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Hospital readmission with *Clostridium difficile* infection as a secondary diagnosis is associated with worsened outcomes and greater revenue loss relative to principal diagnosis

A retrospective cohort study

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Abstract

Recurrent *Clostridium difficile* infection (rCDI) requiring rehospitalization contributes to poor outcomes, which may differ between patients hospitalized with versus for it.

We performed a multicenter retrospective cohort study of rehospitalized adults surviving initial CDI hospitalization. Hospital mortality, length of stay (LOS), 30-day readmission, and mean gap between hospital costs and Diagnosis Related Group (DRG) reimbursement served as outcomes.

Among the 25.7% (n = 99,175) survivors requiring rehospitalization, 36,504 (36.8%) had rCDI (14,005 [38.4%] principal diagnosis rCDI [PrCDI]). Compared with non-CDI, PrCDI, and secondary diagnosis rCDI [SrCDI] carried lower risk of death (PrCDI odds ratio [OR] 0.52; 95% confidence interval [CI] 0.46, 0.58; SrCDI OR 0.80; 95% CI 0.75, 0.85) and 30-day readmission (PrCDI OR 0.84; 95% CI 0.80, 0.88; SrCDI OR 0.97; 95% CI 0.94, 1.01), and excess LOS (PrCDI 1.8 days; 95% CI 1.7, 2.0; SrCDI 1.4 days; 95% CI 1.3, 1.5), and costs (PrCDI $1399; 95% CI $858, $1939; SrCDI $2809; 95% CI $2307, $3311). Mean gap between hospital costs and DRG reimbursements was highest in SrCDI ($13,803).

A rehospitalization within 60-days of an initial CDI hospitalization occurs in approximately 25% of all survivors, 1/3 with rCDI. SrCDI carries worse outcomes than PrCDI. The potential loss of revenue incurred by the hospital is nearly 3-fold higher for SrCDI than PrCDI.

Abbreviations: AHRQ = Agency for Healthcare Research and Quality, CA = community-acquired, CO-HCFA = community-onset healthcare facility associated, GLM = generalized linear model, HCUP = Health Care Utilization Project, HO-HCFA = hospital-onset healthcare facility associated, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IQR = interquartile range, LOS = length of stay, MS-DRG = Medicare Severity Diagnosis Related Group, PrCDI = principal diagnosis rCDI, rCDI = recurrent *Clostridium difficile* infection, SD = standard deviation, SID = State Inpatient Databases, SrCDI = secondary diagnosis rCDI.

Keywords: *C difficile*, hospital costs, mortality, outcomes, rehospitalization

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1. Introduction

Although clinical trials suggest that certain therapies can reduce recurrent *Clostridium difficile* infection (rCDI) rates by ≥50%, the condition remains both prevalent and burdensome.[1–4] Reasons include the increasing complexity of patients potentially at risk for rCDI, the suboptimal use of the newer therapies, and the general differences between the quasi-artificial construct of clinical trials and real-world clinical practice.[5–7] Regardless of the underlying reasons, rCDI continues to vex clinicians, torment patients, and affect hospitals.

Patients who have survived an initial hospitalization with CDI and then require a rehospitalization with a recurrence consume a disproportionate share of healthcare resources. In a cohort of such Medicare patients, we noted a recurrence rate of 33%, of whom 2/3 required a readmission to the hospital within a short interval.[4] Although rCDI did not raise the risk of death in these subjects, the associated excess hospital days and costs were considerable.

While studies conflict as to whether rCDI increases mortality, its economic burden is not in question. What is less certain is what drives this burden.[4,8–11] For example, there may be differences between patients who are admitted explicitly for the treatment of their rCDI and those who are admitted with another condition, where rCDI is a concurrent but not primary affliction. It is likely that those hospitalized *for* rCDI differ in important and potentially actionable ways from those hospitalized *with* rCDI. It is also unclear how much reimbursements for rCDI hospitalizations compare with the actual costs hospitals incur caring for these patients, as it is possible that the lengths of stay for patients with rCDI readmission exceed standard payments for these admissions. Finally, as the US healthcare system moves to a "value based" purchasing approach with a diminished willingness of payors to cover costs associated with readmissions, it is important to understand the current rates of 30-day readmissions among patients with a rCDI.[12]

2. Methods

2.1. Study design

We performed a retrospective cohort study to explore the epidemiology and outcomes of adult (age ≥18 years) rehospitalizations with rCDI in the United States. Outcomes of interest were hospital mortality, length of stay (LOS), hospital costs, 30-day readmission rates, and the reimbursements gap (defined below).

