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Loss in Overall and Quality-Adjusted Life Expectancy for Patients With Chronic-Phase Chronic Myeloid Leukemia

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ABSTRACT

The introduction of tyrosine kinase inhibitors has considerably improved the life expectancy (LE) for patients with chronic myeloid leukemia (CML). Evaluating health-related quality of life within the treatment pathway remains crucial. Using the Swedish CML register, we included 991 adult patients with chronic-phase (CP) CML diagnosed 2007 to 2017, with follow-up until 2018. We developed a multistate model to estimate the loss in LE (LLE) and loss in quality-adjusted life expectancy (LQALE) for the patient population compared to the general population, along with the respective proportions of losses relative to the general population. All patients with CP-CML had a relatively low reduced LE but with larger LQALE. The maximum LLE within age/sex subgroups was 5.7 years (general population LE: 43.2 years vs. CP-CML LE: 37.5 years) for females diagnosed at age 45 years, with LQALE of 12.0 quality-adjusted life years (QALYs) (general population QALE: 38.2 QALYs vs. CP-CML QALE: 26.3 QALYs). Across all ages, the proportions of LLE ranged from 9% to 15%, and the proportions of LQALE were 29% to 33%. Despite a low LLE, our findings reveal a greater LQALE for patients with CP-CML. Further improvements in management of CP-CML are thus warranted to successfully address the prevailing medical needs.

1 | Background

Chronic-phase chronic myeloid leukemia (CP-CML) is a slowly progressing leukemia that typically becomes fatal without treatment [1]. The introduction of tyrosine kinase inhibitors (TKIs), a targeted therapy administered orally, has revolutionized the prognosis of patients with CML [2, 3]. Imatinib, approved as the first TKI in 2001, has been followed by later-generation TKIs. While it was initially considered that patients with CML would need to take TKIs for their entire lifespan, studies during the last decade have suggested that approximately 40% to 50% of patients who achieve deep molecular response (DMR) may safely discontinue TKI treatment and still maintain DMR for longer periods [4–8]. These findings have important implications for the long-term management of CML and may help reduce the burden of treatment for patients.

Life expectancy (LE) refers to the average number of years an individual, such as a patient with cancer, is expected to live over their remaining lifespan. The loss in life expectancy (LLE) quantifies the difference in LE between the patients and that of the general population [9, 10]. These survival measures provide useful information on the burden of a disease. For example, previous studies have shown that the LE of patients with CML in Sweden [11] and the Netherlands [12] has gradually approached that of the general population.

To assess health outcomes comprehensively, incorporating gains from reduced mortality and reduced morbidity, both survival and quality of life should be taken into account [13, 14]. Quality-adjusted life years (QALYs) are, thus, more suitable than life years alone for evaluating the utility of medical care. QALYs combine both quantity gains (survival) and quality gains (quality of life) into one single measure [13]. Typically, QALYs can be computed using multistate models [15], where the duration of each health state is multiplied by its corresponding health utility value. Over a lifetime horizon [16], the sum of QALYs across all states except the absorbing state (e.g., death state) can be considered as quality-adjusted LE (QALE) [17].

While previous studies have employed multistate models to calculate QALYs for assessing the cost-effectiveness of CML treatments [18–20], these models often extrapolate survival within an all-cause survival framework instead of a relative survival framework, which was shown to be a more accurate approach for estimating LE [9]. Moreover, to our knowledge, no study has yet investigated QALE in patients with CML using a multistate model with large-scale register-based data.

We focus specifically on CP-CML because all patients with CML begin their treatment with TKIs. To develop an appropriate model for estimating LE and QALE, it is crucial to balance model complexity with the availability of the Swedish register data. Accordingly, we developed a multistate model that incorporates relative survival extrapolation [9] to predict LE and QALE. The aim of this study was to estimate LE and QALE for patients with CP-CML in Sweden. By comparing these estimates with those of the general population, we also calculated the loss in LE and QALE, as well as the respective proportions of these losses.

2 | Methods

2.1 | Cancer Registers and Study Population

This study included all patients aged 18 to 99 years who had a record of CP-CML diagnosis in the Swedish CML register [2] between January 1, 2007, and December 31, 2017. Patients were followed up until the date of death, date of emigration, or end of follow-up (December 31, 2018), whichever occurred first. The Swedish CML register contains information on age, sex, date of diagnosis, drug treatment, stage of disease, date of start and end of treatment-free remission (TFR), and other routine laboratory tests for clinical or molecular disease characteristics. A previous validation study showed that the coverage of patients in this register is as high as 98% [2]. Complete records for TFR were only available for patients diagnosed during 2007 to 2012. Patients who were recorded with a diagnosis of acute myeloid leukemia or acute lymphoblastic leukemia in the Swedish Cancer Registry were classified as blastic phase. Entry to accelerated phase or blastic phase was defined as progression in this study. Using the unique personal identity number assigned to all residents of Sweden, we linked all patients with the nationwide Cause of Death Register to obtain their date of death. Information on prescribed TKIs was retrieved from the nationwide Prescribed Drug Register [21] and the Swedish CML register [2]. Patients who underwent allogeneic stem cell transplantation (alloSCT) were identified through linkage with the Swedish Patient Register [22] and the Swedish CML register [2]. The study was approved by the Swedish Ethical Review Authority (DNR 2020-05425 and 2020-06544).

