The prolongation of length of stay due to *Clostridium difficile* infection

Abstract

Objective: *Clostridium difficile* infection (CDI) possibly extends hospital length of stay (LOS), however the current evidence does not account for the time-dependent bias - when infection, is incorrectly analysed as a baseline covariate. The aim of this study was to determine whether CDI increases LOS after managing this bias.

Design and setting: We examined the estimated extra LOS due to CDI using a multistate model. Data from all persons hospitalized > 48 hours over four years in a tertiary hospital in Australia were analysed. Persons with healthcare associated CDIs were identified. Cox proportional hazards models were applied together with multistate modeling.

Results: 158 of 58,942 admissions examined had CDI. The mean extra LOS due to infection was 0.9 days (95%CI: –1.8,3.6 days, P=0.51) when a multistate model was applied. The hazard of discharge was lower in persons who had CDI (adjusted hazard ratio 0.42, P<0.001) when a Cox proportional hazard model was applied.

Conclusion: This study is the first to use multistate models to determine the extra LOS due to CDI. Results suggest CDI does not significantly contribute to hospital LOS, contradicting findings published elsewhere. Conversely, when methods prone to result in time-dependent bias were applied to the data, the hazard of discharge significantly increased. These findings contribute to discussion on methods used to evaluate LOS and healthcare associated infections.

Introduction

A fundamental issue in evaluating the costs of CDI and HAIs is the accurate assessment of the prolongation of LOS due to the infection. The use of accurate methods to determine LOS due to CDI and other HAIs, can assist decision makers in formulating informed choices about investing in infection prevention and control prevention activities. The determination of prolonged LOS due to a HAI is challenging as it requires management of bias, more specifically the time-dependent bias. This bias occurs when a time-dependent exposure, such as infection, is incorrectly analysed as a baseline covariate.[1] Methods used to determine LOS should account for the fact that a HAI, such as *C.difficile*, can occur at any point during a hospitalization.[2] If the timing of infections is not taken into account, costs associated pre and post infection are included and can dramatically amplify confounding and lead to time-dependent bias. [3-5] Several studies have demonstrated the effect of time-dependent bias when examining LOS and a HAI.[3-6] Even the inclusion of time to infection as a baseline covariate in Cox proportional hazard model does not adjust for time-dependent bias as the time to infection itself is a time-dependent covariate.[5] Methods used to determine LOS should account for the fact that a HAI, such as *C.difficile*, can occur at any point during a hospitalization.[2]

Statistical models, such as multistate models (MSM), can be used to address this issue at the data analysis stage, rather than at the design stage. A model can be built to describe the relationship between LOS and its predictors. [2] To the best of our knowledge, no published study has used multistate modelling to examine the prolongation of LOS due to CDI.[7] The research presented in this paper, used MSM to investigate any impact of CDI may have on LOS, and compared this to a method that did not manage time-dependent bias.

Methods

Study design and population

The study population was all persons aged two years and above, who were hospitalised for more than 48 hours in the Royal Hobart Hospital (RHH), Tasmania, Australia, between 1st January 2007 and 30th December 2010. From the study population, persons who developed CDI more than 48 hours after their admission, were identified. Therefore, all cases of CDI in this study were healthcare associated, healthcare facility onset (HCA HFO).[8] A hospitalised person with a positive result for *C. difficile* (using either a laboratory assay for detecting toxin A and/or toxin B, or a culture, resulting in the isolation of *C. difficile* that is subsequently shown to produce toxin A and/or toxin B) in the diarrhoeal stool sample was considered to have had CDI. [8, 9] During the four-year study period, the Microbiology Department tested all diarrhoeal samples for *C. difficile* from hospitalised persons, thus minimizing potential for an underestimation of cases of infection.

Data Collection

Data were retrieved from the Clinical Coding department of the RHH, the Tasmanian Infection Prevention and Control Unit (TIPCU), a patient administration system and medical records of each participant. Data were collected on date of birth, sex, age, admission and discharge dates from hospital, diagnosis related group (DRG), and date of death where applicable (in-hospital mortality). The DRG is a patient classification system used internationally, to provide a clinically meaningful way of relating types of diagnosis.

Ethical Considerations

This research was granted ethical approval by the Tasmanian Human Research Ethics Committee (HREC) (H0011484) and by Australian Catholic University (N201150).

Data management and analysis

Univariate analysis was used to compare the clinical characteristics of persons with and without CDI using a chi-square test or Fisher's exact test where numbers were small. A Cox proportional hazard model was used to determine the hazards of discharge, while adjusting for clinical variables significant at the 0.1 level in univariate analysis, using a forward stepwise selection process. In addition, to adjust for time-dependent bias, a MSM was used to determine the prolongation of LOS due to CDI, with infection as an intermediate state.[5] The use of a multistate model manages time-dependent bias and length bias.[1] .The MSM was fitted using *R*, version 2.13.2. (*R* Foundation for Statistical Computing, Vienna). Infection was modelled as a time-dependent covariate in order to avoid the time-dependent bias. Descriptive analysis was performed in IBM SPSS Version 20.0 (International Business Machines Corporation, New York).

