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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.<sup>1,2</sup> 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,<sup>1,3-10</sup> higher severity of illness,<sup>4,6</sup> hospitalization after initial CDI,<sup>10,11</sup> receipt of antibiotics during the period after initial CDI,<sup>1,3,4,6,7,11,12</sup> and receipt of antacids.<sup>1,3,7,13</sup> In addition, Pepin et al<sup>9</sup> and Petrella et al<sup>14</sup> 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<sup>8</sup> 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 emer-

gence 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,<sup>18</sup> 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.<sup>19</sup> 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.<sup>20</sup>

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.<sup>21</sup> 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 | y All | Variables |
|----------|-------------|---------|-------------|----------|-------|-----------|
|----------|-------------|---------|-------------|----------|-------|-----------|

| Recurrent CDI 45 (10.7) 37 (99.3) 421 (30.7) 1,426 (40.3) 3,637 (32.9) 49 (37.9) 1,426 (40.3) 3,637 (32.9) 49 (37.9) 1,426 (40.3) 3,637 (32.9) 49 (37.9) 1,426 (40.3) 3,637 (32.9) 49 (37.9) 1,426 (40.3) 398 (37.7) 1,030 (32.10 (37.9) 49 (37.9) 1,030 (37.9) 49 (37.9) 1,030 (37.9) 49 (37.   | Variable   | Zero cost, no. (%)       | Nonzero cost, no. (%) | Total $(n = 3,958)$ |
|--|--|--------------------------|-----------------------|---------------------|
| No recurrent CDI         2.111 (95.7)         1.42c (40.3)         3.637           seq years         485 (50.8)         470 (49.2)         955           seq to sc2 years         530 (54.6)         441 (45.4)         971           Sc1 oc 74 years         530 (54.6)         441 (45.4)         971           Sc2 to sc4 years         1.069 (55.8)         846 (44.2)         1.915           Male         1.087 (53.2)         956 (46.8)         2.043           Race           1.925 (56.2)         1.192 (43.8)         2.721           Make         1.089 (55.1)         654 (64.9)         1.083         1.040 (55.1)         1.94 (46.9)         318           Normal weight         1.09 (55.1)         1.94 (46.9)         318         1.042         1.042           Or rewight         1.09 (55.1)         1.94 (46.9)         1.043         1.042         1.044           O ta sca sca sca sca sca sca sca sca sca sc  | Recurrent CDI  | 45 (10.7)                | 376 (89.3)            | 421                 |
| Age quartile   | No recurrent CDI   | 2,111 (59.7)             | 1,426 (40.3)          | 3,637               |
| -e49 years         445 (50.8)         470 (492, 955           49 to c52 years         537 (52.1)         497 (47.9)         1,030           62 to c74 years         530 (54.6)         441 (45.4)         971           274 years         604 (60.3)         398 (39.7)         1,002           Sec  | Age quartile   |                          |                       |                     |
| 49 to <22 years  | <49 years  | 485 (50.8)               | 470 (49.2)            | 955                 |
| 62 to $2^4$ years       530 (54.6)       441 (45.4)       971         274 years       604 (60.3)       398 (39.7)       1.002         Set  | 49 to <62 years  | 537 (52.1)               | 493 (47.9)            | 1,030               |
| $2^{74}$ years       604 (60.3)       398 (39.7)       1.002         Sex   | 62 to <74 years  | 530 (54.6)               | 441 (45.4)            | 971                 |
| Sec<br>Fernale<br>Pernale<br>Male<br>Pernale<br>Male<br>1,087 (53.2)<br>956 (46.8)<br>2,043<br>Race<br>White<br>Nonvhite<br>1,529 (56.2)<br>1,192 (43.8)<br>2,721<br>Nonvhite<br>627 (50.7)<br>101 (49.3)<br>1,237<br>120<br>Normal weight<br>109 (53.1)<br>149 (46.9)<br>318<br>Normal weight<br>109 (53.1)<br>149 (46.9)<br>318<br>Normal weight<br>100<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | ≥74 years  | 604 (60.3)               | 398 (39.7)            | 1,002               |
| Female         1,069 (55.8)         846 (42.)         1,915           Male         1,057 (53.2)         956 (46.8)         2,043           Race           1,922 (43.8)         2,721           Nonwhite         6.27 (50.7)         610 (49.3)         1,237           Body mass index           149 (46.9)         318           Overweight         169 (53.1)         149 (46.9)         318           Normal weight         592 (53.2)         520 (46.8)         1,112           Obece         621 (56.8)         473 (43.2)         1,094           Charlson composite score          391 (61.6)         244 (48.8)         514           0         439 (65.5)         231 (34.5)         670         12         263 (51.2)         251 (48.8)         514           3         22 (53.9)         452 (46.1)         981         34         452         253           4         125 (45.3)         151 (48.4)         514         34         34         34           6         50.39         444 (42.2)         983         344 (46.2)         290         26           Charlson comprobidities          155 (53.8)         134 (46.2) <td< td=""><td>Sex</td><td></td><td></td><td></td></td<>  | Sex  |                          |                       |                     |
| Male         1,087 (53.2)         956 (46.8)         2,043           Racc         White         1,529 (56.2)         1,192 (43.8)         2,721           Nonwhite         627 (50.7)         610 (49.3)         1,237           Body mass index         627 (50.7)         610 (49.3)         1,237           Missing         29 (93.5)         2 (5.5)         31           Underweight         169 (53.1)         149 (46.9)         318           Normal weight         592 (53.2)         520 (46.8)         1,112           Obese         621 (56.8)         473 (43.2)         675           Carlston composite score         72         529 (53.9)         452 (46.1)         981           2         529 (53.9)         452 (46.1)         981         514           4         125 (45.3)         151 (54.7)         276           5         409 (46.4)         473 (53.6)         882           Charlson comorbidities         73         127 (45.7)         278           Myocardial infarction         161 (48.2)         179 (51.8)         34           Congestive heart failure         449 (50.8)         134 (46.2)         290           Carerborvascular disease         15 (53.4)         11 (45.7)  | Female   | 1,069 (55.8)             | 846 (44.2)            | 1,915               |
| Race         Non-white         1,529 (56.2)         1,192 (43.8)         2,721           Non-white         627 (50.7)         610 (49.3)         1,237           Dody mass index           318           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          70         1         321 (61.6)         244 (38.4)         635           2         529 (53.9)         452 (46.1)         981         3         5         5         76         2           Carlson comorbidities         125 (54.3)         127 (53.6)         382         334         6         6         38.3         344         6         5         2         14         2         290         12         25         6         14         12         120         22         246.1)         14         46.2         290         22         22         23  | Male   | 1,087 (53.2)             | 956 (46.8)            | 2,043               |
