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SHORT REPORT

Medical history and lifestyle factors have limited impact on time-to-first-treatment in patients with chronic lymphocytic leukemia

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is a heterogeneous disease. Whereas some patients have an indolent disease, others experience an aggressive course and early death. Our aim was to investigate if modifiable and non-modifiable medical history and lifestyle factors prior to diagnosis had an impact on the natural course of the disease.

Method: In 1154 CLL patients, we assessed if the weight, physical activity, smoking, and alcohol consumption or non-modifiable characteristics including family history of lymphoid malignancy and medical history were associated with time-to-first-treatment (TTFT) and adjusted all results for the CLL-International Prognostic Index (CLL-IPI).

Results: TTFT was shorter for patients with high/very high-risk CLL-IPI than those with low/intermediate risk CLL-IPI. In the adjusted analysis we did not find additional impact on TTFT besides CLL-IPI from any environmental characteristics assessed.

Ingrid Glimelius and Geffen Kleinstern contributed equally to first authorship.

Susan L. Slager and Karin E. Smedby contributed equally to last authorship.

Conclusions: We found limited impact of environmental factors on the natural course of CLL (measured as the TTFT in treatment naïve patients) providing valuable knowledge, and potential relief, to share with patients at the time of diagnosis.

KEYWORDS
chronic lymphocytic leukemia, CLL-IPI, environmental factors, family history, IGHV mutation status, time-to-first-treatment

1 | INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a clinically and biologically heterogeneous disease. Finding lifestyle factors that have an additional impact on the time to need treatment can inform patients and treating physicians about potential tools to modify their risk of disease progression in CLL and the need for treatment. Patients often ask what has caused the cancer they have been diagnosed with, but also if any lifestyle changes can alter the natural course of their disease; such as smoking, alcohol consumption, and/or physical activity [1]. Patients might also recall other diseases or health-related factors they have experienced earlier in life and wonder if they have had an impact on their disease course, such as prior infections, for example, mononucleosis, prior human herpes virus infections, history of autoimmune diseases, blood transfusion, height/weight and history of atopic disorders (allergies, food allergies, asthma, hay fever, and eczema). In addition, if they have had a relative with a hematological malignancy they might ask if family history might affect the natural course of the disease. In two case-control studies, the Mayo Clinic CLL study and the SCALE study [2, 3] we aimed to investigate the risk of progression of CLL during the natural course of the disease based on those different environmental risk factors.

2 | METHOD

The Mayo Clinic study included patients diagnosed between September 1, 2002, and December 31, 2012, who were older than 20 years and residents of the Midwest United States [3]. The SCALE study included patients between 18 and 74 years diagnosed in Sweden between October 1, 1999, and April 15, 2002, and between January 1, 2000, and August 2002 in Denmark [2]. All Mayo cases were followed every 6 months for the first 3 years after diagnosis and annually thereafter. For SCALE cases, a medical record review was conducted retrospectively 12 years after the last inclusion of a patient.

Information on environmental exposures was obtained through standardized telephone interviews (SCALE) or through self-administered risk-factor questionnaires (Mayo). The exposures selected were based on earlier studies and predefined hypotheses [4]. We studied family history of hematological malignancies in first-degree relatives (through questionnaires and through the Swedish multi-generation register and the Danish civil registration system), tobacco history (former and current smokers pooled into ever smokers), alcohol consumption (ever/never), and as continuous variables; bodyweight (per-5 kg), height (per-10 cm) and body mass index (BMI) (per-5 kg/m^2 increase). BMI was also specified in young adulthood (age 18–21 years), sun exposure (high vs. low), physical activity (high vs. low), and ever having had a blood transfusion. We studied the history of mononucleosis (delayed Epstein Barr Virus [EBV] infection), human herpes virus (HHV)-infections, and history of autoimmune and atopic disorders (allergies, food allergies, asthma, hay fever, and eczema) [2, 4, 5].

