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ORIGINAL ARTICLE

Readmission, healthcare consumption, and mortality in *Clostridioides difficile* infection hospitalizations: a nationwide cohort study

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Abstract

Objective Despite being the most common healthcare-related infection in the US, nationwide data on readmission, healthcare consumption, and mortality in *Clostridioides difficile* infection (CDI) remain limited. We examined these outcomes in a US-based cohort of patients with CDI.

Methods We queried the 2017 Nationwide Readmission Database using ICD-10-CM codes to identify all adult patients admitted with a principal diagnosis of CDI. Primary outcomes were 30- and 90-day readmission rates. Secondary outcomes included mortality rates and healthcare consumption.

Results Of the 83,865 patients discharged from an index hospitalization for CDI, 22.37% were readmitted within 30 days, and an additional 15.01% were readmitted within 90 days. Recurrent CDI was responsible for more than 30% of readmissions at both 30 and 90 days. Compared to the index hospitalization, readmissions were characterized by higher mortality (1.41% index vs. 4.86% 30-day vs. 4.40% 90-day) and increased hospital length of stay and charges. Medicaid insurance (HR 1.16), cirrhosis (HR 1.31), Type 1 diabetes mellitus (HR 1.38), and end-stage renal disease (HR 1.36) were independently associated with 30-day readmission (all $p < 0.01$), with similar findings in 90-day readmissions.

Conclusions In a large cohort of patients hospitalized for CDI, we found that approximately 1 in 5 were readmitted within 30-days, and more than 1 in 3 within 90-days. Readmission was characterized by increased mortality and greater healthcare consumption. Additionally, we found independent associations for readmission that may help identify patients at high-risk. Prospective investigation is needed to identify means to reduce the healthcare consumption and mortality in CDI.

Keywords Clostridioides difficile infection · Readmission · Outcomes · Healthcare utilization · Mortality

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Introduction

Clostridioides difficile infection (CDI) is notorious for its propensity to cause severe inflammatory diarrhea, extensive colitis, and numerous other complications. According to a 2015 US survey, CDI accounts for approximately 15% of healthcare-related infections, making it the most common etiology of such infections [1]. In addition, CDI is responsible for nearly 30,000 deaths per annum in the US, with an increased risk in certain groups—namely those who are immune-compromised or elderly [2–4]. Given an overall aging general population and increasing levels of patient complexity, CDI undoubtedly remains a prevalent healthcare concern [2, 3].

CDI poses a significant burden on US healthcare systems as infected patients have been shown to have longer, more expensive hospitalizations compared to uninfected patients [3–6].One study estimated CDI to cost the US healthcare system $1.62 billion per year. In addition, this problem appears to only be worsening as rates of recurrent CDI have increased by more than three-fold over an 11-year period studied, many of which translated into hospital readmissions [6].

Considering the burden CDI has on the healthcare system, the US Department of Health and Human Services initiated a National Action Plan to prevent such infections [7]. Moreover, numerous major insurance companies require public reporting of CDI rates with financial penalties for underperforming hospitals and/or those with increasing all-cause readmissions [8, 9].

Despite these initiatives, data on CDI readmission, mortality, and healthcare utilization are largely limited to studies with small sample sizes, inadequate adjustment for confounding factors, single-center experiences, and/or older data [6–11]. We hypothesize that CDI is associated with significant mortality, healthcare expenditures and increased readmission at both 30- and 90-days. As such, we examined these clinical outcomes in a cohort of patients with CDI using a large, nationally-representative database.

Methods

Data source

In this retrospective cohort study, we queried the National Readmission database (NRD) from January 2017 to November 2017 for 30-day follow-up and to September 2017 for 90-day follow-up. The NRD is the largest database of hospital readmissions in the US and is derived from billing data submitted to statewide organizations based upon discharge abstracts. The NRD 2017 database is nationally representative as it contains data from almost 20 million hospital stays in 2,454 hospitals in 28 states, accounting for almost 60% of the US population. It contains de-identified clinical and non-clinical elements at both the patient- and hospital-level using the International Classification of Diseases-10th revision (ICD-10) coding system.

Study population

Patients with a primary diagnosis of CDI during hospitalization (based upon ICD-10 diagnostic codes A04.71, A04.72) were included in the study. Patients were excluded if they were less than 18 years of age, the admission was elective, or discharge disposition was unknown (Fig. 1). All-cause mortality, length of stay (LOS), and charges during the index hospital admission were identified. All-cause hospitalization mortality, length of stay (LOS), and charges upon readmission were identified and compared to that of the index hospital admission. Patient demographics, hospital demographics, and comorbid risk factors (based on ICD-10 diagnostic and procedural codes) for readmission, along with the most common diagnoses/causes of readmission, were recorded. The ICD-10-CM diagnostic and procedural codes used in this study are presented in Supplementary Table 1. These codes have been used successfully in previous work on this topic [11, 12].

