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Carolyn Chi Date

The Likelihood of Hospital Readmissions Based on Exposure to Central Line-Associated Bloodstream Infection

By

Carolyn Chi
Master of Public Health

Epidemiology

_____

David Kleinbaum, PhD

Committee Chair

_____

Ronda Cochran, MPH

Committee Member

_____

James Baggs, PhD

Committee Member

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By

Carolyn Chi

Bachelor of Science
University of California, San Diego
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Thesis Committee Chair: David Kleinbaum, PhD

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Abstract

The Likelihood of Hospital Readmissions Based on Exposure to Central Line-Associated Bloodstream Infection
By Carolyn Chi

Research on healthcare-associated infections suggests a potential association with hospital readmissions. A secondary data analysis was conducted on a retrospective matched cohort study to determine if there was an association between central line-associated bloodstream infection (CLABSI) status during the index hospitalization and later re-hospitalization. Readmission was measured from the patient's index discharge to the following 30 days via logistic regression analysis and as the first hospitalization following index discharge, regardless of timing, via survival analysis. The final logistic regression model determined a statistically significant association between CLABSI status and readmission, with effect modifiers length of stay and rheumatoid arthritis. The odds of readmission were 1.59 times more likely among CLABSI patients with rheumatoid arthritis than those without rheumatoid arthritis, for a median length of stay between 13 and 22 days [OR=1.588, 95% CI (1.030, 2.447)]. The odds ratio for the shortest length of stay between zero and six days was 11.17 for patients without rheumatoid arthritis [OR=11.172, 95% CI (2.307, 54.093)]. Similarly, the final stratified Cox model determined a statistically significant association between CLABSI status and readmission, with effect modifiers length of stay, rheumatoid arthritis, depression, and chronic kidney disease. The hazard of readmission was 1.59 times more likely among CLABSI patients with rheumatoid arthritis than those without rheumatoid arthritis, for a median length of stay between 13 and 22 days [HR=1.589, 95% CI (1.228, 2.056)]. The hazard ratio for the shortest length of stay between zero and six days was 3.09 for patients without rheumatoid arthritis, depression, or chronic kidney disease [HR=3.093, 95% CI (1.647, 5.808)]. Both the adjusted odds and hazard ratios for the effect of CLABSI on readmission decreased as length of stay increased, given fixed rheumatoid arthritis status. Also, both the adjusted odds and hazard ratios were higher for patients diagnosed with rheumatoid arthritis than for patients not diagnosed with rheumatoid arthritis, for a fixed length of stay. The adjusted logistic regression and survival analyses resulted in a statistically significant association between CLABSI status and readmission. These findings suggest that a focus on the prevention of CLABSIs could reduce re-hospitalizations, improving patient safety and public health.

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Introduction

Research has found that healthcare-associated infections (HAIs) contribute to the growing issue of readmissions in acute care hospitals. Re-hospitalizations not only create a burden for patients and their health but also account for increased costs, resources, and time for healthcare providers, payers, and ultimately the healthcare system.

HAIs are characterized as a localized or systemic condition that arises from the body's interaction with an infectious agent(s) or its toxin(s), causing a detrimental clinical reaction (1). An HAI must meet body site-specific standards and occur during a hospital stay; there cannot be any indication that the infection had previously existed or was incubating at or prior to the hospital admission. HAIs generally occur within 30 days after the hospital stay or within a year, in the event that an insertion or a prosthetic device has caused the infection (2). HAIs can develop with any healthcare encounter: within hospitals, ambulatory and long-term care facilities, and via home health agencies (3).

One out of every 20 hospitalized patients will be infected with an HAI (4). HAIs impact almost two million people in the United States each year, giving rise to great morbidity and mortality while affecting five to ten percent of hospitalized patients each year (1). The World Health Organization approximates that seven out of 100 hospitalized patients are infected with an HAI at any given time (5). Furthermore, research suggests that HAIs create about $28 to $34 billion in excess healthcare costs each year and up to $45 billion can be spent in direct annual hospital costs due to HAIs (6). The majority of HAIs are represented by endemic issues, such as central line-associated bloodstream infections (CLABSIs). A recent study indicated that 14% of HAIs are attributable to

CLABSIs (1). Of the 1.7 million HAIs that bring about 99,000 deaths each year, 30,665 of these deaths are the result of bloodstream infections (1).

CLABSIs are device-associated infections that may occur when a central line or central catheter tube is inserted into the patient's large vein. The central line is implemented to draw blood or administer fluids or medications. The lines can be maintained in place for up to several weeks (7). A bloodstream infection can occur when bacteria or other germs enter the blood from the central line. Catheters can become contaminated by direct hand contact, dirtied devices and fluids, or with the movement of skin organisms from the insertion site to the catheter tract and its surface, which allows for colonization around the tip of the catheter (8). Major CLABSI risk factors also include skin-related colonization around the insertion site, moist dressings, extended use of the catheter, and improper techniques implemented to place the central line (8, 9).

To be classified as a CLABSI, a central line must be placed in the vein during or up to 48 hours prior to the infection (10). CLABSIs are required to be laboratory-confirmed primary bloodstream infections, which would signify that the infection itself is not accountable for infections at other sites. They must have one or more positive blood cultures with a recognized pathogen and/or more positive blood cultures for skin contaminants. CLABSIs are most commonly found in hospital intensive care units (ICUs), inpatient units, and outpatient hemodialysis clinics (4).

CLABSIs generate other problems, such as extending the length of hospitalization and increasing hospital costs (11). There are approximately 249,000 bloodstream infections in hospitals within the United States annually (1), which may lead to longer

hospital stays by seven to 21 days (12). Crnich et al. concludes that the length of hospitalization due to a CLABSI can range from five to 20 days, depending on one's age and the severity of his or her illness (13). About 500-4,000 deaths occur in the United States each year due to CLABSIs, which are known to be associated with an in-hospital mortality rate of 12% to 35%, increasing complications associated with the treatment of these infections (14). In 2002, the estimated attributable cost of a bloodstream infection was between $36,441 and $37,078 (15) and according to Marschall et al., the non-inflation-adjusted attributable cost of CLABSIs generally range from $3,700 to $29,000 per case (16). Similarly, the Centers for Disease Control and Prevention (CDC) report that the marginal cost to the healthcare system for CLABSIs is about $25,000 per episode (8).

CLABSIs are avoidable and can save $9 million in excess costs annually (17) by implementing strategies such as education, hand hygiene, and maximal sterile barrier precautions. Research on hospital policies and procedures discovered that 88% of surveyed hospitals arranged education for nursing staff on central vascular catheter care and maintenance, but only 52% administered education on insertion techniques to physicians (18). Healthcare personnel need to be educated on the indications for catheter use, correct procedures on inserting and maintaining catheters, and proper infection control measures (8). Only trained personnel who are capable of demonstrating appropriate insertion techniques and maintaining catheters should be designated to administer such procedures. In addition, standard hand hygiene procedures that include the act of washing hands with soap and water or with alcohol-based hand rub should be

applied (8). Hand hygiene should be observed both before and after being in contact with the catheter.

A study by Rubinson et al. surveyed 526 physicians on their adherence to maximum barrier precautions (19). About 99% claimed to wear sterile gloves, yet a smaller percentage reported compliance with use of other components such as sterile gowns, masks, and drapes. Only 28% in total were found following all of the maximum barrier precautions recommendations. This often occurs due to a lack of proper education and insufficient quantities of equipment and supplies (20). Maximal sterile barriers require that the staff member who is inserting the central line wear a head cap, face mask, sterile body gown, and sterile gloves (9). The patient should be using a full-sized drape to protect him or her from head to toe. Simply applying minimal sterile barriers, such as sterile gloves and a small drape is insufficient; patients are still at risk for a six-fold higher rate of catheter-related infection (21). Another mechanism to avoid CLABSI-related events includes the use of chlorhexidine to clean the skin before inserting the catheter line and selecting an appropriate site for insertion (8). But most importantly, collaboration by multidisciplinary teams is important to help overcome the burden of CLABSIs (20). By integrating the knowledge and expertise of epidemiologists, nurse specialists, management, staff nurses, quality improvement professionals, and physicians, these teams could efficiently identify barriers while consistently exercising evidence-based practices and following recommendations. These teams could then apply useful solutions to overcome such obstacles and prevent the acquisition of CLABSIs in their healthcare facilities.

CLABSIs can be averted and have shown a decrease in rates with increased prevention intervention. For instance, Pronovost et al. studied physicians' use of CDC recommended measures and how they affect the rate of CLABSIs (22). Such measurements included washing one's hands, implementing full-barrier precautions while inserting central venous catheters, wiping with chlorhexidine, evading the femoral site, and eliminating unnecessary catheters (22). Among the participating ICUs, the state-wide intervention resulted in a 62% overall decrease in the rate of CLABSIs after zero to three months of applying recommended measures (22). Similarly, the Pittsburgh Regional Healthcare Initiative conducted a four-year intervention effort to reduce CLABSI rates that followed recommended practices (23). The results indicated that in some ICUs, there were no incidents of CLABSIs for consecutive months after applying an integrated, multi-institutional infection control program to pursue prevention efforts (23). During the study period, BSI rates among ICU patients decreased by 68%, from 4.31 to 1.36 per 1,000 central line days. If there is no prevention intervention to reduce CLABSIs, the issue of HAIs could become more problematic to both patients and hospitals, thereby also complicating the already challenging situation with hospital readmissions.

Readmissions or re-hospitalization can be used as an indicator to assess hospital quality, which brings about challenges because hospital readmissions often occur frequently and are costly to payers such as Medicare (24, 25). Rates of hospital readmission among adults can vary from five to 29% (26-30) and are responsible for up to 60% of hospital expenditure (31). Medicare presently pays for all hospital readmissions, aside from those in which patients are re-hospitalized within 24 hours of

discharge for the same condition they were originally admitted (25). The program spends up to $12 billion a year on re-hospitalization issues that are likely preventable (32). In 2004, approximately 20% of Medicare beneficiaries who were discharged from a hospital were readmitted within 30 days, and 34% within 90 days. The program spent about $17.4 billion of the $102.6 billion in Medicare hospital payments on re-hospitalizations alone that year (25, 33). These expenses have driven healthcare facilities to better aim at reducing costs associated with re-hospitalizations (25).

Prior research indicates that there exists an association between having an HAI and becoming re-hospitalized. Within a three-month period of a study that examined the proportion of patients who were readmitted to a hospital due to an HAI, it was determined that HAI incidents were the cause of 14.3% of readmissions within the study's hospital (34). Mattner et al. studied the persistence of methicillin-resistant *Staphylococcus aureus* (MRSA) among 1,032 patients who were admitted into the university hospital and tested positive for MRSA at least once during a four-year period (35). It was discovered that of these patients, 403 (39.1%) were readmitted more than once, from anywhere between two to 21 times (35). Murphy et al. studied the frequency of *Clostridium difficile* infection (CDI) occurrence during the hospital visit and within 12 weeks of being discharged (36). They found that the risk of being readmitted due to CDI was higher within the first 12 weeks from being discharged, but highest within the first four weeks of discharge (36).

Demographic factors such as male gender and older age have been found to be positively associated with re-hospitalization within the first 28 days of discharge (37). Marcantonio et al. performed a matched case-control study on patients with Medicare

managed care plans who were admitted to an academic hospital (38). They too measured readmission within 30 days of discharge and discovered that five factors were independently associated with readmission. These included characteristics such as age 80 years or older, previous hospital visits within 30 days, five or more comorbidities, a diagnosis of depression, and one discharge measurement such as lack of documented patient or family education (38). Silverstein et al. used the Elixhauser comorbidity scale to assess which comorbidity variables were associated with an increased risk of 30-day re-hospitalization (39). According to their analysis, variables that were independent predictors of readmission included being older than 75 years, male sex, and African American race (39). Consequently, re-hospitalizations can be alleviated by improving inpatient care, creating better discharge planning, increasing access to outpatient services, and promoting community support (26).