| White         1,529         (5.2)         (1,92)         (1,32)         (1,32)           Body mass index $$  | Race   |                          |                       |                     |
| Nonwhite       627 (50.7)       610 (49.3)       1,237         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  | White  | 1,529 (56.2)             | 1,192 (43.8)          | 2,721               |
| Body mass index<br>Missing 29 (93.5) 2 (6.5) 31<br>Underweight 745 (33.1) 449 (46.9) 3.18<br>Normal weight 745 (33.1) 658 (46.9) 1.403<br>Overweight 759 (33.2) 520 (46.8) 1.112<br>Obese 6.21 (56.8) 473 (43.2) 1.094<br>Charlson composite score<br>0 439 (65.5) 2.31 (34.5) 670<br>1 39 (65.5) 2.31 (34.5) 670<br>2 1 44 (38.4) 6.635<br>2  | Nonwhite   | 627 (50.7)               | 610 (49.3)            | 1,237               |
| Missing         29 (93.5)         2 (6.5)         31           Underweight         169 (33.1)         149 (46.9)         318           Normal weight         745 (33.1)         658 (46.9)         1.403           Overweight         592 (33.2)         520 (46.8)         1.112           Obese         621 (56.8)         473 (43.2)         1.094           Charlson composite score         739 (65.5)         231 (34.5)         670           1         391 (61.6)         244 (38.4)         635           2         529 (33.9)         452 (46.1)         981           3         263 (51.2)         251 (48.8)         514           4         125 (45.3)         151 (54.7)         276           Carson comorbidities         733 (51.8)         334         66.6)         332 (46.2)         283           Peripheral vascular disease         151 (54.3)         127 (45.7)         278         278           Chronic obstructive pulmonary disease         153 (53.6)         13 (46.4)         28         967           Rheumatologic disease         92 (57.5)         68 (42.5)         160         444 (40.2)         156           Paraplegia/hemiplegia         43 (50.0)         43 (50.0)         86         26   | Body mass index  |                          |                       |                     |
|  | Missing  | 29 (93.5)                | 2 (6.5)               | 31                  |
| Normal weight       745 (53.1)       658 (46.9)       1,102         Overweight       592 (53.2)       520 (46.8)       1,112         Obese       621 (56.8)       473 (43.2)       1,094         Charlson composite score       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       Charlson comorbidities       734 (65.8)       134 (46.2)       981         Myocardial infarction       161 (48.2)       173 (51.8)       334         Congestive heart failure       449 (50.8)       134 (46.2)       290         Cerborivascular disease       151 (54.3)       127 (45.7)       278         Chronic roal 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       92 (57.5)       68 (42.2)       160         Ary tiver disease       521 (49.7)       527 (50.   | Underweight  | 169 (53.1)               | 149 (46.9)            | 318                 |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$   | Normal weight  | 745 (53.1)               | 658 (46.9)            | 1,403               |
| Obese         621 (56.8)         473 (43.2)         1,094           0         439 (65.5)         231 (34.5)         670           1         231 (34.5)         670         931 (61.6)         244 (38.4)         635           2         259 (53.9)         452 (46.1)         981         3         635 (51.2)         251 (48.8)         514           3         263 (51.2)         251 (48.8)         514         25         Charlson comorbidities         776 (23.3)         151 (54.7)         276           ≥5         409 (46.4)         473 (53.6)         882         Charlson comorbidities         882           Myocardial infarction         161 (48.2)         173 (51.8)         334           Congestive heart failure         49 (50.8)         434 (49.2)         883           Peripheral vascular disease         156 (53.8)         134 (46.2)         290           Chronic obstructive plumonary disease         152 (45.4)         443 (48.8)         967           Rheumatologic disease         87 (55.8)         69 (44.2)         156           Peptic ulcer disease         92 (57.5)         68 (42.5)         160           Any liver disease         521 (49.7)         538 (56.3)         688           Cancorer (excluding l  | Overweight   | 592 (53.2)               | 520 (46.8)            | 1,112               |
| Charlson composite score $439 (65.5)$ 231 (34.5) 670<br>1 391 (61.6) 244 (38.4) 635<br>2 259 (53.9) 452 (46.1) 981<br>3 263 (51.2) 251 (48.8) 514<br>4 125 (45.3) 151 (54.7) 276<br>$\geq 5$ 409 (46.4) 473 (53.6) 882<br>Charlson comorbidities<br>Myocardial infarction 161 (48.2) 173 (51.8) 334<br>Congestive heart failure 449 (50.8) 434 (49.2) 883<br>Peripheral vascular disease 156 (53.8) 134 (46.2) 290<br>Cerebrovascular disease 156 (53.8) 134 (46.4) 28<br>Chronic renal failure 83 (41.1) 119 (58.9) 202<br>Dementia 15 (53.6) 13 (46.4) 28<br>Chronic obstructive pulmonary disease 524 (54.2) 443 (45.8) 967<br>Rheumatologic disease 87 (55.8) 69 (44.2) 156<br>Peptic ulcer disease 107 (47.6) 118 (52.4) 225<br>Any diabetes 252 (49.7) 527 (50.3) 1,048<br>Paraplegia/hemiplegia 43 (50.0) 43 (50.0) 86<br>Cancer (excluding leukenia/lymphoma) 404 (50.6) 395 (49.4) 799<br>Leukenia/lymphoma 299 (43.5) 389 (56.5) 688<br>Metastatic solid tumor 236 (50.3) 233 (49.7) 469<br>HUV/AIDS 26 (53.1) 448 (64.9) 74<br>MDC<br>0 (unassigned principal diagnosis) 404 (60.4) 265 (39.6) 669<br>Metastatic solid tumor 236 (50.3) 233 (49.7) 366<br>5 (diseases of the nervous system) 160 (52.3) 146 (47.7) 306<br>5 (diseases of the enervous system) 161 (52.3) 48 (44.3) 193<br>88 (diseases of the enervous system) 160 (55.8) 84 (43.5) 193<br>84 (diseases of the enervous system) 160 (52.3) 48 (44.6) 130<br>10 (uncostigned principal diagnosis) 43 (40.2) 50 (53.8) 93<br>11 (diseases of the enervous system) 28 (70.0) 12 (30.0) 40<br>13 (diseases of the enervous system and connective tissue) 72 (55.4) 58 (44.6) 130<br>10 (chocrine, nutritional, and metabolic disease) 43 (46.2) 50 (53.8) 93<br>11 (diseases of the enervous system and connective tissue) 109 (56.5) 84 (43.5) 193<br>84 (diseases of the enervous system and connective tissue) 109 (56.5) 84 (43.5) 193<br>13 (diseases of the female reproductive system) 28 (70.0) 12 (30.0) 40<br>16 (diseases of the enervous system and connecti | Obese  | 621 (56.8)               | 473 (43.2)            | 1,094               |
| 0  | Charlson composite score   |                          |                       |                     |
| 1  | 0  | 439 (65.5)               | 231 (34.5)            | 670                 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$   | 1  | 391 (61.6)               | 244 (38.4)            | 635                 |
| 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  | 2  | 529 (53.9)               | 452 (46.1)            | 981                 |