Ethical considerations

Institutional Review Board approval was not required for this study as it was performed using de-identified and nationally available data.

Study variables

Patient demographics included age, sex, median household income, primary expected payer, and burden of comorbidities—as assessed by the Charlson Comorbidity Index (CCI). Hospital demographics included hospital size (based on the number of beds), teaching status, region, and location. These variables were included as we hypothesize that perhaps ethno-racial disparities and or hospital teaching status or location/region may play a role in predicting hospital outcomes in CDI as seen in other infections and inflammatory diseases in the biomedical literature [11].

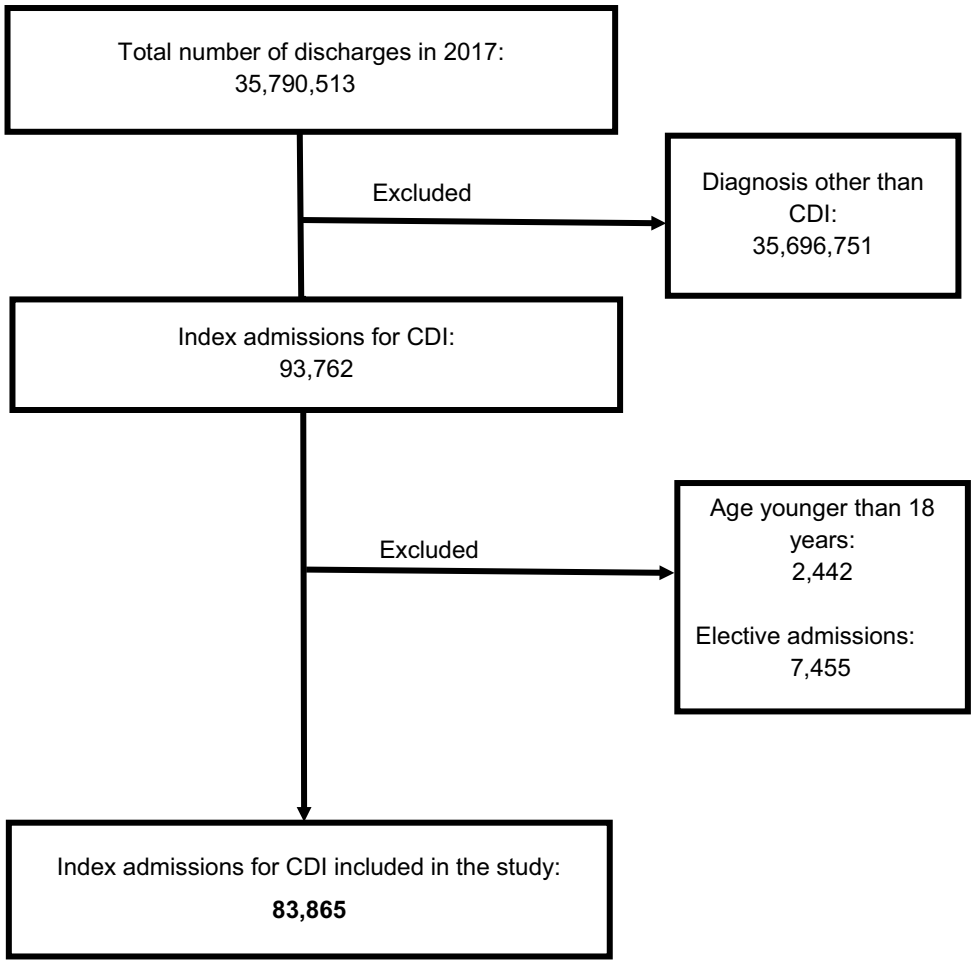

Fig. 1 Flow diagram used to conduct our study

Study outcomes

The primary outcome was the 30- and 90-day readmission rates. Secondary outcomes were as follows: (a) primary diagnoses upon readmission; (b) risk factors associated with readmission; and (c) all-cause inpatient mortality, mean hospitalization LOS, and mean hospitalization charges upon i) index admission, ii) 30-day readmission, iii) 90-day readmission, and iv) readmission as compared to the index admission.

