ONLINE APPENDIX

The evolution of the loss of life expectancy in patients with chronic myeloid leukemia: a population-based study in the Netherlands, 1989-2018

Carolien C.H.M. Maas[1,2], David van Klaveren[1], Geneviève I.C.G. Ector[3], Eduardus F.M. Posthuma[4,5], Otto Visser[6], Peter E. Westerweel[7], Jeroen J.W.M. Janssen[8], Nicole M.A. Blijlevens[3], Avinash G. Dinmohamed[1,2,8,9]

[1]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands; [3]Department of Hematology, Radboudumc, Nijmegen, The Netherlands; [4]Department of Internal Medicine, Reinier de Graaf Gasthuis, Delft, The Netherlands; [5]Department of Hematology, Leiden University Medical Center, Leiden, The Netherlands; [6]Department of Registration, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands; [7]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands, [8]Amsterdam UMC, Location VUmc, Department of Hematology, Cancer Center Amsterdam, Amsterdam, The Netherlands; [9]Amsterdam UMC, Universiteit van Amsterdam, Department of Hematology, Cancer Center Amsterdam, Amsterdam, The Netherlands

Supplemental methods

Flexible parametric survival model

The loss of life expectancy (LOLE) of patients with chronic myeloid leukemia (CML) was defined as the difference between the area under the survival curve of the general population (that is, the expected survival) and CML patients (that is, the observed survival). The LOLE can be estimated using the following equation $LOLE(z) = \int_0^{t_{\max}} S^*(u;z)du - \int_0^{t_{\max}} S(u;z)du$, where $S^*(t)$ denotes expected survival, $S(t)$ denotes observed survival, z includes patient characteristics such as sex, age at diagnosis, and calendar year at diagnosis, and $t_{\max}$ a time point at which the patient is assumed dead[1]. For example, if it is assumed that patients do not live beyond 100 years, the life expectancy of a 60-year-old CML patient is obtained by integrating the life expectancy curve of CML patients from 0 to $t_{\max} = 40$.

The survival curves are not fully observed until individuals die ($t_{\max}$). Therefore, it needs to be extrapolated. The expected survival $S^*(t)$ is assumed to be complete and obtained from population life tables. Constant mortality for expected mortality beyond 2018 is assumed. The observed survival $S(t)$ can be rewritten in terms of relative survival or excess hazard. Specifically, relative survival $R(t)$ is defined as the observed survival $S(t)$ divided by the expected survival $S^*(t)$, such that observed survival can be expressed as $S(t) = S^*(t)R(t)$. Relative survival $R(t)$ can be expressed in terms of cumulative excess hazard $\Lambda(t)$ by $R(t) = \exp\big(-\Lambda(t)\big)$.

The flexible parametric survival model uses restricted cubic splines to model the log cumulative excess hazard $\ln\big(\Lambda(t)\big)$ with the log baseline cumulative hazard, log hazard ratio, and time-varying effects, i.e. $\ln\big(\Lambda(t)\big) = s(\ln(t)\,|\boldsymbol{\gamma_0}) + \boldsymbol{x\beta} + \sum_{d=1}^{D} s(\ln(t)\,|\boldsymbol{\gamma_d})\,\boldsymbol{x_d}$, where $\ln(\cdot)$ denotes the natural logarithm, D is the number of time-dependent covariate effects, $s(\cdot\,|\boldsymbol{\gamma})$ is a restricted cubic spline function with $\boldsymbol{\gamma}$ degrees of freedom, and $\boldsymbol{x}$ the explanatory variables sex, calendar year at diagnosis, and age at diagnosis[1]. Calendar year and age at diagnosis were modelled continuously using restricted cubic splines and were allowed to be time-dependent. Interaction terms are included in the model between sex and age at diagnosis, sex and calendar year, and calendar year and age at diagnosis.

