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ORIGINAL ARTICLE

Attributable Inpatient Costs of Recurrent *Clostridium difficile* Infections

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OBJECTIVE. To determine the attributable inpatient costs of recurrent *Clostridium difficile* infections (CDIs).

DESIGN. Retrospective cohort study.

SETTING. Academic, urban, tertiary care hospital.

PATIENTS. A total of 3,958 patients aged 18 years or more who developed an initial CDI episode from 2003 through 2009.

METHODS. Data were collected electronically from hospital administrative databases and were supplemented with chart review. Patients with an index CDI episode during the study period were followed up for 180 days from the end of their index hospitalization or the end of their index CDI antibiotic treatment (whichever occurred later). Total hospital costs during the outcome period for patients with recurrent versus a single episode of CDI were analyzed using zero-inflated lognormal models.

RESULTS. There were 421 persons with recurrent CDI (recurrence rate, 10.6%). Recurrent CDI case patients were significantly more likely than persons without recurrence to have any hospital costs during the outcome period ($P < .001$). The estimated attributable cost of recurrent CDI was $11,631 (95% confidence interval, $8,937–$14,588).

CONCLUSIONS. The attributable costs of recurrent CDI are considerable. Patients with recurrent CDI are significantly more likely to have inpatient hospital costs than patients who do not develop recurrences. Better strategies to predict and prevent CDI recurrences are needed.

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Clostridium difficile infection (CDI) is a formidable challenge. Although most cases of CDI are successfully treated, 10%–30% of patients experience a CDI recurrence.[1,2] There are relatively few published studies that specifically examine recurrent CDI. A number of risk factors for recurrent CDI have been reported, most commonly older age,[1,3-10] higher severity of illness,[4,6] hospitalization after initial CDI,[10,11] receipt of antibiotics during the period after initial CDI,[1,3,4,6,7,11,12] and receipt of antacids.[1,3,7,13] In addition, Pepin et al[9] and Petrella et al[14] have reported increased recurrence rates associated with the 027/NAP1/BI strain.

Data on the economic burden of recurrent CDI on the healthcare system are extremely sparse. McFarland et al[8] have published the only estimates of costs associated with recurrent CDI, estimating that recurrent CDI costs $3,103 per episode and $10,970 over a patient's lifetime. While these estimates are the best data currently available, they predate the emergence of the 027/NAP1/BI strain and do not estimate the attributable costs associated with recurrent CDI. The objective of this study was to determine the attributable inpatient costs of recurrent CDI in a large retrospective cohort of CDI patients.

METHODS

Study Design

This study was conducted at Barnes-Jewish Hospital (BJH), an academic tertiary care facility in St. Louis, Missouri. Data were collected electronically from the hospital's electronic medical records and from the Medical Informatics and Trendstar financial databases. The Informatics database was queried to identify all patients with positive *C. difficile* toxin assay results collected from January 1, 2003, through December 31, 2009. The BJH laboratory accepts only diarrheal stool

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samples for *C. difficile* testing. Two toxin assays were used during the study period (TechLab *C. difficile* Toxin A/B II before July 2004 and again after May 2009; Remel ProSpec T *C. difficile* A/B from July 2004 through May 2009). Additional electronic data included demographics, admission and discharge dates, admission type (eg, inpatient, outpatient, or emergency department), *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes, inpatient medications, and laboratory results. In addition, medical records were reviewed to identify medications on hospital admission and discharge and whether the patient received a diagnosis of recurrent CDI. Total hospital costs (direct, indirect, and fixed) and major diagnostic category (MDC) codes were collected from Trendstar. Death dates were collected from the Informatics database and the Social Security Death Index. ICD-9-CM discharge codes from the index admission and any admissions within the previous year were classified according to Charlson-Deyo categories.[15,16]

