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Title

Escherichia coli bloodstream infections in the western interior of British Columbia, Canada: a population-based cohort study

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**Summary**

Our population-based study objectives were to describe characteristics and outcomes of *Escherichia coli* bloodstream infections (BSIs), and to evaluate factors associated with outcomes. We included incident *E. coli* BSIs from western interior residents (British Columbia, Canada; 04/2010–03/2020). We obtained data including patient demographics, location of onset, infection focus, Charlson comorbidity index (CCI), antimicrobial resistance, 30-day all-cause mortality, and length of hospital stay (LOS). Using multivariable logistic regression models fitted with generalized estimating equations, we estimated factors associated with 30-day mortality and long post-infection LOS (>75th percentile). We identified 1,080 incident *E. coli* BSIs in 1,009 patients. The crude incidence and 30-day mortality rates were 59.1 BSIs and 6.8 deaths/100,000 person-years, respectively. The 30-day case fatality risk was 11.5%. Compared to community-acquired *E. coli* BSIs, either healthcare-associated or nosocomial cases had higher odds of 30-day mortality. Older cases, non-urogenital BSI foci and CCI≥3 had higher odds of 30-day mortality compared to younger cases, urogenital foci and CCI<3. In patients that survived to discharge, those with ESBL-producing *E. coli* BSIs, nosocomial BSIs, and CCI≥3 had higher odds of long post-infection LOS compared to those with non-ESBL-producing, community-acquired and healthcare-associated, and CCI<3. There is a substantial disease burden from *E. coli* BSIs.
**Introduction**

*Escherichia coli* causes a significant burden of disease in humans since it is the most common cause of bacterial bloodstream infections (BSIs) [1-3]. The importance of using population-based study designs for BSI research has been established [4-6]. By including all incident BSIs in a defined and isolated geographical area, selection biases are minimized and the area population can be used as the population-at-risk [5]. This allows BSI epidemiology to be studied at a population-level and gain insight into the burden of disease. Population-based studies are essential when researching *E. coli* BSIs because the vast majority of cases are community-onset [7-12], and not all require hospitalization [7]. Therefore, a solely hospital-based data collection approach for *E. coli* BSI research does not achieve complete case ascertainment and defining the population-at-risk will not be possible.

Mortality and length of hospital stay (LOS) are important measures of burden of disease from the patient and healthcare system perspectives [13]. Two previous population-based *E. coli* BSI studies used logistic regression analyses to explore factors associated with all-cause mortality while adjusting for confounding (in-hospital mortality [7] and 30-day mortality [12]). Median total LOS has been reported by two previous population-based studies [7, 8]. Both used non-parametric tests to assess whether median LOS differed between location of onset types [7, 8]. We are not aware of a previously published population-based *E. coli* BSI study using multivariable regression analysis to explore post-infection LOS. Multivariable regression analyses facilitate more accurate estimation of the measures of associations by controlling for confounding variables and exploration of interaction effects. Detailed analyses of *E. coli* BSI characteristics and outcomes in the western interior area of British Columbia (BC), Canada have not been previously reported.
Using population-based data from a geographically isolated Canadian area, we aimed to: 1) describe characteristics, antimicrobial resistance (AMR), and outcomes of *E. coli* BSIs; and 2) evaluate factors associated with 30-day mortality and long post-infection LOS.

**Methods**

**Study protocol**

Our population-based cohort study included all incident *E. coli* BSIs in western interior area residents (BC, Canada; 2018 population 191000) [14] from 1 April 2010 to 31 March 2020, which were the first ten years of data from the surveillance database. A subsequent *E. coli* BSI in the same patient was only included as a separate incident case if it was diagnosed at least one month from the preceding BSI that had clinically resolved after treatment [8, 11, 15-17]. Details regarding the area’s healthcare infrastructure, population, surveillance database, and microbiological methodology have been previously published [18, 19]. The Interior Health and University of Guelph Research Ethics Boards approved this study and granted waivers of individual informed consent (2013-14-052-I and 2018-10-050, respectively).