The choice of the number of degrees of freedom to model continuous variables, baseline hazard, and time-dependent effects was investigated through sensitivity analysis (Fig S1-3). We used one degree of freedom to model calendar year at diagnosis, two degrees of freedom to model age at diagnosis, three degrees of freedom to model the log baseline cumulative hazard, and one degree of freedom to model the time-varying effects. The point of cure was assumed at ten years post-diagnosis, i.e., the excess hazard was assumed to be zero after ten years of follow-up.

The flexible parametric model cannot accurately estimate life expectancy in a setting where observations, and therefore events, are sparse; for example, for very old patients. Therefore, the effect of age on excess mortality was considered equal for CML patients aged 90 years and older.

Supplemental figures

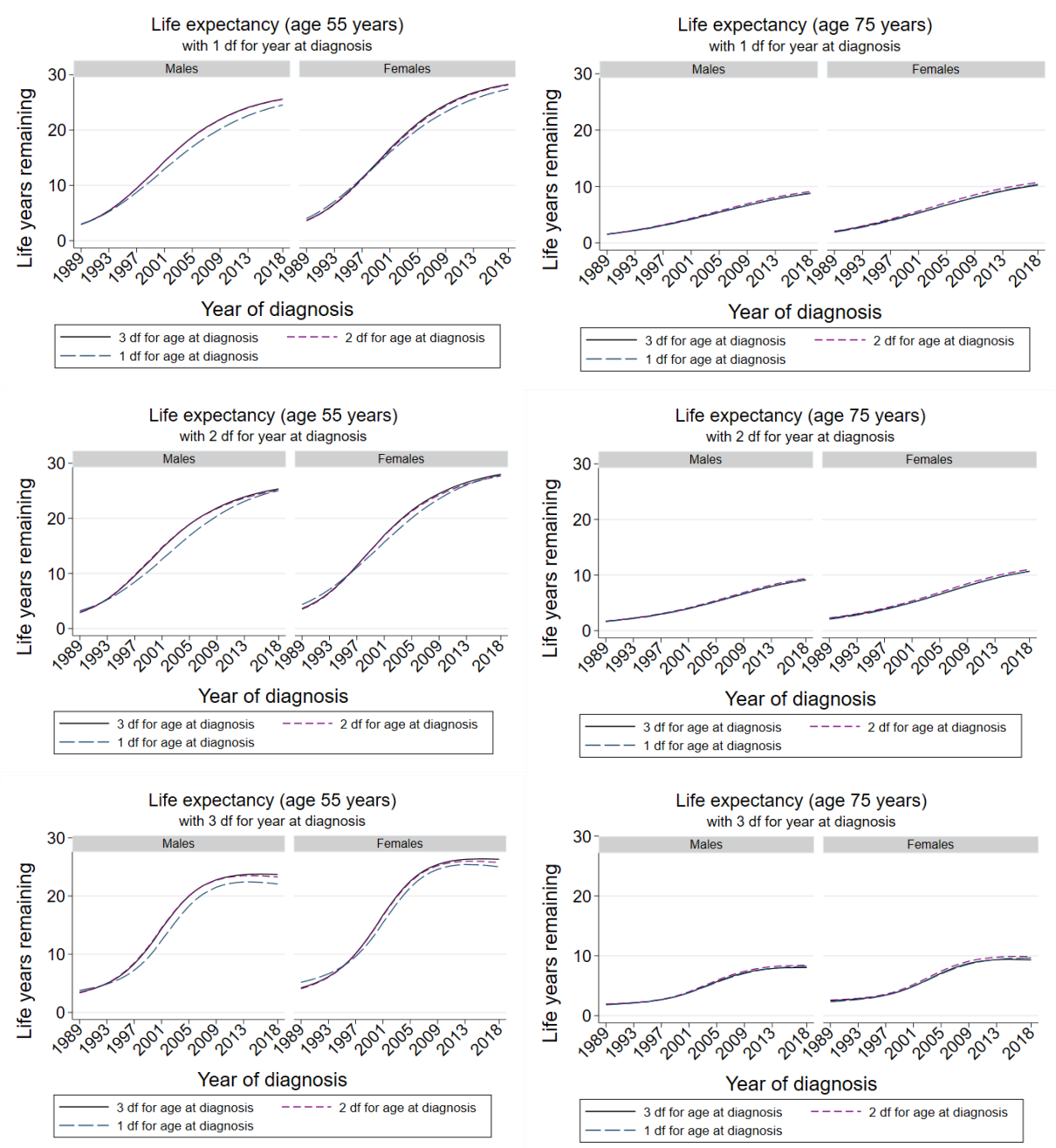

Fig S1. The observed survival curves when varying the degrees of freedom to model the continuous variables. Based on the AIC, the calendar year at diagnosis should be modelled using three degrees of freedom and age at diagnosis two