Universitat de Girona

# SURVIVAL ANALYSIS OF LYMPHOID NEOPLASMS AND IMPACT OF COMORBIDITY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA IN GIRONA: A POPULATION-BASED STUDY

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*DOCTORAL THESIS*

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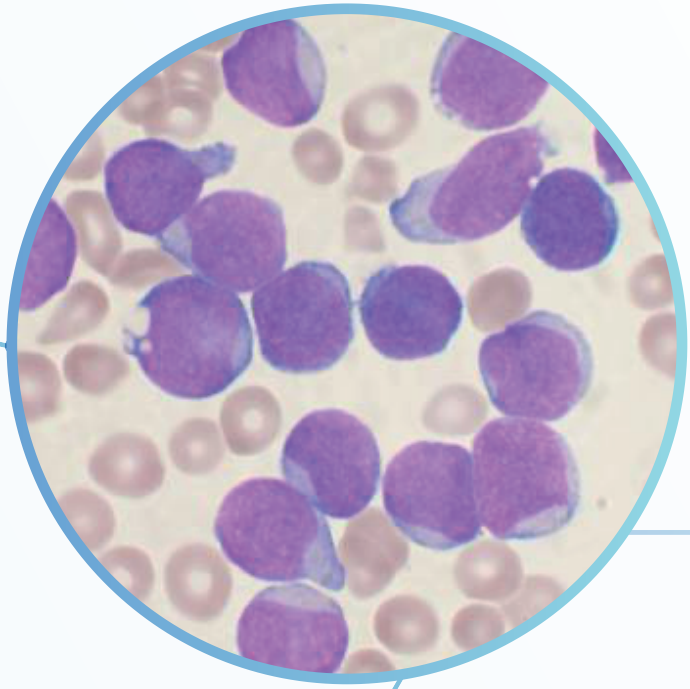

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# Survival analysis of lymphoid neoplasms and impact of comorbidity in patients with chronic lymphocytic leukemia in Girona: a population-based study

**Alicia Silvana Villavicencio Obando**
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PhD program in Molecular Biology, Biomedicine and Health

Under the direction of:

Prof. Dr. Marc Saez Zafra  Dr. Rafael Marcos Gragera  Dra. Marta Solans Margalef

Thesis delivered to obtain the doctoral degree by the Universitat de Girona

Prof. Dr. Marc Saez Zafra

Catedràtic del Departament d'Economia de la Universitat de Girona i Investigador Principal del Grup de Recerca en Estadística, Econometria i Salut (GRECS) de la Universitat de Girona.

Dr. Rafael Marcos Gragera

Professor associat del Departament d'Infermeria i Ciències mèdiques de la Universitat de Girona, coordinador de la Unitat d'Epidemiologia i Registre de Càncer de Girona (UERCG) de l'Institut Català d'Oncologia (ICO), i membre del Grup de Recerca en Estadística, Econometria i Salut (GRECS) de la Universitat de Girona.

Dra. Marta Solans Margalef

Investigadora post-doctoral del CIBER d'Epidemiologia i Salut Pública (CIBERESP). Professora associada del Departament d'Economia de la Universitat de Girona i membre del Grup de Recerca en Estadística, Econometria i Salut (GRECS) de la Universitat de Girona.

Certifiquem:

Que Alicia Silvana Villavicencio Obando ha dut a terme sota la nostra direcció el treball titulat **Survival analysis of lymphoid neoplasms and impact of comorbidity in patients with chronic lymphocytic leukemia in Girona: a population-based study** que es presenta en aquesta memòria, la qual constitueix la seva Tesi per optar al Grau de Doctor per la Universitat de Girona.

A Girona, 10 de febrer de 2021.

Prof. Dr. Marc Saez Zafra  Dr. Rafael Marcos Gragera  Dra. Marta Solans Margalef

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# ACKNOWLEDGEMENTS

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# FUNDING

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# LIST OF PUBLICATIONS

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PAPER I

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PAPER II

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# LIST OF ABBREVIATIONS

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**AIDS**, Acquired Immunodeficiency Syndrome
**ALC**, Absolute lymphocyte count
**ALK**, Anaplastic Lymphoma Kinase
**BL**, Burkitt Lymphoma
**B2M**, Beta 2 microglobulin
**CAP**, Cyclophosphamide, Doxorubicin, Prednisone
**CCI**, Charlson Comorbidity Index
**CHL**, classical Hodgkin lymphoma
**CHOP,** Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
**CI**, Confidence Interval
**CIRS**, Cumulative Illness Rating Scale
**CLL/SLL**, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
**DCO**, Death Certificate Only
**DLBCL**, Diffuse Large B-Cell Lymphoma
**EBV**, Epstein Barr Virus
**EUROCARE**, European Cancer Registry
**FCR**, Cyclophosphamide and rituximab
**FISH**, Fluorescent In-Situ Hybridization
**FL**, Follicular Lymphoma
**FRANCIM**, French Network of Cancer Registries
**GCR**, Girona Cancer Registry
**HAEMACARE**, Cancer Registry based Project on Hematologic Malignancies
**Hb**, Hemoglobin
**HCL**, Hairy Cell Leukemia
**Hct**, Hematocrit
**HL**, Hodgkin Lymphoma
**HMRN**, Haematological Malignancy Research Network
**HR**, Hazard Ratio
**ICD-O-3**, International Classification of Diseases for Oncology third edition
**ICD-10-ES,** International Classification of Diseases 10th edition
**IDESCAT**, Institut d'Estadística de Catalunya
**IGHV**, Immunoglobulin Heavy Chain gene
**InterLymph**, International Lymphoma Epidemiology Consortium
**IWCLL**, International Workshop on Chronic Lymphocytic Leukemia
**LNs**, Lymphoid Neoplasms
**LPL/WM**, Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia
**MBL**, Monoclonal B lymphocytosis
**MCL**, Mantle Cell Lymphoma
**MF/SS**, Mycosis Fungoides/Sezary Syndrome
**MZL,** Marginal Zone Lymphoma
**NAACCR**, North American Association of Central Cancer Registries

**NCI-WG**, National Cancer Institute-Sponsored Working Group
**NHL**, Non-Hodgkin Lymphoma
**NK**, Natural Killer
**NLPHL**, Nodular lymphocyte predominant Hodgkin lymphoma
**NOS**, Not Otherwise Specified
**NS**, Net Survival
**OS**, Observed Survival
**PCN**, Plasma Cell Neoplasms
**PET-CT**, Positron Emission Tomography - Computed Tomography
**PS**, performance status
**PTCL**, Peripheral T-Cell Lymphoma
**REAL**, Revised European American Lymphoma
**RS**, Relative Survival
**TK**, thymidine kinase
**WHO**, World Health Organization
**ZAP-70**, Zeta-associated Protein 70

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# ABSTRACT

# ABSTRACT

Comprehensive population-based studies assessing the survival of hematological entities are scarce and typically conducted using old classifications schemes, which hampers their interpretation and international comparisons. Therefore, this thesis is aimed at studying the survival of lymphoid neoplasms (LNs) and its subtypes in the province of Girona, according to the 2008 World Health Organization (WHO) classification. It further provides a sub-analysis focused on estimating the prevalence of comorbidities and their potential impact on survival and mortality (related or not to chronic lymphocytic leukemia (CLL)) of patients diagnosed with CLL.

Data were extracted from the Girona Cancer Registry between 1996-2015 for all LNs and observed survival (OS) and relative survival (RS) were calculated using the Kaplan Meier and Pohar Perme methods, respectively. For the CLL sub-analysis, we focused on a more recent period (2008-2016) in order to have access to computerized medical records. Clinical variables were collected at diagnoses and comorbidities were assessed using Charlson Comorbidity Index (CCI).

The 5-year RS of the LNs was 62.3% (95% confidence interval (CI): 60.4–64.4) and varied notably according to the different subtypes. The RS of all LNs progressively decreased with advancing patient age, and an increase in RS was observed during 1996-2002 and 2003-2008. In the CLL sub-analysis, survival decreased markedly with increasing CCI scores, but the effect of CCI score disappeared when age and stage are also considered. On the other hand, the CCI score does not play a role predictor of mortality.

In conclusion, the LNs survival analysis related possible changes in survival probability to improvements in both diagnostic approach and treatment of the different LNs. Moreover, the high-resolution sub-analysis of CLL cases further allowed us to identify how survival was conditioned by comorbidities at diagnosis.

# RESUMEN

# RESUMEN

Los estudios exhaustivos de base poblacional que evalúan la supervivencia de las entidades hematológicas son escasos y suelen realizarse utilizando esquemas de clasificación antiguos, lo que dificulta su interpretación y las comparaciones internacionales. Por ello, esta tesis tiene como objetivo estudiar la supervivencia de las neoplasias linfoides (NLs) y sus subtipos en la provincia de Girona, según la clasificación de la Organización Mundial de la Salud (OMS) de 2008. Además, se realiza un subanálisis centrado en la estimación de la prevalencia de comorbilidades y su potencial impacto en la supervivencia y mortalidad (relacionada o no con la leucemia linfocítica crónica (LLC)) de los pacientes diagnosticados de LLC.

Los datos se extrajeron del Registro de Cáncer de Girona entre 1996-2015 para todas las NLs y se calcularon la supervivencia observada (SO) y la supervivencia relativa (SR) mediante los métodos de Kaplan Meier y Pohar Perme, respectivamente. Para el subanálisis de la LLC, nos centramos en un período más reciente (2008-2016) para tener acceso a las historias clínicas informatizadas. Las variables clínicas se recogieron en el diagnóstico y las comorbilidades se evaluaron mediante el Índice de Comorbilidad de Charlson (ICC).

La SR a 5 años de las NLs fue del 62,3% (intervalo de confianza (IC) del 95%: 60,4-64,4) y varió notablemente según los distintos subtipos. La SR de todas las NLs disminuyó progresivamente con el avance de la edad de los pacientes, y se observó un aumento de la SR durante 1996-2002 y 2003-2008. En el subanálisis de la LLC, la supervivencia disminuyó notablemente con el aumento del ICC, pero el efecto del ICC desapareció cuando se consideraron también la edad y el estadio. Por otro lado, el ICC no juega un papel predictor de la mortalidad.

En conclusión, el análisis de supervivencia de las NLs relacionó los posibles cambios en las probabilidades de supervivencia con las mejoras tanto en el enfoque diagnóstico como en el tratamiento de los diferentes NLs. Además, el

subanálisis de alta resolución de los casos de LLC nos permitió identificar además cómo la supervivencia estaba condicionada por las comorbilidades en el momento del diagnóstico.

# RESUM

# RESUM

Els estudis complets basats en la població que avaluen la supervivència de les entitats hematològiques són rars i sovint es duen a terme utilitzant antics esquemes de classificació, cosa que dificulta la interpretació i dificulta les comparacions internacionals. Per això, aquesta tesi té com a objectiu estudiar la supervivència de les neoplàsies limfoides (NLs) i els seus subtipus a la província de Girona, segons la classificació de l'Organització Mundial de la Salut (OMS) de 2008. A més, es realitza un subanàlisi centrat en l'estimació de la prevalença de comorbiditats i el seu impacte potencial en la supervivència i mortalitat (relacionada o no amb la leucèmia limfàtica crònica (LLC)) dels pacients diagnosticats de LLC.

Les dades es van extreure del Registre del Càncer de Girona entre 1996 i 2015 per a tots els NLs i es van calcular la supervivència observada (SO) i la supervivència relativa (SR) utilitzant els mètodes de Kaplan Meier i Pohar Perme, respectivament. Per al subanàlisi de LLC, ens vam centrar en un període més recent (2008-2016) per tenir accés a registres mèdics informatitzats. Les variables clíniques es van recollir en el diagnòstic i les comorbiditats es van avaluar utilitzant l'índex de comorbiditat de Charlson (ICC).

La SR a 5 anys per als NLs va ser 62,3% (interval de confiança del 95%: 60,4-64,4) i va variar notablement entre subtipus. La SR de totes les NLs va disminuir progressivament amb l'edat avançada dels pacients, i es va observar un augment de SR durant 1996-2002 i 2003-2008. Al subanàlisi de LLC, la supervivència va disminuir notablement amb l'augment de la puntuació de l'ICC, però l'efecte de la puntuació de l'ICC va desaparèixer quan també es va considerar l'edat i l' estadi. D'altra banda, la puntuació de la ICC no juga un paper predictiu de la mortalitat.

En conclusió, l'anàlisi de supervivència de NLs va relacionar possibles canvis en les probabilitats de supervivència a millores tant en l'enfocament diagnòstic com en el tractament de diferents NLs. A més, el subanàlisi d'alta resolució dels casos de LLC

també va permetre identificar com la supervivència estava condicionada per les comorbiditats en el moment del diagnòstic.

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# INTRODUCTION

# 1. INTRODUCTION

## 1.1 Lymphoid neoplasms

### *1.1.1 Definition*

Lymphoid neoplasms (LNs) are a heterogeneous group of cancers that arise from lymphoid tissue (**Figure 1**). There are various types of LNs which are classified according to type of lymphocyte affected: B-cell (85–90% of LNs are derived from these lymphocytes)[1], T-cell, and natural killer (NK)cell.

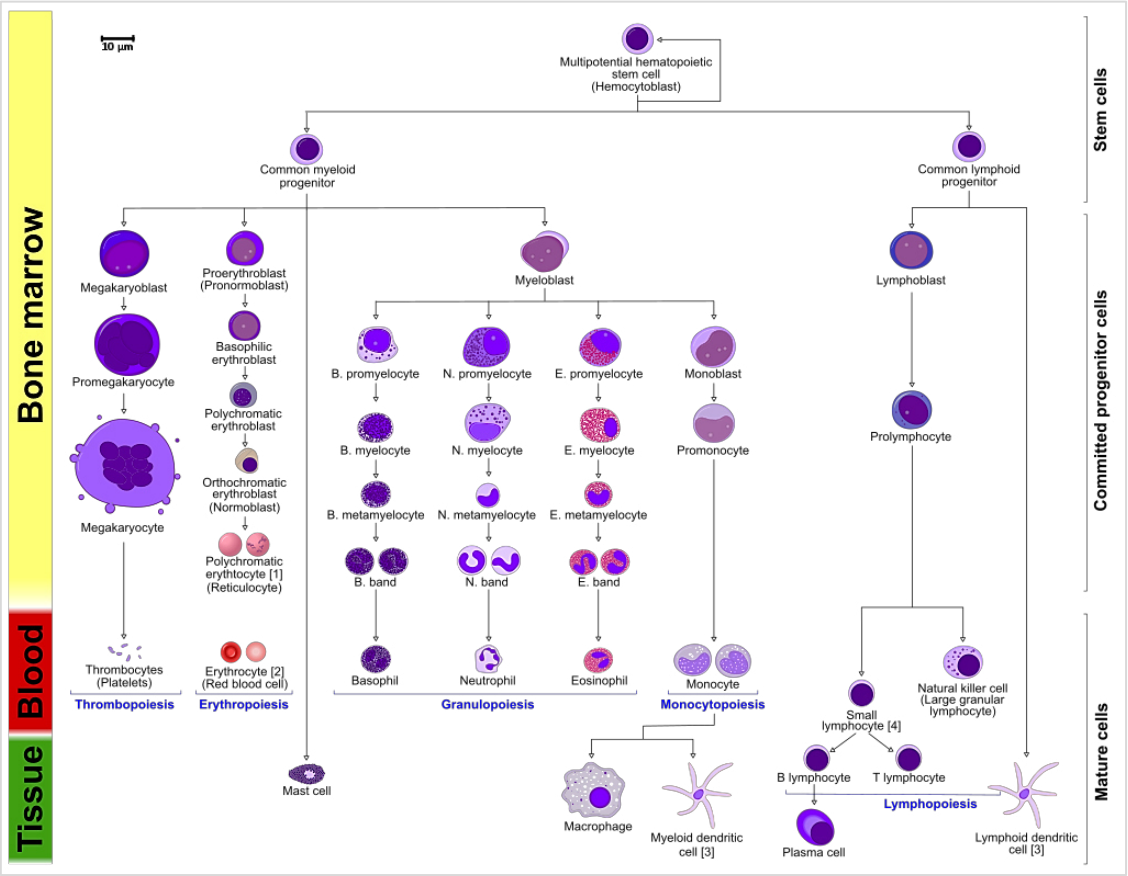


**Figure 1.** Diagram of hematopoiesis. Development of different blood cells from hematopoietic stem cell to mature cells in both myeloid and lymphoid lineages [original illustration by A. Rad., CC BY-SA 3.0].

### *1.1.2 Classification*

Historically, the classification of hematological neoplasms has undergone several changes due to advances in the understanding of their origin and natural history (**Figure 2**). Initially, their classification was based on morphological patterns (Rappaport classification, 1966[2]), on cell differentiation (Lukes and Collis, 1974[3]; or Kiel, 1975[4]) or prognosis (Working Formulation, 1982[5,6]).

In the early 1990s, based on the introduction of immunophenotyping and molecular biology techniques, the Revised European American Lymphoma (REAL)[7] made a new classification of hematological neoplasms considering morphology, immunology, cytogenetics, and molecular techniques. In 1999 the World Health Organization (WHO) updated the REAL classification by stratifying hematological diseases based on cell lineage: myeloid neoplasms, LNs, histiocyte and dendritic cell neoplasms and mast cell neoplasms. The WHO classification is currently considered the "gold standard" in the classification of the different hematopoietic neoplasms and has been updated in 2001[8], 2008[9] and 2016[10]. This system allows differentiation between Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), as well as cell lineage, differentiation, and other morphological, immunological, and molecular characteristics, which allow a broader view of the hematopoietic neoplasms.

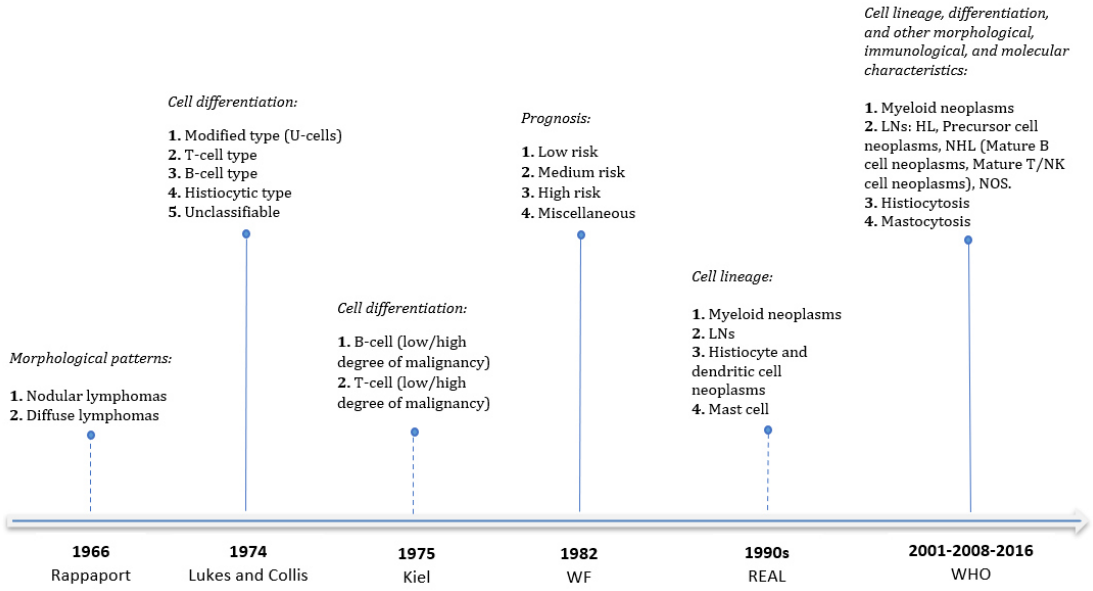


**Figure 2.** Evolution of the classification of hematological neoplasms over the years (Source: own elaboration).

In relation to the coding of neoplasms, the WHO follows the International Classification of Diseases for Oncology third edition (ICD-O-3)[11], which allows the coding of neoplasms according to anatomical location, histology, biological behavior and degree of differentiation. However, the implementation of these classifications in epidemiological research is not straightforward, given that several subtypes are too rare to allow robust estimates in most studies. To overcome this limitation, the HAEMACARE[12], a European cancer-registry based projected funded by the European Commission, was set up in 2005 in order to improve the standardization of population-based data on hematological neoplasms. Under the aegis of HAEMACARE, hematologists, pathologists and epidemiologists from several countries reached a consensus on how to group hematological neoplasms following the ICD-O-3 morphological codes and WHO recommendations. Broadly, the HAEMACARE scheme groups LNs into six major categories: HL, mature B-cell neoplasms, mature T-cell and NK cell neoplasms, precursor cell neoplasms, composite HL and NHL, and lymphoid neoplasm of unknown type (NOS). Each of these categories is further divided into subcategories of similar cell lineage and prognosis, as detailed in **Table 1**.

