Received: 31 August 2019 | Revised: 28 October 2019 | Accepted: 4 November 2019

DOI: 10.1002/ajh.25681

Increasing prevalence of chronic lymphocytic leukemia with an estimated future rise: A nationwide population-based study

To the Editor:

Population-based data on the prevalence of chronic lymphocytic leukemia (CLL) are lacking. Our aims were to investigate: (i) the prevalence of CLL in Sweden; (ii) changes in the prevalence over time; and (iii) to estimate the future prevalence.

Using national health registries, we calculated the yearly prevalence from 1990 to 2015. The future prevalence was estimated using a model that predicted relative survival for two scenarios: (i) unchanged survival, or (ii) improvement in survival, based on data from pivotal randomized controlled trials.

CLL is the most common leukemia in adults in the Western world, and approximately 60% of all CLL patients require treatment at diagnosis or during follow-up, and have a significantly reduced survival.[1]

New treatment options are being implemented for CLL. Historically, the introduction of more effective first line therapies coincides with a gradual improvement in overall survival,[2] hence the adoption of novel therapeutics into clinical routine is likely to lead to a marked increase in the future prevalence of the disease.

In contrast to available data detailing the incidence of CLL, knowledge about the true prevalence of CLL is scarce and primarily consists of estimates from non-population based cohorts, and do not account for survival improvements.

Sweden has a public health-care system with a well-developed organization of health-care databases and population-based registries, providing an optimal setting for epidemiological studies.[3]

Individuals with a diagnosis of CLL (ICD7, ICD9 204.1 and ICD10 C91.1) between 1958-2015 were identified in the National Cancer Register (National Board of Health and Welfare), established in 1958. Background population sizes, predictions of future population sizes and death rates (from the Swedish Cause of Death register) and data concerning emigration and immigration (from the Register of the Total Population and Population Changes) were obtained from Statistics Sweden. Follow-up data on individuals with a diagnosis of CLL was obtained from the Cause of death register ((National Board of Health and Welfare) and emigration/immigration was considered.

To construct a model to calculate future prevalence (Figure S1), we used data from randomized controlled trials as well as data from the Swedish National CLL Register. The latter to estimate the time elapsed from the publication of novel data until their widespread use in clinical practice, and to retrieve data on the proportion of patients within different age groups and the preferred treatments used.

This study was approved by the Regional Board of Ethics in Uppsala and conducted according to the Helsinki declaration (Dnr 2016/178).

The number of CLL cases at the end of each year, from 1990 to 2015, was calculated based on the total number of individuals diagnosed with CLL, that were still alive and living in Sweden.

Future age-specific incidence rates were assumed to be equal to the average age-specific incidence rates in the previous 10 years (2006-2015) and estimated for the following years.

To estimate the proportion of CLL patients that will survive a specific number of years into the future, relative survival was estimated using a period analysis based on 2011-2015. Relative survival rates were computed as means of the relative survival during this time period. This calculates excessive mortality associated with the diagnosis of CLL whether directly associated with the disease or not. The estimates of relative survival were then used in conjunction with predictions of future (expected) mortality rates, to predict overall survival among living CLL patients at the end of 2015, and among predicted future cases (2016-2060).

The future estimated mortality rates were based on the prognostication of population sizes and death rates from the Database of Statistics, Sweden.

Relative survival was estimated up to 10 years after diagnosis, and extrapolated by assuming a constant excess mortality rate after 10 years, equal to the average between 8 and 10 years after diagnosis. By using a flexible parametric model, with age at diagnosis included as a restricted cubic spline, relative survival could be estimated for all ages (Figure 1A).[4] This enabled us to calculate the prevalence, as well as the absolute number of patients with CLL for each year.

Future prevalence was estimated using two scenarios: (i) unchanged relative survival; (ii) a "best case" scenario with improvement in survival.

We found that the age-standardized incidence of CLL in Sweden has remained stable for both men and women since 2000 (Figure 1B). New treatments were fully implemented in Sweden within 5 years of the publication of robust, large-scale data and there were no major changes in disease characteristics at diagnosis over time. (Figure S2 and Table S1).

We calculated the actual prevalence of CLL in Sweden in 2015 to 52.0/100000 inhabitants. A continuous improvement in 5-year overall and relative survival over time was seen (Figure 1C). Between 2000 and 2015, an increase in the prevalence of CLL was observed from 33.3/100000 to 52.0/100000 inhabitants, that is, an increase of 56% [52.0 / 33.3 = 1.56] over 15 years. This corresponds to an increase in the absolute number of patients from 2954 to 5124 cases [5124/2954 = 1.73), i.e., of 73%.

We then estimated the future prevalence assuming the relative survival to remain unchanged. This leading to an estimated increase of the prevalence from 52.0 cases/100000 in 2015 to 60.6 cases/100000 in 2025 and 66.5 cases/100000 in 2035, that is, an increase of 17% and 28% over 10 and 20 years respectively.

