CELLULITIS: COMORBIDITIES AS A DETERMINANT OF HOSPITAL LENGTH-OF-STAY

by

Celia Mayol

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Abstract

Background: Cellulitis is a common skin and soft-tissue infection that often recurs in some patients. Patients with presenting comorbid conditions may require hospitalization which increases the cost of treatment. However, little is known about comorbid conditions as determinants for a patient’s hospital length-of-stay.

Objective: 1) To profile the characteristics of patients admitted to Ontario hospitals with a diagnosis of cellulitis according to key demographic, clinical and geographic factors; 2) To examine, among patients hospitalized with cellulitis, comorbidities as possible determinants of hospital length-of-stay.

Methods: A retrospective cohort of 7863 patients was identified from the Discharge Abstract Database from April 1, 2006 to March 31, 2008. The Charlson Comorbidity Index was used to measure patients’ comorbidities. Univariate analyses were performed to describe the study population. The chi-square test was used to assess the association between categorical variables. The Kaplan-Meier product-limit method and log-rank test were used to estimate and to test the difference in the distributions of hospital lengths-of-stay between patients with and without comorbidities. Cox regression modeling was used to estimate the comorbidities’ effect on hospital length-of-stay while adjusting for confounding factors. The restricted means of lengths-of-stay were given to estimate and compare the average duration of hospitalization. The effects of specific Charlson comorbidities on hospital length-of-stay were similarly investigated.
Results: Forty-six percent (3588/7863) of patients were diagnosed with Charlson comorbidities. Those patients were significantly older ($p<.0001$), and more likely to be female ($p=.006$) and to have lower limb cellulitis ($p<.001$) and *C. difficile* infections ($p<.0001$), compared to patients without comorbidities. Patients with comorbidities stayed significantly longer in hospital (8.0 vs. 5.3 days, $p<.0001$). Comorbidities independently decreased the instantaneous discharge rate by 37% (95% CI, 34% to 40%, $p<.001$). Hospital lengths-of-stay increased with increasing index of comorbidity. The means of hospital lengths-of-stay for patients with a cumulative index of 1, 2, 3, and 4 (or more than 4) were 7.4, 7.6, 8.8, and 9.7 days, respectively.

Conclusion: The Charlson Comorbidity Index is predictive of longer hospital lengths-of-stay in adult patients diagnosed with cellulitis and may be a useful tool in the decision-making process during clinical management of these patients.
Acknowledgements

Dr. Mackillop, Department chairman, once wisely advised this candidate that the composition of the supervisory committee is the single best predictor of success of a candidate’s project. No truer words could have been spoken.

To Dr. Keyue Ding, my primary supervisor, I gratefully acknowledge his unfailing support, statistical insight and expertise, and guidance. To Dr. William Pickett, whose experience and direction helped to guide this project smoothly, I am also indebted. And many thanks to Dr. Kieran Moore, who with his imagination and intellectual curiosity, helped to lead me on this path of enquiry, and gave me support and encouragement.

I also wish to acknowledge the staff of Kingston General Hospital who provided invaluable assistance: to director Barbara Nayler who graciously directed her staff to extend all assistance I may require; to Diane Guthrie, Rajanpreet Gill, Suzanne Burt and Eric Chase, for their time and patience in helping me to become familiarized with ICD-10 CA diagnoses coding and coding standards, and with the Discharge Abstract Database data elements.

To Strategic Information Development staff Rory Skelly, I am thankful for his support and encouragement, and for providing me with electronic copies of CIHI materials. To Rod Albrough, Data Management Coordinator, my thanks for his patience in filling my data request.

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Chapter 1
Introduction

1.1 Background and Rationale

Cellulitis is a common skin and soft-tissue infection and often recurs in some patients. It affects patients of all age-groups and sex. The presence and the stability of comorbid conditions that may complicate or delay the resolution of the infection, influence the clinical management of the disease (1,2). Several decisions need to be made, including, which type and route of antimicrobial agent to initiate, and whether to treat on an outpatient basis or to hospitalize the patient. The decisions that are made have an impact on the cost of the treatment. The average unit cost to hospitalize a patient with cellulitis in Canada (2004-2005) was $5,951 (3). Of this, 24.8% was attributed to the presence or treatment of complexities.

1.2 Objectives

The objectives of this study were:

- to profile characteristics of patients admitted to Ontario hospitals with a diagnosis of cellulitis according to key demographic, clinical and geographic factors;
- to examine, among patients hospitalized with cellulitis, comorbidities as possible determinants of hospital length-of-stay.

These study objectives are important because a better understanding of the relationship between specific comorbidities and hospital length-of-stay for patients with cellulitis may help
physicians to identify patients at risk for longer hospitalization and to aid in their treatment decisions at initial patient contact. During the patient’s hospital stay, this knowledge may help the health care team to develop clinical pathways, and to allocate resources that may improve the patient’s outcome and shorten their hospital stay.
Chapter 2
Literature Review

2.1 Literature Search Keywords

The CINAHL and MEDLINE databases were searched using the MESH keywords (and combinations thereof): skin and soft tissue infections, risk factors, hospital length-of-stay, cellulitis, methicillin-resistant Staphylococcus aureus, (re)admission, epidemiology, comorbidity, comorbidities, and Canada. An online PubMed search was also conducted using similar keywords. Citations in both searches were tracked. Studies that were shown as related to the original results in PubMed were also tracked. Reference lists of relevant articles were then exhaustively reviewed to identify studies for inclusion.

2.2 Symptoms of Cellulitis

Cellulitis is an acute infection of the lower dermis and subcutaneous soft tissue that is commonly treated in ambulatory and hospitalized patients. It is characterized by a rapidly spreading area of edema, redness, and heat, accompanied by pain and tenderness. Regional lymph nodes and vessels may become inflamed and swollen. Signs and symptoms of systemic toxicity may include fever or hypothermia, tachycardia, hypotension, confusion, and abnormal laboratory values (4-6). Among patients treated in emergency departments or admitted as inpatients, the lower limbs are the most commonly affected sites (7-10).
2.3 Causative Agents and Identification

Numerous organisms can cause cellulitis. The most commonly isolated organisms are gram-positive beta-haemolytic streptococci and *Staphylococcus aureus* (4,5,11). Other gram-positive, gram-negative and anaerobic bacteria are also known pathogens (8,12). Unusual organisms may cause infections in circumstances such as in animal bites, fresh/saltwater exposure, and certain occupational exposures (4,11). Obtaining a specimen for culture is often difficult in cases of non-purulent cellulitis. Needle aspirations and punch biopsies may yield an organism in 5-40% and 20-30% percent of cases respectively, and positive blood cultures are rare (<5% cases) (4).

2.4 Incidence of Cellulitis and Methicillin-resistant *Staphylococcus aureus*

Disease incidence and rates of admissions to hospitals due to cellulitis may be increasing globally (13,14). The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) has been clearly linked to increased visits to emergency departments for skin and soft-tissue infections (15), but there is no clear evidence that it has led to an increase of community-onset cellulitis. There is potential for concern because MRSA infection has been associated with higher mortality rates and is an independent risk factor for increased hospital length-of-stay in patients with skin, bone and soft-tissue infections (12).

2.5 Global Risk Factors Associated with Cellulitis

Global comorbid conditions such as diabetes, obesity, smoking, intravenous drug use, cancer, and immunosuppression are often associated with cellulitis (8-10,12,16-18). Only
diabetes and obesity have been shown to be proven risk factors and the evidence is far from conclusive (10,16,19). Ethnicity, as a proxy for biological and physiological differences between white and dark skin, may also be a determinant (19).

2.6 Local Risk Factors Associated with Cellulitis

Local risk factors are the most strongly associated with the development of cellulitis (16,17,19). The disruptions of the cutaneous barrier by cuts, blisters, fungal infections between the toes, cracks and fissures, scaling, macerations, and ulcers provide means by which a pathogen can enter the skin, although a point of entry may not always be identified (16,17,20,21). Local predisposing factors such as oedema (due to lymphatic obstruction or venous insufficiency) and a previous history of cellulitis are also important risk factors (16,17,19). Comorbid conditions affecting the local area, such as venous insufficiency and peripheral vascular disease, are also predisposing factors (10,16-18). A history of previous surgery on the affected side may also predispose a patient to the development of cellulitis, as in the case of saphenectomy (17) and orthopaedic surgery (19) in lower limb cellulitis, and breast conservation procedure in breast cellulitis (11). A history of deep vein thrombosis may also be an important risk factor (19).

2.7 Mortality and Morbidity

Mortality in patients hospitalized with a diagnosis of cellulitis is low and estimates of mean length-of-hospital stay have ranged between 4 and 11 days (8-10,12,18,22). A two-year study of 4668 patients with a diagnosis of cellulitis in 134 US institutions reported that 0.07% of
patients died during their hospital stay (12). In contrast, a 6-year study of 332 patients in one hospital in Spain found 5% mortality during hospitalization (10). An Italian hospital review of patients admitted during an 8-year period identified 107 patients diagnosed with cellulitis, all of whom were cured by the time of discharge (8). Variations in hospital lengths-of-stay may be due to differences in the study population characteristics, medical treatment provided, and other factors.

