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LONG-TERM SURVIVAL AND SURVIVORSHIP IN NON-HODGKIN LYMPHOMA PATIENTS IN SWEDEN

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LONG-TERM SURVIVAL AND SURVIVORSHIP IN NON-HODGKIN LYMPHOMA PATIENTS IN SWEDEN

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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POPULAR SCIENCE SUMMARY OF THE THESIS

This thesis contains four studies about survival and survivorship (life after cancer) in patients diagnosed with lymphoma in Sweden. All studies in the thesis are population-based register studies, i.e. patients are followed via national health registers.

Lymphoma is a collective name for cancers that develop from cells in the lymphatic system, so-called lymphocytes. Lymphocytes are a type of white blood cells that are part of our immune system. There are at least 70 different subtypes of lymphoma where the course of the disease and prognosis vary greatly. Aggressive subtypes require immediate treatment but can be cured, while slow-growing, indolent subtypes are, in most cases, considered chronic diseases. Patients with disseminated indolent lymphoma can however live a long time with their disease and any treatment is primarily aimed at suppressing the disease and relieving symptoms - not to cure. The most common subtype is diffuse large B-cell lymphoma (DLBCL), which has an aggressive clinical course and affects about 600 people annually in Sweden. Since the mid-00s, the chemotherapy against DLBCL has been combined with an antibody treatment, which has improved the survival of the patients.

In **Study I**, we examined how the number of patients living with different lymphoma subtypes has changed between the years 2000 and 2016, and how the number of newly diagnosed patients and their survival have changed during the same period. The background to the study is that lymphoma, despite the large variations between the subtypes, is often presented as one disease, and we therefore lack statistics at subtype level that are important for understanding the disease burden and for health care planning.

We found that the number of patients living with lymphoma in Sweden has increased and that this applies to the vast majority of subtypes, both the aggressive and the indolent. The increase was a result of improved survival at the same time as more and more patients have been diagnosed. The fact that more and more people are living with a lymphoma diagnosis has consequences for how we plan the follow-up of the patients, especially with regard to patients with indolent subtypes who are followed-up at the clinic for many years.

In **Study II**, we estimated life expectancy in patients diagnosed with DLBCL. We also compared the patients' life expectancy with the corresponding life expectancy of the Swedish population. In this way, we were able to calculate how many life years the patients were expected to lose, on average, as a result of their cancer diagnosis.

The result was that the life expectancy increased in all patient groups between the years 2000 and 2013. For example, 70-year-old male patients diagnosed with DLBCL in 2000 were expected to live, on average, another 6 years and 6 months, while patients of the same age diagnosed in 2013 were expected to live 10 years and 1 month, on average. In 2013, 70-year-old men diagnosed with DLBCL were expected to lose an average of 4 years and 10 months of their life as a result of their cancer. Despite the positive trend, patients still lost many years

due to their lymphoma. This was especially true for young patients with advanced disease (patients with several risk factors that together contribute to a worse prognosis).

The remaining life expectancy for patients who were alive two years after their DLBCL diagnosis did not differ as much compared to the life expectancy of the general population. On average, these patients lost less than two years of their lives to the cancer, regardless of age at diagnosis, sex or how advanced their disease was at the time of diagnosis.

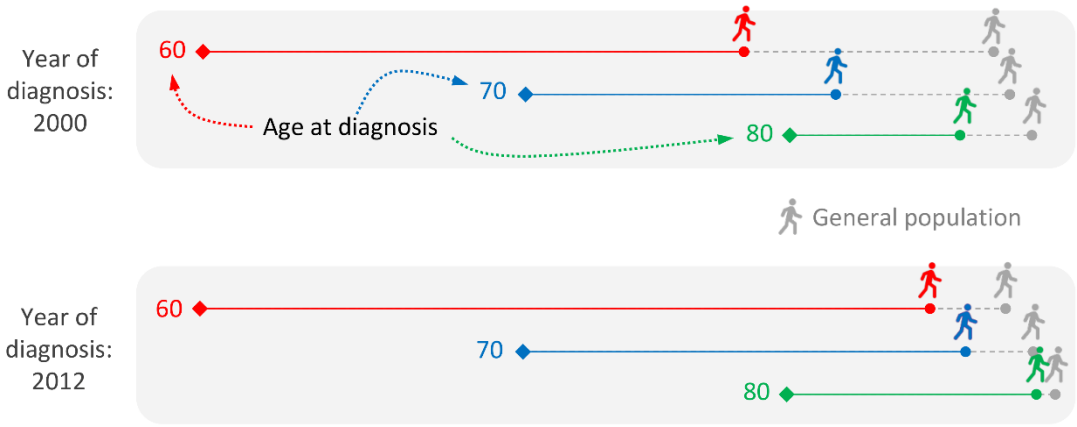


Figure 1: Life expectancy of patients diagnosed with DLBCL at 60, 70 and 80 years of age and surviving the first two years after diagnosis compared to life expectancy in the general population. The solid lines represent the life expectancy of the patients and the dashed lines represent the life expectancy of the general population.

Study III aimed to study whether patients treated for DLBCL had an increased risk of having a heart attack after diagnosis compared to the general population. The background to the study is that one type of chemotherapy (doxorubicin) that is included in the standard treatment can cause damage to the heart and thus lead to an increased risk of e.g. heart failure and possibly also other heart diseases. In addition, many patients are older (about half of all patients are over 70 years of age at diagnosis), and often have other underlying diseases which by themselves increase the risk of having a heart attack.

We followed the patients for up to 10 years after diagnosis and saw that the risk of suffering a heart attack was 33% higher for the patients compared to a control group when taking into account age and sex. However, the excess risk was highest immediately after diagnosis and then gradually decreased. After about two years, there was no longer an increased risk for patients to have a heart attack compared to the control group. Another positive result was that DLBCL patients received treatment for their heart attack to the same extent as the control group

and that an equal proportion of DLBCL patients and controls were alive 30 days after being hospitalized due to a heart attack.

An important milestone for patients with DLBCL is to be disease-free for at least two years after end of treatment. **In Study IV**, we examined probabilities of being in different stages of the disease at different times for DLBCL patients who initially responded to treatment and for whom no further disease could be detected. We also examined how different patient- and lymphoma-specific factors were linked to the chance of remaining disease-free for more than two years.

Patients who had several risk factors associated with a worse prognosis (e.g. old age, widespread disease or poor general condition) were less likely to remain disease-free for at least two years. However, there was no difference between men and women.

Five years after end of treatment, 7 out of 10 patients were still disease-free, while almost 2 out of 10 had a relapse of their disease. One in 10 had died without having had a relapse of their disease (i.e. probably due to reasons other than their cancer).

Figure 2: The proportion of patients with DLBCL who are disease-free immediately after treatment and who after 5 years are still disease-free (green), have had a relapse (orange) or who have died without having a relapse (gray).

Overall, the prognosis for patients diagnosed with DLBCL has improved during the 2000s, and for patients who survive the first two years, the prognosis today is very favorable. However, much remains to be done to further improve the prognosis for people affected by DLBCL. Patients who are not expected to tolerate treatment, who are unable to complete the treatment, who do not respond to treatment or have early relapses have a poor prognosis. The number of patients living with lymphoma has increased and is likely to continue to do so as survival improves even more. This means that more and more patients are living with their disease and need to be followed up for relapses or side effects.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Den här avhandlingen innehåller fyra studier som på olika sätt behandlar överlevnad och överlevarskap (livet efter cancer) hos patienter diagnosticerade med lymfom i Sverige. Alla studier i avhandlingen är populationsbaserade registerstudier, det vill säga, patienterna följs upp via nationella hälsoregister.

Lymfom är ett samlingsnamn för cancerformer som utvecklas från celler i lymfsystemet, så kallade lymfocyter. Lymfocyter är en typ av vita blodkroppar som utgör en del av vårt immunsystem och som delas in i B-celler, T-celler och NK-celler. Det finns minst ett 70-tal olika underdiagnoser till lymfom där sjukdomsförlopp och prognos varierar stort. Aggressiva lymfom kräver omedelbar behandling, men går att bota, medan långsamt växande, indolenta lymfom, är mer att betrakta som kroniska sjukdomar i de flesta fall. Patienter med spritt indolent lymfom kan leva länge med sin sjukdom och eventuell behandling syftar främst till att trycka tillbaka sjukdomen och lindra symptom – inte till att bota. Den allra vanligaste underdiagnosen till lymfom är diffust storcelligt B-cellslymfom (Diffuse large B-cell lymphoma, DLBCL) som har ett aggressivt sjukdomsförlopp och drabbar cirka 600 personer årligen i Sverige. Sedan mitten på 00-talet kombineras cellgifterna mot DLBCL med en antikroppsbehandling vilket har förbättrat överlevnaden hos patienterna.

I **Studie I** undersökte vi hur antalet patienter som lever med olika lymfomdiagnoser har förändrats mellan år 2000 och 2016, samt hur antalet nyinsjuknade och överlevnaden hos patienterna har förändrats under samma period. Bakgrunden till studien är att lymfom, trots de stora variationerna mellan underdiagnoserna, ofta studeras som en sjukdom, och att det därför har saknats denna typ av statistik på underdiagnosnivå som är viktig för att förstå sjukdomsbördan i samhället och för att planera vården.

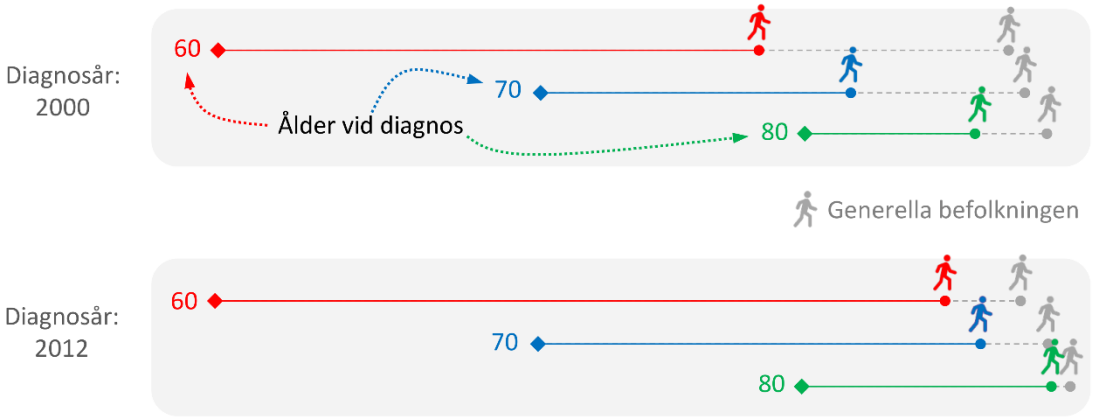
Vi fann att antalet patienter som lever med en lymfomdiagnos i Sverige har ökat kraftigt och att detta gäller de allra flesta lymfomdiagnoserna, både de aggressiva och de indolenta. Ökningen var en följd av att överlevnaden förbättrades samtidigt som allt fler insjuknade. Att fler och fler lever med en lymfomdiagnos har konsekvenser för hur vi planerar uppföljningen av patienterna, framförallt vad gäller patienter med indolenta lymfomdiagnoser som följs kliniskt under många år.

I **Studie II** skattade vi förväntad livslängd hos patienter som diagnosticerats med DLBCL. Vi jämförde även patienternas förväntade livslängd med motsvarande förväntad livslängd hos den svenska befolkningen. På så vis kunde vi beräkna hur många levnadsår patienterna i snitt förväntades förlora till följd av sin cancerdiagnos.

Resultatet var att den förväntade livslängden hos patienterna ökade i alla patientgrupper mellan åren 2000 och 2013. Till exempel förväntades 70-åriga manliga patienter som diagnosticerades med DLBCL år 2000 att i snitt leva i ytterligare 6 år och 6 månader, medan patienter i samma ålder diagnosticerade år 2013 förväntades leva snitt i ytterligare 10 år och 1 månad. År 2013 förväntades 70-åriga män diagnosticerade med DLBCL förlora i snitt 4 år och 10 månader till

följd av sin cancer. Trots den positiva trenden kunde vi konstatera att framförallt unga patienter med avancerad sjukdom (patienter med flera riskfaktorer som tillsammans bidrar till sämre prognos) fortfarande förlorar många år på grund av sin lymfomsjukdom.

Den återstående livslängden för patienter som var vid liv två år efter sin DLBCL-diagnos skiljde sig inte lika mycket jämfört med den förväntade livslängden i befolkningen i stort. I snitt förlorade dessa patienter mindre än två år av sitt liv till cancern oavsett ålder vid diagnos, kön eller hur avancerad sjukdom man hade från början.



Figur 3: Förväntad återstående livslängd hos patienter som diagnosticerats med DLBCL vid 60, 70 och 80 års ålder och som överlevt de två första åren efter diagnos jämfört med den förväntade livslängden i befolkningen i stort. De heldragna linjerna representerar patienternas förväntade livslängd och de streckade linjerna representerar den generella befolkningens förväntade livslängd.

Studie III syftade till att studera om patienter som behandlas för DLBCL hade en ökad risk att drabbas av hjärtinfarkt efter diagnos jämfört med befolkningen i övrigt. Bakgrunden till studien är att en typ av cellgift som ingår i standardbehandlingen kan ge skador på hjärtat och på så sätt medföra en förhöjd risk för till exempel hjärtsvikt och eventuellt också andra hjärtsjukdomar. Dessutom är många patienter äldre (ungefär hälften av alla patienter är över 70 år vid diagnos) och många har andra bakomliggande sjukdomar, vilka i sig ökar risken för att drabbas av hjärtinfarkt.

Vi följde patienterna i upp till 10 år efter diagnos och såg att risken att drabbas av en hjärtinfarkt var 33% högre för patienterna jämfört med en kontrollgrupp när hänsyn togs till ålder och kön. Överrisken var dock högst i anslutning till diagnos och minskade sedan successivt. Efter ungefär två år fanns inte längre någon ökad risk för patienterna att drabbas av hjärtinfarkt jämfört med kontrollgruppen. Ett annat positivt resultat var att DLBCL-patienterna fick behandling för sin hjärtinfarkt i samma utsträckning som kontrollgruppen, och att en lika stor

andel av DLBCL-patienterna som i kontrollgruppen var vid liv 30 dagar efter sjukhusinläggning för hjärtinfarkt.

En viktig milstolpe för patienter med DLBCL är att vara sjukdomsfri åtminstone två år efter avslutad behandling. I **Studie IV** undersökte vi sannolikheter för att befinna sig i olika sjukdomsstadier vid olika tidpunkter för DLBCL-patienter som initialt svarat på behandlingen och för vilka man inte längre kunde påvisa kvarvarande sjukdom. Vi undersökte även hur olika patient- och lymfomspecifika faktorer var kopplade till chansen att vara fortsatt sjukdomsfri i minst två år.

Patienter som hade flera riskfaktorer som kopplats ihop med sämre prognos (t.ex. hög ålder, att sjukdomen är spridd eller dåligt allmäntillstånd) hade lägre sannolikhet att förbli sjukdomsfria i minst 2 år, däremot var det ingen skillnad mellan män och kvinnor.

Fem år efter behandlingsslut var sju av 10 patienter fortfarande sjukdomsfria, medan nästan två av 10 fått återfall av sin sjukdom. En av 10 hade dött utan att först återfalla i sjukdom (det vill säga, troligen av andra orsaker än av sin cancer).

Figur 4: Andelen patienter med DLBCL som är sjukdomsfria direkt efter behandling och som efter 5 år är fortsatt sjukdomsfria (gröna), har fått återfall (orangea) samt andelen som dött utan att först få återfall (gråa).

Sammantaget kan vi konstatera att prognosen för patienter som diagnosticerats med DLBCL har förbättrats under 2000-talet, och för patienter som överlever de första två åren är prognosen idag väldigt god. Dock finns det fortfarande mycket kvar att göra för att ytterligare förbättra prognosen för personer som drabbas. Patienter som inte anses tåla behandling, som tvingas avbryta behandling, som inte svarar på behandling eller får tidiga återfall har fortsatt dålig prognos. Antalet patienter som lever med en lymfomdiagnos har ökat och kommer troligtvis fortsätta att öka i takt med att överlevnaden förbättras än mer. Detta innebär att fler och fler patienter lever med sin sjukdom och behöver följas upp för eventuella återfall eller biverkningar.

ABSTRACT

Non-Hodgkin lymphoma (NHL) is one of the top ten most common cancer types in Sweden. Although sometimes referred to as one disease, NHL is truly an umbrella term representing a heterogeneous group of diseases with varying clinical course and prognosis. The main data source for all four studies included in this thesis is the Swedish lymphoma register (SLR). This national quality register provides population-based data, detailed clinical information and the possibility to distinguish between different morphological subtypes of NHL.

In **Study I** we provide a systematic presentation of temporal trends in absolute numbers of prevalent patients by NHL subtypes, linking them to trends in incidence, survival and mortality. Poisson regression was used to test for temporal trends. We found that an increasing incidence and improved survival have led to an increase in the prevalence of NHL overall and for almost all investigated subtypes between 2000 and 2016. This increase was most notable for diffuse large B-cell lymphomas (DLBCL) among aggressive subtypes and marginal zone lymphomas among indolent subtypes. The prevalence provides a measure of burden of disease, useful for health care planning and to optimize resource allocation. The prevalence also represents the number of survivors in the population, at risk for relapses and psychological and physiological side effects of their lymphoma or treatment. The increase in number of prevalent NHL patients underscores the need to develop and evaluate alternative follow-up schemes of lymphoma survivors since especially patients diagnosed with indolent lymphoma subtypes are followed in the clinic for many years.

The most common subtype of NHL, DLBCL is the focus in study II-IV. In recent years, the addition of rituximab to the standard combination chemotherapy has improved outcomes in patients with DLBCL. Nevertheless, every fourth patient treated curatively is expected to experience progressive disease or relapse.

Study II aimed to quantify trends and remaining loss in life expectancy due to DLBCL in a population-based cohort. Loss in life expectancy was predicted using flexible parametric models from diagnosis and among two-year survivors, by age, sex and age-adjusted international prognostic index (aaIPI). The number of life-years lost decreased over the study period 2000-2013 in all patient groups. However, especially younger patients (≤60 years) with aaIPI≥2 were still estimated to lose many life years in 2013. Among two-year survivors, the loss in life-expectancy was reduced to two years or less by the end of the study period, regardless of age, sex and aaIPI. By using novel measures, we illustrated the improvement of DLBCL survival in a population-based context and over the entire life-span.

