The life expectancy of chronic myeloid leukemia patients is approaching the life expectancy of the general population

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Abstract

PURPOSE A dramatic improvement in the survival of chronic myeloid leukemia (CML) patients occurred after the introduction of imatinib myeselate (IM), the first tyrosine kinase inhibitor (TKI). We assess how these changes affect the life expectancy of CML patients and life years lost due to a diagnosis of CML between 1973 and 2013 in Sweden.

MATERIALS AND METHODS Patients recorded as having CML in the Swedish Cancer registry from 1973 to 2013 were included in the study and followed until death, censoring or end of follow-up. The life expectancy and loss in expectation of life were predicted from a flexible parametric relative survival model.

RESULTS 2,662 CML patients were diagnosed between 1973 and 2013. Vast improvements in the life expectancy of CML patients were seen over the study period; larger improvements were seen in the youngest ages. The great improvements in life expectancy translated into great reductions in the loss in expectation of life. Patients of all ages diagnosed in 2013 will on average lose less than 3 life years due to their diagnosis of CML.

CONCLUSION Imatinib mesylate, new TKIs along with allogeneic stem cell transplantation and other factors have contributed to the life expectancy in CML patients approaching that in the general population today. This will be a very important message to convey to patients in order to understand the impact of a CML diagnosis on their life. In addition, the increasing prevalence of CML patients will have a great effect on future healthcare costs as long as continuous TKI treatment is required.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by an acquired balanced chromosomal translocation, giving rise to a constitutively active tyrosine kinase (BCR–ABL1) [1]. Untreated or symptomatically treated CML is a fatal disease, with a reported median survival of approximately 2–3 years in seemingly unselected CML populations [4]. Over 90% of Swedish patients are diagnosed in the chronic phase, and the major treatment goal is to prevent the disease from progressing into more advanced phases [3]. Treatment for CML patients has changed dramatically over the years. CML therapy was restricted to busulphan and hydroxyurea prior to the 1980s [4]. During the 1980s allogeneic stem cell transplantations (allo-SCT) and interferon-α were the treatments of choice.[6]. A dramatic improvement occurred after 2000 due to the introduction of imatinib mesylate (IM), the first tyrosine kinase inhibitor (TKI) specifically targeting the BCR–ABL1 oncoprotein [1]. IM treatment significantly increased the survival and quality of life for patients of all ages, particularly for patients in chronic phase [7,8].

The improved survival has led to an increasing prevalence, a trend that is projected to continue during coming decades[2,3,9]. The increased prevalence in combination with, for the large majority of patients, the recommended life-long IM treatment will have a great impact on costs [9]. It will be very important to, in an accessible way, guide health care professionals, educators, and policy makers regarding present and future achievements with a focus on population-based data. It is also important for these groups, as well as for patients and clinicians, that survival statistics are presented in a comprehendible way, that enhance the understanding of the impact of a cancer diagnosis on a patient's life expectancy, especially for chronic diseases such as CML.

Life expectancy is a simple, well-known concept that quantifies the expected number of life years remaining. The loss in expectation of life (LEL) is a survival measure that presents the number of life years lost, or the reduction in the life expectancy, due to a diagnosis of cancer [13,14]. These measures have many advantages including being easily comprehendible, and thus easily communicated, and providing a survival measure over a whole time scale.

The aim of this study is to assess how the life expectancy of CML patients and life years lost due to a diagnosis of CML have changed between 1973 and 2013 in patients diagnosed in Sweden. Particular interest lies in the survival of patients after the introduction of the TKIs. An additional aim is to determine whether improvements previously reported in the survival of CML patients in Sweden have continued between 2008 and 2013.

Methods

Cancer registries and patients

The study included CML patients recorded within the nationwide Swedish Cancer Registry established in 1958. By law every incidence of cancer must be reported to this registry by each physician and pathologist/cytologist. The Swedish Cancer registry contains information on age, sex, date and type of diagnosis but does not contain detailed information such as symptoms, routine laboratory tests, treatments and comorbidities [15]. Patients with CML were identified using International Classification Version 8 (code 2051). All residents in Sweden are given a unique national registration number which was used for linkage with the national Cause of Death Register to obtain the date of death.