**Laboratory procedures**

A single draw was used to collect blood into a pair of aerobic and anaerobic bottles (blood culture set). During the study, it was standard protocol to draw two blood culture sets from different sites on each patient. The BacT/Alert 3D system was used for blood culturing (bioMérieux, France). Standard methodology and established protocols were used for bacterial isolation and speciation. Antimicrobial susceptibility testing (AST) was performed using microbroth dilution (Vitek 2XL, bioMérieux, France), ETEST®, or Kirby Bauer disk diffusion depending on the antimicrobial. Antimicrobials assessed for susceptibility in BSI *E. coli* isolates
included, but were not limited to: ampicillin, cefazolin, ceftriaxone, ciprofloxacin, gentamicin, and trimethoprim sulfamethoxazole (TMS). The results of AST were interpreted as susceptible, intermediate and resistant using Clinical Laboratory Standards Institute (CLSI) clinical breakpoints at the time of AST [20]. *Escherichia coli* isolates were screened and confirmed for extended-spectrum β-lactamase (ESBL)-production using ESBL detection disc sets (MASTDISC® Combi, Mast Group Ltd, United Kingdom).

**Data and definitions**

*Escherichia coli* BSIs were identified by the regional microbiology laboratory and an experienced infectious disease specialist (KBL) confirmed incident cases. KBL reviewed electronic medical records from the regional clinical information system to obtain and determine case data including: bacterial species isolated from blood culture, blood culture date, patient’s age and sex, hospital admission date, location of onset, infection focus, Charlson comorbidity index (CCI), antimicrobial susceptibility data, LOS, and 30-day all-cause mortality. The electronic medical record is directly linked to the regional enterprise master patient index and provincial vital statistics database, which provided the date of death for deceased patients. The BSI location of onset was characterized as nosocomial if the first positive blood culture was obtained at least 48 hours after hospital admission or within 48 hours of hospital discharge; otherwise, it was characterized as community-onset [21]. Using the definitions proposed by Friedman *et al.* 2002, community-onset BSIs were categorized into healthcare-associated or community-acquired [21]. Detailed medical record review by KBL facilitated determination of the infection foci category: no focus (primary), soft tissue, pneumonia, cardiovascular, intra-abdominal and biliary, and urogenital. The CCI was constructed from medical record data using established methodology [22]. Intermediate susceptibility was considered resistant for analyses.
Bloodstream infections were classified as multidrug resistant (MDR) if resistant to three or more antimicrobial categories [23]. Polymicrobial infections were *E. coli* BSIs that had at least one more bacterial species isolated within two days of the *E. coli* culture [2, 24]. Thirty-day all-cause mortality was defined as death from any cause within 30-days after the *E. coli* blood culture. In-hospital all-cause mortality was defined as death from any cause during hospitalization. Thirty-day in-hospital all-cause mortality was death from any cause during the first 30-days of hospitalization after the *E. coli* blood culture. Total LOS was the difference in days between hospital admission and discharge. Pre-infection LOS was the difference in days between hospital admission and the day the blood culture was drawn. Post-infection LOS was the difference between the day the blood culture was drawn and hospital discharge.

**Statistical analysis**

We performed data analyses in Stata 16.1 [25]. To summarize categorical variables, we calculated proportions (sex, location of onset, focus of infection (urogenital and non-urogenital), AMR data) and determined median and interquartile range (IQR) to summarize continuous variables (age, CCI, pre-infection LOS). We calculated incidence and mortality rates by dividing the number of incident *E. coli* BSIs or 30-day deaths by the surveillance population during the study period [14, 26]. We calculated 30-day case fatality risk by dividing the number of 30-day deaths by the number of incident *E. coli* BSIs [26]. To summarize LOS measures, median and IQR were calculated.