The standard chemotherapy for curative treatment of DLBCL contains the cardiotoxic anthracycline doxorubicin. An increased rate of heart failure is well documented following this treatment, whereas incidence and outcome of other cardiac complications, e.g. myocardial infarction, are less well studied.

In **Study III** we assessed the incidence, characteristics and outcome of acute myocardial infarctions (AMI) in curatively treated patients with DLBCL. Patients were matched to lymphoma-free comparators and the rate of AMI was estimated using flexible parametric survival models incorporating repeated events. Overall, DLBCL patients had a 33% excess rate of AMI compared to the general population. However, the excess rate was most pronounced during the first year after diagnosis and diminished after 2 years. The strongest risk factors for AMI were advanced age, male sex and pre-existing comorbidity. There was no difference in AMI characteristics, extent of treatment or 30-day survival following hospitalization for AMI between DLBCL patients and comparators. The increased risk of AMI especially during the first 2 years and among elderly patients calls for improved cardiac monitoring.

In **Study IV** we estimated real-world probabilities for lasting remission by clinical disease characteristics using a multi-state model approach. DLBCL patients who achieved remission after primary treatment were followed for repeated relapses and death. Flexible parametric models were used to model transition rates between disease stages accounting for competing events at each transition. At 2 years after end of primary treatment, 81% of the patients remained in remission, 13% had relapsed and 6 % of patients had died in first remission. The probability of remaining in remission for at least 2 years was reduced by 24 percentage units for patients with international prognostic index, IPI 4-5 compared to patients with IPI 0-1. On average, these patients lost 4.4 months of being in remission the first 2 years. Only 43% of relapsing patients achieved a second remission and half of them (51%) relapsed again - reflecting the difficulties in treating relapsing patients.

LIST OF SCIENTIFIC PAPERS

I. Sara Ekberg, Karin E Smedby, Ingrid Glimelius, Herman Nilsson-Ehle, Christina Goldkuhl, Catharina Lewerin, Mats Jerkeman and Sandra Eloranta
Trends in the prevalence, incidence and survival of Non-Hodgkin lymphoma subtypes during the 21st century – A Swedish lymphoma register study
British Journal of Haematology, 2020. 189(6): p. 1083-1092.

II. Sara Ekberg, Mats Jerkeman, Per-Ola Andersson, Gunilla Enblad, Björn E Wahlin, Sverker Hasselblom, Therese M Andersson, Sandra Eloranta and Karin E Smedby
Long-term survival and loss in expectancy of life in a population-based cohort of 7114 patients with diffuse large B-cell lymphoma
American Journal of Hematology 2018 93: p. 1020-1028.

III. Sara Ekberg*, Sara Harrysson*, Tomas Jernberg, Karolina Szummer, Per-Ola Andersson, Mats Jerkeman, Karin E Smedby and Sandra Eloranta
*Both authors contributed equally to this study
Incidence, timing and characteristics of acute myocardial infarction among 3548 patients treated for diffuse large B-cell lymphoma in Sweden – a population-based matched cohort study
Manuscript

IV. Sara Ekberg, Michael Crowther, Sara Harrysson, Mats Jerkeman, Karin E Smedby and Sandra Eloranta
Patient trajectories after diagnosis of diffuse large B-cell lymphoma - a multi-state modelling approach to estimating the chance of lasting remission
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

aaIPI	Age adjusted international prognostic index
ABC-DLBCL	Activated B-cell diffuse large B-cell lymphoma
ASCT	Autologous stem cell transplantation
BMI	Body mass index
CAR T	Chimeric antigen receptor T-cell therapy
CHF	Congestive heart failure
CHOEP	Cyclophosphamide, Doxorubicin, Vincristine, Etoposide and Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete remission
CVD	Cardiovascular disease
DHAP	Dexamethasone, cytarabine, cisplatin
DLBCL	Diffuse large B-cell lymphoma
FDA	Food and drug administration
FL	Follicular lymphoma
FPM	Flexible parametric models
GCB-DLBCL	Germinal center B-cell diffuse large B-cell lymphoma
GDP	Gemcitabine, Dexamethasone, and Cisplatin
GEMOX	Gemcitabine and oxaliplatin
HMD	Human mortality database
HR	Hazard ratio
ICE	Ifosfamide, carboplatin and etoposide
IME	Ifosfamide, mitoxantrone and etoposide
IPI	International prognostic index
LEL	Loss in life expectancy
NHL	Non-Hodgkin lymphoma

NK cell	Natural killer cell
PD	Progressive disease
R	Rituximab
RCT	Randomized clinical trial
RIKS-HIA	Register of information and knowledge about Swedish heart intensive care admissions
R-RCT	Register-based randomized clinical trial
SCAAR	Swedish coronary angiography and angioplasty register
SD	Stable disease
SEPHIA	Secondary prevention after heart intensive care admission
S-LDH	Lactate dehydrogenase in serum
SLL	Small lymphocytic lymphoma
SLR	Swedish lymphoma register
SWEDEHEART	The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies
WHO	World Health Organization

1 INTRODUCTION

1.1 NON-HODGKIN LYMPHOMA

Non-Hodgkin lymphoma (NHL) is one of the top ten most common cancer types in Sweden and responsible for approximately 4% of all new cancers[1]. In 2016, the Swedish population comprised a total of 22 671 NHL survivors, or prevalent NHL patients[1].

Lymphoma develop from a type of white blood cells called lymphocytes. Lymphocytes are part of the immune system and include B cells, T cells and natural killer cells (NK cells). NHL can arise in any of these types of cells, although about 85-90 % of NHL arise from B cells.

The term NHL originate from the traditional division into Hodgkin and non-Hodgkin lymphoma but is not used that often anymore as a more refined subtype classification system has been developed. Although sometimes still referred to as one disease, NHL is truly an umbrella term representing a heterogeneous group of diseases with varying clinical course and prognosis. A more clinically relevant division distinguishes between aggressive lymphomas and indolent lymphomas.

1.1.1 Aggressive/Indolent lymphoma

Aggressive lymphomas show an aggressive growth pattern. These tumors grow rapidly and often cause general symptoms in the form of fever, night sweats and weight loss (B symptoms). Without treatment, survival is short. Treatment is started immediately after diagnosis and can be curative.

Indolent lymphomas grow slowly. Treatment is given if the disease causes symptoms or has a large tumor burden, however some patients can be followed without requiring treatment for many years. Indolent lymphomas are mostly regarded as chronic diseases and the purpose of the treatment is not curative but to push back the disease and prolong the time to progression. However, if the disease is diagnosed at an early stage, when localized to only one nodal site, cure may be possible with local radiotherapy. Although most patients are diagnosed with more widespread disease and thus cannot be treated curatively, long remissions are seen and survival is often long. Indolent lymphomas can transform into aggressive lymphomas.

1.1.2 Subtype classification

A more refined subtype classification system of NHL has been implemented based on clinical findings, morphology, immunophenotyping and molecular genetics[2] and the classification system is continually revised based on advancement in the understanding of the disease. In the widely established WHO classification, the term lymphoma has been replaced by mature lymphoid neoplasms. This group also encompasses chronic lymphocytic leukemia and multiple myeloma; however, the latter entities are not included in the definition of NHL in this thesis.

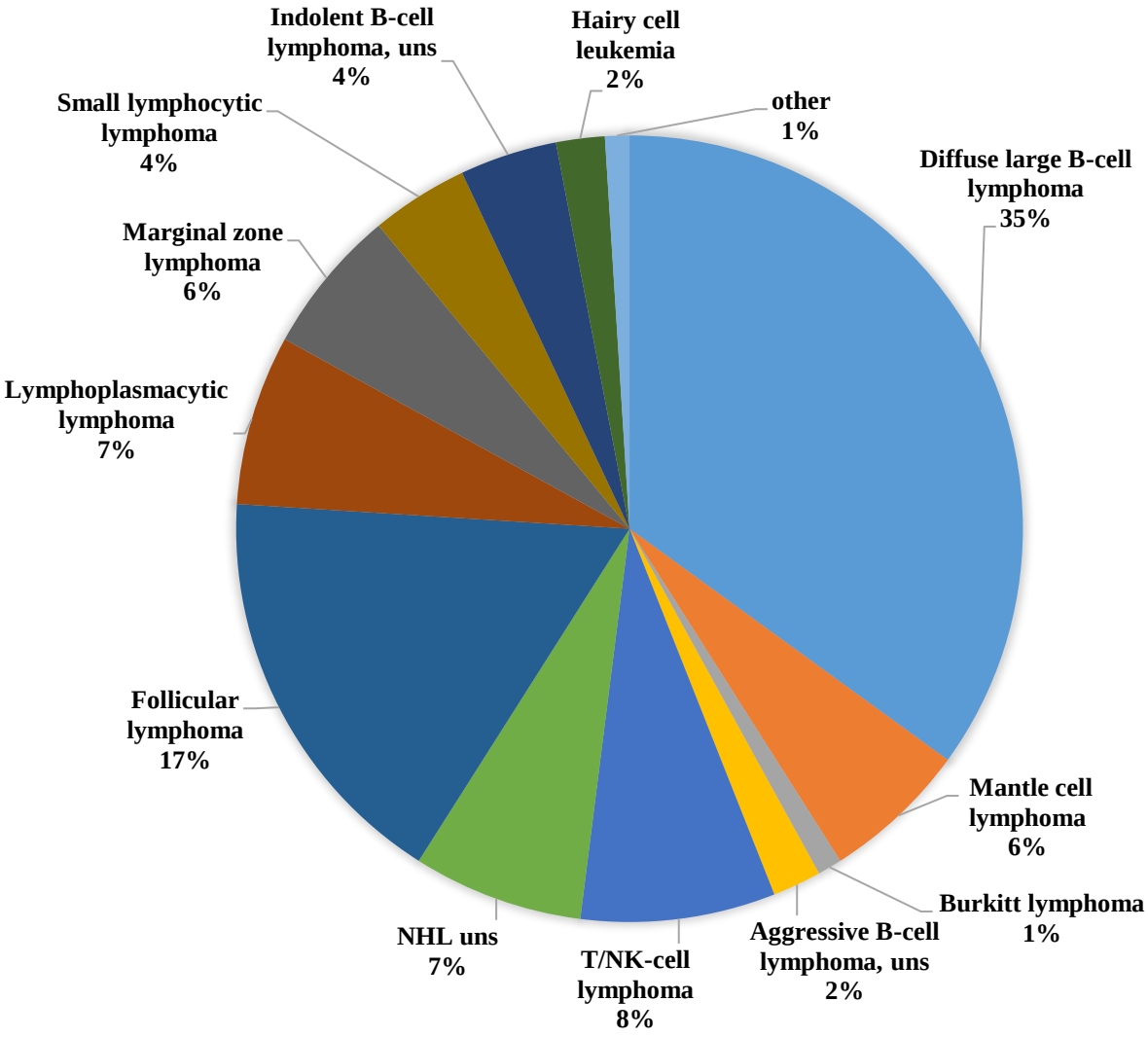


Figure 1.1: Distribution of NHL subtypes from 2000 to 2016 based on data from the Swedish lymphoma register

1.2 DIFFUSE LARGE B-CELL LYMPHOMA

The most common lymphoma subtype (and the main focus in three of the four studies included in this thesis) is diffuse large B-cell lymphoma (DLBCL)[3]. DLBCL is an aggressive type of lymphoma that develops from B cells.

The term diffuse large B-cell lymphoma describes the histological picture. The cells are large, grow diffusely and express B-cell markers such as CD20 and CD19. The cell-of-origin is a B cell from the germinal center (GCB-DLBCL) in the secondary lymph follicles or a cell that has passed the germinal center and has just begun its development towards plasma cell differentiation, a so-called activated B cell (ABC-DLBCL)[4].

In the latest WHO classification of tumors in lymphatic and hematopoietic tissue, from 2016, DLBCL is in turn further divided into several subgroups[2]. The most common is the unspecified group (DLBCL without further specification, UNS). In addition, several groups are distinguished based on, among other things, localization (mediastinum, CNS) and histology (T-cell-rich, ALK-positive, etc.).

1.2.1 Presentation

The first sign of illness is typically a rapidly growing mass, often in lymph nodes but it can arise in any organ, sometimes in combination with the so-called B symptoms; night sweat, weight loss and fever.

1.2.2 Risk factors

The incidence of DLBCL increases with age, median age at diagnosis is 70 years and it is more common in men than women. Risk factors for DLBCL include; immune suppression as in HIV/AIDS or following solid organ transplantation, autoimmune diseases (e.g. Sjögrens syndrome, systemic lupus erythematosus, rheumatoid arthritis etc.), Hepatitis C virus seropositivity, a family history of lymphoma and a high BMI[5-8].

1.2.3 International Prognostic Index, IPI

A prognostic scoring system called “International Prognostic Index” or IPI is used in clinical practice to determine risk categories and prognosis[9]. The score is calculated by summing risk factors where one point is given for each of the following:

- age >60 years
- elevated lactate dehydrogenase in serum (S-LDH)
- WHO/ECOG performance status >1
- Ann Arbor stage III-IV
- involvement of two or more extranodal sites.

A simplified score called the age-adjusted IPI (aaIPI) can be used to compare patients within age categories[9]. One point is then given for each of the following:

- Ann Arbor stage III-IV
- elevated S-LDH
- WHO/ECOG performance status >1.

Since the development of IPI back in 1993, several other prognostic scores have been suggested with the goal to further improve risk stratification, e.g., NCCN-IPI[10], R-IPI[11], DLBCL-PI[12]. However, IPI has been shown to remain a valid prognostic score[13, 14] and age-adjusted IPI is still used in clinical practice in Sweden to guide treatment decisions.

1.2.4 Treatment

According to the Swedish clinical guidelines[15], the standard treatment for patients diagnosed with DLBCL is 6 cycles (given with a 14- or 21- day interval) of the combination of cyclophosphamide, doxorubicin, vincristine and prednisone together with the anti-CD20 monoclonal antibody rituximab (R-CHOP). For younger patients (≤65 years) with aaIPI = 2-3, etoposide may be added to R-CHOP (R-CHOEP). The antibody rituximab targets the CD20 cell surface protein, present on most B-cell malignancies.

A reduced R-CHOP treatment called R-miniCHOP is increasingly used in very old patients (guideline > 80 years). The dose of doxorubicin and cyclophosphamide in R-miniCHOP has been halved while the doses of rituximab, vincristine and prednisone are unchanged.

For patients with impaired cardiac function, doxorubicin can either be replaced by etoposide (R-CEOP) or alternatively, the infusion time for doxorubicin can be prolonged.

1.2.5 Changes in treatment praxis during the study period (2000-2016)

The most significant change in the treatment guidelines during the study period was the addition of the antibody rituximab to the standard treatment. Rituximab was approved by the US Food and Drug Administration in 1997[16] and was gradually introduced in Sweden within clinical trials in the beginning of the 21st century. Rituximab was adopted in the national treatment guidelines as standard treatment for all DLBCL patients regardless of aaIPI in 2006.

The national guidelines are continuously updated as new evidence of treatment efficacy becomes available and other, minor, changes have been made over the years regarding, e.g., number of recommended treatment cycles, or the indications for administration of CNS-prophylaxis.

1.2.6 Follow-up guidelines

Patients in complete remission (CR) after completion of treatment are followed with regular visits to the clinic during two years (in general every three months during the first year and every 6 months during the second year but with large local variation). The purpose of the visits is to control for potential relapse, control and treat potential late effects, provide psychosocial support and evaluate needs of sick-leave and rehabilitation etc. The recommended follow-up has been shortened from previously five years to the current two years due to the reduced relapse risk after two years.

1.2.7 Relapsed/refractory disease

Approximately 20-30% of curatively treated patients are either refractory to first line treatment or relapse within 5 years[17].

Curative treatment for younger and fit relapsing patients (age ≤70 years, performance status and comorbidity load are also considered) include high-dose chemotherapy and autologous stem cell transplant (ASCT). Eligible patients are started on second-line chemotherapy (GDP,

DHAP, ICE with or without rituximab) and patients demonstrating chemosensitive disease are considered for high-dose chemotherapy after 3-4 cycles. Younger patients <65-70 years with recurrence after high-dose treatment can also occasionally be considered for allogeneic stem cell transplantation.

Many patients are however not eligible for ASCT, mainly due to high age. Among these, fit patients are recommended R-GEMOX, R-Bendamustine or R-IME or the possibility of inclusion in a clinical trial. Non-curative intent treatment, with the purpose of relieving symptoms include radiotherapy or low-toxic chemotherapy e.g. cyclophosphamide, trophosphamide or steroids.

For patients with primary refractory disease, experimental treatment in clinical trials is recommended.

2 LITERATURE REVIEW

The following literature review contains three sections and examines the current literature related to the studies in this thesis. The first section reviews the literature on recent trends in prevalence, incidence, mortality and survival of NHL and its subtypes in populations similar to the Swedish population (Study I). The following two sections focus on survival and survivorship following a diagnosis of DLBCL. First, by reviewing the literature regarding long-term survival after DLBCL, especially following the introduction of rituximab (Study II & IV). Secondly, by reviewing the literature on cardiovascular morbidity and risk of myocardial infarction among patients treated for DLBCL (Study III).

2.1 RECENT TRENDS IN PREVALENCE, INCIDENCE, MORTALITY AND SURVIVAL OF NHL AND ITS SUBTYPES

While there are several examples of studies on trends in incidence, survival and mortality of NHL, the knowledge about prevalence trends is sparse. However, the number of prevalent patients in the population will depend both on the number of newly diagnosed patients (incidence) and the survival of those patients (survival and mortality). It is therefore natural to review the literature regarding those metrics in order to indirectly capture what is known about the trends in prevalence of NHL.

2.1.1 Incidence trends

The number of newly diagnosed patients with NHL in Sweden has grown dramatically since the 1960s but after decades of a steeply increasing incidence of NHL, the increase started to level off in the 1990s[18]. Similar shifts in incidence trends have been seen in most high-income countries[18-22]. Notably, the incidence has continued to increase in some countries, although the level of increase is markedly lower than a few decades ago[23, 24], while it has stabilized[21, 22] or even started to decline in others[25].

Less is known about the incidence trends of the NHL-subtypes; however, a few studies exist that have systematically estimated subtype-specific trends. Despite the attenuation of the incidence of NHL overall, the incidence of several subtypes of NHL have been reported to increase in more recent years, including Burkitt lymphoma[3, 21, 26], marginal zone lymphoma[3, 21] and mantle cell lymphoma[3, 21, 27]. A pronounced increase in incidence of mantle cell lymphoma has been noted among white males over 70-75 years of age[21, 27]. On the other hand, the incidence of small lymphocytic lymphoma (SLL)/chronic lymphocytic lymphoma (CLL) has been reported to plateau or even decline[3, 21, 22].

