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Original Article

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Trends and Disparities in Outcomes of *Clostridioides difficile* Infection Hospitalizations in the United States: A Ten-Year Joinpoint Trend Analysis

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Abstract

Background: *Clostridioides difficile* infection (CDI) is the most frequently reported nosocomial infection. This study aimed to describe epidemiological trends, sex, race, and economic disparities in clinical and mortality outcomes among CDI hospitalizations over a decade.

Methods: We queried Nationwide Inpatient Sample databases from 2010 to 2019, identified hospitalizations with CDI, and obtained the incidence and admission rate of CDI per 100,000 adult hospitalizations each year. We analyzed trends in mortality rate, mean length of hospital stay (LOS), and mean total hospital charge (THC). We highlighted disparities in outcomes stratified by sex, race, and mean household income quartile.

Results: Of the 305 million hospitalizations included in our study, over 3.3 million were complicated by CDI, with 1.01 million principal admissions for CDI. Among primary admissions for CDI, the mortality rate decreased from 3.2% in 2010 to 1.4% in 2019. Mean LOS reduced from 6.6 to 5.3 days while mean THC increased from US$40,593 to US$42,934 between 2010 and 2019. Females had a 21% decrease in adjusted odds of mortality compared to males (all P-trends < 0.001). Middle-aged and elderly patients had aOR of 4.96 and 14.74 respectively for mortality when compared to young adults (P < 0.001). Mortality rates showed a steady decline among Whites over the study period. Mean LOS trends were similar across racial subgroups.

Conclusions: Outcomes of CDI hospitalizations improved over the studied decade. Older age, male sex, and being from a minority racial group were associated with worse clinical and mortality outcomes. Further studies are needed to elucidate the reasons for these findings.

Keywords: *Clostridioides difficile* infection; Hospitalization; Disparities; Trends; Mortality

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Introduction

Clostridioides difficile infection (CDI) is the most frequently reported pathogen in nosocomial infections and accounts for 12.1% of healthcare-associated infections in the United States [1]. The clinical severity of CDI is a spectrum ranging from a mild, self-limited diarrheal illness to fulminant, life-threatening colitis [2]. Data from active population- and laboratory-based surveillance show that approximately half a million cases of CDI occur each year in the United States, with almost 30,000 deaths reported in 2011 [3]. The total annual CDI-attributable health care cost in the United States is estimated at US$6.3 billion with nearly 2.4 million days of inpatient stay attributable to CDI [4].

The Centers for Disease Control and Prevention's Emerging Infections Program demonstrated a decrease in the estimated national burden of CDI and associated hospitalizations from 2011 through 2017 [5]. However, the proportion of community-acquired CDI has been increasing over time. Cases of CDI have been increasingly reported outside of acute care facilities over the last few years with progressively more cases being diagnosed and treated without hospitalization [3, 6].

While the above-stated changes in the epidemiology of CDI have been extensively documented in the literature, there is a relative paucity of research on the impact of sociodemographic indices on CDI hospitalizations and outcomes. This study aimed to describe the epidemiological trends, sex, race, and economic disparities in clinical and mortality outcomes among hospitalizations with CDI over a decade.

Materials and Methods

Design and data source

This was a retrospective longitudinal trends study involving

hospitalizations with CDI in the US from 2010 to 2019. We sourced data from the Nationwide Inpatient Sample (NIS) databases from 2010 through 2019. The NIS is developed by the Healthcare Cost and Utilization Project (HCUP), a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is a database of hospital inpatient stays derived from billing data submitted by hospitals to statewide data organizations across the US, covering more than 97% of the US population [7]. The provided dataset for a given calendar year approximates a 20% stratified sample of discharges from US hospitals, excluding rehabilitation and long-term acute care hospitals. This dataset is weighted to obtain US national estimates [8]. Databases before 2016 were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification/ Procedure Coding System (ICD-9-CM/PCS). Databases from 2016 were coded using the ICD-10-CM/PCS. The 2015 NIS has both ICD-9 and 10 codes, hence requiring a combination of both codes to obtain the studied cohort in keeping with the HCUP regulations [9]. In this study, we weighted the 9 months of ICD-9 data in 2015 for the entire year. In the NIS, diagnoses are divided into two separate categories: principal diagnosis and secondary diagnoses. A principal diagnosis was the ICD code attributed as the reason for hospitalization. Secondary diagnoses were any ICD code discharge diagnosis other than the principal diagnosis. We obtained total yearly adult hospitalizations from the NIS databases. This manuscript conforms with the STROBE statement for reporting observational studies.

Study population and variables

We queried NIS databases from 2010 to 2019 for this study. The study involved two cohorts of hospitalizations: any hospitalization with CDI and hospitalizations with a principal admitting diagnosis of CDI. We searched the databases for hospitalizations using ICD codes (008.45 and A04.7x). We excluded hospitalizations involving patients less than 18 years. The NIS includes variables on patient demographics, including age, sex, race, median household income (MHOI) for patient's zip code (income quartiles referred to patients as 1 - low income, 2 - middle income, 3 - upper middle income, 4 - high income), and primary payer. It also contains hospital-specific variables including bed size, teaching status, and location. We assessed the comorbidity burden using Sundararajan's adaptation of the modified Deyo's Charlson comorbidity index (CCI). This modification groups CCI into four groups in increasing risk for mortality. It has been adapted to population-based research. A score of > 3 has about a 25% 10-year mortality, while a score of 2 or 1 has a 10% and 4% 10-year mortality, respectively. This cutoff point was chosen as a means of assessment of the increased risk of mortality [10]. Total hospital charge (THC) was adjusted for inflation using the Medical Expenditure Panel Survey index for hospital care, with 2019 as the reference point [11].

Outcome measures

We highlighted the biodemographic trends over time of CDI hospitalizations. Specifically, we obtained the CDI admission rate and the incidence of CDI among all hospitalizations. We calculated the crude CDI admission rate per 100,000 adult hospitalizations and the incidence of CDI per 100,000 adult hospitalizations during each calendar year. We analyzed trends in inpatient mortality rate, mean length of hospital stay (LOS), and mean THC of both cohorts. We also highlighted disparities in outcomes of CDI hospitalizations stratified by sex (male and female), race (Whites, Blacks, and Hispanics), and MHOI quartile (low-income quartile - LIQ and high-income quartile - HIQ).

