Journal of Hospital Infection 103 (2019) 85–91

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Short report

Predictors of mortality and length of stay in patients with hospital-acquired *Clostridioides difficile* infection: a population-based study in Alberta, Canada

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ARTICLE INFO

Article history:
Received 23 January 2019
Accepted 8 April 2019
Available online 13 April 2019

Keywords:
Clostridioides difficile
Attributable mortality
Epidemiology
Length of stay

SUMMARY

In a population-based, five-year retrospective cohort study of 5304 adult patients with hospital-acquired *Clostridioides difficile* infection across Alberta (*N*=101 hospitals), 30-day all-cause and attributable mortality were 12.2% and 4.5%, respectively. Patients >75 years of age had the highest odds of attributable mortality (odds ratio (OR) 9.34, 95% confidence interval (CI) 2.92–29.83) and largest difference in mean length of stay (11.7 days, 95% CI 8.2–15.2). A novel finding was that elevated white blood cell count at admission was associated with reduced attributable mortality (OR 0.67, 95% CI 0.50–0.90) which deserves further study. Advancing age was incrementally and significantly associated with all outcomes.

Introduction

Clostridioides difficile infection (CDI) is the most common cause of hospital-acquired diarrhoea and has replaced meticillin-resistant *Staphylococcus aureus* as the most common hospital-acquired infection [1,2]. Recent evidence has shown a modest decrease in the incidence of healthcare-associated CDI, however it remains an important healthcare concern because all-cause and attributable mortality at 30 days may vary from 9 to 38% and from 5.7 to 6.9%, respectively [3,4].

It is critical to define patients with CDI who are at highest risk for attributable mortality to enable optimal treatment and to facilitate efficient allocation of resources to this high-risk patient population. Currently there is no consensus on which factors best predict severity and outcomes of CDI [5]. This

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https://doi.org/10.1016/j.jhin.2019.04.007
0195-6701/

study builds on previous studies by using population-based data from Alberta, Canada to determine predictors of mortality and length of stay (LOS) among patients with hospital-acquired CDI (HA-CDI).

Methods

Study population

This was a multicentre, retrospective, population-based cohort study of all adult patients (≥18 years) admitted to any of Alberta's acute-care facilities (N=101) and diagnosed with HA-CDI between 1st April 2011 and 31st March 2016.

Definitions and data sources

Since 1st April 2011, all hospital facilities were required to participate in the Alberta Health Services/Covenant Health (AHS/CH) Infection Prevention and Control (IPC) provincial surveillance CDI programme. All patient-level incidents of CDI, location of acquisition and related outcome information were manually recorded in a centralized, online provincial database. All cases were reviewed by the IPC Surveillance and Standards team to ensure compliance with clinical surveillance definitions.

C. difficile infection was defined as either a laboratory confirmation of *C. difficile* toxin in the stool plus diarrhoea; or a laboratory confirmation with fever and abdominal pain and/or ileus if no diarrhoea was present; or a diagnosis of pseudomembranes seen during endoscopy. Incident cases of CDI were defined as 56 days or more without CDI and identified during hospitalization. Only the first incident case of CDI was included in this study.

HA-CDI was defined as an incident of CDI identified >3 days after admission to a hospital facility or CDI ≤3 days from admission and the patient had a previous admission in the last 4 weeks and the patient was not a long-term care resident or dialysis patient.

HA-CDI-attributable mortality was defined as death in hospital within 30 days of a CDI diagnosis where CDI was the cause of death with no other condition that would have caused death, or CDI exacerbated an existing disease condition that led to the patient's death (all confirmed using pre-determined criteria and reviewed by an IPC physician or Medical Officer of Health, ensuring uniformity of attribution). Thirty-day all-cause mortality was defined as death due to any cause within 30 days of a CDI diagnosis. Total LOS was the time from CDI diagnosis date to discharge date, including the LOS of any subsequent direct transfers.

All data on potential predictors of mortality and LOS were collected from administrative and laboratory databases. Patient demographics, admission status, comorbidities, previous hospitalizations, intensive care unit admissions, and surgeries were extracted from the Discharge Abstract Database (DAD). Patient comorbidity was defined using the Elixhauser comorbidity list within the two-year period prior to the first incident HA-CDI case using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada* (ICD-10-CA) discharge codes within the DAD [6]. Previous hospitalizations were hospitalizations with a discharge date within one year of the HA-CDI diagnosis date. Previous intensive care unit visits and surgeries occurred prior to the HA-CDI diagnosis date, either in the hospitalization where the CDI was identified or in a previous hospitalization where the CDI was acquired.