2.8 Factors Associated with Patients’ Length-of-Hospital Stay

Few studies exist that have investigated factors associated with length-of-hospital stay in patients with cellulitis. A New Zealand study of 51 inpatients investigated 85 clinical variables and their association with hospital length-of-stay (18). Diuretic use was the only factor that was independently associated with longer stays (> 7 days) in multivariate analyses. Diuretic use may be a proxy for an underlying comorbid conditions. However, chronic oedema, vascular disease and congestive heart failure were not each independently associated with hospital length-of-stay. A second study (10) that examined complications and mortality among patients with cellulitis found that being male, having 2 or more comorbid conditions, cutaneous necrosis at presentation, or hypoalbuminemia were each significantly associated with complications during hospitalization, leading to longer hospital stays. Male sex, comorbid conditions of congestive heart failure, morbid obesity, having two or more comorbid conditions, shock/multi-organ failure, hypoalbuminemia and renal insufficiency, and Pseudomonas aeruginosa cellulitis were factors associated with mortality in univariate analysis. Of the comorbid conditions, congestive heart failure was the most strongly associated with death. Multivariate analyses were not performed in this study due to small sample sizes. Other factors that may be associated with
longer hospital stays are complicated and polymicrobial infections (12). An infection was considered complicated if there was a documented skin and soft-tissue-related procedure code within 2 days of admission or if comorbid conditions were present (12).

2.9 Long term Morbidity of Patients after an Episode of Cellulitis

Long-term morbidity from cellulitis includes persistent/chronic oedema, ulceration, and susceptibility to further recurrence (20,21). The probability of recurrence within 2 years varies from 5 to 93% depending on the presence or absence of additional risk factors (23).

2.10 Summary

There are few studies in Canada that examine the role of comorbidities in the length-of-hospital stay in patients admitted for cellulitis. Research to date has focused more on the role of comorbidities as predisposing risk factors and less on their role as prognostic factors. Morbidity related to complications arising from hospitalization, frequent recurrence of infection, and their associated costs, warrant efforts to explore the roles that these comorbidities play in prolonging hospital admissions. Prevention strategies have been recommended in the literature, but increased efforts need to be directed towards those at greater risk for longer hospital stays.
Chapter 3
Study Design and Measurement of Exposure and Outcome

3.1 Study Design

I performed a retrospective cohort study. The study period spanned two years ending on March 31, 2008. The primary exposure measures were patients’ comorbidities associated with specific disease types. The primary outcome measure was the patients’ hospital lengths-of-stay.

3.2 Study Population

The study population included patients discharged from Ontario hospitals with a main problem diagnosis of cellulitis during the period April 1, 2006 to March 31, 2008. The Canadian Enhancement to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10 CA) codes (24) for the diagnoses of interest were used to identify these patients.

3.2.1 Inclusion Criteria

Inclusion criteria were as follows:

1) Patients admitted to any Ontario hospital during the period April 1, 2006 to March 31, 2008;
2) Patient age of 15 years or more;
3) Diagnosis of cellulitis (L03.0-L03.9). Table 3.1 lists all the diagnoses of cellulitis that were included in subsequent analyses.

Table 3.1 ICD-10 CA Codes for Cellulitis Diagnoses and Descriptions (24)

<table>
<thead>
<tr>
<th>ICD-10 CA Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L03</td>
<td>Cellulitis</td>
</tr>
<tr>
<td>L03.0</td>
<td>Cellulitis of finger and toe</td>
</tr>
<tr>
<td>L03.00</td>
<td>Cellulitis of finger</td>
</tr>
<tr>
<td>L03.01</td>
<td>Cellulitis of toe</td>
</tr>
<tr>
<td>L03.1</td>
<td>Cellulitis of other parts of limb</td>
</tr>
<tr>
<td>L03.10</td>
<td>Cellulitis of upper limb</td>
</tr>
<tr>
<td>L03.11</td>
<td>Cellulitis of lower limb</td>
</tr>
<tr>
<td>L03.2</td>
<td>Cellulitis of face</td>
</tr>
<tr>
<td>L03.3</td>
<td>Cellulitis of trunk</td>
</tr>
<tr>
<td>L03.30</td>
<td>Cellulitis of chest wall</td>
</tr>
<tr>
<td>L03.31</td>
<td>Cellulitis of abdominal wall</td>
</tr>
<tr>
<td>L03.32</td>
<td>Cellulitis of umbilicus</td>
</tr>
<tr>
<td>L03.33</td>
<td>Cellulitis of groin</td>
</tr>
<tr>
<td>L03.34</td>
<td>Cellulitis of back</td>
</tr>
<tr>
<td>L03.35</td>
<td>Cellulitis of buttock</td>
</tr>
<tr>
<td>L03.36</td>
<td>Cellulitis of perineum</td>
</tr>
<tr>
<td>L03.39</td>
<td>Cellulitis of trunk, unspecified</td>
</tr>
<tr>
<td>L03.8</td>
<td>Cellulitis of other sites</td>
</tr>
<tr>
<td>L03.9</td>
<td>Cellulitis, unspecified</td>
</tr>
</tbody>
</table>

3.3 Exclusion Criteria

Exclusion criteria were as follows:

1) Cellulitis attributable to any external cause, specifically, traumatic wound, cellulitis complicating a diabetic ulcer, surgical complication, animal bites, and intravenous drug use;
2) Cellulitis of the breast were excluded because it is primarily limited to a certain population group and because ICD10-CA coding for breast mastitis includes carbuncles/abscesses with cellulitis (24)

3.4 Source of Data

The Canadian Institute for Health Information (CIHI) manages the Discharge Abstract Database (DAD). The DAD compiles demographic, administrative and clinical data for all patients who are discharged from hospitals (inpatient acute, chronic, rehabilitation) and day surgeries in Ontario (25).

Mandatory and optional (depending on the province) data elements are abstracted from hospital patient information by trained facility nosologists. This is done using abstraction software developed according to CIHI’s specifications. Records are submitted by hospitals electronically to CIHI. Data submission and facility access to CIHI’s national data holdings are facilitated through service packages called Core Plans. Provincial and Territorial Ministries of Health purchase these packages on behalf of their facilities and mandate submission to various CIHI databases. The DAD data for this study was made available by request through Kingston General Hospital’s Strategic Information Development department that has access to CIHI’s national data holdings through the Ministry’s Core Plan.
3.4.1 Validity of Data Source

CIHI’s data quality study utilizing DAD data for 2005-2006 (26) found that only 76% of all significant diagnoses on patients’ charts were captured in the abstract. Among the clinical conditions reported, ischemic heart diseases (e.g. myocardial infarction) were found to be reported 86% of the time, while congestive heart failure was more likely to be underreported at 76%. Chronic lower respiratory diseases were reported 79% of the time. Although diabetes was found to be significantly underreported at 52%, CIHI’s mandatory requirement starting in 2006 to abstract diabetes diagnoses whenever documented in the patient chart regardless of whether there is supporting documentation that the disease had a significant impact on the patient’s length-of-stay should have addressed this problem of underreporting. There was no information regarding the other clinical conditions in the Charlson Comorbidity Index and they can be assumed to be, on average, underreported 24% of the time. The review also found that 86% of therapeutic interventions on the musculoskeletal system documented in the chart were found in the DAD abstract.

When the DAD abstract was compared with the original documentation in the patient’s chart to determine whether chart documentation supported the inclusion of the diagnoses and interventions in the abstract, the study found that 25% of diagnoses were not supported by chart documentation. Diagnoses of chronic lower respiratory diseases were overreported 14% of the time, while ischaemic heart diseases (e.g. myocardial infarction) were overreported 16% of the time. Diagnoses of other forms of heart disease (e.g., congestive heart failure) were overreported 33% of the time, and diabetes 21% of the time. On average in Ontario, 73% of diagnoses and 81% of interventions in DAD abstracts were confirmed in chart review.
With respect to correctness of diagnoses coding, the chart review found exact ICD-10-CA code agreement (A.NN.NN format) for 80% of the significant diagnoses and 92% agreement to the code category (A.NN format). Similar results were found for codes for interventions.

3.5 Measurement of the Exposure Variable

The main exposure variable in the study was patients’ comorbidities. Comorbidity refers to coexisting medical conditions or disease processes that are additional to an initial diagnosis (27). The Charlson Comorbidity Index was the primary tool to measure comorbidity (28). The two functional forms of measures of comorbidity were:

1) the presence/absence of a Charlson comorbidity (a binary outcome); and,

2) an index of comorbidity. Each of Charlson comorbidities has a corresponding weight that was applied as a factor when the comorbidity was present. The value of the index is the sum of all the comorbidity weights. For this study, the values ranged from 0-4, where 0 indicated no comorbidity and 4 included all values greater than or equal to 4.