This corresponds to an increase in the absolute number of patients with CLL from 5124 in 2015 to 6641 in 2025 and 7737 in

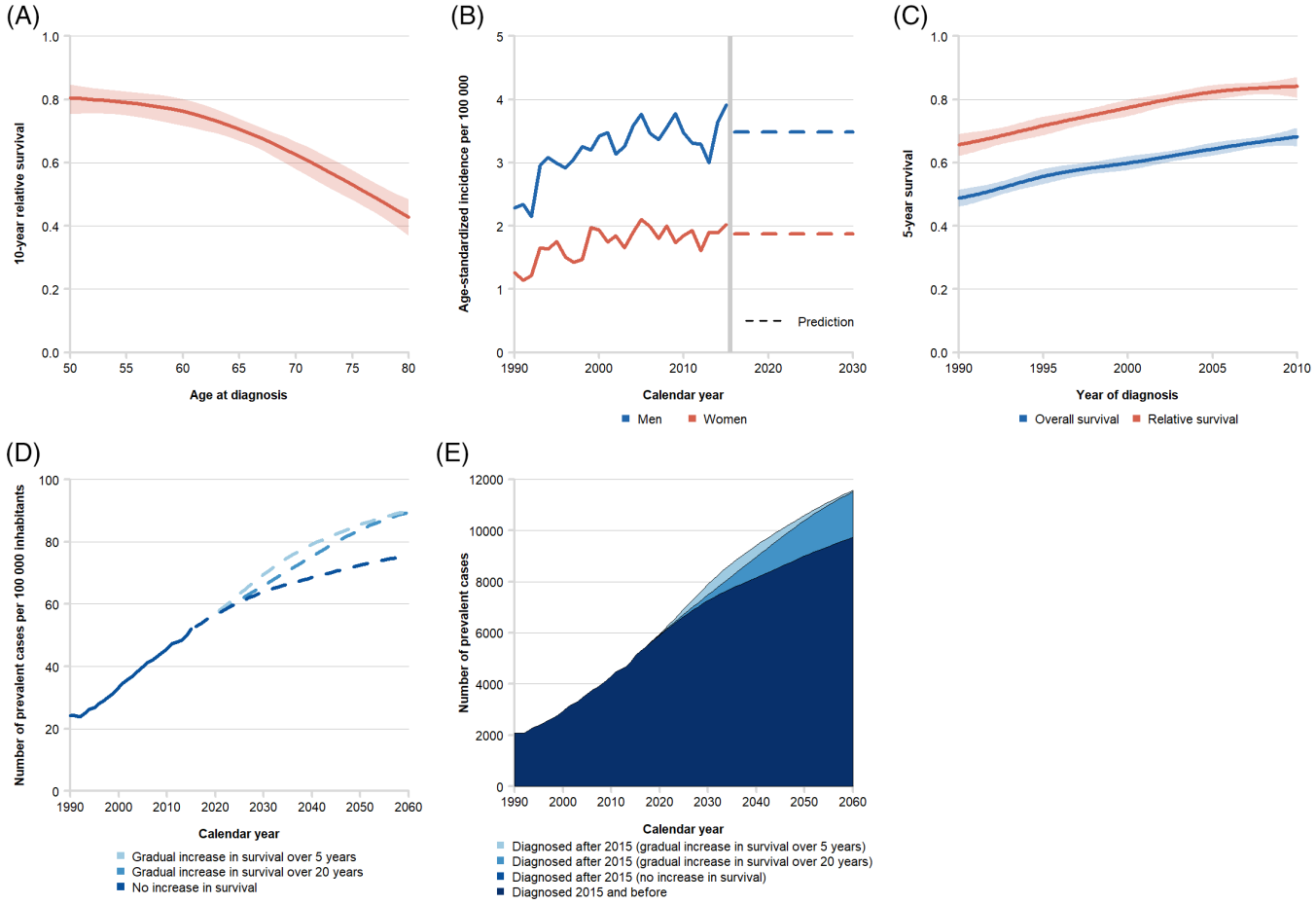

FIGURE 1 A, Estimates of relative survival according to age at diagnosis. B, Age-standardized incidence (per 100 000 person per year) of CLL cases in Sweden. Data from 1990-2015 along with the predicted future incidence of CLL. Age-standardized according to the World population. C, Five-year relative and overall survival for CLL patients diagnosed in Sweden between 1990 and 2010. D, Prevalence of CLL/100000 inhabitants in Sweden, with predictions up until the year 2060 included and (E) Prevalence of CLL in Sweden in absolute numbers, with predictions up until the year 2060 included

2035, that is, an increase in absolute numbers of 30% and 51% over 10 and 20 years respectively.

Next, we assumed an increase in survival using a "best-case" scenario, using our model as described above, and assuming that the implementation of new treatments would be complete within 5 years.

This resulted in an estimated increase of the prevalence, from 52.0 cases/100000 in 2015 to 63.1 cases/100000, in 2025 and 74.9 cases/100000 in 2035, that is, an increase of 21% and 44% over 10 and 20 years respectively. This corresponds to an increase in the absolute number of patients with CLL from 5124 in 2015 to 6920 in 2025 and 8724 in 2035, that is, an increase in absolute numbers of 35% and 70% over 10 and 20 years respectively.

All these data are summarized in Figure 1D,E and in Table S3.