Laboratory measures used as biomarkers of CDI adverse outcomes (including serum albumin, serum creatinine, glucose, platelets, sodium, troponin, blood urea nitrogen, white blood cell (WBC) count, and arterial blood pH) were extracted from the Alberta provincial general laboratory repository [7,8]. This dataset included results from all hospital and emergency-room laboratories across Alberta. For each measure, the first laboratory result taken in the first ±24 h of the admission where the HA-CDI was acquired was included. Patients who did not have a particular measure on admission were treated as not clinically indicated and coded as normal. The normal ranges of each measure were defined according to local laboratory reference ranges.

Consistent with prior guidelines and studies, severe CDI was defined as leukocytosis with a WBC count >15,000 cells/μL or an elevated serum creatinine (i.e. 200 μmol/L or greater) within ±3 days of the CDI diagnosis date [9–11].

Microbiology

During the study period, Calgary Laboratory Services (which services Calgary and all surrounding areas) performed *C. difficile* testing using a two-step algorithm. All samples were screened by a chemiluminescent immunoassay to detect the glutamate dehydrogenase (GDH) specific for *C. difficile*. If it was negative, *C. difficile* was ruled out. If the GDH was positive, Cepheid GeneXpert® Dx System, a real-time polymerase chain reaction (PCR) test for rapid detection of toxin B gene sequences, was used to confirm the presence of a toxigenic *C. difficile* strain. Up until 2013, all other laboratories across Alberta used a single enzyme-linked immunosorbent assay test for *C. difficile* toxins, which would be re-run if results were indeterminate. As of April 2013, all other laboratories across the province standardized to a rapid enzyme immunoassay (TechLab® C. diff Quik Check Complete™) for the simultaneous detection of *C. difficile* GDH antigen and toxins A and B in fecal specimens. If the result was indeterminate it was sent for confirmatory PCR testing.

Statistical analysis

Frequencies and percentages for categorical variables were used. HA-CDI incidence was calculated as number of incident cases per 10,000 hospital patient-days. All-cause mortality and attributable mortality was calculated as the number of deaths per 100 HA-CDI cases. Test of proportions was used to compare mortality rates. Predictors of mortality and LOS with P-values <0.20 from univariate analyses served as independent predictor variables in a subsequent multivariate model.

Multivariate models were reduced by backward elimination starting with predictors with P-values >0.05. The final model represented the most parsimonious model with the strongest predictors. Model results were presented as odds ratios (ORs) for the mortality outcomes and as difference in means for the LOS outcome with 95% confidence intervals (95% CIs). Statistical significance was observed at an alpha level of 0.05. Statistical analyses were conducted using STATA/IC Version 14.0 (StataCorp, College Station, TX, USA).

Ethics

This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary and the Alberta Health Services' Research, Innovation and Analytics department.

Results

Incidence

The overall incidence of HA-CDI for the study period was 3.9/10,000 hospital patient-days. The overall incidence had a relative decline of 31.2%, from 4.3/10,000 patient-days in the fiscal year 2011 to 3.3/10,000 patient-days in fiscal year 2015 ($P<0.0001$).

Predictors of attributable mortality

Of the 5304 incident cases of HA-CDI, 650 patients died, with 238 (36.6%) attributed to CDI. Overall attributable mortality in patients with HA-CDI was 4.5%. There was no significant decline in attributable mortality between 2011 (4.5%) and 2015 (3.6 %) ($P=0.2996$).

