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Effects of Longitudinal Changes in Charlson Comorbidity on Prognostic Survival Model Performance Among Newly Diagnosed Patients with Hypertension

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Effects of Longitudinal Changes in Charlson Comorbidity on Prognostic Survival Model Performance Among Newly Diagnosed Patients with Hypertension

by

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Abstract

Objectives: To assess methods of defining comorbidities by comparing risk adjusted mortality predictive model fit and performance among newly diagnosed hypertensive population.

Methods: We included nearly all patients 18 year and older with an incident diagnosis of hypertension from one Canadian Province. We compared prognostic model performance for Cox regression models using Charlson comorbidities as time-invariant covariates (TIC) at baseline and time-varying covariates (TVC). Cox regression was used to calculate hazard ratios. Model fit and performance was based on the comparison of the AIC and Likelihood Ratio.

Results: All Cox regression time-varying covariate models (TVCMs) outperformed time-invariant covariate (TIVMs) baseline models, based on a comparison of AIC and Likelihood Ratio, regardless of the method used to adjust for individual risk using the Charlson Comorbidities. TVCMs included all 17 Charlson comorbidities as individual independent variables showed the best fit and performance compared with similar baseline models, AIC (1,670,491 to 1,720,126) and Likelihood Ratio (112,941.72 to 63,239.78) respectively.

Conclusion: Accounting for changes in patient comorbidity status over time more accurately capture a patient's health risk and improves predictive model fit and performance over longer follow-up periods than traditional baseline method.

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Finally, I would like to recognize and thank my supervisor Dr. Hude Quan. He has been instrumental in guiding me. His ability to understand when to help and when to step away was key in the progress of my work and my personal development.

Dedication

To my wife Alicja, and to Olivia and Max, my children.

Thank you for your ongoing love and support.

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List of Symbols, Abbreviations and Nomenclature

ACGs	Adjusted Clinical Groups
AH	Alberta Health
aHRs	Adjusted hazard ratios
AHS	Alberta Health Services
CHREB	Conjoint Health Research Ethics Board
AHCIP	Alberta Health Care Insurance Plan
CI	Confidence interval
cHRs	Crude hazard ratios
CMGs	Case Mix Groups
CRGs	Clinical Risk Groups
HR	Hazard ratio
DA	Dissemination Area
DAD	Discharge Abstract Database
ICD	International Classification of Diseases
PHN	Personal health number
CCI	Charlson comorbidity Index
RUB	Resource Utilization Bands
TIC(s)	Time- invariant covariate(s)
TIVM(s)	Time-invariant covariate model(s)
TVC(s)	Time-varying covariate(s)
TVCM(s)	Time-varying covariate model(s)

Chapter One: Study Objective and Significance

1.1 Objective

The objective of the study is to use a large population based administrative data to compare survival model fit and performance between models adjusting for comorbidities present at baseline and models adjusting for longitudinal comorbidity, changes in disease state over a longer follow-up period. This study looks at a 12-year follow-up period in a newly diagnosed hypertension population in Alberta, Canada.

1.2 Significance

Comorbidity is an important component of individual risk and health status. It has been shown to be an important determinant of health care utilization, predictive of health outcomes and of mortality. Studies using large administrative data sets to predict death have historically adjusted for individual risk on the basis of comorbidities present at the beginning of studies (Wang, 2009, Giolo, 2012). Little is known about the onset of comorbidities or effects of medical events during long study follow-up periods, and how the change in individual risk reflects on ability to predict survival.

The Charlson comorbidity index (CCI), (Charlson, 1987) was developed as a prognostic classification and weighting methodology-predicting mortality based on disease burden. The CCI has demonstrated prognostic value. Short-term studies predicting 30-day and 1-year mortality using time-invariant baseline Charlson comorbidity adjustment have shown good performance. Recent studies have suggested that predictive models solely relying on baseline measures of comorbidity may have less predictive ability in longer follow-up studies (Giolo, 2012; Kovesdy,

2007; Fleishman, 2010;Wong, 2012). Diseases could occur in the follow-up and thus longitudinal comorbidity should be considered as predictor of survival (Giolo 2012, Wong 2012). However, few studies have accounted for changes in disease state after baseline.

Because of variation in the length of follow-up and study populations, there is contradictory evidence about the value of time-varying effects and improvement in prognostic model performance (Wang 2009, Ahern 2009).

Our study was aimed to understand the impact of longitudinal comorbidity on patient survival. Models accounting for changes in patient comorbidity status over time may more accurately capture a patient's health risk and improve a model's ability to predict survival over long follow-up periods than baseline method.

Chapter Two: Background

2.1 Health Care System Performance

2.1.1 Evaluation of Health System Performance

Decision makers at all levels need comparable and meaningful information to make policy, operational and clinical decisions. This requires a systematic approach to the assessment of health system performance. Understanding variation between different parts of the health system in different subpopulations is vital to evaluating health system delivery, and determining factors that drive it. Explaining key factors responsible for variation can lead to improved comparability in health outcomes between different parts of the health system and between various populations, leading to reductions in inequality and improvements in policies applicable to multiple settings (Iezzoni, 2010).

A health system includes structures such as facilities, equipment and human resources. The system is required to deliver health care services through the efficient use of organizational resources and processes focused on activities that are intended to maintain or improve population health (Donabedian, 1997).

2.1.2 Conceptual Evaluation Frameworks

Various conceptual evaluation frameworks have been proposed to examine health services and evaluate quality of patient care (RAND 2010, Donabedian 1997, www.hqca.ca). The frameworks support informed policy, and operational and clinical decisions in an effort to reduce information asymmetry ensuring evidence based decisions leading to improved patient care. The intention of conceptual frameworks is to outline a set of steps, assumptions and definitions to guide evaluation processes and activities focused on the measurement of specific

objectives. They also define a set of measures and goals that are vital in quantifying improvement in the health system. They can focus on defining a common set of definitions and conceptual approaches (HQCA, Quality Matrix For Health).

Selection of an appropriate conceptual framework largely depends on the alignment between the outcomes of research being done and the context provided by the supporting framework. Researchers have used various frameworks for evaluation of health system performance.

2.1.2.1 Alberta Quality Matrix for Health

The Health Quality Counsel of Alberta (HQCA) has developed a conceptual framework that summarizes the definition of quality according to six dimensions (Acceptability, Accessibility, Appropriateness, Effectiveness, Efficiency and Safety) and an additional four dimensions of patient need (Being Healthy, Getting Better, Living with Illness or Disability and End of Life). The framework emphasizes a common understanding of the complexity of the healthcare system, components that contribute to quality health care and the interrelated nature of all six-quality dimensions. The framework is intended to help individuals and organizations to enter into dialogue using a common language and understanding of the foundations of quality and how these impact areas of patient need (www.hqca.ca, Alberta Quality Matrix for Health).

2.1.2.2 RAND Health Service Planning Framework

In 2010, the RAND corporation developed a framework to assess and optimize health services planning; RAND report (Framework for assessing, improving and enhancing health service planning) identified three core themes required for health system assessment. The three

themes include the development of long-term goals and objectives with emphasis on strong unified leadership and accountability structures linked to long-term goals and objectives. Most importantly, the RAND model emphasizes the need for analytical capacity to support health system change with appropriate and relevant information.

The goal of the framework is to support health system governance through processes and tools that inform decision makers to ensure that the current planning approaches taken would meet their objectives (RAND, 2010).

2.1.2.3 The Donabedian Model

The Donabedien framework was developed to support health system research to better assess quality of health care. Quality is grouped into three areas: structure, process, and outcomes. Structures refer to facilities, equipment and human resource required to deliver health care services. Processes are defined as the activities related to the delivery of health services. Outcomes are the results of the structures and processes of the medical system, and should be easily measured, allowing for precision and validation. Outcome measures should be related to recovery, restoration of function, and survival. Patients' survival is often selected as an outcome measure because it is easily measured and cannot be disputed as an invalid outcome.

Donabedian outlined several considerations when outcomes were used as quality of care indicators. Researchers need to ensure that metrics are relevant for the conditions being studied, and that metrics are sensitive to effectively applied medical intervention. Factors such as severity of disease, patient socioeconomic status and care setting should be adjusted to ensure comparability of outcomes across jurisdictions. To ensure that we are able to draw valid conclusions, factors outside of medical intervention, which have been known to influence patient outcomes, need to be included in the analysis (Donabedian 1997).

2.2 Disease Severity and Risk Adjustment

Historically, therapeutic efficacy was evaluated under controlled conditions restricting patient eligibility based on the presence or absence of comorbid disease. Rather than controlling for confounding, scientists controlled study eligibility criteria to achieve homogenous patient populations (Charlson, 1987). The problem with this approach was that the study findings were limited in their generalizability and had difficulty reaching an appropriate sample size. Clinical trials used randomization to control for the effects of confounding to ensure accuracy when comparing between various groups. Since observational studies did not randomize patients, risk adjustment methods were needed to control for unbalanced distribution of individual level confounders such as age, sex, socio-economic status and disease comorbidity known to affect outcomes. Risk adjustment was required to ensure that results are comparable between patient groups (Charlson, 1987, Nieto, 1996).

2.2.1 Disease severity

Clinical outcomes such as mortality may be used in the assessment and comparison of competing medical interventions, or more broadly, in observational studies looking at the effects of various external or environmental risk factors on overall population survival. Studies strive to understand differences in outcomes resulting from therapeutic intervention, quality of care delivered or efficiency in the process of care delivery. To ensure that study findings are accurate and representative, adjusting for individual patient disease severity is required (Iezzoni, 2010).

Disease severity refers to the presence and progression of one or more diseases. Disease severity and progression could be determined through diagnostic testing, and physical medical exams in the assessment of organ and tissue damage (Finlayson, 2004).

Determination of disease severity is based on clinical judgment supported by diagnostic information (Charlson, 1985). Clinical measures such as blood pressure are indicators of disease severity and considered predictors of multiple cardiovascular events and mortality (Parati, 2013, Rapsomaniki, 2014). While clinical information is important in assessing severity, it is often unavailable and patient case-mix is used as an alternative. Christensen et al. found that using case-mix adjustment tools such as the CCI, a proxy for disease burden and severity, performed as well as physiologically acute care based measures such as the APACHEII and SAPSIII in models predicting mortality (Christensen, 2011). Patients with multiple chronic conditions have a higher risk of death and complications than those with a single condition. Subsequently, high-risk patients with complications have a high level of functional impairment and disability (Iezzoni, 2010).

2.2.2 Disease Classification and Patient Case-mix

Classification of disease and causes of death evolved from Bertillons Classification of Cause of Disease. Through an iterative process, disease classification underwent various revisions. Eventually, diseases and causes of death were included in the International Classification of Death and Disease (ICD)(Dean, 2007). The ICD system evolved to form a 4-digit classification system in ICD 9. Subsequently, a 5-digit ICD 9 CM classification was developed to increase specificity and capture new disease categories (Iezzoni, 2010). Most recently the ICD 10 was adopted and deployed in the Canadian acute care system (CIHI, 2001). The system enabled very detailed disease classification, and supported administrative, clinical and epidemiological reporting (Dean, 2007).

Increasing complexity of the ICD has made it difficult for researchers to identify a reasonable number of potential risk factors that could be used to account for patient risk. In response to the increasing complexity of the ICD, alternative methods were created to group highly variable and complex patients into a smaller number of manageable and clinically meaningful categories. These categories could be used to measure and evaluated health care costs, utilization and patient outcomes (Iezzoni, 2010; Fetter, 1980)

Patient case-mix groups patients into homogenous groups according to specific risk factors using clinical and administrative health data (CIHI, 2001). Various methods of case-mix have been used for risk adjustment. The adjustment is for accounting for various risk factors that affect specific outcomes over a defined period of time (Greenfield, 1994). Selection and use of case-mix methods depends on study outcomes and objectives.

2.2.2.1 Diagnosis Related Groups (DRGs)

In 1980, Fetter et al. developed Diagnosis Related Groups (DRGs) based on ICD9 CM diagnosis and procedure information from abstracted hospital discharge data. The DRG system classifies patients into clinically meaningful groups based on similar resource use for given service events. The primary users of the DRG system are hospital administrators who are interested in improving their understanding of inpatient services, processes, cost accounting, budgeting, and quality improvement.

2.2.2.2 Case Mix Groups (CMGs)

Similarly, Case Mix Groups (CMG), a Canadian risk adjustment method assigned patients to homogeneous patient groups based on routinely collected hospital discharge data.