**Table 1.** Classification of lymphoid neoplasms according to the WHO 2008 and HAEMACARE groupings and their correspondence with the codes of the ICD-O-3.

| Subtype | ICD-O-3 codes |
|---|---|
| **Hodgkin lymphoma** | |
| Classical Hodgkin lymphoma | |
| Lymphocyte rich classical Hodgkin lymphoma | 9651 |
| Nodular sclerosis classical Hodgkin lymphoma | 9663-9667 |
| Mixed cellularity classical Hodgkin lymphoma | 9652 |
| Lymphocyte-depleted classical Hodgkin lymphoma | 9653-9655 |
| Classical Hodgkin lymphoma, NOS | 9650,9661-9662 |
| Nodular lymphocyte predominant Hodgkin lymphoma | 9659 |
| **Non-Hodgkin lymphoma** | |
| **Precursor lymphoid neoplasms** | |
| B-lymphoblastic leukemia/lymphoma | 9728, 9811-9818, 9836 |
| T-lymphoblastic leukemia/lymphoma | 9729, 9837 |
| Lymphoblastic leukemia/lymphoma, NOS | 9727, 9835 |
| **Mature B-cell neoplasms** | |
| Chronic lymphocytic leukemia/small lymphocytic lymphoma | 9670, 9823 |

| | |
|---|---|
| B-cell prolymphocytic leukemia | 9833 |
| Mantle cell lymphoma | 9673 |
| Lymphoplasmacytic lymphoma/ Waldenström's Macroglobulinemia | 9671, 9761 |
| Diffuse large B-cell lymphoma | |
| DLBCL, NOS | 9684, 9680 (excluding C44.0-44.9, C49.9, C71.0-71.9) |
| T-cell/histiocyte-rich large B-cell lymphoma | 9688 |
| Primary DLBCL of the central nervous system | 9680 (C71.0-71.9) |
| Primary cutaneous DLCBL, leg type | 9680 (C44.0-44.9) |
| Intravascular large B-cell lymphoma | 9712, 9680 (C49.9) |
| ALK+ large B-cell lymphoma | 9737 |
| Plasmablastic lymphoma | 9735 |
| Large B-cell (plasmablastic) lymphoma arising in HHV-8 associated multicentric Castleman's disease | 9738 |
| Primary effusion lymphoma | 9678 |
| Primary mediastinal (thymic) large B-cell lymphoma | 9679 |
| Burkitt lymphoma/leukemia | 9687, 9826 |
| Marginal lymphoma | |
| Splenic marginal zone lymphoma | 9689 |
| Extranodal marginal zone lymphoma | 9699 (excluding C77.0-C77.9) |
| Nodal marginal zone lymphoma | 9699 (C77.0-C77.9) |
| Follicular lymphoma | |
| Primary cutaneous follicle Centre lymphoma | 9597, 9690 (C44.0-C44.9) |
| Follicular lymphoma | 9691, 9695, 9698 |
| Hairy cell leukemia | 9940 |
| Plasma cell neoplasms | |
| Solitary plasmocytoma of bone | 9731 |
| Extraosseus plasmocytoma | 9734 |
| Plasma cell myeloma/leukemia | 9732-9733 |
| Heavy chain disease | 9762 |
| B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL | 9596 |
| B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical and Burkitt lymphoma | 9680 |
| **Mature-T-cell and NK-cell neoplasms** | |
| Mycosis fungoides/Sezary syndrome | 9700, 9701 |
| Peripheral T/NK-cell lymphoma | |
| Peripheral T-cell lymphoma, NOS | 9702 |
| Angioimmunoblastic T-cell lymphoma | 9705 |
| Subcutaneous panniculitis-like T-cell lymphoma | 9708 |
| Anaplastic large cell lymphoma, ALK-positive | 9714 |
| Hepatosplenic T-cell lymphoma | 9716 |
| Enteropathy-associated T-cell lymphoma | 9717 |
| Primary cutaneous gamma-delta T-cell lymphoma | 9726 |

| | |
|---|---|
| Primary cutaneous T-cell lymphoma, NOS | 9709 |
| Systemic EBV-positive T-cell lymphoproliferative disease of childhood | 9724 |
| Hydroa vacciniforme-like lymphoma | 9725 |
| Adult T-cell leukemia/lymphoma | 9827 |
| Extranodal NK/Tcell lymphoma, nasal type | 9719 |
| T-cell large granular lymphocytic leukemia | 9831 |
| T-cell prolymphocytic leukemia | 9834 |
| Aggressive NK cell leukemia | 9948 |
| Primary cutaneous CD30 + T-cell lymphoproliferative disorders | 9718 |
| **Lymphoid neoplasms, NOS** | **9590, 9591, 9820, 9970, 9971** |

NOS, not otherwise specified; DLBCL, diffuse large B-cell lymphoma; ALK, anaplastic lymphoma kinase; HL, Hodgkin lymphoma; EBV, Epstein Barr virus.

### *1.1.3 Epidemiology*

Overall, LNs are ranked as the 6th to 7th most common cancer in both men and women worldwide[13]. Incidence rates of LNs are higher in men than in women (**Figure 3**) and rates increase with increasing age occurs in most LNs, reaching a maximum at 75-99 years (with exception of HL and Burkitt lymphoma (BL), as the incidence varies markedly in these neoplasms)[14].

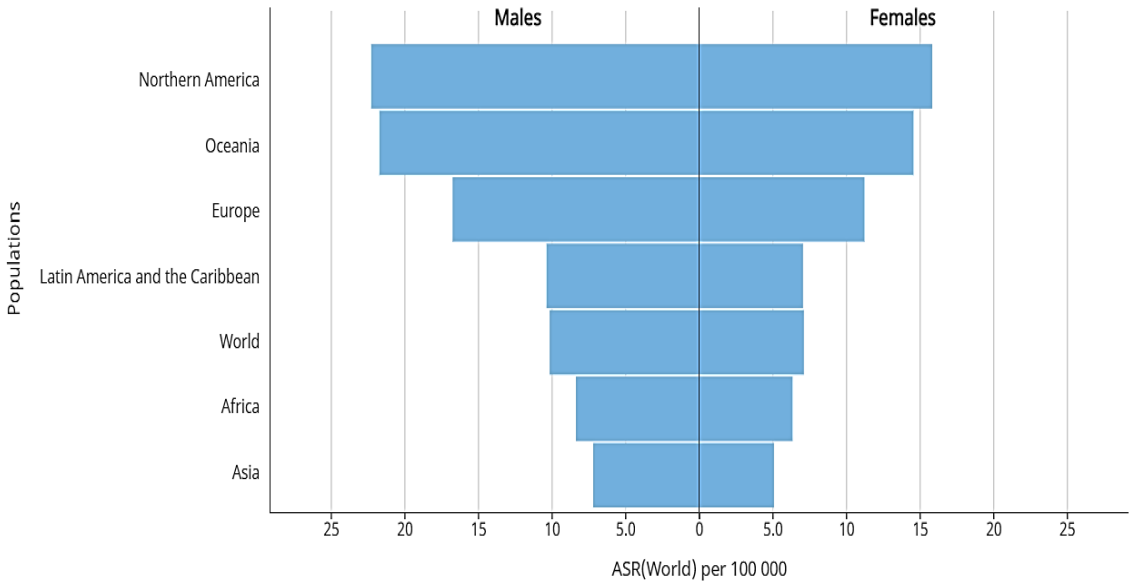


**Figure 3.** Estimated age-standardized incidence rates per 100,000 inhabitants of lymphoma (NHL, HL and multiple myeloma combined) according to sex in 2020 (Source: GLOBOCAN 2020[13]).

There are geographical variations in the incidence of LNs, with the highest rates in North America, Oceania and western Europe[13] (**Figure 4**). In Europe, the HAEMACARE study found that LNs occur at an incidence rate of 24.5 cases per 100,000 inhabitants/year, the most common being plasma cell neoplasms (PCN) (4.64), chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) (3.79), diffuse large B-cell lymphoma (DLBCL) (3.13), and HL (2.41)[14]. In a study of children and adolescents in Spain, the global incidence rate of LNs was found to be 24.8 cases per 100,000 inhabitants/year (31.4 for boys and 17.9 for girls, respectively)[15].

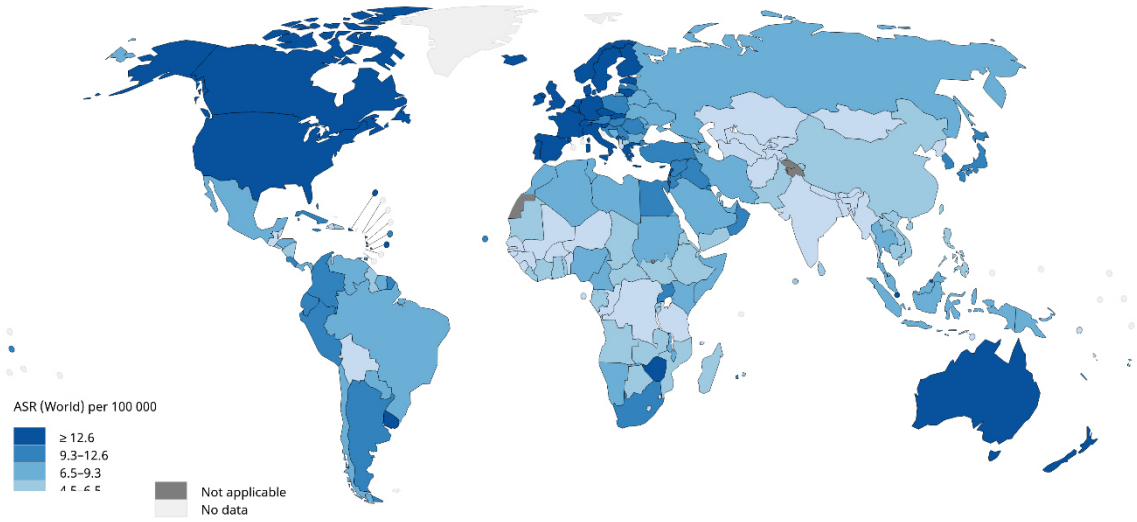


**Figure 4.** Estimated age-standardized incidence rates per 100,000 inhabitants of lymphoma (NHL, HL and multiple myeloma combined) for both sexes in 2020 (Source: GLOBOCAN 2020[13]).

Survival of LNs has been widely studied in population-based studies. Findings from large-scale European conducted during 1997-2008[16] or 2000-2007[17] have reported detailed 5-year observed (OS) and relative survival (RS) for the whole spectrum of LNs. Overall 5-y RS is around 57%, but notable differences have been reported according to age, gender, country, and subtype. Particularly, survival decreases with advancing age at diagnosis and is significantly higher in women for several subtypes, such as CLL/SLL. In addition, 5-y RS varies strikingly across subtypes, with the highest 5-y RS reported in Hodgkin lymphoma (ranging from 95.8% to 81% according to subtype) and the poorest estimates found for plasma cell neoplasms (39% to 40.4%) and precursor cell lymphoblastic leukemia

(ranging from 40% to 59%, with notable differences according to age at diagnosis). Regarding geographical differences, survival is generally lower in Easter European countries than in the rest of Europe, although marked inter-country variations have been also observed. These findings are line with the largest study conducted in United States, analyzing data from the Surveillance, Epidemiology, and End Results (SEER) during 2005-2011[18]. In addition, Teras et al. report differences according to ethnicity, evidencing the lowest survival in black individuals. Finally, other European studies have been conducted at a national[19] or regional scale[20,21]. The latter, despite including a smaller set of cases, are relevant since were conducted in UK and French areas covered by hematology specialized cancer registries, which are more likely to provide accurate and complete data, particularly for subtypes, such as CLL/SLL, that might be under-reported in general cancer registries.

## 1.2 Chronic Lymphocytic Leukemia/small lymphocytic lymphoma

### *1.2.1 Definition*

According to WHO classification CLL/SLL is defined as a lymphoproliferative disorder, composed by monomorphic round B lymphocytes involving peripheral blood, bone marrow and lymphoid tissues[22–24]. From a pathologic and immunophenotypic standpoint, CLL and SLL are identical. CLL and SLL are both caused by aberrant B-cell lymphocytes; however, the symptoms vary depending on where the abnormal cells are located. The initial leukemic phase is usually CLL, in which the cells are found in the blood. The lymphoma phase, which represents SLL, advances to the lymphoma phase, when the cells are located in the lymph nodes. SLL is a term used to describe a lymphoproliferative condition that is restricted to the lymph nodes[25–28].

### *1.2.1 Epidemiology*

CLL is the most common leukemia in the adult population in Western countries, with an annual incidence rate of 4.92 cases per 100,000 inhabitants/year in Europe[29]. The incidence of CLL is higher in males than in females (with a ratio of 2:1, respectively) and increases with increasing age, over 65 years old, while less than 2% of cases are under 45 years old[30]. The median age at diagnosis is approximately 72 years[31]. In addition to gender and age, there is a large difference between Caucasians (7.3 and 3.8 cases per 100,000 inhabitants/year for males and females, respectively), African Americans (4.9 and 2.4 cases per 100,000 inhabitants/year for males and females, respectively) and Asians (1.5 and 0.7 cases per 100,000 inhabitants/year for males and females, respectively)[32]. In Spain, the incidence is estimated to be 4.2 and 3.1 cases each 100,000 inhabitants per year in males and females, respectively, resulting in about 1,600 new cases each year[33]. Finally, the incidence rate in Girona province (Spain) is around 6.62 cases per 100,000 inhabitants/year[34].

Five-year OS probability for CLL patients observed in studies conducted in periods between 1980 and 2011 is greater than 60%, while 5-year RS probability differ based on age, race, and time after diagnosis, but are generally above 65%[12,18,21,35]. Furthermore, RS can vary by region, as evidenced by a European study carried out during the period 2000-2007, that found higher RS in northern and central Europe (74%), as well as by country, with lower RS in Bulgaria (45.5%), Croatia (52 %), and Poland (53%)[17]. In another study conducted between 1996-2000 and 2006-2010, the RS of CLL patients was longer in the United States (US) than in England at all ages, with a greater difference observed at older versus younger ages. Survival of CLL patients varied considerably both between the two countries examined and with age[36].

### *1.2.2 Diagnosis and etiology*

According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008[26], updating the National Cancer Institute-Sponsored Working Group (NCI-WG) 1996 guidelines[37], CLL diagnosis requires a monoclonal B- lymphocyte

count of 5 x $10^9$/L or more and a characteristic cell- surface phenotype of B cells (i.e., the presence of CD5, CD19, and CD23, weak expression of CD20 and CD79b, and either kappa or lambda immunoglobulin light chains). In otherwise healthy persons with an absolute rise in clonal B lymphocytes but fewer than 5 x $10^9$/L B lymphocytes in the blood, CLL or SLL may be considered. However, in the absence of lymphadenopathy or organomegaly (as determined by physical examination or CT scans), cytopenias, or disease-related symptoms, the presence of less than 5 x $10^9$/L B lymphocytes in the blood is classified as "monoclonal B-lymphocytosis" (MBL)[26]. CLL has a wide range of clinical manifestations, ranging from indolent, stable disease to aggressive leukemia patients who succumb to their disease and die quickly. Most patients are asymptomatic at the time of diagnosis, and the disease is discovered after blood tests for unrelated causes reveal an elevated lymphocyte count. In some cases, visible lymphadenopathies and/or splenomegaly characterize the clinical presentation[24,38].

To the date, the cause of CLL is unknown, yet few risk factors have been established. Several lines of evidence suggest a genetic component, such as the increased prevalence of CLL among first-degree relatives, the phenomenon of anticipation, where there is an increased of severity and earlier age of onset with each generation and the increased frequency of autoimmune disorders in relatives of CLL patients[24,39–41]. On the other hand, several studies have revealed a link between CLL diagnosis and occupational and lifestyle characteristics, with those who live or work on a farm being at a higher risk of developing CLL, while sun exposure acting as a protective factor[40,42–45].

### *1.2.3 Staging*

Two systems for staging CLL are now in use. The revised Rai[46] and Binet[47] staging systems are based on results of the physical examination and blood tests.

### *1.2.3.1 Rai staging system*

The Rai system was proposed on the premise that CLL is a progressive disorder in which non-functional lymphocytes (>15,000/μL) first accumulate initially in blood and bone marrow, then invade lymph nodes, spleen, and liver, and subsequently result in thrombocytopenia (<100,000/μL), anemia (hemoglobin (Hb) level <10 g/dL or hematocrit (Hct) <33%), and death. This system was modified to reduce the number of prognostic subgroups from the original 5 (0, I, II, III and IV stage) to a more clinically relevant 3 (Low, Intermediate and High Risk[40]) (**Table 2**).

**Table 2.** Rai staging system[40]

| **Clinical features** | **Stage** | | |
|---|---|---|---|
| | **Low** | **Intermediate** | **High** |
| | **0** | **I / II** | **III / IV** |
| Lymphocytosis (>5 x $10^9$ /L) | + | + | + |
| Splenomegaly-hepatomegaly | - | - / + | ± |
| Lymphadenopathy | - | + / ± | ± |
| Thrombocytopenia (<100 x $10^9$ /L) | - | - | ± / + |
| Anemia (Hb <10 g/dL or Hct <33%) | - | - | + / ± |
| Survival (years) | >10 | 6-8 | 1-2 |

Hb, hemoglobin; L, liter; Hct, hematocrit.

### *1.2.3.2 Binet staging system*

The Binet staging system is dependent on the number of affected areas, which is determined by the presence of swollen lymph nodes with a diameter greater than 1 cm or organomegaly, as well as whether there is anemia or thrombocytopenia. The areas of involvement considered are head and neck, axillae, groins, palpable spleen, and palpable liver (clinically enlarged)[48]. This staging system defines stage A as Hb ≥10 g/dL and platelets ≥100 × $10^9$/L and up to two of the above involved; stage B as Hb ≥10 g/dL and platelets ≥100 × $10^9$/L and organomegaly greater than that defined for stage A (i.e., three or more areas of nodal or organ enlargement);

and stage C as Hb less than 10 g/dL and/or a platelet count of less than 100 × $10^9$/L[40] (**Table 3** ).

**Table 3.** Binet Staging system[49,50]

| Stage | Risk | Clinical features | Survival (years) |
|---|---|---|---|
| **A** | Low | Hb ≥10g/dL, platelets ≥100 × $10^9$/L, and lymphadenopathy in up to 2 sites*. | >10 |
| **B** | Intermediate | Hb ≥10g/dL, platelets ≥100 × $10^9$/L, and lymphadenopathy in 3 or more sites*. | 5 |
| **C** | High | All patients who have Hb <10g/dL (anemia) or platelets <100 × $10^9$/L (thrombocytopenia), regardless of lymphadenopathy. | 2 |

*Sites: Head and neck; axillae; groin; palpable spleen; palpable liver.

### *1.2.4 Treatment*

The decision to treat is guided by the stage of the disease, the presence of symptoms, and the disease activity[51]. Patients with CLL do not need treatment with chemotherapy until they become symptomatic or show evidence of rapid disease progression. Alkylating agent monotherapy has served as initial first-line therapy for CLL, and chlorambucil has been considered the therapeutic "gold standard" for several decades due to its low toxicity, low cost, and convenience as an oral drug. However, its prolonged use produces some side effects prolonged cytopenia, myelodysplasia and secondary acute leukemia, so that currently chlorambucil monotherapy is mainly used as a cost-effective option to achieve palliation in elderly or unfit patients[48,52].

On the other hand, fludarabine monotherapy produces superior overall response rates compared to other treatment regimens containing alkylating agents or

corticosteroids. Fludarabine induces more remissions than other conventional chemotherapies such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone) or chlorambucil, but does not improve overall survival when used as a single agent. However, combination chemotherapy of fludarabine, cyclophosphamide and rituximab (FCR) is usually the best choice for initiation of treatment[53–58]. A randomized phase III study published in 2010 demonstrated that this combination increased the overall response, complete remission rate, progression-free survival and, most importantly, overall survival, thus demonstrating for the first time the superiority in overall survival of one scheme over another in CLL[59].

Second-line treatment decisions follow the same indications as those used for initiation of first-line treatment. Patients who have refractory disease, a short time to progression after first treatment, and/or del(17p)-positive leukemia cells often do not respond to standard chemotherapy and have relatively short survival. Therefore, these patients should be offered investigational clinical protocols, including allogeneic hematopoietic stem cell transplantation[26].

### *1.2.5 Prognostic factors*

#### *1.2.5.1 Well-established prognostic factors*

In addition to staging, age (>50 years), male sex, black race, and poor performance status are all unfavorable prognostic variables, regardless of clinical stage. In terms of presenting symptoms, response rates, or length of response, there are no differences between older and younger CLL patients[49,60–63].

#### *1.2.5.2 Novel prognostic factors*

##### *1.2.5.2.1 Genetic prognostic factors*

Genetic risk stratification should be performed at the time of diagnosis. Fluorescent in-situ hybridization (FISH) determines interphase cytogenetics,

which provides valuable prognostic information and can affect therapeutic decisions. The most common cytogenetic aberration is del(13q14), occurring in approximately 55% of all cases[48] and which is associated with a favorable disease prognosis and therefore increased survival.

Trisomy 12 is found in 10-20% of CLL patients. However, the genes involved in the pathogenesis of CLL with trisomy 12 are largely unknown. Furthermore, the prognostic significance of trisomy 12 remains unknown[64]. Patients with a del(11q) clone have a bulky lymphadenopathy, fast development, and a lower overall survival probability[40,48]. Finally, patients with a del(17p13) account for 5-8% of all genetic aberrations and have a poorer prognosis because the TP53 tumor suppressor gene is lost, resulting in a shorter survival[24,48,50].

CD38 and zeta-associated protein 70 (ZAP-70) expression as assessed by flow cytometry, on the other hand, are related with clinical outcomes in CLL patients, despite being imperfect surrogates for IGHV (immunoglobulin heavy chain gene) status. CD38 positive (defined arbitrarily as a threshold of 30% CD38-expressing cells) and ZAP-70 positivity (defined arbitrarily as a cutoff of 20% expressing ZAP-70) are also linked to resistance to standard therapy, shorter time to first treatment, and longer overall survival[22,65,66].

## 1.3 Comorbidity

### *1.3.1 Definition and background*

Comorbidity is defined as the "coexistence of disorders in addition to a primary disease of interest"[67]. Comorbidity may have a positive or negative impact on the timing of cancer diagnosis. Comorbidity symptoms, for example, can prompt a patient to seek medical attention sooner, possibly leading to an earlier diagnosis. Alternatively, cancer symptoms could be masked by those of a pre-existing medical condition, delaying its diagnosis[68]. Disorders of the heart, lungs, liver, or kidneys pose an additional obstacle to treating physicians because cancer patients with such comorbidities are likely to be less tolerant to traditional chemotherapy-based

regimens. As a result, evaluating comorbid illness history in relation to care channeling is a common clinical issue when diagnosing adult and elderly patients. Although there is widespread consensus that comorbidity is common among cancer patients, determining how common it is difficult. This is because the prevalence of measured comorbidity varies, often dramatically, depending on the comorbidity measure used, the study population, and the type of cancer[69]. Comorbidity is particularly important in elderly patients with biologically indolent or morphologically localized cancers (i.e., not rapidly fatal)[70], such as prostate[71], colon and rectum[72,73], ovary[74], breast[74,75], and NHL[76]. However, the impact of comorbidities on the outcome of CLL is much less studied than in other types of cancer. According to a previous study, CLL patients have a median of two concurrent medical disorders, with 46% having at least one significant comorbidity (e.g., cerebrovascular disease, coronary artery disease, diabetes mellitus or a concurrent disease)[77]. In addition, several studies have shown that the number of diseases that subjects with CLL have increases with age[78–80].

