



# Excess length of stay and mortality due to *Clostridium difficile* infection: a multi-state modelling approach

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## SUMMARY

**Background:** The burden of healthcare-associated infections, such as healthcare-acquired *Clostridium difficile* (HA-CDI), can be expressed in terms of additional length of stay (LOS) and mortality. However, previous estimates have varied widely. Although some have considered time of infection onset (time-dependent bias), none considered the impact of severity of HA-CDI; this was the primary aim of this study.

**Methods:** The daily risk of in-hospital death or discharge was modelled using a Cox proportional hazards model, fitted to data on patients discharged in 2012 from a large English teaching hospital. We treated HA-CDI status as a time-dependent variable and adjusted for confounders. In addition, a multi-state model was developed to provide a clinically intuitive metric of delayed discharge associated with non-severe and severe HA-CDI respectively.

**Findings:** Data comprised 157 (including 48 severe) HA-CDI cases among 42,618 patients. HA-CDI reduced the daily discharge rate by nearly one-quarter [hazard ratio (HR): 0.72; 95% confidence interval (CI): 0.61–0.84] and increased the in-hospital death rate by 75% compared with non-HA-CDI patients (HR: 1.75; 95% CI: 1.16–2.62). Whereas overall HA-CDI resulted in a mean excess LOS of about seven days (95% CI: 3.5–10.9), severe cases had an average excess LOS which was twice (~11.6 days; 95% CI: 3.6–19.6) that of the non-severe cases (about five days; 95% CI: 1.1–9.5).

**Conclusion:** HA-CDI contributes to patients' expected LOS and risk of mortality. However, when quantifying the health and economic burden of hospital-onset of HA-CDI, the heterogeneity in the impact of HA-CDI should be accounted for.

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## Introduction

*Clostridium difficile* is a considerable cause of healthcare-associated infections in Europe and the USA.<sup>1,2</sup> In common with other healthcare-associated infections, patients with healthcare-associated *Clostridium difficile* infection (HA-CDI)

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place a serious health and economic burden on the hospital system. Previous economic analyses of HA-CDI have shown that direct healthcare, and opportunity, costs due to excess length of hospital stay (LOS) were the main HA-CDI cost drivers.<sup>3–6</sup> However, a recent review of publications on HA-CDI-associated additional hospital stay showed wide variation in excess LOS, ranging from 2.8 to 16.1 days.<sup>7</sup> These studies primarily used simple regression models, which did not account for the timing of onset of infection ('time-dependent bias').<sup>8</sup> Hence, they may overestimate the duration of excess hospitalization, as a longer stay in hospital may increase the risk of infection. This has been demonstrated rigorously for other healthcare-associated infections but has rarely been explicitly explored for HA-CDI.<sup>7–10</sup>

Two recent publications, which implicitly adjusted for time-dependent bias, reported very different results.<sup>11,12</sup> Using a Cox proportional hazards model, Forster *et al.* concluded that HA-CDI patients had a median excess LOS of six days, whereas Mitchell *et al.* found no significant impact of HA-CDI on hospital stay.<sup>11,12</sup> Mitchell *et al.* used multi-state modelling (MSM), which – in addition to appropriately adjusting for both time to event bias and the competing end-points related to nosocomial infections, namely discharge and death – also provided more easily interpretable results than the proportional hazards model.<sup>11</sup> In their conclusion, Mitchell *et al.* posit that their results, and the difference from earlier estimates, could potentially be explained by milder HA-CDI due to a lack of circulating hypervirulent polymerase chain reaction (PCR) ribotype 027 in their locality (Tasmania, Australia).

As the clinical presentation of HA-CDI can range from mild diarrhoea to pseudomembranous colitis and even death, and the prevalence of severe HA-CDI can vary regionally, due to differences in ribotype prevalence and case-mix, it is important for any estimation of attributable LOS and mortality to consider these heterogeneities.<sup>13–16</sup> In this study, we investigate the effect of severe infection on the expected delayed discharge and mortality associated with HA-CDI based on a Cox proportional hazards model as well as MSM techniques.