Definitions

A CDI index hospitalization was defined as the first inpatient hospitalization during the study period in which the patient had a positive *C. difficile* toxin assay. All index CDI cases had a positive toxin assay at BJH. The outcome period was defined as 180 days after the end of the index hospitalization or the end of the patient's index CDI antibiotic treatment, whichever occurred later. A recurrent CDI case was defined as a patient who had documentation of recurrent CDI within 42 days of the end of CDI antibiotic treatment, either by positive toxin assay or by clinical diagnosis documented in the medical record (history of a positive laboratory test as an outpatient or at an outside healthcare facility and symptoms consistent with CDI). We used 42 days as the risk period to develop recurrent CDI on the basis of the current surveillance definition of 8 weeks (ie, 56 days) between episodes to be considered recurrent CDI.[17] Since the recommended CDI treatment duration is 10–14 days,[18] the risk period for recurrent CDI after the end of treatment using the surveillance definition is 42–46 days. Patients were included in the study only once.

Exclusion Criteria

Patients who were less than 18 years old, had a documented history of CDI (either by positive toxin assay or recorded in the medical record) in the 60 days before the study period, or were admitted for less than 0.75 days during their index CDI admission were excluded. Patients who experienced a CDI recurrence during the index hospitalization were also excluded because of the difficulty in separating costs associated with each CDI episode. Patients who died during their index hospitalization or were discharged on hospice were excluded. Readmissions that began during the 180-day outcome period but ended after the 180-day outcome period were excluded. For readmissions that began prior to the outcome period, costs were prorated to include only those days that occurred within the outcome period.

Statistical Analyses

The total hospital cost during the outcome period was defined as the cumulative sum of all costs for hospital readmissions during the 180-day outcome period. All hospital readmission costs were inflated to 2010 dollars based on the year of discharge using the medical care component of the consumer price index.

Zero-inflated lognormal models were used to identify factors associated with total hospital readmission costs during the outcome period because 55% of patients had no readmissions during the 180-day outcome period and thus no readmission costs.[19] The models had 2 components: a logistic regression component modeling the probability of zero costs (ie, no readmissions during the outcome period), and a lognormal regression component modeling the mean of log costs given nonzero costs (ie, 1 or more readmissions during the outcome period). Cost data were normally distributed after log transformation.

Two models were fitted. The first model included only recurrent CDI status. The full model included recurrent CDI status and other relevant covariates. Missing body mass index (BMI) values ($n = 31$; 0.8%) were imputed at the median of 26. All covariates were included in both components of the model.

Odds ratios (ORs) were calculated for the logistic component and cost ratios (CRs) were calculated for the lognormal component for all covariates in the model, with corresponding 95% confidence intervals (CI). Quartiles of age were used in the model since exploratory graphical methods and spline fits indicated nonlinear associations, especially for the lognormal component. All other variables were categorical. The quasi-maximum-likelihood estimator was used to back-transform log costs to actual dollar costs.[20]

Overall mean costs were calculated by multiplying the estimated probability of nonzero cost from the logistic model times the expected cost from the lognormal portion of the model. Differences in overall mean costs between exposures (eg, recurrent CDI vs no recurrent CDI) were calculated using the average predicted value (APV) method.[21] The APV method is useful to understand how overall mean costs differ by covariates, regardless of the mechanism(s) by which the differences may arise. The APV method was applied by calculating predicted costs from the fitted model for both levels of the variable of interest (eg, recurrent CDI vs no recurrent CDI) separately for all patients in the data set. Then, the mean difference was calculated across all patients. The method was applied separately for all covariates in the model to obtain differences in overall mean costs for all covariates. Bootstrapping (500 samples) and the percentile method were used to calculate 95% CIs. The difference in overall mean

