Improved survival in chronic lymphocytic leukemia in the past decade: a population-based study including 11,179 patients diagnosed between 1973-2003 in Sweden

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ABSTRACT

Background

Clinical management of chronic lymphocytic leukemia patients has changed considerably over the last years, reflected in an increased use of prognostic markers, new therapeutic agents and procedures, and supportive care measures. However, to date, clinical trials have not shown a survival benefit.

Design and Methods

Using population-based data from Sweden, we assessed variations in survival among all chronic lymphocytic leukemia patients (n=11,179) reported from 1973-2003. Relative survival ratios were computed as measures of patient survival.

Results

Overall we found significantly improved (p<0.0001) 5-, 10-, and 20-year relative survival ratio for the entire cohort during the study period. Improved 5- and 10-year relative survival ratio was found for all age-groups (p<0.0001) and both sexes. Compared to females, however, males had a significantly inferior survival in all age groups and calendar periods (p<0.0001). Younger chronic lymphocytic leukemia patients had a superior survival compared to older chronic lymphocytic leukemia patients, in all calendar periods (p<0.0001). Five-year relative survival ratio has not improved in the youngest chronic lymphocytic leukemia patients since the 1980s; however, older patients have had a continuous improvement in 5 year-relative survival ratio.

Conclusions

The observed improvements are likely due to improved therapeutic developments and supportive care. Our findings suggest that elderly chronic lymphocytic leukemia patients might benefit more from the recently introduced drugs in chronic lymphocytic leukemia. Future clinical trials are needed to better define underlying mechanisms of observed heterogeneity in chronic lymphocytic leukemia survival by age and sex, and evaluate the role of newer chronic lymphocytic leukemia therapy in the elderly.

Key words: chronic lymphocytic leukemia, prognosis, survival, sex, older age, population-based.

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia of adults in Western countries with an annual incidence of 2-4.5 per 100,000 in the general population.[1,2] It affects males twice as frequently as females and is a disease of older individuals (median age 73.0 years for whites).[2]

After decades of therapeutic stability, clinical management of CLL patients is now rapidly evolving.[3] Initially, CLL was considered an indolent, relatively homogeneous but incurable disease. The introduction of purine analogs in the early 1980s followed by monoclonal antibodies and immunomodulatory drugs (IMiDs) have revitalized clinical research in CLL.[4] Complementing these new therapies have been the identification of biomarkers such as CD38, immunoglobulin (Ig) mutational status and ZAP-70, that augment prognostication, reflect disease pathogenesis and heterogeneity of the disease, offering the opportunity for risk adjusted treatments.[3,4] Despite such advances, however, clinical trials have yet to show improved overall survival in CLL.[5-8]

Clinical trials, compared to general practice, are associated with a certain degree of patient selection, reflected in under-ascertainment of elderly patients. Typically, the average age at diagnosis of CLL is around ten years younger in clinical trials[5-8] compared to that reported in the general population.[1,2] Indeed, there are only sparse population-based data available on survival patterns in CLL. Using the publicly available US National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) database, Brenner *et al.* recently conducted a population-based study designed to evaluate survival patterns among CLL patients diagnosed in 2000-2004 compared to those diagnosed in 1980-1984.[9] In their study, 5-year survival has improved for all age groups over the past two decades; and increased 10-year survival was observed for all except the oldest patients.[9] Although these findings are intriguing, there are data indicating both a significant delay and under-reporting of CLL to the applied database, and an increase in earlier stage CLL due to changes in diagnostic practices over time.[10,11] As pointed out by Brenner *et al.*, delayed registration and potential under-registration for CLL might impact survival trend analyses for CLL based on the NCI-SEER database while additional studies are needed to confirm and expand their findings.[9]

In order to overcome these deficiencies and assess survival in a whole population, we conducted a large population-based study in Sweden which has provided universal medical health care available for its entire population (currently approximately 9 million people) since the mid-1950s. We identified all CLL patients (n=11,179) diagnosed in the period 1973-2003, with follow-up until December 31, 2004. The aims of the study were to define CLL survival patterns in the Swedish population and evaluate the effect of newly introduced therapeutic agents on survival in the entire population. Since previous studies have suggested that older CLL patients have more aggressive clinical disease and an adverse biomarker profile,[12,13] we hypothesized that it may be possible to detect heterogeneity in survival benefits (i.e. more aggressive disease may receive greater benefit from more effective therapy), measured by longitudinal survival patterns by age.