Results

Overview

Data from 58,942 admissions were obtained, of which 158 resulted in persons having CDI (Table 1). The incidence of CDI per 1,000 admissions was 2.68 (95% CI: 2.28, 3.13), ranging from 1.71 (95% CI: 1.12, 2.50) in 2007 to 3.89 (95% CI: 2.96, 5.01) in 2010. The median age of persons who had CDI was 67 compared to 55 in persons without CDI, Significantly more

persons in the DRG categories digestive system (P < 0.01), kidney system (P < 0.01) and neoplastic disease (P < 0.01) had CDI were compared to persons without CDI. Conversely, more persons with a DRG category of mental health (P<0.01) and pregnancy (P < 0.01) did not have CDI. For persons who had CDI, the median time for the commencement of infection from admission date was eight days (range 2-104).

Prolongation of LOS using a MSM

A MSM was developed to estimate the prolongation of LOS due to CDI. The mean extra LOS due to infection was calculated to be 0.9 days, P = 0.51, (95% CI: –1.8-3.6 days). Figure 1 displays the estimated LOS and shows that there was little difference between those with and without an infection. The estimated extra LOS for admissions who were ultimately discharged and for those who ultimately died in hospital were 0.9 days and 0 days, respectively.

Prolongation of LOS using a Cox proportional hazard model

A Cox proportional hazard model, which does not control for time-dependent bias, was used to estimate the hazard of discharge (dead or alive), for patients with and without CDI (n=58,942). Six variables (presence of CDI, age and DRG categories mental health, pregnancy, kidney and digestive were included in the final model using a conditional (likelihood ratio) process. The entire LOS for people who had CDI was used. Contrary to the calculated results from the MSM, the influence of CDI in extending LOS in a proportional

hazard model was found to be statistically significant. Acquisition of CDI significantly reduced ($P < 0.001$) the discharge hazard (i.e., it prolonged the LOS) (Figure 2).

Discussion

This study examined whether there was prolongation of LOS in hospital associated with CDI. Acquiring a CDI did not significantly increase the prolongation of LOS, when multistate modelling was applied to the data. This conclusion is contrary to the findings of other studies that did not use the multi-state approach. When the same data were analysed using a Cox proportional hazards model, a model in standard use to analyse HAI that ignored the time-dependent bias, CDI was associated with an increase LOS. These conflicting findings support recent literature suggesting that data analysis methods that do not account for the timing of infection are likely to bias findings. This is the first known study that examines CDI and prolongation of LOS in a hospital by using a multistate model.

Estimating the effect of CDI on LOS

Our study found no significant increase in the LOS due to CDI when a MSM was used. Many studies have examined the prolongation of LOS due to CDI by using approaches other than multistate modelling.[7] Thus, limited comparisons between our study and others are possible. Studies included in two reviews examining CDI and LOS, suggest that the additional LOS in persons who had CDI compared to persons without, ranged from 2.8 days to 16.1 days. [7, 10] However, none of the studies included in these reviews reported on the timing of CDI infection relative to admission period in hospital and or used a MSM. [11-20]. Therefore, these studies may suffer from reverse causality as a longer LOS in hospital may increase the risk of CDI (time-dependent bias).

A Canadian study has attempted to manage CDI as a time-varying covariate in examining its effect on LOS. [21] In doing so, the authors found that CDI was significantly decreased the hazard of discharge (HR 0.55, 95% CI: 0.39, 0.70). [21] Although not stated as a MSM, the authors clearly used a process to control the time-varying nature of the infection. They too demonstrated that failure to account for the time to infection could result in an overestimation of the LOS attributable to CDI. However, contrary to our study, even when accounting for timing of infection, they found that CDI significantly increased LOS in hospital. The findings from both Forster's study [21] and our study suggest that the failure to account for the time-varying nature of infection can lead to bias, as confirmed by others. [6, 22]

We believe in presenting credible data to policy makers that can withstand critical examination. The use of sound data analysis techniques and study design that account for time-dependent bias are required for studies that evaluate the impact of HAIs on LOS in hospital. It is also important to consider that our study only examines the impact that CDI has on LOS and does not consider the human cost.

Implications for future studies examining the LOS

Future studies may wish to examine the impact of multiple infections. These studies would require a model that not only allows a person with an infection to return to a susceptible status again, but also allow for the possibilities of other or concurrent HAIs. Further work is required in this area for MSM to accommodate this. In addition, the adjustment for variables, such as co-morbidity, needs to be considered in the context of MSM. This could potentially managed through a process of matching on specific variables. Until such time, direct

comparisons between regression models and multistate models should be cautiously undertaken as these methods analyse the data differently.

Limitations

The MSM used in our study, and that of others studies using MSM do not account for variables such as co-morbidity, which is a considerable limitation of multistate models at the present time. Therefore, comparisons between regression models, such as Cox proportional hazards and multistate models, need to be undertaken with caution.

