Annals of Hematology
https://doi.org/10.1007/s00277-025-06595-5

RESEARCH

Real-world study on patient characteristics, treatment patterns and outcomes for treated patients with chronic lymphocytic leukemia during 2013–2022 in Finland

Juha Ranti[1] · Sanaz Jamalzadeh[2] · Eleonora Mäkelä[3] · Johanna Vikkula[2] · Essi Havula[2] · Sari Luopajärvi[4] · Vesa Lindström[5]

Received: 10 June 2025 / Accepted: 20 August 2025

Abstract

The aim of this study was to describe the chronic lymphocytic leukemia (CLL) patient population characteristics, treatments, outcomes, and healthcare resource utilization (HCRU) in Finland. All adult patients diagnosed with CLL (ICD-10: C91.1) and small lymphocytic lymphoma (SLL, ICD-10: C83.0) in the regions of Helsinki and Uusimaa (HUS), Southwest Finland (HDSF) and Pirkanmaa (PHD) were identified. The study focused on treated patients initiating first line treatment in 2013–2022. Treatment lines were constructed using all available medication administration and prescription data, categorized into targeted therapies, chemotherapies, chemoimmunotherapies, and other regimens. Analysis employed descriptive statistics, Kaplan-Meier for outcomes, and Sankey plots for treatment patterns. Targeted therapies were most commonly used as the first treatment line during 2018–2022, while between 2013 and 2017, the most common treatments were chemotherapy and chemoimmunotherapy. The 3-year survival rate of CLL patients in HUS, HDSF and PHD areas increased from 69% (95% CI: 64.3, 72.5) during 2013–2017 to 73% (95% CI: 66.8, 77.3) during 2018–2022. A notable proportion of patients ($N=596$, 64%) had unknown del(17)p/TP53 status, and 79% ($N=740$) lacked information on IGHV mutational status during the study period, despite an increase in genetic testing over time. No change in total HCRU events was observed, however a change in the types of outpatient contacts was identified over time. New treatments have been introduced as they have emerged, concurring with improved outcomes.

Keywords Chronic lymphocytic leukemia (CLL) · Real-world evidence (RWE) · Hematology · Healthcare resource utilization (HCRU)

Introduction

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by accumulation of immunologically dysfunctional mature B lymphocytes within the blood, bone marrow, lymph nodes, and spleen [1, 2]. CLL is the most common type of adult leukemia with an incidence of 4.2 per 100 000 per year [3]. CLL affects primarily older adults and the median age at diagnosis is 72 years [3], and males are more often affected than females. In Finland, during 2017–2021, the CLL incidence rate for men was 7.40 per 100 000 and for women of 4.25 per 100 000 [4]. The median 5-year survival rate has consistently increased and is currently over 80% for women and approximately 75% for men [5].

✉ Vesa Lindström
vesa.lindstrom@hus.fi

1 Department of Hematology, Turku University Hospital, Wellbeing Services County of Southwest Finland, Turku, Finland

2 Medaffcon Oy, Espoo, Finland

3 Janssen-Cilag Oy, Espoo, Finland

4 Department of Hematology, Tampere University Hospital, The Wellbeing Services County of Pirkanmaa, Tampere, Finland

5 Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center and University of Helsinki, Helsinki, Finland

Published online: 19 September 2025

CLL is a chronic illness without a known cure, and it exhibits varying survival rates. The immunoglobulin heavy chain variable region gene (IGHV) mutation status has been one of the most important prognostic factors. Approximately 50% of CLL patients have an unmutated *IGHV* (uIGHV), which especially in the era of chemoimmunotherapies (CITs), has been associated with more aggressive disease and inferior outcomes [6, 7]. Other genetic drivers of CLL, which can act as either initiating factors or acquired alterations during the course of the disease, include alterations of certain chromosomal areas, namely del(13q), del(11q), del(17p), and trisomy 12 [2]. An estimated 80% of all CLL patients carry at least one of these chromosomal alterations [3]. Most deletions in 17p disrupt the TP53 tumor suppression gene, and both del(17p) and TP53 mutations (collectively referred to as aberrant TP53), are associated with worse prognosis even in the era of targeted therapies [8]. Moreover, the presence of a complex karyotype (CK), which is defined as three or more independent chromosomal aberrations and found in approximately 15% of CLL patients, is both a negative prognostic marker and associated with a poor response to treatment, including both CITs and targeted therapies [9]. In 2018, the International Workshop on CLL (iwCLL) recommended that IGHV mutational status, and both TP53 mutational status and del(17p)-status should be tested in all CLL patients to guide therapeutic decisions [10]. In addition to IGHV and TP53 mutation status, age, clinical stage and serum β_2-microglobulin concentration are considered as the most important prognostic factors in CLL [11].

The decision to treat CLL depends on the stage of the disease and presence of symptoms [3, 12, 13]. For patients with an early asymptomatic disease, the standard treatment follows a watch-and-wait strategy. For patients with symptomatic early-stage or advanced-stage CLL, the choice of front-line therapy depends on the IGHV and del(17)p/TP53 mutation status and patient's fitness [3, 13].

Chemotherapy with chlorambucil was the standard treatment for CLL for decades before the introduction of fludarabine-based therapies that were first used in combination with cyclophosphamide (fludarabine-cyclophosphamide, FC). Since the introduction of the monoclonal antiCD20 antibodies (mCD20Ab) including rituximab and obinutuzumab, CITs, namely fludarabine-cyclophosphamide-rituximab (FCR), and for unfit patients bendamustine-rituximab (BR) or chlorambucil-mCD20Ab (Ch+mCD20Ab) have been the standard of care. A significant milestone in the treatment of CLL has been the introduction of targeted therapies, including Bruton's tyrosine kinase (BTK)-inhibitors ibrutinib, acalabrutinib and zanubrutinib, PI3K-inhibitor idelalisib and BCL2 inhibitor venetoclax, which have benefited especially the patients with aberrant TP53 or uIGHV [3, 13].

As frail patients are often under-represented in clinical trials, the golden standard of evaluating new therapies, real-world data (RWD) is needed to evaluate new therapies and understand the current treatment practices in the real-world population [14]. Furthermore, real-world evidence (RWE) studies are in constant demand to support decision making as the therapeutic options for CLL are constantly evolving. Previous RWE studies in Finland, both conducted in a single-center, have studied the treatment landscape of CLL patients during 2005–2015 [15] and 2014–2019 [16]. Here, in this descriptive retrospective RWE study, we utilized the Finnish healthcare registries and three hospital data lakes covering approximately 50% of the Finnish population and studied the patient characteristics, treatment patterns, outcomes and healthcare resource utilization (HCRU) of CLL patients, thus expanding on the previous RWE studies conducted in Finland. Furthermore, we studied the treatment evolution in two time periods of 2013–2017 and 2018–2022, corresponding to the time before and after targeted CLL therapies gained national reimbursement in Finland.