2.2 | Multistate Model and Statistical Methods

We developed a multistate model to describe the natural history of CML treatments, which consists of the following states: first-line TKI (1 L TKI), second-line TKI (2 L TKI), third-line or later TKI (3 L+ TKI), TFR, progression, alloSCT, and death (excess or expected) (Figure 1). All patients with CP-CML started from 1 L TKI, where they were all prescribed 1 L TKI after diagnosis. Over time, patients can transition from one state to another. Individuals who experienced a competing event were censored for other events of interest [23]. We incorporated relative survival extrapolation [9] into the multistate model by distinguishing between excess and expected mortality (death). The expected mortality rates were obtained from the general population mortality file of Sweden [24] up to 2022, stratified by age, sex, and calendar year, along with predictions beyond 2022 by Statistics Sweden [25].

The LLE or LQALE among patients with CP-CML is the difference between the LE or QALE, respectively, of a patient with CP-CML and that of a matched (by age, sex, and calendar year) individual from the general population. The interpretation of LLE/LQALE is the average number of years or QALYs a patient is expected to lose compared to if they did not have the disease. Additionally, we presented the proportion of loss in LE (PLLE) and the proportion of loss in quality-adjusted LE (PLQALE), defined as the LLE or LQALE divided by the general population's LE or QALE, respectively [26].

Details on all the survival transition models can be found at Appendix A. We used a microsimulation approach to simulate 1 000 000 individuals to obtain point estimates of LE and QALE. Ninety-five percent confidence intervals (CIs) were derived through bootstrapping. This multistate microsimulation model was implemented in R version 4.4.1 using the microsimulation package version 1.4.2 [27] (https://CRAN.R-project.org/package=microsimulation) and the rstpm2 package version 1.6.2 [28].

To compare with our previous study on LE for patients with CML (including patients in chronic, accelerated, and blastic phase) in Sweden [11], we present the LLE and PLLE for patients with CML diagnosed in 2010. Moreover, we provided updated results with extended follow-up until 2020, based on data from the Swedish Cancer Registry (Appendix D).

2.3 | Health Utility Values

To calculate QALYs, we utilized health utility values specific to CML treatments, drawn from the studies by Foulon et al. [29] and Szabo et al. [30] (Table 1A). The utility value of the progression state was measured by using the time-trade-off approach [30], while the utility values for other health states were obtained using the EQ-5D-3L instrument

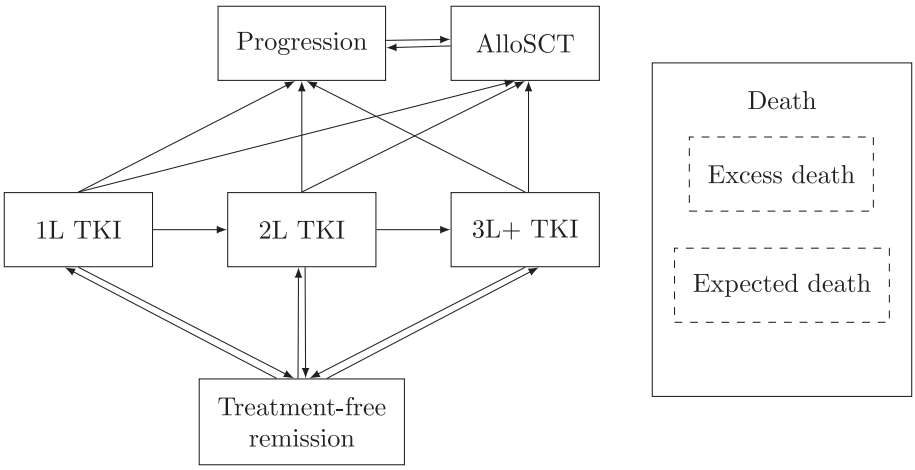

FIGURE 1 | A multistate microsimulation model for chronic-phase chronic myeloid leukemia. Transitions are also assumed from every live state to the excess or expected death state (arrows not shown). 1 L, first-line; 2 L, second-line; 3 L+, third-line and later; TKI, tyrosine kinase inhibitor; AlloSCT, allogeneic stem cell transplantation.

