A).

The most common cause of re-admission in the study group was CDI (578, 41.1%), followed by complications of transplant (233, 16.5%), sepsis (160, 11.4%), acute kidney injury (51, 3.6%), and pneumonia (48, 3.4%), whereas the complication of the liver transplant was the most common cause of re-admission in the non-CDI liver transplant population (Table 4).

3.2 | Secondary outcomes

After the liver transplant, the mortality rate was higher (OR: 1.36, 95% CI: 1.14–1.61, $p < .001$) in the *C. difficile* population. The liver transplant patients with a history of alcohol liver disease (OR: 1.26, 95% CI: 1.05–1.52) and hepatocellular cancer (OR: 1.54, 95% CI: 1.27–1.87) also had higher mortality. The other independent predictors associated with higher in-hospital mortality were older age, gastrointestinal bleed, acute kidney injury, history of renal transplant, post-liver transplant complications, pneumonia, and coronary artery disease (Figure 2 and Table S4B).

The patients with *C. difficile* had more complicated hospital stay requiring intensive care unit (ICU) admission (OR: 1.76, 95% CI: 1.55–2.00), intubations (OR: 1.85, 95% CI: 1.60–2.13, $p < .001$), esophagogastroduodenoscopy (EGD) (OR: 1.39, 95% CI: 1.17–1.67,

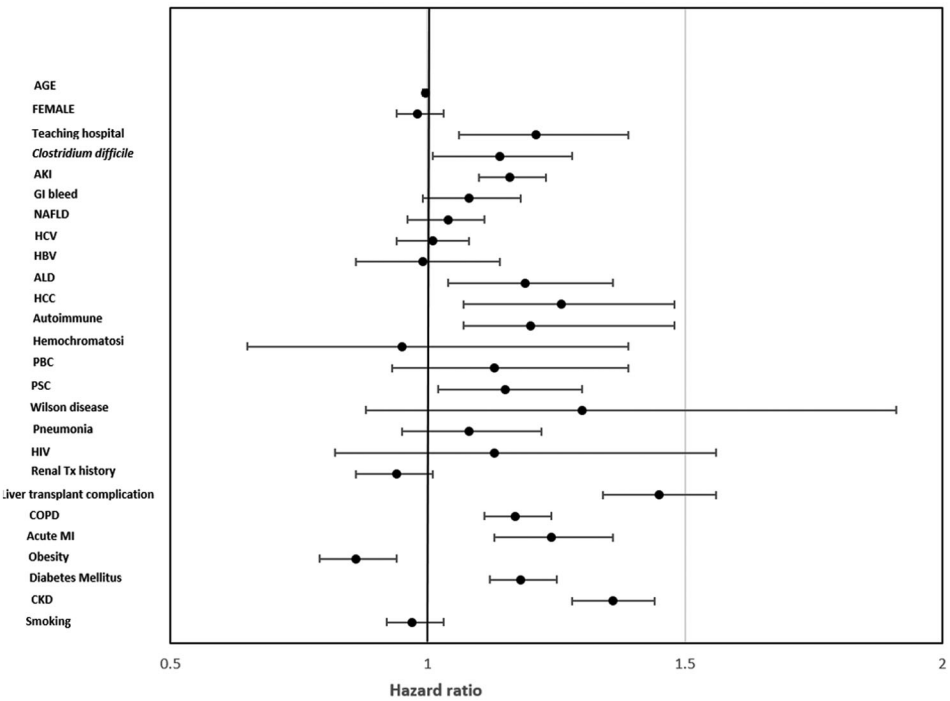

FIGURE 1 Forest plot showing the predictors of the 30-days re-admission in hospitalized liver transplant patients