The ongoing problem of hospital readmissions continues to result in serious public health consequences by creating a burden on patients and generating unnecessary healthcare costs. Therefore it is beneficial to study the issue of re-hospitalizations, especially among CLABSI patients. The purpose of the thesis is to conduct a secondary data analysis to determine whether there is an association between patients who have been identified as having a CLABSI and being readmitted to acute care hospitals. The frequency of readmission to acute care hospitals will be studied among those with a CLABSI and matched controls.

Methods

NULL HYPOTHESIS

There is no association between CLABSI status during a patient's index hospitalization and later re-hospitalization.

STUDY DESIGN

The study design is a retrospective frequency-matched cohort study involving 11,802 subjects. The exposed subjects (i.e., index group) were CLABSI patients and the unexposed patients (i.e., comparison group) were those without CLABSI. The study dataset was collected from January 1, 2008 to December 30, 2009 on adult patients between the ages of 65 and 102 years from various US hospitals. These data were obtained from two different sources including the National Healthcare Safety Network (NHSN) and the Centers for Medicare & Medicaid Services' Medical Provider and Analysis Review (MEDPAR).

The CDC established NHSN in 2005, which would serve as a combination of three major surveillance systems: the National Nosocomial Infections Surveillance system, the Dialysis Surveillance Network, and the National Surveillance System for Healthcare Workers (40). NHSN collects, reports, and analyzes data by applying methods and definitions that have been standardized and follow particular module procedures (10, 41). For instance, denominator data must be collected consistently and at the same time every day. Infections are based on CDC definitions (42). CLABSI is defined by a primary laboratory confirmed bloodstream infection; the infection cannot be

associated with infections at other body sites. Also, in order for the infection to be considered central line-associated, a central line or umbilical catheter must have been in position 48 hours prior to or at the time of the event. Facilities may contribute surveillance data voluntarily or due to obligatory reporting requirements by their respective states. Surveillance can take place within inpatient settings, including critical and intensive care units (ICU), specialty care areas, neonatal units, step down units, wards, and long term care units (10). Once the reports have been received, NHSN generates a conglomerate database for analysis.

The second data source, MEDPAR, provides data based on beneficiary claims for services provided to patients admitted to Medicare certified inpatient hospitals and skilled nursing facilities (43). Generally MEDPAR records contain documentation on beneficiary demographics, diagnosis, surgery information, charges, and days of care. Information on a patient's death is included up to three years after discharge. The dataset used for the analysis provided inpatient claims and helped identify hospitalizations and skilled nurse visits for each patient. It also included information on each patient's admission date, date of birth, sex, facility, diagnosis and procedures using ICD-9-CM codes, reimbursement cost of the claim, and beneficiary status. ICD-9-CM codes classify morbidity data from patient records (International Classification of Diseases, Clinical Modification). Available states included Colorado, Illinois, New Hampshire, New York, Pennsylvania, South Carolina, Tennessee, and Virginia. There were no typical personal identifiers associated with the data, such as patient name, social security number, or medical record.

The two separate datasets provided by NHSN and MEDPAR ultimately helped identify CLABSI patients and those who were readmitted based on this status. The MEDPAR dataset used ICD-9-CM codes, but it has previously been shown that ICD-9-CM codes are not able to sufficiently identify all CLABSI cases in administrative files (44); thus an alternative method of finding CLABSI cases had to be applied. On the other hand, NHSN relied on surveillance data to capture CLABSI cases, which were more reliable in helping distinguish cases. However, re-hospitalization and additional information on the index hospitalization could only be obtained through MEDPAR. Thus the two datasets had to be linked to properly identify patients with the infection. The information in the MEDPAR database would then help determine readmission rates and potential confounders using a large sample.

In order to identify a study population that would allow for estimating risk of subsequent hospitalization, certain adjustments were applied to each dataset. Since the MEDPAR datafile only had observations from January 1, 2008 to December 31, 2009, this became the study time period. Only patients who were aged 65 years or older were included to avoid confounding by age, since Medicare beneficiaries tend to be typically 65 years or older (45). The records for these patients also required that their date of birth, sex, and facility were documented. There were additional restraints placed on patients filed under the MEDPAR source, in order to include patients who may have had more conclusive data to analyze. Beneficiaries were included in the study only if they had naturally aged into the cohort, regardless of whether they were diagnosed with end stage renal disease or not, enlisted in Medicare Part A and B, and had not enrolled in a Medicare Advantage program. Lastly, patients who were admitted to psychiatric or

swing units were excluded from the study to prevent misclassified linkages. The NHSN datafile was adjusted as well, limiting this group's study population to patients who were 65 years or older, the eight available states, and those who were admitted during the study time period. States included were Colorado, Illinois, New Hampshire, New York, Pennsylvania, South Carolina, Tennessee, and Virginia. This provided 4,736 patients with CLABSI within the NHSN datafile and 3.95 million hospitalization events within the MEDPAR datafile prior to combing the two datafiles. There were 1,052,920 non-CLABSI patients available to match.

To create the final dataset, the two data sources from NHSN and MEDPAR were first linked, and then frequency matching of specific variables was carried out to control for potential confounding. The linked datafile contained hospitalizations in which a patient was identified as having a CLABSI (i.e., exposed group) as well as the remaining hospitalizations in which no CLABSI cases (i.e., unexposed group) were identified.

Since these populations were different in terms of important clinical and demographic characteristics, it was necessary to further limit and to match the patients using a frequency matching procedure (described below). This would help control for possible confounders related to the risk of having a CLABSI especially due to the expected length of stay. The variables involved in the frequency matching were procedure code (125 categories) and ICU status (yes or no). Note that the primary ICD-9-CM code procedure status is based on the Agency for Healthcare Research and Quality's Clinical Classification Software (CCS), which is a software tool that categorizes diagnoses and procedures (46). Also, ICU status was classified as having spent no time in the ICU or having spent at least one day in the ICU. It was an important

variable to control for, since previous research has shown that about 20% of patients who stay in the ICU are infected with a CLABSI (1). Patients who have both an ICU stay and a longer length of stay generally have a higher chance of being re-hospitalized (47). Frequency matching was carried out with five unexposed matches for each exposed participant such that the distribution of the ICU status and the procedure category was identical between the exposed participants and the unexposed participants. The total number of matched sets was 197 and due to this large size, a conditional logistic regression was executed. The dataset contained a stratum variable with 196 dummy variables. Other potential confounding variables included facility, demographics, and GAGNE scores. GAGNE scores were calculated based on morbidity scores that had combined conditions from other measures such as the Charlson Index and the Elixhauser comorbidity classification system (48).

For the purposes of this analysis, the exposure variable of interest was whether patients were identified by their CLABSI status during their index hospital stay. This was reported as "has a CLABSI" or "does not have a CLABSI." The date of the CLABSI incidence and the number of days from admission to the CLABSI occurrence were also recorded.

Unplanned readmissions between 1-30 days of the initial hospital discharge represented the primary outcome of the study. This variable was reported as "readmitted" or "not readmitted". Patients who were discharged from their first CLABSI visit and readmitted on the same day were considered transfers, and were excluded from the analyses. Any patient who died either during the index hospitalization or 1-30 days following hospitalization was eliminated from analysis as well.

Covariates also included patient demographic information including age, race, sex, and the variable describing a patient's length of stay during his or her index CLABSI visit. Race was sorted into white, black, or other. Length of stay was considered a confounder since increased hospital stays, especially those longer than seven days, have been found to be associated with an increased 30-day readmission (49). GAGNE scores were assigned a value between zero and six for the analysis, which were used to help better predict the outcome. A higher score generally indicated a poorer health condition for the patient. Lastly, the presence or absence of other chronic conditions that a patient was also diagnosed with was documented, since these variables could serve as possible confounders. Some examples of noted conditions include chronic heart failure, diabetes, chronic kidney disease, and rheumatoid arthritis.

DATA ANALYSIS

Analyses were conducted using SAS 9.3 statistical software (SAS Institute, Cary, NC). Alpha was set to 0.05 for all statistical analyses.

Univariate analyses were performed on CLABSI, readmission between 1-30 days of discharge, and risk factors to acquire descriptive statistics. Bivariate analyses were conducted to determine relationships between individual predictors, including the exposure variable (CLABSI status) and other potential risk factors, to the outcome variable (i.e., hospital readmission). The chi-squared test was used to analyze the presence of associations between the CLABSI variable and categorical risk factors, as well as readmission variables. If expected cell counts were less than five, Fisher's exact

test was used. One-sample t-tests were used to compare CLABSI and readmission variables to normally distributed continuous risk factor variables. Wilcoxon rank-sum tests were performed on non-parametric variables. A crude measure of association was assessed between CLABSI status and hospital re-admission within 1-30 days of discharge using a risk ratio estimate and the corresponding 95% confidence interval for this risk ratio.

Potential confounders and interaction terms were identified for both stratified and multivariable analyses. Confounders were based on the patient's index hospital stay. During stratified analysis, the association between the exposure and outcome variables was determined by adjusting for each co-variable using Mantel-Haenszel risk ratios and corresponding 95% confidence intervals. Adjusted risk ratios were compared to the crude risk ratio to determine if the co-variables potentially confounded the exposure outcome association. If the adjusted estimates differed from the unadjusted crude estimate by more than 10%, confounding was determined to be present. Interaction was assessed in the stratified analysis by applying the Breslow-Day (i.e., B-D) test. If the B-D test's p-value was significant when controlling for a given risk factor, we would then conclude that there was interaction between CLABSI status and that risk factor. If a term's p-value was not found to be significant, its crude risk ratio and 95% confidence interval would be reported instead. If the term's p-value was found to be significant, the risk ratio and 95% confidence intervals for each level of the effect modifier would be reported. The results obtained from the stratified analyses about assessment of confounding and interaction were used to guide the model building (described below).

A full logistic regression model for the outcome variable, readmission within 30 days, was built for the exposure variable CLABSI, containing relevant confounders and interaction terms (i.e., as guided by the results of the stratified analyses). The initial model contained the variables age, race, sex, patient's length of stay during his or her index CLABSI visit as well as previously determined significant interaction terms obtained from the stratified analyses.

$$logit\ P(X) = \alpha + \beta CLABSI + \sum_{i=1}^{196} \gamma_{1i} V_{1i} + \sum_{j=1}^{34} \gamma_{2j} V_{2j} + CLABSI \sum_{k=1}^{6} \delta_k W_k$$

where

V_{1i}= dummy variables for matching strata
V_{2j}= other covariates that were not matched (see Table 7)
W_k= effect modifiers defined from other covariates (see Table 7)

Any product terms found to be significant remained in the model. A likelihood ratio test was performed to assess that significance of such interaction terms. Confounders were assessed through the hierarchical backward elimination approach as described by Kleinbaum and Klein (50). Potential confounding terms that were not components of significant product terms were considered for removal from the model using a 10% change rule for assessing confounding (other than the frequency matched variables, which remain in the model). Note, however, that if some product terms were found significant, then the 10% change rule had to be assessed using tables of odds ratios derived from combined categories of effect modifiers. Since the number of eligible potential confounders was large, application of the 10% rule using an all-possible subsets approach was considered unwieldy and much subjective. Consequently, as an alternative approach to assessing confounding, a "reduced" model that dropped all covariates that

were not components of a significant product term was compared to the "gold standard" model that controlled for all such covariates. Tables of odds ratios and 95% confidence intervals were compared for these two models. If these two tables were essentially similar (i.e., collectively corresponding odds ratios in each table were within 10% of each other), the reduced model was determined to be the best model since it controlled for confounding and provided improved precision. On the other hand, if comparison of these two tables determined that they were meaningfully different, then covariates would be added to the model until a model that was comparable to the gold standard model was found.

Also, regression diagnostics were performed on both the initial and final models to test assumptions and assess the fit. Such analysis included testing for multi-collinearity and outliers. The presence of multi-collinearity was determined by the assessment of condition indices and variance decomposition proportions using a SAS macro (51). Outliers were identified by calculating Cook's distance-type indices.

