Outcomes associated with Hospital Acquired Complications in patients with Chronic Kidney Diseases

By

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Abstract

Improving the quality of healthcare has been a focus for researchers and policy makers during the last two decades. Hospital acquired complications (HACs) are unintended harms to patient (e.g. urinary tract infection, wound infection), yet many are potentially preventable. They are common and associated with deleterious clinical and economic outcomes. Patients with chronic disease may be at increased risk of preventable HACs, partly due to complexity of those patients' clinical condition. Chronic kidney disease (CKD) is common, patients with CKD are hospitalized frequently, and the nature of CKD may make them particularly vulnerable to complications. It is not yet clearly known the extent to which HACs and clinical and economic consequences attributable to HACs occur with CKD. Reducing the incidence of preventable HACs in hospitals is a critical component of efforts to provide higher quality of health care. A greater understanding will facilitate targeted implementation of preventative strategies aimed at reducing complications in this readily identifiable high-risk population to improve medical and surgical safety, and efficiency of care in hospitals in Canada.

In this thesis, population based linked administrative and laboratory data were used to create a population based cohort of hospitalized adult patients from April 2003 to March 2008 in Alberta (Appendix A). Outpatient creatinine and proteinuria measurements were used to define CKD within 365 to 90 days prior to hospitalization and were categorized according to Clinical Practice Guidelines developed by Kidney Disease Improving Global Outcome (KDIGO)in 2012. A specific indicator in administrative data was used to identify HACs, and published literature was used to identify potentially preventable HACs.

Regression models were used to assess the independent association of CKD with any severity with risk of developing ≥1 HACs. Further, the association of HACs and outcomes were assessed; mortality in the index hospitalization and within 90 days after hospital discharge, incremental length of stay, readmission within 90 days, and incremental hospital costs from admission to 90 days after discharge in patients with CKD with ≥1 HACs, accounting for potential clinical confounders.

Of 536,549 eligible patients, 8.5% had CKD who were older and more likely to be admitted for cardiovascular diseases than those without CKD. In fully adjusted models the odds ratio (OR) of ≥ 1 preventable HAC in patients with CKD (reference: no CKD) was 1.20 (95% CI: 1.16 – 1.24). There was a graded relation between the risk of HACs and CKD severity, with an OR of 1.81 (95% CI: 1.51 – 2.17) in those with the most severe CKD. In patients with CKD, 9.8% had preventable HACs vs 5.4% in patients without CKD. Fully adjusted odds ratio (OR) of mortality during index hospitalization and from hospital discharge to 90 days in patients with ≥ 1 preventable HAC (reference: no preventable HAC) was 4.67 (95% CI: 4.17 – 5.22) and 1.08 (95% CI: 0.94 – 1.25), respectively. Median incremental length of stay in patients with CKD and with ≥ 1 preventable HAC was 9.86 days (95% CI 9.25 – 10.47). The OR for readmission in patients with CKD and with preventable HAC was 1.24 (95% CI: 1.15 – 1.34). In the cohort with and without CKD the fully adjusted OR of mortality during index hospitalization in patients with CKD and no preventable HACs, patients without CKD and with preventable HACs, and patients with CKD and preventable HACs, were 2.22 (95%CI; 1.69 – 2.94), 5.26 (95%CI; 4.98 – 5.55), and 9.56 (95% CI; 7.23 – 12.56), respectively (referenced to patients without CKD or HAC).

In fully adjusted models, the median incremental index hospitalization cost and in-hospital physician claims were $4,047 (95 %CI; 3,918 – 4,176) and $765 (95% CI; 738 – 792) in CKD patients with ≥ 1 preventable HACs, compared with those without. Post-discharge incremental costs in physician claim, ambulatory care, and readmission cost were $71 (95% CI; 54 – 89), $119 (95% CI; 74 – 164), and $1,429 (95% CI; 844 – 1,709), respectively. The incremental costs over 90 days from admission with ≥1 preventable HAC in patients with CKD was $7,522 (95% CI; 7,219 – 7,824). In patients without CKD but with a preventable HACs incremental costs within 90 days from hospital admission was $6,688 (95% CI: 6,612 – 6,723).

Patients with CKD are at higher risk of preventable HACs. The presence of ≥ 1 preventable hospital acquired complication, including those are deemed to be preventable, was associated with greater risk of mortality, longer length of stay in hospital, readmission, and incremental healthcare cost in patients with CKD. In the cohort of patients with and without CKD (referenced to patients without CKD or HAC), negative clinical and economic outcomes increase with presence of CKD and preventable HACs. Further studies are proposed to examine the effect of evidence-based strategies on the risk of potentially preventable hospital acquired complications, with the goal of improving quality of care and associated with poor outcomes in patients with CKD.

Preface

This thesis is an original work by Babak Bohlouli. Research ethics was approved by the University of Alberta and the University of Calgary Research Ethics Board, Project Name “Outcomes associated with Hospital Acquired Complications in patients with Chronic Kidney Diseases: a cohort study using data from Interdisciplinary Chronic Diseases Collaboration (ICDC), No Pro00036226_REN3

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In addition, a version of Chapter 4 and a version of Chapter 5 of this thesis have been submitted for publications as as Bohlouli B. Jackson T. Tonelli M. Hemmelgarn B. Klarenbach S. *“*Adverse outcomes associated with preventable complications in hospitalized patients with chronic kidney disease” and Bohlouli B. Jackson T. Tonelli M. Hemmelgarn B. Klarenbach S. “Healthcare associated with preventable hospital acquired complications in patients with chronic kidney disease”, respectively.

Babak Bohlouli was responsible for study design and data analyses as well as writing manuscript for the above studies. Scott Klarenbach provided comments and guidance to the manuscript preparation and revision. Marcello Tonelli, Terri Jackson, Brenda Hemmelgarn contributed to the manuscript preparation and revision.

Dedication

This dissertation is dedicated to my loving daughters, Sanaz and Solmaz for all the happiness they brought to me.

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List of abbreviations:

ACC: Ambulatory Care Cost

CHADX: Classification of Hospital Acquired Diagnoses

CIHI: Canadian Institute for Health Information

COPD: Chronic Obstructive Pulmonary Disease

CPWC: Cost Per Weighted Case

CKD: Chronic Kidney Disease

DRG: Diagnostic related group

ED: Emergency Department

ELOS: Estimated Length of Stay

GFR: Glomerular Filtration Rate

ICD 10: International Classification of Diseases 10 version

IOM: Institute of Medicine

HAC: Hospital Acquired Complications

LOS: Length of Stay

MDRD: Modification of Diet in Renal Disease

NHANES: National Health and Nutrition Examination Survey

NHS: National Health System

POA: Present on Admission

PPC: Potentially preventable Complications

RIW: Resource Intensity Weight

CHAPTER 1: Introduction

1.1. Statement of problem

The quality and safety of medical care is under increasing scrutiny recently. Healthcare practitioners and the general public are now more aware of the inherent risks of medical care, and healthcare policy makers are also paying close attention to this issue because of clinical and economic outcomes to patients and health systems.

Hospital acquired complications (HACs) are unintended clinical events distinct from the admitting diagnoses that occur after hospital admission, and result from the process of clinical care and treatment rather than from a natural progression of underlying disease, for example, urinary tract infection, deep vein thrombosis, wound infection. Studies in Britain, New Zealand, and the United States report that HACs are common[1]. Similarly, in Canada, the occurrence and consequences of HACs are concerning [2].

HACs may intensify hospitalized patients' clinical conditions leading to more medications administration, laboratory tests, and multiple curative procedures compared to patients without complications.

The Institute of Medicine (IOM) estimates that 44,000 to 98,000 Americans die each year as a result of potentially preventable complications [3-5]. Length of stay in hospital is longer in the patients with HACs than those patients without HACs. Consequences of HACs may extend beyond the discharge from hospital and result in frequent physician visits, emergency department visits and readmission to hospitals.

HACs are costly and result in consumption of healthcare resources for additional nursing time, medications, procedures, interventions, and lab tests before discharge is possible. Estimation of the cost implications of HACs for organizations and health systems may establish a business case for quality improvement and may facilitate the implementation of quality enhancement initiatives[6,7].

A significant proportion of HACs are deemed to be potentially preventable. There is evidence that HACs can be reduced through implementation of Agency for Healthcare Research and Quality (AHRQ) recommendations on best practices to prevent hospital acquired complications in the US[8].

Certain patient populations may be at greater risk of HACs, partly due to the complexity of their clinical conditions. Chronic diseases such as congestive heart failure, hypertension, diabetes, and chronic kidney disease increase the intensity of patients' clinical conditions compared with those without any underlying disease [9,10].

Patients with chronic kidney disease (CKD) are frequently hospitalized and pre-disposed to complications during hospitalization[11,12], potentially due to the nature of disease. Under recognition of CKD may contribute to high frequency of HACs observed, particularly with milder severity of kidney impairment [13].

As CKD is readily identifiable using routine laboratory tests that are commonly conducted in hospitalized patients, and targeted strategies to prevent HACs have been demonstrated to be effective in some settings, patients with CKD may be an ideal high

risk population to implement evidence-based strategies to reduce HACs, which may subsequently improve patient and health care system outcomes.

Current studies have investigated the association of HACs with poor clinical and economic outcomes in the general inpatient population but there are only two published studies that have investigated the HACs in patients with CKD.

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1.2. Study Objectives

This dissertation aims to determine the independent association of chronic kidney disease and its severity with the risk of those hospital acquired complications that are deemed to be potentially preventable and determine the association of those complications with mortality, length of stay, readmission, and healthcare costs in patients with CKD.

Objectives:

- To determine the association of CKD with all HACs, as well as potentially and always preventable complications.
- To determine the association of mortality in the index hospitalization, incremental length of stay in hospital, mortality within 90 days after hospital discharge, readmission within 90 days after hospital discharge in patients with potentially preventable HACs.
- To determine the association of incremental Index hospitalization costs (including hospital costs and inpatient physician claims), incremental costs within 90 days after discharge (including; ambulatory care costs, physician claims, and readmission costs) in patients with potentially preventable complications.

- To determine above outcomes in a full cohort with and without CKD who develop potentially preventable complications.

1.3. Thesis Submitted for Partial Fulfillment of PhD

This thesis consists of a comprehensive literature review on hospital acquired conditions including those that are deemed to be potentially preventable and their effects on quality of care in patients with chronic kidney disease and healthcare system resources (Chapter 2). Three studies (Chapter 3, 4, 5) have been designed to address each of the specific objectives.

Chapter 2 consists of a literature review of what is known about hospital acquired complications and what are the consequences of those complications in the general inpatient population, as well as in patients with CKD. In section 2.1 introduction and definition of HACs is summarized, followed by section 2.2 explaining the burden of HACs in the hospitalized population. Section 2.3 presents approaches to identify HACs. In section 2.4 consequences of HACs including mortality, morbidity, length of stay in hospital, hospital readmission, healthcare costs of HACs are provided. Determining those complications that are deemed to be always preventable (never events) and potentially preventable HACs are discussed in section 2.5. In section 2.6 the burden of HACs in patients with chronic disease with the focus on CKD are presented, and conclusions are presented in section 2.7.

In Chapter 3, results of the first study “risk of hospital acquired complications in patients with CKD” are presented. A version of chapter 3 has been published in the *Clinical Journal of the American Society of Nephrology (CJASN) in June 2016*.

In Chapter 4, results of the second study are presented. In this chapter “Adverse outcomes associated with potentially preventable complications in hospitalized patients with chronic kidney disease” were examined. A version of Chapter 4 has been submitted to the *Journal of the American Society of Nephrology (JASN).*

In Chapter 5, results of the third study are provided. “Health care costs associated with hospital acquired complications in patients with chronic kidney disease” are presented in this chapter and a version has been submitted to *Nephrology Dialysis Transplantation (NDT).*

In the final chapter, Chapter 6, general discussion and conclusions are presented. This chapter includes an overview of the thesis research, a summary of the results from three studies, discussion of the importance of the research, strength and limitations of the studies, conclusions and implications for future research and recommendations for clinical care and policy makers.

CHAPTER 2:

Hospital acquired complications (HACs) in the general inpatient population and patients with chronic kidney disease (CKD)

2.1. Introduction and definition of HACs

Quality of healthcare is a worldwide priority in healthcare systems and is a major area of investigation in health research. Hospital acquired complications (HACs) are undesirable harms or complications that are not caused by the patient's underlying nature of diseases. The Institute of Medicine (IOM) released a report in 1999 called "*To Err is Human": Building a Safer Health System*[1]. The Agency for Healthcare Research and Quality in the US defines medical error as:

> *"The failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. Errors can include problems in practice, products, procedures, and systems*[2]*."*

Patients are generally hospitalized to treat a medical condition, e.g. community acquired pneumonia or to undergo a surgery, e.g. total knee arthroplasty. They may have some co-morbid conditions for the time before hospital admission, e.g. diabetes. During delivery of healthcare, administration of medications or curative procedures, patients may experience clinical conditions that they have not previously had and unintendedly occur in hospital, causing patients to suffer. Examples of HACs include accidental injuries, disabilities, or mortality associated with complications of: surgical procedures and anesthesia (e.g. surgery performed on the wrong patients or wrong part of body, foreign body left within after surgery), medication (e.g. any error in dose, preparation, time, and route of administration), medical device (e.g. contaminated or unsafe

injections), blood or blood product transfusion (e.g. ABO incompatibility), post-operative patient care (e.g. deep vein thrombosis), and environmental (e.g. falls)[3]. Some combination of individual, system, and communication failures during clinical care in both public and private practice is considered to be a factor in most HACs [2,4]. Investigation of patients' underlying clinical conditions may provide more information about risk factors of HACs in hospitalized patients. Any co-morbid condition may alter the likelihood of development of a complication (e.g., the process of patients' treatment in hospital causing more procedures, medications dose adjustment, etc.) and making them vulnerable to HACs.

Some HACs may have minor impact on patients, but others may cause death, and disability after discharge, increase the intensity of patients' care that may lead to longer hospital stays, and incremental healthcare costs [5,6].

Prevention of harm and injury is a significant aspect of medical practice. The long standing foundation of medicine "first, do no harm" indicates that the medical expert's understanding that human beings are fragile and can be harmed in health care systems and processes that intend to heal [3].

2.2. Burden of HACs in the general hospitalized patient population

In literature reviews Medical Subject Headings (MeSH) terms (Appendix B) were used to search relevant studies. Systematic search was not conducted and that some articles may have been missed.

Through literature review, several studies were found that have investigated the occurrence of HACs in a general hospitalized population. Most studies provide general information about the rate of HACs and clinical consequences in general population. Alternatively, other studies have analysed HACs within specific types of hospitalization, including specific surgical or medical admissions, specific age categories, and or particular complications, limiting the generalizability of those studies to a broad population. Findings from these studies, both at the patient and hospital level, inform medical practitioners and policy makers. They may inform priority-setting for HAC preventive programs conducted by health system managers. The frequency of the complications, the severity of outcomes, the absolute numbers of hospitalization with HACs, the evidence base for the success of preventive strategies, the feasibility and acceptability of such interventions, and the economic burden of complications[7] may all be considered in planning for HAC prevention.

In the general hospitalized patient population, hospital-based studies in Britain, New Zealand, and United State have reported that HACs occur in 2.9% to 11.7% of hospitalizations[6]. In a systematic review of Medline (January 1966 to February 2007), Cochrane and Embase (January 1980 to February 2007) by E.N. de. Vires and M.A. Ramrattan in 2008, eight studies reporting on a total of 74,485 patient records were analyzed. They defined HACs as an unintended injury to patients resulting in prolonged hospital stay, disability at the time of discharge or death and caused by healthcare management rather than by the patient's underlying disease process (adverse drug events, and specific populations, for example children and ICU patients were excluded from their study). The overall proportion of hospitalizations with HACs was 9.6% [8].

Canadian studies that examine HACs are based on a 1984 protocol set out in the Harvard Medical Practice Study of hospital complications in New York State hospitals. The Harvard Medical Study to identify HACs was based on a two stage chart review. First, nurses screened patient records for those that were likely to include a HAC. Selected charts were then reviewed by physicians to confirm the presence of HACs and to assess the extent to which these conditions indicated substandard care. Since that study, this protocol has been applied and modified in subsequent studies in Australia, the United Kingdom, New Zealand, Denmark and the US other states[6] . In the first Canadian chart review study, in a random sample of patients over 18 years of age for the fiscal year 2000, identified an overall rate of HACs of 7.5% [6]. In another study, reviewing patients' charts in a sample of adults admitted to the Ottawa (Canada) Hospital for acute care of non-psychiatric illnesses over a 1-year period, 12.7% of hospitalizations had ≥ 1 HAC [9]. In eight Alberta, Canada teaching and urban hospitals in 2008, using administrative data, 23.9% of episodes had at least one recorded HAC[10].

Published papers to date indicate that HACs are common and a significant proportion of hospitalized patients experience ≥ 1 HACs.

2.3. Approaches to identify HACs

Differences in the proportion of hospitalized patients with identified HACs can arise from inconsistencies in the definitions used in practice and from the detection method employed. A variety of methods may be used to identify HACs, but, there is no optimal method for measuring those complications[11,12] . Administrative data analyses and chart

review are the common approaches to identify HACs, each with specific advantages and drawbacks [13].

2.3.1. Identification of HACs using Administrative Data analyses

Administrative health data is produced through the routine administration of health care programs in healthcare settings. In addition to basic demographic data (age, sex, place of residence), trained coders assign diagnosis codes from the International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10) from notes in the patient medical record. While not originally intended primarily for research purposes, administrative data can be a rich source of information for investigators to conduct epidemiological research, pharmaco-epidemiology and other types of observational research[13] . The administrative hospital data can be linked to many types of contacts with the healthcare system, including physicians, hospitals, long term healthcare facilities, home care, and pharmaceutical prescriptions.

The Canadian Institute for Health Information Discharge Abstract Data, and the National Ambulatory Care Reporting System are examples of healthcare databases [14,15]. In recent decades, healthcare data is widely used as an efficient approach to define HACs in United States, United Kingdom, Australia, and Canada. The largest administrative health database is the Discharge Abstract Data that contains administrative, clinical, and demographic information relating to all episode of hospitalizations. In different health settings hospital administrative data includes data elements that specify the timing of any clinical condition or diagnosis of hospitalized patients. This allows

identification of conditions that arise during hospitalization. Examples of these indicators include “not present on admission”, “condition onset”, and “diagnosis type 2” that flag conditions that occur during the hospital admission in the US, Australia, and Canada, respectively. Trained coders in hospitals assign indicators to all diagnoses (clinical conditions) by abstracting information from the inpatients medical records.

2.3.2. Identification of HACs using medical Chart review

Chart review is considered the “gold standard” approach to identify complications in hospital [16-18]. Like the coded data, it relies on reviewing medical records to provide comprehensive information about hospitalized patients. Data captured in the patient chart may include a wide range of information (e.g., results of lab tests, nursing and physician notes, discharge notes and consultant reports, and raw data from electrophysiological or imaging tests, etc.) that can be expertly evaluated by clinically trained staff (usually doctors or nurses). Clinical review can better preserve timing of events beyond the ‘present/absent on admission’ criteria used by coders.

2.3.3. Pros and cons of using administrative data analyses and clinical chart review to identify HACs

The main advantages of using administrative data are that a large population can be studied, analyses can examine more exposures and outcomes variables, and such data provides a substantially cheaper and often more timely way of monitoring rates of HACs. Implementing computerized programming allows for rapid identification of any change in complication rates[17,19].

Ambiguities in the description of the code itself (e.g. hypotension) raises concerns about the interpretation of recorded diagnoses by individual coders [17].
Administrative data may not be sensitive for some types of hospital acquired conditions, and on average leads to underestimation of HACs rates[20] . Coding standards require coders to record only conditions that have an impact on patients' clinical outcomes, and this may also lead to under-reporting of HACs.

An important advantage of clinical chart review is that it is possible to extract more details of each patient's clinical course than the simpler administrative data. Coders are trained to review the patient's chart and record several diagnoses, including nominating the 'most responsible diagnosis' for admission, any comorbid conditions, and post admission conditions in administrative data, but in chart review methods, researchers can be trained to identify specific hospital complications.

