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## Original Article

# Impact of *Clostridioides difficile* infection on patient-reported quality of life

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**Abstract**

Objective: We investigated the quality of life (QoL) of patients hospitalized with *C. difficile* infection (CDI).

Design: Prospective survey study.

Setting: US tertiary-care referral center, acute-care setting.

Participants: Adults hospitalized with a diagnosis of CDI, defined as ≥3 episodes of unformed stool in 24 hours and a positive laboratory test for *C. difficile*.

Methods: We surveyed patients from July 2019 to March 2020 using the disease-specific Cdiff32 questionnaire and the generic PROMIS GH survey. We compared differences in Cdiff32 scores among demographic and clinical subgroups (including CDI severity, CDI recurrence, and various comorbidities) using 2-sample *t* tests. We compared PROMIS GH scores to the general population T score of 50 using 1-sample *t* tests. We performed multivariable linear regression to identify predictors of Cdiff32 scores.

Results: In total, 100 inpatients (mean age, 58.6 ±17.1 years; 53.0% male; 87.0% white) diagnosed with CDI completed QoL surveys. PROMIS GH physical health summary scores (T = 37.3; $P < .001$) and mental health summary scores (T = 43.4; $P < .001$) were significantly lower than those of the general population. In bivariate analysis, recurrent CDI, severe CDI, and number of stools were associated with lower Cdiff32 scores. In multivariable linear regression, recurrent CDI, severe CDI, and each additional stool in the previous 24 hours were associated with significantly decreased Cdiff32 scores.

Conclusions: Patients hospitalized with CDI reported low scores on the Cdiff32 and PROMIS GH, demonstrating a negative impact of CDI on QoL in multiple health domains. The Cdiff32 questionnaire is particularly sensitive to QoL changes in patients with recurrent or severe disease.

**Keywords:** Clostridioides difficile; quality of life; survey; patient-reported outcomes

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*Clostridioides difficile* is one of the leading causes of healthcare-associated infections.[1,2] In most studies of *Clostridioides difficile* infection (CDI), clinical end points such as resolution of symptoms, hospitalization, and mortality are used to assess disease outcomes and effectiveness of new treatments. However, these traditional outcome measures fail to capture changes in health-related quality of life (HR-QoL).

Although HR-QoL has been studied extensively in chronic conditions such as hypertension and diabetes, fewer data are available on HR-QoL in CDI. The paucity of data on CDI HR-QoL is highlighted by the fact that cost-effectiveness analyses of CDI therapies have had to use health-utility scores attributed to more extensively studied forms of diarrhea associated with prostate cancer, ulcerative colitis, and chemotherapy instead.[3–5] Of the available CDI studies, several have quantitatively studied the impact of CDI on HR-QoL using the Short Form 36-Item Health Survey (SF-36) and the European Quality of Life – 5 Dimensions (EQ-5D).[6–8] Although they are broadly applicable to a wide range of medical conditions, the SF-36 and EQ-5D are generic questionnaires that may lack the sensitivity to detect HR-QoL changes specific to diseases such as CDI. To better evaluate the unique impacts of CDI on HR-QoL, efforts have since been made to develop CDI-specific patient reported outcome (PRO) instruments. Recently, Garey et al[9] developed the Cdiff32 questionnaire, a CDI-specific PRO instrument inspired by the SF-36 that quantitatively measures

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not only the physical health domain but also mental and social health domains of HR-QoL. Although it is the most comprehensive CDI-specific PRO instrument developed to date, the Cdiff32 questionnaire was only preliminarily validated in an outpatient sample of ~100 patients. Therefore, we aimed to describe the impact of CDI on HR-QoL using the Cdiff32 questionnaire. Secondly, we aimed to further validate the Cdiff32 questionnaire in a population of patients currently hospitalized with CDI. Finally, we aimed to identify predictors of HR-QoL as represented by Cdiff32 scores in CDI patients.