Design and Methods

Central registers

Information on every patient diagnosed with a malignant disorder in Sweden has been reported to the centralized, nationwide Swedish Cancer Register since 1958 with a nearly complete capture.[14,15] The Swedish Cancer Register contains diagnosis, sex, date of birth, date at diagnosis, and hospital where the diagnosis was made. All physicians are obliged by law to report every cancer case to the registry. In contrast to many other countries, patients with lymphoproliferative malignancies in Sweden are typically diagnosed, treated and followed clinically by physicians at a few hospital-based hematology or oncology centers. Each individual in Sweden receives a unique national registration number and every death date is recorded in the Causes of Death Register. Information on the number of stem cell transplantations in CLL patients reported from Swedish centers during the study period was obtained from the EBMT register.

Patient cohort

Information on all patients diagnosed with CLL from January 1, 1973 to December 31, 2003 was identified in the Swedish Cancer Register (ICD-7 code 204.1); incomplete data were excluded. By linking the registration number to the Causes of Death Register, data on date of death was collected from January 1, 1973 to December 31, 2004. Information was gathered for sex, date of birth, date of diagnosis, date of death, and hospital where the patient was diagnosed. During the study period, hematology/oncology clinics were confined to a few regional university hospitals, which offer inpatient hospital care to a defined primary catchment area in addition to being the referral center for a whole health care region. The remaining hospitals in the country serve regions with fewer inhabitants and offer inpatient care.

We had no access to information on clinical stage, prognostic markers, treatment, or other clinical or laboratory data for the collected cohort. Approval was obtained from the Karolinska and the NIH institutional review boards for these studies. Informed consent was waived because we had no contact with study subjects.

Survival analyses

Relative survival ratios (RSR) were used as the measure of patient survival.[16] RSR has key advantages in that it does not rely on the accurate classification of cause of death; instead it provides a measure of the total CLL associated excess mortality irrespective of whether the excess mortality is directly or indirectly related to CLL. Estimated from life tables, RSR is defined as the observed survival in the patient group (where all deaths are considered events) divided by the expected survival of a comparable group from the general population. Expected survival was estimated using the Hakulinen

method from Swedish population life tables stratified by age, sex, and calendar period.[17] Five-, 10-, and 20-year RSR with 95% confidence intervals (CI) were calculated for CLL patients during four calendar periods: 1973-1979, 1980-1986, 1987-1993, and 1994-2003. Thus, 5-, 10-, and 20-year RSR provide a measure of the fraction of CLL patients who survived their malignancy at five, ten and 20 years.

Using Poisson regression models adjusted for sex, age group (<50, 50-70, and >70 years), calendar period, and hospital category (university *vs.* non-university) at diagnosis, we estimated excess hazard ratios (EHR) of death among CLL patients. All calculations were performed using SAS 8.1 (SAS Institute, Cary, NC, USA).

Results

Between January 1, 1973 and December 31, 2003 a total of 11,179 patients with CLL (mean age 70 years; 62% males) were reported to the Swedish Cancer Registry in Sweden. During the study period, the annual age-adjusted mean incidence for CLL was 6.5 per 100,000 for males and 3.1 per 100,000 for females, respectively. Although rates in men briefly rose to 8.1 per 100,000 in the mid-1980s and declined to 4.7 per 100,000 in the mid-1990s, the overall incidence pattern was stable; for females the age-adjusted incidence pattern was stable. The fraction of CLL patients being diagnosed at University hospitals was 29% (Table 1). Patients diagnosed in non-university hospitals had a 1.12-fold (95% CI 1.04-1.21) higher excess mortality (Table 2). A total of 73 stem cell transplantations [43 allogeneic and 30 autologous (ASCT)] were reported to the EBMT register during the study period, the majority (95%) in the last calendar period.

