Risk of Depressive or Anxiety Disorders in Commercially Insured Patients with Non-Hodgkin Lymphoma (NHL) in the US: A Retrospective Analysis

Lucille Sun

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Joshua J. Carlson

Ryan Hansen

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Abstract

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Lucille Sun

Chair of the Supervisory Committee:
Joshua J. Carlson
Pharmaceutical Outcomes Research & Policy Program

Background: Non-Hodgkin Lymphoma (NHL) is one of the most common cancers in the United States, with an expected incidence of 72,000 new cases in 2017. Compared to rapidly fatal cancers, such as lung or pancreatic, NHL is associated with a relatively high 5-year survival of 70%. Prior epidemiological studies suggest that NHL patients may experience higher rates of depressive or anxiety disorders, and have an associated unmet mental health need.

Objective: To estimate the incidence of depressive and anxiety disorders in patients newly diagnosed with NHL compared to matched, cancer-free controls in the US commercially insured population.

Methods: A retrospective cohort analysis was conducted using MarketScan® claims data from 2008 to 2015. Patients with NHL were identified by ICD-9 code and matched on a 1:1 ratio to cancer-free controls using propensity scores generated from age, region, and Charlson comorbidity index (CCI) score. Incidence rate ratios and hazard ratios were estimated using Poisson regression and Cox proportional hazards models. The odds of experiencing a depressive or anxiety disorder within one year of diagnosis was also estimated using logistic regression.

Results: A total of 24,055 NHL patients were identified and matched to cancer-free controls, with a total study population of 48,110. NHL patients had a 36% higher instantaneous risk of experiencing a depressive or anxiety disorder, 31% higher risk of only a depressive disorder, and 39% higher risk of only an anxiety disorder, compared to cancer-free controls ($p < 0.00005$). Within one year of diagnosis, NHL patients had 122% higher odds of experiencing any type of depressive or anxiety disorder, 112% higher odds of experiencing a depressive disorder, and 127% higher odds of experiencing an anxiety disorder.

Conclusion: Diagnosis with NHL is associated with a significantly higher risk of experiencing depressive or anxiety disorders compared to cancer-free controls, which may indicate an important clinical need within this patient population.

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Chapter 1. Introduction

Non-Hodgkin lymphoma (NHL) is a hematological malignancy that accounts for 4% of all cancers in the United States.[1] In 2017 alone, the American Cancer Society estimates an incidence of 72,000 new cases and over 20,000 NHL-attributable deaths. The vast majority of NHL cases develop during adulthood, and life expectancy can vary widely. Further, NHL can be broadly classified by indolent or aggressive subtype, which are associated with different disease trajectories. Compared to more rapidly fatal cancers, however, NHL has a relatively high 5-year survival of 70.7% based on SEER data from 2006 to 2012.[2] While recent treatment advances have extended patient survival, there has been little work regarding the impact of comorbidities and mental health needs on NHL patient outcomes.

Literature indicates that comorbid depression and anxiety are highly prevalent in cancer patients, which has a negative impact on health-related quality of life (HRQoL).[3,4] More broadly, evidence suggests that the presence of depression as a comorbidity leads to worsened HRQoL and disease outcomes than if it were present alone.[5] HRQoL deficits have also been reported in cancer survivors, suggesting that depression and anxiety may have persistent long-term consequences.[6] Furthermore, surveys of hematological cancer survivors indicate that the most commonly reported unmet patient needs were related to emotional health.[7] Impacts on survival have also been demonstrated in studies of cancer patients, where depressive or anxiety disorders were associated with worse survival outcomes.[8,9] In a study of cancer patients with no history of mental disorder, new onset of mood disorders after cancer diagnosis were associated with a higher risk of cancer-specific death.[9]

Evidence suggests that the psychological burden that can accompany a hematologic cancer diagnosis may also be under recognized by oncology providers.[10] A study in follicular lymphoma (FL), the most common subtype of indolent NHL, found that patients consistently report higher rates of persistent fatigue and worry, which are common symptoms of anxiety and depression.[11] Depressed or anxious patients are also less likely to return to work and more likely to report functional impairment.[6,12,13] Since NHL is associated with relatively high 5-year survival, the

clinical impact of experiencing a depressive or anxiety disorder may persist longer in this patient population versus other cancers.