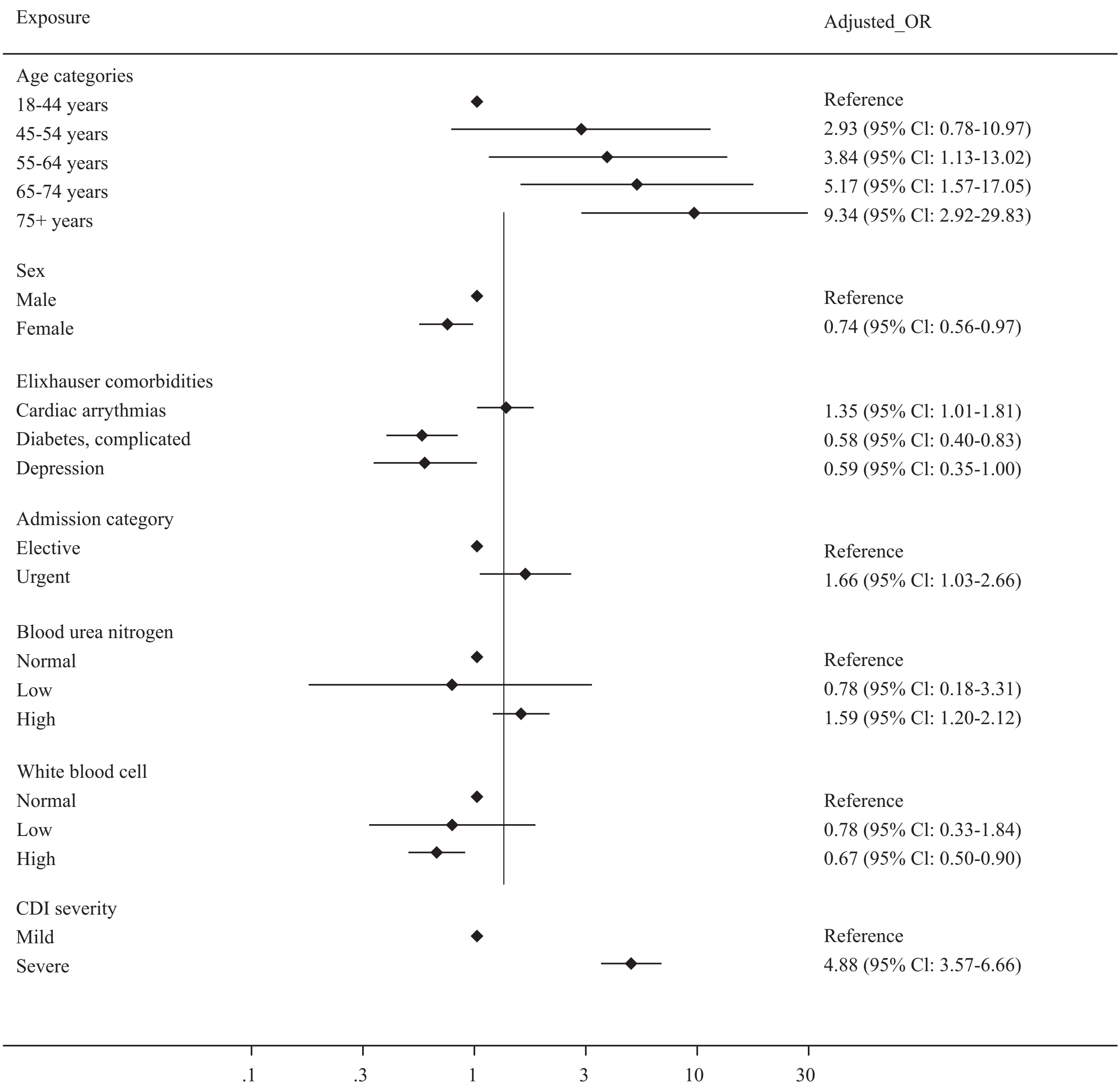

Figure 1. Visual representation of multivariate analysis of attributable mortality among patients with hospital-acquired *Clostridioides difficile* infection (CDI). Significant predictors of attributable mortality that were retained in a multivariate logistic regression model and produced the best model fit. CI, confidence interval; OR, odds ratio.