Patients are assigned to a manageable number of patient categories, each category containing clinically similar patients consuming comparable resources (CIHI). Both CMGs and DRGs are used to classify episodes of patient care with associated weightings to estimate relative cost of each service (Manitoba Centre for Health Policy, Concept: Case Mix Groups (CMGs™) versus Diagnosis Related Groups (DRGs™).

2.2.2.3 Adjusted Clinical Groups (ACGs)

The John's Hopkins ACG case-mix system is a statistically validated tool that has been used by researchers, health system administrators and clinicians. The goal of the tool is to evaluate current resource use, as well as to predict future healthcare utilization. ACGs assign patients to one of 32 mutually exclusive diagnostic clusters using ICD 9, 9-CM, 10, and 10-CM as part of five clinical dimensions. Patients within each group are expected to have similar morbidity and are expected to use similar level of healthcare resources. The ACGs can be further collapsed into Resource Utilization Bands (RUBs), classes categorizing patients to one of six groups ranging from 1- Non-User to 5 - Very High. The ACGs is developed to support comparability of health system utilization across aggregate patient groups. In 2002, the Manitoba Centre for Health Policy validated its use using Canadian health data. Reid et al concluded that the ACG was correlated with premature death, socio-economic status and physician use (Reid, 2002).

Similar to ACGs, Clinical Risk Groups (CRGs) apply diagnosis and procedure data to categorize individuals into mutually exclusive severity adjusted risk groups. CRGs are used for risk assessment to better understand resource use, control costs and improve quality of care. Both ACGs and CRGs are considered population based risk assessment models, and are used to ensure

appropriate funding allocation to reduce treatment inequality and to prevent patient selection based on financial incentives (http://solutions.3m.com).

Unlike DRGs and CMGs which classified inpatient service events and could be deemed limited considering the rarity of inpatient admission, ACGs and CRGs are considered population based classification systems, offering a more comprehensive assessment of patient risk by using diagnosis and procedure information for each patient recorded across the continuum of care using multiple information sources including physicians claims, DAD and Ambulatory care data over a longer period of time (Dean, 2007).

2.2.2.4 Charlson Comorbidity Index (CCI)

In 1987 Charlson et al. developed a predictive risk model that assigned individual risk at the time of enrolment into therapeutic trials based on presence or absence of specific disease comorbidities. Charlson et al. identified a series of comorbid conditions that were shown to have an independent association with a higher risk of death. Comparing 1-year mortality rates for each disease, weights were assigned based on the relative risk (RR) of death for each comorbidity. The weighted scores where then added and originally reported patients as having one of the following scores: 0,1-2,3-4 to >=5. The study reported a stepwise increase in 1-year mortality rates of 12%, 26%, 52% and 85% respectively (Charlson, 1987). The study assigned outcomes based on an individual weighted risk scores predictive of death during a 1-year follow-up period. This risk-adjustment methodology allowed studies to be more inclusive of their patient populations and subsequently generalizable with improved study sample sizes.

The CCI that was initially developed using clinical data has been subsequently translated to use ICD data. Since then, large administrative databases have promoted adoption of CCI. A

systematic review of 54 comorbidity indices comparing short-term and long-term mortality and concluded that comorbidity adjustment improves prognostic model performance over adjustment for age and sex alone (Sharabiani, 2012). Of the 54 papers reviewed, the CCI is the most frequently cited index.

2.2.2.5 Selecting a risk adjustment model

When selecting a risk adjustment model, researchers need to understand how risk is defined. An appropriate definition of risk needs to be considered to ensure that the study achieves its objective. The definition is related to outcomes. Outcomes could be broadly classified into three areas, 1) clinical outcomes of care, 2) resource use, and 3) patient-reported outcomes. Once researchers understand their study outcome, they can select a specific risk adjustment method that ensures their findings are comparable within and across their study populations, and potentially generalizable to other research (Iezzoni, 2010).

2.2.3 Comorbidity Adjustment in Statistical Models

Charlson comorbidities have been incorporated into regression models in several different ways. Some studies include each disease as a single dichotomous variable (present or absent) within regression models, while other studies have opted to use summary measures such as the CCI, or the count of Charlson comorbidities (Austin, 2003).

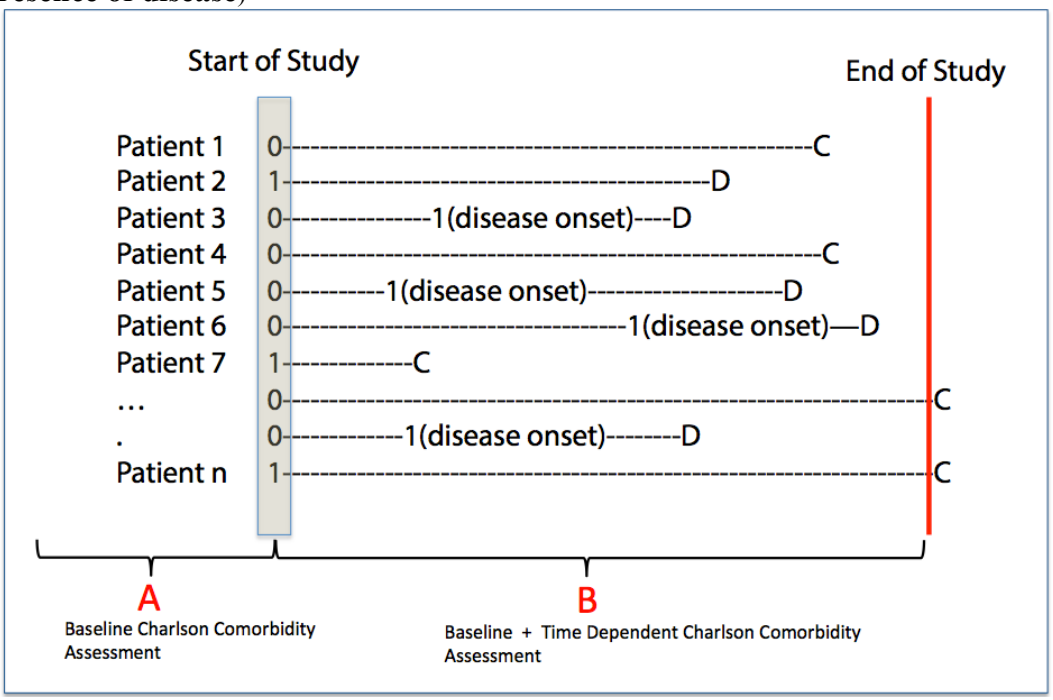
Summary measures for the CCI were built from individual weighted scores for each of 17 Charlson comorbidities assigned based on the original relative risk of 1-year mortality by Charlson et al. In 2011, Quan et al. developed an updated Charlson comorbidity score,

concluding that the original CCI should be updated to account for advances in chronic disease management and improvements in treatment and technology. Their study found that 12 comorbidities continued to be associated with 1-year mortality and proposed an updated summary score using 12 of the original 17 comorbidities to calculate an updated CCI yielding similar prognostic characteristics (Quan, 2011).

Summary measures may also include the count of Charlson comorbidities, and have also been used to adjust for patient risk. Fleishman et al. found the summary measure is least able to predictive mortality (Fleishman, 2010).

2.3 Survival Analysis

Figure 1. Survival Analysis Design (D – Death, C- Censored, 0-absence of disease, 1-presence of disease)



2.3.1 Survival Analysis Background

Survival analysis can be defined as a set of statistical methods looking at elapsed time between the beginning of a study and the occurrence of one or more events of interest. Studies are characterized by a start date and end date. Sometimes survival analysis is referred to as time to event analyses. Using survival analysis, researchers compare the effectiveness of various medical or surgical interventions, and changes in health policy.

The conceptual model presented in Figure 1, shows a sample cohort of patients (patient 1 to patient n). The study observation period starts at time 1 (start of the study) and finishes at time 2 (end of the study). Patient comorbidities can be defined in one of two ways (A and B). A) Time-invariant covariate baseline method (TIVM) - the baseline definition of patient comorbidities is based on a period of time up to and including the start of the study observation

period. This time frame includes various look back periods. Once the study begins, comorbidities defined at baseline are static through out the study. B) Time-varying covariate model (TVCM) – the period of defining comorbidities includes the baseline comorbidity assessment and changes in disease state over the remaining study follow-up, until a patient is lost to follow-up, died, exits the study or the study finishes.

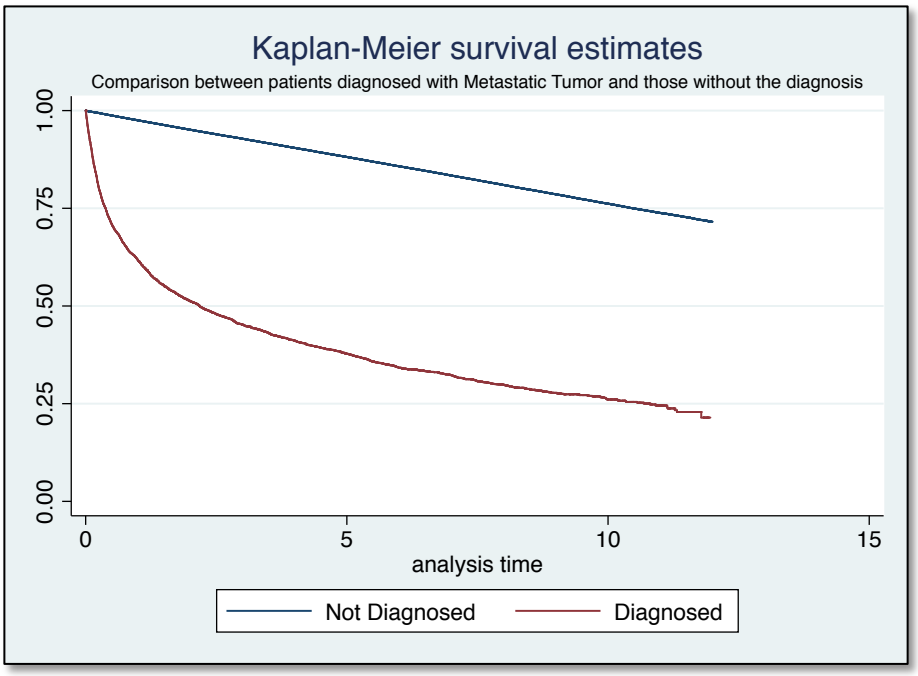
2.3.2 Failure (Event)

Death or failure (Figure 1. D- death) is an event in survival analysis (Kleinbaum, 2012). Researchers are interested in the occurrence of an event over the elapsed period between the beginning of the study and in the remaining study period from diagnosis. Survival time or time to event is the primary variable of interest and helps researchers to understand the differences in survival characteristics among various patient populations.

2.3.3 Censoring

There are various instances where patient data in a survival analysis may be censored, or considered incomplete. Censoring of patient information, identified in Figure 1 as C-censoring, means that researchers are unsure of exact survival time for the individuals in the study. This occurs if a patient is lost to follow-up, or chooses to withdraw from the study in the study period. Censoring occurs if a patient does not experience the event of interest before the end of the study. Even though a patient may be censored, their survival time prior to censorship is still incorporated in to the calculation of survival probabilities and contributes to assessment of population survival.

Figure 2. Comparison of Kaplan-Meier survival estimated for patients Diagnosed with metastatic cancer as compared to patients without the diagnosis.



2.3.4 Univariate Survival Analysis (Kaplan- Meier survival curves)

Researchers are able to calculate both survivor function and hazard functions to help them understand patient mortality. The survivor function gives the probability that a person survives longer than a specific time. Data is typically presented in the form of survivor tables or graphically in a survivor curve. Kaplan-Meier curves (K-M), a simple univariate analysis, can be used to compare survival curves by splitting the cohorts of patients into two or more groups using a single categorical variable (Figure 2). Using the Log-Rank test, a test of statistical significance, we can test differences in the survival characteristics between two or more K-M curves. The K-M method is useful to determine if independent variables have a statistical association with patient survival and should be included in a multivariate analysis. However,

these models are limited because they only allow the use of one independent categorical variable at a time.