## Methods

### Data

Data were collected from Guy's and St Thomas' National Health Service (NHS) Foundation Trust, a teaching hospital including two sites with ~1200 beds. Details of all inpatients discharged in 2012 (namely: age, primary diagnosis code, dates of admission and discharge, and discharge status; i.e. discharge alive or death) were extracted from the Trust's electronic patient record database. These data were linked to the Trust's voluntarily collected HA-CDI surveillance database containing information on date of onset of symptoms, markers of HA-CDI severity, antibiotic treatment, and, where known, the ribotype that caused the infection. In order to evaluate only those infections that were hospital-acquired, patients with symptom onset  $\leq 48$  h after admission and all patients with LOS  $\leq 48$  h were excluded from analyses.

### Severe HA-CDI

Severe HA-CDI was defined by the clinical presence of one or more of four indicators: (i) peripheral white blood cell count

$>15 \times 10^9/L$ ; (ii) acutely rising serum creatinine ( $>50\%$  increase above baseline); (iii) temperature  $>38.5^\circ\text{C}$ ; or (iv) radiographic evidence of colitis or endoscopic appearance of pseudomembranous colitis.<sup>17</sup>

### Procedure

Proportions and medians were compared using the  $\chi^2$ -test and Mann–Whitney–Wilcoxon test, respectively. A Cox proportional hazards model was used to estimate the impact of HA-CDI on the risk of hospital discharge alive or death. This method can adjust for time-dependent bias and take into account the impact of important non-healthcare-associated infection variables such as age and comorbidity score on LOS. Hence, the method can identify and adjust for important confounders. Nonetheless, it does not produce an easily interpretable metric (namely hazard ratios) for economic analysis. Therefore we constructed a suitable MSM, to quantify the average excess LOS caused by the event of interest, i.e. HA-CDI. However, using established methodology, MSM does not account for the potential confounding effect of other variables. As an alternative, we stratified our data by each of the relevant confounders, and performed the MSM on these subsamples.

### Statistical analysis

#### Cox regression model

The risk of in-hospital death or discharge was modelled with a Cox proportional hazards model, with HA-CDI treated as a time-dependent risk factor. We added the covariates age and comorbidity to assess their confounding effects on the risk of in-hospital death or discharge. Comorbidity was expressed in a Charlson Comorbidity Index (CCI) score based on the patients' primary diagnosis code.<sup>18</sup> These primary diagnoses were classified using International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes.<sup>18</sup>

#### Multi-state model

The first MSM comprised four states; admission with no HA-CDI (state 0), HA-CDI (state 1), discharge alive (state 2), and death in hospital (state 3).<sup>19</sup> Since we were solely concerned with HA-CDI, it was assumed that all patients were admitted to the hospital without infection. Uninfected patients remained in state 0 from admission until discharge (state 2) or in-hospital death (state 3). Infected patients entered state 1 and then remained in that state until discharge or death. This competing end-points approach allowed for assessment of the impact of mortality due to HA-CDI on patients' expected excess stay, e.g. whether HA-CDI-related mortality may shorten expected LOS. Second, prolonged LOS associated with HA-CDI was estimated by constructing an MSM in which the two competing end-points were combined as a single state.<sup>20</sup> Transitions between states were determined by time-varying hazards, which were estimated using the Aalen–Johansen estimator.<sup>21</sup> For each point in time  $t$  (in days), the expected LOS for HA-CDI and non-infected patients was compared. The unadjusted expected change in LOS was then calculated as the average difference in LOS of HA-CDI and non-HA-CDI cases across all days, weighted relative to the frequency of the possible events (i.e. HA-CDI, discharge alive and in-hospital death) on each day.<sup>22</sup> Bootstrapping was

used to obtain robust standard error-based confidence intervals.<sup>23</sup>

To assess the effect of specific confounders identified by the Cox regression model, the MSM compared patients within their risk group by stratification, for each potential confounding variable separately. To evaluate the effect of severe HA-CDI on excess LOS, a stratified analysis was conducted, comparing mean differences in LOS of non-severe HA-CDI and severe HA-CDI cases respectively to non-infected patients.