To assess the rate of first re-hospitalization, the rate of initial readmission among those with a CLABSI and those without was determined using a survival analysis involving Cox regression. Patients were censored at death or the end of the study period.

A Cox proportional hazard model was developed to evaluate the association between CLABSI and first re-admission. A likelihood ratio test was performed to compare log-likelihood statistics for models with and without interaction. As with the risk (i.e., logistic regression) analyses, model building using the Cox model was guided by the results previously obtained from the stratified analyses on assessment of both

confounding and interaction. Significant interaction terms remained in the initial model and confounders were assessed through hierarchical backward elimination. Potential confounding terms that were not lower-order terms of the interaction variables were considered for removal from the final model by applying a 10% change rule to assess confounding. If some of the interaction terms were found significant, the 10% rule was applied using tables of hazard ratios obtained from combinations of effect modifiers. As with the logistic regression analysis, because there was a large number of potential confounders, using the 10% rule with an all-possible subsets approach would have been subjective and unmanageable. Thus, a reduced model that dropped all covariates except for lower-order components of significant interaction terms were compared to the gold standard model, which controlled for all such covariates. Tables of hazard ratios and 95% confidence intervals were compared for these two models and if found similar (i.e., collectively within 10% of each other), the reduced model would be determined as the best model, provided the reduced model would control for confounding and improve precision. However, if the two tables were collectively meaningfully different from one another, covariates would be added to the model until a final model that was comparable to the gold standard was found. The hazard model that satisfied the PH assumption and considered for these analyses is given below:

$$h_g(t, X) = h_{0g}(t)\exp[\sum_{p=1}^{49} \beta_p X_p]$$

where

g= 1, 2 …7 (GAGNE scores)

X= covariates that satisfy the proportional hazard assumption (see Table 10)

Note that the above hazard model does not stratify on the 197 frequency matched strata that resulted from the matched study design. Nevertheless, since the study was a follow-up rather than a case-control study, it was assumed that controlling for the matched strata was not necessary in order to obtain valid estimates of hazard ratios of interest. This decision was based on assuming the widely known result that the analysis of matched follow-up data leads to unbiased odds ratio estimates of effect in logistic regression modeling, which carries over to Cox regression for matched cohort data (50).

Results

MEDPAR and NHSN data from eight states were linked to determine those experiencing a CLABSI during their primary visit as well as hospital readmissions after discharge from the primary visit for all selected patients. A total of 11,802 patients were selected for the study.

To assess the risk of re-hospitalization among the study population using logistic regression analysis, certain exclusions were applied such as death and transfers. Among the total 11,802 patients selected for the study, 7,107 patients survived the index hospitalization, were not transferred or re-hospitalized on the same day of discharge, and survived at least 30 days after discharge from the primary visit (Figure 1). These 7,107 patients were used to analyze risk of readmission, and among them, 726 (10.22%) had a CLABSI during the primary visit and 6,381 did not have a CLABSI (89.78%). Furthermore, 283 patients (38.98%) with a CLABSI were re-hospitalized at least once within 1-30 days of discharge from their index CLABSI visit and 1,677 patients (26.28%) without a CLABSI were re-hospitalized (Table 1). The average age among the 7,107 patients was 76.5 years and 4,951 patients (69.66%) spent at least one day in the ICU. There were 3,704 male patients (52.12%) and 5,937 white patients (83.54%).

The criteria to assess the rate of first re-hospitalization using survival analysis did not include death during the readmission period since data were right censored. Therefore, among the total 11,802 patients selected for the study, 8,097 patients were evaluated for the rate analysis (Figure 2). This was based on the number of patients surviving their primary stay and who were not transferred or readmitted on the same day they were discharged from the index visit. Demographic and clinical characteristics were

similar to the risk population used to analyze the logistic regression (Table 2). These patients experienced at least one of the following: death, readmission, or survival to the end of the study period. If patients were readmitted during the study period after the primary hospitalization, an "event" had occurred; 4,512 of these patients (55.72%) were readmitted during the study period, and 3,585 patients (44.28%) were censored from the analysis (Table 2). The rate of first readmissions was about 1.5 events per person-year for the total population. The rate of first readmission was about 2.5 events per person-year for patients who were exposed to CLABSI and about 1.4 events per person-year for patients who were not exposed to CLABSI.

RISK ANALYSIS FROM CRUDE AND STRATIFIED DATA

Crude risk ratios between CLABSI status during a patient's index hospitalization (exposure) and re-hospitalization within 30 days of initial discharge (outcome) were calculated, as well as their respective confidence intervals. Patients who were infected with a CLABSI were about 1.48 times more likely to be readmitted within 30 days than patients without a CLABSI [RR=1.483, 95% CI (1.342, 1.639)] (Table 3).

In addition, adjusted risk ratios computed from stratified analysis between CLABSI and readmission were calculated to assess the potential for confounding and interaction. Risk ratios obtained from stratified analyses indicated significant interactions between having a central line procedure code during the index hospital visit and readmission ($p=0.027$), between length of stay and readmission ($p<0.001$), and between patients diagnosed with rheumatoid arthritis and readmission ($p=0.006$) (Table 4). Only

for length of stay was there more than a 10% difference between the crude and adjusted risk ratios (Tables 3 and 4).

RATE ANALYSIS FROM CRUDE AND STRATIFIED DATA

Crude rate ratios between CLABSI status during a patient's index hospitalization and first re-hospitalization within the study period were calculated, as well as their respective confidence intervals. The rate of readmission was about 1.76 times higher among patients infected with a CLABSI than among patients without a CLABSI [IDR=1.755, 95% CI (1.606, 1.919)] (Table 5).

In our assessment of confounding and interaction, the stratified analysis obtained by comparing rate ratios in different strata revealed that 12 statistically significant variables would be evaluated as terms interacting with CLABSI in survival analysis: central line procedure code, length of stay during the index hospital visit, GAGNE score, and the following chronic conditions: Alzheimer's disease and related disorders, acute myocardial infarction, breast cancer, depression, diabetes, chronic kidney disease, rheumatoid arthritis, rectal cancer, and stroke or transient Ischemic attack (Table 6). Possible confounders were determined using screening one covariate at a time to identify whether or not there was more than a 10% difference between crude rate ratios and adjusted rate ratios. Length of stay was found to be the only possible confounder since there was more than a 10% difference between the crude and adjusted rate ratio (Tables 5 and 6).

LOGISTIC REGRESSION

A likelihood ratio test for comparing the full interaction model with a no-interaction model was statistically significant with a p-value of <0.001, indicating that an interaction model would be better than a model without interaction (Table 7). Hence backwards elimination was performed on the full model, revealing that the interaction term containing CLABSI and the central line procedure code during the first hospital visit was not found significant (p=0.256). After this term was excluded, the remaining interaction terms were found significant; the gold standard model contained two product terms, CLABSI and length of stay as well as CLABSI and rheumatoid arthritis. The initial model with the interaction variables also controlled for race, length of stay, sex, central line procedure code, GAGNE score, and the individual chronic conditions.

Odds ratios were obtained for the reduced model without potential confounders (i.e., race, sex, central line procedure code, and individual chronic conditions other than rheumatoid arthritis) to compare against the gold standard (i.e., full model). The odds ratios for the reduced models were compared to the odds ratios of the gold standard, and evaluated for a meaningful difference of 10%. Because the reduced model was within 10% of the gold standard, 95% confidence intervals were calculated for precision. The 95% confidence intervals indicated that precision improved with the reduced model, which was determined as the final model (Table 8-9):

$$logit\ P(X)$$

$$= \alpha + \beta CLABSI + \sum_{i=1}^{196} \gamma_{1i} V_{1i} + \gamma_{21} Length\ of\ stay + \gamma_{22} Rheumatoid\ arthritis$$

$$+ \delta_{11} CLABSI * Length\ of\ stay + \delta_{12} CLABSI * Rheumatoid\ arthritis$$

where

V_{1i}= dummy variables for matching strata

Additional modeling diagnostic procedures were applied to determine the final models, specifically an assessment of multi-collinearity by using a SAS macro (51) and influential observations. No multi-collinearity issues were found. Influential observations were detected using the INLUENCE and IPLOTS options on SAS's LOGISTIC procedure, but after reviewing the data, none were due to data inaccuracies.

A final logistic model indicated a statistically significant association between CLABSI and readmission to an acute care hospital, but this varied by length of stay and an indication of rheumatoid arthritis as a chronic disease, (i.e., these two variables were found to be effect modifiers of exposure status). As length of stay increased, the odds ratio for the effect of CLABSI on readmissions decreased, adjusted for rheumatoid arthritis (Table 9). Patients with rheumatoid arthritis and a length of stay of 0-6 days had an odds ratio of 18.376 [95% CI (3.777, 89.409)] whereas patients with a rheumatoid arthritis and a length of stay greater than 22 days had an odds ratio of 1.845 [95% CI (1.262, 2.697)]. For fixed length of stay, odds ratios were higher when patients were diagnosed with rheumatoid arthritis than when patients were not diagnosed with rheumatoid arthritis. For instance, there was an odds ratio of 18.376 among patients with

rheumatoid arthritis and a length of stay between zero and six days [95% CI (3.777, 89.409)]. But there was a lower odds ratio of 11.172 among patients without rheumatoid arthritis and the same length of stay [95% CI (2.307, 54.093)].

SURVIVAL ANALYSIS

To evaluate the proportional hazard (PH) assumption, three approaches were implemented: examining graphical curves, testing the goodness of fit (GOF), and comparing time-dependent variables. For each approach, covariates were tested one at a time and assessed to see which variable violated the assumption. The only variable whose PH assumption was not met for all three approaches was GAGNE score. The log-log survival curves were not parallel and intersected, while the p-value for GAGNE in the GOF test was <0.001. The extended Cox model that contained the time-dependent GAGNE variable indicated its p-value as <0.001. Since the PH assumption for GAGNE scores was not met, a stratified Cox procedure was carried out; GAGNE scores were controlled for by stratification while including the rest of the variables (that satisfied the PH assumption) in the model.

A likelihood ratio test comparing the log-likelihood statistics for the interaction model and the no-interaction model was statistically significant with a p-value of <0.001, indicating that an interaction model would be better than a model without interaction terms (Table 10). Backwards elimination was performed on the interaction terms and the resulting gold standard model contained four product terms including CLABSI and length of stay, CLABSI and depression, CLABSI and chronic kidney disease, and

CLABSI and rheumatoid arthritis. The gold standard also controlled for race, length of stay, sex, central line procedure code, and individual chronic conditions.

Hazard ratios were obtained for the reduced model without remaining potential confounders (i.e., race, sex, central line procedure code, and individual chronic conditions other than depression, chronic kidney disease and rheumatoid arthritis) to compare against the gold standard (i.e., full model). The hazard ratios for the reduced models were compared to the hazard ratios of the gold standard, and evaluated for a meaningful difference of 10%. Because the hazard ratios of the reduced model were within 10% of the odds ratios of the gold standard, 95% confidence intervals were calculated for precision. The 95% confidence intervals indicated that precision improved with the reduced model, which was determined as the final model (Tables 11-12):

$$h_g(t,X) = h_{0g}(t)\exp[\sum_{p=1}^{14}\beta_{pg}X_p]$$

where

g= 1, 2 …7 (GAGNE scores)
X= covariates that satisfy the proportional hazard assumption (see Table 11)

The final stratified Cox model demonstrated a statistically significant association between CLABSI and readmission to an acute care hospital that is modified by the following four effect modifiers: length of stay, depression, chronic kidney disease, and rheumatoid arthritis. As length of stay increased, the hazard ratio for the effect of CLABSI on readmission decreased, adjusted for rheumatoid arthritis, depression, and chronic kidney disease (Table 12). For a fixed length of stay, depression, and chronic kidney disease, the hazard ratios were higher for patients diagnosed with rheumatoid

arthritis than for patients not diagnosed with rheumatoid arthritis. For instance, the hazard ratio for a length of stay of zero to six days was 4.094 for rheumatoid arthritis patients, without depression and chronic kidney disease [95% CI (2.209, 7.587)]. On the other hand, the hazard ratio for the same length of stay was 3.093 for patients without rheumatoid arthritis, depression, or chronic kidney disease [95% CI (1.647, 5.808)]. The hazard ratios were higher for patients without depression than for patients with depression, at various levels of length of stay, rheumatoid arthritis, and chronic kidney disease. Similarly, the hazard ratios were higher for patients without chronic kidney disease than for patients with chronic kidney disease at various levels of length of stay, rheumatoid arthritis, and depression. The hazard for CLABSI was generally significantly higher for the shortest length of stay (between zero and six days). Lastly, the hazard ratios were significantly less than one for patients who had longer lengths of stay and were diagnosed with depression and chronic kidney disease, but not with rheumatoid arthritis. For instance, patients with a length of stay between 13 and 22 days and diagnosed with depression and chronic kidney disease but not with rheumatoid arthritis had a hazard ratio of 0.744 [95% CI (0.569, 0.972)]. Similarly, patients with the same diagnoses but a length of stay greater than 22 days had a hazard ratio of 0.708 [95% CI (0.556, 0.902)].