While most research has examined the burden of mental illness by using validated patient-reported outcomes (PRO) instruments, claims database analyses can offer a real-world perspective on incidence and treatment patterns in commercially insured populations. Compared to randomized controlled trials, large observational studies using claims data can provide information on effectiveness, typical clinical practice, patient behaviors, epidemiological patterns, and resource utilization. Real-world evidence of healthcare practices can also inform health policy and identify areas of unmet need. Previous work, including studies conducted in pediatric Crohn's Disease and psoriasis, have also shown that methods of identifying incident depression or anxiety in claims data are feasible and valid.[14–17]

The objective of this study is to compare the incidence of depressive and anxiety disorders in patients newly diagnosed with NHL to cancer-free controls in a U.S. commercially insured population. Secondary aims include evaluating the risk of developing depressive or anxiety disorders at one year after NHL diagnosis, and stratification by age group and year of diagnosis.

Chapter 2. Methods

2.1 Data Source

The *Truven Health Analytics MarketScan*® Commercial Claims and Encounters (CCAE) database is constructed from privately insured medical and prescription drug claims from approximately 150 payers in the United States, including individual employers and health plans. Data from 2007 to 2015 were used for this analysis to reflect the healthcare experiences of over 100 million covered lives in all census regions. The MarketScan® data are de-identified and comply with patient privacy requirements of the Health Insurance Portability and Accountability Act (HIPAA).

2.2 Sample Selection and Study Cohorts

We performed a retrospective matched-cohort study consisting of two patient cohorts: (1) those newly diagnosed with NHL, and (2) their matched, cancer-free controls.

Patients with NHL were defined as those with least one inpatient or two separate outpatient NHL-related claims (ICD-9: 200.00 to 200.88, 202.00 to 202.98, or 204.10 to 204.12). All patients were required to have at least 12 months of continuous enrollment data before and after the index date, and to be at least 18 years of age as of the index date. Patients were excluded if they have any history of pre-index depressive or anxiety disorder based on claims or medications. Patients with any history of cancer prior to diagnosis with NHL or during the study period were also excluded.

Cancer-free controls were matched on a 1:1 ratio to NHL patients using propensity scores estimated from: birth year, region, and Charlson comorbidity index (CCI) score. Controls met the same inclusion and exclusion criteria, with the exception that they had no record of any cancer-related claims.

Demographic and clinical characteristics were compared between the two cohorts using the Student's t-test for continuous variables and χ^2 tests for categorical variables. Significant differences in patient characteristics were considered influential factors in regression analyses.

2.3 Study Period

For NHL patients, we defined a diagnosis period as the time starting 1 month prior to the first NHL-related claim to 2 months after the first claim (Figure 5.1). This is based on SEER's definition for date of diagnosis, in which including both the month prior and immediately following the month of first claim gives the highest concordance between SEER and Medicare claims data.[18,19]

The index date was defined as one month prior to the date of the first NHL-related claim within the study period. By setting the index date one month prior to the first NHL-related claim, the study period includes any incident cases of depression that may be identified during the diagnosis period, which may be related to diagnostic workup for NHL-related signs or

symptoms. Cancer-free controls were assigned the same index date (calendar date) as their matched NHL contemporary. The study period of interest will be the extent of post-index follow-up data available for each patient. Patients may also be censored within the time of study (2008 to 2015) due to death, terminating coverage, or changing health plans.

2.4 Definition of Outcomes

Incident cases of depressive or anxiety disorder were defined as meeting the following criteria during the study period:

- At least two depressive or anxiety disorder-related claims on different dates within 6 months of each other (Appendix A), ***or***
- At least one depressive or anxiety disorder-related claim and at least one outpatient prescription for an antidepressant or anxiolytic within 6 months of each other

This definition was constructed as a composite outcome for depressive or anxiety disorders. A secondary, claims-based definition was also used, which was restricted to having at least two inpatient or outpatient claims for depressive or anxiety disorders within 6 months of each other. Outcomes for depressive disorder or anxiety disorder were also identified independently, using the composite and claims-based definitions.

2.5 Incidence of Depressive or Anxiety Disorders

A Poisson regression model was generated to estimate incidence risk ratios, as follows:

$$Log(\lambda) = \beta_0 + \beta_1 NHL$$

where λ is the incidence rate of depressive or anxiety disorder, and the exponentiated slope, β_1 gives the unadjusted incidence rate ratio between those newly diagnosed with NHL and their matched cancer-free controls.