## Methods

### Study population and design

We conducted a prospective observational study at the main campus of Cleveland Clinic (Cleveland, Ohio) from July 2019 to March 2020. Positive laboratory testing for *C. difficile* was defined as positive toxin gene polymerase chain reaction (PCR) and/or toxin enzyme immunoassay (EIA). Notably, the hospital in which the study was conducted employed a 2-step C. *difficile* testing algorithm in which patients suspected of having CDI receive a PCR test for *C. difficile* toxin B gene first, and subsequently receive a reflex EIA for toxin A/B only if they tested positive by PCR. Patients were included if they (1) were aged ≥18 years, (2) were hospital inpatients, (3) were positive on laboratory testing for *C. difficile*, and (4) were symptomatic (≥3 unformed stools over the past 24 hours). Patients were excluded if they (1) were deemed by clinical staff to lack the capacity for consent, (2) were not able to read English at a proficient level, or (3) were unable to communicate with the study coordinator. Based on surveillance trends in incidence of CDI at the study center, sample sizes achieved in previous studies of quality of life in CDI, and time and resource limitations, a sample size of 100 was determined to be feasible. A power analysis performed a priori demonstrated at least 80% power for each aim of the study.

### Data collection

Patients who consented to participation in the study were administered the Cdiff32 questionnaire and the PROMIS Global Health (PROMIS GH) survey at the bedside. Patients were given the option to complete surveys by pen and paper on their own or to have the surveys verbally administered and recorded by the study coordinator. All surveys were conducted in private rooms because CDI patients had been placed on contact isolation according to protocol following diagnosis. Briefly, the Cdiff32 questionnaire consists of 32 different questions about the patient's physical, mental, and social well-being in relation to their CDI diagnosis. Supplementary Figure 1 (online) shows the full list of questions from the Cdiff32 questionnaire, the mean scores for patients in this study, and the mean scores from the initial validation by Garey et al.[9] Questions related to community living were framed for patients to respond as if they were at home and not currently hospitalized, without alteration of the original survey questions. The PROMIS GH is a questionnaire comprising 10 general questions that can be used to generate physical and mental health summary T scores centered on the 2000 US Census with respect to age, sex, education, and race or ethnicity with a mean score of 50 and standard deviation of 10, which reflects the general population mean.[10,11] For both surveys, higher scores indicate better HR-QoL.

Following completion of surveys, relevant demographic and clinical data were collected from the electronic medical records. Clinical variables related to CDI, hospitalization, and relevant comorbidities were collected. Notably, CDI was classified as nonsevere, severe, or fulminant, based on the 2018 SHEA/IDSA guidelines,[12] as summarized in Supplementary Figure 2 (online). In addition to the clinical classification of CDI severity, patients were asked to report the number of bowel movements they had had within the previous 24 hours as an indirect measure of disease severity at the time of survey. Patients were considered to have recurrent CDI if they had documented evidence for a successfully treated previous episode of CDI in the electronic medical records within the previous 2–8 weeks, according to Society for Healthcare Epidemiology of America/Infections Diseases Society of America (IDSA/SHEA) guidelines.[12]

### Statistical analysis

HR-QoL scores for the Cdiff32 were calculated according to directions outlined by the original authors.[9] Briefly, each Cdiff32 item was converted from a numeric value on a 5-point Likert scale to a score between 0 and 100, with 100 being the best HR-QoL. For the PROMIS GH, physical and mental health scores were generated according to the official scoring service. To help better describe the impact of CDI on HR-QoL, we performed 1-sample *t* tests comparing the PROMIS GH physical and mental scores to the general population average T score of 50. Additionally, the PROMIS GH physical and mental scores were mapped to EQ-5D health utility indices using methods previously described by Thompson et al.[13]