Materials and methods

Data collection

This retrospective study analyzed data from Helsinki and Uusimaa (HUS), Southwest Finland (HDSF), and Pirkanmaa (PHD) from 2013 to 2022. The study focused on adult patients diagnosed with CLL (ICD-10: C91.1) (including patients with small lymphocytic leukemia, SLL, ICD-10: C83.0) within these regions. For the identified cohort, data was collected from electronic health records and other hospital databases via the respective data lakes as well as Care register for healthcare (AvoHILMO), Social Insurance Institution (SII), Statistics Finland, Center for Pensions (FCP), and Digital and population services agency (DVV).

Patient population

For the study population patients were included if they were diagnosed with CLL/SLL and had the treatment initiation date in 2013–2022 and were at least 18 years of age at time of diagnosis. From the initial cohort, patients were excluded if they had CLL/SLL treatment prior to 2013, and their home municipality was not within HUS, HDSF or PHD region at EOF. The index was defined as the initiation date of the first treatment line during 2013–2022. CLL/SLL

patients were followed from the index, until death or end of study (December 31, 2022), whichever came first. Patients were stratified to early (2013–2017) and late (2018–2022) subgroups according to the year their first-line treatment was initiated.

Constructing treatment lines

Treatment lines (TLs) were constructed using comprehensive data sources including hospital-administered medications, pharmacy records, electronic prescriptions, and reimbursed outpatient purchases. The start and end dates of the treatment lines were defined based on the records of CLL specific drugs. The medications included here were cyclophosphamide, fludarabine, doxorubicin, vincristine, bendamustine, chlorambucil, obinutuzumab, ibrutinib, acalabrutinib, venetoclax, idelalisib and ofatumumab. Generally, treatment lines were considered to change when the regimen changed. For ibrutinib, acalabrutinib, venetoclax, and idelalisib, an infinite gap was allowed within a treatment line to still consider it as one line of therapy. For other drugs, a gap lasting longer than one year marked a change of line of therapy. The records of the supportive medication (prednisolone) were not used to identify the start and end dates of the regimens.

High level grouping of the treatment options in CLL was categorized in four groups including targeted therapies, chemotherapies, chemoimmunotherapies and 'other'. The treatment options used in each group were:

Targeted therapies

- BTKi (ibrutinib, acalabrutinib).
- Venetoclax, with or without obinutuzumab.
- Idelalisib, with or without rituximab.
- Other targeted therapies: unfeasible to determine the exact combination.

Chemotherapies

- Chlorambucil-based, without rituximab, ofatumumab and obinutuzumab.
- Fludarabine-cyclophosphamide.
- Cyclophosphamide-based, without rituximab, ofatumumab and obinutuzumab.
- Other chemotherapies, including fludarabine, vincristine, doxorubicin, or bendamustine without rituximab, ofatumumab and obinutuzumab.

Chemoimmunotherapies

- Bendamustine-rituximab (BR).
- Cyclophosphamide-fludarabine-rituximab (FCR).
- Chlorambucil- CD20 antibodies including rituximab, ofatumumab and obinutuzumab (Ch + mCD20Ab).
- Other chemoimmunotherapies, including chemotherapy + rituximab, obinutuzumab, or ofatumumab.

Other

- Treatment options which could not be classified into the previous groups.

Statistical analysis

Data was analysed using primarily descriptive measures, with mean and standard deviation (SD) and median with 1 st and 3rd quartiles (IQR) for continuous variables. Categorical variables were presented as the number and proportion of patients in each class, and the differences between strata were tested using chi-squared/Fisher's exact test (categorical variables), t-test/Kruskal-Wallis test (continuous variables). Demographical (age, sex, hospital district), and clinical (mutation status, laboratory values, comorbidities) variables, were summarized at index. For laboratory values, records within a ± 3-month time-window around the index were considered. If multiple records were available per patient, the record closest to index was utilized. For mutation status, data from the diagnosis to the index was used. For baseline comorbidities and Charlson Comorbidity Index (CCI [17]), diagnosis data (excluding CLL and SLL) from primary and secondary care from 5 years before the index was used. Patient numbers 1–4 were replaced with '<5' and the corresponding results for these small patient groups were not reported according to Finland's authority (Findata) guidelines for secondary use of health and social data [15]. All analyses were performed using R version 4.0.5 [18]. The study was approved by The Finnish Social and Health Data Permit Authority Findata (data permit number THL/6570/14.02.00/2021 findata-rems-2021/694). All gathered data was recorded at the medical records during the everyday practices and stored in structured format, and therefore high-quality data was expected. However, as with all real-world data RWD, it is plausible to have erroneous entries or missing data, which was difficult to identify.

Treatment outcomes and patterns

Treatment outcomes were assessed using time to event analysis, namely Kaplan-Meier fit (OS) and competing risk model (TTNT, DoT). In competing risk models, the median times were reported from the event-free survival. The overall survival (OS) was defined as time from the index until death (event) or to end of study follow-up (31.12.2022; censoring event). The time to next treatment (TTNT) was defined as

time from initiation of treatment line until initiation of the next treatment line (event), death (competing risk), or end of study follow-up. The duration of treatment (DoT) was defined as time from initiation for a treatment line until end of treatment (event), death (competing risk), or end of the study follow-up. If the death or end of study follow-up were less than a grace period of 2 months apart from the end of the last treatment line, the treatment was expected to last until death/end of study follow-up. The treatment lines were visualized using Sankey plots and the number (N) and proportion (%) of patients per treatment type were reported. The plot illustrates the distribution of patients within treatment lines and paths between treatment lines. The first four lines were visualized when applicable.

Cause of death

The number and proportion of patients for each recorded cause of death was calculated using the immediate cause of death reported in the cause of death registers (Statistics Finland) via ICD10 codes. Data on causes of death are available up until the end of 2021, so deaths from 2013 to 2021 are analyzed in this study. The time-stratified analysis represents the causes of death for patients who died between 2013–2017 and 2018–2021, respectively, as separate bars.

Secondary malignancies

Malignancies other than CLL/SLL have been identified using ICD10 code diagnosis after TL1 initiation, excluding cases where the patient has secondary malignancies at baseline. The secondary malignancies in groups with more than 5 patients have been then reported.