degrees of freedom. However, the observed survival curves become too flexible when modelling the calendar year at diagnosis with three degrees of freedom. On the other hand, the BIC prefers one and two degrees of freedom to model the calendar year and age at diagnosis, respectively, which results in stable life expectancy estimations and are therefore chosen in the final model. Using more than three degrees of freedom to model the continuous variables results in too flexible observed survival curves, and are therefore not considered.

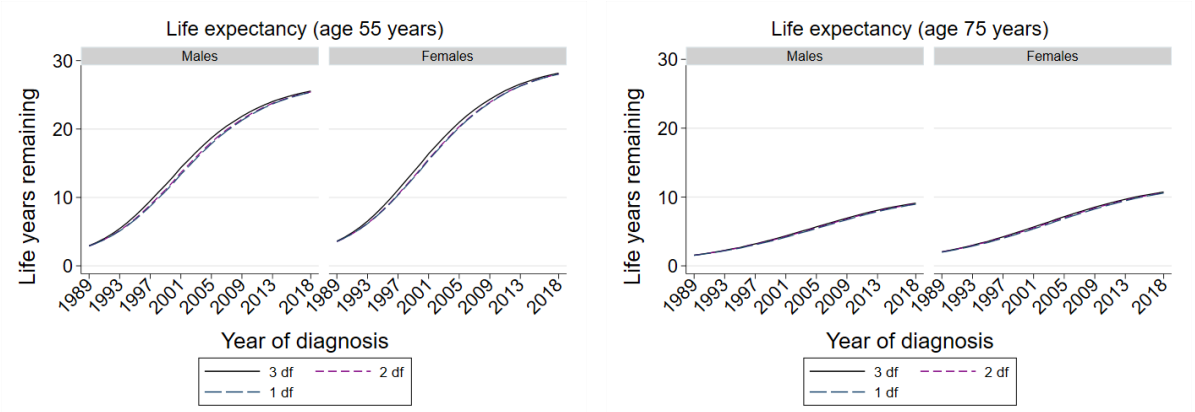

Fig S2. The observed survival curve when varying the degrees of freedom to model the baseline hazard. The observed survival curves were similar when altering the number of degrees of freedom to model the baseline. The AIC and BIC prefer the model with three degrees of freedom to model the baseline and is therefore chosen in the final model. Due to convergence issues, the baseline hazard could only be modelled with a maximum of three degrees of freedom. This issue arises from few events among younger aged patients, resulting in a negative predicted excess mortality.