Patients who were diagnosed between January 1, 1973 and December 31, 2013 were included within the cohort. Patients were followed until their date of death, date of emigration or to the end of follow-up (31 December 2013), whichever occurred first. Diagnoses were included from 1973 since the registry is known to have reached a high coverage for hematological malignancies by then [16]. Only the first diagnosis of CML of patients diagnosed at 50 years of age or above which were histologically verified were considered. The reason for including patients aged 50 years and above at diagnosis was so that long extrapolation was not required when calculating the loss in expectation of life. Incidental autopsy findings and misclassified cases were excluded. The study was approved by the Stockholm Regional Ethics Review Board. Informed consent was waived since there was no contact with study participants.

Statistical methods

The loss in expectation of life (LEL) is the difference between the life expectancy of a cancer patient and the life expectancy of a similar individual, in terms of age and sex, from the general population. This measure estimates the average number of life years lost, or the reduction in the life expectancy, due to a diagnosis of cancer. The LEL can also be presented as a proportion, in the form of the proportion of expected life lost (PELL). This is the proportion of remaining life years that are lost due to a diagnosis of cancer. The LEL and PELL can be estimated based on the relative survival of the cancer patients and the survival of the general population [13]. Relative survival is defined as the all-cause observed survival in the cancer population under study divided by the expected survival of a comparable group in the general population [17,18].

The LEL and PELL were predicted from a flexible parametric relative survival model with 5 degrees of freedom to model the baseline excess hazard [19,20]. Age at diagnosis, year of diagnosis and sex were all modeled (age and year continuously using restricted cubic splines [21]) and interactions between all these covariates were included. The model included time-dependent effects with 2 degrees of freedom for all covariates to allow for non-proportional excess hazards. The expected survival was obtained from population mortality files up to 2012 and predictions beyond 2012 by Statistics Sweden [22] stratified on age at diagnosis, year of diagnosis and sex.

All analyses were performed in Stata 13 [23].

Results

A total of 2,662 CML patients diagnosed between 1973 and 2013 at age 50 years and over, 1,446 (54.3%) males and 1,216 (45.7%) females were included. The median age at diagnosis for the included cohort was 69 years. See Table 1 for descriptive statistics.

Results are presented for four selected ages at diagnosis; 55, 65, 75 and 85 years. The life expectancy of the general population for males and females increased over the follow-up period; this increase was larger for the younger populations presented. The life expectancy of the CML patients steadily increased for all ages between 1973 and 1990. For younger CML patients presented in this study, a large increase in the life expectancy was seen after 1990, this increase was not as great in the older patients and began later, see Figure 1. The increase seen in the life expectancy in those aged 55 at diagnosis after 1990 continued until 2013; however the largest increase was seen between approximately 1990 and 2000, with a more steady increase after 2000. In those CML patients aged 85 years at diagnosis the greatest increase in life expectancy began from approximately 2000. The life expectancy of CML patients of all ages increased dramatically over the whole of the study period which resulted in the life expectancy of CML patients in 2013 was approaching that in the general population. For example, a 55-year old male CML patient diagnosed in 1980 would on average have 3.5 (95% CI: 2.9, 4.1) life years remaining whereas a 55-year old male diagnosed in 2010 would have 27.3 (95% CI: 25.7, 28.8) life years remaining. An 85-year old male patient would on average have 0.8 (95% CI: 0.7, 1.1) life years remaining if he was diagnosed in 1980 and 4.1 (95% CI: 3.4, 4.7) life years remaining if he was diagnosed in 2010. The life expectancy of all aged CML patients

was within 3 years of the life expectancy in the general population for diagnoses in 2010, as shown in the LEL estimates; see Table 2 and Figure 2.

The LEL decreased for all ages over the study period but the most dramatic decrease was seen in diagnoses after 1990 in younger patients presented. This was due to the huge increase in the life expectancy of CML patients at this time; see Figure 2 and Table 2. For example, a male diagnosed with CML in 1980 at age 55 on average had a reduced life expectancy of 20.8 (95% CI: 20.2, 21.4). In contrast, a 55-year old male diagnosed in 2010 would on average have a reduced life expectancy of only 2.6 (95% CI: 1.0, 4.1) years For older patients, improvements were still seen, with a more rapid decrease after the 1990s, but not to the same scale as in the younger patients since older patients have on average fewer potential remaining life years.