Healthcare resource utilization and expenses

All-cause HCRU was assessed based on recorded in- and outpatient contacts in primary and secondary healthcare. The cumulative number of contacts per patient and the accompanying 95% confidence intervals were estimated using mean cumulative functions. The direct costs were estimated by linking publicly available standard unit costs [19] to inpatient and outpatient visits (by contact type and/or specialty).

Results

Patient population

A total of 3386 adult CLL patients were identified (Fig. 1a). Of the 3386 patients, 931 patients had their 1 st treatment line (TL1) initiated between 2013 and 2022, and these patients formed the study cohort. To study the treatment evolution of CLL, we further divided the study cohort into early (2013–2017), and late (2018–2022) cohorts based on treatment initiation dates. The split was based on the year when the first targeted therapeutic agents, including ibrutinib and venetoclax gained national reimbursement in Finland. The patient characteristics are presented in Table 1 and Supplementary table S1.

The median age at the start of the TL1 was higher in the late cohort than in the early cohort (73.3 vs. 70.1 years, respectively). Men were more frequently affected than women (63% vs. 34% during the whole study period) and no statistically significant difference was observed between the proportion of men and women across different age groups over time. The median follow-up time for the whole cohort was 34.3 months (range 13.7–66.5 months). For the early and late cohorts, the median follow-up time was 64.4 and 20.4 months, respectively.

The proportion of patients who had a Charlson's comorbidity index (CCI)$\leq$2, was 70.5% in the early cohort and 86.8% in the late cohort (Table 1), indicating that patients in the earlier time period presented with more comorbidities at start of TL1 ($p<0.001$). Among the most common co-diagnoses recorded at baseline in both time-stratified cohorts were primary hypertension (I10), several dental related diagnoses including dental caries (K02), acute respiratory infections (J06), pneumonia (J18), non-insulin-dependent diabetes mellitus (E11), disorders of lipoprotein metabolism and other lipidemias (E78), and atrial fibrillation and flutter (I48) (Supplementary table S2).

While IGHV mutational and TP53 aberration statuses are currently tested in HUS, PHD and HDSF hospital districts upon treatment initiation for the vast majority of patients, the proportion of "unknown" remained high particularly for IGHV status throughout the study period. A notable increase in the number of direct TP53 mutational status testing was observed over time. Overall, better data coverage regarding the molecular genetic testing was observed in the latter cohort. 92% of the patients who had their TL1 initiation during 2013-2017 were reported to have unknown IGHV mutational status, and an equal 4% of patients had mutated (mIGHV) and unmutated IGHV (uIGHV) CLL. For patients who had their TL1 initiated during 2018-2022, 21% were reported to have mIGHV, 14% uIGHV and for 65%, IGHV mutational status was unknown. Del(17p)-testing increased during the study period; unknown status 43% vs. 20% in early and late cohorts, respectively. At the beginning of the TL1, del(17p) was reported in 6% and 9% of the CLL patients