To identify factors significantly associated with 30-day all-cause mortality in *E. coli* BSIs, we used a logistic regression model [25, 26], which was also used to estimate factors significantly associated with long post-infection LOS (defined as post-infection LOS greater than the 75th percentile) [15]. The latter model was restricted to the subset of *E. coli* BSI patients that were
hospitalized and survived to hospital discharge. The models were fitted with generalized estimating equations using exchangeable correlation structures to account for the lack of independence from some patients having more than one incident BSI during the study [25, 26]. For inclusion in each logistic regression model, we considered the following 12 explanatory variables: age (years); sex (female, male); polymicrobial (monomicrobial, polymicrobial); ESBL (non-ESBL, ESBL); ciprofloxacin resistance (susceptible, resistant); MDR (non-MDR, MDR); infection focus (urogenital, non-urogenital); location of onset (community-acquired, healthcare-associated, nosocomial); pre-infection LOS (days); CCI; season (spring (March-May), summer (June-August), fall (September-November), winter (December-February)); and study year (1 through 10, e.g., study year 1 – 1 April 2010 to 31 March 2011). Escherichia coli BSI patients that did not require hospitalization were assigned a pre-infection LOS of zero days to facilitate regression modeling. First, we assessed the linearity assumption for continuous variables (age, pre-infection LOS, and CCI) by examining a locally weighted regression (lowess) of the log odds of the outcome and continuous variable. If it was not appropriate to model them as a continuous variable, then they were modeled as a categorical variable. Next, we completed univariable analysis, and to avoid collinearity in subsequent multivariable model fitting we checked for high correlation between explanatory variables using a Phi coefficient or Spearman’s rank correlation coefficient, as appropriate ($\rho \geq |0.8|$ was the cut-off value). Multivariable logistic regression models were built using a backwards stepwise model building process starting with all of the explanatory variables that met the liberal p-value threshold of $p < 0.2$ in univariable analysis, and were not highly correlated [26]. If the explanatory variables, MDR and either ESBL or ciprofloxacin resistance, met the criteria to be considered in the multivariable model, separate multivariable models were built for inclusion of MDR, and ESBL and ciprofloxacin resistance.
resistance since the latter variables could be a component of MDR. We considered the following two-way interaction effects for inclusion in the multivariable regression models: age and sex, ESBL and ciprofloxacin resistance, age and explanatory variables in the final main effects multivariable model, and sex and explanatory variables in the final main effects multivariable model. Variables remained in the final multivariable model if statistically significant (α=0.05), part of a significant interaction term, and/or a confounding variable (based on >20% change in another variable’s coefficient and meeting causal criteria) [26]. Odds ratios (OR) were reported with 95% confidence intervals (CI).

**Missing data**

Data were complete for the main descriptive and regression modelling analyses. Incident *E. coli* BSIs were removed from specific analyses if data were incomplete. The only missing data were for susceptibility to gentamicin, ampicillin and TMS where data for four, two, and 43 incident *E. coli* BSIs were missing, respectively.

**Results**

**Incidence and characteristics**

From 1 April 2010 to 31 March 2020, we identified 1080 incident *E. coli* BSIs from 1009 patients. Three patients had four incident *E. coli* BSIs, six patients had three, 50 patients had two, and the remaining 950 patients had a single *E. coli* BSI. Our population-based study had 1.8 million person-years of follow-up. The overall crude incidence rate was 59.1 *E. coli* BSIs/100,000 person-years. The age distribution of incident *E. coli* BSIs was left skewed with a median of 70.8 years (IQR 58.6-81.3) and 57.8% of BSIs were in females (624/1080) [Figure S1, Table 1].
Polymicrobial infections occurred in 7.8% of incident *E. coli* BSIs (84/1080) with one *E. coli* BSI case involving a total of four bacterial species, 12 having three bacterial species, and 71 having two bacterial species [Table 1, Table S1]. The five most common bacterial species that were present in polymicrobial infections with *E. coli* were: *Klebsiella* spp. (28 BSIs), *Enterococcus* spp. (16), *Pseudomonas* spp. (12), *Staphylococcus* spp. (7), and *Streptococcus* spp. (7) [Table S1]. Almost half of incident *E. coli* BSIs were pansusceptible (48.4%, 523/1080). The proportion of *E. coli* BSIs that were resistant to ciprofloxacin, ceftriaxone, gentamicin, cefazolin, ampicillin, and TMS was 24.7% (267/1080), 10.6% (114/1080), 8.6% (92/1076), 18.6% (201/1080), 44.3% (478/1078), and 22.8% (236/1037), respectively. No meropenem resistance was reported and 8.4% of *E. coli* BSIs were ESBL-producing (91/1080) [Table 1]. Overall, there were a small number of *E. coli* BSIs that were intermediate, and therefore considered resistant to ciprofloxacin (3 isolates), gentamicin (1), cefazolin (3), and ampicillin (10), and there were no intermediate isolates for ceftriaxone or TMS. Multidrug resistance was present in 22.3% of *E. coli* BSIs (241/1080) [Table 1], with resistance in three (39.0%, 94/241) to seven (5.4%, 13/241) antimicrobial categories in these infections. *Escherichia coli* BSIs were 90.1% (973/1080) community-onset with healthcare-associated (48.8%, 527/1080) occurring more frequently than community-acquired (41.3%, 446/1080) [Table 1]. The underlying *E. coli* BSI foci from most to least common were urogenital (65.4%, 706/1080), intra-abdominal or biliary (23.5%, 254/1080), no focus (7.0%, 76/1080), respiratory (2.5%, 27/1080), soft tissue (0.9%, 10/1080), and orthopedic (0.6%, 7/1080).