To perform adequate adjustments, we used the CLL-International Prognostic Index (CLL-IPI). To calculate the CLL-IPI we investigated the immunoglobulin heavy variable (IGHV) gene somatic hypermutation (SHM) status (unmuted or mutated) at diagnosis [6]. Sequences with ≥ 98% identity were considered unmutated [7]. Cases were also evaluated for *TP53* disruption (either through deletion 17p or *TP53* mutations) [8]. Stage (Binet A or Rai 0 vs. Binet B-C or Rai I-IV) and age (≤65 years vs. > 65 years) were abstracted from medical records. Information on β_2-microglobulin concentration was retrieved from medical records or by central analysis of stored plasma using an accredited lab (cut-off ≤3.5 mg/L vs. > 3.5 mg/L). We next computed the CLL-IPI [9] and also combined low to intermediate-risk groups, and high to very high-risk groups into a two-level CLL-IPI. Overall, 323 cases were excluded from the analyses due to missing clinical values.

The outcome used to study the natural course of the disease was time to first treatment (TTFT). TTFT was calculated from the date of CLL diagnosis to the date of first CLL treatment, date of last date known to be untreated, or date of death. Patients were censored at the date of last follow-up or death. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to assess associations between exposures and TTFT, with adjustment for sex, study, and CLL-IPI score in two categories. We also investigated potential differences by sex in a stratified Cox regression model.

The studies were ethically approved according to the Declaration of Helsinki and written informed consent was obtained. The cohort protocol for the Mayo Clinic participants was approved by the Mayo Clinic Institutional Review Board.

3 | RESULTS

In total, 1154 patients were included (793 from the Mayo study and 361 from the SCALE study) with 64% male, and the mean age at the time of diagnosis was 62.3 years (range: 23–90) (Table S1). A history of atopy, human herpes virus (HHV) cold blisters, and HHV zoster was

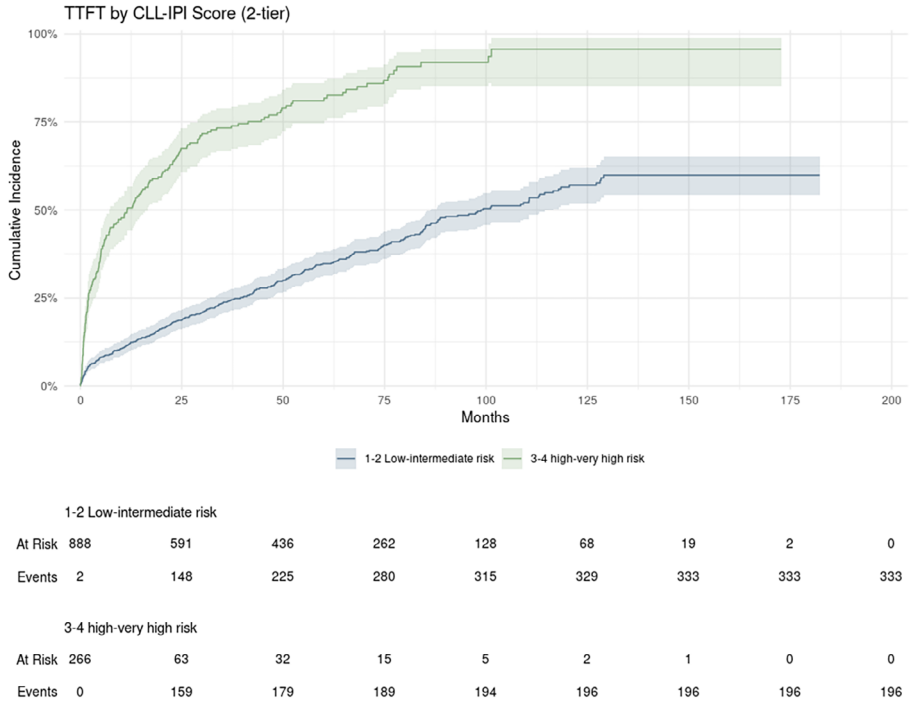


FIGURE 1 Time-to-first treatment (TTFT) stratified by chronic lymphocytic leukemia-international prognostic index (CLL-IPI) with a green curve representing cases with high or very high-risk profile and a blue line representing cases with low or intermediate risk profile.