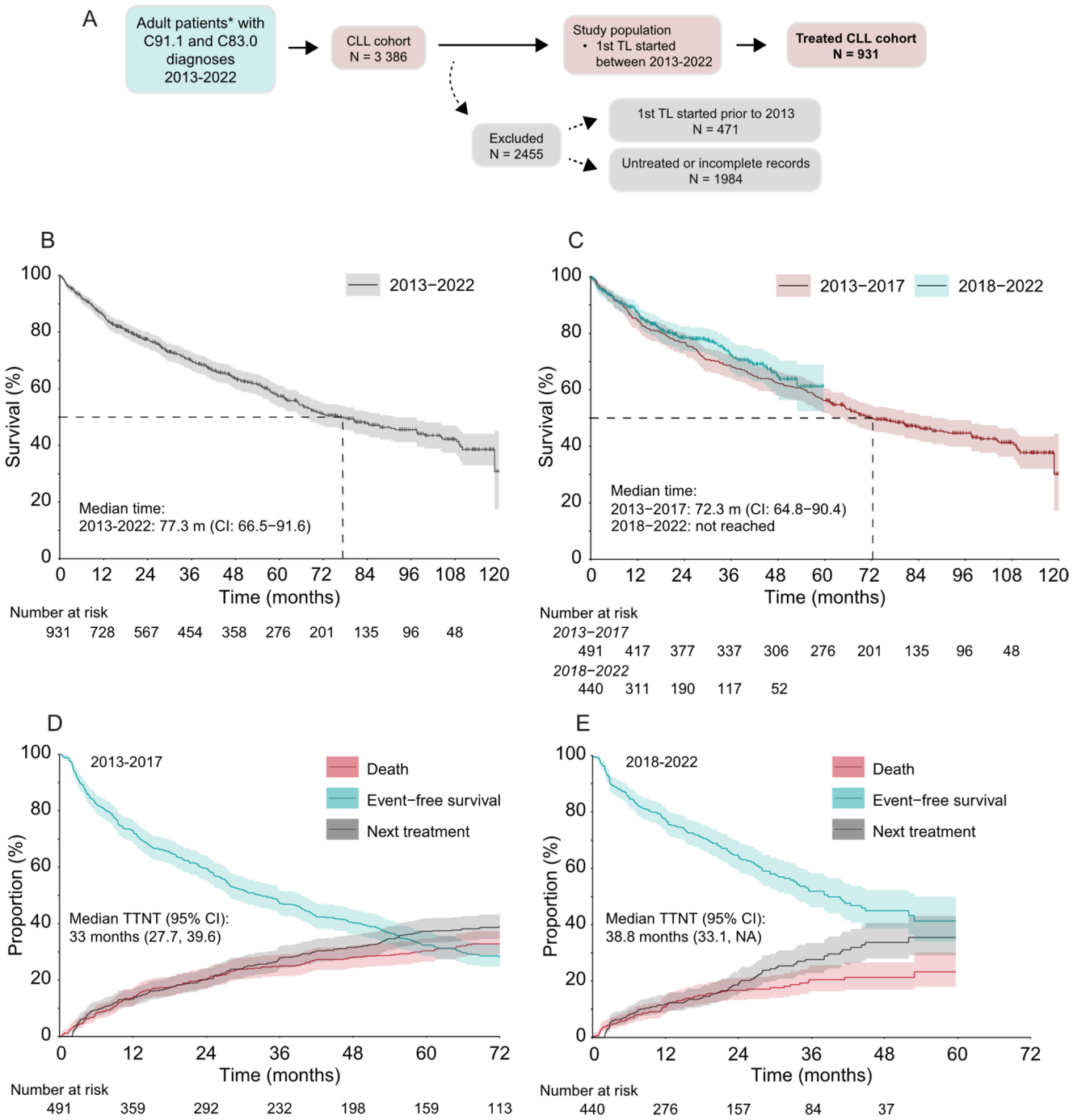

Fig. 1 Cohort formation and treatment outcomes of CLL patients in Finland during 2013–2022 (**a**) Cohort formation. Adult patients with a C91.1 or C83.0 diagnosis during 2013–2022 in HUS, HDSF, and PHD region were included. The study population included patients who started their first-line treatment between 2013 and 2022. The Kaplan-Meier OS curve of the treated CLL patients in HUS, PHD and HDSF in **(b)** 2013–2022, and **(c)** in the early (2013–2017) and in the late (2018–2022) cohorts. The mOS for the late cohort was not reached. Time to next treatment (TTNT) of TL1 using a competing risk model (death as competing risk) in **(d)** the early (2013–2017) and **(e)** in the late (2018–2022) cohorts. Event-free survival indicates the composite event of start of the next treatment line and death. 95% CIs are presented

for the early and late cohorts, respectively. TP53-mutation testing showed a marked increase within our study period, with 98% unknown status in the early cohort and only 36% in the late cohort. Mutated TP53 was reported at the beginning of the TL1 in 8% of patients in the late cohort.

Table 1 Clinical characteristics of the Finnish CLL patients from HUS, HDSF and PHD hospital districts having first line treatment initiation between 2013–2022 (study cohort)

Variable	Estimate/level	Overall	2013–2017	2018–2022	*p*
		(*N*=931)	(*N*=491)	(*N*=440)	
Age at index, years	**mean (SD)**	70.4 (11.3)	69.3 (11.7)	71.6 (10.7)	0.001
	median [IQR]	71.8 [64.7, 78.2]	70.1 [64.4, 77.1]	73.3 [65.5, 78.8]	0.001
Time from CLL diagnosis to start of 1 L, months	**mean (SD)**	39.6 (46.6)	34.2 (41.3)	45.5 (51.3)	<0.001
	median [IQR]	23.2 [2.0, 60.3]	18.7 [0.8, 55.7]	28.7 [4.9, 68.4]	<0.001
Length of follow-up, months	**mean (SD)**	42.8 (33.6)	59.4 (36.0)	24.1 (16.8)	<0.001
	median [IQR]	34.3 [13.7, 66.5]	64.4 [26.3, 86.4]	20.4 [10.3, 37.9]	
Sex, N (%)	**Female**	344 (36.9)	188 (38.3)	156 (35.5)	0.408
	Male	587 (63.1)	303 (61.7)	284 (64.5)	
Hospital district	**HUS**	467 (50.2)	241 (49.1)	226 (51.4)	0.073
	PHD	253 (27.2)	148 (30.1)	105 (23.9)	
	HDSF	211 (22.7)	102 (20.8)	109 (24.8)	
IGHV	**unmutated**	80 (8.6)	19 (3.9)	61 (13.9)	<0.001
	mutated	111 (11.9)	19 (3.9)	92 (20.9)	
	unknown	740 (79.5)	453 (92.3)	287 (65.2)	
TP53	**unmutated**	260 (27.9)	12 (2.4)	248 (56.4)	<0.001
	mutated	35 (3.8)	0 (0.0)	35 (8.0)	
	unknown	636 (68.3)	479 (97.6)	157 (35.7)	
del(17p)	**no del(17p)**	565 (60.7)	251 (51.1)	314 (71.4)	<0.001
	del(17p)	67 (7.2)	28 (5.7)	39 (8.9)	
	unknown	299 (32.1)	212 (43.2)	87 (19.8)	
CCI	**0**	353 (37.9)	134 (27.3)	219 (49.8)	<0.001
	1–2	378 (40.6)	215 (43.8)	163 (37.0)	
	3–4	123 (13.2)	82 (16.7)	41 (9.3)	
	5+	77 (8.3)	60 (12.2)	17 (3.9)	

The statistical differences between the characteristics of early and late cohorts were tested using chisquared/ Fisher's exact test for categorical variables, t-test for continuousnormally distributed variables, and Kruskal-Wallis test for continuous nonnormally distributed variables. Index = Initiation of treatment

CCI: Charlson comorbidity index; IGHV: immunoglobulin heavy chain variable region gene; IQR: interquartile range; SD: standard deviation; TP53: tumor suppressor gene

Treatment outcomes

The median overall survival (mOS) for treated CLL patients from start of the TL1 during 2013-2022 was 6.4 years (77.3 months) (Fig. 1b). We also compared the mOS between the two time periods. While the mOS in the early cohort was 6 years (72.3 months), the mOS was not reached for the late cohort (Figure 1c, log rank p=0.3). The 3-year survival rate was 69% (95% CI: 64.3, 72.5) in the early cohort and 73% (95% CI: 66.8, 77.3) in the late cohort.

We also analyzed the time to next treatment (TTNT) and duration of treatment (DOT). From the start of the TL1, the median event-free survival (i.e. time to the start of the TL2 or death) was 33 months in the early and 38.8. months in the late cohort (Figs. 1d and 1e). The median DoT was 3.8 months in the early and 4.8 months in the late cohort (Supplementary Fig. S1).

Treatment evolution

Next, we identified the treatment lines for the early and late cohorts. CLL treatments were divided into four categories: chemotherapy, chemoimmunotherapy, targeted and other therapies. In the early cohort, chemotherapies (51%) and chemoimmunotherapies (47%) were the most common in TL1, while in the late cohort, chemoimmunotherapies (47%) and targeted therapies (29%) were the most common (Fig. 2 and Supplementary Table S3). In a more detailed analysis, the most commonly used TL1 regimens in the early cohort were bendamustine-rituximab (BR, 23%) and chlorambucil-based chemotherapy (16%), whereas in the late cohort, the most commonly used were BR (25%) and venetoclax-based targeted therapy (16%) (Supplementary Figure S2 and Supplementary Table S4). Targeted therapies were very rarely used as TL1 in the early cohort (2%), but in the late cohort they were used in 29% of patients, with the