### *1.3.2 Charlson Comorbidity Index*

Comorbidities are frequent in elderly CLL patients[81]. Choices must be made regarding the extent and assessment of comorbid diseases when looking at the relationships and effect of comorbidity in general on cancer outcomes. Researchers have proposed multiple models to identify and quantify comorbid diseases to this end. There are different comorbidity indices that allow the reduction of a person's diseases to a final score. The most commonly used general comorbidity measure is the Charlson Comorbidity Index (CCI)[82,83]. CCI is a prognostic method focused on the idea that advancing age, as well as the presence and severity of comorbidities, raise the risk of death in chronic disease patients, such as CLL. Seventeen comorbid conditions (acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, peptic ulcer, mild liver disease, mild/moderate diabetes, diabetes with chronic complications, hemiplegia/paraplegia, kidney disease, malignant tumors, moderate/serious liver disease, metastatic tumor, and AIDS)

are assigned weights of 1, 2, 3, or 6, based on the ratio of the mortality risk for patients with the comorbidity of interest versus the mortality risk for those without (**Table 4**). The sum of the weights for all the conditions is calculated to create a comorbidity index for each patient.

**Table 4.** Charlson comorbidity index (CCI)[82,83]

| Assigned weights for diseases | Conditions |
|---|---|
| 1 | Acute myocardial infarction |
| | Congestive heart failure |
| | Peripheral vascular disease |
| | Cerebrovascular disease |
| | Dementia |
| | Chronic lung disease |
| | Rheumatic disease |
| | Peptic ulcer |
| | Mild liver disease |
| | Mild/moderate diabetes |
| 2 | Diabetes with chronic complications |
| | Hemiplegia/paraplegia |
| | Kidney disease |
| | Malignant tumors |
| 3 | Moderate/serious liver disease |
| 6 | Metastatic tumor |
| | AIDS |

**AIDS**, Acquired Immunodeficiency syndrome

Each decade of age above 40 years adds 1 point to the risk (e.g., 50-59 years, 1 point; 60-69 years, 2 points; 70-79 years, 3 points), and these age points are added to the CCI score (e.g., 0, 1, 2, 3, etc.) Thus, a 60-year-old patient with a CCI score of 3 would have a combined age and comorbidity score of 5 and a 50-year-old patient with a CCI score of 2 would have an age-comorbidity of 3[83].

There are also other systems for measuring comorbidity in CLL patients, such as the Cumulative Illness Rating Scale (CIRS)[84], which measures the burden of chronic medical illness taking into account the severity of the disease.

### *1.3.3 Impact of comorbidity on CLL outcomes*

Previous studies show that comorbidities appear to influence cancer treatment options, outcomes, and overall survival[69,70,85,86]. However, although CLL is the most common form of adult leukemia in Europe and North America and accounts for approximately 25% of mature B-cell neoplasms[87], there are few studies assessing the impact of comorbidities on CLL survival, and much more limited literature focused on the study of comorbidities and their relationship with CLL-related and CLL-unrelated cause of death.

Previous studies have shown lower survival in CLL patients with a greater number of comorbidities[77,79,88–93]. The main comorbidities observed in most previous studies correspond to diabetes mellitus, congestive heart failure and chronic lung disease[77,88,91,92,94,95]. The results obtained in the different studies further indicate that comorbidity plays an important role in the survival of CLL. Thus, for example, in the study conducted in patients who participated in two phase III trials conducted by the German CLL research group, a trend towards poorer survival was observed in patients with significant comorbidity (multiple comorbidities or extreme comorbidities), regardless of age[86]. Similarly, in studies conducted in the periods 1998-2007[89], 2006-2016[90] and 2000-2017[79], comorbidities are associated with worse survival, independently and in comparison with factors such as age, functional status, Rai stage, previous treatment or del(17p). This could be interpreted to mean that the prognosis of CLL patients tends to be influenced by both relevant factors such as age as well as comorbidities.

On the other hand, Strati and colleagues at the Mayo Clinic prospectively evaluated the influence of interacting diseases on survival and cause of death in CLL[93]. They found that 93% of patients had at least one comorbid disease at the time of CLL diagnosis. They further reported that an elevated CCI score and a history of stroke

and heart disease increased the risk of dying from a cause unrelated to CLL. However, 89% of patients presented were classified with low-intermediate CCI, comorbidities did not affect CLL-associated survival and, importantly, approximately half of the deaths in this cohort were directly related to CLL complications. In another study conducted between 1999-2003[92], it was observed that mainly deaths considered CLL-associated by treating physicians were the main factor contributing to higher mortality in patients with higher comorbidity. Similarly, several studies indicate that the presence of comorbidities in patients with CLL influences both overall mortality, CLL-related mortality, and CLL-unrelated mortality[91,94]. These findings may challenge prevailing views that elderly patients with CLL generally die of another disease and are crucial for therapeutic decisions.

# HYPOTHESIS

# 2. HYPOTHESIS

Limited population-based data on survival of LNs according to the WHO 2008 classification, and the scarce information on the impact of comorbidities on survival and cause of death in patients with CLL, have led us to formulate the following hypotheses in this thesis:

Paper I

- Survival of all LNs vary according to each subtype proposed by the WHO 2008 classification. Sex, age of patients and period of diagnosis are prognostic factors that can influence the survival time of LNs.

Paper II

- The presence of comorbidities can negatively influence survival and mortality (overall and CLL-related or CLL-unrelated) in the patients with newly CLL diagnosis.

# OBJECTIVES

# 3. OBJECTIVES

This thesis aims to evaluate the survival of LNs, as well as to examine the influence of comorbidities on survival and cause of death in patients with CLL. To address these general objectives, the following specific objectives were defined:

Paper I

- To estimate the OS and RS of LNs subtypes according to the 2008 WHO classification, overall and by sex, age group and period of diagnosis, in the Girona province during 1996–2015.

Paper II

- To examine the prevalence of comorbidities and their influence on survival and mortality (overall and CLL-related or CLL-unrelated) in patients diagnosed with CLL, in the province of Girona, during 2008–2016.

# METHODS

# 4. METHODS

## 4.1 Paper I. Population-based survival of lymphoid neoplasms: Twenty years of epidemiological data in the Girona province, Spain

### *4.1.1 Data*

Data were extracted from the population-based Girona Cancer Registry (GCR), located in the Northeast of Catalonia, in Spain, and covering a population of 738,976 inhabitants in 2015. The population covered by the GCR is the province of Girona, which includes the counties of Gironès, Selva, Alt Empordà, Baix Empordà, Cerdanya, Garrotxa, Ripollès and Pla de l'Estany (**Figure 5**).


**Figure 5.** Study area. Geographical location of the Girona Cancer Registry (GCR).

LNs incident cases during the period 1996-2015 (n=4,367) were registered using the ICD-O-3[11], following the 2008 WHO classification, and grouped into major sub-categories based on the HAEMACARE project scheme[12]. The WHO classification system is currently considered the "gold standard" for classifying all hematopoietic neoplasms. That classification scheme takes into account many aspects of the disease, such as morphology, immunophenotype, cytogenetic and molecular

features. Although some updates have been made, and a new WHO manual was published in 2016, the surveillance data available are up to 2015 and do not reflect these updates.

After exclusion of Death certificate only (DCOs) and cases diagnosed at autopsy, 4,294 LNs were finally included in the survival analysis. Data on the vital status of patients were obtained by linking records to the Catalan Registry of Mortality and the National Death Index[96]. Mid-year population estimates and mortality rates in the Girona province were obtained from the Institut d'Estadística de Catalunya, IDESCAT[97]. Finally, the date of diagnosis and vital status on 12/31/2015 were used for statistical analyses.

### *4.1.2 Statistical Analysis*

Kaplan-Meier method was used to calculate OS. The RS probability were estimated using the Pohar–Perme method[98] as the ratio of observed survival in the study population, to expected survival in the general population of the same age, sex, year, and province (Girona)[99]. In our analysis, we used the Pohar-Perme method, which is an unbiased estimator when compared to conventional methods such as Ederer II, which is especially important when age-unstandardized survival probabilities are reported. Expected survival probability were taken from the life tables for the population covered by the GCR. Comparison of OS and RS curves were performed using a log-rank type test[100]. All analyses were performed using free R statistical software (R Development Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

## 4.2 Paper II. Comorbidities at Diagnosis, Survival, and Cause of Death in Patients with Chronic Lymphocytic Leukemia: A Population-Based Study

### *4.2.1 Data*

A subset based on all CLL cases diagnosed in the province of Girona during the period of 2008–2016 (n=400) was used in the survival and mortality CLL sub-analysis. We focused on a more recent period (2008-2016) in order to have access to computerized medical records. Following WHO recommendations, CLL and SLL cases were classified together, since both share clinical and pathological features[10].

#### *4.2.1.1 Comorbidity Assessment*

Data on the Rai stage, indicating severity of CLL and comorbidities present at diagnosis were retrospectively obtained by reviewing the medical records. Comorbidities were assigned to one of the following categories—acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, peptic ulcer, mild liver disease, mild/moderate diabetes, diabetes with chronic complications, hemiplegia/paraplegia, kidney disease, malignant tumors, moderate/serious liver disease, metastatic tumor, and AIDS[93]. The age-adjusted CCI[82,83] was calculated for each patient, based on the health conditions present at the time of diagnosis. Based on their CCI scores, patients were grouped into five groups (i.e., absence of comorbidity (0), low risk (1–2), moderate risk (3), high risk (>4), and unknown CCI status). In addition, for each decade of age above 40 years, 1 point was added to the CCI score.

#### *4.2.1.2 Survival and Mortality Data*

Patients were followed up until death or last follow-up date (31 December 2019), whichever came first. In our region, the cause of death was initially determined by the treating physician, based on the available clinical information, and sometimes on autopsy reports. This information was then transferred to the Catalan Registry of Mortality Data[101], which was responsible for coding the underlying causes of death (basic cause of death), following the guidelines of the International Classification of Diseases, 10th edition (ICD-10-ES)[102]. In our study, causes of death were categorized into CLL-related (including all hematological malignancies) and CLL-unrelated death. Those patients with unknown cause of death (n= 13) were excluded for both the CLL-related and CLL-unrelated survival analyses.

### *4.2.2 Statistical Analysis*

Descriptive statistics were used to summarize the baseline clinical characteristics, overall and by the CCI score and cause of death. Differences in the clinical characteristics by CCI score and cause of death were assessed by the chi-square test. The same methods were used to calculate OS and RS as in the first study (see statistical analysis in part 4.1.2 of this section). To assess the association of CCI score after adjusting for other covariates (gender, age, Rai stage, and period of diagnosis), Cox proportional hazards models were constructed, and a Wald test was used. The adjusted hazard ratios (HR) of death and the corresponding 95% confidence intervals (95% CI) were estimated. For all analyses, a p-value $<0.05$ was considered to be significant.

# RESULTS

# 5. RESULTS

The results of this thesis are presented as two original articles:

**Paper I:** Villavicencio A, Solans M, Auñon-Sanz C, Roncero JM, Marcos-Gragera R. Population-based survival of lymphoid neoplasms: Twenty years of epidemiological data in the Girona province, Spain. Cancer Epidemiol. 2020, 69: 101841. doi: 10.1016/j.canep.2020.101841.

[**2020 Impact factor: 2.984**; Q2 Public, Environmental & Occupational Health, position 88 of 203].

**Paper II:** Villavicencio A, Solans M, Zacarías-Pons L, Vidal A, Puigdemont M, Roncero JM, Saez M, Marcos-Gragera R. Comorbidities at Diagnosis, Survival, and Cause of Death in Patients with Chronic Lymphocytic Leukemia: A Population-Based Study. Int. J. Environ. Res. Public Health. 2021,18(2):701. doi: 10.3390/ijerph18020701.

[**2020 Impact factor: 3.390**; Q1 Public, Environmental & Occupational Health, position 41 of 176].

## 5.1 Paper I

### Population-based survival of lymphoid neoplasms: Twenty years of epidemiological data in the Girona province, Spain

Villavicencio A*, Solans M*, Auñon-Sanz C, Roncero JM, Marcos-Gragera R.

Cancer Epidemiology. 2020, 69: 101841. doi: 10.1016/j.canep.2020.101841.

*Equal contribution

**Box 1|** Overview of paper I

**What is already known on this subject**

- LNs are a heterogeneous group of hematologic malignancies which exhibit diverse etiology, presentation, and prognosis.
- In our setting, information on the survival of LNs over a prolonged period is scarce.

**What this study adds**

- This study provides survival data of LNs its subtypes in the Girona province during a 20-year period. We covered a relative long-term period (1996–2015) in which new therapeutic agents for the management of LNs have been introduced.
- The indicators observed in this study can provide valuable information to monitor survival at a population level and to evaluate national cancer plans.

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# Population-based survival of lymphoid neoplasms: Twenty years of epidemiological data in the Girona province, Spain

Alicia Villavicencio [a,b,c,1], Marta Solans [b,c,d,*,1], Carmen Auñon-Sanz [c,e], Josep Maria Roncero [f], Rafael Marcos-Gragera [a,b,c,d,g]

[a] Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Catalan Institute of Oncology, Carrer del Sol 15, 17004 Girona, Spain
[b] Research Group on Statistics, Econometrics and Health (GRECS), University of Girona, C/ Universitat de Girona 10, 17003 Girona, Spain
[c] Descriptive Epidemiology, Genetics and Cancer Prevention Group, Biomedical Research Institute (IDIBGI), Girona, Spain
[d] Centro de Investigación Biomédica en Red: Epidemiología y Salud Pública (CIBERESP), Av. Monforte de Lemos 3-5, 28029 Madrid, Spain
[e] Radiation Oncology Service, Josep Trueta University Hospital, Catalan Institute of Oncology, Avinguda de França, S/N, 17007 Girona, Spain
[f] Hematological Service, Josep Trueta University Hospital, Catalan Institute of Oncology, Avinguda de França, S/N, 17007 Girona, Spain
[g] Josep Carreras Leukemia Research Institute, Girona, Spain

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ABSTRACT

*Background:* The aim of this study was to describe survival of lymphoid neoplasms (LNs) in the Girona province (Spain) during 1996–2015.
*Methods:* Data were extracted from the Girona cancer registry. LN incident cases were registered using the ICD-O-3, following the 2008 WHO classification scheme and HAEMACARE grouping. Follow-up was available until the 31/12/2015. Observed and relative survival (RS) were estimated with Kaplan-Meier and Pohar Perme methods, respectively.
*Results:* 4294 LNs diagnosed over a 20-year period were included in the survival analyses. 5-year RS was 62.3 % (95 % confidence interval (CI): 60.4–64.4), and ranged from 88.5%–41.1% according to subtype. Findings were similar between men and women, while survival decreased markedly with age. RS for all LNs improved during the first two periods of study, being 56.5 % (95 % CI: 53.1–60.0) in 1996–2002, 64.8 % (95 % CI: 61.7–68.2) in 2003–2008, and 65.6 % (95 % CI: 62.0–69.5) in 2009–2015. This pattern was mostly attributed to an improved survival of mature B-cell neoplasms, yet only statistically significant differences were reported for follicular lymphoma and mantle cell lymphoma subtypes.
*Conclusions:* Our study provides estimates of survival in LNs and its subtypes, allowing comparisons between countries. Survival for overall cases improved across the period of study, yet rates are still poor for most subtypes, evidencing the need of therapeutic research programs.

## 1. Introduction

Lymphoid neoplasms (LNs) are a heterogeneous group of hematologic malignancies which exhibit diverse etiology, presentation and prognosis. Together, they are ranked as the 6th to 7th most common cancer worldwide [1]. Changes in our understanding of LNs have resulted in the evolution of multiple classification schemes over the past 60 years [2]. Since 2001 [3], the World Health Organization (WHO) classification is the gold standard for classifying hematological neoplasms. Lately updated in 2008 [4] and 2016 [5], it represents a consensus classification for clinical and pathologic use which has been adopted worldwide, including the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) [6]. The aim of this study was to estimate relative survival of LNs subtypes – according to the 2008 WHO classification – in the Girona province (Spain) during 1996–2015.

*Abbreviations:* CI, confidence interval; ICD-O-3, international classification of diseases for oncology, third edition; ICCC-3, international classification of childhood cancer, third edition; LN, lymphoid neoplasm; OS, observed survival; RS, relative survival; WHO, World Health Organization.

* Corresponding author at: Centro de Investigación Biomédica en Red: Epidemiología y Salud Pública (CIBERESP) and Research Group on Statistics, Econometrics and Health (GRECS), University of Girona. Carrer de la Universitat de Girona 10, Campus de Montilivi, 17003 Girona, Spain.
*E-mail address:* marta.solans@udg.edu (M. Solans).
[1] These authors contributed equally to this work.

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## 2. Material and methods

Data were extracted from the population-based Girona cancer registry, covering a population of 738,976 inhabitants in 2015. LN incident cases were registered using the ICD-O-3 [6], following the 2008 WHO classification, and grouped into major sub-categories based on the HAEMACARE project scheme [7].

Death certificate only (DCOs) cases and those diagnosed at autopsy were excluded from the survival analysis. Data on the vital status of patients were obtained by linking records to the Catalan Registry of Mortality and the National Death Index [8]. The date of diagnosis and vital status on 12/31/2015 were used to calculate observed survival (OS) by the Kaplan-Meier method. Relative survival (RS), defined as the ratio of the OS to the expected survival, was analyzed using the Pohar Perme method [9]. The expected mortality rates were available by sex, age, and year of diagnosis [10]. Comparison of RS curves across period of diagnosis were performed using a log-rank type test [11]. All analyses were performed using free software R (RStudio version 1.1.463).

## 3. Results

Over the 20-year period, 4367 LNs were diagnosed in the Girona province. Incidence rates have been previously detailed elsewhere [12]. After exclusion of DCOs and cases diagnosed at autopsy, 4294 LNs were included in the survival analysis. Among them, there were 1831 (0.43 %) women. The dataset included 110 pediatric cases (0–14 years), 60 adolescent cases (15–19 years), and 4124 adult cases (>19 years), being 67 years the median age at diagnosis. Table 1 lists the number of cases of each subgroup according to the ICD-O-3 codes, median age (min-max), follow-up characteristics, and the 5-year survival estimates. 5-y OS and RS for overall LNs were 54.4 % (95 % confidence interval (CI): 52.8–56.0) and 62.3 % (95 % CI: 60.4–64.4), respectively. Regarding specific lymphoma subtypes, Hodgkin lymphoma showed a high 5-y RS (75.3 % (95 % CI: 70.3–80.6)), with rates being higher in nodular lymphocyte predominant subtypes (91.0 % (95 % CI: 79.8–100.0)) than in classical Hodgkin lymphoma (73.9 % (95 % CI: 68.7–79.5)). By contrast, 5-y RS in precursor cell neoplasms was low (46.3 % (95 % CI: 39.8–53.9), regardless of B- or T-cell origin. Mature T/NK-cell neoplasms encompassed subtypes in opposite extremes in terms of survival, with mycosis fungoides/Sezary syndrome being the lymphoma subtype with most favorable prognosis (88.5 % (95 % CI: 76.6–100.0) and peripheral T-cell lymphoma showing 5-y RS estimates of 43.5 % (95 % CI: 34.3–55.0). Likewise, mature B-cell neoplasms included subtypes with high survival rates [i.e. marginal lymphoma (82.3 % (95 % CI: 76.0–89.2)), chronic lymphocytic leukemia/small lymphocytic lymphoma (82.2 % (95 % CI: 77.1–87.7)), and follicular lymphoma (75.1 % (95 % CI: 69.3–81.5))], together with entities with poor prognosis, such as plasma cell neoplasms (41.1 % (95 % CI: 36.9–45.9)) or diffuse large B-cell lymphoma (49.4 % (95 % CI: 45.1–54.0). Finally, NOS cases showed the worst 5-y RS estimates (26.3 % (95 % CI: 16.4–42.2)).

Sex- and age-specific estimates of 5-year RS are displayed in Fig. 1 (specific values and p-values for log-rank type test are detailed in supplementary material, **Table S1** and **Table S2**). We reported similar rates across sexes (Fig. 1A), while age at diagnosis was a major prognostic factor (Fig. 1B). 5-y RS of all LNs decreased progressively across age-groups, being 91.3 % (95 % CI: 86.0–97.0) in children, 76 % (95 %

**Table 1**
5-year observed and relative survival for patients with lymphoid neoplasms diagnosed in 1996-2015 in the Girona province.

| Subtype | ICD-O-3 codes | N | Median age (min-max) years | Loss to follow-up (%) | 5-year observed survival (95 % CI) | 5-year relative survival (95 % CI) |
|---|---|---|---|---|---|---|
| **Lymphoid neoplasms, total** | | **4294** | **67 (0–98)** | **1.4** | **54.4 (52.8–56.0)** | **62.3 (60.4–64.4)** |
| **Hodgkin lymphoma** | | **362** | **39 (3–92)** | **1.4** | **73.2 (68.6–78.2)** | **75.3 (70.3–80.6)** |
| • Classical Hodgkin lymphoma | 9650–9655, 9661–9667 | 334 | 38.5 (3–92) | 1.2 | 71.9 (67.0–77.2) | 73.9 (68.7–79.5) |
| • Hodgkin lymphoma, nodular lymphocyte predominant | 9659 | 28 | 44 (7–85) | 3.6 | 89.1 (78.3–100.0) | 91.0 (79.8–100.0) |
| **Precursor cell neoplasms** | | **206** | **25 (0–93)** | **0.5** | **46.0 (39.6–53.5)** | **46.3 (39.8–53.9)** |
| • Precursor B-cell lymphoblastic lymphoma/leukemia | 9728, 9811–9818, 9836 | 138 | 17 (0–86) | 0 | 53.5 (45.7–62.6) | 53.8 (46.0–63.0) |
| • Precursor T-cell lymphoblastic lymphoma/leukemia | 9729, 9837 | 46 | 20 (1–80) | 2.8 | 44.0 (31.0–62.3) | 44.1 (31.3–62.0) |
| • Precursor cell lymphoblastic lymphoma/leukemia, NOS | 9727, 9835 | 22 | 81 (22–93) | 0 | – | – |
| **Mature B-cell neoplasms** | | **3371** | **69 (2–98)** | **1.3** | **53.7 (51.9–55.5)** | **62.7 (60.4–65.0)** |
| • Chronic lymphocytic leukemia/small lymphocytic lymphom | 9670, 9823 | 746 | 72 (30–95) | 0.8 | 65.1 (61.5–68.9) | 82.2 (77.1–87.7) |
| • Mantle cell lymphoma | 9673 | 105 | 68 (31–89) | 0 | 44.3 (34.9–56.2) | 50.7 (39.3–65.2) |
| • Lymphoplasmacytic lymphoma/ Waldenström's Macroglobulinemia | 9671, 9761 | 126 | 72.5 (24–91) | 1.6 | 56.1 (47.2–66.7) | 66.4 (55.0–80.2) |
| • Diffuse large B-cell lymphoma | 9678–9680,9688, 9684, 9712, 9735, 97,379,738 | 730 | 66 (2–98) | 2.2 | 44.6 (40.9–48.6) | 49.4 (45.1–54.0) |
| • Burkitt lymphoma/leukemia | 9687, 9826 | 60 | 37.5 (2–92) | 1.7 | 49.8 (38.3–64.7) | 50.2 (38.8–65.0) |
| • Marginal zone lymphoma | 9689, 9699 | 339 | 68 (17–91) | 0.3 | 72.1 (67.2–77.5) | 82.3 (76.0–89.2) |
| • Follicular lymphoma | 9597, 9690, 9691, 9695, 9698 | 439 | 62 (16–94) | 1.6 | 69.1 (64.5–74.0) | 75.1 (69.3–81.5) |
| • Plasma cell neoplasms | 9731,9734, 9732–9733 | 790 | 72 (34–96) | 1.1 | 35.1 (31.7–38.9) | 41.1 (36.9–45.9) |
| • Other B-cell neoplasms[1] | 9596, 9940 | 36 | 58 (18–88) | 8.3 | 79.1 (66.3–94.2) | 91.0 (75.9–100.0) |
| **Mature T/NK-cell neoplasms** | | **261** | **64 (6–92)** | **3.1** | **56.1 (49.9–63.0)** | **65.1 (57.7–73.4)** |
| • Mycosis fungoides/Sezary syndrome | 9700, 9701 | 80 | 63.5 (10–89) | 8.7 | 77.0 (67.4–88.0) | 88.5 (76.6–100.0) |
| • Peripheral T-cell lymphoma | 9702 | 130 | 64.5 (13–90) | 0.8 | 37.8 (29.9–47.8) | 43.5 (34.3–55.0) |
| • Other mature T/NK-cell neoplasms[2] | 9827, 9719, 9831, 9834, 9948, 9718 | 51 | 65 (6–92) | 0 | 72.3 (59.9–87.1) | 80.8 (66.2–98.8) |
| **Lymphoid neoplasms, NOS** | 9590, 9591, 9820, 9970, 9971 | **94** | **76 (32–96)** | **2.1** | **19.6 (12.9–30.0)** | **26.3 (16.4–42.2)** |

95 % CI, 95 % confidence interval; NOS, not otherwise specified.

