Clostridioides (Formerly *Clostridium*) *difficile* Infection During Hospitalization Increases the Likelihood of Nonhome Patient Discharge

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Background. *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) is associated with significant morbidity and mortality, including frequent hospitalizations. However, the impact of CDI after hospital discharge is poorly understood. The purpose of this study was to assess patient discharge disposition and understand CDI-related risk factors for nonhome discharge.

Methods. Using a nationally representative database of Veterans Health Administration (VHA) patients (2003–2014) and a validation database from hospitalized non-VHA patients in Houston, Texas, admission and discharge disposition was obtained for patients with CDI and matched controls. Incidence of and clinical/microbiologic risk factors for nonhome discharge were assessed using these databases.

Results. A total of 15173 VHA patients with CDI and 48599 non-CDI control patients originally admitted from the community were included. Significantly more patients with CDI were discharged to a nonhome location compared with controls (18% vs 8%; *P* < .0001), most commonly hospice/death (12%) or nursing home/long-term care facility (6%). Results were confirmed using a propensity-matched analysis and a validation cohort of 1941 hospitalized patients with CDI in Houston, Texas. Age, comorbidities, severe CDI, and ribotypes F027, F001, and F053-163 were associated with a nonhome discharge (*P* < .05 for all).

Conclusions. Hospitalized patients with CDI frequently required a higher level of medical care residence at discharge compared with non-CDI patients. Risk factors for discharge to a higher level of care included CDI disease severity and variables associated with recurrent CDI.

Keywords. outcomes research; epidemiology; anaerobic infections; healthcare-associated infections; strain typing.

Clostridioides (formerly *Clostridium*) *difficile* is the most common organism implicated in healthcare-associated infections in the United States [1], likely attributed to an epidemic, so-called hypervirulent ribotype 027 strain [2, 3]. *Clostridioides difficile* infection (CDI) is associated with significant morbidity and mortality, including frequent hospitalizations. CDI-attributable hospital costs have been estimated to be $21448 per case, resulting in a total financial burden of $6.3 billion in the United States in 2015 [4, 5]. One-fifth of hospitalized patients with a first episode of CDI treated with vancomycin or metronidazole will experience recurrent CDI, with risk increasing with each subsequent episode [6–10]. Up to half of these patients with recurrent CDI will be rehospitalized, further contributing to the high patient and economic burden [11]. Despite a heightened awareness of the disease burden during

hospitalization, very little is known about how a patient with CDI progresses through the continuum of healthcare after hospital discharge. Specifically, CDI is associated with long-term poor patient outcomes posthospitalization, including decreased quality of life and a high incidence of irritable bowel syndrome [12, 13]. We hypothesized that CDI would increase the likelihood for a nonhome discharge among hospitalized patients. Given that certain *C. difficile* ribotypes are associated with increased disease severity and outcomes [14], we also hypothesized that certain ribotypes would be associated with increased risk for a nonhome discharge. The purpose of this study was to assess patient discharge disposition and assess CDI-related patient and strain risk factors for a nonhome discharge. To accomplish these aims, we used data available from the nationwide inpatient Veterans Health Administration (VHA) facilities in the United States [15] and an ongoing cohort study of hospitalized patients with CDI in Houston, Texas [16]. In separate analyses, we used the large, nationwide VHA database to assess the incidence of nonhome discharge in hospitalized veterans with CDI compared with non-CDI control patients. Clinical risk factors for a nonhome discharge were also assessed. Incidence and risk factors were validated in the Houston cohort with an additional analysis investigating whether certain strain types are associated with a nonhome discharge.

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METHODS

VHA Database

Study Design

This was a retrospective cohort study of patients with their first occurrence of CDI receiving care at any inpatient VHA facility in the United States. Data for this study were obtained from the Department of Veterans Affairs Informatics and Computing Infrastructure, which includes administrative, clinical, laboratory, and pharmacy data repositories that are linked using unique patient identifiers. This study was approved by the institutional review boards at the University of Texas Health Science Center at San Antonio and the South Texas Veterans Health Care System Research and Development Committee.