Adjusted hazard ratios (HR) were estimated using multivariate Cox proportional hazard models with adjustments for sex as a confounder, where controls were matched on age, region, and CCI score:

$$Log(\lambda) = \beta_0 + \beta_1 NHL + \beta_2 male$$

The Cox proportional hazards models defined time-at-risk for each patient as the period following the index date until the outcome occurs or end of enrollment, whichever is first. A regression including year of index was also run to assess time trends.

2.6 One-year Odds of Diagnosis with Depressive or Anxiety Disorder

A multivariate logistic regression was generated comparing the odds of outcome diagnosis at or within one year post-index of NHL patients versus their matched, cancer-free controls. Both the crude odds ratio (OR), and the OR adjusted for sex was calculated. The following model was used to generate adjusted ORs:

$$Log(Odds) = \beta_0 + \beta_1 NHL + \beta_2 male$$

where the exponentiated slope β_1 gives the odds ratio of depressive or anxiety disorder within one year of index date, adjusting for sex with controls matched on age, region, and CCI score. This regression was also run across two age strata: those under and over 40 years of age.

Chapter 3. Results

A total of 24,055 NHL patients were included in the study and matched on a 1:1 ratio to cancer-free controls. The patient selection flowchart is shown in Figure 5.2. The NHL patient cohort and cancer-free control cohort had a statistically significant difference in age, sex, and index year. Compared to the cancer-free controls, the NHL cohort had a mean age that was 0.4 years older, a 13.3% higher proportion of males, and a significantly different distribution across index year and type of health plan (Table 6.1). The two cohorts were identical on matching variables region and CCI score.

There was a statistically significant difference in the proportion of patients with depressive or anxiety disorder, depressive disorder only, or anxiety disorder only, using both the composite and claims-based definitions of outcome ($p < 0.00005$, Table 6.2). Compared to cancer-free controls, the NHL cohort had consistently higher proportions of patients diagnosed with depressive or anxiety disorders, both, or either alone. A total of 14% of NHL patients met criteria for a depressive or anxiety disorder, with 4.5% diagnosed with both, 8.7% diagnosed with a depressive disorder only, and 9.5% diagnosed with an anxiety disorder only. Using the more

restrictive, claims-based definition, the proportions are comparable, at 11.8% for any depressive or anxiety disorder, 3.3% for both types of disorder, 7.0% for depressive disorders, and 7.7% for anxiety disorders.

The most common subtypes of depressive disorder identified in both cohorts are major depressive disorder and adjustment disorders with depressive features (Table 6.3). The most common subtypes of anxiety disorders in both cohorts are anxiety states, which include generalized anxiety disorder (GAD), followed by adjustment disorders with anxious features. The distribution of depressive and anxiety disorders is similar between NHL patients and cancer-free controls with the exception of anxiety states. There is a statistically significant difference in the proportion of patients with incident anxiety states, with NHL patients having the higher proportion.

Using both the composite and claims-based definitions of outcome, the NHL cohort was associated with over 50% higher incidence rates as measured by incidence rate ratios (IRRs) when compared to cancer-free controls for all depressive or anxiety-related outcomes (Table 6.4). When comparing hazard ratios (HRs) adjusted for sex, patients with NHL had 36% higher instantaneous risk of any depressive or anxiety disorder, 31% higher risk of depressive disorder, and 39% higher risk of anxiety disorder. Compared to unadjusted IRRs estimated by Poisson regression, all HRs in the adjusted Cox proportional hazards model were attenuated toward the null. There was a statistically significant difference in incidence rates between the NHL and control cohorts as measured in all regressions shown in Table 6.4 ($p < 0.00005$).

The risk of having been diagnosed with incident depressive or anxiety disorder within one year of the index date is also higher for new NHL patients compared to cancer-free controls (Table 6.5). Compared to the crude ORs, adjusting for sex increases the odds ratio of experiencing depressive or anxiety disorder within one year by over two-fold. NHL is associated with 122% higher odds of experiencing any type of depressive or anxiety disorder, 112% higher odds of experiencing depressive disorder, and 127% higher odds of experiencing anxiety disorder ($p < 0.00005$). The time-failure curve for risk of experiencing the outcome within one year of the index date is shown in Figure 5.3.

Lastly, a logistic regression adjusting for sex and year of index indicates that there is a statistically significant but opposing association between year of index and odds of experiencing either depressive disorder or anxiety disorder (Table 6.6). While the overall OR for experiencing any type of depressive or anxiety disorder is not significantly associated with year of index, there is a 5% lower odds of experiencing depressive disorder and a 3% higher odds of experiencing anxiety disorder with each year after 2008 that the patient was indexed.