To further validate the Cdiff32 questionnaire in our population of hospitalized tertiary-care patients, we calculated the convergent and discriminant validity, known-groups validity, and internal consistency. Convergent and discriminant validities were examined by calculating the Pearson correlation coefficients between Cdiff32 and PROMIS GH subdomain scores. We hypothesized domains measuring similar constructs would be more highly correlated (convergent validity) than those measuring dissimilar constructs (discriminant validity). Known-groups validity was assessed by comparing the overall Cdiff32 subdomain scores between patients classified as having nonsevere, severe, or fulminant CDI using analysis of variance (ANOVA). Because few CDI cases of fulminant severity were expected, known-groups validity was assessed by comparing the Cdiff32 scores in the nonsevere CDI group to the combined severe and fulminant severity group using a 2-sample *t* test. To assess the internal consistency of the Cdiff32, we calculated Cronbach α for each of the physical, mental, and social subdomains separately, as well as for the questionnaire overall.

Demographic, clinical, and HR-QoL variables were presented as means ± standard deviation, median ± interquartile range, or counts with percentages for the overall CDI cohort and for the primary and recurrent CDI subgroups. Overall Cdiff32 HR-QoL scores between various demographic and clinical subgroups were calculated and compared using the 2-sample *t* test for categorical variables and simple linear regression for continuous variables. To further assess the relationship between CDI recurrence status and Cdiff32 HR-QoL scores, we performed multivariable linear regression of Cdiff32 scores on demographic and clinical variables. Age, sex, and the Charlson comorbidity index were included in the regression model based on potential clinical relevance. Additional variables with statistical significance ($P < .05$) on the bivariate analysis were also included in the multivariable model.

For all comparisons, $P$ values of <.05 were considered statistically significant. All statistical analyses were conducted using

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R: A Language and Environment for Statistical Computing version 3.5.1 software (R Foundation for Statistical Computing, Vienna, Austria). A full list of R packages is included in the Supplementary Material (online). The results of our study are hypothesis generating, and there was no formal adjustment for multiple comparisons.

## Results

### Patient characteristics

From July 2019 to March 2020, 362 patients were hospitalized with a diagnosis of CDI. We excluded 127 patients based on exclusion criteria, and 135 patients declined to participate in the study. Surveys were completed by 100 patients. Demographic and clinical characteristics are shown in Table 1. Notably, 49 of the 100 patients tested positive for both *C. difficile* toxin EIA and toxin gene PCR, whereas 51 patients tested positive on PCR only. Moreover, 44 patients had CDI that could be categorized as nonsevere based on SHEA/IDSA criteria, whereas 50 patients had severe CDI and 6 patients had fulminant CDI. The mean (±SD) number of stools over the past 24 hours prior to survey completion was 5.3 ± 3.54. Moreover, 30 patients stayed in the ICU at some point during their admission prior to time of survey. Also, 86 of 100 patients were experiencing their first CDI episode, whereas 14 patients were experiencing a recurrent episode of CDI. The mean time (±SD) between CDI test order and survey was 3.56 days (±3.62). All patients were being treated for CDI at time of survey.

### Survey results

Cdiff32 and PROMIS GH scores are presented in Table 2. The mean PROMIS GH physical health score was 37.3 ± 8.3, which was significantly lower compared to the general population T score of 50 ($P < .001$). Likewise, the mean PROMIS GH mental health score was 43.4 ± 7.9 and was significantly lower than that of the general population ($P < .001$). The estimated EQ-5D index from mapping the PROMIS GH scores was 0.60 ± 0.20.

In the Cdiff32 questionnaire, patients with recurrent CDI reported decreased overall HR-QoL scores compared to patients with primary CDI (40.7 vs 50.0; $P = .04$). The same was found for the PROMIS GH mental scale (39.3 vs 44.1; $P = .02$) and the PROMIS GH physical scale (33.1 vs 38.0; $P = .06$), though the result for the physical score was not statistically significant. For the individual Cdiff32 subdomains, lower HR-QoL scores were seen in recurrent CDI compared to primary CDI, but only the decrease in the Cdiff32 mental subdomain was statistically significant (33.4 vs 46.2; $P = .004$). Notably, Cdiff32 scores did not differ significantly between EIA-positive and EIA-negative patients.