Study Population

The CDI cohort was created by identifying patients 18–89 years old who had any inpatient or outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code for CDI (008.45) plus a positive CDI stool test (eg, toxin enzyme immunoassay or nucleic acid amplification test with or without glutamate dehydrogenase antigen test) during the visit or within 7 days of the visit from 1 October 2002 through 30 September 2014. A control group was created by identifying a random sample of VHA patients without a CDI *ICD-9-CM* code for the duration of the study period and matching 2:1 (control:CDI) by treatment setting (inpatient or outpatient) and fiscal year of visit. Following cohort creation, we limited both cohorts to those patients who were hospitalized, were admitted directly from the community (ie, direct admission) or an outpatient clinic/treatment setting, had complete admission and discharge information, and received active CDI therapy (CDI group only: metronidazole, oral vancomycin, fidaxomicin, rifaximin, nitazoxanide, or fecal microbiota transplantation). Patients with an *ICD-9-CM* code for CDI (008.45) in the year prior to study inclusion were excluded.

Study Definitions

Data collected included admission and discharge sources for first, second, and third occurrence of CDI. Nonhome discharge was categorized as discharge to nursing home/long-term care facility (LTCF), another hospital, hospice, or death. CDI first recurrence was defined as a second inpatient visit during which a patient received an *ICD-9-CM* code for CDI, plus a minimum 3-day gap between the visit and the end of active CDI therapy for the initial episode. A second CDI recurrence was defined in the same manner as the first, but using the third CDI diagnosis over the cohort period.

Patient demographics included age, sex, race, and ethnicity. Charlson comorbidities and other relevant diagnoses, as defined by *ICD-9-CM* codes, were collected for the year prior to the CDI encounter (Supplementary Appendix 1). The Charlson comorbidity score was calculated as modified by Deyo et al [17]. In addition, concomitant infections were collected that occurred during an encounter (between CDI episode start date and end of CDI therapy for CDI patients and during hospitalization for control group), including bacteremia, pneumonia, skin infection, intra-abdominal infection, urinary tract infection, device-related infection, endocarditis, and acute respiratory infection. Other markers of CDI severity that occurred during an encounter were also captured, including sepsis/septicemia, shock, megacolon, prolonged ileus, perforated intestine, acute renal failure, and intensive care unit admission. Patients were considered "severe" if they had any one of these CDI severity indicators, though this definition differs slightly from the CDI clinical practice guidelines (ie, combination of severe and fulminant criteria).

Data on prior and concomitant non-CDI antibiotics (excludes oral vancomycin, metronidazole, fidaxomicin, rifaximin, and nitazoxanide), gastric acid suppressant (GAS) drugs (antacids, H2 receptor antagonists, proton pump inhibitors), and narcotics were collected. Prior use was defined as any use in the 90 days prior to the encounter, and concomitant use was defined as any use during or within 60 days following the encounter. The 60-day follow-up period for concomitant medication use was chosen because this time period is likely to capture the majority of medication use between initial CDI and recurrence; recurrent CDI is most common within 1–3 weeks posttreatment discontinuation, but late recurrences are also common [6].

Data and Statistical Analyses

Data extraction and variable creation were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina). All other data and statistical analyses were conducted using JMP 13.0 (SAS Institute). First, baseline characteristics were presented descriptively and compared between CDI and control group patients using the χ^2 or Wilcoxon rank-sum test as appropriate. Next, discharge dispositions were presented descriptively for each CDI episode and compared between episodes using the McNemar χ^2 test. In CDI patients only, independent predictors for nonhome discharge following first occurrence were determined using logistic regression with the following covariates: age, sex, race/ethnicity, 21 comorbidities, 8 concomitant infections, severe CDI, and concomitant medications (antibiotics, GAS drugs, and narcotics) (Table 1).

