Survival continues to increase in chronic lymphocytic leukaemia: a population-based analysis among 20 468 patients diagnosed in the Netherlands between 1989 and 2016

Chronic lymphocytic leukaemia (CLL) is the most frequently diagnosed and prevalent form of leukaemia among adults in Western countries (Brenner *et al.*, 2008; Kristinsson *et al.*, 2009; Van den Broek *et al.*, 2012). The gradual increase in life expectancy in Western countries over the past decades is one of the contributing factors that brought about the increasing incidence and prevalence of CLL, particularly among the elderly (Van den Broek *et al.*, 2012). Also, diagnostic procedures have been refined, leading to increased detection of CLL at an earlier stage (Bennett *et al.*, 1989). Besides, the therapeutic armamentarium of CLL has rapidly evolved with improvements in supportive care and risk-adapted therapy, and, more importantly, the advent of purine analogues, anti-CD20 agents, kinase inhibitors, and pro-apoptotic agents (Hallek, 2017). Despite the significant advances in diagnosis, prognostication, and treatment of CLL over the past decades, it is mostly unknown how these advances have impacted the survival of patients with CLL at the population level, especially among contemporarily diagnosed patients.

At present, large, representative population-based studies on this issue are scant and mostly do not encompass patients managed with first- and second-generation anti-CD20 agents, kinase inhibitors, and pro-apoptotic agents (Brenner *et al.*, 2008; Kristinsson *et al.*, 2009; Thygesen *et al.*, 2009; Van den Broek *et al.*, 2012). Therefore, the aim of this contemporary, nationwide, population-based study was to assess trends in short-term and long-term excess mortality among patients with CLL diagnosed during a 28-year period in the Netherlands.

We selected all patients with CLL diagnosed between January 1, 1989 and December 31, 2016 – with follow-up for survival until January 1, 2019 – from the nationwide population-based Netherlands Cancer Registry (NCR), using International Classification of Diseases for Oncology morphology code 9823. Details about the registry are provided in the Supporting Information (Data S1).

Relative survival rates (RSRs) were calculated for four calendar periods of diagnosis (1989–1995, 1996–2002, 2003–2008 and 2009–2016) and four age categories at diagnosis (18–59, 60–69, 70–79 and ≥80 years) and measured from the time of diagnosis to death, emigration, or end of follow-up, whichever occurred first. Relative survival (RS) is the overall survival (OS) in the patient cohort divided by the expected OS of an equivalent group from the general population, matched to the patient group by age, sex, and period (Dickman & Adami, 2006). Multivariable evaluation of RS using Poisson regression was performed to assess linear trends in RS over time and the relative excess risk of mortality. A $P < 0{\cdot}05$ indicated statistical significance. Further details about the statistical analyses are provided in Data S1. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

Baseline characteristics of 20 468 patients with CLL (median age, 69 years; range 21–101 years; 61% males) included in this study are presented in Table SI. The overall age-standardised incidence rate (ASR) of CLL gradually increased over time, but remained comparatively steady from 2003 onwards (Table SI and Figure S1). Throughout the entire study period, a consistent male predominance was observed (Table SI and Figure S1). The age-specific incidence rises sharply with older age (Figure S2).

Patients across all age groups experienced ongoing excess mortality – as compared to the general population – in all calendar periods studied (Figure 1). Nevertheless, RSRs improved with each calendar period across all age groups. The multivariable model confirmed an improvement of RS across all age groups in the most recent calendar period (2009–2016) – as compared to the calendar period 2003–2008 – and showed a poor prognostic effect of male sex (up to age 80) and a previous malignancy before CLL diagnosis (Table I).

In this contemporary, nationwide, population-based study, we demonstrated that the overall ASR of CLL gradually increased until it remained comparatively steady from 2003 onwards. Similar trends were observed in Denmark and Sweden (Kristinsson *et al.*, 2009; Thygesen *et al.*, 2009). The initial increase can probably be explained by several factors. First, general practitioners and hospital-based physicians might nowadays be more diligent in requesting routine blood tests, potentially leading to the enhanced detection of early, asymptomatic CLL. Furthermore, the incidence of CLL might be overestimated, because most patients diagnosed with Rai stage 0 or I before 2008 can be reclassified into monoclonal B-cell leukaemia according to the most recent diagnostic criteria (Hallek *et al.*, 2008). On the other hand, the incidence might be underestimated in these earlier calendar periods, because CLL is most frequently diagnosed by flow cytometry