All analyses were performed with R 3.0.1 (Team R Development Core: <http://cran.r-project.org/>). The R-packages *mvna* and *etm* were used to estimate the excess LOS and standard errors, and the R-package 'survival' was used for the Cox model.<sup>21,24</sup>

## Results

### Descriptive statistics

The data comprised a total sample of 42,618 patients; 157 (0.4%) had an episode of HA-CDI, of which 48 (30.6%) were severe (Table I). The median age of the infected patients was 72 years [interquartile range (IQR): 57–82], which was significantly higher than the median age of non-infected patients (47 years; IQR: 26–68;  $P < 0.0001$ ). The vast majority of all patients had no reported comorbidities (91.6%, 39,146 patients). This percentage was slightly lower in the HA-CDI-infected patient group (84.7%, 133 patients) than in the non-infected group (91.9%, 39,013 patients;  $P = 0.002$ ). On average, patients with severe HA-CDI had spent a shorter time in hospital until identification of the infection than non-severe cases (Table I). Moreover, after detection, the median LOS was longer for severely infected patients (Table I). Finally, the causative PCR ribotypes were known for 113 (72.0%) of the HA-CDI patients. None of these patients had an infection caused by hypervirulent PCR ribotype 027.

### Cox regression model results

HA-CDI-positive patients had a lower daily chance of being discharged (alive or dead) than non-infected patients (Table II). Both age of the patient (i.e. >65 or <65 years), and the patient's comorbidity were significant confounders, and the adjusted daily hazard of discharge (hazard ratio: HR) for

HA-CDI patients was 0.72 [95% confidence interval (CI): 0.61–0.84] (Table II). Moreover, HA-CDI patients were at higher risk of experiencing in-hospital death than HA-CDI-negative patients (HR: 1.75; 95% CI: 1.16–2.62). Accounting for severity of the infection revealed that both non-severe and severe cases had a significantly reduced daily likelihood of discharge compared to non-infected cases, with a further reduction for the severe CDI group (Table II, Figure 1). However, severe infection did not result in a further elevated chance of dying in hospital (Table II).

### Multi-state model results

The four-state multi-state model, which allowed for competing end-points, and the three-state combined end-point model yielded similar estimates for the excess LOS. Thus mortality due to HA-CDI did not seem to have an impact on the estimated additional days of hospitalization associated with HA-CDI. For this reason, only the outcomes of the combined end-point model are presented. The average extra number of days (unadjusted for confounders) spent in hospital due to HA-CDI was about seven days (95% CI: 4–11) (Table II). Patients with severe HA-CDI had, on average, twice the additional LOS of non-severe cases, but with overlapping confidence intervals (Table II). Stratification of our sample by age and comorbidity score still showed an impact of HA-CDI on the patients' stay. Among HA-CDI patients aged <65 years (55 in total), there was an average excess LOS of about seven days (95% CI: 1–14) associated with HA-CDI; for patients aged >65 years (133 in total) this was about six days (95% CI: 2–11). A sample restricted to patients with a comorbidity score <1 (133 patients) showed an excess LOS of about seven days (95% CI: 3–11) whereas an average excess LOS of ~10 days (95% CI: –1 to 21) associated with HA-CDI was found for patients with a score of >1 (24 patients).

## Discussion

This study showed that HA-CDI resulted in a prolonged LOS of about seven days. Moreover, the daily mortality rate of HA-CDI patients was almost twice that of non-HA-CDI-infected patients, as has been suggested elsewhere.<sup>26</sup> Severe infection increased the average expected excess LOS associated with HA-CDI. Our LOS estimates are comparable to the median additional six days estimated by a Canadian study, which also adjusted for

**Table I**

Demographic characteristics of the Guy's and St Thomas' hospital patients discharged in 2012

Variable	Non-infected ( <i>N</i> = 42,461)	Infected ( <i>N</i> = 157)	Non-severe HA-CDI ( <i>N</i> = 109)	Severe HA-CDI ( <i>N</i> = 48)	Total ( <i>N</i> = 42,618)
Age >65 years	13,446 (31.7%)	102 (65.0%)	73 (67.0%)	29 (60.4%)	13,548 (31.8%)
CCI score					
0	39,013 (91.9%)	133 (84.7%)	96 (88.1%)	37 (77.1%)	39,146 (91.9%)
≥1	3448 (8.1%)	24 (15.3%)	13 (11.9%)	11 (22.9%)	3472 (8.1%)
Death	801 (1.9%)	24 (15.3%)	15 (13.8%)	9 (18.7%)	825 (1.9%)
Length of stay <sup>a</sup>	4.0/7.6 (2.0–8.0)	25.0/36.6 (15.0–50.0)	29.0/36.6 (15.0–50.0)	22.5/36.8 (14.8–44.8)	4.0/7.7 (2.0–8.0)
Length of stay pre infection <sup>a</sup>	NA	9.0/15.8 (4.0–18.0)	10.0/17.1 (4.0–22.0)	7.0/12.1 (3.8–12.3)	NA
Length of stay post infection <sup>a</sup>	NA	12.0/21.1 (6.0–25.0)	11.0/19.5 (6.0–24.0)	13.5/24.6 (7.8–27.8)	NA