[1] There were 4 cases of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL (9596), and 32 cases of hairy cell leukemia (9940).

[2] There were 3 adult T-cell leukemia/lymphoma (9827), 10 extranodal NK/T-cell lymphoma nasal type (9719), 22 T-cell large granular lymphocytic leukemia (9831), 3 T-cell prolymphocytic leukemia (9834), 1 aggressive NK cell leukemia (9948), and 12 primary cutaneous CD30 + T-cell lymphoproliferative disorders (9718).

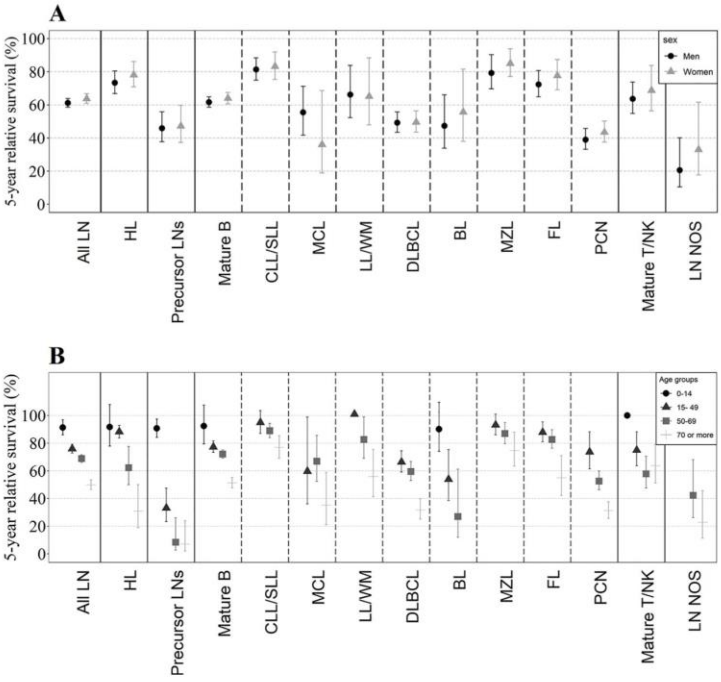


**Fig. 1.** Estimates of 5-year relative survival for patients with lymphoid neoplasms diagnosed in 1996–2015.
In the Girona province, according to (A) sex and (B) age-group. Number of cases included in each subgroup: women (n = 1831), men (n = 2463); age 0–14 (n = 110), age 15–49 (n = 812), age 50–69 (n = 1469), age ≥70 (n = 1903). **LN,** Lymphoid neoplasm**, HL,** Hodgkin lymphoma, CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; **MCL**, mantle cell lymphoma; **LL/WM**, lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia; **DLBCL**, diffuse large B-cell lymphoma; **BL**, Burkitt lymphoma/leukemia; **MZL**, marginal zone lymphoma; **FL**, follicular lymphoma; **PCN**, plasma cell neoplasms; **NOS**, not otherwise specified.

CI: 72.9–79.2) in 15–49 years, 68.9 % (95 % CI: 66.1–71.7) in 50–69 years, and 49.9 % (95 % CI: 46.5–53.5) in those aged ≥70 years (p-value for log-rank type test <0.001). This pattern was observed for most lymphoma subgroups.

Changes in 5-year RS according to period of diagnosis (i.e. 1996–2002, 2003–2008, and 2009–2015) are displayed in Fig. 2 (specific values and p-values for log-rank type test are detailed in supplementary material, **Table S3**). Survival for all LNs increased during the first two periods of study, being 56.5 % (95 % CI: 53.1–60.0) in 1996–2002, 64.8 % (95 % CI: 61.7–68.2) in 2003–2008, and 65.6 % (95 % CI: 62.0–69.5) in 2009–2015 (p-value for log-rank type test = 0.016). This increase was mostly attributed to an improved survival of mature B-cell neoplasms, yet only statistically significant differences were reported for follicular lymphoma and mantle cell lymphoma (p-values: 0.006 and 0.046, respectively). By contrast, survival for mature T/NK-cell neoplasms, Hodgkin lymphoma, precursor cell-neoplasms, and NOS cases, remained stable across the period of study.

## 4. Discussion

This paper presents population-based survival of LNs in the Girona province during a 20-year period. We provided data following the 2008 WHO classification and HAEMACARE grouping of LNs, based on cell lineage and prognosis, easing comparisons between countries.

As expected, RS varied widely across lymphoma subtypes, with our results being in accordance with findings from the largest European [7, 13–15] and North American [16] datasets, as well as hematology-specialized cancer registries [17,18]. However, our survival estimates for most subtypes were lower than those reported by the UK's Haematological Malignancy Research Network [18]. Likewise, survival of Hodgkin lymphoma and follicular lymphoma in our region were lower than those reported by large European datasets [7,13–15] and the SEER [16], respectively. By contrast, some of these studies showed lower 5-y RS rates for some mature B-cell neoplasms subtypes, such as chronic lymphocytic leukemia/small lymphocytic lymphoma [7,13,14], plasma cell neoplasms [7], or precursor cell neoplasms [15]. A plausible

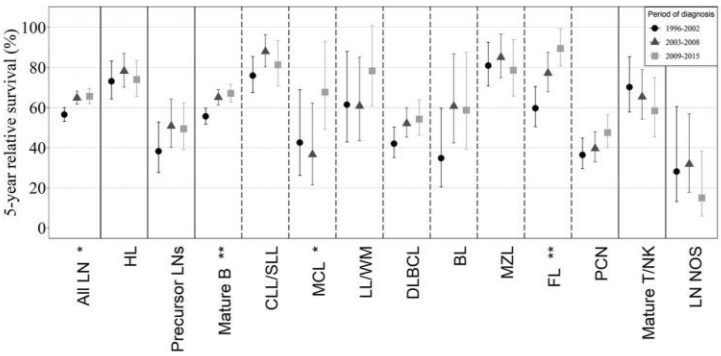


**Fig. 2.** Estimates of 5-year relative survival for patients with lymphoid neoplasms diagnosed in 1996-2015 according to period of diagnosis (1996-2002, 2003-2008, 2009-2015).
Number of cases included in each subgroup: 1996–2002 (n = 1220), 2003–2008 (n = 1385); 2009–2015 (n = 1689). **LN,** Lymphoid neoplasm**, HL,** Hodgkin lymphoma, CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; **MCL**, mantle cell lymphoma; **LL/WM**, lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia; **DLBCL**, diffuse large B-cell lymphoma; **BL**, Burkitt lymphoma/leukemia; **MZL**, marginal zone lymphoma; **FL**, follicular lymphoma; **PCN**, plasma cell neoplasms; **NOS**, not otherwise specified. Statistically significant differences between survival curves by period of diagnosis based on log-rank type test: * **p < 0.05;** ** **p < 0.01**.

explanation for disparities in chronic lymphocytic leukemia/small lymphocytic lymphoma could be a different registration coverage of indolent cases. In particular, chronic lymphocytic leukemia diagnosis is not based on tissue pathology and early-stage cases do not require treatment; thus, are likely to be underreported by cancer registries. We recently made an effort to recover such cases in our region [19], which may have improved survival estimates for this malignancy, being now in agreement with those reported by specialized French cancer registries [15,17]. However, comparisons must be made with caution, given that studies comprised different periods of study, some of them reported age-standardized data [13–15], and different statistical methods were used to estimate RS (e.g. Hakulinen [7], Ederer II [13,14], or Pohar Perme [15]). In our study we used the Pohar-Perme method, which, in comparison to conventional methods, is an unbiased estimator – a particularly relevant property when reporting nonage-standardized survival rates [20].

While most mature B-cell subtypes are increasingly being analyzed separately in recent epidemiological literature, still most studies provide overall results for Hodgkin lymphoma, precursor, and mature T/NK-cell neoplasms, mainly due to limited sample size. However, and in line with previous studies [7,16–18], we evidenced marked differences in survival probabilities among entities classified under such broad categories. This is the case, for instance, of T-cell lymphoma and mycosis fungoides, which are in opposite extremes in terms of survival. Unfortunately, we were limited by sample size to run stratified analyses by age, sex, or period of diagnosis within those subtypes. Overall, further well-powered studies including real world data are needed to deepen into the study of such less incident subtypes.

Survival rates were similar between men and women, while there were marked differences across age-groups. As for most cancers, age at diagnosis is a strong and well-established prognostic factor, even after adjusting survival for competitive mortality risks [13]. Poor survival in elderly patients is namely attributed to the presence of comorbidities or frail status, which hampers the application of several treatment protocols, such as aggressive chemotherapy or stem-cell transplantation. While LNs typically affect patients of advanced age, several subtypes, such as Hodgkin lymphoma (first incidence peak), Burkitt lymphoma/leukemia, or precursor neoplasms, mainly occur in children or adolescents. We were limited by sample size to deepen into the analysis of such cases; however, survival of childhood and adolescent LNs in Spain during 1983–2007, including data from all Spanish cancer registries, have been recently published [21]. Results can be only tentatively compared, though, given that survival rates were provided for categories based on the International classification of childhood cancer (ICCC-3) [22], which, for example, includes Burkitt lymphoma as a separate entity from mature B-cell lymphomas.

Prognosis for LNs as a whole improved across period of study, which was mostly attributed to better survival rates of mature B-cell neoplasms. This could be explained by changes in treatment patterns, such as the introduction in 2004 of rituximab for diffuse large B-cell lymphoma, and soon thereafter, during 2004–2005, for follicular lymphoma and mantle cell lymphoma. In addition, novel agents (i.e. thalidomide, bortezomib, lenalidomide) were introduced between 2005–2008, together with autologous stem cell transplantation in 2009 for the treatment of multiple myeloma. Indeed, several population-based registries have already evidenced the favorable impact of such therapeutic changes on the general population [23–25]. Furthermore, research towards more accurate diagnosis (e.g. the introduction of PET-TC) and better supportive care could have improved the prognosis of patients diagnosed in more recent years. Again, this results should be interpreted with caution, given the numerous changes in the classification of LNs that took place during the period of study and the difficulties in stablishing an accurate diagnosis. High-resolution studies collecting disease stage at diagnosis and therapeutic patterns could provide further evidence of treatment effectiveness, as well as to explain geographic variations in survival [14]. Overall, prognosis for several subtypes is still poor, and research efforts aimed at developing new therapeutic agents are needed to improve patients' outcomes.

## 5. Conclusion

This study provides survival data of LNs its subtypes in the Girona province during a 20-year period. We covered a relative long-term period (1996–2015) in which new therapeutic agents for the management of LNs have been introduced. Survival for overall cases – namely mature B-cell neoplasms – improved across the period of study, yet rates are still poor for precursor neoplasms and most mature non-Hodgkin lymphoma subtypes. These indicators will provide valuable information to monitor survival at a population level and to evaluate national cancer plans.

## Author contribution

Study conception: RMG, MS
Acquisition of data: RMG, CAS, JMR
Data analysis: AV
Manuscript writing: MS, AV
Critical review of the article and final approval: all authors

## Declaration of Competing Interest

None.

## CRediT authorship contribution statement

**Alicia Villavicencio:** Formal analysis, Writing - original draft. **Marta Solans:** Conceptualization, Methodology, Writing - original draft. **Carmen Auñon-Sanz:** Investigation, Writing - review & editing. **Josep Maria Roncero:** Investigation, Writing - review & editing. **Rafael Marcos-Gragera:** Conceptualization, Methodology, Resources, Supervision, Writing - review & editing.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2020.101841.

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## Supplementary material

**Table S1**. 5-year relative survival for patients with lymphoid neoplasms diagnosed in 1996-2015 in the Girona province according to sex.

| Subtype | Men | | Women | | P-value |
|---|---|---|---|---|---|
| | N | 5-year RS (95% CI) | N | 5-year RS (95% CI) | |
| **Lymphoid neoplasms, total** | **2463** | **61.2 (58.6; 63.9)** | **1831** | **63.7 (60.8; 66.8)** | **0.362** |
| **Hodgkin lymphoma** | **222** | **73.4 (66.8; 80.5)** | **140** | **78.1 (70.9; 86.1)** | **0.532** |
| **Precursor cell neoplasms** | **125** | **45.9 (37.8; 55.9)** | **81** | **47.2 (37.3; 59.7)** | **0.622** |
| **Mature B-cell neoplasms** | **1884** | **61.6 (58.6; 64.8)** | **1487** | **64.0 (60.6; 67.5)** | **0.449** |
| • Chronic lymphocytic leukemia/small lymphocytic lymphoma | 438 | 81.4 (74.9; 88.4) | 308 | 83.2 (75.3; 91.9) | 0.993 |
| • Mantel cell lymphoma | 83 | 55.5 (41.7; 71.2) | 22 | 36.0 (18.9; 68.6) | 0.996 |
| • Lymphoplasmacytic lymphoma/ Waldenström's Macroglobulinemia | 80 | 66.2 (52.2; 83.9) | 46 | 65.1 (47.9; 88.4) | 0.187 |
| • Diffuse large B-cell lymphoma | 402 | 49.2 (43.4; 55.7) | 328 | 49.5 (43.5; 56.4) | 0.707 |
| • Burkitt lymphoma/leukemia | 39 | 47.3 (33.8; 66.1) | 21 | 55.7 (38.0; 81.6) | 0.479 |
| • Marginal zone lymphoma | 167 | 79.3 (69.6; 90.3) | 172 | 85.0 (7.1; 93.8) | 0.763 |
| • Follicular lymphoma | 222 | 72.3 (64.9; 80.7) | 217 | 77.7 (69.1; 87.3) | 0.969 |
| • Plasma cell neoplasms | 423 | 39.0 (33.2; 45.8) | 367 | 43.5 (37.6; 50.3) | 0.354 |
| **Mature T/NK-cell neoplasms** | **184** | **63.6 (54.8; 73.8)** | **77** | **68.7 (56.3; 83.8)** | **0.161** |
| **Lymphoid neoplasms, NOS** | **48** | **20.5 (10.5; 40.1)** | **46** | **33.0 (17.7; 61.6)** | **0.771** |

RS, relative survival; p-value indicates p-value of log-rank test.

**Table S2**: 5-year relative survival for patients with lymphoid neoplasms diagnosed in 1996-2015 in the Girona province, according to age-group.

| Subtype | 0-14 years | | 15-49 years | | 50-69 years | | 70 years or more | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | N | 5-year RS (95% CI) | N | 5-year RS (95% CI) | N | 5-year RS (95% CI) | N | 5-year RS (95% CI) | |
| **Lymphoid neoplasms, total** | **110** | **91.3 (86.0; 97.0)** | **812** | **76.0 (72.9; 79.2)** | **1469** | **68.9 (66.1; 71.7)** | **1903** | **49.9 (46.5; 53.5)** | **<0.0001** |
| **Hodgkin lymphoma** | **14** | **91.7 (77.9; 108.0)** | **229** | **88.3 (83.9; 92.9)** | **61** | **62.3 (50.0; 77.6)** | **58** | **30.9 (19.0; 50.1)** | **<0.001** |
| **Precursor cell neoplasms** | **76** | **90.7 (84.2; 97.5)** | **61** | **33.2 (23.3; 47.5)** | **34** | **8.4 (2.7; 26.0)** | **35** | **7.1 (2.1; 24.0)** | **<0.0001** |
| **Mature B-cell neoplasms** | **16** | **92.4 (79.5; 107.5)** | **457** | **77.3 (73.3; 81.6)** | **1254** | **72.1 (69.2; 75.2)** | **1644** | **51.3 (47.7; 55.2)** | **<0.0001** |
| • Chronic lymphocytic leukemia/small lymphocytic lymphoma | 0 | - | 34 | 95.0 (87.0; 103.6) | 279 | 89.0 (84.0; 94.3) | 433 | 76.9 (69.1; 85.5) | 0.043 |
| • Mantel cell lymphoma | 0 | - | 13 | 59.7 (36.1; 98.9) | 46 | 67.0 (52.4; 85.7) | 46 | 35.2 (21.0; 58.9) | 0.522 |
| • Lymphoplasmacytic lymphoma/ Waldenström's Macroglobulinemia | 0 | - | 7 | 101.0 (101.0; 101.0) | 40 | 82.7 (69.1; 99.0) | 79 | 55.9 (41.4; 75.6) | 0.009 |
| • Diffuse large B-cell lymphoma | 3 | - | 162 | 66.4 (59.1; 74.5) | 251 | 59.5 (53.0; 66.8) | 314 | 31.7 (25.1; 39.9) | <0.0001 |
| • Burkitt lymphoma/leukemia | 13 | 90.1 (74.1; 109.6) | 28 | 53.9 (38.5; 75.4) | 14 | 27.0 (11.9; 61.2) | 5 | - | 0.001 |
| • Marginal zone lymphoma | 0 | - | 54 | 93.2 (86.0; 101.0) | 129 | 87.0 (79.7; 95.0) | 156 | 74.7 (63.5; 87.9) | 0.048 |
| • Follicular lymphoma | 0 | - | 98 | 87.9 (80.9; 95.4) | 207 | 82.7 (76.3; 89.7) | 134 | 54.9 (42.3; 71.1) | 0.019 |
| • Plasma cell neoplasms | 0 | - | 50 | 73.7 (61.5; 88.3) | 276 | 52.6 (46.3; 59.9) | 464 | 31.3 (25.7; 37.6) | <0.0001 |
| **Mature T/NK-cell neoplasms** | **4** | **100.0 (100.0; 100.0)** | **56** | **75.0 (63.7; 88.3)** | **96** | **57.9 (47.5; 70.6)** | **105** | **63.7 (51.2; 79.1)** | **<0.0001** |
| **Lymphoid neoplasms, NOS** | **0** | **-** | **9** | **-** | **24** | **42.3 (26.2; 68.1)** | **61** | **22.8 (11.4; 45.7)** | **0.010** |

RS, relative survival; p-value indicates p-value of log-rank test.

**Table S3**: 5-year relative survival for patients with lymphoid neoplasms diagnosed in 1996-2015 in the Girona province, according to period of diagnosis.

| Subtype | 1996-2002 | | 2003-2008 | | 2009-2015 | | P-value |
|---|---|---|---|---|---|---|---|
| | N | 5-year RS (95% CI) | N | 5-year RS (95% CI) | N | 5-year RS (95% CI) | |
| **Lymphoid neoplasms, total** | **1220** | **56.5 (53.1; 60.0)** | **1385** | **64.8 (61.7; 68.2)** | **1689** | **65.6 (62.0; 69.5)** | **0.016** |
| **Hodgkin lymphoma** | **105** | **73.1 (64.3; 83.2)** | **107** | **78.2 (70.2; 87.0)** | **150** | **74.0 (65.6; 83.5)** | **0.408** |
| **Precursor cell neoplasms** | **59** | **38.2 (27.6; 52.8)** | **69** | **50.8 (40.2; 64.2)** | **78** | **49.4 (39.0; 62.4)** | **0.696** |
| **Mature B-cell neoplasms** | **950** | **55.6 (51.8; 59.7)** | **1083** | **65.1 (61.4; 69.0)** | **1338** | **67.1 (62.8; 71.7)** | **0.008** |
| • Chronic lymphocytic leukemia/small lymphocytic lymphoma | 209 | 75.9 (67.4; 85.5) | 254 | 88.0 (80.4; 96.4) | 283 | 81.3 (70.8; 93.4) | 0.829 |
| • Mantel cell lymphoma | 31 | 42.5 (26.2; 68.9) | 27 | 36.6 (21.5; 62.2) | 47 | 67.7 (49.2; 93.1) | 0.046 |
| • Lymphoplasmacytic lymphoma/ Waldenström's Macroglobulinemia | 34 | 61.4 (42.9; 88.0) | 37 | 60.8 (43.4; 85.1) | 55 | 78.3 (60.8; 100.9) | 0.795 |
| • Diffuse large B-cell lymphoma | 209 | 42.0 (35.1; 50.2) | 233 | 52.1 (45.3; 59.8) | 288 | 54.3 (46.2; 63.9) | 0.124 |
| • Burkitt lymphoma/leukemia | 23 | 34.8 (20.4; 59.7) | 18 | 60.7 (42.4; 86.8) | 19 | 58.7 (39.3; 87.7) | 0.329 |
| • Marginal zone lymphoma | 98 | 80.9 (70.8; 92.5) | 101 | 85.1 (74.9; 96.7) | 140 | 78.6 (65.7; 93.9) | 0.769 |
| • Follicular lymphoma | 117 | 59.7 (50.5; 70.5) | 151 | 77.2 (67.9; 87.7) | 171 | 89.5 (80.8; 99.3) | 0.006 |
| • Plasma cell neoplasms | 221 | 36.4 (29.6; 44.8) | 247 | 39.6 (32.9; 47.8) | 322 | 47.5 (40.1; 56.4) | 0.198 |
| **Mature T/NK-cell neoplasms** | **70** | **70.2 (57.8; 85.3)** | **94** | **65.4 (54.3; 78.9)** | **97** | **58.4 (45.5; 75.0)** | **0.291** |
| **Lymphoid neoplasms, NOS** | **36** | **28.1 (13.1; 60.5)** | **32** | **31.8 (17.8; 56.8)** | **26** | **15.0 (5.9; 38.4)** | **0.358** |

RS, relative survival; p-value indicates p-value of log-rank test.