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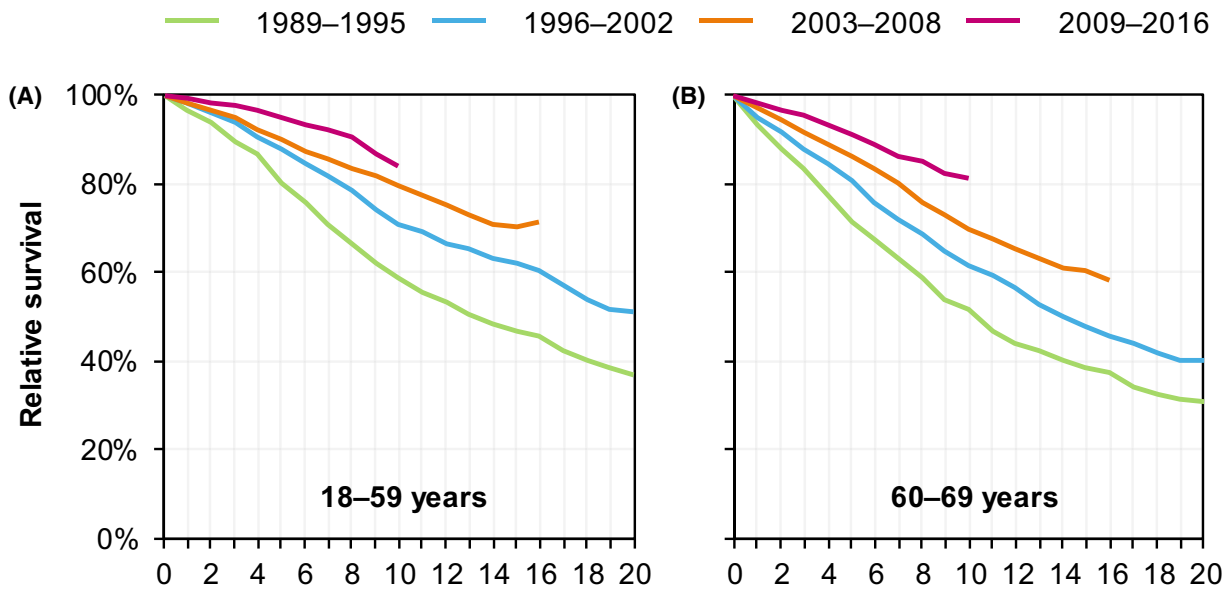
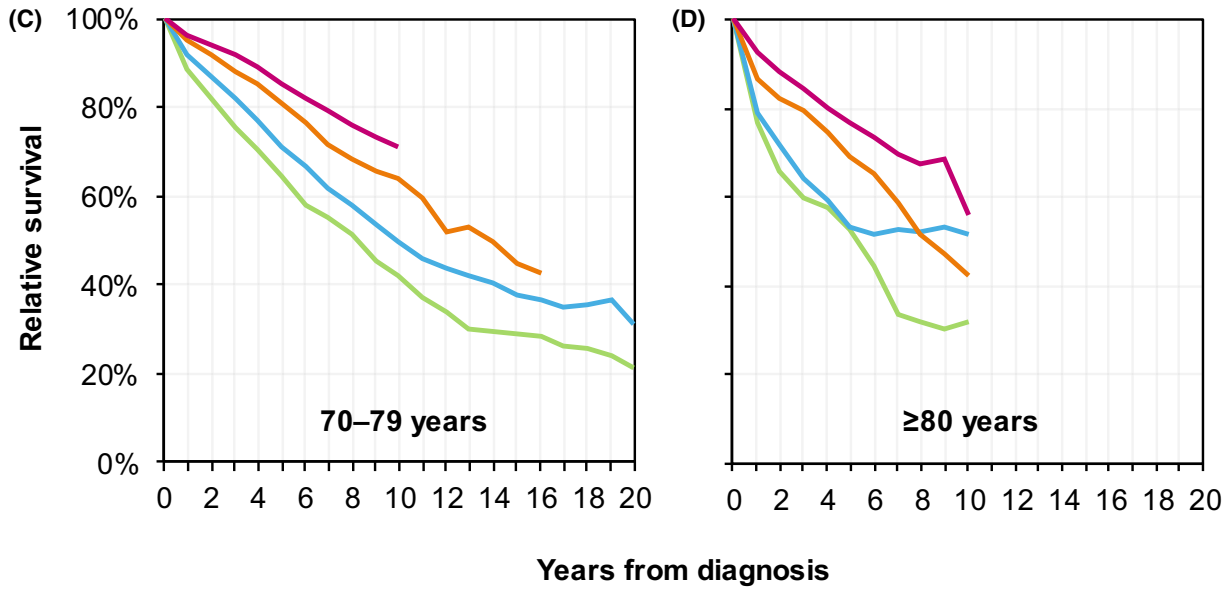