Overall survival pattern

For patients in all age groups and sexes, the overall 5-year RSR improved with patients diagnosed in the last (1994-2003) calendar period showing a significantly lower excess mortality (EHR=0.30, 95% CI 0.27-0.34) compared to patients diagnosed in the first (1973-1979) calendar period (Table 2). We found that 5-, 10-, and 20-year RSR improved significantly (p<0.0001, likelihood ratio test) for the complete cohort during the study period (Figure 1). The 5-year RSR estimates for the four calendar periods were 0.46, 0.57, 0.62, and 0.73, respectively. The 10-year RSR estimates were 0.24, 0.35, 0.38, and 0.53, respectively. Twenty-year RSR estimates could only be computed for the first and second calendar periods; the estimates for these calendar periods were 0.12 and 0.19, respectively (Table 3).

Survival trends by age

Patients diagnosed at an older age (71+ years) had a 2.64-fold (95% CI 2.22-3.13) higher excess mortality compared to patients diagnosed at a younger age (<50 years) (Table 2). Given the survival variations among age groups, we conducted RSR analyses stratified by age. The youngest (<50 years) patients (n=491) showed improved survival over every time period: 5-, 10-, and 20-year RSR (p<0.0001, likelihood ratio test) (Figure 2 and Table 3). For older (50-70 years) patients (n=4,461), the 5-, 10-, and 20-year RSR all significantly improved (p<0.0001, likelihood ratio test; Table 3). Improvements in RSR for all time periods were also observed for the oldest (>70 years) patients (n=6,227) (p<0.0001, likelihood ratio test; Table 3).

Survival trends by sex

We found a significantly reduced (EHR=0.71, 95% CI 0.66-0.77, p<0.0001, likelihood ratio test) excess mortal-

Table 1. Patients' characteristics at diagnosis.

Variable	N (%)
Total number of CLL patients	11,179 (100)
Sex	
Male	6,880 (62)
Female	4,299 (38)
Age group	
≤50 years	491 (4)
51-70 years	4,461 (40)
71+ years	6,227 (56)
Hospital category	
University hospital	3,220 (29)
Non-university hospital	7,959 (71)
Calendar period	
1973-1979	2,067 (18)
1980-1986	2,594 (22)
1987-1993	2,288 (21)
1994-2003	4,230 (39)
Mean age (years, SD), per calendar period	
1973-1979	70.2 (10.7)
1980-1986	70.7 (11.0)
1987-1993	71.7 (10.3)
1994-2003	70.6 (11.2)

CLL: chronic lymphocytic leukemia; SD: standard deviation.

Table 2. Excess hazard ratios and 95% confidence intervals (CI) of dying during the first ten years after chronic lymphocytic leukemia (CLL) diagnosis, stratified by sex, age group, hospital category, and calendar period at CLL diagnosis.

Variable	Relative hazard[1]	95% CI	p value[#]
Sex			
Male	1.00 (ref.)	NA	<0.0001
Female	0.71	(0.66-0.77)	
Age group			
<50 years	1.00 (ref.)	NA	<0.0001
51-70 years	1.51	(1.27-1.79)	
71+ years	2.64	(2.22-3.13)	
Hospital category			
University hospital	1.00 (ref.)	NA	0.004
Non-university hospital	1.12	(1.04-1.21)	
Calendar period			
1973-1979	1.00 (ref.)	NA	<0.0001
1980-1986	0.71	(0.65-0.78)	
1987-1993	0.60	(0.55-0.66)	
1994-2003	0.30	(0.27-0.34)	

ref: reference; NA: not applicable; #: likelihood ratio test. [1]All risk estimates are simultaneously adjusted for all other variables in the table.

ity for females compared to males (Table 2 and Figure 3). Females had a significantly superior survival in all age groups and calendar periods (p<0.001; Figure 3).