Results were validated using a propensity score–matched analysis. Specifically, logistic regression was used to generate propensity scores using the cohort (CDI vs control) as the dependent variable and the following covariates: age, sex, race/ethnicity, prior hospitalization, 21 comorbidities, 8 concomitant infections, and 3 prior medication classes (Supplementary Appendix 2). Propensity scores were then matched 1:1 CDI to control cohort using nearest neighbor matching without replacement and a caliper of 0.001. Following matching, discharge to a nonhome location was compared between groups using the χ^2 test.

Houston External Validation Cohort

To validate and extend the findings from the VHA population, we utilized data from an ongoing, multicenter, cohort study of non-VHA patients with CDI in Houston, Texas [11]. In brief,

Table 1.   Baseline Characteristics of Propensity Score–matched Veterans Health Administration Population

Characteristic	CDI Group (n = 10970)	Control Group (n = 10970)	P Value
Age, y, median (IQR)	66 (59–77)	66 (59–77)	.2604
Male sex, %	95.6	95.8	.4241
Race/ethnicity, %			.0010
Non-Hispanic white	65.4	66.7	
Non-Hispanic black	21.0	19.6	
Hispanic	6.0	5.6	
Other	4.3	5.2	
Missing	3.2	3.0	
Prior hospitalization, %	32.9	32.7	.7957
Comorbidities, %			
Hypertension	73.9	74.6	.2228
Dyslipidemia	53.5	53.1	.5426
Obesity	16.1	15.5	.1765
Myocardial infarction	8.2	8.2	.9021
Congestive heart failure	19.0	19.1	.7570
Peripheral vascular disease	15.1	15.0	.7198
Cerebrovascular disease	15.2	14.9	.4851
Dementia	2.7	2.3	.0929
COPD	33.7	34.8	.0878
Rheumatologic disease	2.4	2.3	.4734
Peptic ulcer disease	3.8	3.9	.6999
Liver disease	5.7	6.1	.2173
Diabetes	36.0	36.1	.8882
Hemiplegia or paraplegia	2.0	1.8	.2369
Renal disease	19.8	20.0	.7737
Cancer	25.6	26.6	.1031
HIV/AIDS	1.7	1.8	.4112
GERD	26.1	26.3	.7588
Transplant	0.1	0.1	.4129
Inflammatory bowel disease	2.0	2.0	1.0000
Irritable bowel syndrome	1.1	1.0	.2285
Charlson score, median (IQR)	3 (1–5)	3 (1–5)	.0170
Concomitant infections, %			
Bacteremia	3.0	2.6	.0693
Pneumonia	17.1	17.6	.3449
Skin infection	8.5	8.6	.8471
Intra-abdominal infection	3.6	3.7	.4713
Device-related infection	1.2	1.1	.4072
Acute respiratory infection	2.7	2.9	.3065
Endocarditis	0.3	0.3	1.0000
Urinary tract infection	2.8	3.3	.0296
Medications, %			
Prior antibiotics	42.0	42.5	.4440
Prior GAS drugs	45.8	45.7	.8815
Prior narcotics	31.9	31.7	.8505

Abbreviations: CDI, *Clostridioides difficile*; COPD, chronic obstructive pulmonary disease; GAS, gastric acid suppressant; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; IQR, interquartile range.

patients were included in the study if they were at least 18 years old with a positive liquid stool test for *C. difficile* toxin(s), were receiving CDI therapy, and had at least 1 of the following signs or symptoms of CDI: diarrhea, fever, leukocytosis (white blood cell count >10 000/mL^3), nausea, anorexia, or abdominal pain,

cramping, or discomfort. Data collected for this study included patient demographics, comorbidities, inpatient hospital admission, and discharge disposition. As part of this study, leftover stool samples from patients with CDI were collected. Stool samples were incubated under anaerobic conditions for 48 hours for *C. difficile* growth. Isolates were confirmed to be *C. difficile* on the basis of Gram stain results, typical odor, and the presence of *C. difficile* antigen on Microscreen latex agglutination (Microgen Bioproducts). *Clostridioides difficile i*solates were then strain typed using polymerase chain reaction–based ribotyping method as previously described [18]. This study was approved by the Institutional Review Board at the University of Houston.