2.3.5 Hazard Function and Hazard Ratio

Survival data allows us to calculate the Hazard function (HF). The HF is another way to explore patient survival and is defined as a rate and probability of an event (death) at a specific time. The HF is analogous to the rate of speed per unit time (km/h). It can be graphically represented to help us understand the probability of death for patients at any point over a study period. The HF can be used to derive the shape of the survival and cumulative hazard curves. Depending on the patient population or patient intervention, the HF can be constant or change over time. To illustrate this relationship we can use a 2012 European study conducted in 28 countries looked at 60-day patient survival rates for inpatient non-cardiac surgery. The study found higher then expected 60-day mortality rates that decreased over time (Pearse, 2012). In this scenario, we would expect the post-surgical hazard rate to be very high initially, and dropping over time. Survival probabilities would reflect this, initially dropping quickly because of high mortality, then flattening out over time (Figure 2. Diagnosed Patients).

The HF is used to calculate Hazard Ratios (HRs). The HR is a ratio of the rate of death per unit time comparing one population to another. It can be calculated using two or more levels of any explanatory variable and is typically used to compare the rate of death between baseline and intervention populations.

2.3.6 Multivariate analysis, Survivor Curves and Hazard Rate

The Cox Proportional Hazards Regression model allows us to study more complex relationships between our independent study variables and survival time. The HR, the primary measure of effect in a Cox regression model describes the increase in relative hazard and quantifies the impact of each independent variable on patient survival while accounting for confounding of all other independent variables in the regression model.

A key assumption of the Cox Proportional Hazard Model is that covariates are multiplicative relative to the baseline hazard. For example, a treatment may reduce patient death by half at any given time relative to the baseline hazard. This relationship does not vary in the study period, making the baseline and treatment survival curves proportional. The model assumption dictates that the HR must be constant over time. In the case of K-M survival curves this can be visually interpreted by seeing if the survival curves of two groups cross (Kleinbaum, 2012).

Evaluating statistical performance of our prognostic models allows us to understand how well our predicted outcomes measure up relative to actual patient outcomes. This gives us a basis for model comparison.

Model fit and performance is concerned with the comparison of nested and non-nested models. Nested models are derived from one another and include an increasing number of predictive variables. Non-nested models on the other hand are unrelated and use a completely different set of independent variables to predict outcomes.

Tests of model fit are derived from the likelihood function. This is an iterative process that is used to calculate model coefficients by testing for the maximum likelihood, and ensures a

statistical model most likely to fit the data. The maximum likelihood function is used to derive two tests of model fit and performance, the Likelihood Ratio (LR) test and the Akaike Information Criterion Statistic (AIC). The LR test compares the fit of two models using changes of models log-likelihood. Using this test we can determine if the addition or deletion of predictive variable improves model fit. AIC allows us to look at the relative loss of information, and assess goodness-of-fit between nested or non-nested models. This enables a comparison of relative strength of one model over another. The AIC penalizes complexity and over-fitting of statistical models to compensate for the addition of predictive variables that naturally raises the maximum likelihood. Relative probability of information loss may be calculated using the AIC values from each model using the following formula $\exp(AIC_{min} - AIC_i)/2$. The resulting value is used to comment on the model probability to minimize information loss relative to the model with the lowest AIC.

Studies have used the C-statistic as a measure of a model's ability to discriminate in assigning a binary outcome. Discrimination refers to a model's ability to predict individuals who experience and those who don't experience a dichotomous outcome such as death. Models with excellent discrimination should assign higher probability of mortality to those patients who actually died. The concordance statistic compares pairs of individuals. Each member in a pair is assigned a probability of death. Then model probabilities are compared to assess concordance with actual observed outcomes. Within each pair a better models should assign a higher probability of death to patients experiencing the outcome (concordant pair). When the reverse happens, pairs are considered discordant while ties are treated as ties. The following formula: *C-index = (concordant pairs + ½ tied pairs)/all pairs is* able to quantify a model's ability to predict

death (Tripepi Part I, 2010). The C-statistic ranges between 0.5 and 1, where value close to 0.5 indicates that the model predicts death no better than chance while 1 is perfect prediction. Previous studies have suggested that C-statistics of 0.7-0.8 should be considered as acceptable and 0.8-0.9 as excellent (Scheeweiss, 2001). In addition to comparing prognostic model performance based on discrimination, calibration is used to compare how well prognostic models correctly estimate the probability of a given event across a range of prognostic estimates (Tripepi part II, 2010). This methodology compares the predicted probability of an outcome estimated by a prognostic model to the real observed probability of the outcome. Patients are group into deciles based on their estimated probability of death. The sum of predicted and observed deaths is calculated and the model is assessed using the Hosmer-Lemeshow test (H-L test). Good model calibration is supported by a non-significant low p-value indicating that the predicted and observed numbers of deaths across deciles are not statistically different. Finally, studies look at potential improvements in calibration by calculating the Net Reclassification Improvement. Net reclassification improvement is used to compare gains in prognostic accuracy of a given model when new covariates are added to the previous predictive model (Tripepi part II, 2010).

2.4 Literature review on modeling

To the best of our knowledge our literature review shows limited, and in some cases contradictory evidence that comorbidity defined as a time-varying covariate improves predictive model performance (See Table 1). The table shows the variation in study design might cause difficulties in generalizing findings from one clinical setting to another.

Stukenborg et al. compared two risk adjustment methods, the Deyo Adaptation of the CCI and Elixhauser Method (Stukenborg, 2001). Their study compared model performance based on comorbidity risk adjustment determined at baseline, at the time of the index hospitalization with model based on historical data from prior hospitalizations (Stukenborg, 2001). Using the C-statistic, they concluded that information from prior hospitalization marginally improved model performance.

Granau et al., a Canadian survival study comparing comorbidity adjustment methods for post acute myocardial infarction (AMI) patients using administrative data and focusing on long-term mortality. Comorbidity risk adjustment tools included OAIMPR and D'Hoore adaptation of the CCI. The study concluded that the presence of specific comorbidities and comorbidities emerging over time should be considered when individual risks are adjusted.

Ahern et al. used the CCI as a measure of comorbidity to investigate the TVC effects on all cause mortality among patients with breast cancer. The study compared HRs per unit increase between baseline method of defining CCI and the method of defining CCI based on as time-varying covariates. The study concluded that there was no statistical difference in the HRs between these two methods (Ahern, 2009).

Wang et al. compared the fit and performance of 11 predictive models using the Romano adaptation of the CCI. Cox regression models were fit using baseline and time-varying covariate methods. The study found longitudinal comorbidity, using baseline and prior year rolling comorbidity, improved cox regression model fit and performance compared with baseline. While the study concluded improvements in model fit and performance using the TVCM comparing

AIC and LR, the improvement was marginal. That raised questions if capturing changes in comorbidity over time is meaningful or not in analysis.

In 2011, Porta et al. compared various methods of risk adjustment in patients diagnosed with myelodysplastic syndrome (MDS). They included a comparative analysis and validation of a new TVCM using a MDS -specific comorbidity index (MDS-CI). Performance of the new methods was compared with existing risk adjustment methods, Hematopoietic cell transplantation comorbidity index (HCT-CI) and the CCI. The MDS-CI index was found to work better then the CCI in the MDS population. The study found no significant difference between the MDS-CI for baseline and TVCM case-mix adjustment.

Giolo et al. quantified the impact of modeling heart failure survival using a TVCM. The study found that the implementation of TVC reduced bias and improved specificity of prognostic models. The authors also concluded that the findings of the study had limitations because of the lack of validated analytical procedures to compare TVCM and TIVM prognostic performance (Giolo, 2012). Sattar et al. looked the effects of diabetes on cause specific and all-cause mortality in patients with end stage renal disease. The study found that the risk of death associate with diabetes in an ESRD population increased with time and concluded that TVCMs improved model performance by capturing changes in disease comorbidity not captured by baseline models (Sattar, 2012).

Table 1: Literature review

	Study Objectives	Study Population	Method(s) of Comorbidity adjustment	Study Statistics	Conclusion
Wang *et al.* 2009	To evaluate the performance of to longitudinal comorbidity measurement in predicting survival.	44,016 Cancer free individuals, 66 years or older enrolled in Medicare between 1991 and 1999 and followed for at least 1-year	Romano adaptation of the Charlson Comorbidity Index	Likelihood Ratio, AIC	Longitudinal comorbidity is an important predictor of survival
Ahern *et al.* 2009	To examine if longitudinal comorbidities acquired after baseline influences the HR for all-cause mortality compared with analysis using baseline comorbidity	865 women diagnosed with early breast cancer between 1996 and 1999	Charlson Comorbidity Index	Comparison of Hazard ratios and confidence intervals	HRs were the same for baseline comorbidities oand for models accounting for acquired comorbidity over the study follow-up
Sattar *et al.* 2012	The Study examines the influence of diabetes risk of death in diabetic patients in a hemodialysis study	823 diabetic patients in a hemodialysis study between March 1995 and October 2000	Index of Coexistent Disease (ICED), Index of Disease Severity (IDS), Index of Physical Severity (IPI)	Hazard Ratios, PH test (Schoenfeld Residuals)	Risk of death among diabetes patients in ESRD increase over time Time-Varying covariate model improves performance.
Granau *et al.* 2005	The study examines methods of risk adjustment in patients with AMI	4,874 patients >= 66 years of age who had an AMI in 1994 or 1995 followed for <=5-years	Ontario AMI prediction Rule (OAMIPR), D'Hoore adaptation of the Charlson Comorbidity Index, Total number of distinct comorbidities	Logistic Regression, C-statistic and R^2	The AMI specific Comorbidities adjustment model, OAIMIPR out performed the CCI. Both comorbidity indexes showed that emerging comobidities over time contribute to risk prediction
Porta *et al.* 2011	The study examined the prognostic impact of comorbidity adjustment aimed at improving risk assessment using baseline vs. time dependent assessments.	840 patients diagnosed with myelodysplastic syndrome. 540 patients used as a validation cohort.	Myelodysplastic syndrome comorbidity index (MDS-CI), WHO-Classification Based Prognostic Scoring System(WPSS)	HRs, LR and AIC, comparing model's goodness of fit and complexity	Comorbidities had a significant impact patient risk stratification. Time dependent assessment did not show improvement over baseline models.
Chang *et al.* 2010	To evaluate clinical characteristics of patients on hemodialysis. To determine if accounting for updated comorbidity assessment over time yields an improved association with mortality over baseline comorbidity alone	1846 Hemodialysis patients between 18 years of age and 80 years of age enrolled between March 1995 and October 2000 and followed for a median of 2.5 years.	Index of Coexistent Disease (ICED), Index of Disease Severity (IDS), Index of Physical Severity (IPI)	Hazard Ratios, X^2,	Updated assessment of comorbidity predictive model ability in Hemodialysis

Chapter Three: METHODS

3.1 Study Design and Period

We used a survival analysis design to understand the impact of Charlson comorbidities used as TVC in predicting mortality in Alberta patients with newly diagnosed hypertension. Patients with newly diagnosed hypertension were selected as a subset of a previous national study and were identified for a 12-year period between April 1 1997 and March 31 2009, and having at least one year of comorbidity data. Hypertensive patients that we identified with an index date between April1 1994 and March 31 1997, three years prior to the beginning of the study, or 30 days following the diagnosis of hypertension were considered to be part of the washout period and were excluded from the study.

3.2 Data Sources and Linkages

We linked Alberta's administrative healthcare data sources using an anonymous unique person identifier using methods previously described (Quan, 2013). Administrative databases used in the study included: (1) Hospital discharge abstracts (DAD), (2) Provincial health care insurance registry, Alberta Health Care Insurance Plan (AHCIP), (3) Physician billing claims, and (4) Vital Statistics.

3.2.1 Alberta Health Care Insurance Plan

The AHCIP is used for demographic information including personal health number (PHN), date of birth, sex, postal code and address for all Albertans residents. The AHCIP is administered and funded by Alberta Health (AH) and provides coverage for insured hospital and physician services for new and returning Alberta residents. The registry did not include

individuals who are not eligible for the AHCIP. This includes members of the Royal Canadian Mounted Police, armed forces, expatriates, visitors, travelers and inmates. AHCIP is one of two data source used for population counts. This is relevant and insures that researchers know that underlying patient population tables are reliable and reconcilable to one another. Combining AHCIP registry data with census data is supported by a 2009 Alberta Health (AH) study. AH conducted a systematic comparison of AHCIP and census to investigate potential differences between datasets. The study concluded that there was only 0.1 percent difference in population counts and differences became larger when smaller sub-populations were compared. Comparison of age and sex groups in total population yielded difference of less than 2 percent. The study found that the AHCIP registry had higher population counts for children and lower counts for seniors compared with census. Possible reasons for the difference included differences in inclusion criteria, geographical assignment interprovincial migration and uninsured populations (Alberta Health and Wellness, 2009). Residents could formally opt out of the AHCIP (www.health.alberta.ca/AHCIP). In 2012, 216 out of 3.9 million, <1% of Albertans chose to opt out (Alberta Health 2011-2012)

The AHCIP dataset was used to identify patients 18 years of age and older enrolled in the plan between April 1 1997 and March 31, 2009. The identified population was linked to Physician Claims, DAD and Vital Statistics databases using PHN (Li, 2006).