TABLE 1. Percentages of Zero and Nonzero Costs by All Variables

Variable	Zero cost, no. (%)	Nonzero cost, no. (%)	Total (n = 3,958)
Recurrent CDI	45 (10.7)	376 (89.3)	421
No recurrent CDI	2,111 (59.7)	1,426 (40.3)	3,637
Age quartile			
<49 years	485 (50.8)	470 (49.2)	955
49 to <62 years	537 (52.1)	493 (47.9)	1,030
62 to <74 years	530 (54.6)	441 (45.4)	971
≥74 years	604 (60.3)	398 (39.7)	1,002
Sex			
Female	1,069 (55.8)	846 (44.2)	1,915
Male	1,087 (53.2)	956 (46.8)	2,043
Race			
White	1,529 (56.2)	1,192 (43.8)	2,721
Nonwhite	627 (50.7)	610 (49.3)	1,237
Body mass index			
Missing	29 (93.5)	2 (6.5)	31
Underweight	169 (53.1)	149 (46.9)	318
Normal weight	745 (53.1)	658 (46.9)	1,403
Overweight	592 (53.2)	520 (46.8)	1,112
Obese	621 (56.8)	473 (43.2)	1,094
Charlson composite score			
0	439 (65.5)	231 (34.5)	670
1	391 (61.6)	244 (38.4)	635
2	529 (53.9)	452 (46.1)	981
3	263 (51.2)	251 (48.8)	514
4	125 (45.3)	151 (54.7)	276
≥5	409 (46.4)	473 (53.6)	882
Charlson comorbidities			
Myocardial infarction	161 (48.2)	173 (51.8)	334
Congestive heart failure	449 (50.8)	434 (49.2)	883
Peripheral vascular disease	156 (53.8)	134 (46.2)	290
Cerebrovascular disease	151 (54.3)	127 (45.7)	278
Chronic renal failure	83 (41.1)	119 (58.9)	202
Dementia	15 (53.6)	13 (46.4)	28
Chronic obstructive pulmonary disease	524 (54.2)	443 (45.8)	967
Rheumatologic disease	87 (55.8)	69 (44.2)	156
Peptic ulcer disease	92 (57.5)	68 (42.5)	160
Any liver disease	107 (47.6)	118 (52.4)	225
Any diabetes	521 (49.7)	527 (50.3)	1,048
Paraplegia/hemiplegia	43 (50.0)	43 (50.0)	86
Cancer (excluding leukemia/lymphoma)	404 (50.6)	395 (49.4)	799
Leukemia/lymphoma	299 (43.5)	389 (56.5)	688
Metastatic solid tumor	236 (50.3)	233 (49.7)	469
HIV/AIDS	26 (35.1)	48 (64.9)	74
MDC			
0 (unassigned principal diagnosis)	404 (60.4)	265 (39.6)	669
1 (diseases of the nervous system)	90 (60.8)	58 (39.2)	148
4 (diseases of the respiratory system)	160 (52.3)	146 (47.7)	306
5 (diseases of the circulatory system)	188 (51.6)	176 (48.4)	364
6 (diseases of the digestive system)	615 (58.8)	431 (41.2)	1,046
7 (diseases of the hepatobiliary system and pancreas)	109 (56.5)	84 (43.5)	193
8 (diseases of the musculoskeletal system and connective tissue)	72 (55.4)	58 (44.6)	130
10 (endocrine, nutritional, and metabolic diseases)	43 (46.2)	50 (53.8)	93
11 (diseases of the kidney and urinary tract)	140 (49.6)	142 (50.4)	282
13 (diseases of the female reproductive system)	28 (70.0)	12 (30.0)	40
16 (diseases of blood, blood-forming organs, immunologic)	24 (36.9)	41 (63.1)	65
17 (myeloproliferative diseases)	79 (33.8)	155 (66.2)	234
18 (infectious and parasitic diseases)	108 (49.3)	111 (50.7)	219
21 (injuries, poisonings, toxic effects of drugs)	18 (56.3)	14 (43.8)	32
25 (HIV infections)	16 (42.1)	22 (57.9)	38
All others	62 (62.6)	37 (37.4)	99

NOTE. Row percentages are used. CDI, *Clostridium difficile* infection; HIV, human immunodeficiency virus; MDC, major diagnostic category.