Chapter 4. Discussion

We evaluated the relationship between a new diagnosis of NHL and the incidence of depression and/or anxiety disorders in a U.S commercially insured population. We found that patients newly diagnosed with NHL had significantly higher incidence rates of depressive or anxiety disorder. This risk is over two-fold higher within the first year of NHL diagnosis compared to cancer-free controls. Furthermore, patients with NHL also have higher risks of experiencing depressive or anxiety disorders when analyzed independently. These results were significant using both the composite definition of outcome, which accounted for outpatient medication use, and the claims-based definition. These findings underscore the mental health burden that can accompany cancer diagnoses.

A diagnosis of NHL is associated with a higher burden of incident depression or anxiety independent of comorbidity burden. For a relatively indolent cancer such as NHL, this represents a potential area for healthcare intervention. Particularly for those who present with less aggressive disease, persistent depressive or anxiety disorders may have a sustained negative impact on patient quality of life. Furthermore, comorbid depression in cancer patients results in greater clinical consequences than depression alone. Given the body of evidence that indicates a link between mood disorders and worse survival outcomes in cancer, higher incidence of depressive or anxiety disorders may also lead to poorer survival in NHL, representing an area for further study and potential intervention.

In addition to having higher incidence rates of depressive or anxiety disorder overall, results indicate that the risk of developing comorbid depressive or anxiety disorder is highest within the first year of NHL diagnosis. This supports the hypothesis that onset of depressive or anxiety disorder may be linked to diagnosis or the diagnostic workup period. Whether or not patients begin treatment for NHL at this point depends on presentation of disease. In the early stages of disease recognition, patients may also be making important treatment decisions that will affect the trajectory of their disease. The added burden of mental health stressors at this point may make it more difficult for a patient to achieve optimal outcomes as they may have difficulty learning to manage their NHL. Under these circumstances, consistent and reliable patient participation is crucial, and early management of any psychiatric burden may be important.

Lastly, exploratory analyses indicate a divergent time trend associated with incidence of depressive disorders versus anxiety disorders. Patients captured in more recent years have an increased risk of anxiety, but decreased risk of depression in both NHL and cancer-free cohorts. The difference is most pronounced in 2014 and 2015, and may indicate a shift in diagnostic practices, changing patterns of disease incidence, or even an operational change in how claims are coded. However, the overall association between NHL and higher risk of depressive or anxiety disorders persisted.

Strengths of this study include the use of real world data to identify depressive or anxiety disorders, which are usually underestimated in claims data. Despite, the potential underestimation, the effect sizes in our analysis were relatively large and likely clinically meaningful and were uniformly statistically significant. Furthermore, while there is abundant evidence that cancer patients have a high prevalence of depressive or anxiety disorder, claims data also allowed us to estimate incidence rates and risk within the first year of NHL diagnosis.

Limitations of this study include those related to MarketScan data, which lacks certain types of patient and clinical information, and is subject to error. In the context of oncology, MarketScan data does not provide detail on histology or staging of disease. Thus, we are only able to draw broad conclusions about NHL patients, without addressing the heterogeneity of disease across subtypes. Furthermore, the population for which data is captured consists only of those that are

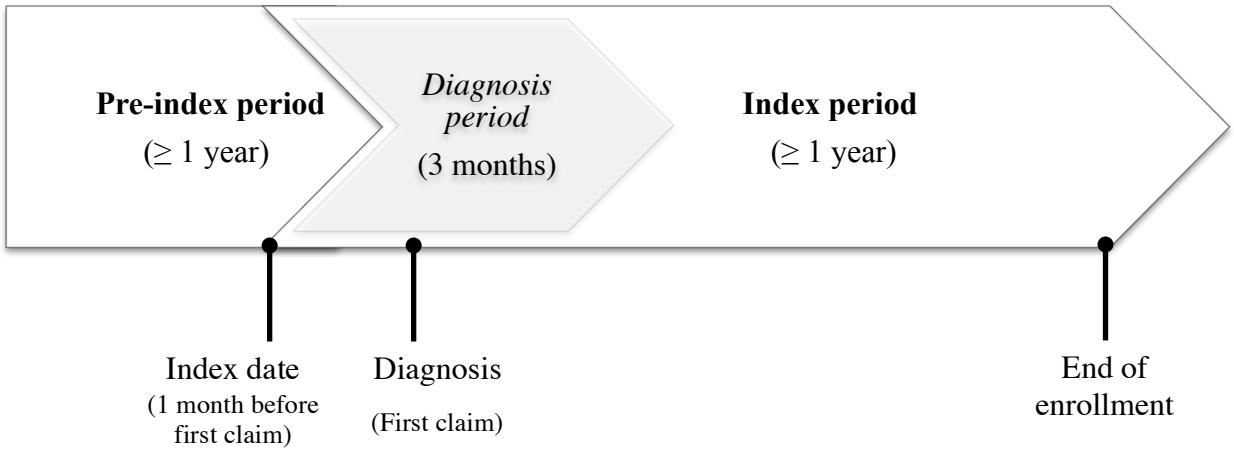
commercially insured, and this study will only capture those patients who seek medical services frequently enough to be identified for inclusion. Therefore, the conclusions drawn from this study may not necessarily apply to those who are uninsured, underinsured, or unlikely to be compliant.