RSR	Calender period				*P* for trend*
	1989–1995	1995–2002		2009–2016	
	RSR (in%) with 95% CI				
5-year	80 (77–84)	88 (86–90)	90 (88–92)	95 (94–96)	<0·001
10-year	59 (54–63)	71 (68–74)	80 (77–82)	84 (79–88)	<0·001

	Calender period				*P* for trend*
	1989–1995	1995–2002	2003–2008	2009–2016	
	RSR (in%) with 95% CI				
5-year	72 (68–75)	81 (78–83)	86 (84–88)	91 (89–93)	<0·001
10-year	51 (48–55)	62 (58–65)	70 (67–73)	81 (77–85)	<0·001



RSR	Calender period				*P* for trend*
	1989–1995	1995–2002	2003–2008	2009–2016	
	RSR (in%) with 95% CI				
5-year	64 (61–68)	71 (68–74)	81 (78–84)	85 (83–88)	<0·001
10-year	42 (37–47)	50 (46–54)	64 (60–68)	71 (64–78)	<0·001

	Calender period				*P* for trend*
	1989–1995	1995–2002	2003–2008	2009–2016	
	RSR (in%) with 95% CI				
5-year	52 (46–59)	53 (47–60)	69 (63–75)	77 (71–82)	<0·001
10-year	32 (23–43)	51 (40–64)	42 (34–52)	56 (37–79)	<0·001

Fig 1. Relative survival of patients with chronic lymphocytic leukaemia diagnosed in the Netherlands according to calendar period of diagnosis and age at diagnosis, 1989–2016. Relative survival is shown for four calendar periods according to the following four age categories: (A) 18–59, (B) 60–69, (C) 70–79, and (D) ≥80 years. The tables present the projected 5- and 10-year relative survival rates (RSRs) with 95% confidence intervals (CIs) according to calendar period of diagnosis for the four age categories. *, *P*-value for likelihood ratio test assessing linear trends between the first and last calendar period. RSRs for patients aged ≥80 years were truncated at 10 years, since comparatively few patients in this age group were alive 10 years after their diagnosis.

Table I. Excess mortality ratio during the first 10 years after chronic lymphocytic leukaemia diagnosis across different age groups.

Age at diagnosis	Covariate	EMR*	95% CI	P†
18–59	Period of diagnosis			
	1989–1995	2·30	1·89–2·80	<0·001
	1996–2002	1·47	1·21–1·79	<0·001
	2003–2008	1	(ref)	
	2009–2016	0·62	0·48–0·81	<0·001
	Female sex	0·65	0·55–0·77	<0·001
	Previous malignancy	1·65	1·21–2·25	0·002
60–69	Period of diagnosis			
	1989–1995	2·00	1·71–2·35	<0·001
	1996–2002	1·40	1·19–1·65	<0·001
	2003–2008	1	(ref)	
	2009–2016	0·59	0·48–0·72	<0·001
	Female sex	0·60	0·52–0·68	<0·001
	Previous malignancy	1·40	1·14–1·72	0·001
70–79	Period of diagnosis			
	1989–1995	2·13	1·80–2·51	<0·001
	1996–2002	1·59	1·35–1·88	<0·001
	2003–2008	1	(ref)	
	2009–2016	0·72	0·60–0·87	0·001
	Female sex	0·59	0·52–0·67	<0·001
	Previous malignancy	1·94	1·67–2·25	<0·001
≥80	Period of diagnosis			
	1989–1995	1·88	1·50–2·34	<0·001
	1996–2002	1·44	1·14–1·82	0·002
	2003–2008	1	(ref)	
	2009–2016	0·58	0·44–0·76	<0·001
	Female sex	0·98	0·83–1·16	0·830
	Previous malignancy	1·49	1·20–1·84	<0·001

EMR, excess mortality ratio; CI, confidence interval.
*All covariates are simultaneously adjusted.
†*P*-values are compared with the reference category.

and most cancer registries primarily rely on pathology reports for case notification (Zent *et al.*, 2001). Thus, although the NCR does not solely rely on pathology reports for case notification, the ascertainment of early, asymptomatic CLL might be underestimated in the NCR in earlier periods (i.e. between 1989 and 2003).

A noteworthy finding of our study was that RS of CLL improved continuously over the calendar periods studied. This finding is congruent with results observed in the paucity of prior population-based studies from the United States (1980–2011), Germany (1997–2011), Denmark (1943–2003) and Sweden (1973–2003). Encouragingly enough, RSRs in the most recent calendar period of our study (2009–2016) surpassed those reported in the aforementioned studies (Brenner *et al.*, 2008; Kristinsson *et al.*, 2009; Thygesen *et al.*, 2009; Pulte *et al.*, 2016). Advances in supportive care (i.e. transfusions, growth factors, and antibiotics) and therapy are key factors that contributed to the improvement in RS over time. However, a normalised plateau in RS has not been reached, suggesting ongoing excess mortality for the overall patient population. Recent progress with kinase inhibitors (e.g. ibrutinib) and pro-apoptotic agents (e.g. venetoclax) might further reduce excess mortality in CLL. However, the benefit of these novel agents cannot be entirely objectivated in this study, since these modalities were not widely implemented for routine application in CLL in the Netherlands during the study period.