2.2. Data sources

We analyzed the State Inpatient Databases (SID), a part of the Health Care Utilization Project (HCUP) administered by the Agency for Healthcare Research and Quality (AHRQ), from 4 geographically diverse US states (California [only available for years 2009–2011], Florida, Iowa, and New York) for years 2009 to 2013.[13] For further details on SID, please, view Supplemental material.

The 4 states representing each of the 4 Census Bureau regions of the United States were chosen because their geographic diversity increases the generalizability of our findings.[14]

2.3. Case identification

An initial CDI hospitalization episode was defined as a discharge with a CDI International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code (008.45) between March 1 and October 31 of any year and no CDI codes during any hospitalization within prior 60 days. All rehospitalizations within 60 days following initial CDI discharge were included in the cohort. Those whose rehospitalizations included a CDI code were assigned to the rCDI group.[4] Admissions with rCDI were subdivided into those whose rCDI was listed as the principal diagnosis (PrCDI), connoting the primary reason for admission, and those with rCDI as a secondary diagnosis (SrCDI), where rCDI was incidental to the hospitalization. For further definitions of rCDI categories (Community-onset healthcare facility associated [CO-HCFA], hospital-onset healthcare facility associated [HO-HCFA], and community-acquired [CA]), please, see Supplemental material.[15]

2.4. Follow-up

The groups were followed until in-hospital death or discharge from the hospital. For the 30-day readmission outcome, the survivors of the index rCDI hospitalization were followed for an additional 30 days with the sole purpose of quantifying this outcome.

2.5. Outcome variables

We examined mortality, hospital LOS in days, hospital costs in $US, as well as 30-day readmission rates among survivors of the readmission. HCUP collects hospital charges and provides Center for Medicare and Medicaid Services-defined individual hospital cost-to-charge conversion ratios as a part of the National Inpatient Database. Comparator groups were those readmitted with no evidence of rCDI (non-rCDI), those with PrCDI, and SrCDI. In addition, we explored the mean reimbursement gap between the top 5 Medicare Severity Diagnosis Related Groups (MS-DRG) within each comparator group (see below).[16] While hospital costs represent a fixed fraction of that which is billed by the hospital for a service (charge), a DRG reflects the actual amount reimbursed to the hospital by the payor. The gap between costs and reimbursements may also be related to further negotiated discounting or penalties and rewards based on value delivered.

2.6. Statistical analyses

We compared demographic, clinical, hospital, and discharge characteristics among the 3 groups, as well as their outcomes—mortality, LOS, costs, and 30-day readmission rates. Differences between mean MS-DRG reimbursements and mean costs for the top 5 MS-DRGs in each of the comparator groups were examined as a measure of the gap between costs and reimbursements.[16]

Mean (standard deviation, SD), and median (interquartile range, 25%–75% [IQR]) were calculated for continuous variables, and counts and proportions for categorical variables. One-way ANOVA, Student *t* test or the Wilcoxon rank-sum test were used to examine the differences in continuous variables as appropriate, while the chi-square test was used for categorical variables comparisons.

To adjust for confounding, we developed generalized linear models (GLM) to compare the differences in the continuous outcomes of interest (LOS and costs) between groups. Since the continuous outcomes were positive and non-normal (skewed), we ran the GLMs with a logarithmic link and used a Gamma family

distribution. Robust standard errors were derived based on the hospital of the patient encounter.[17] For binary outcome models (mortality, 30-day readmission), a multilevel mixed-effects logistic regression model structure was used with hospitals of the patient encounters treated as random effects.

All inferences were two-tailed. Statistical significance was defined to be present at $\alpha = 0.05$. Unless otherwise stated, the P-values are reported for comparisons between all 3 groups. Statistical analyses were performed using Stata/MP 15.1 for Windows for Windows (StataCorp, College Station, TX).

2.7. Ethics statement

Because this study used already existing publicly available fully de-identified retrospective data, it was exempt from ethics review.

3. Results

Among 385,682 initial CDI hospitalizations identified between years 2009 and 2013 in the 4 states examined, 99,175 (25.7%) required a rehospitalization (Fig. 1). Of them, 36,504 (36.8%) had a rCDI (14,005 [14.1%] as PrCDI), while the majority, 62,671 (63.2%), had no code for CDI. In each group, Florida contributed the plurality of admissions, followed by New York, California, and Iowa (Table 1). Nearly all rCDI were present on admission (POA) (99.7% PrCDI, 88.4% SrCDI) (Table 1), and nearly all were CO-HCFA (33,838, 92.7%) (Fig. 1).