Estimates of PELL also suggest a vast improvement in the outcomes of CML patients of all ages over the study period; see Figure 3 and Table 2. Prior to approximately 1990, the PELL was higher in younger patients included in the study, whereas after this time the PELL was higher in the older patients. For example, the PELL for a 55-year old male and an 85-year old male diagnosed in 1980 were 86% (95% CI: 83%, 88%) and 80% (95% CI: 76%, 85%) respectively, in 2010 these values were 9% (95% CI: 4%, 14%) and 28% (95% CI: 16%, 40%) respectively.

Discussion

Our results show that there has been a dramatic reduction in the life years lost in patients diagnosed in Sweden with CML between 1973 and 2013. Patients aged 55 years at diagnosis benefitted greatly from 1990, and life expectancy improvements continued to 2013 but less dramatically from 2000. For older patients, improvements in life expectancy began a little later. The results indicate that the life expectancy of CML patients is now close to the life expectancy of the general population for all ages[10-12]. However, reports suggesting an increased incidence of other cancers [10,11] and cardiovascular morbidity [12] associated with the use of TKIs, could have a negative impact on survival gains. Thus the life expectancy of CML patients may never reach that seen in the general population. Also, approximately 10% of CML patients diagnosed in Sweden are diagnosed in an advanced phase, and it is therefore unlikely that the life expectancy for the whole group of CML patients will reach the life expectancy of the whole population. Even so, the life expectancy of CML patients was within 3 years of the life expectancy in the general population for diagnoses in 2010, which must be seen as a great success of CML treatment.

Treatment for CML patients has changed dramatically over the years, and IM was approved as CML treatment in Sweden in 2001 (second line) and 2002 (first line). However, the implementation of imatinib differed between age groups: during the period 2002–2008 it was on average 79% in persons below 70 years and 47% in persons older than 70 years, leading to a less conspicuous or no improvement in survival for elderly patients [2]. These proportions increased to 94% for younger (<70 years) and 79% for older (>80 years) patients during 2007-2009 [3]. Although IM remains the gold standard for first-line treatment of CML, the appearance of IM resistance and intolerance has led to the development of several additional TKIs [24].

198 Studies have shown that second-generation TKIs (dasatinib, nilotinib, bosutinib)
199 improve outcome of CML patients in whom IM therapy has failed [24,25]. In addition, a
200 third-generation TKI (ponatinib) targeting the frequently observed mutant T315I has
201 been developed [26]. Thus, CML treatment is progressing rapidly and further
202 advancements are anticipated. Notwithstanding the fact that a small subgroup of
203 patients with an excellent response to treatment have been able to stop taking TKI
204 agents [27], most CML patients will take the drug for life which, along with the
205 increasing prevalence of CML, has high implications for the cost. Ohm et al.
206 evaluated the cost-effectiveness of IM in CML patients and found that incremental
207 cost-effectiveness ratios comparing IM to other treatments were generally acceptable
208 by health authorities [9] meaning that these treatments should continue to be
209 financially feasible.

210 The results shown for the youngest patients presented here suggest that
211 improvements in survival of CML patients began for patients diagnosed in the mid-
212 1990s. Our results also show improvements from the introduction of IM in 2001,
213 however, great improvements are observed prior to its introduction. The
214 improvements seen for older patients began slightly later than the younger patients
215 presented; however there was no immediate improvement after 2001 when IM was
216 introduced. The use of interferon-α[28], more precise diagnostics involving centralised
217 cytogeneic labs and a more structured approach in treating and monitoring CML
218 patients are plausible explanations for the trend.. Although our research suggests
219 that improvements in survival of CML patients over the years may not have been
220 completely due to the introduction of IM, it is clear that the prognosis for CML patients
221 today is extremely positive with the current treatment.

Sasaki et al. concluded from clinical trial data that the five-year survival of chronic-CML patients was almost the same as the general population[29]; our results support this finding. Björkholm et al. followed Swedish CML patients on a population level and saw improvements in the relative survival between 1973 and 2008 for Swedish CML patients of all ages, with vast improvements in those aged 79 years and less at diagnosis from 2001 [2]. Our study shows that these improvements have continued to 2013. We here chose to present outcomes in CML patients using LEL whilst others quantified survival using relative survival. It is important to remember that these two measures are related but describe different aspects of the patients' survival. In particular, the relative survival is an estimate of net survival which is interpreted in a hypothetical situation where cancer patients can only die of their cancer whereas the loss in expectation of life is a measure which represents the real-world survival seen by cancer patients.