Statistical analysis

Stata® Version 16 software (StataCorp, TX, USA) and Joinpoint Regression Program, Version 4.9.1.0 were used for data analysis. We analyzed and reported the weighted sample following HCUP regulations for using the NIS database. Age was grouped as 18 - 44 years representing young adults, 45 - 64 years representing middle-aged adults, and 65 years and above representing elderly. The incidence of CDI among hospitalizations was calculated following the HCUP methodology for disease incidence and prevalence [12]. The crude admission rate was calculated by dividing total CDI hospitalizations as the principal diagnosis by the total adult hospitalization for each calendar year studied and expressed per 100,000 hospitalizations. The incidence of CDI per 100,000 adult hospitalizations was obtained by dividing the total hospitalizations with CDI by the total number of adult hospitalizations. This was also expressed as per 100,000 adult hospitalizations. We used multivariable regression analysis to calculate the incidence and admission rates adjusted for age categories, sex, and race using predictive margins. We subsequently used Joinpoint regression analysis to obtain the trends in rates over the study duration, using the adjusted rates and standard errors. Joinpoint regression analysis has been widely used and validated by the National Institutes of Health (NIH) National Cancer Institute to model non-linear trends in cancer rates over a given period [13]. This has been adopted in prior HCUP database research [14, 15]. We used multivariable regression trend analysis to obtain trends in mortality, LOS, and THC adjusted for age categories, sex, and race. All P values were two-sided, with 0.05 set as the threshold for statistical significance.

Ethical compliance with human/animal study

The NIS database lacks patient and hospital level identifiers. This study, therefore, did not require Cook County Health Institutional Review Board approval.

Data availability statement

The NIS is a large publicly available all-payer inpatient care database in the United States, containing data on more than seven million hospital stays per year. Its large sample size is ideal for developing national and regional estimates and ena-

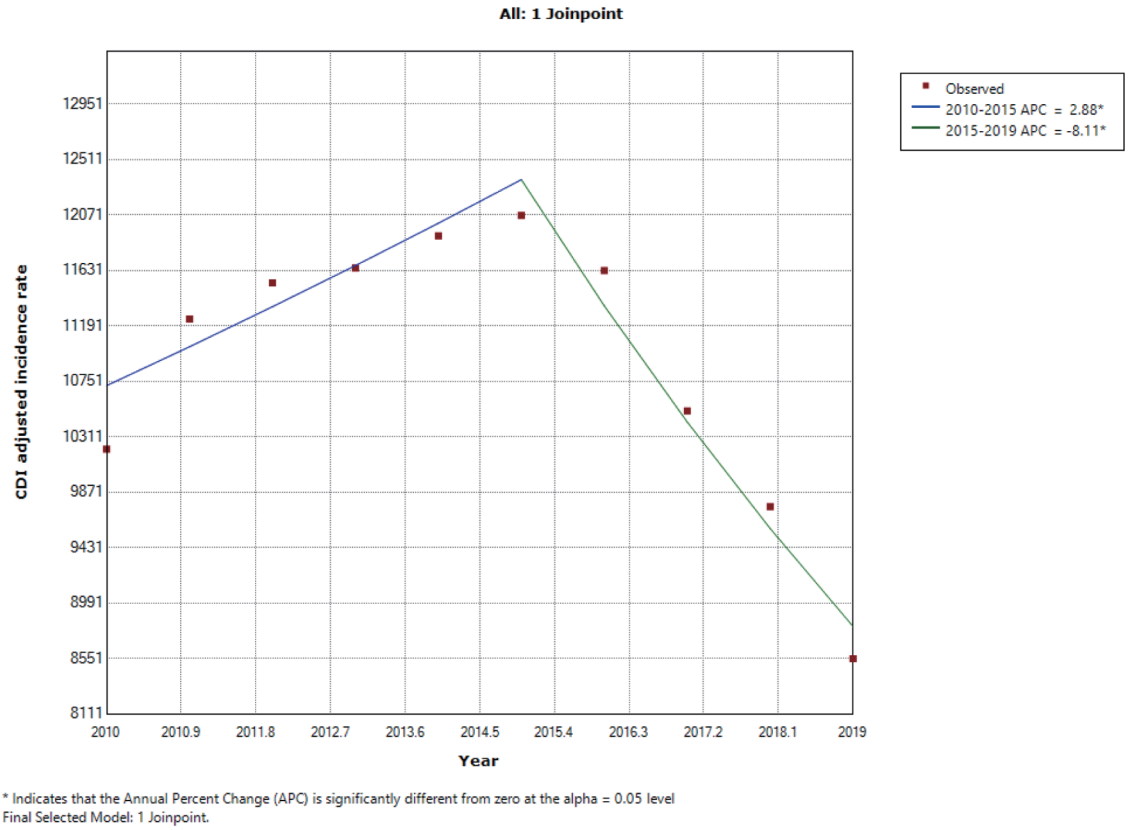

Figure 1. Trend in the adjusted incidence of CDI among all hospitalizations from 2010 to 2019. *Statistically significant. APC: annual percentage change; CDI: *Clostridioides difficile* infection.

bles analyses of rare conditions, uncommon treatments, and special populations. Datasets are available through the HCUP central distributor on request.

Results

Hospitalizations with CDI

Over 300 million hospitalizations were included in our study over the period from 2010 to 2019. Of these hospitalizations, 1.1% (more than 3.3 million) were complicated by CDI with the CDI incidence rate amongst hospitalizations down-trending from 1,001 per 100,000 hospitalizations in 2010 to 871 per 100,000 hospitalizations in 2019. When adjusted for age and sex, there was an average annual percentage change (AAPC) of -2% reduction in the incidence of CDI among hospitalizations over the study period. In 2010, CDI was the principal reason for hospitalization in 33.1% of these hospitalizations with CDI, with a reduction in that proportion to 29% in 2019. Other top reasons for hospitalizations included unspecified sepsis, pneumonia from unspecified organism, and acute kidney injury. Joinpoint regression analysis showed an increase in the adjusted CDI incidence rate from 2010 to 2015 (annual percent change (APC) = 2.88%). There subsequently was a decreased incidence from 2015 to 2019 (APC = -8.11%), as shown in Figure 1.

Table 1 shows the biodemographic distribution of hospitalizations with CDI. Older age groups were consistently at higher odds of hospitalization with CDI compared to young adults with elderly hospitalizations having higher odds than middle-aged hospitalizations. Middle-aged and elderly patients had adjusted odds ratios (aORs) of 2.54 and 3.86 respectively for hospitalization with CDI when compared to young adults ($P < 0.001$). Females had a 12% increase in adjusted odds of hospitalization with CDI compared to males over the study period ($P < 0.001$).