In this study, the term “comorbidity” or “comorbidities” referred to the clinical conditions in the Charlson Comorbidity Index. The term “comorbidity” was also used as the variable representing the presence/absence of any of the Charlson comorbidities. Where it was used as a variable, it was referred to as such in the rest of the thesis.
3.5.1 The Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) is a weighted index that takes into account both the number and the seriousness of comorbid diseases (28). Table 3.2 lists the clinical conditions included in the Charlson Comorbidity Index, their weights, and the corresponding ICD-10 coding algorithms (29-31). Except for one diagnosis code for peripheral vascular disease common in other algorithms (30,31) and added to Table 3.2, the Quan (29) ICD-10 CA algorithm of the Charlson Comorbidity Index. A comparison of the Quan algorithm with other algorithms showed that it has the most additional codes (in addition to codes common across other algorithms). Using data from four countries, the Quan algorithm demonstrated higher median discrimination in its ability to predict mortality compared to other versions (32). In this study, one diagnosis code for peripheral vascular disease, R02 which is a code for gangrene, was added to the list of diagnostic codes because it was common to two other algorithms but was not included in Quan’s.
### Table 3.2 Clinical Conditions of the Charlson Comorbidity Index (28) and ICD-10 CA Algorithms (29-31)

<table>
<thead>
<tr>
<th>Clinical Conditions</th>
<th>Weight</th>
<th>ICD-10 Codes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>I21.x, I22.x, I25.2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
<td>I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, R02, Z95.8, Z95.1, Z95.5, Z95.9</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
<td>G45.x, G46.x, H34.0, I60.x–I69.x</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
<td>F00.x–F03.x, F05.1, G30.x, G31.1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1</td>
<td>I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3, J84.1</td>
</tr>
<tr>
<td>Connective Tissue Disease</td>
<td>1</td>
<td>M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>1</td>
<td>K25.x–K28.x</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1</td>
<td>B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4</td>
</tr>
<tr>
<td>Hemiplegia or paraplegia</td>
<td>2</td>
<td>G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9</td>
</tr>
<tr>
<td>Renal disease</td>
<td>2</td>
<td>I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2</td>
</tr>
<tr>
<td>Any malignancy, including lymphoma and leukemia except for malignant neoplasm of skin</td>
<td>2</td>
<td>C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>3</td>
<td>I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>6</td>
<td>C77.x–C80.x</td>
</tr>
<tr>
<td>Acquired Immune Deficiency Syndrome/HIV</td>
<td>6</td>
<td>B20.x–B22.x, B24.x</td>
</tr>
</tbody>
</table>

* An "x" indicates that all sub-categories are included.
An additional comorbidity, *Clostridium difficile* infection, was considered separately in this study. Like the Charlson comorbidities, this disease process may have been present in addition to the primary disease of cellulitis; however, it is not part of the Charlson Comorbidity Index. Its effect on hospital lengths-of-stay was also considered in the analyses (See section 3.6.5).

### 3.5.2 Validity of the Measurement Tool

Although developed to predict one-year mortality during a cohort study of medical patients, the Charlson Comorbidity Index has been validated in its ability to predict risk for death from comorbid conditions after 10 years in a cohort of 685 breast cancer patients (23), and in larger groups (>10,000) of post-surgical patients, patients with heart disease, and patients with pneumonia (33). It has been demonstrated to have construct validity, good test-retest reliability, and moderate to good inter-rater reliability (33). In a review of 106,673 hospitalization records in Spain, higher Charlson Comorbidity Index scores were found to be associated with longer lengths-of-hospital stay (34).

### 3.6 Potential Confounders and Other Variables

Factors that had the potential to be associated with the exposure (Charlson comorbidities) and the outcome (hospital length-of-stay) required consideration among cellulitis patients. Other variables that had the potential to be independently associated with hospital lengths-of-stay were also included in order to improve the precision of the estimate of association of exposure and outcome.
3.6.1 Age

Age is a potential confounder because comorbid diseases are known to be more common in older populations than in younger populations (35). Average durations of hospital lengths-of-stay among patients hospitalized with cellulitis also appear to increase with age, from 3.8 days for the 15-44 age-group to 5.1 in the 65+ group (22). Whether the increased lengths-of-stay are related to the presence of comorbidities, to normal aging processes (e.g. reduced mobility, slower healing process), or to other factors such as socio-economic conditions, could not be determined. In this thesis, the age variable in the study was treated as a continuous variable as well as categorized into 5 age groups: 15-44, 45-64, 65-74, 75-84, and 85+.

3.6.2 Sex

Male patients hospitalized with cellulitis have been found to experience more complications leading to longer stays and higher rates of mortality (10). This study categorized patients by sex, with males coded as the reference category.

3.6.3 Geographic Designation

Cellulitis is easier to manage when diagnosed and treated early. Accessibility of primary care and health care seeking behaviour may vary by geographic location. The study categorized patients as either rural or urban residents based on their postal code forward sortation area (the first three characters of the postal code). A “0” indicates rural residency (36) and all others were coded as urban residents.
3.6.4 Anatomical Site

Cellulitis of the lower limbs is the most frequently reported in comparison with cellulitis of the upper limb, face, or other parts of the body. Patients admitted with cellulitis of the lower limbs also tend to have more comorbidities (8). It is unclear if lower limb cellulitis is associated with complications that prolong hospital stays compared to cellulitis in other areas, e.g. upper limbs. Anatomical site was categorized into lower limb cellulitis vs. all other anatomical sites.

3.6.5 Clostridium difficile Infection

Clostridium difficile is an anaerobic bacterium responsible for a large proportion of infectious diarrhea associated with antibiotic-use in hospitalized patients. It is also associated with longer hospital lengths-of-stay (37). This variable was categorized into presence or absence of C. difficile infection and represented an additional diagnosis (comorbidity) that is not considered in the Charlson Comorbidity Index (28).

3.6.6 Microorganism Resistance

When a patient fails to respond to empiric treatment, a change in patient management may prolong hospitalization. Since 2006, ICD10-CA has assigned provisional codes for research purposes to identify the type of drug resistant micro-organism (24). Where identified, the analyses included the resistance status of the microorganism.
3.6.7 Complicated Cellulitis

A documented skin and soft-tissue-related procedure code is a factor that may be associated with longer hospital lengths-of-stay (12). Cellulitis cases that involved interventions, namely, amputation of joints or bones, destruction of skin or soft tissue, drainage of the affected area, partial or total excision, release of muscles or tendons, and repair of skin, muscles or phalanges, were coded as complicated cellulitis. This variable was categorized into complicated or uncomplicated cellulitis (10,12).

3.7 Measurement of Outcome

Hospital length-of-stay is defined as the total number days the patient spent in hospital, for treatment of cellulitis as the most responsible diagnosis, until discharged from acute care. This included transfers to other acute care hospitals and readmissions within 28 days for the same diagnosis. It did not include days spent in Alternate Level of Care (ALS) prior to being discharged from the acute care hospital. In 2006, the average length-of-hospital stay for all age groups with abscesses/cellulitis diagnoses in the United States was 4.4 days (14).
Chapter 4
Data Analyses

4.1 Data Selection

Data from the Discharge Abstract Database (DAD) indicated that from April 1, 2006 to March 31, 2007, there were 4941 patients discharged from Ontario hospitals who had a main diagnosis of cellulitis and who were 15 years and older. From April 1, 2007 to March 31, 2008, there were 5084 discharges. In total, there were 10025 discharges during the study period.

The Discharge Abstract Database system created a unique encounter number for each admission/discharge record. When a patient was transferred to another facility or was readmitted to the same facility for the same diagnosis (after initial discharge), an additional unique encounter number was generated. The same patient in the dataset may therefore have more than one encounter number. For each encounter, the patient’s comorbidities, length-of-stay, and other data were recorded. Comorbidities were assigned diagnosis codes by facility coders, consistent with ICD-10 CA coding standards (38).

All of the DAD data elements (39) that were extracted for this study are shown in Table 4.1.
<table>
<thead>
<tr>
<th>Data Element</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiscal Year</td>
<td>2007, 2008</td>
</tr>
<tr>
<td>Encounter Number</td>
<td>Numeric</td>
</tr>
<tr>
<td>Scrambled Health Insurance Number</td>
<td>Alpha Numeric</td>
</tr>
<tr>
<td>Forward Sortation Area (3 characters)</td>
<td>Alpha-Numeric-Alphabet</td>
</tr>
<tr>
<td>Sex</td>
<td>Male, Female</td>
</tr>
<tr>
<td>Age</td>
<td>Numeric</td>
</tr>
<tr>
<td>Date of Admission</td>
<td>yyyymmdd</td>
</tr>
<tr>
<td>Admission Entry Code</td>
<td>D-Direct E-Emergency P-Day Procedure C-Clinic</td>
</tr>
<tr>
<td>Readmission Code</td>
<td>1- Planned readmission from previous acute care</td>
</tr>
<tr>
<td></td>
<td>2- Acute ≤7 days, unplanned, same facility, same/related diagnosis</td>
</tr>
<tr>
<td></td>
<td>3- Acute 8-28 days, unplanned, same facility, same/related diagnosis</td>
</tr>
<tr>
<td></td>
<td>4- ≤7 days, unplanned from day surgery, same/related diagnosis</td>
</tr>
<tr>
<td></td>
<td>5- New patient to acute care unit</td>
</tr>
<tr>
<td></td>
<td>9 - Unplanned readmission &gt;28 days, unplanned not same/related diagnosis</td>
</tr>
<tr>
<td>Date of Discharge</td>
<td>yyyymmdd</td>
</tr>
<tr>
<td>Diagnosis Prefix</td>
<td>C- Cause of death codes Q- Questionable or query diagnoses</td>
</tr>
<tr>
<td>Diagnosis Code</td>
<td>ICD-10 CA</td>
</tr>
<tr>
<td>Diagnosis Type</td>
<td>M-Most Responsible Diagnosis</td>
</tr>
<tr>
<td></td>
<td>1- Pre-admit Comorbidity 6-Asterisk Code for Case Mix Group Assignment</td>
</tr>
<tr>
<td></td>
<td>2- Post-admit Comorbidity 7,8- Restricted to CIHI</td>
</tr>
<tr>
<td></td>
<td>3- Secondary Diagnosis 9- V01-Y98, U98, U99 - external cause of injury code</td>
</tr>
<tr>
<td></td>
<td>4- Morphology Code 0- Restricted to newborn codes</td>
</tr>
<tr>
<td></td>
<td>5- Admitting Diagnosis</td>
</tr>
</tbody>
</table>
Table 4.1 Discharge Abstract Database (DAD) Data Elements