Not all subtypes show consistent incidence trends across populations. For the most common subtype, DLBCL, the incidence trends are somewhat divergent. For instance, during the past 15-20 years, the incidence rates of DLBCL increased in Australia[21] and Canada[22], remained stable in the Netherlands[26], while starting to decrease in the US[25]. In a Swedish study from 2014, estimated DLBCL trends 2000-2010 where stable among women but there was a yearly increase in incidence among men[28]. As for follicular lymphoma (FL), a stable

incidence trend was seen in Sweden 2003-2007 which is in line with data in a Canadian study from 2017 where there was no statistical change in incidence of FL in either sex between 2003 and 2013[22]. In contrast, FL incidence increased prior to 2007 in the US and Australia[21, 25]. In the US, FL incidence rates have started to decline after 2007[25].

Diagnosis and classification of NHL is not always straightforward and despite the detailed categorization developed by WHO, there are non-negligible numbers of lymphoid malignancies recorded in the registers as unclassified, possibly due limited diagnostic material, or patients unfit for further diagnostic work-up. Several studies have, however, reported that this number is decreasing[3, 21, 24]. The unclassified lymphomas are a heterogeneous group that is difficult to study and the subtype to which these cases truly belong will be underestimated.

2.1.2 Mortality trends

Up to the mid/late 1990s, there was a steady increase in NHL-related mortality, but from the beginning of the 21st century, the mortality started to decline. This pattern has been observed in most high-income countries[19, 20, 24, 25].

It is not directly possible to decompose mortality rates into trends for NHL subtypes because death certificates often do not record subtypes. However, in a US SEER study, deaths were linked to incident cases for calculation of so-called incidence-based mortality rates (IBM) in order to estimate subtype-specific mortality trends[25]. Follicular lymphoma IBM was flat during 1990-1997 and then declined steeply, while the mortality observed for DLBCL and CLL/SLL peaked in 1995-1998 and then declined.

2.1.3 Survival trends

Survival after NHL has improved over the past decades[20, 29], although the extent of the improvement varies by sex, age and lymphoma subtype[22]. The improvement has been especially dramatic for patients diagnosed with B-cell lymphomas[3, 25, 26, 28-30]. The improved survival follows treatment advancements over the past decades that include introduction of new chemotherapy drugs and monoclonal antibodies (rituximab), autologous stem cell transplantation and optimized radiation therapy to reduce toxicity.

2.1.4 Prevalence

The data on prevalence at the subtype level is meager. In a study from 2014, the prevalence of different lymphoma subtypes in the UK were presented[31].The authors concluded that the prevalence estimates tend to be higher for men than women across all main subtypes, largely due to underlying differences in incidence patterns while there was no difference in survival between the sexes. However, this study did not investigate temporal trends.

Overall, the reported incidence, mortality and survival trends combined point to an increasing prevalence of NHL in the population. Although the steep increase in incidence of NHL overall observed in Scandinavia prior to the 1990s has leveled off, more recent studies have

demonstrated increasing incidences in specific subtypes of NHL and as new treatment options have become available during the past few decades, survival has improved dramatically.

While the increasing incidence, decreasing mortality and improving survival imply increasing prevalence, no systematic review on prevalence trends at the subtype level has been performed. As trends vary between populations it is not clear how the trends reported in other high-income countries can be generalized to the Swedish population nor how these trends translate into actual numbers of prevalent patients.

2.2 DLBCL SURVIVAL FOLLOWING THE INTRODUCTION OF RITUXIMAB

As stated in the previous section, survival in patients with B-cell lymphomas has improved dramatically during the past 1-2 decades following the addition of the anti-CD20 antibody rituximab to standard chemotherapy. As first shown in clinical trials, the addition of rituximab to CHOP-like chemotherapy improved the outcome of all subgroups of DLBCL patients, regardless of age and risk group without increased toxicity[16, 32-34].

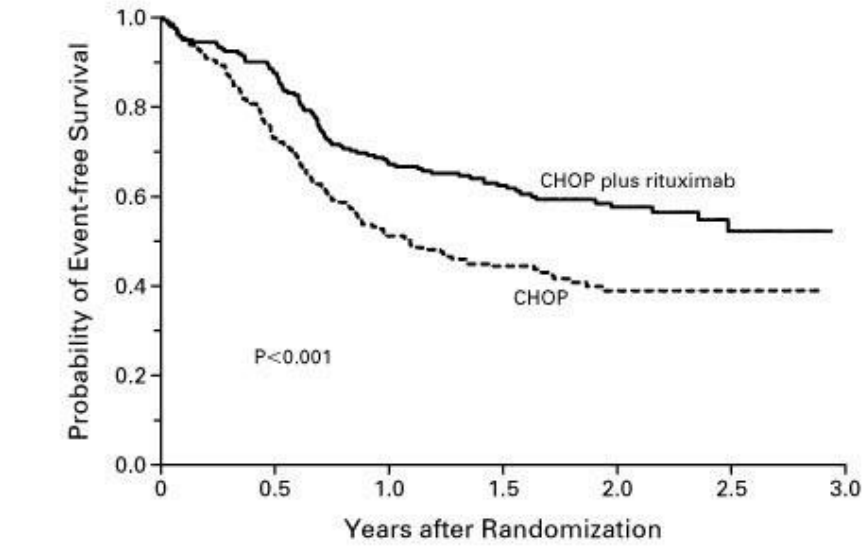


Figure 2.1: Event-free Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab. Reproduced with permission from New England Journal of Medicine Coiffier et al 2002[32] Copyright Massachusetts Medical Society.

Observations from controlled trials with selected patients have further been generalized to "real world patient groups" composed of a wide mixture of patients, including many who would not be eligible for participation in randomized clinical trials[35-37].

The addition of rituximab has prolonged survival due to a lower rate of disease progression during therapy and fewer relapses among patients in complete remission[32, 33, 38, 39] yet 20-30% are still either primary progressive or relapse within a few years from diagnosis[17, 36, 40].

The majority of relapses occur early but there is a pattern of continuous relapse risk[35, 36, 38, 40, 41] and 5-8% of patients achieving CR on primary treatment relapse after more than 5 years[39, 42, 43]. The survival after relapse is poor[40, 44-49] although late occurring relapses seem to have slightly better prognosis[39, 43, 50].

At least two studies exist that have compared DLBCL survival to that of the general population. In a study by Maurer et al, patients achieving 24 months of event-free survival had a subsequent survival comparable to that of the general population matched on age and sex[36]. In a study by Jakobsen et al, survival of patients with DLBCL responding to immunochemotherapy with complete remission, was compared to an age-and sex matched general population[35]. This study confirmed the favorable outcome shown by Maurer et al although the survival was slightly reduced relative the general population despite many years in complete remission. However, patients younger than 50 years at diagnosis had a survival comparable to that of the general population. Maurer and Jakobsen both stress the importance of avoiding relapse since the excess mortality after 24 months was mainly driven by relapses.

In conclusion, rituximab has substantially improved the survival after DLBCL and patients who successfully respond to primary treatment and have no adverse events during the first 2 years thereafter seem to have only a slightly reduced survival compared to the general population. However, despite advancements in the primary treatment, many patients still experience relapses and even after years in remission the persistent risk of relapse may prevent a normalization of survival. Therefore, quantifying the potential loss in life expectancy in a population-based setting (study II) as well as describing how patients move through different states (relapse, second remission, death etc.) following their disease (study IV) can provide new insight in long-term survival and survivorship after DLBCL.

2.3 CARDIOVASCULAR MORBIDITY AND RISK OF MYOCARDIAL INFARCTION IN PATIENTS TREATED FOR DLBCL

The anthracycline doxorubicin (abbreviated with an H in R-CHOP, as it was initially described as hydroxydaunorubicin) is known to be cardio-toxic and increases the risk of later cardiomyopathy and heart failure (CHF), and possibly also of cardiovascular diseases (CVD) such as AMI[51-54].

According to clinical guidelines, doxorubicin should be avoided in patients with severe cardiac comorbidity and low left ventricular ejection fraction at primary lymphoma diagnosis, and

modified chemotherapy regimens should be used. However, many patients are older and/or have milder comorbidity at diagnosis, such as hypertension or diabetes, which could also have implications for risk of adverse cardiac events[55].

Chemotherapy-associated CHF has been well described[53, 56-61] and the risk of doxorubicin-induced CHF has been shown to be dose dependent, i.e. the risk increases with increased life time cumulative dose[53, 60, 61]. Nevertheless, low to moderate doses of anthracycline-based chemotherapy have been associated with early development of subclinical abnormalities of cardiac and vascular function that in other populations are associated with future occurrence of a range of cardiovascular events[52, 62].

In a study based on SEER-data, DLBCL patients older than 65 years at diagnosis were compared to cancer-free controls. DLBCL patients were found to have a significantly increased risk of AMI, especially during the first 6 months after diagnosis[63]. The relative risk of AMI was higher for patients without prior CVD (when compared to controls without prior CVD) than the relative risk of AMI among patients with prior CVD (when compared to controls with CVD). The authors claim that this unintuitive finding can be explained by the fact that patients without a history of CVD receive more doxorubicin than patients with a history of CVD. However, even if the relative risks are reported higher for patients without CVD compared to the controls[63], the absolute risk of AMI is probably higher among patients with history of CVD than among patients without prior CVD.

Patients with a pre-existing CVD may receive fewer cycles and/or lower doses of chemotherapy and are less likely to be treated with doxorubicin[53, 59, 63]. Lowering the dose of doxorubicin in patients with cardiovascular disease reduces risk of secondary cardiovascular events but also increases the risk of death, presumably due to an increase in risk of disease progression[63].

Whether or not a patient should be disqualified for potentially life-saving treatment due to baseline CVD is a difficult but important question since many DLBCL patients are older and do have milder comorbidity at diagnosis.

3 RESEARCH AIMS

The overall aims of this thesis were to:

- Advance the understanding of the NHL disease burden by describing recent trends in the prevalence (i.e. the number of survivors in the population) of NHL subtypes and correlate those to trends in incidence, survival and mortality.

- Quantify loss in life-expectancy following a diagnosis of DLBCL in a population-based setting.

- Describe the excess risk and timing of myocardial infarction in patients treated curatively for DLBCL (when contrasted to a DLBCL-free comparison group).

- Describe patient trajectories following DLBCL using multistate models with emphasis on predicting real-world probabilities of lasting remission in a population-based setting.

4 MATERIALS AND METHODS

All studies included in this thesis are population-based register studies.

4.1 DATA SOURCES

4.1.1 The Swedish Lymphoma Register

The main data source in the four studies included in this thesis is the Swedish Lymphoma Register (SLR). Due to the heterogeneity of the lymphoma diagnoses and their subclassification, SLR is essential for follow-up of patients in subgroups that can otherwise not be distinguished in the National Cancer Register.

SLR was initiated in 2000 on behalf of the Swedish Lymphoma Group with the purpose to optimize the care of patients with malignant lymphomas. Chronic lymphocytic leukemia (CLL, which belongs to the same group of mature lymphoid malignancies) has a separate quality register since 2007 and hence this diagnosis is not included in SLR.

The SLR includes all incident lymphomas diagnosed in patients aged 18 years and above. Pure autopsy findings are not included. SLR includes detailed level information of lymphoma subtype (the register contains 78 subtypes, unspecified lymphomas included). From 2007 the register collects data on first line treatment and response to treatment, and from 2010 information on relapse is also collected. Compared to the National Cancer Register to which reporting is mandatory by law, the coverage is around 95%[64]. There is however a lag in the registration, where the median time from diagnosis to registration is about 6 months (80% are registered within 14 months from diagnosis)[64].

During 2017-2019 we initiated an extensive nationwide data collection and update of the SLR (Figure 4.1). In phase one, approximately 5000 patients diagnosed with DLBCL between 2007 and 2014 were identified in SLR and medical charts for 98% were localized and reviewed by trained research nurses. The purpose was to ensure the completeness of the information regarding treatment, response to treatment and relapse information.

4.1.2 Data collection

In addition to the update of SLR, in phase two, data including information on later line treatment and clinical presentation at relapse, were collected for relapsing patients and patients not responding to first line treatment. After the first chart review, a total of 822 patients were found to meet these criteria.

When the data collection ended in 2019, the final cohort with relapse or progressive or stable disease (PD/SD) as best response to first-line treatment encompassed 761 (92.6%) patients. Live patients had been asked to give their informed consent to have their data collected, 15 patients (1.8%) declined to participate and were therefor not included, and in addition 46 patients (5.5%) never had their data collected due to administrative reasons (e.g. that the

patients had moved between different hospitals which made it difficult to localize the full medical chart or that the informed consent was received after the data collection had ended).

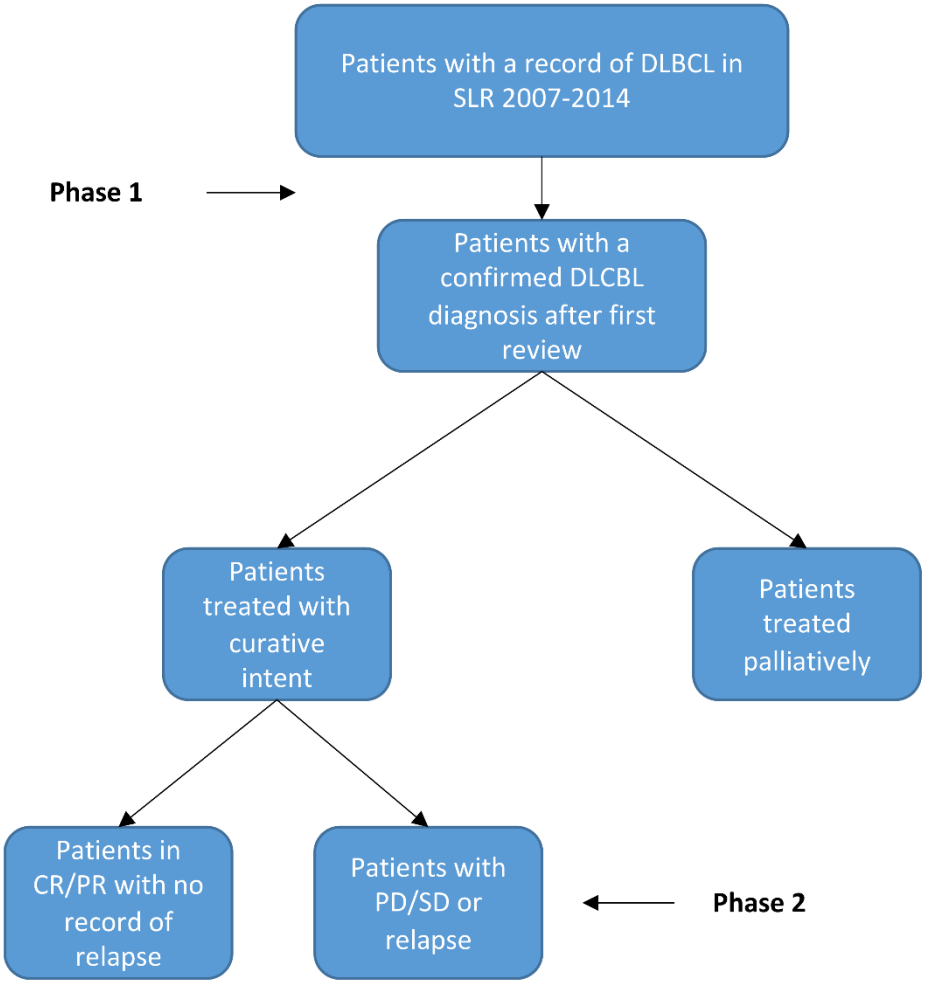


Figure 4.1: Schematic overview of the data collection.

4.1.3 SWEDEHEART

In the third study in this thesis, SLR was linked to the Swedish national quality register SWEDEHEART. SWEDEHEART started in 2009 by the merge of four already existing quality registers (RIKS-HIA, SEPHIA, SCAAR, and the Swedish Cardiac Surgery Registry) - forming Sweden's largest quality register. Patients eligible for registration in SWEDEHEART receive written information about the register, their voluntary participation and about the possibility to decline participation[65].

We mainly use data from RIKS-HIA, this register includes all patients who are treated in coronary care units or other specialized facilities due to acute coronary syndrome/myocardial infarction. The register includes detailed information on clinical characteristics, symptoms, diagnoses and medications during hospitalization and at discharge. When the RIKS-HIA register started in 1991, 19 hospitals participated but today the register is nationwide and includes all Swedish hospitals treating acute cardiac diseases. The register has a 95-96% agreement with health records[65].

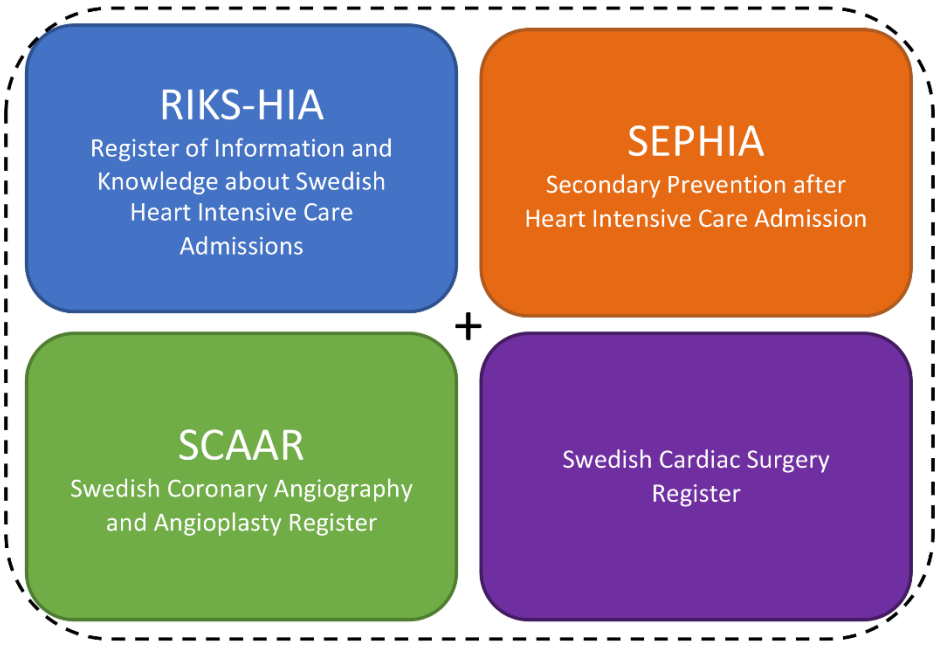


Figure 4.2: SWEDEHEART is a merger of four quality register: RIKS-HIA, SEPHIA, SCAAR and Swedish Cardiac Surgery Register

4.1.4 Additional data sources

SLR is regularly linked to the Swedish Cause of Death Register to retrieve information on dates of death (if applicable). In addition, the data was further linked by the use of personal numbers[66] to: The National in- and outpatient registers, the National Cancer Register and the Prescribed Drug Register.