The mortality rate in the cohort of hospitalizations with CDI was 6.9% over the study period and decreased from 8.4% in 2010 to 5.8% in 2019. The mean LOS decreased from 11.6 to 9.8 days and the mean THC increased from US$93,521 to US$108,357 (all P-trends < 0.001). When adjusted for age and sex, there was a -4% APC in mortality among hospitalizations with CDI over the study period. On sex subgroup analysis, females had a significantly lower mortality rate (Fig. 2). On racial subgroup analysis, mortality rates were lowest among Whites over the study period, most improved in Hispanics over the study period with the least improvement in Blacks (Fig. 3). Mean LOS trends were also similar to mortality trends across the three racial subgroups. Mortality rates, mean LOS, and mean THC followed similar trends over the study period in

Table 1. Biodemographic Data of Hospitalizations With CDI

Variable	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	P-value
Total hospitalizations, million, N = 305	31.4	31.5	30.7	30.0	29.8	30.2	30.2	30.4	30.3	30.2	
Total hospitalizations with CDI, N = 3,318,533	314,147	352,831	352,580	347,835	352,290	363,385	351,040	322,545	298,930	262,950	
CDI incidence rate, per 100,000 hospitalizations	1001	1120	1148	1159	1182	1203	1162	1061	987	871	
Mean age ± SD, years	68.9 ± 17.2	69.1 ± 17.4	67.9 ± 16.9	67.3 ± 17.0	66.6 ± 17.0	66.3 ± 17.0	66.0 ± 16.9	66.2 ± 16.8	66.3 ± 16.5	66.2 ± 16.5	< 0.001
Age categories, %											< 0.001
Young adults (18 - 44)	9.8	9.5	10.5	11.1	11.7	12.0	12.0	11.8	11.4	11.6	
Middle aged (45 - 64)	25.3	25.2	26.3	27.1	28.3	28.8	29.3	28.9	29.2	29.0	
Elderly (≥ 65)	64.9	65.3	63.1	61.8	60.0	59.2	58.7	59.3	59.4	59.4	
Female, %	57.7	58.8	58.9	58.4	58.6	58.2	57.6	57.4	57.3	57.4	< 0.001
Race, %											< 0.001
White	67.3	68.2	71.6	70.9	71.1	71.0	71.1	71.5	72.0	72.2	
Black	11.8	11.8	12.0	12.3	12.3	12.6	12.4	12.6	12.7	13.1	
Hispanic	6.2	7.3	6.9	7.4	7.3	7.5	7.9	8.0	8.2	8.0	
Others	14.6	12.7	9.4	9.4	9.3	8.9	8.6	7.9	7.0	6.7	
CCI score, %											< 0.001
0	23.4	22.4	22.8	22.6	22.4	25.5	17.1	16.9	16.1	16.3	
1	19.7	19.2	18.7	18.3	18.1	16.9	17.3	16.9	16.3	15.8	
2	19.4	18.9	18.7	18.8	17.9	17.0	17.7	17.4	17.4	16.8	
≥ 3	37.6	39.5	39.8	40.3	41.6	40.6	47.9	48.8	50.2	51.2	
Primary payer, %											< 0.001
Medicare	69.8	71.4	70.6	69.6	67.9	67.4	66.8	67.3	67.7	66.9	
Medicaid	9.4	8.9	9.2	9.7	11.6	12.0	12.7	12.3	12.0	12.3	
Private insurance	18.5	17.5	17.6	17.9	18.5	18.7	18.5	18.3	18.1	18.3	
No insurance	2.4	2.2	2.6	2.9	2.1	2.0	2.0	2.1	2.2	2.5	
MHOI quartile, %											< 0.001
1	25.1	25.9	27.2	27.0	27.3	29.2	29.0	28.6	28.2	28.8	
2	24.8	23.8	24.4	26.2	27.6	24.9	26.0	27.0	27.9	26.0	
3	25.6	26.3	24.9	24.8	23.8	24.7	24.4	24.0	24.4	24.8	
4	24.6	24.0	23.6	22.0	21.3	21.3	20.6	20.4	19.5	20.5	
Hospital bed-size, %											< 0.001
Small	10.7	11.3	13.2	13.0	17.5	17.0	17.5	18.9	20.0	21.7	
Medium	23.2	23.8	25.1	25.4	28.7	29.1	28.3	28.7	28.5	28.1	
Large	66.2	64.9	61.7	61.6	53.8	54.0	54.3	52.4	51.5	50.3	
Hospital region, %											0.513
Northeast	23.8	22.1	22.0	21.5	20.4	19.5	18.8	18.5	18.7	19.1	
Midwest	25.2	24.6	24.4	24.0	23.6	23.2	23.4	24.5	25.2	25.0	
South	33.9	34.2	34.8	36.1	36.9	37.8	37.4	37.4	37.8	37.4	
West	17.2	19.1	18.8	18.5	19.2	19.6	20.5	19.6	18.4	18.5	
Location/teaching status of hospital, %											< 0.001
Rural	9.9	9.8	9.4	9.9	7.9	8.4	8.2	8.7	9.0	9.0	
Urban nonteaching	43.0	41.7	38.4	37.3	26.3	27.0	26.5	23.2	20.1	18.7	
Urban teaching	47.1	48.6	52.3	52.8	65.7	64.6	65.3	68.1	70.9	72.3	

CCI: Charlson comorbidity index; CDI: *Clostridioides difficile* infection; MHOI: median household income national quartile for patient ZIP code; SD: standard deviation from the mean.

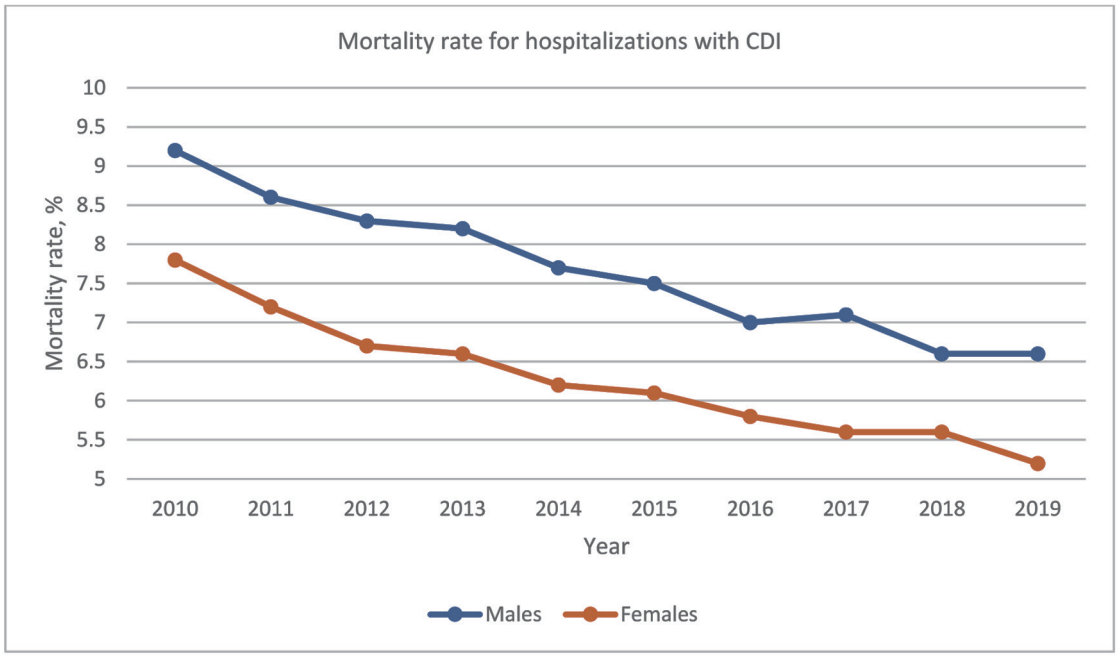

Figure 2. Trend in the mortality rate for hospitalizations with CDI (sex subgroup analysis). CDI: *Clostridioides difficile* infection.

hospitalizations with mean household income (MHOI) quartile 1 when compared to those with MHOI quartile 4 (Table 2).