Statistical Analysis

Proportion of patients with a nonhome discharge and each discharge disposition were calculated. Risk factors for nonhome discharge identified in the VHA cohort were tested in the Houston cohort using logistic regression. Finally, incidence of nonhome discharge for any *C. difficile* ribotype identified in at least 25 unique patients compared to all other ribotypes was assessed using logistic regression.

RESULTS

VHA Database Results

Baseline Characteristics

A total 15 173 hospitalized patients admitted from the community or outpatient clinic were included in the CDI cohort and 48 599 in the control group. Supplementary Appendix 2 describes the patients' baseline characteristics. Patients with CDI were predominately older (median age, 67 years), male (96%), and non-Hispanic white (66%). Compared to the control group, CDI patients more commonly had chronic comorbidities and recent or concomitant medication use.

CDI Discharge Disposition and Clinical Risk Factor for a Nonhome Discharge

The most common discharge locations for CDI patients included community (78%), nursing home/LTCF (8%), hospice/death (12%), or other (2%) (Figure 1). Compared to non-CDI controls, CDI patients were more often discharged to a nursing home/LTCF (8% vs 3%; *P* < .0001) or hospice/death (12% vs 3%; *P* < .0001). A total of 3190 (18%) CDI patients were discharged to a nonhome location following their first CDI episode compared with 3686 (8%) in the control group (*P* < .0001).

For propensity score analyses, 10 970 CDI patients were matched to 10 970 controls. CDI and control patients were well matched for demographics and comorbidities (Table 1). Compared to controls, CDI patients were more often discharged to a nursing home/LTCF (8% vs 4%; *P* < .0001) or hospice/death (10% vs 5%; *P* < .0001). Overall, discharge to a nonhome location was more common in the CDI cohort (19%) compared with the control cohort (11%) (*P* < .0001).

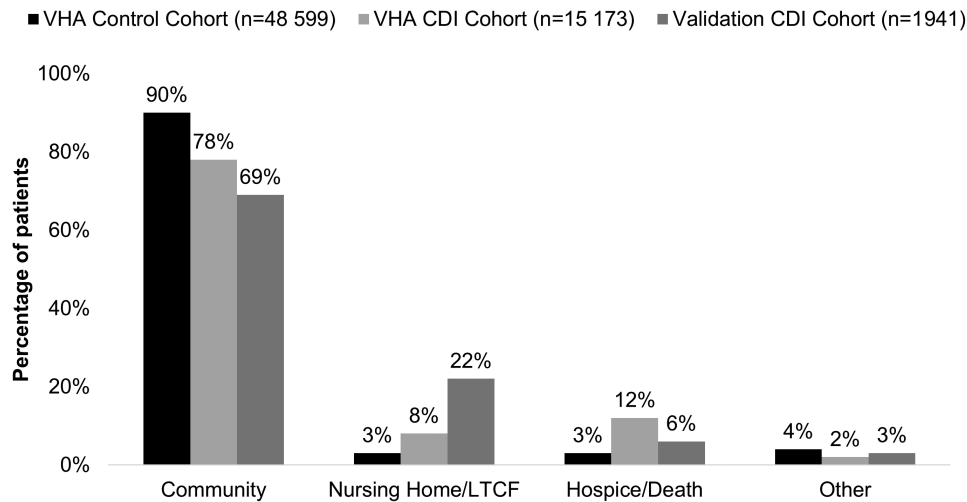■ VHA Control Cohort (n=48 599) ■ VHA CDI Cohort (n=15 173) ■ Validation CDI Cohort (n=1941)

Figure 1. Discharge destination of *Clostridioides difficile* patients and controls admitted from the community in Veterans Health Administration and external validation cohorts. Abbreviations: CDI, *Clostridioides difficile*; LTCF, long-term care facility; VHA, Veterans Health Administration.