Population life tables stratified on age, sex and calendar year obtained from the Human Mortality Database project (HMD) were used in study II. HMD receives raw data from Statistics Sweden and convert it to life-tables according to a common methods protocol[67]. The life-tables are available for public use at http://mortality.org.

4.2 ETHICAL CONSIDERATIONS

The studies included in this thesis are all observational register-based studies. This means that there are no interventions done to the patients (as compared to in clinical trials) and therefore no risk of directly harming the patients involved. However, we are handling personal- and highly sensitive information about the patients included in the studies. Therefore, ethical considerations in register-based studies naturally revolves around how researchers handle this data and how we make sure that the public's confidence in research is preserved. It is crucial that:

- We handle the data in a secure way to protect the patients' privacy and security. This means that access to data is limited to researchers directly involved in data analysis, that data is stored in a secure way (on encrypted servers set up for this purpose) and that it is at least pseudoanonymized (e.g. by the use of random identification number instead of personal number and that we limit the number of variables as much as possible to obstruct indirect identification).
- We as researchers secure the quality of the data so that it can be used to pursue valid and important research, for the group under study and the society.
- We choose appropriate methodology, design and statistical methods for the research question at hand.

Processing of sensitive personal data without explicit consent is prohibited, according to the general Data Protection Regulation (GDPR), but there are a number of exceptions, for example research with approval from the Ethical Review Board before the research begins. When informed consent is not required from the participants, we need to bear in mind that most people are probably not even aware of their data being used, and while it seems an impossible task to keep track of the numerous studies that are pursued based on these data, we need to ensure that we facilitate such work by e.g., reporting new data linkages to the data protection officer.

One could also argue that the research conducted is not always beneficial for the individuals included (but can potentially be beneficial for future patients). On the other hand, the general inclusion is an important aspect that allow for true population-based research that makes the results applicable also to patient-groups that are normally not included in e.g., randomized clinical trials.

4.3 METHODOLOGICAL CONSIDERATIONS

4.3.1 Study I

4.3.1.1 Different measures capture different aspects of disease burden

Incidence, survival, mortality and prevalence are all measures that are important indicators of disease burden and that form the basis for cancer control activities[68]. The different measures capture different aspects of a dynamic, time-dependent process. Hence it is important to explore

trends in all metrics jointly in order to interpret the overall progress in cancer prevention and control[69, 70].

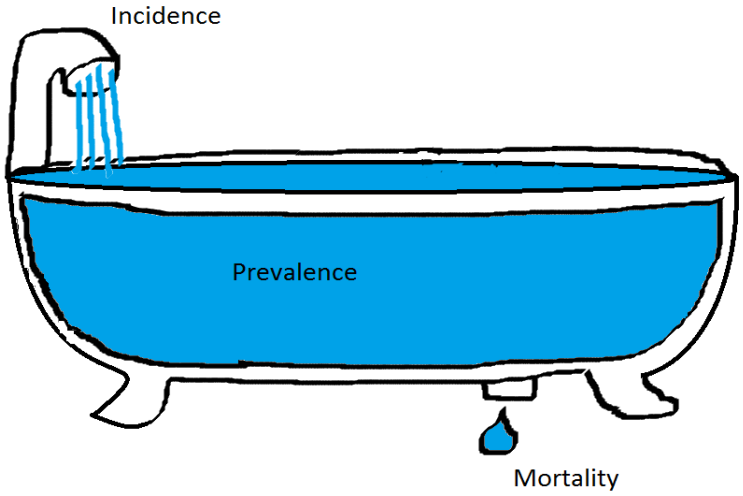


Figure 4.3: The "Epidemiologist's bathtub" shows the relationship between Incidence, mortality, survival and prevalence. The incidence is represented by the water entering the tub from the tap, the mortality is represented by the water leaving the tub through the drain, the survival time is the time the water stays in the tub and the prevalence is represented by the amount of water that is in the tub at any given moment.

4.3.1.2 Incidence

Trends in incidence may be explained by changes in the distribution of risk factors (disease ethology), clinical work-up leading up to the diagnosis and/or the cancer registration process itself. Because age is such a strong risk factor for cancer, incidence rates are often age-standardized to facilitate comparison between groups or over time. This can be done directly or indirectly, either by applying the age-distribution of a standard population (e.g. the World Standard Population) or by applying the age-distribution from one of the groups under comparison. In this study, incidence and mortality rates were age standardized using the age-distribution in Sweden in 2000 as the standard population.

4.3.1.3 Prevalence

Prevalence can be defined as the number of persons alive at a given time point who have had a cancer diagnosis (ever) or expressed as the number of persons alive that have been diagnosed with cancer in a certain time-window e.g. in the previous five years. Different time windows may capture different aspects of the disease burden. A short time window may reflect the number of patients in the population with an active disease undergoing treatment while a wider

time window may capture a larger number of patients in remission that may experience late effects of their cancer. The prevalence in a specified time window also reflects the number of patients that are actively monitored in health care.

We defined the prevalence as the number of patients alive December 31st each year and who had a recorded diagnosis of NHL in the previous 2, 5 or 10 years. The different time-windows were chosen to reflect both varying clinical course by subtype, and differences in the recommended duration of active patient monitoring in clinical practice over time[71-75].

4.3.1.4 Survival

Survival refers to the proportion of patients diagnosed with the cancer under study who are still alive at various points in time after diagnosis. Often when we want to measure the survival after cancer, we are interested in deaths associated with the diagnosis of cancer itself. However, cancer patients may die from a number of causes, sometimes completely unrelated to their cancer diagnosis. These deaths are known as competing events, meaning that they effectively prevent all other events from eventually occurring. Since we can only die once, having died from another cause means you are no longer at risk to die from cancer.

When estimating cancer survival, we therefore have two options: we can either eliminate deaths due to other causes, i.e. ignore them and estimate a quantity called net survival that assumes that competing events did not happen, or accommodate them and estimate the cancer survival in the presence of the competing events (sometimes called crude survival). The choice between the two approaches depends on the research question and intended target audience.

4.3.1.5 Net survival or net probability of death

We can estimate net probability of cancer death by censoring the survival time when a competing event occurs (e.g. at death from another cause based on information from death certificates). The strict interpretation of net probability of death due to cancer is: *the probability of death in a hypothetical world where cancer is the only possible cause of death*. This can sound a bit awkward, however, eliminating any background mortality makes comparisons across groups of patients more meaningful in many epidemiological investigations (e.g. across age-groups or between countries).

Lymphoma subtypes are not specified on death certificates so in order to capture subtype-specific deaths we can instead contrast the number of deaths (all-cause) in our patient population to the number of deaths that we would expect if the cancer patients did not have cancer. This is known as excess mortality and is defined as:

$$Excess\ mortality = Observed\ mortality - Expected\ mortality$$

The survival analogue to excess mortality is relative survival and is defined as:

$$Relative\ survival\ ratio = \frac{Observed\ survival\ proportion}{Expected\ survival\ proportion}$$

The advantage of this approach is that information on cause of death is not required. Another advantage is that excess mortality captures all deaths, both directly and indirectly due to the cancer (e.g. including also treatment related side effects)[76].

Expected mortality is often taken from population life tables stratified by age, sex and calendar year (see section 4.1.4). In theory, the expected mortality would be from a population completely free from the cancer under study but in reality, we use population life tables that contain deaths due to the cancer under study. It has been shown that this introduced bias in practice is so small that it does not affect the estimated survival proportions of cancer forms as rare as lymphoma[77].

When estimating excess mortality, we make the following assumption:

- exchangeability i.e. that the only difference between the cancer patients and the general population is the fact that the cancer patients were diagnosed with cancer and that the potential difference in mortality is directly or indirectly due to the cancer.

- Independence i.e. that the time to death from the cancer in question is conditionally independent of the time to death from other causes. i.e. there should be no factors that influence both the cancer and non-cancer mortality other than those controlled for in the estimation.

Unfortunately, we cannot test the validity of this assumption in a given data set but must rely on subject matter knowledge.

Table 4.1: Different population measures of cancer burden, their interpretation and factors affecting them.

Measure	Interpretation	Affected by:
Incidence	Number of newly diagnosed patients per person-years at risk in the population	Risk factors (disease etiology), diagnostic routines, cancer registration process
Mortality	Number of deaths per person-years at risk *in the population*	Incidence, survival
Prevalence	Number of live patients at a specific time point	Incidence, survival
Survival	Proportion alive *among the patients* (Often reported as net survival or overall survival)	Treatment, prognostic factors (age, comorbidity etc), care, incidence (e.g. if more cases are detected early due to screening this will affect survival)

4.3.1.6 Estimating trends

Poisson regression models (adjusted for age at diagnosis and sex) were used to test for trends in incidence, excess mortality and prevalence by assuming a linear effect of calendar year on each outcome. The Poisson regression model is commonly used to model counts or event rates i.e. number of deaths or number of new cases (incidence) per 100 000 person-years. These models estimate rate ratios with 95% confidence intervals, which can be interpreted as the average annual effect on the incidence or mortality.

Interactions between calendar year and age at diagnosis (≤70/>70 years) and sex were included to test for effect modification. A sandwich estimator[78] of the standard errors was used in the prevalence models to account for non-independent observations since the same patient may attribute to the prevalence many years in a row.

This framework also enables a straightforward and commonly used extension of the Poisson regression model (via a user defined link function) to allow for modelling of excess mortality (relative survival) in studies of cancer patient survival[79].

4.3.2 Study II

4.3.2.1 Estimating loss in life expectancy

Survival is commonly expressed as a summary measure at arbitrary time points e.g. proportion of patients alive at five years after diagnosis. In this study, we instead estimate the loss in life expectancy (LEL) a clinically relevant and easy-to-interpret measure of survival of the patient that summarizes the prognosis over the entire life-span.

The LEL provides a useful summary measure for how close (within how many years) the life expectancy for the patients is predicted in comparison to that in the general population. The loss in expectation of life is of specific interest in young patients (potential life years that can be lost is higher compared to chronologically older patients).

The LEL is defined as the difference between the life expectancy (mean all-cause survival) in the cancer population and that in the general population (matched on age, sex and year). Since we seldomly have follow-up data until all patients are dead (i.e. when the survival function reaches zero), estimation of life expectancy generally requires extrapolation of the survival function beyond the available data. Hakama and Hakulinen[80] suggested extrapolation of the relative survival and to use the relationship between relative survival, observed and expected survival to obtain the all-cause survival function rather than extrapolating the all-cause survival function directly. The all-cause survival function may extrapolate poorly but the excess mortality is typically low at the time of follow-up where extrapolation is used (i.e. several years after the cancer diagnosis).

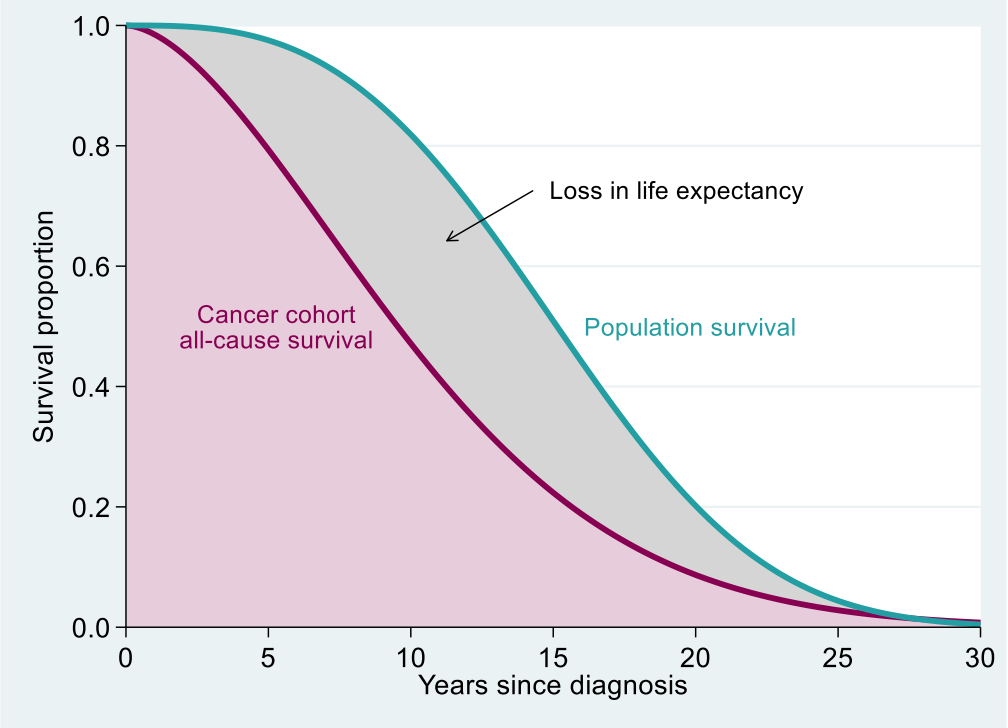


Figure 4.4: The loss in life-expectancy is defined as the difference between the mean all-cause survival in the general population and that in the cancer population.

We used methods developed by Andersson et al[81] where the cumulative excess mortality is extrapolated by using a flexible parametric survival model. When evaluated against historical data, the extrapolated relative survival gave a good estimate of the mean survival time in most age groups and for most cancer sites[81].

4.3.2.2 The flexible parametric survival model

The flexible parametric survival models (FPM) were first introduced by Royston and Parmar[82]. In contrast to the widely used Cox model, FPM explicitly estimates the baseline hazard function. In a Cox model, no parametric shape of the baseline hazard needs to be assumed. However, using parametric models have several advantages when it comes to prediction, quantifications (e.g. absolute and relative differences in risk) and modelling time-dependent effects or on multiple time scales. The flexible parametric model has also been extended to a relative survival framework and can be used to estimate excess hazards (relative survival)[83, 84].

The baseline hazard function is estimated in FPM by using restricted cubic splines. The baseline rate is modelled on the log cumulative hazard scale (or the log cumulative excess hazard scale if we are using relative survival).

$$ln[H(t|\boldsymbol{x}_i)] = ln[H_0(t)] + \boldsymbol{x}_i\boldsymbol{\beta}$$

Restricted cubic splines are restricted to be linear before first knot and after last knot. For knots,$k_1, \cdots, k_k$ a restricted cubic spline function can be written:

$$s(x) = \gamma_0 + \gamma_1 z_1 + \gamma_2 z_2 + \cdots + \gamma_{k-1} z_{k-1}$$

For example, with a flexible parametric model using 4 knots to model the baseline hazard we can write:

$$ln[H(t|x_i)] = \eta_{\,i} = \gamma_0 + \gamma_1 z_1 + \gamma_2 z_2 + \gamma_3 z_3 + x_i\beta$$

Where $\gamma_0 + \gamma_1 z_1 + \gamma_2 z_2 + \gamma_3 z_3$ is the log baseline cumulative hazard and $x_i\beta$ is the log hazard ratio. This is a proportional hazards model and the estimates that we obtain from the flexible parametric survival models are similar to those obtained from a standard Cox model if a sufficiently large number of degrees-of-freedom is used to model the spline function.

4.3.2.3 Sensitivity analysis

Although flexible parametric models are parametric "by nature", the use of splines to model the baseline has previously been shown to allow for sufficient flexibility to capture the complexities of the data, provided an appropriate number of knots for the spline is used[85].

Typically, the sensitivity of the results due to the knot figuration (i.e. the parametric shape of the baseline hazard) is assessed by re-fitting the model with a range of knot numbers and localization, and to compare the AIC (Akaike Information Criterium) and BIC (Bayesian Information Criterium). Such sensitivity analysis (figure 4.5) show only minimal differences

in the estimated number of life-years lost in study II, and the conclusions drawn are independent of the number of knots used to estimate the baseline cumulative excess hazard.

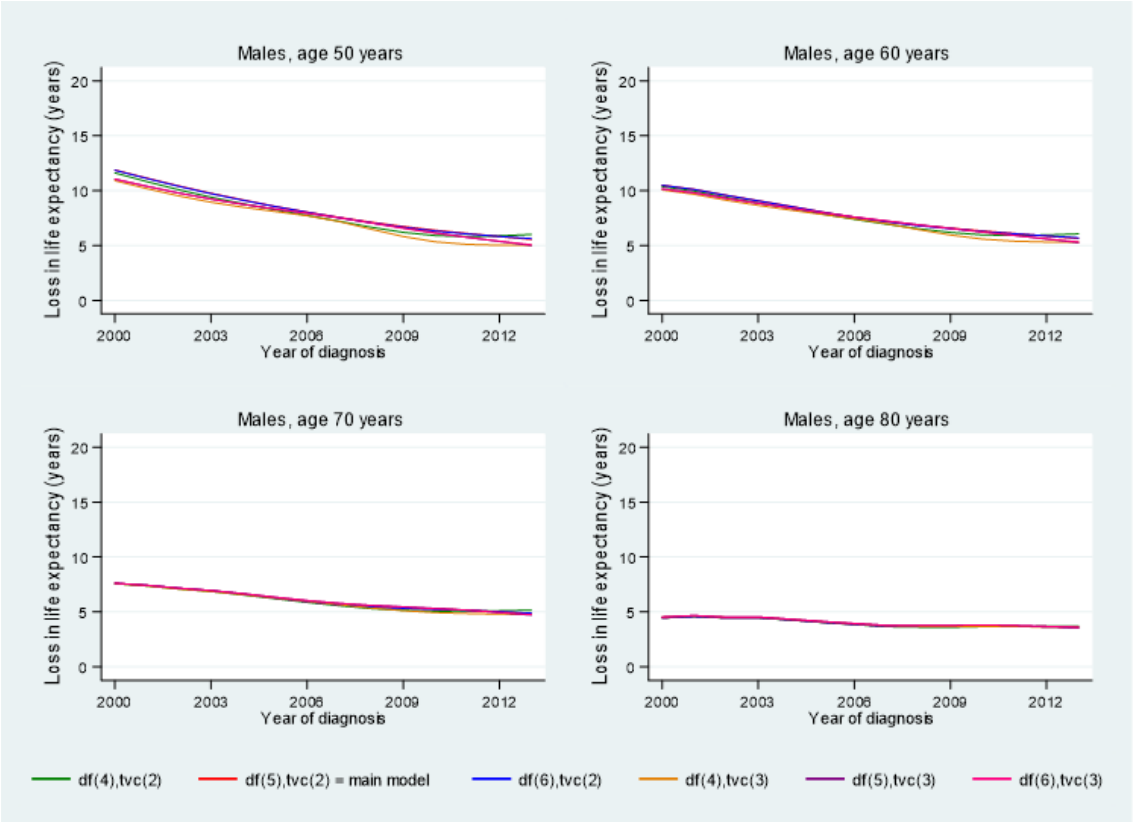


Figure 4.5: Temporal trends in loss in expectation of life (LEL) for male Diffuse Large B-cell Lymphoma (DLBCL) patients at ages 50, 60, 70 and 80 years at diagnosis estimated from different models with degrees-of-freedom (df) for the baseline hazard ranging from 4 to 6 and time-dependent effects (tvc) with degrees-of-freedom 2 or 3.