3.2.2 Alberta Postal Code File

The analysis of health data involves the use of geographic areas and boundaries. The Alberta postal code file includes a mapping of all Alberta based geographies including census divisions, census subdivisions, counties, health regions, Regional health authorities (RHAs) and Dissemination Areas (DAs). Canada Post provides these data to AH who in turn makes this data available to Alberta Health Services (AHS) and other partners.

We used the postal code file to link Alberta residents to the 2006 Canadian census dissemination area (DAs). Patient socio-economic status was derived using median household income as a proxy assigning patients with postal codes within a specific DA. Given that individual level income varies within the geographic area, assigning a median household income to each individual within a DA raises concerns over ecological fallacy. Ecological fallacy is an associations or interpretation of statistics applied to individuals when those associations or interpretations were developed based on the group to which those individuals belong. Studies have looked at comparison between household income and individual income and found that a decline in household income was associated with a progressive decline in survival, but did not find the trend when individual income was used (Southern, 2006). However, other studies showed an ongoing association between mortality and median household income, supporting the use of median income as a valuable proxy for socio-economic status (Southern, 2005)

3.2.3 Physician Claims

The Physician Claims data set is collected as part of a routinely submitted fee-for-service physicians remuneration system to the AHCIP. The data collected includes information on

provider, patients and services. Providers submit up to 3 ICD-9 diagnosis codes for each patient visit. Alberta physicians submitted their services to Albertan residents who have registered under the AHCIP.

The validity and use of physician claims data in research has been called into question because of the introduction of alternative payment models. A recent study by Cunningham et al. compared the face validity of submitted claims by physicians remunerated under the fee for service (FFS) model, receiving reimbursement for submitting claims outlining delivered clinical services, as compared to Alternate Payment Plans (APP), where physicians received fix remuneration independent of the volume of services delivered. Physicians operating under the APP model that required them to submit shadow billings, not for reimbursement but to track services delivered, submitted less than half of the claims compared with their FFS counterparts. This raised the issue of data accuracy. Face validity was found to vary between reimbursement models, requiring policy to protect accurate data collection. The study concluded that physician claims data were valuable and supported health research, surveillance and the development of health care policy (Cunningham, 2014)

3.2.4 Discharge Abstract Database

The discharge abstract database contains all acute care inpatient visit information, from time of admission until discharge or death. Clinical visit information for all patients discharged from Alberta hospitals was abstracted and recorded. DAD includes administrative, clinical and diagnostic data, capturing up to 25 diagnoses, which are coded in ICD-9, ICD-9 Clinical Modification (ICD-9-CM) or after 2002, ICD-10 Clinical Modification (i.e. ICD-10-CA).

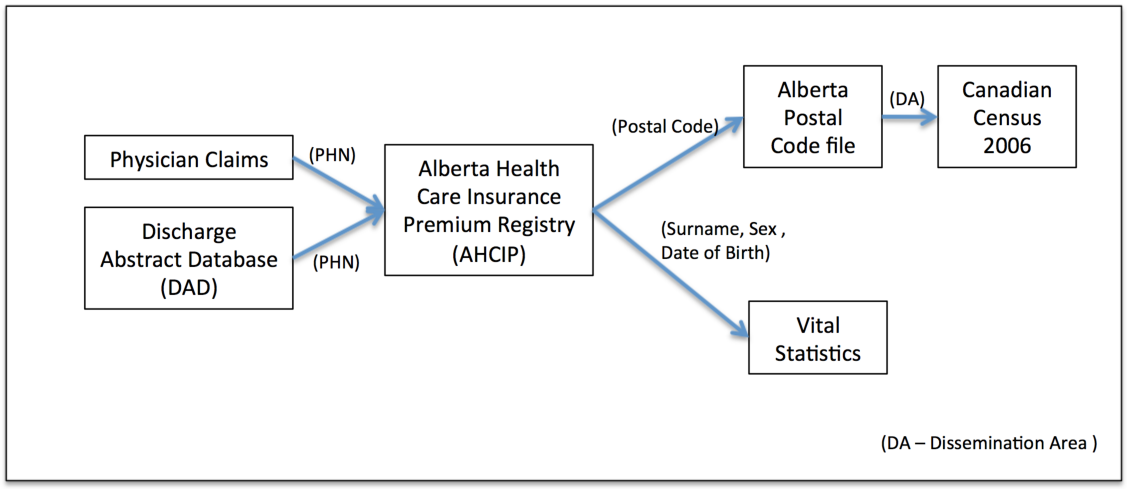
We used the DAD data in combinations with the physician claims data set to identify incident hypertensive patients as well as the onset of chronic conditions before and after the index hypertension date.

*3.2.5 **Alberta Vital Statistics File***

The vital statistics file is a registration of all vital events occurring in Alberta and includes a date and cause of death. All Alberta deaths are legally required to be registered and form a permanent legal record of death (http://www.servicealberta.ca/1148.cfm). Because registration of death is legally required for settling estate matters and legal burial or disposal of a body, the Alberta vital statistics file has a low error rate of <0.1% (Statistics Canada Vital Statistics, Death database) Abstracted health data was linked to vital statistics using a combination of surname, sex and date of birth (Li, 2006). Li et al. found high linkage rates between vital statistics and AHCIP and between Vital Statistics and the DAD, 96.9% and 98.9 respectively.

We linked Census data to all other administrative data sets using the AHCIP Alberta residential postal code. Alberta residential postal codes were linked to the Census data using Dissemination Area (DA), the smallest identified geographic area in the Canadian Census file.

Figure 3. Administrative data set and linkage relationships



3.3 Study Population

3.3.1 Inclusion Criteria

The study population is a subset of a larger national hypertension study using incident hypertension cases (Quan, 2013). The study included all adults who were residents of the Province of Alberta, were age 18 years and older, and registered in the AHCIP on April 1, 1997 (Figure 6). The AHCIP was linked with physician claims and DAD using PHN to identify newly diagnosed hypertensive Albertans using a validated ICD case definition (Quan, 2009). The previously defined case definition identified patients with 2 physician claims within 2 years or 1 hospital discharge within a 3-year observation period. The index hypertension diagnosis was considered to be the discharge date or the initial claim date, whichever was earliest. The case definition had a high specificity (95% to 97%) and but low sensitivity (66% to 72%), potentially under sampling low risk hypertensive patients (Quan, 2009). Cases were defined using both ICD-9 (401.x, 402.x, 403.x, 404.x or 405.x) and ICD10-CA (I10.x, I11.x, I12.x, I13.x or I15.x).

Newly diagnosed hypertensive patients between April 1 1997 and March 31 2009 having at least one year of comorbidity data were considered part of the study. However, hypertensive patients identified with an index date between April 1 1994 and March 31 1997 were part of the washout period. The washout period is the period leading up to the start of the study. Researchers use the washout period to identify prevalent hypertension cases to be excluded. This ensures consistency with the incident hypertensive case definition.

The case definition used to identify newly diagnosed hypertensive patients was based on a combination of DAD, and physician claims. The use of drug and blood pressure data while useful in identifying patients with hypertension was rarely available, systematically collected, or followed longitudinally. This selection strategy may have under-sampled low risk hypertensive patients. These patients may have been unaware of their condition, and less likely to seek and receive medical care, and be captured within one of the administrative data sets (Quan, 2013).

A subsequent study looking an alternative methods of identifying and reporting incidence and prevalence of hypertension, found that self-reported surveys such as the Canadian Community Health Survey (CCHS) underestimated hypertension prevalence (18% vs. 23 %). Although administrative data did not capture individuals who did not contact universal health care system, the sampling strategy of the CCHS survey, reported lower prevalence than administrative data (Quan, 2013; Quan, 2014). The lower hypertension prevalence was attributed by the lower likelihood of patient's response from patients in institutions. These people were the least healthy. The low prevalence was also related to recall bias and unawareness of hypertension

among patients who received blood pressure medication and perceived that they were not hypertensive.

3.3.2 Exclusion Criteria

We excluded patients from the study if they met any of the following criteria. 1) age less than 18 years 2) hypertensive patients diagnosed in the washout period (between April1 1994 and March 31 1997); 3) having myocardial infarction, heart failure or stroke during the 3 years leading up to the study or within 30 days following the diagnosis of hypertension; 4) died the same day that they were diagnosed with hypertension; 5) patients with less then 1-year of comorbidity data (Quan, 2013).

3.4 Study Variables

3.4.1 Dependent Variable

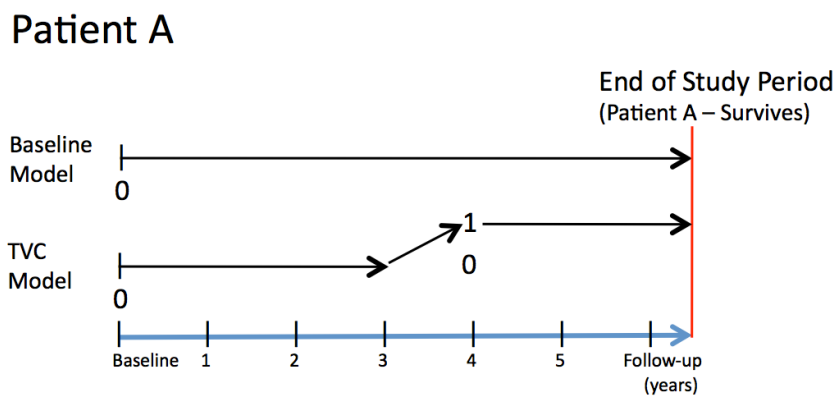
The outcome variable was all-cause mortality between April 1 1997 and March 31 2009. We followed patients from diagnosis until death or the end of the study (March 31 2009), which ever came first. Survival time was calculated as time between the initial hypertension diagnosis date and date of death and for censored patients, between diagnosis and loss to follow-up, withdrawal from the study or the end of the follow-up. Deaths were identified from Vital Statistics (Li, 2006).

3.4.2 Independent Variables

Our primary independent variables of interest were 17 Charlson comorbidities present at baseline and between April 1 1997 and March 31 2009. Comorbidities were derived from the physician claims, and DAD databases. We included age and sex from the provincial health insurance registry data. We assigned median household income quintiles (Q1 to Q5), a proxy for socioeconomic status, and rural or urban residential location based on their residential postal code, mapped to 2006 Statistics Canada Census data.

The onset of a patient's disease comorbidity was determined as the earliest date of diagnosis obtained from DAD and physician claims data following a patient's index of hypertension diagnosis date (see Appendix A, and B). If more than one record was identified for the same condition, we chose the first date of service as date of chronic condition. Survival time was the number of days between the initial hypertension diagnosis and the end of the study period (March 31 2010) or date of death, whichever came first. We used last observed carry forward (LOCF) for each comorbidity in our TVCMs. Once identified, each condition was considered ongoing (Wang, 2009).

Figure 4. Capture of disease comorbidity comparing baseline with time-varying covariate method.



The primary difference between baseline and TVCMs was that TVCMs enabled us to capture the onset of comorbidity along with time at risk in the period between diagnosis and the remainder of the study (Figure 4). Patient outcomes (death) were consistent between TIVM and TVCM while the assessment of comorbidity varied between models.

We included 17 comorbidities at baseline, coding each variable with a dichotomous status, present or absent, if identified within a year, prior to the initial hypertension diagnosis date. We captured time varying comorbidities as serial measurements for each patient. We divided each patient's follow-up period into a sequential series of time windows. Each time window started with the onset of a new chronic condition, and represented an increase in disease burden. Comorbidities were assumed to persist and were counted over the remaining study period from diagnosis or until death, whichever came first. Using a two-step process, we calculate the time-varying impact of each comorbidity on survival. First, a Cox analysis was carried out to calculate the hazard ratio for each follow-up time window. Then a single weighted average HR was calculated based on the series of shorter time windows (Figure 11).