A total of 2712 CDI patients (15%) had a first recurrence, of whom 1213 (45%) were rehospitalized and 858 (32%) had discharge disposition data available for the subsequent hospitalization. These patients were most often admitted from the community (83%) for their recurrence. Compared to first episodes, the proportion of CDI patients discharged to a nonhome setting was significantly lower for first recurrences (8%; *P* < .0001). A total of 858 (32% of first recurrence patients) experienced a second recurrence, of whom 249 were rehospitalized (29%) and 15 (2%) had discharge disposition information available. Second recurrence patients were most often admitted from the community (20%) or outpatient clinics (67%). No (0%) second recurrence patients were discharged to a nonhome setting.

Overall, 17 variables independently predicted discharge to a higher level of care following the initial CDI episode (Table 2). Those with the strongest association included severe CDI (odds ratio [OR], 1.85 [95% confidence interval {CI}, 1.69–2.01]), liver disease (OR, 1.80 [95% CI, 1.55–2.09]), and age ≥65 years (OR, 1.74 [95% CI, 1.58–1.91]).

Houston External Validation Cohort
Baseline Characteristics and Discharge Disposition
Discharge status was available for 1953 hospitalized CDI patients aged 63 ± 18 years (mean ± standard deviation) (58% female) admitted from the community in the external validation cohort. Of those CDI patients admitted from the community, most

Table 2. Independent Predictors of Discharge to Higher Level of Care Among Veterans Health Administration (VHA) *Clostridioides difficile* (CDI) Patients Admitted From the Community (n = 15 173; VHA CDI Cohort) and Hospitalized Patients From a Quaternary Care Hospital (n = 574; Validation Cohort)

Characteristic	VHA CDI Cohort		Validation Cohort	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Severe CDI	1.85 (1.69–2.01)	<.0001	1.61 (1.03–2.50)	.025
Liver disease	1.80 (1.55–2.09)	<.0001		
Age ≥65 y	1.74 (1.58–1.91)	<.0001	3.48 (2.20–5.53)	<.0001
Concomitant antibiotics	1.59 (1.41–1.78)	<.0001	2.06 (1.28–3.31)	.003
Pneumonia	1.59 (1.45–1.75)	<.0001		
Male sex	1.52 (1.15–1.99)	.0028		
Hemiplegia/paraplegia	1.48 (1.19–1.84)	.0004		
White race	1.35 (1.21–1.51)	<.0001		
Congestive heart failure	1.29 (1.17–1.43)	<.0001	3.33 (2.10–5.28)	<.0001
Dementia	1.25 (1.01–1.54)	.0413		
Concomitant narcotics	1.24 (1.14–1.35)	<.0001		
Cancer	1.20 (1.09–1.31)	<.0001		
Bacteremia	1.18 (1.03–1.37)	.0238		
Concomitant acid suppressants	1.15 (1.02–1.28)	.0160		
Cerebrovascular disease	1.12 (1.00–1.25)	.0436		

Abbreviations: CDI, *Clostridioides difficile*; CI, confidence interval; OR, odds ratio; VHA, Veterans Health Administration.

(69%) were discharged back to the community followed by nursing home/LTCF (22%), hospice/death (6%), or other (3%).