## 5.2 Paper II

### Comorbidities at Diagnosis, Survival, and Cause of Death in Patients with Chronic Lymphocytic Leukemia: A Population-Based Study

Villavicencio A, Solans M, Zacarías-Pons L, Vidal A, Puigdemont M, Roncero JM, Saez M, Marcos-Gragera R.

International Journal of Environmental Research and Public Health. 2021,18(2):701. doi: 10.3390/ijerph18020701.

**Box 2** | Overview of paper II

**What is already known on this subject**

- CLL typically occurs in patients with advanced ages which are prone to present comorbidites at diagnosis.
- Overall survival of cancer populations decreases as the burden of co-morbid diseases increases, but the impact of comorbidities on CLL outcomes remains less explored.

**What this study adds**

- This population-based study is one of the few to explore the role of comorbidities on mortality in patients with CLL in a real-world setting, considering the specific cause of death.
- The use of the CCI score shows the impact that comorbidities have on adverse outcomes in CLL, which may contribute to better define the optimal treatment of CLL patients, mainly those elderly patients with comorbidity.

International Journal of
*Environmental Research and Public Health*

MDPI

*Article*

# Comorbidities at Diagnosis, Survival, and Cause of Death in Patients with Chronic Lymphocytic Leukemia: A Population-Based Study

**Alicia Villavicencio [1,2,3,*], Marta Solans [2,3,4], Lluís Zacarías-Pons [5], Anna Vidal [1,3], Montse Puigdemont [1,3], Josep Maria Roncero [6], Marc Saez [2,4] and Rafael Marcos-Gragera [1,2,3,4,7]**

1 Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Catalan Institute of Oncology, Carrer del Sol 15, 17004 Girona, Spain; marianna.vidal@iconcologia.net (A.V.); mpuigdemont@iconcologia.net (M.P.); rmarcos@iconcologia.net (R.M.-G.)
2 Research Group on Statistics, Econometrics and Health (GRECS), University of Girona, C/Universitat de Girona 10, 17003 Girona, Spain; marta.solans@udg.edu (M.S.); marc.saez@udg.edu (M.S.)
3 Descriptive Epidemiology, Genetics and Cancer Prevention Group, Biomedical Research Institute (IDIBGI), 17190 Girona, Spain
4 Centro de Investigación Biomédica en Red: Epidemiología y Salud Pública (CIBERESP), Av. Monforte de Lemos 3-5, 28029 Madrid, Spain
5 Research Group on Aging, Disability and Health, Girona Biomedical Research Institute (IDIBGI), 17190 Girona, Spain; lzacarias@idibgi.org
6 Hematological Service, Josep Trueta University Hospital, Catalan Institute of Oncology, Avinguda de França, S/N, 17007 Girona, Spain; jroncero@iconcologia.net
7 Josep Carreras Leukemia Research Institute, 08916 Badalona, Spain
* Correspondence: alicia.villavicencio@udg.edu



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**Abstract:** This study aimed to examine the prevalence of comorbidities in patients diagnosed with chronic lymphocytic leukemia (CLL), and to assess its influence on survival and cause-specific mortality at a population-based level. Incident CLL cases diagnosed in the Girona province (Spain) during 2008–2016 were extracted from the Girona Cancer Registry. Rai stage and presence of comorbidities at diagnosis, further categorized using the Charlson comorbidity index (CCI), were obtained from clinical records. Observed (OS) and relative survival (RS) were estimated and Cox's proportional hazard models were used to explore the impact of comorbidity on mortality. Among the 400 cases included in the study, 380 (99.5%) presented at least one comorbidity at CLL diagnosis, with diabetes without end organ damage (21%) being the most common disease. 5-year OS and RS were 68.8 (95% CI: 64.4–73.6) and 99.5 (95% CI 3.13–106.0), respectively, which decreased markedly with increasing CCI, particularly in patients with CCI $\geq$ 3. Multivariate analysis identified no statistically significant association between the CCI and overall CLL-related or CLL-unrelated mortality. In conclusion, a high CCI score negatively influenced the OS and RS of CLL patients, yet its effect on mortality was statistically non-significant when also considering age and the Rai stage.

**Keywords:** chronic lymphocytic leukemia; comorbidities; causes of death; survival; population-based

## 1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries, with an incidence of 3.79 [1] and a 5-year relative survival (RS) of 69 years (95% confidence interval (CI):68.1; 69.8) [2], in 2006–2008 in Europe. Although CLL is often classified as an indolent disease with a relatively good prognosis, it has an unpredictable clinical course and can become resistant to conventional treatments. Despite recent progress in its management, this disease remains incurable, and patients with CLL still have a reduced life expectancy as compared to the general population [3].

CLL typically occurs in advanced ages (its median age at diagnosis is >70 years) [1,4]. Elderly patients are often compromised by concurrent pathological conditions [5], and

particularly in cancer, comorbidities are a significant concern (i.e., they preclude some treatments or are a competing cause of death) [6]. Indeed, cumulative evidence reflects that the overall survival of cancer populations decreases as the burden of comorbid diseases increases [7]. The impact of comorbidities on CLL outcomes, however, remains less explored. Several studies assessed the impact of comorbidities on CLL survival/mortality [8–15] and treatment tolerance or feasibility [10,16–18]. However, few include population-based data [12,15,19], and thus, there is a lack of real-word data addressing CLL outcomes in comorbid patients, especially when considering the specific causes of death.

Therefore, the aim of this study was to examine the prevalence of comorbidities and their influence on survival and mortality (overall and CLL-related or CLL-unrelated) of patients diagnosed with CLL, in the province of Girona (Spain), during 2008–2016.

## 2. Materials and Methods

### *2.1. Study Population*

Incident CLL cases diagnosed during the period of 2008–2016 were extracted from the population-based Girona Cancer Registry (GCR). The GCR is located in the Northeast of Catalonia, in Spain, covering a population of 739,607 inhabitants in 2016. Following WHO recommendations, CLL and small lymphocytic lymphoma (SLL) cases were classified together, since both share clinical and pathological features [20]. We excluded death certificate only (DCOs) and those cases diagnosed at autopsy.

### *2.2. Comorbidity Assessment*

Data on the Rai stage, indicating severity of CLL and comorbidities present at diagnosis were retrospectively obtained by reviewing the medical records. Comorbidities were assigned to one of the following categories—acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, peptic ulcer, mild liver disease, mild/moderate diabetes, diabetes with chronic complications, hemiplegia/paraplegia, kidney disease, malignant tumors, moderate/serious liver disease, metastatic tumor, and AIDs [14]. The Charlson comorbidity index (CCI) [21,22] was calculated for each patient, based on the health conditions present at the time of diagnosis. The CCI is a prognostic tool based on the principle that age and the presence and severity of comorbidities increase the likelihood of mortality among patients who receive treatment for chronic illnesses. Based on their CCI scores, patients were grouped into five groups (i.e., absence of comorbidity (0), low risk (1–2), moderate risk (3), high risk (>4), and unknown CCI status).

### *2.3. Survival and Mortality Data*

Patients were followed up until death or last follow-up date (31 December 2019), whichever came first. Data on the vital status of patients were obtained by linking records to the Catalan Registry of Mortality and the National Death Index [23]. Mid-year population estimates and mortality rates in the Girona province were obtained from the Institut d'Estadística de Catalunya, IDESCAT [24].

In our region, the cause of death was initially determined by the treating physician, based on the available clinical information, and sometimes on autopsy reports. This information was then transferred to the Catalan Registry of Mortality Data [25], which was responsible for coding the underlying causes of death (basic cause of death), following the guidelines of the International Classification of Diseases, 10th edition (CIE-10-ES) [26]. In our study, causes of death were categorized into CLL-related (including all hematological malignancies) and CLL-unrelated death (Supplementary Table S1). Those patients with unknown cause of death ($n = 13$) were excluded for both the CLL-related and CLL-unrelated survival analyses.

### 2.4. Statistical Analysis

Descriptive statistics were used to summarize the baseline clinical characteristics, overall and by the CCI score and cause of death. Differences in the clinical characteristics by CCI score and cause of death were assessed by the chi-square test. Observed survival (OS) was modelled using the Kaplan-Meier method. The relative survival (RS) rates were estimated using the Pohar–Perme method [27] as the ratio of observed survival in the study population, to expected survival in the general population of the same age, sex, year, and province (Girona) [28]. Expected survival rates were taken from the life tables for the population covered by the GCR. Comparison of OS and RS curves were performed using a log-rank type test [29]. To assess the effect of CCI score after adjusting for other covariates (gender, age, Rai stage, and period of diagnosis), multifactor Cox proportional hazards models were constructed, and a Wald test was used. The adjusted hazard ratios of death (HR) and the corresponding 95% confidence intervals (95% CI) were estimated. For all analyses, a $p$-value <0.05 was considered to be significant. All analyses were performed using the free software R (RStudio version 1.1.463) (Free Software Foundation, Inc., Boston, MA, USA).

## 3. Results

### 3.1. Prevalence of Comorbidity

A total of 400 incident CLL with a median follow-up time of 5.2 years were included in the study. Clinical characteristics of patients at diagnosis, overall and by CCI score, are detailed in Table 1. Median age at diagnosis was 72 years (interquartile range, 60–80 years); there were 230 (57.5%) males, and most patients (56.7%) had early stage CLL (Rai stage 0) at diagnosis. As expected, patients with higher CCI score were older and more prone to be diagnosed with advanced Rai stages, while we did not find differences according to sex or period of diagnosis. Except for 20 patients (0.5%), the population studied presented at least one comorbidity at the time of diagnosis (Table 1). Among the comorbid patients, the CCI score was low (1–2) in 86 (21.5%), moderate (3–4) in 151 (37.7%), high (>4) in 118 (29.5%), and unknown in 25 (6.2%).

**Table 1.** Distribution of baseline characteristics of chronic lymphocytic leukemia patients according to the Charlson comorbidity index score.

| Clinical Characteristics | Total | Charlson Comorbidity Index (CCI) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Absence of Comorbidity | Low Risk | Moderate Risk | High Risk | Unknown | |
| | | 0 | 1–2 | 3–4 | >4 | | $p$-Value |
| | *n* (%) a | *n* (%) a | *n* (%) a | *n* (%) a | *n* (%) a | *n* (%) a | |
| **Total** | 400 (100.0) | 20 (5.0) | 86 (21.5) | 151 (37.7) | 118 (29.5) | 25 (6.2) | |
| **Age** | | | | | | | |
| Mean (SD) | 70.8 (12.2) | 43.6 (5.5) | 59.41(5.6) | 73.11 (7.2) | 80.58 (7.7) | 70.96 (11.8) | <0.001 |
| Median (Range) | 72 (62–80) | 46 (39.7–48) | 59 (55–63.7) | 74 (69–78) | 83 (75.2–86) | 69 (60–79) | |
| **Gender** | | | | | | | |
| Male | 230 (57.5) | 9 (45.0) | 46 (53.5) | 84 (55.6) | 74 (62.7) | 17 (68.0) | 0.342 |
| Female | 170 (42.5) | 11 (55.0) | 40 (46.5) | 67 (44.4) | 44 (37.3) | 8 (32.0) | |
| **Age group** | | | | | | | |
| <65 | 122 (30.5) | 20 (100.0) | 65 (75.6) | 22 (14.6) | 5 (4.2) | 10 (40.0) | <0.001 |
| 65–78 | 158 (39.5) | - | 21 (24.4) | 97 (64.2) | 32 (27.1) | 8 (32.0) | |
| >78 | 120 (30.0) | - | - | 32 (21.2) | 81 (68.6) | 7 (28.0) | |
| **Rai stage** | | | | | | | |
| 0 | 227 (56.7) | 12 (60.0) | 57 (66.3) | 85 (56.3) | 68 (57.6) | 5 (20.0) | <0.001 |
| I-II | 60 (15.0) | 5 (25.0) | 15 (17.4) | 29 (19.2) | 11 (9.3) | - | |
| III-IV | 35 (8.7) | 2 (10.0) | 6 (7.0) | 12 (7.9) | 15 (12.7) | - | |
| Unknown | 78 (19.5) | 1 (5.0) | 8 (9.3) | 25 (16.6) | 24 (20.3) | 20 (80.0) | |
| **Period of diagnostic** | | | | | | | |
| 2008–2010 | 141 (35.2) | 6 (30.0) | 27 (31.4) | 54 (35.8) | 45 (38.1) | 9 (36.0) | 0.320 |
| 2011–2013 | 136 (34.0) | 12 (60.0) | 27 (31.4) | 51 (33.8) | 37 (31.4) | 9 (36.0) | |
| 2014–2016 | 123 (30.7) | 2 (10.0) | 32 (37.2) | 46 (30.5) | 36 (30.5) | 7 (28.0) | |

a Except when specified.

At diagnosis, 21% patients had diabetes, 18% had congestive heart failure, and 11% of patients had malignant tumors and chronic lung disease. Figure 1 shows the prevalence of comorbidities by sex. In general, diabetes without end-organ damage, congestive heart failure, cancer, chronic lung disease, and dementia were the most frequent comorbidities, being more predominant in men (except for dementia, which was more frequent in women). Additionally, in our cohort, 5 (1.25%) patients with CLL progressed to aggressive lymphoma (Richter syndrome).

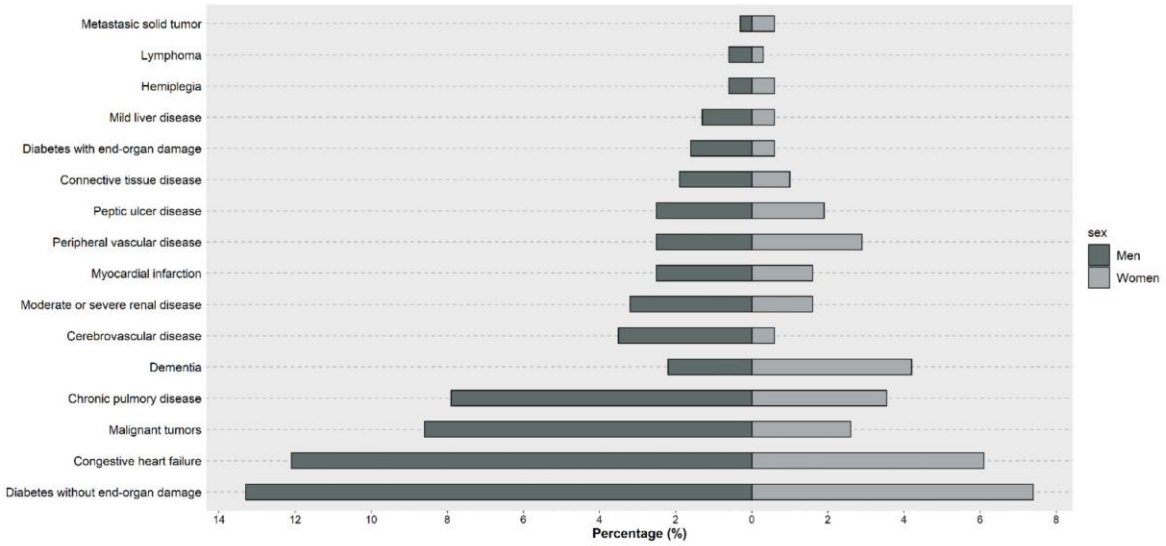


**Figure 1.** Frequency by sex of comorbidities included in the Charlson comorbidity index among patients with chronic lymphocytic leukemia in Girona, Spain ($n$ = 400).

### *3.2. Comorbidity and Survival*

1, 3, and 5-year OS and RS survival of CLL patients, according to the CCI is displayed in Table 2. Overall, 5-year OS and RS were 68.8 (95% CI: 64.6–73.6) and 99.5 (95% CI: 93.6–106.0), respectively. Survival estimates decreased markedly with increasing CCI scores, particularly in patients with 3 or more comorbidities.

**Table 2.** Observed and relative survival of chronic lymphocytic leukemia patients according to the Charlson comorbidity index at diagnosis in Girona, 2008–2016.

| CCI Core | 1-Year | | 3-Years | | 5-Years | |
|---|---|---|---|---|---|---|
| | **OS (95% CI)** | **RS (95% CI)** | **OS (95% CI)** | **RS (95% CI)** | **OS (95% CI)** | **RS (95% CI)** |
| 0 | 100.0 (100.0–100.0) | 100.0 (100.0–100.0) | 100.0 (100.0–100.0) | 100.0 (100.0–100.0) | 94.7 (85.2; 100.0) | 95.4 (86.1; 106.0) |
| 1–2 | 100.0 (100.0–100.0) | 100.0 (100.0–100.0) | 97.7 (94.5; 100.0) | 99.7 (96.5; 103.0) | 95.1 (90.4; 99.9) | 98.8 (94.0; 104.0) |
| 3–4 | 94.0 (90.3; 97.9) | 96.5 (92.7; 100.5) | 80.8 (74.7; 87.3) | 88.1 (81.2; 95.6) | 70.7 (63.7; 78.5) | 82.9 (73.5; 93.4) |
| >4 | 83.0 (76.5; 90.1) | 89.3 (82.3; 96.9) | 64.4 56.3; 73.6) | 82.2 (71.6; 94.3) | 47.2 (38.7; 57.5) | 72.2 (57.7; 90.5) |
| Unknown | 76.6 (61.0; 94.7) | 81.2 (66.1; 99.9) | 56.0 (39.6; 79.3) | 62.6 (44.1; 88.7) | 47.0 (30.7; 71.9) | 52.7 (33.8; 82.3) |
| Overall | 91.2 (88.5; 94.1) | 104.0 (104.0–104.0) | 79.0 (75.1; 83.1) | 113.0 (113.0–113.0) | 68.8 (64.4; 73.6) | 99.5 (93.6; 106.0) |

CCI—Charlson comorbidity index; OS—observed survival; RS—relative survival; 95% CI, 95% confidence interval.

Figure 2 further depicts these differences among the OS curves ($p$-value of log rank test <0.001; also for RS survival curves—data not shown).

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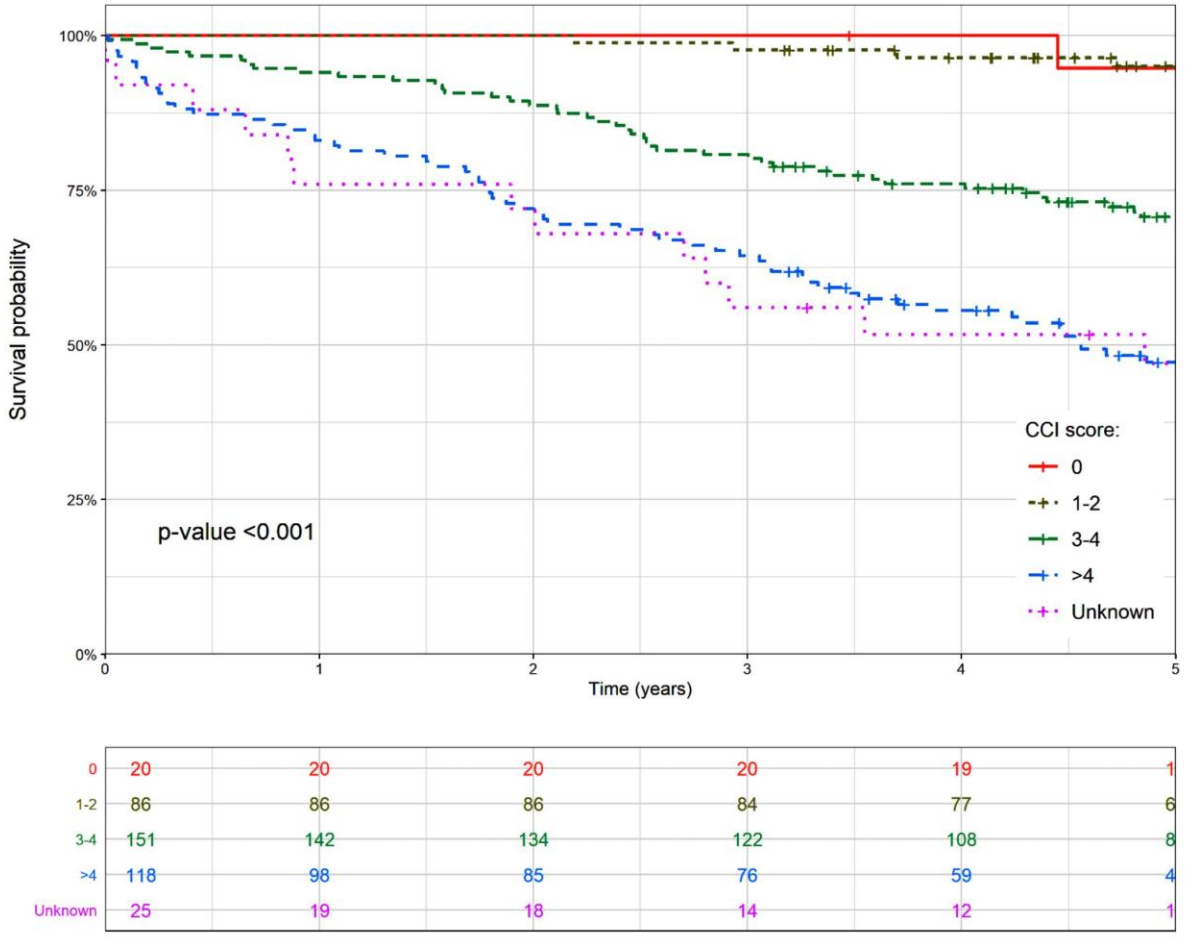


**Figure 2.** Observed survival of patients with chronic lymphocytic leukemia by the Charlson comorbidity index at diagnosis. Events included both types of death, CLL-related and CLL-unrelated. The differences between the survival curves that had a *p*-value <0.05 were considered to be statistically significant.