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis Description</td>
<td></td>
</tr>
<tr>
<td>Intervention Date</td>
<td></td>
</tr>
<tr>
<td>Intervention Code</td>
<td>Canadian Classification of Health Intervention (CCI) – Most principal intervention</td>
</tr>
<tr>
<td>Intervention Description</td>
<td></td>
</tr>
<tr>
<td>Special Care Unit Number</td>
<td>2 digits identifying where critical care was received</td>
</tr>
<tr>
<td>Special Care Hours</td>
<td></td>
</tr>
<tr>
<td>Place</td>
<td>Institution location</td>
</tr>
<tr>
<td>Hospital Local Health Integration Network (LHIN)</td>
<td>1-14</td>
</tr>
<tr>
<td>Patient Local Health Integration Network (LHIN)</td>
<td>1-14</td>
</tr>
<tr>
<td>Acute Length-of-Stay (LOS)</td>
<td>Numeric (days)</td>
</tr>
<tr>
<td>Alternate Level of Care (ALC) LOS</td>
<td>Numeric (days)</td>
</tr>
<tr>
<td>Total Length-of-stay</td>
<td>Numeric (days = Acute LOS + Alternate Level of Care LOS)</td>
</tr>
<tr>
<td>Alternate Level of Care Flag</td>
<td>Yes - ALC LOS No - No ALC LOS</td>
</tr>
<tr>
<td>Discharge Disposition</td>
<td>01- Transferred to an acute care inpatient institution</td>
</tr>
<tr>
<td></td>
<td>02- Transferred to continuing care</td>
</tr>
<tr>
<td></td>
<td>03- Transferred to other facility including ambulatory care, hospice, jails, etc.</td>
</tr>
<tr>
<td></td>
<td>04- Transferred to home setting with support services</td>
</tr>
<tr>
<td></td>
<td>05- Discharged home with no support services</td>
</tr>
<tr>
<td></td>
<td>06- Left against medical advice</td>
</tr>
<tr>
<td></td>
<td>07- Died</td>
</tr>
<tr>
<td></td>
<td>08 - Cadaveric donor admitted for organ/tissue retrieval</td>
</tr>
<tr>
<td></td>
<td>09- Stillbirth</td>
</tr>
<tr>
<td>Institution Number, Institution Name</td>
<td>CIHI Institution Number, Institution Name</td>
</tr>
<tr>
<td>Institution From (Name &amp; Type)</td>
<td></td>
</tr>
<tr>
<td>Institution To (Name &amp; Type)</td>
<td></td>
</tr>
</tbody>
</table>
4.2 Creation of Dataset for Analysis

Several steps were taken to create the final dataset that was used in the analysis. They are as follows:

4.2.1 Creation of Sub-datasets

The first step was to analyze the comorbidity diagnosis codes of each encounter to determine if any of the 17 Charlson comorbidities, resistant microorganism, *C. difficile* infection, and the exclusion criteria (injection drug use, animal bites, post-surgical complication, trauma, and complication of a diabetic ulcer) were identified. A diagnosis variable was created for each diagnosis of interest. When any diagnosis code of interest was identified, the diagnosis variable was coded as “1”, or coded as “0” if otherwise. Separate sub-datasets were created for Charlson comorbidities, other diagnoses of interest (resistant microorganism and, *C. difficile* infection), and exclusion criteria diagnoses. Comorbidity diagnoses that did not contribute to the analysis were then deleted.

Subsets of data were also created for other data of interest, namely demographic data (age, sex, gender, geographic designation, scrambled Health Insurance Number), anatomical site, procedures or interventions, admission and discharge information (including acute length-of-stay), and hospital information (size and location by Local Health Integration Network). The common variable in all sub-datasets was the encounter number.
4.2.2 Combining Sub-datasets

The data set was then re-created by combining all sub-datasets according to the common encounter number. Of the 10025 encounters, 200 had no Health Insurance Number (scrambled), 8067 were single admission/discharge, and 1758 were multiple admission/discharge (772 patients). The Health Insurance Number was missing when the insured patient did not have available their Health Insurance Number, had chosen not to register for provincial health insurance, or had out-of-country or Federal government insurance.

4.2.3 Adjustments for Transfers and Readmissions

The dataset was then reviewed for patient transfers and readmissions. When a patient had one or more transfers to an acute care facility prior to being discharged home or to a non-acute care facility, the total hospital length-of-stay was calculated as the sum of all the acute lengths-of-stay. An admission for the same diagnosis in 28 days or less was considered a readmission, and the total length-of-stay became the sum of admission and readmissions. After adjusting for transfers and readmissions, only the first admission was included in the dataset. This was done in order to satisfy the assumption of independence for each observation. Subsequent admissions could not be determined as being independent without reviewing record-level patient data which were not accessible. The resulting dataset had 9039 observations.
4.3 Application of Exclusion Criteria and Censoring

The next step was to apply the exclusion criteria. Where any exclusion criteria diagnosis (traumatic wound, cellulitis complicating a diabetic ulcer, surgical complication, animal bites, and intravenous drug use/injury) was present, the observation was deleted. The dataset was reduced to 7863 observations.

In the final step, censoring was applied to determine the primary outcome of hospital length-of-stay. Hospital length-of-stay is defined as the total number of days the patient spent in hospital for the treatment of cellulitis as the most responsible diagnosis, until discharged from acute care. This included transfers to other acute care hospitals and readmissions within 28 days for the same diagnosis. It did not include days spent in Alternate Level of Care (ALS) prior to being discharged from the acute care hospital. For patients who died during their hospitalization, the hospital lengths-of-stay were censored at death date. For patients with lengths-of-stay greater than 28 days, their lengths-of-stay were censored at the 28th day. Patients that were coded as transferred to another acute care facility, but where no further information was found, were also censored at the date of transfer. A comorbidity index was calculated for each observation by applying the weights in the Charlson Comorbidity Index (28).

A flow chart of the dataset creation is shown in Figure 4.1.
Figure 4.1 Preparation of the Discharge Abstract Database (DAD) Data to Create the Dataset for Analysis

Discharge Abstract Database
Fiscal Years 2006 & 2007

Cellulitis as main diagnosis
n=10025 unique encounters (admissions/discharges)

Admissions with no health care number n=200

Patients with single admissions n=8067

772 patients with multiple admissions n=1758

Adjusted for transfers and readmissions n=1371

First visits only n=772

Combined dataset n=9039

Reduced by exclusion criteria n=7863

Censored (n=267)
Final Dataset n=7863

IV drug injection (n=37)
Animal bites (n=121)
Post-surgical complications (n=200)
Traumatic wounds (n=298)
Diabetic ulcers (n=666)
(An encounter may have more than 1 exclusion criteria).
4.4 Analysis: Objective 1

The first objective of this study was to profile characteristics of patients admitted to hospital with a diagnosis of cellulitis according to key demographic and clinical factors.

Descriptive analyses were conducted for the continuous variable age, and the categorical variables age-group, sex, geographic designation, anatomical site, C. difficile infection, microorganism resistance, and complicated cellulitis.

The continuous variable, age, was summarized in univariate analyses using the mean, standard deviation, and minimum and maximum values. The association with Charlson comorbidity was tested with logistic regression. For categorical variables (age-group, sex, geographic designation, anatomical site, C. difficile infection, microorganism resistance, and complicated cellulitis), frequency tables were created. The Chi-square test statistic was used to test the statistical significance of their associations with the Charlson comorbidity variable.

Frequency tables were also created for comorbidity index values (0-4+) and the 17 clinical conditions in the Charlson Comorbidity Index.

4.5 Analysis: Objective 2

The second objective was to examine comorbidities as possible determinants of hospital length-of-stay. Survival analysis methods were conducted to analyze the data.
4.5.1 Survival Analysis

Survival analysis methods are designed for longitudinal studies where the outcome is measured as time to certain event (T) (40). Survival analysis methods are also able to incorporate observations where the exact time to event is unknown (right censoring). Therefore, survival analysis was the suitable method of analysis for this study.

The event of interest in this study was patient discharge from acute care. The time to event was the acute length-of-stay. Censoring occurred when lengths-of-stay were greater than 28 days, when patients died, or when patients were transferred to another acute care facility and no further information was found. It was assumed that the transferred patients’ most responsible diagnosis had changed with the transfer, and therefore was not captured in the available data. Kaplan-Meier methods and Cox proportional hazards modeling were used to analyze the data.

4.5.2 Kaplan-Meier Procedure

A non-parametric method of analysis, the Kaplan-Meier (KM) method uses the actual survival times and the probability of survival over time T. The KM method provides an intuitive summary of the distribution of censored variables.

The restricted mean (41), the area under the Kaplan–Meier curve, is the estimation of the mean length-of-stay that is restricted to a chosen maximum time T, i.e., 28 days. In survival analysis, the mean survival time is underestimated because of censoring. The absolute difference in hospital lengths-of-stay was estimated using the difference in restricted means between patients with and patients without Charlson comorbidities.
4.5.3 Cox Proportional Hazards Model

The Cox proportional hazards model (42) is a semi-parametric regression approach to survival analysis that can study multiple factors’ (categorical and continuous variables) effects on the censored outcome. The Cox model makes no assumption on the distribution of the hazard function, but assumes that changes in levels of the independent variables will produce proportional changes in the hazard function, independent of time. The hazards rates may vary over time but the hazard ratios of the independent predictors must be roughly constant over time. It is expressed as a log relative hazard,

$$\ln \left( \frac{h(t)}{h_0(t)} \right) = b_1X_1 + b_2X_2 + \ldots + b_kX_k$$

Where

$$h(t) = \text{the hazard function at time } t$$

$$h_0(t) = \text{the baseline hazard for an individual when the value of all the independent variables equal zero.}$$

To check the proportionality assumption, the graph of log-negative-log survival function against log time of the two groups should be close to parallel.
4.6 The Effect of Comorbidities (as a Binary Variable) on Hospital Length-of-Stay

4.6.1 The Kaplan-Meier Survival Function

The first measure of comorbidity was binary and grouped patients into two groups: patients with comorbidities or patients without comorbidities. The Kaplan-Meier method was applied to summarize the distributions of hospital lengths-of-stay within the two groups. The restricted means which summarize the duration of lengths-of-stay were given and the 2-sample t-test was used to test any observed difference.