Discussion

Previous studies have observed that HAIs impact re-hospitalizations, which further contributes to the growing issue of HAIs and the problem they create for patients and healthcare providers (34-36, 52). The aim of this secondary data analysis was to determine an association between CLABSI infection during a patient's index hospitalization and readmission to an acute care hospital. Patients were identified as either having a CLABSI or not having a CLABSI, and the frequency of readmission was measured either during the 30 days following hospital discharge or as time till first re-admission.

The final logistic regression model indicated a statistically significant association between CLABSI status and readmission to an acute care hospital, which varied by the effect modifiers length of stay and the chronic condition, rheumatoid arthritis. Odds ratios for readmission decreased as length of stay increased for patients exposed to a CLABSI, regardless of rheumatoid arthritis status (Table 9). CLABSI infection also increased the odds of readmission among patients diagnosed with rheumatoid arthritis, for a fixed length of stay. For example, the odds ratio among patients with rheumatoid arthritis and length of stay between zero and six days was 18.376 [95% CI (3.777, 89.409), whereas the odds ratio among patients without rheumatoid arthritis and the same length of stay was 11.172 [95% CI (2.307, 54.093)]. The odds ratio among patients without rheumatoid arthritis but with a length of stay over 22 days was 0.965 [95% CI (0.674, 1.384)], which did not indicate that the odds of readmission for those with a CLABSI was significantly higher compared to those without a CLABSI.

The final stratified Cox model also demonstrated a statistically significant association between the exposure and the outcome, modified by effect modifiers such as length of stay, rheumatoid arthritis, depression, and chronic kidney disease. Similar to logistic models, the hazard ratios decreased as length of stay increased for CLABSI patients, regardless of rheumatoid arthritis, depression, and chronic kidney disease (Table 12). CLABSI increased the hazard of readmission among rheumatoid arthritis patients for a fixed length of stay, depression, and chronic kidney disease. The hazard for re-hospitalization was almost always significantly higher for CLABSI patients with the shortest length of stay. For the most part, CLABSI was not associated with a higher hazard of re-hospitalization for patients with depression or chronic kidney disease, at various levels of length of stay. However the hazard ratios were significantly less than one for patients who had a longer length of stay (i.e., between 13 and 22 days or greater than 22 days) and diagnosed with depression and chronic kidney disease, but not with rheumatoid arthritis. For example, the hazard ratio for patients with a length of stay greater than 22 days and diagnosed with depression and chronic kidney disease but not with rheumatoid arthritis was 0.708 [95% CI (0.556, 0.902)]. The findings on depression and chronic kidney disease should be interpreted with caution as they may not imply clinical significance; while these hazard ratios were statistically significant, their effects were small in comparison to those of length of stay and rheumatoid arthritis. The hazard ratios were higher for patients without depression than for patients with depression, at various levels of length of stay, rheumatoid arthritis, and chronic kidney disease. The same pattern was seen for chronic kidney disease; the hazard ratios were higher for

patients without chronic kidney disease than for those with the diagnosis, at various levels of length of stay, rheumatoid arthritis, and depression.

Prior research has demonstrated how HAIs can be indicators of adverse events (34). Results from our analysis were parallel; CLABSI was determined to be significantly associated with readmission to an acute care hospital, for patients with shorter lengths of stays during the index visit and rheumatoid arthritis (Tables 9 and 12).

There are few studies that have established relationships between re-hospitalization and the variables interacting with CLABSI. Kaboli et al. concluded that patients with an increased length of stay had a higher likelihood of readmission, a three percent increase for every one extra day of stay (53). In this analysis, a longer length of stay during the primary hospital stay was also associated with both a higher risk and rate of re-hospitalization (Tables 3, 5). Interestingly, this study found that if a patient was exposed to CLABSI in the index hospitalization, a shorter length of stay indicated both a higher odds and hazard of readmission, given fixed rheumatoid arthritis status (Tables 9, 12). This analysis also demonstrated that exposure to CLABSI increased both the odds and hazard of re-hospitalization if the patient was also diagnosed with rheumatoid arthritis (Tables 9, 12). Kartha et al. concluded that patients who were hospitalized within the past six months and were depressed were three times more likely to be readmitted within 90 days (54). This was parallel to the findings of this analysis; the rate of re-hospitalization within 30 days was 1.66 times higher for non-CLABSI patients with depression [IDR= 1.655, 95% CI (1.542, 1.778)] (Table 5). But it was also concluded that patients who were exposed to CLABSI, diagnosed with both depression and chronic

kidney disease, and had a longer length of stay (i.e. between 13 and 22 days or greater than 22 days) had a significantly decreased hazard of hospital readmission (Table 12).

HAIs are a source of unnecessary cost issues to hospitals (6). Re-hospitalizations are just as costly by accounting for up to two thirds of a hospital's spending (55). A previous research study indicated that HAIs were found responsible for at least 14% of hospital readmissions (34). Similarly, the current data analysis has shown that exposure to CLABSI is a strong indicator of re-hospitalizations. As this trend may continue, healthcare administrators and patients would benefit from studies that analyze the costs created by these readmission issues. Presently, there is little research on specific HAIs such as CLABSI, and their impact on re-hospitalization, let alone cost issues that are the result of this impact. Future investigations could estimate the increased costs for patients who were readmitted to acute care hospitals due to their exposure to CLABSI, and analyze hospital or insurance provider savings if readmissions and HAIs were prevented.

In addition, hospitals could focus on applying evidence-based practices to prevent CLABSIs, which would in turn reduce the number of re-hospitalizations. Studies have shown that activities such as practicing hand hygiene, applying maximal sterile barriers and chlorhexidine for skin asepsis, avoiding the femoral site, and removing unnecessary lines are strategies to decrease the number of CLABSI cases (9, 22). As a result, the number of readmission cases should follow suit and decrease as well.

Strengths and Limitations

Data from the NHSN and MEDPAR were linked to identify patients who were both infected with CLABSI and re-hospitalized and therefore did not solely depend on patients' ICD-9-CM codes. Although ICD-9-CM codes are commonly used to define infections for hospital bills and other administrative data, previous research has shown their inability to properly differentiate HAIs (53). In fact, a previous study found that administrative data often misclassified non-CLABSI cases as true CLABSI cases, which produced a different number of cases compared to that of surveillance data (44). This was no different prior to the linkage of datasets in this analysis; thus the linkage allowed for CLABSI patients to be more appropriately identified and closely matched to non-CLABSI study participants, creating a sample of patients who were comparable, allowing for better control of confounding. Previous studies using only ICD-9-CM codes for identification of CLABSI would suffer from strong misclassification bias in determining the exposure status.

The data for readmissions were based on the MEDPAR dataset that used beneficiary claims. Thus according to beneficiary claims, any hospital visit following the primary hospitalization could have been defined as a re-hospitalization. Therefore it is unclear whether these claims differentiated between a true, unplanned re-hospitalization and a planned hospital visit following discharge. Though this analysis defined a readmission as something that occurs unplanned, it is possible that some of the "readmissions" included in the analysis were incorrectly defined or incorporated. In addition, using administrative data such as claims information could entail more complications. For instance, diagnosis information could have been misrepresented

because the physician did not properly recognize nor diagnose the disease, documentation was not legibly written, the health record abstractor did not correctly interpret or enter the data, or the proper code was not identified for the diagnosed disease (56). If any of the above occurred, there would be no way the analyst would know or be able to fix the issues. Therefore the use of surveillance data via NHSN was critical in properly identifying and differentiating between CLABSI and non-CLABSI patients. Note that determining CLABSI status based on NHSN data minimized the misclassification bias due to exposure, but there could have been further misclassification bias in the demographic or readmission data if the claims were not linked properly. Future studies can avoid bias by using methods such as hospital surveillance, to carefully measure readmission and other demographic data.

A large sample size with a considerable number of CLABSI cases was available for the analysis. This allowed for precise estimates of effects and the ability to detect small differences in exposure. Data were collected from eight states but state information was excluded from the models since the data were assumed to be representative of a national sample, especially since readmission data (provided by the MEDPAR dataset) were based on all US hospital inpatient stays for Medicare beneficiaries. The benefit of having data from multiple hospitals allowed for the findings to be generalized on a large-scale national level, unlike research performed on one hospital, where the findings could only be generalized to the study population or institutions that admit high-risk patients such as a particular study's hospital (57). However, the effect of patient's location on his/her exposure status or readmission could not be examined in this analysis.

Two types of analyses were conducted to explore the study question: logistic regression analysis and survival analysis. With the logistic regression analysis, the occurrence of readmission was observed within the first 30 days from hospital discharge. The survival analysis measured time to first readmission. Both the logistic regression and survival analyses were multivariate analyses, which accounted for effect modification and confounding from other demographic and clinical characteristics. However, both analyses only took into account the first occurrence of re-hospitalization rather than the total number of readmissions over the 30-day period. The logistic regression analysis focused on readmissions that occurred within the first 30 days of discharge, which meant there was a short period allowed for readmission. The statistically significant association between exposure and outcome meant the outcome event was closely related to the index visit. On the other hand, the logistic regression analysis was unable to look at events greater than 30 days of discharge whereas the survival analysis followed individuals well beyond 30 days. Observations analyzed within the survival analysis would be censored due to loss of follow-up, dropout, or by the end of the new study period. Both the logistic regression analysis and the survival analysis observed a statistically significant association between CLABSI and 30-day readmission. This association was modified by effect modifiers such as length of stay and rheumatoid arthritis for the logistic regression analysis, while the final model for the survival analysis was modified by length of stay, rheumatoid arthritis, depression, and chronic kidney disease. Similar findings were observed by previous studies. Sreeramoju et al. determined a significant association between readmission and HAIs, according to a multivariate logistic regression model including age, sex, Hispanic ethnicity, and the need for an interpreter. The need for an

interpreter appeared to be significantly associated with the outcome due to exposure (34). Emerson et al. concluded from their research that patients with a positive clinical culture for various HAIs such as MRSA, vancomycin-resistant enterococci, or *Clostridium difficile* acquired more than 48 hours after the index hospital visit had a higher hazard of re-hospitalization, adjusting for age, sex, length of stay, ICU status, Charlson comorbidity index, and year of hospital visit (52). The findings of this data analysis contribute to the validity of these previous studies on HAIs and readmission. In addition, these findings further examine the role of CLABSI and its impact on re-hospitalizations, which has yet to be addressed.