TABLE 2. Estimated Probabilities and Overall Mean Costs Adjusted for Recurrent *Clostridium difficile* Infection (CDI) Status Only

Recurrent CDI	Probability of zero cost	Expected mean cost given nonzero costs, $	Overall mean costs,[a] $
No	0.597	20,964	8,448
Yes	0.107	21,942	19,594

[a] Overall mean costs = (1 − probability of zero cost) × expected mean cost given nonzero cost.

cost between patients with recurrent CDI and patients without recurrent CDI was used as the measure for attributable cost.

The data set included patients who died during the 180-day outcome period. A sensitivity analysis was performed to determine the effect of death on the final cost estimates for recurrent CDI. The zero-inflated lognormal models were refit to the data set excluding patients who died during the outcome period. The APV with bootstrapping was used to estimate attributable costs of recurrent CDI.

This study was approved by the Washington University School of Medicine Human Research Protection Office. Statistical analyses were performed with SAS version 9.3 and R version 3.0.1.

RESULTS

A total of 4,615 patients were evaluated for the study; 3,958 patients met the inclusion criteria and were included. The CDI recurrence rate was 10.6% ($n = 421$). Of the 421 patients with recurrent CDI, 302 (72%) had a positive toxin assay at BJH. The study population consisted of 2 distinct subpopulations: patients with zero costs (ie, no readmissions) during the outcome period ($n = 2{,}156$; 55%), and patients with nonzero costs (ie, 1 or more readmissions) during the outcome period ($n = 1{,}802$; 45%; Table 1). Total hospital costs for the subpopulation with nonzero costs were highly skewed, with a median of $10,560 and a distribution that ranged from $213 to $1,014,000 (interquartile range, $4,333–$23,980); 89% of recurrent CDI cases had nonzero costs ($n = 376$), compared with 40% of patients without recurrent CDI ($n = 1{,}426$; $P < .001$).

For the base regression model, which included only recurrent CDI status, the logistic portion of the model indicated that the odds of zero costs (ie, no readmissions) for patients with recurrent CDI were 0.08 (95% CI, 0.06–0.11; $P < .001$) compared with patients without recurrent CDI. The model also indicated that, given nonzero total cost (ie, 1 or more readmissions), patients with recurrent CDI had an average of 5% larger total costs (CR, 1.05) than patients without recurrent CDI (95% CI, 0.91–1.20; $P = 0.52$). Stated conversely, patients with recurrent CDI were 12.5 times more likely to accrue any readmission costs (ie, be readmitted) than were patients without recurrent CDI. However, patients with recurrent CDI who were readmitted had only 5% larger costs than patients without recurrent CDI who were readmitted.

The expected probabilities of zero and nonzero costs and the overall mean costs of recurrent CDI status are shown in Table 2. Patients without recurrent CDI had a 0.597 probability of zero costs, compared with a 0.107 probability for recurrent CDI patients. For patients with recurrent CDI who had nonzero costs, the expected mean cost was $21,942, and the expected overall mean cost for recurrent CDI was $19,594; this value includes both the probability of zero costs and the expected mean cost given nonzero costs. The difference in overall mean costs between groups was $11,146 ($19,594 − $8,448).

For the regression model that included recurrent CDI status and adjustments for other demographic variables ("full model"), recurrent CDI was significantly associated with lower odds of zero costs (OR, 0.07 [95% CI, 0.05–0.10]; $P < .001$) compared with patients without recurrent CDI (Table 3). Nonwhite race, various MDC codes, and several comorbidities were also associated with significantly lower odds of zero cost. Increasing age was associated with higher odds of zero cost.

For the subpopulation with nonzero costs, recurrent CDI status was marginally associated ($P = .07$) with increased costs (CR, 1.13 [95% CI, 0.99–1.30]). MDC codes 17 (myeloproliferative disease), 0 (not classified), 7 (hepatobiliary and pancreas disease), and 18 (infectious and parasitic diseases) were associated with increased costs relative to MDC code 6 (diseases of the digestive system; this was chosen as the reference category because it was the most commonly identified MDC category in the data). Myocardial infarction, rheumatologic disease, and leukemia/lymphoma were also associated with increased costs. Older age (more than or equal to 74 years) and cerebrovascular disease were associated with decreased costs.