Discussion

In this large population-based cohort study of over 11,000 CLL patients diagnosed in Sweden between 1973 and 2003, we found significantly improved 5-year and, most importantly 10-year CLL survival trends in all age groups. Older CLL patients had a continuous improvement in survival during the whole study period, while younger CLL patients have had a stable survival since the 1980s. Females had consistently better survival over the study period in all age groups. Our survival analyses showed that an increasing proportion of CLL patients survive their malignancy for 20 years, particularly younger patients. To improve our understanding of these survival patterns, we investigated several hypotheses including the influence of therapeutic-, diagnostic-, disease-, and host-related factors.

Initiation of therapy in early stage patients has not been shown to prolong survival,[18] allowing asymptomatic patients to be followed clinically without treatment. Chlorambucil, the standard of care in Sweden throughout the study period,[19] can induce partial remissions but few complete remissions, and survival with this agent has been 3-5 years.[7,20] The purine analog, fludarabine, as a single agent or in combination with cyclophospamide, has been shown to improve response compared to chlorambucil but not survival.[7, 21] Fludarabine had been used as second-line agent in Sweden since the 1990s and has only recently been widely adopted as first-line treatment. Alemtuzumab, a monoclonal antibody targeting CD52 was registered in Sweden in 2001[22] for fludarabine-refractory patients. While it can induce good responses, the effect on survival remains unclear.[23] Rituximab, which targets CD20, has single agent activity[24] and is particularly useful in combination therapy,[25] but was not routinely used during the study period. No prospective randomized clinical trial has found ASCT to improve survival in CLL patients, and it was not used frequently (n=30) during the study period.[26] Allogeneic transplantation is associated with a prolonged overall survival but considerable treatment-related mortality.[27] In our study, allogeneic transplantation was only used in selected patients (n=43) and could only marginally affect the survival estimates. We were able to confirm and expand on the only prior population-based study by Brenner *et al.*,[9] designed to

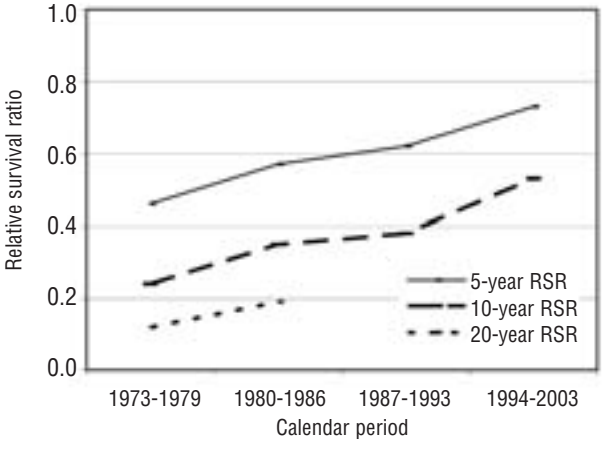

Figure 1. Overall relative survival ratios among chronic lymphocytic leukemia patients diagnosed in Sweden 1973-2003.