The distribution of CCI for incident *E. coli* BSIs was right skewed with a median of 2 (IQR 0-3) [Table 1]. The CCI ranged from zero (35.1%, 379/1080) to 11 (0.2%, 2/1080). The three most
common comorbidities were diabetes mellitus (23.5%, 254/1080), cancer (20.8%, 225/1080), and chronic pulmonary disease (15.1%, 163/1080) [Table 1].

Mortality

The 30-day all-cause case fatality risk was 11.5% (124/1080) and the crude 30-day mortality rate was 6.8 deaths/100,000 person-years. The descriptive statistics for characteristics of E. coli BSI cases that did and did not survive to 30 days after blood culture are in Table 1. Most cases with E. coli BSIs required hospitalization (85.7%, 926/1080) and the in-hospital case fatality risk was 10.7% (99/926). The 30-day in-hospital case fatality risk was 9.9% (92/926). The continuous variables age, pre-infection LOS, and CCI did not meet the linearity assumption and they were categorized as follows: age category (<65-years-old, ≥65-years-old); pre-infection LOS category (not hospitalized, pre-infection LOS <2 days, pre-infection LOS ≥ 2 days); and CCI category (CCI<3, CCI≥3). We identified high correlation (ρ≥|0.8|) between the variables for location of onset and pre-infection LOS category and we decided to proceed with the location of onset variable for multivariable modelling since this variable provided data on community-acquired and healthcare-associated E. coli BSIs. Age category, sex, polymicrobial, location of onset, infection focus, and CCI category were all considered for inclusion in our multivariable logistic regression model for 30-day mortality in E. coli BSIs [Table S2]. When individual comorbidities were evaluated for their association with 30-day mortality using univariable logistic regression models, E. coli BSI cases with cancer, chronic pulmonary disease, congestive heart failure, myocardial infarction, dementia, mild liver disease, or cerebrovascular disease had significantly higher odds of dying within 30 days compared to those without the specific comorbidity [Table S2]. Our final multivariable logistic regression model for 30-day mortality included age category, location of onset, infection focus and CCI category [Table 2]. None of the
interactions tested were statistically significant. Older E. coli BSI cases had significantly higher odds of 30-day mortality compared to younger cases [Table 2]. Compared to community-acquired E. coli BSIs, cases with either healthcare-associated or nosocomial had significantly higher odds of 30-day mortality, and the odds were significantly higher for nosocomial E. coli BSIs compared to healthcare-associated (p=0.004) [Table 2]. Cases with a BSI focus that was anything other than urogenital had higher odds of dying within 30 days compared to those with a urogenital focus [Table 2]. Cases with a CCI≥3 had higher odds of 30-day mortality compared to those with a CCI<3 [Table 2].

**Length of hospital stay**

The distributions for all LOS measures were right skewed. For cases with incident E. coli BSIs that required hospitalization and survived to discharge (n=827), the median LOS prior to infection was 0 days (IQR 0-0), the median total LOS was 7 days (IQR 4-12), and the median post-infection LOS was 6 days (IQR 4-11). For cases that died in hospital (n=99), the median LOS prior to infection was 0 days (IQR 0-7), the median total LOS was 7 days (IQR 2-20), and the median post-infection LOS prior to in-hospital death was 3 days (IQR 1-11). The median post-infection LOS in E. coli BSIs that survived to discharge stratified by demographics and characteristics are presented in Table S3. The continuous variables age, pre-infection LOS, and CCI did not meet the linearity assumption and they were categorized as follows: age category (<65-years-old, ≥65-years-old); pre-infection LOS category (pre-infection LOS <2 days, pre-infection LOS ≥ 2 days); and CCI category (CCI<3, CCI≥3). We identified high correlation ($\rho\geq|0.8|$) between the variables for location of onset and pre-infection LOS category and we decided to proceed with the location of onset variable for multivariable modelling since this variable provided data on community-acquired and healthcare-associated E. coli BSIs. Age
category, polymicrobial, ESBL, ciprofloxacin resistance, MDR, location of onset, infection focus and CCI category were all considered for inclusion in our multivariable logistic regression model for long post-infection LOS in patients that survived to discharge [Table S4]. When individual comorbidities were evaluated for their association with long post-infection LOS in patients that survived to discharge using univariable logistic regression models, *E. coli* BSI cases with diabetes mellitus, chronic pulmonary disease, congestive heart failure, renal disease, dementia, cerebrovascular disease, or diabetes mellitus with end organ damage had significantly higher odds of long post-infection LOS compared to those without the specific comorbidity [Table S4]. Our final multivariable logistic regression model for long post-infection LOS in patients that survived to discharge included ESBL, location of onset, and CCI category [Table 3]. None of the interactions tested were significant. In patients that survived to discharge, those with ESBL-producing *E. coli* BSIs had significantly higher odds of long post-infection LOS compared to those with non-ESBL-producing *E. coli* BSIs [Table 3]. Compared to community-acquired and healthcare-associated *E. coli* BSIs, nosocomial cases had significantly higher odds of long post-infection LOS in patients that survived to discharge [Table 3]. In patients that survived to discharge, those with a CCI≥3 had significantly higher odds of long post-infection LOS compared to those with a CCI<3 [Table 3]. A separate multivariable model was constructed for MDR, but MDR was not statistically significant (results not shown).