Middle-aged and elderly patients had aOR of 2.15 and 3.58 respectively for mortality when compared to young patients ($P < 0.001$). Females had a 22% decrease in adjusted odds of mortality compared to males over the study period ($P < 0.001$).

When adjusted for age and sex, there was an annual 0.19 decrease in LOS over the study period ($P < 0.001$), with this finding similar across the different racial subgroups.

Patients hospitalized for CDI

There were over 1 million hospitalizations with CDI as the

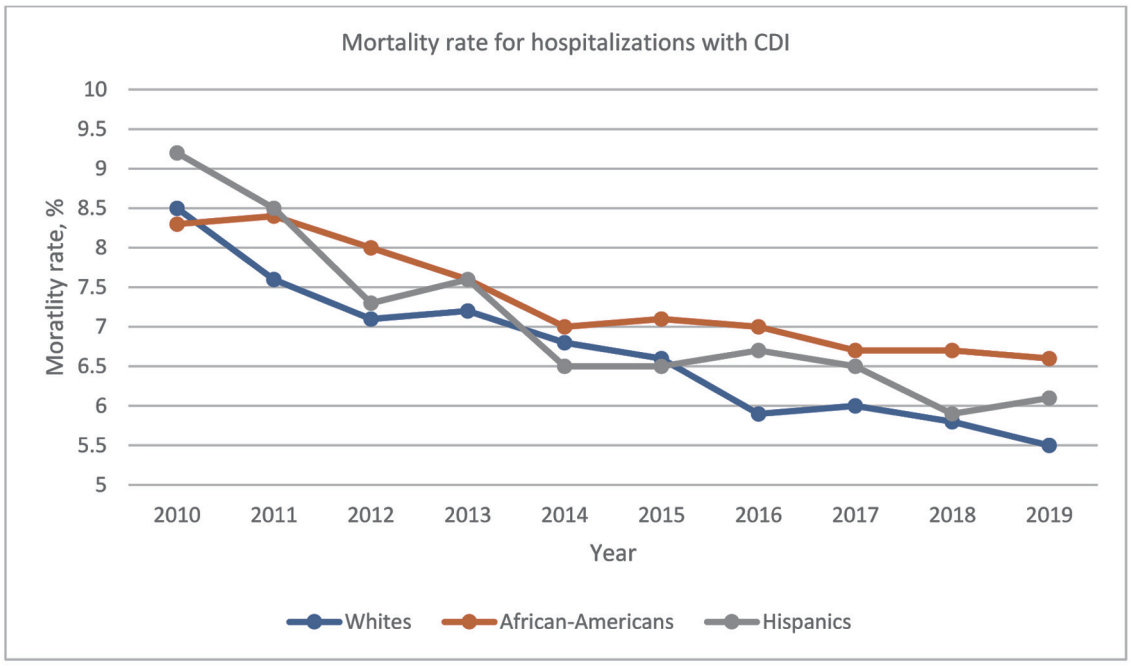

Figure 3. Trend in the mortality rate for hospitalizations with CDI (racial subgroup analysis). CDI: *Clostridioides difficile* infection.

Table 2. Outcomes of Hospitalizations With CDI

Variable	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	P-value
Mortality rate, %	8.4	7.8	7.3	7.3	6.8	6.7	6.3	6.3	6.0	5.8	< 0.001
Mean LOS, days	11.6	11.1	10.6	10.4	10.5	10.2	10.1	9.9	9.9	9.8	< 0.001
Mean THC, US$	93,521	98,649	95,012	96,702	99,163	99,015	105,120	104,320	105,737	108,357	< 0.001
Mortality rate among females, %	7.8	7.2	6.7	6.6	6.2	6.1	5.8	5.6	5.6	5.2	< 0.001
Mean LOS among females, days	10.7	10.2	9.8	9.6	9.7	9.5	9.3	9.2	9.1	9.1	< 0.001
Mean THC among females, US$	82,867	85,353	82,873	84,388	87,269	87,730	92,126	91,928	92,296	94,855	< 0.001
Mortality rate among males, %	9.2	8.6	8.3	8.2	7.7	7.5	7.0	7.1	6.6	6.6	< 0.001
Mean LOS among males, days	12.9	12.3	11.8	11.6	11.6	11.1	11.2	10.8	11.0	10.8	< 0.001
Mean THC among males, US$	108,090	117,624	112,425	114,003	116,022	114,722	122,790	121,033	123,781	126,518	< 0.001
Mortality rate among Whites, %	8.5	7.6	7.1	7.2	6.8	6.6	5.9	6.0	5.8	5.5	< 0.001
Mean LOS among Whites, days	10.9	10.6	10.0	9.8	9.9	9.5	9.4	9.2	9.2	9.1	< 0.001
Mean THC among Whites, US$	85,867	91,878	86,144	87,836	90,581	88,521	92,767	92,202	93,560	95,882	< 0.001
Mortality rate among Blacks, %	8.3	8.4	8.0	7.6	7.0	7.1	7.0	6.7	6.7	6.6	< 0.001
Mean LOS among Blacks, days	15.1	13.4	12.6	12.5	12.6	12.2	12.4	12.0	12.1	12.3	< 0.001
Mean THC among Blacks, US$	114,929	117,850	111,413	115,006	116,800	118,518	125,221	123,995	126,158	125,050	< 0.001
Mortality rate among Hispanics, %	9.2	8.5	7.3	7.6	6.5	6.5	6.7	6.5	5.9	6.1	< 0.001
Mean LOS among Hispanics, days	14.5	12.7	11.9	11.9	11.5	11.8	11.5	11.0	10.7	10.9	< 0.001
Mean THC among Hispanics, US$	140,462	146,273	139,345	140,193	139,799	142,846	151,262	146,579	145,180	153,481	< 0.001
Mortality rate among MHOI quartile 1, %	8.6	7.6	7.5	7.3	6.8	6.9	6.6	6.5	6.3	5.8	< 0.001
Mean LOS among MHOI quartile 1, days	12.3	11.4	10.9	10.9	10.9	10.6	10.6	10.3	10.3	10.2	< 0.001
Mean THC among MHOI quartile 1, US$	93,751	98,105	92,696	94,431	99,437	100,402	104,595	105,356	105,723	105,756	< 0.001
Mortality rate among MHOI quartile 4, %	8.7	8.2	7.4	7.8	6.9	6.6	6.2	6.3	6.1	6.0	< 0.001
Mean LOS among MHOI quartile 4, days	11.5	11.0	10.6	10.5	10.5	10.1	10.2	10.0	9.9	9.7	< 0.001
Mean THC among MHOI quartile 4, US$	98,532	99,403	103,701	106,578	109,072	105,922	116,261	117,153	118,548	117,650	< 0.001

LOS: length of hospital stay; MHOI: median household income national quartile for patient ZIP code; THC: total hospital charges.