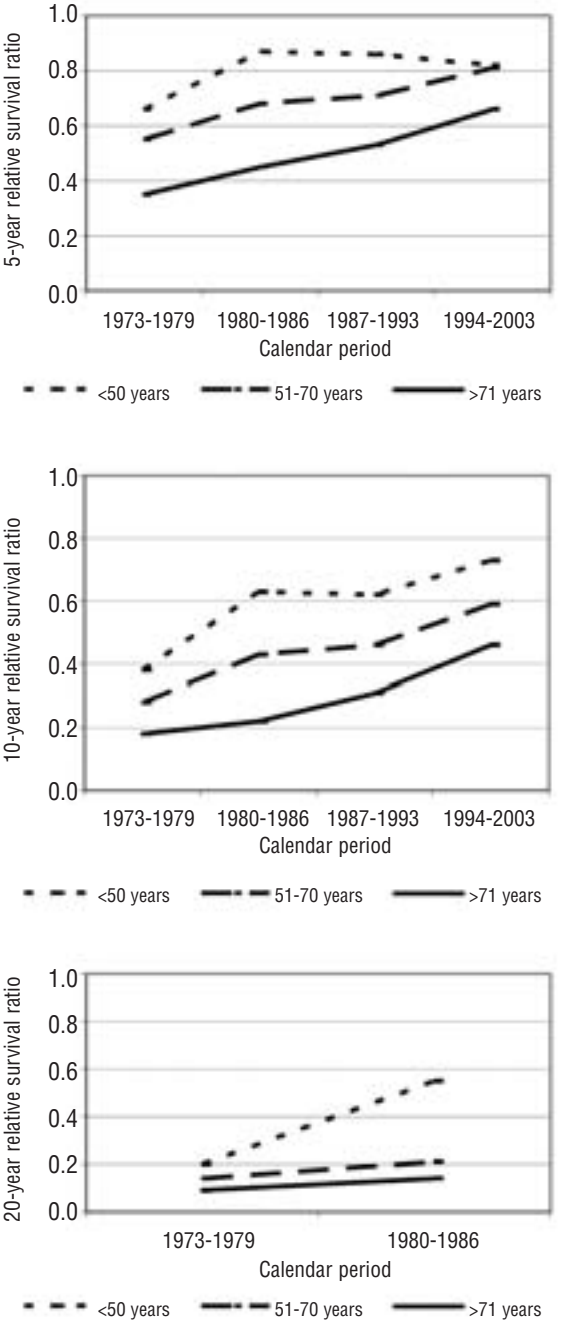

Figure 2. Relative survival ratios among chronic lymphocytic leukemia patients diagnosed in Sweden 1973-2003, stratified by age group at CLL diagnosis.

Table 3. Relative survival ratios (RSR) and 95% confidence intervals (CI) among chronic lymphocytic leukemia (CLL) patients diagnosed in Sweden 1973-2003, stratified by age group at CLL diagnosis.

Age group/calendar period	5-year RSR (95% CI)	10-year RSR (95% CI)	20-year RSR (95% CI)
Combined			
All ages (n=11,179)			
1973-1979	0.46 (0.43-0.49)	0.24 (0.22-0.27)	0.12 (0.10-0.15)
1980-1986	0.57 (0.55-0.60)	0.35 (0.32-0.37)	0.19 (0.16-0.22)
1987-1993	0.62 (0.59-0.64)	0.38 (0.36-0.41)	NA
1994-2003	0.73 (0.71-0.75)	0.53 (0.49-0.57)	NA
<50 years (n=491)			
1973-1979	0.66 (0.54-0.75)	0.38 (0.28-0.49)	0.20 (0.12-0.29)
1980-1986	0.87 (0.79-0.92)	0.63 (0.53-0.72)	0.55 (0.44-0.65)
1987-1993	0.86 (0.76-0.92)	0.62 (0.51-0.72)	NA
1994-2003	0.82 (0.74-0.88)	0.73 (0.62-0.82)	NA
51-70 years (n=4,461)			
1973-1979	0.55 (0.51-0.58)	0.28 (0.25-0.32)	0.14 (0.11-0.17)
1980-1986	0.68 (0.64-0.71)	0.43 (0.39-0.47)	0.21 (0.17-0.25)
1987-1993	0.71 (0.68-0.75)	0.46 (0.41-0.50)	NA
1994-2003	0.81 (0.78-0.83)	0.59 (0.53-0.64)	NA
71+ years (n=6,227)			
1973-1979	0.35 (0.32-0.39)	0.18 (0.14-0.23)	0.09 (0.03-0.21)
1980-1986	0.45 (0.41-0.49)	0.22 (0.19-0.27)	0.14 (0.07-0.23)
1987-1993	0.53 (0.49-0.57)	0.31 (0.26-0.35)	NA
1994-2003	0.66 (0.63-0.70)	0.46 (0.39-0.53)	NA

assess trends in CLL survival patterns over the past decades. In their study, based on US NCI-SEER data, between 1980-1984 and 2000-2004 they observed an improved 5-year survival among CLL patients of all age groups, and improved 10-year survival in all except the oldest patient population.[9] In our study, we observed improved 5- and 10-year survival in all age groups. Differences between these two studies include the fact that we used the total Swedish population as reference group when calculating RSR estimates. In contrast, in the study by Brenner *et al.*, CLL survival from the included states was related to the entire United States population survival. Secondly, Sweden has a well established government-funded public health care system where all residents by law are entitled to equal access to health services. Furthermore, patients with CLL in Sweden are almost exclusively diagnosed, treated, and followed clinically by physicians at non-private hospital-based hematology units.