Future Steps

Final models were created by performing a logistic regression analysis and a survival analysis. This provided insight on the proportion of readmission within 30 days and the time to first event such as readmission, death, or December 31, 2009, the end of the study period. In addition, a Poisson longitudinal analysis would have been appropriate to carry out by counting the number of readmissions on a weekly basis and extending the window for readmission from 30 days to 90 days. By doing so, data on the number of readmissions could be collected and analyzed to determine a trend of whether readmissions occur immediately following discharge, after some time from discharge, or displaying no pattern at all. In addition, other healthcare facilities were excluded from the analysis since the data analysis solely focused on acute care hospitals. Similar studies could be implemented at long-term care facilities or nursing homes to see if there are differences in the likelihood of readmission among patients who were exposed to CLABSI.

It is important to note that there have not been many studies pertaining to the topic of CLABSI and hospital readmissions. Though the current results may bear statistical significance, they may not necessarily hold clinical significance. For instance, it was concluded from both the logistic regression and survival analyses that a shorter length of stay and a diagnosis of rheumatoid arthritis were associated with a higher odds and hazard of readmission for patients exposed to CLABSI (Tables 9, 12). In addition, hazard ratios were significantly less than one for patients who had a longer length of stay (i.e. between 13 and 22 days or greater than 22 days) and diagnosed with depression and chronic kidney disease, but not with rheumatoid arthritis. These findings have yet to be

confirmed with other epidemiological and clinical research. Studies on HAIs, such as CLABSI, and their role in re-hospitalizations are still being explored, thus the results of this analysis indicate the need for further research studies to be performed in order to draw firmer conclusions. The analysis should be repeated among different populations for consistency.

The results of this analysis draw attention to the consequence of HAIs, as demonstrated by the significant association between CLABSI and hospital readmissions. By addressing this public health issue, patient burden and excess healthcare costs could be averted. Future studies on re-hospitalizations based on exposure to other HAIs would be beneficial; if findings can be validated through other studies, hospital administrators and healthcare professionals would have more incentive to work towards preventing HAIs from occurring. This would help decrease the number of both HAI incidence and HAI-related re-hospitalizations, allowing for healthier patients and safer healthcare practices.

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Table 1. Baseline characteristics of the population used for logistic regression analysis, US, January 1, 2008-December 30, 2009

	Total Population		**Exposed to CLABSI**					
	Total		**Yes**		**No**			
	n=7107	%	n=726	%	n=6381	%	χ^2	p-value
Readmitted within 30 days	1960	27.58%	283	38.98%	1677	26.28%	52.636	<0.001
CLABSI	726	10.22%	----	----	----	----	----	----
Race							22.606	<0.001
White	5937	83.54%	586	80.72%	5351	83.86%		
Black	941	13.24%	130	17.91%	811	12.71%		
Other	229	3.22%	10	1.38%	219	3.43%		
Sex							0.570	0.450
Male	3704	52.12%	388	53.44%	3316	51.97%		
Age§	76.543	(7.606)	75.018	(7.297)	76.717	(7.621)		<0.001
ICU Status§§	4951	69.66%	496	68.32%	4455	69.82%	0.691	0.406
Central line procedure code§§	1916	26.96%	357	49.17%	1559	24.43%	202.639	<0.001
Length of stay§§							1425.182	<0.001
1 (0-6 days)	1999	28.13%	11	1.52%	1988	31.15%		
2 (7-12 days)	2276	32.02%	52	7.16%	2224	34.85%		
3 (13-22 days)	1580	22.23%	186	25.62%	1394	21.85%		
4 (over 22 days)	1252	17.62%	477	65.70%	775	12.15%		
GAGNE score							137.015	<0.001
0	475	6.68%	105	14.46%	370	5.80%		
1	375	5.28%	16	2.20%	359	5.63%		
2	581	8.18%	19	2.62%	562	8.81%		
3	1325	18.64%	126	17.36%	1199	18.79%		
4	1239	17.43%	163	22.45%	1076	16.86%		
5	1153	16.22%	128	17.63%	1025	16.06%		
6	1959	27.56%	169	23.28%	1790	28.05%		

Alzheimer's disease	542	7.63%	46	6.34%	496	7.77%	1.911	0.167
Alzheimer's disease and related disorders	1385	19.49%	136	18.73%	1249	19.57%	0.294	0.588
Acute myocardial infarction	276	3.88%	28	3.86%	248	3.89%	0.002	0.969
Atrial fibrillation	1521	21.40%	147	20.25%	1374	21.53%	0.640	0.424
Breast cancer	150	2.11%	15	2.07%	135	2.12%	0.008	0.930
Cataracts	1303	18.33%	130	17.91%	1173	18.38%	0.099	0.753
Chronic heart failure	3621	50.95%	399	54.96%	3222	50.49%	5.200	0.023
Chronic obstructive pulmonary disease	2239	31.50%	242	33.33%	1997	31.30%	1.254	0.263
Depression	1335	18.78%	157	21.63%	1178	18.46%	4.278	0.039
Diabetes	3112	43.79%	333	45.87%	2779	43.55%	1.421	0.233
Endometrial cancer	23	0.32%	1	0.14%	22	0.34%	0.866	0.725
Glaucoma	645	9.08%	58	7.99%	587	9.20%	1.157	0.282
Hip/pelvic fracture	102	1.44%	9	1.24%	93	1.46%	0.219	0.640
Ischemic heart disease	4762	67.00%	486	66.94%	4276	67.01%	0.001	0.970
Chronic kidney disease	2789	39.24%	340	46.83%	2449	38.38%	19.532	<0.001
Lung cancer	215	3.03%	24	3.31%	191	2.99%	0.217	0.641
Osteoporosis	878	12.35%	73	10.06%	805	12.62%	3.947	0.047
Prostate cancer	360	5.07%	29	3.99%	331	5.19%	1.929	0.165
Rheumatoid Arthritis	1799	25.31%	181	24.93%	1618	25.36%	0.062	0.803
Rectal cancer	363	5.11%	37	5.10%	326	5.11%	0.000	0.988
Stroke or transient Ischemic attack	820	11.54%	98	13.50%	722	11.31%	3.046	0.081

§Values expressed as mean (standard deviation)

§§During the index CLABSI visit

Table 2. Baseline characteristics of the population used for survival analysis, US, January 1, 2008-December 30, 2009

	Total Population		**Exposed to CLABSI**					
	Total		**Yes**		**No**			
	n=8097	%	n=917	%	n=7180	%	χ^2	p-value
Follow up time†	2991.617	----	219.247	----	2772.370	----	----	----
Readmitted (failure)	4512	55.72 %	550	59.98%	3962	55.18%	----	----
Censored	3585	44.28 %	367	40.02%	3218	44.82%	----	----
CLABSI	917	11.33%	----	----	----	----	----	----
Race							17.996	<0.001
White	6740	83.24%	739	80.59%	6001	83.58%		
Black	1094	13.51%	160	17.45%	934	13.01%		
Other	263	3.25%	18	1.96%	245	3.41%		
Sex							0.201	0.654
Male	4235	52.30%	486	53.00%	3749	52.21%		
Age§	76.886	(7.696)	75.485	(7.422)	77.065	(7.712)		<0.001
ICU Status§§	5661	69.91%	626	68.27%	5035	70.13%	1.336	0.248
Central line procedure code§§	2322	28.68%	472	51.47%	1850	25.77%	262.711	<0.001
Length of stay§§							1569.583	<0.001
1 (0-6 days)	2170	26.80%	13	1.42%	2157	30.04%		
2 (7-12 days)	2532	31.27%	71	7.74%	2461	34.28%		
3 (13-22 days)	1859	22.96%	241	26.28%	1618	22.53%		
4 (over 22 days)	1536	18.97%	592	64.56%	944	13.15%		
Died within 30 days of discharge	1010	12.47%	192	20.94%	818	11.39%	67.857	<0.001
Died after 30 days of discharge	1873	23.13%	241	26.28%	1632	22.73%	5.768	0.016
GAGNE score							162.600	<0.001

0	549	6.78%	129	14.07%	420	5.85%		
1	388	4.79%	19	2.07%	369	5.14%		
2	607	7.50%	21	2.29%	586	8.16%		
3	1481	18.29%	154	16.79%	1327	18.48%		
4	1436	17.73%	212	23.12%	1224	17.05%		
5	1310	16.18%	163	17.78%	1147	15.97%		
6	2326	28.73%	219	23.88%	2107	29.35%		
Alzheimer's disease	704	8.69%	72	7.85%	632	8.80%	0.926	0.336
Alzheimer's disease and related disorders	1767	21.82%	204	22.25%	1563	21.77%	0.109	0.742
Acute myocardial infarction	329	4.06%	40	4.36%	289	4.03%	0.237	0.627
Atrial fibrillation	1806	22.30%	218	23.77%	1588	22.12%	1.287	0.257
Breast cancer	172	2.12%	23	2.51%	149	2.08%	0.733	0.392
Cataracts	1430	17.66%	149	16.25%	1281	17.84%	1.418	0.234
Chronic heart failure	4237	52.33%	525	57.25%	3712	51.70%	10.051	0.002
Chronic obstructive pulmonary disease	2618	32.33%	307	33.48%	2311	32.19%	0.621	0.431
Depression	1560	19.27%	202	22.03%	1358	18.91%	5.072	0.024
Diabetes	3592	44.36%	435	47.44%	3157	43.97%	3.962	0.047
Endometrial cancer	26	0.32%	1	0.11%	25	0.35%	1.453	0.354
Glaucoma	722	8.92%	75	8.18%	647	9.01%	0.694	0.405
Hip/pelvic fracture	121	1.49%	14	1.53%	107	1.49%	0.007	0.932
Ischemic heart disease	5445	67.25%	620	67.61%	4825	67.20%	0.062	0.803
Chronic kidney disease	3299	40.74%	457	49.84%	2842	39.58%	35.415	<0.001
Lung cancer	268	3.31%	31	3.38%	237	3.30%	0.016	0.899
Osteoporosis	981	12.12%	90	9.81%	891	12.41%	5.142	0.023
Prostate cancer	404	4.99%	39	4.25%	365	5.08%	1.183	0.277
Rheumatoid arthritis	2074	25.61%	242	26.39%	1832	25.52%	0.327	0.568
Rectal cancer	391	4.83%	45	4.91%	346	4.82%	0.014	0.906

Stroke or transient Ischemic attack	968	11.96%	128	13.96%	840	11.70%	3.944	0.047

†Values expressed as person-years

§Values expressed as mean (standard deviation)

§§During the index CLABSI visit

Table 3. Crude measures of association (risk ratio) between readmission and potential confounders

	Readmitted within 30 days	
	Crude Risk Ratio*	95% CI
CLABSI	1.483	(1.342, 1.639)
Race		
White†	----	----
Black	1.227	(1.109, 1.358)
Other	1.335	(1.115, 1.598)
Sex		
Male	1.032	(0.957,1.113)
ICU Status§§	1.024	(0.943, 1.111)
Central line procedure code§§	1.256	(1.160, 1.360)
Length of stay§§		
1 (0-6 days)†	----	----
2 (7-12 days)	1.218	(1.092, 1.359)
3 (13-22 days)	1.361	(1.213, 1.526)
4 (over 22 days)	1.853	(1.661, 2.066)
GAGNE score		
0†	----	----
1	0.481	(0.366, 0.633)
2	0.692	(0.565, 0.848)
3	0.782	(0.664, 0.919)
4	0.920	(0.785, 1.078)
5	0.882	(0.750, 1.036)
6	0.999	(0.862, 1.158)
Alzheimer's disease	1.308	(1.159, 1.476)
Alzheimer's disease and related disorders	1.281	(1.176, 1.396)
Acute myocardial infarction	1.094	(0.910, 1.315)
Atrial fibrillation	1.155	(1.059, 1.260)
Breast cancer	0.991	(0.761, 1.290)
Cataracts	0.885	(0.799, 0.981)
Chronic heart failure	1.313	(1.217, 1.418)
Chronic obstructive pulmonary disease	1.282	(1.187, 1.384)
Depression	1.274	(1.167, 1.390)
Diabetes	1.230	(1.141, 1.326)
Endometrial cancer	1.104	(0.594, 2.050)
Glaucoma	0.903	(0.786, 1.037)
Hip/pelvic fracture	1.031	(0.756, 1.406)