### Validity

Pearson correlation coefficients were obtained to evaluate convergent and discriminant validities between the corresponding Cdiff32 and PROMIS GH subdomains (Table 3). All correlations were statistically significant. The Cdiff32 overall score was strongly correlated with the Cdiff32 physical ($r = 0.91$) and mental ($r = 0.93$) subdomains and was only moderately correlated with the PROMIS GH physical ($r = 0.36$) and mental ($r = 0.46$) subdomains. With respect to convergent validity, the Cdiff32 physical subdomain was moderately correlated with the PROMIS-GH physical subdomain ($r = 0.30$). Similarly, the Cdiff32 mental

**Table 1.** Demographic and Clinical Characteristics of Survey Participants

| Characteristic | Total Respondents (n=100), No. (%)[a] |
|---|---|
| Age, mean y (SD) | 58.56 (17.1) |
| Sex, male | 53 (53.0) |
| **Race** | |
| White | 87 (87.0) |
| Black | 9 (9.0) |
| BMI, mean (SD) | 26.89 (6.6) |
| Estimated household income, mean USD (SD) | 49,096 (16,925) |
| PCR positive/EIA negative | 51 (51.0) |
| PCR positive/EIA positive | 49 (49.0) |
| No. of stools past 24 h, mean (SD) | 5.29 (3.54) |
| Days between CDI test order and survey, mean (SD) | 3.56 (3.62) |
| ICU stay during admission | 30 (30.0) |
| **CDI severity** | |
| Nonsevere | 44 (44.0) |
| Severe | 50 (50.0) |
| Fulminant | 6 (6.0) |
| **CDI recurrence** | |
| Primary CDI | 86 (86.0) |
| Recurrent CDI | 14 (14.0) |
| **Treatment** | |
| Vancomycin PO | 96 (96.0) |
| Metronidazole IV | 14 (14.0) |
| Metronidazole PO | 4 (4.0) |
| Fidaxomicin | 3 (3.0) |
| Colectomy | 2 (2.0) |
| **Comorbidities** | |
| Charlson comorbidity index, mean (SD) | 4.33 (2.8) |
| Cancer | 37 (37.0) |
| Immunosuppressants/Chemotherapy | 51 (51.0) |
| Inflammatory bowel disease | 16 (16.0) |
| Congestive heart failure | 23 (23.0) |
| Diabetes mellitus | 27 (27.0) |
| Chronic kidney disease | 32 (32.0) |
| **CDI risk factors in past 90 days** | |
| Prior antibiotic use | 93 (93.0) |
| Penicillins | 57 (57.0) |
| Fluoroquinolones | 46 (46.0) |
| Cephalosporins | 42 (42.0) |
| Prior hospitalization | 78 (78.0) |
| Prior PPI use | 67 (67.0) |

Note. CI, confidence interval; CDI, *C. difficile* infection; SD, standard deviation; BMI, body mass index; ICU, intensive care unit; PO, administered orally; IV, administered intravenously; USD, US dollars; PPI, proton pump inhibitor; PCR, polymerase chain reaction; EIA, toxin enzyme immunoassay.
[a]No. (%) unless otherwise indicated.