Table 2. Four alternative methods of comorbidity adjustment used for regression models

Methods	Description (Number of Variables)
Individual Comorbidities	
1. 17 Individual Comorbidities	17 dichotomous variables Should we include all the conditions
Weighted Methods	
2.Original Charlson Weighting	One variable summary measure (0 to 24 maximum)
3. Updated Charlson Weighting	One variable summary measure (0 to 24 maximum)
Count of Conditions	
4. Count of up to 17 Conditions	One variable summary measure (0 to 17 conditions)

We used four methods to adjust for patient case-mix, for both baseline and TVCMs, using 17 individual comorbidities and 3 summary measures (Table2). We included individual weighted scores for each of 17 comorbidities assigned based on the original relative risk of 1-year mortality by Charlson et al. We also used an updated CCI proposed in a recent study (Quan, 2011). The study concluded that the original CCI should be updated to account for advances in chronic disease management and improvements in treatment and technology. Their study found that 12 comorbidities continued to be associated with 1-year mortality and proposed an updated summary score using 12 of the original 17 comorbidities to calculate an updated CCI yielding similar prognostic characteristics. We also used a count of Charlson comorbidities, while Fleishman et al. found this measure to be the least predictive of mortality, it is also the easiest to calculate and implement.

3.5 Ethical Approval

The Conjoint Health Research Ethics Boards of the University of Calgary (CHREB) approved the study.

3.6 Statistical Analysis

A 5% significance level ($p<0.05$) was considered statistically significant for all tests. Univariate and multivariate Cox regression analyses were performed using Stata/IC 12.1 for Mac (64-bit Intel), Revision 25 Nov 2013 Copyright 1985-2011 StataCorp LP

3.6.1 Descriptive Statistics

We performed and reported demographic and socio-economic characteristics of our newly diagnosed hypertensive patients. Our summary included mean age, sex, socio-economic status, area of residence, mortality rate, median years of follow-up, and all-cause mortality.

3.6.2 Univariate Analysis

Univariate analysis was carried out using both the K-M survival estimates and Cox regression to determine the difference in median survival between two or more groups for each categorical covariate. We reported median survival time and association with mortality for each Charlson comorbidity. Our univariate analysis could not report median survival time for eight comorbidities. This indicated that half of the patients were still alive at the end of the study and that alone these comorbidities did not materially impact patient survival unless present in combination with other comorbidities. Continuous variables such as age were converted into groups. Statistically significant differences in the survival estimates were determined using the log-rank test p-values ($p<0.05$).

3.6.3 Multivariate Analysis

Using the findings of the univariate analyses we determined independent variables that were included in our multivariate Cox regression models. The univariate and multivariate Cox proportional hazard models were used to calculate unadjusted hazard ratios (HR) and adjusted hazard ratios (aHR) respectively, including 95% Confidence Intervals (95% CI) for baseline and TVCMs. Each model used 4 alternative methods adjusting for CCI, along with controlling for other potential confounders, including age, sex, median household income, and area of residence. All models included all comorbidity variables regardless of significance to ensure consistency with other CCI studies.

Eight multivariate prognostic survival models were fit, 4 models using the traditional Cox regression, recording comorbidities at baseline, and 4 TVCM Cox regression models, which includes baseline comorbidity as well as changes in disease status in the remaining study period from diagnosis.

3.6.3.1 Time Invariant Baseline Cox Regression Models (TIVM)

Model 1: The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), individual Charlson comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hemiplegia or paraplegia, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, diabetes without chronic complications, diabetes with chronic complications, renal disease, any

malignancy, including leukemia and lymphoma, metastatic solid tumor, mild liver disease, moderate or severe liver disease, AIDS/HIV). All comorbidities were defined at the start of the study.

Model 2: The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), and original Charlson weighting. All comorbidities were defined at the start of the study.

Model 3: The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), and updated Charlson weighting. All comorbidities were defined at the start of the study.

Model 4: The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), and count of conditions at baseline. All comorbidities were defined at the start of the study.

3.6.3.2 Time Varying Covariate Models (TVCM)

Model 5: The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), and individual Charlson comorbidities. Comorbidities were identified throughout the study follow-up period. Once identified, each condition was assumed to persist in the remaining study period after diagnosis.

Model 6: The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), and original Charlson weighting. Comorbidities were identified throughout the study follow-up period. Once identified, each condition was assumed to persist in the remaining study period from diagnosis.

Model 7: The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), and updated Charlson weighting. Comorbidities were identified throughout the study follow-up period. Once identified, each condition was assumed to persist in the remaining study period from diagnosis.

Model 8:

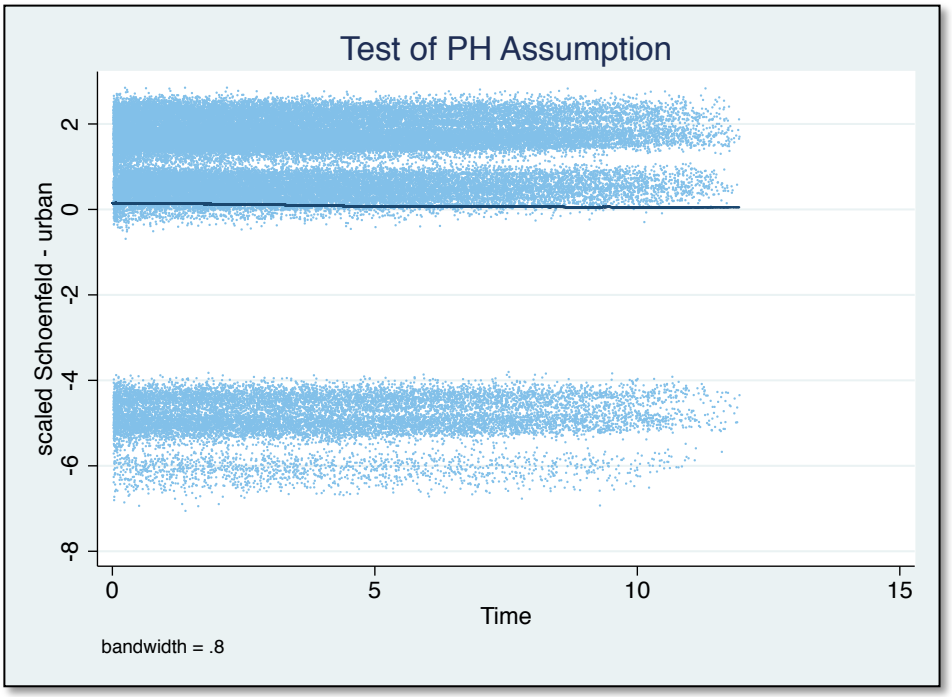
The dependent variable was time to event (years) and the independent variables were age (continuous), sex (male, female), median household income quintiles (q1 to q5), area of residence (rural, urban), and count of conditions at baseline. Comorbidities were identified throughout the study follow-up period. Once identified, each condition was assumed to persist in the remaining study period from diagnosis.

3.6.4 Assessment of Proportional Hazards

A typical assessment of proportional hazards would include both empirical and visual inspections. The Schoenfeld residuals can be interpreted as the observed minus the expected values of the covariates at each failure time (Figure 5). If residuals were random they would not exhibit a pattern at each failure time, indicating that there is no evidence that the covariate is changing with time; In other words it met the proportional hazard assumption (Hosmer and Lemeshow 1999).

Our assessment of the proportional hazards assumption had to consider our large study sample size, which would detect even very small slopes in the Schoenfeld residuals over time at a 5% two-side significance level. We pre-specified that the PH criterion would be met if the coefficients of the slope were within 0 ± 0.05. In sensitivity analyses we checked if the log-HRs differed by more than 10% when time was split in quarterly segment.

Figure 5. Assessment of Proportional hazards for a Covariate (Urban/ Rural) using Schoenfeld residuals



Chapter Four: Results

4.1 Study Population Characteristics

Descriptive statistics for all study variables included in (Table 3) show that newly diagnosed patients with hypertension (n=453,734) predominantly lived in an urban setting (80.7%) and 50.6% were male. The median age was 57.5 and 67.9% were younger than 65 years. There were 29,717(6.5%) patients with missing information on income quintile. The median follow-up time and interquartile range was 5.75 (5.74- 5.76) years, with an overall population mortality of 21.53% (95% CI 21.44 -21.62).

Figure 6. Study Population derivation for newly diagnosed Alberta hypertensive patients 18 years and older identified between April 1 1997 and March 31 2009.

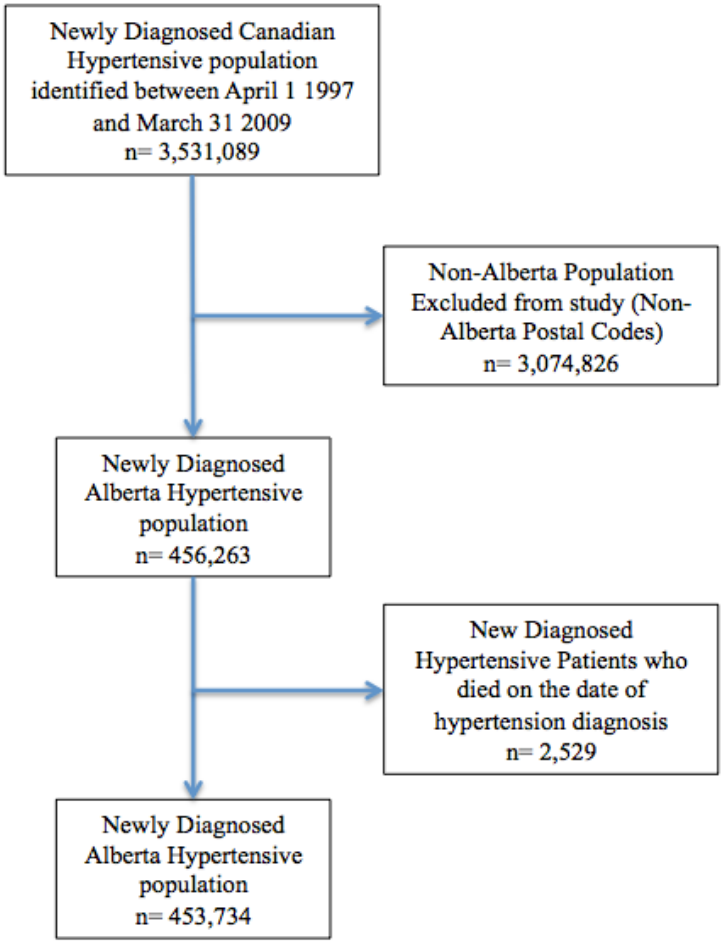


Table 3. Study population characteristics

	Number	(%)
Total Patients	453,734	100
Age, years		
20-49	139,110	30.6
50-64	168,998	37.2
65-74	81,930	18.1
75+	63,696	14.0
Mean (SD)	57.52(14.63)	
Median Income quintile		
1 (Lowest)	91,891	20.3
2	86,694	19.1
3	84,876	18.7
4	81,269	17.9
5 (Highest)	79,287	17.5
Missing	29,717	6.5
Total	453,734	100.0
Number of Charlson Comorbidities at baseline		
0	285,417	63.2
1-2	140,101	28.1
>=3	28,216	8.7
Total	453,734	100
Region of Residence		
Urban	366,226	80.7
Rural	86,253	19.0
Missing	1,255	0.3
Mortality Rate (%)	21.53 (21.44-21.62)	
Duration of Follow-up		
Median Years (IRQ)	5.75 (5.74-5.76)	

4.2 Disease prevalence at baseline and at the end of study period

We found the prevalence of Charlson Comorbidities differed substantially between baseline and the end of the study period (Table 4 and Table 5). The TIVMs underestimated the number of individuals with one or more Charlson comorbidities by 23.6% compared with TVCMs. At the end of study, disease prevalence for each comorbidity increased dramatically using the TVCM, ranging from 1.74 times (chronic obstructive pulmonary disease) to 3.81 times (metastatic solid tumors)(Table 4).

Table 4. Prevalence of 17 individual Charlson comorbidities at baseline and at the end of the study

	Baseline		At End of Study	
	n	(%)	n	(%)
Charlson Comorbidities				
Myocardial infarction	27,304	(6.02)	53,774	(11.85)
Congestive heart failure	26,041	(5.74)	60,426	(13.32)
Peripheral vascular disease	13,399	(2.95)	33,863	(7.46)
Cerebrovascular disease	23,881	(5.26)	56,297	(12.41)
Hemiplegia or paraplegia	3,738	(0.82)	8,536	(1.88)
Dementia	8,890	(1.96)	31,659	(6.98)
Chronic pulmonary disease	70,227	(15.48)	122,785	(27.06)
Rheumatologic disease	8,161	(1.80)	18,223	(4.02)
Peptic ulcer disease	11,674	(2.57)	27,142	(5.98)
Diabetes without chronic complications	31,098	(6.85)	58,389	(12.87)
Diabetes with chronic complications	7,503	(1.65)	23,390	(5.16)
Renal disease	10,231	(2.25)	34,560	(7.62)
Any malignancy, including leukemia and lymphoma	26,853	(5.92)	69,637	(15.35)
Metastatic solid tumor	4,784	(1.05)	18,231	(4.02)
Mild liver disease	6,524	(1.44)	16,860	(3.72)
Moderate or severe liver disease	968	(0.21)	2,782	(0.61)
AIDS/HIV	230	(0.05)	407	(0.09)

Table 5. Population distribution by number of Charlson comorbidities at baseline and at the end of the study period

Number of Charlson Comorbidities	Baseline		At End of Study	
	n	(%)	n	(%)
0	285,417	(63.2)	179,802	(39.6)
1-2	140,101	(28.1)	181,353	(40.0)
>=3	28,216	(8.7)	92,579	(20.4)
Total	453,734	(100)	453,734	(100)

4.3 Univariate Assessment of Median Survival

Univariate Cox Regression was used to determine the difference in median survival between categories of each independent variable. This allowed us to report median survival times for individual variables and their association with patient mortality (Table 6).

A non-reportable endpoint (NR) indicated a median survival time longer than the 12-year study follow-up for a given population.

Patient survival was affected by all 21 independent variables. However, only 10 comorbidities were able to report a median survival time. Comorbidities associated with the shortest median survival time included metastatic solid tumors (n=4784) with median survival time of 2.17 [1.97-2.39] years, dementia (n=8,890) with 3.67 [3.58-3.79] years median survival and moderate or sever liver disease (n=968) with median survival time of 4.10 [3.72-5.15] years. Comorbidities associated with increased mortality included hemiplegia and paraplegia 7.90 [7.51-8.43], renal disease 8.67 [8.34-9.08], cerebrovascular disease 9.84 [9.58-10.14], peripheral vascular disease 9.16 [8.80-9.44], malignancy 10.38 [10.00- 10.73].

Table 6. Univariate Cox regression reporting median survival time (years)

Variable	Number	Median Survival Time (95% CI)	P (log-rank)
Sex			
Male	229,553	NR [NR-NR]	<0.001
Female	224,181	NR [NR-NR]	
Age 65			
<65	145,626	NR [NR-NR]	<0.001
>=65	308,108		
Urban			
Urban	366,226	NR [NR-NR]	<0.001
Rural	86,253	NR [NR-NR]	
Median Income quintile			
1 (Lowest)	91,891	NR [NR-NR]	<0.001
2	86,694	NR [NR-NR]	
3	84,876	NR [NR-NR]	
4	81,269	NR [NR-NR]	
5 (Highest)	79,287	NR [NR-NR]	
Myocardial infarction			
Yes	27,304	NR [11.73-NR]	<0.001
No	426,430	NR [NR-NR]	
Congestive heart failure			
Yes	26,041	NR [NR-NR]	<0.001
No	427,693	NR [NR-NR]	
Peripheral vascular disease			
Yes	13,399	9.16[8.80-9.44]	<0.001
No	440,335	NR [NR-NR]	
Cerebrovascular disease			
Yes	23,881	9.84 [9.58-10.14]	<0.001
No	429,853	NR [NR-NR]	
Hemiplegia or paraplegia			
Yes	3,738	7.90 [7.51-8.43]	<0.001
No	449,996	NR [NR-NR]	
Dementia			
Yes	8,890	3.67 [3.58-3.79]	<0.001
No	444,844	NR [NR-NR]	
Chronic pulmonary disease			
Yes	70,227	NR [NR-NR]	<0.001
No	383,507	NR [NR-NR]	
Rheumatologic disease			
Yes	8,161	NR [NR-NR]	<0.001
No	445,573	NR [NR-NR]	

Table 6. Univariate Cox regression reporting median survival time (years) (Continued)

Variable	Number	Median Survival Time (95% CI)	P (log-rank)
Peptic ulcer disease			
Yes	11,674	NR [NR-NR]	<0.001
No	442,060	NR [NR-NR]	
Diabetes without chronic complications			
Yes	31,098	NR [NR-NR]	<0.001
No	422,636	NR [NR-NR]	
Diabetes with chronic complications			
Yes	7,503	NR [NR-NR]	<0.001
No	446,231	NR [NR-NR]	
Renal disease			
Yes	10,231	8.67 [8.34-9.08]	<0.001
No	443,503	NR [NR-NR]	
Any malignancy, including leukemia and lymphoma			
Yes	26,853	10.38 [10.00-10.73]	<0.001
No	426,881	NR [NR-NR]	
Metastatic solid tumor			
Yes	4,784	2.17 [1.97-2.39]	<0.001
No	448,950	NR [NR-NR]	
Mild liver disease			
Yes	6,524	NR [NR-NR]	<0.001
No	447,210	NR [NR-NR]	
Moderate or severe liver disease			
Yes	968	4.10 [3.72-5.15]	<0.001
No	452,766	NR [NR-NR]	
AIDS/HIV			
Yes	230	NR [NR-NR]	<0.001
No	453,504	NR [NR-NR]	

Figure 7. Kaplan-Meier Survival Estimates for patients with (0,1-2,3+) Chronic conditions based in baseline disease assessment.

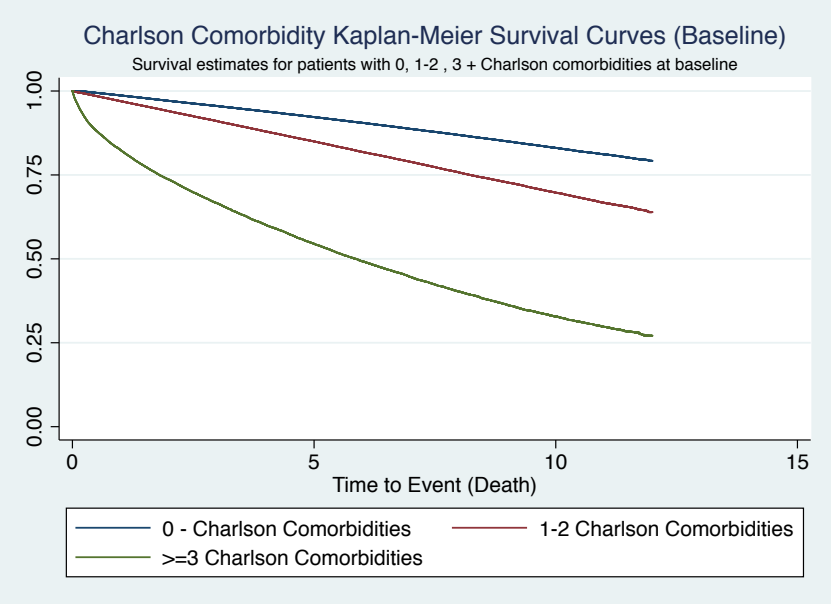


Figure 8. Kaplan-Meier Survival Estimates for patients with (0,1-2,3+) Chronic conditions based on disease assessment at the end of the study period.

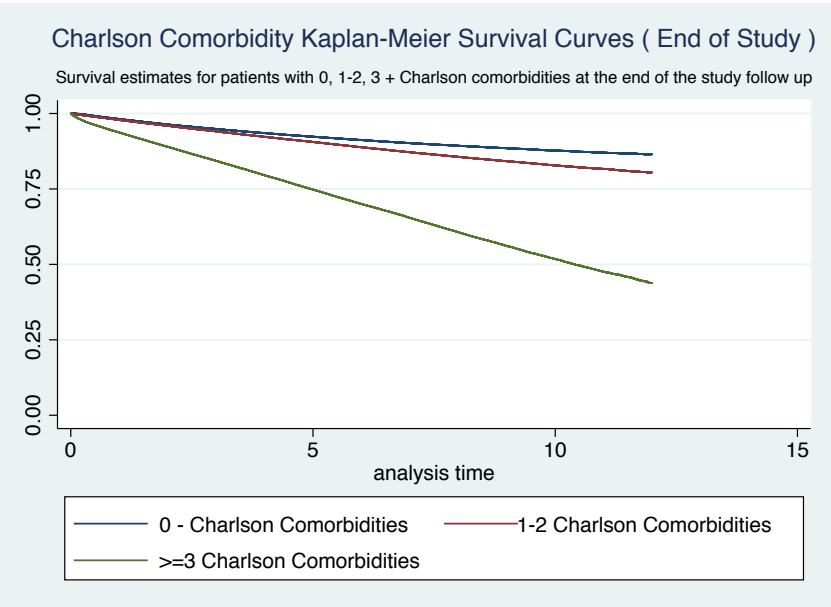
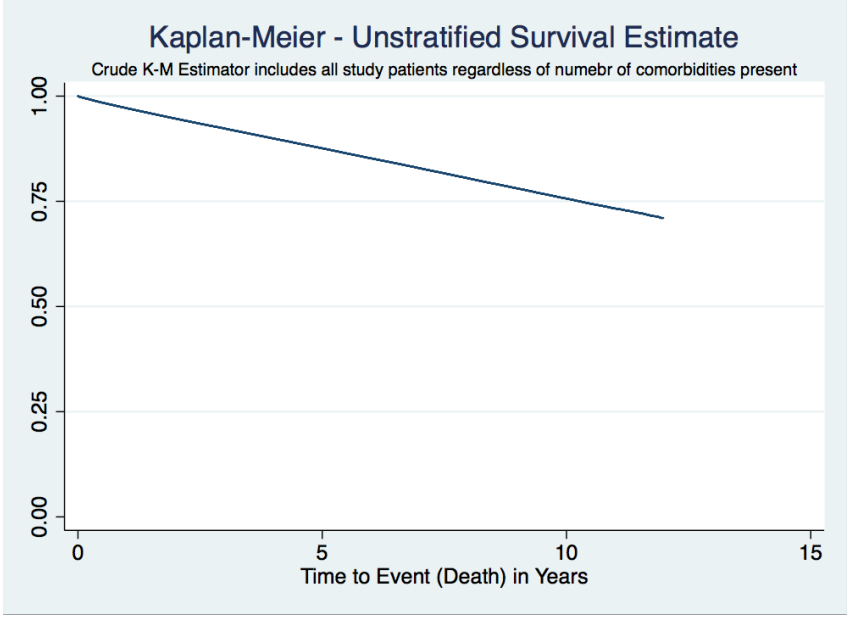


Figure 9. Unstratified Kaplan-Meier Survival Estimates for the entire study population



The association between each comorbidity and mortality varied substantially between baseline data and data in the remaining study period from diagnosis (Table 7). aHR estimates for 7 comorbidities increased from the baseline to TVCM, myocardial infarction, congestive heart failure, cerebrovascular disease, hemiplegia/paraplegia, mild or sever liver disease, cancer, metastatic solid tumors). Six comorbidities show decrease in the estimate of aHR indicating a potential reduction in the comorbidity contributions to mortality in the near term.

Table 7. Comparison of crude and adjusted hazard ratios between the baseline and TVCMs for all 17 individual Charlson comorbidities

	Baseline		TVCM	
	cHR* (95%CI)	**aHR** (95%CI)**	**cHR* (95%CI)**	**aHR**(95%CI)**
Sex (Male)	1.15 (1.14-1.17)	1.23 (1.22-1.26)	1.15 (1.14-1.17)	1.15 (1.14-1.17)
Age	1.05 (1.05-1.06)	1.04 (1.04-1.04)	1.06 (1.05-1.06)	1.03 (1.03-1.03)
Area of Residence				
Urban	1.01 (.99-1.03)	1.10 (1.08-1.12)	1.01 (.99-1.03)	1.09 (1.07-1.11)
Income Quintile				
(Compared to 1- Lowest)				
2	.88 (.86-.90)	.95 (.93-.98)	.88 (.86-.90)	.97 (.95-.99)
3	.81 (.79-.83)	.92 (.90-.94)	.81 (.79-.83)	.94 (.92-96)
4	.69 (.67-.71)	.86 (.85-.89)	.69 (.67-.71)	.91 (.88-.95)
5 – Highest Income Quintile	.65 (.63-.66)	.85 (.82-.87)	.65 (.63-.66)	.93 (.90-.95)
Charlson Comorbidities				
Myocardial infarction	2.2 (2.15-2.25)	1.07 (1.05-1.1)	2.89 (2.84-2.94)	1.2 (1.18-1.22)
Congestive heart failure	4.19 (4.11-4.27)	1.77 (1.73-1.81)	5.21 (5.13-5.29)	1.88 (1.84-1.92)
Peripheral vascular disease	2.99 (2.9-3.07)	1.24 (1.2-1.28)	3.31 (3.24-3.38)	1.16 (1.14-1.19)
Cerebrovascular disease	2.87 (2.8-2.93)	1.28 (1.24-1.31)	3.65 (3.59-3.72)	1.41 (1.38-1.43)
Hemiplegia or paraplegia	7.64 (7.43-7.85)	2.36 (2.29-2.43)	8.82 (8.66-8.98)	2.89 (2.83-2.95)
Dementia	1.88 (1.85-1.91)	1.31 (1.29-1.34)	2.16 (2.12-2.19)	1.3 (1.28-1.32)
Chronic pulmonary disease	1.69 (1.61-1.76)	1.18 (1.13-1.24)	1.62 (1.56-1.67)	1.03 (0.99-1.07)
Rheumatologic disease	1.67 (1.61-1.73)	1.1 (1.06-1.14)	2.02 (1.96-2.07)	1.1 (1.08-1.13)
Peptic ulcer disease	2.31 (2.21-2.42)	1.69 (1.6-1.78)	2.66 (2.58-2.74)	1.56 (1.51-1.62)
Diabetes without chronic complications	2.18 (2.13-2.23)	1.3 (1.27-1.33)	2.16 (2.12-2.2)	1.1 (1.07-1.12)
Diabetes with chronic complications	3.27 (3.14-3.4)	1.41 (1.35-1.48)	3.8 (3.71-3.9)	1.27 (1.23-1.31)
Renal disease	3.45 (3.28-3.62)	1.44 (1.36-1.52)	4.18 (4.04-4.33)	1.36 (1.31-1.41)
Any malignancy, including leukemia and lymphoma	3.52 (3.41-3.64)	1.63 (1.57-1.69)	4.78 (4.68-4.87)	1.72 (1.69-1.76)
Metastatic solid tumor	3.11 (3.04-3.18)	1.5 (1.47-1.54)	4.49 (4.42-4.57)	1.87 (1.83-1.90)
Mild liver disease	5.7 (5.23-6.21)	1.97 (1.79-2.17)	7.1 (6.73-7.49)	2.1 (1.98-2.23)
Moderate or severe liver disease	8.34 (8.04-8.65)	3.58 (3.43-3.73)	13.26 (12.99-13.53)	5.15 (5.03-5.28)
AIDS/HIV	1.86 (1.42-2.44)	1.72 (1.28-2.31)	2 (1.62-2.46)	1.65 (1.32-2.06)

**aHR - Adjusted Hazard Ratio-adjusted model included sex age area of residence and median household income

The statistical performance between 4 time invariant and 4 time dependent models is presented in Table 8. Generally, improved model performance is evident by increases in the LR score accompanied by a decrease in AICs scores.

A comparison of LRs for nested Cox regression models showed that models including all 17 Charlson comorbidities as individual covariates outperformed regression models using summary measures (Table 8). These results were consistent in nested model comparisons for

both TIVMs and TVCMs. Based on these findings; we compared the best TIVM and TVCM, which included all 17 Charlson comorbidities as individual covariates. The TVCM outperformed the baseline model achieving the highest LR = 112,941.72 and lowest AIC = 1,670,491 (Table 8).

Table 8. Comparison of model fit and performance between baseline and TVCMs using (Likelihood Ratio and AIC)

	Baseline		TVCM	
Modeling Methods	Likelihood Ratio	AIC	Likelihood Ratio	AIC
Individual Comorbidities				
1. 17 Individual Conditions (17 variables)	63,239.78	1,720,126	112,941.72	1,670,491
Weighting Method				
2. Original Charlson Weighting Method (one variable)	60,217.07	1,723,116	104,264.62	1,679,069
3. Updated Charlson Weighting Method (one variable)	58,723.42	1,724,610	106,169.71	1,677,164
Count of Conditions				
4. Count of up to 17 conditions (one variable)	58,674.36	1,724,769	91,986.08	1,691,347

Chapter Five: Discussion

Our study used a large number of hypertensive patients to compare survival model fit and performance between two methods of defining comorbidities, baseline and TVC. The TVC method captured changes in disease state in the time between hypertension diagnosis and the remainder of the study. We analyzed 475,345 newly diagnosed hypertension patients within 12 years in Alberta, Canada. Our study highlighted that the prevalence of comorbidities was much higher using TVC methods than baseline methods and TVCM performs slightly better than baseline method model.

The prevalence of Charlson comorbidities differed substantially between baseline and the conclusion of the study follow-up. Baseline models underestimated comorbidities by 23.6%. This was consistent with another study that evaluated different approaches to longitudinal comorbidity measurement (Wang, 2009). A possible reason includes additional diagnoses captured from visits over a longer follow-up period. We compared K-M survival curves between baseline and TVCMs to visually assess the effect of misclassification of patient comorbidities and raised awareness to potential errors in reporting.

Surprisingly, we did not notice a large difference in model fit and performance between baseline model and TVCMs even if occurrence of comorbidities in the study period was captured. This was related to length of study follow-up and the sensitivity of mortality as an outcomes measure among newly diagnosed hypertensive patients.

Hypertension is not a cause of mortality; rather, it is on a causal pathway. Hypertension is a leading risk factor for chronic conditions or medical events associated with mortality (Rapsomaniki, 2014). To capture mortality well from hypertension diagnosis, we need long term of follow-up. We used our non-stratified KM survival estimate to project a 20-year median survival time for study population (Figure 9). Combining this figure with median patient follow-up time of 5.75 years. We concluded that it would be difficult to capture mortality in a population living on average 14.25 years longer than the median patient follow-up time. These findings were supported by our literature review. We observed that studies with more stable, healthier populations were less likely to conclude dramatic improvements in model performance between TIVM and TVCMs, as compared to studies with high-risk patient populations. Future studies should consider a comparison of median patient follow-up time and median population survival time to determine the frequency and sensitivity of outcomes within the specific study population. This would allow us to consider model improvements in the context of similar study populations.

A possible alternative to increasing the length of the follow-up is to select outcome measures sensitive to change over shorter study follow-up periods; including measures such as patient satisfaction or patient related symptoms as outcomes. This highlights the importance of understanding the natural history and etiology of a disease and the need to consider the sensitivity of outcomes measures and length of study follow-up for specific study populations.

TVCM captured incremental changes in disease state over time based on the serial measurements method (Dekker, 2008)(Figure 11). Based on this we interpreted aHRs for TVCMs as the relatively short-term effects of the risk of death for patients with a specific comorbidity as compared to those without that comorbidity. aHRs for TVCMs are considered

short-term predictors of death as compared to baseline aHRs, which look at risk of death over the long term ignoring disease occurrence in the follow-up period (Figure10). Baseline survival models captured disease at a single point in time. As a result, the interpretations of aHRs for each chronic condition, collected at a single point in time, were attributed to the entire study period (Dekker, 2008). This allowed us to quantify the long-term effects of each condition on mortality over the entire 12-year study (Figure 10). TVCMs use an alternative method of calculating aHRs. We calculated a series of measures, breaking up the patient follow-up time into smaller time windows. The start of each time window coincides with the onset of each additional disease and represents an increase in risk (Figure 11). First, aHRs were calculated for each time window using a Cox regression analysis. Then a single weighted aHR for the entire study period is calculated using all the aHRs in the previous step. This allowed TVCMs to incorporate disease onset, changes in patient severity and exposure time, more accurately reflecting overall patient risk.

Our baseline model (Figure 7), showed that patients with 3 or more comorbidities had a median survival of over 5 years. Patients were then correctly classified using the count of chronic conditions from the end of the study. The net effect of reclassification was to increase the average number of comorbidities for each patient while patient survival time remained the same. As expected, the result of correctly classifying patients was seen in the increased median survival and visually confirmed by flatter survival curves (Figure 7 and Figure 8). Specifically, patients with 3 or more conditions, considered most sick, doubled their median survival time to over 10 years from the original baseline figure. This increase in median survival gave us further evidence that our 12-year study follow-up period was not a long enough to observe variation in mortality based on comorbidity. These findings have implications for existing and future studies using

baseline assessment of comorbidity and highlight how disease misclassification could lead to errors in reporting.

Comparison between individual and summary measures shows that predictive models adjusting for all 17 individual comorbidities outperformed models using summary measures. Literature shows mixed results. Austin et al. validated the performance and use of summary measures like the CCI and Elixhauser score as substitutes for the use of individual comorbidities (Austin 2013). Sundararajan et al reported that using individual comorbidities performed better than the CCI, while Lieffer et al. reported opposing results (Sundararjan 2007, Lieffer 2011). Ghali et al. suggested that summary measures calculated using study specific data had superior performance (Ghali, 1996). Acknowledging variation in the literature, case mix adjustment using summary scores continues to be important in research for studies with small sample sizes.

Figure 10. Long-term effects on baseline risk factors on mortality

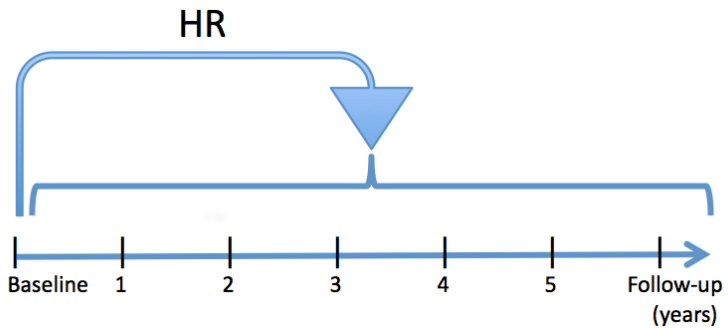
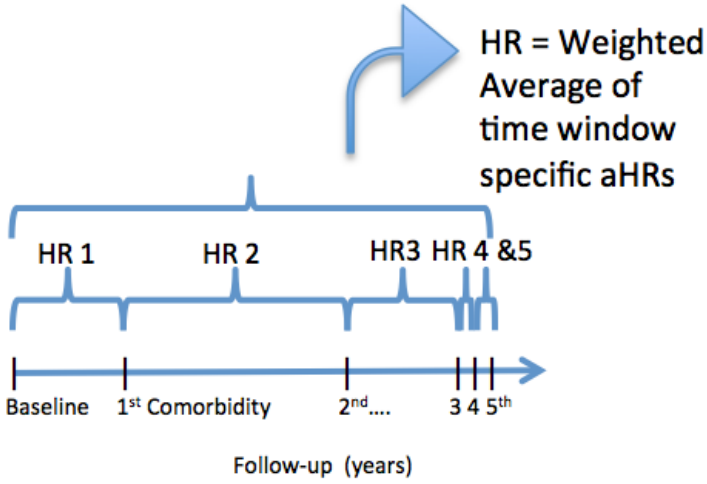


Figure 11. Effect of time-varying risk on Mortality (Dekker, 2008)



Our comparisons and interpretations of aHRs between models took into consideration the natural history and etiology of each of the 17 Charlson comorbidities. Comorbidities with higher aHRs in TVCMs compared to baseline were considered to have higher risk or mortality in the short-term verses the entire study follow-up. Consistent with this interpretation, the aHRs for hemiplagie or paraplegia (2.36(2.29-2.43), 2.89(2.83-2.95) baseline and TVCM respectively, were interpreted as a higher risk of death immediately following the onset of a disease or condition (Table 7). Supporting this interpretation, Divanoglou et al., reported that the highest mortality rate for hemiplagie or paraplegia was within the 1-year of injury, with a 1-year mortality of 18.8% (Divanoglou, 2010). Conversely, a higher COPD aHR in the baseline model could be interpreted as patients experiencing a lower risk of death over the short term, with increasing risk over time. Shah et al. demonstrated that the natural history of COPD was slow to develop, with patients initially seeing minimal decline followed by an increased severity over the long-term.

Chapter Six: Limitations

Our study focused on a newly diagnosed hypertensive patient population, a relatively healthy population requiring a long-term follow-up to observe mortality as outcome. Patients with newly diagnosed hypertension were identified for a 12-year period between April 1 1997 and March 31 2009. Patients had a median follow-up time of 5.75 years, well short of median survival for most patients in the study (Median survival time of over 20 years). This resulted in poor capture of patient outcomes (death), contributing to limited improvements in model performance. Future research studies using mortality as a study outcome should focus on populations with a high risk of death. This would include patients with acute conditions or post intervention patient population where chronic disease burden is known to impact patient survival.

Use of administrative datasets may underestimate the identification of comorbidities in a relatively healthy, newly diagnosed hypertensive populations. Without blood pressure measurement, asymptomatic hypertensive patients may not seek primary or acute care, excluding them from our study.

Our study median follow-up period of 5.75 years was not long enough to capture mortality. Future studies should also consider a comparison of median follow-up time and median survival time for a given study population.

Chapter Seven: Conclusion

To the best of our knowledge this is the first large scale, population based Canadian study using administrative data investigating the onset of chronic disease over time and it's impact on predicting patient mortality. In an incident population of newly diagnosed hypertensive adults we were able to show that accounting for changes in patient comorbidity over time more accurately reflected a patient's health risk. This leads to slight improvement in predictive model fit and performance.

Future research may improve understanding and support for the use of TVCMs to determine the impact of chronic disease on patient survival/prognosis of disease through comparing 1) longer and shorter observation periods to determine the exact effect of length of study follow-up on HRs and 2) the use of alternative outcome variables that are more sensitive.

Chapter Eight: References

Abeysekera W, Sooriyarachchi R. Use of Schoenfeld's global test to test the proportional hazards assumption in the Cox proportional hazards model: an application to a clinical study 2009.

Ahern TP. Lash TL. Thwin SS. Silliman RA.,Impact of acquired comorbidities on all-cause mortality rates among older breast cancer survivors.Medical Care. 47(1):73-9, 2009 Jan.

Alberta Health and Wellness, Comparison of Alberta Population Counts Between the AHCIP Registry and the 2006 Census, December 2009

Alberta Health and Wellness AHCIP Statistical Supplement 2011 – 2012, http://www.health.alberta.ca/documents/AHCIP-Stats-Supplement-12.pdf

Alberta Health and Wellness Insurance Plan AHCIP
http://www.health.alberta.ca/health-care-insurance-plan.html

Alberta Health and Wellness Health Data sets
http://www.health.alberta.ca/documents/Research-Health-Datasets.pdf

Austin SR[1], Wong YN, Uzzo RG, Beck JR, Egleston BL,Why Summary Comorbidity Measures Such As the Charlson Comorbidity Index and Elixhauser Score Work.,Med Care. 2013 May 23.

Canadian Institute Of Health Information
http://www.cihi.ca/CIHI-ext portal/pdf/internet/NACRS_DATA_ELEMENTS_2012_13_EN\

Chang TI, Paik J, Greene T, Miskulin DC, Chertow GM. Updated comorbidity assessments and outcomes in prevalent hemodialysis patients. Hemodialysis International 2010;14:478–85.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987; 40:373–383.

Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of Clinical Epidemiology 1994;47:1245–51.

Charlson ME, Sax FL, MacKenzie CR, Fields SD, Braham RL, Douglas RG. Assessing illness severity: does clinical judgment work? J Chronic Dis 1986;39:439–52.

Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. Diabetes Research and Clinical Practice 2010;89:189–95.

Christensen, Johansen M, Christiansen C, Jensen, Lemeshow. Comparison of Charlson comorbidity index with SAPS and APACHE scores for prediction of mortality following intensive care. Clep 2011:203.

Cunningham CT, Cai P, Topps D, Svenson LW, Jetté N, Quan H. Mining rich health data from Canadian physician claims: features and face validity. BMC Res Notes 2014;7:682–2.

Degroot V, Beckerman H, Lankhorst G, Bouter L. How to measure comorbiditya critical review of available methods. Journal of Clinical Epidemiology 2003;56:221–9.

Dekker FW, de Mutsert R, van Dijk PC, Zoccali C, Jager KJ. Survival analysis: time-dependent effects and time-varying risk factors. Kidney Int 2008;74:994–7.

Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45:613–619.

Divanoglou A, Westgren N, Seiger A, Hulting C, Levi R. Late mortality during the first year after acute traumatic spinal cord injury: a prospective, population-based study. J Spinal Cord Med 2010;33:117–27.

D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol. 1996;49:1429–1433.

D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. Methods Inf Med. 1993;32: 382–387.

Finlayson TL, Moyer CA, Sonnad SS. Assessing symptoms, disease severity, and quality of life in the clinical context: a theoretical framework. Am J Manag Care 2004;10:336–44.

Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. Annu Rev Public Health 1999;20:145–57.

Gao D, Grunwald GK, Rumsfeld JS, Schooley L, MacKenzie T, Shroyer ALW. Time-Varying Risk Factors for Long-Term Mortality After Coronary Artery Bypass Graft Surgery. The Annals of Thoracic Surgery 2006;81:793–9.

Ghali WA, Hall RE, Rosen AK, et al. Searching for an improved clinical comorbidity index for use with ICD-9-CM administrative data. J Clin Epidemiol. 1996;49:273–278.

Giolo SR, Krieger JE, Mansur AJ, Pereira AC. Survival Analysis of Patients with Heart Failure: Implications of Time-Varying Regression Effects in Modeling Mortality. PLoS ONE 2012;7:e37392.

Greenfield S. Sullivan L. Silliman RA. Dukes K. Kaplan SH. ,Principles and practice of case mix adjustment: applications to end-stage renal disease. ,American Journal of Kidney Diseases. 24(2): 298-307, 1994 Aug.

Grosso G, di Francesco F, Vizzini G, Mistretta A, Pagano D, Echeverri GJ, et al. Association of

population and primary healthcare factors with hospital admission rates for chronic obstructive pulmonary disease in England: national cross-sectional study. Thorax 2011;66:191–6.

Grunau GL, Sheps S, Goldner EM, Ratner PA. Specific comorbidity risk adjustment was a better predictor of 5-year acute myocardial infarction mortality than general methods. Journal of Clinical Epidemiology 2006;59:274–80.

Kleinbaum David G., Mitchel Klein , Survival Analysis, A Self-Learning Text 3rd Edition, 2012

Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical Association Between Body Mass Index and Mortality in Men With CKD Not Yet on Dialysis. American Journal of Kidney Diseases 2007;49:581–91.

Lee, S. J., A. S. Go, K. Lindquist, D. Bertenthal, and K. E. Covinsky. 2008b. Chronic Conditions and Mortality Among the Oldest Old. American Journal of Public Health 98(7):1209–14.

Li B, Evans D, Faris P, Dean S, Quan H. Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. BMC Health Services Research 2008;8:12.

Li B, Quan H, Fong A, Lu M. Assessing record linkage between health care and Vital Statistics databases using deterministic methods. BMC Health Services Research 2006;6:48.

Lieffers JR, Baracos VE, Winget M, Fassbender K. A comparison of Charlson and Elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data. Cancer 2011;117:1957–65.

Nieto FJ, Coresh J. Prognostic Value of Blood Pressure Variability and Average Blood Pressure Levels in Patients With Hypertension and Diabetes. Diabetes Care 2013;36:S312–24.

Miskulin DC, Meyer KB, Martin AA, Fink NE, Coresh J, Powe NR, et al. Comorbidity and its change predict survival in incident dialysis patients. Am J Kidney Dis 2003;41:149–61.

Parati G, Ochoa JE, Salvi P, Lombardi C, Bilo G. Prognostic Value of Blood Pressure Variability and Average Blood Pressure Levels in Patients With Hypertension and Diabetes. Diabetes Care 2013;36:S312–24.

Perkins AJ, Kroenke K, Unützer J, Katon W, Williams JW, Hope C, et al. Common comorbidity scales were similar in their ability to predict health care costs and mortality. Journal of Clinical Epidemiology 2004;57:1040–8.

Porta Della MG, Malcovati L, Strupp C, Ambaglio I, Kuendgen A, Zipperer E, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. Haematologica 2011;96:441–9.

Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. Hypertension 2009;54:1423–8.

Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. American Journal of Epidemiology 2011;173:676–82.

Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, D Shah A, Denaxas S, et al. Blood pressure and incidence of twelve cardiovasculardiseases: lifetime risks, healthy life-years lost, andage-specific associations in 1·25 million people. The Lancet 2014;383:1899–911.

Reid RJ, Roos NP, MacWilliam L, Frohlich N, Black C. Assessing population health care need using a claims-based ACG morbidity measure: a validation analysis in the Province of Manitoba. Health Services Research 2002;37:1345–64.

Shah R, Kotloff R. Lung Transplantation for Obstructive Lung Diseases. Semin Respir Crit Care Med 2013;34:288–96.

Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Med Care 2012;50:1109–18.

Southern DA, Ghali WA, Faris PD, Norris CM, Galbraith PD, Graham MM, et al. Misclassification of income quintiles derived from area-based measures. A comparison of enumeration area and forward sortation area. Can J Public Health 2002;93:465–9.

Southern DA, Faris PD, Knudtson ML, Ghali WA. Prognostic relevance of census-derived individual respondent incomes versus household incomes. Can J Public Health 2006:114–7.

Southern DA, McLaren L, Hawe P, Knudtson ML, Ghali WA, APPROACH Investigators. Individual-level and neighborhood-level income measures: agreement and association with outcomes in a cardiac disease cohort. Med Care 2005;43:1116–22.

Statistics Canada (http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3233).

Stukenborg GJ, Wagner DP, Connors AF. Comparison of the performance of two comorbidity measures, with and without information from prior hospitalizations. Med Care 2001;39:727–39.

Sundararajan V, Quan H, Halfon P, et al. Cross-National comparative performance of three versions of the ICD-10 Charlson Index. Med Care. 2007;45:1210–1215.

Tripepi G, Jager KJ, Dekker FW, Zoccali C. Statistical methods for the assessment of prognostic biomarkers(part II): calibration and re-classification. Nephrology Dialysis Transplantation 2010;25:1402–5.

Tripepi G, Jager KJ, Dekker FW, Zoccali C. Statistical methods for the assessment of prognostic biomarkers (Part I): Discrimination. Nephrology Dialysis Transplantation 2010;25:1399–401.

Wang CY, Baldwin L-M, Saver BG, Dobie SA, Green PK, Cai Y, et al. The contribution of longitudinal comorbidity measurements to survival analysis. Med Care 2009;47:813–21.

Wong J, Taljaard M, Forster AJ, Escobar GJ, van Walraven C. Journal of Evaluation in Clinical Practice 2012;19:351.

Appendix A. **ICD-9 Charlson Comorbidities**

Comorbidities	**ICD-10 Codes**
Myocardial infarction	410.x, 412.x
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4
Cerebrovascular disease	362.34, 430.x–438.x
Dementia	290.x, 294.1, 331.2
Chronic pulmonary disease	416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8
Rheumatic disease	446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x
Peptic ulcer disease	531.x–534.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Diabetes without chronic complication	250.0–250.3, 250.8, 250.9
Diabetes with chronic complication	250.4–250.7
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0–344.6, 344.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6
Moderate or severe liver disease	196.x–199.x
Metastatic solid tumor	042.x–044.x

Appendix B. **ICD-10 Charlson Comorbidities**

Comorbidities	**ICD-10 Codes**
Myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x--I69.x
Dementia	F00.x--F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40.x--J47.x, J60.x--J67.x, J68.4, J70.1, J70.3
Rheumatic disease	M05.x, M06.x, M31.5, M32.x--M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	K25.x--K28.x
Mild liver disease	B18.x, K70.0--K70.3, K70.9, K71.3--K71.5, K71.7, K73.x, K74.x, K76.0, K76.2--K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complication	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, El2.6, E12.8, El2.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complication	E10.2--E10.5, E10.7, E11.2, E11.5, E11.7, E12.2--E12.5, E12.7, E13.2--E13.5, E13.7, E14.2--E14.5, E14.7
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0--G83.4, G83.9
Renal disease	I12.0, I13.1, N03.2--N03.7, N05.2--N05.7, N18.x, N19.x, N25.0, Z49.0--Z49.2, Z94.0, Z99.2
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	C00.x--C26.x, C30.x--C34.x, C37.x--C41.x, C43.x, C45.x--C58.x, C60.x--C76.x, C81.x--C85.x, C88.x, C90.x--C97.x
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	C77.x--C80.x