Differences in overall mean costs as estimated by the APV method are shown in Figure 1. After adjusting for all other variables in the model, older age was associated with lower overall mean costs, while recurrent CDI was associated with higher overall mean costs. After adjusting for age, sex, race, BMI, MDC code, and comorbidities, the attributable cost of recurrent CDI was $11,631 (95% CI, $8,937–$14,588).

Sensitivity analysis. Twenty-seven percent of the study population ($n = 1{,}065$) died during the 180-day outcome period. Patients who died were more likely to have nonzero costs (52% vs 43%) and higher median costs ($14,618 vs $9,255) than patients who survived for the full 180 days. Patients with recurrent CDI were more likely to die during the outcome period (36.6% vs 25.8%) than patients without recurrent CDI. After adjusting for all demographic variables in the data set that excluded individuals who died and after applying the APV method, the attributable cost of recurrent CDI was $8,709 (95% CI, $6,219–$11,529).

TABLE 3. Estimated Odds Ratios (ORs) and Cost Ratios (CRs) with 95% Confidence Intervals (CIs) from the Model That Adjusted for All Variables

Variable	OR (95% CI) for zero cost	*P*	CR (95% CI) given nonzero cost	*P*
Recurrent CDI (vs none)	0.07 (0.05–0.10)	<.001	1.13 (0.99–1.30)	.07
Age quartile				
<49 years	1.00 (reference)		1.00 (reference)	
49 to <62 years	1.22 (1.01–1.49)	.04	0.90 (0.77–1.05)	.18
62 to <74 years	1.44 (1.17–1.76)	<.001	0.92 (0.78–1.08)	.32
≥74 years	1.86 (1.50–2.30)	<.001	0.79 (0.67–0.94)	.009
Male (vs female)	0.98 (0.85–1.13)	.83	0.95 (0.85–1.07)	.41
Nonwhite (vs white)	0.79 (0.68–0.92)	.003	1.02 (0.90–1.16)	.74
Body mass index				
Normal weight	1.00 (reference)		1.00 (reference)	
Underweight	1.08 (0.82–1.41)	.59	0.99 (0.80–1.22)	.94
Overweight	1.07 (0.90–1.27)	.46	0.96 (0.84–1.10)	.60
Obese	1.22 (1.02–1.46)	.03	1.01 (0.88–1.17)	.87
MDC				
6 (diseases of the digestive system)	1.00 (reference)		1.00 (reference)	
0 (unassigned principal diagnosis)	1.09 (0.86–1.37)	.47	1.49 (1.23–1.81)	<.001
1 (diseases of the nervous system)	0.99 (0.66–1.47)	.95	1.55 (1.11–2.18)	.01