Ischemic heart disease	1.160	(1.068, 1.261)
Chronic kidney disease	1.361	(1.263, 1.467)
Lung cancer	1.187	(0.976, 1.445)
Osteoporosis	0.879	(0.777, 0.993)
Prostate cancer	0.965	(0.810, 1.150)
Rheumatoid Arthritis	1.060	(0.974, 1.154)
Rectal cancer	0.915	(0.764, 1.096)
Stroke or transient Ischemic attack	1.353	(1.224, 1.496)

§§During the index CLABSI visit

†Reference categories

Table 4. Stratified and adjusted measures of association (risk ratio) between CLABSI and readmission, adjusted for potential confounders

	Readmission within 30 days			
	Stratified Risk Ratio	Adjusted Risk Ratio*	95% CI	Breslow-Day p-value
Race		1.479	(1.338, 1.635)	0.844
White	1.493			
Black	1.459			
Other	1.138			
Sex		1.482	(1.347, 1.645)	0.143
Male	1.378			
Female	1.608			
Central line procedure code§§		1.412	(1.277, 1.562)	0.027
Yes	1.236			
No	1.599			
Length of stay§§		1.149	(1.029, 1.282)	<0.001
1 (0-6 days)	3.476			
2 (7-12 days)	1.662			
3 (13-22 days)	1.092			
4 (over 22 days)	1.067			
GAGNE score		1.438	(1.300, 1.591)	0.146
0	1.510			
1	2.640			
2	2.805			
3	1.289			
4	1.373			
5	1.478			
6	1.353			
Alzheimer's disease		1.490	(1.348, 1.646)	0.794
Yes	1.476			
No	1.491			
Alzheimer's disease and related disorders		1.487	(1.346, 1.642)	0.779
Yes	1.470			
No	1.492			
Acute myocardial infarction		1.483	(1.342, 1.639)	0.119
Yes	0.945			
No	1.508			
Atrial fibrillation		1.486	(1.345, 1.642)	0.338
Yes	1.585			

No	1.457			
Breast cancer		1.483	(1.342, 1.639)	0.913
Yes	1.543			
No	1.482			
Cataracts		1.482	(1.342, 1.638)	0.921
Yes	1.526			
No	1.474			
Chronic heart failure		1.466	(1.327, 1.619)	0.981
Yes	1.438			
No	1.509			
Chronic obstructive pulmonary disease		1.475	(1.335, 1.630)	0.418
Yes	1.362			
No	1.548			
Depression		1.471	(1.331, 1.625)	0.073
Yes	1.211			
No	1.563			
Diabetes		1.476	(1.336, 1.631)	0.256
Yes	1.367			
No	1.590			
Endometrial cancer		1.484	(1.343, 1.640)	0.370
Yes	0.000			
No	1.486			
Glaucoma		1.482	(1.341, 1.637)	0.371
Yes	1.265			
No	1.499			
Hip/pelvic fracture		1.483	(1.342, 1.639)	0.318
Yes	2.153			
No	1.475			
Ischemic heart disease		1.483	(1.342, 1.639)	0.833
Yes	1.461			
No	1.535			
Chronic kidney disease		1.446	(1.309, 1.597)	0.481
Yes	1.364			
No	1.540			
Lung cancer		1.482	(1.342, 1.638)	0.750
Yes	1.326			
No	1.489			
Osteoporosis		1.479	(1.338, 1.634)	0.271
Yes	1.779			
No	1.449			
Prostate cancer		1.483	(1.342, 1.639)	0.206

Yes	1.038			
No	1.502			
Rheumatoid Arthritis		1.483	(1.343, 1.639)	0.006
Yes	1.829			
No	1.367			
Rectal cancer		1.483	(1.342, 1.639)	0.364
Yes	1.196			
No	1.498			
Stroke or transient Ischemic attack		1.472	(1.333, 1.627)	0.339
Yes	1.262			
No	1.517			

§§During the index CLABSI visit

Table 5. Crude measures of association (rate ratio) between first readmission and potential confounders

	Rate to first readmission	
	Crude Rate Ratio	95% CI
CLABSI	1.755	(1.606, 1.919)
Race		
White†	----	----
Black	1.476	(1.361, 1.601)
Other	1.312	(1.121, 1.535)
Sex		
Male	1.001	(0.945, 1.062)
ICU Status§§	0.912	(0.856, 0.971)
Central line procedure code§§	1.425	(1.337, 1.518)
Length of stay§§		
1 (0-6 days)†	----	----
2 (7-12 days)	1.171	(1.082, 1.268)
3 (13-22 days)	1.489	(1.369, 1.619)
4 (over 22 days)	2.251	(2.064, 2.455)
Died within 30 days of discharge	9.454	(8.409, 10.630)
GAGNE score		
0†	----	----
1	0.411	(0.338, 0.500)
2	0.617	(0.525, 0.724)
3	0.904	(0.792, 1.032)
4	1.090	(0.955, 1.244)
5	1.192	(1.043, 1.363)
6	1.542	(1.362, 1.746)
Alzheimer's disease	1.609	(1.451, 1.783)
Alzheimer's disease and related disorders	1.816	(1.694, 1.946)
Acute myocardial infarction	1.445	(1.257, 1.660)
Atrial fibrillation	1.429	(1.334, 1.530)
Breast cancer	0.973	(0.791, 1.196)
Cataracts	0.832	(0.770, 0.899)
Chronic heart failure	1.851	(1.745, 1.963)
Chronic obstructive pulmonary disease	1.601	(1.506, 1.702)
Depression	1.655	(1.542, 1.778)
Diabetes	1.553	(1.465, 1.646)
Endometrial cancer	1.494	(0.867, 2.575)
Glaucoma	0.946	(0.853, 1.048)
Hip/pelvic fracture	1.428	(1.128, 1.809)

Ischemic heart disease	1.401	(1.315, 1.493)
Chronic kidney disease	1.987	(1.874, 2.107)
Lung cancer	1.402	(1.197, 1.643)
Osteoporosis	0.969	(0.885, 1.061)
Prostate cancer	1.042	(0.911, 1.193)
Rheumatoid Arthritis	1.249	(1.169, 1.334)
Rectal cancer	0.866	(0.755, 0.993)
Stroke or transient Ischemic attack	1.832	(1.682, 1.996)

§§During the index CLABSI visit

†Reference categories

Table 6. Stratified and adjusted measures of association (rate ratio) between CLABSI and first readmission, adjusted for potential confounders

	Rate to first readmission			
	Stratified Rate Ratio	Adjusted Rate Ratio	95% CI	Breslow-Day p-value
Race		1.734	(1.585, 1.896)	0.786
White	1.756			
Black	1.633			
Other	1.937			
Sex		1.756	(1.606, 1.919)	0.113
Male	1.646			
Female	1.902			
Central line procedure code§§		1.592	(1.455, 1.743)	<0.001
Yes	1.281			
No	2.003			
Length of stay§§		1.195	(1.082, 1.320)	<0.001
1 (0-6 days)	4.527			
2 (7-12 days)	1.959			
3 (13-22 days)	1.182			
4 (over 22 days)	1.098			
Died within 30 days of discharge		1.616	(1.478, 1.767)	0.006
Yes	1.111			
No	1.695			
GAGNE score		1.657	(1.515, 1.814)	0.002
0	1.693			
1	1.971			
2	3.284			
3	1.465			
4	2.117			
5	1.800			
6	1.320			
Alzheimer's disease		1.753	(1.604, 1.917)	0.087
Yes	1.331			
No	1.797			
Alzheimer's disease and related disorders		1.734	(1.586, 1.896)	0.022
Yes	1.428			
No	1.840			
Acute myocardial infarction		1.746	(1.597, 1.909)	0.047
Yes	1.141			

No	1.786			
Atrial fibrillation		1.756	(1.606, 1.920)	0.880
Yes	1.734			
No	1.763			
Breast cancer		1.755	(1.605, 1.918)	0.005
Yes	3.951			
No	1.729			
Cataracts		1.755	(1.605, 1.918)	0.589
Yes	1.851			
No	1.735			
Chronic heart failure		1.690	(1.546, 1.848)	0.074
Yes	1.583			
No	1.867			
Chronic obstructive pulmonary disease		1.747	(1.598, 1.910)	0.743
Yes	1.712			
No	1.766			
Depression		1.683	(1.540, 1.840)	<0.001
Yes	1.179			
No	1.900			
Diabetes		1.700	(1.555, 1.858)	<0.001
Yes	1.436			
No	2.032			
Endometrial cancer		1.756	(1.606, 1.920)	----
Yes	0			
No	1.760			
Glaucoma		1.754	(1.604, 1.918)	0.508
Yes	1.940			
No	1.739			
Hip/pelvic fracture		1.759	(1.609, 1.923)	0.214
Yes	2.802			
No	1.749			
Ischemic heart disease		1.758	(1.608, 1.922)	0.766
Yes	1.743			
No	1.795			
Chronic kidney disease		1.616	(1.478, 1.767)	<0.001
Yes	1.379			
No	1.927			
Lung cancer		1.759	(1.609, 1.923)	0.301
Yes	2.246			
No	1.744			

Osteoporosis		1.754	(1.605, 1.918)	0.618
Yes	1.877			
No	1.741			
Prostate cancer		1.755	(1.605, 1.919)	0.091
Yes	1.203			
No	1.787			
Rheumatoid Arthritis		1.774	(1.623, 1.939)	<0.001
Yes	2.282			
No	1.630			
Rectal cancer		1.759	(1.609, 1.923)	0.039
Yes	1.121			
No	1.801			
Stroke or transient Ischemic attack		1.704	(1.559, 1.863)	0.007
Yes	1.273			
No	1.804			

§§During the index CLABSI visit

Table 7. Unadjusted logistic regression model with interaction terms

Variable	Parameter Estimate	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
CLABSI	0.1721	0.1540	1.2497	0.264	1.188	(0.878, 1.606)
Race						
White†	----	----	----	----	1.000	---- ----
Black	0.1348	0.0824	2.6773	0.102	1.144	(0.974, 1.345)
Other	0.3437	0.1493	5.2979	0.021	1.410	(1.052, 1.890)
Length of stay§§						
1 (0-6 days)	-0.6280	0.1110	31.9834	<0.001	0.534	(0.429, 0.663)
2 (7-12 days)	-0.3714	0.1002	13.7424	0.000	0.690	(0.567, 0.839)
3 (13-22 days)	-0.3185	0.1021	9.7261	0.002	0.727	(0.595, 0.888)
4 (over 22 days)†	----	----	----	----	1.000	---- ----
Sex						
Male	0.0423	0.0612	0.4776	0.490	1.043	(0.925, 1.176)
Central line procedure code§§	0.1216	0.0768	2.5102	0.113	1.129	(0.972, 1.313)
GAGNE score						
0	-0.0158	0.1209	0.0171	0.896	0.984	(0.777, 1.247)
1	-0.4526	0.1633	7.6829	0.006	0.636	(0.462, 0.876)
2	-0.1431	0.1224	1.3661	0.243	0.867	(0.682, 1.102)
3	-0.1876	0.0879	4.5569	0.033	0.829	(0.698, 0.985)
4	-0.0787	0.0842	0.8741	0.350	0.924	(0.784, 1.090)
5	-0.2014	0.0864	5.4279	0.020	0.818	(0.690, 0.969)
6†	----	----	----	----	1.000	---- ----
Alzheimer's disease	0.1260	0.1223	1.0621	0.303	1.134	(0.893, 1.441)
Alzheimer's disease and related disorders	0.0466	0.0879	0.2814	0.596	1.048	(0.882, 1.245)
Acute myocardial infarction	0.0291	0.1424	0.0418	0.838	1.030	(0.779, 1.361)
Atrial fibrillation	0.0833	0.0698	1.4212	0.233	1.087	(0.948, 1.246)