| 4       125 (45.3)       151 (54.7)       276 $255$ 409 (46.4)       473 (53.6)       882         Charlson comorbidities       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         Cerebrowscular 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         Perptic 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 (64.9)       74         MDC       0       (unassigned principal diagnosis)       404 (60.4)       265 (39.6)       669         1 (diseases of the nervous system)       160 (52.3)       146   | 3  | 263 (51.2)               | 251 (48.8)            | 514                 |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $  | 4  | 125 (45.3)               | 151 (54.7)            | 276                 |
| Charlson comorbidites<br>Myocardial infarction $161 (48.2)$ 173 (51.8) 334<br>Congestive heart failure $449 (50.8)$ 434 (49.2) 883<br>Peripheral vascular disease 156 (53.8) 134 (46.2) 290<br>Cerebrovascular disease 151 (54.3) 127 (45.7) 278<br>Chronic renal failure $83 (41.1)$ 119 (58.9) 202<br>Dementia 15 (53.6) 13 (46.4) 28<br>Chronic obstructive pulmonary disease 524 (54.2) 443 (45.8) 967<br>Rheumatologic disease 87 (55.8) 69 (44.2) 156<br>Peptic ulcer disease 92 (57.5) 68 (42.5) 160<br>Any liver disease 107 (47.6) 118 (52.4) 225<br>Any diabetes 521 (49.7) 527 (50.3) 1,048<br>Paraplegia/hemiplegia 43 (50.0) 43 (50.0) 86<br>Cancer (excluding leukemia/lymphoma) 404 (50.6) 395 (49.4) 799<br>Leukemia/lymphoma 299 (43.5) 389 (56.5) 6688<br>Metastatic solid tumor 236 (53.1) 48 (64.9) 74<br>MDC<br>0 (unassigned principal diagnosis) 404 (60.4) 265 (39.6) 669<br>11 (diseases of the respiratory system) 90 (60.8) 58 (39.2) 148<br>4 (diseases of the respiratory system) 160 (52.3) 146 (47.7) 306<br>5 (diseases of the directive system) 615 (58.8) 431 (41.2) 1,046<br>7 (diseases of the directive system) 618 (51.6) 176 (48.4) 364<br>6 (diseases of the hepatobiliary system and pancreas) 109 (56.5) 84 (43.5) 193<br>10 (endocrine, nutritional, and metabolic disease) 43 (46.2) 50 (53.8) 93<br>11 (diseases of the kipestite system) 28 (70.0) 12 (30.0) 40<br>16 (diseases of the kipestite system) 28 (70.0) 12 (30.0) 40<br>16 (diseases of the kipestite system) 28 (70.0) 12 (30.0) 40<br>16 (diseases of the kipestite system) 28 (70.0) 12 (30.0) 40<br>16 (diseases of the kipestite system) 28 (70.0) 12 (30.0) 40<br>16 (diseases of the kipestite system) 28 (70.0) 12 (30.0) 40<br>16 (diseases of the kipestite system) 108 (55.3) 144 (43.8) 32<br>13 (diseases of the kipestite diseases) 79 (33.8) 155 (66.2) 234<br>13 (diseases of the kipestite diseases) 79 (33.8) 155 (66.2) 234<br>13 (diseases of the kinely and urinary tract) 140 (49.6) 142 (50.4) 282<br>13 (diseases of the kinely and urinary tract) 140 (49.6) 142 (50.4) 282<br>13 (diseases of the kinely and urinary tract) 140 (49.6) 142 (50.4) 282<br>13 (disea          |  | 409 (46.4)               | 473 (53.6)            | 882                 |
| Myocardial infarction161 (48.2)173 (51.8)534Congestive heart failure449 (50.8)434 (49.2)883Peripheral vascular disease156 (53.8)134 (46.2)290Cerebrovascular disease151 (54.3)127 (45.7)278Chronic renal failure83 (41.1)119 (58.9)202Dementia15 (53.6)13 (46.4)28Chronic obstructive pulmonary disease524 (54.2)443 (45.8)967Rheumatologic disease87 (55.8)69 (44.2)156Peptic ulcer disease92 (57.5)68 (42.5)160Any liver disease107 (47.6)118 (52.4)225Any diabetes521 (49.7)527 (50.3)1,048Paraplegia/hemiplegia43 (50.0)43 (50.0)86Cancer (excluding leukemia/lymphoma)404 (50.6)395 (49.4)799Leukemia/lymphoma299 (43.5)389 (56.5)688MDC0(massigned principal diagnosis)404 (60.4)265 (39.6)6691 (diseases of the nervous system)100 (52.3)146 (47.7)3065 (diseases of the circulatory system)160 (52.3)146 (47.7)3065 (diseases of the digestive system)163 (56.5)84 (43.5)19310 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the heighter system and pancreas)109 (56.5)84 (43.6)13010 (endocrine, nutritional, and metabolic diseases)79 (33.8)155 (66.2)234 <td< td=""><td>Charlson comorbidities</td><td>1(1(10.0))</td><td>152 (51.0)</td><td>224</td></td<>   | Charlson comorbidities   | 1(1(10.0))               | 152 (51.0)            | 224                 |
| Congestive near failure449 (30.8)434 (42.2)885Peripheral vascular disease156 (53.8)134 (46.2)290Cerebrovascular disease151 (54.3)127 (45.7)278Chronic renal failure83 (41.1)119 (58.9)202Dementia15 (53.6)13 (46.4)28Chronic obstructive pulmonary disease524 (54.2)443 (45.8)967Rheumatologic disease87 (55.8)69 (44.2)156Any liver disease22 (57.5)68 (42.5)160Any liver disease107 (47.6)118 (52.4)225Any diabetes521 (49.7)527 (50.3)1,048Paraplegia/hemiplegia43 (50.0)86Cancer (excluding leukemia/lymphoma)404 (50.6)395 (49.4)799Leukemia/lymphoma299 (43.5)389 (56.5)668Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74MDC0060.8)58 (39.2)1484 (diseases of the nervous system)160 (52.3)146 (47.7)3065 (diseases of the digestive system)615 (58.8)431 (41.2)1,0466 (diseases of the digestive system)169 (55.3)84 (43.5)19310 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the kidney and urinary tract)120 (56.5)84 (43.5)19313 (diseases of the kidney and urinary tract)120 (56.5)44 (43.5)19314  | Myocardial infarction  | 161 (48.2)               | 173 (51.8)            | 334                 |
| Perpheral vascular disease15b (35.8)134 (46.2)290Cerebrovascular disease151 (54.3)127 (45.7)278Chronic renal failure83 (41.1)119 (58.9)202Dementia15 (55.6)13 (46.4)28Chronic obstructive pulmonary disease524 (54.2)443 (45.8)967Rheumatologic disease87 (55.8)69 (44.2)156Peptic ulcer disease92 (57.5)68 (42.5)160Any liver disease107 (47.6)118 (52.4)225Any diabetes521 (49.7)527 (50.3)1.048Paraplegia/hemiplegia43 (50.0)43 (50.0)86Cancer (excluding leukemia/lymphoma)404 (50.6)395 (49.4)799Leukemia/lymphoma299 (43.5)389 (56.5)668Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74 $MDC$ 0(unassigned principal diagnosis)404 (60.4)265 (39.6)6691 (diseases of the nervous system)160 (52.3)146 (47.7)3065 (diseases of the circulatory system)160 (52.3)146 (47.7)3065 (diseases of the digestive system)165 (58.8)431 (41.2)1.0467 (diseases of the digestive system)163 (46.2)50 (53.8)9311 (diseases of the king and urinary tract)140 (49.6)142 (50.4)28213 (diseases of the king and urinary tract)140 (40.6)142 (50.4)28214 (diseases of the king and urinary t   | Congestive heart failure   | 449 (50.8)               | 434 (49.2)            | 883                 |
| Cerebrovascuar disease151127127278Chronic renal failure83(41.1)119(58.9)202Dementia15(53.6)13(46.4)28Chronic obstructive pulmonary disease524(54.2)443(45.8)967Rheumatologic disease87(55.8)69(44.2)156Peptic ulcer disease92(57.5)68(42.5)160Any liver disease107(47.6)118(52.4)225Any diabetes521(49.7)527(50.3)1,048Paraplegia/hemiplegia43(50.0)43(50.0)86Cancer (excluding leukemia/lymphoma)404(50.6)395(49.4)799Leukemia/lymphoma299(43.5)389(56.5)688Metastatic solid tumor236(50.3)233(49.7)469HIV/AIDS26(35.1)48(64.9)74MDC77306404(60.4)265(39.6)6691(diseases of the erespiratory system)160(52.3)146(47.7)3065(diseases of the circulatory system)618(51.6)176(48.4)3646(diseases of the hepatobiliary system and pancreas)109(56.5)84(43.5)1938(diseases of the hepatobiliary system and connective tissue)72(55.4)58(44.6)13010(endocrine, nutrit   | Peripheral vascular disease                                      | 156 (53.8)               | 134 (46.2)            | 290                 |