HA-CDI, healthcare-associated *Clostridium difficile* infection; CCI, Charlson Comorbidity Index; NA, not applicable.

<sup>a</sup> Median/mean (interquartile range).

**Table II**

Hazard ratios for in-hospital death or discharge alive and excess length of stay estimated from the Cox regression model and multi-state model

Exposure	Hazard ratio (95% CI) for discharge alive <sup>a</sup>		Hazard ratio (95% CI) for in-hospital death <sup>a</sup>		Hazard ratio (95% CI) for discharge alive or death <sup>a</sup>		Excess LOS (95% CI) <sup>d</sup>
	Time-adjusted <sup>b</sup>	Fully adjusted <sup>c</sup>	Time-adjusted <sup>b</sup>	Fully adjusted <sup>c</sup>	Time-adjusted <sup>b</sup>	Fully adjusted <sup>c</sup>	
All CDI	0.66 (0.56–0.77)	0.72 (0.61–0.84)	1.98 (1.33–2.96)	1.75 (1.16–2.62)	0.73 (0.64–0.84)	0.79 (0.69–0.92)	7.2 (3.5–10.9)
Severe CDI	0.53 (0.39–0.71)	0.59 (0.44–0.79)	2.11 (1.17–3.79)	1.76 (0.95–3.25)	0.62 (0.49–0.76)	0.69 (0.54–0.85)	11.6 (3.6–19.6)
Non-severe CDI	0.73 (0.60–0.88)	0.79 (0.66–0.96)	1.91 (1.13–3.22)	1.74 (1.03–2.93)	0.80 (0.67–0.95)	0.86 (0.71–1.03)	5.3 (1.1–9.5)

CI, confidence interval; LOS, length of hospital stay; CDI, *Clostridium difficile* infection.

To estimate the hazard ratios for discharge alive and in-hospital death respectively, the observations on patients who experienced a competing risk event were censored, i.e. removed from the risk set used for the hazard calculation at time of occurrence of the event, based on the principles of the cause-specific hazard function.<sup>25</sup>

<sup>a</sup> Cox regression model.

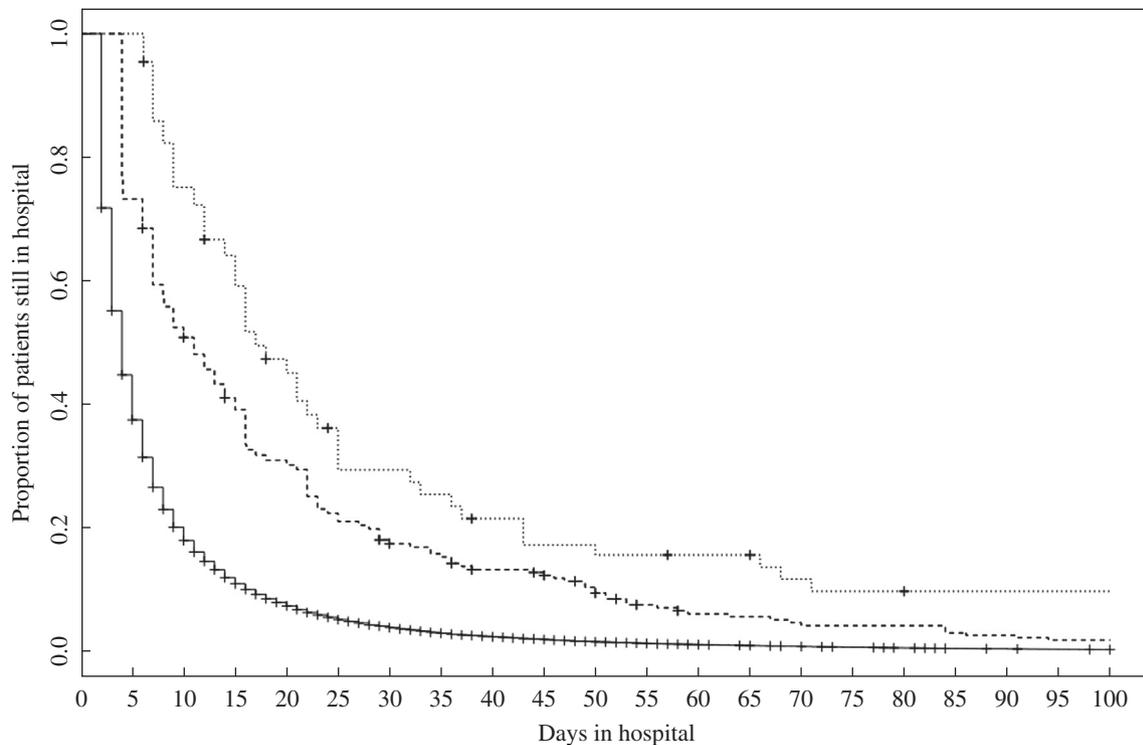
<sup>b</sup> Cox regression model with time to infection included as a time-dependent variable.