Breast cancer	0.0006	0.1973	0.0000	0.997	1.001	(0.680,	1.473)
Cataracts	-0.1471	0.074	3.9444	0.047	0.863	(0.747,	0.998)
Chronic heart failure	0.0919	0.0677	1.8427	0.175	1.096	(0.960,	1.252)
Chronic obstructive pulmonary disease	0.2242	0.0633	12.5423	0.000	1.251	(1.105,	1.417)
Depression	0.1939	0.0715	7.3580	0.007	1.214	(1.055,	1.396)
Diabetes	0.1034	0.0597	2.9971	0.083	1.109	(0.986,	1.247)
Endometrial cancer	0.2088	0.5181	0.1625	0.687	1.232	(0.446,	3.402)
Glaucoma	-0.1117	0.0997	1.2549	0.263	0.894	(0.736,	1.087)
Hip/pelvic fracture	-0.0353	0.2359	0.0224	0.881	0.965	(0.608,	1.533)
Ischemic heart disease	0.0352	0.0675	0.2718	0.602	1.036	(0.907,	1.182)
Chronic kidney disease	0.2164	0.0636	11.577	0.001	1.242	(1.096,	1.406)
Lung cancer	0.2796	0.165	2.8703	0.090	1.323	(0.957,	1.828)
Osteoporosis	-0.1019	0.0921	1.2248	0.268	0.903	(0.754,	1.082)
Prostate cancer	-0.0116	0.1313	0.0078	0.930	0.988	(0.764,	1.279)
Rheumatoid arthritis	0.0231	0.0702	0.1079	0.743	1.023	(0.892,	1.174)
Rectal cancer	-0.0192	0.1375	0.0196	0.889	0.981	(0.749,	1.284)
Stroke or transient Ischemic attack	0.2202	0.0859	6.5685	0.010	1.246	(1.053,	1.475)
CLABSI*Central line procedure code	-0.2003	0.1762	1.2924	0.256	0.972	(0.701,	1.349)
CLABSI*Length of stay§§							
1 (0-6 days)	2.1978	0.8124	7.3179	0.007	10.696	(2.208,	51.827)
2 (7-12 days)	0.4149	0.3241	1.6386	0.201	1.799	(0.963,	3.358)
3 (13-22 days)	-0.1196	0.2165	0.3052	0.581	1.054	(0.702,	1.581)
4 (over 22 days)†	0.1721	0.1540	1.2497	0.264	1.188	(0.878,	1.606)
CLABSI*Rheumatoid arthritis	0.5411	0.1960	7.6170	0.006	2.041	(1.336,	3.117)

§§During the index CLABSI visit

†Reference category

Log likelihood= 7287.593

Likelihood chi-square= 22.830
Likelihood p-value <0.001

Table 8. Final logistic regression model containing the interaction terms, CLABSI*Length of stay and CLABSI*Rheumatoid Arthritis

Variable	Parameter Estimate	Standard Error	Wald χ^2	p-value	Odds Ratio	95% CI
CLABSI	0.1148	0.1317	0.7600	0.383	1.122	(0.867, 1.452)
Length of stay§§						
1 (0-6 days)	-0.7239	0.1066	46.1269	<0.001	0.485	(0.394, 0.598)
2 (7-12 days)	-0.4117	0.0977	17.7498	<0.001	0.663	(0.547, 0.802)
3 (13-22 days)	-0.3052	0.1004	9.2309	0.002	0.737	(0.605, 0.897)
4 (over 22 days)†	----	----	----	----	1.000	---- ----
Rheumatoid arthritis	0.0617	0.0674	0.8376	0.360	1.064	(0.932, 1.214)
CLABSI*Length of stay§§				0.004*		
1 (0-6 days)	2.2986	0.8105	8.0429	0.005	----	---- ----
2 (7-12 days)	0.4082	0.3189	1.6384	0.201	----	---- ----
3 (13-22 days)	-0.1501	0.2129	0.4969	0.481	----	---- ----
4 (over 22 days)†	0.1148	0.1317	0.7600	0.383	----	---- ----
CLABSI*Rheumatoid arthritis	0.4976	0.1926	6.6754	0.010	----	---- ----

§§During the index CLABSI visit
†Reference categories

Log likelihood of CLABSI*Length of stay=7410.140
Likelihood chi-square of CLABSI*Length of stay=13.326
*Likelihood p-value of CLABSI*Length of stay=0.004

Table 9. Final odds ratios and 95% CI for CLABSI at the specific levels for the interaction terms, Length of stay and Rheumatoid arthritis

	Rheumatoid arthritis			
	Yes		No	
Length of stay§§	Odds Ratio	95% CI	Odds Ratio	95% CI
1 (0-6 days)	18.376	(3.777 89.409)	11.172	(2.307 54.093)
2 (7-12 days)	2.775	(1.483 5.193)	1.687	(0.936 3.041)
3 (13-22 days)	1.588	(1.030 2.447)	0.965	(0.674 1.384)
4 (over 22 days)†	1.845	(1.262 2.697)	1.122	(0.867 1.452)

§§During the index CLABSI visit

†Reference category

Table 10. Unadjusted stratified Cox model with interaction terms

Variable	Parameter Estimate	Standard Error	Wald χ^2	p-value	Hazard Ratio	95% CI
CLABSI	0.1432	0.1299	1.2138	0.271	1.154	(0.895, 1.489)
Race						
White†	----	----	----	----	1.000	---- ----
Black	0.1359	0.0435	9.7738	0.002	1.146	(1.052, 1.247)
Other	0.2336	0.0813	8.2613	0.004	1.263	(1.077, 1.481)
Length of stay§§						
1 (0-6 days)	-0.4590	0.0535	73.7224	<0.001	0.632	(0.569, 0.702)
2 (7-12 days)	-0.3571	0.0508	49.4794	<0.001	0.700	(0.634, 0.773)
3 (13-22 days)	-0.2641	0.0533	24.5322	<0.001	0.768	(0.692, 0.853)
4 (over 22 days)†	----	----	----	----	1.000	---- ----
Sex						
Male	0.0344	0.0330	1.0891	0.297	1.035	(0.970, 1.104)
Central line procedure code§§	0.0759	0.0347	4.7847	0.029	1.079	(1.008, 1.155)
Alzheimer's disease	-0.0250	0.0643	0.1507	0.698	0.975	(0.860, 1.106)
Alzheimer's disease and related disorders	0.1855	0.0473	15.3483	<0.001	1.204	(1.097, 1.321)
Acute myocardial infarction	0.1463	0.0765	3.6596	0.056	1.158	(0.996, 1.345)
Atrial fibrillation	0.0695	0.0373	3.4695	0.063	1.072	(0.996, 1.153)
Breast cancer	-0.0490	0.1162	0.1774	0.674	0.952	(0.758, 1.196)
Cataracts	-0.1163	0.0400	8.4450	0.004	0.890	(0.823, 0.963)
Chronic heart failure	0.1070	0.0363	8.7015	0.003	1.113	(1.037, 1.195)
Chronic obstructive pulmonary disease	0.1506	0.0335	20.1755	<0.001	1.163	(1.089, 1.241)
Depression	0.1658	0.0411	16.2872	<0.001	1.180	(1.089, 1.279)
Diabetes	0.1497	0.0341	19.2966	<0.001	1.162	(1.087, 1.242)
Endometrial cancer	0.2831	0.2793	1.0272	0.311	1.327	(0.768, 2.294)

Glaucoma	-0.0431	0.0530	0.6614	0.416	0.958	(0.863,	1.063)
Hip/pelvic fracture	0.0223	0.1221	0.0334	0.855	1.023	(0.805,	1.299)
Ischemic heart disease	0.0533	0.0359	2.2085	0.137	1.055	(0.983,	1.132)
Chronic kidney disease	0.2483	0.0356	48.5268	<0.001	1.282	(1.195,	1.375)
Lung cancer	0.1520	0.0832	3.3351	0.068	1.164	(0.989,	1.371)
Osteoporosis	-0.0211	0.0491	0.1848	0.667	0.979	(0.889,	1.078)
Prostate cancer	-0.0219	0.0713	0.0940	0.759	0.978	(0.851,	1.125)
Rheumatoid arthritis	0.0652	0.0372	3.0620	0.080	1.067	(0.992,	1.148)
Rectal cancer	0.0035	0.0751	0.0021	0.963	1.004	(0.866,	1.163)
Stroke or transient Ischemic attack	0.2275	0.0489	21.6854	<0.001	1.256	(1.141,	1.382)
CLABSI*GAGNE score							
0	0.0843	0.1643	0.2630	0.608	1.255	(0.932,	1.691)
1	0.0241	0.3794	0.0040	0.949	1.182	(0.566,	2.469)
2	0.3978	0.3155	1.5898	0.207	1.718	(0.928,	3.180)
3	0.0143	0.1488	0.0092	0.924	1.171	(0.894,	1.532)
4	0.2198	0.1346	2.6674	0.102	1.438	(1.127,	1.834)
5	0.1812	0.1453	1.5561	0.212	1.383	(1.048,	1.489)
6†	0.1432	0.1299	1.2138	0.271	1.154	(0.895,	1.489)
CLABSI*Length of stay§§							
1 (0-6 days)	0.9185	0.3376	7.4028	0.007	2.891	(1.442,	5.799)
2 (7-12 days)	0.2457	0.1864	1.7375	0.188	1.475	(0.999,	2.178)
3 (13-22 days)	0.0493	0.1142	0.1862	0.666	1.212	(0.910,	1.615)
4 (over 22 days)†	0.1432	0.1299	1.2138	0.271	1.154	(0.895,	1.489)
CLABSI*Alzheimer's disease and related disorders	-0.0662	0.1215	0.2973	0.586	1.080	(0.778,	1.500)
CLABSI*Acute myocardial infarction	-0.2575	0.2302	1.2509	0.263	0.892	(0.538,	1.480)
CLABSI*Breast cancer	0.4117	0.3011	1.8694	0.172	1.742	(0.933,	3.251)
CLABSI*Depression	-0.2589	0.1175	4.8525	0.028	0.891	(0.636,	1.247)

CLABSI*Diabetes	-0.1431	0.0955	2.2440	0.134	1.000	(0.760,	1.316)
CLABSI*Chronic kidney disease	-0.1779	0.0988	3.2458	0.072	0.966	(0.739,	1.262)
CLABSI*Rheumatoid arthritis	0.3030	0.1062	8.1465	0.004	1.562	(1.150,	2.122)
CLABSI*Rectal cancer	-0.3782	0.2334	2.6251	0.105	0.791	(0.489,	1.279)
CLABSI*Stroke or transient Ischemic attack	-0.1372	0.1364	1.0115	0.315	1.006	(0.702,	1.441)

§§During the index CLABSI visit
†Reference category

Log likelihood= 58616.521
Likelihood chi-square= 49.518
Likelihood p-value <0.001

Table 11. Final stratified Cox model containing the interaction terms, CLABSI*Length of stay, CLABSI*Depression, CLABSI*Chronic kidney disease, and CLABSI*Rheumatoid Arthritis

Variable	Parameter Estimate	Standard Error	Wald χ^2	p-value	Hazard Ratio	95% CI
CLABSI	0.1334	0.0850	2.4650	0.116	1.143	(0.967, 1.350)
Length of stay§§						
1 (0-6 days)	-0.5099	0.0522	95.6219	<0.001	0.601	(0.542, 0.665)
2 (7-12 days)	-0.3949	0.0502	61.9521	<0.001	0.674	(0.611, 0.743)
3 (13-22 days)	-0.2772	0.0531	27.2926	<0.001	0.758	(0.683, 0.841)
4 (over 22 days)†	----	----	----	----	1.000	---- ----
Depression	0.2446	0.0395	38.4035	<0.001	1.277	(1.182, 1.380)
Chronic kidney disease	0.3715	0.0335	123.0348	<0.001	1.450	(1.358, 1.548)
Rheumatoid arthritis	0.0914	0.0362	6.3776	0.012	1.096	(1.021, 1.176)
CLABSI*Length of stay§§				0.030*		
1 (0-6 days)	0.9958	0.3182	9.7948	0.002	----	---- ----
2 (7-12 days)	0.2548	0.1822	1.9571	0.162	----	---- ----
3 (13-22 days)	0.0494	0.1131	0.1905	0.663	----	---- ----
4 (over 22 days)†	0.1334	0.0850	2.4650	0.116	----	---- ----
CLABSI*Depression	-0.2750	0.1138	5.8372	0.016	----	---- ----
CLABSI*Chronic kidney disease	-0.2038	0.0925	4.8522	0.028	----	---- ----
CLABSI*Rheumatoid arthritis	0.2804	0.1048	7.1607	0.008	----	---- ----