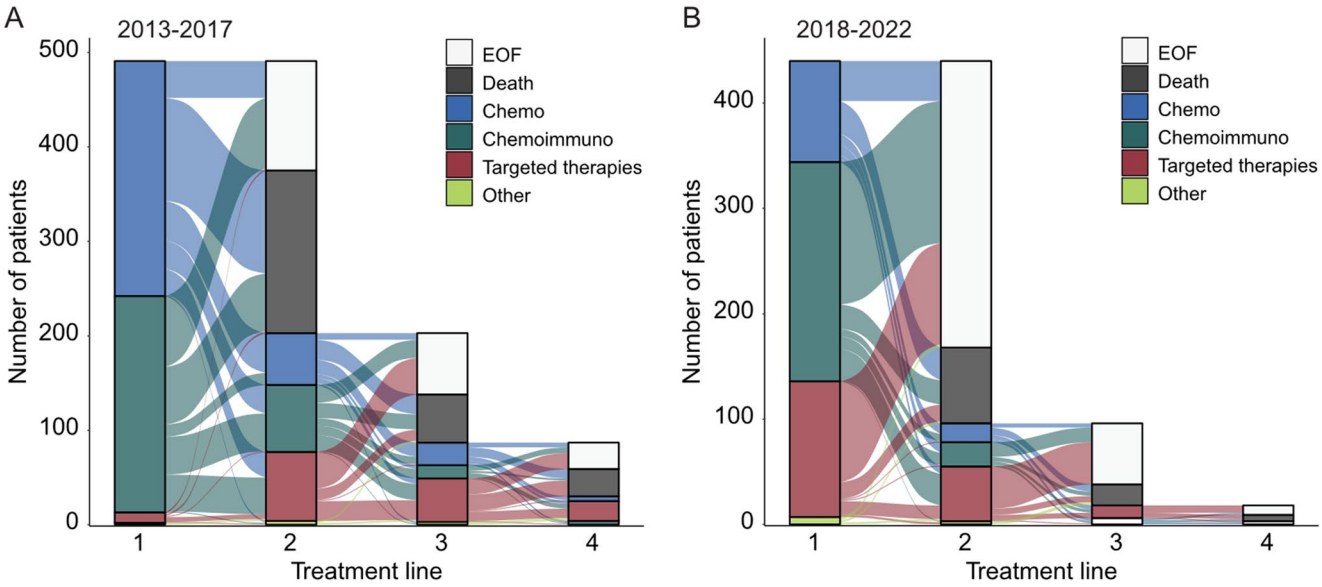

Fig. 2 Treatment lines of CLL patients in Finland. Treatment lines visualized by Sankey plots for CLL patients **(a)** in the early (2013–2017) and **(b)** late (2018–2022) cohorts. Chemoimmunotherapies include bendamustine-rituximab (BR), cyclophosphamide-fludarabine-rituximab (FCR), chlorambucil-CD20 antibodies (Ch + mCD20Ab), and "other chemoimmunotherapies", chemotherapies include chlorambucil-based, fludarabine-cyclophosphamide, cyclophosphamide-based and "other chemotherapies", targeted therapies include Bruton tyrosine kinase inhibitor (BTKi)- (ibrutinib, acalabrutinib), venetoclax-, idelalisib- based, and "other targeted therapies". EOF = end of study (December 31, 2022)

venetoclaxbased (16%) and Bruton tyrosine kinase inhibitor (BTKi)-based (12%) therapies being the most common.

For patients who received second line treatment (TL2), targeted therapies were the most common both in early (36%) and late (54%) cohorts (Fig. 2 and Supplementary Table S3). The most used targeted therapies in the early cohort were BTKi- (13%), venetoclax- (12%) and idelalisib-based (9%) therapies, while in the late cohort BTKi- (25%) and venetoclax-based (26%) were mainly used in TL2. BR (13%) and the "other chemoimmunotherapies" (15%) were still relatively commonly used in TL2 in the early cohort, while in the late cohort, the "other chemoimmunotherapies" with 8% were the most common chemo(immuno)therapy (Supplementary Figure S2 and Supplementary Table S4). It is important to note that the follow-up time was shorter for the patients in the late cohort starting their TL1 in 2018–2022 compared to those in the early cohort starting the TL1 in 2013–2017, as the patients in the early cohort were followed until death or December 31, 2022. Due to this, the proportion of patients reaching later treatment lines is not comparable between the two time windows.

Causes of death and secondary malignancies in CLL patients

Next, we looked at the causes of deaths among CLL patients (Fig. 3). The time-stratified analysis here represents the causes of death for patients who died between 2013 and 2017 and 2018–2021 (in contrast to the other analyses where the stratification was done based on the treatment initiation date). In 2013–2017 and 2018–2021, there were 134 and 177 recorded deaths, respectively. Notably, the cause of death data was only available up to the end of 2021, and the patients from the early cohort may have experienced death in later years (2018–2021). CLL was recorded as the most common immediate cause of death in both cohorts. There were no significant differences in the immediate causes of deaths between the cohorts. Furthermore, we examined secondary malignancies among the CLL patients for the entire study period. A total of 141 secondary malignancies were reported, with the most commonly diagnosed being non-melanoma skin cancers, followed by prostate and breast cancer (Fig. 3b).

Healthcare resource utilization

Finally, the HCRU among CLL patients in time stratified cohorts were analyzed. The majority of HCRU events originated from primary care contracts, followed by outpatient contacts at specialized care and purchases of reimbursed outpatient medications (Fig. 4a-b, Supplementary Table S5). Interestingly, despite the improvements in treatment patterns and outcomes, we did not observe changes in the HCRU events between the two periods. We also analyzed