<sup>c</sup> Cox regression model with time to infection included as a time-dependent variable, and age (<65 and >65 years) and comorbidity (Charlson Comorbidity Index score <1 and ≥1) included as covariates.

<sup>d</sup> Multi-state model.

the time dependency of the impact of HA-CDI, but contradict the findings of a recent study by Mitchell *et al.* in an Australian hospital using a comparable MSM, suggesting that HA-CDI did not result in excess LOS.<sup>7,12</sup> As the MSM of Mitchell *et al.* did not implicitly adjust for such potential confounders, difference in case-mix among the different hospital settings (UK and Australia) could have been responsible for the differences in measured excess LOS.<sup>27</sup> However, stratified MSM results (by age, and comorbidity index score respectively) revealed that both younger and older HA-CDI patients had an increased average LOS of about six or seven days, and patients of both comorbidity

groups had an increased expected LOS related to CDI, so this is unlikely to supply the explanation. Moreover, the non-severe HA-CDI patients in our sample still had a significantly increased LOS of about five days; thus, even the potential lack of severely infected patients in the Australian sample would have most likely resulted in an effect on LOS. However, with only three published studies using appropriate methods, little can be concluded with regard to the heterogeneity in the findings. More appropriate analyses of existing datasets (e.g. those reviewed by Mitchell *et al.*) might be a sensible way forward.<sup>7</sup>



**Figure 1.** Kaplan–Meier curve for the time-adjusted length of hospital stay for patients without healthcare-associated *Clostridium difficile* infection (HA-CDI) (solid line), non-severe HA-CDI (dashed line), and severe HA-CDI (dotted line). + denote censored observations (i.e. death).

Our dataset was collected as part of routine record keeping in a large teaching hospital, which led to a number of limitations in our study. First, the number of patients with HA-CDI was small, resulting in relatively large standard errors for the risk-group-stratified MSM analysis. A larger dataset would have allowed sufficient power to sub-stratify the analysis further. Second, the comorbidity index was calculated using only the primary diagnosis code of each patient, as more detailed information was not available to the researchers. Therefore, our analysis might not have fully adjusted for the effect of concomitant conditions. Finally, patients who spend a longer time in hospital are at increased risk of acquiring healthcare-associated infections other than HA-CDI, which could have extended their LOS rather than HA-CDI. However, considering the construction of the MSM, this may be explained as follows: HA-CDI-positive patients who were in hospital for a given number of days post onset were compared to admitted HA-CDI-negative patients still in hospital after this number of days. Thus, both these populations were arguably equally at risk of acquiring healthcare-associated infections other than HA-CDI.

In conclusion, the present work confirms the heterogeneity among patients concerning the health and economic burden of CDI. To our knowledge, these results have yielded the first severity-specific estimate of the additional LOS and excess mortality due to CDI. We believe that the techniques presented here could supply policy-makers – locally, nationally, and regionally – with an estimate of the burden of CDI for their patient population and severity of CDI.

#### Conflict of interest statement

None declared.

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