There are some disadvantages to identifying HACs using chart review. Increasing the number of reviewers may increase the low agreement between experts on HAC identifications[21] . Standardization of methods and eligibility criteria to identify HACs increases the interrater reliability and agreement between researchers. Other strategies that may improve low agreement are: additional training, reducing the number of response categories, improving operational definitions. Studies using this method focus on smaller sample sizes of hospitals, patients, and specific reasons for admission or HACs of interest. Using chart reviews is a labour intensive and expensive approach to identify HACs, as it needs trained reviewers, and often it takes a longer time to capture and analyze data.

2.4. Consequences of HACs

HACs may lead to adverse clinical outcomes for patients, and increased healthcare resource utilization. In the following paragraphs clinical and economic consequences of HACs are discussed in the general hospitalized population.

2.4.1 Impacts of HACs on patients' clinical outcomes

2.4.1.1. Association of HACs with mortality

HACs are associated with and are thought to contribute to increased risk of death[10,22-24]. The Institute of Medicine (IOM) estimates that 44,000 to 98,000 Americans die each year as a result of hospital complications[1]. Analyses of 5.15 million discharges from all California hospitals from 1999 and 2000 indicated that mortality in patients with at least one potentially preventable HACs was 2.5 fold greater than expected[25]. In another study, a literature reviews from 2006 to 2012 identified 4 studies investigating death attributable to HACs. Extrapolating the findings from these studies, they estimated that 210, 000 – 400, 000 deaths a year were associated with HACs among hospital patients in the US. This estimate of HAC-related mortality was higher than the earlier study by the IOM. The authors believe this is because of new methods that are better able to identify HACs. Further it is also possible that from 1984 to 2008 the frequency of patient harms has increased because of the increased complexity of medical practice and technology, the increased incidence of antibiotic-resistant bacteria, overuse/misuse of medications, and/or an aging population[25].

In addition to studies that describe the association of mortality and HAC in general hospitalized patients, other studies consider specific reasons for hospital admission. For example, HACs occurred in 11.3% of all patients undergoing radical cystectomy, and

were associated with a higher odds of in-hospital death (OR 8.07, p<0.001) [26]. Of patients undergoing surgical treatment of a cranial neoplasm; 5.4% had any HAC and those with HACs faced a higher risk of mortality (6.47% vs 1.53%; P < .01) [27].

In summary HACs are common and associated with an increased risk of death. Risk of mortality in patients with HACs is greater than in patients without HACs in the general inpatient population and in specific types of hospitalizations, including specific surgical or medical admissions, and on a population basis may account for a large number of deaths.

2.4.1.2. Association of HACs with Morbidity

In addition to mortality, HACs may lead to harm without causing death. Morbidity describes a diseased state, disability, or poor health due to any cause. HACs increase the risk of disabilities at time of discharge from hospital. Up to 17% of HACs were found to result in permanent disability in the US, Australia, New Zealand, Britain, and Canada[22]. In a study of HACs in Canada, physician reviewers were asked to determine, based on data in the patients' medical chart and their professional judgement, the extent to which physical impairment on the day of discharge was attributable to the HACs, considering underlying disease states. They found that 7.5% of hospitalizations had at least one HAC, most resulted in no disability, or in minimal to moderate impairment with recovery lasting less than 6 months. However, 5% of HACs led to permanent (impairment lasting more than one year) disability[22].

An increased risk of morbidity, ranging from events that are trivial to those that result in permanent disability, are associated with HACs.

2.4.2. Length of stay (LOS) in hospitalized patients with HACs

Some hospital complications intensify patients' clinical condition and lead to more procedures, medication or close observation resulting in longer stay in hospital. We found two studies investigating effects of HACs on length of stay in hospitals. In a study conducted in Spain in 2004, hospitalized patients for major surgery between 1995 and 1999 were analyzed and divided into subgroups with and without complications. Using a program screening for complications, the percentage of hospitalization with any HAC ranged from 17.5% (in cholecystectomy except by laparoscope) to 52.4% (in peritoneal adhesiolysis). Hospital complications were associated with 2.48-fold increase in LOS[28] . An important limiting factor of this study was related to the insensitivity of the screening program itself in differentiating between comorbidity and complications, which may affect validity as it cannot be confirmed that HACs were causal.

In another study, 6.68% of hospitalizations in 5 hospitals in western Australia (excluding same day admission, maternity, and neonatal admissions) from 2010 to 2011 had at least one HAC code assigned in the administrative data. The unadjusted mean LOS was longer in the patients with HACs than those patients without HACs (17.4 days vs 5.4 days) and after adjusting for age, hospital, indigenous status, diagnostic related group category, medical/surgical admission type, elective/urgent admission type, sex and adjusted comorbidity index score, there was an almost fourfold increase in LOS in patients with HACs (IRR=3.84 95% CI 3.73 – 3.96)[29]. The crude and adjusted LOS difference emphasizes the influence of case mix and intensity of patients' clinic conditions and hence the importance of adjusting estimates for these factors.

A case study investigated selected potentially preventable HACs in Syracuse (New York) hospitals to identify the impact of complications on lengths of stay and concluded that, in the patient populations with the same diagnosis related groups and severity of illness, patients with complications of urinary tract infection and pneumonia stayed in hospital 8.9 - 11.9 days and 13.0 - 16.3 days longer, respectively, compared with those without complications[30].

Alternatively, longer LOS exposes hospitalized patients to hazards and makes them vulnerable to acquire complications; risk of pressure ulcer would be a good example for patients with longer stay. Timing of complications within hospitalization is a key point in understanding any causality relation between HAC and LOS. In analyses of administrative data in retrospective studies, the findings show only an association between complications and differences in LOS. Using chart review to identify HACs, provides the opportunity for researchers to determine the causal pathway of HAC and LOS.

2.4.3. Hospital readmission in patients with HACs

Clinical events attributable to HACs may extend beyond the index hospitalization; e.g. readmission. Hospital readmission is defined as a hospitalization that occurs shortly after a discharge; which is most often measured as within 30 days, but may be shorter or longer [31,32] . Assessing the impact of HACs after hospital discharge provides more information about the impact of HACs on patients and health system.

In a study of almost 1.5 million adult surgical admissions, researchers selected 9 HACs relevant for surgical patients. The main data sources were hospital databases in 7

states in the US in 2004, maintained by the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project. 2.6% of hospitalizations had at least one HAC, and the 3-month readmission rate was 17% for those with no HACs, but was 25% with any HACs. This study also found, after risk adjustment for the severity of illness, chronic comorbidities, and age, the relative risk of readmission within 3 months was 1.20 (95% CI 1.14 to 1.56) for specific types of events [33,34].

It is possible that burden of HACs in index hospitalization extend to after hospital discharge. Knowing that HACs are associated with readmission may prioritize practices to reduce HACs to improve patients care and health system outcomes.

2.4.4. Incremental health care costs associated with HACs

With increasing medical care costs, increased efforts are made to ensure health care systems are sustainable. As described above, HACs result in longer stay in hospital, readmission to hospitals, and consequently will lead to increased healthcare costs. Using computerized clinical costing systems that identify the costs of hospital care for individual patients, it is estimated that HACs added AU$790 million to the costs of inpatient care in Australian public hospitals in Victoria (2005/06) and Queensland (2006/07), representing 14.8% of total expenditures and additional costs of 17.3% [7]. A study from Texas, assessing potentially preventable HACs found that 6 percent of Medicaid adult and obstetric populations had at least one potentially preventable HACs in fiscal year 2012 and overall, the estimated economic burden of potentially preventable HACs was $97.4 million, or 3.7 percent, to the hospital costs of caring for these patients[35]. In Alberta, Canada, discharge abstracts of patients admitted from 2008 to 2009 in eight large urban and teaching hospitals were analysed to identify the

proportion of hospitalized patients with ≥1 HAC and to estimate incremental hospital costs attributable to HACs. Using Canada Information Health Information Case Mix Group (CMG) methodology (Appendix C) HACs were associated with increased costs of C$10,866 per patient, or more than double the mean cost of an uncomplicated hospital admission for the same CMG[10].

Readmission due to any HACs in the index hospitalization also increases healthcare costs. In an observational study, all records of inpatient admissions to California hospitals from July 2006 to June 2007 were analyzed. Readmission to hospital within 183 days for complications including poor glycemic control, iatrogenic air emboli, incompatible blood transfusions, catheter-associated urinary tract infections and vascular catheter-associated infections; deep vein thromboses or pulmonary emboli following hip or knee replacement surgery; and foreign objects retained after surgery, mediastinitis following coronary artery bypass grafts, injuries sustained during inpatient care, infections following specific joint or bariatric surgery procedures, and pressure ulcers stages III & IV were investigated. The study found that readmissions that are a consequence of a HAC in the index hospitalizations attract annual Medicare payments of $103 million in this California sample [36].

Other than costs of readmission associated with HACs, some studies have assessed the economic and clinical burden of HACs occurring after hospital discharge due to interventions or medications in index hospitalizations. In a study in the US, the clinical outcomes and costs in the 8-weeks after discharge associated with surgical site infections (excluding obstetric patients) were assessed. After hospital discharge, investigators analyzed questionnaires and surgical site infection was found in 1.9% of

procedures from May 1997 to October 1998. Significantly more outpatient visits, emergency room visits, X-ray services, readmissions, and home health aide services were observed in patients with surgical site infections compared with study controls. On average total costs during the 8 weeks after discharge were US$5,155 for patients with surgical site infections and $1,773 for controls ($p<0.001$)[37].

Understanding the economic dimensions of HACs, including those that are potentially preventable, emphasizes the negative consequences of HACs and may prioritize efforts and guide investment in reducing potentially preventable HACs.

2.5. Some HACs are preventable

While some adverse outcomes occurring in the process of curative interventions in hospitals are not preventable even with optimal care, many may be partially or completely preventable.

Assessing preventability can provide greater understanding of the causes of hospital acquired conditions, which provides information not only for clinicians to prioritize care plans but at a policy level they can be used to develop actionable solutions to the systemic problems that lead to these complications. Any reduction in potentially preventable HACs may decrease resource use and improve patients' clinical outcomes. Specific criteria have been proposed to designate potentially preventable complications: the condition is not redundant with admitting diagnoses (e.g., a diagnosis of stroke in a patient admitted with intracranial hemorrhage), it is not natural, or expected consequence of admitting diagnoses (e.g., stroke in a patient admitted with a brain malignancy), may cause short- or long-term debility, mortality, or impact on costs. In addition, the condition should have a narrow

spectrum of manifestation and its impact on patients or on resource use must not be significant for some patients, but trivial for others[38].

2.5.1. Always preventable complications (never event)

Some hospital acquired complications are thought to be completely avoidable through adherence to best practice. The term "Never Event" or “always preventable HACs" was first introduced in 2001[39] with reporting of particularly shocking HACs that should never occur, e.g., wrong-site surgery. The list has been expanded since then, and in 2011, consisted of 29 complications grouped into 6 classes: surgical, product or device, patient protection, care management, environmental, radiologic, and criminal[40]. In a major “pay for quality” initiative in 2005, the US Congress required Medicare to decrease payment when a diagnoses related group (DRG) includes particular complications that could reasonably have been prevented through the application of evidence-based guidelines. Nonpayment policies for completely preventable HACs are gaining in prominence and are viewed as powerful incentive to reduce the incidence of HACs. As a part of an effort to become a more active purchaser of health care, Medicare will not pay for additional costs associated with preventable HACs [41,42]. (Appendix: Always preventable complications).

2.5.2. Potentially preventable HACs

Studies have assessed whether HACs are preventable and describe the circumstances associated with these conditions. A specific algorithm, developed by 3M Health Information Systems, was used to identify and classify potentially preventable complications (PPCs). The patient’s risk of any HAC is related to the reason for admission, their underlying medical condition, and severity of illness at the time of hospital admission. The present on admission

indicator is important because hospitals use it to determine whether each condition was present on admission or developed during the admission. Panels of 3M clinicians, after reviewing diagnosis values in the ICD-9-CM coding scheme and physician claims, created 66 potentially preventable groups of conditions among identified hospital complications codes. Obstetric admissions were excluded from this analysis. Of the 66 groups of potentially preventable complications evaluated by Maryland and California, statistically significant estimates of PPCs were obtained for 48 categories of events[35,38] (Appendix: list of preventable HACs).

13% of hospitalized Medicare beneficiaries in 2008 had at least one HAC that resulted in some degree of harm, and 44% of these complications were deemed to be potentially or definitely preventable. A study from Texas, based on the potentially preventable HACs analytical approach developed by 3M Health Information Systems, 6 percent of Medicaid adult and obstetric populations had at least one potentially preventable HACs in fiscal year 2012, with higher risk of complications in surgical versus medical patients [35]. Different hospital case mix between the two studies, e.g. high volume of obstetrics admissions in the Texas study, was one of the factors for different proportions of potentially preventable HACs in them. Severity of admitting diagnoses and other comorbid conditions led to considerable variation in potentially preventable HAC rates, so case mix adjustment is essential in producing fair comparisons across hospitals.

In Canada, based on a protocol developed by the Harvard Medical Practice Study, reviewers screened a sample of patient charts, and physicians reviewed the positively screened charts to identify HACs and determine their preventability. They estimated 7.5% of hospitalized patients in fiscal year 2000 experienced ≥ 1 HACs and 37% of these patients

(using their own preventability scale) were judged to have highly preventable HACs. By extrapolation, their study results suggest that, in 2000, between 141 000 and 232 000 of 2.5 million hospitalizations in Canada were associated with HACs and that 9250 to 23 750 deaths from HACs could have been prevented[6].

Implementation of preventive evidence-based strategies suggest many HACs are potentially preventable; e.g. ventilator -associated pneumonia or even always preventable; e.g. foreign body left after surgery. Following training of nurses in how to prevent ventilator-associated pneumonia (e.g. continuous aspiration of subglottic secretions), the rate of this complication decreased from 12.6 per 1,000 ventilator days to 5.7 per 1,000 ventilator days, a decrease of 57.6 percent ($P < 0.001$)[43].

2.6. Burden of HACs in patients with chronic diseases

Hospitalized patients with chronic diseases (e.g. diabetes, hypertension, congestive heart failure, and CKD) may be at greater risk of complications compared with patients without those chronic diseases. These co-morbid conditions interact with the process of illness and conventional care plans and procedures, leading to potential hospital acquired complications.

In our literature review, few studies have investigated the association of HACs in patients with chronic disease. Review of hospitalizations over 12 months at Northern Hospital in Australia using administrative data, indicated 4.5% of admission episodes treated patients with diabetes mellitus. 30% of admissions with diabetes mellitus and with end organ damage had at least one HACs vs 13% in patients without diabetes.

Patients with other comorbid chronic conditions but not diabetes were found to have a HAC rate of 17%. [44].

In a 2005 study in the US [45], analyses of a claims database of 3.5 million privately insured members and dependents under age 65 for six chronic conditions (congestive heart failure, coronary artery disease, diabetes, hypertension, chronic obstructive pulmonary disorder (COPD), and asthma) indicated that preventable HACs consume an estimated average of 28.6 percent of costs of these chronic conditions. In this study, their literature review found that current potentially preventable hospital complication rates might be reduced by about 50% for CHF and CAD, 40% for diabetes, 60% for COPD and asthma, and 75% for hypertension. They concluded, by extrapolation, the estimated total costs associated with potentially preventable HACs in patients with these six chronic conditions could decrease by 3.8 percent. Generalizability of findings are limited: the study did not include Medicaid, Medicare members, or self-pay patients; participants had high level of health care coverage, and the demographic distribution of the database is not nationally representative.

Chronic medical conditions may place patients at a greater risk of HACs. We could find few studies to comprehensively investigate risk of HACs in those patients with underlying chronic diseases.

2.6.1. Definition of chronic kidney diseases (CKD)

CKD is defined as abnormalities of kidney function present for more than three months. The 'Kidney Disease: Improving Global Outcomes' (KDIGO) 2012 Clinical Practice Guideline, categorizes CKD severity status according to GFR and proteinuria levels[46] (Appendix:

KDIGO classification of CKD severity). In older people the prevalence of CKD is rapidly increasing. Between the period 1988–1994 and the 2003–2006 period, prevalence of CKD in people over 60 increased from 18.8 to 24.5 percent according to National Health and Nutrition Examination Survey study [47].

2.6.2 Introduction to HACs in patients with CKD

CKD is thus common, and may be associated with increased risk of bleeding, drug toxicity, drug dosing issues, susceptibility to infection, and associated with a wide range of complications leading to adverse health outcomes [48,49]. The hospital setting is also a place for frequent use of medications including those that contribute to accelerated loss of kidney function or other complications. As such, patients with CKD may be uniquely at risk for HACs. Under-recognition of CKD may be a main contributor to risks for HAC in this patient population [50]. Early recognition of CKD would be an effective means to ensure appropriate doses of medications e.g. NSAIDs, aminoglycosides, or other medications which need dose adjustment in this disease [51]. Furthermore, any reduction of HACs through implementing preventive strategies may be even more beneficial in high risk patients such as those with CKD.

In literature review of HACs in patients with chronic kidney disease, only two studies of HACs and CKD (by the same author in a similar patient population) were found. In a cross-sectional study of associations between CKD and several HACs using Veterans Health Administration data[52] in 2004 to 2005, 29% of hospitalized veterans (surgical, non-surgical) had CKD. These patients had a higher risk for several HACs, even after case-mix adjustment (adjusted incidence rate ratios:1.19; 95% CI 1.13 -1.25). Among several

complications studied, infection had the highest risk in patients with CKD (IRR 2.33; 95% CI 1.92 to 2.82). Further, they found that in surgical hospital admissions, CKD was associated with increased complications of anesthesia (IRR 1.60; 95% CI 1.07 to 2.37), postoperative hip fracture (IRR 4.89; 95% CI 2.79 to 8.57), and respiratory failure (IRR 1.37; 95% CI 1.19 to 1.57. In another study, in 2005 again using the Veterans Health Administration data, they found that approximately half of the sample of 70,000 patients with CKD, had ≥ 1 HAC, whereas 7% experienced three or four (multiple) distinct conditions. Hospital complications were defined as one or more selected AHRQ PSIs, hypoglycemia, hyperkalemia, and/or medication errors[53] . For the first time, both Veteran studies analysed HACs in CKD patients across an integrated national health system, including a large number of hospitals. Furthermore, they used outpatient lab data, creatinine measures, to define CKD prior to hospitalization to minimize the probability of misclassification of acute renal failure as CKD. However, they included only a small number of complications and examined only the Veterans population, which may reduce generalizability of results.

2.6.3. Clinical and economic outcomes of HACs in patients with CKD

We could not find a comprehensive study that analyses mortality attributable to HACs in hospitalized patients (medical and surgical) with CKD and furthermore, no study investigated the association of HACs with mortality after hospital discharge in this patients population.

While there was some data on the length of stay in hospital and health care costs associated with HACs in a general patient population, to our knowledge no study has determined the incremental LOS and healthcare costs of HACs in patients with CKD.It is not clear the extent to which HACs are potentially preventable or reducible in patients

with CKD. In this literature review, no study was found to explain approaches to identifying potentially preventable complications in this high risk patients' population.

2.7. Conclusion

HACs are unintended conditions that occur during hospitalizations and are not present on admission. HACs are common and associated with higher risk of poor clinical outcomes such as increased mortality, greater probability of readmission to hospital, increased length of stay and associated significant economic impact on the health care system. Knowledge of the magnitude of clinical consequences and costs implications of hospital complications may allow priority setting and cost-effective implementation of preventive program and strategies.

A significant proportion of HACs are deemed to be always or potentially preventable. Implementing evidence based preventive strategies has been shown to reduce the occurrence of HACs.

Patients with chronic disease may be at increased risk of HACs but much less is known about HACs and clinical consequences in this population. Chronic kidney disease is common, frequently under-recognized, and may be associated with increased risk of bleeding, drug toxicity, drug dosing issues, susceptibility to infection, and other complications, but HACs have only been examined to a limited extent in one US patient population.