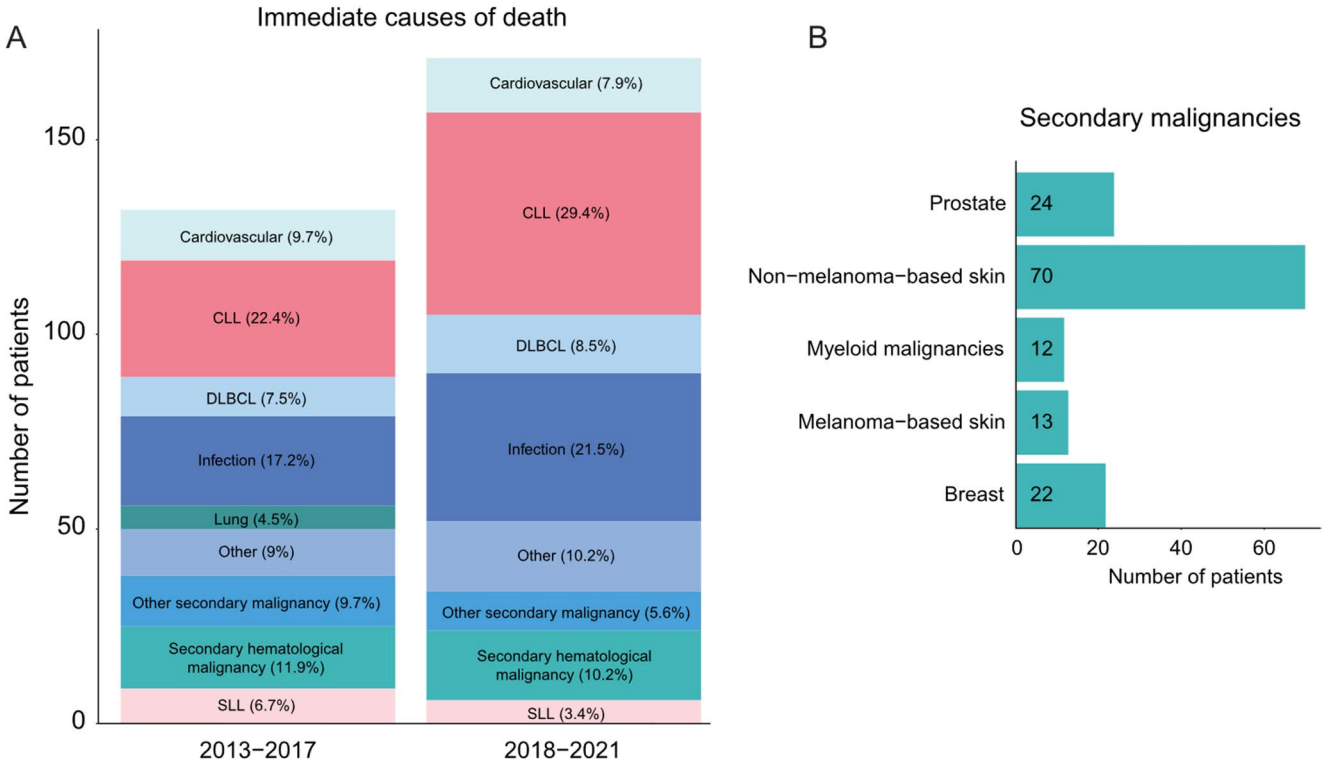

Fig. 3 Causes of death and secondary malignancies in CLL patients (a) Causes of deaths among CLL-patients who died during 2013–2017 and 2018–2021. Note that the stratification here is done according to the year of death, not according to the initiation of treatment. **(b)** Secondary malignancies in CLL patients during 2013–2022. Abbreviations: DLBCL: Diffuse large B cell lymphoma, Cardiovascular (ICD-10 codes starting with I), Infection (ICD-10 codes starting with A, B, J, and U07), Myeloid malignancies include AML (Acute myeloid leukemia) and MDS (myelodysplastic syndrome). Other secondary malignancies (ICD-10 codes C18, C19, C22, C24, C25, C30, C32, C44, C56, C57, C61, C64, C71, C78, C79), and Secondary hematological malignancies (ICD-10 codes C81, C82, C84, C86, C88, C90, C92, C94, C95, D46). Any additional secondary malignancies classified under "Other"

the direct costs by using publicly available standard unit costs [19], and found a notable increase in the outpatient medication costs during the latter time period (Fig. 4c-d, Supplementary Table S5). With the advent of new targeted therapies, we hypothesize that the types of outpatient events have evolved over time. Consequently, we conducted a more detailed analysis of the outpatient contacts. Notably, we observed a decrease in the outpatient clinic visits for IV-treatments and routine appointments (clinic visits), accompanied by an increase in other types of contacts (Fig. e-f, Supplementary Table S5).

Discussion

To our knowledge, this represents the most comprehensive RWE study conducted on Finnish CLL patients. While previous RWE studies primarily relied on manual data collection [15, 16], this study utilized the extensive healthcare registries of Finland and three hospital data lakes covering approximately 50% of the Finnish population. In this study, we examined the CLL treatment practices, outcomes, and healthcare resource utilization in real-world clinical practice in Finland between 2013 and 2022.

The mOS for all treated CLL patients from the start of the TL1 during 2013–2022 was 6.4 years (77 months, median age 71.8 years at the start of TL1). This is consistent with the most recent Finnish RWE study from 2005–2015, which reported a mOS of 6.8 years following the initiation of TL1 [15]. The slight difference between these two studies may largely be attributed to the younger median age of the patients in the latter study. An earlier Finnish RWE study reported a mOS of 4.8 years (57 months, median age 71 years at the start of TL1) following the initiation of TL1 during 2005–2013 [16]. Similar outcomes were reported by a Swedish RWE study conducted in 2007–2013, with a mOS of 4.8 years (58 months, median age 71 years at the start of TL1) for treated CLL patients [20]. Although the mOS for the late cohort was not reached in this study, a modest increase in the 3-year survival was observed. Together with the data from previous RWE studies, these findings suggest an improvement in the OS of CLL patients in Finland over time. Nevertheless, the expected improvements associated with changes in treatment patterns are not fully reflected in