| $\begin{array}{c} \text{Chronic renar fautre} & 83 (41.1) & 119 (58.9) & 202 \\ \text{Dementia} & 15 (53.6) & 13 (46.4) & 28 \\ \text{Chronic obstructive pulmonary disease} & 524 (54.2) & 443 (45.8) & 967 \\ \text{Rheumatologic disease} & 87 (55.8) & 69 (44.2) & 156 \\ \text{Peptic ulcer disease} & 92 (57.5) & 68 (42.5) & 160 \\ \text{Any liver disease} & 107 (47.6) & 118 (52.4) & 225 \\ \text{Any diabetes} & 521 (49.7) & 527 (50.3) & 1,048 \\ \text{Paraplegia/hemiplegia} & 43 (50.0) & 43 (50.0) & 86 \\ \text{Cancer (excluding leukemia/lymphoma} & 299 (43.5) & 389 (56.5) & 688 \\ \text{Metastatic solid tumor} & 236 (50.3) & 233 (49.7) & 469 \\ \text{HIV/AIDS} & 26 (53.1) & 48 (64.9) & 74 \\ \text{MDC} & & & & & & & & & & & & & & & & & & &$  | Cerebrovascular disease  | 151 (54.3)               | 127 (45.7)            | 2/8                 |
| Dementia15 (35.6)15 (46.4)28Chronic obstructive pulmonary disease524 (54.2)443 (45.8)967Rheumatologic disease87 (55.8)69 (44.2)156Peptic ulcer disease92 (57.5)68 (42.5)160Any liver disease107 (47.6)118 (52.4)225Any diabetes521 (49.7)527 (50.3)1,048Paraplegia/hemiplegia43 (50.0)43 (50.0)86Cancer (excluding leukemia/lymphoma)404 (50.6)395 (49.4)799Leukemia/lymphoma299 (43.5)389 (56.5)688Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74MDC0(unassigned principal diagnosis)404 (60.4)265 (39.6)6691 (diseases of the nervous system)90 (60.8)58 (39.2)1484 (diseases of the circulatory system)160 (52.3)146 (47.7)3065 (diseases of the digestive system)615 (58.8)431 (41.2)1,0467 (diseases of the digestive system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the musculoskeletal system and connective tissue)72 (55.4)58 (44.6)13010 (endocrine, nutritional, and metabolic diseases)73 (46.2)50 (53.8)931111 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of the female reproductive system)28 (70.0)12 (30.0)4016 (diseases of blood, blood-forming orga   | Chronic renal failure  | 83 (41.1)                | 119 (58.9)            | 202                 |
| Chronic constructive 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 digestive system) $615 (58.8)$ $431 (41.2)$ $1,046$ 7(diseases of the digestive system and pancreas) $109 (56.5)$ $84 (43.5)$ $193$ 8(diseases of the female reproductive system) $28 (70.0)$ $12 (30.0)$ $40$ 10(endocrine, nutritional, and metabolic diseases) $79 (33.8)$ $155 (66.2)$ $234$ 13(diseases of the female reproductive system) $28 (70.0)$ $12 (30.0)$ $40$ 16(diseases of blood, blood-forming organs, immunologic) $24 (36.9)$ <td>Changing the structure and the second disease</td> <td>15 (55.0)</td> <td>13 (46.4)</td> <td>28</td>  | Changing the structure and the second disease                    | 15 (55.0)                | 13 (46.4)             | 28                  |
| International curves $(35.6)$ $(6)$ $(44.2)$ $(150)$ 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 $26$ $(35.1)$ $48$ $(64.9)$ $74$ MDC0(unassigned principal diagnosis) $404$ $(60.8)$ $58$ $(39.2)$ $148$ 4(diseases of the revous system) $90$ $(60.8)$ $58$ $(39.2)$ $148$ 4(diseases of the revous system) $160$ $(52.3)$ $146$ $(47.7)$ $306$ 5(diseases of the digestive system) $615$ $58.8$ $431$ $(41.2)$ $1,046$ 7(diseases of the hepatobiliary system and pancreas) $109$ $(56.5)$ $84$ $(4.6)$ $130$ 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   | Dhoumatologic disease  | 524 (54.2)<br>97 (55.8)  | 445 (45.8)            | 967                 |
| Priput uter disease $32$ (37.3) $05$ (42.3) $100$ Any liver disease $107$ (47.6) $118$ (52.4) $225$ Any diabetes $521$ (49.7) $527$ (50.3) $1,048$ Paraplegia/hemiplegia43 (50.0)43 (50.0)86Cancer (excluding leukemia/lymphoma)404 (50.6)395 (49.4)799Leukemia/lymphoma299 (43.5)389 (56.5)688Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74MDC $0$ $0$ $0$ (0.8)58 (39.2)1484 (disease of the nervous system)90 (60.8)58 (39.2)1484 (diseases of the respiratory system)160 (52.3)146 (47.7)3065 (diseases of the digestive system)615 (58.8)431 (41.2)1,0467 (diseases of the digestive system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the hepatobiliary system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of the female reproductive system)28 (70.0)12 (30.0)4016 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV  | Paptic ulcar disease   | 07 (55.0)                | 68 (42.5)             | 150                 |
| Any liver disease107 (47.6)118 (52.4)22.5Any diabetes521 (49.7)527 (50.3)1,048Paraplegia/hemiplegia43 (50.0)43 (50.0)86Cancer (excluding leukemia/lymphoma)404 (50.6)395 (49.4)799Leukemia/lymphoma299 (43.5)389 (56.5)688Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74MDC70 (unassigned principal diagnosis)26 (35.1)48 (64.9)0 (unassigned principal diagnosis)90 (60.8)58 (39.2)1484 (diseases of the respiratory system)160 (52.3)146 (47.7)3065 (diseases of the circulatory system)160 (52.3)146 (47.7)3066 (diseases of the digestive system)1615 (58.8)431 (41.2)1,0467 (diseases of the hepatobiliary system and panceas)109 (56.5)84 (43.5)1938 (diseases of the hepatobiliary system and panceas)140 (49.6)142 (50.4)28213 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99  | A pur liver disease  | 92(37.3)                 | 118(52.4)             | 100                 |
| Arry diadets $321 (9.7.7)$ $327 (90.5.7)$ $1940$ Paraplegi/hemiplegia43 (50.0)43 (50.0)86Cancer (excluding leukemia/lymphoma)404 (50.6)395 (49.4)799Leukemia/lymphoma299 (43.5)389 (56.5)688Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74MDC0 (unassigned principal diagnosis)404 (60.4)265 (39.6)6691 (diseases of the nervous system)90 (60.8)58 (39.2)1484 (diseases of the respiratory system)160 (52.3)146 (47.7)3065 (diseases of the digestive system)615 (58.8)431 (41.2)1,0466 (diseases of the digestive system)615 (58.8)431 (41.2)1,0467 (diseases of the hepatobiliary system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the hepatobiliary system and connective tissue)72 (55.4)58 (44.6)13010 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of the kidney and urinary tract)120 (436.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9) <t< td=""><td>Any diabetes</td><td>107 (47.0)<br/>521 (49.7)</td><td>527 (50.3)</td><td>1 048</td></t<>   | Any diabetes   | 107 (47.0)<br>521 (49.7) | 527 (50.3)            | 1 048               |
| Tarapegar (an trippegar40(50.6)39(50.6)39Cancer (excluding leukemia/lymphoma)404(50.6)395(50.9)79Leukemia/lymphoma299(43.5)389(56.5)688Metastatic solid tumor236(50.3)233(49.7)469HIV/AIDS26(35.1)48(64.9)74MDC0(unassigned principal diagnosis)404(60.4)265(39.6)6691(diseases of the nervous system)90(60.8)58(39.2)1484(diseases of the respiratory system)160(52.3)146(47.7)3065(diseases of the digestive system)160(55.3)84(43.5)1938(diseases of the hepatobilizry system and pancreas)109(56.5)84(43.5)1938(diseases of the hepatobilizry system and connective tissue)72(55.4)58(44.6)13010(endocrine, nutritional, and metabolic diseases)43(46.2)50(53.8)9311(diseases of the kidney and urinary tract)140(49.6)142(50.4)28213(diseases of blood, blood-forming organs, immunologic)24(36.9)41(63.1)6517(myeloproliferative diseases)79(33.8)155(66.2)23418(infectious and parasitic diseases)108(49.3)111(50.7)21921(injurie   | Paranlegia/heminlegia  | 321(49.7)<br>43(50.0)    | 43(50.0)              | 1,040               |