In the general inpatient population, the association of HACs with mortality, readmission, incremental length of stay, incremental hospital cost in patient have already been studied and well known, however in hospitalized patients with CKD, the association of

those outcomes with potentially preventable HACs have not been determined to our knowledge. Only two papers were found to investigate several HACs in patients with CKD using Veterans Administration Health Data in US. These studies for the first time investigated the association of HACs and CKD, however, the non-veteran population, and other potentially preventable complications have not been analyzed.

Assessment of the clinical outcomes and health care resource use associated with potentially preventable HACs are important to understand and to frame the potential benefit of strategies aimed at reducing complications. Healthcare systems would benefit from determining the impact and rate of those conditions in order to best target preventative strategies.

While CKD patients may benefit from implementing general preventive strategies, strategies targeting this readily identifiable high-risk population may lead to greater reduction of potentially preventable HACs more efficiently, and subsequently improve patient and health care system outcomes in hospitalized patients.

Further studies are needed to examine the effect of evidence-based strategies on the risk of potentially preventable HACs, potential needs to improve available best practice guidelines, and to define disease specific strategies, with the goal of improving quality of care and outcomes for hospitalized patients with CKD.

Appendix A: List of databases were used in this study

The Alberta Kidney Disease Network (AKDN) is a collaborative nephrology research organization based on a central repository of laboratory and administrative data from Alberta. Discharge Abstract Data (DAD), The National Ambulatory Care Reporting System (NARS), Population Registry, Laboratory data, physician claims.

Appendix B: Mesh terms and keywords were used in literature review:

The following MeSH terms are relevant for our paper: Renal insufficiency, Chronic; Patient Safety; Cohort Studies; Safety Management; Medical Errors; Near miss, Mortality, Readmission, Cost analysis.

Terms were searched for literature review were: Hospital acquired diagnosis (adverse events AND hospital*[ti] AND Canada) OR ((((cross infection) OR (infectious disease transmission, Professional-to-Patient) OR (infectious disease transmission, professional-to-patient) OR (iatrogenic disease) OR (medical errors) OR (patient safety) OR (safety management) OR (iatrogenic disease*[ti]) OR (iatrogenic disease*[ti]) OR (hospital infection*[ti]) OR ("hospital acquired "[ti]) OR (nosocomial infection*[ti]) OR ("acquired diagnoses"[ti]) OR ("acquired diagnoses"[ti]) OR ("acquired diagnosis"[ti]) OR (adverse events AND hospital*[ti] AND Canada)) AND ((health facilities[mh]) OR (hospitals[mh]) OR (hospital*[ti]))) AND ((Alberta) OR (Alberta) OR (Canada[ti]) OR (Canadian[ti]) OR (Alberta[ti])) AND (("1999"[PDat] : "3000"[PDat])))

Appendix C: How to measure hospital and ambulatory care costs:

The Canadian Institute of Health Information (CIHI) in April 2007 has introduced the CMG+ methodology which groups the hospitalizations to clinically similar and/or homogenous group with respect to resources used [54]. Using most responsible diagnoses or (principal condition) or based on procedures, this methodology defines patients' major clinical category (MCCs) and CMGs. The average index hospitalization cost calculated by multiplying "Cost Per Weighted Case" (CPWC) and resource intensity weight (RIW) of each CMGs. Average financial cost a hospital incurs to treat a single inpatient is presented by the CPWC measure by dividing total inpatients cost for a facility by the total weighted cases in that facility. "Resource Intensity Weights" (RIWs) presents the relative resource used by a patient. The RIW and CPWC are being calculated and updated annually from CIHI's Canadian MIS database, based on data provided by all hospitals [55].

The National Ambulatory Care Reporting System which was developed by CIHI includes data for all hospital-based and community-based ambulatory care. Specific categories include emergency visits, ambulatory interventions, rehabilitation and clinic visits with the exception of telephone visits and direct diagnostic imaging. In this data costs of all outpatients' health resource use including complete cost of each encounter of allied healthcare professional, diagnostic imaging, and interventions. Most physicians in Alberta are paid for each service they deliver through fee-for-service where compensation occurs with submitting a claim

CHAPTER 3: Risk of hospital acquired complications in patients with CKD

3.1. Abstract:

Background and objectives: Unintended injuries or complications that occur in hospitalized patients are common, potentially preventable, and associated with adverse consequences including greater mortality and health care costs. Patients with chronic kidney disease (CKD) may be at higher risk of hospital acquired complications.

Design, setting, participants, and measurements: Adults hospitalized from April 1, 2003 to March 31, 2008 from a population based cohort (Alberta Kidney Disease Network) comprised the study cohort. Kidney function was defined using outpatient eGFR and proteinuria (protein/creatinine ratio or dipstick) in the year prior to index hospitalization. Co-morbid conditions were identified using validated algorithms applied to administrative data. A specific diagnostic indicator was used to identify hospital acquired complications (HACs). Complications were classified into clinically homogeneous groups, and sub classified as potentially preventable complications (p-HACs) or always preventable (a-HACs). Multivariable logistic regressions models were used to examine the association of CKD with HACs, accounting for confounders.

Results: Of 536,549 patients, 8.5% had CKD and they were older and more likely to be admitted for circulatory system diseases than those without CKD. In fully adjusted models the odds ratio (OR) of any hospital complication in patients with CKD (reference: no CKD) was 1.19 (95% CI: 1.18 – 1.26); there was a graded relation between the risk of HACs and CKD severity, with an OR of 1.81 (95% CI: 1.51 – 2.17) in those with the most severe CKD (eGFR = 15-29 ml/min/1.73m^2 and proteinuria > 30 mg/mmol).

Findings were similar for p-HACs (OR=1.20, 95% CI: 1.16 – 1.24 and 1.78, 95% CI: 1.43 – 2.11, respectively). Always preventable events had similar point estimates.

Conclusions: The presence of CKD and its severity is associated with a higher risk of HACs, including those considered potentially preventable. Targeted strategies to reduce complications in patients with CKD admitted to hospital should be considered.

3.2. Introduction:

Hospital acquired complications (HACs) are undesirable and unintended clinical conditions, distinct from the admitting diagnosis that may occur during a hospitalization episode. Specific diagnostic indicators in administrative hospital data are used that by definition refer to new diagnoses or events that occur during hospitalization ("Diagnosis type 2" in Canada, "not - present on admission" (n-POA) in US, and "condition-onset flag (C prefix)" in Australia). HACs are common and associated with adverse consequences including prolonged hospital stay, increased disability at discharge, and higher risk of death[4-6,28]. Studies in Britain, New Zealand, and the United States report that HACs occur in 2.9% to 11.7% of hospitalizations[1] . In Canada the proportion of hospital episodes with at least one reported HAC has been estimated to be between 7.5% [3] and 23.9% [(6)] , and prolonged length of stay by 4.7 days[(6)] .Chronic kidney disease (CKD) is common, and associated with high risk of hospitalization and higher risk of complications, including bleeding, drug toxicity, drug dosing issues, susceptibility to infection, and other complications[23,24]. To date, limited data is available on HACs in patients with CKD. An analyses of the Veteran's Administrative data for 2004-2005

showed patients with CKD had a higher risk for several hospital acquired complications than patients with normal kidney function (adjusted incidence rate ratios:1.19; 95% CI 1.13 -1.25)[29] , however non – veteran patient populations with CKD have not been examined.

A significant proportion of HACs are deemed to be potentially preventable. The percentage of hospitalizations episodes with potentially preventable hospital complications range from 2.8% [3] to 6% [19]. There is evidence that these complications can be reduced. Two hospitals with relatively high p-HACs rates (48.73 and 58.17 per 1000 discharge) reduced this rate to 32.36, 48.15, respectively through implementation of various strategies by administrative and clinical staff [30]. In a “pay for quality” initiative in 2005, Medicare decreased payment when a diagnosis related group (DRG) includes particular complications that could reasonably have been prevented through the application of evidence-based guidelines, and “no payment” initiatives have been associated with reductions in the rate of 2 a-HACs (central line-associated bloodstream infections and catheter-associated urinary tract infections) [31].

The risk of hospital acquired complications, including those that are potentially preventable, have not been determined in patients with CKD in a population based cohort. Given the high hospitalization rate in CKD patients, the potential for HACs in this high risk group, and the potential to prevent some of these complications, we sought to determine the association of the presence of CKD and its severity with HACs (including potentially preventable types of HACs) in a large population based cohort of adults.

3.3 METHODS:

Study Population

The study cohort comprised all adults (age ≥ 18) in Alberta hospitalized from April 1, 2003 to March 31, 2008 (Figure 1) from the population based Alberta Kidney Disease Network (AKDN) [23]. The first hospitalization was considered for each individual. Medical and surgical admissions with the exception of maternity/neonatal, congenital malformation, convalescence, and same day admission were included. Patients with kidney failure (dialysis, renal transplant, eGFR<15 ml/min/1.73m^2) were excluded. We used known designation Case Mix Groups (CMGs) to stratify admissions into medical or surgical, where possible (due to data limitation, 25% could not be classified). Population attributable risk percent (PAR %) was used to determine the proportion of hospitalization with ≥ 1 potentially preventable HAC in the population (CKD and non-CKD) that may be attributable to CKD; Poisson regression was used to determine the adjusted risk ratio needed for this calculation.

Assessment of patients' characteristics:

Kidney function was determined from outpatient serum creatinine measurement and urine studies. Average eGFR was estimated using the Modification of Diet in Renal Disease equation (MDRD). The primary exposure variable of CKD was defined by eGFR < 60 ml/min/1.73m^2 and /or moderate to high proteinuria defined as an albumin/creatinine ratio >3-30 mg/mmol or protein/creatinine ratio >15-50 mg/mmol or > 2+ protein dipstick in the year prior to index hospitalization. All outpatient eGFR measurements in the time frame from 365 days to 90 days prior to admission were

considered; we excluded eGFR measurement within 3 months of admission to ensure that AKI did not impact CKD determination. Further categorization of CKD using the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guidelines was employed. We assumed those patients without any serum creatinine and proteinuria data had normal kidney function. 15% of patients had no lab data to present kidney function in the year before hospitalization. The effect of excluding those patients was tested using sensitivity analyses and produced very close ORs. Co-morbid conditions including; cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, renal disease, rheumatologic disease were identified using validated algorithms applied to hospitalization discharge abstracts and physician claims data [32]. The reason for hospitalizations was categorized into 16 homogeneous groups using ICD 10 CA.

Hospital administrative data includes “diagnoses type 2” which indicates hospital acquired complications. Using the International Classification of Disease version 10 (ICD 10), hospital coders record all clinical conditions and signs not present at hospital admission during reviewing patients’ charts. These 4000+ ICD 10 CA diagnostic codes were mapped into 10 groups and with 38 subgroups according to clinical similarity (Appendix A). We used published data to identify 63 potentially preventable HACs[19] by manually re-mapping ICD 9 diagnostic codes to ICD 10 CA. Briefly, panels of clinicians (two general internists and one pediatrician supplemented by surgical, obstetric specialist as needed) reviewed each of approximately 14,400 diagnosis values in the

ICD-9-CM coding scheme and classified 1,562 codes that as being potentially preventable in-hospital complications. Always preventable HACs were defined based on Medicare “never event” diagnoses [33], and the US ICD 9 codes for these conditions manually were re-mapped to the Canadian version.

3.3.1 Statistical analysis

Continuous variables were described using mean and standard deviation or median with 25th and 75th percentiles, as appropriate. The linearity assumption for age was satisfied. Categorical variables were described as proportions of the cohort with or without each condition or characteristics. A multivariable logistic regression analysis was used to determine the independent association of CKD and its severity with risk of developing ≥1 HAC, after controlling for potential confounders. In the primary analysis, all HACs were used to define the dependent variable, in secondary analyses we considered p-HACs and a-HACs as the dependent variable. Purposeful selection model building was used. The fully adjusted models included reason for admission, age, gender, admission type (urgent vs. elective admission as defined in hospital administrative data), CKD, LOS, and 17 co-morbid conditions. We did sensitivity analysis to assess the association of increasing number of HAC with dependent variable of LOS. Multivariable regression analyses was used and adjusted for gender, age, admission type (elective vs urgent admission as defined in hospital administrative data), and 17 comorbid conditions. The analysis was done using Stata, version 13. The health research ethics board of the University of Alberta and University of Calgary approved the study.

3.4. RESULTS

Patient characteristics

Of 765,234 adults hospitalized in Alberta during the study period, 536,549 (70.1%) met inclusion criteria (Figure 3.1). Mean age of patients with CKD was greater than non-CKD cases and median hospital length of stay for the cohort was 4 days (25th-75th percentile; 2-11 days) and 3 days (25th-75th percentile; 2-6 days) in patients with and without CKD, respectively. Cardiovascular diseases comprised the largest 'most responsible diagnosis category' in patients with CKD accounting for 20% of admissions. Patients with CKD were also more likely to be admitted for cancers and endocrine disorders as the most responsible diagnoses, and less likely to be admitted for respiratory or digestive system conditions compared with those without CKD. In the entire cohort 6.7% and 2.6% of patients had eGFR < 60 mL/min/1.73m^2 and moderate to heavy proteinuria, respectively and 45,733 patients (8.5% of cohort) had CKD (Table 1).

Risk of HAC:

In the entire cohort, 42,036 (7.8%) had at least one HAC, and the proportion of hospitalization episodes with complications was approximately two-fold higher in patients with CKD compared to no CKD (13% and 7% respectively). The proportion of patients with ≥ 1 HAC were similar when stratified by medical or surgical admission. The proportion of hospital admissions with any HAC, potentially preventable, and always preventable complications in each year appeared numerically stable of the study period. In a fully adjusted analysis the odds ratio of HACs in patients with CKD (reference: no CKD) was 1.19 (95% CI: 1.18 – 1.26) (Table 2). Every 5 ml/min/1.73m^2 lower eGFR

was associated with a 1% higher risk of HAC (OR= 1.01 95% 1.01 – 1.01). A graded association with severity of CKD was observed, with the most severe category of CKD associated with OR of 1.81 (95% CI: 1.51 – 2.17) (Table 3a).

Risk of potentially preventable complications:

9.8% of CKD patients had at least one p-HAC compared with 5.4% in those without CKD. Adjusted relative risk of preventable HAC was 1.17 (95% CI: 1.14 – 1.21) in CKD patients, and the population attributable risk percent of HAC that may be due to CKD was 1.2% (with the proportion of cohort with CKD=8.5%). Patients with CKD had a 20% higher risk of developing a p-HACs (OR=1.20 95% CI; 1.18 – 1.27) (Table 2). Patients with more severe kidney disease were also at higher risk of p-HACs. In the most severe CKD category the OR was 1.78 (95% CI: 1.43 – 2.11) (Table 3b). Post-procedural complications including; cardiovascular, respiratory and other complications of surgical and medical care were the most common p-HACs in patients with CKD. Anemia and acid-base, fluid and electrolyte balance, metabolic disorder infections were the second and third most common p-HACs. (Appendix B)

Risk of always preventable complications:

In a fully adjusted logistic regression analyses, patients with CKD were at higher risk of a-HAC (OR =1.16 95% CI: 1.07 – 1.26) (Table 2). A similar graded association of more severe CKD and larger OR was observed, although 95% confidence intervals crossed unity. Post-surgical site infections, falls and trauma, and deep vein thrombosis were the most common a-HACs in patients with CKD (Table 4).

Sensitivity analyses:

Excluding patients with no eGFR measurement did not alter results. The OR of HAC in medical or surgical CKD patients were 1.14 (95% 1.08 – 1.19) and 1.24 (95% CI 1.17 – 1.30), respectively. After adjustment, a graded association of LOS with number of HACs was observed; patients with one HAC and 3 to 5 HACs stayed at hospital 9.38 days (95% CI: 8.73 – 10.02), and 24.09 days (95% CI: 22.43 – 25.75) longer, respectively.

3.5. Discussion:

In this large population based cohort of hospitalized patients, we found that risk of HACs (including those that are considered potentially preventable or always preventable) were more likely in patients with CKD. The risk of these complications increases in a graded fashion with severity of CKD. We found that patients with CKD had 19% higher risk of HACs, and that the excess risk was as much as 81% higher in those with the most severe kidney impairment (eGFR = 15-29 ml/min/1.73m^2 and proteinuria > 30mg/mmol). As CKD is readily identifiable using routine laboratory tests that are commonly conducted in hospitalized patients, and targeted strategies to prevent HACs have been demonstrated to be effective in some settings, patients with CKD may be an ideal high

risk population to implement evidence-based strategies to reduce HACs, which may subsequently improve patient and health care system outcomes.

Patients with CKD may be uniquely pre-disposed to complications during hospitalization, due to known factors such as impaired coagulation, altered renal handling of medications requiring drug dosing changes and predisposition to drug toxicity, susceptibility to infection, and other complications. Under-recognition of CKD may contribute to high frequency of HACs observed, particularly with milder severity of kidney impairment. It is also possible that CKD may be a marker for sicker patients, as CKD often occurs in patients that are older and have multiple comorbid conditions; however, we attempted to control for potential confounders.

Our findings are consistent with previous studies that have examined hospital complication rates in patients with CKD. In the US Veterans population, the association of CKD with 13 hospital acquired complications (Patient Safety Indicators or PSIs) reported a 19% higher risk for patients with CKD, as defined by eGFR alone. A similar linear trend was observed across varying CKD severity [29]. Our results are congruent; however, we used both eGFR and proteinuria level, and assessed outpatient values prior to hospitalization to define CKD patients. Further, we studied a population based cohort, and considered all hospital complications in addition to those deemed to be potentially or always preventable.

A large proportion of HACs are considered to be always or potentially preventable. Payment reform by the US Centers for Medicare and Medicaid (CMS) was found to alter the rate of central line associated blood stream infections and catheter associated

urinary tract infections after hospital implemented preventive strategies in response to these payment incentives [31].

In our study we found that 9.8% of CKD patients had at least one potentially preventable complication in hospital compared with 5.3% in those without CKD. Patients with CKD had a 20% higher risk of developing potentially preventable complications (OR 1.20 95% CI; 1.18 – 1.27). Post-procedural complications were the most frequent cause of HACs in people with underlying CKD compared to those without. The risk of "always preventable" complications also increases with CKD and its severity; however the graded association is not significant in some stages of kidney function, which may be due to lack of statistical power given the infrequent occurrence of these HACs. To highlight the importance of our findings, extrapolation of our data to 38 million admissions in North America in 2013 [22, 23] suggests that 2.18 million patients had ≥ 1 potentially preventable complications (5.75%), and the excess number of admissions with ≥ 1 potentially preventable hospital complication that may be attributable to CKD was 26,000 (based on the PAR of 1.2%).

Strengths of this study include the use of a population based cohort and inclusion of community, teaching, and specialized hospitals, which strengthens generalizability. Further, we determined baseline kidney function prior to hospitalization using outpatient lab data to define both eGFR and proteinuria. Prior studies have focused largely on specific populations of hospitalized patients, such as those defined by age, diagnostic category (cardiac surgery, intensive care unit, and after myocardial infarction) or treated by a specific health care provider or institution, thereby limiting their generalizability[34-39] .

There also are limitations to our study. Administrative data lacks information regarding severity of comorbid conditions and of the 'most responsible diagnoses' for admission. Access to certain clinical variables such as blood pressure control and life style factors (smoking, exercise, and diet) is also limited. A second limitation is underestimation of HACs. Administrative data may not be sensitive for some types of hospital acquired conditions[24]. As such, the number of hospital acquired complications is likely to be underestimated, however this is unlikely to invalidate results as incomplete ascertainment would be expected to occur in both CKD and non-CKD patients. Third, it is possible that the association of CKD and HAC is mediated through other pathways, such as greater burden of illness or greater LOS (greater exposure to develop HAC), although our HACs analysis adjusted for available data on comorbidity as well as days in hospital. Fourth, due to limitations of our source data, we were unable to obtain information on hospital level factors including hospital type, volume, and location. Fifth, we made the assumption that patients with no measure of proteinuria should be in the category of no proteinuria. However, this is a test ordered by providers based on clinical suspicion, therefore the probability of significant proteinuria in patients where the test is not ordered is likely lower than in those in whom it was measured. Sixth, in recent years increased efforts to improve hospital safety and quality of care have been implemented, which may modify the absolute risk of potentially preventable HACs. Finally, our source data does not allow accurate classification of attribution such as medication error causing a complication. As patients with CKD may be uniquely predisposed to complications of medications, this should be a focus of future study using chart review or a prospective study.