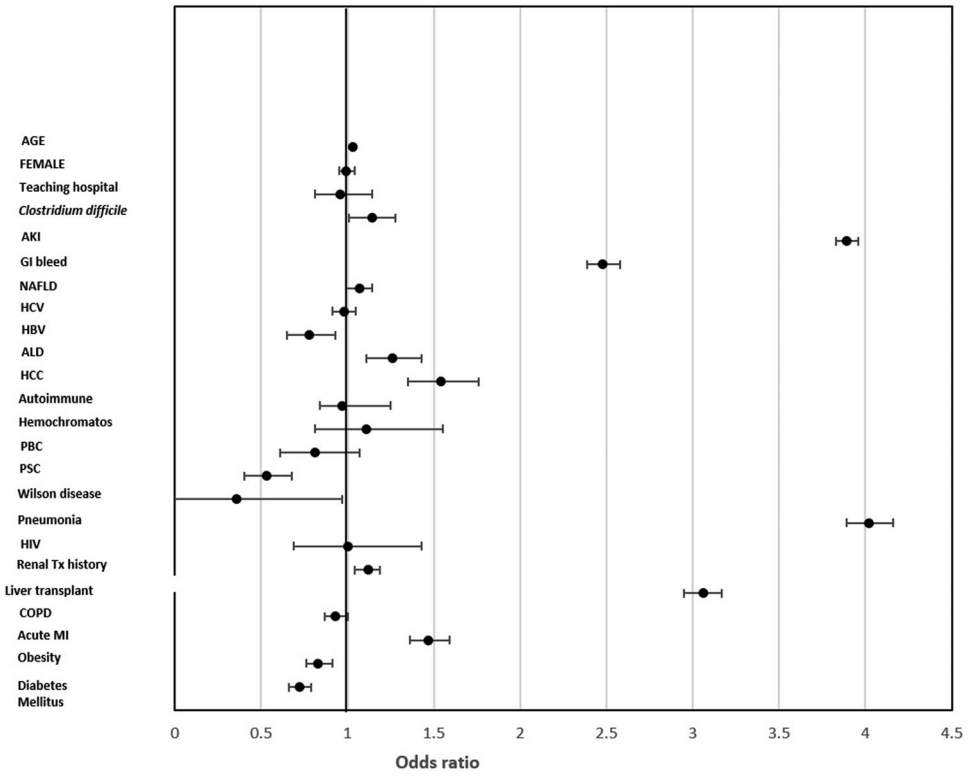

FIGURE 2 Forest plot showing predictors of inpatient mortality in hospitalized liver transplant patients

TABLE 3 Association of *Clostridioides difficile* infection with secondary outcomes

Outcomes	Odds ratio (95% CI)	*p*-Value
ICU admission	1.76 (1.55–2.00)	<.001
Intubation	1.85 (1.60–2.13)	<.001
Pressors use	1.22 (0.85–1.76)	.27
Esophagogastroendoscopy	1.39 (1.17–1.67)	<.001
Colonoscopy	1.95 (1.64–2.31)	<.001

TABLE 4 Top five major causes of re-admissions in *Clostridioides difficile* infection patients

Etiologies	*N*
Clostridioides difficile	578
Complications of liver transplant	233
Sepsis	160
Acute kidney injury	51
Pneumonia	48

$p < .001$), and colonoscopies (OR: 1.95, 95% CI: 1.64–2.31, $p < .001$) (Table 3).

3.3 | Hospital cost

The data suggested that the liver transplant patients with CDI had a higher inflation adjusted cost of $53 064 (IQR: $24 970–$134 830) vs. $35 703 (IQR: $18 793–$73 871) as compared to non-CDI liver transplant patients; $p < .001$. This difference stays statistically significant in survivors (Table 2).

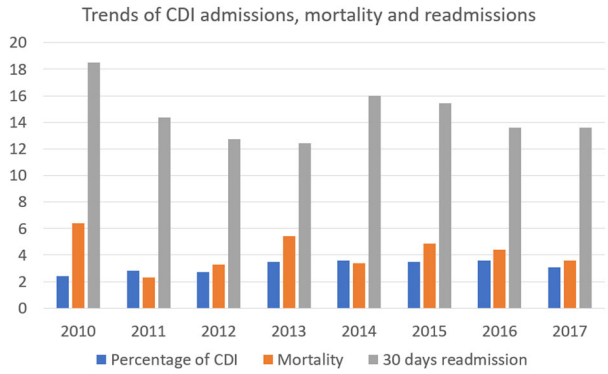

FIGURE 3 Trends of *Clostridioides difficile* infection in liver transplant patients (2010–2017)

3.4 | Trends of CDI in liver transplant patients

The trends of CDI prevalence had increased modestly from 2010 to 2017 (2.4% vs. 3.1%), whereas in-hospital mortality (18.5% vs. 14%) and 30-day re-admission (6.4% vs. 3.6%) had slightly improved in the last decade (Figure 3 and Table S3).

4 | DISCUSSION

This study of the liver transplant cohort demonstrated CDI prevalence of 32 per 1000 patients. The patients hospitalized with *C. difficile* had a more severe illness, and the CDI was independently associated with 36% higher mortality and 14% higher 30-day re-admission. The patients with alcoholic liver disease and hepatocellular cancer were associated with higher 30-day re-admission rates and mortality. The length of stay, ICU admissions, and hence total costs were also higher in CDI. The trend of the CDI rate in liver transplant patients has increased in the last decade. Interestingly, CDI was the most common cause of re-admission as compared to non-CDI patients, who were mostly readmitted because of liver transplant-related complications.