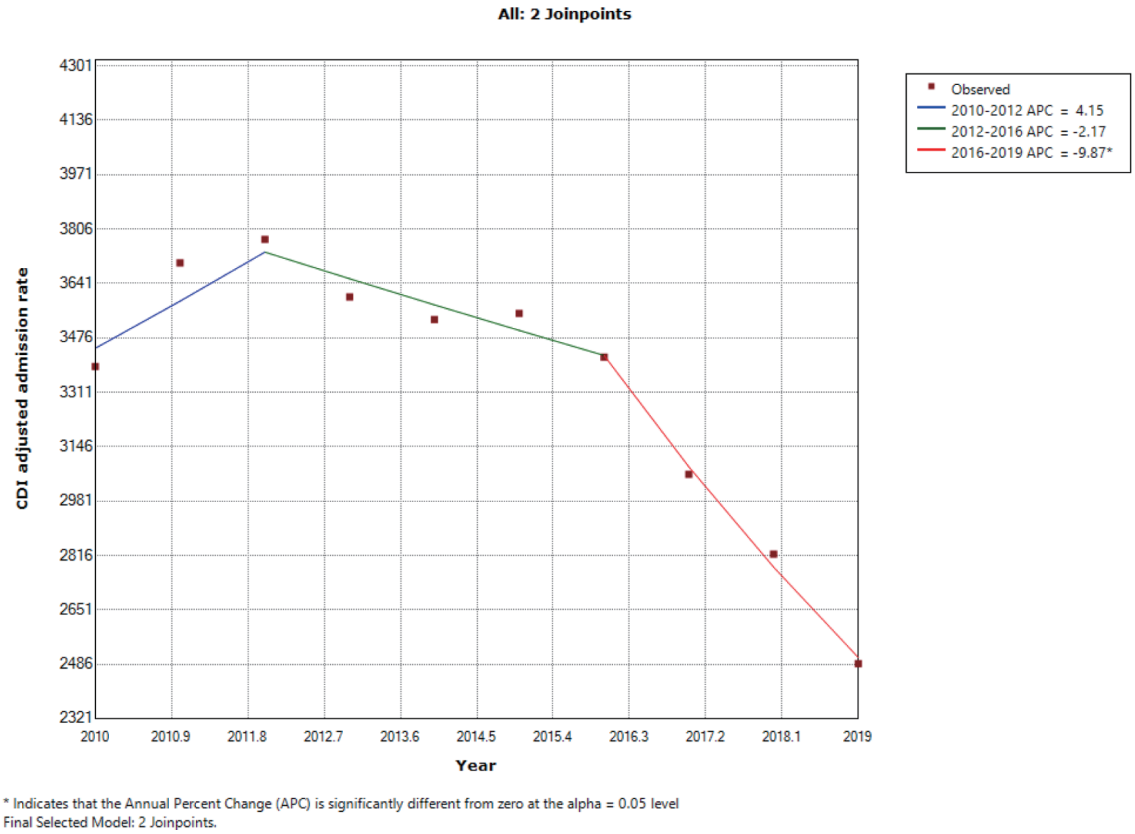

Figure 4. Trends in adjusted CDI admission rate from 2010 to 2019. *Statistically significant. APC: annual percentage change; CDI: *Clostridioides difficile* infection.

reason for inpatient stay, representing 30.6% of all hospitalizations with CDI over the study period. The AAPC for CDI admissions was -3.2% over the study period. Joinpoint regression analysis showed a non-statistically significant increase in adjusted CDI admission rate from 2010 to 2012 (APC = 4.15%), with a subsequent reduction in adjusted CDI admission rate from 2012 to 2016 (APC = -2.17%) which was also not statistically significant. From 2016 to 2019, there was a statistically significant trend towards reduction in adjusted CDI admission rate (APC = -9.87%) (Fig. 4).

The mean age of CDI admissions decreased from 69.4 years in 2010 to 66.6 years in 2019 with the proportion of elderly patients similarly down-trending from 66.3% in 2010 to 60.3% in 2019 (both P-trends < 0.001). The proportion of CDI admissions with CCI scores ≥ 3 increased from 28.4% in 2010 to 39.3% in 2019 (P-trend < 0.001). The highest proportion of the primary payer across each year was Medicare, and most patients were managed at large hospitals (both P < 0.001) (Table 3).

The mortality rate in patients admitted for CDI was 1.9% over the study period, down-trending from 3.2% in 2010 to 1.4% in 2019. When adjusted for age and sex, the AAPC for mortality was -10.2%. The mean LOS reduced from 6.6 days in 2010 to 5.3 days in 2019 and the mean THC increased from US$40,593 to US$42,934 (all P-trends < 0.001). On sex subgroup analysis, mortality rates showed a downtrend in males and females over the study period (Fig. 5). A similar trend was observed in mean LOS in males and females while mean THC increased in both groups over the study period (Table 4). On racial subgroup analysis, mortality rates showed a steady decline among Whites and Blacks over the study period (Fig. 6). Mean LOS trends were also similar across the three racial subgroups. Mortality rates, mean LOS, and mean THC followed similar trends over the study period in hospitalizations among LIQ and HIQ patients.

Middle-aged and elderly patients had aOR of 4.96 and 14.74 respectively for mortality when compared to young adults (P < 0.001). Females had a 21% decrease in adjusted odds of mortality compared to males over the study period (P < 0.001).

When adjusted for age and sex, there was a 0.14 annual decrease in the mean LOS in days over the study period (P < 0.001), with this finding similar across the different racial subgroups and MHOC quartiles. However, there was no significant change in the adjusted mean THC over the study period (P = 0.249).