4.3.2.4 Survival in the presence of competing risks

In this study we also estimated the probability of dying from lymphoma in the presence of competing risks, e.g., cardiovascular diseases, malignancy other than lymphoma, or other causes of death (Figure 4.6b). In terminology used for population-based cancer patient survival this measure is also known as the crude probability of death, as compared to the net probability discussed in section 4.3.1.5.

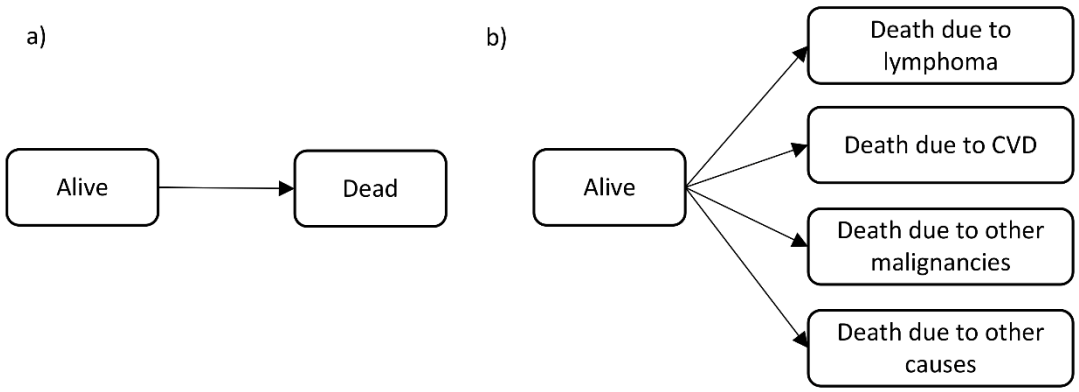


Figure 4.6: Illustration of a) standard survival setting and b) competing risk setting

As stated in section 4.3.1.5, net survival is useful for comparisons between groups when we want to eliminate death due to competing events. However, the somewhat awkward interpretation has limitations in the context of absolute risk estimation for patients. If we instead incorporate the competing risk of dying from other causes we can estimate crude survival. The interpretation of crude probability of death is: *the probability of death in the real world where patients can die from other causes than cancer.* This measure is useful in risk communication and treatment planning to understand the real-world probability of death. However, it is less useful for understanding mechanisms e.g. the effect of different exposures.

4.3.3 Study III

4.3.3.1 Allowing for repeated events

Survival models are often used to study time to death but are not restricted to this outcome, we can use survival models for any type of event when also time to the event needs to be taken into account. When the outcome is death, it is only possible to have one event per study participant – we can only die once. After an individual has experienced the event then the individual is no longer at risk for the outcome i.e. is no longer contributing either any risk time or events to the analysis. In this study, the outcome of interest, acute myocardial infarction (AMI) can occur multiple times, and to capture this situation we incorporated repeated events into the model.

Extensions to the Cox model have been developed to allow for repeated events[86] and we can implement similar models in the Flexible parametric model framework[87]. In general, repeated events in survival analysis are enabled by splitting the time-scale at event times so that we end up with several rows of data per individual that consist of non-overlapping follow-up intervals (figure 4.7). These intervals ensure that individuals are at not at risk for their second event until after they have experienced their first event.

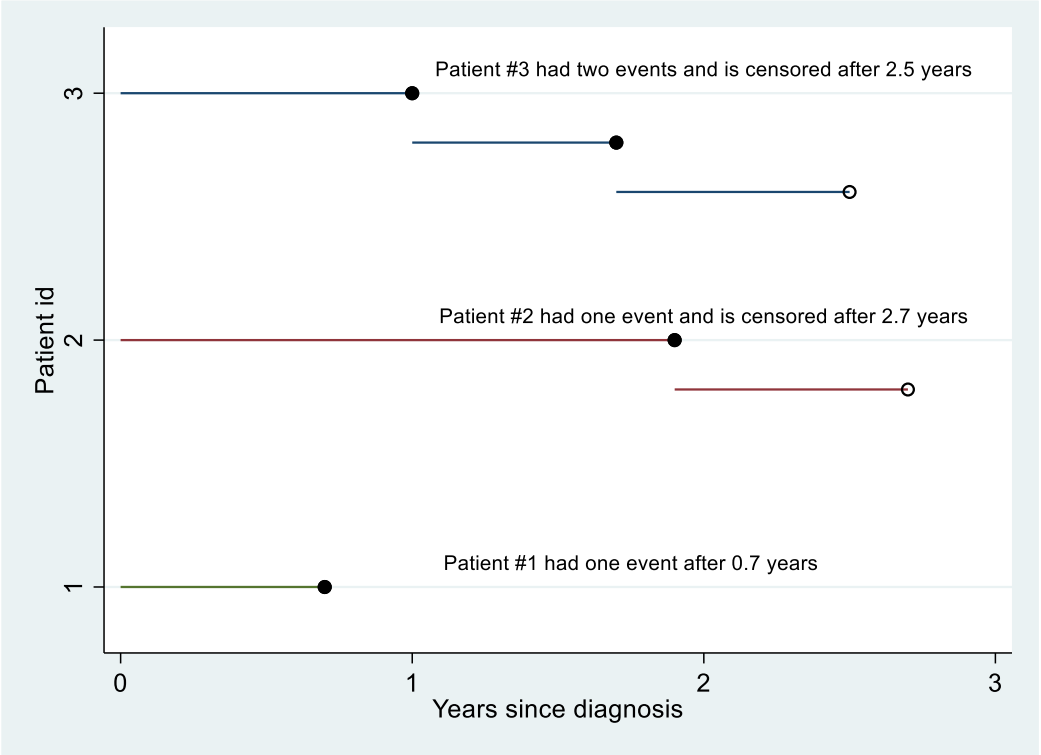


Figure 4.7: Schematic graph showing the time at risk and stratum for three hypothetical patients.

The underlying shape of the baseline hazard is assumed to be the same for all events (first, second, third etc.) but we can relax this assumption by stratifying the survival model on event number. In a flexible parametric model this is done by fitting a time-dependent effect i.e. include an interaction between the baseline cumulative hazard and a covariate containing the interval number. However, including interval number in the models in this paper did not alter any conclusions (figure 4.8) and therefore we opted for a simpler model where the underlying shape of the baseline hazard was assumed to be the same for all intervals.

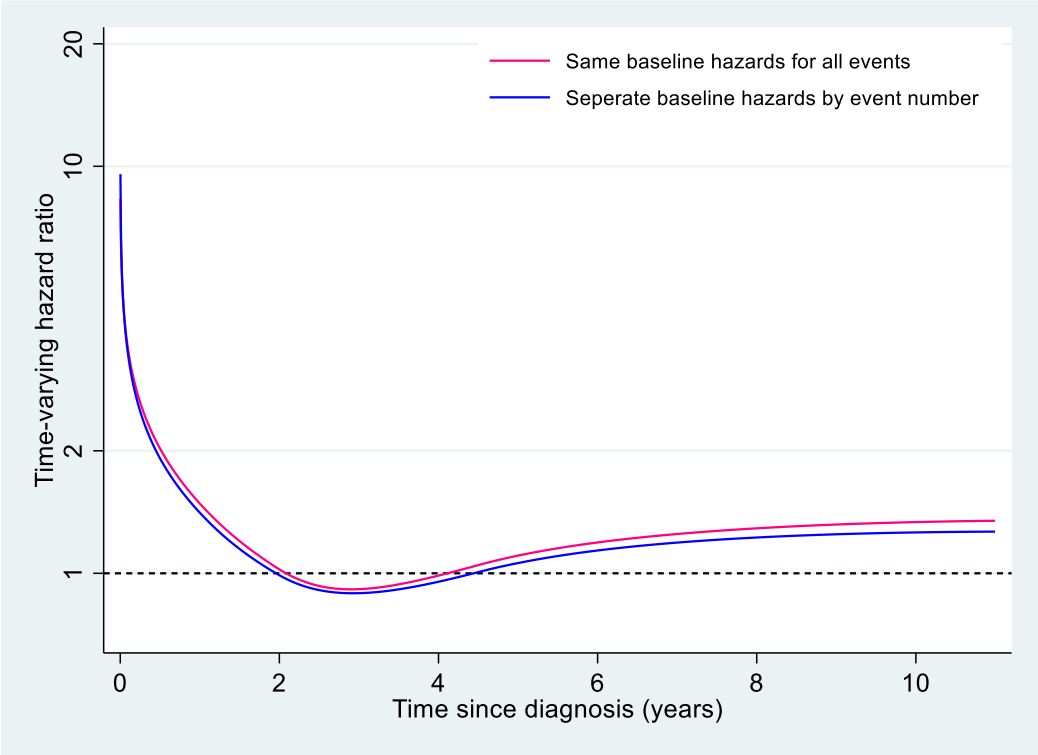


Figure 4.8: Time-varying hazard ratio illustrating the relative risk of AMI among DLBCL patients compared to matched population comparators estimated from two different models, one where the shape of the baseline hazard is assumed to be the same for all events (pink) and one where event number has been included as a time-dependent effect (blue).

4.3.4 Study IV

4.3.4.1 Estimating real-world probabilities of patient trajectories using a Multi-state model approach

Multi-state models can be used to quantify patient trajectories through different disease stages. We can think of the multistate model as a generalization of the competing risk model (Figure 4.6b), where also intermediate states of interest can be added. A multistate model can be simple or complex, all depending on the number of states and the structure of the model e.g. if it is

possible to re-enter a state. States can be classified as "transient states" (that can be both entered and exited) and absorbing states from where it is impossible to leave (e.g. death) (Figure 4.9).

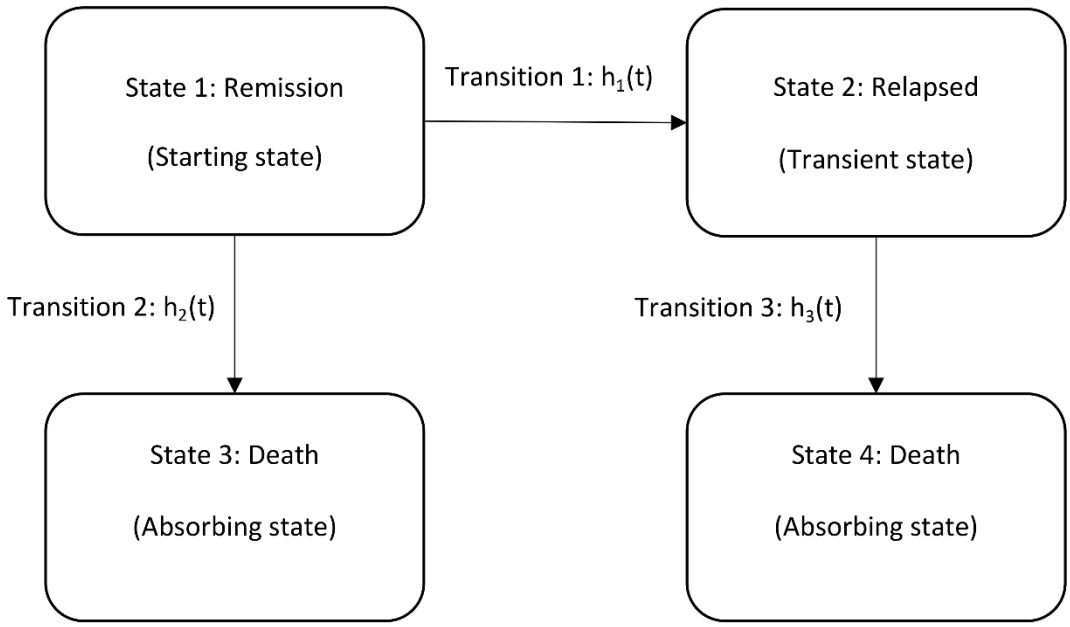


Figure 4.9: Illustration of a multistate model with four states. All patients start in the state "Remission". Each arrow between states is a transition and can be seen as a survival model. The state "Relapsed" is a transient state that can be both entered and exited and the two death states are absorbing i.e. once entered it is impossible to leave.

The multistate models can be described as stochastic processes, $\{Y(t), t \geq 0\}$ taking values in a finite state space S. The transition probability, or the probability of being in a state b at time t, given that the process is in some state a at time s and the process history before s, can be defined as:

$$P(Y(t) = b | Y(s) = a, \mathcal{H}_{s-})$$

where $(a, b) \in S$ and the history $\mathcal{H}_s = \{Y(u); 0 \leq u \leq s\}$ contains all previous observations of the process.

4.3.4.2 The Markov model

The expression of the transition probability can further be simplified by assuming that the probability of future transitions only depends on the current state and not the history leading up to it. This is known as the Markov property. The transition probability in a Markov model can be written as:

$$P(Y(t) = b|Y(s) = a, \mathcal{H}_{s-}) = P(Y(t) = b|Y(s) = a)$$

The transition intensity i.e. the hazard rate of going to one state to the next is now defined as:

$$h_{ab}(t) = \lim_{\Delta t \to 0} \frac{P(Y(t + \Delta t) = b|Y(t) = a)}{\Delta t}$$

The interpretation of the transition intensity is the instantaneous probability of going from state a to state b, given that you were in state a at time t. This is equivalent to the interpretation of the hazard rate of survival models in general. Essentially, a multi-state model can be specified by a combination of transition-specific survival models.

The Markov assumption can be relaxed by allowing the probability of future transition to not only depend on the current state but to also depend on the time the current state was entered.

$$P(Y(t) = b|Y(s) = a, \mathcal{H}_{s-}) = P(Y(t) = b|Y(s) = a, T_a)$$

where T_a is the time when state a was entered. This can be done in different ways, for example by including the enter time as a fixed covariate in the model, called the Semi Markov model. Another example is Markov renewal or clock-reset process. Time since entry in the current state, t-Ta, is then used as the underlying time scale. This is especially useful when the time since entry in the current state is of greater importance for the transition probability than the time since entry of starting state. This is often the case when the current state is more severe, such as recurrence of cancer for example.

4.3.4.3 Estimating transition probabilities

The fact that each transition can be viewed as a survival model makes the estimation of transition intensities straightforward. Predicting the transition probabilities is however more complicated. A variety of approaches has been suggested within a parametric framework; analytic calculations using maximum likelihood, numerical integration and ordinary differential equations[88-91]. In this study we used a simulation-based approach[92]. Simulation together with parametric transition models have the advantage of being less computer intensive and more generalizable especially when we want to include time-varying effect etc.

We estimated transition intensities by fitting separate flexible parametric models for each transition. In this way, we are not restricted to the same distributional form for all transition models. Figure 4.10 show the model-based transition probabilities overlaid by the Aalen-Johanssen estimator (non-parametric estimates of the transition probabilities).

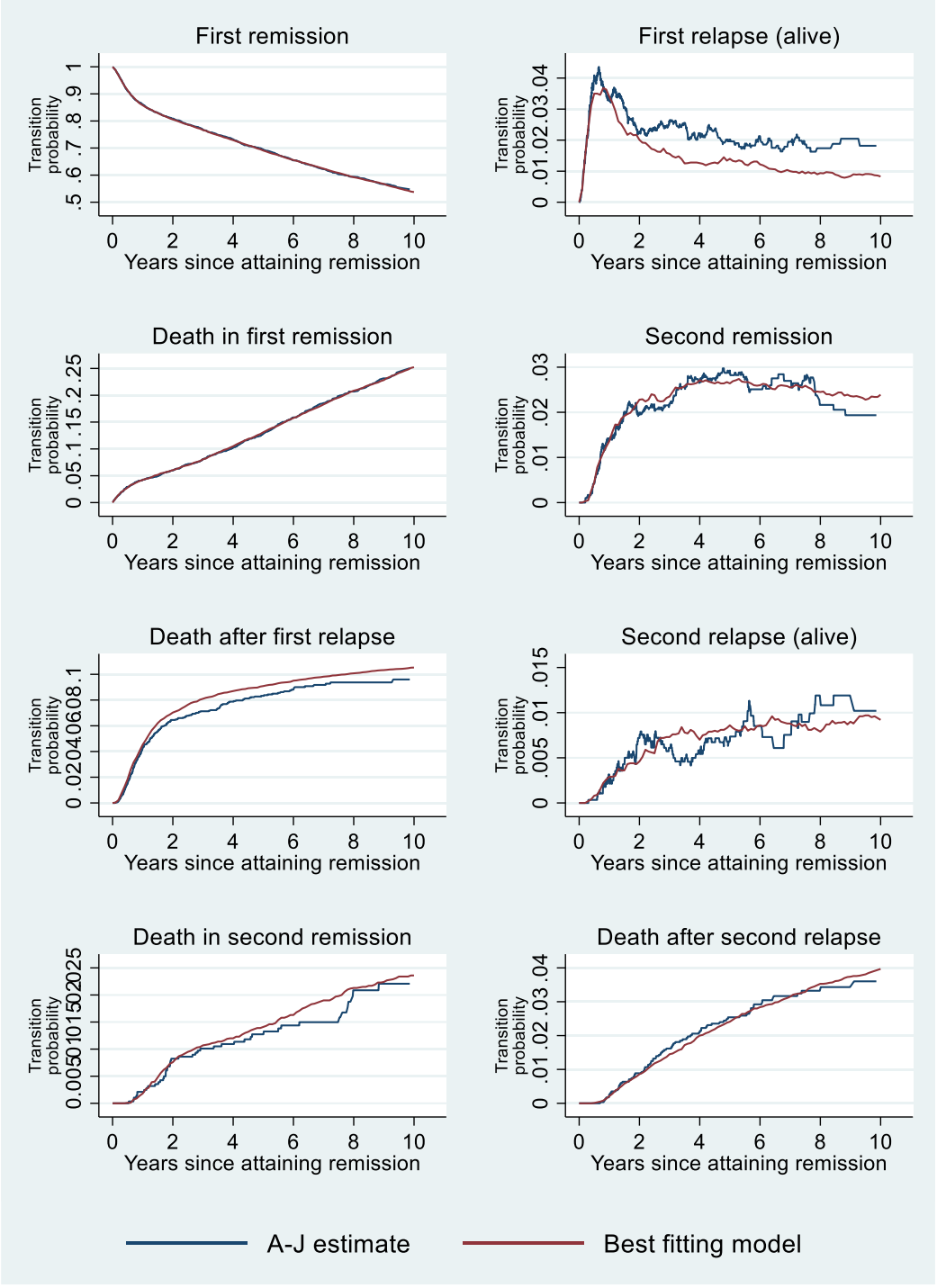


Figure 4.10: Comparison of the Aalen-Johanssen (non-parametric) estimates (A-J estimates) and the model-based estimates of the transition probability for the eight different disease-stages included in the full multistate model in study IV. Note that the scale of the y-axis differs between the plots.