3.6. Conclusion:

The presence of CKD and its severity was associated with a higher risk for hospital acquired complications, many of which may be potentially preventable. Further investigations are needed to examine the effect of evidence-based strategies on the risk of p-HACs, with the goal of improving quality of care and outcomes for hospitalized patients with CKD.

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Disclosure: This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the view of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta, Alberta Health nor Alberta Health Services express any opinion in relation to this study.

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Table 3.1. Patient characteristics

		All Patients	No CKD	CKD
Demographics				
Number of patients (%)		*536,549 (100)*	*490,816 (91.5)*	*45,733 (8.5)*
Age, mean(SD)		*52.4 (22.8)*	*50.6 (22.5)*	*72.1 (15)*
Male (%)		*49.3*	*49.8*	*43.9*
Most responsible diagnosis category (%)				
Disease of digestive system		*13.9*	*14.2*	*11.1*
Injury, poisoning		*13.5*	*14*	*8.1*
Disease of circulatory system		*12.7*	*12*	*20.8*
Neoplasm		*9.5*	*9.4*	*11.4*
Disease of musculoskeletal system		*9.2*	*9.1*	*10.3*
Disease of genitourinary system		*9.2*	*9.1*	*9.6*
Disease of respiratory system		*8.8*	*8.9*	*7.6*
Mental behavioral		*6.9*	*7.2*	*3.1*
Symptom, signs of abnormal clinical and lab		*5.8*	*5.8*	*5.8**
Endocrine		*3.4*	*3.2*	*5*
Disease of nervous system		*2.4*	*2.4*	*2.2*
Certain infectious and parasitic disease		*1.5*	*1.6*	*1.6**
Disease of skin and subcutaneous		*1.2*	*1.2*	*1.1**
Disease of eye		*0.9*	*0.9*	*1**
Disease of blood and blood forming organs		*0.7*	*0.7*	*1.9*
Disease of ear		*0.4*	*0.4*	*0.3*
Admission type (Urgent %)		*69.7*	*69.6*	*71*
Medical admission (N) (%)		*228,450 (42.6)*	*208,926 (42.6)*	*19,524 (42.7)*
Surgical admission (N) (%)		*172,636 (32.2)*	*156,361(31.8)*	*16.275 (35.6)*
Other admission (N) (%)		*135,463 (25.2)*	*125,529 (25.6)*	*9,934 (21.7)*
Length of stay (LOS) mean (median)(25th to 75th percentile)		*7.4(3)(2-7)*	*7.1(3)(2-6)*	*10.6(4)(2-11)*
Any aHAC (n) (%)		*5,419(1)*	*4,711(0.9)*	*722(1.6)*
Any pHAC (n) (%)		*3,0851(5.7)*	*263,568(5.4)*	*4,490(9.8)*
Any HAC (n) (%)		*42,036 (7.8)*	*351,65 (7.2)*	*5,911(12.9)*
Medical admission with any HAC (N) (%)		*16,194 (7.1)*	*13,038 (6.7)*	*2,256 (11.6)*
Surgical admission with any HAC (N) (%)		*16,540 (9.6)*	*14,113 (9)*	*2,427 (14.9)*
Other admission with any HAC (N) (%)		*9,302 (6.9)*	*8,014 (6.4)*	*1,288 (13)*
eGFR mL/min/1.73 m^2 (n)(%)	*>60*	*500,199(93.2)*	*500,199(93.2)*	*0*
	45 – 59	*22,736(4.2)*	*0*	*22,736(4.2)*
	30 – 44	*9,402(1.7)*	*0*	*9,402(1.7)*
	15-29	*4,212(0.8)*	*0*	*4,212(0.8)*
Proteinuria	*None* (<3 mg/mmol)	*522,613(97.4)*	*522,613(97.4)*	*0*
	Moderate (3-30 mg/mmol)	*8,341(1.5)*	*0*	*8,341(1.5)*
	Heavy (> 30 mg/mmol)	*5,595(1)*	*0*	*5,595(1)*

In CKD patients: Serum creatinine (mean, SD): 122.95 (105) and eGFR mL/min/1.73 m^2 (mean, SD: 49.39(15.54)

**Non-significant*

Table 3.2. Risk of hospital acquired complications in patients with CKD

	OR (95 % CI)
All complications *	1.19 (1.15 - 1.23)
Potentially preventable complications**	1.20 (1.16 – 1.24)
Preventable complications**	1.14 (1.05 – 1.24)

* Fully adjusted for age, admission type (elective vs urgent), gender, LOS, and 17 comorbid conditions

** Fully adjusted for age, admission type (elective vs urgent), gender, LOS, and 17 comorbid conditions, except for reason for admission.

Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, renal disease, and rheumatologic disease.

Table 3.3a. Adjusted Odds ratio (95% CI) of HACs by GFR and albuminuria categories

CKD by GFR and Albuminuria Categories: KDIGO 2012			**Persistent albuminuria categories Description and range**		
			Normal to mildly increased	**Moderately increased**	**Severely increased**
			<30 mg/g <3 mg/mmol	**30-300 mg/g 3-30 mg/mmol**	**>300 mg/g >30 mg/mmol**
GFR categories (ml/min/ 1.73 m ^{2})Description and range	**Normal or high**	**>90**	References N = 490,816	**HACs:**1.25 (1.15 – 1.35) N = 6,195	**HACs:**1.33 (1.89 – 1.48) N = 3,188
	Mildly decreased	**60 – 89**			
	Mildly to moderately decreased	**45 – 59**	**HACs:** 1.13 (1.08 – 1.18) N = 20,735	**HACs:** 1.14 (0.93 – 1.35) N = 1,155	**HACs:**1.38 (1.14 – 1.6 N = 846
	Moderately to severely decreased	**30 – 44**	**HACs:** 1.23 (1.16 – 1.32) N = 8,021	**HACs:**1.38 (1.11 – 1.70) N = 655	**HACs:**1.29 (1.05 – 1.60) N = 726
	Severely decreased	**15 – 29**	**HACs:**1.43 (1.29 – 1.58) N = 3,041	**HACs:**1.29 (0.95 – 1.74) N = 336	**HACs:**1.81 (1.51 – 2.17) N = 835

* Fully adjusted for age, admission type (elective vs urgent), gender, LOS, and 17 comorbid conditions including; cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, renal disease, and rheumatologic disease.

Table 3. 3b. Adjusted Odds ratio (95% CI) pHACs by GFR and albuminuria categories

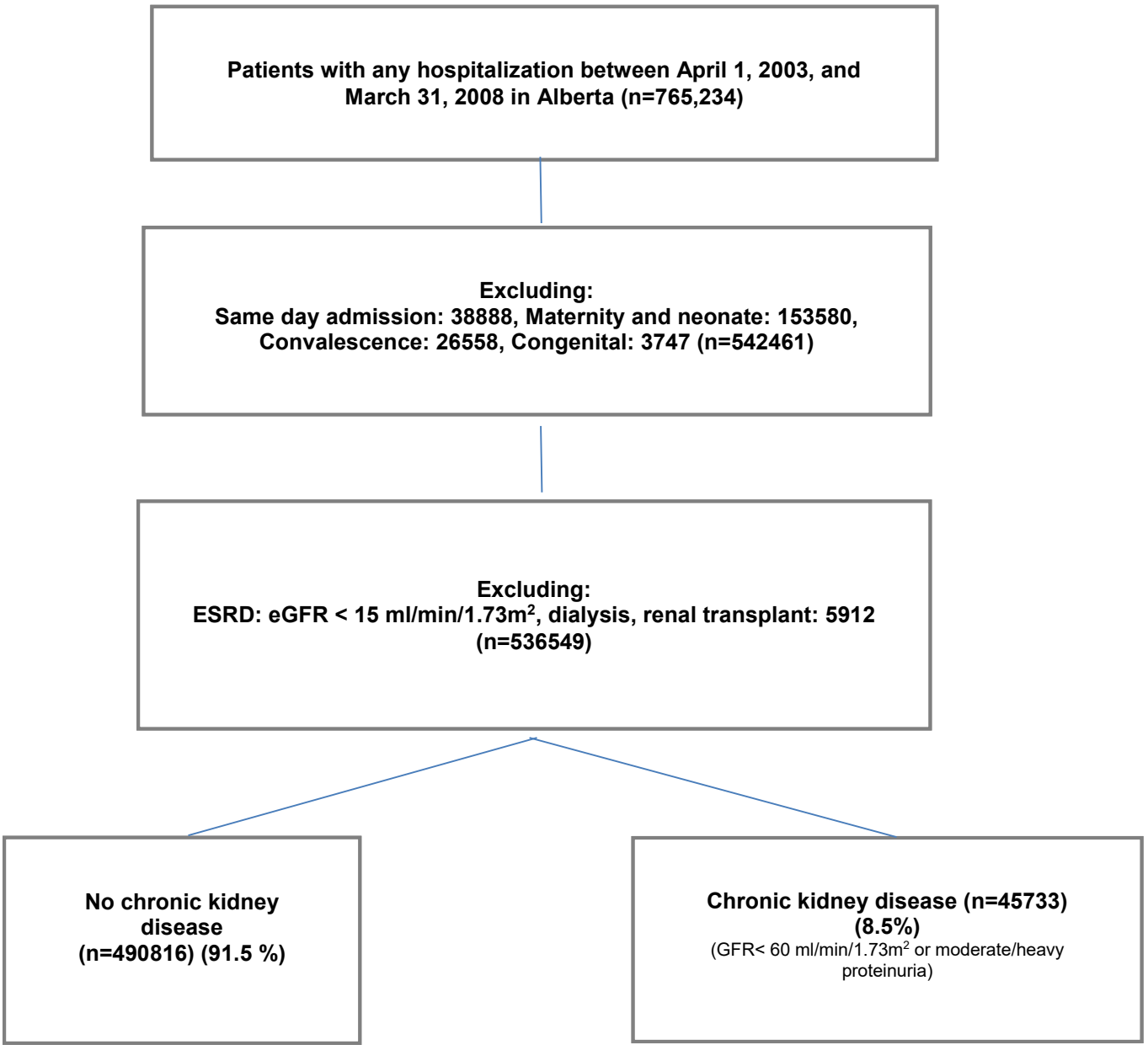
CKD by GFR and Albuminuria Categories: KDIGO 2012			Persistent albuminuria categories Description and range		
			Normal to mildly increased	**Moderately increased**	**Severely increased**
			<30 mg/g <3 mg/mmol	**30-300 mg/g 3-30 mg/mmol**	**>300 mg/g >30 mg/mmol**
GFR categories (ml/min/ 1.73 m ^{2})Description and range	**Normal or high**	**>90**	References N = 490,816	**p-HACs:** 1.21 (1.07 – 1.36) N = 6,195	**p-HACs:** 1.36 (1.18 – 1.58) N = 3,188
	Mildly decreased	**60 – 89**			
	Mildly to moderately decreased	**45 – 59**	**p-HACs:** 1.15 (1.05 – 1.25) N = 20,735	**p-HACs:** 1.05 (0.84 – 1.30) N = 1,155	**p-HACs:** 1.33 (1.05 – 1.69) N = 846
	Moderately to severely decreased	**30 – 44**	**p-HACs:** 1.21 (1.09 – 1.35) N = 8,021	**p-HACs:** 1.28(0.90 – 1.84) N = 655	**p-HACs:** 1.15 (0.88 – 1.49) N = 726
	Severely decreased	**15 – 29**	**p-HACs:** 1.41 (1.23 – 1.62) N = 3,041	**p-HACs:** 1.36 (1.18 – 1.58) N = 336	**p-HACs:** 1.78 (1.43 – 2.11) N = 835

* Fully adjusted for age, admission type (elective vs urgent), gender, LOS, and 17 comorbid conditions including; cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, renal disease, and rheumatologic diseases.

Table 3.4. Most common always preventable complications in patients with CKD

Complications	number	%
Surgical Site Infection including: post CABG, bariatric surgery, orthopedic procedures	2334	39.1
Falls and Trauma including: fracture, dislocation, intracranial injury crushing injury, other injuries	1173	19.7
Deep Vein Thrombosis and Pulmonary Embolism	642*	10.8
Post procedural pneumothorax	564	9.5
Others	1207	23.8
Total	***5920***	***100***

Figure 3.1. Flow chart to construct the cohort with and without CKD



Appendix A

Example for HAC group and subgroup classification using ICD 10 codes

Group	Subgroups	ICD 10 CA Codes
A: Infections	**A_2: Central nervous system(meningitis, brain abscess, encephalitis .....), intracranial phlebitis**	**G002:** Streptococcal meningitis Includes: Non-pneumococcal, streptococci (Streptococcus, Group A) (Streptococcus, Group B) **G008:** Other bacterial meningitis Includes: Meningitis due to: Escherichia coli, Friedlander bacillus, Klebsiella **G009:** Bacterial meningitis, unspecified Includes: Meningitis: purulent NOS, pyogenic NOS. suppurative NOS **G030:** Non-pyogenic meningitis Includes: Nonbacterial meningitis **G039:** Meningitis, unspecified Includes: Arachnoiditis (spinal) NOS **G048:** Other encephalitis, myelitis and encephalomyelitis Includes: Post-infectious encephalitis and encephalomyelitis NOS **G049:** myelitis and encephalomyelitis, unspecified Includes: Ventriculitis (cerebral) NOS **G060:** Intracranial abscess and granuloma Includes: Abscess (embolic)(of): brain [any part],cerebellar, cerebral, otogenic, Intracranial abscess or granuloma: epidural, extradural, subdural **G061:**Intra-spinal abscess and granuloma Includes: Abscess (embolic) of spinal cord [any part]Intra-spinal abscess or granuloma: epidural, extradural subdural **G062:** Extradural and subdural abscess, unspecified D432: G08 C760 A858 D352 A178 D320 A879 G062 B004 C700 G008 G040 C793 G060 G061 G003 G049 A170 G042

Appendix B:

Potentially preventable complications in patients with CKD

Complications	Description	N of	%
A. Infections	A_3: Respiratory (pneumonia, mediastinitis, pulmonary abscess ...)	455	4
	A_5: Genitourinary infection (UTI, cystitis, pyelonephritis ...)	481	4
	A_7: Septicemia	143	1
B: Electrolyte imbalance	B_1: Hypo / hyper glycaemia and related complications	52	0.01
	B_2: Volume depletion	80	1
	B_3: Acid-base, fluid, and electrolyte balance, metabolic disorders	493	4
	B_4: Hospital acquired nutrition deficiencies	15	0.01
C: Neurological complications	C_6: Post procedural disorders	23	0.01
D: Cardiovascular complications	D_2: Shock/hypotension	345	3
	D_3: Ischemic Heart Diseases	36	0.01
	D_4: Acute myocardial infarction	449	4
	D_6: Heart arrest	158	1
	D_7: Heart failure	212	2
	D_8: Arrhythmias	404	3
	D_9: Emboli	8	0.01
	D_10: Pulmonary embolism	80	1
	D_11: Phlebitis , Thrombophlebitis, and Deep vein thrombosis	74	1
	D_12: Complications of cardiac and vascular prosthetic device, implant and graft	155	1
	D_16: Post procedural complications	542	4
E: Respiratory complications	E_1: ARDS	58	0.01
	E_2: Pulmonary oedema	14	0.01
	E_4: Pneumothorax	13	0.01
	E_5: Aspiration pneumonia	229	2
	E_6: Post procedural disorders (Pneumothorax included)	528	4
	E_11: Respiratory failure	197	2
	E_12: Pulmonary collapse	129	1
F: Gastrointestinal complications	F_4: Post procedural disorders	280	2
G: Post procedural disorders	G_1: Post procedural disorders	216	2
K: Skin complications	K_2: Decubitus Ulcer	69	1
M: Hematologic complications	M_4: Anemia due to bleeding	494	4
	M_6: Syncope and collapse	24	0.01
P: Surgical medical complications	P_2: Other complications of surgical and medical care , not elsewhere classified	439	4
	P_3: Following infusion, Transfusion, therapeutic injections	58	0.01
	P_4: Haemorrhage and hematoma complicating a procedure	411	3
	P_5: Accidental puncture and laceration during procedure	161	1
	P_6: Infection following a procedure	216	2
	P_7: Disruption of the operation wound	76	1
	P_8: Foreign body left in body	3	0.01
Potentially preventable complications (pHACs)		7820	63.1
Total recorded complications (HACs)		12126	100

CHAPTER 4: Adverse outcomes associated with potentially preventable complications in hospitalized patients with chronic kidney disease

4.1. Abstract:

Background and objectives: Patients with CKD are at risk of hospital acquired complications (HACs). We sought to determine the association of potentially preventable HACs with mortality, length of stay (LOS), and readmission.

Design, setting, participants, and measurements: All adults hospitalized from April 2003 to March 2008 in Alberta were characterized by kidney function, comorbidity, and occurrence of potentially preventable HAC. Regression models examined the association of HACs with mortality during the index hospitalization and within 90 days after discharge, LOS and readmission.

Results: In patients with CKD, the adjusted odds ratio (OR) of mortality during the index hospitalization and from hospital discharge to 90 days in patients with ≥ 1 potentially preventable HAC was 4.67 (95% CI: 4.17 – 5.22) and 1.08 (95% CI: 0.94 – 1.25), respectively. Median incremental LOS in patients with ≥ 1 potentially preventable HAC was 9.86 days (95% CI 9.25 – 10.48). The OR for readmission with potentially preventable HAC was 1.24 (95% CI: 1.15 – 1.34).

In a cohort with and without CKD, the adjusted OR of mortality during index hospitalization in patients with CKD and no potentially preventable HACs, patients without CKD and with potentially preventable HACs, and patients with CKD and potentially preventable HACs, were 2.22 (95%CI; 1.69 – 2.94), 5.26 (95%CI; 4.98 –

5.55), and 9.56 (95% CI; 7.23 – 12.56), respectively (referenced to patients with neither CKD nor potentially preventable HAC).

Conclusions: Potentially preventable HACs are associated with higher mortality, increased LOS and greater risk of readmission, especially in people with CKD. Targeted strategies to reduce complications should be a high priority.

4.2. Introduction

Hospital acquired complications (HACs) are undesirable and unintended clinical conditions, distinct from the admitting diagnosis and other conditions present at admission, that may occur during hospitalization. HACs are common and occur in 2.9% to 23% of all hospitalizations[1-3] and in a general population are associated with poor outcomes including higher mortality, greater readmission, and longer length of stay in hospital, compared with those without complications[4-7]. Hospitalization is common among patients with chronic kidney disease (CKD), and may confer susceptibility to hospital acquired complications due to increased risk of bleeding, electrolyte abnormalities, and adverse drug effects, among others. Studies conducted in the US and Canada have demonstrated that the presence of CKD is associated with a greater risk of potentially preventable HAC than patients with normal kidney function[8,9]. Targeting prevention efforts on patients at high risk of HAC, such as those with CKD, readily identified through commonly conducted laboratory tests, may be warranted.

In hospitalized patients with CKD, the association of mortality, length of stay (LOS), and readmission with preventable HACs has not been determined to our knowledge. The clinical outcomes associated with preventable HACs are important to understand to frame the potential benefit of strategies aimed at reducing complications. Understanding the consequences of these complications on outcomes will inform prioritization and the scope of investment in prevention efforts.

Using a population based cohort from Alberta, Canada, we sought to determine the association of preventable hospital acquired complications on clinical outcomes of mortality, LOS, and readmission, in hospitalized patients including those with CKD.

4.3. Methodology

Study Population

The study cohort comprised all adults (age ≥ 18) in Alberta hospitalized from April 1, 2003 to March 31, 2008 (Figure 1) from the population based Alberta Kidney Disease Network (AKDN) [10]. The first ('index') hospitalization was considered for each patient. All medical and surgical admissions with the exception of maternity/neonatal, congenital malformation, convalescence, and same day admission, were included. We used inpatient administrative data to stratify admissions into medical or surgical, where possible[11].