The log-rank test was used to test the significance of any difference in the distribution of lengths-of-stay of the two groups. This statistic was used to test the null hypothesis that among patients admitted with a diagnosis of cellulitis, there was no significant difference in the hospital lengths-of-stay for patients with and without comorbidities. The significance level for rejecting a true null hypothesis was 5%.

To check the proportionality assumption of the Cox proportional hazards model, the log-negative-log survival functions of the two groups were plotted to confirm that they were parallel over time. Cox regression was then used to analyze the effect of comorbidities on lengths-of-stay while adjusting for potential confounders.

4.6.2 Cox Regression Modeling

Univariate modeling was first done to show the unadjusted effect of comorbidities and potential confounders on hospital length-of-stay. A multivariate Cox regression model was then used to study the effect of comorbidities on hospital length-of-stay while adjusting for potential confounding variables such as demographic variables (age, sex, rural residence) and clinical
variables (lower limb cellulitis, C. difficile infection, microorganism resistance, and complicated cellulitis). Stepwise variable selection procedures with a significance level of 5% were used for independent variables to enter and stay in the final model.

4.7 The Effect of Comorbidities (as an Index of Comorbidity) on Hospital Length-of-Stay

Similar analytical procedures were performed to analyze the effect of cumulative comorbidities, measured as an index with values of 0, 1, 2, 3, and 4 (includes cumulative scores of 4+), on hospital length-of-stay.

Kaplan Meier curves were created to summarize the distribution of lengths-of-stay among patients with different levels for the comorbidity index (0-4+). Cox regression modeling was performed to evaluate the hypothesis that a higher index was associated with a longer hospital length-of-stay, while adjusting for potential confounders. Similarly, stepwise variable selection procedures with a significance level of 5% were used for independent variables to enter and stay in the multivariable model. Independent variables from the previous univariate analyses that were significant at 5% level were entered in the multivariable model. Results from a model with comorbidity index as a continuous variable were also included, and compared to the results of the model with comorbidity index as a categorical variable.
4.8 The Effects of Specific Charlson Comorbidities

In a secondary analysis, associations between specific Charlson comorbidities and hospital length-of-stay were estimated. Specifically, associations between cardiovascular disease, malignancy, compromised immune function, diabetes, renal disease, connective tissue disease, and liver disease with lengths-of-stay were of interest. First, the unadjusted hazard ratios for each of the 17 comorbidities were calculated in univariate analyses. Next, specific comorbidities of interest were entered into a multivariable model if their proportion in the patient population was at least 5%. Only those potential confounders included in the previous multivariate analyses were included in the model, and these were forced into the model.

4.9 Statistical Software Used in Analyses

The data analyses for this paper were generated using SAS software, Version 9.1 of the SAS System for Windows. Procs of freq, lifetest, and phreg were the primary SAS procedures used in the data analyses.

4.10 Ethical Considerations

No personal identifying information, such as name, street address, and date of birth, that would violate a patient’s privacy and confidentiality, were included in the data. Health Insurance Numbers were scrambled by CIHI using a standard algorithm (25). Only the forward sortation areas (the first 3 digits of a postal code) were obtained. The Health Sciences Human Research Ethics Committee at Queen’s University approved the study proposal (Appendix 1).
Chapter 5

Results

5.1 First Objective: Profile of the Study Population

There were 7863 patients in the study population with 3588 (45.6%) having at least 1 recorded Charlson comorbidity, while 4275 (54.4%) had no Charlson comorbidity recorded on their discharge record.

5.1.1 Demographic Variables

Age ranged from 15-104 years and the mean age was 61.0 years (95% CI, 60.6-61.4) for the study population. The mean age for patients in the comorbidity group was 66.9 years (95% CI, 66.4-67.4) while the mean age for those in the no-comorbidity group was 56.0 years (95% CI, 55.4-56.6). Ages in the two groups ranged from 15-98 and 15-104, respectively.

The 45-64 age-group had the highest proportion of the total number of patients (32.7%), and in the comorbidity group (33.4%) and no-comorbidity group (32.2%). Older age-groups had higher proportions of patients with comorbidities, with 60% in the 65-74 age-group and 58% in the 75-84 age-group. Younger age-groups had lower proportions, 46% of patients in the 45-64 age-group and 19% in the 15-44 age-group. The older age-groups were associated with higher reports of comorbidity ($p<.0001$).
There were more male patients than female patients (53.1% vs. 46.9%). The trend was similar in the comorbidity and no-comorbidity groups, 54.5% and 51.4% respectively. The proportion of females with comorbidities was higher compared to the proportion of males with recorded comorbidities (47% vs. 44%, \(p=.006\)).

Most patients were urban residents (81.3%), and they were more likely to have recorded comorbidities (46%) than rural residents (43%) \(p=.012\).

### 5.1.2 Clinical Variables

Lower limb cellulitis was the most common diagnosis (67.5%). Cellulitis of the upper limbs (14.9%) and the face (5.8%) were the next most common. Among patients with comorbidities, the proportion with lower limb cellulitis was higher at 74.3%, compared to 61.7% in the no-comorbidity group. Lower limb cellulitis was associated with a higher rate of comorbidities (50% vs. 36%, \(p<.0001\)).

Few patients (0.6%) were reported to have a *Clostridium difficile* infection during their hospital stay. However, among those with comorbidities the proportion with *C. difficile* was almost 4 times those in the no-comorbidity group (1.1% vs. 0.3%). A *C. difficile* infection was significantly associated with comorbidities \(p<.0001\).

Only 191 (2.4%) cases reported an antibiotic-resistant organism. This proportion was similar in the two groups, 2.5% in the comorbidity group and 2.4% in the no-comorbidity group. An antibiotic-resistant infection was not associated with comorbidities \(p=.79\).
The proportion of all patients that had a documented cellulitis-related procedure was 6.2%. The proportion of patients with a cellulitis-related procedure was higher in the no-comorbidity group than in the comorbidity group (7.3% vs. 5.0%). A cellulitis-related procedure was associated with having no comorbidities ($p<.001$).

Table 5.1 summarizes the demographic and clinical characteristics of the study population and the association of these characteristics with Charlson comorbidities.
Table 5.1 Demographic and Clinical Characteristics of the Study Population, and their Association with Charlson Comorbidities

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with no comorbidity</th>
<th>Patients with comorbidity*</th>
<th>Subset totals</th>
<th>Patients with comorbidity % of subset total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of patients</td>
<td>No. (%) of patients</td>
<td>No. (%) of Total</td>
<td>% of subset total</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>n=4275</td>
<td>n=3588</td>
<td>N=7863</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>15-44</td>
<td>1387 (32.4)</td>
<td>327 (9.1)</td>
<td>1714 (21.8)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>45-64</td>
<td>1374 (32.2)</td>
<td>1199 (33.4)</td>
<td>2573 (32.7)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>477 (11.2)</td>
<td>704 (19.6)</td>
<td>1181 (15.0)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>75-84</td>
<td>640 (15.0)</td>
<td>892 (24.9)</td>
<td>1532 (19.5)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>397 (9.3)</td>
<td>466 (13.0)</td>
<td>863 (11.0)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Female</td>
<td>1945 (45.5)</td>
<td>1744 (48.5)</td>
<td>3689 (46.9)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2330 (54.5)</td>
<td>1844 (51.4)</td>
<td>4174 (53.1)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Geographic designation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Rural</td>
<td>844 (19.7)</td>
<td>629 (17.5)</td>
<td>1473 (18.7)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>3431 (80.3)</td>
<td>2959 (82.5)</td>
<td>6390 (81.3)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Anatomical site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lower limb</td>
<td>2638 (61.7)</td>
<td>2666 (74.3)</td>
<td>5304 (67.5)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1636 (38.3)</td>
<td>922 (25.7)</td>
<td>2558 (32.5)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>C. difficile infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>With infection</td>
<td>13 (0.3)</td>
<td>38 (1.1)</td>
<td>51 (0.6)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>No infection</td>
<td>4262 (99.7)</td>
<td>3550 (98.9)</td>
<td>7812 (99.4)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Resistant microorganism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>With resistance</td>
<td>102 (2.4)</td>
<td>89 (2.5)</td>
<td>191 (2.4)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>No resistance</td>
<td>4173 (97.6)</td>
<td>3499 (95.5)</td>
<td>7812 (99.4)</td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.1 Demographic and Clinical Characteristics of the Study Population, and their Association with Charlson Comorbidities

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with no comorbidity n=4275</th>
<th>Patients with comorbidity* n=3588</th>
<th>Subset totals N=7863</th>
<th>Patients with comorbidity % of subset total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>With complication</td>
<td>311 (7.3)</td>
<td>178 (5.0)</td>
<td>489 (6.2)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Without complication</td>
<td>3964 (92.7)</td>
<td>3410 (95.0)</td>
<td>7374 (93.8)</td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

* Patients with at least 1 Charlson comorbidity.
5.2 Second Objective: Effects of Comorbidities on Hospital Length-of-stay

The effects of comorbidities with different functional forms (i.e., as a binary variable and as an index of cumulative comorbidity) were examined. The effects of specific comorbidities of focused interest were also investigated.