4 (diseases of the respiratory system)	0.79 (0.59–1.04)	.10	1.26 (1.00–1.58)	.05
5 (diseases of the circulatory system)	0.74 (0.56–0.97)	.03	1.12 (0.90–1.40)	.30
7 (diseases of the hepatobiliary system and pancreas)	1.06 (0.75–1.50)	.73	1.48 (1.12–1.97)	.006
8 (diseases of the musculoskeletal system and connective tissue)	0.70 (0.47–1.03)	.07	1.14 (0.82–1.58)	.43
10 (endocrine, nutritional, and metabolic diseases)	0.65 (0.41–1.04)	.07	1.21 (0.86–1.71)	.28
11 (diseases of the kidney and urinary tract)	0.67 (0.50–0.89)	.006	1.16 (0.93–1.45)	.20
13 (diseases of the female reproductive system)	1.82 (0.86–3.86)	.12	1.24 (0.63–2.43)	.54
16 (diseases of blood, blood-forming organs, immunologic)	0.49 (0.28–0.85)	.01	1.18 (0.80–1.73)	.40
17 (myeloproliferative diseases)	0.45 (0.32–0.65)	<.001	2.25 (1.74–2.91)	<.001
18 (infectious and parasitic diseases)	0.68 (0.49–0.93)	.02	1.30 (1.02–1.67)	.04
21 (injuries, poisonings, toxic effects of drugs)	0.72 (0.34–1.52)	.39	1.29 (0.69–2.41)	.42
25 (HIV infections)	1.55 (0.55–4.36)	.40	1.15 (0.58–2.25)	.69
All others	1.18 (0.74–1.87)	.48	0.98 (0.66–1.45)	.92
Charlson comorbidities				
Myocardial infarction	0.71 (0.54–0.92)	.009	1.23 (1.01–1.51)	.04
Congestive heart failure	0.75 (0.63–0.90)	.002	1.13 (0.98–1.30)	.10
Peripheral vascular disease	0.99 (0.75–1.30)	.95	1.22 (0.98–1.52)	.07
Cerebrovascular disease	1.08 (0.80–1.46)	.63	0.77 (0.61–0.98)	.03
Chronic renal failure	0.60 (0.44–0.83)	.002	1.02 (0.81–1.29)	.85
Dementia	0.97 (0.40–2.33)	.94	1.39 (0.71–2.71)	.34
Chronic obstructive pulmonary disease	0.97 (0.82–1.15)	.75	1.00 (0.88–1.15)	.96
Rheumatologic disease	1.06 (0.74–1.52)	.74	1.45 (1.09–1.94)	.01
Peptic ulcer disease	1.22 (0.85–1.75)	.27	1.04 (0.78–1.40)	.77
Any liver disease	0.60 (0.44–0.81)	<.001	1.15 (0.91–1.45)	.25
Any diabetes	0.81 (0.69–0.95)	.01	1.08 (0.95–1.23)	.23
Paraplegia/hemiplegia	0.78 (0.48–1.26)	.31	0.96 (0.67–1.38)	.84
Cancer (excluding leukemia/lymphoma)	0.63 (0.50–0.79)	<.001	0.96 (0.80–1.14)	.62
Leukemia/lymphoma	0.53 (0.42–0.67)	<.001	1.37 (1.15–1.63)	<.001
Metastatic solid tumor	0.94 (0.71–1.23)	.65	0.98 (0.80–1.22)	.88
HIV/AIDS	0.40 (0.18–0.87)	.02	1.17 (0.74–1.87)	.50