While patients with PrCDI and SrCDI were older than the non-CDI subjects, SrCDI and non-CDI groups had fewer females than PrCDI group (Table 1). PrCDI group had the lowest and SrCDI's

the highest comorbidity burden, with non-CDI falling in-between (Table 1). Sepsis prevalence was nearly 8 times higher in SrCDI (39.2%) than in PrCDI (5.2%), and twice that in non-CDI (19.3%, $P < .001$). The prevalence of severe sepsis and septic shock followed a similar pattern (Table 1).

Both unadjusted hospital mortality and costs were highest in the SrCDI group and lowest in PrCDI (Supplement Table 1, http://links.lww.com/MD/C461). LOS, on the other hand, was similar in PrCDI and non-CDI groups and both were lower than in SrCDI (Supplement Table 1, http://links.lww.com/MD/C461). Interestingly, 30-day readmissions were highest among non-CDI and lowest in PrCDI, though in all groups the rate was over 30% (Supplement Table 1, http://links.lww.com/MD/C461).

In the adjusted analyses, comparing PrCDI and SrCDI outcomes to the reference group of non-CDI, PrCDI (odds ratio [OR] 0.52; 95% confidence interval [CI] 0.46, 0.58) and SrCDI (0.80; 95%CI 0.75, 0.85) were associated with a lower risk of death than non-CDI (Table 2). However, among both groups of rCDI patients we noted excess LOS (PrCDI 1.8 days; 95% CI 1.7, 2.0 and SrCDI 1.4 days; 95% CI 1.3, 1.5) and costs (PrCDI $1399; 95% CI $858, $1939 and SrCDI $2809; 95% CI $2307, $3311) relative to the non-CDI group (Table 2). Similar to mortality, however, adjusted 30-day readmission risk was lower in PrCDI (OR = 0.84; 95% CI 0.80, 0.88) and SrCDI (OR = 0.97; 95% CI 0.94, 1.01) than non-CDI (Table 2).

Among the top 5 DRGs, gastrointestinal disorders predominated in PrCDI, and sepsis did in SrCDI and non-CDI (Table 3). The mean gap between hospital costs and DRG-reimbursements was highest in SrCDI ($13,803) and lowest in PrCDI ($4881) (Table 3).
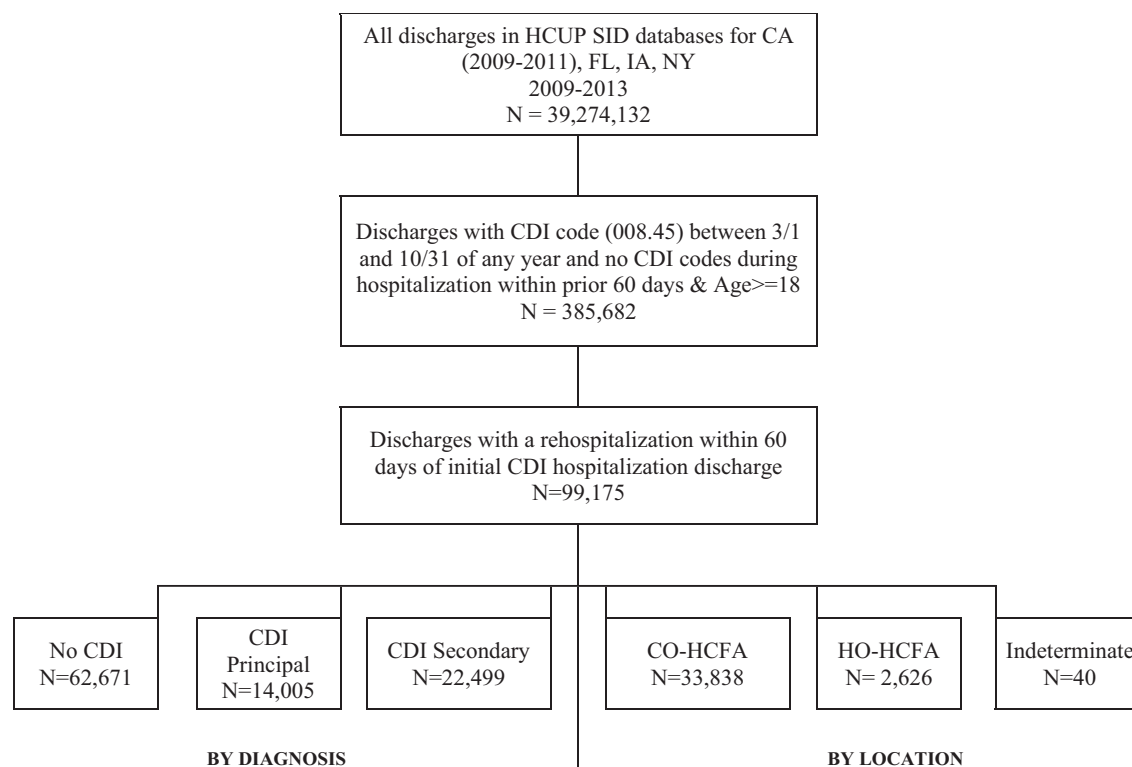

Figure 1. Enrollment chart. CDI = C difficile infection, CO = community-onset, HCFA = healthcare facility associated, HCUP = Health Care Utilization Project, HO = hospital-onset, SID = State Inpatient Database.