A recent study on health-costs in CLL by Chen et al,[5] using SEER data and including estimates of future survival based on the introduction of new drugs, estimated the absolute number of CLL cases as 130 000 in the US in 2011 (a prevalence of approximately 42 cases/100000 inhabitants [our calculation]). They estimated an increase in the prevalence of 26% in the case of unchanged treatments with CIT as the backbone, and 55% when incorporating new treatments. It is noteworthy that the estimated rise in the absolute number of patients from 2010 to 2025 in the event of improved survival is very similar in our study (61%) and the study by Chen *et al* (55%).

The scenario we present, with a near doubling in the number of patients with CLL over the next 20 years, will have direct implications on healthcare systems.

For Sweden (population: 10 million), when calculating the costs based on the most moderate health economic data available, the direct extra yearly cost due to the estimated increase of CLL cases over the next 10 to 20 years would be approximately US$ 8 100 000 and US$ 16 200 000, respectively (Tables S2, S4). [6]

Our estimation of the future prevalence of CLL has limitations. The calculations on improvements in survival are based on results from clinical trials that do not always reflect the real-world scenario. Economical and health-political decisions could slow the implementation of new treatments. There is also a lack of data regarding the long-term outcomes of these. On the other hand, novel treatments currently in development, and/or new treatment combinations, may

further improve the survival in CLL, leading to a scenario whereby our prediction underestimates the increase in prevalence.

In summary, this first population-based study on the prevalence of CLL found this to be 52.0 cases/100000 inhabitants in 2015, with a steep and steady increase over time, and no tendency to abate. This increase can be explained by the continuous improvment in survival, largely due to the introduction of more efficient treatments, including better risk stratification and supportive measures, and not by changes in: (i) population distribution; (ii) time of diagnosis; or (iii) an increase in the incidence of the disease.

We predict the increase in the absolute number of patients with CLL to be approximately 70% over the next 20 years.

Our results have obvious pharmacoeconomic implications, and could also be used in discussing future resource utilization and the planning of care for CLL patients. Finally, we believe that our results can serve as a valid base-line for future population-based studies investigating the effects of new treatments on survival and prevalence of CLL.

ACKNOWLEDGMENTS

The authors want to thank Lesley-Ann Sutton, PhD for valuable help in reviewing the manuscript regarding content and language and Fereshte Ebrahim, statistician at Regional Cancer Centre Stockholm/Gotland for help with CLL Register data.

We want to thank the data managers at the respective Regional Cancer Centers as well as all Swedish hematologists who have carefully reported patients to the Swedish CLL Register.

Finally, we want to thank the Swedish CLL-group for their valuable support of this study.

This work was supported by funding from the Swedish CLL-group. IGs work was supported by Cancerfonden.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

MM, FS, EK, IG and MH designed the study and wrote the manuscript. MM contributed summary of studies used to calculate improvement in survival. FS performed the statistical analysis.

Mattias Mattsson[1,2], Fredrik Sandin[3], Eva Kimby[4], Martin Höglund[2,5], Ingrid Glimelius[6]

[1]*Department of Immunology, Genetics and Pathology Uppsala University, Uppsala, Sweden*

[2]*Department of Hematology, Uppsala University Hospital, Uppsala, Sweden*

[3]*Regional Cancer Centre Uppsala/Örebro, Uppsala, Sweden*

[4]*Department of Hematology Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden*

[5]*Department of Medical Sciences, Uppsala University, Uppsala, Sweden*

[6]*Department of Immunology, Genetics and Pathology, Unit of Clinical and Experimental Oncology, Uppsala University, Uppsala, Sweden*

Correspondence

Mattias Mattsson, MD, Department of Haematology. Uppsala University Hospital, S-751 85 Uppsala, Sweden.

Email: mattias.mattsson@akademiska.se

ORCID

Mattias Mattsson https://orcid.org/0000-0002-9510-8801

REFERENCES

1. Scarfo L, Ferreri AJ, Ghia P. Chronic lymphocytic leukaemia. *Crit Rev Oncol Hematol*. 2016;104:169-182.
2. da Cunha-Bang C, Simonsen J, Rostgaard K, Geisler C, Hjalgrim H, Niemann CU. Improved survival for patients diagnosed with chronic lymphocytic leukemia in the era of chemo-immunotherapy: a Danish population-based study of 10455 patients. *Blood Cancer J*. 2016;6(11):e499.
3. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish cancer register: a sample survey for year 1998. *Acta Oncol*. 2009;48(1):27-33.
4. Lambert PC, Wilkes SR, Crowther MJ. Flexible parametric modelling of the cause-specific cumulative incidence function. *Stat Med*. 2017;36(9):1429-1446.
5. Chen Q, Jain N, Ayer T, et al. Economic burden of chronic lymphocytic leukemia in the era of oral targeted therapies in the United States. *J Clin Oncol*. 2017;35(2):166-174.
6. Frey S, Blankart CR, Stargardt T. Economic burden and quality-of-life effects of chronic lymphocytic leukemia: a systematic review of the literature. *Pharmacoeconomics*. 2016;34(5):479-498.

SUPPORTING INFORMATION

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