Methodological limitations may also introduce bias in how NHL and the outcome are identified within this study. For example, we exclude patients with other cancer-related claims from our study, which narrows our population more specifically to those with NHL only, but may unintentionally exclude those who underwent a broader diagnostic workup. There are also challenges to defining incident depressive or anxiety disorder using claims data. It is possible that if patients had long gaps in making physician appointments or adhering to medications, some episodes of recurrent depression or anxiety may have been misclassified as incident cases. We also define relevant medication use as drug claims for any antidepressants or anxiolytics. However, many of these drugs may be prescribed for other indications, and may not be flagged with specific diagnoses. However, this potential misclassification would likely bias our results toward the null hypothesis.

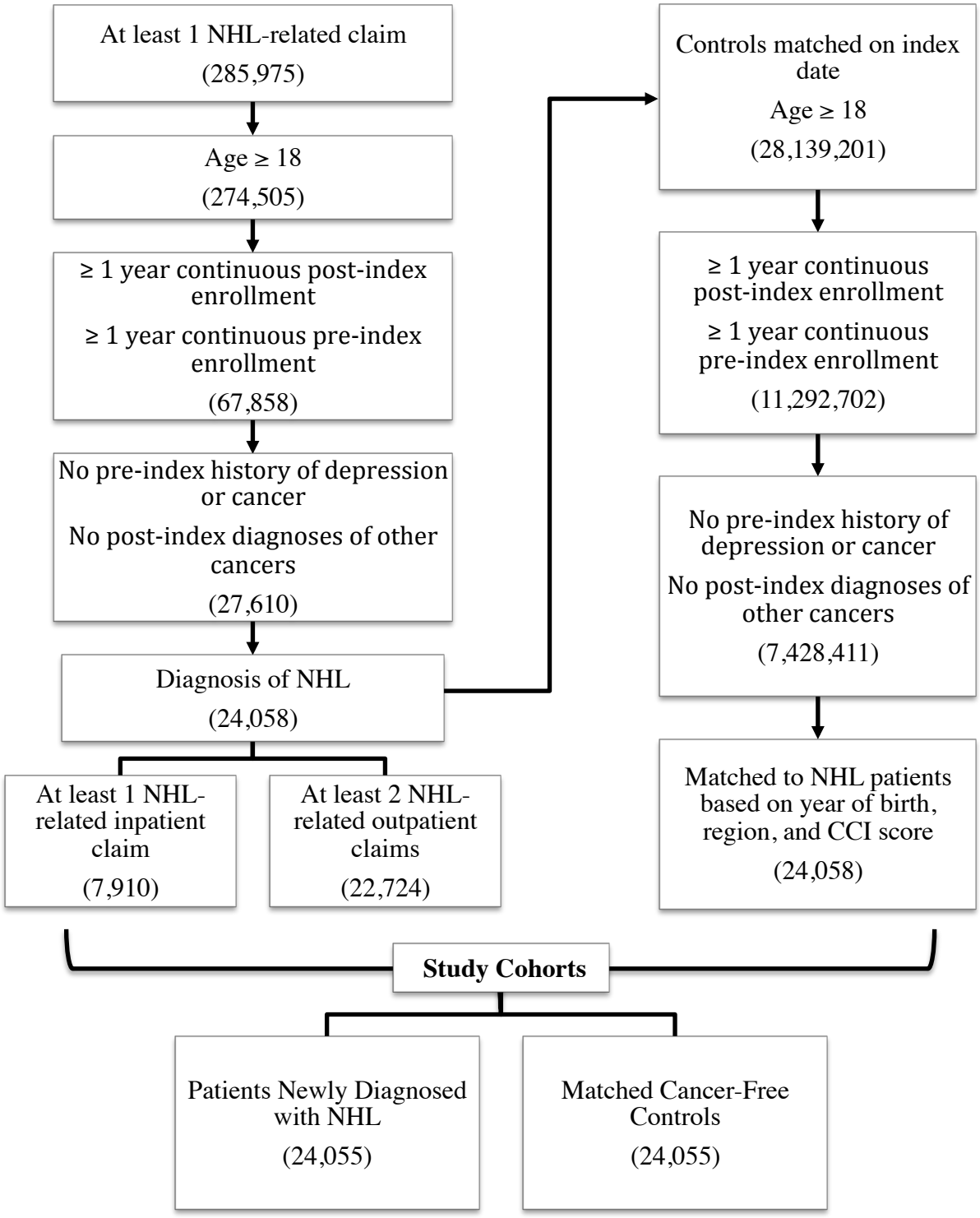
The onset of depression or anxiety as a cancer comorbidity may have important consequences for patient mortality and quality of life, and may be managed differently than if the condition were present alone. While we have established that NHL patients are at a higher risk of depressive and anxiety disorder, especially within the first year of NHL diagnosis, it may also be clinically useful to assess any differences in outcomes depending on NHL treatment or management. Further directions for research include assessing treatment rates for comorbid depressive or anxiety disorder, assessing the duration of comorbid disorders, and comparison of outcomes across NHL subtype, stage, or histology.