5 RESULTS

In summary, the main findings were:

- The number of prevalent cases of NHL has increased between 2000 and 2016. The increase was seen in all three larger subgroups investigated: aggressive B-cell lymphoma, indolent B-cell lymphoma and T/NK-cell lymphoma and in all major morphological subtypes investigated. DLBCL, the most common subtype, was responsible for the largest increase in absolute number of prevalent cases.

- The loss in life expectancy for patients diagnosed with DLBCL between 2000 and 2013 has decreased overall, but a substantial number of life-years are still lost despite the addition of rituximab to the standard tretment, especially in high-risk patient groups. However, patients surviving the first two years after diagnosis have a favorable prognosis thereafter, with only minimal loss in life-expectancy compared to the general population regardless of age, sex or IPI-score.

- DLCBL-patients receiving curative intent treatment have an increased risk of acute myocardial infarction compared to the general population. The excess risk was found to be highest immediately after diagnosis and to decrease to expected levels i.e. no excess risk around two years after diagnosis. The excess risk was driven by patients older than 70 years at diagnosis and with history of comorbidity. When restricting to DLBCL patients, advanced age, male sex and pre-existing comorbidity was associated with a higher risk of AMI but the investigated characteristics of the DLCBL were not. Patients and comparators with AMI had similar clinical presentation at the cardiac intensive care unit and similar 30-day survival.

- More than 80% of all DLCBL patients achieving first line remission are alive and remain in remission after two years. An additional 2% are in second remission after relapse. The proportion of first-line remissions varied from 84% for the youngest patients (≤60 years) with aaIPI<2 to 50% for the oldest patients (>80 years) with aaIPI≥2. Patients with intermediate IPI-score (2-3) and with a high IPI-score (4-5) had 12 and 24 percentage units lower probability of achieving this milestone, respectively, compared to patients with low IPI-score (0-1) when adjusting for age, sex and calendar year of diagnosis.

5.1 STUDY I

The number of prevalent NHL patients in Sweden increased between 2000 and 2016 as a result of both an increase in incidence and improved survival. In the beginning of the study period, 2000-2007, the incidence of NHL remained virtually unchanged, but the incidence increased in the later years. On average, over the entire study period, the incidence increased by 1.3% annually ($p<0.001$). The increasing incidence trend was particularly pronounced among older males (aged >70 years, $p_{interaction}=0.008$). The relative survival of NHL overall improved continuously during the period (Figure 1). The two-year relative survival increased from 0.69 (95%CI: 0.66-0.71) among patients diagnosed in 2000 to 0.82 (95%CI: 0.79-0.84) among those diagnosed in 2016. This corresponded to an annual decrease in NHL mortality of 3.6% ($p<0.001$).

The increase of prevalent patients was observed in all clinical subgroups of NHL; aggressive B-cell lymphomas, indolent B-cell lymphomas and T/NK-cell lymphomas. The prevalence of almost all morphological subtypes increased during the study period. The only two subtypes with a decreasing trend in prevalence across the study period was small lymphocytic lymphoma (SLL) and aggressive B-cell lymphoma unspecified (ABCLU). The decreasing prevalence trends in these subtypes coincided with a decrease in incidence.

The subtype responsible for the largest increase in the absolute number of patients was DLBCL. The number of prevalent patients diagnosed within the past 5 years increased by 66% from 1,347 patients in 2004 to 2,236 patients in 2016. The incidence of DLBCL increased by 2.2% annually ($p<0.001$) and at the same time, the mortality rate decreased by 2.5% per year ($p<0.001$).

The increase in incidence was seen especially among patients older than 70 years, the incidence increased on average by 2.6% per year compared to 1.7% among younger patients (≤70 years) ($p_{interaction}=0.044$). On the other hand, the excess mortality decreased primarily among younger patients (≤70 years), where the mortality rate decreased by 4.2% annually compared to 1.6% decrease among elderly patients (>70 years) ($p_{interaction}<0.001$). There were no interactions by sex, i.e. neither the trend in incidence nor that of excess mortality were different for males and females ($p_{interaction}=0.350$ and $p_{interaction}=0.779$).

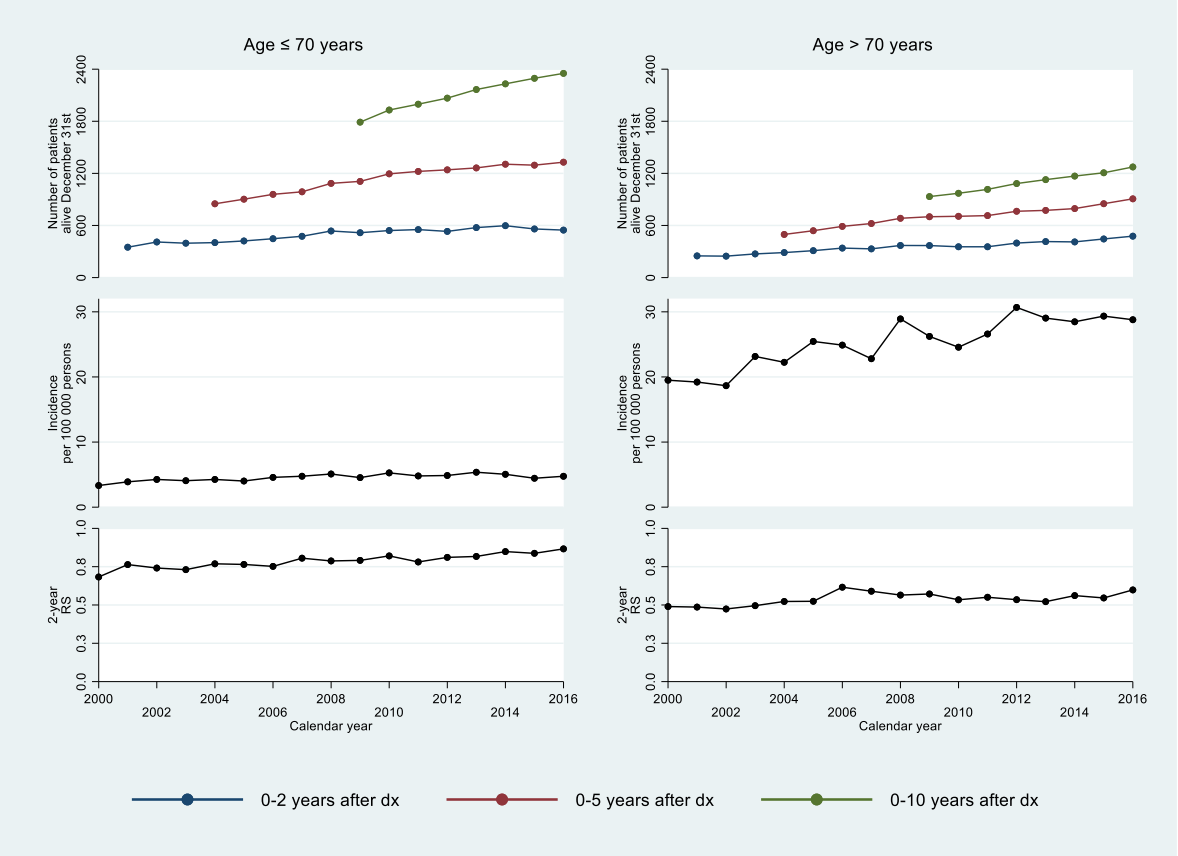


Figure 5.1: Prevalence, incidence per 100,000 persons and 2-year relative survival 2000-2016 for patients diagnosed with diffuse large B-cell lymphoma (DLBCL) by age-group. Left panel: age ≤ 70 years at diagnosis. Right panel: age > 70 years at diagnosis.

5.2 STUDY II

The life expectancy for patients diagnosed with DLBCL increased during the study period. However, there was still a significant loss in life expectancy, compared to the general population in all patient groups in 2013. For example, the life expectancy for a 70-year-old male patients increased from 6.5 years (95% CI 5.8-7.2) in 2000 to 10.1 years (95% CI 8.8-11.4) in 2013, corresponding to an estimated loss in life expectancy of 7.6 years (95% CI 6.9-8.3) and 4.8 years (95% CI 3.6-6.1), respectively. Expressed differently, the proportion of life lost was reduced from 54% (95% CI 49-59) to 32% (95% CI 24-41).

Among patients alive two years after diagnosis, a clear increase in remaining life expectancy from two years post diagnosis and onwards was also noted over calendar time. Patients diagnosed in 2012 and who were alive two years after diagnosis lost two years or less compared to the general population regardless of aaIPI risk group, age at diagnosis or sex.

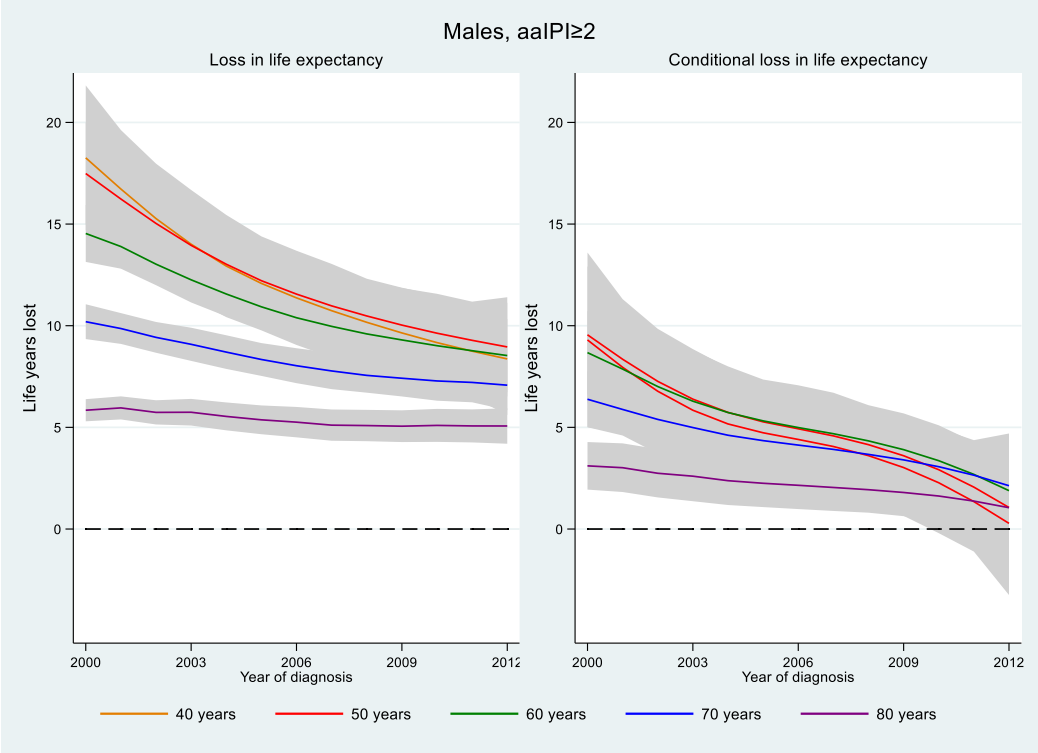


Figure 5.2: Temporal trends in loss in life expectancy (LEL) for male Diffuse Large B-cell Lymphoma (DLBCL) patients with age adjusted International Prognostic Index (aaIPI) score ≥2 at ages 40, 50, 60, 70 and 80 years at diagnosis. Estimates are shown for patients followed from diagnosis (left panel), and conditioned on 2-year survival (right panel)

Lymphoma was the dominant cause of death in patients of all ages, sex and calendar year of diagnosis. However, the probability of lymphoma death was substantially reduced for patients who survived the first two years after diagnosis. It was primarily patients older than 70 years at diagnosis who died due to other causes than lymphoma. Notably, a majority of elderly low risk patients (age >70 years at diagnosis, aaIPI<2) treated in the rituximab era, and who survived the first two years after diagnosis, died from causes other than lymphoma (Figure 5.3).

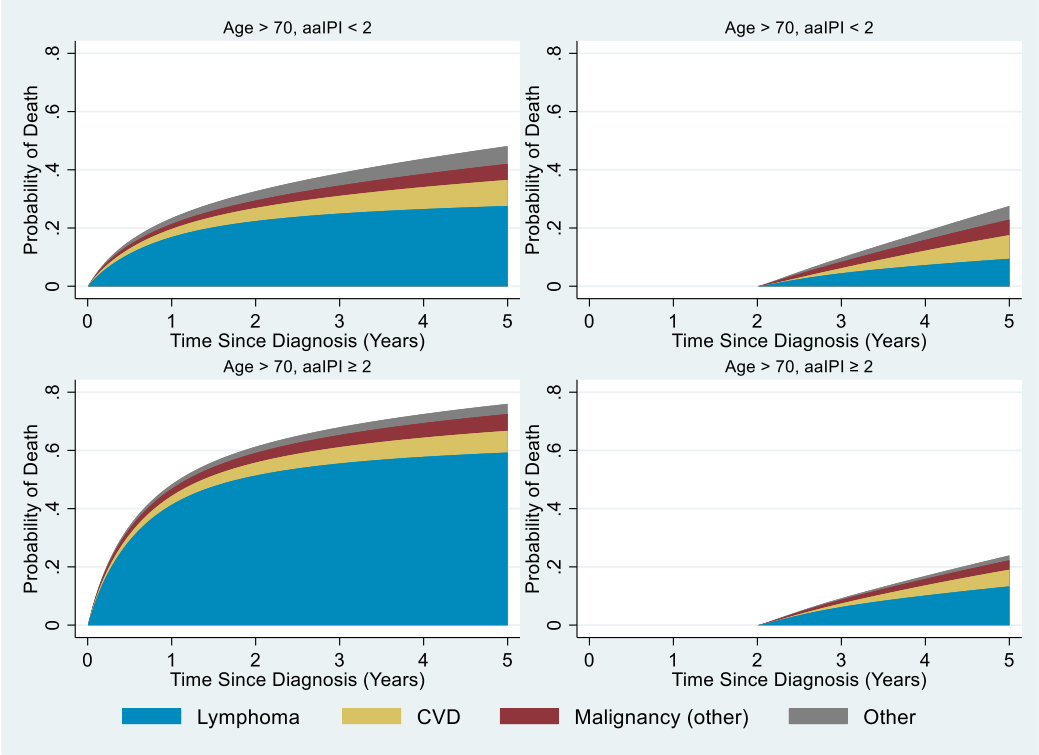


Figure 5.3: Probabilities of death due to lymphoma, cardiovascular disease (CVD), malignancy other than lymphoma, and other causes by age adjusted International Prognostic Index (aaIPI) score in Diffuse Large B-Cell Lymphoma (DLBCL) patients in Sweden older than 70 years at diagnosis and diagnosed 2007-2013. Estimates are shown for patients followed from diagnosis (left panel), and conditioned on 2-year survival (right panel)

5.3 STUDY III

Median age at diagnosis among patients treated curatively for DLBCL was 69 years and a majority of patients had pre-existing comorbidities. A total of 34.4% of patients had a history of severe comorbidities, sufficiently severe to motivate treatment alteration (e.g. reduced anthracycline dose) according to clinical experience. In addition, 22.1% of patients had only milder comorbidities (unlikely to motivate treatment alterations) e.g. hypertension.

Patients treated curatively for DLBCL had an increased risk of AMI compared to the general population (HR: 1.33, 95% CI: 1.14-1.55). The excess rate was most pronounced shortly after lymphoma diagnosis and remained elevated for up to two years, but we found no long-term excess rate with up to 10 years of follow-up.

When stratifying age at diagnosis (≤70/>70 years) and level of pre-existing comorbidity (none/mild/severe) we found that elderly DLBCL patients (>70 years at diagnosis), regardless of comorbidity level, and patients younger than 70 years with severe comorbidity had a

significantly higher AMI risk up to two years after diagnosis. Younger DLBCL patients (≤ 70 years) without comorbidity had no excess rate of AMI within the observable follow-up.

Risk factors for AMI after DLBCL diagnosis were older age, male sex and pre-existing comorbidities. For example, patients with only mild/moderate pre-existing comorbidity had a two-fold risk of AMI (HR: 2.11 95%CI 1.33-3.34) and patients with severe comorbidity had a three-fold risk of AMI (HR: 3.13 95% CI 2.01-4.85) compared to DLBCL patients without pre-existing comorbidities. However, characteristics of the DLBCL-diagnosis, such as stage, S-LDH level and performance status were not associated with risk for AMI.