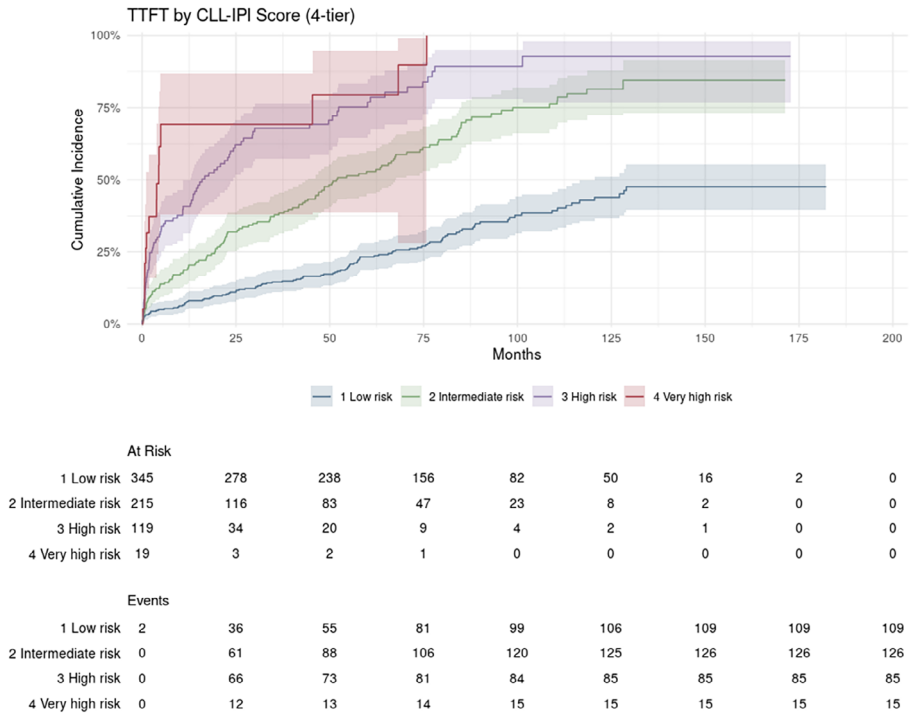
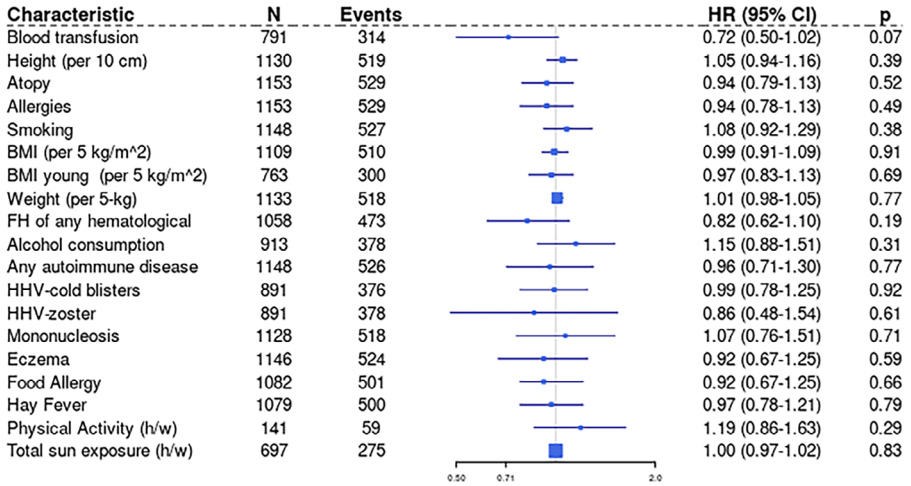