**Discussion**

Our population-based study contributes important information regarding factors associated with mortality and LOS to the *E. coli* BSI literature. There were several key strengths of our study, including ten years of population-based surveillance data, the geographically isolated
nature of the area, and the availability of detailed clinical data. Notably, we have results on the burden of disease from *E. coli* BSIs at the population-level for the western interior of BC, since we have all incident *E. coli* BSIs, and associated 30-day deaths and hospitalizations. When we examine burden from the absolute perspective, the number of *E. coli* BSIs in the population, we report a considerable burden of disease with a crude incidence rate of 59.1 *E. coli* BSIs/100,000 person-years and a crude 30-day mortality rate of 6.8 deaths/100,000 person-years.

The epidemiological characteristics of the incident *E. coli* BSIs in our study are mostly similar to those from previous population-based studies. In previous studies, 72.8-91.1% of *E. coli* BSIs were community-onset, which consisted of 31.7-40.0% healthcare-associated and 34.0-59.4% community-acquired [7-10, 12]. Our study had a similar proportion of community-onset *E. coli* BSIs (90.1%), but we had more healthcare-associated (48.8%) than previous studies. When previous studies reported *E. coli* BSI foci, urogenital foci were the most common and this is consistent with our results [3, 9, 10, 12]. Resistance to ceftriaxone and ciprofloxacin, ESBL-production, and MDR are of particular importance for *E. coli* infections due to their potential implications for treatment and their prevalence can vary widely between different studies. Previous studies reported third-generation cephalosporin resistance of 1.0-10.4% [7-10, 12], ciprofloxacin resistance of 7.0-18.4% [7-10, 12], and ESBL-producing *E. coli* in 2.0-26.8% [7, 8, 11]. We had a higher prevalence of ciprofloxacin resistance (24.7%), however, differences in population and time periods make interpreting this difference difficult. We did not identify a previous population-based *E. coli* BSI study that reported MDR. Future studies could easily include the MDR metric generated from AMR data [23]. Previous population-based *E. coli* BSI studies did not indicate if *E. coli* BSIs were polymicrobial or monomicrobial. In our study, 7.8%
of incident *E. coli* BSIs were polymicrobial and we contend that this is an important detail to include, especially if performing risk factor analyses of health outcomes.

Mortality is an important measure of burden of disease [13]. Population-based studies have reported *E. coli* 30-day all-cause case fatality risks of 8.0-18.2% [1, 12, 16] and our 30-day all-cause case fatality risk of 11.5% is within the lower half of the range. Another previously-used definition of mortality is in-hospital all-cause mortality. If we compare our 30-day case fatality risk (11.5%) to our 30-day in-hospital case fatality risk (9.9%), we note that the in-hospital measure is lower. If we take the in-hospital deaths that occurred within 30 days (n=92) and used the total number of incident *E. coli* BSIs (n=1080), then we have a 30-day in-hospital case fatality risk of 8.5%, which is considerably lower. In-hospital mortality has been shown to be a biased measure of mortality in population-based studies [27] and our results provide further support of this bias. In-hospital mortality does not accurately reflect mortality in population-based studies because any deaths in patients that were never hospitalized or in those that died after discharge but before 30 days are not captured. Bacterium-attributable mortality where deaths are confirmed to be a result of the BSI is a less frequently used definition of mortality, and is often not practical or even possible to confirm. Patients with BSIs often have comorbidities and commonly this information is determined from medical record review, which makes the accurate attribution of cause of death to the BSI difficult. Therefore, all-cause mortality without restriction to in-hospital is the best definition for mortality in population-based studies and this is often done with a 30-day post-infection timeframe [27].