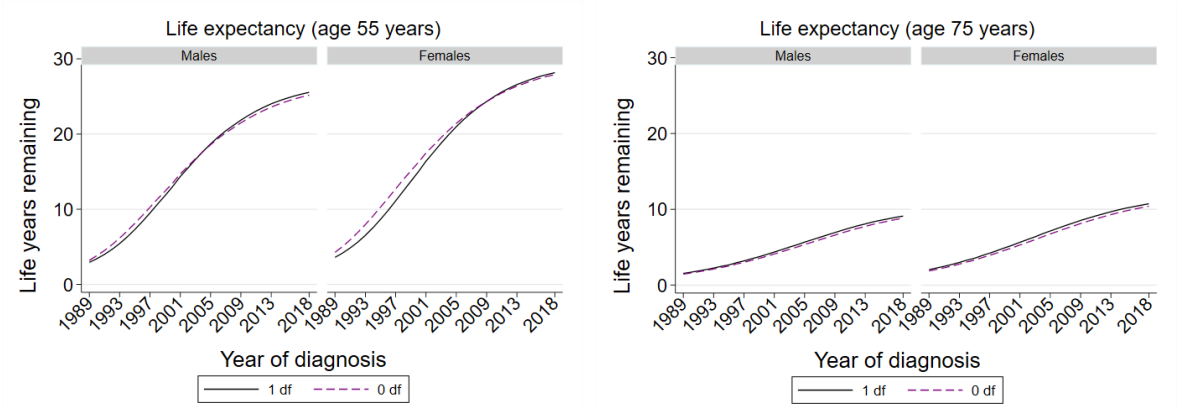

Fig S3. The observed survival curve when varying the degrees of freedom to model the time-varying effects. The observed survival curves were similar when altering the number of degrees of freedom to model time-dependent effects. Based on the AIC and BIC, one degree of freedom is needed to model the time-dependent effects and is therefore chosen in the final model. Due to convergence issues, the time-varying effects could only be modelled with a maximum of one degree of freedom. This issue arises from few events among younger aged patients, resulting in a negative predicted excess mortality.

Table SI. Demographic characteristics of CML patients in the Netherlands in the period 1989-2018.

	Total		1989 – 2000		2001 - 2010		2011 – 2018	
Characteristics	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Total patients	4,702	100.0	1,740	37.0	1,515	32.2	1,447	30.8
Age [median; IQR]	61	[47; 74]	65	[49; 76]	59	[45; 73]	60	[48; 71]
18-29	271	5.8	108	6.2	81	5.3	82	5.7
30-39	420	8.9	147	8.4	162	10.7	111	7.7
40-49	655	13.9	197	11.3	247	16.3	211	14.6
50-59	833	17.7	260	14.9	272	18.0	301	20.8
60-69	933	19.8	330	19.0	272	18.0	331	22.9
70-79	996	21.2	431	24.8	295	19.5	270	18.7
80-97	594	12.6	267	15.3	186	12.3	141	9.7
Females	2,079	44.2	728	41.8	721	47.6	630	43.5
Deaths	2,600	55.3	1,522	87.5	774	51.1	304	21.0
First-line SCT	263	5.6	155	8.9	73	4.8	35	2.4

Abbreviations: IQR, interquartile range; SCT, stem cell transplantation.

Table SII. The life expectancy of the general population and patients with chronic myeloid leukemia, the loss of life expectancy of patients with chronic myeloid leukemia, and the proportional loss of life expectancy of patients with chronic myeloid leukemia. These survival measures, with associated 95% confidence intervals, are presented for four selected calendar years and ages at diagnosis in the Netherlands.