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**Table 2.** Summary Scores for HR-QoL Instruments Overall and by Recurrence Status

| Instrument | Overall Score (SD) | Primary Score CDI | Recurrent Score CDI | *P* Value[a] |
|---|---|---|---|---|
| Cdiff32 Overall | 48.7 (15.3) | 50.0 (15.1) | 40.7 (14.7) | .04 |
| Cdiff32 Physical | 51.5 (17.4) | 52.6 (17.1) | 45.0 (18.7) | .18 |
| Cdiff32 Mental | 44.4 (16.7) | 46.2 (16.5) | 33.4 (13.4) | .004 |
| Cdiff32 Social | 57.8 (21.6) | 58.2 (21.6) | 55.4 (22.6) | .66 |
| **PROMIS GH** | | | | |
| PROMIS GH Physical | 37.3 (8.3) | 38.0 (8.1) | 33.1 (8.4) | .06 |
| PROMIS GH Mental | 43.4 (7.9) | 44.1 (8.0) | 39.3 (6.1) | .02 |
| Estimated EQ-5D index | 0.60 (0.20) | 0.62 (0.20) | 0.52 (0.21) | .13 |

Note. HR-QOL, health-related quality of life; SD, standard deviation; PROMIS GH, Patient Reported Outcomes Measurement Information System – Global Health; EQ-5D, EuroQol – 5 Dimension.
[a]*P* values for 2-sample *t* test.

**Table 3.** Interscale Correlation Coefficients between the Cdiff32 and PROMIS GH

| Instrument | Cdiff32 Overall | Cdiff32 Physical | Cdiff32 Mental |
|---|---|---|---|
| Cdiff32 physical | 0.91[a] | | |
| Cdiff32 mental | 0.93[a] | | |
| PROMIS GH physical | 0.36[a] | 0.30[b] | 0.35[a] |
| PROMIS GH mental | 0.46[a] | 0.36[a] | 0.48[a] |

Note. PROMIS-GH, Patient Reported Outcomes Measurement Information System – Global Health.
[a]$P < .001$.
[b]$P < .01$.

subdomain was also moderately correlated with the PROMIS GH mental subdomain, though that correlation was stronger (r = 0.48). With respect to discriminant validity, both the Cdiff32 physical subdomain and the Cdiff32 mental subdomain exhibited moderate correlation with the opposite PROMIS GH subdomain.

Overall, the Cdiff32 demonstrated excellent internal consistency among its individual items (α = 0.93). The physical (α = 0.86) and mental (α = 0.88) health subdomains demonstrated good internal consistency. Finally, the social subdomain demonstrated acceptable internal consistency (α = 0.70).

Figure 1 shows the known groups validity of the Cdiff32 based on CDI severity. The overall Cdiff32 HR-QoL score significantly differed among patients with nonsevere, severe and fulminant CDI ($P = .021$). Similarly, both the Cdiff32 physical ($P = .040$) and mental ($P = .029$) subdomain scores also significantly differed among patients with varying CDI severity. In the individual comparisons among CDI severity groups, patients with severe and fulminant CDI reported significantly lower Cdiff32 scores compared to patients with nonsevere CDI, except for the difference in Cdiff32 mental subdomain scores between the nonsevere and severe groups, which was not statistically significant.

### *Variables associated with Cdiff32 HR-QoL scores*

On bivariate analysis of Cdiff32 HR-QoL scores with demographic and clinical variables, severe CDI ($P = .030$) and recurrent CDI ($P = .042$) were both significantly associated with decreased HR-QoL (Supplementary Table 1 online). Fulminant CDI was also significantly associated with decreased Cdiff32 scores ($P = .024$). For each additional stool in the past 24 hours, the Cdiff32 HR-QoL score decreased by 1.54 points ($P = .0018$) (Supplementary Table 2 online). No other variables examined were significantly associated with Cdiff32 scores.

**Table 4.** Multivariable Linear Regression of Cdiff32 Scores

| Variable | Parameter Estimate (95% CI) | *P* Value |
|---|---|---|
| Intercept | 74.51 (57.27 to 91.75) | <.001 |
| Age, y | −0.21 (−0.52 to 0.10)[a] | .19 |
| Sex, male | −1.64 (−8.14 to 4.87) | .62 |
| Charlson Comorbidity Index | 0.59 (−1.21 to 2.39)[a] | .51 |
| Recurrent CDI (vs primary) | −11.21 (−20.77 to −1.65) | .02 |
| Severe CDI (vs nonsevere) | −6.79 (−13.35 to −0.22) | .04 |
| Fulminant CDI (vs nonsevere) | −5.74 (−23.94 to 12.46) | .53 |
| No. of stools past 24 hs | −1.71 (−2.67 to −0.76)[a] | <.001 |

Note. CI, confidence interval; CDI, *C. difficile* infection.
[a]Change in Cdiff32 Score per unit change in variable.