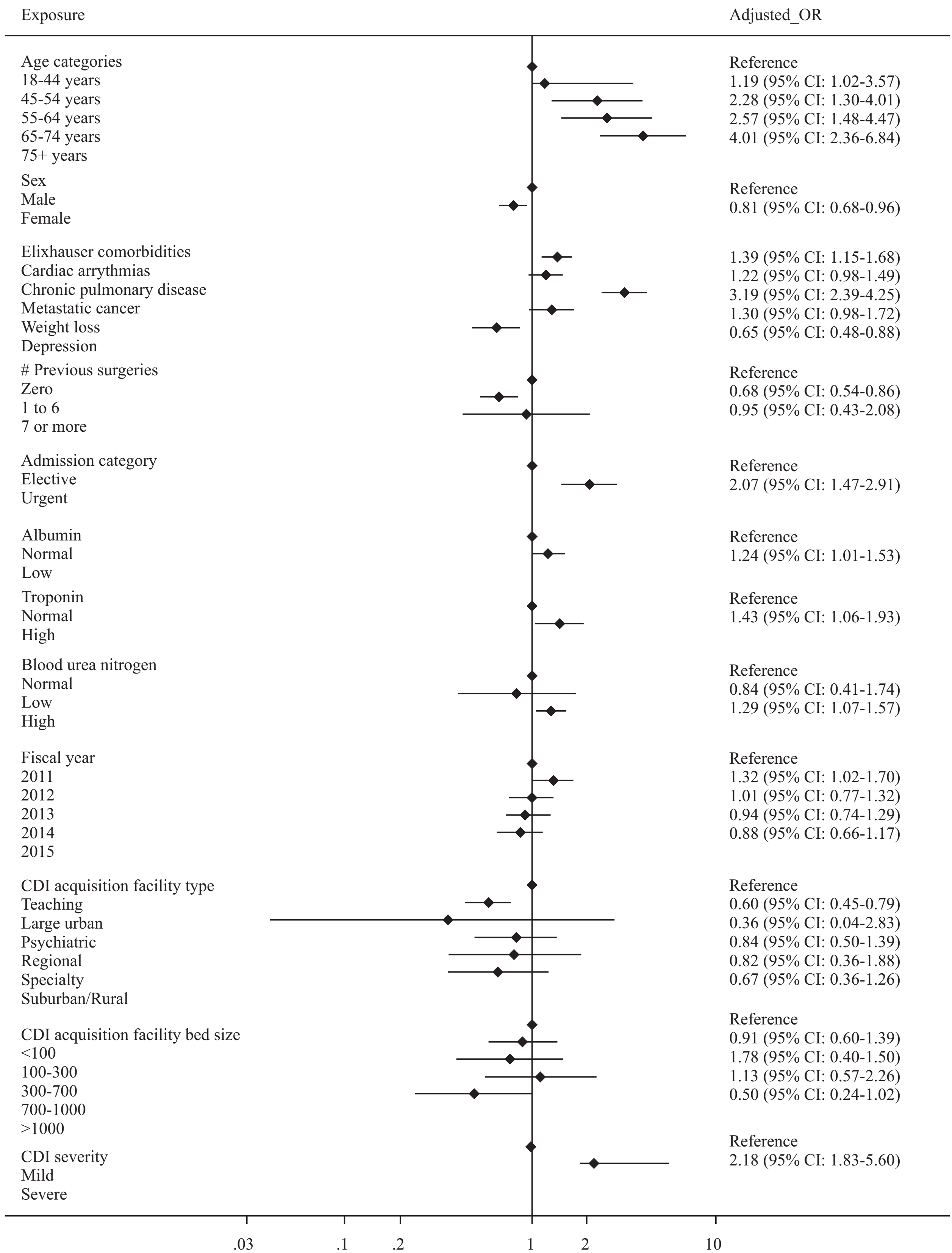

Figure 2. Visual representation of multivariate analysis of 30-day all-cause mortality among patients with hospital-acquired *Clostridioides difficile* infection (CDI). Significant predictors of 30-day all-cause mortality that were retained in a multivariate logistic regression model and produced the best model fit. CI, confidence interval; OR, odds ratio.