The main strengths of our study include the use of a nationwide population-based cancer registry with comprehensive data available for individual patients. Limitations of our study include a lack of information on cytogenetic and molecular diagnostics and treatment throughout most of the registry. Therefore, it is not possible to correct for changes in the classification of CLL over time.

In summary, in this large, contemporary, nationwide population-based study, RS improved significantly over time among patients with CLL across all age groups. The current study provides a benchmark for future research to evaluate the impact of a broader application of kinase inhibitors and anti-apoptotic agents on RS.

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Conflicts of interest

The authors declare to have no potential conflicts of interest regarding the present work.

Author contributions

AGD and LvdS designed the study; LvdS analysed the data; AGD supervised the data analyses; OV collected the data; LvdS wrote the manuscript with contributions from all authors, who also interpreted the data, and read, commented on, and approved the final version of the manuscript.

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Supporting Information

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

Figure S1. Age-specific incidence rates of patients with chronic lymphocytic leukaemia in the Netherlands according to age, 1989–2016. Incidence rates are presented per 100 000 person-years and shown according to the following sexes: (A) males and females together, (B) males alone, and (C) females alone.

Figure S2. Age-specific incidence rates of patients with chronic lymphocytic leukaemia in the Netherlands per quinquennial years of age, 2003–2016. Incidence rates are presented per 100 000 person-years and shown according to sex. The period of 2003–2016 was chosen, as the incidence of CLL in the Netherlands remained comparatively steady as from 2003.

Table SI. Patient characteristics.

Data S1. Supplemental methods.

References

Bennett, J.M., Catovsky, D., Daniel, M.T., Flandrin, G., Galton, D.A., Gralnick, H.R. & Sultan, C. (1989) Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. French-American-British (FAB) Cooperative Group. *Journal of Clinical Pathology*, **42**, 567–584.

Brenner, H., Gondos, A. & Pulte, D. (2008) Trends in long-term survival of patients with chronic lymphocytic leukemia from the 1980s to the early 21st century. *Blood*, **111**, 4916–4921. https://doi.org/10.1182/blood-2007-12-129379.

Dickman, P. & Adami, H. (2006) Interpreting trends in cancer patient survival. *Journal of Internal Medicine*, **260**, 103–117. https://doi.org/10.1111/j.1365-2796.2006.01677.x.

Hallek, M. (2017) Role and timing of new drugs in CLL. *Hematological Oncology*, **35**, 30–32. https://doi.org/10.1002/hon.2397.

Hallek, M., Cheson, B.D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Döhner, H., Hillmen, P., Keating, M.J., Montserrat, E., Rai, K.R. & Kipps, T.J. (2008) Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*, **111**, 5446–5456. https://doi.org/10.1182/blood-2007-06-093906.

Kristinsson, S.Y., Dickman, P.W., Wilson, W.H., Caporaso, N., Björkholm, M. & Landgren, O. (2009) Improved survival in chronic lymphocytic leukemia in the past decade: a population-based study including 11,179 patients diagnosed between 1973–2003 in Sweden. *Haematologica*, **94**, 1259–1265.

Pulte, D., Castro, F.A., Jansen, L., Luttmann, S., Holleczek, B., Nennecke, A., Ressing, M., Katalinic, A. & Brenner, H. (2016) Trends in survival of chronic lymphocytic leukemia patients in Germany and the USA in the first decade of the twenty-first century. *Journal of Hematology & Oncology*, **9**, 28.

Thygesen, L.C., Nielsen, O.J. & Johansen, C. (2009) Trends in adult leukemia incidence and survival in Denmark, 1943–2003. *Cancer Causes & Control*, **20**, 1671.

Van den Broek, E., Kater, A., van de Schans, S., Karim-Kos, H., Janssen-Heijnen, M., Peters, W., Nooijen, P., Coebergh, J. & Posthuma, E. (2012) Chronic lymphocytic leukaemia in the Netherlands: trends in incidence, treatment and survival, 1989–2008. *European Journal of Cancer*, **48**, 889–895.

Zent, C.S., Kyasa, M.J., Evans, R. & Schichman, S.A. (2001) Chronic lymphocytic leukemia incidence is substantially higher than estimated from tumor registry data. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, **92**, 1325–1330.