5.2.1 The Effect of the Presence of Comorbidities on Hospital Length-of-stay

For the 4275 patients with no comorbidity, the restricted mean hospital length-of-stay was 5.3 days (95% CI, 5.2-5.4). The median was 4 days. Among the 3588 patients with comorbidities, the restricted mean hospital length-of-stay was 8.0 days (95% CI, 7.9-8.1), with a median of 6 days. Table 5.2 presents the summary statistics for length-of-stay. Patients with comorbidities had significantly longer hospital lengths-of-stay (mean of 8.0 vs. 5.3 days, \( p < .0001 \)). The absolute difference in mean hospital length-of-stay between patients with and without Charlson comorbidities was 2.7 days (\( p < .0001 \)).
Table 5.2 Summary Statistics for Length-of-Stay (in Days) for Cellulitis Patients in Ontario Hospitals, 2006-2008

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Patients with no comorbidity</th>
<th>Patients with comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point</td>
<td>95 %CI</td>
</tr>
<tr>
<td>Percent</td>
<td>Estimate</td>
<td>Lower</td>
</tr>
<tr>
<td>75</td>
<td>7.0</td>
<td>6.0</td>
</tr>
<tr>
<td>50</td>
<td>4.0</td>
<td>*</td>
</tr>
<tr>
<td>25</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Mean</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Censored (%)</td>
<td>69 (1.6)</td>
<td></td>
</tr>
</tbody>
</table>

*No estimate.
Kaplan-Meier estimates of the distributions of hospital lengths-of-stay are displayed in Figure 5.1. Patients in the comorbidity group had longer hospital lengths-of-stay. For each day in hospital after admission, i.e., hospital length-of-stay, the proportion of patients in the comorbidity group that remained in hospital was higher than the proportion of patients in the no-comorbidity group that remained. The log-rank test, which tests the difference in the distributions of the hospital lengths-of-stay, had a $p$ value of less than .0001. This indicated that the difference in the distribution of the lengths-of-stays between the two groups was highly significant.

Figure 5.1 Kaplan-Meier Survival Functions by Comorbidity

Survival Curves by Charlson Comorbidity

- **No comorbidity** $N = 4275$ Mean $= 5.3$
- **With comorbidity** $N = 3588$ Mean $= 8.0$

$p < .0001$
To check the proportionality assumption of the Cox proportional hazards model, the log-negative-log survival function vs. log time (days) was produced (Figure 5.2). The curves of the two groups remained fairly parallel indicating that the hazard rates were proportional over time, thus satisfying the assumption of Cox’s regression model.

Figure 5.2 Log-Negative-Log Survival Functions by Comorbidity Group
A Cox regression model was also used to study the effect of comorbidities on the hospital lengths-of-stay. Univariate analysis showed that having any Charlson comorbidity decreased the instantaneous rate of discharge by 37% (95% CI, 34% to 40%, \( p < .0001 \)). This reduction of the discharge rate was equivalent to increased hospital length-of-stay by roughly 51%.

Similar analyses were performed on potential confounders. Compared to the reference group (16-44 age-group), hazard ratios for other age-groups declined correspondingly with increasing age. The greatest effect was seen in the oldest group. Being aged 45-64 decreased the instantaneous discharge rate by 27% (95% CI, 22% to 32%) compared to the reference group; the instantaneous rate of discharge decreased by 38% (95% CI, 33% to 42%) in the 64-74 age-group, 44% (95% CI, 39% to 47%) in the 75-84 age-group, and 48% (95% CI, 44% to 53%) in the 85+ age-group.

Female sex decreased the instantaneous discharge rate by 11% (95% CI, 7% to 15%) compared to male sex. Similarly, it was found in univariate analyses that lower limb cellulitis (32%), \textit{C. difficile} infections (57%), resistant organisms (39%) and complicated cellulitis (29%), reduced the instantaneous discharge rate, i.e. they were associated with a longer hospital lengths-of-stay. Rural residence was not associated with hospital length-of-stay (hazard ratio = 1.0) compared to urban residence.

To adjust for confounding, multivariable Cox regression modeling was performed by adding the potential confounders individually to the univariate model with the variable comorbidity as the main exposure variable. When dummy variables for age-groups were added
to the model, the parameter estimate for comorbidity $\beta_1$ changed from $-0.459$ to $-0.387$; this 16% change indicated that age-group is a confounding variable. Adding the other variables to the multivariable model had negligible impact on the parameter estimate. In the final model the parameter estimate of the variable comorbidity $\beta_1$ was $-0.376$. No significant interactions between the variable comorbidity and the other variables were found for the hospital length-of-stay outcome. The final model included the variables comorbidity, age-groups, sex, lower limb cellulitis, $C.\ difficile$ infection, resistant microorganism, and complicated cellulitis. In summary, comorbidities decreased the instantaneous discharge rate by 31% (95% CI, 28% to 35%), after adjusting for potential confounders. Table 5.3 summarizes the unadjusted and adjusted effects of comorbidities and other significant factors on patients’ hospital length-of-stay.
Table 5.3 Demographic and Clinical Variables and their Association with Hospital Length-of-Stay

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity (any in the Charlson Index)</td>
<td>0.63 (0.60-0.66)</td>
<td>0.69 (0.65-0.72)</td>
</tr>
<tr>
<td>Age-group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-44</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
</tr>
<tr>
<td>45-64</td>
<td>0.73 (0.68-0.78)</td>
<td>0.81 (0.76-0.87)</td>
</tr>
<tr>
<td>64-74</td>
<td>0.62 (0.58-0.67)</td>
<td>0.72 (0.66-0.78)</td>
</tr>
<tr>
<td>75-84</td>
<td>0.56 (0.53-0.61)</td>
<td>0.65 (0.61-0.70)</td>
</tr>
<tr>
<td>85+</td>
<td>0.52 (0.47-0.56)</td>
<td>0.60 (0.54-0.65)</td>
</tr>
<tr>
<td>Female</td>
<td>0.89 (0.85-0.93)</td>
<td>0.94 (0.90-0.98)</td>
</tr>
<tr>
<td>Rural residence</td>
<td>1.00 (0.95-1.06)</td>
<td></td>
</tr>
<tr>
<td>Lower limb cellulitis</td>
<td>0.68 (0.65-0.71)</td>
<td>0.71 (0.68-0.75)</td>
</tr>
<tr>
<td><em>C. difficile</em> infection</td>
<td>0.43 (0.32-0.57)</td>
<td>0.51 (0.38-0.68)</td>
</tr>
<tr>
<td>Resistant microorganism</td>
<td>0.61 (0.53-0.71)</td>
<td>0.57 (0.49-0.66)</td>
</tr>
<tr>
<td>Complicated cellulitis</td>
<td>0.71 (0.74-0.78)</td>
<td>0.57 (0.51-0.62)</td>
</tr>
</tbody>
</table>
5.2.2 The Effect of Comorbidities as a Comorbidity Index on Hospital Length-of-stay

A patient index of comorbidity was calculated as the cumulative sum of the weights of their Charlson comorbidities (Table 3.2), and values ranged from 0-12. Values of 4 or more were grouped into one category. Kaplan-Meier survival distributions for these index values are shown in Figure 5.3.

Figure 5.3 Kaplan-Meier Survival Functions by Comorbidity Index

Survival Curves by Charlson Comorbidity Index (CCI)
Hospital lengths-of-stay increased with an increase in the comorbidity index. Patients with a comorbidity index of 1 had a mean hospital length-of-stay of 7.4 days. Patients with comorbidity index values of 2, 3, and ≥4 had mean hospital lengths-of-stay of 7.6, 8.8, and 9.7, respectively. The distributions of hospital lengths-of-stays were significantly different among the groups, with the p-value from the log-rank test less than 0.0001.

The Cox regression model showed that when the comorbidity index increased, the instantaneous discharge rate decreased. A comorbidity index of 2 decreased the instantaneous discharge rate by 27% (95% CI, 21% to 30%) while an index of 3 decreased it by 37% (95% CI, 31% to 43%) after adjusting for potential confounders. Similar results were found when the comorbidity index was modeled as a continuous variable.

In the multivariable model, the parameter estimate for comorbidity index (as a continuous variable) \( \beta_1 \) was −0.158. An increase of the index by 1 unit decreased the hazard ratio to 0.85 (95% CI, 0.84-0.87). An increase by 2 and 3 units decreased the hazard ratio to 0.73 and 0.62, respectively. The parameter estimates for potential confounders in all three models (comorbidity as a binary variable, comorbidity index as a categorical variable, and comorbidity index as a continuous variable) remained stable (not shown).

Table 5.4 summarizes the hazard ratios by categorical levels of comorbidity index.
Table 5.4 Multivariate Analysis of Comorbidity Index and Association with Length-of-stay

<table>
<thead>
<tr>
<th>Charlson Comorbidity Index</th>
<th>No (%) of patients</th>
<th>Adjusted Hazard Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4275 (54.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>1608 (20.4)</td>
<td>0.74 (0.70-0.79)</td>
</tr>
<tr>
<td>2</td>
<td>953 (12.1)</td>
<td>0.73 (0.70-0.79)</td>
</tr>
<tr>
<td>3</td>
<td>494 (6.3)</td>
<td>0.62 (0.56-0.69)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>533 (6.8)</td>
<td>0.54 (0.49-0.60)</td>
</tr>
</tbody>
</table>

*Adjusted for age-group, sex, anatomical site, *C. difficile* infection, resistant microorganism, and complicated cellulitis.
5.2.3 The Effects of Specific Charlson Comorbidities on Hospital Length-of-stay

The effects of specific clinical conditions in the Charlson Comorbidity Index on hospital length-of-stay were explored in univariate analyses. Congestive heart failure decreased the discharge rate by 56%. Peripheral vascular disease decreased it by 47%, diabetes by 29%, diabetes with end-organ-damage by 42%, moderate to severe renal damage by 46%, and malignancy by 30%. These specific comorbidities were entered into a multivariable model, based on the criteria that the proportion of patients with these conditions was at least 5%. Peripheral vascular disease and malignancy were slightly less than 5% but were forced into the model because they were comorbidities of special interest.