Additional clinical metadata were available for 585 patients. Comorbidities present in this population with an incidence of at least 10% included chronic obstructive pulmonary disease (11%), cerebrovascular disease (16%), congestive heart failure (21%), solid, nonmetastatic tumor (12%), diabetes with no complications (16%), and hemodialysis (18%). Hospitalization variables present in at least 10% of the population included proton pump inhibitor use (46%), scheduled narcotics (29%), continued use of non–*C. difficile* antibiotics (62%), and scheduled steroid use (14%). Average (± standard deviation) Charlson score was 2.4 ± 2.2. These variables were included in a multivariate stepwise, logistic regression analysis to identify predictors of nonhome discharge disposition. Significant predictors included age >65 years (OR, 3.5 [95% CI, 2.2–5.6]; $P < .0001$); congestive heart failure (OR, 3.3 [95% CI, 2.1–5.2]; $P < .0001$), severe CDI (OR, 1.58 [95% CI, 1.02–2.45]; $P = .04$), and continued use of systemic antibiotics (OR, 2.10 [95% CI, 1.30–3.37]; $P = .0022$).

Seven hundred and eighty-four patients with discharge disposition information also had *C. difficile* ribotype data available. The most common ribotypes present identified in >25 unique patients included F014-020 (n = 126 [16%]), F027 (n = 120 [15%]), F106 (n = 97 [12%]), F002 (n = 83 [11%]); F001 (n = 31 [4%]), F053-163 (n = 29 [4%]), F054 (n = 27 [3%]), and F078 (n = 26 [3%]). In addition to age and gender, these ribotypes were included as unique variables compared to all other ribotypes combined in a multivariate logistic regression model to identify potential ribotype predictors of nonhome discharge. In addition to age >65 years, ribotypes associated with a nonhome discharge included ribotype F027 (OR, 2.60 [95% CI, 1.71–3.94]; $P < .0001$), F001 (OR, 2.49 [95% CI, 1.16–5.32]; $P = .019$), and F053-163 (OR, 4.40 [95% CI, 1.91–10.14]; $P = .0005$). Discharge disposition by ribotype is shown in Figure 2.

DISCUSSION

CDI is common in the United States and associated with many poor outcomes during hospitalization [19]. Despite a high incidence and mortality rate due to CDI, very few studies have focused on transition of care for hospitalized patients with CDI, with a specific focus on discharge disposition in patients originally admitted from the community setting. In this study, we demonstrated that hospitalized patients with CDI have a higher likelihood of requiring a higher level of healthcare at discharge compared with non-CDI controls. These results were demonstrated in a large VHA database and validated using a secondary database comprised of hospitalized patients with CDI in Houston, Texas. Variables associated with a nonhome discharge reflected CDI disease severity, increased age, and patient comorbidities. After controlling for age and comorbidities, patients with CDI were still more likely to be discharged to a nonhome setting. Finally, the recent epidemic ribotype 027 strain was associated with a nonhome discharge, as were 2 other less frequently isolated ribotypes. Taken together, these data provide strong evidence that certain hospitalized patients with CDI are at a higher risk for discharge to a nonhome setting compared to hospitalized patients without CDI. Strengths of the study include a nationally representative, large VHA cohort to provide data that were validated using a separate database. Addition of strain typing to the analysis further helped to confirms these findings including identification of another poor patient outcome associated with ribotype 027.