One potential limitation of the study is that the current analysis is not able to capture any late lethal effects if they were to occur, due to fewer years of follow-up in the later calendar years; the fewer years of follow-up also mean that the estimates presented rely more on the model assumptions. However, it is also possible that any late adverse effects may not impact the life span of patients.

A major strength of the current study is the use of population-based information; we include all CML diagnoses reported to the Swedish Cancer Register between 1973 and 2013. The Swedish Cancer Register has high completeness; in 1998 it was estimated to capture 96% of all cancers in Sweden [16]. Using population-based data is optimal since it captures the mortality of CML patients in Sweden on a whole whilst incorporating changes in treatments, increasing prevalence of CML and potential negative side-effects of treatments for CML patients. Unfortunately, the Swedish

Cancer Register doesn't contain information on treatment and other detailed clinical information. This also means that there is a lack of potential confounder information such as socioeconomic status.

In order to present the LEL for all patients including those diagnosed in the most recent years, extrapolation from models are required. This potential weakness of the LEL has been assessed by Andersson et al.[13] in several different cancers and extrapolation was shown to be accurate. However, further extrapolation is required to calculate the LEL in younger patients due to their larger potential life expectancy. Therefore, the LEL was presented for patients aged 55 years and above.

In conclusion, the life expectancy, and the number of life years lost, has vastly improved in all-aged CML patients in Sweden since 1973 with larger improvements beginning already in the mid-1990s. IM along allo-SCT and other factors have contributed to the life expectancy in CML patients being almost the same as the general population today.

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Figure legends

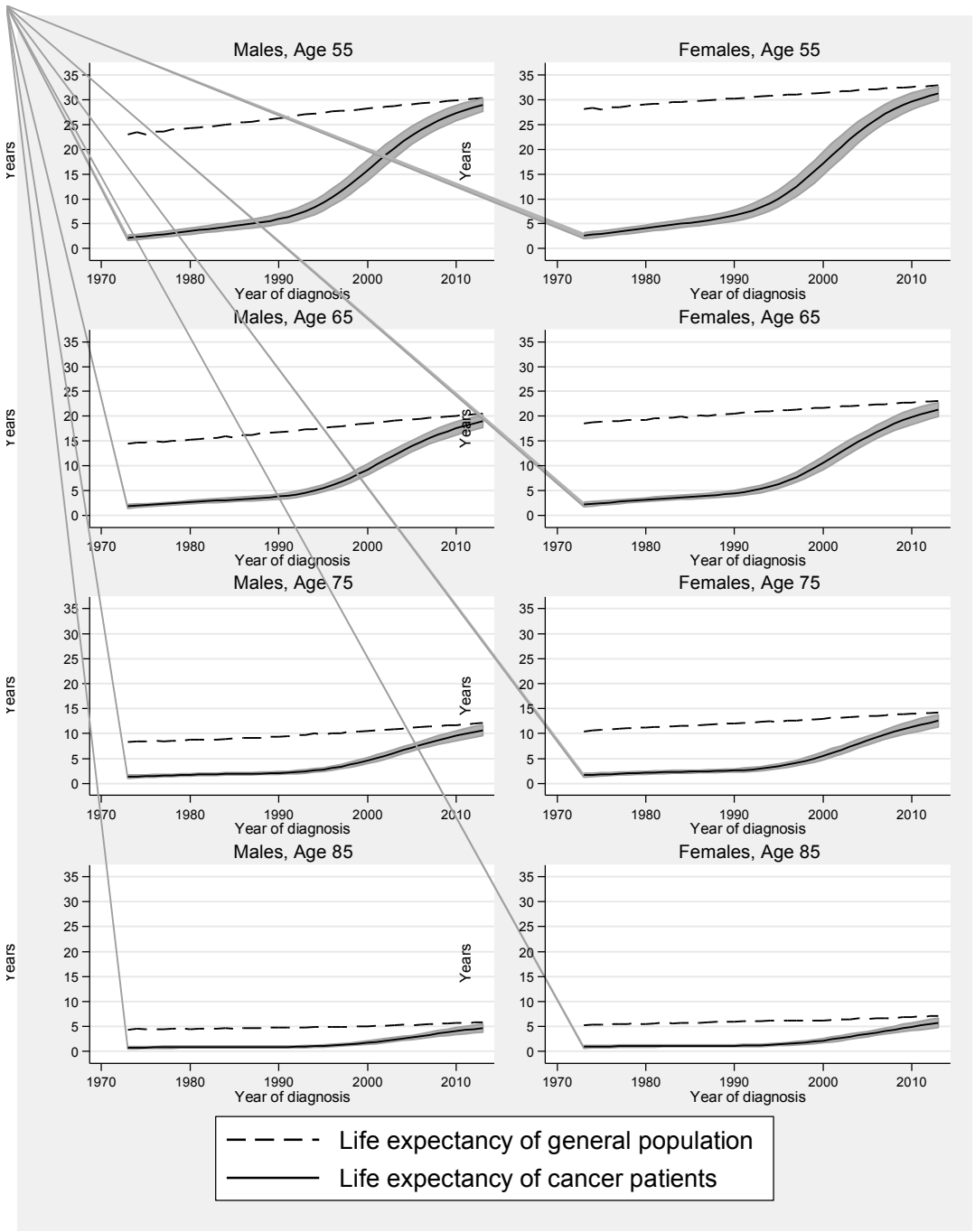
Figure 1: Life expectancy of the general population and of CML patients in Sweden, over year of diagnosis, by age at diagnosis and sex