Measure	Age 55 years		Age 65 years		Age 75 years		Age 85 years	
	Males	Females	Males	Females	Males	Females	Males	Females
1990								
LE	24.9	29.1	15.4	19.8	8.7	11.7	4.6	5.8
LE CML	3.5 (2.9; 4.0)	4.1 (3.3; 4.9)	2.6 (2.2; 2.9)	3.2 (2.7; 3.7)	1.7 (1.5; 2.0)	2.2 (1.9; 2.6)	1.0 (0.8; 1.2)	1.2 (1.0; 1.5)
LOLE	21.5 (20.9; 22.0)	25.0 (24.2; 25.7)	12.9 (12.5; 13.2)	16.6 (16.1; 17.1)	6.9 (6.7; 7.2)	9.4 (9.1; 9.8)	3.6 (3.4; 3.8)	4.5 (4.3; 4.8)
PLOLE (%)	86.1 (84.0; 88.2)	85.8 (83.1; 88.5)	83.2 (81.0; 85.5)	83.9 (81.3; 86.6)	80.1 (77.4; 82.8)	81.0 (78.1; 83.9)	78.5 (74.4; 82.6)	78.6 (74.3; 82.9)
2000								
LE	26.3	29.5	17.4	20.7	9.7	12.3	4.8	6.0
LE CML	13.0 (11.8; 14.1)	15.0 (13.6; 16.5)	7.9 (7.3; 8.5)	9.7 (8.9; 10.5)	4.0 (3.7; 4.3)	5.3 (4.8; 5.7)	1.7 (1.5; 1.9)	2.2 (2.0; 2.5)
LOLE	13.4 (12.2; 14.5)	14.4 (13.0; 15.9)	9.4 (8.8; 10.1)	11.0 (10.1; 11.8)	5.7 (5.4; 6.0)	7.1 (6.6; 7.5)	3.1 (2.9; 3.3)	3.8 (3.5; 4.0)
PLOLE (%)	50.8 (46.4; 55.2)	49.0 (44.0; 53.9)	54.4 (50.8; 57.9)	53.1 (49.1; 57.1)	58.7 (55.4; 61.9)	57.3 (53.8; 60.7)	64.2 (60.1; 68.2)	62.7 (58.6; 66.8)
2010								
LE	27.0	29.7	18.4	20.9	10.9	13.0	5.4	6.5
LE CML	22.4 (21.4; 23.4)	25.0 (23.9; 26.2)	14.0 (13.3; 14.8)	16.3 (15.4; 17.2)	7.2 (6.7; 7.6)	8.9 (8.3; 9.4)	2.8 (2.4; 3.1)	3.6 (3.2; 3.9)
LOLE	4.6 (3.6; 5.6)	4.7 (3.5; 5.9)	4.4 (3.6; 5.1)	4.6 (3.7; 5.5)	3.8 (3.3; 4.3)	4.1 (3.5; 4.7)	2.7 (2.3; 3.0)	3.0 (2.6; 3.3)
PLOLE (%)	17.1 (13.3; 20.9)	15.8 (11.9; 19.8)	23.7 (19.7; 27.7)	22.1 (17.9; 26.3)	34.5 (29.9; 39)	31.8 (27.2; 36.4)	49.0 (42.8; 55.3)	45.4 (39.3; 51.5)
2018								
LE	27.1	29.8	18.6	21.1	11.2	13.1	5.5	6.5
LE CML	25.5 (24.9; 26.1)	28.2 (27.6; 28.8)	16.7 (16.1; 17.2)	19.1 (18.5; 19.7)	9.0 (8.5; 9.5)	10.8 (10.2; 11.3)	3.5 (3.1; 3.9)	4.4 (3.9; 4.8)
LOLE	1.6 (1.1; 2.2)	1.6 (1.0; 2.2)	1.9 (1.4; 2.5)	2.0 (1.4; 2.6)	2.2 (1.7; 2.7)	2.3 (1.7; 2.9)	2.0 (1.6; 2.4)	2.1 (1.6; 2.6)
PLOLE (%)	6.0 (3.9; 8.1)	5.4 (3.3; 7.5)	10.4 (7.5; 13.2)	9.4 (6.5; 12.3)	19.8 (15.5; 24.2)	17.6 (13.3; 21.9)	36.6 (28.7; 44.5)	32.6 (25.2; 40.0)

As a reader's guide, a 55-year-old male in 1990 is estimated, on average, to have 24.9 life-years remaining. On the other hand, a 55-year-old male patient with CML diagnosed in 1990 has, on average, 3.5 life-years remaining. Thus, a 55-year-old male patient with CML loses, on average, 21.5 life-years due to a CML diagnosis in 1990. This corresponds to a 55-year-old male patient with CML losing, on average, 86.1% of his life due to CML diagnosis in 1990. The 95% confidence intervals, shown in the Table in parentheses, are obtained using the Delta method. Abbreviations: LE, life expectancy; CML, chronic myeloid leukemia; LOLE, loss of life expectancy of CML patients; PLOLE, proportional loss of life expectancy of CML patients.