| Called (citating relational) mphonal104 (50.0)505 (51.4)707Leukemia/lymphoma299 (43.5)389 (56.5)688Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74MDC $0$ (unassigned principal diagnosis)404 (60.4)265 (39.6)6691 (diseases of the nervous system)90 (60.8)58 (39.2)1484 (diseases of the respiratory system)160 (52.3)146 (47.7)3065 (diseases of the circulatory system)188 (51.6)176 (48.4)3646 (diseases of the digestive system)615 (58.8)431 (41.2)1,0467 (diseases of the hepatobiliary system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the musculoskeletal system and connective tissue)72 (55.4)58 (44.6)13010 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the female reproductive system)28 (70.0)12 (30.0)4016 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99  | Cancer (excluding leukemia/lymphoma)                             | 404(50.6)                | 395 (49 4)            | 799                 |
| International237 (45.5)500 (50.5)600Metastatic solid tumor236 (50.3)233 (49.7)469HIV/AIDS26 (35.1)48 (64.9)74MDC0 (unassigned principal diagnosis)404 (60.4)265 (39.6)6691 (diseases of the nervous system)90 (60.8)58 (39.2)1484 (diseases of the respiratory system)160 (52.3)146 (47.7)3065 (diseases of the circulatory system)188 (51.6)176 (48.4)3646 (diseases of the digestive system)615 (58.8)431 (41.2)1,0467 (diseases of the musculoskeletal system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the musculoskeletal system and connective tissue)72 (55.4)58 (44.6)13010 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the female reproductive system)28 (70.0)12 (30.0)4016 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)16 (42.1)22 (57.9)3825 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99  | Leukemia/lymphoma  | 299(435)                 | 389 (56 5)            | 688                 |
| Huranian $260 (605)$ $200 (101)$ $100$ 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 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) $18 (56.3)$ $44 (43.8)$ $32$ 25 (HIV infections) $16 (42.1)$ $22 (57.9)$ $38$  | Metastatic solid tumor   | 236 (50.3)               | 233 (497)             | 469                 |
| Intrinued $26 (50.1)$ $10 (61.5)$ $17$ MDC0 (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 digestive 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 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 $62 (62.6)$ $37 (37.4)$ $99$  | HIV/AIDS   | 26 (35.1)                | 48 (64 9)             | 74                  |
| 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 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) $18$ (56.3) $14$ (43.8) $32$ 21 (injuries, poisonings, toxic effects of drugs) $18$ (56.6) $14$ (43.8) $32$ 25 (HIV infections) $16$ (42.1) $22$ (57.9) $38$ All others $62$ (62.6) $37$ (37.4) $99$   | MDC  | 20 (33.1)                | 10 (01.5)             | , 1                 |
| 1 (diseases of the nervous system)90 (60.8)58 (39.2)1484 (diseases of the respiratory system)160 (52.3)146 (47.7)3065 (diseases of the circulatory system)188 (51.6)176 (48.4)3646 (diseases of the digestive system)615 (58.8)431 (41.2)1,0467 (diseases of the hepatobiliary system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the musculoskeletal system and connective tissue)72 (55.4)58 (44.6)13010 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99  | 0 (unassigned principal diagnosis)                               | 404 (60.4)               | 265 (39.6)            | 669                 |
| 1 (diseases of the introduction system)160 (52.3)146 (47.7)3065 (diseases of the circulatory system)188 (51.6)176 (48.4)3646 (diseases of the digestive system)615 (58.8)431 (41.2)1,0467 (diseases of the hepatobiliary system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the musculoskeletal system and connective tissue)72 (55.4)58 (44.6)13010 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99  | 1 (diseases of the nervous system)                               | 90 (60.8)                | 58 (39.2)             | 148                 |
| 111 <th< td=""><td>4 (diseases of the respiratory system)</td><td>160 (52.3)</td><td>146 (47.7)</td><td>306</td></th<>   | 4 (diseases of the respiratory system)                           | 160 (52.3)               | 146 (47.7)            | 306                 |
| 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 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) $16 (42.1)$ $22 (57.9)$ $38$ All others $62 (62.6)$ $37 (37.4)$ $99$   | 5 (diseases of the circulatory system)                           | 188 (51.6)               | 176 (48.4)            | 364                 |
| 7 (diseases of the hepatobiliary system and pancreas)109 (56.5)84 (43.5)1938 (diseases of the musculoskeletal system and connective tissue)72 (55.4)58 (44.6)13010 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of the female reproductive system)28 (70.0)12 (30.0)4016 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99   | 6 (diseases of the digestive system)                             | 615 (58.8)               | 431 (41.2)            | 1,046               |
| 10 (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) $99$  | 7 (diseases of the hepatobiliary system and pancreas)            | 109 (56.5)               | 84 (43.5)             | 193                 |
| 10 (endocrine, nutritional, and metabolic diseases)43 (46.2)50 (53.8)9311 (diseases of the kidney and urinary tract)140 (49.6)142 (50.4)28213 (diseases of the female reproductive system)28 (70.0)12 (30.0)4016 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99   | 8 (diseases of the musculoskeletal system and connective tissue) | 72 (55.4)                | 58 (44.6)             | 130                 |
| 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   | 10 (endocrine, nutritional, and metabolic diseases)              | 43 (46.2)                | 50 (53.8)             | 93                  |
| 13 (diseases of the female reproductive system)28 (70.0)12 (30.0)4016 (diseases of blood, blood-forming organs, immunologic)24 (36.9)41 (63.1)6517 (myeloproliferative diseases)79 (33.8)155 (66.2)23418 (infectious and parasitic diseases)108 (49.3)111 (50.7)21921 (injuries, poisonings, toxic effects of drugs)18 (56.3)14 (43.8)3225 (HIV infections)16 (42.1)22 (57.9)38All others62 (62.6)37 (37.4)99  | 11 (diseases of the kidney and urinary tract)                    | 140 (49.6)               | 142 (50.4)            | 282                 |
| 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  | 13 (diseases of the female reproductive system)                  | 28 (70.0)                | 12 (30.0)             | 40                  |
| 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   | 16 (diseases of blood, blood-forming organs, immunologic)        | 24 (36.9)                | 41 (63.1)             | 65                  |