Statistical analysis

Statistical analyses were performed using STATA, version 16.1 (StataCorp., College Station, Texas, US). Weighting of patient-level observations was implemented. Multivariate cox regression model was built to adjust for patient level, hospital level and comorbidity-related factors [age, sex, insurance, hospital size, income quartiles, hospital teaching status, length of stay, CCI, congestive heart failure (CHF), chronic kidney disease (CKD), end-stage renal disease (ESRD), cirrhosis, acute kidney injury (AKI), diabetes mellitus (DM)] to calculate an adjusted hazard ratio (HR). Logistic regression was used for binary outcomes and linear regression was used for continuous outcomes. Proportions were compared using Fisher's exact test, and continuous variables were compared using Student's *t*-test. All *p*-values were two-sided, with 0.05 as the threshold for statistical significance.

Results

Baseline patient and hospital characteristics

A total of 83,865 adult patients with a principal diagnosis of CDI were included in the study for the 30-day analysis. The mean age was 66.27 years, the majority of patients were female (64.3%), and Medicare (68.38%) was the primary payer insurance. Patients were predominantly admitted to large sized hospitals (53.24%), teaching hospitals (62.10%), in large metropolitan areas (50.68%) (Table 1). A total of 67,123 patients were included for the 90-day analysis.

Table 1 Characteristics of patients admitted for CDI

Variable	*N* (%)
Total population	83,865
Female	53,906 (64.27%)
Mean age in years	66.27
Insurance Provider	
Medicare	57,347(68.38%)
Medicaid	8,663 (10.33%)
Private	16,077 (19.17%)
Uninsured	1,778 (2.12%)
Charlson comorbidity index	
0	22,165 (26.43%)
1	17,159 (20.46%)
2	14,248 (16.99%)
3 or more	30,293 (36.12%)
Median income in patient zip code	
0-25th percentile	23,717 (28.28%)
26th to 50th percentile	24,472 (29.18%)
51st to 75th percentile	20,497 (24.44%)
76th to 100th percentile	15,179 (18.10%)
Hospital Location	
Large metropolitan with at least 1 million residents	42,503 (50.68%)
Small metropolitan with less than 1 million residents	31,508 (37.57%)
Micropolitan areas	7,045 (8.40%)
Nonmetropolitan or micropolitan	2,809 (3.35%)
Hospital size	
Small	16,303 (19.44%)
Medium	22,912 (27.32%)
Large	44,650 (53.24%)
Teaching hospital	52,080 (62.10%)

Readmission rates

Of the 82,670 patients discharged from their index hospitalization and followed for 30-days, 22.69% (18,764) were readmitted (within 30-days). Of the 66,150 patients discharged from the index hospitalization and followed for 90 days, 37.40% (24,732) were readmitted (within 90-days).

Reasons for readmission

CDI was responsible for the plurality of readmissions at both 30- (30.47%) and 90-days (36.65%). Table 2 contains the most common primary diagnoses at 30- and 90-day readmission.

Risk factors associated with readmission

In multivariate analyses, higher CCI (HR 1.08, $p < 0.01$), Medicaid (HR 1.16, $p < 0.01$), longer LOS (HR 1.01, $p < 0.01$), liver cirrhosis (HR 1.31, $p < 0.01$), type-1 diabetes mellitus (DM) (HR 1.38, $p < 0.01$), and end-stage renal disease (ESRD) (HR 1.36, $p < 0.01$) were independently associated with increased 30-day readmission. In contrast, female gender (HR 0.93, $p < 0.01$), age greater than 60 years [60–80 years (HR 0.79, $p < 0.01$), > 80 years (HR 0.81, $p < 0.01$)], and private insurance (HR 0.84, $p < 0.01$) were independently associated with *decreased* 30-day readmission.

With regard to 90-day readmission, multivariate analyses found higher CCI (HR 1.08, $p < 0.01$), Medicaid insurance (HR 1.11, $p < 0.01$), admission to teaching hospital (HR 1.08, $p < 0.01$), longer LOS (HR 1.01, $p < 0.01$), discharge other than home (HR 1.19, $p < 0.01$), type-1 DM (HR 1.07, $p < 0.01$), congestive heart failure (CHF) (HR 1.07, $p < 0.05$), liver cirrhosis (HR 1.27, $P < 0.01$), ESRD (HR 1.43, $p < 0.01$) to be independently associated with increased 90-day readmission rate. In contrast, private insurance (HR 0.80, $p < 0.01$) and age greater than 60 years [60–80 years (HR 0.79, $p < 0.01$), > 80 years (HR 0.77, $p < 0.01$)] were independently associated with *decreased* 90-day readmission (Tables 3 and 4).