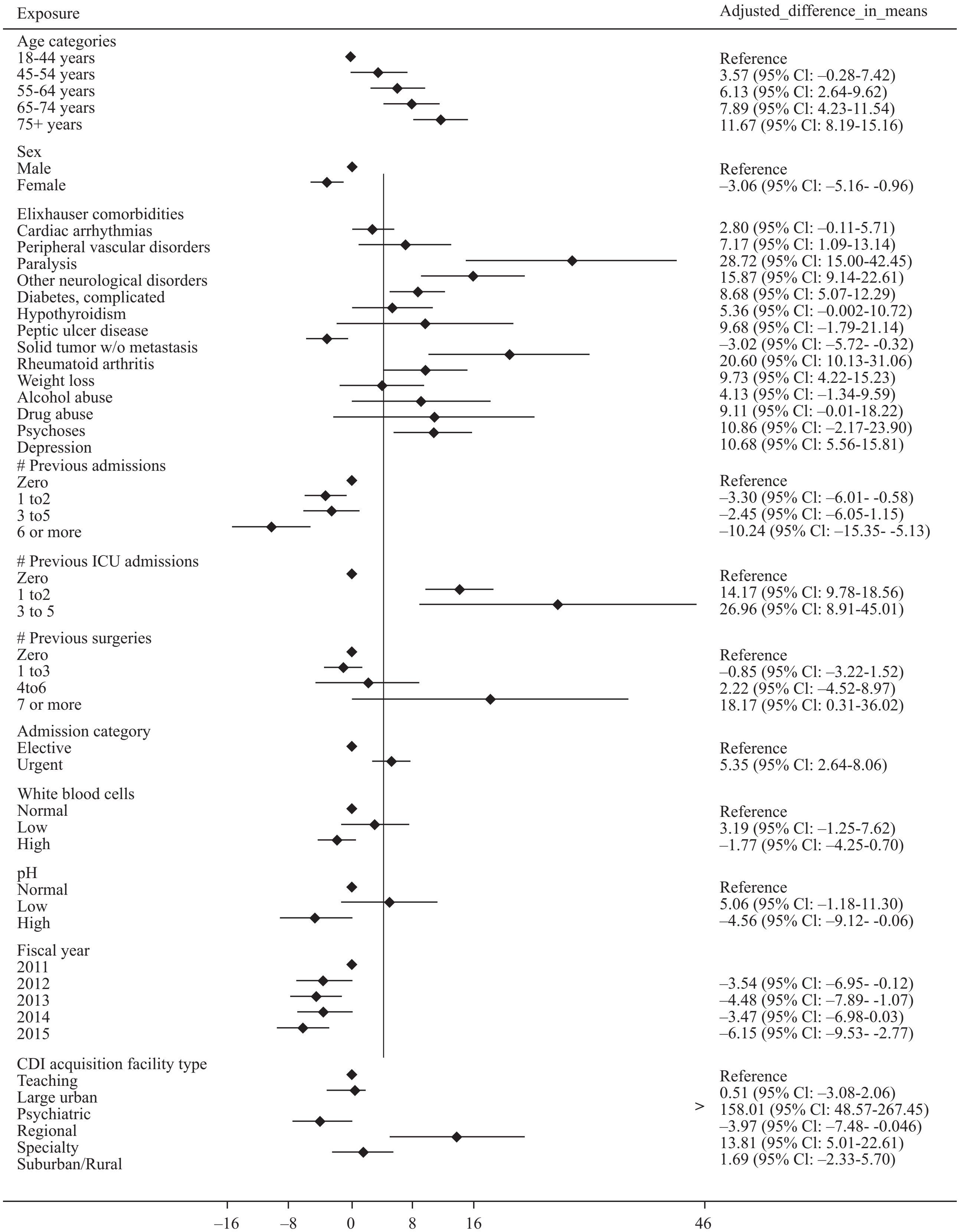

Figure 3. Visual representation of multivariate analysis of length of stay among patients with hospital-acquired *Clostridioides difficile* infection (CDI). The final multivariate model that fit the data well using a generalized linear model with gamma distribution and identity link. CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

Increasing age was associated with a step-wise increase in the odds of attributable mortality (Figure 1). Patients 75 years and older had the highest odds of attributable mortality (OR 9.34, 95% CI 2.92—29.83) compared with the 18- to 44-year-old age group. High WBC count ($>11\times10^9$) at admission (OR 0.67, 95% CI 0.50—0.90) had a protective effect in the multivariate model.

Predictors of 30-day all-cause mortality and length of stay

Overall 30-day all-cause mortality in patients with HA-CDI was 12.2%. This remained stable between 2011 (12.1%) and 2015 (10.5%) (P=0.2350). There was a step-wise increase in the odds of 30-day all-cause mortality with increasing age with patients 75 years and older having the highest odds (OR 4.10, 95% CI 2.36—6.84) compared with the 18- to 44-year-old age group (Figure 2). The overall mean LOS was 36.5 days (standard deviation ±59.8). Increasing age was also significantly associated with a step-wise increase in LOS among patients with HA-CDI (Figure 3).

Discussion

To our knowledge this is the largest population-based cohort study evaluating patient characteristics, clinical parameters on admission and healthcare system level exposures as predictors of attributable and all-cause mortality among a population of patients with HA-CDI. We found that increasing age was consistently associated with all outcomes even after adjustment. Surprisingly, an increased WBC count measured on admission and before CDI diagnosis reduced the odds of attributable mortality.