Table 5.5 tabulates the 17 Charlson comorbidities, their weight, proportion in the patient population, and unadjusted hazard ratios.
Table 5.5 Univariate Analyses of Charlson Comorbidities and their Association with Hospital Length-of-stay

<table>
<thead>
<tr>
<th>Charlson Comorbidities</th>
<th>Weight</th>
<th>No (%) of patients</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>142 (1.8)</td>
<td>0.43 (0.36-0.51)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>460 (5.8)</td>
<td>0.44 (0.39-0.48)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
<td>331 (4.2)</td>
<td>0.53 (0.47-0.60)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
<td>89 (1.1)</td>
<td>0.55 (0.44-0.68)</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
<td>252 (3.2)</td>
<td>0.56 (0.49-0.64)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1</td>
<td>466 (5.9)</td>
<td>0.57 (0.51-0.63)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1</td>
<td>105 (1.3)</td>
<td>0.73 (0.60-0.89)</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>1</td>
<td>17 (0.2)</td>
<td>0.29 (0.12-0.50)</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1</td>
<td>180 (2.3)</td>
<td>0.66 (0.57-0.77)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>1168 (14.8)</td>
<td>0.71 (0.66-0.76)</td>
</tr>
<tr>
<td>Diabetes with end-organ damage</td>
<td>2</td>
<td>990 (12.6)</td>
<td>0.58 (0.54-0.63)</td>
</tr>
<tr>
<td>Hemiplegia or paraplegia</td>
<td>2</td>
<td>69 (0.9)</td>
<td>0.63 (0.50-0.81)</td>
</tr>
<tr>
<td>Moderate to severe renal damage</td>
<td>2</td>
<td>406 (5.2)</td>
<td>0.54 (0.49-0.60)</td>
</tr>
<tr>
<td>Any malignancy including leukemia and lymphoma</td>
<td>2</td>
<td>375 (4.8)</td>
<td>0.70 (0.63-0.78)</td>
</tr>
<tr>
<td>Moderate to severe liver disease</td>
<td>3</td>
<td>26 (0.3)</td>
<td>0.42 (0.28-0.63)</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>6</td>
<td>125 (1.6)</td>
<td>0.58 (0.48-0.71)</td>
</tr>
<tr>
<td>AIDS</td>
<td>6</td>
<td>18 (0.2)</td>
<td>0.96 (0.61-1.53)</td>
</tr>
</tbody>
</table>
Kaplan-Meier survival curves were produced to demonstrate the differences in the hospital lengths-of-stay among patients with specific comorbidities. Because the survival curves overlap thus making it difficult to distinguish them from each other, only five specific comorbidities (congestive heart failure, peripheral vascular disease, chronic pulmonary disease, moderate to severe renal damage, and malignancy) are shown in Figure 5.4.

**Figure 5.4 Kaplan-Meier Curves by Specific Charlson Comorbidities**

Legend:
- CHF  Congestive Heart Failure
- CPD  Chronic pulmonary disease
- NEO  Malignancy
- PVD  Peripheral vascular disease
- RD   Moderate to severe renal damage

p < .0001
Congestive heart failure showed the longest hospital lengths-of-stay, malignancy had the shortest, and the other comorbidities were in between. At least 2 of the survival distributions were significantly different from each other; \( p \)-value of the log-rank test was less than .0001.

After adjusting for all other Charlson comorbidities and potential confounders, the specific Charlson comorbidities were found to significantly affect hospital lengths-of-stay. Congestive heart failure decreased the instantaneous discharge rate by 37% (95% CI, 30% to 43%). A malignancy decreased the risk of discharge by 11% (95% CI, 1% to 21%). Peripheral vascular disease decreased it by 21% (95% CI, 11% to 30%), chronic pulmonary disease by 21% (95% CI, 13% to 28%), diabetes mellitus by 19%, (95% CI, 14% to 24%) diabetes with end-organ damage by 17% (95% CI, 11% to 23%), and moderate to severe renal damage by 18% (95% CI, 9% to 27%). Table 5.6 summarizes the effects of the specific Charlson comorbidities adjusted for all other comorbidities and potential confounders.

Table 5.6 Multivariate Analysis of Charlson Comorbidities Association with Length-of-stay

<table>
<thead>
<tr>
<th>Charlson Comorbidities</th>
<th>Adjusted Hazard Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>0.63 (0.57-0.70)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.79 (0.70-0.89)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>0.79 (0.72-0.87)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.81 (0.76-0.86)</td>
</tr>
<tr>
<td>Diabetes with end-organ damage</td>
<td>0.83 (0.77-0.89)</td>
</tr>
<tr>
<td>Moderate to severe renal damage</td>
<td>0.82 (0.73-0.91)</td>
</tr>
<tr>
<td>Any malignancy including leukemia and lymphoma</td>
<td>0.89 (0.79-0.99)</td>
</tr>
</tbody>
</table>

*Adjusted for all other Charlson comorbidities, age-group, sex, anatomical site, \( C. \) difficile infection, resistant microorganism, and complicated cellulitis.
Chapter 6
Discussion

6.1 Key Findings and Interpretations

Patients diagnosed with Charlson comorbidities were significantly older than patients without diagnosed Charlson comorbidities, consistent with the well-known biological relationship between aging and the development of chronic diseases (35). The higher proportion of comorbidities among female patients and their longer lengths-of-stay may largely reflect the demographics of the Ontario adult population. Females have a longer life expectancy, 82 vs. 77 years (43); there are more females than males in all age-groups greater than 65. In addition, the proportion of women living alone is higher than males in all age-groups, after the age of 55 (44). Females may have longer hospital lengths-of-stay because in the Ontario population they are proportionally older and therefore have more comorbidities and are more likely to live alone.

Lower limb cellulitis was the most common diagnosis identified in this study population, a finding reported previously in the literature (8,45). This diagnosis was also independently associated with increased lengths-of-stay. Lower limb cellulitis may be associated with specific clinical conditions in the Charlson Comorbidity Index. However, the interaction term for the variables comorbidity and lower limb cellulitis was not statistically significant.

A patient diagnosed with Charlson comorbidities was also at increased risk for an infection with *C. difficile*. Longer hospital length-of-stay is a known risk factor for a *C. difficile* infection, and *C. difficile* infection is also associated with increased lengths-of-stay (37). It is unknown whether the infections in this study were an adverse result of antibiotic treatment or
attributable to exposure during an outbreak of *C. difficile*, the risk of which increases with longer hospital stays.

Our findings demonstrated that cellulitis infections caused by antibiotic-resistant microorganisms were not associated with comorbidities. This is consistent with reports that methicillin-resistant *Staphylococcus aureus*, previously found only in health care settings, have been implicated in community outbreaks (46,47). Patients without comorbidities were just as likely to be infected with an antibiotic-resistant organism as patients with comorbidities.

A cellulitis infection that required a related procedure or intervention was not associated with Charlson comorbidities. This implied that patients without comorbidities may have been hospitalized because their infections were more severe or more complex, while patients with comorbidities may have been hospitalized because of the presence of unstable comorbidities, or because of other factors not considered in this study. A complicated cellulitis infection was independently associated with longer hospital stays.

Adding R02 (a code for peripheral vascular disease found in other algorithm) to the Quan algorithm, increased detection of the number of patients with peripheral vascular disease by 36 patients or 0.5% of the total number of patients.

The most common Charlson comorbidity reported in the study population was diabetes, both with and without end-organ damage. This may be largely attributable to the fact that since 2006, CIHI required that this medical condition be abstracted whenever it found in the patient chart regardless of whether there is documentation to support that the disease had a significant impact on the patient’s stay in hospital.
This study found that 27.4% of patients had diabetes with or without end-organ damage. This was slightly higher than the 25% in a Spanish study (10), and much higher than the 13% in a New Zealand study (18), and 16.5% (9) in a United Kingdom study. The increased reporting of diabetes in the DAD abstract due to the requirement to report any diabetic condition regardless of whether or not it had a significant impact on the patient’s hospital stay meant that even non-insulin dependent diabetes conditions were coded. This may not have been the case for the other studies where only those patients on insulin while in hospital may have been reported. The Spanish study reported a higher proportion of the population with diabetes, whereas the proportions in the other two study populations were relatively similar to each other. This may be attributable to differences in the study population and to culturally-based diets, life-styles, and other unknown factors that influence the health of a population.

This study found congestive heart failure and myocardial infarction in 5.8% and 1.8% of the population respectively. The Spanish study reported 11% had congestive heart failure but did not report any cases of myocardial infarction. The New Zealand study reported that 41% had atherosclerotic vascular disease (with no breakdown of specific diseases), while the UK study reported that 19.9% had a previous MI. It is very likely that the 41% of patients that had atherosclerotic vascular disease in the New Zealand study included those that had myocardial infarction or congestive heart failure. The study noted congestive heart failure conditions in patients without indicating specific numbers. The higher rates on all three studies compared to the results in this thesis may be attributable to differences in study populations. This study collected data from all Ontario hospitals including small and community hospitals with typically less seriously acute patient populations while the other studies were done in larger urban
tertiary care hospitals where patients with more serious cases may have been admitted. A similar trend is noted in the proportion of patients with peripheral vascular disease. In this study, 4.2% of the study population had peripheral vascular disease compared to 7% in the Spanish study, 10% in the New Zealand study, and 7.6% in the UK study.