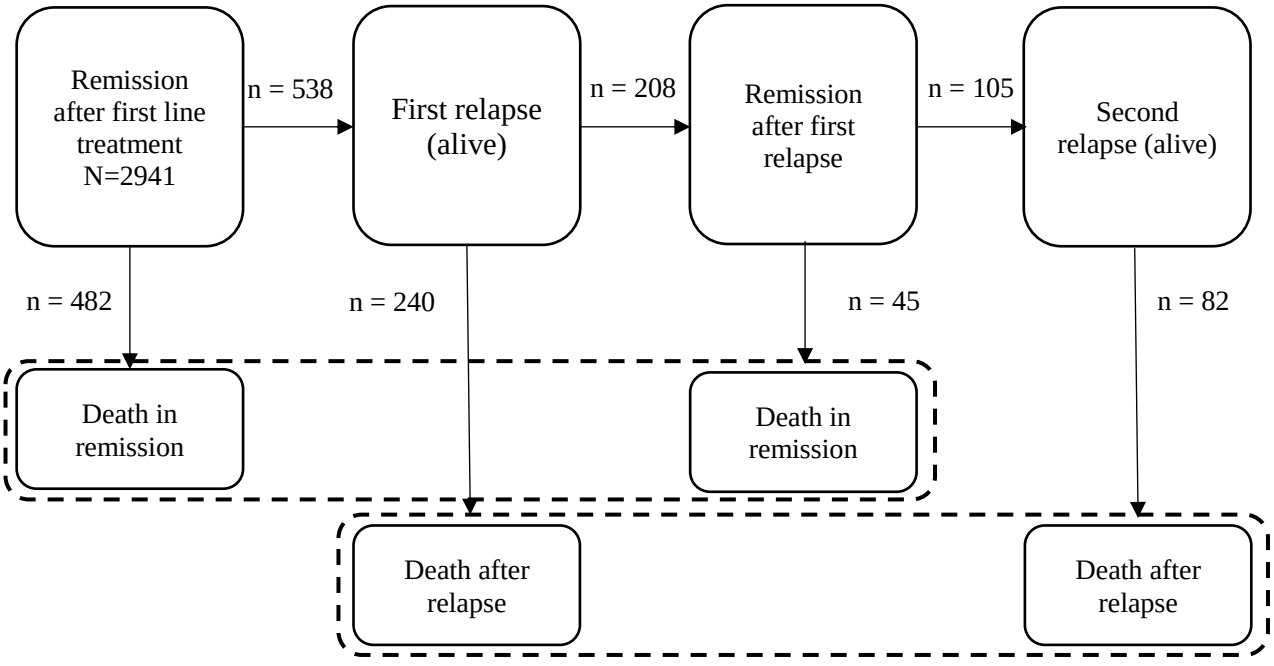
The AMIs occurring among DLBCL patients had similar characteristics (e.g. ECG rhythm, Killip class and infarction type etc) as the AMIs among the matched comparators. In addition, DLCBL patients received AMI treatment to the same extent as comparators and did have a similar 30-day survival after AMI.

5.4 STUDY IV

The prognosis for patients treated during the rituximab era and achieving remission after first-line remission was generally favorable, with over 80 % of patients still alive and in remission after 2 years.

Out of the 538 (18%) patients who experienced a relapse during follow-up, 72% relapsed within two years, and only 33 patients (6% of relapses, 1% of all patients) relapsed after more than five years. Among relapsing patients, 43% achieved a second remission although 51% of those also had a second relapse.

Figure 5.4: The multistate model illustrating of the different stages that the patients may go through following remission after first line treatment.



The proportion of patients still in remission after two years varied by age and IPI-score, mainly reflecting the risk of early relapse among patients with higher IPI scores. At two years, a total of 8% (95% CI: 5-12) and 9% (95% CI: 7-12) of patients aged 61-70 and 71-80 years with aaIPI<2 had experienced a relapse compared to 17% (95% CI 12-21) and 22% (95% CI: 17-26) of patients with aaIPI≥2.

When controlling for age at diagnosis, sex and calendar year; clinical characteristics such as advanced stage (stage III-IV), poor performance status (ECOG ≥1), elevated S-LDH, more than one extranodal site and high IPI score (> 1) were all associated with lower probability of two-year remission. Patients with IPI 2-3 had a 12-percentage unit reduced probability of remaining in remission at two years and patients with IPI 4-5 had 24 percentage units reduced probability compared to patients with IPI 0-1

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6 DISCUSSION

6.1 PUTTING THE RESULTS INTO CONTEXT

We found a substantial increase in the number of prevalent patients in all clinical subgroups of NHL: aggressive B-cell lymphoma, indolent B-cell lymphoma and T/NK-cell lymphoma and in almost all major subtypes during the period 2000-2016. The prevalent patients are a mix of patients at different disease stages, living through and beyond treatment, including some with relapses and/or late effects of their cancer or treatment.

Being the most common subtype, DLBCL was responsible for the largest increase in absolute numbers of prevalent patients which coincided with an increase in both incidence and survival.

6.1.1 Improved survival

The improved survival among DLBCL patients that we have demonstrated, aligns with the undisputed trend towards improved survival during the last decades. In fact, the 5-year relative survival has increased for NHL overall[20, 29], although the extent of the improvement has varied by sex, age group and lymphoma subtype[22]. DLBCL is one of the NHL subtypes that have seen the largest increase in 5-year relative survival[25, 29].

One explanation for the survival improvement is the addition of the anti-CD20 antibody rituximab to standard treatment. In combination with chemotherapy, rituximab has significantly improved both response rates and progression free survival in patients with B-cell malignancies[32, 93, 94]. However, rituximab was not stated as standard of care in the Swedish clinical guidelines until May 2006 (after which it was recommended to all patients regardless of stage and IPI). The life-expectancy among DLBCL-patients increased steadily even before that which could have been due in part to rituximab treatment within clinical trials prior to 2006. Other possible explanations for improved survival during the 21st century include that larger fractions of elderly patients are considered eligible for more intensive treatment and that the supportive care during both primary and second-line treatments has improved. Today, novel drugs are also more widely recommended in the relapsed/refractory setting in national treatment guidelines.

6.1.2 The results highlight patient groups in need of novel therapies

Despite the survival improvements, the life-expectancy for patients diagnosed with DLBCL still remained substantially reduced compared to the general population, highlighting the needs of further improvements regarding treatment and care. Especially young high-risk patients still lost a considerable number of life-years due to the disease on average. For example, although halved between 2000 and 2013, the number of life-years lost for male patients age 50 years at diagnosis, with aaIPI≥2 was still 8.6 years in 2013 (17.5 years in 2000).

Patients not eligible for curative intent treatment, who fail to complete planned treatment, who are refractory to treatment or patients that relapse represent the groups of patients where large challenges remain. Approximately 14% of all DLBCL in Sweden are not eligible for treatment

with curative intent and the median survival in this group of, mostly older, patients is only 2.9 months [17]. Also, failure to complete planned R-CHOP treatment is associated with inferior survival[95]. Among patients treated with curative intent, 23% are either primary refractory of relapse within 5 years[17]. The survival after refractory/relapse is poor[36, 40, 45, 46, 49].

6.1.3 The importance of reporting prognosis conditioned on duration of follow-up

On the other hand, by the end of the study period, the loss in life-expectancy for patients surviving the first two critical years after diagnosis was minimal, less than a couple of years, regardless of age, sex and even risk-group according to aaIPI. We speculate that this could be a consequence of a reduced and low risk of late relapses after this point. Similar results have been demonstrated in other populations, that patients that are event-free at two years after diagnosis have a life-expectancy similar to that of the general population[35, 36].

The reassuring results for patients alive two years after diagnosis demonstrate the importance of reporting prognosis conditioned on duration of follow-up - both from a patient's perspective and for health care planning reasons. As a consequence of the minimal loss in life-expectancy after two years from diagnosis, reported by us and others, the recommended follow-up of patients has been shortened from five to two years in several clinical guidelines[71, 73-75].

Naturally, the prognosis after a cancer diagnosis changes depending on if the patient is eligible for and tolerate curative treatment, the response to the treatment, and whether or not the cancer progresses or relapses. By using a multistate model approach, we were able to estimate real-world probabilities of transitioning between different disease stages (first remission, relapse, second remission, second relapse, and death). In our study we demonstrate that the proportion remaining in first-line remission for at least two years (and hence reaching the two-year milestone discussed above) was over 80% for patients treated in the rituximab era and achieving remission following first-line therapy. The probability varied with age and IPI score, reflecting the different risks of early relapse and death while in remission from the DLBCL. The results also illustrate the difficulties in treating relapsing patients, second remissions were much less common and those remissions were less durable as half of the patients relapsed again.

6.1.4 Patients have an increased risk of AMI

The prevalent pool of patients is not only a mix of patients at different disease stages (and hence with different prognosis). The prevalent pool of patients is also representing patients with varying risk of physical and psychological late effects of their cancer diagnosis and treatment.

We found that there was an increased risk of AMI among curatively treated DLBCL-patients compared to the general population. However, the excess risk varied over follow-up time and was most pronounced early after diagnosis and subsequently diminished after two years. With a maximum of 10 years of follow-up, there was no indication of long-term risk. Advanced age, male sex and comorbidity were associated with an increased rate of AMI among DLBCL-patient. In patients older than 70 years at diagnosis the excess risk of AMI was seen even for

patients with only milder comorbidity such as hypertension or diabetes while among younger patients, an excess risk was only associated with severe pre-existing comorbidity.

In line with our results, a study based on SEER-Medicare data, found an increased rate of AMI, most pronounced during the first 6 months after DLBCL-diagnosis among older patients (>65 years) compared to cancer-free controls[63].

There can be several explanations to why DLCBL patients have an increased risk of AMI, where the treatment is one of them. In a Swedish study from 2012, most cancer sites, including NHL, are associated with an initial higher risk of CVD diseases according[96]. In a SEER-data study, several cancer sites, again including NHL, were associated with an initial increased risk of myocardial infarction and stroke[97]. The increased risk may of course have different underlying causes for different cancer sites. Possible causes are common risk factors, cancer related inflammation and hemostatic activation, stress related to receiving a cancer diagnosis or side effects of treatment[96, 97].

The standard chemotherapy regimen administered to DLBCL patients contains the anthracycline doxorubicin with cardiotoxic effects that have been known for decades[61]. Doxorubicin is considered the most important drug when aiming for cure of DLCBL and therefore also elderly patients and patients with relatively severe comorbidity are often considered for treatment. There is a lack of specific guidelines on how to treat DLBCL patients with risk of cardiovascular disease, but the field is rapidly growing with initiatives such as large cardio-oncology units and also guidelines for assessment and monitoring risk [98, 99].

6.2 STRENGTHS AND LIMITATIONS

A strength of the studies in this thesis is the use of data from the SLR. Compared to the National Cancer Register to which reporting is mandatory by law, the coverage is around 95%[64]. The high coverage of SLR provides a truly population-based cohort and in addition the SLR allow us to identify lymphoma subtypes.

SLR was launched in year 2000 and over the years, there have been changes in registration practice and accuracy of subtype classification. The morphological coding of subtypes has successively been revised as diagnostic techniques have improved, leading to new definitions of subtypes. A limitation is that it was not possible to fully distinguish between more detailed subtypes of DLBCL (e.g. primary mediastinal B-cell lymphoma, T-cell rich DLBCL and ALK-positive DLBCL) already from the year 2000. Another consequence, that could possibly affect subtype specific trends in incidence and survival, is that the number of unspecified lymphoma diagnoses has decreased which leads to larger underestimation of subtype-specific measures early in the study period.

The SLR contains detailed information about patient characteristics which enabled us to study risk-groups based on IPI. Although IPI was developed back in the 1990s it has been shown to be a robust prognostic score even in the rituximab era and is still used in clinical practice. A

common critique against IPI is that it is too simplistic and could lead to loss of predictive accuracy[100].

Unfortunately, the SLR does not include more recent prognostic markers such as cell of origin or double-/triple-hit lymphoma (MYC/BCL-2/BCL-6 translocations). Cell-of origin strongly predict the outcome, where patients with ABC-DLBCL have a less favorable outcome[4, 101, 102]. Still, additional genetic complexity remains to be defined to provide insights into disease pathogenesis, identify candidate treatment targets, tailor treatment and better predict outcome[101, 103-107].

Progressively more information has been included in SLR since the start. Data on primary treatment and response to primary treatment have been registered in SLR since 2007 and relapse information is collected since 2010. However, SLR lack information for example regarding anthracycline dose reductions which was a limitation when studying risk of AMI in patients treated for DLBCL in Study III.

During 2017-2019 we performed a national update of the SLR to ensure the completeness of primary treatment and relapse information for patients diagnosed with DLBCL between 2007 and 2014. The chart review together with the extensive data collection on refractory/relapsing patients has generated access to unique, high quality and rich data. Unfortunately, at the time when the second study in this thesis was performed, this information was not yet available which prevented us from studying event-free survival and test the hypothesis of a trend towards reduced risk of later relapses. Another limitation was that thus far, the collected data on later relapses/later line treatments has not been linked to other Swedish health registers, such as the National Patient Register or the Prescribed Drug Register.

Another strength is the use of novel statistical methodology to provide clinical useful and easy-to-interpret measures of disease burden. Population-based cancer survival is often reported using cause-specific survival or relative survival[69]. Although these are valid and useful measures for comparisons between groups (when we want to eliminate any differences in background mortality) it is less useful for risk communication purposes and in health care planning[76].

In contrast to summarizing survival at e.g. five years after diagnosis, loss in life expectancy summarizes the prognosis over the entire life-span to fully capture the impact of treatment regimens and patient management on survival. However, estimating loss in life expectancy requires extrapolation of survival beyond the range of available data. The extrapolated rates should be interpreted with care, especially in young patients, as the models assume that no unpredictable changes in the trends of the mortality occur.

7 CONCLUSIONS

The number of prevalent patients has increased for almost all major subtypes of NHL during the 21st century. DLBCL, being the most common subtype is responsible for the largest increase in absolute numbers.

The prognosis for patients diagnosed with DLBCL has improved during the past decades and more and more patients are living through and beyond their diagnosis and treatment. In particular, patients surviving the first two years have a favorable prognosis. However, despite improvements following the introduction of rituximab, the results highlight continued large losses of life among young high-risk patients, driven by primary refractory disease and early relapse in some patients.

The general improvement in the outcome for DLBCL patients in combination with an aging population will increase the need for adequate cardiology monitoring. The excess risk of AMI among primarily older patients and within the first two years of diagnosis and treatment should be a signal to the treating hematologist/oncologist that cardiac monitoring is of importance, even for patients with milder comorbidities.

However, given the poor prognosis for patients when treatment fails, it does not seem appropriate to withhold doxorubicin from all of the comorbid older patients as the absolute risk of a cardiovascular event is still low. Primary refractory disease and early relapses remain the most important challenges of current DLBCL practice.

8 POINTS OF PERSPECTIVE

Patients refractory to first-line immunochemotherapy or with early relapse remain the main challenge in DLBCL patient care. The treatment options when initial therapy fails are limited, especially among elderly patients (>70 years) and population-based studies show that more than half of the refractory/relapsing patients only received palliative treatment or no treatment at relapse[44, 108].

Patients 70 years or younger with refractory disease or relapse are recommended second-line chemotherapy and consolidation with ASCT aiming for cure. However, remission on second-line therapy cannot always be obtained and relapses following ASCT are common. Therefore, new therapeutic strategies are needed for relapsed/refractory patients in all age groups. A range of novel therapies are currently undergoing evaluation in clinical trials or have recently been approved in relapsed/refractory DLBCL. One of the most important is the chimeric antigen receptor t-cell therapy (CAR T) that has demonstrated promising results in phase II-studies in relapsed/refractory DLBCL patients[109, 110]. Currently two CAR T-cell therapies are approved by FDA and EMA but several other are undergoing clinical trials. Another promising group of agents are the bispecific antibody therapies.

CAR T-cell therapy is still at the beginning of its development and much work remains to reduce manufacturing times, lower toxicity and make it tolerable for broader patient groups. To this point, only a few DLBCL-patients have been treated in Sweden with CAR T-cell therapy. A preliminary evaluation of the eligibility of CAR T-cell therapy in a population-based setting (based on the data collection on refractory/relapsed DLBCL-patients described in section 4.1.2) indicate that only about 17% of first-relapse and even fewer second-relapse patients would be eligible for CAR T-cell therapy with today's eligibility criteria from ongoing clinical trials[111]. However, given the poor prognosis with standard treatment options, the hope is that these new drugs will bring new possibilities for cure and also that they eventually will be tolerated among broader patient groups.

A majority of new drugs are designed based on the increasing understanding of genetic differences of DLBCL. As opposed to the current standard of care, i.e., R-CHOP treatment and a "one size fits all" approach, the aim of personalized medicine is to optimize the choice of treatment for each individual patient based on their genetic tumor profile and thus sparing them the unnecessary toxicity of a drug less likely to work for them. Another aspect is that some of the more targeted therapies are associated with high costs, therefore it is even more important that they are administered to patients who will actually benefit from them.

Population-based statistics play an important role to identify patient groups in need of modified or alternative treatments, and to evaluate long-term effects and efficacy of new therapies/drugs in the "real-world" after drug approval. Although randomized clinical trials (RCT) are gold standard for evaluating the effect of new treatments, they are often limited to small sample sizes, short follow-up and highly selected patient groups. All factors that may limit the generalizability into the clinical reality.

The number of prevalent NHL patients has increased in Sweden since the beginning of the 21st century and will likely continue to do so due to improved survival. This means that more and more patients are living beyond their diagnosis which raises questions about how these patients should best be cared for in the long run. When the outcome of the cancer improves, more and more focus shifts towards survivorship issues e.g. quality of life, fertility, physical or psychological late-effects etc. AMI, as studied in one of the papers in this thesis, is only one of many health conditions that DLBCL-patients are at increased risk of as a consequence of their cancer (either the cancer itself or its treatment).

Population-based quality registers, such as SLR are a gold mine for research as it enables long follow-up of all patients, including patients who may not be represented in clinical trials, e.g. older patients or patients with comorbidity. In addition, the data collection that we performed on refractory/relapsing DLBCL patients (described in section 4.1.2) has provided detailed clinical information on a group of patients that is difficult to treat today. When used in combination with the SLR it is therefore a valuable source of increased knowledge about this vulnerable patient group.

Lastly, a rather new concept in population-based research is register-based randomized clinical trials (R-RCT), a field in which the Swedish quality register SWEDEHEART is world-leading today. The idea is that patients can be recruited, randomized and followed within the infrastructure of the registry. Advantages, besides it being cost-effective, is that it enables recruitment of large numbers of unselected patients and thereby a better reflection of the clinical reality[112]. R-RCTs should be seen as a complement to standard RCT and is particularly useful when comparing treatments already in use in clinical practice. Examples of potential applications related to the studies in this thesis could be to use R-RCTs to evaluate the real-world efficacy of newly approved drugs, evaluate prophylactic treatments/routines to reduce cardiovascular diseases among patients or evaluate alternative follow-up schemes of the increasing number of lymphoma survivors.