Figure 2: Loss in expectation of life of CML patients in Sweden, over year of diagnosis, by age at diagnosis and sex

Figure 3: Proportion of expected life lost of CML patients in Sweden, over year of diagnosis, by age at diagnosis and sex.

Figures

Figure 1: Life expectancy of the general population and of CML patients in Sweden, over year of diagnosis, by age at diagnosis and sex



278 **Figure 2:** Loss in expectation of life of CML patients in Sweden, over year of

279 diagnosis, by age at diagnosis and sex

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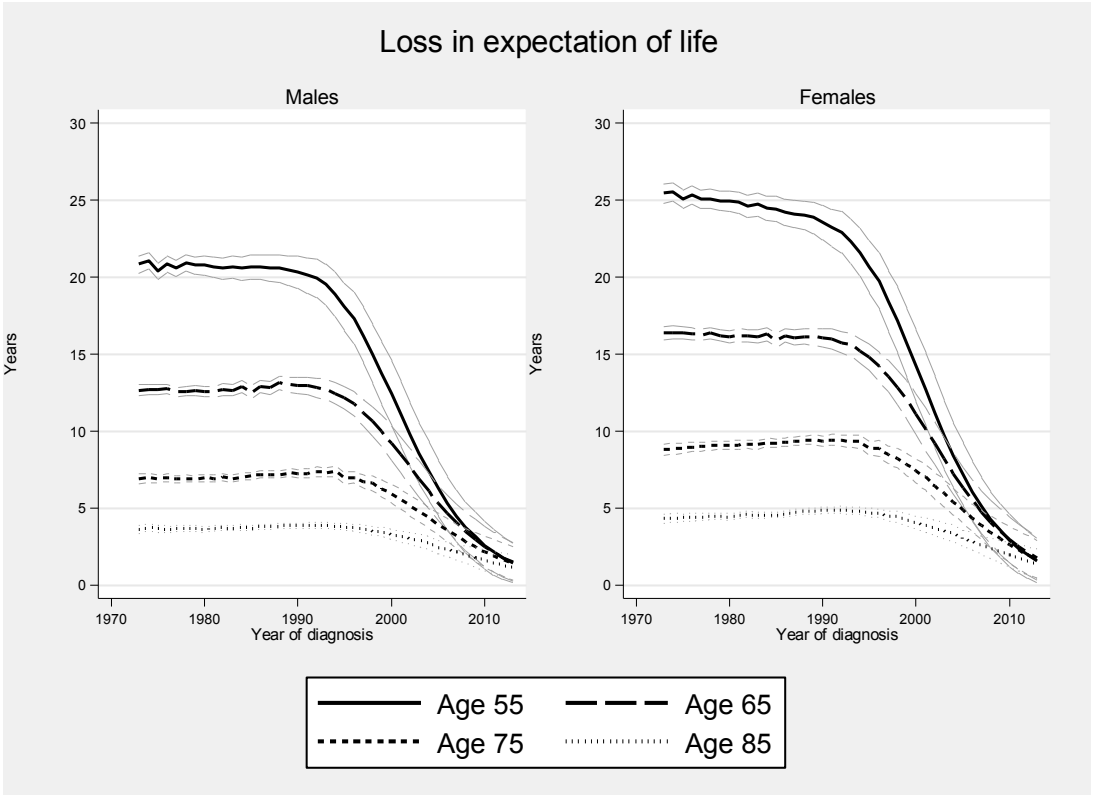