Assessment of patients' characteristics:

CKD was defined by eGFR < 60 ml/min/1.73m^2 (estimated using the Modification of Diet in Renal Disease equation) and /or moderate to high albuminuria defined as an albumin/creatinine ratio >3-30 mg/mmol. The average of all outpatient eGFR measurements from 365 days to 90 days prior to admission were used; we excluded eGFR measurements within 3 months of admission to ensure that acute kidney injury (AKI) did not impact CKD determination. Patients with end-stage renal disease (dialysis, renal transplant, eGFR<15 ml/min/1.73m^2) were excluded. Further categorization using the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice

Guidelines[12] was employed to categorize CKD to moderate, high, and very high risk; the remaining patients were classified as non-CKD.

Co-morbid conditions including; cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications and without complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic disease were identified using validated algorithms applied to hospitalization discharge abstracts and physician claims data[9,13] . The reason for hospitalization was categorized into 16 homogeneous groups using International Classification of Disease version 10 Canadian Modifications (ICD 10 CA) (Appendix A).

Hospital administrative data includes “diagnoses type 2” which captures all HACs. These 4000+ ICD 10 CA diagnostic codes were mapped into 16 groups and 76 subgroups according to clinical similarity (Appendix B). In the US, 3M health system released list of hospital complications deemed to be potentially preventable. Briefly, panels of clinicians (two general internists and one pediatrician supplemented by surgical, obstetric specialist as needed) reviewed each of approximately 14,400 diagnosis values in the ICD-9-CM coding scheme and classified 1,562 codes that as being potentially preventable in-hospital complications[14,15]. Pulmonary embolism, deep vein thrombosis, major gastro-intestinal complications with significant bleeding, and decubitus ulcer are examples of potentially preventable complications. That information was used to identify 63 potentially preventable complications by manually re-mapping ICD 9 diagnostic codes to ICD 10 CA. (Appendix c)

Hospitalization and vital statistics data were used to determine study outcomes including LOS of the index hospitalization, mortality during hospitalization and up to 90 days after discharge, and all cause re-admission 90 days after discharge. Patients who migrated out of province (n=22) within 90 days after discharge were excluded from analyses of post discharge events.

4.3.1. Statistical analysis

In patients with CKD we compared outcomes in patients with and without preventable HACs, and a second analysis included all patients with and without CKD. Mean, standard deviation, and 25th and 75th percentiles and median were used to describe continuous variables. Categorical variables were described as proportions of the cohort with or without a condition. Multivariable regression, logistic regression, Poisson, and quantile analyses (where appropriate) were used in this study. To determine the independent association of ≥1 potentially preventable HAC with risk of mortality within index hospitalization, mortality from discharge to 90 days, re-admission within 90 days logistic regression model was used. All primary analyses used logistic regression model; alternate models were used in sensitivity analyses. To analyze incremental LOS associated with ≥1 potentially preventable HAC multivariable regression model was used. Poisson regression was used to calculate population attributable risk. Quantile regression was used to determine association of outcomes with ≥1 potentially preventable HAC within quantiles of LOS. Quantile regression models allow one to assess how any quantile of a conditional distribution changes with patient characteristics, for example LOS (0 -25%, 25 – 50%)[16]. All models were accounted for potential confounders. We used purposeful selection model building. The fully adjusted

models included reason for admission, age, gender, admission type (categorical; urgent vs. elective defined in hospital administrative data), length of stay (LOS), severity of CKD (where appropriate), and 16 co-morbid conditions. All analyses were also adjusted for complications deemed not to be preventable. The attributable risk percent was calculated to determine the proportion of mortality and readmission that may be attributable to preventable HACs in patients with CKD and this formula was used: "PAR%= Pe (RRe-1) / [1 + Pe (RRe-1)]" Relative Risk (RRe), Pe (proportion of outcomes in cohort of patients with and without HACs)[17]. In additional analyses, we categorized the number of preventable HACs as; one, 2-3, 4-5, and ≥ 5 preventable HACs. We stratified CKD patients to examine moderate risk, high risk, and very high risk CKD as defined by KDIGO, and determined outcomes in these subgroups in sensitivity analysis. Analyses were conducted among patients with CKD only, as well as the larger cohort with and without CKD. In additional sensitivity analyses, we considered all HACs (preventable and non-preventable) as the exposure variable. Longer length of stay may increase exposure of patients to complications; as such a quantile regression model was used to determine association of preventable HAC and outcomes of interest by length of stay quantile. In other sensitivity analyses, the association of mortality with preventable HACs was determined considering the time frame from hospital admission to 90 days after hospital discharge in CKD patients. The analysis was undertaken using Stata, version 13. The Health Research Ethics Board of the University of Alberta and University of Calgary approved the study.

4.4. Results

Patients' characteristics:

During the study period, 765,234 patients were admitted to hospitals in Alberta, Canada, and 536,549 hospitalizations met inclusion criteria (Figure 1). In the full cohort 6.7% and 2.6% of patients had eGFR < 60 mL/min/1.73m^2 and moderate to heavy proteinuria, respectively, and 45,733 patients (8.5% of cohort) had CKD. In patients with CKD the proportion of hospitalizations with ≥1 preventable HAC was 9.8%, vs 5.4% in patients without CKD (Table 1). Patients with preventable HACs experienced a high proportion of non-preventable complications in both those with CKD (32.8%) and without CKD (27%); only 2.1-3.6% of patients without preventable HACs had non-preventable complications. The mean age of CKD patients with preventable HACs was greater than patients without preventable HAC cases. In patients with CKD, the median length of stay in hospitalizations without preventable HAC was 5 days (25th - 75th percentile; 2 – 9 days) compared with 13 days (25th - 75th percentile; 7 – 29 days) in those hospitalizations with preventable HAC. Patients without CKD were younger and experienced a shorter length of stay. Cardiovascular disease comprised the highest proportion of 'most responsible' (principal) diagnosis in CKD patients with any preventable HAC, accounting for 28.9% of admissions vs 23% in non-CKD patients with preventable HACs. Post-procedural complications (cardiovascular, respiratory and other complications of surgical and medical care) were the most common preventable HACs, followed by anemia and acid-base, fluid electrolyte balance, or metabolic disorders[9] in patients with CKD. (Appendix D)

Risk of mortality in index hospitalization among patients with CKD

The unadjusted probability of hospital mortality in patients with and without preventable HACs was 17.6% and 3.7%, respectively and was similar when stratified by medical or surgical admission. In fully adjusted analysis the OR of death during index hospitalization in patients with ≥ 1 preventable hospital complications were 4.67 (95% CI; 4.17 – 5.22). The OR of mortality increased with increasing numbers of preventable HACs in a graded fashion (Table 2). The population attributable risk percent of in-hospital mortality that may be due to a preventable HAC was 27%.

Risk of mortality from discharge to 90 days:

Among patients surviving the index admission, 6.8% with any preventable HAC died within 90 day post discharge, compared with 4.8% in patients without preventable HACs. The fully adjusted OR of mortality from discharge to 90 days in patients with ≥ 1 preventable HAC was 1.08 (0.94 – 1.25) (Table 2).

Incremental length of stay in index hospitalization:

After controlling for all variables, incremental LOS was 10 days (95% CI: 9.25 – 10.47) in patients with ≥ 1 preventable HAC, and a graded association was observed with increasing number of preventable HACs, with an incremental 17 days (95% CI: 14.94 – 19.34) in patients with 4-5 preventable HACs. (Table 2)

Risks of re-admission from discharge to 90 days:

Among surviving patients, 29.5% of those with ≥ 1 preventable HAC were re-admitted

within 90 days of discharge, compared with 24.1% in those without. In fully adjusted analyses, patients with ≥ 1 preventable HAC were more likely to be re-admitted to hospital with an OR of 1.24 (95% CI; 1.15 – 1.34). Patients with one preventable HAC re-hospitalized 21% more than those without HACs (OR=1.23; 95%; 1.17 – 1.35) and the OR was1.48 (95% CI: 1.08 – 2.34) in CKD patients with > 5 HACs. (Table 2). Population attributable risk of readmission due to preventable HACs was 2.6%

Population attributable risk percent:

PAR estimates are useful for providing a measure of the proportion of outcomes that can be attributed to individual or multiple causal factors. Given the proportion of patients with CKD and potentially preventable complications (Table 1 and Figure 1), hospital admissions with ≥1 (mean 1.7) potentially preventable HACs may lead to an additional 45,000 in-hospital patient deaths, 21,000 readmissions within 90 days, and 4.5 million additional hospital days when extrapolated to the population of North America.

Outcomes in entire cohort:

Further analyses were done to determine the impact of the presence or absence of both potentially preventable HACs as well as CKD. A new cohort that included patients with and without CKD was assembled. The presence of both CKD and potentially preventable HACs were associated with all outcomes of interest (Table 3). A graded increase in the risk of mortality in index hospitalization, mortality from discharge to 90 days, length of stay, and readmission within 90 days were noted with the presence of

CKD and preventable complications. For example, the OR of index mortality and incremental LOS were of 9.56 (95% CI; 7.23 – 12.65) and11.42 (95%CI; 9.93 – 12.91), respectively.

Sensitivity analyses:

The association of higher mortality with preventable HACs persisted when patients with CKD were subdivided into length of stay quantiles. The OR of in hospital mortality in patients who developed preventable HAC was numerically largest in the 0 - 25% quantile (all patients LOS ≤7 days) with an OR 20.6 (95% CI 16.44 – 25.8), and decreased but was still significant in the subsequent quantiles. (Table 4) The absolute risk of mortality was low in patients without potentially preventable HACs which is a contributor to the large value of the odds ratio in first quantile. When mortality was assessed over a time frame from admission to 90 days after discharge the OR associated with ≥ 1 preventable HACs was 3.06 (95% CI 2.77 – 3.37).

4.5. Discussion

In this large population based cohort of hospitalized patients, we found that the risk of mortality, length of stay in hospital, and 90 day readmission was higher in patients who experienced one or more potentially preventable complication during a hospitalization; this risk was even greater among patients with CKD. The risk of these clinically important outcomes increased in a graded fashion with increasing number of preventable complications that occurred. The magnitude of this association is large, with a fivefold higher risk of mortality in index hospitalization, and almost 30% higher risk of

re-hospitalization within 90 days after discharge in CKD patients with ≥ 1 preventable HACs. As an example of the potential implications, we extrapolated our findings to North America. It is estimated that in 2013 approximately 3.25 million patients with CKD (8.5%) were admitted in North America[18,19]. While there are acknowledged limitations and potential biases, using the population attributable risk percent and if the association of preventable complications and adverse outcomes is causal, they lead to an additional 45,000 in-hospital patient deaths, 21,000 readmissions within 90 days, and 4.5 million additional hospital days. Considerable gains in health outcomes would be achieved if even a proportion of these attributable consequences can be reduced.

Hospital acquired complications can be reduced, although the approach can be complex. In a general hospitalized population various strategies have been implemented, including environmental efforts to control hospital infections and procedures for management of patients with foley catheters, leading to a relatively high preventable HAC rate (48.73 and 58.17 per 1000 discharge) becoming reduced to 32.36 and 48.15, respectively[20] . Preventive strategies targeted at patients with greater risk of preventable HACs may result in a proportionately greater reduction of poor clinical outcomes.

Patients with CKD are pre-disposed to complications during hospitalization[21], possibly due to factors such as impaired coagulation, altered renal handling of medications requiring drug dosing changes and predisposition to drug toxicity, susceptibility to infection, among others. An analysis of the Veteran's Administrative data for 2004-2005, demonstrated that patients with CKD had a higher risk for a several hospital acquired complications compared with patients with normal kidney function (adjusted incidence

rate ratios:1.19; 95% CI 1.13 -1.25)[8]. Similarly, our previous work examining a population based cohort, found that patients with CKD had an OR of preventable HACs of 1.20 (95% CI 1.16 – 1.24)[9]. As CKD is readily identifiable using routine and commonly performed laboratory tests, targeting CKD patients to prevent complications may be feasible. Implementing preventive strategies in general population including CKD patients may improve quality of care, however patients with CKD may benefit more from such interventions.

Other findings from our study merit consideration. First, patients with preventable HACs also had more non-preventable complications, compared to those with no preventable HACs. It is not clear why complications cluster in certain patients, but we speculate that this may occur in more complex patients, may accrue as patients stay in hospital longer, or be a follow-on effect (for example, management of a complication may predispose to other complications). The effect of any preventative strategy on this clustering of complications is unknown. Second, while in general greater severity of CKD is associated with poorer clinical outcomes in a graded fashion[22], this was not observed in our study. (Appendix F) While CKD is a risk factor for the occurrence of preventable HACs, we speculate that over this very short time frame of observation, preventable HACs appears to have primacy with respect to adverse outcomes, and the severity of CKD may not exert its influence.

To our knowledge no study has investigated the association of clinical outcomes with preventable HACs in patients with CKD. Prior studies on hospital complications and subsequent clinical outcomes in general hospitalized patients have reported significant

consequences for patients and healthcare networks including: 6 days longer length of stay, 4 more deaths in 1000 hospitalizations, and $US 40,000 incremental cost[15]. While the results of our study examining the combined CKD and non-CKD patients are similar to other studies, the magnitude in the CKD population who develop preventable HACs appears larger, perhaps a reflection of this sicker patient population examined.

Strengths of this study include the use of a population based cohort and inclusion of community, teaching, and specialized hospitals, which may improve generalizability. Outpatient lab data; eGFR and proteinuria level values were used prior to hospitalization to define CKD patients. We adjusted our model for LOS, age, gender, admission type (urgent vs elective), severity of CKD, and comorbid conditions, as well as for hospital complications that are not considered to be preventable, the latter of which has not been performed in other studies to the best of our knowledge.

Our findings are subject to a number of limitations. First, we do not have access to certain clinical variables such as blood pressure control, life style factors (smoking, exercise, and diet), and severity of admitting disease and comorbid conditions. Second, hospital level factors including volume, location, and hospital type were not available. Third, the nature and behaviour of preventable HACs is not precisely defined given the use of administrative data to identify these complications; details including circumstances leading to a complication, the extent to which complications alter the process of disease and care, and how complications and comorbid conditions interact are unknown. This limitation could only be overcome by conducting a chart review or prospective study, which would lack the power of a population based analysis. Fourth, misclassification of preventable complications may take place, however this should not

invalidate results as sensitivity analysis examining all HACs showed similar results. (Appendix E). Fifth, there are limitations and potential biases in using the population attributable risk percent which may alter results of PAR%. Finally, the association of outcomes of interest with preventable HACs may mediate through other pathways, such as greater exposure to develop HACs by longer LOS or burden of illness, although our analyses adjusted for available data on comorbidity as well as days in hospital. In sensitivity analyses, this association was persistent in all quantiles of LOS which may indicate that preventable HACs independent from LOS lead to higher risk of mortality. Although absolute mortality was smaller in the 0 – 25% quantile of LOS (< 7 days), the magnitude of association of preventable HACs and mortality was greater. The explanation for this has yet to be fully explored; we speculate that HAC that occur earlier in a hospital admission when patients may be more unwell may have a greater impact.

4.6. Conclusion

Preventable hospital acquired complications are associated with a dramatic increase in risk of in-hospital mortality, as well as longer LOS, mortality at 90 days after discharge, and readmission at 90 days. The magnitude of this association is larger in patients with CKD compared with those without. Our findings may inform prioritization of prevention efforts and reduce the rate of preventable complications with attributable clinical outcomes, eventually improving health care in this patient population. Further investigations are needed to examine evidence-based preventive strategies on the risk

of potentially preventable hospital acquired complications, with the goal of improving quality of care and outcomes for hospitalized patients with CKD.

Acknowledgments:

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Table 4.1. Cohort characteristics

Demographics			All Patients	With preventable HAC	No preventable HAC
Number of patients (%)		With CKD	45,733 (100)	4.494 (9.8)	41,239 (90.2)
		No CKD	490,816 (100)	26,374 (5.4)	464,442 (94.6)
Age, mean(SD)		With CKD	72 (14)	74 (13)	71 (15)
		No CKD	50 (22)	61 (20)	50 (22)
Male (%)		With CKD	43.6	45.9	43.4
		No CKD	50	51	49
Top 3 most responsible diagnosis (reason for admission) categories (%) in patients with CKD					
Diseases of circulatory system		With CKD	21	29	20
		No CKD	12	23	11
Neoplasm		With CKD	11	15	11
		No CKD	9	17	9
Diseases of the digestive system		With CKD	11	10	11
		No CKD	14	13	14
Admission type (Urgent %)		With CKD	70	67	71
		No CKD	71	65	72
Medical admission (%)**		With CKD	19,524 (54)	1,581 (45)	17,943 (55)
		No CKD	208,926(57)	9,640 (46)	199,286 (57)
Surgical admission (%)**		With CKD	16,275 (45)	1,928 (54)	14,347 (44)
		No CKD	156,361 (42)	10,966 (53)	145,395 (42)
Preventable HACs	None	With CKD	-	-	41,239 (90.2)
		No CKD	-	-	464,442 (94.6)
	one	With CKD	-	2,861 (6.3)	-
		No CKD	-	18083 (3.7)	-
	2 -3	With CKD	-	1,231 (2.7)	-
		No CKD	-	6,488 (1.3)	-
	4 - 5	With CKD	-	284 (0.6)	-
		No CKD	-	1,244 (0.2)	-
	>5	With CKD	-	118 (0.3)	-
		No CKD	-	599 (0.1)	-
Non preventable HACs (%)		With CKD	2,952 (6.5)	1,475 (32.8)	1,477 (3.6)
		No CKD		7139 (27.0)	9,691 (2.1)
CKD category (%) *** (Only CKD cohort)		Moderate risk	26,930 (58.9)	2,249 (54.1)	24,501 (59.4)
		High risk	12,364 (27.0)	1,287 (28.7)	11,077 (26.8)
		Very high risk	6,439 (14.1)	778 (17.3)	5,661 (13.7)
Length of stay (LOS) mean(SD) (25^{th} – 75^{th})		With CKD	10 (20) (2 -11)	23 (30) (7 -29)	9 (17) (2 – 9)
		No CKD	7 (21) (2- 6)	20 (35) (6 – 23)	6 (19) (1 - 6)
Length of stay (LOS) median		With CKD	5	13	5
		No CKD	3	11	3
Mortality in index hospitalization (%)		With CKD	2,315 (5.1)	790 (17.7)	1,525 (3.7)
		No CKD	8,858 (1.8)	2,884 (11.0)	5,974 (1.3)
Mortality from discharge to 90 days (%)		With CKD	2,228 (5.0)	304 (6.8)	1,978 (4.8)
		No CKD	10,034 (2.0)	1,085 (4.1)	8,049 (1.9)
All cause re-admission within 90 days		With CKD	11,281 (24.7)	1,326 (29.5)	9,955 (24.1)
		No CKD	85,816 (17.5)	7,027 (26.4)	78,710 (17.0)

*P_value < 0.001 in all characteristics
** Some admissions could not be classified as medical/surgical
***Using KDIGO risk classification

Table 4.2. OR of outcomes in patients with CKD by increasing number of potentially preventable HAC

	Mortality: Index hospitalization [A] (95% CI)	Mortality: Discharge to 90-days[A] (95% CI)	Incremental LOS [B] (mean) 95% (CI)	Re-Admission Discharge to 90-days[A] (95% CI)
≥ 1 P_HACs	4.67(4.17 – 5.22)	1.08 (0.94 – 1.25) *	9.86 (9.25 – 10.47)	1.24 (1.15 – 1.34)
One	3.56 (3.11 – 4.07)	1.17(0.99 – 1.38) *	7.20 (6.54 – 7.96)	1.21(1.11 – 1.32)
2-3	6.52 (5.50 – 7.73)	0.91 (0.71 – 1.18) *	12.09 (11.81 – 13.98)	1.28 (1.12 – 1.46)
4-5	10.47 (7.78 – 14.08)	0.88 (0.54 – 1.44) *	17.14 (14.94 – 19.34)	1.35 (1.04 – 1.75)
>5	18.89 (12.12 – 29.44)	1.29 (0.67 – 2.47) *	39.92 (36.54 – 43.30)	1.48 (1.00 – 219)

A. Fully adjusted for age, admission type (elective vs urgent), gender, LOS, severity of CKD, non-preventable complications, and 17 comorbid conditions
B. Fully adjusted for age, admission type (elective vs urgent), gender, severity of CKD, non-preventable complications, and 17 comorbid condition: Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic diseases.
- Reference; admissions without HAC
*Non-significant

Table 4.3. OR of outcomes in patients with and without CKD and potentially preventable HACs.