### *3.3. Comorbidity and Mortality*

Among the 168 patients that died during the follow-up, the cause of death could be accurately determined in 155 (92.2%), 86 (55.5%) being CLL-related (Supplementary Table S1). The distribution of clinical features according to the causes of death is shown in Supplementary Table S2. No statistically significant differences were observed according to CCI, age, sex, Rai stage, or period of diagnosis. Table 3 examines the relationship between the CCI score and other clinical variables with mortality. On univariate analysis, a higher CCI score was associated with higher overall mortality (HR: 5.82; 95% CI: 1.44–23.49), but not with CLL-related (HR: 1.28; 95% CI: 0.17–9.18) or and CLL-unrelated (HR: 2.83; 95% CI: 0.39–20.72) mortality. On multivariate analysis, after adjusting for age, sex, Rai stage, and period of diagnosis, a higher CCI score was not associated with a higher overall mortality (HR: 2.05; 95% CI: 0.47–8.90) and CLL-related mortality (HR: 0.62; 95% CI: 0.07–5.30).

**Table 3.** Univariate and multivariate analysis of mortality (overall, CLL-related, and CLL-unrelated) in patients with chronic lymphocytic leukemia in Girona (2008–2016).

| Variable | | | Univariate Analysis | | | | | | Multivariate Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | | Overall Mortality (*n* = 400) | | CLL-Related Mortality (*n* = 86) | | CLL-Unrelated Mortality (*n* = 69) | | Overall Mortality (*n* = 400) | | CLL-Related Mortality (*n* = 86) | | Unrelated to CLL Mortality (*n* = 69) | |
| | | | HR (95% CI) | *p*-Value | HR (95% CI) | *p*-Value | HR (95% CI) | *p*-Value | HR (95% CI) | *p*-Value | HR (95% CI) | *p*-Value | HR (95% CI) | *p*-Value |
| **Sex** | Female | 170 | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| | Male | 230 | 1.28 (0.94; 1.75) | 0.118 | 0.85 (0.54–1.31) | 0.457 | 1.11 (0.68–1.81) | 0.680 | 1.38 (1.01; 1.90) | 0.042 | 0.81 (0.47; 1.39) | 0.447 | 1.18 (0.70–2.01) | 0.529 |
| **Age (y)** | <65 | 122 | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| | 65–78 | 158 | 8.45 (5.18; 13.78) | <0.001 | 2.53 (1.17–5.46) | 0.018 | 1.42 (0.60–3.34) | 0.426 | 2.72 (1.59; 4.66) | <0.001 | 2.16 (0.92;5.09) | 0.078 | 1.54 (0.57–4.16) | 0.391 |
| | >78 | 120 | 2.75 (1.65; 4.58) | <0.001 | 2.78 (1.34–5.78) | 0.006 | 1.37 (0.60–3.15) | 0.455 | 9.96 (5.86; 16.92) | <0.001 | 2.20 (0.94; 5.13) | 0.068 | 2.05 (0.76–5.51) | 0.157 |
| | p-trend [1] | | | <0.001 | | <0.001 | | 0.07 | | <0.001 | | 0.015 | | 0.396 |
| **Rai stage** | 0 | 227 | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| | I-II | 60 | 1.49 (0.97; 2.31) | 0.067 | 0.61 (0.34–1.09) | 0.094 | 0.66 (0.28–1.59) | 0.361 | 1.91 (1.23–2.96) | 0.004 | 0.75 (0.39; 1.41) | 0.366 | 1.13 (0.44–2.91) | 0.804 |
| | III-IV | 35 | 2.68 (1.68; 4.27) | <0.001 | 1.04 (0.55–1.97) | 0.901 | 1.83 (0.87-3.84) | 0.111 | 4.17 (2.56; 6.80) | <0.001 | 1.18 (0.57; 2.44) | 0.650 | 8.24 (3.26–20.83) | <0.001 |
| | Unknown | 78 | 2.17 (1.47; 3.18) | <0.001 | 1.70 (0.96–3.02) | 0.069 | 1.71 (0.95–3.06) | 0.072 | 1.95 (1.25; 3.04) | 0.003 | 1.82 (0.79; 4.22) | 0.159 | 1.56 (0.79–3.09) | 0.202 |
| | p-trend [1] | | | 0.002 | | 0.06 | | 0.2 | | <0.001 | | 0.428 | | <0.001 |
| **Period of diagnosis** | 2008–2010 | 141 | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| | 2011–2013 | 136 | 1.02 (0.73; 1.42) | 0.900 | 1.15 (0.72–1.84) | 0.567 | 2.77 (1.52–5.04) | <0.001 | 1.35 (0.96; 1.91) | 0.088 | 1.13 (0.66–1.95) | 0.651 | 3.71 (1.95–7.07) | <0.001 |
| | 2014–2016 | 123 | 0.50 (0.31; 0.81) | 0.004 | 1.80 (0.86–3.76) | 0.121 | 5.06 (2.33–10.98) | <0.001 | 0.65 (0.39; 1.07) | 0.092 | 1.04 (0.37–2.88) | 0.946 | 9.95 (4.10–24.12) | <0.001 |
| | p-trend [1] | | | 0.1 | | 0.08 | | 0.003 | | 0.765 | | 0.003 | | <0.001 |
| **CCI** | 0 | 20 | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| | ≥1 | 355 | 5.82 (1.44-23.49) | 0.013 | 1.28 (0.17–9.18) | 0.815 | 2.83 (0.39–20.72) | 0.305 | 2.05 (0.47–8.90) | 0.340 | 0.62 (0.07–5.30) | 0.660 | 8.67 (0.87–85.96) | 0.065 |
| | Unknown | 25 | 10.08 (2.30-44.42) | 0.002 | 1.81 (0.22–14.55) | 0.576 | 8.34 (0.89–78.36) | 0.063 | 4.11 (0.85–19.90) | 0.078 | 0.50 (0.05–5.20) | 0.560 | 68.08 (4.73–980.51) | 0.002 |
| **CCI continuous** | | 375 | 1.45 (1.34-1.57) | <0.001 | 1.19 (1.04–1.37) | 0.01 | 1.21 (1.05–1.39) | 0.01 | 1.16 (1.01–1.33) | 0.034 | 0.96 (0.77–1.20) | 0.717 | 1.27 (1.06–1.53) | 0.01 |

CLL—chronic lymphocytic leukemia; 95% CI, 95% confidence interval; CCI—Charlson comorbidity index; HR—hazard ratio. [1] *p*-value of the Cox proportional model fitted with the ordinal variable as continuous to test for the lineal trend (the unknown category was excluded from the calculation).

## 4. Discussion

This population-based study provides prevalence data of comorbidities in CLL patients and evaluates its impact, through the CCI score, on survival and mortality in the Girona province, over a period of 8 years. Our results indicate that almost all patients had, at least, one comorbidity at CLL diagnosis, and that the 5-year OS and RS decreased markedly with higher CCI scores, particularly with CCI $\geq 3$. However, in multivariate analysis, a higher CCI score was not related to an increased mortality (both overall, CLL-related, and CLL- unrelated).

The association between comorbidities and poorer outcomes in cancer patients is well established [7], yet specific data on CLL are scarce. To the best of our knowledge, two clinical trials [10,30], one prospective cohort [14], two population-based [12,15], two multicenter [11,31], and three hospital series [8,9,13] assessed the relationship between comorbidities at diagnosis and survival or mortality in CLL patients. In line with our results, most studies evidenced lower survival rates in patients with a higher level of comorbidities [8–10,12–14], yet there were mixed results regarding their independent effect on survival or mortality [10,12–14,30]. However, comparisons must be made with caution, especially because there were different study designs and settings. This could be evidenced when comparing the median age of study populations, which was lower ($\leq$65 years) in the clinical trials [10,30] or prospective cohorts [14]. This might have influenced the outcomes of patients, not only if different treatment patterns were used, but also if the prevalence and type of comorbidities at diagnostic varied within them. Nevertheless, most authors found, in line with our study, that the most frequent comorbidities at CLL diagnosis were diabetes mellitus, congestive heart failure, and chronic lung disease [8,10,15,30,32]. It is likely that a higher prevalence of diabetes mellitus is related to these patients having continuous check-ups and therefore the finding of CLL is incidental. Indeed, among the 65 patients with diabetes mellitus, 45 had a low Rai (0–1), which suggests that if these patients were under continuous control and follow-up, CLL could probably be diagnosed at an early stage.

To date, no comorbidity score was prospectively validated in CLL, and thus, there is a marked heterogeneity in the study methodology when assessing comorbidities in such patients. For instance, different range of disease codes were considered, different scales or scoring systems were used (i.e., number of comorbidities [8,15,30] vs. CCI [10,14] vs. Cumulative Illness Rating Scale [9,11–13,31]), and within the CCI, different diseases codes were included and final score groupings were used. Overall, this reinforced the need to standardize the assessment of comorbidity in patients with CLL.

Our research is one of the few to explore the role of comorbidities on mortality in patients with CLL, considering the specific cause of death. Previous studies yielded mixed results, indicating that comorbidities might affect the overall mortality [10,12–14], CLL-related [10,15] and CLL-unrelated [14,30]. In our multivariate analysis, after adjusting for age and Rai stage, we did not find a statistically significant association between the CCI and mortality (overall or both when considering CLL-related or CLL-unrelated causes). However, our results must be interpreted with caution, since we might have been limited by sample size and, particularly, by death cause misclassification [33]. We relied on official data on the basic cause of death—and not the secondary cause of death [25]. Thus, we were unable to subclassify CLL-related mortality into more informative categories (e.g., disease progression, second primary cancer, infection, and other health conditions). In CLL-related causes, we included all hematological malignancies, suspecting misclassifications of CLL cases and treatment-related diseases. However, there might be some real secondary primary hematological malignancies that were wrongly located in CLL-related causes.

To date, several prognostic tools were developed to predict outcomes of CLL patients [34]. Among them, the CLL-IPI is prognostic index most widely used [35] that has been validated in an elderly population [36]. Although overall survival is currently undergoing significant changes with the introduction of novel agents [3], most still hold the potential to support clinical patient management. However, due to drug interactions

and a different side effect profile, specific comorbidities and comedication might have a larger impact on survival in the future [34]. Overall, further real-world data including clinical and treatment variables are warranted to deepen into the role of comorbidities on CLL outcomes, and to provide better-tailored prognostic tools for the comorbid and elderly populations.

Several limitations must be considered when interpreting our results, including the limited sample size and, particularly, potential misclassification or categorization of the underlying cause of death [33], as previously discussed. Similarly, clinical data were gathered from electronic health records, which cannot be assumed to provide complete, accurate, and standardized information of individual's health status. In addition, our study evaluated comorbid health conditions only at diagnosis; however, during follow-up, some patients might acquire new comorbid conditions or face a decline in their organ function. Furthermore, we lacked data on additional variables that could influence the prognosis, such as treatment patterns or the presence of several genetic or biochemical markers (e.g., TP53 dysfunction or a complex karyotype) [34]. Finally, race/ethnicity was not recorded in our study, which might also influence survival rates, as previously reported [37].

## 5. Conclusions

Pre-diagnostic comorbidities are extremely common in CLL patients. Survival estimates decrease markedly with higher CCI scores, especially in patients with a CCI score $\geq$3. However, comorbidities are less important than age and stage in predicting mortality (both CLL-related or CLL-unrelated) in newly diagnosed patients with CLL. These population-based data will provide insights into the relationship between comorbidities and CLL in a real-world setting. Prioritizing comorbid CLL patients in future clinical trials is warranted, to further inform treatment guidelines and improve outcomes for these patients.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/1660-4601/18/2/701/s1. Table S1: Specific cause of death by age group of patients with chronic lymphocytic leukemia in Girona, Spain. Table S2: Causes of death by reference characteristics in patients diagnosed with CLL.

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## Supplementary material

**Table S1.** Specific cause of death by age group of patients with chronic lymphocytic leukemia in Girona, Spain.

| Cause of death | ICD-10-ES code | Age group | | | |
|---|---|---|---|---|---|
| | | Total | <65 years | 65-78 years | >78 years |
| | | *n (%)* | *n (%)* | *n (%)* | *n (%)* |
| **All** | | **155 (100.0)** | **18 (11.6)** | **51 (32.9)** | **86 (55.5)** |
| **Hematological disease** | | **86 (55.5)** | **10 (55.5)** | **29 (56.8)** | **47 (54.6)** |
| • Non-Hodgkin's lymphoma, unspecified | C859 | 8 (5.2) | - | 4 (7.8) | 4 (4.7) |
| • Chronic lymphocytic leukemia/small | C911 | 25 (16.1) | 3 (16.7) | 10 (19.6) | 12 (14.0) |
| • Leukemia, unspecified | C959 | 4 (2.6) | - | - | 4 (4.7) |
| • Other lymphoid leukemias | C917 | 35 (22.6) | 4 (22.2) | 9 (17.6) | 22 (25.6) |
| • Lymphoid leukemia,unspecified | C919 | 3 (1.9) | - | 2 (3.9) | 1 (1.2) |
| • Acute leukemia, cells of unspecified type | C950 | 2 (1.3) | 2 (11.1) | - | - |
| • Myelodysplastic syndrome, unspecified | D469 | 1 (0.6) | 1 (5.6) | - | - |
| • Chronic leukemia of unspecified cell type | C951 | 2 (1.3) | - | 1 (2.0) | 1 (1.2) |
| • Myeloid Leukemia | C920 | 1 (0.6) | - | - | 1 (1.2) |
| • Other myeloid leukemias | C927 | 1 (0.6) | - | 1 (2.0) | - |
| • Small cell B-cell lymphoma | C830 | 2 (1.3) | - | 1 (2.0) | 1 (1.2) |
| • Unclassified peripheral T-cell lymphoma | C844 | 1 (0.6) | - | 1 (2.0) | - |
| • Uncertain behavioral neoplasm of lymphatic, hematopoietic and related tissue, unspecified | D479 | 1 (0.6) | - | - | 1 (1.2) |
| **Cardiovascular disease** | | **11 (7.1)** | **1 (5.6)** | **1 (2.0)** | **9 (10.5)** |
| • Atrial fibrillation and flutter | I48 | 3 (1.9) | - | - | 3 (3.5) |
| • Acute myocardial infarction, unspecified | I219 | 3 (1.9) | 1 (5.6) | 1 (2.0) | 1 (1.2) |
| • Dilated myocardiopathy | I420 | 1 (0.6) | - | - | 1 (1.2) |
| • Heart failure, unspecified | I509 | 1 (0.6) | - | - | 1 (1.2) |
| • Left ventricular failure, unspecified | I501 | 1 (0.6) | - | - | 1 (1.2) |
| • Chronic ischemic heart disease, unspecified | I259 | 1 (0.6) | - | - | 1 (1.2) |
| • Other Hypertrophic Cardiomyopathies | I422 | 1 (0.6) | - | - | 1 (1.2) |
| **Cerebrovascular disease** | | **6 (3.9)** | **1 (5.6)** | **2 (3.9)** | **3 (3.5)** |
| • Cerebral infarction due to cerebral | I634 | 1 (0.6) | 1 (5.6) | - | - |

| | | | | | |
|---|---|---|---|---|---|
| artery embolism | | | | | |
| • Cerebral infarction, unspecified | I639 | 3 (1.9) | - | - | 3 (3.5) |
| • Other specified cerebrovascular diseases | I678 | 2 (1.3) | - | 2 (3.9) | - |
| **Pulmonary disease** | | **12 (7.7)** | **-** | **3 (5.9)** | **9 (10.5)** |
| • Chronic respiratory insufficiency | J961 | 1 (0.6) | - | - | 1 (1.2) |
| • Unspecified respiratory failure | J969 | 1 (0.6) | - | - | 1 (1.2) |
| • Chronic obstructive pulmonary disease with acute lower respiratory tract infection | J440 | 1 (0.6) | - | 1 (2.0) | - |
| • Chronic obstructive pulmonary disease, unspecified | J449 | 3 (1.9) | - | 2 (3.9) | 1 (1.2) |
| • Diseases of the bronchi, not otherwise classified | J980 | 1 (0.6) | - | - | 1 (1.2) |
| • Streptococcus pneumoniae pneumonia | J13 | 1 (0.6) | - | - | 1 (1.2) |
| • Pneumonia, unspecified microorganism | J189 | 1 (0.6) | - | - | 1 (1.2) |
| • Other lung disorders | J984 | 1 (0.6) | - | - | 1 (1.2) |
| • Other specified respiratory disorders | J988 | 1 (0.6) | - | - | 1 (1.2) |
| • Influenza due to other types of flu viruses identified with other respiratory manifestations | J101 | 1 (0.6) | - | - | 1 (1.2) |
| **Renal disease** | | **3 (1.9)** | **-** | **1 (2.0)** | **2 (2.3)** |
| • Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end-stage renal disease | I120 | 1 (0.6) | - | - | 1 (1.2) |
| • Acute renal failure, unspecified | N179 | 1 (0.6) | - | 1 (2.0) | - |
| • Hypertensive chronic heart and kidney disease without heart failure | I131 | 1 (0.6) | - | - | 1 (1.2) |
| **Metabolic disease** | | **3 (1.9)** | **-** | **2 (3.9)** | **1 (1.2)** |
| • Diabetes Mellitus | E145 | 1 (0.6) | - | 1 (2.0) | - |
| • Diabetes Mellitus unspecified | E149 | 1 (0.6) | - | 1 (2.0) | - |
| • Chronic or unspecified duodenal ulcer with perforation | K265 | 1 (0.6) | - | - | 1 (1.2) |
| **Cognitive disease** | | **4 (2.6)** | **-** | **-** | **4 (4.6)** |
| • Unspecified dementia | F03 | 1 (0.6) | - | - | 1 (1.2) |
| • Late-onset Alzheimer's disease | G301 | 1 (0.6) | - | - | 1 (1.2) |
| • Alzheimer's disease, unspecified | G309 | 1 (0.6) | - | - | 1 (1.2) |
| • Epilepsy, type not specified | G409 | 1 (0.6) | - | - | 1 (1.2) |
| **Neoplasm** | | **19 (12.3)** | **4 (22.2)** | **10 (19.6)** | **5 (5.8)** |
| • Lung | C349 | 4 (2.6) | - | 3 (5.9) | 1 (1.2) |
| • Colon | C189 | 3 (1.9) | - | 3 (5.9) | - |

| | | | | | |
|---|---|---|---|---|---|
| • Lip, oral cavity and pharynx | D000 | 1 (0.6) | - | - | 1 (1.2) |
| • Location not specified | C809 | 1 (0.6) | - | - | 1 (1.2) |
| • Pancreas | C259 | 1 (0.6) | 1 (5.6) | - | - |
| • Prostate | C61 | 1 (0.6) | 1 (5.6) | - | - |
| • Kidney | C64 | 4 (2.6) | 1 (5.6) | 2 (3.9) | 1 (1.2) |
| • Thorax | C493 | 1 (0.6) | - | 1 (2.0) | - |
| • Uterus | C55 | 1 (0.6) | 1 (5.6) | - | - |
| • Uterus (endometrium) | C541 | 1 (0.6) | - | 1 (2.0) | - |
| • Bladder | C679 | 1 (0.6) | - | - | 1 (1.2) |
| **Other causes** | | **11 (7.1)** | **2 (11.1)** | **3 (5.9)** | **6 (7.0)** |
| • Liver abscess | K750 | 1 (0.6) | - | 1 (2.0) | - |
| • Acute appendicitis | K359 | 1 (0.6) | 1 (5.6) | - | - |
| • Atherosclerosis of native limb arteries | I702 | 1 (0.6) | - | - | 1 (1.2) |
| • Bleeding from anus and rectum | K625 | 1 (0.6) | - | - | 1 (1.2) |
| • Vascular bowel disorder, unspecified | K559 | 1 (0.6) | - | 1 (2.0) | - |
| • Essential (primary) hypertension | I10 | 1 (0.6) | - | 1 (2.0) | - |
| • Urinary tract infection, location not specified | N390 | 1 (0.6) | - | - | 1 (1.2) |
| • Pathological fracture, not otherwise classified | M844 | 1 (0.6) | - | - | 1 (1.2) |
| • Inhalation and ingestion of other objects that cause airway obstruction, in an unspecified location | W809 | 1 (0.6) | - | - | 1 (1.2) |
| • Pedestrian injured in traffic accident with other motorized and unspecified vehicles | V092 | 1 (0.6) | 1 (5.6) | - | - |
| • Poorly defined and unknown causes of mortality | R99 | 1 (0.6) | - | - | 1 (1.2) |

CIE-10-ES, Clasificación Internacional de Enfermedades-décima edición española.

**Table S2.** Causes of death by reference characteristics in patients diagnosed with CLL.

| Clinical features | Cause of death | | | |
|---|---|---|---|---|
| | Total | CLL-related | Unrelated to CLL | |
| | *n* (%)*a* | *n* (%)*a* | *n* (%)*a* | p-value |
| **All** | **155** | **86 (55.5)** | **69 (44.5)** | |
| **Age** | | | | |
| Mean (SD) | 77.5 (10.1) | 77.2 (10.3) | 78.0 (10.0) | 0.463 |
| Median (Range) | 79 (74-85) | 79 (72.2-84.7) | 80 (74-85) | |
| **Sex** | | | | |
| Male | 95 (61.3) | 54 (62.8) | 41 (59.4) | 0.669 |
| Female | 60 (38.7) | 32 (37.2) | 28 (40.6) | |
| **Age group** | | | | |
| <65 | 18 (11.6) | 10 (11.6) | 8 (11.6) | 0.969 |
| 65-78 | 51 (32.9) | 29 (33.7) | 22 (31.9) | |
| >78 | 86 (55.5) | 47 (54.7) | 39 (56.5) | |
| **Rai stage** | | | | |
| 0 | 67 (43.2) | 32 (37.2) | 35 (50.7) | 0.091 |
| I-II | 28 (18.1) | 21 (24.4) | 7 (10.1) | |
| III-IV | 23 (14.8) | 14 (16.3) | 9 (13.0) | |
| Unknown | 37 (23.9) | 19 (22.1) | 18 (26.1) | |
| **Period of diagnostic** | | | | |
| 2008-2010 | 76 (49.0) | 46 (53.5) | 30 (43.5) | 0.327 |
| 2011-2013 | 58 (37.4) | 31 (36.0) | 27 (39.1) | |
| 2014-2016 | 21 (13.5) | 9 (10.5) | 12 (17.4) | |
| **CCI score** | | | | |
| 0 | 2 (1.3) | 1 (1.2) | 1 (1.4) | 0.243 |
| 1-2 | 8 (5.2) | 7 (8.1) | 1 (1.4) | |
| 3-4 | 59 (38.1) | 34 (39.5) | 25 (36.2) | |
| >4 | 74 (47.7) | 36 (41.9) | 38 (55.1) | |
| Unknown | 12 (7.7) | 8 (9.3) | 4 (5.8) | |

*a* Except when specified; SD, standard deviation; CLL, Chronic lymphocytic leukemia; CCI, Charlson comorbidity index

# DISCUSSION

# 6. DISCUSSION

The research undertaken in this thesis aimed to assess the survival of LNs in the province of Girona, as well as the impact of comorbidities on survival and cause of death in patients with CLL. The following sections provide a global discussion of the main results, as well as their possible shortcomings and strengths.