Conclusion

To the best of our knowledge, this study is the first to use multistate data analysis techniques to determine the potential prolongation of LOS due to CDI. The findings suggest that CDI does not significantly contribute to a longer hospital LOS. Conversely, when other data analysis methods were used, a significant increase in LOS was found for people infected with *C. difficile*. These findings have implications for future researchers exploring the consequences of HAIs and for senior healthcare managers responsible for policy and practice in this field. Multistate models may manage the issue of time-dependent bias, but there is scope for further refinement in these methods.

Conflict of interest statement

None declared.

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Table 1

Demographic characteristics of the cohort, Royal Hobart Hospital, 2007–2010

Characteristic	Developed CDI (n=158)	Did not develop CDI (n=58,784)	Total (N=58,942)
Sex			
Male	79 (50%)	25 915 (44.1%)	25,994
Female	79 (50%)	32 857 (55.9%)	32,936
Intersex	-	11 (<1%)	11
Not specified	-	1 (<1%)	1
Age (years)			
Median	67	55	55
Range	2–102	2–106	2–106
Age Group (years)			
2–9	3 (1.9%)	1523 (2.6%)	1526 (2.6%)
10–19	6 (3.8%)	3471 (5.9%)	3477 (5.9%)
20–29	3 (1.9%)	7977 (13.6%)	7980 (13.5%)
30–39	5 (3.2%)	6928 (11.8%)	6933 (11.8%)
40–49	13 (8.2%)	5748 (9.8%)	5761 (9.8%)
50–59	24 (15.2%)	6759 (11.5%)	6783 (11.5%)
60–69	31 (19.6%)	8609 (14.6%)	8640 (14.7%)
70–79	38 (24.1%)	9159 (15.6%)	9197 (15.6%)
80–89	30 (19.0%)	7057 (12.0%)	7087 (12.0%)
≥ 90	5 (3.2%)	1553 (2.6%)	1558 (2.6%)

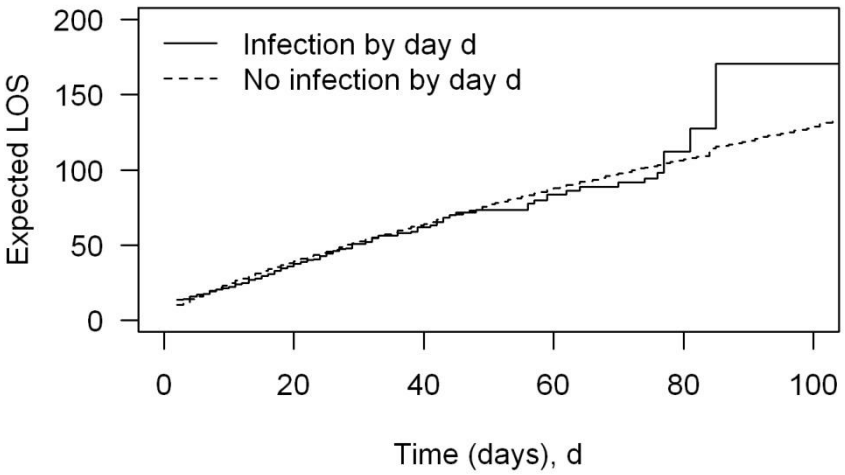

Figure 1. Estimated length of stay by day of *Clostridium difficile* infection in persons admitted to the Royal Hobart Hospital, 2007–2010.

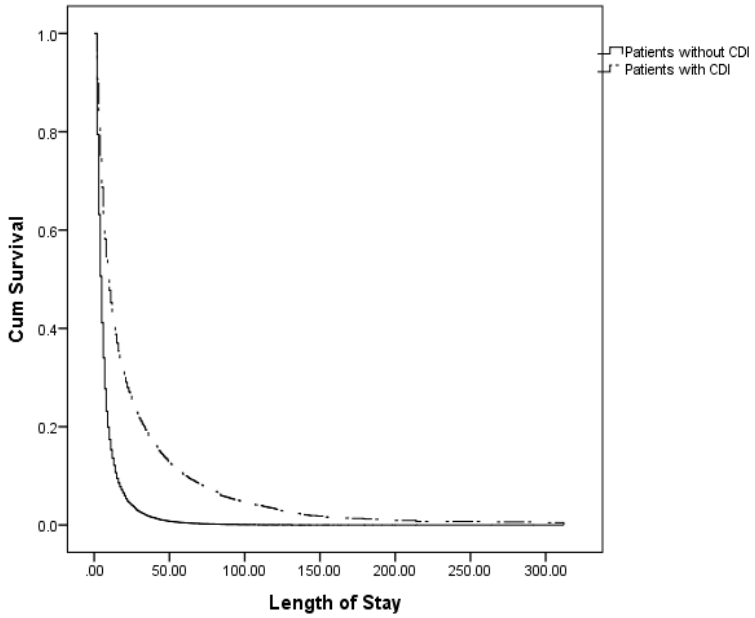

Figure 2. Effect of *Clostridium difficile* infection on the cumulative survival (proportion still in hospital) for admissions to the Royal Hobart Hospital, 2007–2010, as estimated using Cox Proportional Hazard Model.