	Mortality: Index hospitalization [A] (95% CI)	Discharge to 90-day Mortality [A] (95% CI)	Incremental LOS[B] (mean) 95% (CI)	Re-Admission Discharge to 90-days[A] (95% CI)
With CKD and no Preventable HAC	**2.22 (1.69 – 2.94)**	**1.49 (1.11 – 2.00)**	**1.67 (0.29 – 3.06)**	**1.45 (1.25 – 1.69)**
Non-CKD and with Preventable HAC	**5.26 (4.98 – 5.55)**	**1.20 (1.12 – 1.29)**	**9.73 (9.4 – 9.98)**	**1.41 (1.36 – 1.45)**
With CKD and Preventable HAC	**9.56 (7.23 – 12.65)**	**1.68 (1.23 – 2.29)**	**11.42 (9.93 – 12.91)**	**1.67 (1.42 – 1.96)**
Reference: *Non-CKD and no preventable HACs patients*				

A. Fully adjusted for age, admission type (elective vs urgent), gender, LOS, non-preventable complications, and 17 comorbid conditions: Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic diseases
B. Fully adjusted for age, admission type (elective vs urgent), gender, non-preventable complications, and 17 comorbid condition: Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic diseases

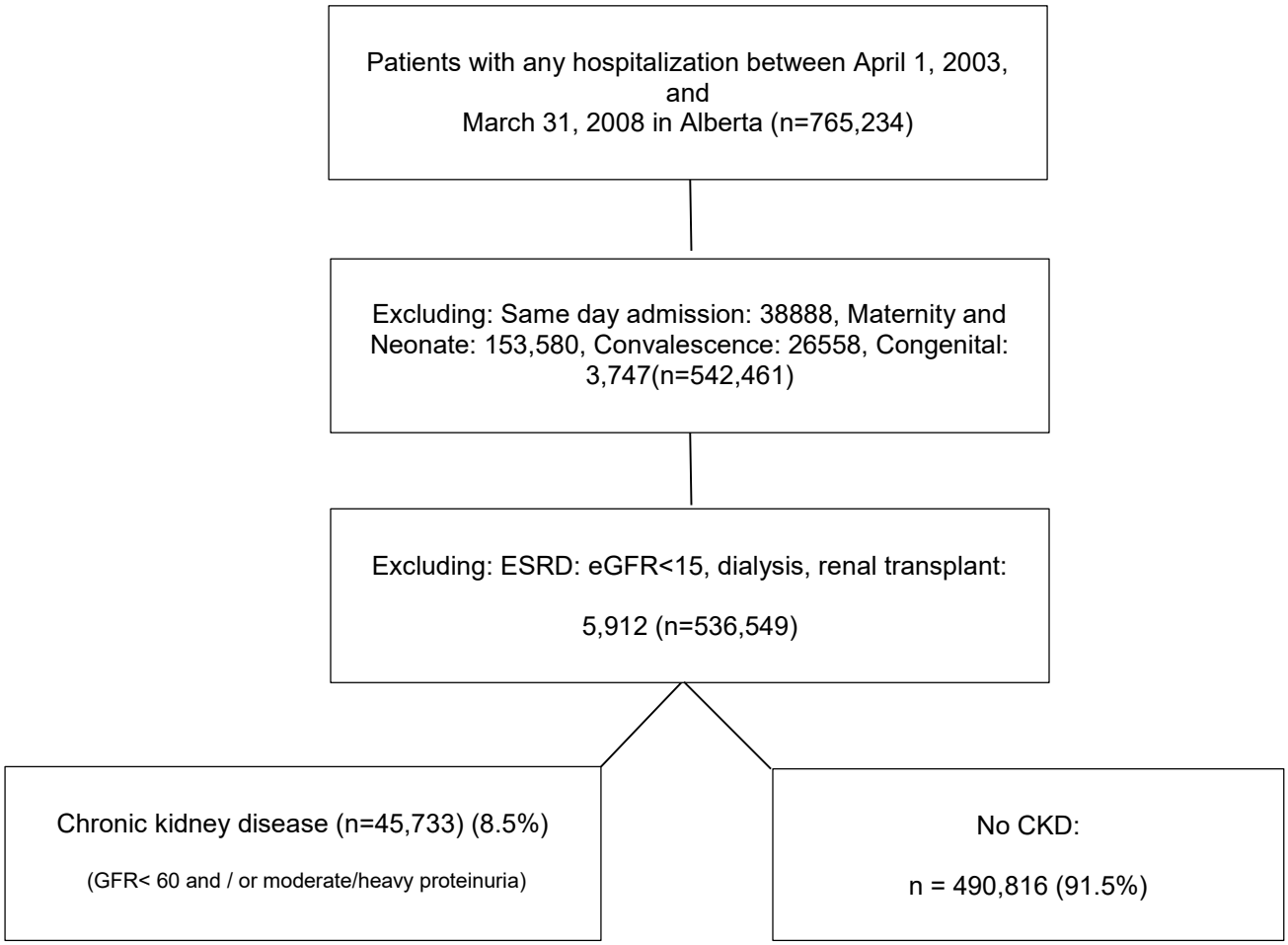
Table 4.4. ORs of index hospitalization mortality, by LOS quantiles, in CKD cohort with potentially preventable HACs

Quantile	0 – 25%	25 – 50%	50 – 70%	75 – 100%
LOS	< 7	7 < LOS < 23	23 < LOS < 29	> 29
OR (95% CI)	20.60 (16.44 – 25.80)	3.6 (3.02 – 4.29)	2.20 (1.45 – 3.34)	2.37 (1.89 – 2.97)
Absolute # of death (%)	224 (25%)	277 (33%)	62 (41%)	227 (50%)

Fully adjusted for age, admission type (elective vs urgent), gender, severity of CKD, non-preventable complications, and 17 comorbid condition: Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic diseases

- Reference; admissions without HAC

Figure 4.1. Study flowchart to construct cohort of patients with and without CKD



Supplementary:

Appendix A. Classification of reason for admission

Chapter Number	ICD-10-CA Chapter Title	Code Range
I	Certain infectious and parasitic diseases	A00–B99
II	Neoplasms	C00–D48
III	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50–D89
IV	Endocrine, nutritional and metabolic diseases	E00–E90
V	Mental and behavioural disorders	F00–F99
VI	Diseases of the nervous system	G00–G99
VII	Diseases of the eye and adnexa	H00–H59
VIII	Diseases of the ear and mastoid process	H60–H95
IX	Diseases of the circulatory system	I00–I99
X	Diseases of the respiratory system	J00–J99
XI	Diseases of the digestive system	K00–K93
XII	Diseases of the skin and subcutaneous tissue	L00–L99
XIII	Diseases of the musculoskeletal system and connective tissue	M00–M99
XIV	Diseases of the genitourinary system	N00–N99
XV	Pregnancy, childbirth and the puerperium	O00–O99
XVI	Certain conditions originating in the perinatal period	P00–P96
XVII	Congenital malformations, deformations, and chromosomal abnormalities	Q00–Q99
XVIII	Symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified	R00–R99
XIX	Injury, poisoning and certain other consequences of external causes	S00–T98
XX	External causes of morbidity and mortality	V01–Y98
XXI	Factors influencing health status and contact with health services	Z01–Z99
XXII	Morphology of Neoplasms	8000/0-9989/1
XXIII	Provisional codes for research and temporary assignment	U00-U99

Appendix B. Example for HAC group and subgroup classification using ICD 10 codes

Group	Subgroups	ICD 10 CA Codes
A: Infections	**A_2: Central nervous system(meningitis, brain abscess, encephalitis .....), intracranial phlebitis**	**G002:** Streptococcal meningitis Includes: Non-pneumococcal, streptococci (Streptococcus, Group A) (Streptococcus, Group B) **G008:** Other bacterial meningitis Includes: Meningitis due to: Escherichia coli, Friedlander bacillus, Klebsiella **G009:** Bacterial meningitis, unspecified Includes: Meningitis: purulent NOS, pyogenic NOS. suppurative NOS **G030:** Non-pyogenic meningitis Includes: Nonbacterial meningitis **G039:** Meningitis, unspecified Includes: Arachnoiditis (spinal) NOS **G048:** Other encephalitis, myelitis and encephalomyelitis Includes: Post-infectious encephalitis and encephalomyelitis NOS **G049:** myelitis and encephalomyelitis, unspecified Includes: Ventriculitis (cerebral) NOS **G060:** Intracranial abscess and granuloma Includes: Abscess (embolic)(of): brain [any part], cerebellar, cerebral, otogenic, Intracranial abscess or granuloma: epidural, extradural, subdural **G061:** Intra-spinal abscess and granuloma Includes: Abscess (embolic) of spinal cord [any part]Intra-spinal abscess or granuloma: epidural, extradural subdural **G062:** Extradural and subdural abscess, unspecified D432: G08 C760 A858 D352 A178 D320 A879 G062 B004 C700 G008 G040 C793 G060 G061 G003 G049 A170 G042

Appendix c

PPC Description

01 Stroke & Intracranial Hemorrhage
02 Extreme CNS Complications
03 Acute Pulmonary Edema and Respiratory Failure without Ventilation
04 Acute Pulmonary Edema and Respiratory Failure with Ventilation
05 Pneumonia & Other Lung Infections
06 Aspiration Pneumonia
07 Pulmonary Embolism
08 Other Pulmonary Complications
09 Shock
10 Congestive Heart Failure
11 Acute Myocardial Infarction
12 Cardiac Arrythmias & Conduction Disturbances
13 Other Cardiac Complications
14 Ventricular Fibrillation/Cardiac Arrest
15 Peripheral Vascular Complications Except Venous Thrombosis
16 Venous Thrombosis
17 Major Gastrointestinal Complications without Transfusion or Significant Bleeding
18 Major Gastrointestinal Complications with Transfusion or Significant Bleeding
19 Major Liver Complications
20 Other Gastrointestinal Complications without Transfusion or Significant Bleeding
21 Clostridium Difficile Colitis
22 Urinary Tract Infection
23 GU Complications Except UTI
24 Renal Failure without Dialysis
25 Renal Failure with Dialysis
26 Diabetic Ketoacidosis & Coma
27 Post-Hemorrhagic & Other Acute Anemia with Transfusion
28 In-Hospital Trauma and Fractures
29 Poisonings Except from Anesthesia
30 Poisonings due to Anesthesia
31 Decubitus Ulcer
32 Transfusion Incompatibility Reaction
33 Cellulitis
34 Moderate Infections
35 Septicemia & Severe Infections
36 Acute Mental Health Changes
37 Post-Operative Infection & Deep Wound Disruption without Procedure
38 Post-Operative Wound Infection & Deep Wound Disruption with Procedure
39 Reopening Surgical Site

40 Post-Operative Hemorrhage & Hematoma without Hemorrhage Control Procedure or I&D Procedure

41 Post-Operative Hemorrhage & Hematoma with Hemorrhage Control Procedure or I&D Procedure
42 Accidental Puncture/Laceration During Invasive Procedure

43 Accidental Cut or Hemorrhage During Other Medical Care
44 Other Surgical Complication - Moderate
45 Post-procedure Foreign Bodies
46 Post-Operative Substance Reaction & Non-O.R. Procedure for Foreign Body
47 Encephalopathy
48 Other Complications of Medical Care
49 Iatrogenic Pneumothrax
50 Mechanical Complication of Device, Implant & Graft
51 Gastrointestinal Ostomy Complications
52 Inflammation & Other Complications of Devices, Implants or Grafts Except Vascular Infection
53 Infection, Inflammation and Clotting Complications of Peripheral Vascular Catheters and Infusions
54 Infections due to Central Venous Catheters
55 Obstetrical Hemorrhage without Transfusion
56 Obstetrical Hemorrhage with Transfusion
57 Obstetric Lacerations & Other Trauma without Instrumentation
58 Obstetric Lacerations & Other Trauma with Instrumentation
59 Medical & Anesthesia Obstetric Complications
60 Major Puerperal Infection and Other Major Obstetric Complications
61 Other Complications of Obstetrical Surgical & Perineal Wounds
62 Delivery with Placental Complications
63 Post-Operative Respiratory Failure with Tracheostomy
64 Other In-Hospital Adverse Events

Appendix D. Potentially preventable HAC in patients with CKD

Complications	Description	N of cases	%
A. Infections	A_3: Respiratory (pneumonia, mediastinitis, pulmonary abscess ...)	455	4
	A_5: Genitourinary infection (UTI, cystitis, pyelonephritis ...)	481	4
B: Electrolyte imbalance	B_3: Acid-base, fluid, and electrolyte balance, metabolic disorders	493	4
D: Cardiovascular complications	D_4: Acute myocardial infarction	449	4
	D_16: Post procedural complications	542	4
E: Respiratory complications	E_6: Post procedural disorders (Pneumothorax included)	528	4
M: Hematologic complications	M_4: Anemia due to bleeding	494	4
P: Surgical medical complications	P_2: Other complications of surgical and medical care , not elsewhere classified	439	4
Others		3939	50
Potentially preventable complications		7820	63.11
Total recorded complications (HACs)		12126	100

Appendix E. OR of outcomes in patients with CKD by all HACs and increasing number of complications

	Index hospitalization Mortality [A] (95% CI)	Discharge to 90-day Mortality [A] (95% CI)	Incremental LOS [B] (mean) (95% CI)	90-days re-admission [A](95% CI)
≥ 1 HACs	5.28(4.79 – 5.82)	1.37 (1.22 – 1.53)	14.32 (13.81 – 14.83)	1.27 (1.19 – 1.35)
One	3.55 (3.13 – 4.03)	1.40 (1.21 – 1.61)	9.31 (8.67 – 9.96)	1.21 (1.11 – 1.31)
2-3	6.26 (5.42 – 7.24)	1.34 (1.11 – 1.62)	16.12 (15.24 – 17.00)	1.34 (1.21 – 1.49)
4-5	14.86 (11.85 – 18.64)	1.04 (0.71 – 1.53) *	24.05 (22.39 – 25.71)	1.37 (1.12 – 1.67)
>5	17.40 (13.15 – 23.03	1.71 (1.15 – 2.53)	42.91 (40.88 – 44.94)	1.50 (1.18 – 1.90)

A. Fully adjusted for age, admission type (elective vs urgent), gender, LOS, severity of CKD, non-preventable complications, and 16 comorbid conditions.
B. Fully adjusted for age, admission type (elective vs urgent), gender, severity of CKD, non-preventable complications, and 16 comorbid condition.
- Reference; admissions without HAC

*Non-significant

Appendix F. ORs of outcomes with ≥ 1 preventable HAC by severity of CKD

CKD Severity	Mortality: Index hospitalization [A] (95% CI)	Mortality: Discharge to 90-days[A] (95% CI)	Length of stay [B] (mean) (95% CI)	Re-Admission Discharge to 90-days[A] (95% CI)
Moderate	4.81 (4.09 – 5.67)	1.06 (0.81 –1.31) *	9.86 (8.91 – 10.32)	1.32 (1.20 – 1.43)
High	4.51 (3.71 – 5.46)	1.32 (1.04 – 1.69)	10.24 (8.87 – 11.61)	1.15 (1.00 – 1.32)
Very high	4.81 (3.76 – 6.13)	0.84 (0.61 – 1.15) *	10.23 (8.54 – 11.91)	1.12 (0.94 – 1.35) *

A. Fully adjusted for age, admission type (elective vs urgent), gender, LOS, severity of CKD, non-preventable complications, and 17 comorbid conditions

B. Fully adjusted for age, admission type (elective vs urgent), gender, severity of CKD, non-preventable complications, and 17 comorbid condition; Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic diseases

- Reference; admissions without HAC

*Non-significant

CHAPTER 5: Health care costs associated with hospital acquired complications in patients with chronic kidney disease

5.1. Abstract

Background: Patients with CKD are at increased risk of potentially preventable hospital acquired complications (HACs). Understanding the economic consequences of potentially preventable HACs, may define the scope and investment of initiatives aimed at prevention.

Methods: All adults patients hospitalized from April, 2003 to March, 2008 in Alberta, Canada comprised the study cohort. Healthcare costs were determined and categorized into 'index hospitalization' comprising hospital cost and in-hospital physician claims, and 'post discharge' including ambulatory care, physician claims, and readmission from discharge to 90 days. Multivariable regression was used to estimate the incremental healthcare costs associated with potentially preventable complications.

Results: In fully adjusted models, the median incremental index hospitalization cost and in-hospital physician claims were $4,047 (95 %CI; 3,918 – 4,176) and $765 (95% CI; 738 – 792) in CKD patients with ≥ 1 potentially preventable HACs, compared with those without. Post-discharge incremental costs in physician claim, ambulatory care, and readmission cost were $71 (95% CI; 54 – 89), $119 (95% CI; 74 – 164), and $1,429 (95% CI; 844 – 1,709), respectively. The incremental costs over 90 days from admission with ≥1 potentially preventable HAC in patients with CKD was $7,522 (95% CI; 7,219 – 7,824). A graded increase in cost was noted with increasing number of complications. In patients without CKD but with a potentially preventable HACs

incremental costs within 90 days from hospital admission was $6,688 (95% CI: 6,612 – 6,723).

Conclusions: Potentially preventable HACs are associated with substantial increases in healthcare costs especially in people with CKD. Investment in implementing targeted strategies to reduce HACs may have a significant benefit for patient and health system outcomes.

5.2. Introduction

With escalating costs of medical care and focus on health care system sustainability, increasing attention is being placed on gaining efficiency and maximizing value of health care. A significant proportion of health care costs are attributable to hospital acquired complication (HACs), defined as unintended clinical conditions, distinct from the admitting diagnosis, that may occur in hospitalized patients. HACs are common and occur in 2.9% to 23% of hospitalizations [1-4]. They are associated with poor outcomes including higher mortality, greater 30-day readmission, longer length of stay in hospital, and incremental costs compared with those without complications in general hospitalized patient populations[5,6]. In a general population, HACs are associated with an additional CAN $10,866 per patient, or more than double the mean cost of an uncomplicated hospital admission, and estimated to add 17.3% to treatment costs[4]. Complications deemed to be potentially preventable are estimated to add 9.7% to the costs of inpatient care[7]. Patients with chronic kidney disease (CKD) are hospitalized frequently[8] and data from the US and Canada have demonstrated that CKD patients are at increased risk of developing hospital complications compared with patients without CKD [9,10].

To our knowledge, the economic consequences of HAC, including those complications that are potentially preventable, have not been determined in patients with CKD. The health care resource use associated with potentially preventable HACs is important to frame the potential benefit of strategies aimed at reducing complications. Understanding the cost association with potentially preventable complications may inform prioritization of prevention efforts in patients with CKD and may inform the scope of investment in prevention efforts.

5.3. Methodology

Study Population and Characteristics:

We assembled a cohort of hospitalized patients as previously described[10]. Briefly, all adults (age ≥ 18) in Alberta hospitalized from April 1, 2003 to March 31, 2008 (Figure 1) were included, and the first hospitalization (excluding maternity/neonatal, congenital malformation, convalescence, same day admission) was defined as the index encounter. CKD and its severity, comorbid conditions, all HACs, and potentially preventable HACs were determined using laboratory and administrative data[10].