Table 1

Baseline characteristics, admission, sources, and hospital events.

Characteristic	Principal rCDI	Percent/ SD/IQR	Secondary rCDI	Percent/ SD/IQR	Any CDI	Percent/ SD/IQR	No CDI code	Percent/ SD/IQR	P value (across all)	P value (between CDI and no CDI)
Baseline characteristics										
N	14,005	100.00%	22,499	100.00%	36,504	100.00%	62,671	100.00%		
Sex (%)										
Male	5256	37.53%	10,157	45.14%	15,413	42.22%	27,941	44.58%	<.001	<.001
Female	8746	62.45%	12,338	54.84%	21,084	57.76%	34714	55.39%		
Missing	3	0.02%	4	0.02%	7	0.02%	16	0.03%		
Age (%)										
18–44	1095	7.82%	1660	7.38%	2755	7.55%	7164	11.43%		
45–54	1166	8.33%	1689	7.51%	2855	7.82%	7202	11.49%	<.001	<.001
55–64	1748	12.48%	3166	14.07%	4914	13.46%	10,715	17.10%		
≥65	9996	71.37%	15,984	71.04%	25,980	71.17%	37590	59.98%		
Mean	71.2	16.4		16.1		16.2		17.3		
Median	75	62, 84		62, 83		62, 83		56, 81	<.001	<.001
Race (%)										
White	9892	70.63%	15,352	68.23%	25,244	69.15%	39,334	62.76%		
Black	1430	10.21%	2813	12.50%	4243	11.62%	9756	15.57%		
Hispanic	1991	14.22%	2715	12.07%	4706	12.89%	8970	14.31%		
Asian or Pacific Islander	242	1.73%	690	3.07%	932	2.55%	1799	2.87%	<.001	<.001
Native American	19	0.14%	40	0.18%	59	0.16%	108	0.17%		
Other	340	2.43%	690	3.07%	1030	2.82%	2080	3.32%		
Missing	91	0.65%	199	0.88%	290	0.79%	624	1.00%		
Primary expected payer (%)										
Medicare	10,708	76.46%	17,231	76.59%	27,939	76.54%	43,136	68.83%		
Medicaid	1264	9.03%	2171	9.65%	3435	9.41%	8874	14.16%		
Private	1548	11.05%	2535	11.27%	4083	11.19%	8189	13.07%	<.001	<.001
Self-pay	228	1.63%	208	0.92%	436	1.19%	1058	1.69%		
No charge	64	0.46%	39	0.17%	103	0.28%	254	0.41%		
Other	193	1.38%	314	1.40%	507	1.39%	1160	1.85%		
Missing	0	0.00%	1	0.00%	1	0.00%	0	0.00%		
Year of admission[*] (%)										
2009	3211	22.93%	4697	20.88%	7908	21.66%	14,062	22.44%		
2010	3255	23.24%	5012	22.28%	8267	22.65%	14,370	22.93%	<.001	.003
2011	3303	23.58%	5820	25.87%	9123	24.99%	15056	23.84%		
2012	2199	15.70%	3516	15.63%	5715	15.66%	9739	15.42%		
2013	2037	14.54%	3454	15.35%	5491	15.04%	9444	14.95%		
State										
California	3014	21.52%	5657	25.14%	8671	23.75%	14,246	22.73%	<.001	<.001
Florida	6722	48.00%	8770	38.98%	15,492	42.44%	27,568	43.99%		
Iowa	403	2.88%	529	2.35%	932	2.55%	1187	1.89%		
New York	3866	27.60%	7543	33.53%	11,409	31.25%	19,670	31.39%		
Hospital ownership and size										
Investor-owned, under 100 beds	252	1.80%	266	1.18%	518	1.42%	920	1.47%		
Investor-owned, 100+ beds	2338	16.69%	3176	14.12%	5514	15.11%	10,683	17.05%		
Not-for-profit, rural, under 100 beds	158	1.13%	155	0.69%	313	0.86%	498	0.79%		
Not-for-profit, rural, 100+ beds	328	2.34%	425	1.89%	753	2.06%	1011	1.61%	<.001	<.001
Not-for-profit, urban, under 100 beds	265	1.89%	386	1.72%	651	1.78%	916	1.46%		
Not-for-profit, urban, 100 to 299 beds	2995	21.39%	4840	21.51%	7835	21.46%	13,040	20.81%		
Not-for-profit, urban, 300+ beds	7357	52.53%	12,789	56.84%	20,146	55.19%	34,613	55.23%		
Missing	312	2.23%	462	2.05%	774	2.12%	990	1.58%		
Comorbidities (%)										
AIDS/HIV	118	0.84%	90	0.40%	208	0.57%	357	0.57%	<.001	1.00
Alcohol abuse	418	2.98%	664	2.95%	1082	2.96%	2534	4.04%	<.001	<.001
Blood loss anemia	209	1.49%	467	2.08%	676	1.85%	1073	1.71%	<.001	.11
Chronic pulmonary disease	3649	26.05%	6344	28.20%	9993	27.38%	16,591	26.47%	<.001	.002
Coagulopathy	710	5.07%	2275	10.11%	2985	8.18%	5159	8.23%	<.001	.76
Congestive heart failure	2628	18.76%	5380	23.91%	8008	21.94%	11,876	18.95%	<.001	<.001
Deficiency anemia	5335	38.09%	9241	41.07%	14,576	39.93%	23,840	38.04%	<.001	<.001
Depression	2343	16.73%	2998	13.33%	5341	14.63%	8289	13.23%	<.001	<.001
Diabetes, complicated	1088	7.77%	2154	9.57%	3242	8.88%	5891	9.40%	<.001	.006
Diabetes, uncomplicated	3211	22.93%	5745	25.53%	8956	24.53%	16,897	26.96%	<.001	<.001
Drug abuse	352	2.51%	473	2.10%	825	2.26%	2230	3.56%	<.001	<.001
Fluid and electrolyte disorders	8988	64.18%	11,901	52.90%	20,889	57.22%	25,112	40.07%	<.001	<.001