Mortality and healthcare consumption upon index admission and readmission

When compared to the index admission, 30-day readmissions were characterized by significantly higher inpatient mortality (4.86% vs 1.41%, $p < 0.01$), longer mean LOS

Table 2 Most common primary diagnoses at 30-day and 90-day readmission after CDI

	30-day readmission		90-day readmission	
	Primary diagnosis at readmission	(%)	Primary diagnosis at readmission	(%)
1	"Enterocolitis due to Clostridium difficile"	20.47%	"Enterocolitis due to Clostridium difficile"	20.65%
2	"Sepsis, unspecified organism"	9.85%	"Sepsis, unspecified organism"	9.78%
3	"Enterocolitis due to Clostridium difficile, recurrent"	3.48%	"Acute kidney failure, unspecified"	2.45%
4	"Acute kidney failure, unspecified"	2.35%	"Urinary tract infection, site not specified"	2.00%
5	"Enterocolitis due to Clostridium difficile, not specified as recurrent"	1.95%	"Enterocolitis due to Clostridium difficile, recurrent"	1.74%

Table 3 Significant predictors of 30-day readmission in patients with CDI

Variable	Adjusted Hazard Ratio (95% CI)	*p*-value
Female	0.93 (0.88–0.98)	**<0.01**
Age	0.995 (0.993–0.998)	**<0.01**
Age 18–40	Reference	Reference
Age 41–60	0.94 (0.86–1.04)	0.28
Age 61–80	0.79 (0.71–0.89)	**<0.01**
Age > 80	0.81 (0.71–0.92)	**<0.01**
Medicare insurance	Reference	Reference
Medicaid insurance	1.16 (1.06–1.28)	**<0.01**
Private insurance	0.84 (0.78–0.91)	**<0.01**
Charlson comorbidity index	1.08 (1.06–1.09)	**<0.01**
Length of stay (LOS)	1.01 (1.006–1.015)	**<0.01**
Cirrhosis	1.31 (1.18–1.46)	**<0.01**
Type 1 DM	1.38 (1.15–1.66)	**<0.01**
ESRD	1.36 (1.23–1.49)	**<0.01**

(6.56 days vs 5.59 days, $p < 0.01$), and higher mean hospitalization charges ($58,854 vs $41,146, $p < 0.01$).

When compared to the original index admission, 90-day readmissions were also characterized by significantly higher inpatient mortality (4.4% vs 1.43%, $p < 0.01$), longer mean LOS (6.39 days vs 5.58 days, $p < 0.01$), and higher mean hospitalization charges ($57,857 vs $40,995, $p < 0.01$).

Table 4 Significant predictors of 90-day readmission in patients with CDI

Variable	Adjusted Hazard Ratio (95% CI)	*p*-value
Age	0.995 (0.993–0.997)	**<0.01**
Age 18–40	Reference	Reference
Age 41–60	0.93 (0.86–1.02)	0.15
Age 61–80	0.79 (0.72–0.86)	**<0.01**
Age > 80	0.77 (0.69–0.85)	**<0.01**
Medicare insurance	Reference	Reference
Medicaid insurance	1.11 (1.03–1.20)	**<0.01**
Private insurance	0.80 (0.75–0.85)	**<0.01**
Teaching hospital	1.08 (1.03–1.13)	**<0.01**
Other than home discharge	1.19 (1.13–1.25)	**<0.01**
Charlson comorbidity index	1.08 (1.06–1.10)	**<0.01**
Length of stay (LOS)	1.01 (1.006–1.014)	**<0.01**
Cirrhosis	1.27 (1.15–1.39)	**<0.01**
Type 1 DM	1.07 (1.01–1.11)	**<0.01**
ESRD	1.43 (1.31–1.57)	**<0.01**
CHF	1.07 (1.01–1.14)	**<0.05**

Discussion

In a large, nationwide cohort of patients admitted for CDI, we found that 1 in 5 were readmitted within 30-days and more than 1 in 3 were readmitted within 90-days of discharge. The plurality of readmissions (over 30%) were due to recurrent CDI at both 30 and 90-days post discharge. Higher CCI, being enrolled in Medicaid insurance, longer LOS, liver cirrhosis, Type-1 DM, and ESRD were independently associated with 30-day readmission; with the additional risk factors of admission to a teaching hospital, being discharged to a rehabilitation facility, and CHF independently associated with 90-day readmission. Age greater than 60 years and private insurance were found to be protective factors for readmission at both 30- and 90-days, with female gender being an additional protective factor for readmission at 30-days. Finally, readmission at both 30 and 90-days was significantly associated with increased mortality and higher healthcare consumption.