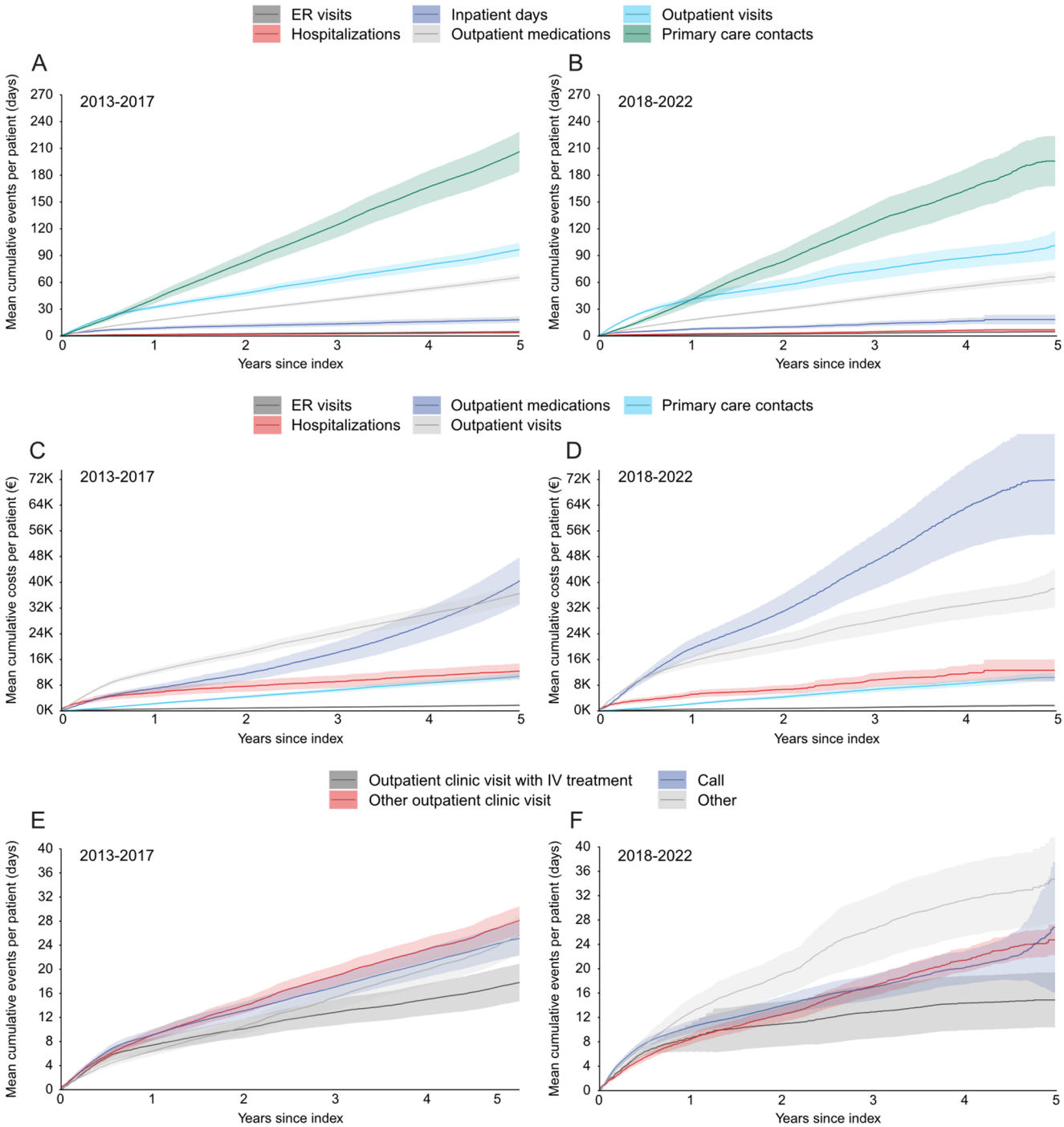

Fig. 4 Cumulative HCRU of CLL/SLL patients in Finland in the early (2013–2017) and late (2018–2022) cohorts. Cumulative HCRU of CLL patients over time due to ER visits, hospitalizations, inpatient days, outpatient medications, outpatient visits and primary contacts. Data is presented as **(a-b)** mean cumulative events per patient (days) and **(c-d)** mean cumulative costs per patient (euros) **(e-f)** Cumulative HCRU of CLL patients over time due to outpatient visits including calls, outpatient clinic visits, serial IV treatments and other. Abbreviations: ER = emergency room

the outcomes presented in this study. It is also important to note that compared to patients in the early cohort, those in the late cohort were older and exhibited a higher CCI at TL1 initiation, suggesting that patients in the latter cohort were frailer. However, as indicated by the increase in TTNT, and along with the fact that mOS was not reached during the study period, it is likely that the expected improvements in survival were not fully captured due to the relatively short follow-up time for the latter time-period. The observed DoT was 3.8 months in the early cohort and 4.8 months

in the late cohort. The relatively short treatment durations are likely attributable to the extensive use of fixed-duration chemotherapy and chemoimmunotherapy regimens in both cohorts. The potentially lower tolerability of these treatments may also contribute to the shorter treatment duration. It will be interesting to observe whether the improved tolerability associated with targeted therapies [21] translates into even longer DoTs for CLL in future RWE studies.

The national treatment guidelines for CLL have been in use in Finland for 10 years, roughly corresponding to the study period. The national guidelines have changed over the years when the new therapies have become available and received reimbursement in Finland. As expected, we observed a change in treatment patterns between the two follow-up periods, with targeted therapies now being the most commonly used in TL1. The increased use of targeted therapies aligns with the international treatment guidelines for CLL [3, 10, 13]. Prominently, in the early cohort chemotherapy remained the most commonly used first line treatment. The use of chemotherapy in TL1 decreased from 51% in the early cohort to 22% in the late cohort, and especially the use of cyclophosphamide-based treatments decreased from 11 to 4%. Chemotherapy was still used relatively frequently in the late cohort in TL2 (19% of treated patients). However, it is important to note that for most of the follow-up period of this study, targeted therapies were reimbursed only for the specific subpopulations, namely patients with del(17p)/TP53 mutations or those with relapsed or refractory CLL. Nevertheless, in the late cohort, chemotherapies were not used in TL3 (compared to 28% in the early cohort). The overall use of chemoimmunotherapy in TL1 was similar between the two cohorts (47% in both). However, the specific treatments have evolved over time, with chlorambucil-CD20 antibody (Ch+mCD20Ab) treatment being more common in the late cohort compared to the early cohort (10.7% vs. 2.9%, respectively). Additionally, even though IGHV and TP53 mutational status testing has been a standard practice since 2018, following the iwCLL guidelines [10], a significant proportion of patients still had an unknown del(17)p/TP53, and particularly IGHV mutational status, in the latter period. This is likely reflective of insufficient testing. However, it is important to note that certain reimbursement conditions are tied to specific aberrations, and if the medication has not been available for other reasons, testing has likely not been done either. There has also been a change in the recording practices during the study period, which may have contributed to inconsistent data in some cases.

This is the first study to investigate the causes of death among Finnish patients with CLL. CLL remained the most common immediate cause of death in both follow-up groups, consistent with a study covering the same follow-up period [22]. As expected, the proportion of CLL-related causes of death, such as infections and secondary malignancies, was high in both follow-up groups. The proportion of infections as a cause of death was higher in the latter follow-up group, possibly related to the coinciding COVID-19 pandemic.

Our analysis of HCRU demonstrated an expected increase in the outpatient medication costs, coinciding with the national reimbursement approval of targeted therapies for CLL. Although no notable changes in the HCRU events were observed over the study period, a closer examination of outpatient contacts revealed a decrease in the outpatient clinic visits for IV-treatments. This finding suggests a shift from chemotherapy to immunotherapies and targeted therapies. It is important to note that the costs of reimbursed medications were estimated using list prices. However, the actual costs are often subject to confidential price agreements between the pharmaceutical companies, and in the case, the Finnish Pharmaceutical Pricing Board.

Conclusions

Targeted therapies have increased in the first line treatment of CLL. Although outcomes for CLL patients have improved, it remains an incurable disease with a significant healthcare burden. With the rapidly evolving treatment landscape of CLL, RWD remains invaluable for providing insights into current outcomes in the real-world CLL patient population. The wider implementation of targeted therapies in Finland and their impact on treatment outcomes should be assessed in future studies.