(continued)

Table 1

(continued).

Characteristic	Principal rCDI	Percent/ SD/IQR	Secondary rCDI	Percent/ SD/IQR	Any CDI	Percent/ SD/IQR	No CDI code	Percent/ SD/IQR	P value (across all)	P value (between CDI and no CDI)
Hypertension	9563	68.28%	14,017	62.30%	23,580	64.60%	38,124	60.83%	<.001	<.001
Hypothyroidism	2316	16.54%	3659	16.26%	5975	16.37%	9309	14.85%	<.001	<.001
Liver disease	597	4.26%	1086	4.83%	1683	4.61%	3455	5.51%	<.001	<.001
Lymphoma	317	2.26%	618	2.75%	935	2.56%	1522	2.43%	<.001	.19
Metastatic cancer	483	3.45%	952	4.23%	1435	3.93%	2619	4.18%	<.001	.06
Neurological disorders	1791	12.79%	3524	15.66%	5315	14.56%	8788	14.02%	<.001	.02
Obesity	1057	7.55%	1923	8.55%	2980	8.16%	5345	8.53%	<.001	.05
Paralysis	548	3.91%	1558	6.92%	2106	5.77%	4028	6.43%	<.001	<.001
Peptic ulcer disease, no bleeding	12	0.09%	21	0.09%	33	0.09%	44	0.07%	.53	.27
Peripheral vascular disorders	1393	9.95%	2640	11.73%	4033	11.05%	6540	10.44%	<.001	.003
Psychosis	775	5.53%	1266	5.63%	2041	5.59%	3790	6.05%	<.001	.003
Pulmonary circulation disorders	471	3.36%	1131	5.03%	1602	4.39%	2339	3.73%	<.001	<.001
Renal failure	3435	24.53%	6909	30.71%	10,344	28.34%	17,675	28.20%	<.001	.65
Collagen vascular diseases	696	4.97%	945	4.20%	1641	4.50%	2520	4.02%	<.001	<.001
Solid tumor without metastasis	520	3.71%	917	4.08%	1437	3.94%	2416	3.86%	.18	.52
Valvular disease	911	6.50%	1442	6.41%	2353	6.45%	3500	5.58%	<.001	<.001
Weight loss	2330	16.64%	4916	21.85%	7246	19.85%	8233	13.14%	<.001	<.001
Charlson comorbidity score										
Mean	6.2	3.1	7.4	3.2	7.0	3.2	6.9	3.3	<.001	.34
Median	6	4, 8	7	5, 9	7	5, 9	7	5, 9		
Admission sources and hospital events										
CDI POA	13,956	99.65%	19,881	88.36%	33,837	92.69%	0	0.00%	NA	NA
Admission source										
Emergency department	12,455	88.93%	18,575	82.56%	31,030	85.00%	51,799	82.65%		
Transfer from another acute or long-term care facility	717	5.12%	2488	11.06%	3205	8.78%	5603	8.94%		
Other[†]	777	5.55%	1333	5.92%	2110	5.78%	4929	7.86%		
Missing	56	0.40%	103	0.46%	159	0.44%	343	0.55%		
Admission type[‡]										
Emergent	9722	69.42%	14,734	65.49%	24,456	67.00%	40,619	64.81%		
Urgent	935	6.68%	1317	5.85%	2252	6.17%	4119	6.57%		
Elective	331	2.36%	773	3.44%	1104	3.02%	3622	5.78%	<.001	<.001
Trauma	0	0.00%	13	0.06%	13	0.04%	43	0.07%		
Other/Missing	3017	21.54%	5662	25.17%	8679	23.78%	14,268	22.77%		
Hospital events										
Toxic megacolon	170	1.21%	203	0.90%	373	1.02%	566	0.90%	.002	.06
Sepsis	731	5.22%	8829	39.24%	9560	26.19%	12,105	19.32%	<.001	<.001
Severe sepsis	240	1.71%	4256	18.92%	4496	12.32%	5279	8.42%	<.001	<.001
Septic shock	158	1.13%	2947	13.10%	3105	8.51%	3391	5.41%	<.001	<.001
Abdominal procedure/surgery	87	0.62%	380	1.69%	467	1.28%	1028	1.64%	<.001	<.001
Colectomy	47	0.34%	164	0.73%	211	0.58%	193	0.31%	<.001	<.001
Number of discharge diagnoses										
Mean	13.0	5.6	16.8	6.1	15.3	6.2	13.9	6.1	<.001	<.001
Median	12	9, 16	15	13, 21	15	11, 19	14	9, 17		
Number of procedures										
Mean	1.0	1.7	2.5	3.0	1.9	2.7	2.0	2.5	<.001	<.001
Median	0	0, 1	1	0, 4	1	0, 3	1	0, 3		