Most, but not all studies, examining age as a predictor of prognosis, have found older individuals to have poorer survival, and previous studies have reported more lethal CLL disease among older patients.[12,13] The observed improved CLL survival among older patients could be due to better effects of newer therapies on more aggressive CLL or to the fact that improvements in supportive care over time may permit the elderly to benefit more from newer treatments.

We found a stable 5-year RSR of approximately 80-85% among CLL patients diagnosed at the age of 50 or lower over the time period of the study. In contrast to older patients, we found no evidence of improved survival among younger patients since the early 1980s. This age group poses a great clinical and public health challenge due to the impact of shortened life expectancy. Future clinical trials are needed to assess the optimal therapy for younger CLL patients. Also, the number of patients that can be evaluated for 20-year RSR is limited but it does document overall improved survival from the 1973-1979 through the 1980-1986 period, particularly in the younger subjects. Interestingly, females with CLL have been found to have a more favorable prognostic disease profile, for example, less advanced stage and chromosomal abnormalities.[28] We found females to have a 29% lower excess mortality, compared to males, and a consistently superior survival, in all calendar periods and across all age groups, as has been previously reported[29] and similar to the findings from the SEER database.[9] The observed superior survival in females may be due to underlying biological differences, social factors, or differential effects of therapy. Future research is needed to explore underlying mechanisms of these observations.

We found CLL patients diagnosed at university hospitals had a significant 12% lower excess mortality compared to those diagnosed at non-university hospitals. In Sweden, a similar difference has been observed among multiple myeloma patients.[30] The underlying mechanism for the observed differences is probably multifactorial, and could be due to differences in diagnostics, treatment, and supportive care. Alternatively, it could be due to underlying referral mechanisms. For these reasons, the present finding needs to be interpreted with caution. Future work is needed to clarify the exact underlying causes.

An important consideration when interpreting our findings is the potential effect of lead time bias due to early CLL detection. This issue is raised by the increased