Study strengths and limitations

This study is subject to limitations commonly associated with registry-based RWE studies. The data reflects routine clinical coding practices and may therefore be non-standardized, incomplete, and subject to missing data or variations in coding practices. TLs were defined post hoc based on administration, prescription, and reimbursed purchase data; therefore, misclassification of TLs is possible. However, the start dates of the treatments were expected to be recorded with reasonable precision, and clinical considerations were taken into account when constructing TLs. Therefore, the majority of TLs were expected to be accurately defined. Treatment practices in CLL are evolving rapidly. Consequently, the treatments presented here for the late cohort may already be outdated and may not reflect the current clinical landscape. Text mining was applied to extract IGHV, TP53 and del(17p) status: therefore, misclassification of patients is possible to a small extent. Additionally, IGHV and TP53 testing were

gradually introduced into standard practice during the later years of this study. Consequently, the proportion of patients classified as having unknown IGHV/TP53 status remained relatively high. The data for this study was retrieved from three regional data lakes in Finland, covering 50% of the population, and is therefore expected to be representative of the nationwide population. A strength of this study is the use of RWD collected in a real-world setting, encompassing all diagnoses, procedures, and visits, without strict inclusion and exclusion criteria. Finland has a universal healthcare system primarily funded through taxation. All permanent residents in Finland, regardless of financial situation, are entitled to the same level of public healthcare. Therefore, the RWD in hospital data lakes are not biased by selection criteria. With the rapidly evolving treatment landscape of CLL, RWE studies have been considered especially valuable for addressing the rapidly emerging clinical questions in the field [14].

Supplementary Information The online version contains supplementary material available athttps://doi.org/10.1007/s00277-025-06595-5.

Acknowledgements Kai Kysenius, current employee at Medaffcon Oy, is acknowledged for providing medical writing support.

Author contributions JR, SJ, EM, JV, EM, SL and VL contributed to the study design and objectives, interpretation of results and revising the manuscript. JV and SJ analyzed the data. EH, SJ and JV wrote the first manuscript draft. EM, SL, VL, and JR critically reviewed the results and revised the manuscript. All authors have reviewed and approved the final version of the manuscript.

Funding This study was funded by Johnson & Johnson.

Data availability Data can be accessed with data permission by following the guidance and application process set by the registries. All authors had access to the aggregate data, whereas pseudonymized single-level registry data were available only to authors conducting the data analysis. Only the registry personnel had full access to patient data. The single-level data cannot be shared. Only the registry holders have the authority to grant rights to third parties for data usage in accordance with the Act on Secondary Use of Health and Social Data.

Declarations

Ethics approval The study was approved by the Finnish Social and Health data permit authority Findata (THL/4633).

Consent to participate According to the Finnish Act on Secondary use of health and social data (552/2019), no patient consent was required.

Competing interests SJ, EH, and JV are employees of Medaffcon Oy. EM is employed by Johnson & Johnson. VL has received honoraria from AbbVie, AstraZeneca, Johnson & Johnson, SL from Abbvie and Johnson & Johnson, and JR from AbbVie, Astra-Zeneca, Beigene and Johnson & Johnson. Medaffcon provided support for planning the study, analyzing the data and interpretation of the results, drafting the manuscript, and medical writing.

References

1. Shadman M (2023) Diagnosis and treatment of chronic lymphocytic leukemia: a review. JAMA 329:918
2. Hallek M, Shanafelt TD, Eichhorst B (2018) Chronic lymphocytic leukaemia. Lancet 391:1524–1537
3. Eichhorst B, Robak T, Montserrat E et al (2021) Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 32:23–33
4. Cancer registry F (2023) Cancer statistics. *Syöpärekisteri*, https://cancerregistry.fi/statistics/cancer-statistics/ Accessed 22 May 2023
5. Seppä K, Tanskanen T, Heikkinen S et al (2023) *Syöpä 2021. Tilastoraportti Suomen syöpätilanteesta (eg. Cancer 2021. Statistical Report on Finnish Cancer Status)*. Suomen Syöpäyhdistys. https://syoparekisteri.fi/assets/files/2023/05/Syopa_2021_final_31052023.pdf
6. Damle RN, Wasil T, Fais F et al (1999) Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 94:1840–1847
7. Hamblin TJ, Davis Z, Gardiner A et al (1999) Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 94:1848–1854
8. Kang S, Ahn IE (2024) Prognostic markers in the era of targeted therapies. Acta Haematol 147:33–46
9. Baliakas P, Jeromin S, Iskas M et al (2019) Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. Blood 133:1205–1216
10. Hallek M, Cheson BD, Catovsky D et al (2018) IwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 131:2745–2760
11. An international prognostic (2016) Index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol 17:779–790
12. Hallek M, Al-Sawaf O (2021) Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol 96:1679–1705
13. Eichhorst B, Ghia P, Niemann CU et al (2024) Esmo clinical practice guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Ann Oncol 35:762–768
14. Islam P, Mato AR (2019) Real-World evidence for chronic lymphocytic leukemia in the era of targeted therapies. Cancer J 25:442–448
15. Lindström V, Hakkarainen KM, Mehtälä J et al (2019) Observational evidence from patients diagnosed with chronic lymphocytic leukaemia (CLL) in Finland between 2005-2015 show improved survival over time. Eur J Haematol 103:190–199

16. Ranti J, Perkonoja K, Kauko T et al (2022) Characterization of real-world treatment practices and outcomes among patients with chronic lymphocytic leukemia treated in a Finnish tertiary center. eJHaem 3:291–300
17. Quan H, Li B, Couris CM et al (2011) Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 173:676–682
18. Team RC (2022) R: A Language and environment for statistical computing. Austria: R Foundation for Statistical Computing, Vienna. https://www.R-project.org/
19. Mäklin S (2017) Terveyden- ja sosiaalihuollon yksikkökustannukset Suomessa vuonna 2017. 55
20. Sylvan SE, Asklid A, Johansson H et al (2019) First-line therapy in chronic lymphocytic leukemia: a Swedish nation-wide real-world study on 1053 consecutive patients treated between 2007 and 2013. Haematologica 104:797–804
21. Zhong L, Li Y, Xiong L et al (2021) Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. Sig Transduct Target Ther 6:201
22. Van Der Straten L, Levin M, Dinnessen MAW et al (2024) Causes of death among patients diagnosed with chronic lymphocytic leukemia: a population-based study in the Netherlands, 1996–2020. HemaSphere 8:e70015