281 **Figure 3:** Proportion of expected life lost of CML patients in Sweden, over year of

282 diagnosis, by age at diagnosis and sex

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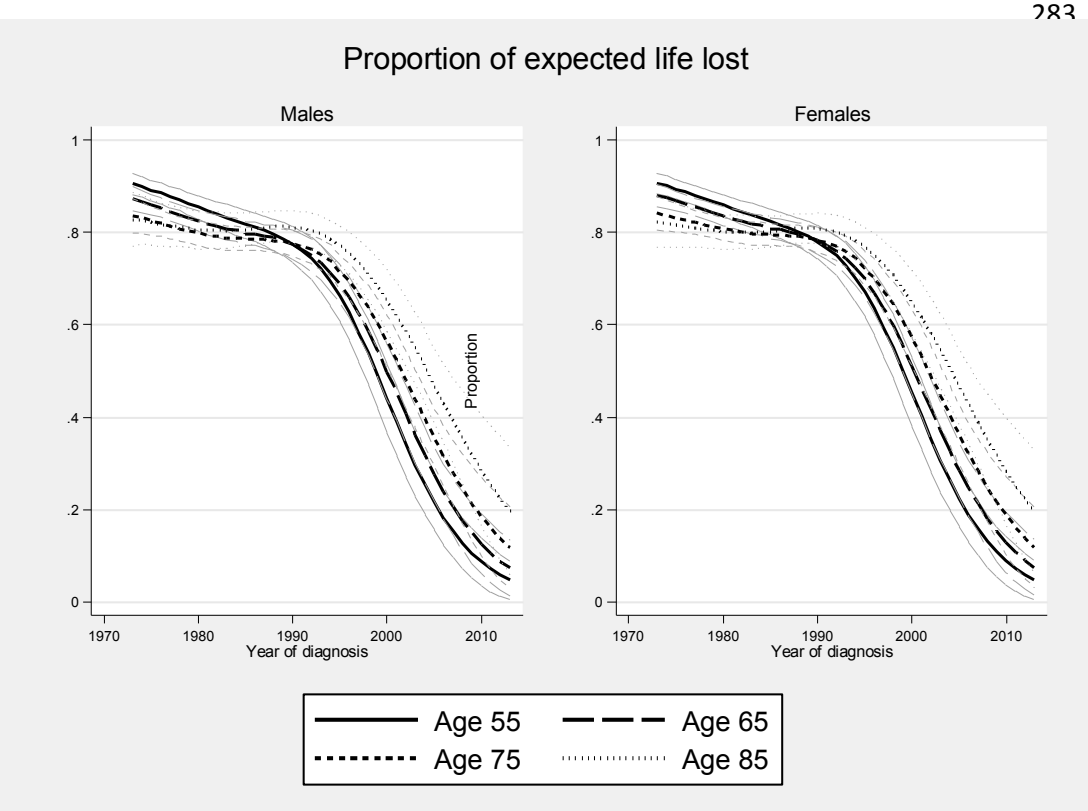

Tables

Table 1: Demographic characteristics of CML patients diagnosed in Sweden between 1973 and 2013 at 50 years of age or above

Characteristic	Calendar period								Total	
	1973-1982		1983-1992		1993-2002		2003-2013			
	No.	%	No.	%	No.	%	No.	%	No.	%
Total patients with CML	679	25.5	690	25.9	573	21.5	720	27.1	2662	100
Age, years										
50-59	138	20.3	136	19.7	162	28.3	182	25.3	618	23.2
60-69	227	33.4	197	28.6	142	24.8	223	31.0	789	29.6
70-79	214	31.5	240	34.8	179	31.2	180	25.0	813	30.5
>79	100	14.7	119	17.0	90	15.7	135	18.8	442	16.6
Sex										
Male	371	54.6	363	52.6	322	56.2	390	54.2	1446	54.3
Female	308	45.4	327	47.4	251	43.8	330	45.8	1216	45.7