Multivariable linear regression of the Cdiff32 overall score was performed on the variables age, sex, and the Charlson comorbidity index, as well as significant variables from the bivariate analysis, which included recurrent CDI, CDI severity, and number of stools in the past 24 hours (Table 4). Recurrent CDI was associated with an 11.2-point decrease in Cdiff32 score compared to primary CDI ($P = .02$). Severe CDI was associated with a 6.79-point decrease in Cdiff32 score compared to nonsevere CDI ($P = .04$). Finally, each additional increase in number of stools in the past 24 hours prior to survey completion was associated with a 1.71-point decrease in Cdiff32 score ($P < .001$). Notably, the association between fulminant CDI and Cdiff32 scores was no longer statistically significant after adjusting for other covariates.

## Discussion

In this study of HR-QoL in hospitalized CDI patients using a recently developed and disease-specific survey instrument, we demonstrated that patients with active CDI report substantially decreased HR-QoL as represented by the Cdiff32 scores. Results from the PROMIS GH showed that CDI patients experience significantly lower HR-QOL compared to the general population. Moreover, PROMIS GH scores reported by CDI patients in this study are lower or comparable to other medical conditions.[14–19] One caveat for the comparison of these results is that most studies examining HR-QoL are done in the outpatient setting, whereas our study was conducted in the inpatient setting with acutely ill patients. This distinction is highlighted by the fact that the Cdiff32 scores reported by hospitalized patients in our study appear to be lower compared to those reported in the original study by Garey et al,[9] in which preliminary validation was conducted in outpatients.

To our knowledge, this is one of the only studies to examine HR-QoL in CDI using a disease specific questionnaire and HR-QoL in a diarrheal illness using the PROMIS GH. To compare the impact of CDI on HR-QoL in relation to the impact of other diarrheal illnesses on HR-QoL, we mapped the PROMIS GH

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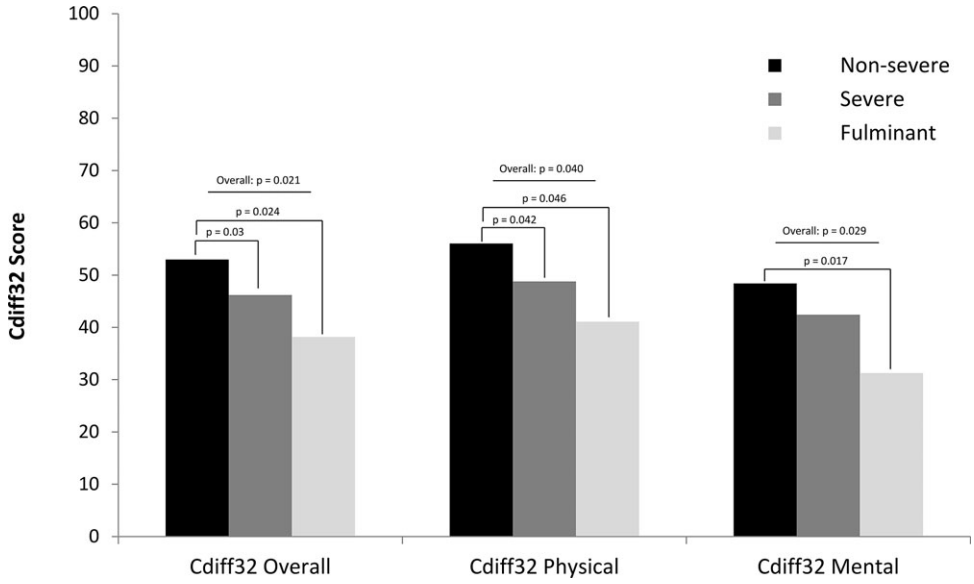