The factors with significantly higher odds of 30-day mortality in *E. coli* BSIs in our study included cases ≥ 65-years-old, healthcare-associated or nosocomial BSIs, infection foci other than urogenital, and CCI≥3. We used a generalized estimating equation for the logistic
regression models to account for the lack of independence due to 59 patients having more than one *E. coli* BSI during the study and therefore, correctly estimated coefficients and standard errors. Managing the lack of independence is important, because *E. coli* BSIs from the same patient will be more similar to each other than those from other patients. Our findings are consistent with previous studies, including those that identified associations between increasing age and higher case fatality risks [7, 12, 15, 28]. Also similar to our findings, studies established that nosocomial *E. coli* BSIs are associated with increased mortality [7, 8, 29], and specifically, the odds of mortality are higher with nosocomial than healthcare-associated when compared to community-acquired [7, 8]. Our study is also consistent with others in identifying that a BSI focus other than urogenital is associated with increased case fatality risk [7, 12, 15, 28, 30-32]. Some previous studies found an association between higher CCI or Elixhauser comorbidity score and increased mortality [15, 31]. We used CCI in the multivariable logistic regression model and found that a higher CCI was associated with higher odds of 30-day mortality. We went further and evaluated common comorbid conditions with univariable logistic regression models to gain insight into comorbidities that might be contributing to the CCI mortality association.

*Escherichia coli* BSI cases with diabetes mellitus, cancer, chronic pulmonary disease, congestive heart failure, myocardial infarction, dementia, mild liver disease, and cerebrovascular disease all had significantly higher odds of mortality, which is important from a clinical perspective. Other variables, including sex, ESBL, ciprofloxacin resistance, MDR, and season are not consistently significantly associated with mortality in the literature; some previous studies found that males, ESBL production, ciprofloxacin resistance, MDR, and winter were significantly associated with higher mortality, whereas others, including our study, did not [7, 11, 12, 15, 28-31, 33, 34]. The inconsistent associations for sex, AMR, and season between studies are likely due to differences
in healthcare practices, population, and geography. Studies also found significant associations between inappropriate initial antimicrobial therapy and higher mortality [32, 33] and this could be explored in future western interior studies.

Longer LOS is associated with increased hospital costs and therefore is an important measure of the burden of disease [13]. When exploring burden of disease, post-infection LOS is the appropriate LOS measure since it only covers LOS during the BSI. Blandy et al. 2019, estimated factors associated with long post-infection LOS in *E. coli* BSIs, but used hospital-based data [15]. They included *E. coli* BSIs from three teaching hospitals in West London, United Kingdom from January 2011 to June 2015 [15]. In our study and theirs, having an ESBL-producing or third-generation cephalosporin-resistant *E. coli* BSI significantly increased the odds of having a long post-infection LOS [15]. This is an important finding because third-generation cephalosporin resistance in *E. coli* has been increasing globally [35]. Third-generation cephalosporin-resistant *E. coli* is considered a critical priority pathogen for research and development of new antibiotics by the World Health Organization and a serious threat to human health by the Centers for Disease Control and Prevention [35, 36]. Blandy et al. found that patients with nosocomial *E. coli* BSIs had significantly higher odds of long post-infection LOS compared to those with community-onset [15]. Similarly, we found that cases with nosocomial *E. coli* BSIs had significantly higher odds of long post-infection LOS compared to those with community-acquired and healthcare-associated. There were two significant associations identified by Blandy et al. that were not significant in our analysis, patients being 60-years-old or older, and ciprofloxacin resistance, which both had greater odds of having a long post-infection LOS [15]. In both studies, sex and urinary focus of BSIs were not associated with long post-infection LOS [15]. It is interesting that a urogenital focus of infection was protective for
mortality but did not impact the odds of having a long post-infection LOS. We found that having a CCI ≥ 3 increased the odds of having a long post-infection LOS; comparatively, Blandy et al. did not find a significant association between Elixhauser comorbidity score and long post-infection LOS [15]. Differences in the comorbidity indices used by the two studies and the number of categories used for the categorical comorbidity index variable likely contributed to the contradictory results. By exploring individual comorbidities with univariable analyses, we found that *E. coli* BSI cases with diabetes mellitus, chronic pulmonary disease, congestive heart failure, renal disease, dementia, cerebrovascular disease, or diabetes mellitus with end organ damage had significantly higher odds of having a long post-infection LOS. In future studies, we could explore an alternative approach to modelling the post-infection LOS data using a Cox proportional hazard model with death as a competing risk for being discharged alive from hospital.