The overall attributable mortality among HA-CDI patients in Alberta (4.5%) was similar to the Canadian national average of 4.4% [3]. We did not identify a statistically significant decrease in mortality, which may be related to the highly virulent and epidemic strain of *C. difficile* (BI/NAP1/027) that remains the most prevalent strain in Alberta and other western regions of Canada despite the decline and shift in strains observed elsewhere in Canada [3].

This study demonstrated a strong relationship between increasing age and mortality outcomes. Patients older than 75 years had the highest odds of mortality compared with patients between 18 and 44 years of age, even after adjustment for a wide range of comorbidities. The association between older age and increased mortality, even after adjustment, may suggest that the frail nature of these patients and potentially weakened immune system could be responsible for the increase in mortality as opposed to comorbid conditions [12].

Severe CDI measured by increased WBC count or serum creatinine at or near the time of CDI diagnosis was a significant predictor of attributable and all-cause mortality. Previous studies found that age, increased WBC count and serum creatinine, and decreased serum albumin measured at or near the time of diagnosis had the most evidence to support their use as markers of risk for mortality in CDI [8].

In contrast, increased WBC count, measured on admission in our study before the diagnosis of CDI, appeared protective against attributable mortality. This finding may suggest that the ability to mount an innate immune response prior to onset of CDI may be beneficial but additional studies would be required to examine this. Because increased WBC count was measured at admission and was not consistent with the results of studies using this measure around CDI diagnosis in multivariate analysis, the timing of its measurement may influence its usefulness as a predictor of mortality among CDI patients [13].

The average LOS decreased in 2015 compared with 2011 by 6.15 days, possibly due to improved and timely diagnosis of CDI enabling prompt treatment and isolation as well as the overall pressures to reduce patients' LOS to increase efficiencies in the healthcare system.

This study should be interpreted in light of its limitations. Firstly, approximately 6% of cases were missing laboratory measures to define severe CDI and thus recoded as having mild disease, which may have underestimated the impact of severe CDI on the outcomes. Secondly, laboratory methods for detecting *C. difficile* toxin varied in the province across the study timeframe. Although the introduction of molecular tests with increased sensitivity may increase the incidence of CDI, we did not observe an increase in the incidence rate given that included cases of CDI required confirmation of symptoms and that the molecular tests are reserved for confirmatory testing only. Lastly, the determination of death attributable to CDI was subjective, but cases were reviewed by an infection control physician using uniform criteria, so ascertainment bias should be low.

This study has a number of advantages over previously published articles evaluating predictors of death and LOS among CDI patients, including that it was population-based, with over five years of information from a number of validated provincial data sources. Elixhauser comorbidity, which includes more comorbid conditions and is a better predictor of in-hospital mortality, was used rather than the commonly reported Charlson comorbidity index [14]. Finally, a number of laboratory values at admission and at the time of diagnosis were evaluated in the models, which were not reflected in many other studies, leading to a novel observation related to WBC counts.

Conclusion

This study found that advancing age was associated with all outcomes even after adjusting for a number of factors. Given the novel finding that WBC count on admission reduces the odds of attributable mortality, further studies are needed to verify this association in the HA-CDI population.

Acknowledgements

The authors would like to acknowledge and thank the following individuals and departments that supported this work: Deanne Thibeault, Analytics (DIMR), Alberta Health Services; Troy Lohnes and Jodi Kluchky, Pharmacy Informatics & Technology Integration; Terry Ross, Laboratory Process Excellence; Infection Prevention and Control; and Rob Weaver and James Wick, University of Calgary for statistical advice.

Conflict of interest statement

J. Conly reports receiving relevant financial activities outside the submitted work including a consulting fee from

Pfizer Prevnar 13 in 2016; a grant from Pfizer for the STRIVE study (*Staphylococcus aureus* vaccine randomized control trial in vertebral spinal surgery with instrumentation); a peer reviewed research grant on the development of a rapid assay for detection of MRSA from the Canadian Institutes for Health Research (CIHR); a grant from CIHR for a stewardship application to improve antibiotic prescribing; a grant for a peer reviewed initiative on the use of probiotics as primary prophylaxis for *C. difficile* colitis from Alberta Innovates Health Solutions and travel expenses to a ThinkTank meeting at the Centers for Disease Prevention and Control. All other authors have no conflicts of interest to declare.

Funding sources

This work was supported by the Vanier Canada Graduate Scholarship; Alberta Innovates-Health Solutions Graduate Studentship; and the University of Calgary's Eyes High Doctoral Recruitment award.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.04.007.

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