**Fig. 1.** Known groups validity of the Cdiff32 questionnaire and its physical and mental health subdomains as represented by overall and pairwise comparisons of mean Cdiff32 scores by CDI severity.

scores to the EQ-5D, which has been in use longer. Notably, the estimated EQ-5D index from this study appears to be lower compared to that in Crohn's disease, ulcerative colitis, or irritable bowel syndrome.[20,21] With respect to CDI in hospitalized patients, previous studies have reported even lower EQ-5D indices than our study.[6,8] Taken together, these results indicate a considerable impact of CDI on HR-QoL that is comparable to, if not more significant than, that of other diarrheal illnesses.

The Cdiff32 demonstrated strong internal consistency and known-groups validity. The lack of strong correlations between noncorresponding subdomains of the Cdiff32 and PROMIS GH suggests adequate discriminant validity of the Cdiff32. In contrast, we did not find high correlation between Cdiff32 and PROMIS GH subdomains measuring similar constructs to suggest a strong convergent validity as expected. Although this finding may reflect a lack of convergent validity in the Cdiff32 survey, it may also indicate that the Cdiff32 may be capturing aspects of HR-QoL change in CDI that may be missed by generic questionnaires.

The association of recurrent CDI with lower Cdiff32 score was statistically significant even after adjusting for various demographic and clinical comorbidities, including severity of CDI and number of stools experienced by the patient. These findings are consistent with the lasting and debilitating impact of recurrent CDI that has been previously demonstrated.[9,22] Combined with the increased healthcare costs associated with treatment of a recurrent CDI episode compared to a primary CDI episode,[6] these findings highlight the need for the development and reinforcement of new strategies to treat and prevent recurrent CDI.

Our study had several limitations. First, the survey was conducted at a tertiary-care hospital, and most patients were medically complex with multiple comorbidities that could impact their HR-QoL in addition to their CDI. This is especially true for patients with ongoing IBD or undergoing cancer chemotherapy, who may experience decrements to their HR-QoL as a result of diarrhea independent of CDI. From the bivariate analysis, however, it appears that patients with IBD and cancer did not experience significant differences to HR-QoL compared to patients without these diagnoses. Second, owing to the lack of a previously validated CDI-specific PRO instrument to which the Cdiff32 can be compared, we were unable to demonstrate a high degree of construct validity. As discussed previously, this may instead indicate the ability of the Cdiff32 to capture subtle HR-QoL changes that are specific to CDI rather than an inability for the Cdiff32 to measure physical or mental health. Third, our study population was influenced by selection bias, in that patients with the most severe cases of CDI were often unable or unwilling to participate due to their ongoing acute illness. Therefore, we likely underestimated the overall impact of CDI on HR-QoL in the hospitalized population. Fourth, because patients were given the option to complete the surveys independently or with the aid of a study coordinator, the presence of the study coordinator may have led to some patients answering differently. Fifth, because our study did not include a non-CDI comparator, the low HR-QoL scores in isolation should be interpreted with caution. Sixth, *C. difficile* colonized patients with positive PCR but negative EIA were included in our study, which may have introduced bias that affected the results toward the null hypothesis. However, we found that patients with negative and positive EIA reported similar Cdiff32 scores, suggesting a similar level of impairment among all PCR-positive patients.

In summary, patients hospitalized with CDI reported low scores on the Cdiff32 and PROMIS GH, demonstrating a negative impact of CDI on HR-QoL in multiple health domains. The Cdiff32 questionnaire is particularly sensitive to HR-QoL differences between patients with recurrent and/or severe disease, and may be a valuable tool for the study of novel therapies in the future.

**Supplementary material.** To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.413

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