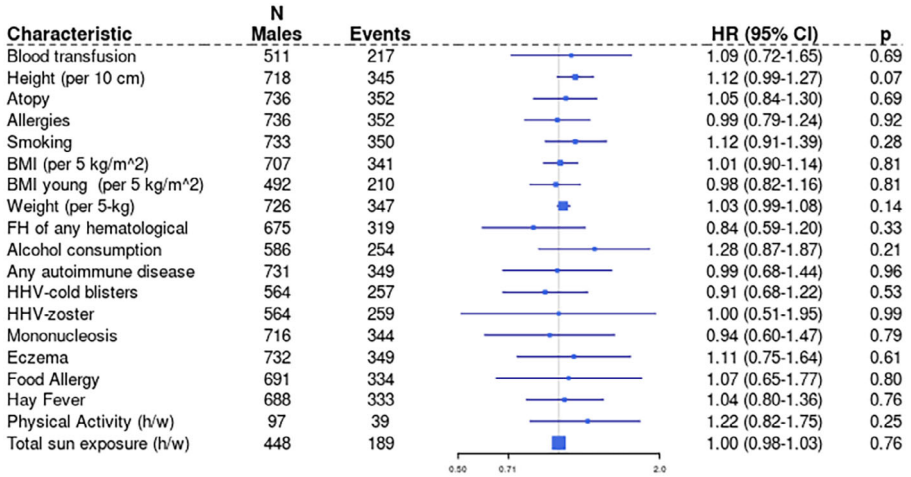
FIGURE 2 Time-to-first treatment (TTFT) stratified by chronic lymphocytic leukemia-international prognostic index (CLL-IPI) score with a red curve representing cases with red very high risk, purple high risk, green intermediate risk, and blue low risk.

more frequently reported in SCALE cases while a history of mononucleosis, having a family history of hematological malignancy, or being a never drinker was more common in Mayo cases (Table S1). Of the 1154 CLL patients, the median follow-up was 6.8 years, and the median TTFT was 3.5 years where 529 received a first-line treatment. TTFT was shorter in cases with high/very high risk CLL-IPI than low/intermediate risk CLL-IPI; (HR = 1.80, 95%CI: 1.65–1.97, $p < 0.0001$, adjusted for sex and study, Figures 1 and 2).



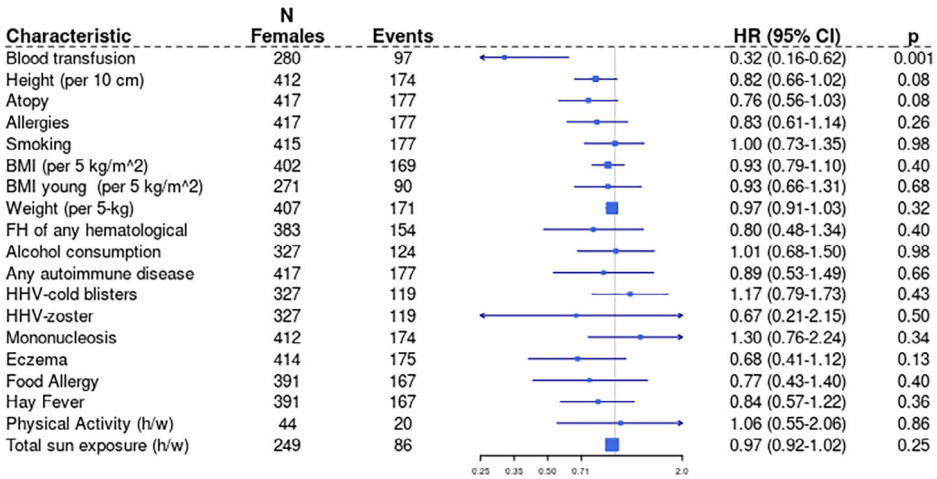
Characteristic	N	Events	HR (95% CI)	p
Blood transfusion	791	314	0.72 (0.50-1.02)	0.07
Height (per 10 cm)	1130	519	1.05 (0.94-1.16)	0.39
Atopy	1153	529	0.94 (0.79-1.13)	0.52
Allergies	1153	529	0.94 (0.78-1.13)	0.49
Smoking	1148	527	1.08 (0.92-1.29)	0.38
BMI (per 5 kg/m^2)	1109	510	0.99 (0.91-1.09)	0.91
BMI young (per 5 kg/m^2)	763	300	0.97 (0.83-1.13)	0.69
Weight (per 5-kg)	1133	518	1.01 (0.98-1.05)	0.77
FH of any hematological	1058	473	0.82 (0.62-1.10)	0.19
Alcohol consumption	913	378	1.15 (0.88-1.51)	0.31
Any autoimmune disease	1148	526	0.96 (0.71-1.30)	0.77
HHV-cold blisters	891	376	0.99 (0.78-1.25)	0.92
HHV-zoster	891	378	0.86 (0.48-1.54)	0.61
Mononucleosis	1128	518	1.07 (0.76-1.51)	0.71
Eczema	1146	524	0.92 (0.67-1.25)	0.59
Food Allergy	1082	501	0.92 (0.67-1.25)	0.66
Hay Fever	1079	500	0.97 (0.78-1.21)	0.79
Physical Activity (h/w)	141	59	1.19 (0.86-1.63)	0.29
Total sun exposure (h/w)	697	275	1.00 (0.97-1.02)	0.83