| 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   | 17 (myeloproliferative diseases)                                 | 79 (33.8)                | 155 (66.2)            | 234                 |
| 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  | 18 (infectious and parasitic diseases)                           | 108 (49.3)               | 111 (50.7)            | 219                 |
| 25 (HIV infections)       16 (42.1)       22 (57.9)       38         All others       62 (62.6)       37 (37.4)       99   | 21 (injuries, poisonings, toxic effects of drugs)                | 18 (56.3)                | 14 (43.8)             | 32                  |
| All others 62 (62.6) 37 (37.4) 99  | 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 | Probability of | Expected<br>mean cost given | Overall mean |  |  |
|-----------|----------------|-----------------------------|--------------|--|--|
| No        | 0.597          | 20,964                      | 8,448        |  |  |
| Yes       | 0.107          | 21,942                      | 19,594       |  |  |

<sup>a</sup> Overall mean costs =  $(1 - \text{probability of zero cost}) \times \text{expected mean cost given nonzero cost.}$ 

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 180day 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.

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 Odd    | ds Ratios (C | ORs) and | Cost Ratios | (CRs) v | with 95% | Confidence | Intervals | (CIs) | from | the 1 | Model | That |
|-------------|------------------|--------------|----------|-------------|---------|----------|------------|-----------|-------|------|-------|-------|------|
| Adjusted fo | or All Variables |              |          |             |         |          |            |           |       |      |       |       |      |

| Variable         zero cost $P$ nonzero cost $P$ Recurrent CDI (vs none)         0.07 (0.05–0.10)         <.001         1.13 (0.99–1.30)         .07 $\leq$ 9 quarti  |  | OR (95% CI) for    |       | CR (95% CI) given  |       |
|--|--|--------------------|-------|--------------------|-------|
| Recurrent CDI (vs none)         0.07 ( $0.05-0.10$ )         <.001   | Variable   | zero cost          | P     | nonzero cost       | Р     |
| Age quartile1.00 (reference)1.00 (reference)<49 years  | Recurrent CDI (vs none)  | 0.07 (0.05-0.10)   | <.001 | 1.13 (0.99–1.30)   | .07   |
|  | Age quartile   | · · · · · ·        |       |                    |       |
| 49 to $c<62$ years $1.22$ $(1.0-1.49)$ $.04$ $0.90$ $(0.77-1.05)$ $.18$ 62 to $c74$ years $1.44$ $(1.17-1.76)$ $<001$ $0.92$ $(0.78-1.08)$ $.32$ $Z^2$ years $1.68$ $(1.50-2.30)$ $<001$ $0.79$ $(0.67-0.94)$ $.009$ Male (vs female) $0.98$ $(0.85-1.13)$ $.83$ $0.95$ $(0.85-1.07)$ $.41$ Normkite (vs white) $0.79$ $(0.68-0.92)$ $.003$ $1.02$ $(0.90-1.16)$ $.74$ Body mass index $1.00$ (reference) $1.00$ $(reference)$ $1.00$ $(reference)$ Underweight $1.07$ $(0.90-1.27)$ $.46$ $0.96$ $(0.84-1.10)$ $.60$ Obese $1.22$ $(1.02-1.46)$ $.03$ $1.01$ $(0.88-1.37)$ $.47$ $1.49$ $(1.23-1.81)$ $<001$ 1 d (diseases of the arrows system) $0.99$ $(0.66-1.47)$ $.95$ $1.55$ $(1.1-2.18)$ $.001$ 1 d (diseases of the enrous system) $0.79$ $(0.5-0.97)$ $.31$ $1.12$ $(0.90-1.40)$ $.30$ 2 d (diseases of the musculoskeletal system and connective tissue) $0.70$ $(0.47-1.03)$ $.07$ $1.14$ $(0.82-1.58)$ $.43$ 10 (endoctine, nutritional, and metabolic diseases) $0.65$ $(0.41-1.04)$ $.07$ $1.14$ $(0.82-1.58)$ $.43$ 10 (diseases of the musculoskeletal system and connective tissue) $0.70$ $(0.47-1.03)$ $.07$ $1.14$ $(0.82-1.58)$ $.43$ 10 (diseases of the musculos   | <49 years  | 1.00 (reference)   |       | 1.00 (reference)   |       |
| 62 to <74 years  | 49 to <62 years  | 1.22 (1.01–1.49)   | .04   | 0.90 (0.77-1.05)   | .18   |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $   | 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  |
| Norwhite (vs white) $0.79$ (0.68– $0.92$ ).003 $1.02$ (0.90– $1.16$ ).74Body mass index  | Male (vs female)   | 0.98 (0.85–1.13)   | .83   | 0.95 (0.85–1.07)   | .41   |
| Body mass index1.00 (reference)1.00 (reference)Normal weight1.00 (reference)1.00 (reference)Underweight1.07 (0.90–1.27)460.96 (0.84–1.20)Overweight1.07 (0.90–1.27)460.96 (0.84–1.10).60Obese1.22 (1.02–1.46)0.31.01 (0.88–1.17).87MDC11.00 (reference)1.00 (reference)1.00 (reference)0 (unassigned principal diagnosis)1.09 (0.86–1.37)471.49 (1.23–1.81)<001  | Nonwhite (vs white)  | 0.79 (0.68–0.92)   | .003  | 1.02 (0.90-1.16)   | .74   |
| Normal weight1.00 (reference)1.00 (reference)Underweight1.08 (0.82-1.41).590.99 (0.80-1.22).94Overweight1.07 (0.09-1.27).460.96 (0.84-1.10).60Obese1.22 (1.02-1.46).031.01 (0.88-1.17).87MDC.946 (diseases of the digestive system)1.00 (reference)1.00 (reference)1 (diseases of the respiratory system)0.99 (0.66-1.47).951.55 (1.11-2.18).014 (diseases of the respiratory system)0.79 (0.59-1.04).101.26 (1.00-1.58).055 (diseases of the musculoskeletal system and pancreas)1.06 (0.75-1.50).731.48 (1.12-1.87).0068 (diseases of the musculoskeletal system and connective tissue)0.70 (0.47-1.03).071.14 (0.82-1.58).4310 (endocrine, nutritional, and metabolic diseases)0.65 (0.41-1.04).071.21 (0.86-1.71).2813 (diseases of the female reproductive system)1.82 (0.86-3.86).121.24 (0.63-2.43).4014 (diseases of bloed-forming organs, immunologic)0.49 (0.28-0.85).011.18 (0.80-1.73).4017 (myeloproliferative diseases)0.57 (0.53-4.36).401.15 (0.58-2.25).69All others1.18 (0.74-1.87).480.98 (0.66-1.45).92Charlson comorbidites0.70 (0.47-1.83).021.30 (1.02-1.67).4425 (HIV infections)1.55 (0.55-4.36).401.15 (0.58-2.25).69All diseases of b   | Body mass index  | · · · · · ·        |       |                    |       |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | Normal weight  | 1.00 (reference)   |       | 1.00 (reference)   |       |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $   | Underweight  | 1.08 (0.82–1.41)   | .59   | 0.99 (0.80-1.22)   | .94   |
| Obese         1.22 (1.02–1.4)         .03         1.01 (0.88–1.17)         .87           MDC         6         (diseases of the digestive system)         1.00 (reference)         1.00 (reference)         0           0 (unassigned principal diagnosis)         1.09 (0.86–1.37)         .47         1.49 (1.23–1.81)         <.001   | Overweight   | 1.07 (0.90-1.27)   | .46   | 0.96 (0.84–1.10)   | .60   |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $  | Obese  | 1.22(1.02-1.46)    | .03   | 1.01 (0.88–1.17)   | .87   |
|  | MDC  |                    |       | (                  |       |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$   | 6 (diseases of the digestive system)                             | 1.00 (reference)   |       | 1.00 (reference)   |       |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$  | 0 (unassigned principal diagnosis)                               | 1.09 (0.86 - 1.37) | .47   | 1.49(1.23-1.81)    | <.001 |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$  | 1 (diseases of the nervous system)                               | 0.99(0.66-1.47)    | .95   | 1.55 (1.11-2.18)   | .01   |