## 6.1 Comparison with previous studies

### *6.1.1 Paper I: Survival of LNs*

One of the purposes of population-based cancer registries is to provide survival data for a particular pathology in order to understand its prognosis in a given population, as well as to assess the effects of treatments and to inform patients about their survival prospects. In this context, the first work of this thesis focused on estimating the 5-year survival probability of the main subtypes of LNs in the province of Girona according to the WHO 2008 classification. In addition, this study also analyzed survival data by sex, patient age at diagnosis and period of diagnosis.

The survival of LNs has been studied in several population-based and European-wide studies[12,16–21]. While proper registration of the various hematological lymphoid entities is the first step in the publication of good survival results, it is well recognized that this is often hampered by ongoing changes in LNs classification.

As it is well known, LNs are a heterogeneous group of cancers that present a prognosis according to the hematological entity. In this study, 5-year OS and RS for all LNs were 54.4% (95% CI: 52.8-56.0) and 62.3% (95% CI: 60.4-64.4), respectively. This was slightly lower than the probability reported in epidemiological studies reporting overall RS of LNs (**Figure 6**). However, this variation may be due in part to the difference depending on the regions studied as well as the study period considered in each investigation.

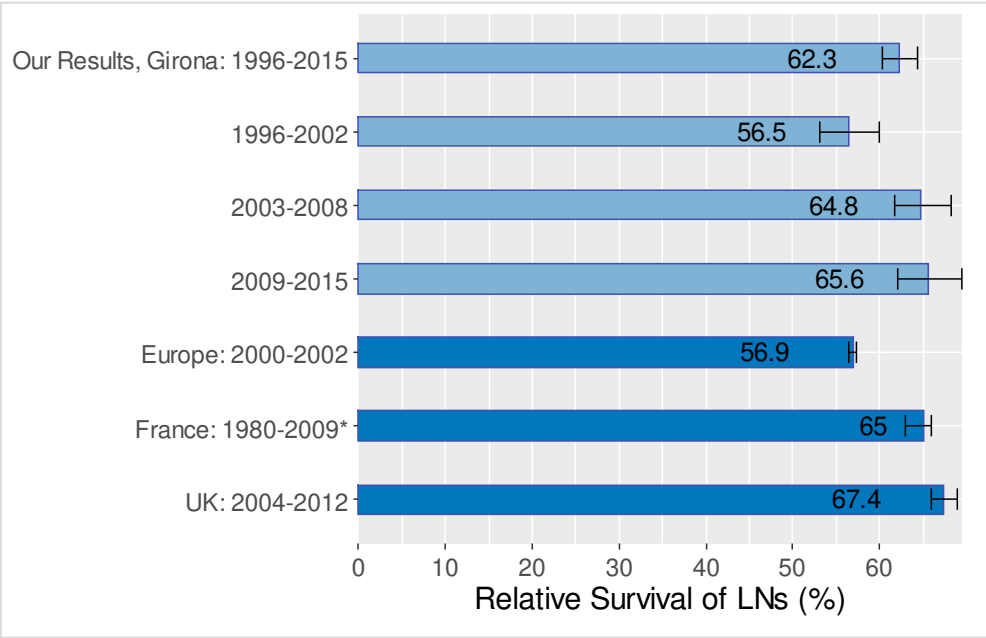


**Figure 6.** Five-year survival probability of overall lymphoid neoplasms.
Our Results (Girona: periods 1996-2015); Europe: 2000-2002[12]; France: 1980-2009[21]; UK: 2004-2012[20] (Source: own elaboration).
*Net survival

On the other hand, several published studies indicate that at the European level the 5-year RS of LNs varies according to subtype (**Table 5**). Thus, the entities with the worst survival correspond to precursor, PCN and peripheral T/NK-cell lymphoma (PTCL) with a 5-year survival of about 35-39%, 33-48% and 36-56% respectively, while on the contrary mycosis fungoides/Sezary syndrome (MF/SS), marginal zone lymphoma (MZL) and HL are the entities with the best survival, with a 5-year survival of about 79-93%, 77-91% and 78-85% respectively. In addition, some subtypes of LNs have intermediate 5-year survival such as FL and CLL/SLL with 67-87% and 68-82% respectively. Our results also show a variation of RS according to the different hematological entities. However, our study shows variations in survival probability of LNs in contrast to those reported by some authors.

**Table 5.** Five-year relative survival of lymphoid neoplasm subtypes from the different studies.

| Study | Hematological classification used | Subtype | 5-year RS (95% CI) |
|---|---|---|---|
| Europe: 2000-2002[12] | | | |
| | HAEMACARE (based on ICD-O-3 morphological codes and WHO 2001 recommendations) | -HL | 84.5 (83.2-85.7) |
| | | -CHL | 84.0 (82.8-85.3) |
| | | -NLPHL | 95.8 (91.4-100.0) |
| | | -CLL/SLL | 69.1 (67.7-70.5) |
| | | -DLBCL | 49.3 (47.8-50.6) |
| | | -PCN | 32.6 (31.5-33.7) |
| | | -FL | 72.8 (71.0-74.6) |
| | | -MCL | 43.8 (39.7-47.8) |
| | | -MZL | 81.4 (77.7-85.2) |
| | | -MF/SS | 83.4 (80.0-86.7) |
| | | -PTCL | 38.6 (35.2-41.9) |
| | | -HCL | 93.9 (90.1-97.7) |
| | | -T lymphoma cutaneous | 83.4 (80.0-86.7) |
| | | -NOS | 48.2 (46.9-49.6) |
| Europe: 2000-2007[17] | | | |
| | HAEMACARE (based on ICD-O-3 morphological codes and WHO 2001 recommendations) | -HL | 80.8 (80.2–81.5) |
| | | -Precursor | 39.4 (37.9–40.9) |
| | | -CLL/SLL | 70.4 (-) |
| | | -DLBCL | 51.4 (50.6-52.2) |
| | | -PCN | 39.2 (38.6–39.8) |
| | | -FL | 71.6 (70.2-73.1) |
| Europe: 1997-2008[16] | | | |
| | HAEMACARE (based on ICD-O-3 morphological codes and WHO 2008 recommendations) | -HL | ~ 78 (-) |
| | | -Precursor | ~35 (-) |
| | | -CLL/SLL | ~68 (-) |
| | | -DLBCL | ~48 (-) |
| | | -PCN | ~34 (-) |
| | | -FL | ~67 (-) |
| France: 1989-2004[19] | | | |
| | International Lymphoma Epidemiology Consortium (InterLymph) (based on ICD-O-3 morphological codes and WHO 2001 recommendations) | -CHL | 81 (80–83) |
| | | -Precursor | 35 (31–39) |
| | | -CLL/SLL | 78 (77– 80) |
| | | -DLBCL | 47 (45–49) |
| | | -PCN | 45 (43–46) |
| | | -FL | 70 (67–73) |
| | | -LPL/WM | 73 (70–76) |
| France: 1980-2009[21] * | | | |
| | InterLymph (based on ICD-O-3 morphological codes and WHO 2001 Recommendations) | -HL | 81 (76-85) |
| | | -Precursor | 58 (51-65) |
| | | -CLL/SLL | 80 (76-84) |
| | | -DLBCL | 51 (47-56) |
| | | -PCN | 42 (38-46) |
| | | -LPL/WM | 71 (64-79) |
| | | -HCL | 83 (72-95) |
| | | -BL | 66 (53-81) |
| | | -FL | 77 (72-82) |
| | | -MCL | 50 (38-66) |
| | | -MZL | 88 (80-97) |

| | | | |
|---|---|---|---|
| | | -MF/SS | 93 (84-103) |
| | | -PTCL | 41 (33-52) |
| | | -NOS | 49 (41-58) |
| **Study** | **Hematological classification used** | **Subtype** | **5-year RS (95% CI)** |
| US: 2005-2011[18] | | | |
| | ICD-O-3 morphological codes and WHO 2008 recommendations | -CLL/SLL | 69-82 (-) |
| | | -DLBCL | 55-62 (-) |
| | | -PCN | 44-48 (-) |
| | | -LPL/WM | 58-81 (-) |
| | | -HCL | 84-94 (-) |
| | | -BL | 47-63 (-) |
| | | -FL | 81-87 (-) |
| | | -MCL | 55-62 (-) |
| | | -MZL | 83-91 (-) |
| | | -MF/SS | 79-92 (-) |
| | | -PTCL | 36-56 (-) |
| UK: 2004-2012[20] | | | |
| | ICD-O-3 morphological codes and WHO 2008 recommendations | -HL | 84.9 (81.7–87.6) |
| | | -CHL | 82.5 (78.9–85.5) |
| | | -DLBCL | 54.8 (52.4–57.1) |
| | | -BL | 52.9 (42.4–62.4) |
| | | -FL | 86.5 (83.0–89.4) |
| | | -MCL | 31.4 (23.6–39.5) |
| | | -MZL | 77.2 (72.9–80.8) |
| | | -MF/SS | 86.6 (61.1–95.8) |
| Our results, Girona: | | | |
| 1996-2015 | | | |
| | HAEMACARE (based on ICD-O-3 morphological codes and WHO 2008 recommendations) | -HL | 75.3 (70.3–80.6) |
| | | -CHL | 73.9 (68.7–79.5) |
| | | -NLPHL | 91.0 (79.8–100.0) |
| | | -Precursor | 46.3 (39.8–53.9) |
| | | -CLL/SLL | 82.2 (77.1–87.7) |
| | | -DLBCL | 49.4 (45.1–54.0) |
| | | -PCN | 41.1 (36.9–45.9) |
| | | -LPL/WM | 66.4 (55.0–80.2) |
| | | -BL | 50.2 (38.8–65.0) |
| | | -FL | 75.1 (69.3–81.5) |
| | | -MCL | 50.7 (39.3–65.2) |
| | | -MZL | 82.3 (76.0–89.2) |
| | | -Other B-cell neoplasms | 91.0 (75.9–100.0) |
| | | -MF/SS | 88.5 (76.6–100.0) |
| | | -PTCL | 43.5 (34.3–55.0) |
| | | -Other mature T/NK-cell neoplasms | 80.8 (66.2–98.8) |
| | | -NOS | 26.3 (16.4–42.2) |
| 1996-2002 | | | |
| | | -HL | 73.1 (64.3-83.2) |
| | | -Precursor | 38.2 (27.6-52.8) |
| | | -CLL/SLL | 75.9 (67.4-85.5) |
| | | -DLBCL | 42.0 (35.1-50.2) |
| | | -PCN | 36.4 (29.6-44.8) |
| | | -LPL/WM | 61.4 (42.9-88.0) |
| | | -BL | 34.8 (20.4-59.7) |
| | | -FL | 59.7 (50.5-70.5) |
| | | -MCL | 42.5 (26.2-68.9) |
| | | -MZL | 80.9 (70.8-92.5) |
| | | -Mature T/NK-cell | 70.2 (57.8-85.3) |

| | | |
|---|---|---|
| | neoplasms | |
| | -NOS | 28.1 (13.1-60.5) |
| 2003-2008 | | |
| | -HL | 78.2 (70.2-87.0) |
| | -Precursor | 50.8 (40.2-64.2) |
| | -CLL/SLL | 88.0 (80.4-96.4) |
| | -DLBCL | 52.1 (45.3-59.8) |
| | -PCN | 39.6 (32.9-47.8) |
| | -LPL/WM | 60.8 (43.4-85.1) |
| | -BL | 60.7 (42.4-86.8) |
| | -FL | 77.2 (67.9-87.7) |
| | -MCL | 36.6 (21.5-62.2) |
| | -MZL | 85.1 (74.9-96.7) |
| | -Mature T/NK-cell neoplasms | 65.4 (54.3-78.9) |
| | -NOS | 31.8 (17.8-56.8) |
| 2009-2015 | | |
| | -HL | 74.0 (65.6-83.5) |
| | -Precursor | 49.4 (39.0-62.4) |
| | -CLL/SLL | 81.3 (70.8-93.4) |
| | -DLBCL | 54.3 (46.2-63.9) |
| | -PCN | 47.5 (40.1-56.4) |
| | -LPL/WM | 78.3 (60.8-100.9) |
| | -BL | 58.7 (39.3-87.7) |
| | -FL | 89.5 (80.8-99.3) |
| | -MCL | 67.7 (49.2-93.1) |
| | -MZL | 78.6 (65.7-93.9) |
| | -Mature T/NK-cell neoplasms | 58.4 (45.5-75.0) |
| | -NOS | 15.0 (5.9-38.4) |

**,* net survival; -, no data; RS, relative survival; 95% CI, 95% confidence interval; CHL, classical Hodgkin lymphoma; NLPHL, Nodular lymphocyte predominant Hodgkin lymphoma; HCL, hairy cell leukemia; LPL/WM, Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia; MCL, mantle cell lymphoma.

Data published by the HAEMACARE group[12], whose study was conducted between 1995-2002 with data from 41 cancer registries from 20 European countries and whose 5-year RS was calculated from cases registered in the period 2000-2002, provides data for several LNs based on sex, age and region. In the HAEMACARE publication most subtypes of LNs revealed much lower survival probability than those observed in our study, this variation was mainly observed in CLL/SLL, PCN and mantle cell lymphoma (MCL) whose 5-year RS probability were 69. 1% (95% CI: 67.7-70.5), 32.6 (95% CI: 31.5-33.7) and 43.8% (95% CI: 39.7-47.8) respectively, while in our study the survival probability of the mentioned entities were 82.2% (95% CI: 77.1-87.7), 41.1% (95% CI: 36.9-45.9) and 50.7% (95% CI: 39.3-65.2) respectively. However, HL has a better survival probability of 84.5%

(95% CI: 83.2-85.7) while our analysis shows a survival probability of 75.3% (95% CI: 70.3-80.6). Survival varies between the different regions of Europe and is similar in males (57.0%) and females (56.7%), although better survival was found in females than in males for CLL/SLL, results comparable to our analysis where there was no notable difference between males (61.2%) and females (63.7%) in the different subtypes. On the other hand, survival decreases with age and mainly after the age of 50 years, with a worse decrease in precursor cell neoplasms (decrease from 84.4% in patients younger than 14 years to 8.8% in patients older than 70 years), similar to our study where a decrease in survival was observed in most LNs (with the exception of MCL), including precursor cell neoplasms (with a decrease from 90.7% in patients younger than 14 years to 7.1% in patients older than 70 years). Analysis by study period was not performed so there is no data with which to compare our results.

The French network of cancer registries (FRANCIM)[19] in its study conducted between 1989-2004 with information on patients >15 years old from 16 cancer registries, reports survival probability s for haematological malignancies, including some subtypes of LNs. Like the HAEMACARE study, survival probability for haematological entities are lower than those in our study, with a lower 5-year RS for precursor cell neoplasms at 35% (95% CI: 31-39), while in contrast the 5-year RS for HL at 81% (95% CI: 80-83) is much better than that reported in our study. Regarding sex, females have better survival than males in several subtypes such as CLL/SLL (81% vs 76%), DLBCL (50% vs 45%), LPL/WM (77% vs 70%) and Mature T/NK-cell neoplasms (64% vs 57%), data that differ from those found in our analysis since no significant sex-related results were observed. As in our study, survival of LNs decreases with advancing age, and in this case from the age of 65 years onwards the decrease is more noticeable. FL went from 62% (95% CI: 54-70) in the period 1992-1994 to 77% (95% CI: 71-83) in 2001-2004, as did precursor B-cell lymphoblastic lymphoma/leukaemia from 22% (95% CI: 15-33) in 1989-1991 to 46% (95% CI: 37-56) in 2001-2004, results that are in agreement with those obtained in our study where an improvement in the RS of FL of 59. 7% (95% CI: 50.5; 70.5) in 1966-2002 to 89.5% (95% CI: 80.8; 99.3) in 2009-2015. The EUROCARE-5 studies (1997-2008[16] and 2000-2007[17]) also indicate variation

in survival as a function of sex, age, region and period of diagnosis, with low general survival probability for CLL/SLL (~68% and 70% respectively) and for precursor cell neoplasms (~35% and 39% respectively), while better survival is observed for HL (~78% and 81%). Worse survival is observed in Eastern Europe compared to the other European regions. As in the FRANCIM study, survival decreases with age and is higher in women in most of the NLs, being more marked in FL (74.3% vs. 60.8%). A significant increase is also observed throughout the study period (1997-1999 to 2006-2008) for all LNs. However, it is important to note that the FRANCIM and EUROCARE-5 studies use age-standardised RS, so we could not compare it with our results.

Another population-based study conducted in France in the period 1980-2009 including 4,790 cases of patients residing in the Department of Cote d'Or, provides survival by sex and by period of diagnosis and indicates an increase in net survival (NS) for all LNs over the study period[21]. This increase is most notable for MF/SS, MZL, HL and BL with survival probability of 93%, 88%, 81% and 66% respectively, which are better than those in our analysis. Females have a better survival than males (67% vs 63%) and depending on the period of diagnosis an increase in NS is observed for HL, CLL/SLL, FL, BL, PCN, LPL/ WM, HCL, MF/SS and precursor NHL.

Finally, the paper conducted by the UK's population-based Haematological Malignancy Research Network (HMRN)[20] with 5,796 cases registered during the period 2004-2012, indicates a better survival in most LNs mainly for HL, FL and DLBCL with 5-year survival probability of 84.9% (95% CI: 81.7-87.6), 86.5% (95% CI: 83.0-89.4) and 54.8% (95% CI: 52.4-57.1) respectively. However, in the case of MZL and MCL survival is much lower than in our analysis, with a 5-year RS of 77.2% (95% CI: 72.9-80.8) and 31.4% (95% CI: 23.6-39.5) respectively, whereas in our study the probability were 82.3% (95% CI: 76.0-89.2) and 50.7% (95% CI: 39.3-65.2) respectively. As in our study, no differences were detected between males and females (67.2% vs. 67.8%). This study does not present analysis by age group or study period. Similarly, the study conducted by the North American Association of Central Cancer Registries (NAACCR) with data from 18 cancer registries between 2005-2011, shows the survival probability of LNs by race and

sex[18]. Like the English study, the NAACCR study shows better survival probability than those observed in our study, as well as lower survival for black men in all subtypes of LNs.

Differences in LNs survival between our results and those obtained in different studies could be attributed to the different time periods analysed, ethnicity and variability between regions and countries, as demonstrated in some publications [12,16–18]. However, although this variation in LNs survival exists, both our results and those obtained by other authors indicate better survival for MF/SS, MZL, FL, CLL/SLL and HL and worse survival for precursor cell neoplasms, PCN and PTCL.

On the other hand, in most of the articles reviewed, HL survival is higher than in our study[12,17,19–21]. Several publications have noted an improvement in HL survival in recent years, which can be attributed in part to the improvement in anatomopathological diagnosis over the years in the different Anatomic Pathology Services and the changes in the management of HL. The increased use of positron emission tomography–computed tomography (PET-CT) has improved the information on the extent of the disease compared to conventional methods and allowed for better control and management of the disease, thus playing a fundamental role in the therapeutic activity of these patients[103–105]. One of the possible reasons for the lower survival in our study may be the number of the sample, since of the 362 cases of HL, only 28 cases correspond to nodular lymphocyte predominant HL, which is the one with the best survival, so it cannot be ruled out that this variation in survival may be due to this limitation. Hence the importance of participating in larger projects that can include a greater number of cases and therefore present a greater statistical significance. As mentioned above, another reason could be the differences found between different geographical regions[16,17]. On the other hand, in recent years the management in HL has varied both at the level of chemotherapy and radiotherapy, in our case there are patients since 1996, and therefore we cannot rule out that these changes in treatment have not been implemented in some patients especially in the early years. Similarly, given the progressive improvement in anatomopathological diagnosis over the years at the various Anatomic Pathology Departments, we cannot rule out the

potential that some HL identified in our analysis are truly NHL, especially in the early years. Finally, although the survival of HL in our study is lower than that observed by other authors, we agree that HL is one of the best-positioned entities with a very favorable RS compared to other LNs.

In contrast, our study shows a better survival of CLL/SLL compared to that observed by other authors[12,16–18,21]. A possible plausible explanation for these discrepancies could be a different registration coverage of indolent cases, possibly due to poor collection or under-registration of these cases. CLL/SLL is an indolent disease, and its diagnosis is not based on tissue pathology, and early-stage cases do not require treatment[22,105–107]; therefore, it is likely that cancer registries are underreporting. In our region, every effort has recently been made to retrieve all these cases[108], where in addition to the information provided by the GCR, other sources of information (i.e. records of flow cytometry laboratories, hospital registries and hematologists' databases) have been used, which may have improved overall survival estimates for this neoplasm.

In most of the studies reviewed, survival probability was similar between men and women, while there were marked differences between age groups, with lower survival probability observed in older patients, demonstrating that age at diagnosis plays an important role in the prognosis of the disease. The poor survival of elderly patients is mainly attributed to the presence of comorbidities or to their frail state, which hinders the application of various treatment protocols, such as aggressive chemotherapy or stem cell transplantation. Although most LNs usually affect older patients, several subtypes, such as HL, BL or precursor cell neoplasms occur mainly in children or adolescents, however, the analysis of these cases in our study was limited by the sample size.