Discussion

We analyzed the trends in CDI hospitalizations during the decade under review and found that the incidence and admission

Table 3. Biodemographic Data of Hospitalizations With Principal Admitting Diagnosis of CDI

Variable	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	P-value
Total principal admissions for CDI	103,845	116,138	115,830	107,730	104,695	106,905	103,135	93,810	86,285	76,325	
CDI admission rate, per 100,000 hospitalizations	331	369	377	359	351	354	342	309	285	253	
Mean age ± SD, years	69.4 ± 17.5	69.2 ± 18.0	67.9 ± 17.5	67.3 ± 17.7	66.4 ± 17.8	65.9 ± 17.9	65.8 ± 17.7	66.1 ± 17.5	66.5 ± 17.2	66.6 ± 16.9	< 0.001
Age categories, %											< 0.001
Young adults	10.0	10.5	11.8	12.6	13.4	14.0	13.7	13.1	12.4	12.2	
Middle aged	23.7	23.4	24.5	25.8	26.9	27.4	27.9	27.9	27.5	27.5	
Elderly	66.3	66.1	63.7	61.7	59.7	58.6	58.5	59.0	60.1	60.3	
Female, %	64.3	65.8	65.3	65.1	65.5	64.8	65.1	64.2	64.4	63.9	0.002
Race, %											< 0.001
White	71.2	71.5	75.2	75.2	74.8	75.0	75.2	75.8	75.9	75.8	
Black	8.9	9.2	9.6	9.8	10.1	10.7	10.3	10.4	10.6	11.0	
Hispanic	5.9	7.1	6.8	6.8	7.2	6.9	7.5	7.5	7.8	7.5	
Others	14.0	12.2	8.4	8.3	7.9	7.4	7.0	6.3	5.8	5.7	
CCI score, %											< 0.001
0	31.7	31.3	32.0	32.8	32.1	33.2	26.8	25.9	24.5	24.5	
1	22.1	21.8	20.8	20.4	21.3	20.3	21.0	20.5	19.9	19.5	
2	17.8	17.9	17.6	17.2	16.3	16.1	17.0	17.1	17.2	16.7	
≥ 3	28.4	29.1	29.6	29.6	30.4	30.5	35.2	36.6	38.4	39.3	
Primary payer, %											< 0.001
Medicare	70.5	71.1	70.5	68.5	67.3	66.0	66.2	66.9	68.4	66.8	
Medicaid	7.1	7.3	7.9	8.1	10.8	11.0	11.6	10.9	10.4	10.4	
Private insurance	20.0	19.1	18.8	20.2	19.6	20.8	20.0	19.8	18.8	20.1	
No insurance	2.5	2.5	2.9	3.2	2.3	2.1	2.3	2.4	2.4	2.7	
MHOI quartile, %											< 0.001
1	23.9	25.4	26.9	26.9	26.9	28.6	27.9	27.8	27.2	27.8	
2	26.1	24.2	24.5	27.0	28.0	25.5	27.0	27.7	28.3	26.5	
3	25.7	26.5	25.2	24.8	24.2	25.0	24.7	23.8	24.7	24.6	
4	24.4	23.9	23.5	21.3	20.8	20.9	20.4	20.8	19.9	21.1	
Hospital bed-size, %											< 0.001
Small	12.3	13.0	15.1	15.0	19.8	19.5	20.8	21.4	23.1	24.4	
Medium	24.3	25.2	25.8	26.6	30.1	30.2	29.1	30.2	29.7	29.6	
Large	63.4	61.8	59.2	58.5	50.0	50.3	50.1	48.4	47.3	46.0	
Hospital region, %											0.76
Northeast	22.9	21.3	21.2	20.5	19.7	19.1	18.6	18.8	18.6	19.1	
Midwest	25.3	24.9	24.6	24.5	24.1	23.9	23.7	24.7	24.5	24.6	
South	35.9	36.8	36.8	38.4	38.9	39.8	39.6	39.6	40.3	39.7	
West	15.9	17.0	17.4	16.7	17.3	17.2	18.1	16.9	16.5	16.6	
Location/teaching status of hospital, %											< 0.001
Rural	12.3	12.9	12.3	12.7	10.3	10.9	11.1	11.3	11.5	11.3	
Urban nonteaching	47.5	45.7	42.6	41.8	30.4	31.1	30.1	26.3	23.2	21.7	
Urban teaching	40.3	41.4	45.1	45.4	59.3	58.0	58.9	62.4	65.3	67.0	

CCI: Charlson comorbidity index; CDI: *Clostridioides difficile* infection; MHOI: median household income national quartile for patient ZIP code; SD: standard deviation from the mean.

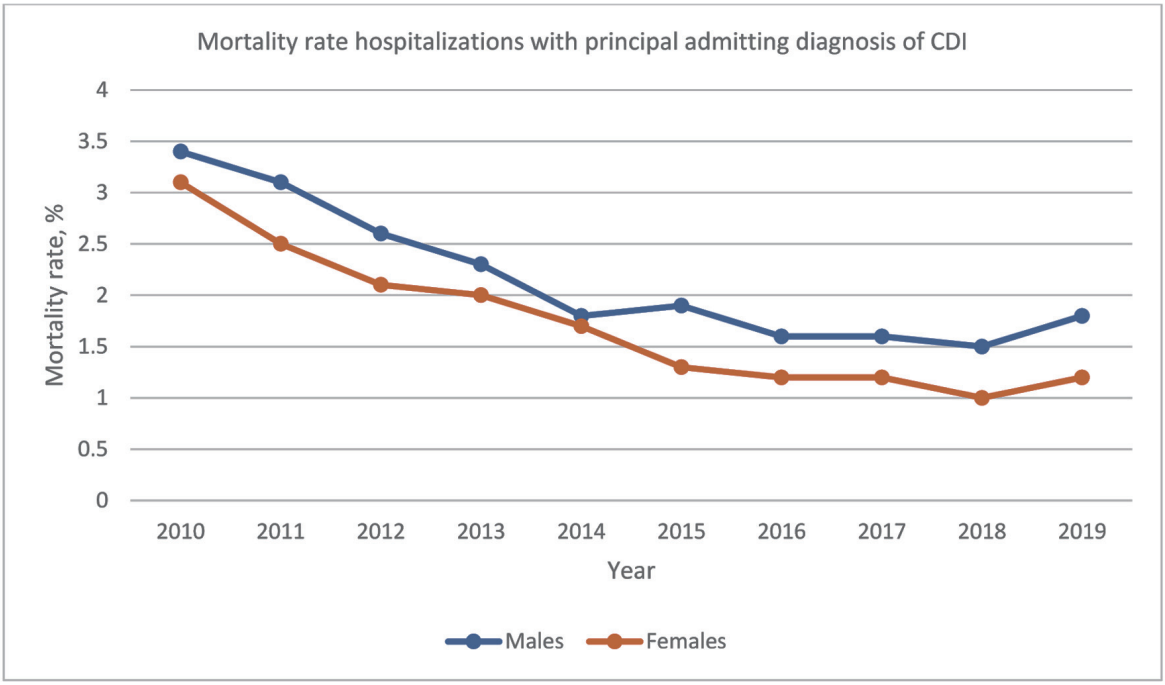

Figure 5. Trend in mortality rate hospitalizations with a principal admitting diagnosis of CDI (sex subgroup analysis). CDI: *Clostridioides difficile* infection.

rates of CDI initially trended up, likely representing a continuation of the increasing trend in CDI incidence in the first decade of the 21st century [16-18]. After 2015, there was a marked decline in incidence and admission rates among hospitalizations with CDI. Given the transition from ICD-9 to ICD-10 codes in 2015, we ensured that the change in administrative code for the disease was accounted for. The sensitivity and specificity of these administrative codes at identifying CDI has been established at 88% and 100% respectively [19].