Costs of inpatient care were determined using Canadian Institute for Health Information methods[11], developed to estimate average cost of services delivered to patients in all acute care facilities. The estimated cost corresponds to clinical services provided to the average typical patients in hospitals. Each case is assigned to one of 17 major clinical categories and case mix group (CMGs) according to clinical and similarities in health resource use, modified by complexity (including increased resource use due to the

occurrence of HACs). The National Ambulatory Care Reporting System, developed by Canadian Institute for Health Information, includes data for all hospital-based and community-based ambulatory care including: day surgery, outpatient and community-based clinics, emergency departments. Specific categories include emergency department visits, ambulatory interventions, rehabilitation and clinic visits with the exception of telephone visits and direct diagnostic imaging. In this data costs of all outpatients' health resource use including complete cost of each encounter of allied healthcare professional, diagnostic imaging, and interventions. More details on costing are provided in Appendix A. Most physicians in Alberta are paid for each service they deliver through fee-for-service where compensation occurs with submission of a claim.

We considered healthcare cost during three distinct but overlapping intervals. The first interval was the index hospitalization, and included costs of hospitalization and physician claims during hospitalization that is of varying length depending on the length of stay. The second Interval was from discharge date to 90 days and included ambulatory care, hospitalization costs of readmission, and physician claim. The third interval began at admission and ended at 90 days following admission, and excluded hospitalizations lasting longer than 90 days (n=371). In the post-discharge period, only the first readmission was included (if it occurred); the costs of readmissions that extended beyond the 90 day observation period were included in the main analyses, but excluded in sensitivity analysis (n=508). We have reported all costs in Canadian dollars.

5.3.1 Statistical analysis

The primary analysis was conducted in a cohort of patients with CKD comparing incremental costs in patients with potentially preventable HACs to those without; a second analysis considered subjects with and without CKD. Median, mean, and standard deviation of each cost category was determined. Data transformation, e.g. logarithmic, is frequently used with skewed cost data, although may not be required with large sample sizes[12]. Multivariable regression analysis was used to determine the independent association of ≥1 potentially preventable HAC on incremental costs for each cost category and time frame. Tobit models were used for costs of readmission given the large number of subjects not readmitted (i.e. with zero costs). Purposeful selection model building was used. The fully adjusted models included reason for admission, age, gender, admission type (categorical; urgent vs. elective defined in hospital administrative data), length of stay (LOS), severity of CKD (where appropriate), and 16 co-morbid conditions. All analyses were also adjusted for HACs deemed not to be potentially preventable. In additional analyses, we categorized the number of potentially preventable HACs as one, 2-3, 4-5, and ≥ 5. We stratified the cohort of subjects with CKD to examine moderate risk, high risk, and very high risk CKD as defined by KDIGO. We replicated all analyses using generalized linear models. In sensitivity analyses, we considered all HACs (both preventable and non-preventable) as the exposure variable. LOS is a main driver of hospital cost, and as such we assessed the association of cost with potentially preventable HACs in patients grouped by LOS categories using a quantile model. The analysis was undertaken using Stata, version

13. The Health Research Ethics Board of the University of Alberta and University of Calgary approved the study.

5.4. Results

Patients characteristics:

Baseline characteristics have been previously described[10] and are presented in Table 1. The unadjusted median length of hospital stay in patients without potentially preventable HAC was 5 days (25^{th} - 75^{th} percentile; 2 – 9 days) compared with 13 days (25^{th} - 75^{th} percentile; 7 – 29 days) in patients with potentially preventable HACs. (Table 1)

Incremental index hospitalization cost (hospital cost and in-hospital physician claims) in patients with CKD:

Unadjusted median index hospitalization cost including hospital cost and physician claims within hospital in patients with ≥1 potentially preventable HAC was $18,883 (SD= 39,649), almost three fold greater than patients with no preventable HAC (Table 1). In fully adjusted analyses median incremental index hospitalization cost was $6,169 (95% CI; 6,003 – 6,336) (Table 2A). Costs increased dramatically in a graded fashion with increasing number of potentially preventable HACs; for example, patients with 4-5 potentially preventable complications were associated with incremental costs of $19,083 (95% CI: 18,498 – 19,667). (Table 2A.)

Incremental healthcare cost over 90 days after discharge (including; physician claims, ambulatory care cost, readmission) in patients with CKD:

Unadjusted median ambulatory health care cost and physician claims over 90 days after hospital discharge in patients with ≥1 potentially preventable HAC was 50% greater than those patients without potentially preventable complications (Table 1). In patients with ≥1 potentially preventable HACs who were readmitted within 90 days after discharge, the cost of hospital readmission was $6,133, two-fold higher than for patients without complications. (Table 1) In fully adjusted models, incremental ambulatory care cost and readmission costs associated with ≥1 potentially preventable HAC were $119 (95% CI; 74 – 164), $1,429 (95% CI; 1,150 – 1,709), respectively. Considering all cost categories within 90 days after discharge in patients with ≥1 potentially preventable HAC, adjusted median incremental cost was $1,471(95% CI; 844 – 2,099). (Table 2B.) We did not find significant differences in fully adjusted physician claims in patients with and without potentially preventable HACs $71 (95% CI; 54 – 89). (Table 2B.) Results were similar when readmissions extending beyond the 90 day observation period (n=133) were excluded.

Incremental costs of potentially preventable HACs within 90 days from hospital admission:

Within 90 days from hospital admission in CKD patients with ≥1 potentially preventable HACs, unadjusted median health care cost was $24,137 (SD=32,500) compared to $8,528 (SD= 18,276) in those patients without preventable HACs. In fully adjusted models median incremental cost in patients with ≥1 potentially preventable HACs was

$7,522 (95% CI; 7,219 - 7,824). Incremental costs increase with the number of complications in a graded fashion, for example in patients with 4 or 5 potentially preventable HACs median incremental cost was $21,882 (95% CI; 20,809 – 22,955) (Tables 3 and 5). When readmissions extending beyond 90 days (n= 198) were excluded similar results were obtained.

Sensitivity analyses in CKD cohort:

Similar results were obtained when generalized linear models were used. In quantile analyses, the higher incremental cost of the index hospitalization persisted in all LOS quantiles; in the 0 – 25% (LOS ≤ 7) percentile, the incremental cost with ≥ 1 potentially preventable HACs was $3,304 (95% CI: 3,096 – 3,512) and increased in the subsequent quantiles. (Table 4)

Incremental costs of potentially preventable HACs within 90 day from hospital admission in cohort without CKD:

In fully adjusted analyses the median incremental costs within 90 days period in patients without CKD who had potentially preventable HACs was $6,688 (95% CI; 6,612 – 6,723). (Table 5).

5.5. Discussion

We found that patients with potentially preventable complications had substantially greater costs during their index hospitalization as well as in the post-discharge period, and these costs were even greater when potentially preventable complications occurred

in patients with CKD. The association of potentially preventable HACs with healthcare costs increased in a graded fashion with increasing number of complications. In patients with CKD, the magnitude of this association was large and the incremental costs of the index hospitalization with 2-3 potentially preventable HACs was a three-fold increase of index hospitalization costs of those patients without potentially preventable complications. As an example of the potential real world implications, we extrapolated our findings to all of North America; we estimate that in 2013 approximately 3.25 million patients with CKD (8.5%) were admitted in North America[13,14] . If the association of potentially preventable complications and incremental health care costs are causal, potentially preventable HACs may be responsible for approximately C$2.4 billion in additional costs per year. If prevention leads to averting even a fraction of attributable costs this would represent considerable savings, in addition to the potential for better patient outcomes.

To our knowledge, no study has determined the incremental costs of potentially preventable HAC in patients with CKD, although other work has examined general hospitalized patient populations. However, our findings, including the magnitude of incremental cost in patients with ≥ 1 potentially preventable HACs in a cohort of patients with and without CKD, are congruent with these other studies in general inpatient populations. In a retrospective study conducted in Alberta, Canada in 2008, 24% of hospitalization episodes had at least one HAC, and were associated with additional costs of C$10,866, more than double the mean cost of an uncomplicated admission[4]. Our incremental results are slightly lower, but we have reported median incremental cost (numerically lower than the mean in skewed data). Internationally, other studies

also report the economic impact of HAC. Using the definition of potentially preventable HACs developed by 3M Health Information Systems, 6% of Medicaid adult and obstetric populations had at least one potentially preventable HACs in fiscal year 2012. It was estimated that the economic burden of potentially preventable HACs was $97.4 million, or 3.7 percent, in addition to the hospital cost of caring for these patients[15].

Targeted strategies to prevent HACs may be effective in some settings[16-18], and could lead to a corresponding decrease in health care costs. An observational retrospective study by the Agency for Healthcare Research and Quality[19] suggests that, through implementation of specific recommendations on best practices to prevent hospital acquired complications in the US (including prevention of pressure ulcers, catheter induced blood stream infections, deep vein thrombosis, etc.), hospitalized patients had 17% (1.3 million) fewer HACs over a 3-year period. This reduction in the rate of potentially preventable HACs was estimated to lead to approximately $12 billion savings in health care costs.

Effective strategies to prevent HACs targeted at vulnerable patient populations may result in a proportionately greater reduction of health expenditure. Patients with CKD are at increased risk of complications during hospitalization[9,10], potentially due to known factors such as impaired coagulation, susceptibility to infection, altered renal handling of medications requiring drug dosing changes and predisposition to drug toxicity, among others. While CKD patients may benefit from implementing general preventive strategies, strategies targeting this readily identifiable high-risk population may lead to greater reduction of potentially preventable HACs more efficiently, and subsequently improve patient and health care system outcomes in hospitalized patients.

Strengths of our study include the consideration of all HACs and those deemed to be potentially preventable as exposure variables in a population based cohort of patients with CKD. Prior studies have analyzed only cost within index hospitalization associated with potentially preventable HACs which may underestimate the incremental cost estimation associated with those conditions in short term. Shortly after discharge, services such as physician office visits, emergency department visits, ambulatory care, and readmission may occur as extended consequences of potentially preventable HACs. Capturing costs attributable to potentially preventable HACs following discharge may provide close to real cost estimation. We adjusted our model for LOS, age, gender, admission type (urgent vs elective), severity of CKD, and comorbid conditions, as well as for hospital complications that are not preventable, the latter of which has not been performed in other studies to the best of our knowledge.

In addition to these limitations[10], it is also possible that the aggregated costing approach used by Canadian Institute for Health Information may underestimate the incremental cost association with potentially preventable HACs, as their methodology may not fully capture the incremental cost attributable to those complications within a CMG. Secondly, administrative data lacks information regarding unmeasured confounders (such as frailty, blood pressure, etc.), however we captured all important co-morbid conditions that were available. Finally, association of incremental cost and potentially preventable HACs may be mediated by longer LOS which is closely correlated with cost, a potential endogeneity bias. Endogeneity bias may result in inflated estimates of the cost impact of potentially preventable HACs, although our analyses adjusted for available data on days in hospital. Results of quantile analyses

indicate that conclusions are not altered when analyses are performed by quantiles of LOS where HAC independently leads to incremental cost among patients categorized by LOS.

5.6. Conclusion

The presence of ≥1 hospital acquired complications and those deemed to be potentially preventable was associated with incremental healthcare costs. This cost is numerically greater in patients with CKD. Further studies are proposed to examine the effect of evidence-based strategies on the risk of potentially preventable hospital acquired complications, with the goal of improving quality of care and reducing costs.

Acknowledgments:

Disclosure: This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the view of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta, Alberta Health nor Alberta Health Services express any opinion in relation to this study.

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Table 5.1. Characteristics of patients.

Demographics			All patients	With preventable HAC	No preventable HAC
Number of subjects (%)		With CKD	45,521 (100)	4,463 (9.8)	41,058(92.2)
		No CKD	490,719 (100)	26,374 (5.4)	464,345 (94.6)
Age, mean		With CKD	72	75	72
		No CKD	50	61	50
Male (%)		With CKD	43	46.02	43.4
		No CKD	50	51	50
Top 3 reason for admission in patients with CKD					
Disease of circulatory system (%)		With CKD	20.8	29.1	19.9
		No CKD	12	23	11
Neoplasm (%)		With CKD	11.4	15.3	11
		No CKD	9	17	9
Disease of the digestive system (%)		With CKD	11.1	10.1	11.3
		No CKD	14	13	14
Admission type (Urgent %)		With CKD	71	67.5	71.6
		No CKD	71	65	70
Preventable HACs (n) (%)	no P_HAC	With CKD	41,508 (92.2)	-	41,508 (92.2)
		No CKD	464,442 (94.6)		464442 (94.6)
	One	With CKD	-	2,836 (63.5)	-
		No CKD		18,083 (3.7)	
	2-3	With CKD	-	1,225 (26.8)	-
		No CKD		6,488 (1.3)	
	4-5	With CKD	-	284 (6.4)	-
		No CKD		1,244 (0.2)	
	>5	With CKD	-	118 (2.6)	-
		No CKD		599 (0.1)	
Length of stay (LOS) mean (25% - 75%)		With CKD	10 (2 - 7)	23 (7 - 29)	9 (2 - 9)
		No CKD	10 (2 – 11)	20 (6 – 23)	6 (1 – 6)
Length of stay (LOS) (Median)		With CKD	5	13	5
		No CKD	5	11	3
Index hospitalization cost (hospital + physician claims) (SD)**		With CKD	6,397 (18,051)	18,883 (39,649)	5,848 (12,034)
		No CKD	5,057 (16,879)	16,362 (44,628)	4,883 (12,283)
Post index cost (ambulatory care + physician claims) (SD)**		With CKD	559 (13,202)	797 (20,171)	539 (12,159)
		No CKD	348 (11,511)	646 (23,808)	337 (10198)
Readmission cost (SD)**		With CKD	3,310 (12,934)	6,133 (19,910)	3,001 (11,890)
		No CKD	2,038 (11,317)	5,888 (23,555)	1,796 (10,010)

* All differences statistically significant p< 0.01

** $ Can

Table 5.2A Median Incremental in-hospital cost by cost category associated with potentially preventable HACs

# of preventable HACs	In hospital *(95 % CI)***	Physician claims *(95 % CI)***	Total *(95 % CI)***
≥ 1	4,047 (3,918 – 4176)	765 (738 – 792)	6,169 (6,003 – 6,336)
One	3,191 (3,007 – 3,375)	712 (672 – 751)	3,970 (3,779 – 4,162)
2 - 3	7,434 (7,183 – 7,684)	1,323 (1,270 – 1,377)	11,769 (11,482 – 12,056)
4 - 5	14,609 (14,162 – 15,057)	2,537 (2,441 – 2,632)	19,083 (18,498 – 19,667)
>5	24,639 (24,102 – 25,175)	5,899 (5784 – 6014)	39,584 (38,675 - 40,493)

* Adjusted for age, admission type (elective vs urgent), gender, LOS, severity of CKD, other complications, and16 comorbid conditions including: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications and without complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic disease.

** $ Can

Table 5.2B Incremental cost associated with potentially preventable HACs within 90 days after discharge

Discharge to 90 days cost	*Incremental cost (95 % CI)***
Ambulatory care costs with ≥ 1 preventable complications (mean)	119 (74 – 164)
Physician claim costs with ≥ 1 preventable complications (mean)	71 (54 – 89)[#]
Readmission (mean)	1,429 (1,150 – 1,709)
Total	1,471(844 – 2099)

* Adjusted for age, admission type (elective vs urgent), gender, LOS, severity of CKD, other complications, an16 comorbid conditions including: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications and without complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic disease.

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[#] Non-significant

Table 5.3. Median incremental costs in CKD patients with hospital complications within 90 days from hospital admission

		Potentially preventable complications	All complications
Incremental cost (95% CI)*	≥ 1 complication	7,522 (7,219 - 7,824)	6,612 (6,278 – 6,946)
	One	4,676 (4,332 – 5,020)	4,755 (4,428 – 5,122)
	2 - 3	14,184 (13,658 – 14,73)	12,163 (11,659 – 12,557)
	4 - 5	21,882 (20,809 – 22,955)	21,062 (20184 – 21,940)
	>5	38,632 (36,870– 40394)	35,843 (34,733 – 36,953)

* $ Can
Adjusted for age, admission type (elective vs urgent), gender, severity of CKD, non-preventable complications, and 16 comorbid conditions
- Reference; admissions without HAC or P-HAC
Comorbid conditions including: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications and without complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic disease.

Table 5.4. Median unadjusted and adjusted incremental index hospitalization costs by LOS quantiles in CKD cohort with potentially preventable HACs

Quantile		**0 – 25%**	**25 – 50%**	**50 – 70%**	**75 – 100%**
LOS		< 7	7 to < 13	13 to < 29	> 29
Median unadjusted Costs*	*With HAC*	9,687	16,576	22,352	48,620
	No HAC	4,635	8,588	11,946	29,127
	Cost difference	5,052	7,988	10,220	19,493
Median adjusted incremental costs* (95% CI) **		3,304 (3,096– 3,512)	5,998 (5,722 – 6,720)	8,775 (8,177 – 9,372)	13,749 (12,425 – 15,073)

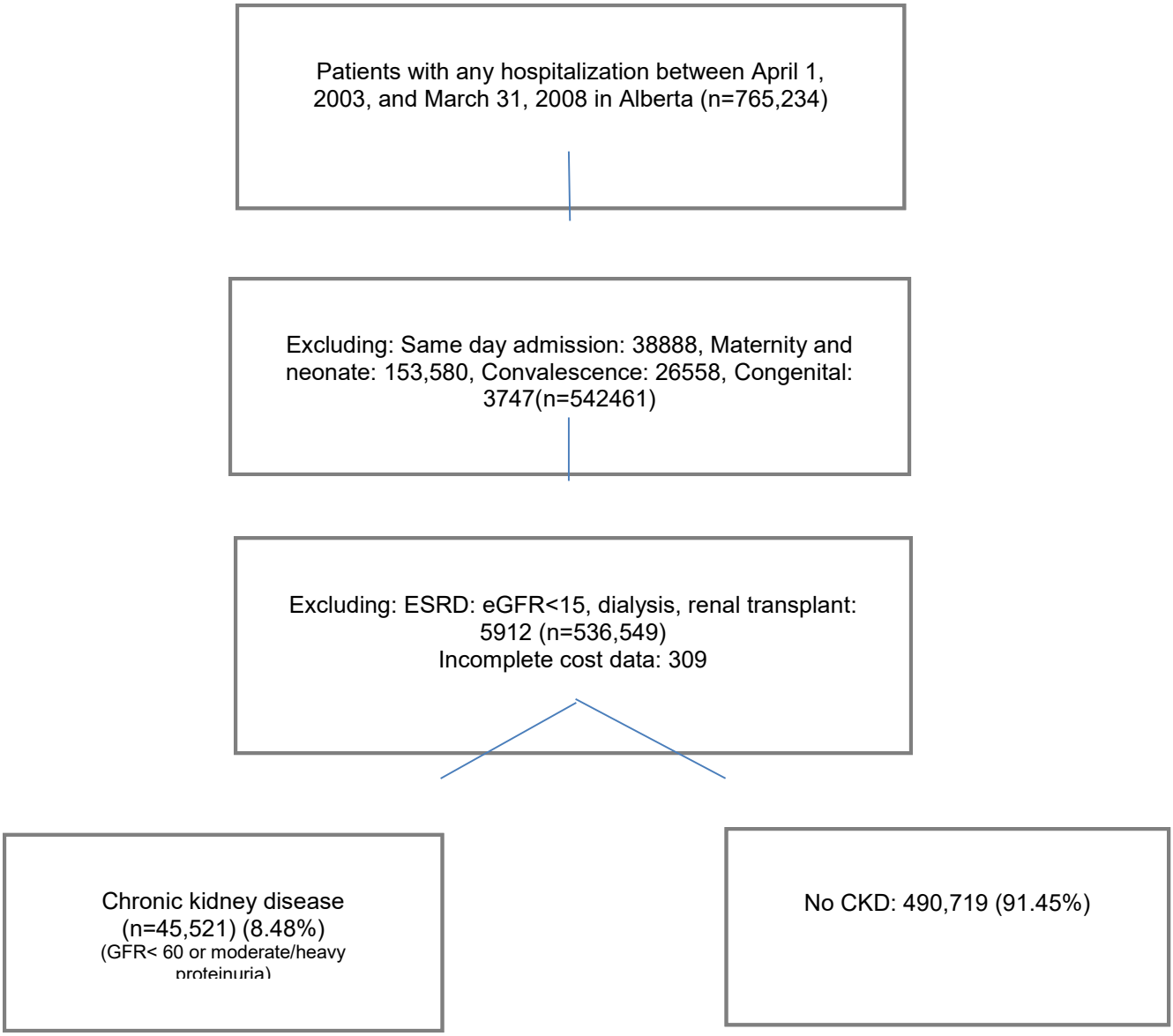
* $ Can
**Adjusted for age, admission type (elective vs urgent), gender, LOS, non-preventable complications (where appropriate), and 16 comorbid conditions including: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications and without complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic disease.