| 5 (diseases of the circulatory system) 0.74 (0.56-0.97) 0.3 1.12 (0.90-1.40) 3.0 7 (diseases of the hepatobiliary system and pancreas) 1.06 (0.75-1.50) 7.3 1.48 (1.12-1.97) 0.06 8 (diseases of the musuloskeletal system and connective tissue) 0.70 (0.47-1.03) 0.7 1.14 (0.82-1.58) 4.3 10 (endocrine, nutritional, and metabolic diseases) 0.65 (0.41-1.04) 0.7 1.21 (0.86-1.71) 2.8 11 (diseases of the kidney and urinary tract) 0.65 (0.41-1.04) 0.7 1.21 (0.86-1.71) 2.8 11 (diseases of the female reproductive system) 1.82 (0.86-3.86) 1.12 1.24 (0.63-2.43) 5.4 16 (diseases of blood, blood-forming organs, immunologic) 0.49 (0.28-0.85) 0.01 1.18 (0.80-1.73) 4.0 17 (myeloproliferative diseases) 0.45 (0.32-0.65) <0.01 2.25 (1.74-2.91) <0.01 18 (infectious and parasitic diseases) 0.68 (0.49-0.93) 0.2 1.30 (1.02-1.67) 0.4 21 (injuries, poisonings, toxic effects of drugs) 0.72 (0.34-1.52) 3.9 1.29 (0.69-2.41) 4.2 5 (HV infections) 1.55 (0.55-4.36) 4.0 1.15 (0.58-2.25) 6.9 All others 1.18 (0.74-1.87) 4.8 0.98 (0.66-1.45) 9.2 Charlson comorbidities 1.18 (0.74-1.87) 4.8 0.98 (0.66-1.45) 9.2 Charlson comorbidities 0.77 (0.64-0.92) 0.00 1.23 (1.01-1.51) 0.4 Congestive heart failure 0.75 (0.63-0.90) 0.02 1.13 (0.98-1.30) 1.10 Peripheral vascular disease 0.99 (0.75-1.30) 9.5 1.22 (0.98-1.52) 0.70 Cerebrovascular disease 1.08 (0.80-1.46) 6.3 0.77 (0.61-0.98) 0.37 Chronic obstructive pulmonary disease 1.08 (0.84-1.48) 0.94 (1.92-1.94) 0.11 Pertic ulcer disease 1.06 (0.44-0.83) 0.02 1.02 (0.88-1.15) 9.6 Rheumatologic disease 1.06 (0.44-0.81) <0.01 1.15 (0.91-1.45) 2.5 Any diabetes 0.66 (0.44-0.81) <0.01 1.15 (0.91-1.45) 2.5 Any diabetes 0.66 (0.44-0.81) <0.01 1.15 (0.91-1.45) 2.5 Any diabetes 0.66 (0.44-0.81) <0.01 1.15 (0.91-1.45) 2.5 Any diabetes 0.63 (0.50-0.79) <0.01 0.16 (0.78-1.40) 7.77 Any liver disease 0.60 (0.44-0.81) <0.01 1.15 (0.91-1.45) 2.5 Any diabetes 0.63 (0.50-0.79) <0.01 0.96 (0.67-1.38) 8.4 Cancer (excluding leukemia/lymphoma) 0.53 (0.42-0.67) <0.01 1.37 (1.15-1.63) <0.01 Metast  | 4 (diseases of the respiratory system)                           | 0.79 (0.59–1.04)   | .10   | 1.26 (1.00–1.58)   | .05   |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$   | 5 (diseases of the circulatory system)                           | 0.74 (0.56-0.97)   | .03   | 1.12 (0.90–1.40)   | .30   |
| 8 (diseases of the musculoskeletal system and connective tissue)0.70 $(0.47-1.03)$ .071.14 $(0.82-1.58)$ .4310 (endocrine, nutritional, and metabolic diseases)0.65 $(0.41-1.04)$ .071.21 $(0.86-1.71)$ .2811 (diseases of the kidney and urinary tract)0.65 $(0.50-0.89)$ .0061.16 $(0.93-1.45)$ .2013 (diseases of blood, blood-forming organs, immunologic)0.49 $(0.28-0.85)$ .011.18 $(0.80-1.73)$ .4017 (myeloproliferative diseases)0.45 $(0.32-0.65)$ <.001   | 7 (diseases of the hepatobiliary system and pancreas)            | 1.06(0.75 - 1.50)  | .73   | 1.48 (1.12–1.97)   | .006  |
| 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) $0.49$ ( $0.28-0.85$ ) $.011$ $1.18$ ( $0.80-1.73$ ) $.40$ 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 $.071$ ( $0.54-0.92$ ) $.009$ $1.23$ ( $1.01-1.51$ ) $.04$ Myocardial infarction $0.71$ ( $0.54-0.92$ ) $.009$ $1.23$ ( $1.01-1.51$ ) $.04$ Corgestive heart failure $0.60$ ( $0.44-0.83$ ) $.002$ $1.13$ ( $0.98-1.52$ ) $.07$ Cerebrovascular disease $0.97$ ( $0.82-1.15$ ) $.75$ $1.00$ ( $0.8-1.12$ ) $.85$ Dementia $0.97$ ( $0.82-1.15$ ) $.75$ $1.00$ ( $0.88-1.15$ ) $.96$ Rheumatologic disease $1.06$ ( $0.74-1.52$ ) $.74$ $1.45$ ( $1.09-1.94$ ) $.01$ <t< td=""><td>8 (diseases of the musculoskeletal system and connective tissue)</td><td>0.70 (0.47–1.03)</td><td>.07</td><td>1.14 (0.82–1.58)</td><td>.43</td></t<>   | 8 (diseases of the musculoskeletal system and connective tissue) | 0.70 (0.47–1.03)   | .07   | 1.14 (0.82–1.58)   | .43   |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$   | 10 (endocrine, nutritional, and metabolic diseases)              | 0.65 (0.41 - 1.04) | .07   | 1.21 (0.86 - 1.71) | .28   |
| 13 (diseases of the female reproductive system)1.82 (0.86-3.86)1.22 (0.63-2.43).5416 (diseases of blood, blood-forming organs, immunologic)0.49 (0.28-0.85)0.011.18 (0.63-2.43).4017 (myeloproliferative diseases)0.45 (0.32-0.65)<001   | 11 (diseases of the kidney and urinary tract)                    | 0.67 (0.50 - 0.89) | .006  | 1.16 (0.93 - 1.45) | .20   |
| 16 (diseases of blood, blood-forming organs, immunologic)0.49 (0.28-0.85)0.11.18 (0.80-1.73).4017 (myeloproliferative diseases)0.45 (0.32-0.65)<.001   | 13 (diseases of the female reproductive system)                  | 1.82 (0.86–3.86)   | .12   | 1.24 (0.63 - 2.43) | .54   |
| 17 (myeloproliferative diseases)0.45 ( $0.32-0.65$ )<.0012.25 ( $1.74-2.91$ )<.00118 (infectious and parasitic diseases)0.68 ( $0.49-0.93$ ).021.30 ( $1.02-1.67$ ).0421 (injuries, poisonings, toxic effects of drugs)0.72 ( $0.34-1.52$ ).391.29 ( $0.69-2.41$ ).4225 (HIV infections)1.55 ( $0.55-4.36$ ).401.15 ( $0.58-2.25$ ).69All others1.18 ( $0.74-1.87$ ).480.98 ( $0.66-1.45$ ).92Charlson comorbidities0.71 ( $0.54-0.92$ ).0091.23 ( $1.01-1.51$ ).04Myocardial infarction0.71 ( $0.54-0.92$ ).0091.23 ( $1.01-1.51$ ).04Congestive heart failure0.75 ( $0.63-0.90$ ).0021.13 ( $0.98-1.30$ ).10Peripheral vascular disease0.99 ( $0.75-1.30$ ).951.22 ( $0.88-1.52$ ).07Cerebrovascular disease0.99 ( $0.75-1.30$ ).951.22 ( $0.88-1.52$ ).07Cerebrovascular disease0.97 ( $0.40-2.33$ ).941.39 ( $0.71-2.71$ ).34Chronic renal failure0.60 ( $0.44-0.83$ ).0021.02 ( $0.81-1.29$ ).85Dementia0.97 ( $0.82-1.15$ ).741.45 ( $1.09-1.94$ ).01Peric ulcer disease1.06 ( $0.74-1.52$ ).741.45 ( $1.09-1.94$ ).01Peric ulcer disease0.60 ( $0.44-0.81$ )<.001   | 16 (diseases of blood, blood-forming organs, immunologic)        | 0.49 (0.28 - 0.85) | .01   | 1.18 (0.80 - 1.73) | .40   |
| 18 (infectious and parasitic diseases)0.68 $(0.49-0.93)$ 0.021.30 $(1.02-1.67)$ 0.421 (injuries, poisonings, toxic effects of drugs)0.72 $(0.34-1.52)$ 391.29 $(0.69-2.41)$ 4225 (HIV infections)1.55 $(0.55-4.36)$ .401.15 $(0.58-2.25)$ .69All others1.18 $(0.74-1.87)$ .480.98 $(0.66-1.45)$ .92Charlson comorbidities0.71 $(0.54-0.92)$ .0091.23 $(1.01-1.51)$ .04Congestive heart failure0.75 $(0.63-0.90)$ .0021.13 $(0.98-1.30)$ .10Peripheral vascular disease0.99 $(0.75-1.30)$ .951.22 $(0.98-1.52)$ .07Cerebrovascular disease0.99 $(0.75-1.30)$ .951.22 $(0.88-1.52)$ .07Chronic renal failure0.60 $(0.44-0.83)$ .0021.02 $(0.88-1.12)$ .85Dementia0.97 $(0.40-2.33)$ .941.39 $(0.71-2.71)$ .34Chronic obstructive pulmonary disease1.06 $(0.74-1.52)$ .741.45 $(1.09-1.94)$ .01Peptic ulcer disease1.22 $(0.85-1.75)$ .271.04 $(0.78-1.40)$ .77Any liver disease0.60 $(0.44-0.81)$ <.001  | 17 (myeloproliferative diseases)                                 | 0.45 (0.32 - 0.65) | <.001 | 2.25(1.74-2.91)    | <.001 |
| 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 $0.71 (0.54-0.92)$ $.009$ $1.23 (1.01-1.51)$ $.04$ 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 $0.99 (0.75-1.30)$ $.95$ $1.22 (0.88-1.52)$ $.07$ Cerebrovascular disease $0.60 (0.44-0.83)$ $.002 (1.02 (0.81-1.29))$ $.85$ 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) $0.63 (0.50-0.79)$ $<.001 1.37 (1.15-1.63)$ $<.001$ Metastatic solid tumor $0.94 (0.71-1.23)$ $.65 0.98 (0.80-1.22)$ $.88$ HIV/AIDS  | 18 (infectious and parasitic diseases)                           | 0.68 (0.49–0.93)   | .02   | 1.30 (1.02–1.67)   | .04   |