When the cohort of admissions with a primary diagnosis of CDI was analyzed, we found that this downward trend in incidence predated 2015 and began in 2012. This is likely explained by increased caution with antimicrobial drug use following the widespread initiation of antibiotic stewardship programs. A report by the Blue Cross Blue Shield Association in 2017 showed that the fill rate of outpatient antibiotic prescriptions declined 9% among commercially insured Americans from 2010 to 2016 with broad-spectrum antibiotic fill rates dropping the most at 13% [20]. Several studies have shown that antimicrobial stewardship programs and formulary restrictions have resulted in significant reductions in the rates of occurrence of CDI [2]. An interrupted time-series analysis conducted by Valiquette et al [21] in a secondary/tertiary-care hospital in Quebec showed that there was no significant change in nosocomial CDI incidence after strengthening of infection control procedures ($P = 0.63$), but the implementation of an antimicrobial stewardship program was followed by a 60% reduction in CDI incidence ($P = 0.007$). Similar findings were observed in two other interrupted time-series studies conducted by Fowler et al [22] and Talpaert et al [23] among acute medical admissions which showed that CDI rates fell by 65% ($P = 0.009$) and 66% ($P < 0.0001$) respectively compared to controls when "narrow-spectrum" antibiotic policies were applied.

Most of the hospitalizations for CDI in our study were among elderly patients, although the mean age of both cohorts progressively reduced while the proportion of patients with CCI scores of 3 or more increased over the study period. When adjusted for race and sex, elderly patients were found to have increased odds of hospitalizations for CDI. An older age group and multiple medical comorbidities are established risk factors for CDI [24]. Other risk factors include immunocompromised states (as seen in patients with human immunodeficiency virus infection or patients with cancer who are receiving chemotherapy), broad-spectrum antibiotic therapy (especially clindamycin, cephalosporins, amoxicillin, and fluoroquinolones), gastric acid suppression therapy, intensive care unit admission, recent non-surgical gastrointestinal procedures, and tube feeding [4, 22, 24].

We noted improvements in adjusted mortality rates and LOS amongst hospitalizations with CDI and admissions with a principal admitting diagnosis of CDI over the study period. This is likely due to new treatment strategies which were implemented over the decade under review. Between 2010 and 2019, therapeutic options including oral vancomycin, fidaxomicin, fecal microbiota transplantation, and bezlotoxumab were approved for the treatment of index episodes or recurrences of CDI and have been incorporated into clinical guidelines [25]. Another possible explanation for the improvement in mortality and LOS is the increased use of *Clostridium difficile* toxin polymerase chain reaction (PCR) testing assays over the study period. The rapid stool PCR test was approved by the FDA in 2011 [26] after the test was shown to have higher sen-

Table 4. Outcomes of Hospitalizations With Principal Admitting Diagnosis of CDI

Variable	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	P-value
Mortality rate, %	3.2	2.7	2.3	2.1	1.7	1.5	1.3	1.4	1.2	1.4	< 0.001
Mean LOS, days	6.6	6.3	6.1	6.0	5.8	5.6	5.5	5.4	5.4	5.3	< 0.001
Mean THC, US$	40,593	41,035	39,855	39,975	39,015	38,587	39,981	40,313	41,104	42,934	< 0.001
Mortality rate among females, %	3.1	2.5	2.1	2.0	1.7	1.3	1.2	1.2	1.0	1.2	< 0.001
Mean LOS among females, days	6.5	6.2	6.1	5.9	5.8	5.5	5.5	5.3	5.3	5.3	< 0.001
Mean THC among females, US$	38,966	39,259	39,073	38,867	38,331	38,018	39,246	38,873	40,153	41,527	< 0.001
Mortality rate among males, %	3.4	3.1	2.6	2.3	1.8	1.9	1.6	1.6	1.5	1.8	< 0.001
Mean LOS among males, days	6.9	6.5	6.1	6.0	5.9	5.6	5.6	5.6	5.4	5.5	< 0.001
Mean THC among males, US$	43,526	44,453	41,331	42,050	40,318	39,634	41,355	42,894	42,822	45,421	< 0.001
Mortality rate among Whites, %	3.4	2.9	2.4	2.1	1.8	1.6	1.4	1.4	1.3	1.4	< 0.001
Mean LOS among Whites, days	6.6	6.3	6.1	5.9	5.7	5.5	5.5	5.3	5.3	5.2	< 0.001
Mean THC among Whites, US$	39,861	39,694	38,553	37,984	37,559	36,737	38,036	37,878	39,079	40,739	< 0.001
Mortality rate among Blacks, %	2.8	2.4	1.9	1.9	1.4	1.1	1.1	1.0	0.7	1.3	< 0.001
Mean LOS among Blacks, days	7.5	7.1	6.5	6.4	6.4	6.1	5.9	6.0	5.9	5.8	< 0.001
Mean THC among Blacks, US$	46,705	49,212	43,996	42,940	43,114	42,634	45,342	47,192	46,100	45,873	< 0.001
Mortality rate among Hispanics, %	2.3	2.3	1.2	2.3	1.5	1.1	1.3	1.0	0.9	2.0	0.002
Mean LOS among Hispanics, days	6.9	6.5	6.4	6.1	6.0	5.6	5.8	5.3	5.3	5.4	< 0.001
Mean THC among Hispanics, US$	55,307	56,655	53,541	56,429	51,889	50,918	52,029	52,115	53,860	57,604	< 0.001
Mortality rate among MHOI quartile 1, %	3.4	2.8	2.2	2.2	1.6	1.5	1.5	1.6	1.1	1.5	< 0.001
Mean LOS among MHOI quartile 1, days	6.7	6.4	6.1	6.0	5.9	5.6	5.7	5.6	5.5	5.4	< 0.001
Mean THC among MHOI quartile 1, US$	37,409	38,967	37,114	39,224	38,616	37,799	39,635	49,742	39,250	40,536	< 0.001
Mortality rate among MHOI quartile 4, %	3.6	2.5	2.2	1.9	1.6	1.6	1.2	1.5	1.3	1.5	< 0.001
Mean LOS among MHOI quartile 4, days	6.8	6.4	6.2	5.9	5.9	5.5	5.5	5.4	5.4	5.3	< 0.001
Mean THC among MHOI quartile 4, US$	45,677	42,582	44,961	44,014	43,551	42,678	44,947	44,702	46,938	47,737	< 0.001

LOS: length of hospital stay; MHOI: median household income national quartile for patient ZIP code; THC: total hospital charges.