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10 REFERENCES

1. Cancerfonden, S., *Cancer i siffror 2018 Populärvetenskapliga fakta om cancer*. 2018.
2. Swerdlow, S.H., et al., *The 2016 revision of the World Health Organization classification of lymphoid neoplasms.* Blood, 2016. **127**(20): p. 2375-90.
3. Teras, L.R., et al., *2016 US lymphoid malignancy statistics by World Health Organization subtypes.* CA Cancer J Clin, 2016.
4. Alizadeh, A.A., et al., *Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling.* Nature, 2000. **403**(6769): p. 503-11.
5. Cerhan, J.R., et al., *Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project.* J Natl Cancer Inst Monogr, 2014. **2014**(48): p. 15-25.
6. Fallah, M., et al., *Familial risk of non-Hodgkin lymphoma by sex, relationship, age at diagnosis and histology: a joint study from five Nordic countries.* Leukemia, 2016. **30**(2): p. 373-8.
7. Fallah, M., et al., *Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study.* Ann Oncol, 2014. **25**(10): p. 2025-30.
8. Morton, L.M., et al., *Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project.* J Natl Cancer Inst Monogr, 2014. **2014**(48): p. 130-44.
9. *A predictive model for aggressive non-Hodgkin's lymphoma.* N Engl J Med, 1993. **329**(14): p. 987-94.
10. Zhou, Z., et al., *An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era.* Blood, 2014. **123**(6): p. 837-42.
11. Sehn, L.H., et al., *The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP.* Blood, 2007. **109**(5): p. 1857-61.
12. Gang, A.O., et al., *A clinically based prognostic index for diffuse large B-cell lymphoma with a cut-off at 70 years of age significantly improves prognostic stratification: population-based analysis from the Danish Lymphoma Registry.* Leuk Lymphoma, 2015. **56**(9): p. 2556-62.
13. El-Galaly, T.C., et al., *Outcome prediction by extranodal involvement, IPI, R-IPI, and NCCN-IPI in the PET/CT and rituximab era: A Danish-Canadian study of 443 patients with diffuse-large B-cell lymphoma.* Am J Hematol, 2015. **90**(11): p. 1041-6.
14. Ziepert, M., et al., *Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era.* J Clin Oncol, 2010. **28**(14): p. 2373-80.
15. *Aggressiva B-cellslymfom Nationellt vårdprogram 2019-09-10 Version 4.0*. 2019.
16. Feugier, P., *A review of rituximab, the first anti-CD20 monoclonal antibody used in the treatment of B non-Hodgkin's lymphomas.* Future Oncol, 2015. **11**(9): p. 1327-42.

17. Harrysson, S., et al., *Incidence of Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) Including CNS Relapse in a Population-Based Cohort of 4205 Patients in Sweden.* Blood Cancer Journal, 2020. **In press**.

18. Sandin, S., et al., *Incidence of non-Hodgkin's lymphoma in Sweden, Denmark, and Finland from 1960 through 2003: an epidemic that was.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(7): p. 1295-300.

19. Bosetti, C., et al., *Incidence and mortality from non-Hodgkin lymphoma in Europe: the end of an epidemic?* Int J Cancer, 2008. **123**(8): p. 1917-23.

20. Storm, H.H., et al., *Trends in the survival of patients diagnosed with malignant neoplasms of lymphoid, haematopoietic, and related tissue in the Nordic countries 1964-2003 followed up to the end of 2006.* Acta Oncol, 2010. **49**(5): p. 694-712.

21. van Leeuwen, M.T., et al., *Lymphoid neoplasm incidence by WHO subtype in Australia 1982-2006.* Int J Cancer, 2014. **135**(9): p. 2146-56.

22. Ye, X., et al., *Long-term time trends in incidence, survival and mortality of lymphomas by subtype among adults in Manitoba, Canada: a population-based study using cancer registry data.* BMJ Open, 2017. **7**(7): p. e015106.

23. Ocias, L.F., et al., *Trends in hematological cancer in the elderly in Denmark, 1980-2012.* Acta Oncol, 2016. **55 Suppl 1**: p. 98-107.

24. van de Schans, S.A., et al., *Diverging trends in incidence and mortality, and improved survival of non-Hodgkin's lymphoma, in the Netherlands, 1989-2007.* Ann Oncol, 2012. **23**(1): p. 171-82.

25. Howlader, N., et al., *Contributions of Subtypes of Non-Hodgkin Lymphoma to Mortality Trends.* Cancer Epidemiol Biomarkers Prev, 2016. **25**(1): p. 174-9.

26. Issa, D.E., et al., *Trends in incidence, treatment and survival of aggressive B-cell lymphoma in the Netherlands 1989-2010.* Haematologica, 2015. **100**(4): p. 525-33.

27. Aschebrook-Kilfoy, B., et al., *An upward trend in the age-specific incidence patterns for mantle cell lymphoma in the USA.* Leuk Lymphoma, 2013. **54**(8): p. 1677-83.

28. Szekely, E., et al., *Improvement in survival of diffuse large B-cell lymphoma in relation to age, gender, International Prognostic Index and extranodal presentation: a population based Swedish Lymphoma Registry study.* Leuk Lymphoma, 2014. **55**(8): p. 1838-43.

29. Sant, M., et al., *Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study.* Lancet Oncol, 2014. **15**(9): p. 931-42.

30. Junlen, H.R., et al., *Follicular lymphoma in Sweden: nationwide improved survival in the rituximab era, particularly in elderly women: a Swedish Lymphoma Registry study.* Leukemia, 2015. **29**(3): p. 668-76.

31. Smith, A., et al., *Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's Haematological Malignancy Research Network.* Br J Cancer, 2015. **112**(9): p. 1575-84.

32. Coiffier, B., et al., *CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.* N Engl J Med, 2002. **346**(4): p. 235-42.

33. Habermann, T.M., et al., *Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma.* J Clin Oncol, 2006. **24**(19): p. 3121-7.

34. Pfreundschuh, M., et al., *CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group.* Lancet Oncol, 2006. **7**(5): p. 379-91.

35. Jakobsen, L.H., et al., *Minimal Loss of Lifetime for Patients With Diffuse Large B-Cell Lymphoma in Remission and Event Free 24 Months After Treatment: A Danish Population-Based Study.* J Clin Oncol, 2017. **35**(7): p. 778-784.

36. Maurer, M.J., et al., *Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy.* J Clin Oncol, 2014. **32**(10): p. 1066-73.

37. Sehn, L.H., et al., *Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia.* J Clin Oncol, 2005. **23**(22): p. 5027-33.

38. Modvig, L., M. Vase, and F. d'Amore, *Clinical and treatment-related features determining the risk of late relapse in patients with diffuse large B-cell lymphoma.* Br J Haematol, 2017. **179**(1): p. 75-82.

39. Vannata, B., et al., *Late relapse in patients with diffuse large B-cell lymphoma: impact of rituximab on their incidence and outcome.* Br J Haematol, 2019. **187**(4): p. 478-487.

40. Coiffier, B., et al., *Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte.* Blood, 2010. **116**(12): p. 2040-5.

41. Stephens, D.M., et al., *Continued Risk of Relapse Independent of Treatment Modality in Limited-Stage Diffuse Large B-Cell Lymphoma: Final and Long-Term Analysis of Southwest Oncology Group Study S8736.* J Clin Oncol, 2016. **34**(25): p. 2997-3004.

42. Wang, Y., et al., *Late Relapses in Patients With Diffuse Large B-Cell Lymphoma Treated With Immunochemotherapy.* J Clin Oncol, 2019. **37**(21): p. 1819-1827.

43. Vose, J.M., et al., *Late relapse in patients with diffuse large B-cell lymphoma*. Br J Haematol, 2010. **151**(4): p. 354-8.

44. Arboe, B., et al., *Treatment intensity and survival in patients with relapsed or refractory diffuse large B-cell lymphoma in Denmark: a real-life population-based study.* Clin Epidemiol, 2019. **11**: p. 207-216.

45. Crump, M., et al., *Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study.* Blood, 2017. **130**(16): p. 1800-1808.

46. Epperla, N., et al., *Postrelapse survival in diffuse large B-cell lymphoma after therapy failure following autologous transplantation.* Blood Adv, 2019. **3**(11): p. 1661-1669.

47. Friedberg, J.W., *Relapsed/refractory diffuse large B-cell lymphoma.* Hematology Am Soc Hematol Educ Program, 2011. **2011**: p. 498-505.

48. Maurer, M.J., et al., *Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) enrolled on randomized clinical trials.* Ann Oncol, 2018. **29**(8): p. 1822-1827.

49. Rovira, J., et al., *Prognosis of patients with diffuse large B cell lymphoma not reaching complete response or relapsing after frontline chemotherapy or immunochemotherapy.* Ann Hematol, 2015. **94**(5): p. 803-12.

50. Gisselbrecht, C., et al., *Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era.* J Clin Oncol, 2010. **28**(27): p. 4184-90.

51. Baech, J., et al., *Cumulative anthracycline exposure and risk of cardiotoxicity; a Danish nationwide cohort study of 2440 lymphoma patients treated with or without anthracyclines.* Br J Haematol, 2018. **183**(5): p. 717-726.

52. Hequet, O., et al., *Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults.* J Clin Oncol, 2004. **22**(10): p. 1864-71.

53. Hershman, D.L., et al., *Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma.* J Clin Oncol, 2008. **26**(19): p. 3159-65.

54. Moser, E.C., et al., *Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma.* Blood, 2006. **107**(7): p. 2912-9.

55. Thieblemont, C. and B. Coiffier, *Lymphoma in older patients.* J Clin Oncol, 2007. **25**(14): p. 1916-23.

56. Limat, S., et al., *Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma.* J Clin Pharm Ther, 2014. **39**(2): p. 168-74.

57. Limat, S., et al., *Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma.* Ann Oncol, 2003. **14**(2): p. 277-81.

58. Linschoten, M., et al., *Cardiovascular adverse events in patients with non-Hodgkin lymphoma treated with first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP with rituximab (R-CHOP): a systematic review and meta-analysis.* Lancet Haematol, 2020. **7**(4): p. e295-e308.

59. Salz, T., et al., *Preexisting Cardiovascular Risk and Subsequent Heart Failure Among Non-Hodgkin Lymphoma Survivors.* J Clin Oncol, 2017. **35**(34): p. 3837-3843.

60. Swain, S.M., F.S. Whaley, and M.S. Ewer, *Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials.* Cancer, 2003. **97**(11): p. 2869-79.

61. Von Hoff, D.D., et al., *Risk factors for doxorubicin-induced congestive heart failure.* Ann Intern Med, 1979. **91**(5): p. 710-7.

62. Drafts, B.C., et al., *Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease.* JACC Cardiovasc Imaging, 2013. **6**(8): p. 877-85.

63. Tsai, H.T., et al., *The effects of cardiovascular disease on the clinical outcome of elderly patients with diffuse large B-cell lymphoma.* Leuk Lymphoma, 2015. **56**(3): p. 682-7.

64. RCC, R.c.c., *Nationella kvalitetsregistret för lymfom; Årsrapport från Nationell kvalitetsregistret för lymfom, diagnosperioden 2000-2017.*

65. Jernberg, T., et al., *The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART).* Heart, 2010. **96**(20): p. 1617-21.

66. Ludvigsson, J.F., et al., *The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research.* Eur J Epidemiol, 2009. **24**(11): p. 659-67.

67. J.R. Wilmoth, K.A., D. Jdanov, D.A. Glei and T. Rie with the assistance of C. Boe, M. and D.P. Bubenheim, V. Shkolnikov, P. Vachon, C. Winant, M. Barbieri, *Methods Protocol for the Human Mortality Database*. 2020.

68. Armstrong, B.K., *The role of the cancer registry in cancer control.* Cancer Causes Control, 1992. **3**(6): p. 569-79.

69. Dickman, P.W. and H.O. Adami, *Interpreting trends in cancer patient survival.* J Intern Med, 2006. **260**(2): p. 103-17.

70. Ellis, L., et al., *Cancer incidence, survival and mortality: explaining the concepts.* Int J Cancer, 2014. **135**(8): p. 1774-82.

71. Chaganti, S., et al., *Guidelines for the management of diffuse large B-cell lymphoma.* Br J Haematol, 2016. **174**(1): p. 43-56.

72. Dreyling, M., et al., *Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2017. **28**(12): p. 3109.

73. Excellence, N.I.f.H.a.C., *Non-Hodgkin's Lymphoma: Diagnosis and Management, NICE guideline: methods, evidence and recommendations*. 2016, National Institute for Health and Care Excellence (UK)

74. National Comprehensive Cancer Network, N. *B-cell Lymphomas (Version 4.2019).* 2019 August 23, 2019]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

75. Tilly, H., et al., *Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2015. **26 Suppl 5**: p. v116-25.

76. Eloranta, S., et al., *Cancer survival statistics for patients and healthcare professionals - a tutorial of real-world data analysis.* J Intern Med, 2020.

77. Talback, M. and P.W. Dickman, *Estimating expected survival probabilities for relative survival analysis--exploring the impact of including cancer patient mortality in the calculations.* Eur J Cancer, 2011. **47**(17): p. 2626-32.

78. Huber, P.J. *The behavior of maximum likelihood estimates under nonstandard conditions*. in *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability, Volume 1: Statistics*. 1967. Berkeley, Calif.: University of California Press.

79. Dickman, P.W., et al., *Regression models for relative survival.* Stat Med, 2004. **23**(1): p. 51-64.

80. Hakama, M. and T. Hakulinen, *Estimating the expectation of life in cancer survival studies with incomplete follow-up information.* J Chronic Dis, 1977. **30**(9): p. 585-97.

81. Andersson, T.M., et al., *Estimating the loss in expectation of life due to cancer using flexible parametric survival models.* Stat Med, 2013. **32**(30): p. 5286-300.

82. Royston, P. and M.K. Parmar, *Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects.* Stat Med, 2002. **21**(15): p. 2175-97.

83. Lambert, P.C. and P. Royston, *Further development of flexible parametric models for survival analysis.* Stata Journal, 2009. **9**(2): p. 265-290.

84. Nelson, C.P., et al., *Flexible parametric models for relative survival, with application in coronary heart disease.* Stat Med, 2007. **26**(30): p. 5486-98.

85. Rutherford, M.J., M.J. Crowther, and P.C. Lambert, *The use of restricted cubic splines to approximate complex hazard functions in the analysis of time-to-event data: a simulation study.* Journal of Statistical Computation and Simulation, 2015. **85**(4): p. 777-793.

86. Andersen, P.K. and R.D. Gill, *Cox's Regression Model for Counting Processes: A Large Sample Study.* The Annals of Statistics, 1982. **10**(4): p. 1100-1120.

87. Patrick Royston, P.C.L., *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model*. 2011: Stata Press.

88. Andersen, P.K. and N. Keiding, *Multi-state models for event history analysis.* Stat Methods Med Res, 2002. **11**(2): p. 91-115.

89. Hinchliffe, S.R., D.A. Scott, and P.C. Lambert, *Flexible parametric illness-death models.* Stata Journal, 2013. **13**(4): p. 759-775.

90. Hsieh, H.J., T.H. Chen, and S.H. Chang, *Assessing chronic disease progression using non-homogeneous exponential regression Markov models: an illustration using a selective breast cancer screening in Taiwan.* Stat Med, 2002. **21**(22): p. 3369-82.

91. Titman, A.C., *Flexible nonhomogeneous markov models for panel observed data.* Biometrics, 2011. **67**(3): p. 780-7.

92. Crowther, M.J. and P.C. Lambert, *Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences.* Stat Med, 2017. **36**(29): p. 4719-4742.

93. Pfreundschuh, M., et al., *CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group.* Lancet Oncol, 2011. **12**(11): p. 1013-22.

94. Pfreundschuh, M., et al., *Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60).* The Lancet Oncology, 2008. **9**(2): p. 105-116.

95. Wästerlid, T., et al., *Outcome and determinants of failure to complete primary R-CHOP treatment for reasons other than non-response among patients with diffuse large B-cell lymphoma.* Am J Hematol, 2020. **95**(7): p. 740-748.

96. Zöller, B., et al., *Risk of coronary heart disease in patients with cancer: a nationwide follow-up study from Sweden.* Eur J Cancer, 2012. **48**(1): p. 121-8.

97. Navi, B.B., et al., *Risk of Arterial Thromboembolism in Patients With Cancer.* J Am Coll Cardiol, 2017. **70**(8): p. 926-938.

98. Herrmann, J., et al., *Evaluation and management of patients with heart disease and cancer: cardio-oncology.* Mayo Clin Proc, 2014. **89**(9): p. 1287-306.

99. Zamorano, J.L., et al., *2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC).* Eur Heart J, 2016. **37**(36): p. 2768-2801.

100. Biccler, J., et al., *Simplicity at the cost of predictive accuracy in diffuse large B-cell lymphoma: a critical assessment of the R-IPI, IPI, and NCCN-IPI.* Cancer Med, 2018. **7**(1): p. 114-122.

101. Rosenwald, A., et al., *The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma.* N Engl J Med, 2002. **346**(25): p. 1937-47.

102. Wright, G.W., et al., *A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications.* Cancer Cell, 2020. **37**(4): p. 551-568.e14.

103. Chapuy, B., et al., *Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes.* Nat Med, 2018. **24**(5): p. 679-690.

104. Phelan, J.D., et al., *A multiprotein supercomplex controlling oncogenic signalling in lymphoma.* Nature, 2018. **560**(7718): p. 387-391.

105. Shipp, M.A., et al., *Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning.* Nat Med, 2002. **8**(1): p. 68-74.

106. Staiger, A.M., et al., *Clinical Impact of the Cell-of-Origin Classification and the MYC/ BCL2 Dual Expresser Status in Diffuse Large B-Cell Lymphoma Treated Within Prospective Clinical Trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group.* J Clin Oncol, 2017. **35**(22): p. 2515-2526.

107. Wright, G., et al., *A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma.* Proc Natl Acad Sci U S A, 2003. **100**(17): p. 9991-6.

108. Hitz, F., et al., *Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment.* Ann Hematol, 2015. **94**(11): p. 1839-43.

109. Locke, F.L., et al., *Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial.* Lancet Oncol, 2019. **20**(1): p. 31-42.

110. Schuster, S.J., et al., *Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma.* N Engl J Med, 2019. **380**(1): p. 45-56.

111. Ekström Smedby, K., et al., *Evaluation of Eligibility for CAR-T Cell Therapy in a Population-Based Cohort of 3550 Patients with Incident Diffuse Large B-Cell Lymphoma (DLBCL) in Sweden.* Blood, 2020. **136**(Supplement 1): p. 38-39.

112. Jernberg, T. and M. Janzon, *[The truth about the clinical reality is in the registries. A register-based randomized clinical trial could provide representative picture]*. Lakartidningen, 2015. **112**.