NOTE. CDI, *Clostridium difficile* infection; HIV, human immunodeficiency virus; MDC, major diagnostic category.

DISCUSSION

This study is the first to estimate the attributable inpatient costs of recurrent CDI. Previous estimates by Dubberke et al[22] and Kyne et al[23] of the attributable costs of any CDI per hospitalization were between $2,400 and $3,700, but neither of these studies included recurrent CDI. Dubberke et al[22] estimated the attributable cost of CDI over the 180 days after initial infection as $5,042–$7,179, and while this estimate surely includes some of the costs associated with recurrence, the analysis was not limited specifically to recurrent CDI cases. As mentioned previously, only McFarland et al[8] have studied the costs associated with recurrent CDI; their esti-

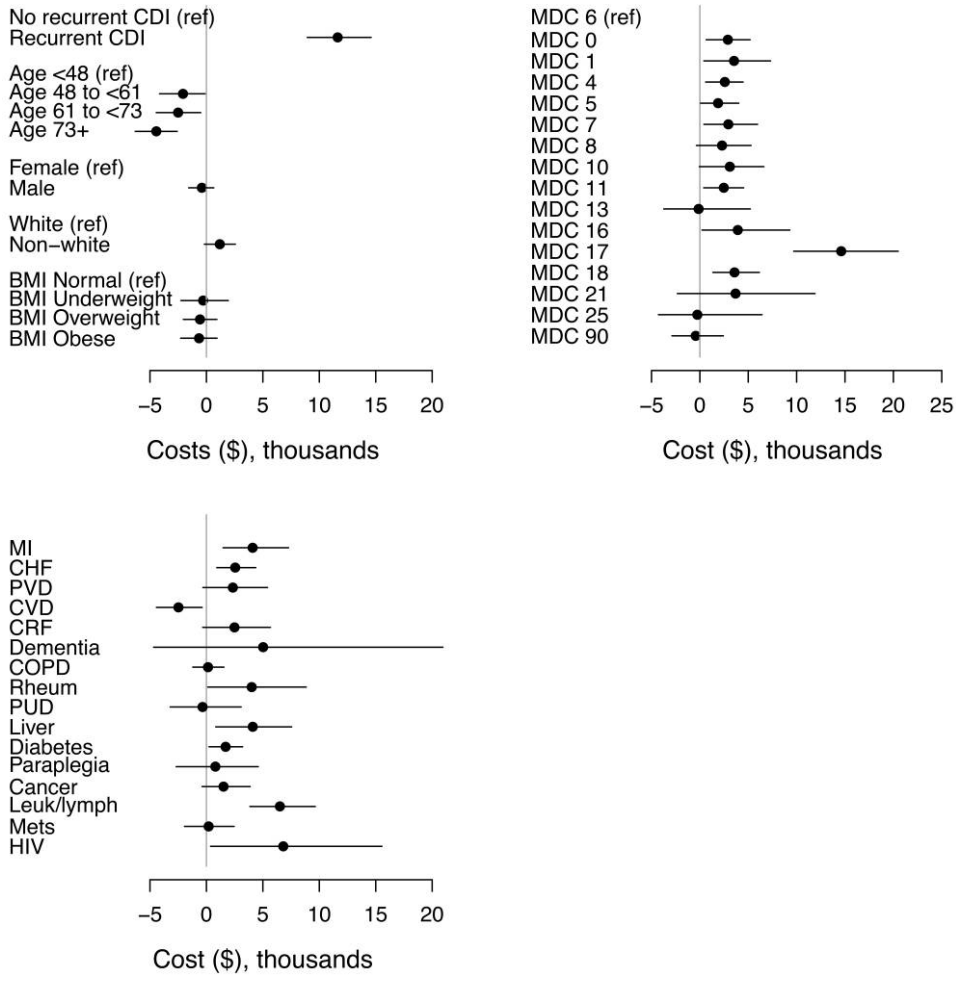

FIGURE 1. Forest plots of overall mean differences in total costs (filled circles) with 95% confidence intervals (line segments) for each covariate relative to the reference group. BMI, body mass index; CDI, *Clostridium difficile* infection; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVD, cerebrovascular disease; HIV, human immunodeficiency virus; Leuk/lymph, leukemia/lymphoma; MDC, major diagnostic category; Mets, metastatic solid tumor; MI, myocardial infarction; PUD, peptic ulcer disease; PVD, peripheral vascular disease; Rheum, rheumatologic disease.

mates were $3,103 per recurrent CDI episode and $10,970 over a patient's lifetime ($4,152 per episode and $14,675 lifetime in 2010 dollars, assuming that McFarland et al's estimates used 1998 dollars), but they did not determine attributable costs.

The estimated attributable inpatient costs of recurrent CDI over the 180 days after the initial episode of CDI reported in this study was $11,631 (95% CI, $8,937–$14,588). This value reflects that patients with recurrent CDI would be expected to accrue about $11,000 more per patient, on average, than those without recurrent CDI. This estimate is significantly larger than McFarland et al's per-episode estimate of $3,103 ($4,152 in 2010 dollars) and is comparable to their lifetime estimate of $10,970 ($14,675 in 2010 dollars). These estimates suggest that the attributable cost of recurrent CDI has increased since publication of McFarland et al's study in 1999. They were able to capture some outpatient costs (clinic visits), whereas outpatient costs were not included in our study. McFarland et al's definition of "lifetime" costs was from a patient's first episode of CDI through enrollment into a clinical trial of combination treatment for recurrent CDI (and the next recurrence after enrollment); many patients were followed up for more than 180 days. If outpatient costs had been included in our current study and patients had been followed up for a longer period of time, the attributable cost of CDI would likely have been even larger.