Table 5.5. Median incremental costs within 90 days after hospital admission in patients with and without CKD and potentially preventable HACs.

	Patients	
	Without CKD	With CKD
Incremental costs of preventable HACs (95% CI)**	6,688 (6,612 – 6,723)	7,522 (7,219 - 7,824)

*Adjusted for age, admission type (elective vs urgent), gender, LOS, non-preventable complications, and 1 comorbid conditions including: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications and without complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, renal disease(where appropriate), rheumatologic disease; in cases with CKD adjusted for severity of CKD.
** $ Can
# Incremental costs of preventable HACs were non-significant when patients with CKD were referred to those without CKD.

Figure 5.1. Study flowchart to construct cohort of patients with CKD



CHAPTER 6: GENERAL DISCUSSION AND CONCLUSIONS

6.1 Summary of the results

This thesis examined the risk of hospital acquired complications, including those considered to be preventable, in a large population based cohort of all adults with CKD hospitalized in Alberta (2003 - 2008). The findings, summarized in Tables 1, showed that the proportion of hospitalized patients with HACs were greater in patients with CKD. In a fully adjusted analysis, the risk of all complications, potentially preventable HACs, and always preventable complications, were higher in patients with CKD. Additionally, with increasing severity of CKD, the risk of HACs increases (19% in all patients with CKD vs 81% risk of HACs in those with the most severe CKD (eGFR = 15 - 29 ml/min/1.73m^2 and proteinuria > 30mg/mmol)).

In addition, this thesis analysed negative clinical consequences of HACs in patients with CKD during and after an admission (summarized in Table 2). The magnitude of these associations was large, with a fivefold higher risk of mortality in the index hospitalization, 10 days longer stay in hospital, and almost 30% increased risk of re-hospitalization within 90 days after discharge in CKD patients with ≥ 1 preventable HACs compared to patients with CKD but without preventable HACs.

When this thesis considered the full cohort analysis, including patients with and without CKD, patients without CKD and without preventable HACs were used as the reference. A graded increase in the risk of mortality in the index hospitalization, mortality from

discharge to 90 days, length of stay, and readmission within 90 days was noted with the greatest risk in those with both CKD and preventable complications.

This thesis also examined the association of incremental healthcare costs attributable to preventable HACs in hospitalized patients. In a population of patients with CKD, hospitalizations with potentially preventable complications had substantially greater costs during the index hospitalization, as well as in the post-discharge period (including physician claim, ambulatory care costs and readmissions). These costs remained greater when compared to costs in patients with preventable complications but without CKD. In patients with CKD, the magnitude of this association was large and the incremental costs of the index hospitalization with 2-3 preventable HACs was three-fold of index hospitalization costs of those patients without preventable complications.

Two other findings, in this thesis, deserve consideration. First, patients with CKD who had preventable HACs also had more non-preventable complications, compared to those with patients with no preventable HACs. It is not clear why complications cluster in certain patients, but we speculate that this may happen in patients with more clinical complexity, may accrue as patients stay in hospital longer, or be a follow-on effect of the preventable complications. The effect of any preventive strategy on this clustering of complications is unknown. Second, greater severity of CKD is associated with greater risk of preventable HACs and this finding is congruent with other studies. However, while in general greater severity of CKD is associated with poorer clinical outcomes in a graded fashion[1-3] in patients with CKD who developed HACs this was not observed in our study. While CKD is a risk factor for the occurrence of preventable HACs, we speculate that over this very short time frame of observation, preventable HACs

appears to have primacy with respect to adverse outcomes, and the severity of CKD may not exert its influence.

In summary, the presence of CKD and its severity increases the risk of HACs, including those considered preventable, and are associated with deleterious clinical and economic outcomes. Targeted strategies to reduce complications should be a high priority as any reduction of preventable HACs may reduce the risk of mortality, extended LOS, readmission to hospital, and additional healthcare costs and result in a significant benefit for patient and health system outcomes especially in people with CKD.

6.2 Importance of the study

In this thesis, health administrative data was used as a major source of patients' clinical and economic information. Aggregating multiple healthcare administrative datasets including: Demographic, Discharge Abstract Data (DAD), the National Ambulatory Care Reporting System (NACRS), physician claims, and out-patients lab data result in an individual-level large and informative longitudinal study dataset. Use of this data enabled the study to look at an entire population, define CKD prior to hospitalization and identify HACs and their consequences at a broad level, that would not be feasible through chart review. Using this approach allows examination of general findings in all population or sub-populations at risk of hospital complications and provides information for further studies to prioritize specific populations or patients.

Heteroskedasticity, an issue of OLS regression, occurs when the standard deviations of a variable, monitored over a specific amount of time, are non-constant, which can often occur in cost data. Along with linearity, independent error, normal distribution of error,

the absence of heteroskedasticity is an assumption of the classical Linear model. Heteroskedasticity has serious consequences for the OLS estimator. OLS estimators remain unbiased and consistent in the presence of this condition, but they are not efficient and the estimated standard errors are inconsistent, so confidence intervals and hypotheses tests cannot be relied on. Heteroskedasticity is detectable by eye-ball test, a simple but casual assessment doe by examining the plot of residuals against predicted values or individual explanatory variables to see if the spread of residuals appears to depend on these variables. Other tests e.g. the Breush Pagan Test, Park Test formalize these visual descriptions, regressing the squared residuals on predicted values or explanatory variables.

Using observational data, researchers can assess the association of exposure with outcome variables, and there are some features that when present may suggest causality. Timing of occurrence of conditions is a main factor to define the causal pathway, however administrative data for this project does not include timing of events. Considering the

Hill's criteria for causation that provides evidence of a causal relation between a putative cause and an effect, it is possible to satisfy some of criteria using administrative data; the greater the association, the more likely that it is causal (strength), temporality: the effect has to occur after the cause, and greater exposure should generally lead to greater incidence of the effect. (biological gradient)

Length of stay is an endogenous risk factor of hospital acquired complications and limited evidence are available to investigate impact of length of stay on risk of hospital complications. Endogeneity can arise as a result of simultaneous causality. Hospital complications may result in longer length of stay and longer length of stay may expose patients to greater risk of HACs. Using administrative data, statistical models of hospital acquired complications which do not control for the potential endogeneity of LOS may generate inconsistent and biased estimates of all factors impacting on HACs.

Both length of stay in hospital and preventable HACs are contributing factors to incremental hospitalization costs. Simultaneous estimation of the impact of these two factors in cost analyses may lead to inflated estimates of results. This thesis is important because quntile regression models were used to examine the impact of preventable HACs on costs in quantiles of LOS. While this model cannot prove causality, the fact that the incremental cost effect of HACs was found in all LOS quantiles suggests an independent relationship between these two factors. Results of quantile analyses indicate that conclusions are not altered when analyses are performed by quantiles of LOS, where HAC independently leads to increased incremental cost among patients categorized by LOS. To our knowledge other studies have not employed this method of analysis.

This thesis showed that hospitalizations with preventable HACs in a general patient population are common. Certain patient populations may be at higher risk of preventable HACs, partly due the complexity of their clinical conditions. Chronic disease including congestive heart failure, hypertension, diabetes, and chronic kidney disease may increase the susceptibility to complications, compared to patients without any

underlying disease [4,5]. The risk of preventable HACs in patients with chronic disease including congestive heart failure, hypertension, COPD, has not been determined yet. This thesis demonstrated that patients with CKD are at higher risk of complications during hospitalization, even when other chronic diseases have been controlled. To date, limited data is available on preventable HACs in patients with CKD. Only two studies that both used Veterans Administration data for 2004-2005 showed patients with CKD had a higher risk for several preventable HACs than patients with normal kidney function [6-8], however non – veteran patient populations with CKD and/or other potentially preventable HACs have not been examined, nor has this been explored in other care settings. While findings in this thesis are congruent, we used both eGFR and proteinuria levels, and assessed outpatient values prior to hospitalization to define CKD patients, a more accurate method to assess CKD. Further, we studied a population based cohort, and considered all hospital complications and those deemed to be potentially or always preventable.

Implementing preventive strategies in the general inpatient population, including CKD patients, may improve quality of care, but patients with CKD may be an ideal high risk population to implement specific strategies or clinical guidelines to reduce preventable HACs. This may subsequently improve patient and health care system outcomes.

We extrapolated our findings to North America as an example of the potential implications. It is estimated that in 2013 approximately 3.25 million patients with CKD (8.5%) were admitted to hospital in North America [9,10] . Assuming causality between preventable complications and adverse outcomes in patients with CKD, preventable HACs may be responsible for an additional 45,000 in-hospital patient deaths, 4.5 million

additional hospital days, 21,000 readmissions within 90 days, and $2.2 billion incremental cost.

To our knowledge no study has investigated the association of clinical outcomes and incremental cost with preventable HACs in patients with CKD. Prior studies have emphasized hospital complications and clinical outcomes in general inpatient populations and found costly consequences for patients and healthcare networks.

Hospital acquired complications can be reduced. In a general hospitalized population various strategies have been implemented leading to reduction in the rate of preventable HACs [11-14]. Preventive strategies targeted at patients with greater risk of preventable HACs may result in a proportionately greater reduction of poor clinical and economic outcomes.

6.3 Strengths of the study

Strengths of this study include the use of a population based cohort and inclusion of community, teaching, and specialized hospitals, which strengthens generalizability. It is the first study to take a broad look at a specific, easily identifiable patient populations that may be at high risk of preventable HACs. This study examined HACs in patients with CKD, a common chronic disease, and defined CKD in a rigorous manner, using outpatient lab data prior to hospitalization.

Healthcare costs were comprehensive, including both in-hospital and post discharge costs; the latter has not been determined yet in any previous study identified. This thesis linked ambulatory care costs, physician claims after hospital discharge and incremental readmission costs. Other studies have analyzed cost only within an index

hospitalization, which may underestimate the incremental cost estimation associated with preventable HACs.

In contrast to previous studies, this thesis is important because of categorization of all the complications into potentially preventable and non-preventable. All analyses were adjusted for hospital complications that are not currently thought to be preventable – if these are not accounted for, it modifies the results, for example risk of mortality in the index hospitalization associated with ≥ 1 preventable HACs was 6.74 (95% CI; 6.45 – 7.05) vs 4.67 (95% CI: 4.17 – 5.22) after accounting for non-preventable HACs (These data were not shown in study). To our knowledge other studies examining the impact of complications did not control for non-preventable HACs in their analysis; if these independently contribute to outcomes, then previous studies that did not control for these may have overestimated the impact. In this thesis, adjusting the analyses for non-preventable HACs decreased the estimated risk of preventable HACs in patients with CKD, avoiding misattribution.

The increasing severity of CKD or number of preventable HACs may increase the risk of the outcomes measured, indicating the robustness of their associations. This thesis is important because in addition to reporting association of outcomes with the average severity of kidney function and average number of complications, as in previous studies, kidney function and preventable HACs were categorized by severity of CKD, and number of preventable complications, respectively to assess for gradients of association from an epidemiological perspective (association vs causality) [15]. This study found graded outcomes associated with increasing numbers of preventable HACs in patients with CKD, consistent with causality.

6.4. Study limitations

In general, there are limitations of studies using administrative data to identify preventable HACs. First, the quality of recording of diagnoses depends on the quality of documentation in the medical record and the expertise of coders. This may alter the identification of complications in different hospitals. Second, administrative data may not be sensitive (low positive predictive value) for some types of hospital acquired conditions [16] and may underestimate the preventable HACs. Third, using this method provides information regarding association but not causation; administrative data lacks timing of events to determine causality (except for the 'hospital acquired' timing flag), and other approaches, e.g. chart review or prospective data collection may be needed. Fourth, using administrative data does not allow accurate classification of attribution such as medication error causing a complication. Fifth, circumstances leading to a complication, the extent to which complications alter the process of disease and care, and how complications and comorbid conditions are associated cannot be easily clarified using administrative data.

There are additional limitations that merit discussion. Due to limitations of our source data, this thesis was unable to obtain information on hospital level factors including hospital type, volume, and location, certain clinical variables such as blood pressure control and life style factors (smoking, exercise, and diet). However, we captured important chronic diseases and controlled for them in our analyses. Further, in this study the cohort included adults' hospitalizations only between 2003 and 2008. Improvements to quality of hospital care through various improvement efforts were implemented over this time. While this was not accounted for in this analysis, the

proportion of patients with preventable HACs was stable over time (Appendix A). Increased efforts to improve hospital safety and quality of care have been implemented in Alberta in recent years, and the extent to which absolute risk of preventable HACs may have changed after 2008 was not examined.

Another limitation is the potential for misclassification of preventability of complications. Misclassification of preventable HACs may change the potential impact of implemented prevention strategies. Identification of preventable complications in this thesis was based on the opinion of 3M Health System clinicians based on ICD 9 CM[17], and then subsequently mapped to ICD 10 Canadian version in this study. In the creation of preventable complications developed by the 3M system, as well as remapping this system to ICD 10 Canadian version, there was the potential to misclassify preventable HACs resulting in over or underestimation of impact of prevention strategies on HACs. Finally, the aggregated costing methodology used by CIHI provides average costs of hospitalizations for each Case Mix Group[18] (clinically similar and/or homogenous groups of patients based on health care resources used). This approach may underestimate the incremental cost association with preventable HACs, as this methodology may not fully capture the incremental cost attributable to those complications within a CMG.

6.5. Implications for Future Research

This study took a high level approach to analyses, and included all preventable complications, in patients hospitalized for a wide variety of reasons, and focused on one chronic disease (CKD). This thesis provides groundwork for further studies. That may include assessing other high risk patient populations, for example those with diabetes, or congestive heart failure.

Preventable hospital acquired complications can be reduced through implementing prevention strategies. Given the greater risk of preventable complications in patients with CKD, another area of further study is analyses of outcomes after implementing evidence based preventive strategies in this high risk patient population. A clinical trial would be a suggested study design to analyze results of prevention strategies in CKD patients. Furthermore, as patients with CKD may be uniquely predisposed to complications of medications, this should be a focus of future study using chart review or a prospective study.

6.6. Conclusion

Hospitalized patients are at risk of acquired complications, many of which are potentially preventable. Patients with chronic kidney disease are at increased risk of preventable HACs. Consequences of HACs in CKD patients are dramatic: increase in risk of in-hospital mortality, as well as longer length of stay, mortality within 90 days after discharge, readmission within 90 days, and incremental in-patient and outpatients' healthcare costs, compared with patients with CKD but without preventable HACs. Our findings may inform prioritization of prevention efforts to reduce the rate of preventable complications and attributable clinical and economic outcomes with the goal of improving quality of care and outcomes for hospitalized patients with CKD, as well as reduced health system costs.

Table 6.1. Summary of proportion and OR of all HACs, potentially preventable HACs, and always preventable HACs by CKD status.

	# of patients	% with All HACs	OR (95% CI) of all HACs*	% with potentially preventable HACs	OR (95% CI) of potentially preventable HACs*	% with always preventable HACs	OR (95% CI) of always preventable HACs*
No CKD	490,816	7.34	Reference	5.37	Reference	0.96	Reference
CKD (all)	45,733	13.05	1.19 (1.15 - 1.23)	9.82	1.20 (1.16 – 1.24)	1.57	1.14 (1.05 – 1.24)
Moderate severity CKD	26,930	7.10	1.08 (1.04 – 1.13)	4.96	1.08 (1.03 – 1.13)	0.88	1.06 (0.95 – 1.17) **
High severity CKD	12,364	3.69	1.11 (1.05 – 1.18)	2.30	1.14 (1.07 – 1.21)	0.43	0.99 (0.86 – 1.15) **
Very high severity CKD	6,439	2.36	1.24 (1.15 – 1.33)	1.20	1.26 (1.16 – 1.36)	0.25	0.97 (0.80 -1.18) **

* Fully adjusted for age, admission type (elective vs urgent), gender, LOS, non-preventable HACS, CKD severity, and 16 comorbid conditions, except for reason for admission. Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, and rheumatologic disease. ** non-significant

Table 6.2. Summary of outcomes associated with potentially preventable HACs (pp-HACs) by CKD status.

Patients	# of patients	OR of mortality: index hospitalization [A] (95% CI)	OR of mortality: discharge to 90-day [A] (95% CI)	Median LOS	Incremental LOS[B] (mean) 95% (CI)	OR of Re-Admission: discharge to 90-days[A] (95% CI)	Incremental Costs within 90 days from hospital admission [A, C]
With CKD & no pp-HACs	41,239	Reference	Reference	3	Reference	Reference	Reference
With CKD & with pp-HACs	4,494	4.67 (4.17 – 5.22)	1.08 (0.94 – 1.25) *	13	9.86 (9.25 – 10.47)	1.24 (1.15 – 1.34)	7,522 (7,219 - 7,824)
No CKD & no pp-HACs	464,442	Reference	Reference	3	Reference	Reference	Reference
With CKD & no pp-HAC	41,239	2.22 (1.69 – 2.94)	1.49 (1.11 – 2.00)	5	1.67 (0.29 – 3.06)	1.45 (1.25 – 1.69)	474 (415 – 532)
Non-CKD & with pp-HAC	26,374	5.26 (4.98 – 5.55)	1.20 (1.12 – 1.29)	11	9.73 (9.4 – 9.98)	1.41 (1.36 – 1.45)	6,688 (6,612 – 6,723)
With CKD & pp-HAC	4494	9.56 (7.23 – 12.65)	1.68 (1.23 – 2.29)	13	11.42 (9.93 – 12.91)	1.67 (1.42 – 1.96)	9,411 (9,245 – 9,576)

A. Fully adjusted for age, admission type (elective vs urgent), gender, LOS, severity of CKD, non-preventable complications, and 16 comorbid conditions
B. Fully adjusted for age, admission type (elective vs urgent), gender, severity of CKD, non-preventable complications, and 16 comorbid condition: Comorbid conditions: cancer, cerebrovascular disease, congestive heart failure, COPD, dementia, diabetes with complications, diabetes with NO complications, HIV/AIDS, metastatic solid tumor, myocardial infarction, mild liver disease, moderate/severe liver disease, para/hemiplegia, peptic ulcer disease, peripheral vascular diseases, rheumatologic diseases.
C. Canadian dollar
*Non-significant

Appendix A.

Study period(year)	03 – 08	03 – 04	04 – 05	05 – 06	06 – 07	07 – 08	
HAC (%)	**7.83**	8.84	7.69	7.17	7.48	7.81	P value < 0.05
pp-HAC (%)	**5.75**	6.50	5.57	5.34	5.45	5.49	P value < 0.05
Never events (%)	**1.01**	1.10	1.03	0.88	0.96	1.05	P value < 0.05

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APPENDIX:

Ethics approval for the study

Notification of Approval (Renewal)

Date:	October 17, 2016
Amendment ID:	Pro00036226_REN3
Principal Investigator:	Scott Klarenbach
Study ID:	MS3_Pro00036226
Study Title:	Outcomes and trends of Hospital Acquired Diagnoses (HAD) in patients with non-communicable chronic diseases
Approval Expiry Date:	Monday, October 16, 2017

Thank you for submitting this renewal application. Your application has been reviewed and approved.

This re-approval is valid for another year. If your study continues past the expiration date as noted above, you will be required to complete another renewal request. Beginning at 30 days prior to the expiration date, you will receive notices that the study is about to expire. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

All study related documents should be retained so as to be available to the Health REB upon request. They should be kept for the duration of the project and for at least 5 years following study completion.

Sincerely,

Dr. Liran Levin
Member, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).