Our study had some limitations that should be noted. We did not have access to data regarding patient history (e.g., previous hospitalization, or travel), BSI treatment, or other burden of disease measures (e.g., measures of morbidity, or hospital costs). The case data were collected retrospectively through medical record review and therefore, are limited to details contained within the medical records, however, it was performed by an experienced infectious disease specialist (KBL). We used the current CLSI clinical breakpoints at the time of AST to interpret the results as susceptible, intermediate, or resistant, and therefore it is possible that some of the breakpoints changed slightly during the study period. Although our study is population-based, it is only from one geographical area in a high-income country with publicly-funded healthcare and this should be taken into consideration when attempting to generalize our results to a different population [14, 37].
In conclusion, our population-based study presented detailed analyses of *E. coli* BSIs in the western interior area of BC and explored several different perspectives of burden of disease in *E. coli* BSIs at the population-level. Our study demonstrated the substantial burden of *E. coli* BSIs with crude incidence and 30-day mortality rates of 59.1 *E. coli* BSIs and 6.8 deaths/100,000 person-years, respectively. We identified having a nosocomial *E. coli* BSIs and a CCI ≥ 3 as risk factors for both 30-day mortality, and long post-infection LOS in patients that survived to discharge. Whereas, older cases, a non-urogenital BSI focus and healthcare-associated BSIs had significantly higher odds of 30-day mortality, and ESBL-producing *E. coli* BSIs were a risk factor for long post-infection LOS in patients that survived to discharge. Several individual comorbidities, including diabetes mellitus, chronic pulmonary disease, congestive heart failure, cerebrovascular disease, and dementia, were risk factors for both 30-day mortality, and long post-infection LOS in patients that survived to discharge. Future research should explore which of these risk factors could be effectively targeted with interventions to reduce mortality in *E. coli* BSIs, and post-infection LOS in patients that survived to discharge.

**Supplementary material**

The supplementary material for this material can be found on the Cambridge Core website.

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**Conflicts of interest**

MCM reports a scholarship from the Canadian Institutes of Health Research and funding for a Federal Student Work Experience Program placement from the Government of Canada – Genome Research Development Initiative, both related to her PhD program, but not directly related to the submitted work.

**Data availability statement**

The dataset analysed during the current study is available from the corresponding author on reasonable request.

**Ethics statement**

The Interior Health and University of Guelph Research Ethics Boards approved this study and granted waivers of individual informed consent (2013-14-052-I and 2018-10-050, respectively).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.
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Table 1 – Characteristics of cases with incident *E. coli* bloodstream infections that did and did not survive 30 days after blood culture collection based on data from a population-based cohort study in the western interior area of British Columbia, Canada (April 2010 to March 2020)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=1080)</th>
<th>Alive at day 30 (n=956)</th>
<th>Died within 30 days (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>456 (42.2%)</td>
<td>393 (41.1%)</td>
<td>63 (50.8%)</td>
</tr>
<tr>
<td><strong>Age in years (median (IQR))</strong></td>
<td>70.8 (58.6-81.3)</td>
<td>69.8 (57.0-80.4)</td>
<td>77.9 (67.4-85.9)</td>
</tr>
<tr>
<td><strong>Polymicrobial BSI</strong></td>
<td>84 (7.8%)</td>
<td>62 (6.5%)</td>
<td>22 (17.7%)</td>
</tr>
<tr>
<td><strong>Antimicrobial resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended-spectrum β-lactamase</td>
<td>91 (8.4%)</td>
<td>79 (8.3%)</td>
<td>12 (9.7%)</td>
</tr>
<tr>
<td>Ciprofloxacin resistance</td>
<td>267 (24.7%)</td>
<td>237 (24.8%)</td>
<td>30 (24.2%)</td>
</tr>
<tr>
<td>Multidrug resistant</td>
<td>241 (22.3%)</td>
<td>217 (22.7%)</td>
<td>24 (19.4%)</td>
</tr>
<tr>
<td><strong>Location of onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community-acquired</td>
<td>446 (41.3%)</td>
<td>422 (44.1%)</td>
<td>24 (19.3%)</td>
</tr>
<tr>
<td>Healthcare-associated</td>
<td>527 (48.8%)</td>
<td>458 (47.9%)</td>
<td>69 (55.7%)</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>107 (9.9%)</td>
<td>76 (8.0%)</td>
<td>31 (25.0%)</td>
</tr>
<tr>
<td><strong>Pre-infection LOS in days (median (IQR))</strong></td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td><strong>Focus of infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urogenital</td>
<td>706 (65.4%)</td>
<td>666 (69.7%)</td>
<td>40 (32.3%)</td>
</tr>
<tr>
<td>Non-urogenital</td>
<td>374 (34.6%)</td>
<td>290 (30.3%)</td>
<td>84 (67.7%)</td>
</tr>
<tr>
<td><strong>CCI (median (IQR))</strong></td>
<td>2 (0-3)</td>
<td>1 (0-3)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td><strong>Comorbidities (prevalence ≥5%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (DM)</td>
<td>254 (23.5%)</td>
<td>234 (24.5%)</td>
<td>20 (16.1%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>225 (20.8%)</td>
<td>182 (19.0%)</td>
<td>43 (34.7%)</td>
</tr>
</tbody>
</table>
Chronic pulmonary disease 163 (15.1%) 136 (14.2%) 27 (21.8%)
Congestive heart failure 105 (9.7%) 78 (8.2%) 27 (21.8%)
Renal disease 102 (9.4%) 87 (9.1%) 15 (12.1%)
Myocardial infarction 89 (8.2%) 72 (7.5%) 17 (13.7%)
Dementia 83 (7.7%) 66 (6.9%) 17 (13.7%)
Mild liver disease 81 (7.5%) 58 (6.1%) 23 (18.6%)
Cerebrovascular disease 66 (6.1%) 52 (5.4%) 14 (11.3%)
DM with end organ damage 59 (5.5%) 52 (5.4%) 7 (5.7%)
Rheumatologic disease 56 (5.2%) 48 (5.0%) 8 (6.5%)