Previously, a single-center study analyzed 10 years of data and demonstrated a high incidence of CDI in liver transplant patients, and a majority of them were observed in the first year of transplant. The predictors of developing CDI were White race, length of stay, and pre-transplant model for end-stage liver disease (MELD) score. The recurrence rate was 16.9%.[13] Similarly, a small study had identified length of stay, pre-transplant antibiotic use, prior history of CDI, CKD, and exposure to proton pump inhibitors as possible risk factors for post-liver transplant CDI.[21] Another retrospective study recaptured similar results, and live donor liver transplant patients had a higher incidence of CDI, although the number of these observations was small.[14] Usually, the MELD score is lower in live donor recipients; it is difficult to establish a pre-transplant MELD score as a true risk factor in these patients.

A national database study had shown a three-fold increase in the prevalence of CDI in the hospitalized liver transplant patients, which was also associated with increased mortality as compared to the non-CDI liver transplant patients.[17] One national inpatient sample (NIS) study utilized 2016 data and showed an increased risk of shock, organ failure, and ICU admission in CDI with a liver transplant, but the mortality was not different from non-transplant patients.[19] Another study utilized NIS and showed the same 2.7% prevalence of CDI in SOT patients, and these patients had adverse outcomes.[25] Our study utilized the same administrative data and reproduced similar results. The prevalence of CDI has increased in hospitalized patients to 3.2% as per our observation. We also looked at the re-admission rates and determined the causes and predictors of 30-day re-admission, which was previously not well described.

Previously, the fidaxomicin and vancomycin had shown better outcomes over metronidazole.[2,26] The recent Infectious Diseases Society of America (IDSA) guidelines recommend fidaxomicin as first-line treatment for initial CDI, and vancomycin as an alternative. In recurrent CDI, fidaxomicin (standard or extended pulsed regimen) is recommended. The vancomycin (tapered and pulsed regimen) is alternative for the first recurrence when fidaxomicin is not available. For multiple CDI recurrence, the alternatives are vancomycin (tapered and pulsed regimen), vancomycin followed by rifaximin, and fecal microbiota transplantation. Co-administration of bezlotoxumab is also suggested in recurrent CDI in the last 6 months to reduce the likelihood of subsequent recurrent infection. If the logistic allows, bezlotoxumab can benefit patients with primary CDI with a high risk of recurrence (advanced age, severe infection, and immunocompromised state).[27] There is no transplant-specific guideline. There is a fear of vancomycin-resistant *Enterococcus* (VRE) with vancomycin use in the immunocompromised population.[28] Our study utilized the data prior to the recent IDSA guidelines. The fecal microbiota transplant in SOT has promising outcomes in the published studies,[29] but there is weak evidence as prospective data are limited.[30]

There are several implications of our study. First, this study shows that having a diagnosis of CDI in the liver transplant population is not benign. It leads to increased mortality, hospital re-admission, and resources utilization, including more procedures, length of stay, hence higher cost. Second, we found that the most common cause of re-admission was the CDI. This suggests more intense treatment in liver transplant patients and consideration of bezlotoxumab as adjunctive treatment in primary infection cases.

There are several limitations due to the retrospective nature of the study. As NRD are often created for financial and administrative purposes, these lack certain pertinent clinical information such as radiological information, laboratory data, sequence of events, medications use, and biomarkers. As a result, we did not comment on the stool colonization and antimicrobial's affectivity. Additionally, it does not fully reflect all national hospitalizations, as NRD account for 20% of all US hospitalizations and the national estimations are generated using discharge weight estimates, it may underestimate the true prevalence of CDI amongst patients with liver transplantation. Finally, only in-hospital outcomes are measured, and the exact cause of death is not available. Despite these limitations, the NRD still provide an important understanding of the effects of hospitalized CDI in the liver transplant population with large statistical power.

The CDI in liver transplant recipients continues to increase. It is associated with higher mortality, prolonged length of stay, higher re-admission, and resource utilization. The judicial use of antibiotics, immunosuppression, acid suppressive medications, and shorter hospital stay can reduce the incidence of CDI. More intense doses and duration of the medical treatment can improve the re-admission rates.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Waseem Amjad and Waqas Qureshi contributed to the acquisition of the data. Waseem Amjad and Adnan Malik collected the ICD codes. Waqas Qureshi ran the analysis. Waseem Amjad interpreted the data. Waseem Amjad, Waqas Qureshi, Adnan Malik, and Ritu Singh wrote the manuscript. Syed-Mohammed Jafri did the critical review and final edits. All authors agreed with the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Amjad W, Qureshi W, Malik A, Singh R, Jafri S-M. The outcomes of *Clostridioides difficile* infection in inpatient liver transplant population. *Transpl Infect Dis*. 2021;e13750. https://doi.org/10.1111/tid.13750