Our findings are in line with prior single-center studies in the past. In 2003, Dubberke et al [20] demonstrated that CDI patients were more likely to be discharged to LTCFs or to another hospital compared with non-CDI control patients (32% vs 23%; OR, 1.62 [95% CI, 1.15–2.28]). Prior to this study, CDI patients with persistent colonization were also at increased risk for discharge to an LTCF [21]. During the recent ribotype 027 outbreak, 37% of CDI patients were discharged to LTCFs from hospitals in the
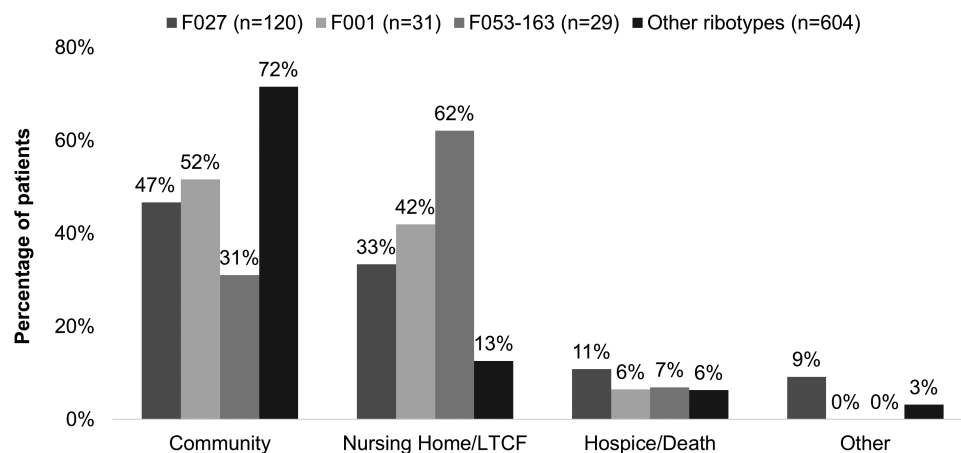

Figure 2. Discharge destination of *Clostridioides difficile* patients stratified by polymerase chain reaction ribotype. Abbreviation: LTCF, long-term care facility.

Chicagoland area [22]. These results were remarkably similar to the 22%–31% of patients in our study discharged to a nonhome setting. The likelihood of a nonhome discharge decreased with subsequent recurrences, likely due to survivor bias; patients with a recurrence have a lower mortality rate compared with initial episodes, as seen in prior studies [11, 15, 23].

Although we were unable to determine the specific reasons for postdischarge site of care in this study, severe CDI disease presentation was a consistent risk factor in the VHA and validation cohorts. Ribotypes shown to increase the likelihood of a nonhome discharge have also been associated with severe CDI. The most recent 027/BI/NAP1 strain was often described as hypervirulent during the epidemic, although other ribotypes have been demonstrated to be equally virulent [2, 3, 14]. Ribotype 001 has been shown to cause severe disease during an epidemic in the Czech Republic [24], and has also been shown to be a significant causative ribotype for transmission events between patients [25]. Our ribotyping assay does not distinguish between ribotypes 053 and 163; however, both ribotypes have been associated with epidemic spread or severe disease in the past [26, 27]. This is one of the first studies documenting a higher level of discharge care associated with these ribotypes. Discharge to a nonhome setting increases global healthcare costs and also increases likelihood for mortality [28, 29].

Once validated, these findings also support routine strain typing of *C. difficile* isolates to identify patient populations at high risk for poor outcomes, including unfavorable discharge disposition, and additional studies identifying the most effective clinical treatment strategies for patients with high-risk strain types.

The study has potential limitations. Data for the primary VHA cohort were collected retrospectively from the VHA electronic medical record system. Relevant diagnoses and admission/discharge information might be subject to misclassification and could not be confirmed through individual chart review. Signs/symptoms associated with CDI and specialty care (ie, infectious diseases consultation) could not be confirmed to aid in CDI diagnosis, nor could recurrences be confirmed with additional laboratory testing or CDI therapy. Misclassification might also occur in patients who were admitted from an outpatient clinic, as it is possible these were LTCF or nursing home residents. The VHA population is predominately older and male and might not be representative of CDI patients in community hospitals; however, our findings were similar in the non-VHA validation cohort. Clinical metadata from our validation database was not available for many of the cases where ribotyping had been performed; therefore, more in-depth multivariate analyses with ribotype and clinical metadata were not possible. Last, study outcomes could not be determined as attributable to CDI; rather, these were all-cause outcomes.

In conclusion, hospitalized patients with CDI more frequently required a higher level of medical care residence at discharge compared with non-CDI controls. Risk factors for a nonhome discharge included CDI disease severity, comorbidities, and variables commonly associated with recurrent CDI (eg, older age, concomitant antibiotics).

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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