FIGURE 3 Time-to-first-treatment (TTFT) for patients with chronic lymphocytic leukemia (CLL) by environmental exposures prior to the time of diagnosis shown overall.



Characteristic	N Males	Events	HR (95% CI)	p
Blood transfusion	511	217	1.09 (0.72-1.65)	0.69
Height (per 10 cm)	718	345	1.12 (0.99-1.27)	0.07
Atopy	736	352	1.05 (0.84-1.30)	0.69
Allergies	736	352	0.99 (0.79-1.24)	0.92
Smoking	733	350	1.12 (0.91-1.39)	0.28
BMI (per 5 kg/m^2)	707	341	1.01 (0.90-1.14)	0.81
BMI young (per 5 kg/m^2)	492	210	0.98 (0.82-1.16)	0.81
Weight (per 5-kg)	726	347	1.03 (0.99-1.08)	0.14
FH of any hematological	675	319	0.84 (0.59-1.20)	0.33
Alcohol consumption	586	254	1.28 (0.87-1.87)	0.21
Any autoimmune disease	731	349	0.99 (0.68-1.44)	0.96
HHV-cold blisters	564	257	0.91 (0.68-1.22)	0.53
HHV-zoster	564	259	1.00 (0.51-1.95)	0.99
Mononucleosis	716	344	0.94 (0.60-1.47)	0.79
Eczema	732	349	1.11 (0.75-1.64)	0.61
Food Allergy	691	334	1.07 (0.65-1.77)	0.80
Hay Fever	688	333	1.04 (0.80-1.36)	0.76
Physical Activity (h/w)	97	39	1.22 (0.82-1.75)	0.25
Total sun exposure (h/w)	448	189	1.00 (0.98-1.03)	0.76

FIGURE 4 Time-to-first-treatment (TTFT) for patients with Chronic Lymphocytic Leukemia (CLL) by environmental exposures prior to the time of diagnosis shown for males.