289 **Table 2:** Life expectancy of the general population (LE), life expectancy of CML
290 patient (LE CML), loss in expectation of life of CML patients (LEL) and proportion of
291 expected life lost of CML patients (PELL) with 95% CIs for males and females at four
292 selected years and four selected ages at diagnosis in Sweden

		Age 55		Age 65		Age 75		Age 85	
		Males	Females	Males	Females	Males	Females	Males	Females
1980	LE	24.3	29.0	15.3	19.3	8.7	11.3	4.5	5.5
	LE CML	3.5 (2.9,4.1)	4.1 (3.4,4.7)	2.7 (2.3,3.0)	3.2 (2.8,3.6)	1.8 (1.5,2.0)	2.2 (1.9,2.4)	0.8 (0.7,1.1)	1.1 (0.9,1.3)
	LEL	20.8 (20.2,21.4)	24.9 (24.3,25.6)	12.6 (12.2,12.9)	16.1 (15.7,16.5)	7.0 (6.7,7.2)	9.1 (8.8,9.4)	3.6 (3.4,3.8)	4.4 (4.2,4.6)
	PELL	0.86 (0.83,0.88)	0.86 (0.84,0.88)	0.83 (0.80,0.85)	0.84 (0.81,0.86)	0.80 (0.77,0.83)	0.81 (0.78,0.83)	0.80 (0.76,0.85)	0.80 (0.76,0.84)
1990	LE	26.3	30.2	16.8	20.5	9.4	12.0	4.8	6.0
	LE CML	5.9 (4.9,7,0)	6.66 (5.6,7.8)	3.8 (3.3,4.3)	4.5 (3.9,5.1)	2.1 (1.8,2.4)	2.6 (2.3,2.9)	0.9 (0.7,1.1)	1.1 (0.9,1.3)
	LEL	20.4 (19.3,21.4)	23.6 (22.4,24.7)	13.0 (12.5,13.5)	16.1 (15.5,16.6)	7.3 (7.0,7.5)	9.4 (9.0,9.7)	3.9 (3.7,4.0)	4.8 (4.6,5.0)
	PELL	0.77 (0.73,0.81)	0.78 (0.74,0.82)	0.77 (0.74,0.80)	0.78 (0.75,0.81)	0.77 (0.75,0.80)	0.78 (0.76,0.81)	0.81 (0.78,0.85)	0.81 (0.78,0.84)
2000	LE	28.2	31.4	18.5	21.7	10.5	13.0	5.0	6.2
	LE CML	15.8 (13.7,17.9)	17.2 (14.8,19.5)	9.3 (8.2,10.4)	10.6 (9.3,11.9)	4.6 (4.0,5.2)	5.5 (4.8,6.3)	1.8 (1.4,2.1)	2.2 (1.8,2.6)
	LEL	12.4 (10.3,14.5)	14.3 (11.9,16.6)	9.2 (8.1,10.3)	11.1 (9.8,12.4)	5.9 (5.3,6.5)	7.4 (6.6,8.2)	3.3 (3.0,3.6)	4.0 (3.6,4.5)
	PELL	0.44 (0.37,0.51)	0.45 (0.38,0.53)	0.50 (0.44,0.56)	0.51 (0.45,0.57)	0.56 (0.51,0.62)	0.57 (0.51,0.63)	0.65 (0.59,0.72)	0.65 (0.58,0.72)
2010	LE	29.9	32.6	20.1	22.8	11.7	14.0	5.7	6.9
	LE CML	27.3 (25.7,28.8)	29.7 (28.0,31.4)	17.5 (16.2,18.9)	19.8 (18.4,21.3)	9.5 (8.5,10.5)	11.3 (10.2,12.5)	4.1 (3.4,4.7)	5.0 (4.2,5.8)
	LEL	2.6 (1.0,4.1)	2.9 (1.2,4.6)	2.5 (1.2,3.8)	2.9 (1.4,4.4)	2.2 (1.2,3.2)	2.6 (1.4,3.8)	1.6 (0.9,2.3)	2.0 (1.2,2.8)
	PELL	0.09 (0.04,0.14)	0.09 (0.04,0.14)	0.13 (0.06,0.20)	0.13 (0.06,0.19)	0.18 (0.10,0.27)	0.19 (0.10,0.27)	0.28 (0.16,0.40)	0.28 (0.17,0.40)

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