Chapter 5. List of Figures

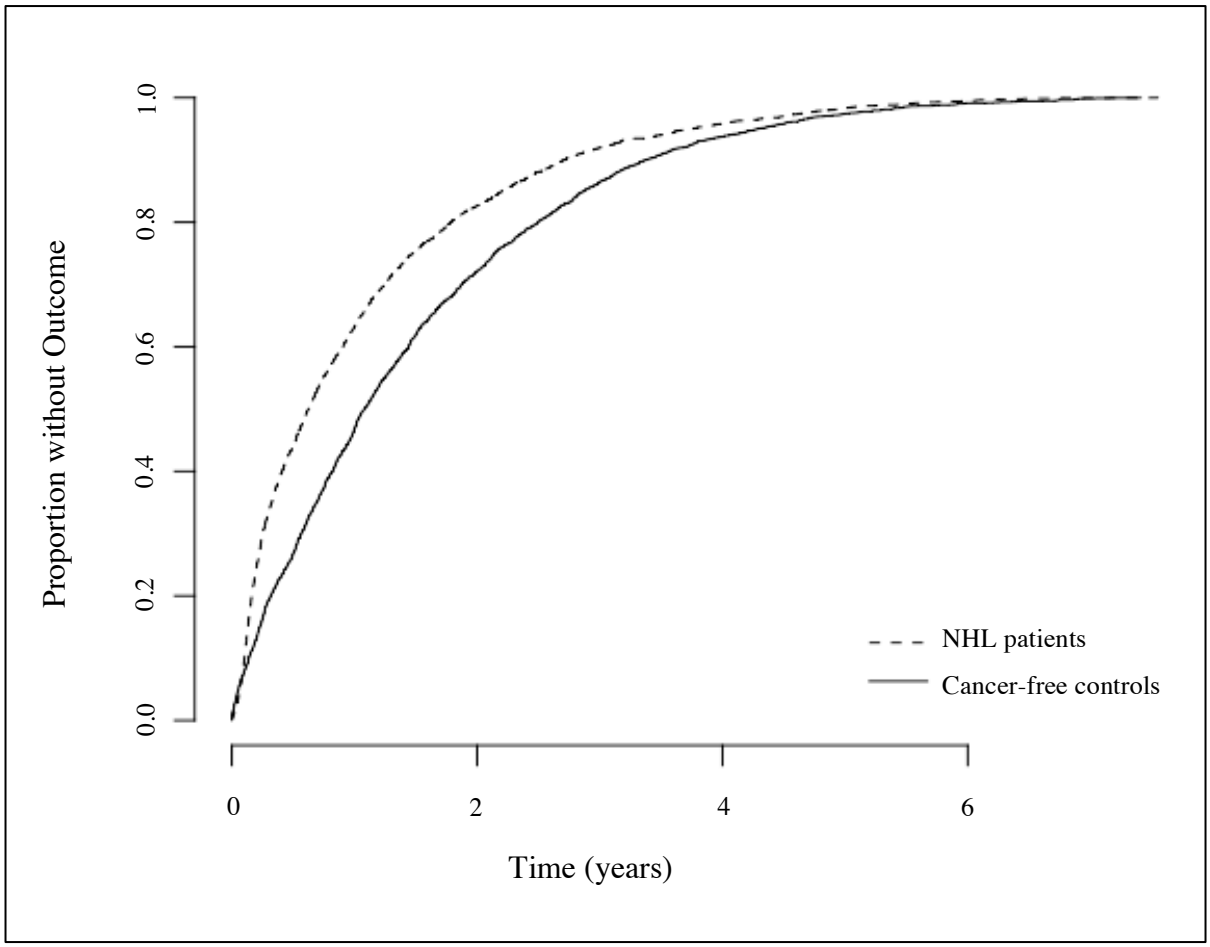
5.1 Diagnosis of NHL and Definition of Study Period