Characteristic	N Females	Events	HR (95% CI)	p
Blood transfusion	280	97	0.32 (0.16-0.62)	0.001
Height (per 10 cm)	412	174	0.82 (0.66-1.02)	0.08
Atopy	417	177	0.76 (0.56-1.03)	0.08
Allergies	417	177	0.83 (0.61-1.14)	0.26
Smoking	415	177	1.00 (0.73-1.35)	0.98
BMI (per 5 kg/m^2)	402	169	0.93 (0.79-1.10)	0.40
BMI young (per 5 kg/m^2)	271	90	0.93 (0.66-1.31)	0.68
Weight (per 5-kg)	407	171	0.97 (0.91-1.03)	0.32
FH of any hematological	383	154	0.80 (0.48-1.34)	0.40
Alcohol consumption	327	124	1.01 (0.68-1.50)	0.98
Any autoimmune disease	417	177	0.89 (0.53-1.49)	0.66
HHV-cold blisters	327	119	1.17 (0.79-1.73)	0.43
HHV-zoster	327	119	0.67 (0.21-2.15)	0.50
Mononucleosis	412	174	1.30 (0.76-2.24)	0.34
Eczema	414	175	0.68 (0.41-1.12)	0.13
Food Allergy	391	167	0.77 (0.43-1.40)	0.40
Hay Fever	391	167	0.84 (0.57-1.22)	0.36
Physical Activity (h/w)	44	20	1.06 (0.55-2.06)	0.86
Total sun exposure (h/w)	249	86	0.97 (0.92-1.02)	0.25

FIGURE 5 Time-to-first-treatment (TTFT) for patients with chronic lymphocytic leukemia (CLL) by environmental exposures prior to the time of diagnosis shown for females.

A shorter TTFT was seen in univariate analyses for taller patients (HR = 1.1, 95%CI: 1.01–1.19, $p = 0.03$) and patients with a higher weight (HR = 1.03, 95%CI: 1.00–1.06, $p = 0.02$) (Table S2); however, this was attenuated when adjusting for sex, study, and CLL-IPI (Figure 3 and Table S2). No other exposures were associated with TTFT overall (Table S2) including family history of hematological malignancy, smoking status, physical activity, or sun exposure. When stratifying the analysis by sex (Figures 4 and 5), history of blood transfusion was associated with a longer TTFT among females both in univariate (HR = 0.5, 95%CI: 0.26-0.95, $p = 0.04$) and multivariable (HR = 0.32, 95%CI: 0.16–0.62, $p = 0.001$) analysis as was adult height and atopy (Figure 5 and Table S2). No evidence for associations was observed among males (Figure 4 and Table S2).

4 | CONCLUSION

TTFT was in our cohort shorter for patients with high/very high-risk CLL-IPI than those with low/intermediate risk CLL-IPI. However, little to no consistent evidence of any associations of the investigated lifestyle exposures was found to be associated with TTFT, univariately or when adjusting for CLL-IPI, except for women having a history of blood transfusion. Family history of hematological malignancy, medical history, and lifestyle factors added no prognostic information beyond CLL-IPI and indicated that these exposures before diagnosis have a limited impact on the natural course of CLL. Thus, patients could be counseled that their personal traits and lifestyle habits investigated here likely will have a very limited impact on TTFT for their CLL disease course.

The risk of CLL has a strong inherited component [10] and pronounced risks have been described in individuals with a family history of CLL [11]. Herein, we demonstrated that familial association is not associated with TTFT. Our finding of a longer TTFT for women with a history of blood transfusion may be explained by these patients likely having had another disease (or planned surgery) and having been investigated (with a full blood count) for that reason, which would lead to an earlier diagnosis of CLL.

The novel findings in this study, that an epidemiologic exposure does not add prognostic information beyond clinical characteristics, can provide valuable information to patients, as they can be told that medical history and lifestyle factors evaluated herein are not likely to affect the aggressiveness of their disease. One might expect that individuals with a normal body mass index (BMI), without medical history conditions (such as atopy/allergy and autoimmunity), non-smokers, and never drinkers would have a more favorable (indolent) disease course, but this was not seen. In case of a later need for treatment for CLL, those factors might however affect treatment tolerance and risk of other severe complications such as secondary infections and secondary malignancies, all different outcomes than TTFT. Moreover, established factors predicting short TTFT in CLL include CLL-IPI [9] and its components, the IPS-E score/tumor mutational load [12, 13], and complex karyotype [14]. These factors are better at predicting TTFT than environmental exposures. The incidence of CLL has also been stable since the millennium, indicating no major changes in risk factor patterns with modern living conditions and strengthening the autoantigen or genetic hypothesis for this disease. The prevalence of CLL is increasing due to improved survival secondary to the impact of novel drugs [15]. Personal traits might also influence other important outcomes for lymphoma patients, such as the risk of second malignancies and secondary infections. Here we believe that having a family history of lymphoma might increase the risk of a new second malignancy as was recently shown in MCL [16]. For secondary infections we believe the need for treatment and given treatment is the strongest predicting factor [17] but personal traits likely also contribute [18]. Those different outcomes were not tested in this study.