§§During the index CLABSI visit

†Reference category

Log likelihood of CLABSI*Length of stay=58782.521

Likelihood chi-square of CLABSI*Length of stay=8.952

*Likelihood p-value of CLABSI*Length of stay=0.030

Table 12. Final hazard ratios and 95% CI for CLABSI at specific values of the interaction terms including Length of stay, Rheumatoid arthritis, Depression, and Chronic kidney disease

	Rheumatoid arthritis		Depression		Chronic kidney disease			
Length of stay§§	Yes	No	Yes	No	Yes	No	Hazard Ratio	95% CI
1 (0-6 days)	x			x		x	4.094	(2.209 7.587)
2 (7-12 days)	x			x		x	1.952	(1.339 2.845)
3 (13-22 days)	x			x		x	1.589	(1.228 2.056)
4 (over 22 days)†	x			x		x	1.513	(1.203 1.902)
1 (0-6 days)	x		x			x	3.340	(1.830 6.093)
2 (7-12 days)	x		x			x	1.592	(1.092 2.321)
3 (13-22 days)	x		x			x	1.296	(0.997 1.686)
4 (over 22 days)†	x		x			x	1.234	(0.974 1.563)
1 (0-6 days)	x			x	x		3.110	(1.613 5.995)
2 (7-12 days)	x			x	x		1.482	(0.992 2.216)
3 (13-22 days)	x			x	x		1.207	(0.903 1.613)
4 (over 22 days)†	x			x	x		1.149	(0.877 1.505)
1 (0-6 days)	x		x		x		2.537	(1.346 4.780)
2 (7-12 days)	x		x		x		1.209	(0.819 1.785)
3 (13-22 days)	x		x		x		0.985	(0.746 1.299)
4 (over 22 days)†	x		x		x		0.937	(0.725 1.212)
1 (0-6 days)		x		x		x	3.093	(1.647 5.808)
2 (7-12 days)		x		x		x	1.474	(1.037 2.097)
3 (13-22 days)		x		x		x	1.201	(0.974 1.480)
4 (over 22 days)†		x		x		x	1.143	(0.967 1.350)
1 (0-6 days)		x	x			x	2.523	(1.364 4.667)
2 (7-12 days)		x	x			x	1.203	(0.845 1.712)
3 (13-22 days)		x	x			x	0.979	(0.788 1.216)
4 (over 22 days)†		x	x			x	0.932	(0.780 1.113)

1 (0-6 days)	x		x	x	2.349	(1.189	4.643)
2 (7-12 days)	x		x	x	1.120	(0.750	1.672)
3 (13-22 days)	x		x	x	0.912	(0.689	1.207)
4 (over 22 days)†	x		x	x	0.868	(0.672	1.120)
1 (0-6 days)	x	x		x	1.916	(0.991	3.707)
2 (7-12 days)	x	x		x	0.913	(0.619	1.347)
3 (13-22 days)	x	x		x	0.744	(0.569	0.972)
4 (over 22 days)†	x	x		x	0.708	(0.556	0.902)

§§During the index CLABSI visit

†Reference category

Figure 1. Population created to analyze risk, which excludes hospital deaths, transfers, and deaths following discharge from index visit, US, January 1, 2008-December 30, 2009

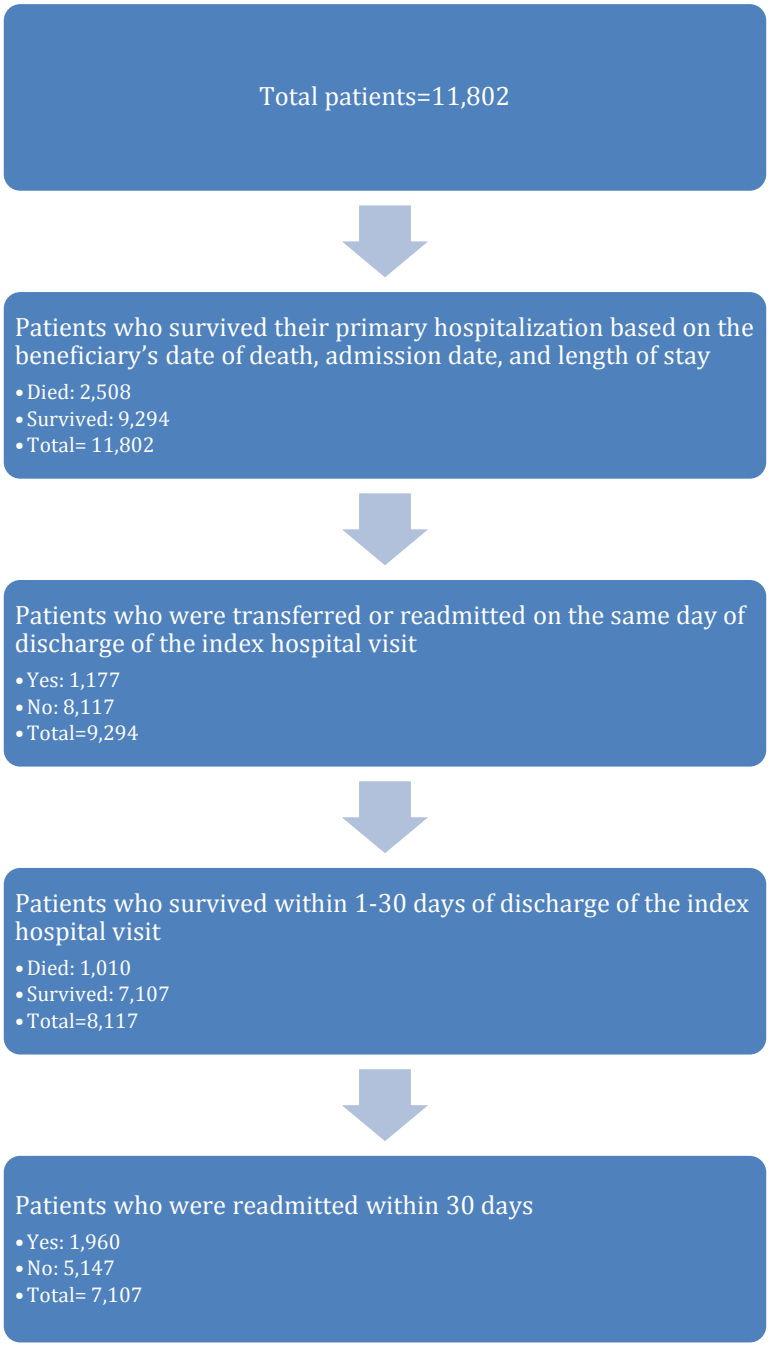
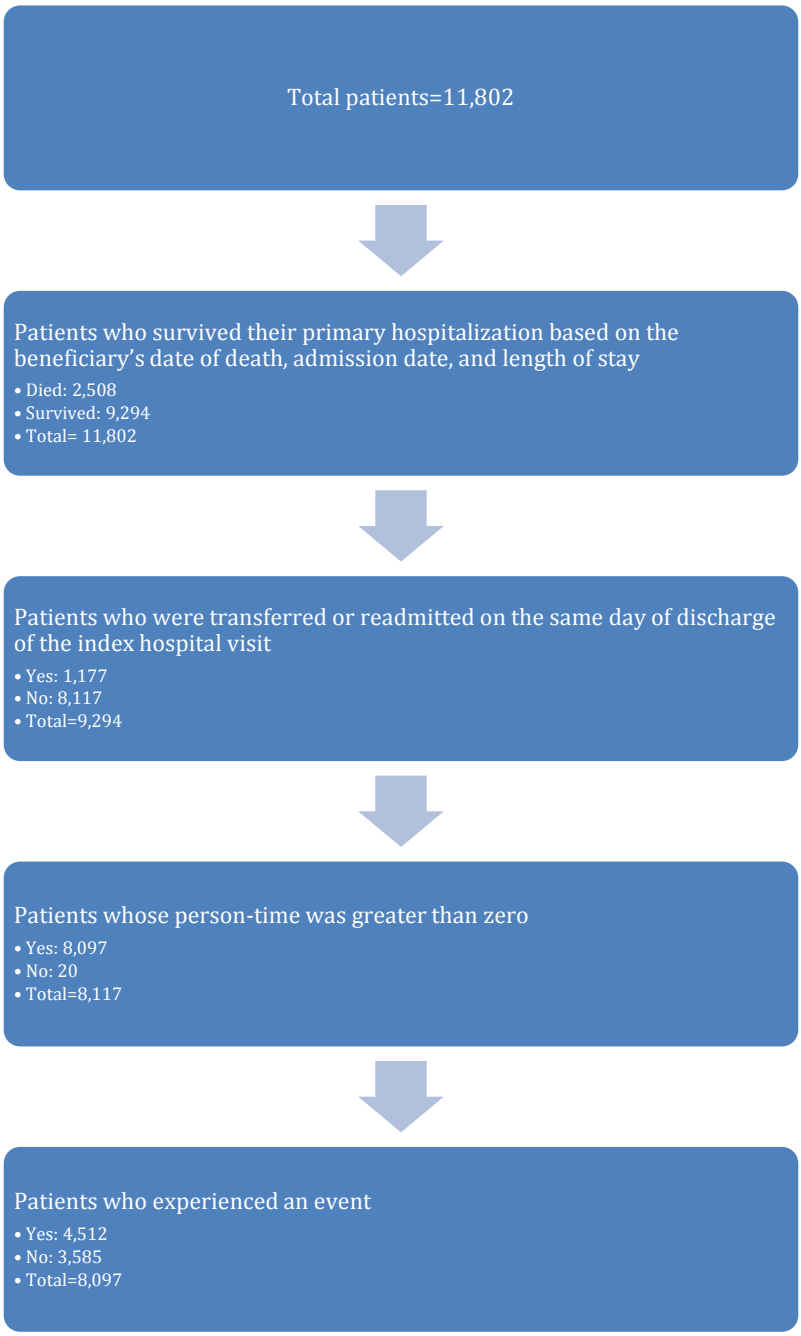


Figure 2. Population created to analyze rate, which excludes hospital deaths and transfers following discharge from index visit, US, January 1, 2008-December 30, 2009



Appendix 1. Emory Institutional Review Board Approval

EMORY UNIVERSITY

Institutional Review Board

TO: Carolyn Chi
Principal Investigator
Public Health

DATE: July 23, 2012

RE: **Expedited Approval**

IRB00058968

The Association between Central Line-Associated Bloodstream Infections and Hospital Readmissions

Thank you for submitting a new application for this protocol. This research is eligible for expedited review under 45 CFR.46.110 and/or 21 CFR 56.110 because it poses minimal risk and fits the regulatory category F[5] as set forth in the Federal Register. The Emory IRB reviewed it by expedited process on 7/22/2012 and granted approval effective from **7/22/2012** through **7/21/2013**. Thereafter, continuation of human subjects research activities requires the submission of a renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above. Please note carefully the following items with respect to this approval:

- CFR # F(5)
- Complete HIPAA waiver was granted
- Approved Forms:
    - Scientific Protocol Carolyn Chi (Vers. 6/29/2012)

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol

deviations) must be reported to the IRB according to our Policies & Procedures at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, study design, you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you

Aric Edwards
Analyst Assistant
This letter has been digitally signed

CC:

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu/