PATTERNS AND PREDICTION OF COMPETING CAUSES OF MORTALITY IN OLDER ADULTS DIAGNOSED WITH INDOLENT NON-HODGKIN LYMPHOMA

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ABSTRACT

Laura L. Hester: Patterns and Prediction of Competing Causes of Mortality in Older Adults Diagnosed with Indolent Non-Hodgkin Lymphoma
(Under the direction Jennifer L. Lund)

Non-Hodgkin lymphoma (NHL) consists of heterogeneous hematological malignancies that are broadly categorized into aggressive or indolent tumor growth groups. In the past two decades, there have been notable increases in the proportion of NHL diagnoses aged ≥65 and cancer-specific survival with the aging US population and improvements in NHL treatments. These population changes have important implications for non-cancer mortality, particularly for indolent NHL subtypes, which display remitting-relapsing patterns and a slower progression. This dissertation sought to address gaps in knowledge about non-cancer mortality in NHL by providing foundational evidence on: 1) cancer-specific and non-cancer mortality patterns in NHL subtypes and 2) characteristics of indolent NHL patients at greatest risk of non-cancer mortality.

We identified adults aged ≥66 at diagnosis with a first, primary NHL diagnosis from 2004-2011 using a database linking the US Surveillance, Epidemiology, and End Results (SEER) cancer registry with Medicare health insurance claims.

Using death certificate data and Fine-Gray competing risks methods, Aim 1 estimated the 5-year cumulative incidence of NHL-specific and non-cancer mortality by prognostic factors (subtype, age, comorbidity level) in 26,809 NHL patients. Among aggressive subtypes, NHL-specific mortality exceeded non-cancer mortality across all ages and comorbidity levels. In indolent subtypes, non-cancer mortality was similar to or exceeded NHL-specific mortality for patients with older ages, higher comorbidity burdens,

or specific subtypes. The results support development of tools predicting non-cancer mortality in older indolent NHL patients.

In Aim 2, we developed and internally validated risk prediction models for short- and long-term mortality outcomes in 9789 indolent NHL patients. We created 16 elastic net penalized regression models predicting 1- and 5-year all-cause and non-cancer mortality (four models per outcome) in 100 randomly resampled training sets. In 100 validation sets, we compared average performance statistics of the elastic net to those from comorbidity score models. For all outcomes, the elastic net models had a higher discrimination and lower false-positive rate than comorbidity score models. However, differences were not statistically significantly.

This project supports development of personalized prediction models integrated into electronic medical records that can be used to inform physicians and patients on non-cancer mortality risk in treatment decision-making.

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LIST OF ABBREVIATIONS AND SYMBOLS

ADL-D	Dependence in Activities of Daily Living
AUC	Area under the (Receiver Operator) Curve
CEVD	Cerebrovascular disease
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CLL/SLL	Chronic lymphocytic leukemia/small lymphocytic lymphoma
CVD	Cardiovascular disease
DLBCL	Diffuse large B-cell lymphoma
DME	Durable Medical Equipment file
FDA	Food and Drug Administration
HCPCS	Health Care Procedure Classification Codes
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
IDI	Integrated Discrimination Improvement
INTERLYMPH	International Lymphoma Epidemiology Consortium
LP/WM	Lymphoplasmacytic lymphoma/Waldenström's macroglobinemia
MCL	Mantle cell lymphoma
MEDPAR	Medicare Provider and Analysis Review file
MSE	Mean squared error
MSPE	Mean squared prediction error
MZL	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network

NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NRI	Net Reclassification Improvement
OUTSAF	Outpatient Hospital Services file
PEDSF	Patient Entitlement and Diagnosis Summary File
PTCL	Peripheral T-cell lymphoma
PVD	Peripheral vascular disease
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
SEER	Surveillance, Epidemiology and End Results
WHO	World Health Organization

CHAPTER 1: STUDY OBJECTIVE, SPECIFIC AIMS AND RATIONALE

In the first five years after diagnosis with cancer, individuals can experience one of three outcomes: death from cancer, death from a cause other than cancer, or survival. The probability of experiencing each of these outcomes is partially determined by the individual's physiological condition at diagnosis. Individuals with pre-existing comorbid conditions or frailty at cancer diagnosis have a higher risk of dying from a non-cancer cause than those without these conditions, even after considering age, sex, and cancer stage.[1-5] Non-cancer mortality is particularly a concern among older adults because they have a higher burden of comorbidities and frailty at diagnosis than their younger counterparts. When making first-line treatment decisions for older adults, the benefits of a cancer treatment should be weighed against a patient's underlying non-cancer prognosis. As the US cancer population ages and the proportion of cancer patients diagnosed at age $\geq$65 increases,[6] we can make more informed treatment decisions in older patients with cancer by understanding their patterns of non-cancer mortality and by developing more advanced tools for predicting non-cancer mortality risk.

Patients with indolent subtypes of non-Hodgkin lymphoma (NHL) have attributes that potentially place them at a higher risk of dying from causes other than their lymphoma than from the lymphoma itself. Indolent subtypes, which account for 57% of NHL,[7] are characterized by slow growth and remitting-relapsing patterns.[8,9] Advancements in treatment have increased lymphoma-specific survival.[10] The longer these patients live without dying of their NHL, the higher their risk of dying from a competing non-cancer cause. Repeated exposure to treatment for relapses may place older patients with indolent NHL at a higher risk of experiencing comorbidity exacerbations, lapses in appropriate

comorbidity management, or adverse non-cancer events than patients with more aggressive subtypes.

Although individuals diagnosed with indolent NHLs have characteristics that place them at a higher risk of non-cancer mortality, limited information is available on 1) *how* the risk of death from non-cancer causes compares to death from cancer in these subtypes, 2) *when* non-cancer risk is greatest after diagnosis for each subtype, or 3) *who* is most at risk of dying from competing non-cancer causes. Traditional comorbidity scores have been suggested as a tool for identifying who is at risk for non-cancer deaths, which can aid treatment decisions.[11] However, these simple scores have multiple limitations that potentially decrease their utility for the indolent NHL population. Notably, the scores were developed in populations that may not reflect the indolent NHL population and use weights from models predicting less relevant short-term (1-year) mortality that do not account for potential interactions between comorbidities or frailty characteristics. Risk prediction models built in an indolent NHL population using machine learning methods could address these limitations and provide better identification of older patients with a high risk of non-cancer mortality for informing treatment decisions. Ultimately, by preventing non-cancer adverse events, an enhanced risk prediction tool could improve the quality of life and life expectancy among patients faced with slow-growing cancers.

The objective of the proposed research is 1) to provide evidence on patterns of cause-specific mortality in older adults with indolent and aggressive NHL subtypes and 2) to develop and internally validate models that address limitations of traditional comorbidity scores and provide better prediction of non-cancer mortality for older adults diagnosed with indolent NHL subtypes. We sought to achieve this objective through the following aims:

A. Specific Aim 1: Patterns of Non-Cancer Mortality by NHL Subtype

Aim 1 seeks to describe patterns of all-cause, cancer-specific, and non-cancer mortality by NHL subtype, age group, comorbidity level, histologic stage, and time since diagnosis in Medicare beneficiaries newly diagnosed with NHL at age ≥66 while living in SEER areas.

Aim 1 Rationale

Aim 1 will provide the first published estimates of the cumulative incidence of non-cancer mortality for older adults by NHL subtype. This analysis specifically seeks to provide evidence for the hypothesis that non-cancer mortality is a more substantial concern in indolent NHL subtypes than in aggressive subtypes. If true, these findings will support targeted interventions focused on care coordination and comorbidity management in indolent NHL. By providing stratified cumulative incidence estimates by age, comorbidity level and stage, we can identify the NHL patient subgroups that are most likely to benefit from these interventions. These estimates also support identification of patient subpopulations in which NHL treatment benefits should be weighed with the risk of mortality from non-cancer causes. In addition, our analytic approach will account for competing risks, and therefore, will provide realistic prognosis estimates acknowledging that patients can die of more than one cause at cancer diagnosis. By examining the patterns in the cumulative incidence of non-cancer mortality over time, we can identify when the risk of non-cancer mortality exceeds the risk of cancer-specific mortality and inform optimal timing of comorbidity interventions in the cancer care trajectory. Our analysis will provide a descriptive foundation for future development of prognosis tools that generate patient-specific estimates of cancer or non-cancer mortality based on a patient's tumor, age, race, gender, and other measures of health status.

B. Specific Aim 2: Predicting Non-Cancer Mortality in Indolent NHL

Aim 2 sought to use penalized regression methods to develop and internally validate a series of indolent NHL risk models predicting short- and long-term non-cancer mortality to improve upon traditional comorbidity scores.

Aim 2 Rationale

Aim 2 will contribute to the evidence base by providing the first population-based prevalence estimates of individual comorbidities at indolent NHL diagnosis. The goal of this aim is to develop a model that improves prediction of non-cancer mortality and could be used within clinical settings to inform risk-benefit decisions in cancer treatment selection.

Prediction of non-cancer mortality is important for informing indolent NHL treatment decisions. Conventional treatments for indolent NHL subtypes include chemotherapy combinations with rituximab. However, due to the slow growth of these malignancies, patients may not benefit from aggressive treatment until their symptoms arise and their disease progresses. In particular, aggressive treatment may not provide a benefit that outweighs the risk of a non-cancer death among patients with a poor non-cancer prognosis at diagnosis. Patient-level non-cancer risks can be used as one source of evidence when deciding whether to give an older patient a less-aggressive treatment, such as a watch-and-wait strategy or rituximab monotherapy, over more aggressive chemoimmunotherapies.

The risk prediction models developed in this aim seek to address limitations of traditional comorbidity scores, the current tools available for non-cancer risk stratification in treatment decisions. This aim will use advanced machine learning algorithms to select comorbidities that are most relevant for older patients with indolent NHL. In addition, this aim will assess how risk prediction changes when examining more long-term mortality outcomes (5 years) that are more relevant for slow-growing indolent NHLs than short-term mortality (1 year) assessed in traditional comorbidity scores. The model will also explore how risk prediction improves when assessing non-cancer mortality instead of using an all-

cause mortality outcome in which the influence of comorbidities and other non-cancer predictors may be diluted by the presence of cancer deaths. Despite the complex health profiles of many older adults that include both multimorbidity and frailty, traditional comorbidity scores do not account for the effect of co-occurring comorbidities or frailty. The risk models developed in this aim will address this gap by assessing comorbidity interactions and by adding claims-based indicators of frailty. The performance of the more complex machine learning risk scores will be compared with that of a traditional comorbidity score using discrimination, reclassification and calibration metrics.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

A. Older Adults and Cancer

Cancer was diagnosed in approximately 1.7 million US individuals and caused 589,430 deaths in 2015, making it the second deadliest disease in the nation and a major public health issue.[12] With the population from the baby boomer generation reaching older ages and 60% of cancer diagnoses among adults aged 65 and over, the proportion of new cancer diagnoses among older adults is increasing.[13,14] Simultaneously, advances in the effectiveness and safety of cancer treatments are allowing older adults to live longer after cancer diagnosis.[6] As a result, an estimated 75% of cancer survivors will be aged 65 and older by 2040. As the prevalence of older patients with cancer grows, research is needed to address the complex health needs that place older patients at a high risk of adverse outcomes, a poor quality-of-life, and early mortality during cancer care and survivorship.

B. Complex Non-Cancer Health Profiles in Older Adults at Cancer Diagnosis

At diagnosis with cancer, older adults are more likely than their younger counterparts to have one or more non-cancer conditions, called comorbidities, or syndromes that increase vulnerability to health stressors, called frailty.[15-18] An estimated 40% of US adults aged $\geq$66 with cancer have at least one pre-existing comorbidity.[5] This percentage increases with age, with up to 85% of adults aged 80 and older diagnosed with at least one pre-existing comorbidity.[18] Among the comorbidities managed by older adults with cancer, approximately half are considered moderate-to-severe, including diabetes, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF).

Frailty, a state of vulnerability that affects recovery after a stressing physiologic event, is another prevalent issue faced by older adults.[19-21] Comorbidities and disability

overlap with the frailty phenotype. An estimated 42% of older cancer patients are considered frail or pre-frail at cancer diagnosis.[22]

Frailty and comorbidities add complexity to cancer care and decision-making for older adults. Both cancer and its systemic treatments are significant stressors that can exacerbate existing comorbidities and lead to development of new comorbidities. They also can challenge a frail patient's physiological reserve to the point where a patient may not recover after treatment.[22] Ongoing treatment for comorbid conditions may result in drug interactions with chemotherapy. Characteristics of other diseases may also alter the pharmacokinetics and pharmacodynamics of chemotherapies and result in greater toxicities.[23] Hematologist/oncologists and patients have to consider whether the benefit of cancer treatment is worthwhile given the potential impact of treatment on a patient's quality of life or non-cancer prognosis.

Although the risk of having non-cancer conditions at cancer diagnosis generally increases with age, there is a large amount of heterogeneity in the prevalence and severity of these conditions in older adults across ages. At cancer diagnosis, an 88-year-old may have one comorbidity but otherwise display adequate physical functioning. In contrast, a 70-year-old may have three co-occurring severe comorbidities and be dependent on a wheelchair. Although age is an important predictor of cancer outcomes, simply making treatment decisions based on age may lead to undertreatment in older adults with less comorbidities and lower frailty and overtreatment in younger adults with more non-cancer conditions.[24] Treatment decisions that incorporate information on a patient's underlying non-cancer prognosis can lead to a higher quality of cancer care.

As the population of clinically complex older adults living with cancer increases, there is a critical need to identify how non-cancer conditions vary in the cancer population and how these patterns impact outcomes during cancer. Tools are also needed that can improve risk stratification of older patients with complex health profiles.

C. Effect of Non-Cancer Conditions on Cause-Specific Mortality

Multiple studies across different cancer sites suggest that frail older adults or those living with a high comorbidity burden at cancer diagnosis have a higher risk of early mortality compared to those without frailty or comorbidities.[1-4,17,25] Prior evidence suggests that non-cancer conditions are as important as stage in predicting all-cause mortality.[26] In order to understand why these conditions affect mortality and to develop the best informed interventions, it is important to first understand how these conditions separately influence cancer and non-cancer causes of death.

Cancer-Specific and Non-Cancer Mortality

After a cancer diagnosis, patients can 1) survive, 2) die of their first, primary cancer, called cancer-specific mortality, or 3) die of another cause (e.g. secondary malignancies, comorbidities, acute infections, treatment toxicities, accidents, and starvation), generally termed non-cancer mortality.[27] Cancer-specific mortality risk is a popular outcome measure used by hematologist/oncologists to decide how aggressively to treat cancer patients. This measure is also used by researchers and policy-makers to examine which interventions should be recommended for improving cancer outcomes.[28] Non-cancer mortality risk is not a common outcome used in the cancer epidemiology literature, but provides important information for identifying risks of cancer treatments and gaps in the care for non-cancer conditions.[27] The importance of studying non-cancer mortality has increased over the past two decades with the aging population and improvements in cancer prevention, screening, and treatment that have lengthened cancer-specific survival.[29]

Addressing Competing Risks in Prognosis Measures

Before estimating cause-specific mortality, such as non-cancer mortality or cancer-specific mortality, it is important to consider how competing risks will be addressed in the analysis. A competing risk is another outcome that precludes the patient from experiencing the outcome of interest.[30] For example, when assessing cancer-specific mortality, the

competing risk is death from a non-cancer cause. When assessing non-cancer mortality, the competing risk is death from cancer.

There are two ways that competing risks can be addressed when calculating mortality (or the inverse of mortality, survival).[31] "Net" measures of survival calculate the probability of surviving cancer in the absence of other causes of death, meaning that they censor the competing risk from the analysis. These measures include relative survival, which compares the proportion of observed survivors in a cancer cohort with the proportion of expected survivors in a comparable cohort without cancer. These measures also include cause-specific estimates calculated with Cox proportional hazards models, in which the competing risks are removed from the analysis. "Crude" probabilities of death, also called cumulative incidence functions in the statistical literature, are calculated using the Fine-Gray subdistribution hazards model or other statistical methods.[32] The subdistribution hazards model addresses inflation of cause-specific estimates by retaining individuals who have experienced a competing risk in the at-risk or survivor group.[33] **Figure 2.1** outlines the four methods for analyzing and addressing competing risks in cancer mortality or survival data.

Net measures that ignore competing risks are not influenced by changes in mortality, and therefore, are useful for tracking mortality (or survival) across time or making comparisons between groups.[31] Crude probabilities (or cumulative incidence functions) are better measures for communicating a patient's actual prognosis. This is because, at diagnosis, a patient will have a probability of dying of cancer, dying of a non-cancer cause or surviving over a set time period. By addressing competing risks, these three probabilities will add to 100%, but if competing risks are not addressed, as in the net measures, the probabilities may add to an unrealistic value >100%. Therefore, crude (or cumulative incidence) measures accounting for competing risks are the best measures to use when assessing patterns of cancer-specific and non-cancer mortality to understand prognosis patterns and identify risk groups.

Impact of Non-Cancer Conditions on Cause-Specific Mortality

Evidence from multiple cancer sites suggest that comorbidities affect both cancer-specific and non-cancer mortality among older adults. However, the impact of comorbidities on each of these outcomes occurs through different mechanisms.[4,34] Older adults who have comorbidities are less likely to receive curative or more aggressive treatments, which in turn increases their risk of cancer-specific mortality.[35-43] Cancer treatment may also exacerbate pre-existing comorbid conditions or cause new disease, affecting compliance to or continuation of subsequent rounds of cancer treatment and increasing the likelihood of a cancer death.[44-51] In turn, cancer care may impact appropriate comorbidity management[52-55] or exacerbate comorbidities,[56,57] resulting in increased risk for non-cancer mortality.

Frailty is also independently associated with increased all-cause mortality (5-year hazard ratio (HR) 1.87, 95% CI: 1.36–2.57).[22,58] Treatment complications are more frequent in those with frailty, including intolerance to cancer treatment (adjusted odds ratio 4.86, 95% CI 2.19–10.78).[22,48,59] Intolerance to chemotherapies can result in non-cancer mortality. Similar to comorbidities, patients with frailty can experience treatment complications that result in them being channeled away from or discontinuing more aggressive, effective treatment, potentially impacting their cancer-specific mortality.

The framework in **Figure 2.2** summarizes the evidence from the literature on the impact of comorbidity and frailty on cancer-specific and non-cancer mortality.

The effect of comorbidities and frailty on both cancer-specific and non-cancer mortality among older adults varies depending upon the individual's demographic, comorbidity, and tumor characteristics. Cancer site is one of the most important factors in the relationship between comorbidities and mortality since other moderating characteristics (e.g. average patient age, rate of progression, average stage at diagnosis, and treatments) vary according to cancer site.[5] Interventions focused on reducing deaths from competing causes adds a layer of complexity to cancer care for older adults. In order to maximize

resources for addressing the negative consequences of comorbidity on mortality, interventions should be prioritized for cancer sites in which patients have a higher risk of comorbidity, frailty, and non-cancer mortality.

D. Impact of Non-Cancer Conditions on Mortality in Indolent Non-Hodgkin Lymphoma (NHL)

Chronic Hematological Malignancies

Chronic hematologic malignancies are a growing group of relapsing-remitting cancers that have characteristics making them particularly important targets for comorbidity-related interventions.[8] With improvements in treatments, patients diagnosed with these malignancies are now living longer with their cancer. From 1999-2007, the 5-year cancer-specific relative survival for these cancers rose 10-20% among the three main chronic hematological cancers.[10,60] In the same period, the 5-year relative cancer-specific survival for all cancer sites only increased 3.8%. As cancer-specific survival increases, the prevalence of survivors living with these relapsing-remitting diseases is also increasing. Due to their slow-growth and relapsing-remitting disease, non-cancer mortality may be a particularly important issue for these increasingly prevalent malignancies.

Epidemiology of Indolent NHL

The most common chronic hematologic malignancy in the United States is indolent non-Hodgkin lymphoma (NHL).[61] Indolent NHL is also one of the 10 most prevalent cancers among older adults in the United States; approximately 1 in 173 US patients aged 65 years and older were living with indolent NHL in 2013.[61] The NHL subtypes considered to be indolent are follicular, marginal zone, chronic/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic lymphoma/Waldenström macroglubulinemia, and mycosis fungoides.[62] These indolent NHL subtypes compose 47% of NHL diagnoses and largely affect older adults, with an average age between 63 (follicular lymphoma) and 72 (lymphoplasmacytic lymphoma).[61]

As observed in other chronic hematologic malignancies, cancer-specific survival is high in indolent NHLs. In 2007, the 5-year relative cancer-specific survival for indolent NHL was 87%, which is higher than the 68% 5-year relative cancer-specific survival of aggressive NHLs.[63] It is estimated that the average survival among indolent NHL patients is now 15-20 years post-diagnosis due to the introduction of the anti-CD20 rituximab, the reintroduction of bendamustine, and improvements in bone marrow transplantation.[64]

Rationale for Studying Non-Cancer Mortality in Indolent NHL

Indolent NHLs have unique characteristics and exposures, which place them at a higher risk of a non-cancer death than patients with aggressive subtypes of NHL.[2,65] First, indolent NHLs are slow-growing. Evidence suggests that individuals with slower-progressing cancers have a lower likelihood of initially dying from their cancer.[66,67] Additionally, NHL-specific survival is lengthening as more effective first- and second-line treatments are being introduced. [68-70] The longer a patient lives without dying from their indolent NHL, the greater their risk of dying from comorbidities or having a poor response to a physiologic stressor.[71] In addition, there is evidence that individuals with indolent NHL have a lower overall and non-cancer survival than individuals without cancer.[72] For a 65-year-old indolent NHL patient diagnosed in 2007, the estimated 5-year non-cancer survival was 67.3% (95% CI: 66.4%-68.2%), which was significantly lower than the expected 5-year non-cancer survival of 82.0% in a population without cancer.[63] This evidence suggests that indolent NHL patients are at a greater risk of dying due to their comorbidities and frailty than the general population, warranting a greater focus on comorbidity management and supportive care in this population.

Indolent NHL patients also face continual relapses, which may contribute to a higher risk of non-cancer mortality compared to patients with aggressive NHL or the general population. Due to their recurring disease, patients with indolent subtypes face more treatment over their lifetime than cancer sites with a higher likelihood of cure, including

aggressive NHL subtypes.[65] Repeated exposure to chemotherapies may exacerbate existing comorbidities or stimulate development of new comorbidities, increasing the risk of non-cancer mortality.[73] In addition, comorbidities may become exacerbated after repeated exposure to toxic or invasive treatments, leading to discontinuation, or failure of effective cancer treatments.[42,74] Patients who are frail may not have the physiological reserves to recover after being exposed to chemotherapy stressors. Another negative side effect of relapses is that they require ongoing surveillance and retreatment, which consumes resources and time that would have otherwise been spent on comorbidity management.[75] Gaps in comorbidity management could lead to comorbidity exacerbations that result in non-cancer deaths. Finally, the burden of constant cancer care may prevent indolent NHL patients from connecting with healthcare providers other than their hematologist/oncologists, resulting in suboptimal comorbidity management.[52-54,76]

The average age at diagnosis of patients with indolent NHL is 69 years, setting this group apart from other cancers with a lower average age at diagnosis (e.g., breast: 62 years, prostate: 66 years).[61] With a greater number and severity of comorbidities among older patients than younger patients,[5,17,27] indolent NHLs are expected to have a greater burden of comorbidities and frailty at diagnosis, and thus, a greater risk of comorbidity-related death than other cancer sites. As the older population increases, so too will the risk of non-cancer mortality in this population. Therefore, non-cancer mortality will become increasingly important to consider when making indolent NHL treatment decisions and prioritizing which subpopulations should receive supportive care for comorbidities.

Gaps in Evidence on Non-Cancer Conditions and Mortality in Indolent NHL

Despite the unique risks for comorbidity exacerbations and non-cancer death faced by patients with indolent NHL, limited research has explored comorbidity or frailty patterns in this population. No studies have examined patterns of non-cancer mortality among these patients. One reason for these gaps is that population-based estimates of comorbidity and

frailty are not available in indolent NHL cohort studies. For example, the National Lymphocare Cohort of follicular lymphoma patients is largely representative of the US but does not collect comorbidity data at diagnosis.[77] The University of Iowa/Mayo Clinic NHL cohort collects data on select comorbidities but the population is not representative of the United States and has not yet published collected comorbidity data.[78] The InterLymph Non-Hodgkin Lymphoma Subtype Project, which pools case-control data from around the globe, focuses on risk factors for cancer diagnosis rather than clinical characteristics of patients at diagnosis.[79] The prevalence of comorbidity has not been reported in large, longitudinal clinical trials, which mostly exclude patients with higher comorbidity burdens and specific comorbidities, including renal disease, liver disease, HIV, and hepatitis B or C.[80,81]

Six studies have reported the comorbidity burden among indolent NHL patients, which are reported in **Table A1.1** in Appendix 1. Three studies conducted in the SEER-Medicare data reported the Charlson comorbidity score or NCI comorbidity score for indolent NHL subtypes; in these studies approximately 30-50% of patients had at least one comorbidity.[70,82-84] One population-level study has described comorbidity severity among indolent NHL patients (subtypes not specified) diagnosed from 1993-2004 in the Southern Netherlands Eindhoven Cancer Registry study,[85] finding that 34% of patients aged >60 had high-impact comorbidities (heart-related conditions, COPD, diabetes, and previous cancer). Another study in an Italian cancer center found that 85% of older indolent NHL patients (follicular, marginal zone, lymphoplasmacytic) diagnosed between 1990-2012 had one or more comorbidities, and 25% had a severe score on the Cumulative Illness Rating Scale-Geriatrics (CIRS-G).[86] However, no known studies have described patterns of individual and co-occurring comorbidities in indolent NHL or the impact of these comorbidity patterns on non-cancer mortality.

E. Identifying Risk of Non-Cancer Mortality in Older Adults with Indolent NHL

In order to prevent comorbidity exacerbations and early non-cancer deaths among older patients with indolent NHL, hematologist/oncologists need tools to identify who may be at risk of dying of a non-cancer cause. These tools can inform decisions on whether a treatment for indolent NHL is beneficial given a patient's underlying non-cancer prognosis.

Traditional Comorbidity Scores

A handful of tools are available for stratifying patients into risk groups according to their comorbidity. These include simple measures of comorbidity burden, including number of comorbidities or binary variables representing the presence or absence of a comorbidity.[4] Comorbidity scores provide a more complex method for calculating comorbidity and represent the number and impact of common comorbidities on an outcome (usually 1-year all-cause mortality) using a simple integer value. A comorbidity score is calculated by assigning an indicator variable to patients given the presence (1) or absence (0) of selected conditions, which is then weighted by an integer representing the rounded effect of the condition on an outcome.[87,88] Weights are summed across conditions for each patient to obtain a score.

The most widely used comorbidity scores are by Charlson et al.[89] and Elixhauser et al.[90] The Charlson comorbidity score was developed to predict 1-year mortality among patients admitted to an acute care hospital in the 1980s. The score assigns empirically derived weights to 17-19 investigator-defined, clinically important conditions. In contrast, the Elixhauser comorbidity score was developed to predict hospital discharges, length of stay, and in-hospital mortality using an inpatient population. The 30 conditions included in the Elixhauser were selected because they are considered to influence hospitalization but are not the primary reason for hospitalization. Multiple variants of these scores have been developed, including different ways to identify comorbidity codes in claims data.[91-95]

The comorbidities used in the Charlson and the Elixhauser comorbidity scores have minimal overlap, with important conditions potentially missing from either or both scores. For example, the Charlson focuses almost exclusively on chronic conditions, excluding acute conditions important for hospitalization risk and mortality. The Elixhauser score uses conditions listed as a secondary diagnosis at hospital discharge, which leads to the exclusion of many common causes of hospitalization and comorbidity burden among older adults, such as myocardial infarction. To address these differences, the combined comorbidity score was developed using a more contemporary, general older adult population from US Medicare claims and a subset of comorbidities from the Charlson and Elixhauser to predict 1-year all-cause mortality.[93]

Comorbidity indices can approximate a patient's risk of an outcome, usually short-term mortality and be used to identify patients who may respond poorly to more toxic treatments or who should receive more intensive comorbidity care during cancer treatment.[96] Another benefit of comorbidity scores is that they can be integrated into clinical treatment guidelines or prognostic indices and used to standardize treatment decisions for patients with comorbidities across physicians, clinics, and regions.[97]

Despite the simplicity and clinical utility of traditional comorbidity scores, these tools have limitations for predicting non-cancer mortality in older adults with indolent NHL. Prior studies have found that the comorbidities and weights in traditional comorbidity scores are not be the same as those identified in specific cancer populations.[98] This may also be true for the indolent NHL population, which may have a different comorbidity mix and outcome prevalence than the general Medicare population used to calculate the combined comorbidity score. Most traditional comorbidity scores were created to assess 1-year all-cause mortality. Short-term mortality may not be an applicable outcome for indolent NHL given the longer survival of these individuals. Due to these differences, important comorbidities may not be considered in the score calculation and weights may provide a

poor reflection of the given comorbidity's importance in the new population. Traditional comorbidity scores also consider each comorbidity to be an independent predictor of the mortality outcome. However, among older indolent NHL patients with multiple non-cancer conditions, the presence of one condition on a mortality outcome may modify the effect of another condition.[99,100] Prior research has found that interactions between comorbidities result in a higher predicted risk of short-term mortality.[99,101] Therefore, by including interactions between conditions in a risk prediction tool, we may improve prediction of non-cancer mortality. A final limitation of traditional comorbidity scores is that they do not consider frailty, and therefore, only capture a portion of predictors important for non-cancer mortality.

Building Risk Prediction Models with Machine Learning

Risk prediction models developed using machine learning can be used to address limitations of traditional comorbidity scores and offer a potentially improved prediction of mortality.[102] Machine learning is a branch of artificial intelligence in which computers employ statistical, probabilistic, and optimization techniques to learn about outcomes and hard-to-detect patterns.[103] Penalized regression is a type of machine learning method that applies a penalty to parametric regression methods, which shrinks less informative predictor coefficients towards zero.[102] This is a powerful method for balancing model bias and variance, and can be used in situations where overfitting may occur in regular situations due to large numbers of predictors (>10). These methods may be especially useful in creating risk prediction models from multiple non-cancer predictors and their interactions.

Importance of Predicting Risk of Non-Cancer Mortality

As we improve treatments for indolent NHL and other chronic hematologic malignancies and as the proportion of older adults in the indolent NHL population grows, we need to identify ways to improve the experience and outcomes of older patients during long-term management of their disease. This planning needs to start at diagnosis, when the

hematologist/oncologist is identifying the optimal treatments. Comorbidities and frailty may have a profound effect on the quality and length of these patients' life, and therefore, should be a key component considered in first-line treatment decisions.

Method of Analysis	Method of Addressing Competing Risks: Net	Method of Addressing Competing Risks: Crude
Cause of death (Kaplan-Meier)	Cause-specific survival	Crude probability of death using cause of death information
Expected life tables (Ederer I/II)	Relative survival	Crude probability of death using expected life tables

Figure 2.1 *Two-by-two table outlining the different methods for analyzing survival and mortality data which account for (crude methods) or do not account for (net methods) competing risks*

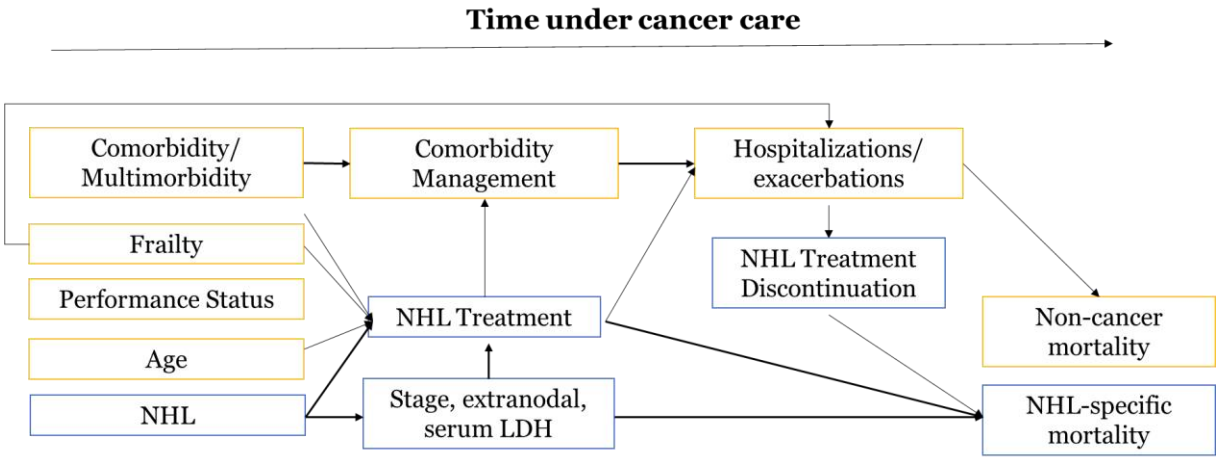

Figure 2.2 *Framework displaying the impact of comorbidities on cancer-specific and non-cancer mortality in chronic hematologic malignancies*

CHAPTER 3: METHODS

In this chapter, we describe the data source used for both aims 1 and 2. Then, we specifically describe the study populations and methods unique to each aim. For Aim 1, we used the Fine-Gray subdistribution hazards model to calculate the cancer-specific and non-cancer mortality risk by NHL subtype, age group, comorbidity level, stage, and time since diagnosis. For Aim 2, we used elastic net machine learning methods to conduct penalized logistic regressions predicting 1- and 5-year all-cause and non-cancer mortality. We compared the discrimination, reclassification, and calibration metrics from the resulting models to those from a model with the combined comorbidity index to assess how our models improved upon traditional comorbidity scores.

This research protocol was approved by the Institutional Review Board and the Office of Human Research Ethics at the University of North Carolina.

A. Data Source

For this analysis, we used data from the National Cancer Institute's (NCI) 18 US Surveillance, Epidemiology, and End Results (SEER) cancer registries linked with Medicare health insurance claims. SEER registries cover approximately 28% of the US and provide information on NHL diagnosis and mortality that are representative of those observed in the general US population, except for a slightly higher proportion of individuals from urban

areas or who were foreign born.[104] Medicare is a federally funded program providing health insurance to persons aged ≥65 that consists of Part A (hospital, skilled-nursing facility) and Part B (physician and outpatient services, durable medical equipment) fee-for-service coverage. Almost all (93%) Medicare beneficiaries are enrolled in either Part A or Part B.[105]

SEER-Medicare claims are organized into a series of files. The Patient Entitlement and Diagnosis Summary File (PEDSF) contains a record for each individual diagnosed in a SEER area who has been matched to Medicare claims. Approximately, 93% of older adults (age ≥65) in the PEDSF are matched to Medicare claims.[106] The PEDSF includes demographic, clinical, tumor, and census tract-level socioeconomic status data for each individual with an incident cancer diagnosis. The Medicare claims files include inpatient hospitalizations claims (MEDPAR), outpatient hospital services claims (OUTSAF), durable medical equipment claims (DME), and carrier claims. The MEDPAR claims file includes data on inpatient service dates, diagnoses, procedures, and injected agents, which are identified with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis and procedure codes. Similarly, the OUTSAF claims include ICD-9 CM diagnosis and procedure codes conducted in outpatient setting. The DME claims file contains HCPCS, which can be used to identify markers of frailty, including home hospital beds, home oxygen use, and wheelchair use. Carrier claims include ICD-9 CM diagnosis codes and HCPCS. Additional information about files used in SEER-Medicare can be found at the SEER-Medicare website (https://healthcaredelivery.cancer.gov/seermedicare/aboutdata/).

B. Methods for Aim 1

Study Population

The study selection flowchart for Aim 1 is provided in **Figure 3.1**. We identified patients aged ≥66 years at diagnosis with first, primary NHL between January 1, 2004 and December 31, 2011. Eligible patients were required to have continuous Medicare Parts A and

B and no managed care coverage for the 12 months before the diagnosis date (set to the first day of the diagnosis month). Our study started in 2004 after the 1997 FDA approval and dissemination of rituximab to ensure that most patients in the study population had a similar opportunity to experience survival advantages from this drug.[69,107] B- and T-cell NHL subtypes were defined using the International Lymphoma Epidemiology Consortium (InterLymph) categories[108] based on the 2008 World Health Organization (WHO) classification system for hematological and lymphoid tissue malignancies.[109] Using clinical expertise, we further excluded malignancies with unspecified/unknown subtypes that primarily affected non-lymphoid tissue or that occurred in precursor or plasma cells (lymphoblastic leukemia/lymphomas (ICD-O-3 9811-9818, 9837), plasma cell/myelomas (ICD-O-3 9731-9732, 9734, 9762), and precursor lymphomas (ICD-O-3 9724-9729, 9735). Patients aged <65 at Medicare enrollment (qualifying due to end-stage renal disease or disability) or diagnosed at autopsy or death were also excluded. See **Table A1.2** in Appendix 1 for histology codes.

Exposure Variables

We grouped NHL into indolent and aggressive subtypes based on clinical expertise and prior knowledge about survival.[85,110,111] Aggressive subtypes included diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL) and Burkitts lymphoma. Although subpopulations of mantle cell lymphoma have exhibited indolent tumor growth,[68] this subtype was categorized as aggressive since it displays an higher NHL-specific mortality than observed in typical indolent NHL.[112] Indolent subtypes included follicular lymphoma, marginal zone lymphoma (MALT extranodal, nodal, and splenic), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic/Waldenström macroglobulinemia, and mycosis fungoides. We removed Sezary syndrome due to small numbers preventing stable stratification.

For the cohort description, we assigned patients to an age group according to their age at diagnosis (60-74, 75-84, 85+ years). We also identified sex, race (white, black, Hispanic, other), and Ann Arbor cancer stage (I/II, III/IV) in the SEER data to further describe the population. The presence or absence of 16 comorbidities were identified in the 12 months before NHL diagnosis, and a Charlson comorbidity score was calculated using weights developed by Mariotto et al.[100] We used comorbidity categories from Cho et al. to stratify patients into no comorbidity, low or moderate comorbidity, and high comorbidity groups.[27]

Outcome Variables

We followed patients from NHL diagnosis until death or the end of follow-up on December 31, 2012. Deaths were identified using state death certificate data compiled by the National Center for Health Statistics and linked to SEER records.[113] We linked deaths to individuals with SEER data regardless of whether they died within or outside of a SEER registry.

Deaths were defined by major site groups on death certificates based on 3-digit ICD-10 codes. We used a definition of cancer death developed by the NCI that adjusts for potential misattribution of NHL-specific deaths by considering tumor site, origin, and order, as well as secondary malignancies and comorbidities that commonly occur with NHL (e.g. HIV/AIDS).[28] Any death not classified as a cancer death was considered a "non-cancer death."

Statistical Analysis

For each NHL subtype, we calculated cumulative risks of all-cause mortality as the complement of overall survival probabilities from Cox proportional hazards models. We used the Fine-Gray subdistribution hazards regression model[32] to estimate the cumulative incidence of NHL-specific and other-cause mortality by subtype, age and comorbidity level. The formula for the subdistribution hazards is presented in **Equation 3.1**.

$$\lambda_j(t) = \lim_{\Delta t \to 0} \left\{ \frac{P(t < T \leq t + \Delta t, J = j \,|T > t \ \cup (T < t \cap J \ \neq j))}{\Delta t} \right\}$$

Equation 3.1

Where t is the time point up to which the person has survived, $J = j$ indicates whether the event of interest or the competing risk is estimated. In continuous time, this model is estimating the probability of experiencing the event of interest j at time $T = t$ given that the person has survived to time t or that the person experienced the competing event ($J \ \neq j$) before time t.

The Fine-Gray subdistribution hazards model accounts for competing causes of death precluding patients from experiencing the event of interest. When calculating the cumulative incidence of NHL-specific mortality, NHL death was the event of interest, and death due to other causes was the competing event. For the cumulative incidence of other-cause mortality, deaths from causes other than NHL were the events of interest, and NHL death was the competing event. We calculated 95% confidence intervals for cumulative incidence estimates using bootstrapping with 1000 replicates.

We estimated 5-year cumulative incidence functions and cumulative incidence curves of NHL-specific and other-cause mortality for each subtype, age group, comorbidity level, and stage, which were graphed using stacked bar charts. We also developed stacked cumulative incidence curves to show change in cause-specific mortality risk over the five years post-diagnosis. The top of the stacked curves represented cumulative all-cause mortality. The area above the curves represented the overall survival probability at each time point after NHL diagnosis. Analyses were conducted using SAS 9.4 statistical software (SAS Inc., Cary, NC).

C. Methods for Aim 2

Study Population

The study selection flowchart for Aim 2 is provided in **Figure 3.2**. We required patients to be aged ≥66 years at diagnosis with a first, primary indolent NHL diagnosis from January 1, 2004 through December 31, 2011. Diagnosis was set to the first day of the diagnosis month. Patients were required to have continuous enrollment in Medicare Parts A and B without managed care coverage during the 12 months before indolent NHL diagnosis so that we could identify pre-existing comorbid conditions and frailty indicators. Patients aged <65 at Medicare enrollment (qualifying due to end-stage renal disease or disability) or diagnosed at autopsy or death were excluded. Patients were also excluded if they had zero months of follow-up and no date of death. The study period was selected to reflect a time period when all patients generally had the same opportunity to receive and experience survival advantages from the anti-CD20 biologic, rituximab.[69,107]

NHL subtypes were defined using the InterLymph[108] categories based on the 2008 WHO classification system for hematological and lymphoid tissue malignancies.[109] Using clinical expertise, we further restricted to indolent B-and T-cell subtypes, which were defined as those with a 5-year relative survival >70% that were not leukemias or plasma cell malignancies.[7,114] The final indolent subtypes in our analysis were follicular lymphoma, marginal zone lymphoma (MZL), lymphoplasmacytic/Waldenström's macroglobulinemia, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mycosis fungoides. See **Table A1.2** in Appendix 1 for histology codes.

Potential Predictors

Age and sex were included in all models. We defined age using 5-year age groups (66-69, 70-74, 75-79, 80-84, 85+). We also described the population by race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), subtype, and Ann Arbor cancer stage (I/II, III/IV). Only subtype was included in the final prediction model.

For each patient, we identified the presence or absence of 36 comorbidities in the 12 months before the patient's diagnosis using validated ICD-9- CM codes from Part A hospitalization, Part B physician/supplier, outpatient, and durable medical equipment claims data. To mirror comorbidity definitions used to create the combined comorbidity index, we included comorbidities from the Romano adaptation of the Charlson Comorbidity Index[89,91] and the Quan/van Walvaren adaptation of the Elixhauser Comorbidity Index.[90,92,115] When the same conditions were included in both scores, we chose the definition with more patients. We also identified comorbidities associated with NHL prognosis, including anxiety and hepatitis B and C using established ICD-9 diagnosis codes.[116] Finally, using ICD-9 diagnosis codes and HCPCS, we identified claims-based markers of frailty as defined by Faurot et al.[117] that had not been listed as a comorbidity in our analysis. These variables served as frailty proxies in our model.

Outcome Variable

Our outcomes of interest were 1- and 5-year all-cause and non-cancer mortality. The ICD-10 codes identifying cause of death were obtained by SEER from state death certificate data provided by the National Center for Health Statistics.[113] Deaths were captured through December 31, 2011, regardless of whether the death occurred within a SEER registry area.

One-year mortality enabled comparison of our model results with most traditional comorbidity scores. Death within 5 years represented long-term mortality, which is more relevant for indolent NHL. We developed models predicting both all-cause and non-cancer mortality to observe whether type of outcome changed the predictors and performance of our model. All-cause mortality was defined as death from any cause and is the most common outcome used to define traditional comorbidity scores. Indolent NHL-specific deaths were identified using the criteria established by the NCI,[27] which adjusts for potential misattribution of NHL-specific deaths by considering tumor site, tumor origin, tumor order,

secondary malignancies and comorbidities that commonly occur with NHL. Non-cancer deaths were defined as those not due to an indolent NHL.

Statistical Analysis

We described the demographic, cancer, comorbidity, and frailty characteristics of older patients with indolent NHL. Models assessing 1-year mortality included all eligible patients. Models assessing 5-year mortality only included individuals diagnosed from January 1, 2004 through December 31, 2007 to allow patients to have at least five years between their diagnosis and the end of follow-up during which mortality could be identified.

To address small sample sizes, we randomly resampled an 80% training set and a 20% validation set in each cohort 100 times using consecutive new seed values 1-100. In each training set, we fit five logistic regression models predicting 1- and 5-year all-cause and non-cancer mortality. **Table 3.1** describes each model. The first model included the combined comorbidity index, age group, and sex. This model was considered the comparison model since our goal was to assess how well our new prediction models improved upon traditional comorbidity scores. The second through the fifth models (Models A-D) each added a component addressing a limitation of traditional comorbidity scores.

Models A-D were developed using elastic net machine learning methods. The equation for the elastic net is presented in **Equation 3.2**. The elastic net applies two types of penalization, the L1-norm penalty and the L2-norm penalty. The L1-norm penalty ($\lambda_1 \sum_{j=1}^{p} |\beta_j|$) generates a sparse matrix in which most of the variables that are considered uninformative are shrunk to zero. However, if the L1-norm is used alone, then it will only select one variable out of a group of highly correlated variables and shrink the rest of the variable coefficients to zero. The strengths of the L1-norm penalty is that is allows for simultaneous selection from the large numbers of potential predictors and their interactions while shrinking those that are generally less informative towards zero (essentially removing them from the model).[118] This method balances model predictive ability and parsimony and

selects comorbidities that are most relevant to indolent NHL and to the outcome being assessed. The quadratic L2-norm part of the model ($\lambda_2 \sum_{j=1}^{p}|\beta_j|^2$) allows for a greater number of predictors to be selected and encourages a grouping effect, which retains or removes strongly correlated predictors from the model as a group. The grouping effect is important since many comorbidity and frailty predictors are collinear. Notably, the conditions commonly grouped as cardiovascular diseases are often correlated, including arrhythmias, congestive heart failure, hypertension, and valvular disease. We used 10-fold cross-validation to identify the tuning parameters of each penalty, λ_1 and λ_2, that minimized the mean square error.

$$\frac{1}{n}\sum_{i}^{n}\left(Y_i - m_\beta(X_i)\right)^2 + \lambda_2 \sum_{j=1}^{p}|\beta_j|^2 + \lambda_1 \sum_{j=1}^{p}|\beta_j|$$

Equation 3.2

In the first elastic net model (Model A), we included the age group, sex, and 36 non-cancer comorbidities from the Charlson and Elixhauser comorbidity scores (which were considered when developing the combined comorbidity index). The second elastic net model (Model B) added two-way interactions between the 10 most prevalent comorbidities in addition to age group, sex, and the 36 previously assessed comorbidities. The third elastic net model (Model C) included variables in Model B plus the 12 claims-based indicators of frailty. The final elastic net model (Model D) added indolent NHL subtypes to assess whether characteristics related to cancer prognosis were also predictive of non-cancer mortality.

We tested the five models in the 100 validation sets and calculated the average model coefficients, predicted probability of 1- and 5-year all-cause and non-cancer mortality, and performance metrics in the 100 resamples. The values at the 97.5 and 2.5 percentiles of the performance metric distributions from the 100 resamples were used to calculate 95% confidence intervals.

We assessed the ability of the five models to discriminate each mortality outcome using the area under the receiver operating characteristics curve, also known as the AUC. The receiver operating characteristics (ROC) curve assesses the change in the true positive rate (sensitivity) and the false positive rate (1-specificity) for various cut-points in the predicted probabilities. Changes in average AUC between each model were assessed.

We calculated the average continuous Net Reclassification Improvement (NRI) (also called the category-free net reclassification index) and the Integrated Discrimination Improvement (IDI) indices to compare true- and false-positive rates of the four elastic net models versus those of the combined comorbidity index model.[119,120]

The continuous NRI, shown in **Equation 3.3**, assesses the degree to which an index model (i.e., one of the four elastic net models) correctly reclassifies events and non-events versus a comparison model (i.e., the combined comorbidity index model). The purpose of the NRI is to assess whether a more effective model increases predicted risks for events and decreases predicted risks or risk categories for nonevents. It is not in itself a proportion but is composed of four proportions.

$$NRI = P(up|event) - P(down|event) + P(down|nonevent) - P(up|nonevent)$$

Equation 3.3

In equation 3.3, the P(up|event) represents the proportion of individuals who actually experience the event who are correctly shifted to a higher risk of the event in the elastic net model versus the combined comorbidity index model. When the models have the same classification, this value equals 0.50. P(down|event) is the proportion that are mistakenly shifted to a lower risk of the event in the elastic net model versus the comorbidity model. The difference in P(up|event) and the P(down|event) is the NRI_{event}, which is the net proportion of events assigned to a higher risk. Similarly, the P(down|nonevent) represents the proportion of individuals who actually do not experience the event who are correctly shifted to a lower risk of the event in the elastic net model versus the combined comorbidity

index model. The P(up|nonevent) is the proportion of non-events that are mistakenly shifted to a higher risk of the event in the elastic net model versus the comorbidity model. Again, a value of 0.5 for these proportions represents no difference. The difference in P(down|nonevent) and the P(up|nonevent) is the $NRI_{nonevent}$, which is the net proportion of nonevents assigned to a lower risk.

The IDI, shown in **Equation 3.4**, assesses the change in sensitivity minus the change in 1-specificity of the index versus the comparison model over all possible cutoff values for the predicted probabilities.

$$IDI = (\bar{\hat{p}}_{new,events} - \bar{\hat{p}}_{old,events}) - (\bar{\hat{p}}_{new,nonevents} - \bar{\hat{p}}_{old,nonevents})$$

Equation 3.4

In equation 3.3, $\bar{\hat{p}}$ is the average of the estimated probabilities for all individuals who are actual events (i.e. die in 1 or 5 years) or all individuals who are actual non-events (i.e. do not die in 1 or 5 years). In the case of this research, the new model is the elastic net model while the old model is the model with the combined comorbidity score. This value can also be interpreted as the difference in the change in sensitivity minus 1-specificity, which is the same as the difference in the discrimination slope between the elastic net and comorbidity score models.[121]

Finally, we assessed model fit using calibration plots. The calibration plots compared observed probabilities, which were binary mortality variables estimated as continuous values using locally-weighted smoothing (loess),[122] and predicted probabilities from each model.[123] Well-calibrated models follow the 45-degree line representing perfect alignment between the observed and predicted probabilities. All analyses were conducted using the *glmnet, pROC, rms*, and *ggplot2* packages in R.

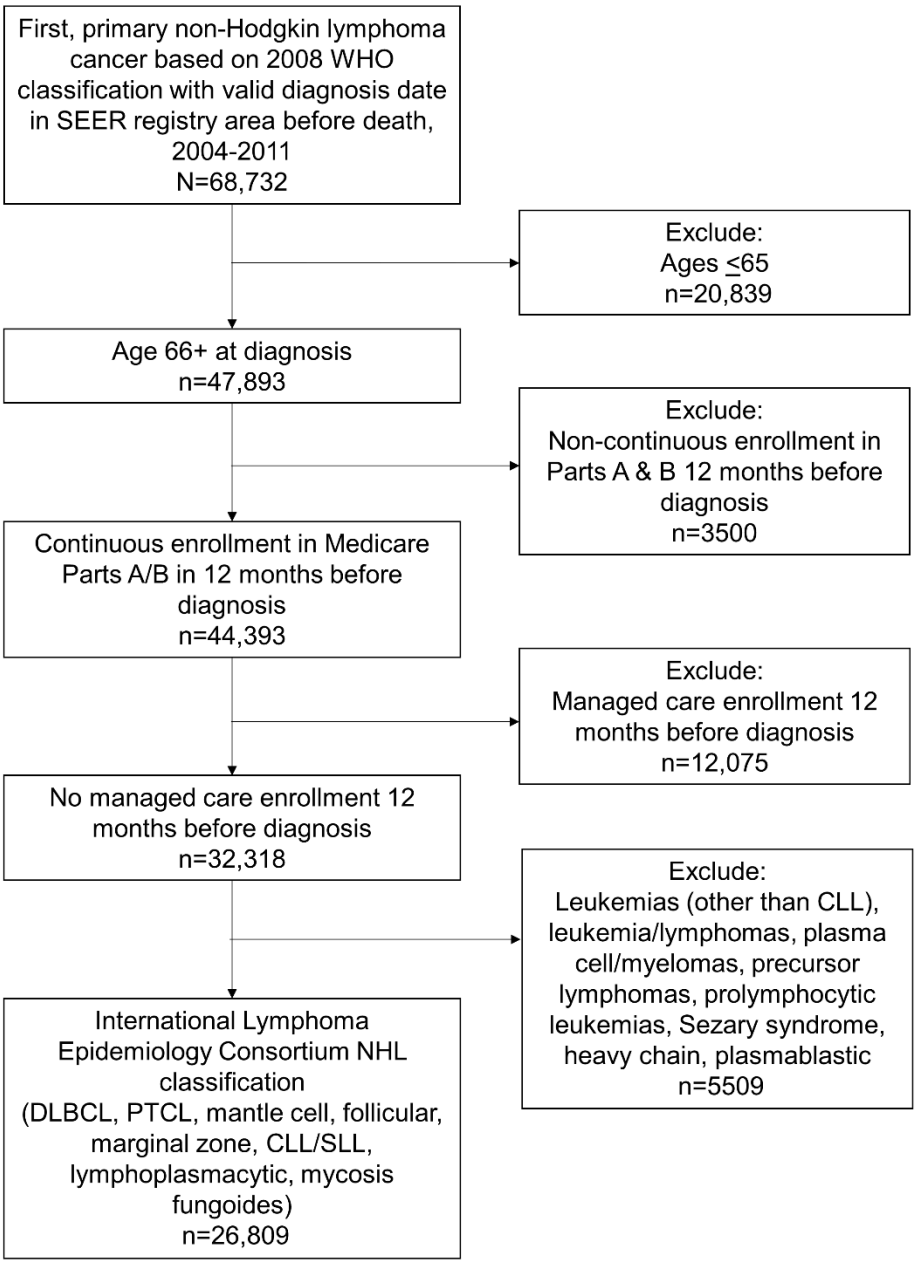

Figure 3.1 *Study selection flowchart for Aim 1 study population*

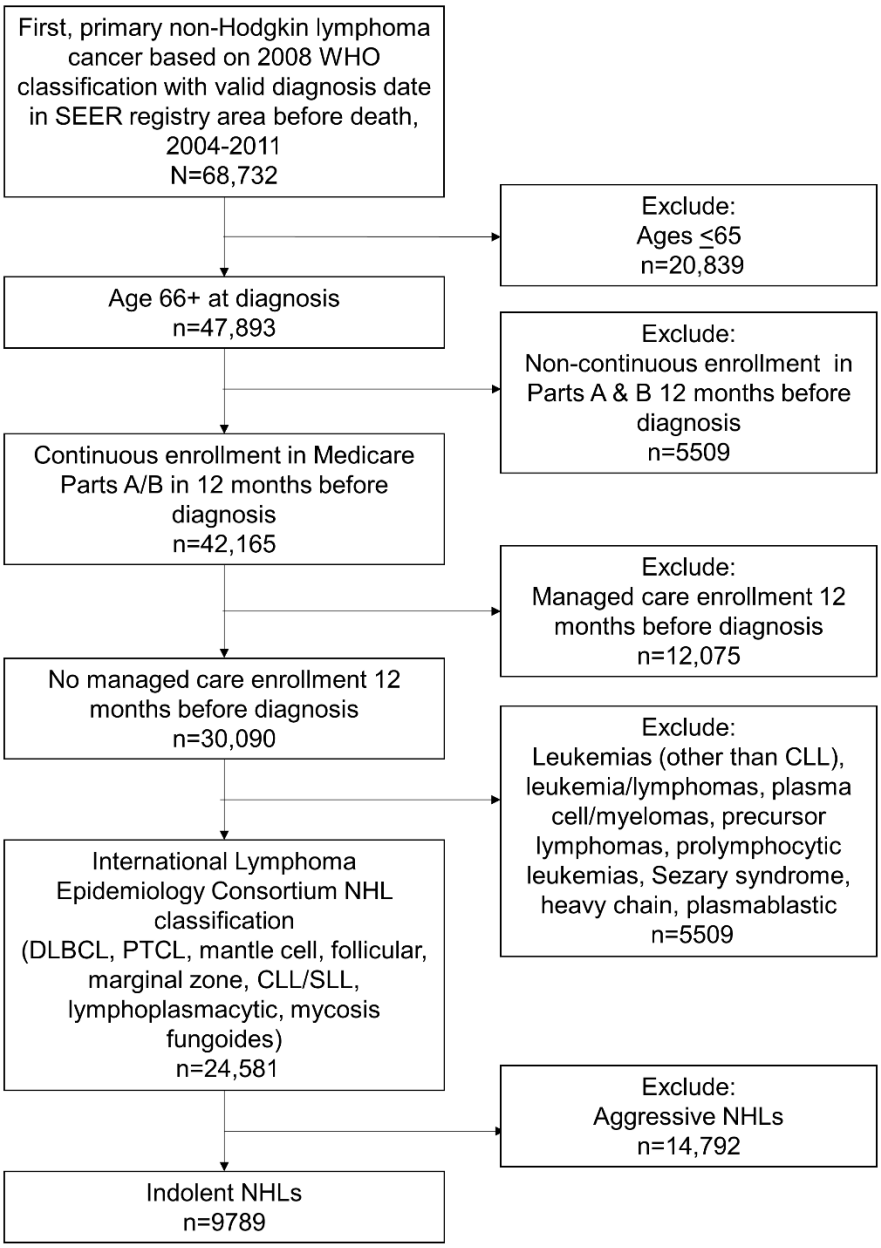

Figure 3.2 *Study selection flowchart for Aim 2 study population*

Table 3.1 *Characteristics of the combined comorbidity index comparator model and elastic net index models (A-D) in Aim 2*

Model	Model Components
Combined Comorbidity Index Model	Combined comorbidity index + age (categorical) + sex
Elastic net Model A	36 comorbidities+ age (categorical) + sex
Elastic net Model B	36 comorbidities + age (categorical) + sex + interactions between 10 most prevalent comorbidities
Elastic net Model C	36 comorbidities + age (categorical) + sex +12 frailty indicators + interactions between 10 most prevalent comorbidities
Elastic net Model D	36 comorbidities + age (categorical) + sex +12 frailty indicators + interactions between 10 most prevalent comorbidities + indolent NHL subtype (proxy for cancer prognosis)

CHAPTER 4: RESULTS OF AIM 1: CAUSE-SPECIFIC MORTALITY AMONG MEDICARE BENEFICIARIES WITH NEWLY DIAGNOSED NON-HODGKIN LYMPHOMA SUBTYPES IN THE RITUXIMAB ERA

A. Introduction

Non-Hodgkin lymphoma (NHL) is the sixth most diagnosed cancer and eighth leading cause of cancer death among US men and women, with an estimated 72,580 new diagnoses and 20,150 deaths in 2016.[7,124] The demographic composition and survival of the NHL population has changed markedly over the past two decades. Notably, the proportion of new NHL diagnoses among older adults has risen since the late 1990s with the aging US population.[7] By 2030, two-thirds of new NHL diagnoses are expected to be aged $\geq$65.[14] The aging NHL population brings unique challenges to NHL treatment decision-making. Older patients are more susceptible to cancer treatment toxicities and have a greater number and severity of comorbidities than younger patients, which increases the likelihood that they will die from causes other than NHL.[4,34,85] As the NHL population has grown older, the NHL-specific mortality has decreased.[7,114] The decreasing mortality in NHL is largely attributable to the introduction of rituximab, a monoclonal antibody against CD20, and other effective second- and third-line treatments.[125] As patients live longer with their NHL, their risk of dying from other causes increases. Going forward, treatment decision-making for older patients with NHL may benefit from information about the risk of mortality from causes other than NHL.

The importance of competing causes of mortality in treatment decisions likely varies across NHL subtypes, which have heterogeneous demographic, clinical, and tumor characteristics that differentially influence NHL-specific prognosis.[110,112] One important prognostic factor that varies between subtypes is the speed of tumor growth. Patients

diagnosed with subtypes exhibiting an aggressive growth have a higher likelihood of NHL-specific mortality and cure after first-line treatment than indolent subtypes.[110] In contrast, indolent subtypes are characterized by patterns of disease remission and relapse requiring long-term management of the cancer, such as additional treatment that can lead to adverse events.[126] Taken together, deaths from causes other than NHL may be more of a concern for treatment decisions among indolent subtypes than aggressive subtypes.

As mortality from competing causes becomes more important among patients with NHL, cause-specific prognosis estimates are needed to inform discussions on the value of NHL treatments given the risks of death from other causes. In the cancer literature, the most commonly reported measures of cause-specific prognosis are net cancer-specific mortality risks, which remove patients from an analytic cohort after they die of causes other than the cancer.[31] Net cancer-specific mortality risks are used to isolate the effect of interventions on cancer mortality and to compare cancer mortality across time or populations. However, these measures assume that patients only die of NHL. In real clinical settings, newly diagnosed patients have a probability of dying from NHL, dying from other causes, and surviving.[31] In order for these three probabilities to add up to 100%, it is necessary to acknowledge that a patient may die of a cause other than NHL and to estimate cause-specific mortalities that account for competing risks. These risks are commonly called crude measures in the surveillance literature or cumulative incidence functions in the statistical literature.[31,32,127] Cumulative incidence functions that account for competing risks retain patients in the denominator population after they die of a competing cause, which prevents inflation of prognosis estimates.[32,33] Though not commonly reported, the cumulative incidence of cause-specific mortality provides the best reflection of a patient's actual prognosis and the most useful measure for informing individual treatment decisions.

This study sought to describe patterns in the cumulative incidence of NHL-specific and non-cancer mortality by prognostic factors for older patients with NHL, including subtype, age and comorbidity level.

B. Methods

Data Source and Study Population

For this analysis, we used data from the 18 US Surveillance, Epidemiology, and End Results (SEER) cancer registries linked with Medicare insurance claims. SEER registries cover approximately 28% of the US and provide information on NHL diagnosis and mortality that are generally representative of those observed in the general US population.[104] Medicare is a federally funded program providing health insurance to persons aged ≥65 that consists of Part A (hospital, skilled-nursing facility, hospice, home health care) and Part B (physician and outpatient services) fee-for-service coverage.

We identified patients aged ≥66 years at diagnosis with first, primary NHL between January 1, 2004 and December 31, 2011. Eligible patients were required to have continuous Medicare Parts A and B and no managed care coverage for the 12 months before the diagnosis date (set to the first day of the diagnosis month). Our study started in 2004 after the 1997 FDA approval and dissemination of rituximab to ensure that most patients in the study population had a similar opportunity to experience survival advantages from this drug.[69,107] B- and T-cell NHL subtypes were defined using the International Lymphoma Epidemiology Consortium (InterLymph) categories[108] based on the 2008 WHO classification system for hematological and lymphoid tissue malignancies.[109] Using clinical expertise, we further excluded malignancies with unspecified/unknown subtypes that primarily affected non-lymphoid tissue or that occurred in precursor or plasma cells (lymphoblastic leukemia/lymphomas (ICD-O-3 9811-9818, 9837), plasma cell/myelomas (ICD-O-3 9731-9732, 9734, 9762), and precursor lymphomas (ICD-O-3 9724-9729, 9735). Patients aged

<65 at Medicare enrollment (qualifying due to end-stage renal disease or disability) or diagnosed at autopsy or death were also excluded.

Demographic and Clinical Variables

We grouped NHL into indolent and aggressive subtypes based on clinical expertise and prior knowledge about survival.[85,110,111] Aggressive subtypes included diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL) and Burkitts lymphoma. Although supbpopulations of mantle cell lymphoma have exhibited indolent tumor growth,[68] this subtype was categorized as aggressive since it displays an higher NHL-specific mortality than observed in typical indolent NHL.[112] Indolent subtypes included follicular lymphoma, marginal zone lymphoma (MALT extranodal, nodal, and splenic), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic/Waldenström macroglobulinemia and mycosis fungoides. We removed Sezary syndrome due to small numbers preventing stable stratification.

For the cohort description, we assigned patients to an age group according to their age at diagnosis (60-74, 75-84, 85+ years). We also identified sex, race (white, black, Hispanic, other), and Ann Arbor cancer stage (I/II, III/IV) in the SEER data to further describe the population. The presence or absence of 16 comorbidities were identified in the 12 months before NHL diagnosis, and a Charlson comorbidity score was calculated using weights developed by Mariotto et al.[100] We also used comorbidity categories from Cho et al. to stratify patients into no comorbidity, low or moderate comorbidity, and high comorbidity.[27]

Cause of Death

We followed patients from NHL diagnosis until death or the end of follow-up on December 31, 2012. We identified deaths using state death certificate data compiled by the National Center for Health Statistics and linked to SEER records.[113] Deaths were linked to

individuals with SEER data regardless of whether they died within or outside of a SEER registry.

Deaths were defined by major site groups on death certificates based on 3-digit International Classification of Disease (ICD) version 10 codes. We used a definition of cancer death developed by the NCI that adjusts for potential misattribution of NHL-specific deaths by considering tumor site, origin and order, as well as secondary malignancies and comorbidities that commonly occur with NHL (e.g. HIV/AIDS).[28] Any death not classified as an NHL death was considered a "non-cancer death."

Statistical Analysis

For each NHL subtype, we calculated cumulative risks of all-cause mortality as the complement of overall survival probabilities from Cox proportional hazards models. We used the Fine-Gray subdistribution hazards regression model[32] to estimate the cumulative incidence of NHL-specific and non-cancer mortality by subtype, age and comorbidity level. The Fine-Gray model accounts for competing causes of death preventing patients from experiencing the event of interest. When calculating the cumulative incidence of NHL-specific mortality, NHL death was the event of interest, and death due to other causes was the competing event. For the cumulative incidence of non-cancer mortality, deaths from causes other than NHL were the events of interest, and NHL death was the competing event. We calculated 95% confidence intervals for cumulative incidence estimates using bootstrapping with 1000 replicates.

We calculated 5-year cumulative incidences and cumulative incidence curves of NHL-specific and non-cancer mortality for each subtype, age group and comorbidity level, which were graphed using stacked bar charts and stacked cumulative incidence curves over the five years post-diagnosis. The top of the stacked curves represented cumulative all-cause mortality. The area above the curves represented the overall survival probability at each time

point after NHL diagnosis. Analyses were conducted using SAS 9.4 statistical software (SAS Inc., Cary, NC).

C. Results

From 2004-2011, 26,809 eligible adults aged 66+ were newly diagnosed with mature B- or T-cell NHL in the SEER-Medicare database (Figure 1). Of these individuals, 40% had indolent subtypes and 60% had aggressive subtypes. The most common subtype was DLBCL (47.4%), followed by follicular (22.5%) and marginal zone lymphoma (13.4%).

Table 4.1a Table 4.1b display the characteristics of older adults newly diagnosed with aggressive and indolent NHL subtypes, respectively. In general, patients diagnosed with indolent subtypes were more likely to be younger, female, white, and have less advanced disease than patients diagnosed with aggressive subtypes. We observed some variation in NHL subtype characteristics within the same tumor growth group. Among aggressive subtypes, the percentage of patients diagnosed at age 85+ years ranged from 14% in Burkitts to 19% in DLBCL. Patients with marginal zone and lymphoplasmacytic lymphoma were generally older than patients with other indolent subtypes. More than half of patients with follicular, CLL/SLL and lymphoplasmacytic lymphoma were diagnosed in advanced stages, while early stage diagnoses were more common among patients with marginal zone lymphoma and mycosis fungoides.

Table 4.2 reports the number of deaths from cancer and other causes in the study period and the 5-year NHL-specific and non-cancer mortality by subtype. There were 12,684 deaths among newly diagnosed patients from 2004-2012. Thirty-three percent of newly diagnosed patients died of NHL (n=8761), while 15% died of other causes (n=3923). The percentage of patients with aggressive subtypes who died of NHL was higher than the percentage of patients with indolent subtypes (44% vs. 19%). In contrast, the percentage of patients with indolent subtypes dying of other causes slightly exceeded the percentage

among patients with aggressive subtypes (16% vs. 14%). Within tumor growth groups, the percentage of newly diagnosed patients dying from NHL and other causes varied by subtype.

Patients diagnosed with indolent subtypes had a lower cumulative incidence of NHL-specific mortality (19% vs. 45%) and higher cumulative incidence of non-cancer mortality (18% vs. 16%) at five years post-diagnosis than aggressive subtypes. Indolent marginal zone and mycosis fungoides subtypes had a higher cumulative incidence of non-cancer mortality than NHL mortality at five years.

Figure 4.1 illustrates the cumulative incidence of NHL-specific mortality, non-cancer mortality, and survival at five years by subtype, age group, and comorbidity level. Five-year NHL-specific mortality was larger for every age and comorbidity level in aggressive subtypes than indolent subtypes. Among aggressive subtypes, 5-year NHL-specific mortality rose with increasing age but changed little with increasing comorbidity level. In contrast, 5-year non-cancer mortality increased with age and comorbidity level and was highest among older patients with indolent subtypes.

Figure 4.2 presents cumulative incidence curves for non-cancer mortality stacked on those for NHL-specific mortality over the five years post-diagnosis for each age group and subtype. Cumulative incidence curves for NHL-specific and non-cancer mortality varied across NHL subtypes, though similar patterns were observed among subtypes with the same speed of tumor growth. Among aggressive subtypes, NHL-specific mortality exceeded non-cancer mortality throughout the five years post-diagnosis, regardless of age group. NHL-specific mortality increased rapidly in the first year among aggressive subtypes; this incline became steeper as patients aged. Cumulative incidence curves for non-cancer mortality also rose more quickly for older than younger age groups. Cumulative incidence curves for mantle cell lymphoma display a unique, hybrid pattern, with a higher NHL-specific mortality at each time point after diagnosis than indolent subtypes but a slower rate of increase in NHL-specific mortality than aggressive subtypes.

Cumulative incidence curves of non-cancer mortality increased more rapidly in older patients diagnosed with indolent subtypes than for aggressive subtypes. Notably, among older patients diagnosed with the indolent marginal zone and mycosis fungoides subtypes, non-cancer mortality exceeded NHL-specific mortality for patients surviving three or more years post-diagnosis.

Figure 4.3 displays the stacked cumulative incidence curves for NHL-specific and non-cancer mortality in the five years post-diagnosis stratified by subtype and comorbidity level. Compared to patients diagnosed with aggressive subtypes with no or low/moderate comorbidity at diagnosis, patients with a high comorbidity level have a greater increase in non-cancer mortality over the five years. This increase is most notable among indolent subtypes.

Figure 4.4 shows that cumulative incidence curves for NHL-specific mortality generally increase at a faster greater rate in advanced stages than early stages among aggressive subtypes. In contrast, non-cancer mortality increased at a slightly faster rate in early versus advanced stages. Similar patterns were observed among indolent subtypes.

D. Discussion

In this population-based study, we explored the risks of NHL-specific and non-cancer mortality among older Medicare beneficiaries diagnosed with NHL during the rituximab era by subtype, age group, comorbidity level, and time since diagnosis. Our findings suggest that, for most subtypes, NHL-specific mortality increases with age, while non-cancer mortality generally increases with age and comorbidity level. Similar patterns have been observed in other cancer sites.[5,27,31,127] At five years post-diagnosis, NHL-specific mortality is higher for aggressive subtypes compared to indolent subtypes. In contrast, the cumulative incidence of non-cancer mortality is higher in indolent subtypes than aggressive subtypes, especially for patients diagnosed with marginal zone lymphoma and mycosis

fungoides. Patterns in indolent subtypes mirror those previously reported for early stage, solid tumor cancers, which are also slower growing.[5,27,128,129]

Prior population-based studies of patients with NHL have also observed variation in overall survival[110,114,130] and net NHL-specific mortality estimates[112,114,130,131] across subtypes, age groups, and comorbidity levels. However, overall survival estimates do not provide specific information about the cumulative incidence of death from NHL or other causes, and net survival measures do not account for competing causes of death.[31] By exploring patterns of NHL-specific and non-cancer mortality, our results contribute unique, population-level evidence about the impact of competing risks on survival in older NHL patients.

A strength of this study is use of the linked SEER-Medicare data, which is generally representative of the US population.[132] Therefore, patterns of crude cause-specific mortality risks observed in the SEER-Medicare data are expected to reflect patterns among all older adults in the US. The SEER-Medicare data also provide an opportunity to measure comorbid conditions present at the time of diagnosis, which are important, but often underreported, prognostic factors for older adults newly diagnosed with NHL.[5] Cancer registries generally do not collect comorbidity data, while clinical trials generally exclude individuals with higher comorbidity levels, affecting our ability to translate prognostic trends observed by comorbidity levels in clinical trials to those expected in the general population. Another strength of this analysis is that we explore the cumulative incidence of cause-specific mortality by NHL subtype, which to our knowledge, have not been explored previously and are important given the potential importance of competing risks in some subtypes. Finally, this study provides information on mortality trends from a time period in which contemporary first-line treatment paradigms with rituximab were used for most patients with the two most common subtypes, follicular lymphoma[133] and DLBCL.[134]

However, there are also limitations of this analysis. SEER-Medicare data only provide information on patients with NHL who are aged $\geq$65 years. Eighty-nine percent of

these patients are missing the International Prognostic Index,[135] which is a score widely used by oncologists to inform treatment decisions. Components of this score are also unavailable in the data, including performance status, number of extranodal sites, and lactate dehydrogenase levels. Future studies should explore how cumulative incidence of NHL-specific and non-cancer mortality vary by these prognostic variables. Despite use of the refined NCI cause-specific death variable, cause of death may still be misclassified and lead the cumulative incidence of NHL-specific mortality to falsely appear higher or lower than non-cancer mortality across subtypes and time periods.[28,136] Additionally, several NHL subtypes cannot be separated exclusively into an indolent and aggressive category. Notably, while mantle cell lymphomas have a low median overall survival, a subset of these malignancies demonstrate slow-growth and characteristics similar to indolent NHLs.[137] Finally, the 5-year crude mortality risks reflect death in the presence of treatments available for the patient at the time of their diagnosis from 2004-2011. There have been advances in NHL treatment since 2004, such as improvements in stem-cell transplants and increased use of rituximab. Due to treatment advances, 5-year crude mortality risks may look different for patients diagnosed in 2004 than those diagnosed in 2011. Although prior studies have shown mortality rates plateauing during this time period,[114] relative measures utilizing expected survival data from life tables may be better for exploring time trends in NHL prognosis.[31]

Our findings describe population-level patterns in the cumulative incidence of NHL-specific and non-cancer mortality. These population-level results suggest that treatment decision-making for patients with indolent subtypes who are older or have higher comorbidity levels may benefit from information on the cumulative incidence of non-cancer mortality compared to NHL-specific mortality. However, to improve outcomes among older NHL patients, individual-level estimates of the cumulative incidence of cancer-specific and non-cancer mortality are needed, as well as tools that predict these outcomes according to a

patient's specific characteristics. Current NHL prognosis tools, such as the International Prognostic Index[135] and Follicular Lymphoma Prognostic Index,[138] were developed to inform providers on a patient's probability of overall mortality. However, these tools do not provide context regarding the patient's cancer-specific mortality risks in the presence of competing risks, nor do they inform providers on the risk of death from causes other than NHL. Currently, the NCI is developing the SEER*CSC tool for prostate, breast, colorectal, and head-and-neck cancers, which will provide nomograms for predicting the cumulative incidence of surviving or dying from cancer or other causes based on a patient's tumor, age, race, gender, and other measures of health status.[139,140] Our study informs the development of predictive tools like the SEER*CSC nomogram for NHL, which would generate highly personalized, actual prognosis measures for informing treatment discussions between providers and older patients with NHL.

Table 4.1 *Individual demographic characteristics by aggressive non-Hodgkin lymphoma subtype in the linked Surveillance, Epidemiology, and End Results cancer registry and Medicare claims database*

Characteristics	Total (n=26,809)		Total Aggressive (n=14,773)		DLBCL (n=11,657)		PTCL (n=1518)		Mantle Cell (n=1367)		Burkitts (n=231)	
	n	**%**	n	%	n	%	n	%	n	%	n	%
Age Group												
66-74	10912	40.7	5646	27.7	4326	37.1	641	42.2	592	43.3	87	37.7
75-84	8453	31.5	3380	22.9	5168	44.3	662	43.6	576	42.1	111	48.1
85+	7444	27.8	5747	38.9	2163	18.6	215	14.2	199	14.6	33	14.3
Sex												
Male	12831	47.9	7317	49.5	5496	47.1	806	53.1	890	65.1	125	54.1
Female	13978	52.1	7456	50.5	6161	52.9	712	46.9	477	34.9	106	45.9
Race/Ethnicity												
White, non-Hispanic	22459	84.5	12167	82.9	9619	83.0	1179	78.8	1189	87.8	180	78.3
Black, non-Hispanic	1169	4.4	626	4.3	438	3.8	128	8.6	47	3.5	13	5.7
Hispanic	1693	6.4	1027	7.0	833	7.2	91	6.1	83	6.1	20	8.7
Other	1250	4.7	857	5.8	706	6.1	99	6.6	35	2.6	17	7.4
Stage												
I	7581	30.5	3933	28.4	3278	29.8	459	33.7	155	12.1	41	18.8
II	3949	15.9	2403	17.4	2097	19.1	154	11.3	114	8.9	38	17.4
III	4397	17.7	2404	17.4	1845	16.8	304	22.3	235	18.4	20	9.2
IV	8923	35.9	5098	36.8	3763	34.3	444	32.6	772	60.5	119	54.6
Comorbidity Level												
None	10566	39.4	5600	37.9	4343	37.3	588	38.7	587	42.9	82	35.5
Low/moderate	5019	18.7	2784	18.8	2203	18.9	291	19.2	239	17.5	51	22.1
High	11224	41.9	6389	43.2	5111	43.8	639	42.1	541	39.6	98	42.4

Table 4.2 *Individual demographic characteristics by aggressive non-Hodgkin lymphoma subtype in the linked Surveillance, Epidemiology, and End Results cancer registry and Medicare claims database*

Characteristics	Total (n=26,809)		Total Indolent (n=12,036)		Follicular (n=5523)		Marginal Zone (n=3301)		CLL/SLL (n=2221)		Lympho-plasmacytic (n=527)		Mycosis fungoides (n=464)	
	n	n	%	n	%	n	%	n	n	n	%	n	%	
Age Group														
66-74	10912	40.7	5266	43.8	2594	47.0	1324	40.1	233	233	198	37.6	233	50.2
75-84	8453	31.5	5073	42.1	2264	41.0	1406	42.6	172	172	244	46.3	172	37.1
85+	7444	27.8	1697	14.1	665	12.0	571	17.3	59	59	85	16.1	59	12.7
Sex														
Male	12831	47.9	5514	45.8	2445	44.3	1389	42.1	244	244	258	49.0	244	52.6
Female	13978	52.1	6522	54.2	3078	55.7	1912	57.9	220	220	269	51.0	220	47.4
Race/Ethnicity														
White, non-Hispanic	22459	84.5	10292	86.5	4853	88.5	2734	83.8	356	356	449	87.5	356	82.8
Black, non-Hispanic	1169	4.4	543	4.6	156	2.8	151	4.6	39	39	13	2.5	39	9.1
Hispanic	1693	6.4	666	5.6	314	5.7	215	6.6	22	22	31	6.0	22	5.1
Other	1250	4.7	393	3.3	161	2.9	164	5.0	13	13	20	3.9	13	3.0
Stage														
I	7581	30.5	3648	33.1	1562	30.5	1388	46.3	254	254	55	11.0	254	77.4
II	3949	15.9	1546	14.0	922	18.0	336	11.2	31	31	11	2.2	31	9.5
III	4397	17.7	1993	18.1	1294	25.2	194	6.5	19	19	26	5.2	19	5.8
IV	8923	35.9	3825	34.7	1348	26.3	1080	36.0	24	24	408	81.6	24	7.3
Comorbidity Level														
None	10566	39.4	4966	41.3	2396	43.4	1294	39.2	195	195	207	39.3	195	42.0
Low/moderate	5019	18.7	2235	18.6	1053	19.1	589	17.8	91	91	88	16.7	91	19.6
High	11224	41.9	4835	40.2	2074	37.6	1418	43.0	178	178	232	44.0	178	38.4

Table 4.3 *Five-year cumulative incidence of all-cause mortality, non-Hodgkin lymphoma-specific mortality and other-cause mortality by tumor growth groups and subtypes for cases in diagnosed from 2004-2012 in the linked Surveillance, Epidemiology and End Results-Medicare data*

Group (n(%))	Cases (N=26,809)	Deaths in 5-years (n=12,684)		5-year all-cause mortality		5-year cancer-specific mortality		5-year other-cause mortality	
		Cancer	Non-cancer	CID (%)	95% CI	CID (%)	95% CI	CID (%)	95% CI
Aggressive Subtypes	14773	6452 (42.6)	2057 (13.9)	61.6	60.7,62.4	45.5	44.7,46.3	16.2	15.6,16.8
Diffuse large B-cell lymphoma	11657	4971 (42.6)	1648 (14.1)	60.4	59.4,61.3	44.1	43.3,44.9	16.4	15.7,17.2
Peripheral T-cell lymphoma	1518	726 (47.8)	215 (14.2)	65.6	63.1,68.4	49.6	47.2,52.2	16.0	14.2,18.0
Mantle cell lymphoma*	1367	602 (44.0)	174 (12.7)	65.5	62.5,68.4	50.1	47.1,53.3	15.5	13.4,18.0
Burkitts lymphoma	231	153 (66.2)	20 (8.7)	75.0	69.0,80.8	64.5	59.1,70.1	10.2	6.9,15.0
Indolent Subtypes	12036	2309 (19.2)	1866 (15.5)	39.3	38.4,40.4	21.1	20.3,21.8	18.3	17.6,18.7
Follicular lymphoma	5523	1093 (19.8)	710 (12.6)	37.7	36.3,39.1	22.0	20.8,23.1	15.8	14.8,16.9
Marginal zone lymphoma	3301	458 (13.9)	538 (16.3)	36.0	34.0,38.0	16.0	14.7,17.5	20.0	18.6,21.7
CLL/SLL	2221	583 (26.2)	448 (20.2)	46.4	44.2,48.7	26.4	24.5,28.3	20.2	18.3,22.2
Lymphoplasmacytic	527	112 (21.3)	95 (18.0)	47.9	42.9,53.5	24.4	20.7,28.6	23.7	19.8,28.3
Mycosis fungoides	464	63 (13.6)	75 (16.2)	37.7	35.0,39.7	16.6	13.3,20.7	21.2	17.4,25.9

CID=cumulative incidence of death; CI=confidence interval; CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma; *Mantle cell lymphoma can be classified as aggressive or indolent but is considered aggressive in this analysis.

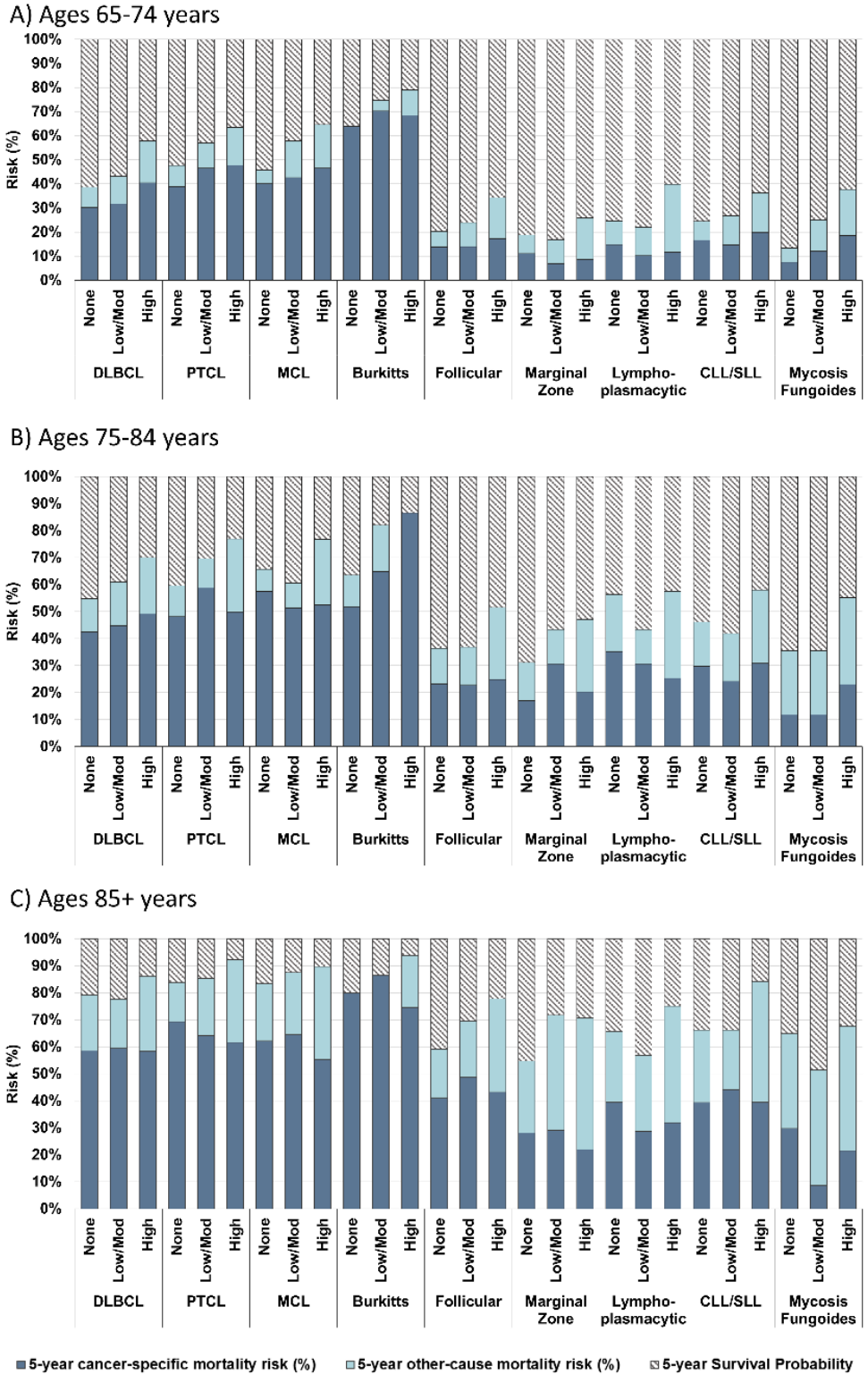

Figure 4.1 *Bar charts displaying NHL-specific and other cause mortality and survival probabilities at 5 years post-diagnosis for patients with NHL by subtype, comorbidity group, and age groups*

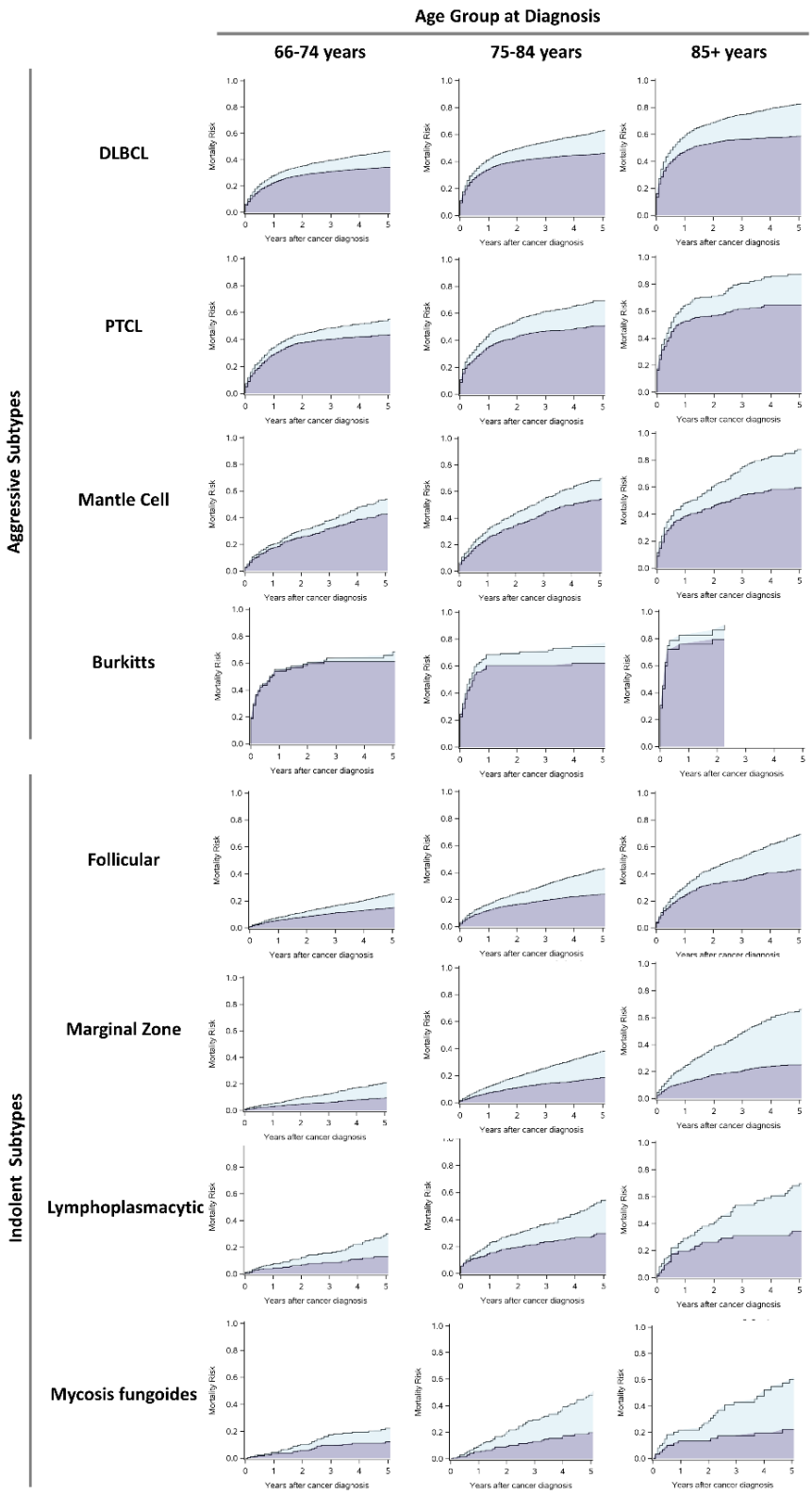

Figure 4.2 *Stacked cumulative NHL-specific (dark blue) and other cause (light blue) mortality curves over five years from NHL diagnosis by subtype and age group*

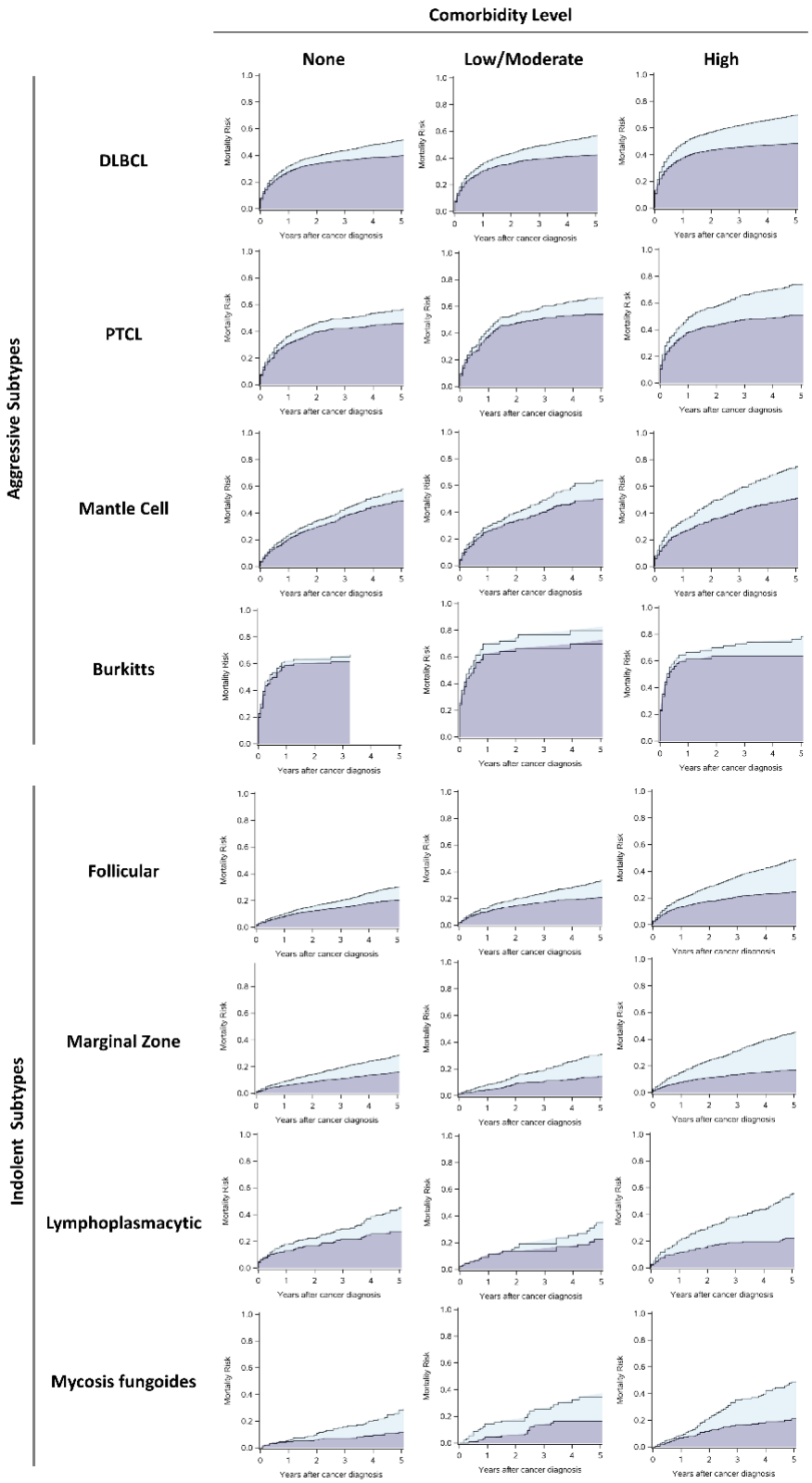

Figure 4.3 *Stacked cumulative NHL-specific (dark blue) and other cause (light blue) mortality over five years after NHL diagnosis by subtype and comorbidity level*

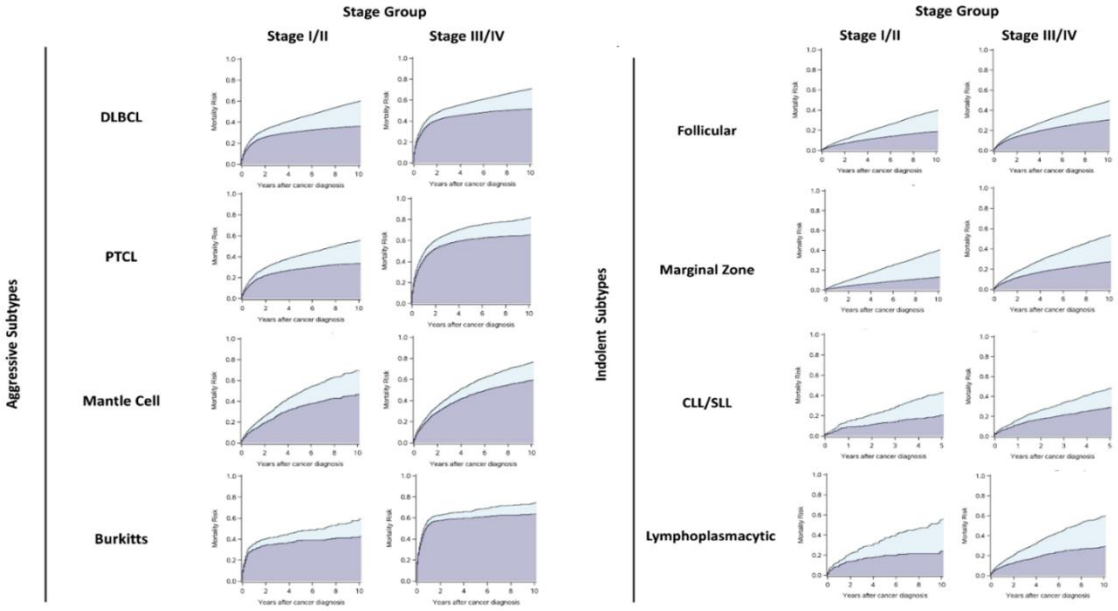

Figure 4.4 *Stacked cumulative NHL-specific (dark blue) and other cause (light blue) mortality curves over five years from NHL diagnosis by subtype and stage*

CHAPTER 5: RESULTS OF AIM 2: PREDICTING NON-CANCER MORTALITY AMONG MEDICARE BENEFICIARIES NEWLY DIAGNOSED WITH INDOLENT NON-HODGKIN LYMPHOMA SUBTYPES

A. Introduction

Non-Hodgkin lymphoma (NHL) is composed of heterogeneous hematological subtypes categorized according to whether they exhibit an indolent or aggressive speed of tumor growth. Indolent NHLs are characterized by patterns of remission and relapse that can continue throughout a patient's lifetime, especially for those diagnosed with advanced disease.[126] The most common indolent NHL subtype is follicular lymphoma, composing a third of indolent diagnoses, followed by chronic lymphocytic leukemias/small lymphocytic lymphomas (CLL/SLL), marginal zone lymphomas (MZL), lymphoplasmacytic/Waldenström's macroglobulinemia, and the T-cell subtype, mycosis fungoides.[7]

Characteristics of indolent NHL place patients at a higher risk of dying from a cause other than their lymphoma. Given the slow growth of indolent NHL, these patients are more likely to survive their initial cancer and die of non-cancer causes than patients with more aggressive NHL.[61] Patients with indolent NHL also face treatment for multiple relapses, increasing their risk of comorbidity exacerbations and diverting resources away from non-cancer conditions. Additionally, over half of indolent NHLs are diagnosed at older ages, with an average age at diagnosis of 68.[61] Older patients with indolent NHL have a higher burden of comorbidity and frailty than their younger counterparts,[85,86] which increases their risk of dying from non-cancer causes. As the proportion of older adults diagnosed with indolent NHL increases with the aging US population, [6,13,14] assessment and consideration of non-

cancer prognosis at the outset of care for older patients diagnosed with indolent NHL is of critical importance.

Initial treatment discussions between older patients diagnosed with indolent NHL and providers should decide whether to follow a less aggressive treatment approach, which includes watch-and-wait or monotherapy with a target anti-CD20 agent such as rituximab, or to pursue more aggressive chemoimmunotherapy regimens.[141] Non-cancer prognosis is particularly relevant to discuss in these scenarios since aggressive chemotherapies can exacerbate non-cancer conditions and increase the risk of dying from a non-cancer cause.[35,142] For older patients with a high burden of comorbidity and/or frailty at the time of their NHL diagnosis, the risk of non-cancer mortality may outweigh the benefit of specific treatment options in reducing NHL deaths. The burden of comorbidity and frailty and the impact of these conditions on non-cancer mortality is heterogeneous across older patients, complicating identification of high-risk patients. Therefore, to better inform treatment decisions, enhanced risk prediction tools are needed to identify indolent NHL patients at diagnosis who have a high probability of dying from non-cancer causes.

Currently, comorbidity scores are the recommended tools for identifying older patients who may not benefit from aggressive treatment.[141] Traditional comorbidity scores use a single integer to represent the number and impact of common comorbid conditions on an outcome, usually short-term (e.g., 30-day, 1-year), all-cause mortality. In the clinic, comorbidity scores can be used to: (1) flag patient whose comorbidity burden might preclude them from a treatment benefit, (2) determine whether an aggressive treatment approach could exacerbate other conditions, or (3) identify patients who might need additional supportive care or care coordination during cancer treatment.[2] The most widely used comorbidity scores, the Charlson[89] and Elixhauser [90] comorbidity indices, were recently aggregated and reduced into the combined comorbidity index.[93] In external validation in a

contemporary cohort of older Medicare beneficiaries, the combined comorbidity index had superior performance in predicting short-term mortality compared to its component indices.

Despite the simplicity and clinical utility of traditional comorbidity scores, they have limitations for predicting a non-cancer death among older patients with indolent NHL. Prior studies have found that the comorbidities, weights, and outcomes in the combined comorbidity index are not directly transferable across patients diagnosed with different cancers.[98,143] While weights used in the general comorbidity scores reflect the rounded effect of comorbidities on 1-year all-cause mortality, 5-year non-cancer mortality may be a more clinically meaningful outcome for informing treatment trade-offs in indolent NHL. Traditional comorbidity scores also ignore that interactions may occur between co-occurring comorbidities that modify their effect on mortality.[99] Additionally, although patient frailty is considered an important predictor of non-cancer mortality, no measures of disability or poor physical performance are included in comorbidity scores. Inclusion of these variables could enhance prediction and improve identification of older patients who have a high probability of dying from non-cancer causes.

In this study, we sought to develop and internally validate more robust and tailored models to predict 1- and 5-year non-cancer mortality among a cohort of older adults newly diagnosed with indolent NHL.

B. Methods

Study Population

We used data from the 18 Surveillance Epidemiology and End Results (SEER) cancer registries linked to Medicare fee-for-service insurance claims. SEER registries cover approximately 28% of the US and provide NHL diagnosis and mortality data that are generally representative of the US cancer population.[104] Medicare is a federally funded health insurance program for eligible disabled or older (age $\geq$65) adults. The program consists of Part A (hospital, skilled-nursing facility) and Part B (physician and outpatient

services, durable medical equipment) fee-for-service coverage.[132] Part D outpatient prescription drug claims were not used for this analysis.

We required patients to be aged ≥66 years at diagnosis with a first, primary indolent NHL diagnosis from January 1, 2004 through December 31, 2011. Diagnosis was set to the first day of the diagnosis month. Patients were required to have continuous enrollment in Medicare Parts A and B without managed care coverage during the 12 months before indolent NHL diagnosis so that we could identify pre-existing comorbid conditions and frailty indicators. Patients aged <65 at Medicare enrollment (qualifying due to end-stage renal disease or disability) or diagnosed at autopsy or death were excluded. The study period was selected to reflect a time period when all patients generally had the same opportunity to receive and experience survival advantages from the anti-CD20 biologic, rituximab.[69,107]

NHL subtypes were defined using the International Lymphoma Epidemiology Consortium (InterLymph)[108] categories based on the 2008 WHO classification system for hematological and lymphoid tissue malignancies.[109] Using clinical expertise, we further restricted to indolent B-and T-cell subtypes, which were defined as those with a 5-year relative survival >70% that were not leukemias or plasma cell malignancies.[7,114] The final indolent subtypes in our analysis included follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic/Waldenström's macroglobulinemia, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mycosis fungoides (see Table S1 in Supplement for histology codes).

Candidate Predictors

Age and sex were included in all models. We defined age using 5-year age groups (66-69, 70-74, 75-79, 80-84, 85+). We also described the population by race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), subtype, and Ann Arbor cancer stage (I/II, III/IV). Subtype was include in the final prediction model (Model D).

For each patient, we identified the presence or absence of 36 comorbidities in the 12 months before the patient's diagnosis using validated ICD-9 codes from Part A hospitalization, Part B physician/supplier, outpatient, and durable medical equipment claims data. We included comorbidities defined using the Romano adaptation of the Charlson Comorbidity Index[89,91] (Quan/van Walvaren adaptation) of the Elixhauser Comorbidity Index.[90,92,115] When similar conditions were included in both scores, we chose a definition with more patients. We also identified comorbidities associated with NHL prognosis, including anxiety and hepatitis B and C using established ICD-9 diagnosis codes.[116] Finally, using ICD-9 diagnosis codes and HCPCS, we identified claims-based markers of frailty as defined by Faurot et al.[117] that had not been listed as a comorbidity in our analysis.

Mortality Outcome

Our outcomes of interest were 1- and 5-year all-cause and non-cancer mortality. The ICD-10 codes identifying cause of death were obtained by SEER from state death certificate data provided by the National Center for Health Statistics.[113] Deaths were captured through December 31, 2011 regardless of whether the death occurred within a SEER registry area.

One-year mortality enabled comparison of our model results with most traditional comorbidity scores. Death within 5 years represented long-term mortality, which is more relevant for indolent NHL. We developed models predicting both all-cause and non-cancer mortality to observe whether type of outcome changed the predictors and performance of our model. All-cause mortality was defined as death from any cause and is the most common outcome used to define traditional comorbidity scores. Indolent NHL-specific deaths were identified using the criteria established by the NCI,[27] which adjusts for potential misattribution of NHL-specific deaths by considering tumor site, tumor origin, tumor order, secondary malignancies and comorbidities that commonly occur with NHL. Non-cancer deaths were defined as those not due to an indolent NHL.

Statistical Analysis

We described the demographic, cancer, and underlying health status of older patients with indolent NHL. Models assessing 1-year mortality included all eligible patients. Models assessing 5-year mortality only included individuals diagnosed from January 1, 2004 through December 31, 2007 to allow patients to have at least five years of follow-up for the 5-year mortality endpoint between their diagnosis.

To address variation due to small sample sizes, we randomly resampled an 80% training set and a 20% validation set in each cohort 100 times using new seed values. In each training set, we fit five logistic regression models predicting 1- and 5-year all-cause and non-cancer mortality. **Table 3.1** describes each model. The first model included the combined comorbidity index, age group and sex. This model was considered the comparison model since our goal was to assess how well our new prediction models improved upon traditional comorbidity scores. The second through the fifth models (Models A-D) each added a component addressing a limitation of traditional comorbidity scores.

Models A-D were developed using elastic net machine learning methods, which simultaneously select from the large numbers of potential predictors and their interactions while shrinking those that are generally less informative towards zero. [118] This method balances model predictive ability and parsimony. Elastic net also uses a grouping effect that retains or removes strongly correlated predictors from the model as a group. This is important since many comorbidity and frailty predictors are collinear. For this analysis, we used 10-fold cross-validation to identify the tuning parameter, $\lambda_{o.5}$, that minimized the partial log likelihood. The utility of this approach is that it selects comorbidities that are most relevant to indolent NHL and to the outcome being assessed.

In the first elastic net model (Model A), we included the age group, sex and 36 comorbidities. The second elastic net model (Model B) added two-way interactions between the 10 most prevalent comorbidities in addition to age group, sex and the 36 previously

assessed comorbidities. The third elastic net model (Model C) included variables in Model B plus the 12 claims-based indicators of frailty. The final elastic net model (Model D) added indolent NHL subtypes to assess whether characteristics related to cancer prognosis were also predictive of non-cancer mortality.

We tested the five models in the 100 validation sets and calculated the average model coefficients, predicted probability of 1- and 5-year all-cause and non-cancer mortality and performance metrics in the 100 resamples. The performance metric distributions in the 100 resamples were used to calculate 95% confidence intervals. We assessed the ability of the five models to discriminate each mortality outcome using the area under the receiver operator curve, also known as the AUC. Changes in average AUC between each model were assessed. We calculated the average continuous Net Reclassification Improvement (NRI) measure and Integrated Discrimination Improvement (IDI) indices to compare true- and false-positive rates of the four elastic net models versus the combined comorbidity index model.[119] The NRI assesses the degree to which an index model (i.e., elastic net models) correctly reclassifies events and non-events versus a comparison model (i.e., combined comorbidity index model). The IDI assesses the change in sensitivity minus the change in 1-specificity of the index versus the comparison model over all possible cutoff values. This can be interpreted as the difference in the discrimination slope between two models.[121] Finally, we assessed external model fit using calibration plots of observed probabilities,[122] estimated as or binary mortality outcomes as continuous values using locally-weighted smoothing (loess), versus predicted probabilities.[123] Well-calibrated models follow the 45-degree line representing perfect alignment between the observed and predicted probabilities.

All analyses were conducted using the *glmnet, pROC, rms*, and *ggplot2* packages in R.

C. Results

Characteristics of Study Population

There were 9789 eligible older adults diagnosed with an indolent subtype of NHL between January 1, 2004 and December 31, 2011 who were included in the cohort assessing 1-year mortality. Within a year of diagnosis, 12.4% died of any cause and 4.1% died of a non-cancer cause. There were 5310 patients diagnosed on or before December 31, 2007 in the cohort assessing 5-year mortality, of which 39% died of any cause and 18% died of a non-cancer cause.

In the cohort, just under half of patients in the 1- and 5-year cohorts were diagnosed with follicular lymphoma, while half of patients were aged ≥75 years (**Table 5.1**). The majority of patients were white, non-Hispanic and female. Approximately 20% of patients with a comorbidity score >2. Follicular lymphoma was the most common NHL subtype (45%). Just over half of patients were diagnosed with advanced stage NHL. There were small differences in demographic and cancer characteristics between the 1- and 5-year cohorts, with a slightly smaller proportion of patients who were aged 85+, minority race/ethnicities, or diagnosed with early stage disease in the 5-year cohort.

In both cohorts, the ten most prevalent comorbidities were uncomplicated hypertension (46%), hyperlipidemia (34%), uncomplicated diabetes (21%), chronic obstructive pulmonary disease (COPD) (15%), cardiac arrhythmias (15%), hypothyroidism (12%), fluid/electrolyte disorders (10%), congestive heart failure (CHF) (9%), cerebrovascular disease (CEVD) (7%), and valvular disease (6%) (**Table 5.2**). Among the indicators of frailty, over 5% of individuals received rehabilitation care in the 12 months before diagnosis.

Selected Predictors in the Models

Tables A2.1-A2.4 in Appendix 2 list the average coefficients (log odds ratios) of the selected predictors for the four elastic net models and outcomes. Across all models, the log odds of 1- and 5-year all-cause and non-cancer mortality increases with subsequent 5-year age group compared to the youngest age group (66-69 years). Regardless of model, females have a lower log odds of each mortality outcome than males. For 1-year all-cause mortality, the most important comorbidity risk predictors across all models are CHF, hepatitis C, mild liver disease, and weight loss. Important comorbidity interactions include those between CEVD and peripheral vascular disease and between uncomplicated diabetes and CEVD or fluid/electrolyte conditions. In Models C and D, individuals with wheelchair use and skin ulcers indicating poor mobility have a higher log odds of 1-year all-cause mortality than those without these codes. CHF and weight loss remain important comorbidity predictors in all four models predicting 1-year non-cancer mortality and are joined by other key predictors, including alcohol and drug abuse, COPD, dementia, moderate-severe liver disease, hemi/paraplegia, renal disease, and rheumatologic diseases join CHF and weight loss as important comorbidity predictors. Skin ulcers and wheelchair use continue to be strong predictors in Models C and D.

When predicting longer-term, 5-year all-cause mortality, CHF, mild liver disease, hepatitis C, and weight loss continue to be important predictors. Other key comorbidity predictors include coagulopathy, COPD, dementia, drug abuse, hepatitis B, neurological disorders, moderate-severe liver diseases, acute myocardial infarctions, and renal disease. The key comorbidity predictors of 5-year non-cancer mortality are CHF, COPD, dementia, hepatitis B, mild liver disease, neurological diseases (including Parkinson's disease), renal disease and rheumatologic disease. Interactions between arrhythmias and CEVD and between individuals with prior fluid/electrolyte disorder and peripheral vascular disease contribute to prediction in Models B-D. For these longer term outcomes, prior use of oxygen

is a strong predictor of non-cancer mortality in Models C and D. Diagnosis with marginal zone lymphoma appears to be protective against 1- and 5-year all-cause mortality (log(OR)=-0.35), but otherwise, the results of Model D suggest that indolent NHL subtype plays a minimal role in predicting all-cause or non-cancer mortality in the short or long-term.

Discrimination Metrics for Models

In general, the average AUCs are similar across the five models and four outcomes (**Table 5.3**). The 95% CI for the average AUC calculated from the combined comorbidity index model overlaps with those of the four elastic net models. Elastic net Model C, which adds frailty indicators to the 36 comorbidities and prevalent comorbidity interactions, has a higher average AUC than the other models when the predicted outcomes are 1-year all-cause mortality (AUC=0.716,95%CI:0.685,0.748) or 1- and 5-year non-cancer mortality (AUC=0.753, 95%CI:0.694,0.786); AUC= 0.716,95%CI:0.683,0.742, respectively). Model C has an average AUC that is $\geq$0.01 higher for 1-year all-cause and non-cancer mortality than the combined comorbidity index model. Model D, which adds indolent NHL subtype, provides a higher discrimination of 5-year all-cause mortality than the combined comorbidity index or other elastic net models (0.740,95%CI:0.709,0.711).

Reclassification Metrics for Models

The NRI indicates that, compared to the comorbidity index model, none of the elastic net models significantly improve classification of 1- or 5-year mortality from any cause or non-cancer causes (i.e. true positive rate) (**Table 5.4**). However, Model C has a significantly lower false-positive rate than the combined comorbidity index model, suggesting that adding frailty improves classification of those who do not experience 1-year all-cause mortality ($NRI_{NonDeaths}$= 0.17,95%CI:0.05,0.30), 1-year non-cancer mortality ($NRI_{NonDeaths}$ =0.10, 95%CI:0.01, 0.20), or 5-year all-cause mortality ($NRI_{NonDeaths}$ = 0.18, 95%CI:0.11,0.26). Compared to the combined comorbidity index model, the IDI index also indicates that the addition of frailty predictors in Model C increases estimated risks of mortality among those

who die and decreased estimated risks among those who do not die of each mortality outcome except 5-year non-cancer mortality. However, the improvements in classification do not differ significantly from those observed in the combined comorbidity index model.

Calibration of Models

For 1-year all-cause mortality, the elastic net models generally predict a higher all-cause mortality than is true (**Figures 5.1-5.4)**. Few patients had a probability of all-cause mortality >50%, leading to a higher amount of uncertainty in predicting higher short-term mortality. This pattern is observed across the five models, though overestimation occurs to a greater degree in models with frailty indicators added and to a lesser degree in the combined comorbidity index model. In all models except Model B, the predicted probabilities of 1-year non-cancer mortality are well-calibrated for individuals with an observed loess-smoothed probability of 1-year non-cancer mortality <25% but over-estimated among remaining individuals. Adding interactions in Models B improved calibration, but adding frailty predictors in Model C and D led to overestimation. For predicting 5-year all-cause mortality, all of the elastic net models appeared relatively well-calibrated. Compared to other models, Model A displayed the best calibration and was less likely to underestimate mortality among those with moderate risks or overestimate mortality among those with higher risks. The combined comorbidity index model showed the best calibration for 5-year non-cancer mortality. Among the elastic net models, the addition of the frailty predictors in Model C reduced overestimation among those with higher observed probabilities of mortality.

D. Discussion

This study sought to improve identification of older adults with a high risk of non-cancer mortality after an indolent NHL diagnosis by developing more complex risk prediction models that address limitations of traditional comorbidity scores. Notably, we assessed how prediction changes when using comorbidities relevant to indolent NHL, examining non-cancer mortality, exploring long-term outcomes, adding interactions

between comorbidities and adding frailty or cancer characteristics. Our AUC results suggest that the more complex, elastic net-based prediction models did not demonstrate superior performance in predicting short- or long-term all-cause or non-cancer mortality compared to traditional comorbidity scores. In fact, the performance metrics and selected comorbidities indicate there are few differences between our model and the combined comorbidity index model when predicting 5-year non-cancer mortality. This result is surprising given that the combined comorbidity index was developed to predict 1-year all-cause mortality. Other studies developing comorbidity scores tailored for specific cancer sites have also reported limited differences between cancer-specific comorbidity scores and traditional comorbidity scores.[143]

Despite limited differences in the predictive performance of traditional comorbidity scores and our elastic net prediction models, the elastic net models provide results that deserve further consideration. Although the AUC confidence intervals overlap for the elastic net models and the combined comorbidity index model, the AUC values are generally higher for the elastic net models. Even slight improvements in predictive ability could result in better identification of patients with a high risk of a non-cancer death. Additionally, prior studies suggest that the AUCs may not be as sensitive for identifying incremental change after addition of useful predictive markers, such as age in our case.[144,145]

Reclassification metrics provide a more clinical perspective on evaluating the utility of a newly developed predictive model. For our analysis, the NRI indicates that the addition of indicators of frailty provide better classification of older adults who will die or survive in the long-term than the combined comorbidity index model. Notably, the NRI examining the classification of patients as alive indicates that the elastic net models incorporating comorbidity interactions and frailty indicators generally have a lower false-positive rate than the combined comorbidity index for all outcomes except 5-year non-cancer mortality. Probabilities from models that perform better at identifying individuals who are unlikely to

die from causes other than cancer can be used by healthcare providers and patients to characterize the potential benefits of treatment.

Additionally, our findings also add important information on the comorbidity and frailty characteristics that influence mortality and how these characteristics vary according to the type of mortality outcome being assessed. For example, we found that congestive heart failure is an important predictor of both short- and long-term mortality. By understanding how specific comorbidities influence mortality, physicians can tailor treatment decisions for patients according to the comorbidities that they have, rather than to a score representing approximate comorbidity burden. Of note, our results suggest that assessment of non-cancer mortality risks cannot rely on comorbidity information alone and should also incorporate information on prior physical functioning, as was done for our model, or more in-depth health status information obtained through a geriatric assessment.[146]

There are practical and theoretical limitations of our models. First, the sample size of older patients with indolent NHL in the SEER-Medicare dataset is small for model building. Individuals who are older or frailer generally have a higher risk of death, and therefore, our model assigns a higher probability of mortality to patients with these characteristics. However, if a few individuals with high-risk characteristics do not die, our model can overestimate mortality for these patients, as is seen in our calibration plots. Additionally the short-term mortality outcomes are uncommon, especially 1-year non-cancer mortality (prevalence <4%). Despite using penalized regression, our calibration plots suggest that some overfitting remains.[147] For longer-term outcomes, future analyses can also use survival analysis to allow for censoring and the occurrence of competing risks over time. Overestimation of the predicted probability of mortality may also occur if less prevalent comorbidities with a strong relationship with the outcome are included in the model. Future model development should conduct sensitivity analyses assessing influential but less prevalent variables. Another limitation is that our validation set is a random sample from

the same population used for training our model. External validation of our model is unknown. However, SEER-Medicare data are considered to be demographically, geographically, and socioeconomically representative of the US cancer population. Therefore, models developed in this population will likely be similar to those developed in other older US adult populations newly diagnosed with indolent NHL.

Finally, our elastic net models have some limitations in clinical utility. Although a physician can quickly calculate a comorbidity score, our model would require a computer application to aid calculation. In addition, the comorbidity and frailty predictors only reflect the information available in claims data. More predictive indicators of frailty from a geriatric assessment may provide better prediction.

Future versions of the risk model could incorporate patient medications, surgeries, and other health care utilization variables available in claims data to better capture comorbidity severity and improve prediction. However, addition of more variables may make it difficult for physicians to use in the clinic setting, even using an electronic application. Additionally, the probability of non-cancer mortality is only informative for decision-making when contrasted with the potential benefit a patient may receive from a cancer treatment (to reduce their risk of dying from their cancer). Decision analytic approaches could be used in the future to contrast alternative treatment strategies (e.g., less or more aggressive treatment) given the patient's cancer and non-cancer prognosis.[148]

Table 5.1 *Demographic and cancer characteristics of older adults with a first, primary indolent non-Hodgkin lymphoma diagnosis who are diagnosed within 1 year or 5 years of the end of follow-up on Dec. 31, 2012*

Characteristics	1-year (n=9789)		5-year (n=5310)	
	No.	%	No.	%
Age group				
66-69	1866	19.1	1004	18.9
70-74	2342	23.9	1249	23.6
75-79	2335	23.9	1294	24.4
80-84	1858	19.0	1038	19.6
85+	1388	14.2	725	13.7
Sex				
Male	4310	44.0	2355	44.4
Female	5479	56.0	2955	55.7
Race/Ethnicity				
White, non-Hispanic	8828	90.2	4829	90.9
Black, non-Hispanic	475	4.9	245	4.6
Hispanic	145	1.5	64	1.2
Other	341	3.5	172	3.2
Subtype				
Follicular	4466	45.6	2444	46
Marginal Zone	2728	27.9	1407	26.5
CLL/SLL	1799	18.4	1059	19.9
Lymphoplasmacytic	431	4.4	213	4
Mycosis fungoides	365	3.7	187	3.5
Stage				
I/II	5186	50.0	2859	47.6
III/IV	5815	50.0	3149	52.4
Combined comorbidity index				
0	3563	36.4	2038	38.4
1-2	4148	42.4	2220	41.8
>2	2078	21.2	1052	19.8

Table 5.2 *Comorbidity and frailty characteristics of older adults with a first, primary indolent non-Hodgkin lymphoma diagnosis who are diagnosed within 1 or 5 years of the end of follow-up on Dec. 31, 2012*

Characteristics	1-year mortality (n=9789)		5-year mortality (n=5310)	
	No.	%	No.	%
Comorbidities				
Alcohol abuse	70	0.7	33	0.6
Anxiety disorder	244	2.5	100	1.9
Blood loss anemia	146	1.5	95	1.8
Deficiency anemias	399	4.1	203	3.8
Cardiac arrhythmias	1473	15.1	773	14.6
Cerebrovascular disease	718	7.3	390	7.3
Chronic pulmonary disease	1509	15.4	799	15.1
Coagulopathy	395	4.0	204	3.8
Congestive Heart Failure	850	8.7	465	8.8
Dementia	61	0.6	41	0.8
Depression	454	4.6	233	4.4
Diabetes (uncomplicated)	2056	21.0	1088	20.5
Diabetes (complicated)	371	3.8	199	3.8
Drug abuse	31	0.3	19	0.4
Fluid/electrolyte disorders	1016	10.4	546	10.3
Hemiplagia/Paraplegia	44	0.5	24	0.5
Hepatitis B	***	***	***	***
Hepatitis C	33	0.3	17	0.3
HIV/AIDS	***	***	***	***
Hyperlipidemia	3329	34.0	1689	31.8
Hypertension uncomplicated	4503	46.0	2327	43.8
Hypertension complicated	541	5.5	257	4.8
Hypothyoidism	1173	12.0	604	11.4
Liver disease (mild)	51	0.5	25	0.5
Liver disease (moderate/severe)	18	0.2	11	0.2
Myocardial infarction (acute)	112	1.1	75	1.4
Neurodegenerative disorder	341	3.5	185	3.5
Obesity	259	2.7	124	2.3
Peptic ulcer disease	218	2.2	130	2.5
Peripheral vascular disorder	452	4.6	234	4.4
Psychoses	77	0.8	41	0.8
Pulmonary circulation disorders	192	2.0	101	1.9
Renal Disease	576	5.9	229	4.3
Rheumatologic disease	303	3.1	143	2.7
Valvular disease	610	6.2	352	6.6
Weight loss	426	4.4	218	4.1
Frailty Indicators				
Ambulance transport/Life Support	131	1.3	72	1.4
Bladder dysfunction	295	3.0	150	2.8
Decubitus ulcer	201	2.1	104	2.0
Home hospital bed	113	1.2	61	1.2
Hypotension/Shock	214	2.2	119	2.2
Podiatric care	59	0.6	35	0.7
Parkinson's Disease	121	1.2	73	1.4
Rehabilitation care	520	5.3	276	5.2
Oxygen	377	3.9	185	3.5
Vertigo	464	4.7	235	4.4
Weakness	247	2.5	100	1.9
Wheelchair	222	2.3	124	2.3

***Less than 11 persons (information not shown for confidentiality reasons)

Table 5.3 *Area under the curve (AUC) and change in area under the curve in the model with the combined comorbidity index model and elastic net models A-D*

	1-year Mortality				5-year			
	All-cause		Non-cancer		All-cause		Non-cancer	
Predictors	**Avg. AUC (95% CI)**	**ΔAUC**	**Avg. AUC (95% CI)**	**ΔAUC**	**Avg. AUC (95% CI)**	**ΔAUC**	**Avg. AUC (95% CI)**	**ΔAUC**
Combined comorbidity index + age and sex	0.706 (0.672,0.745)	---	0.740 (0.692, 0.783)	---	0.730 (0.700,0.761)	---	0.712 (0.779,0.746)	---
Elastic Net Model A: Age+sex+ 36 comorbidities	0.711 (0.683,0.747)	0.005	0.747 (0.697,0.788)	0.007	0.733 (0.702,0.763)	0.003	0.710 (0.677,0.738)	-0.002
Elastic Net Model B: Age+sex+ 36 comorbidities + 10 comorbidity interactions	0.712 (0.691,0.752)	0.006	0.745 (0.704,0.791)	0.005	0.734 (0.703,0.765)	0.004	0.711 (0.678,0.739)	-0.001
Elastic Net Model C: Age+sex+ 36 comorbidities+ 10 comorbidity interactions + 12 frailty markers	0.716 (0.685,0.748)	0.010	0.753 (0.694,0.786)	0.013	0.737 (0.706,0.768)	0.007	0.716 (0.683,0.742)	0.006
Elastic Net Model D: Age+sex+36 comorbidities+ 10 comorbidity interactions + 12 frailty markers +Indolent NHL subtype	0.715 (0.690,0.750)	0.009	0.748 (0.697,0.786)	0.008	0.740 (0.709,0.771)	0.01	0.715 (0.684, 0.742)	0.003

AUC=area under the curve

Table 5.4 *Average Net Reclassification Improvement [NRI] and Integrated Discrimination Improvement [IDI] indices assessing how classification and discrimination of 1-year all-cause mortality is improved in Models A-D versus the combined comorbidity index model*

EN Model vs. comorbidity	Deaths			Non-Deaths						
	p(+)	p(-)	NRI_{Deaths} (95%CI)[a]	p(+)	p(-)	$NRI_{Non\text{-}deaths}$ (95% CI)[b]	NRI_{Total} (95% CI)[c]	Δsens[d]	Δspec[e]	IDI (95% CI)[f]
1-year All-Cause Mortality										
Model A	0.48	0.52	-0.03 (-0.16,0.09)	0.47	0.53	0.05 (-0.07,0.18)	0.02 (-0.12,0.13)	-0.0001	<0.001	-0.001 (-0.008,0.015)
Model B	0.46	0.54	-0.08 (-0.21,0.04)	0.42	0.58	0.16 (0.03,0.28)	0.08 (-0.06,0.13)	-0.002	-0.003	-0.003 (-0.011,0.027)
Model C	0.46	0.53	-0.07 (-0.20,0.05)	0.41	0.59	0.17 (0.05,0.30)	0.10 (-0.03,0.14)	0.002	0.003	0.003 (-0.004,0.011)
Model D	0.49	0.51	-0.02 (-0.14,0.11)	0.43	0.57	0.14 (0.02,0.27)	0.07 (-0.01,0.13)	0.001	<0.001	0.001 (-0.008,0.019)
1-year Non-Cancer Mortality										
Model A	0.51	0.49	0.03 (-0.05,0.11)	0.49	0.51	0.02 (-0.08,0.12)	0.05 (-0.170.27)	-0.001	<0.001	-0.002 (-0.013,0.010)
Model B	0.50	0.50	0 (-0.08.0.08)	0.46	0.54	0.08 (-0.02,0.17)	0.07 (-0.15,0.30)	-0.005	<0.001	-0.004 (-0.019,0.010)
Model C	0.52	0.48	0.04 (-0.03,0.12)	0.45	0.55	0.10 (0.01, 0.20)	0.14 (-0.08,0.37)	0.004	<0.001	0.004 (-0.006,0.015)
Model D	0.53	0.47	0.06 (-0.02,0.14)	0.46	0.54	0.08 (-0.01,0.18)	0.15 (-0.08,0.37)	0.002	<0.001	0.002 (-0.012,0.016)
5-year All-Cause Mortality										
Model A	0.51	0.49	0.02 (-0.08,0.12)	0.52	0.48	-0.03 (-0.11,0.05)	-0.01 (-0.13,0.11)	-0.003	-0.002	-0.005 (-0.015,0.006)
Model B	0.44	0.56	-0.12 (-0.22,-0.02)	0.45	0.55	0.10 (0.02,0.18)	-0.02 (-0.14,0.00)	-0.009	-0.005	-0.014 (-0.025,-0.003)
Model C	0.47	0.53	-0.06 (-0.16,0.03)	0.41	0.59	0.18 (0.11,0.26)	0.12 (0, 0.24)	0.003	0.002	0.004 (-0.004,0.013)
Model D	0.49	0.51	-0.02 (-0.13,0.07)	0.43	0.57	0.14 (0.07,0.22)	0.12 (0 ,0.24)	<0.001	<0.001	-0.001 (-0.011,0.009)
5-year Non-Cancer Mortality										
Model A	0.52	0.48	0.05 (-0.10,0.19)	0.48	0.52	0.04 (-0.11,0.03)	0.08 (-0.08,0.23)	<0.001	<0.001	0 (-0.013,0.013)
Model B	0.55	0.45	0.09 (-0.05,0.23)	0.50	0.50	0 (-0.07,0.07)	0.09 (-0.06,0.24)	-0.007	-0.002	-0.009 (-0.024, 0.007)
Model C	0.53	0.47	0.06 (-0.08,0.20)	0.47	0.53	0.05 (-0.12,0.01)	0.12 (-0.04, 0.27)	<0.001	<0.001	-0.001 (-0.015,0.013)
Model D	0.54	0.46	0.08 (-0.06,0.22)	0.49	0.51	0.01 (-0.09,0.05)	0.09 (-0.06,0.25)	-0.007	-0.002	-0.009 (-0.025,0.008)

Model A:36 comorbidities***; Model B:*** *36 comorbidities + 10 comorbidity interactions****; Model C:*** *36 comorbidities + 10 comorbidity interactions +12 frailty predictors****; Model D:*** *36 comorbidities + 10 comorbidity interactions +12 frailty predictors+ indolent NHL subtype;* ***p***=the proportion of events/non-events, where *p*(+) is the proportion of true events/non-events that were reclassified correctly as events/non-events in the index model versus comparison model and *p*(-) ; NRI=Net Reclassification Improvement; IDI=Integrated Discrimination Improvement; [a]Calculated as the proportion increase - proportion decrease for deaths; [b]Calculated as the proportion decrease - proportion increase for non-deaths; cSum of NRI_{Deaths} and $NRI_{Non\text{-}deaths}$; [d] Mean increase in probability of correctly being classified as a death (sensitivity); [e] Mean decrease in probability of correctly being classified as a non-death (specificity); [f] Difference in the average sensitivitiy-(1-specificity), which is the same as the difference in the Yates' discrimination slopes

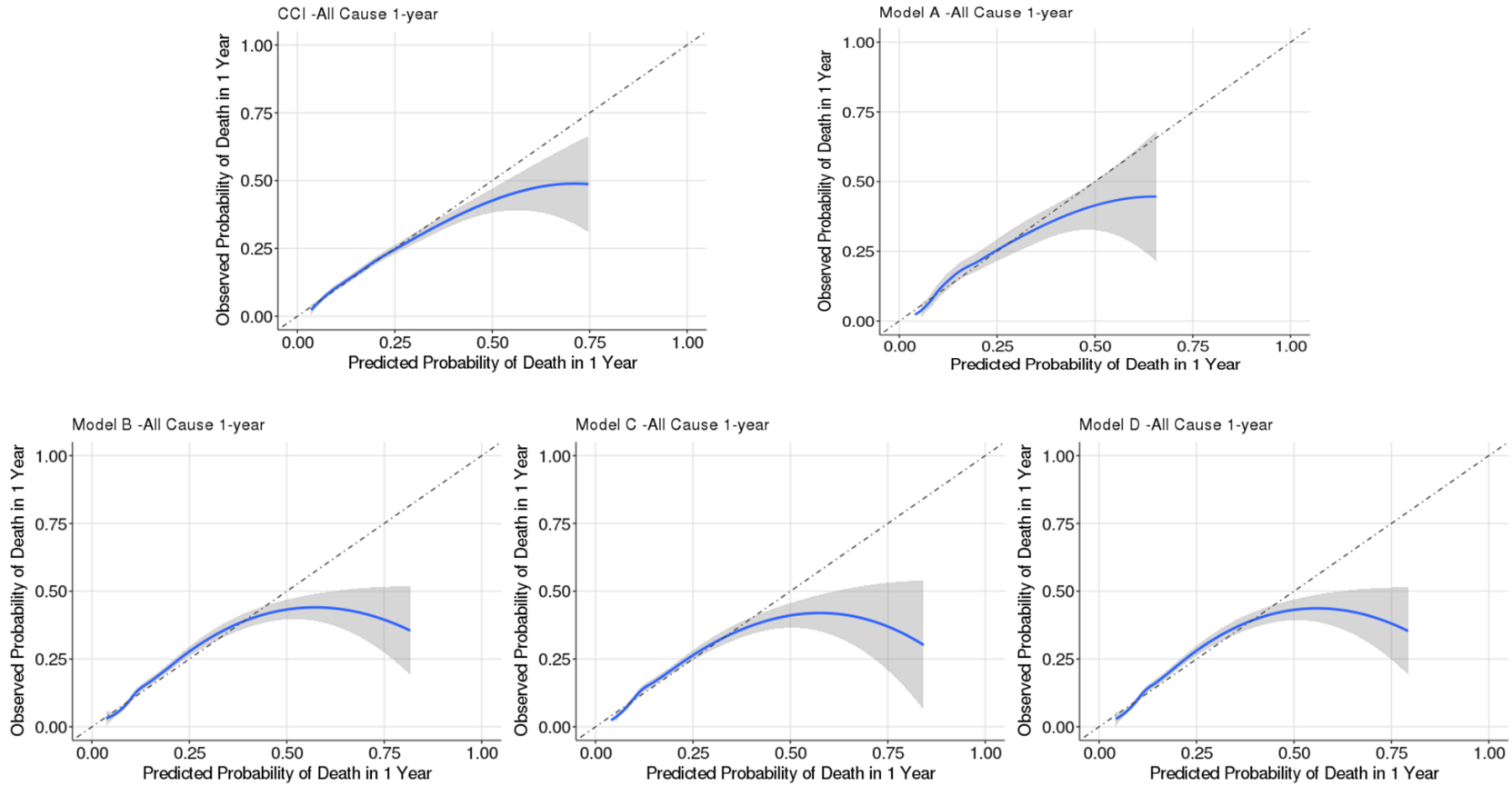

Figure 5.1 *Calibration plots for the combined comorbidity index model and elastic net models A-D comparing loess-smoothed observed probabilities on predictive probabilities of 1-year all-cause mortality*

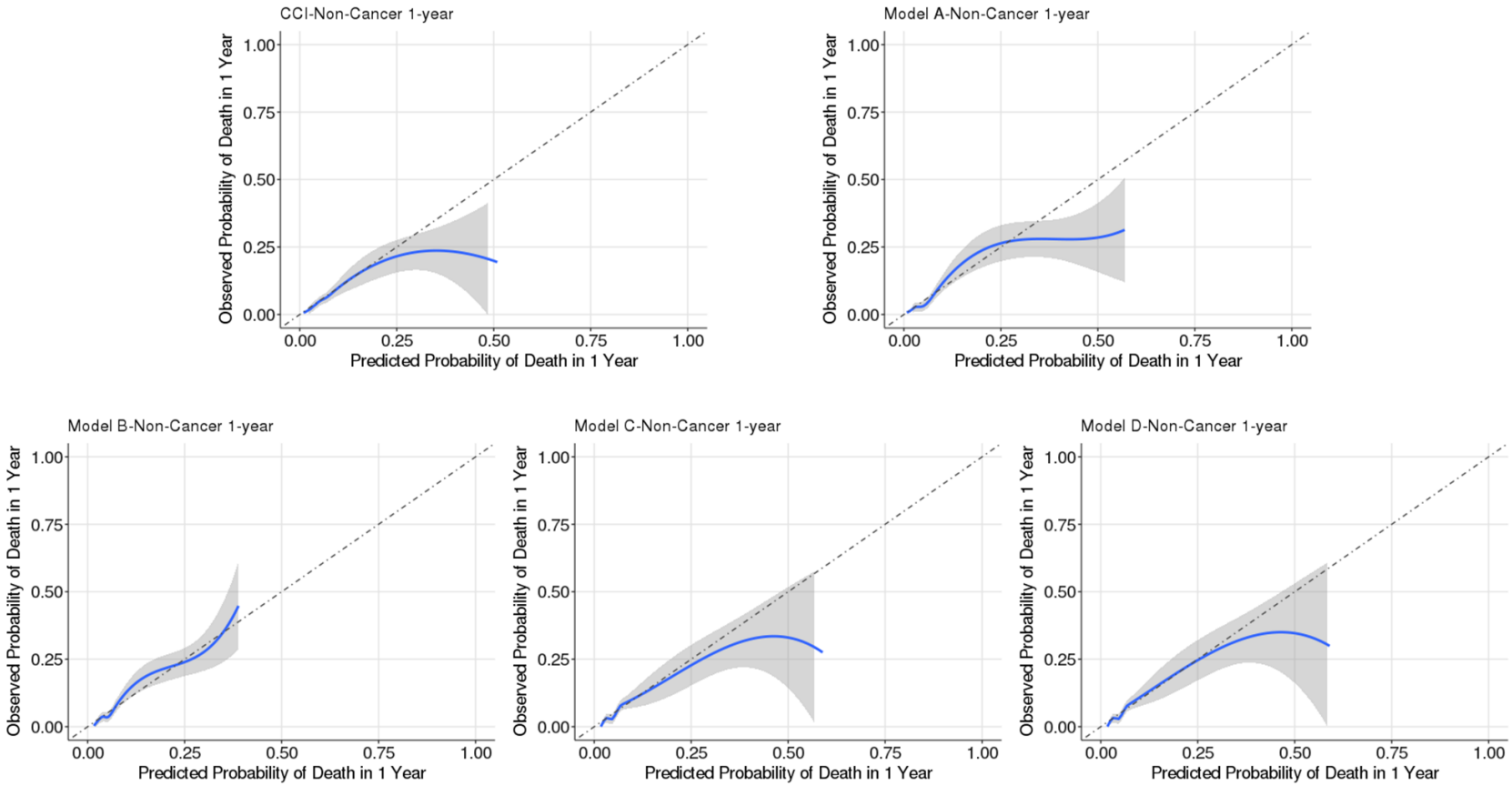

Figure 5.2 *Calibration plots for the combined comorbidity index model and elastic net models A-D comparing loess-smoothed observed probabilities on predictive probabilities of 1-year non-cancer mortality*

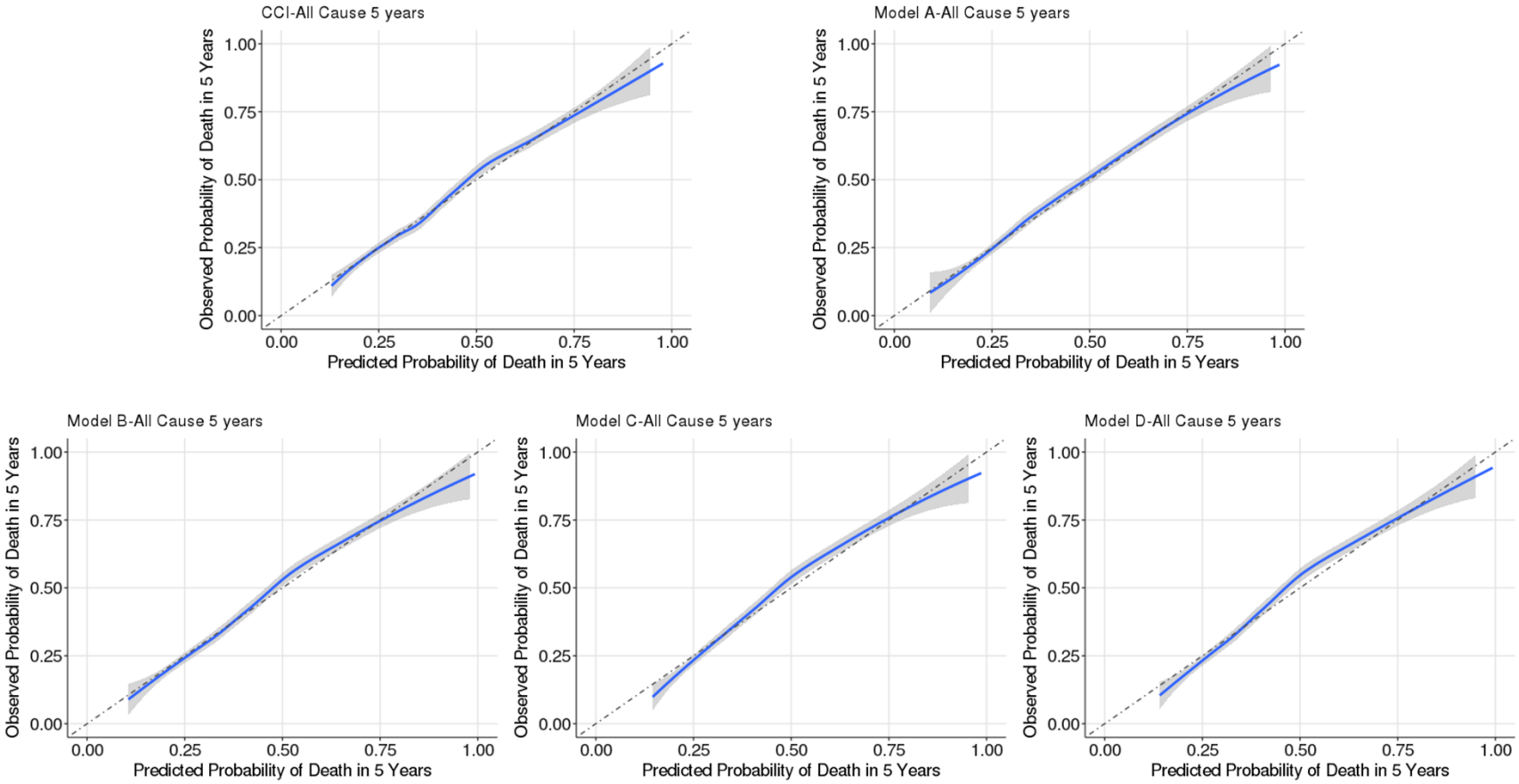

Figure 5.3 *Calibration plots for the combined comorbidity index model and elastic net models A-D comparing loess-smoothed observed probabilities on predictive probabilities of 5-year all-cause mortality*

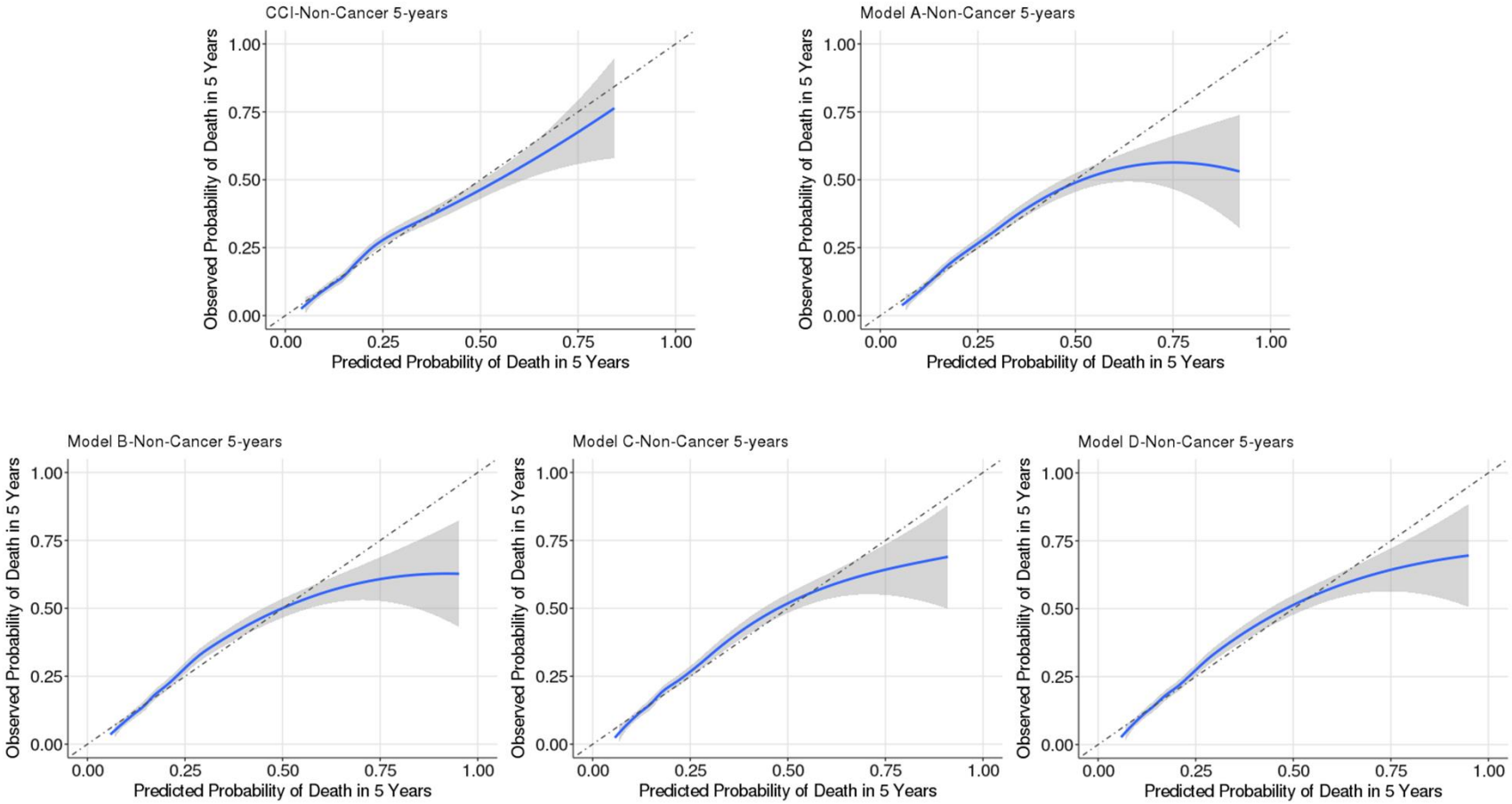

Figure 5.4 *Calibration plots for the combined comorbidity index model and elastic net models A-D comparing loess-smoothed observed probabilities on predictive probabilities of 5-year non-cancer mortality*

CHAPTER 6: CONCLUSIONS

A. Summary of Findings

The objective of this research was two-fold. First, this project sought to identify how estimates of cancer-specific and non-cancer mortality varied across subtypes, age groups, comorbidity levels, stage, and time since diagnosis. A specific goal of this analysis was to confirm or refute the hypothesis that non-cancer mortality risk exceeded cancer-specific mortality risk in the indolent NHL subtypes. This information is important for justifying the development of risk scores and supportive interventions targeting these subtypes. The second aim of this project was to use penalized machine learning regression methods to develop an enhanced risk prediction model that improves identification of older patients with indolent NHL who have a high risk of non-cancer mortality. These new models were assessed against a logistic regression with a traditional comorbidity score to identify whether the machine learning models provided better prediction for informing treatment decision-making.

Aim 1 Conclusions

The findings from Aim 1 suggest that for most subtypes, NHL-specific mortality increases with age, and non-cancer mortality increases with age and comorbidity level. Similar patterns have been observed in other cancer sites.[5,27,31,127] At five years post-diagnosis, NHL-specific mortality is higher for aggressive subtypes compared to indolent subtypes. In contrast, the cumulative incidence of non-cancer mortality is higher in indolent subtypes than aggressive subtypes, especially for patients diagnosed with marginal zone lymphoma and mycosis fungoides. Patterns in indolent subtypes mirror those previously

reported for slower-growing, early stage solid tumors.[5,27,128,129] By exploring patterns of NHL-specific and other-cause mortality, our results contribute unique, population-level evidence about the impact of competing risks on survival in older NHL patients.

Aim 2 Conclusions

Aim 2 sought to improve identification of older adults with a high risk of non-cancer mortality after an indolent NHL diagnosis by developing risk prediction models using elastic net machine learning methods. Four outcomes and up to 141 predictors were assessed. Four elastic net models were built for each outcome to observe how prediction changed when addressing limitations of traditional comorbidity scores. When comparing model discrimination, we found that the elastic net-based prediction models had a higher average AUC than the models with the combined comorbidity score. Even slight improvements in predictive ability can improve identification of patients with a high risk of a non-cancer death.[145] However, there was overlap in the AUC confidence intervals for the elastic net models and the model with the combined comorbidity score, suggesting that improvement in discrimination was not statistically significant.

Prior studies suggest that AUC may not be as sensitive for identifying incremental change after addition of strong predictive markers, such as age in our case.[119] Reclassification metrics, such as the NRI and the IDI, provide interpretable, clinically useful information on the ability of the elastic net models to correctly reclassify individuals in comparison with the combined comorbidity index model. In general, our results suggest that the elastic net models are more likely to assign a lower probability of mortality to those who do not die in comparison with the traditional comorbidity score model (lower false-positive rate). The elastic net model that includes the 36 comorbidities, the interactions between the 10 comorbidities, and the frailty predictors provided the best reclassification in comparison with the traditional comorbidity models. This suggests that comorbidities alone may not provide enough information about non-cancer mortality risk; frailty predictors may improve

accurate assessment of mortality risk. The calibration models support the findings on performance, though they also indicate that our sample size and outcome prevalence may be too small to achieve perfect calibration for the 1-year all-cause and non-cancer mortality outcomes.

Ultimately, the performance metrics did not indicate that the elastic net models were superior at predicting either short- or longer-term all-cause or non-cancer mortality in comparison with the comorbidity score model. In fact, the comorbidities selected by the elastic net models appeared similar to those used in the combined comorbidity score for the 5-year non-cancer mortality outcome. Despite being built to predict 1-year all-cause mortality, the combined comorbidity score model did slightly better (but not statistically significantly better) at predicting 5-year non-cancer mortality. This pattern may arise if the non-cancer risks of an individual 5 years after an indolent NHL diagnosis are similar to the risks of the average Medicare beneficiary in the cohorts used for developing and validating the combined comorbidity index.

B. Public Health Implications of Findings

In order to respond to the growing population of older adults, cancer survivors and patients with complex health profiles, we need informed interventions that reduce the risk of comorbidity exacerbations and help avoid deaths due to non-cancer conditions. The findings from this research have key implications for public health.

Overall, our results from Aim 1 raise awareness of the importance of non-cancer mortality in indolent NHL, specifically among older individuals and those with higher burdens of comorbidities. These results could potentially support resource planning in hospitals or other cancer care facilities. For example, patients with older ages, higher comorbidity scores, and indolent subtypes could be flagged for receiving additional guidance on comorbidity management and care coordination from pharmacists or nurses. Specifically, these results support enhanced care coordination interventions and supportive services

focused in indolent NHL patients aged >75 who have ≥2 comorbidities at baseline. Additionally, our Aim 1 findings support use of actual prognosis measures accounting for competing risks in future development of personalized risk models that guide treatment discussions between hematologist/oncologists and patients.

Our Aim 2 results provide the first description of the comorbidity burden in older adults with indolent NHL. Notably, these results bring attention to the fact that >60% of older patients have comorbidities, and 13 of these comorbidities have a prevalence >5%. Importantly, Aim 2 provides a thorough examination of the limitations of widely used comorbidity scores and how these scores could be improved. Finally, the models developed in this aim provide a foundation for models that can be laid on top of electronic health records systems to aid in identifying whether a patient might experience a benefit from NHL treatment that outweighs the risks of a comorbidity death.

C. Limitations

Aim 1 Limitations

The purpose of Aim 1 is to provide a high-level view of cause-specific mortality patterns to identify the general risk groups in which risk-benefit treatment trade-offs and supportive care interventions would be most beneficial. However, this simple descriptive strategy has some limitations. First, the 5-year crude mortality risks reflect death in the presence of treatments available for the patient at the time of their diagnosis from 2004-2011. There have been advances in NHL treatment since 2004, such as improvements in stem-cell transplants and increased use of rituximab. Due to treatment advances, 5-year crude mortality risks may look different for patients diagnosed in 2004 than those diagnosed in 2011. Although prior studies have shown mortality rates plateauing during this time period,[114] relative measures utilizing expected survival data from life tables may be better for exploring time trends in NHL prognosis.[31] Additionally, Aim 1 results provide baseline risks and do not consider how different treatments impact patterns of cause-specific

mortality. However, patterns by baseline characteristics should be understood before exploring patterns in specific treatment groups because baseline characteristics drive treatment decisions.

There are also limitations associated with using existing registry and claims data. Despite use of the refined NCI cause-specific death variable, cause of death may be misclassified, leading the cumulative incidence of NHL-specific mortality to falsely appear higher or lower than non-cancer mortality across subtypes and time periods.[28,136] Additionally, we are only able to examine patterns of cause-specific mortality by potentially important prognostic factors that are available in the SEER-Medicare data. Approximately 89% of NHL patients are missing the International Prognostic Index (IPI),[135] which is a score widely used by hematologist/oncologists to inform NHL treatment decisions. Cancer-specific and non-cancer mortality may have different patterns by IPI scores. Finally, we define comorbidities in the claims data using a 12-month look-back window. A patient must have accessed their physician and received a comorbidity code during this window in order to be classified as having a comorbidity. Future studies could consider all-available claims and the timing of those claims before the cancer diagnosis to improve classification of those with and without comorbidities.

Aim 2 Limitations

There are practical and theoretical limitations of our elastic net models. First, the sample size of older patients with indolent NHL in the SEER-Medicare dataset is small for model building. Individuals who are older or frailer generally have a higher risk of death, and therefore, our model assigns a higher probability of mortality to patients with these characteristics. However, if a few individuals with high-risk characteristics do not die, our model can overestimate mortality for these patients, as is seen in our calibration plots. Future studies could trim outlying patients and observe how these actions change calibration. Additionally, the short-term mortality outcomes are uncommon, especially 1-

year non-cancer mortality (prevalence <4%), which may contribute to overfitting, as indicated by our calibration plots.[147] We assessed longer term (5-year) outcomes to address these rarer outcomes. However, censoring and competing risks are more of an issue in analyses of longer-term outcomes. Future analyses should use survival analysis to account for competing risks and allow for censoring over time. Overestimation of the predicted probability of mortality may also occur if less prevalent comorbidities with a strong relationship with the outcome are included in the model. Sensitivity analyses could be used to assess the importance of influential but less prevalent variables. Another limitation is that our validation set is a random sample from the same population that is used for training our model. External validation of our model is unknown. However, SEER-Medicare is derived from population-based data considered to be demographically, geographically, and socioeconomically representative of the US cancer population. Therefore, models developed in this population will likely be similar to those developed in other older US adult populations newly diagnosed with indolent NHL. A final limitation is that our elastic net models may be difficult to calculate in the clinic, limiting its utility in clinical decisions. Although a physician can quickly calculate a comorbidity score, our model would require a computer application to aid calculation.

D. Next Steps

The work presented in this research project is foundational. It provides information on the basic patterns of cause-specific mortality in NHL and a simple, claims-based risk prediction tool for identifying older adults with a high risk of non-cancer mortality outcomes. By establishing the basic cause-specific patterns and developing general prediction tools to identify individuals with a high risk of non-cancer mortality, we now have strong evidence to support development of plausible interventions for improving non-cancer outcomes in older adults with indolent NHL and to create complex risk prediction models for use in electronic health records.

The Aim 1 findings describe population-level patterns in the cumulative incidence of NHL-specific and non-cancer mortality. These population-level results suggest that treatment decision-making for patients with indolent subtypes who are older or have higher comorbidity levels may benefit from information on the cumulative incidence of non-cancer mortality compared to NHL-specific mortality. However, to improve outcomes among older NHL patients, individual-level estimates of the cumulative incidence of cancer-specific and non-cancer mortality are needed, as well as tools that predict these outcomes according to a patient's specific characteristics. Current NHL prognosis tools, such as the International Prognostic Index[135] and Follicular Lymphoma Prognostic Index,[138] were developed to inform providers on a patient's probability of overall mortality. However, these tools do not provide evidence about a patient's cancer-specific mortality risk in the presence of competing risks, nor do they inform providers on the risk of death from causes other than NHL. Currently, the NCI is developing the SEER*CSC tool for prostate, breast, colorectal, and head-and-neck cancers, which will provide nomograms for predicting the cumulative incidence of surviving or dying from cancer or other causes based on a patient's tumor, age, race, gender, and other measures of health status.[139,149] Our study informs the development of predictive tools like the SEER*CSC nomogram for NHL, which would generate highly personalized, actual prognosis measures for informing treatment discussions between providers and older patients with NHL.

We want to improve our risk prediction model so that it provides more information about benefit-risk tradeoffs of less vs. more aggressive treatments in indolent NHL. In order to use the elastic net risk prediction models to inform treatment decisions, we will need to build risk prediction models for specific chemoimmunotherapy regimens. These models will provide information on the risk of non-cancer mortality within treatments. However, these models will not provide the actual prognosis for everyone in the population, but rather those channeled into specific treatments. We would expect that younger individuals with a lower

comorbidity burden and less frailty would receive more aggressive treatments, while frailer, older patients with more comorbidities are likely channeled into less aggressive treatments, like rituximab monotherapy and watch-and-wait strategies.[133] Therefore, to provide context for these treatment-specific risk prediction models, more research would be required on how hematologist/oncologists and patients make treatment decisions and what are the comorbidity and frailty characteristics of individuals who receive each treatment.

Future versions of the risk prediction model may also be enhanced by using survival analysis, which can improve upon our logistic regression models by addressing competing risks and administrative censoring. Models created with survival analysis can also be used to predict risk at certain times conditional on the fact that a patient has survived to that point, allowing for identification of non-cancer risk in individuals who have survived the first round of treatment.[112] This information is especially important for informing treatment decisions for relapses.

In order to provide the best information for use by physicians and patients when making treatment decisions, future studies should apply findings from this research in the development of decision curves based in decision–theoretic principle.[148] These curves provide information on how a physician and patient might weigh the harms of overtreatment with more aggressive chemoimmunotherapies (when a patient is identified as being at high risk for a non-cancer death but is actually low risk) with the harms of undertreatment with less aggressive treatment (when a patient is identified as being low risk for a non-cancer death but is actually high risk).

Finally, in order to improve outcomes once a patient with a poor non-cancer prognosis is identified, we need well-designed interventions for reducing non-cancer mortality. Interventions focused on comorbidity management and care coordination would help patients receive recommended preventative and supportive treatment services during and after their cancer treatment.[150] These interventions could include reminder systems,

patient navigation programs, and monitoring of comorbidity medication adherence.[146,150,151] This multi-level intervention approach will require a nationwide change within our healthcare system. However, these changes are critical for addressing the needs of the growing population of older adults faced with managing indolent NHL and other relapsing-remitting chronic hematologic cancers.

APPENDIX 1: BACKGROUND AND CODING INFORMATION

Table A1.1 *Prevalence of comorbidities or comorbidity severity among chronic hematologic cancers or indolent non-Hodgkin lymphoma (NHL) reported in the literature*

Source	Size	Cohort	Years	Ages	Cancer	Comorbidity	Prev. (%)
Breccia et al., 2014[152]	181	Patients aged >75 yrs treated with imatinib from 21 Italian Centers	NR	>75	Chronic myeloid leukemia	CCI* 0	71
						CCI 1	50
						CCI 2	37
						CCI 3+	23
Goede et al., 2014[153]	555	Two trials of the German Chronic Lymphocytic Leukemia Study Group on first-line treatment with fludarabine plus cyclophosphamide, fludarabine, or chlorambucil	N/A	30+	Chronic lymphocytic leukemia	# Comorb 0	47
						#Comorb 1	28
						# Comorb 2+	25
						Cardiac	12
						Vascular	21
						Respiratory	5
						Eyes/ears/nose/ throat	2
						Intestinal	4
						Hepatic	2
						Renal	3
						Urogenital	4
						Metabolic/ Endocrine	26
						Musculoskeletal	5
						Neurologic	2
						Psychiatric	1
Griffiths et al., 2012[154]	1117	SEER-Medicare	2005-2007	≥66	Follicular lymphoma	NCI Combined index 0	71.0
						NCI Combined index 1	20.9
						NCI Combined index 2+	7.8
Gritti et al., 2016[86] (Abstract)	427	1 Italian Cancer Center	1990-2012	60-94	Indolent NHL (Follicular, marginal zone leukemia, lymphoplasmacytic)	CIRS-G*<6	75
						CIRS-G 6+	25
						1+ comorbidity	85
						Vascular	45
						Metabolic/ endocrine	24
						Heart	17
Lin et al., 2016	2164	SEER-Medicare	1995-2007	≥66	Chronic myeloid leukemia	CCI 0	53
						CCI 1	25
						CCI 2	22

Source	Size	Cohort	Years	Ages	Cancer	Comorbidity	Prev. (%)
Mohammadi et al., 2015[155]	2550	Swedish National Registry	2002-2009	>18	Chronic myeloid leukemia	Prior Cancer	13
						CVD	10
						Diabetes	7.2
						Cerebrovascular	5.4
						Chronic pulmonary	5.1
						PVD	3
						Peptic ulcer	3
						Rheumatologic	2
						Renal disease	0.5
						Liver disease	0.8
						Dementia	1
						Psychiatric disorders	1.6
						Hemiplegia/Paraplegia	0.3
						AIDS/HIV	0
Olzewski and Castillo et al., 2013[84]	1134	SEER-Medicare	1997-2007	≥66	Gastric MALT lymphoma (indolent NHL)	CCI 0	56
						CCI 1	26
						CCI 2	15
						CCI 3+	3
Olzewski et al., 2015[83]	6993	SEER-Medicare	1996-2010	≥66	Indolent NHL (follicular lymphoma, nodal marginal zone lymphoma, small lymphocytic leukemia)	NCI Comorbidity index 0	56.9
						NCI Comorbidity index 1	25.1
						NCI Comorbidity index 2+	17.9

CCI=Charlson comorbidity index/score; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; comorb=comorbidities

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Table A1.2 *Hematologic subtypes included and excluded in the indolent non-Hodgkin lymphoma (NHL) definition and categorization of patients into indolent and aggressive tumor growth groups*

Included (ICD-0-3 code)
▪ **Indolent NHL** • Follicular lymphoma (9690-9691, 9695, 9698) • Lymphoplamacytic/Waldenstrom macroglobulinemia (9761) • Marginal-zone lymphoma-MALT, splenic, nodal (9689,9760, 9764, 9699) • Mycosis fungoides (9700) • CLL/SLL in lymph nodes (9760)
Excluded (ICD-0-3 code)
▪ **Aggressive NHL** • Diffuse large B-cell lymphoma (9680, 9688, 9737-9738, 9684, 9712, 9678, 9679) • Burkitt lymphoma (9687,9826) • Mantle Cell lymphoma (9673) • Peripheral T-cell lymphoma (9702, 9675, 9705, 9708, 9714, 9716, 9717,9709, 9826, 9718) • Sezary Syndrome (9701) • **Leukemias** (ICD-0-3 9733, 9742, 9800-9801, 9805-9809, 9811-9818, 9820, 9826-9827 9831-9837, 9840, 9860-9861, 9863, 9865-9867, 9870-9871, 9875-9876, 9891, 9898, 9910-9911, 9920, 9930, 9940, 9945-9946, 9948) • **Lymphoblastic leukemia/lymphomas** (ICD-O-3 9811-9818, 9837) • **Plasma cell/myelomas** (ICD-O-3 9731-9732, 9734, 9762) • **Precursor lymphomas** (ICD-O-3 9724-9729, 9735) • **HHV8-asssociated T-cell lymphomas** (9738)

Table A1.3 *Comorbidity and markers of frailty used in Aim 2 prediction models*

Predictor	ICD-9 CM/HCPCS/CPT	Source
Comorbidities		
Alcohol abuse	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3	Elixhauser/Quan (Van Walvaren)
Anxiety disorder	293.84, 300.00-300.02, 300.10, 300.20-300.23, 300.29, 300.3, 300.5, 300.89, 300.9, 308.0-308.9, 309.81, 313.0, 313.1, 313.22, 313.3, 313.82, 313.83	CMS Chronic Disease Warehouse
Blood loss anemia	280	Elixhauser/Quan (Van Walvaren)
Cardiac arrhythmias	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0-427.4, 427.6-427.9, 785.0, 996.01, 996.04, V45.0, V53.3	Elixhauser/Quan (Van Walvaren)
Cerebrovascular disease	430.x-438.x	Elixhauser/Quan (Van Walvaren)
Chronic obstructive pulmonary disease	490.x-496.x, 500.x-505.x, 506.4	Charlson/Romano
Coagulopathy	286.x, 287.1, 287.3-287.5	Elixhauser/Quan (Van Walvaren)
Congestive Heart Failure	428.x	Charlson/Romano
Deficiency anemias	280.1-280.9, 281.x	Elixhauser/Quan (Van Walvaren)
Dementia	290.x	Charlson/Romano
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311	Elixhauser/Quan (Van Walvaren)
Diabetes (uncomplicated)	250.0–250.3, 250.7	Charlson/Romano
Diabetes (complicated)	250.4–250.6, 250.8-250.9	Charlson/Romano
Drug abuse	292.x, 304.x, 305.2– 305.9, V65.42	Elixhauser/Quan (Van Walvaren)
Fluid/electrolyte disorders	253.6, 276.x	Elixhauser/Quan (Van Walvaren)
Hemiplegia/Paraplegia	342.x, 344.1	Charlson/Rmano
Hepatitis B	070.2, 070.20, 070.21, 070.22, 070.23, 070.30, 070.31, 070.32, 070.33	Niu et al.,
Hepatitis C	070.41, 070.44, 070.51, 070.54, 070.7, 070.70, 070.71	Niu et al.,
HIV/AIDS	42.x-44.x	Charlson/Romano
Hyperlipidemia	272.0, 272.1, 272.2, 272.3, 272.4	Elixhauser/Quan (Van Walvaren)
Hypertension uncomplicated	401.x	Elixhauser/Quan (Van Walvaren)
Hypertension complicated	402.x-405.x	Elixhauser/Quan (Van Walvaren)
Hypothyroidism	240.9, 243.x, 244.x, 246.1, 246.8	Elixhauser/Quan (Van Walvaren)
Liver disease (mild)	571.2, 571.4, 571.5, 571.6	Charlson/Romano
Liver disease (moderate/severe)	456.0–456.2, 572.2–572.8	Charlson/Romano
Myocardial infarction (acute)	410.x,	Charlson/Romano

Predictor	ICD-9 CM/HCPCS/CPT	Source
Comorbidities Cont.		
Neurodegenerative disorder	331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x–335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3	Elixhauser/Quan (Van Walvaren)
Obesity	278	Elixhauser/Quan (Van Walvaren)
Peptic ulcer disease	531.x–534.x	Charlson/Quan
Peripheral vascular disorder	441.x, 443.9, 785.4, V43.4	Charlson/Romano
Psychoses	295.x, 296.04, 296.14, 296.14, 296.44, 296.54, 297.x, 298.x	Elixhauser/Quan (Van Walvaren)
Pulmonary circulation disorders	415.0, 415.1, 416.x, 417.0, 417.8, 417.9	Elixhauser/Van Walvaren
Chronic Renal Failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x	Charlson/Romano
Rheumatologic disease	446.5, 710.0–710.4, 714.0– 714.2, 714.8, 725.x	Charlson/Romano
Valvular disease	093.2, 394.x–397.x, 424.x, 746.3–746.6, V42.2, V43.3	Elixhauser/Quan (Van Walvaren)
Weight loss	260.x-263.x, 783.2, 799.4	Elixhauser/Quan (Van Walvaren)
Markers of Frailty (not included above as comorbidities)		
Bladder Incontinence	788.3, 788.2, 596.5, 599.6	Faurot et al.
Decubitus ulcer	707.x	Faurot et al.
Difficulty walking	719.7, 781.2, 781.3, 438.85, V46.3	Faurot et al.
Parkinson's Disease	332	Faurot et al.
Podiatric care	700., 703., 681.1	Faurot et al.
Rehabilitation care	V57.1, V57.21, V57.3, V57.89, V57.9	Faurot et al.
Shock	458., 785.5, 958.4, 998.0	Faurot et al.
Vertigo	386., 780.4	Faurot et al.
Weakness	728.2, 728.87, 799.3, 728.2, 728.3, V49.84	Faurot et al.
Home hospital bed	E0250, E0251, E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0290, E0291-297, E0301-304, E0316	Faurot et al.
Ambulance transport/Life Support	A0426, A0427, A0428, A0429, A0999	Faurot et al.
Home oxygen	E1390-1392, E0431, E0433-435, E0439, E0441-443	Faurot et al.
Wheelchair	E1050, E1060, E1070, E1083-1093, E1100, E1110, E1120, E1140, E1150, E1160, E1161, E1170, K0001-9	Faurot et al.

APPENDIX 2: ELASTIC NET MODEL COEFFICIENTS

Table A2.1 *Average coefficients (log odds ratios) and interaction terms for Models A-D predicting 1-year all-cause mortality from 100 resampled training and validation sets*

Predictors	Model A	Model B	Model C	Model D
(Intercept)	-2.8611	-2.7192	-2.7331	-2.6782
Demographics				
Age 70-74 vs. 66-69	0	0	0	0
Age 75-79 vs. 66-69	0.5214	0.4430	0.4591	0.4715
Age 80-84 vs. 66-69	0.8398	0.7855	0.7952	0.8149
Age 85+ vs. 66-69	1.3268	1.2786	1.2783	1.3188
Sex (Male vs. Female)	-0.1484	-0.1811	-0.2029	-0.1922
Comorbidities				
Alcohol Abuse	0.1681	0.0494	0.0543	0.0892
Anemia (Blood loss)	0.0947	0.0302	0.0284	0.0584
Anemia (Deficiency)	0	0	0	0
Anxiety	-0.1598	-0.0724	-0.0946	-0.0973
Arrhythmia	0.2933	0.2251	0.2226	0.2217
CEVD	0.3112	0.1098	0.0931	0.1265
CHF	0.5866	0.8107	0.7916	0.8204
Coagulopathy	0.3154	0.2915	0.2751	0.3102
COPD	0.3284	0.4203	0.4255	0.4509
Dementia	0.3050	0.2965	0.2677	0.3026
Depression	0.2389	0.2361	0.2078	0.2294
Diabetes (uncomplicated)	0.1860	0.1612	0.1525	0.1497
Diabetes (complicated)	0.3436	0.3618	0.2403	0.2416
Drug Abuse	0.2134	0.0795	0	0
Fluid/electrolyte disorder	0.3354	0.3649	0.3524	0.3735
Hepatitis B	-1.2849	-0.8190	-0.9718	-0.9617
Hepatitis C	0.8015	0.6924	0.7593	0.7895
HIV/AIDS	-1.039	-0.2616	-0.2578	-0.2540
Hyperlipidemia	-0.3152	-0.2684	-0.2582	-0.2698
Hypertension(uncomplicated)	0.0802	0.1084	0.1206	0.1280
Hypertension (complicated)	-0.0880	-0.0470	-0.0523	-0.0586
Hypothyroidism	0	0	0	0
Liver disease (mild)	0.6239	0.6394	0.6062	0.6715
Liver disease (moderate/severe)	0	0	0	0
Myocardial infarction (acute)	0.2377	0.2160	0.1923	0.2189
Neurological disorder	0.3517	0.3340	0.2654	0.2585
Obesity	0	0	0	0
PCD	0.1156	0.1118	0.1487	0.1252
Hemiplegia/Paraplegia	0.3279	0.1496	0.0324	0.0502
Pscyhosis	0	0	0	0
Peripheral vascular disease	0.0402	0	0	0
Renal disease	0.1408	0.0953	0.0778	0.0752
Rheumatologic/orthopedic disease	0.1439	0.1015	0.0479	0.0603
Peptic ulcer disease	0.0463	0.0241	0	0.0671
Valvular disease	-0.0151	0	0	0
Weightloss	0.7888	0.7670	0.7621	0.7821

Predictors	Model A	Model B	Model C	Model D
Comorbidity Interactions				
Arrhythmia:CEVD		0.089	0	0
Arrhythmia:CHF		-0.2716	-0.3086	-0.3368
Arrhythmia:COPD		0	0	0
Arrhythmia:Diabetes (mild)		0	0	0
Arrhythmia:Diabetes (Moderate/Severe)		0	0	0
Arrhythmia:Fluid Disorder		0.3970	0.4370	0.4472
Arrhythmia:Hyperlipidemia		0	0	0
Arrhythmia:Hypertension (uncomplicated)		0	0	0
Arrhythmia:Hypothyroidism		0.2032	0.2061	0.2148
Arrhythmia:PVD		0	0	0
CEVD:CHF		0	0	0
CEVD:COPD		-0.1507	-0.1695	-0.1890
CEVD:Diabetes (mild)		0.4859	0.4530	0.4777
CEVD:Diabetes (Moderate/Severe)		0.1610	0.3199	0.3185
CEVD:Fluid Disorder		0.1244	0.0972	0.1061
CEVD:Hyperlipidemia		0	0	0
CEVD:Hypertension (uncomplicated)		-0.2105	-0.2017	-0.2455
CEVD:Hypothyroidism		0.6147	0.6053	0.6109
CEVD:PVD		0.5386	0.5629	0.5575
CHF:COPD		0.0126	0	0.029
CHF:Diabetes (mild)		0	0	0
CHF:Diabetes (Moderate/Severe)		-0.2284	-0.3496	-0.4112
CHF:Fluid Disorder		-0.1338	-0.1927	-0.2099
CHF:Hyperlipidemia		0	0	0
CHF:Hypertension (uncomplicated)		0	0	0
CHF:Hypothyroidism		-0.3117	-0.3502	-0.3319
CHF:PVD		0	0	0.0177
COPD:Diabetes (mild)		-0.1370	-0.1472	-0.1613
COPD:Diabetes (Moderate/Severe)		0	0	0
COPD:Fluid Disorder		-0.1812	-0.2119	-0.2324
COPD:Hyperlipidemia		0	0	0
COPD:Hypertension (uncomplicated)		0	0	0
COPD:Hypothyroidism		-0.1165	-0.1418	-0.1568
COPD:PVD		0	0	0
Diabetes (mild):Diabetes (Moderate/Severe)		0	0.0344	0.0454
Diabetes (mild):Fluid Disorder		0	0	0
Diabetes (mild):Hyperlipidemia		-0.0590	-0.0643	-0.0688
Diabetes (mild):Hypertension (uncomplicated)		0	0	0
Diabetes (mild):Hypothyroidism		0.0520	0.0717	0.1159
Diabetes (mild):PVD		0	0	0
Diabetes (Moderate/Severe):Fluid Disorder		0.3815	0.4316	0.4878
Diabetes (Moderate/Severe):Hyperlipidemia		0	0	0
Diabetes (Moderate/Severe):Hypertension (uncomplicated)		0	0	0
Diabetes (Moderate/Severe):Hypothyroidism		-0.1703	-0.1242	-0.1745
Diabetes (Moderate/Severe):PVD		-0.6855	-0.9137	-0.9190
Fluid Disorder:Hypothyroidism		0	0	0
Fluid Disorder:PVD		0	0	0
Hyperlipidemia:Fluid Disorder		-0.0652	-0.0765	-0.0923
Hyperlipidemia:Hypertension (uncomplicated)		0	0	0
Hyperlipidemia:Hypothyroidism		-0.0210	0	0

Predictors	Model A	Model B	Model C	Model D
Hyperlipidemia:PVD		-0.0491	0	0
Hypertension (uncomplicated):Fluid Disorder		-0.1146	-0.1339	-0.1571
Hypertension (uncomplicated):Hypothyroidism		-0.0317	-0.0491	-0.0627
Hypertension (uncomplicated):PVD		-0.0537	-0.1328	-0.1337
Hypothyroidism:PVD		0.3226	0.3218	0.3159
Frailty Indicators				
AMBULANCE			0.1240	0.1483
Bladder Dysfunction			01	0.0138
Home hospital bed			0.1611	0.1665
Oxygen			0.080	0.0860
Parkinson's Disease			0	0
Podiatric Care			0.2590	0.2606
Rehabilitative Care			-0.0742	-0.0744
Shock			0.2126	0.2079
Skin Ulcer			0.4447	0.4434
Vertigo			-0.220	-0.2236
Weak			0.3603	0.3397
Wheelchair			0.5446	0.5303
Indolent NHL Subtypes				
CLL/SLL				0.0649
Follicular				0
Lymphoplasmacytic				0
Mycosis fungoides				-0.2562
Marginal zone lymphoma				-0.3465

Table A2.2 *Average coefficients (log odds ratios) and interaction terms for Models A-D predicting 1-year non-cancer mortality from 100 resampled training and validation sets*

Predictors	Model A	Model B	Model C	Model D
(Intercept)	-1.5091	-1.1655	-1.1725	-1.1737
Demographics				
Age 70-74 vs. 66-69	0.1402	0	0	0
Age 75-79 vs. 66-69	0.5719	0.3870	0.3912	0.4353
Age 80-84 vs. 66-69	1.1153	0.9306	0.9216	0.9701
Age 85+ vs. 66-69	1.8314	1.6352	1.6293	1.6988
Sex (Male vs. Female)	-0.2882	-0.2665	-0.2750	-0.2693
Comorbidities				
Alcohol Abuse	0.2667	0.0073	0	0
Anemia (Blood loss)	-0.0942	0	0	0
Anemia (Deficiency)	0	0	0	0
Anxiety	0.0066	0	0	0
Arrhythmia	0.3448	0.3018	0.2992	0.3131
CEVD	0.1081	0.0209	0.0096	0.0378
CHF	0.5877	0.4968	0.4314	0.4707
Coagulopathy	0.6442	0.5220	0.5019	0.5653
COPD	0.4381	0.3266	0.2447	0.2770
Dementia	1.0512	0.8724	0.8334	0.9618
Depression	-0.0005	0	0	0
Diabetes (uncomplicated)	0.2223	0.1523	0.1411	0.1492
Diabetes (complicated)	0.4190	0.3428	0.2337	0.2485
Drug Abuse	0.6859	0.3857	0.2153	0.2532
Fluid/electrolyte disorder	0.3598	0.2344	0.2200	0.2354
Hepatitis B	3.3299	1.7852	1.8059	1.8586
Hepatitis C	0.9330	0.6200	0.6363	0.6708
HIV/AIDS	-1.7004	-0.2329	-0.1266	-0.5921
Hyperlipidemia	-0.3513	-0.2522	-0.2351	-0.2426
Hypertension(uncomplicated)	0.1194	0.0921	0.0916	0.0922
Hypertension (complicated)	-0.1681	-0.0337	-0.0498	-0.0609
Hypothyroidism	0.0409	0	0.0149	0
Liver disease (mild)	0.9629	0.5792	0.6051	0.6886
Liver disease (moderate/severe)	-0.6192	0	0	0
Myocardial infarction (acute)	0.7552	0.5796	0.6038	0.6301
Neurological disorder	0.6670	0.5759	0.2772	0.2845
Obesity	0.2687	0.1610	0.1234	0.1692
PCD	-0.2148	0	-0.0222	#DIV/0!
Hemiplegia/Paraplegia	0.3590	0.0442	0	0.1051
Pscyhosis	0.4386	0.2429	0.1877	0.1906
Peripheral vascular disease	0.1805	0.0527	0.0108	0.0391
Renal disease	0.5410	0.4318	0.4017	0.4248
Rheumatologic/orthopedic disease	0.4180	0.3280	0.2847	0.3095
Peptic ulcer disease	-0.0599	0	0	0
Valvular disease	0.2006	0.1477	0.1502	0.1694
Weightloss	0.6628	0.5833	0.5893	0.6101
Comorbidity Interactions				
Arrhythmia:CEVD		0.1028	0.1503	0.1699
Arrhythmia:CHF		0	0	0
Arrhythmia:COPD		0	0	0

Predictors	Model A	Model B	Model C	Model D
Arrhythmia:Diabetes (mild)		-0.0540	-0.0688	-0.1229
Arrhythmia:Diabetes (Moderate/Severe)		0	0	0
Arrhythmia:Fluid Disorder		0	0	0
Arrhythmia:Hyperlipidemia		0	0	0
Arrhythmia:Hypertension (uncomplicated)		0	0	0
Arrhythmia:Hypothyroidism		0	0	0
Arrhythmia:PVD		0	0	0
CEVD:CHF		0	0	0
CEVD:COPD		0.1256	0.1271	0.1303
CEVD:Diabetes (mild)		0	0	0
CEVD:Diabetes (Moderate/Severe)		0	0	0
CEVD:Fluid Disorder		0	0	0
CEVD:Hyperlipidemia		0	0	0
CEVD:Hypertension (uncomplicated)		0	0	0
CEVD:Hypothyroidism		0	0	-0.0425
CEVD:PVD		0.1741	0.2568	0.1967
CHF:COPD		0	0	0
CHF:Diabetes (mild)		0	0	0
CHF:Diabetes (Moderate/Severe)		0	0	-0.1141
CHF:Fluid Disorder		0.2875	0.2682	0.2828
CHF:Hyperlipidemia		-0.0068	-0.0256	-0.1111
CHF:Hypertension (uncomplicated)		0	0	0
CHF:Hypothyroidism		-0.0908	-0.1103	-0.1957
CHF:PVD		0.2958	0.3480	0.4933
COPD:Diabetes (mild)		0	0	0
COPD:Diabetes (Moderate/Severe)		0	0	0
COPD:Fluid Disorder		0.2944	0.2555	0.2467
COPD:Hyperlipidemia		0	0	0
COPD:Hypertension (uncomplicated)		0	0	-0.0322
COPD:Hypothyroidism		0	0	0
COPD:PVD		0	0	0
Diabetes (mild):Diabetes (Moderate/Severe)		0	0	0
Diabetes (mild):Fluid Disorder		0.2362	0.1734	0.2184
Diabetes (mild):Hyperlipidemia		0	0	0
Diabetes (mild):Hypertension (uncomplicated)		0	0	0
Diabetes (mild):Hypothyroidism		0	0	0
Diabetes (mild):PVD		0	0	0
Diabetes (Moderate/Severe):Fluid Disorder		0	0.0370	0.1092
Diabetes (Moderate/Severe):Hyperlipidemia		0	0	0
Diabetes (Moderate/Severe):Hypertension (uncomplicated)		0	0.0143	0.0250
Diabetes (Moderate/Severe):Hypothyroidism		0	0	0
Diabetes (Moderate/Severe):PVD		-0.2132	-0.4535	-0.6797
Fluid Disorder:Hypothyroidism		0	0	0
Fluid Disorder:PVD		0	0	0
Hyperlipidemia:Fluid Disorder		-0.1720	-0.1890	-0.2416
Hyperlipidemia:Hypertension (uncomplicated)		0	0	0
Hyperlipidemia:Hypothyroidism		0	0	0
Hyperlipidemia:PVD		0	0	0
Hypertension (uncomplicated):Fluid Disorder		0	0	0
Hypertension (uncomplicated):Hypothyroidism		0	0	0
Hypertension (uncomplicated):PVD		0	0	0

Predictors	Model A	Model B	Model C	Model D
Hypothyroidism:PVD		0	-0.0056	0
Frailty Indicators				
AMBULANCE			0.3549	0.3983
Bladder Dysfunction			0.1975	0.2310
Home hospital bed			0.3380	0.3900
Oxygen			0.5787	0.6149
Parkinson's Disease			0.7007	0.7072
Podiatric Care			0	0
Rehabilitative Care			0	0
Shock			0	0
Skin Ulcer			0.7297	0.7727
Vertigo			-0.1542	-0.1799
Weak			0.0977	0.1005
Wheelchair			0.3457	0.3189
Indolent NHL Subtypes				
CLL/SLL				0.1512
Follicular				0
Lymphoplasmacytic				0.0717
Mycosis fungoides				0.1511
Marginal zone lymphoma				-0.3339

Table A2.3 *Average coefficients (log odds ratios) and interaction terms for Models A-D predicting 5-year all-cause mortality from 100 resampled training and validation sets*

Predictors	Model A	Model B	Model C	Model D
(Intercept)	-4.2019	-3.9973	-3.8209	-3.8170
Demographics				
Age 70-74 vs. 66-69	0	0	-0.0314	-0.0166
Age 75-79 vs. 66-69	0.4916	0.3256	0.1414	0.1795
Age 80-84 vs. 66-69	0.8233	0.6908	0.4771	0.5161
Age 85+ vs. 66-69	1.2012	1.0706	0.8477	0.8801
Sex (Male vs. Female)	-0.2722	-0.2257	-0.1754	-0.1832
Comorbidities				
Alcohol Abuse	0.8215	0.6516	0.6123	0.6503
Anemia (Blood loss)	0.2565	0.1653	0.1216	0.1285
Anemia (Deficiency)	0.2241	0.1775	0.0846	0.0889
Anxiety	0	0	0	0
Arrhythmia	0.0829	0.0547	0	0
CEVD	0.3039	0.3247	0.0383	0.0799
CHF	0.6722	0.8229	0.5885	0.6090
Coagulopathy	0.3317	0.2917	0.2388	0.2433
COPD	0.7219	0.7345	0.5740	0.5854
Dementia	0.7121	0.7273	0.5480	0.5950
Depression	0.0712	0.0611	0	0
Diabetes (uncomplicated)	0.1925	0.0805	0.0157	0.0275
Diabetes (complicated)	0.2584	0.3783	0.0556	0.0841
Drug Abuse	0.5050	0.2935	0	0
Fluid/electrolyte disorder	0.0966	0	0	0
Hepatitis B	-0.6298	-0.2646	0	0
Hepatitis C	0	0	0	0
HIV/AIDS	-0.0204	0	0	0
Hyperlipidemia	-0.2114	-0.1425	-0.0143	-0.0164
Hypertension(uncomplicated)	-0.2002	-0.0013	0	0
Hypertension (complicated)	0.0217	0	0	0
Hypothyroidism	-0.0236	0	0	0
Liver disease (mild)	0.8975	0.8375	0.5559	0.5674
Liver disease (moderate/severe)	0.6277	0.4574	0.4442	0.4765
Myocardial infarction (acute)	0.3049	0.2610	0.1453	0.1629
Neurological disorder	0.7697	0.7314	0.5572	0.5546
Obesity	-0.3402	-0.2269	-0.0979	-0.1330
PCD	0.3549	0.3579	0.2742	#DIV/0!
Hemiplegia/Paraplegia	1.1645	1.1615	0.9628	0.9956
Pscyhosis	-0.5348	-0.3287	0	0
Peripheral vascular disease	0.4124	0.1818	0.0162	0.0303
Renal disease	0.6388	0.5769	0.5343	0.5328
Rheumatologic/orthopedic disease	0.7945	0.7173	0.5664	0.5958
Peptic ulcer disease	0.5935	0.5739	0.4392	0.4404
Valvular disease	-0.0208	0	0	0
Weight loss	0.5296	0.5076	0.4424	0.4571
Comorbidity Interactions				
Arrhythmia:CEVD		0	0	0
Arrhythmia:CHF		-0.1127	0	0
Arrhythmia:COPD		0	0	0
Arrhythmia:Diabetes (mild)		0	0	0

Predictors	Model A	Model B	Model C	Model D
Arrhythmia:Diabetes (Moderate/Severe)		-0.3938	-0.1191	-0.2237
Arrhythmia:Fluid Disorder		0.2867	0.1295	0.1515
Arrhythmia:Hyperlipidemia		0	0	0
Arrhythmia:Hypertension (uncomplicated)		-0.1463	0	0
Arrhythmia:Hypothyroidism		0.4071	0.1110	0.1753
Arrhythmia:PVD		0	0	0
CEVD:CHF		0	0	0
CEVD:COPD		-0.0816	0	0
CEVD:Diabetes (mild)		0.0649	0.0032	0.0172
CEVD:Diabetes (Moderate/Severe)		0.0548	0.1284	0.1586
CEVD:Fluid Disorder		0.2965	0.2164	0.2141
CEVD:Hyperlipidemia		0.0206	0	0
CEVD:Hypertension (uncomplicated)		-0.4933	0	-0.0679
CEVD:Hypothyroidism		0.4721	0.2336	0.2641
CEVD:PVD		0.3844	0.2448	0.2693
CHF:COPD		0	0	0
CHF:Diabetes (mild)		0	0	0
CHF:Diabetes (Moderate/Severe)		0	0	0
CHF:Fluid Disorder		-0.1455	0	0
CHF:Hyperlipidemia		0	0	0
CHF:Hypertension (uncomplicated)		0	0	0
CHF:Hypothyroidism		-0.2819	-0.0109	-0.0584
CHF:PVD		-0.0221	0	0
COPD:Diabetes (mild)		0	0	0
COPD:Diabetes (Moderate/Severe)		-0.2321	0	0
COPD:Fluid Disorder		0	0	0
COPD:Hyperlipidemia		0	0	0
COPD:Hypertension (uncomplicated)		-0.0282	0	0
COPD:Hypothyroidism		0.0310	0	0
COPD:PVD		-0.1418	0	0
Diabetes (mild):Diabetes (Moderate/Severe)		0.1646	0.0483	0.0858
Diabetes (mild):Fluid Disorder		0	0	0
Diabetes (mild):Hyperlipidemia		0	0	0
Diabetes (mild):Hypertension (uncomplicated)		0	0	0
Diabetes (mild):Hypothyroidism		0	0	0
Diabetes (mild):PVD		0.3756	0.1472	0.1457
Diabetes (Moderate/Severe):Fluid Disorder		0	0	0
Diabetes (Moderate/Severe):Hyperlipidemia		0	0	0
Diabetes (Moderate/Severe):Hypertension (uncomplicated)		0	0	0
Diabetes (Moderate/Severe):Hypothyroidism		-0.5065	-0.1469	-0.1963
Diabetes (Moderate/Severe):PVD		-0.3305	0	-0.0330
Fluid Disorder:Hypothyroidism		0	0	0
Fluid Disorder:PVD		0.0998	0	0
Hyperlipidemia:Fluid Disorder		0	0	0
Hyperlipidemia:Hypertension (uncomplicated)		-0.0674	-0.0964	-0.1149
Hyperlipidemia:Hypothyroidism		0	0	0
Hyperlipidemia:PVD		0	0	0
Hypertension (uncomplicated):Fluid Disorder		-0.0154	0	0
Hypertension (uncomplicated):Hypothyroidism		0	0	0
Hypertension (uncomplicated):PVD		-0.1221	0	0
Hypothyroidism:PVD		0.7631	0.5707	0.5918

Predictors	Model A	Model B	Model C	Model D
Frailty Indicators				
AMBULANCE			0	0
Bladder Dysfunction			0	0
Home hospital bed			0.1095	0.1122
Oxygen			0.2868	0.3117
Parkinson's Disease			0.2560	0.2655
Podiatric Care			0	0
Rehabilitative Care			0	0
Shock			0.0055	0.0171
Skin Ulcer			0.6041	0.5864
Vertigo			0	0
Weak			0.1546	0.1536
Wheelchair			0.4304	0.4312
Indolent NHL Subtypes				
CLL/SLL				0.0001
Follicular				-0.0884
Lymphoplasmacytic				0.0333
Mycosis fungoides				0
Marginal zone lymphoma				0

Table A2.4 Average coefficients (log odds ratios) and interaction terms for Models A-D predicting 5-year non-cancer mortality from 100 resampled training and validation sets

Predictors	Model A	Model B	Model C	Model D
(Intercept)	-2.4006	-2.2328	-2.2277	-2.2459
Demographics				
Age 70-74 vs. 66-69	0.0169	0	0	0
Age 75-79 vs. 66-69	0.4165	0.3608	0.3459	0.3672
Age 80-84 vs. 66-69	0.7837	0.7195	0.6787	0.6978
Age 85+ vs. 66-69	1.1057	1.0656	1.0332	1.0487
Sex (Male vs. Female)	-0.1952	-0.1981	-0.1935	-0.2011
Comorbidities				
Alcohol Abuse	0	0	0	0
Anemia (Blood loss)	0	0	0	0
Anemia (Deficiency)	0	0	0	0
Anxiety	0	0	0	0
Arrhythmia	0.2743	0.2232	0.1955	0.1926
CEVD	0.1073	0.2979	0.3071	0.3521
CHF	0.5752	0.6362	0.5611	0.5781
Coagulopathy	0.1225	0.0519	0	0
COPD	0.5896	0.6251	0.4791	0.5004
Dementia	0.8571	0.8434	0.7834	0.7788
Depression	0	0.0113	0	0
Diabetes (uncomplicated)	0.2032	0.0795	0.0757	0.0793
Diabetes (complicated)	0.1568	0.3219	0.2441	0.2713
Drug Abuse	0.2855	0.2634	0.0602	0.1186
Fluid/electrolyte disorder	0.2232	0	0	0
Hepatitis B	2.3729	2.1307	2.1141	2.1522
Hepatitis C	0.2742	0.1222	0.1446	0.1668
HIV/AIDS	0	0	0	0
Hyperlipidemia	-0.1632	-0.0666	-0.0613	-0.0644
Hypertension(uncomplicated)	0	0	0	0
Hypertension (complicated)	0	0	0	0
Hypothyroidism	0	0	0	0
Liver disease (mild)	1.0487	1.0269	0.9873	0.9815
Liver disease (moderate/severe)	0	0	0	0
Myocardial infarction (acute)	0.2341	0.2414	0.2561	0.2684
Neurological disorder	0.7890	0.7570	0.2599	0.2586
Obesity	0.3007	0.1718	0.1334	0.1456
PCD	-0.4361	-0.3779	-0.3506	#DIV/0!
Hemiplegia/Paraplegia	0.0771	0.1939	0.0358	0.0561
Pscyhosis	0.2787	0.1856	0.1749	0.1927
Peripheral vascular disease	0.2338	0.0730	0.0089	0.0061
Renal disease	0.6126	0.5514	0.5063	0.5123
Rheumatologic/orthopedic disease	0.6360	0.6235	0.6036	0.6032
Peptic ulcer disease	0	0	0	0
Valvular disease	0.0534	0.0187	0.0135	0
Weightloss	0.2661	0.2344	0.2293	0.2298
Comorbidity Interactions				
Arrhythmia:CEVD		0.5604	0.5721	0.5971
Arrhythmia:CHF		0	0	0

Predictors	Model A	Model B	Model C	Model D
Arrhythmia:COPD		0	0	-0.0085
Arrhythmia:Diabetes (mild)		-0.0891	-0.0898	-0.1099
Arrhythmia:Diabetes (Moderate/Severe)		-0.4593	-0.4466	-0.4726
Arrhythmia:Fluid Disorder		0	0	0
Arrhythmia:Hyperlipidemia		0	0	0
Arrhythmia:Hypertension (uncomplicated)		0	0	0
Arrhythmia:Hypothyroidism		0	0	0
Arrhythmia:PVD		0.2334	0.3346	0.3705
CEVD:CHF		-1.0980	-1.0170	-1.0405
CEVD:COPD		0.3242	0.2433	0.2780
CEVD:Diabetes (mild)		0	0	0
CEVD:Diabetes (Moderate/Severe)		0	0	0
CEVD:Fluid Disorder		0	0	0
CEVD:Hyperlipidemia		0	0	0
CEVD:Hypertension (uncomplicated)		-0.3816	-0.3290	-0.3963
CEVD:Hypothyroidism		0	0	0
CEVD:PVD		0	0	0
CHF:COPD		0	-0.0119	-0.0611
CHF:Diabetes (mild)		0.0252	0	0
CHF:Diabetes (Moderate/Severe)		0	0	0
CHF:Fluid Disorder		0.3140	0.2577	0.2466
CHF:Hyperlipidemia		-0.0391	-0.0235	-0.0403
CHF:Hypertension (uncomplicated)		0	0	0
CHF:Hypothyroidism		0	0	-0.0343
CHF:PVD		0	0	0
COPD:Diabetes (mild)		0	0	0
COPD:Diabetes (Moderate/Severe)		0	0	0
COPD:Fluid Disorder		0	0	0
COPD:Hyperlipidemia		-0.2384	-0.2482	-0.2667
COPD:Hypertension (uncomplicated)		-0.0278	0	-0.0207
COPD:Hypothyroidism		0	0	0
COPD:PVD		0	0	0
Diabetes (mild):Diabetes (Moderate/Severe)		0	0	0
Diabetes (mild):Fluid Disorder		0.3775	0.3138	0.3088
Diabetes (mild):Hyperlipidemia		0	0	0
Diabetes (mild):Hypertension (uncomplicated)		0.1198	0.1162	0.1343
Diabetes (mild):Hypothyroidism		-0.1834	-0.1804	-0.2098
Diabetes (mild):PVD		0.0613	0	0
Diabetes (Moderate/Severe):Fluid Disorder		0	0	0
Diabetes (Moderate/Severe):Hyperlipidemia		0	0	0
Diabetes (Moderate/Severe):Hypertension (uncomplicated)		0	0	0
Diabetes (Moderate/Severe):Hypothyroidism		0	0	0
Diabetes (Moderate/Severe):PVD		-0.8270	-0.8702	-0.9565
Fluid Disorder:Hypothyroidism		0.1084	0.0244	0.0451
Fluid Disorder:PVD		0.5103	0.4180	0.4400
Hyperlipidemia:Fluid Disorder		0	0	0
Hyperlipidemia:Hypertension (uncomplicated)		0	0	0
Hyperlipidemia:Hypothyroidism		0	-0.0005	0

Predictors	Model A	Model B	Model C	Model D
Hyperlipidemia:PVD		0.0362	0.1086	0.1366
Hypertension (uncomplicated):Fluid Disorder		0	0	0
Hypertension (uncomplicated):Hypothyroidism		0	0	0
Hypertension (uncomplicated):PVD		0	0	0
Hypothyroidism:PVD		-0.0481	-0.0758	-0.0841
Frailty Indicators				
AMBULANCE			0.4685	0.4770
Bladder Dysfunction			0.3294	0.3430
Home hospital bed			-0.0096	-0.0542
Oxygen			0.7627	0.7742
Parkinson's Disease			1.1365	1.1600
Podiatric Care			0	0
Rehabilitative Care			0	0
Shock			0	0
Skin Ulcer			0.3480	0.3454
Vertigo			0	0
Weak			0.0021	0.0208
Wheelchair			0.2394	0.2537
Indolent NHL Subtypes				
CLL/SLL				0
Follicular				-0.0245
Lymphoplasmacytic				0.1260
Mycosis fungoides				0.0965
Marginal zone lymphoma				0

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