The strengths of this investigation were the use of biological knowledge and scoring tools at the same time as the availability of rich environmental data in a large, well-powered cohort of CLL patients from multiple institutions. This facilitated a broad perspective on prognostic factors including biological, clinical, and environmental factors. Limitations include potential recall bias and participation bias, and some of the exposure variables were available only for the Mayo Clinic study.

In this pooled cohort study enriched with key clinical and prognostic molecular data, we examined modifiable and non-modifiable medical history and lifestyle factors for their impact on TTFT. We found limited impact from modifiable factors on the natural history of the disease providing valuable knowledge, and potential relief, to share with patients at the time of diagnosis.

AUTHOR CONTRIBUTIONS

Ingrid Glimelius, Geffen Kleinstern, Susan L. Slager, and Karin E. Smedby designed the study. Dennis P. Robinson performed statistical analyses and Ingrid Glimelius wrote the first draft of the paper. Henrik Hjalgrim, Klaus Rostgaard, Carsten Utoft Niemann, and Karin E. Smedby collected data on SCALE patients and controls, and Susan L. Slager, James R. Cerhan, ML, Paul J. Hampel, and Sameer A. Parikh, collected data on Mayo Clinic patients. Larry Mansouri, Mattias Mattsson, Carsten Utoft Niemann, and Richard Rosenquist contributed molecular data for CLL-IPI. All authors contributed to the revision and approval of the final paper. Ingrid Glimelius and Geffen Kleinstern contributed equally to the first authorship and Susan L. Slager and Karin E. Smedby contributed equally to the last authorship.

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CONFLICT OF INTEREST STATEMENT

Karin E. Smedby: received honoraria from Celgene and research support from Janssen. Ingrid Glimelius received honoraria from Janssen and participated in a real-world data study sponsored by Takeda. Richard Rosenquist received honoraria from AbbVie, AstraZeneca, Illumina, Janssen, and Roche. DSMC (Data Safety Monitoring Committee) for Agios Pharm, Astra Zeneca, Cytomx Therapeutics, Rigel. Advisory Board for Cytomx Therapy, Pharmacyclics, Dava Oncology, Juno Therapeutics, Oncotracker, and Abbvie. Sameer A. Parikh: Research funding has been provided to the institution (Mayo Clinic) from Janssen, AstraZeneca, Merck, and Genentech for clinical studies in which Sameer A. Parikh is a principal investigator. Honoraria has been provided to the institution (Mayo Clinic) from Pharmacyclics, Merck, AstraZeneca, Janssen, Genentech, Amgen, MingSight Pharmaceuticals, TG Therapeutics, Novalgen Limited, Kite Pharma, and AbbVie for Sameer A. Parikh's participation in consulting activities/advisory board meetings. Carsten Utofth Niemann received honoraria and/or research support from AstraZeneca, Abbvie, Janssen, Beigene, Genmab, CSL Behring, Takeda, Octapharma, and MSD. The rest of the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data is a result of two pooled case-control studies and linkages of several nationwide registers as described in the method section. The data is available upon reasonable request from the corresponding author and given that appropriate agreements can be put in place.

ETHICS STATEMENT

The studies were ethically approved according to the Declaration of Helsinki. The cohort protocol for the Mayo Clinic participants was also approved by the Mayo Clinic Institutional Review Board.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all participants.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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