Throughout the study period, survival of mature B-cell neoplasms improved favorably. This may be due in part to changes in treatment regimens, such as the introduction of rituximab for DLBCL in 2004, and shortly thereafter for FL and MCL during 2004-2005[109–114], as well as the introduction of new multiple myeloma treatments such as thalidomide, lenalidomide and bortezomib, and autologous

stem cell transplantation in 2009[115]. Despite this, the prognosis for several LNs remains poor, necessitating more research into new treatment agents in order to improve patient outcomes.

Finally, making comparisons between our findings and those of other authors should be done with caution because some studies present age-standardized data and different statistical methods were employed to estimate the RS of LNs in other investigations[12,16,17,19].

### *6.1.2 Paper II: Impact of comorbidity in chronic lymphocytic leukemia*

Although CLL is the most common cancer in Western countries and occurs mainly in elderly patients with comorbid conditions, the role of comorbidities in the course of this disease has been little studied. Similarly, the cause of death of most newly diagnosed CLL patients and its relationship to comorbid health conditions is poorly defined. In this sense, the second work of this thesis focused on analyzing the impact of comorbidities on the survival and cause of death of patients with CLL in the province of Girona during the period 2008-2016.

Even if there is a well-established relationship between comorbidities and poorer outcomes in cancer patients, data specific to CLL is sparse. To our knowledge there are few studies evaluating the relationship between comorbidities at diagnosis and survival or mortality in patients with CLL. Among the studies analyzed, there are two clinical trials[86,88,94], one prospective cohort[93], two population-based[89,91], two multicenter[79,116], and three hospital series[77,78,90] (**Table 6**).

**Table 6.** Survival and mortality of CLL according to CCI score from the different studies.

| Region and period of study | Design | N | Overall Survival | | Mortality | | | | Covariates |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | CLL-related | | CLL-unrelated | | |
| | | | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis | |
| | | | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | |
| US: 1995-2006[77] | Hospital serie retrospective cohort | 1195 | -All comorbidities: 0.370<br>-Mayor comorbidities: 0.042 | 1.0 (0.7–1.5; p-value=0.97) | - | - | - | - | Rai stage, age, major comorbidities, sex and ALC |
| US: 1998-2007[89] | Population-based retrospective cohort | 8343 | <0.001 | <0.001 | - | - | - | - | Age, sex, race, stage, comorbidity, income, year of diagnosis and geographic region |
| Spain: 1990-2012[78] | Hospital serie retrospective cohort | 949 | 0.064 | 1.4 (1.0-2.0; p-value= 0.035) | - | - | - | - | Binet stage, B2M, high risk FISH, ZAP-70 and CIRS score |

| Region and period of study | Design | N | Mortality | | | | | | Variables included |
|---|---|---|---|---|---|---|---|---|---|
| | | | Overall Survival | | CLL-related | | CLL-unrelated | | |
| | | | Univariate analysis p-value | Multivariate analysis HR (95% CI) | Univariate analysis p-value | Multivariate analysis HR (95% CI) | Univariate analysis p-value | Multivariate analysis HR (95% CI) | |
| France: 2003-2013[116] | Multicenter retrospective cohort | 201 | 0.775 | 1.0 (1.0-1.1; p-value=0.471) | - | - | - | - | Age, living at home, performance status, CIRS score, PS, creatinine clearance, B2M, CD38, del(17p) and Binet stage |
| Italy: 2006-2016[90] | Hospital serie prospective cohort | 335 | <0.001 | 2.9 (1.5-5.5; p-value= 0.001) | - | - | - | - | CLL-IPI, CIRS score and complex karyotype |
| US: 2000-2017[79] | Multicenter retrospective cohort | 145 | 0.005 | 6.4 (1.5-27.9; p-value= 0.01) | - | - | - | - | Age, performance status, Rai stage, prior treatment, del(17p) and CIRS score |
| The Netherlands: 2010-2015[94] | Clinical trial | 272 (262) | - | - | - | - | 3.1 (1.3-7.6; p-value=0.008) | 5.4 (1.7-15.3; p-value=0.004) | WHO PS, del(17p) and comorbidity |

| Region and period of study | Design | N | Overall Survival | | Mortality | | | | Variables included |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | CLL-related | | CLL-unrelated | | |
| | | | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis | |
| | | | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | |
| Denmark: 1997-2017[91] | Population-based retrospective cohort | 8055 | <0.05 | - | <0.05 | - | <0.05 | - | - |
| Germany: 1999-2003[86] | Clinical trial | 555 | <0.001 | ~1.6 (1.2-2.2; p-value <0.05) | <0.05 | - | <0.05 | - | Age, sex, TK, B2M and comorbidity |
| US: 2002-2014[93] | Hospital serie prospective cohort | 1143 | <0.001 | 1.1 (1.0–1.3; p-value= 0.10) | <0.001 | 1.0 (0.8–1.3; p-value= 0.99) | <0.001 | 1.4 (1.0–1.8; p-value= 0.035) | Age, sex, Rai stage and CCI score |
| Our Results (Girona: 2008-2016) | Population-based retrospective cohort | 400 | <0.001 | 2.1(0.5–8.9; p-value= 0.340) | 1.3 (0.2–9.2; p-value= 0.815) | 2.8 (0.4–20.7; p-value=0.305) | 0.6 (0.1–5.3; p-value= 0.660) | 8.7 (0.9–86.0; p-value= 0.065) | Age, sex, Rai stage, period of diagnosis and CCI score |

HR, hazard ratio; 95% CI, 95% confidence interval; ALC, absolute lymphocyte count; B2M, Beta 2 microglobulin; CIRS, Cumulative Index Rating Scale; PS, performance status; TK, thymidine kinase.

The results obtained in our study show that the presence of comorbidities negatively influences the survival of patients with CLL (p-value <0.001). However, comorbidities are not associated with increased mortality (overall, CCL-related, and CLL-unrelated). A study conducted between 1995-2006 in 1,195 patients at the Mayo Clinic (Minnesota, US), whose purpose is to investigate the prognostic implications of comorbid health conditions in patients with CLL[77], presents results similar to ours. The median age is 68 years, and the main comorbidities observed are coronary artery disease/peripheral vascular disease, cardiac disease, and diabetes mellitus. Likewise, the presence of the main comorbidities indicates a negative impact on OS in the studied population (p-value=0.042), however this effect loses weight when compared to other prognostic factors such as age and stage at diagnosis (p-value=0.97).

Another population-based study conducted with data from 8,343 patients >65 years during the period 1998-2007 in the US reflects a negative influence of comorbidities on CLL survival (p-value <0.001)[89]. Contrary to that was observed in our study, comorbidities, when compared with relevant elements such as age, continue to maintain their negative effect on the survival of newly diagnosed CLL patients (p-value <0.001). In addition, the main comorbidities observed in the study population are hypertension, hyperlipidemia, coronary artery disease, diabetes and osteoarthritis. Similar data are shown in the study conducted between 2006-2016 in 335 patients in a hospital in Italy, with a median age of 68.7 years, where a decrease in overall survival is also observed as the number of comorbidities increases, both in the univariate (HR: 3.84 (95% CI: 2.43-6.07; p-value <0.001)) and multivariate analysis (HR: 2.9 (95% CI: 1.52-5.52; p= 0.001))[90]. Likewise, in a study conducted in the period 2000-2017 in 145 patients from five centers in the US, with a median age of 70 years, the main comorbidities observed were hypertension, vascular disease, and respiratory disease[79]. Like the two studies mentioned above, comorbidities are associated with worse survival, independently (p-value= 0.005) and when compared to factors such as age, performance status, Rai stage, prior treatment and del (17p) (p-value= 0.01).

On the other hand, in a multicenter study conducted between 2003-2013 in 201 patients ≥80 years old from 17 French hospitals, with a median age of 83.3 years, thirty patients (15%) had fewer than 2 comorbidities, suffering mainly from cardiovascular or osteoarticular diseases[116]. In contrast to our study, no significant association was observed between a higher number of comorbidities and a lower overall survival (p-value= 0.775). However, the result observed in the multivariate analysis is similar to ours, as comorbidities do not have a relevant impact on the survival of CLL patients when compared to prognostic factors such as age or stage.

The studies realized in Germany in 555 patients in 1999-2003[86] and 97 patients in 2004-2008[117], focus on the analysis of the interaction between comorbidity and CLL treatment. The main comorbidities observed in the study populations correspond to hypertension, metabolic disorders, cardiovascular diseases, and renal dysfunction. The German studies further indicates that 53% of patients have at least one comorbidity, and that patients with ≥2 comorbidities have a significantly shorter median overall survival than patients with <2 comorbidities (p-value <0.001). In addition, in the study conducted between 1999-2003, when including additional variables with potential impact on overall survival (gender, age, performance status, disease stage, thymidine kinase and b2-microglobulin levels, and treatment regimen), comorbidity remains an independent prognostic factor. Moreover, although the higher mortality rates in the group of patients with comorbidities are attributed to a combined increase in treatment-related, CLL-related and CLL-unrelated deaths during and after treatment, it is CLL-related deaths that contribute most to the increased mortality in these patients (mainly in those with ≥2 comorbidities).

In the prospective cohort study conducted between 2002-2014 in 1,143 US patients, the cause of death in newly diagnosed patients with CLL and whether the number of comorbidities predicts the cause of death and survival of newly diagnosed patients is evaluated[93]. The median age is 63 years, and the main comorbidities are rheumatological diseases, dyslipidemia, and hypertension. As in our study, the presence of comorbidities at diagnosis negatively influences CLL survival (p-value <0.001), but when compared with prognostically relevant factors

such as age or Rai stage, the role of comorbidities disappears. The main causes of death are CLL progression, infection and other cancer. Moreover, in contrast to our results, a higher number of comorbidities is associated with higher CLL-related and CLL-unrelated mortality (p-value <0.001), whereas when compared to other prognostic variables the negative association only holds for CLL-unrelated mortality (HR: 1.37 (95% CI: 1.02-1.82; p-value= 0.035)). Also, the population-based study conducted between 1997-2017 in Denmark in 8,055 patients with a median age of 71 years shows that all individual comorbidities are associated with increased all-cause mortality, while most individual types of comorbidities are associated with both CLL-related and CLL-unrelated mortality[91]. The main comorbidities correspond to chronic heart failure, cerebrovascular disease, diabetes and chronic pulmonary disease and for patients with comorbidity death is commonly caused by cardiovascular disease and other causes.

Another study conducted between 1990-2012 at the Hospital Clínic of Barcelona (Spain), investigates the clinico-biological features, outcomes, and prognosis of 949 patients with CLL according to age[78]. The median age is 65 years, and older patients have more advanced stages of disease (p-value <0.001). Older patients with a higher number of comorbidities tend to have a lower overall survival (p-value= 0.064) and have an independent prognostic value (HR: 1.42 (95% CI: 1.02-1.97; p-value= 0.035) in the multivariate analysis. Finally, a study in 272 patients aged 65-75 years, whose main comorbidity is cardiovascular disease, indicates that comorbidity influences CLL-unrelated mortality (HR: 3.12 (95% CI: 1.27-7.62; p-value= 0.008)) in the elderly and that this association is maintained when compared with other variables such as del(17p) and b2-microglobulin (HR: 5.4 (95% CI: 1.66-15.33; p-value= 0.004)). The main causes of death CLL-unrelated are infection and secondary cancer[94].

Overall, most studies showed lower survival probability in patients with a higher number of comorbidities[77–79,86,89,90,93], although there were heterogeneous results regarding the independent effect of comorbidities on survival or mortality[86,89,90,93,94]. This disparity could be primarily due to the fact that there were different types of studies, as well as the sample size and population analyzed.

This can be corroborated by looking at the median age of the populations which was <65 years in some clinical trials[86,94] and prospective cohorts[93], which could influence the observed patient outcomes, with variation in the treatments applied as well as the comorbidities present in the study population. However, as in our study, most authors agree that the main comorbidities found were diabetes mellitus, congestive heart failure and chronic lung disease[77,86,91,94,95]. The fact that diabetes mellitus is one of the main comorbidities found in patients with CLL may be attributed to the fact that this population is under continuous monitoring and follow-up, which could in turn contribute to the diagnosis of CLL at earlier stages.

On the other hand, to date there is no unified comorbidity scoring system respectively, so that there are a variety of methodologies to assess comorbidities in CLL patients. For example, in the studies reviewed, comorbidities have been classified by disease code ranges, scales or scoring systems such as the number of comorbidities[77,91,94], the CCI score[86,93], or the CIRS[78,79,90,116]. Furthermore, within the CCI score, there is disparity in terms of the codes of the diseases included as well as the grouping of the score, which hinders the correct interpretation of the results. All this leads to the need to establish a properly standardized scoring system for the assessment of comorbidity in patients with CLL.

Our study is one of the few to analyze the impact of comorbidities on mortality in patients with CLL, considering the specific cause of death. Contrasting studies showed heterogeneous results in terms of the possible impact of comorbidities on overall mortality[86,89,90,93], CLL-related mortality[86,91], and CLL-unrelated mortality[91,93,94]. In our study, we did not observe a statistically significant association between higher CCI score and mortality (CLL-related, and CLL-unrelated). This could be partly due to our sample size limitation, as well as misclassification on the specific cause of death cannot be ruled out[118], because we relied on official data on the basic cause of death and not on the secondary cause of death[101]. Therefore, subclassification of mortality into more informative categories such as disease progression, second primary cancer or infection could not be performed. In addition, we included all hematological disorders in the CLL-related

causes of death, so it cannot be ruled out that some actual secondary primary hematological malignancies were erroneously included in this category.

Finally, although the continuous implementation of new drugs over time has improved the survival of patients with CLL[119–121], the presence of comorbid health conditions in combination with age affects the correct evolution of these patients, and on many occasions these patients are not considered for certain treatments. Hence the need to focus on the clinical management of patients with CLL and to further explore the role of comorbidities in CLL outcomes, which will provide better prognostic tools adapted to comorbid and elderly populations.

## 6.2 Methodological considerations: strengths and limitations

### *6.2.1 Paper I*

Over the years, the classification of hematologic entities has changed, and in turn, these changes make it difficult to accurately interpret the geographic variation in LN survival (**Figure 2**). An example of the variation in classifications of hematologic entities corresponds to the changes observed in the diagnostic criteria for CLL/SLL, as initially individuals with CLL phenotype cells were classified as CLL if the patient's absolute lymphocyte count was ≥ 5 x $10^9$/L[37], and, as of the WHO 2008 criteria, lymphocytes other than B lymphocytes were excluded from the absolute numerical cut-off, subsequently reclassifying patients with low B-cell counts and no clinical symptoms as BML, which is a premalignant condition to CLL. On the other hand, from WHO 2001 to WHO 2008 new subtypes and categories have been included in the classification of hematological entities. Because these entities have generally arisen as a result of genetic mutations (e.g., primary DLBCL of the central nervous system, primary cutaneous DLBCL leg type and anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma)[122], cancer registries do not have sufficient information to be able to perform a direct reclassification, so that no matter how hard one tries to update the different LNs in the new classification, there will always be an inherent error in the fact of this variability.

Also in our study, the small sample size in some LNs limits statistical power and does not allow a closer estimation of the real value of survival. Therefore, more well-powered studies that include real-world data are needed to further study these fewer incident subtypes. Proposals such as HAEMACARE and InterLymph have suggested groupings of LNs into "clinically meaningful" categories, however different subtypes grouped together can still present differences in their prognosis. Such is the case of DLBCL, which includes subtypes with a somewhat different prognosis.

Another limitations that we face assessing SR is the methodology choosing (e.g., Hakulinen[70], Ederer II[90,93], or Pohar-Perme[91]). Federer II method and other methods are potentially biased when interest lies in an overall average of net survival[123]. In our study we used the Pohar-Perme method, which, compared to conventional methods, is an unbiased estimator, a particularly relevant property when age-unstandardized survival probability is presented, which could be considered in part as a strength of our study. In addition, some studies have age-standardized data, which makes it difficult to compare results between regions.

Finally, since our analysis lacks data on staging or treatment, it is difficult to ascertain whether changes in survival probability are due to improvements in both the diagnostic approach and treatment of the different LNs.

Despite the limitations encountered, the indicators presented in this study provide valuable information for the monitoring of survival at the population level and for the evaluation of national cancer plans.

### *6.2.2 Paper II*

Several limitations must be considered when comparing our results with those presented by other authors, such as the limited sample size makes certain conclusions difficult, particularly regarding the effect of comorbidities in the mortality (overall, CLL-related and CLL-unrelated).

Another limitation is the possible misclassification or categorization of the underlying cause of death[118]. We relied on official data on the basic cause of death—and not the secondary cause of death. Thus, we were unable to subclassify CLL-related mortality into more informative categories (e.g., disease progression, second primary cancer, infection, and other health conditions). In CLL-related causes, we included all hematological malignancies, suspecting misclassifications of CLL cases and treatment-related diseases. However, there might be some real secondary primary hematological malignancies that were wrongly located in CLL-related causes.

Similarly, clinical data were collected from electronic medical records, which cannot be assumed to provide complete, accurate and standardized information on the health status of individuals. Also, like cause of death, errors in reporting comorbidities in medical records can lead to underestimates of survival and mortality probability. Furthermore, our study assessed comorbid health conditions only at the time of diagnosis; however, during follow-up, some patients might acquire new comorbid conditions or face a decline in organ function.

On the other hand, the method used to measure comorbidity in our study (CCI score) could have certain limitations compared to other measurement scales such as the CIRS. Thus, the CCI underestimates the severity of certain important diseases such as congestive heart failure or dementia, which are very frequent alterations in elderly patients with CLL and could act as predictors of adverse outcomes. Likewise, the CCI considers AIDS to be the most serious disease, without taking into account that its prognosis has changed from being a fatal to a chronic pathology and that its prevalence in elderly people is low. In addition, are other measurement systems such as the modified CCI score used by the Royal College of Surgeons (RCS)[124], which only considers 12 comorbidities and does not assign a weight to them and that could have certain advantages over the CCI score, having a much simpler coding that could improve the accuracy of comorbidity measurement. Despite possible limitations and the fact that the CCI score is not a cancer-specific system, it is one of the most widely used scores to measure the

impact of comorbidities, being an accurate predictor of long-term mortality[85,125–127].

In addition, we lack data on additional variables that could influence prognosis, such as treatment patterns or the presence of several genetic or biochemical markers[128]. Finally, race/ethnicity was also not recorded in our study, which could also influence the survival probability of CLL patients, as has been previously reported by other authors[60].

Regardless of the limitations, the data from this study provide insight into the relationship between comorbidities and CLL in a real-world setting and justify prioritizing patients with comorbid CLL in future clinical trials, to better inform treatment guidelines and improve outcomes for these patients.

## 6.1 Public health implications and future perspectives

The results obtained in this thesis provide relevant information for the monitoring of survival at the population level and mainly for the evaluation of cancer at the national level. Over time, following the introduction of new diagnostic methods and therapeutic agents for the management of LNs, it has been possible to visualize improvements in survival probabilities for most LNs, although more emphasis needs to be placed on precursor neoplasms and most mature HL subtypes as survival probabilities for these entities remain poor.

In view of the above, high-resolution studies are needed to determine improvements in survival in LNs with limited sample size. There is also a need to improve the quality of cancer registry data on LNs and to integrate the data with more detailed information (genetic alterations, molecular data, and clinical data) to facilitate classification of LNs and provide a good benchmark for future studies. So too, the next priority is to determine what has driven these improvements in survival in hematologic malignancies. Cancer registries will remain essential for monitoring improvements in cancer survival, while smaller, high-resolution

studies, which collect data on stage at diagnosis and treatments for representative samples of cancer registry cases, may provide further evidence on whether new treatments are primarily responsible for improved survival of LNs.

In the same way, the results of the sub-analysis provides key data for the development of personalized survival plans for patients diagnosed with CLL, considering the presence of comorbidities over time. In addition, this information can lay the groundwork for prevention, early diagnosis, or intervention strategies to mitigate the long-term comorbidity burden in this population. CLL remains incurable, but in the last decade there have been major advances in the understanding of the pathophysiology of CLL and in the treatment of this disease. This has led to a significant increase in response rates and duration of response, as well as improved survival. CLL is a disease of the elderly and, given its comorbidity, not all patients can receive the aggressive initial chemoimmunotherapy regimens that are resulting in improved response rates and survival. The age range of patients participating in clinical trials is not representative of this disease, and more research is needed in patients who are representative of the majority of CLL patients seen in practice before we will see improved outcomes in these older and often frailer patient populations. Moreover, further research is needed to discover the best method for assessing comorbidity and functional status in CLL patients, and to integrate these measures with established prognostic tools at different stages of the disease. In addition, it is expected that in the coming years the method of comorbidity assessment will be standardized, resulting in a considerably closer to reality view of the impact of comorbidities on CLL outcomes at the local level, while allowing comparison at the global level.

# CONCLUSIONS

# 7. CONCLUSIONS

Specific conclusions:

**Paper I:**

- The 5-year OS and RS of the overall LNs were 54.4% (95% CI: 52.8-56.0) and 62.3% (95% CI: 60.4-64.4), respectively.
- RS varies markedly according to the different subtypes. MF/SS, MZL and HL have better survival while PCN, precursor cell neoplasms and PTCL show the lowest probability.
- No gender differences are observed (male 61.2% (95% CI: 58.6-63.9) vs. female 63.7% (95% CI: 60.8-66.8).
- Age at diagnosis is an important prognostic factor in the survival of LNs. 5-year RS of all LNs decreases progressively across age groups, being 91.3% in children, 76% in those aged 15-49 years, 68.9% in those aged 50-69 years and 49.9% in those aged ≥70 years.
- Survival of LNs increased during 1996-2002 and 2003-2008, which could be attributed to the introduction of new treatments, such as rituximab combined with chemotherapy in the treatment of some mature B-cell neoplasms (p-value=0.008).

**Paper II:**

- The main comorbidities observed in CLL patients at diagnosis are diabetes (21%), congestive heart failure (18%), malignant tumors and chronic pulmonary disease (both with 11%).
- In univariate analysis a high CCI score negatively influences the overall survival of CLL patients. OS and 5-year OS and RS decreased markedly with increasing CCI scores (p-value <0.001), mainly in patients with a CCI score ≥3. However, in multivariate analysis, the effect of the CCI score disappears when age and stage are also considered.
- The CCI does not play a role predictor of mortality (both CLL-related or CLL-unrelated) in newly diagnosed CLL patients.

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