5.2 Study Cohort Criteria and Patient Selection



5.3 Time Failure Curves to First Occurrence Among Patients Who Experience Anxiety or Depressive Disorder



Chapter 6. List of Tables

6.1 Demographic and Clinical Characteristics of NHL Patients and Matched Cancer-Free Controls

Characteristic	NHL Patients (N=24055)	Cancer-free Controls (N=24055)	P-value
Demographic			
Age, *mean (SD)*	50.2 (10.7)	49.8 (10.6)	< 0.00005
Male, *n (%)*	14521 (60.4%)	11325 (47.1%)	< 0.00005
Geographic region, *n (%)*			
North East	4846 (20.1%)	4846 (20.1%)	1.0
North Central	5804 (24.1%)	5804 (24.1%)	
South	8590 (35.7%)	8590 (35.7%)	
West	4321 (18.0%)	4321 (18.0%)	
Unknown	494 (2.1%)	494 (2.1%)	
Index year, *n (%)*			
2008	3668 (15.2%)	5400 (22.4%)	< 0.00005
2009	4195 (17.4%)	4657 (19.4%)	
2010	3696 (15.4%)	4088 (17.0%)	
2011	3930 (16.3%)	3604 (15.0%)	
2012	3480 (14.5%)	2640 (11.0%)	
2013	2856 (11.9%)	2197 (9.1%)	
2014	2230 (9.3%)	1469 (6.1%)	
CCI Score			
0	16902 (70.3%)	16902 (70.3%)	1.0
1	4691 (19.5%)	4691 (19.5%)	
2	1237 (5.1%)	1237 (5.1%)	
3+	1225 (5.1%)	1225 (5.1%)	
Type of health plan, *n (%)*			
Comprehensive	736 (3.1%)	690 (3.0%)	0.00186
EPO	458 (2.0%)	427 (1.8%)	
HMO	3084 (13.2%)	3222 (13.8%)	
POS	1993 (8.5%)	2098 (9.0%)	
PPO	15121 (64.7%)	15111 (64.8%)	
POS with capitation	159 (0.7%)	164 (0.7%)	
CDHP	1184 (5.1%)	1041 (4.5%)	
HDHP	643 (2.8%)	563 (2.4%)	

SD, Standard deviation; *EPO,* Exclusive provider organization; *HMO*, Health maintenance organization; *POS,* Point-of-service; *PPO,* Preferred provider organization; *CDHP,* Consumer-directed health plan; *HDHP,* High-deductible health plan

6.2 Depressive and Anxiety Disorders in NHL Patients vs. Matched Cancer-Free Controls

Outcome	NHL Patients (N=24055)	Cancer-free Controls (N=24055)	P-value
Any depressive or anxiety disorders			
Composite*	3343 (13.9%)	2275 (9.5%)	< 0.00005
Claims †	2833 (11.8%)	1946 (8.1%)	< 0.00005
Both depressive and anxiety disorder			
Composite	1083 (4.5%)	770 (3.2%)	< 0.00005
Claims	793 (3.3%)	564 (2.3%)	< 0.00005
Depressive disorders			
Composite	2096 (8.7%)	1440 (6.0%)	< 0.00005
Claims	1678 (7.0%)	1167 (4.9%)	< 0.00005
Anxiety disorders			
Composite	2284 (9.5%)	1570 (6.5%)	< 0.00005
Claims	1855 (7.7%)	1278 (5.3%)	< 0.00005

* Composite: at least two ICD-9 claims or at least one ICD-9 claim and one drug claim for an antidepressant
† Claims: at least two ICD-9 claims