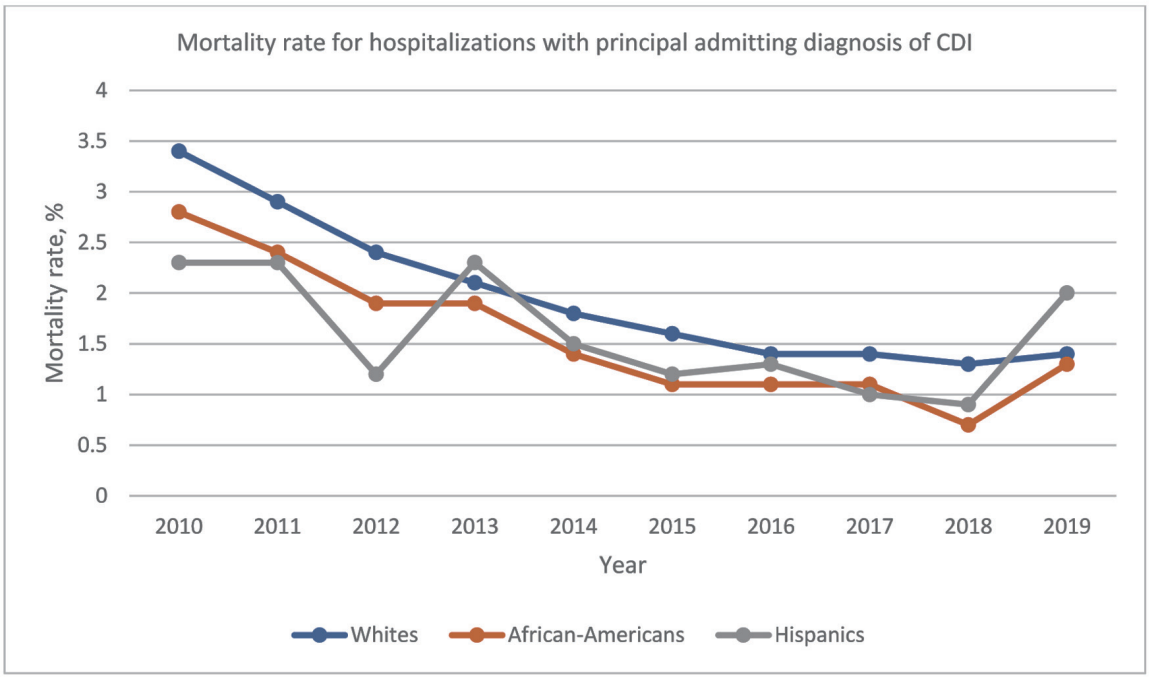

Figure 6. Trend in mortality rate hospitalizations with a principal admitting diagnosis of CDI (racial subgroup analysis). CDI: *Clostridioides difficile* infection.

sitivity and comparable specificity to the previously prevalent enzyme immunoassay [27, 28].

Elderly patients were found to have worse outcomes compared to young and middle-aged individuals. Older patients have previously been shown to be at higher risk of severe and fulminant CDI [29] which invariably have worse outcomes. This increased risk among the elderly is likely related to increased odds of comorbidities and underlying conditions that are also well-recognized risk factors for CDI [28]. Institutionalization, longer hospital stays, and infections that necessitate frequent treatment with antibiotics are more common in the elderly [2].

Females were at increased odds of CDI hospitalization but had better adjusted outcomes. Sex disparities in CDI incidence and prevalence vary across studies, but male sex has previously been associated with severe/complicated CDI [30, 31]. While the reasons behind this are unclear, it may be related to male patients being at higher odds of comorbid conditions that predispose them to CDI [32].

We also found that most hospitalizations were among White patients, but adjusted outcomes were significantly worse in ethnic minorities. Blacks and Hispanics showed significantly worse mortality outcomes, longer hospital stays, and higher total hospitalization costs compared to Whites. These are similar to findings of a retrospective analysis of the US National Hospital Discharge Surveys from 2001 to 2010 which showed that while CDI incidence was higher among White patients (7.7/1,000 discharges vs. 4.9/1,000 discharges in Blacks, $P < 0.0001$), the Black race was independently associated with mortality (odds ratio 1.12, 95% CI 1.09 - 1.15) and severe CDI (odds ratio 1.09, 95 % CI 1.07 - 1.11), despite being a negative predictor for hospital LOS (OR 0.93, 95 % CI 0.93 - 0.94) [33]. The reasons behind these findings are still uncertain and require further studies to elucidate. However, they may suggest socioeconomic and structural inequities disparately affecting minoritized communities including an inequitable distribution of quality healthcare, differential access to public and private insurance, and insufficient research evaluating and addressing these inequities [34].

This study has some important limitations. Firstly, the NIS uses "claims data", and ICD-9 and ICD-10 codes were used to confirm diagnoses that may not completely match clinical/laboratory parameters. Hence our findings were dependent on appropriate data collection and correct representation of these administrative codes. Secondly, the NIS lacks laboratory or radiological data and does not appropriately grade clinical disease severity, hence we could not stratify outcomes specific to severe/fulminant CDI. Thirdly, the NIS reports data on hospitalizations rather than individual patients, hence patients with recurrent CDI infections may count as multiple admissions. Also, the sampling data from NIS do not include rehabilitation and long-term acute care hospitals which is a subset of the population that is at risk for CDI, hence that subset is not accounted for. Lastly, we were unable to determine treatment modalities and the effect of medication adherence on outcomes. Lastly, we were unable to determine treatment modalities and the effect of medication adherence on outcomes.

Conclusions

Outcomes of CDI hospitalizations improved over the studied decade, but CDI still places significant mortality and economic burden on the US health care system. Older age, male sex,

and belonging to a minority racial group were associated with worse outcomes. Further studies are needed to elucidate the reasons for these findings. Continued efforts to address other established risk factors are needed for primary and secondary prevention of CDI.

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Conflict of Interest

The authors have no current or potential conflict to declare.

Informed Consent

Not required as the study involves publicly available data from the Nationwide Inpatient Sample database.

Author Contributions

Pius Ehiremen Ojemolon drafted the manuscript, created the tables and figures, and participated in the review and final approval of the manuscript. Hafeez Shaka conceptualized the manuscript, carried out the data analysis, and participated in the review and final approval of the manuscript. Robert Kwei-Nsoro and Hisham Laswi participated in drafting the introduction and in the review and final approval of the manuscript. Ebehiwele Ebhohon, Abdultawab Shaka and Abdul-Rahman Abusalim participated in drafting the discussion and in the review and final approval of the manuscript. Benjamin Mba revised the manuscript for intellectual content and participated in the review and final approval of the manuscript.

Data Availability

Datasets are available through the HCUP central distributor on request.

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