AIDS = acquired immune deficiency syndrome, HIV = human immunodeficiency virus, IQR = interquartile range, NA = not applicable, POA = present on admission, rCDI = recurrent *C difficile* infection, SD = standard deviation.

[*] California data available through 2011 only.

[†] Category "other" includes court/law enforcement facility and non-healthcare facility.

[‡] State of California does not provide this data point.

4. Discussion

We have demonstrated that in a cohort of patients who have survived an initial hospitalization with a CDI, a full one-quarter gets readmitted within 60 days, of whom over 1/3 has a diagnosis of rCDI during that readmission. While only approximately one-third of all rCDI is PrCDI, nearly all are considered to be POA. We further found that those patients who are readmitted with

PrCDI are different demographically and clinically from those with SrCDI and those without CDI. Indeed, among those 3 groups, patients who are rehospitalized with rCDI as a secondary diagnosis tend to exhibit the highest severity of illness. Nevertheless, both SrCDI and PrCDI patients have a lower adjusted odds of hospital death and 30-day readmission than non-rCDI patients. However, even after adjustment, both PrCDI and SrCDI are associated with increased hospital LOS and costs

Table 2

Adjusted outcomes for principal and secondary rCDI relative to no rCDI[*].

	Principal rCDI		Secondary rCDI	
	Point estimate	95% CI	Point estimate	95% CI
Odds ratios				
Hospital mortality	0.52	0.46, 0.58	0.80	0.75, 0.85
30-day readmission	0.84	0.80, 0.88	0.97	0.94, 1.01
Excess units				
LOS, d	1.82	1.67, 1.98	1.39	1.25, 1.54
Hospital costs ($)	1399	858, 1939	2809	2307, 3311

LOS = length of stay, rCDI = recurrent *C difficile* infection.

[*] The following were used as covariates to adjust for confounding: age, sex, race, insurance payor, year of admission, geographic location, hospital size and urbanicity, admission source, admission type, if emergency department services were rendered, if the patient admission was on a weekend, Elixhauser comorbidities, the total number of procedures, diagnosis, chronic diagnoses, and Elixhauser comorbidities, sepsis, severe sepsis, septic shock, abdominal surgery, colectomy, megacolon, and toxic megacolon.

relative to non-rCDI hospitalizations. Notably, SrCDI carries the highest mean reimbursement gap among the 3 groups examined; nearly $14,000 per hospitalization.