| 25 (HIV infections)1.55 (0.55-4.36).401.15 (0.58-2.25).69All others1.18 (0.74-1.87).480.98 (0.66-1.45).92Charlson comorbidities0.71 (0.54-0.92).0091.23 (1.01-1.51).04Congestive heart failure0.75 (0.63-0.90).0021.13 (0.98-1.30).10Peripheral vascular disease0.99 (0.75-1.30).951.22 (0.98-1.52).07Cerebrovascular disease1.08 (0.80-1.46).630.77 (0.61-0.98).03Chronic renal failure0.60 (0.44-0.83).0021.02 (0.81-1.29).85Dementia0.97 (0.40-2.33).941.39 (0.71-2.71).34Chronic obstructive pulmonary disease0.97 (0.82-1.15).751.00 (0.88-1.15).96Rheumatologic disease1.06 (0.74-1.52).741.45 (1.09-1.94).01Peptic ulcer disease1.02 (0.85-1.75).271.04 (0.78-1.40).77Any liver disease0.60 (0.44-0.81)<.001  | 21 (injuries, poisonings, toxic effects of drugs)                | 0.72(0.34 - 1.52)  | .39   | 1.29 (0.69-2.41)   | .42   |
| All others $1.18(0.74-1.87)$ $.48$ $0.98(0.66-1.45)$ $.92$ Charlson comorbiditiesMyocardial 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 $0.99(0.75-1.30)$ $.95$ $1.22(0.81-1.29)$ $.85$ Dementia $0.60(0.44-0.83)$ $.002$ $1.02(0.81-1.29)$ $.85$ 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 $0.60(0.44-0.81)$ $<.001$ $1.15(0.91-1.45)$ $.25$ Any diabetes $0.61(0.44-0.81)$ $<.001$ $1.15(0.91-1.45)$ $.25$ 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 $0.94(0.71-1.23)$ $.65$ $0.98(0.80-1.22)$ $.88$  | 25 (HIV infections)  | 1.55 (0.55-4.36)   | .40   | 1.15 (0.58-2.25)   | .69   |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$   | All others   | 1.18 (0.74–1.87)   | .48   | 0.98 (0.66–1.45)   | .92   |
| Myocardial infarction $0.71 (0.54-0.92) \\ 0.09 (0.75 (0.63-0.90) \\ 0.02 (0.113 (0.98-1.30) \\ 0.99 (0.75-1.30) \\ 0.95 (0.20 (0.80-1.46) \\ 0.63 (0.77 (0.61-0.98) \\ 0.03 \\ 0.77 (0.61-0.98) \\ 0.03 \\ 0.77 (0.61-0.98) \\ 0.03 \\ 0.77 (0.61-0.98) \\ 0.03 \\ 0.71 (0.40-2.33) \\ 0.97 (0.40-2.33) \\ 0.97 (0.40-2.33) \\ 0.94 (0.74-1.52) \\ 0.97 (0.82-1.15) \\ 0.75 (0.088-1.15) \\ 0.96 \\ Rheumatologic disease \\ 1.06 (0.74-1.52) \\ 0.74 \\ 1.45 (1.09-1.94) \\ 0.11 \\ 0.97 \\ 0.40 \\ 0.78 (0.48-1.26) \\ 0.91 \\ 0.9$ | Charlson comorbidities   |                    |       | (,                 |       |
| 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) $0.63 (0.50-0.79)$ $<.001$ $1.37 (1.15-1.63)$ $<.001$ Metastatic solid tumor $0.94 (0.71-1.23)$ $.65$ $0.98 (0.80-1.22)$ $.88$ HIV/AIDS $0.40 (0.18-0.87)$ $.02$ $1.17 (0.74-1.87)$ $.50$   | Myocardial infarction  | 0.71 (0.54-0.92)   | .009  | 1.23 (1.01-1.51)   | .04   |
| Peripheral vascular disease $0.99 (0.75-1.30)$ $.95 (0.22 (0.98-1.52)$ $.07$ 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) $0.63 (0.50-0.79)$ $<.001 1.37 (1.15-1.63)$ $.001$ Metastatic solid tumor $0.94 (0.71-1.23)$ $.65 0.98 (0.80-1.22)$ $.88$ HIV/AIDS $0.40 (0.18-0.87)$ $.02 1.17 (0.74-1.87)$ $.50$   | Congestive heart failure   | 0.75 (0.63-0.90)   | .002  | 1.13 (0.98–1.30)   | .10   |
| 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 $0.94 (0.71-1.23)$ $.65$ $0.98 (0.80-1.22)$ $.88$ HIV/AIDS $0.40 (0.18-0.87)$ $.02$ $1.17 (0.74-1.87)$ $.50$  | Peripheral vascular disease                                      | 0.99 (0.75–1.30)   | .95   | 1.22 (0.98–1.52)   | .07   |
| 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 $0.60\ (0.44-0.81)\ <.001\ 1.15\ (0.91-1.45)\ .25$ 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 $0.40\ (0.18-0.87)\ .02\ 1.17\ (0.74-1.87)\ .50$   | Cerebrovascular disease  | 1.08(0.80-1.46)    | .63   | 0.77 (0.61-0.98)   | .03   |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$   | Chronic renal failure  | 0.60 (0.44–0.83)   | .002  | 1.02 (0.81–1.29)   | .85   |
| 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 $0.40 (0.18-0.87)$ $.02$ $1.17 (0.74-1.87)$ $.50$   | Dementia   | 0.97 (0.40-2.33)   | .94   | 1.39 (0.71-2.71)   | .34   |
| 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 $0.40 (0.18-0.87)$ $.02$ $1.17 (0.74-1.87)$ $.50$   | Chronic obstructive pulmonary disease                            | 0.97(0.82 - 1.15)  | .75   | 1.00 (0.88–1.15)   | .96   |
| Peptic ulcer disease1.22 (0.85–1.75).271.04 (0.78–1.40).77Any liver disease0.60 (0.44–0.81)<.001   | Rheumatologic disease  | 1.06(0.74 - 1.52)  | .74   | 1.45 (1.09–1.94)   | .01   |
| Any liver disease0.60 (0.44–0.81)<.0011.15 (0.91–1.45).25Any diabetes0.81 (0.69–0.95).011.08 (0.95–1.23).23Paraplegia/hemiplegia0.78 (0.48–1.26).310.96 (0.67–1.38).84Cancer (excluding leukemia/lymphoma)0.63 (0.50–0.79)<.001  | Peptic ulcer disease   | 1.22 (0.85–1.75)   | .27   | 1.04(0.78 - 1.40)  | .77   |
| Any diabetes0.81 (0.69–0.95).011.08 (0.95–1.23).23Paraplegia/hemiplegia0.78 (0.48–1.26).310.96 (0.67–1.38).84Cancer (excluding leukemia/lymphoma)0.63 (0.50–0.79)<.001   | Any liver disease  | 0.60 (0.44–0.81)   | <.001 | 1.15 (0.91–1.45)   | .25   |
| Paraplegia/hemiplegia0.78 (0.48–1.26).310.96 (0.67–1.38).84Cancer (excluding leukemia/lymphoma)0.63 (0.50–0.79)<.001   | Any diabetes   | 0.81 (0.69-0.95)   | .01   | 1.08(0.95 - 1.23)  | .23   |
| Cancer (excluding leukemia/lymphoma)0.63 (0.50-0.79)<.0010.96 (0.80-1.14).62Leukemia/lymphoma0.53 (0.42-0.67)<.001   | Paraplegia/hemiplegia  | 0.78 (0.48 - 1.26) | .31   | 0.96 (0.67 - 1.38) | .84   |
| Leukemia/lymphoma0.53 (0.42–0.67)<.0011.37 (1.15–1.63)<.001Metastatic solid tumor0.94 (0.71–1.23).650.98 (0.80–1.22).88HIV/AIDS0.40 (0.18–0.87).021.17 (0.74–1.87).50  | Cancer (excluding leukemia/lymphoma)                             | 0.63 (0.50-0.79)   | <.001 | 0.96 (0.80 - 1.14) | .62   |
| Metastatic solid tumor0.94 (0.71–1.23).650.98 (0.80–1.22).88HIV/AIDS0.40 (0.18–0.87).021.17 (0.74–1.87).50   | Leukemia/lymphoma  | 0.53 (0.42–0.67)   | <.001 | 1.37 (1.15–1.63)   | <.001 |
| HIV/AIDS 0.40 (0.18–0.87) .02 1.17 (0.74–1.87) .50   | 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<sup>22</sup> and Kyne et al<sup>23</sup> 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<sup>22</sup>

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<sup>8</sup> 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.<sup>24,25</sup> 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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Potential conflicts of interest. E.R.D., K.A.R., M.Z., and M.A.O. report receiving a grant from Cubist Pharmaceuticals for the conduct of this study. E.R.D. reports having been a consultant for Sanofi Pasteur, Merck, and Pfizer and receiving grants from or participating in clinical trials with Sanofi Pasteur, Merck, Cubist Pharmaceuticals, and Viropharma unrelated to this study. M.A.O. reports having been a consultant for Pfizer and Sanofi Pasteur and receiving a grant from Sanofi Pasteur unrelated to this study. M.A.O. reports having been a consultant for Pfizer and Sanofi Pasteur and receiving a grant from Sanofi Pasteur unrelated to this study. M.Z. reports having been a consultant for Pfizer and Astellas. Cubist Pharmaceuticals reviewed the final manuscript but did not influence data collection, management, analysis, interpretation, presentation of data, or description of findings. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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