Verheyen et al. reported similar findings to this study in an analysis of the 2013 NRD [12]. Nontheless, the current study has numerous unique strengths compared to the prior study as it provides data on new questions related to readmission post-hospital discharge for CDI. In the current study, we utilized both 30- and 90-day readmission with double the number of previously assessed patients. Additionally, the current study identified findings of increased mortality at 90-days (4.4% vs 1.43% on index admission) which previously was not known. Moreover, the current study utilized ICD-10 codes (as opposed to ICD-9), a change that facilitates easier comparison with international data and is especially important owning to the changing/emerging literature regarding the diagnosis and treatment of CDI, between our datasets [12–15]. It is interesting to note that even 4 years after the study by Verheyen et al., the all-cause 30-day readmission rate has remained similar, as has the 30-day mortality rate—despite increasing focus on these areas. This may be a result of the disease not having factors that can be mitigated to reduce this rate, or it may be due to a lack of identification of who is at higher risk of readmission. Importantly, it is clear that more studies are needed to evaluate how to reduce the current 30- and 90-day readmission rates.

Hospital readmission is a frequent and expensive problem that myriad researchers are working to solve [16]. Our study has expanded and confirmed the risk factors for readmission after CDI in both the 30- and 90-day time frames. This information has the potential to help allocate therapies known to decrease readmission, such as bezlotoxumab, to those patients who will benefit the most [17]. In addition, these features will aid in the selection of

patients for future prospective studies—namely those at high risk of readmission based upon the present findings.

Although age greater than 65 and shorter LOS during index hospitalization have been associated with decreased rates of all-cause hospital readmission in the US, this study is the first to confirm these associations in CDI [18, 19]. Age, however, is a known risk factor for recurrent CDI [20]. Thus, the association between age and readmission is likely not a function of biology, but rather higher utilization of home healthcare among US seniors [21]. In addition, the NRD does not contain information on deaths outside of the hospital. Thus, it is possible that post-discharge deaths could be contributing to lower readmission rates in the elderly. As shown in previous studies, we confirmed that patients with a higher comorbidity burden, liver cirrhosis, type-1 DM, ESRD, and CHF were more likely to be readmitted, while females and those with private insurance were less likely to be readmitted [12, 21-23].

Our study was subject to limitations common among retrospective analyses of administrative data. Potential confounding variables, including antibiotic course and laboratory values, which are not available in the NRD database, must be considered as they may confound or limit some of our predictive findings. This is especially true as CDI highly varies in its level of seriousness based upon clinical severity. Perhaps patients with a more severe clinical course were at increased risk for readmission—unfortunately, however, owing to the lack of granularity of the dataset, this was unbale to be determined. Additionally, as any study that used administrative data, we might have inherited coding errors or inaccuracy of data entry. Furthermore, some data in the NRD was missing ethno-racial or sex identification and has such been omitted from the outcomes. Finally, while readmission rates were high, we presume the majority of these patients were admitted for CDI—nevertheless, some may have been admitted for something else only to get infected during hospitalization. Despite such limitations, our study has numerous strengths. The biggest strengths being the large sample size (> 80,000 patients) and the accurate representation of the entire US population (> 2,000 hospitals, across 28 states).

In conclusion, in this large, nationwide US cohort, we found that over 20 and 37% of patients with CDI were readmitted within 30- and 90-days of discharge, respectively, with recurrent CDI being the most common reason for readmission at both time-points. Thus, heightened vigilance for recurrent CDI should be emphasized among those hospitalized from previous CDI infection. Readmissions were associated with significantly higher mortality and greater healthcare consumption compared to the index hospitalization. As such, we would suggest more expedient care for those hospitalized for recurrent CDI based upon this finding. In addition, we identified independent predictors of readmission in patients following hospitalization for CDI—namely higher CCI, Medicaid insurance, longer LOS, liver cirrhosis, Type-1 DM, ESRD, admission to a teaching hospital, being discharged to a rehabilitation facility, and CHF. This information may facilitate the recognition of high-risk patients, optimize the distribution of resources, and ultimately result in lower mortality and healthcare consumption among patients with CDI.

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Author contribution SS and SW performed data acquisition, statistical analyses, and manuscript preparation. MA, TW, AA, IV, and JS drafted and critically revised the manuscript. JHT and JDF critically revised the manuscript and provided input regarding methodology. JHT and JDF provided direct supervision and guidance. SS is the article guarantor. All authors agree to the final version of this manuscript.

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