The difference in hospital mortality between those with SrCDI (11.5%) and PrCDI (2.9%) implies that, even in the setting of rCDI, some other factors are likely driving outcomes. For example, sepsis, present in 18.9% of SrCDI as compared with 1.7% of PrCDI, could explain much of the difference. Alternatively, it is possible that this reflects the limited space for billing codes in the HCUP databases. Hence there may be a coding bias wherein those patients with greater disease burden may be less likely to have a CDI code noted if the coder deems it to

Table 3

Reimbursement gap.

Principal rCDI

DRG rank	DRG No.		N (x)	Mean cost (y)	Mean DRG reimbursement (z)	Delta (y−z)	Total (x*[y−z])
1	372	Major gastrointestinal disorders & peritoneal infections w CC	6600	$11,336.00	$7018.97	$4317.03	$28,492,415.90
2	371	Major gastrointestinal disorders and peritoneal infections w MCC	4366	$18,180.00	$11,913.52	$6266.48	$27,359,473.37
3	373	Major gastrointestinal disorders and peritoneal infections w/o CC/MCC	2638	$7488.00	$4786.60	$2701.40	$7,126,300.12
4	356	Other digestive system OR procedures w MCC	146	$46,414.00	$26,277.34	$20,136.66	$2,939,952.76
5	329	Major small and large bowel procedures w MCC	49	$62,466.00	$33,157.23	$29,308.77	$1,436,129.85
Total			13,799				$67,354,272.00
						Mean gap	**$4,881.10**

Secondary rCDI

DRG rank	DRG No.		N (x)	Mean cost (y)	Mean DRG reimbursement (z)	Delta (y−z)	Total (x*[y−z])
1	871	Septicemia w/o MV 96+ hours w MCC	4071	$25,116.00	$11,677.04	$13,438.96	$54,710,024.73
2	872	Septicemia w/o MV 96+ hours w/o MCC	1174	$14,414.00	$6,496.82	$7,917.18	$9,294,766.25
3	870	Septicemia w MV 96+ hours	712	$57,696.00	$39,772.62	$17,923.38	$12,761,445.76
4	853	Infectious and parasitic diseases w OR procedure w MCC	633	$58,600.00	$34,737.12	$23,862.88	$15,105,203.31
5	291	Heart failure and shock w MCC	576	$21,768.00	$9,539.40	$12,228.60	$7,043,672.73
Total			7166				$98,915,112.79
						Mean gap	**$13,803.39**

No rCDI

DRG rank	DRG No.		N (x)	Mean cost (y)	Mean DRG reimbursement (z)	Delta (y−z)	Total (x*[y−z])
1	871	Septicemia w/o MV 96+ hours w MCC	5183	$19,946.00	$11,677.04	$8,268.96	$42,858,043.33
2	392	Esophagitis, gastroenteritis and misc digestive disorders w/o MCC	2648	$8,061.00	$4,400.05	$3,660.95	$9,694,183.35
3	291	Heart failure and shock w MCC	1707	$15,848.00	$9,539.40	$6,308.60	$10,768,777.63
4	690	Kidney and urinary tract infections w/o MCC	1379	$9,184.00	$4,700.41	$4,483.59	$6,182,875.48
5	870	Septicemia w MV 96+ hours	1126	$47,255.00	$39,772.62	$7,482.38	$8,425,158.62
Total			12,043				$77,929,038.41
						Mean gap	**$6,470.90**

CC = complication or comorbidity, DRG = diganosis-realted group, MCC = major complication or comorbidity, MV = mechanical ventilation; misc = miscellaneous, OR = operating room, rCDI = recurrent C. difficile infection, w/o = without, w = with.

be less severe and hence less important than other conditions. This observation may further explain why our findings differ from those of others.[8]

At the same time, we observed a similar relationship between rCDI and death in a cohort of Medicare recipients whose initial CDI hospitalization required discharge to a chronic care facility.[4] In that study, approximately 25% of patients with and without rCDI died within 60 days of rCDI onset. The lower overall rates of death in the current analysis likely reflect a younger population than in other studies, coupled with a shorter observation period limited to the acute hospitalization. In contrast, Olsen et al[8] reported a 33% rise in the adjusted relative risk of death within 180 days in association with rCDI.

One novel aspect of our study is its exploration into the potential differences in outcomes between patients admitted to the hospital specifically to treat the recurrence itself (PrCDI), as opposed to where rCDI is a secondary reason for admission (SrCDI). This distinction appears important, as the outcomes diverge substantially. Therefore, different therapeutic strategies may be necessary in the 2 groups to optimize those outcomes. It is not surprising, for example, that mortality among PrCDI patients is substantially lower than SrCDI, since SrCDI patients were far more likely to be admitted with such high-risk conditions as sepsis.