The studies varied from each other in their methodology. The UK study collected subjects over a 6-year period, the Spanish study over a 2-year period, and the New Zealand study in an 8-month period. The multi-year studies were retrospective and included all patients with certain exclusion criteria. However some cases in the retrospective studies were not independent because they included repeat admissions of the same patient. This may have biased the results by increasing the frequency of certain conditions. The New Zealand study was a smaller prospective study. This smaller study did not indicate how many patients declined to participate and whether this biased the results in some way. These differences in methodology may account for some of the differences in the proportions found in this study.

This study found that diagnoses of Charlson comorbidities significantly increased the restricted mean hospital length-of-stay from 5.3 days among patients with no comorbidity, to 8.0 days. The more clinical conditions that were diagnosed for the patient, the longer their length-of-stay. A patient with a comorbidity index of at least 4 stayed in hospital 46% longer than a patient with a comorbidity index of 0 (no Charlson comorbidities diagnosed), independent of other factors. Different Charlson comorbidities were found to affect hospital lengths-of-stays by varying degrees. Congestive heart failure increased lengths-of-stay by 37% independent of other factors, while diabetes mellitus increased it by 19%.
A patient’s length-of-hospital stay is influenced by disease-specific, patient-specific, and health care system specific factors. This study showed that disease-specific factors such as, a cellulitis that affects the lower limb, the need for surgical intervention which indicates the severity of the infection, and a cellulitis infection caused by an antibiotic resistant microorganisms, each independently increased hospital length-of-stay. This study also found that patient-specific factors such as being older in age and being female also increased a patient’s hospital length-of-stay. Patient psycho-social factors that were not captured in the analyses may have contributed to the length-of-stay. Severity of psycho-social factors has been found to be a significant predictor for length-of-stay that is longer than target length-of stay (48). A patient who is without family or any social support, or is homeless, or is unable to comply with treatment, but is no longer in need of acute care in hospital, may stay in hospital longer until community supports are in place to enable them to leave the hospital and to continue their recovery in the community. Community health care support may not have been available to enable a patient to leave an acute care setting. The availability of home care to support the patient at home during recovery may vary by geographical regions. Patients take up beds in acute care hospitals even when they no longer require the intensity of resources or the resources provided (49) because of the lack of alternatives in the health care system.

The acute hospital length-of-stay in this study ranged from 1-135 days but was censored at 28 days. The database had a variable for alternate level of care days, however an analysis of extreme observations showed that in some cases, the patient was in hospital due to other reasons other than for treatment of the cellulitis disease, but no alternate level of care days were recorded. Almost 98% of patients were discharged by day 27.
6.2 Implications for Clinical Practice and Hospital Policy

The Charlson Comorbidity Index was predictive of the patients’ hospital length-of-stay. Together with other clinical factors and their effects on hospital length-of-stay, this index may be a useful assessment tool in the clinical management of patients with cellulitis. Primary care of patients at risk for developing cellulitis and at higher risk for lengthier hospital stays should routinely include the consideration of prevention strategies. When a cellulitis infection has developed, knowledge of disease-specific degree of effect may be useful when making decisions in clinical management at the initial contact with the physician in an outpatient setting or during the hospital stay. This knowledge may also help in developing strategies for maximizing health outcomes, while reducing the burden to the hospital inpatient system.

A review of the epidemiology, clinical features, management, and prevention of community-acquired methicillin-resistant Staphylococcus aureus skin infections (50) found that direct skin-to-skin contact, damage to skin surface, sharing of personal items, and humid environment were potential mechanisms for the acquisition and transmission of cutaneous infections. Primary health care teaching should include educating patients with comorbid conditions who are at increased risk for longer hospitalization, on how to reduce the risk of acquiring and transmitting of skin infections. Improvements in personal hygiene including handwashing or handsanitizing, and not sharing of personal item such as soap bars, towels may prevent the spread and acquisition of infection. Prompt treatment of cuts, abrasions, and fungal infections may prevent cellulitis infections especially during the warmer months when increased growth and transmission of community acquired S. aureus infections have been observed. Cleaning the area with soap and water and covering with dry clean dressing are simple measures to prevent infection. Sanitizing shared environments, early recognition of
potentially infectious skin lesions, and prompt evaluation and appropriate treatment by health care providers, may minimize the transmission and duration of skin infections.

6.3 Recommendations for Future Studies

A primary goal in patient care would be to prevent infections and to clinically manage the patient on an outpatient basis whenever possible (2). When hospitalization is necessary, optimization of patient outcomes, while reducing the burden to the health care system, would be an ideal goal. Several studies are recommended to help achieve these ends.

Research in other temperate countries has reported a seasonal association with cellulitis (51-54). Prevention strategies for patients should be reviewed and evaluated to determine whether they are targeted at higher risk groups for longer hospital stays, and whether a potential seasonal risk is considered.

Patients with Charlson comorbidities are at greater risk for \textit{C. difficile} infections, a nosocomial infection, in addition to being at increased risk for longer hospital stays. Patients at increased risk for longer hospital stay due to diagnoses of specific comorbidities may benefit from a shorter and more effective course of treatment that would keep them out of hospital or shorten their stay. Cost-benefit analyses may show that more effective but expensive therapies may provide savings from associated shorter stays, among patients with specific risks for longer hospital stays.

In hospital, factors that contribute to longer hospital stays among patients with specific comorbidities require further investigation in order to develop clinical pathways that would
prevent complications, promote healing, and improve patient outcome. The many disciplines that are involved in patient care, including medicine, nursing, physiotherapy, social work, and dietetics, among others, have a role in achieving this goal within their scopes of practice.

6.4 Strengths of the Study

This study had several strengths. First, this was a retrospective cohort study in Ontario with a robust sample size. The total study population was 7863 inpatients which included all inpatients in Ontario (less those who met the exclusion criteria) who were 15 years old or more, and who were admitted with diagnoses of cellulitis during a 2-year period. Second, the data analyses included all known potential confounders. Third, CIHI re-abstraction studies on the Discharge Abstract Database coding of diagnoses have shown 80-92% agreement for the chosen coding diagnoses (26). This high proportion of agreement is due to coding standards established by CIHI and training provided for coders.

6.5 Limitations of the Study

The study results need to be interpreted in the context of the findings of the underreporting and overreporting of comorbidities in the DAD data re-abstraction studies. Ischemic heart diseases like myocardial infarction are the least underreported at 15%, but at the same time overreported 16% of the time. Congestive heart failure on the other hand, is underreported by 24% and overreported 33% of the time. These mixed results require that interpretation of results for this clinical condition be done with some degree of caution. The diagnoses for diabetes, although significantly underreported prior to 2006 by 52%, should, in this study, be closer to reality due to coding requirement changes in fiscal year 2006. Chronic respiratory diseases which were underreported 21% of the time were also overreported 14% of
the time. However, the large sample size, and the not overly large differences in the underreporting and overreporting by clinical conditions, should make the true state similar to what is found in this study, and not negate the study results.

Findings from this study cannot be generalized to other types of cellulitis excluded from the analysis: cellulitis complicating diabetic ulcers, cellulitis as a result of postoperative wound infections, cellulitis due to external causes such as traumatic wounds and animal bites, mastitis, and cellulitis related to intravenous drug use. Results should also not necessarily be generalized to populations outside of Ontario.
Chapter 7
Conclusions

• In Ontario, a person older than 15 years old who is hospitalized for cellulitis and who has any diagnosis of Charlson comorbidities, is more likely to be older, be female, live in an urban location, have a cellulitis that affects the lower limb, and is more likely to become infected with *Clostridium difficile* during the period of hospitalization.

• A diagnosis of one or more Charlson comorbidities increases the restricted mean hospital length-of-stay of an adult patient with cellulitis from 5.3 days to 8.0 days, compared to a patient without any diagnosed Charlson comorbidities.

• A cellulitis patient with congestive heart failure will experience on average, a 37% increase in length-of-hospital stay, compared to a patient without congestive heart failure, independent of other factors.

• The Charlson Comorbidity Index is predictive of hospital length-of-stay for patients with cellulitis. Knowledge of the disease-specific effects of comorbidities may be a useful tool in clinical management of the patient, prevention of the disease, managing the infection, and improving the patient’s outcome during hospitalization.

• Factors that contribute to longer hospital stays among patients with specific comorbidities need further investigation, in order to develop clinical pathways that may prevent complications, promote healing, and improve patient outcome.
References


47. Shorr AF. Epidemiology and economic impact of meticillin-resistant *Staphylococcus aureus*: Review and analysis of the literature. Pharmacoeconomics. 2007;25(9):751-68.


Appendix I

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

February 3, 2009

Ms. Celia Mayol
Department of Community Health & Epidemiology
Artsmeh Hall
Queen's University

Dear Ms. Mayol,

Study Title: Cellulitis: Comorbidities and hospital length of stay
Co-Investigators: Dr. K. Ding, Dr. K. Moore and Dr. W. Pickett

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please adhere carefully to the following list of ethical requirements you must fulfill over the course of your study:

- Reporting of Amendments: If there are any changes to your study (e.g., consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval (see http://www.queens.ca/ep/rep.html).

- Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

- Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

- Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Chair, Research Ethics Board

Date

Study Code: EPID-286-09

Institution please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.