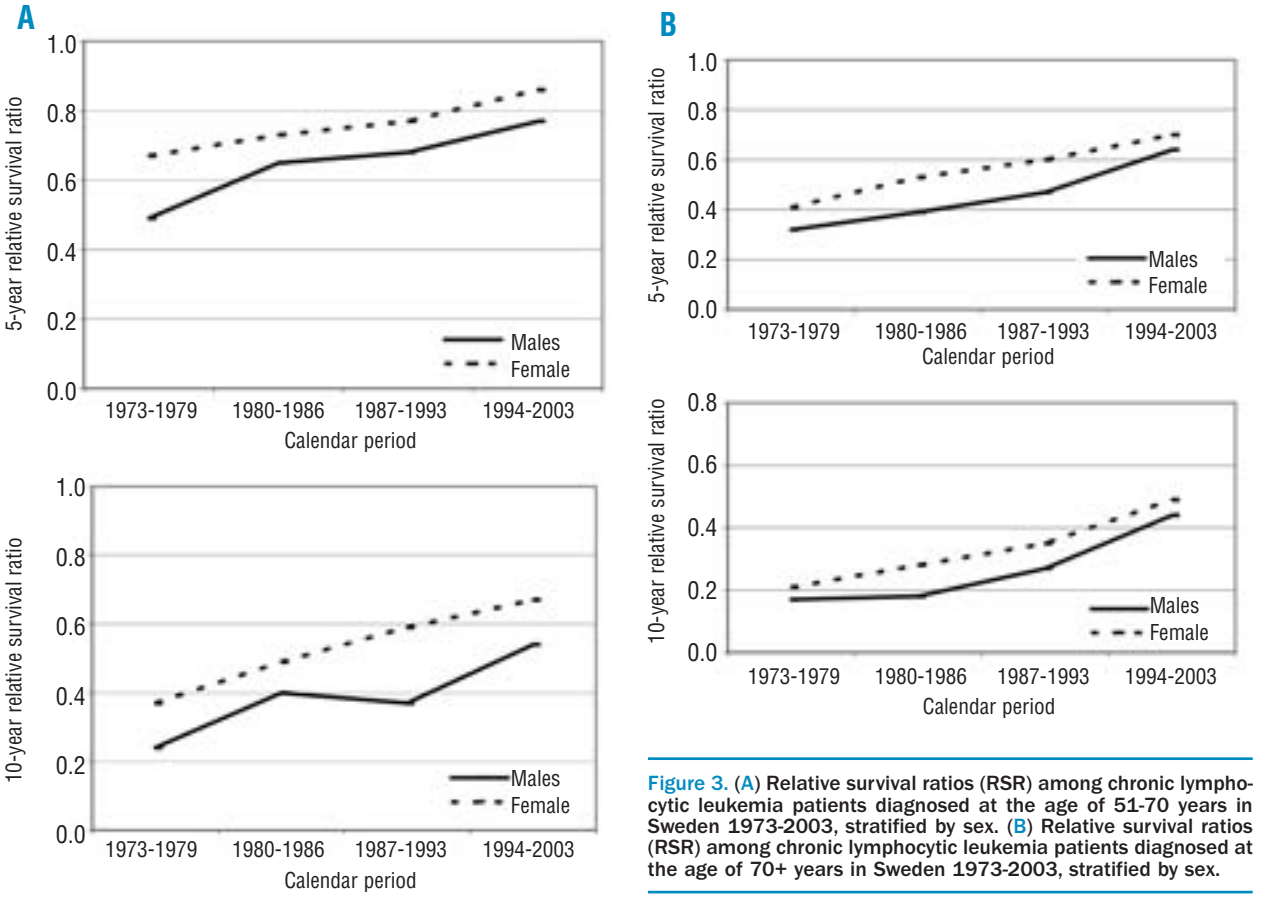

Figure 3. (A) **Relative survival ratios (RSR) among chronic lymphocytic leukemia patients diagnosed at the age of 51-70 years in Sweden 1973-2003, stratified by sex.** (B) **Relative survival ratios (RSR) among chronic lymphocytic leukemia patients diagnosed at the age of 70+ years in Sweden 1973-2003, stratified by sex.**

use of automated cell counters and flow cytometry techniques (employed in Sweden since the early 1990s) and change in diagnostic criteria over time, such as a lower lymphocyte count required to make the diagnosis.[12,31] To help address this question, we recently conducted a nationwide validation study including 202 CLL cases diagnosed in Sweden in the period 1964-2003.[15] In that study, there was about 12% under-reporting of CLL cases to the Swedish Cancer registry. Importantly, when we examined this in greater detail, we observed under-reporting was constant over time and present in all calendar periods; it particularly occurred with elderly CLL patients.[15] In the present study, we evaluated the age-adjusted incidence as well as the mean age at CLL diagnosis (Table 1), and we found both measures to be stable over time. When taken together, we believe these data do not suggest that lead time bias is a major explanation for the improved survival we have observed in CLL.

In our study, we used a register-based cohort design, which ensured a population-based setting and generalization of our findings. Thus, we were able to define the impact of management and treatment strategies in CLL introduced over a 30-year study period in the entire Swedish population. Because the Swedish Cancer Register has a very high diagnostic validity for hematologic malignancies,[14] diagnostic misclassifications should have caused only minimal bias in the present study. Limitations include possible variations in diagnostic practices over time and lack of detailed clinical data.

In conclusion, we found improved 5- and 10-year CLL survival trends for all age groups. Our finding that females had a superior survival confirms a better prognosis compared to males. Younger CLL patients have not improved their survival since the early 1980s. Future clinical trials are needed to assess the role of newer CLL therapies in older patients, with potential major public health implications, given the relatively old average age at diagnosis (about 70 years) for CLL patients in the general population.

Authorship and Disclosures

SYK, MB, WHW, NEC, and OL, designed the study. SYK, MB, and OL obtained data. SYK, PWD, and OL analyzed data. OL initiated this work and SYK and OL wrote the report. All authors were involved in the interpretation of the results, and read, gave comments, and approved the final version of the manuscript. SYK, PWD, and OL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors reported no potential conflicts of interest.

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