IQR – Interquartile range; BSI – Bloodstream infection; LOS – Length of hospital stay;
CCI – Charlson Comorbidity Index

1 Antimicrobial resistance variables used in regression analyses. Details of antimicrobial susceptibility for additional antimicrobials are available in the results section.

2 When those not hospitalized were removed (n=154), the only change was in the 75th percentile for those that died within 30 days; median (IQR) – 0 (0-4).
Table 2 - The adjusted odds ratios for the multivariable logistic regression model estimating the associations between the explanatory variables and 30-day mortality in *E. coli* bloodstream infections based on data from a population-based cohort study in the western interior area of British Columbia, Canada (April 2010 to March 2020)

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65-years-old</td>
<td>1</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥65-years-old</td>
<td>1.97</td>
<td>1.21-3.21</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Location of onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community-acquired</td>
<td>1</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Healthcare-associated</td>
<td>1.97</td>
<td>1.19-3.26</td>
<td>0.009</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>4.26</td>
<td>2.29-7.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Focus of infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urogenital</td>
<td>1</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Non-urogenital</td>
<td>4.21</td>
<td>2.78-6.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Charlson comorbidity index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>1</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>2.57</td>
<td>1.70-3.88</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

aOR – Adjusted odds ratio; CI – Confidence interval

1 Logistic regression model fitted with generalized estimating equation using exchangeable correlation structure to account for lack of independence from some patients having more than one incident bloodstream infection

2 Contrast comparing nosocomial to healthcare-associated aOR:2.16 (95% CI:1.29-3.65) p=0.004

3 Overall p-value for variable estimated using a Wald test
Table 3 - The adjusted odds ratios for the multivariable logistic regression model estimating the associations between the explanatory variables and long post-infection LOS in patients with *E. coli* bloodstream infection that survived to discharge based on data from a population-based cohort study in the western interior area of British Columbia, Canada (April 2010 to March 2020)\(^1\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extended-spectrum β-lactamase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.88</td>
<td>1.09-3.25</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Location of onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community-acquired</td>
<td>1</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Healthcare-associated(^2)</td>
<td>1.40</td>
<td>0.95-2.06</td>
<td>0.085</td>
</tr>
<tr>
<td>Nosocomial(^2)</td>
<td>7.04</td>
<td>4.03-12.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Charlson comorbidity index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>1</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>2.08</td>
<td>1.46-2.96</td>
<td>0.001</td>
</tr>
</tbody>
</table>

aOR – Adjusted odds ratio; CI – Confidence interval

\(^1\) Logistic regression model fitted with generalized estimating equation using exchangeable correlation structure to account for lack of independence from some patients having more than one incident bloodstream infection

\(^2\) Contrast comparing nosocomial to healthcare-associated aOR:5.02 (95% CI:2.97-8.47) p<0.001

\(^3\) Overall p-value for variable estimated using a Wald test