6.3 Depressive and Anxiety Disorders by Subtype in NHL Patients vs. Matched Cancer-Free Controls

Outcome	NHL Patients (N=24055)	Cancer-free Controls (N=24055)	P-value*
Depressive disorder subtypes	2096 (100%)	1440 (100%)	
Major Depressive Disorder	580 (27.7%)	402 (27.9%)	0.903
Dysthymia	373 (17.8%)	279 (19.7)	0.252
Adjustment Disorders	668 (31.9%)	462 (32.1%)	0.923
Anxiety disorder subtypes	2284 (100%)	1570 (100%)	
Anxiety States	1864 (81.6%)	1223 (77.9%)	0.005
Phobias	54 (2.4%)	46 (2.9%)	0.326
Obsessive Compulsive Disorder	21 (0.9%)	26 (1.7%)	0.058
Acute Stress Disorder	38 (1.7%)	37 (2.4%)	0.158
Adjustment Disorders	636 (27.8%)	441 (28.1%)	0.898
Post-traumatic Stress Disorder	69 (3.0%)	60 (3.8%)	0.205

* Percentages and p-values calculated for all patients with depressive disorder, or all patients with anxiety disorder, based on subtype

6.4 Incidence Rate Ratios and Hazard Ratios in NHL Patients and Matched Cancer-Free Controls

Type of disorder	Incidence rate ratios*		Hazard ratios †	
	Unadjusted ratios (95% CI)	P-value	Adjusted ratios (95% CI)	P-value
Any depressive or anxiety disorders				
Composite	1.56 (1.48, 1.64)	< 0.00005	1.36 (1.29, 1.43)	< 0.00005
Claims	1.54 (1.46, 1.63)	< 0.00005	1.37 (1.29, 1.45)	< 0.00005
Depressive disorders				
Composite	1.55 (1.45, 1.65)	< 0.00005	1.31 (1.22, 1.40)	< 0.00005
Claims	1.53 (1.43, 1.65)	< 0.00005	1.28 (1.18, 1.38)	< 0.00005
Anxiety disorders				
Composite	1.55 (1.45, 1.65)	< 0.00005	1.39 (1.33, 1.51)	< 0.00005
Claims	1.54 (1.44, 1.65)	< 0.00005	1.42 (1.32, 1.53)	< 0.00005

CI, Confidence interval

* Estimated using Poisson regression model controlling for sex, after matching controls to NHL patients based on age, region, and CCI score.

† Estimated using Cox proportional hazards regression model controlling for sex, after matching controls to NHL patients based on age, region, and CCI score.

6.5 Risk of Depressive or Anxiety Disorder One Year After Index Date in NHL Patients and Matched Cancer-Free Controls

Outcome	Number of Cases		Odds Ratios (95% CI)	
	NHL patients (N=24055)	Cancer-free controls* (N=24055)	Crude	Adjusted for sex †
Any depressive or anxiety disorders	2110	1066	2.07 (1.92, 2.24)	2.22 (2.05, 2.39)
≤ 40 years	495	263	2.07 (1.77, 2.42)	2.20 (1.88, 2.58)
> 40 years	1615	603	2.09 (1.91, 2.28)	2.23 (2.04, 2.43)
Depressive disorders	1232	634	1.99 (1.81, 2.20)	2.12 (1.92, 2.34)
Anxiety disorders	1453	707	2.12 (1.94, 2.34)	2.27 (2.07, 2.50)

CI, Confidence interval

* Cancer-free controls were matched on a 1:1 ratio to NHL patients based on age, region, and CCI score

† Adjusted for sex; controls matched on age, region, and CCI score

6.6 One-Year Risk of Depressive or Anxiety Disorder Adjusted for Sex and Index Year

Outcome*	Number of Cases		Adjusted Odds Ratios (95% CI)		
	NHL patients (N=24055)	Cancer-free controls † (N=24055)	NHL	Male	Index Year ‡
Any depressive or anxiety disorders	2110	1066	2.22 (2.05, 2.40)	0.62 (0.57, 0.66)	1.00 (0.98, 1.02)
Depressive disorders	1232	634	2.17 (1.96, 2.40)	0.65 (0.59, 0.71)	0.95 (0.92, 0.97)
Anxiety disorders	1453	707	2.24 (2.04, 2.46)	0.61 (0.55, 0.66)	1.03 (1.01, 1.06)

* Based on the composite definition of at least two separate claims, or one claim and one antidepressant/anxiolytic.
† Controls matched on age, region, and CCI score
‡ Calculated as years since 2008

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