Ours is not the first study to demonstrate the excess costs and LOS in association with rCDI. Over a 180-day period following index CDI, Olsen et al[9] found an excess of 11 hospital days among those with rCDI over those without, and the number of readmissions per patient was 1.72 versus 0.81 for the groups, respectively. In a Medicare cohort of older subjects, rCDI resulted in an excess of 20 days of acute hospitalization.[4] Although the number of excess days in the hospital is lower in the current study than in each of the prior 2, this again is likely due to the shorter observation period and a younger population we studied. Nevertheless, despite having no impact on in-hospital mortality, both PrCDI and SrCDI contributed substantially to an increase in the LOS. More importantly, this excess LOS translated into significant excess costs, consistent with prior reports.[4,11]

To the best of our knowledge, ours is the first study to examine 2 additional outcomes in the setting of rCDI hospitalization, namely, 30-day readmission rates and the reimbursement gap. These outcomes carry a particular importance to hospitals whose finances are already strained. It should be reassuring to both patients and institutions that the 30-day readmission rates do not appear to be higher with than without rCDI. However, rCDI admissions pose a major financial challenge since in both cases, patients hospitalized either with or for rCDI consume resources well beyond amounts covered by third party payors. This is particularly true in the instance of SrCDI, where we estimate each hospitalization nets the institution a $14,000 loss per admission. While the SrCDI-associated reimbursement gap is the largest, the other 2 groups' reimbursement shortfalls are also substantial. Even when comparing similar DRG categories, such as 870 and 871 (sepsis) between SrCDI and no rCDI, there is almost twice the magnitude of this gap, defining these values may help hospitals shed a quantitative light on discrepancies they may encounter.

Our study has a number of limitations. As a retrospective study it is subject to a number of biases, most notably selection bias. To mitigate this we developed a priori inclusion criteria. Because we used administrative coding to identify rCDI, there is a possibility for misclassification. However, using ICD-9-CM codes to identify incident CDI is well validated in the hospitalized population.[18] Still, while this method of defining rCDI in the

hospital has been used previously, it has not been widely validated.[4] In fact, the presence of this code may or may not signify the actual presence of active CDI. Wen et al[19] found a relatively low specificity of a combination of ICD-9 codes, stool testing procedure codes, and CDI treatment codes for recurrent CDI. This raises the possibility that at least in a proportion of those identified, rCDI reflects the patient having a documented history of CDI, rather than an active episode. However, this type of misclassification is likely to drive our effect estimates closer to the null and thus mute any differences that exist between comparator groups. This may in part account for our inability to find an association between rCDI and either mortality or readmission rates.

Confounding is an issue in observational studies. Although we dealt with the possibility of confounding by deriving regression models to estimate the effect of rCDI on the outcomes of interest using a large number of additional covariates, the possibility of residual confounding remains. At the same time, our analysis may also suffer from overadjustment.[20] In particular, it is possible that sepsis, for example, at least in some cases, was an intermediary between rCDI and hospital outcomes. In such a case examining it as a confounder may have shifted our effect estimates toward the null, implying that the actual impact of rCDI on the outcomes is likely to be greater than what we found. The risk of this is highest in the SrCDI group, where the prevalence of sepsis was far greater than in PrCDI.

These limitations notwithstanding, our study has a number of strengths that lend credibility to our results. Since we relied on a large geographically representative sample of rCDI discharges, our results are broadly generalizable to US hospitals. We applied rigorous statistical methodologies to derive attributable outcomes. The novel aspects of our study—examining PrCDI and SrCDI separately, computing rCDI's impact on 30-day readmission rates, and the calculation of the reimbursement gap—augment the usefulness and relevance of our data in underscoring the financial pressures that should drive institutions to target intensive preventive efforts.

In summary, a rehospitalization following an index CDI admission is a common occurrence, and a substantial proportion of those readmissions involve rCDI. PrCDI patients differ from those with SrCDI, the latter more similar to those rehospitalized without rCDI, but more severely ill and suffering worse economic outcomes. Although we found no evidence of an increase in mortality or 30-day readmission due to PrCDI or SrCDI relative to no CDI, both increase the LOS and hospital costs. Importantly, all groups, and SrCDI in particular, incurred a substantial deficit in reimbursements when compared with the expenditures, thus suggesting that more efficient models of care may be needed for these patients.

Author contributions

MDZ has participated in study design, results interpretation, manuscript drafting, and revision.
BHN has participated in analysis, and manuscript review and revision. Dr Nathanson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SWM has participated in study design, analysis, and manuscript review and revision.

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