The primary mechanism of the increased costs associated with CDI recurrence was the increased probability of having any costs (ie, being readmitted) during the outcome period for patients with recurrent CDI. While the recurrent CDI attributable cost estimate among patients with any costs (both recurrent CDI and nonrecurrent CDI patients with nonzero costs) during the outcome period was of borderline statistical significance ($P = .07$), recurrent CDI patients were 12.5 times

more likely to have any hospital costs than nonrecurrent CDI patients. Recurrent CDI may have been the primary reason for readmission, or recurrence may have occurred during a readmission and prolonged or complicated the hospitalization. In either situation, recurrent CDI is a potentially modifiable factor that significantly increases inpatient costs.

Although recurrent CDI was associated with only marginally increased hospital costs among all readmitted patients, since recurrent CDI patients were much more likely to be readmitted to the hospital, this translated to an attributable cost estimate of $11,631 (95% CI, $8,937–$14,588) per patient. There were 421 recurrent CDI cases, so the total estimated attributable cost of recurrent CDI would be $4,896,651 (95% CI, $3,762,477–$6,141,548; 2010 dollars) for our single facility over the 7 years examined in our study. These costs reflect only facility costs and do not include provider charges. Furthermore, this estimate does not take into account other quality-of-life issues for patients, such as loss of work, prescription drug costs, or increased morbidity due to recurrence.

The relationship among death, recurrent CDI, and cost estimates is somewhat unclear. Patients who died during the outcome period were necessarily followed up for less than 180 days, suggesting that the total costs were biased downward compared with those for patients followed up for the full period. On the other hand, deaths are typically associated with large hospital costs.[24,25] In our analyses, patients with recurrent CDI were more likely to die, and patients who died were more likely to have nonzero costs. These two findings indicated that the extra deaths during the outcome period for patients with recurrent CDI may have resulted in an increase in costs attributable to recurrent CDI. Indeed, the attributable cost of recurrent CDI was only $8,709 when excluding patient deaths during the outcome period.

There are several limitations to this study. Most of the data used in this study were administrative and collected electronically from hospital databases. Medical records were reviewed to confirm several of the most important variables in this study (e.g., recurrent CDI status and postdischarge antibiotic use). Data on *C. difficile* strain type were not available, so it was not possible to differentiate between CDI relapse and reinfection.

The primary limitation of this study is the use of hospital laboratory results to detect recurrent CDI cases. While we identified all positive *C. difficile* toxin results from our hospital's laboratory and reviewed charts to identify additional CDI recurrences, we likely did not capture recurrent cases that were identified and treated exclusively at other hospitals or at outpatient clinics. These constitute 2 separate patient groups. Bias due to exclusion of cases diagnosed at other inpatient facilities should have been lessened since medical records were reviewed to identify recurrent CDI cases diagnosed at other facilities and transferred to the study hospital for treatment. Exclusion of recurrent CDI patients treated at other inpatient facilities would likely lead to lower estimates of attributable costs because those patients' readmission costs were not included in analyses. In contrast, exclusion of patients diagnosed and treated solely as outpatients may have biased the population toward more severely ill recurrent CDI patients who required hospitalization. In this case, the true odds of zero costs may be lower than reported here. However, the exclusion of outpatient recurrent CDI cases would not impact the CRs given nonzero costs.

Recurrent CDI is known to be an important cause of continued morbidity after initial CDI. The results of this study, which suggests that the attributable costs of a single recurrent CDI case over 6 months are in excess of $11,000, should add further impetus to the need for better prevention of and treatment for recurrent CDI cases. This study also highlights the need for additional research on recurrent CDI, specifically with respect to the relationship between recurrent CDI and mortality, the economic costs of recurrent CDI outside inpatient facilities, and the effect of recurrent CDI on quality of life. Better methods of identifying patients at risk for recurrent CDI and preventing those recurrences would decrease the economic burden of recurrent CDI.

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