[29]. Considering uncertainties, the beta distribution was applied to all health state values for estimating 95% CIs [15]. To estimate LQALE, we retrieved health utility values for the Swedish general population from Teni et al. [31] (Table 1B). These values were multiplied by life years to obtain the general population's QALE, by age and sex.

To account for age-related comorbidity effects on utility values, we adopted the multiplier approach by Brazer et al. [32] For instance, the utility of 1 L TKI, reported as 0.76 (Table 1A), was derived from a study population with a median age of 52 years in Foulon et al. [29], and the general population's utilities in Sweden for this age group were 0.914 for males and 0.895 for females [31] (Table 1B). Consequently, the multipliers were then calculated as 0.76/0.914 = 0.83 for males and 0.76/0.895 = 0.85 for females. These multipliers were then applied across all ages and sexes to adjust for health utility values accordingly. For example, to estimate the utility of 1 L TKI for females aged 65 years, the calculation would be 0.909 * 0.85 = 0.77, where 0.909 represents the general population norm for females aged 65 years in Sweden, and 0.85 is the age-adjusted multiplier for the utility of 1 L TKI.

3 | Results

We identified 991 patients with CP-CML diagnosed from 2007 to 2017 (Table 2). The median age at diagnosis was 61 years, and 44.0% were females. During the follow-up period, 19.6% of the patients ($n = 194$) died, 4.5% ($n = 45$) experienced progression, and 4.9% ($n = 49$) underwent alloSCT. The majority of patients (85.4%, $n = 846$) received imatinib as their 1 L TKI following CP-CML diagnosis. Data on TFR and TKI re-initiation were available only for patients diagnosed between 2007 and 2012. Of these, 124 patients achieved TFR, though 68 of them re-initiated TKI therapy by the end of the follow-up period.

The results are presented for both sexes, covering ages at diagnosis from 45 to 85 years in 10-year intervals. To assess the long-term impact of CP-CML, we present overall survival and quality-adjusted survival curves, using 65-year-old female patients as an illustrative example (Figure 2). Compared to a 65-year-old female in the general population, female patients with CP-CML in this age group showed an LLE of 3.3 years (Figure 2A).

We further evaluated the survival outcome by incorporating health utility values to present the quality-adjusted survival curves for both the patients with CP-CML and the general population (Figure 2B). The curve for the general population reflects the age-stratified population norm in Sweden showed in Table 1B. The LQALE for this group was 6.6 QALYs (Figure 2B), indicating that CP-CML not only reduced LE but also diminished the quality of life in the remaining years. For other age groups and sexes, detailed overall and quality-adjusted survival for patients with CP-CML and their expected survival are provided in Appendix B. In addition, the probability of remaining in each health state and the corresponding QALYs for the patients with CP-CML are presented in stacked plots in Appendix C.

Both the LLE and LQALE of patients with CP-CML declined with increasing age, with LQALE consistently higher than LLE across all ages (Figure 3A). Younger female patients with CP-CML exhibited slightly higher LLE and LQALE than males. The maximum LLE was 5.7 years (95% CIs, 3.1–10.7) for 45-year-old female patients, with the corresponding LQALE being 12.0 QALYs (95% CIs, 5.4–20.6) (Table 3). When looking at the PLLE and PLQALE, the estimates are similar across sexes and ages, ranging from 9% to 15% and 29% to 33%, respectively (Figure 3B, Table 3). In comparison, our previous study [11] on patients with CP-CML showed an increasing PLLE by age, with the lowest estimate of 7% for males at 45 years, and the highest of 28% for both sexes at 85 years (Appendix D). The updated data, which extend follow-up until 2020, predicted similar LE and LLE for CML but with narrower CIs (Appendix D).

4 | Discussion

4.1 | Main Findings

We developed and utilized a multistate model using a population-based CML register to capture CML treatments and disease progression over time. We presented both LE and

TABLE 1 | (A) Chronic myeloid leukemia (CML) treatments' health utility values, by state, and (B) Swedish general population's health utility values, by age group and sex.

(A) CML treatments' health utility values			(B) Swedish general population's health utility values			
State	**Value (SD)**	**Source**	**Age group (years)**	**Males**	**Females**	**Source**
1L TKI	0.76 (0.21)	Table S3, Foulon et al. [29]	30–34	0.925	0.902	Table 1, Teni et al. [31]
2L TKI	0.68 (0.28)	Table S3, Foulon et al. [29]	35–39	0.938	0.910	
3L+ TKI	0.68 (0.23)	Table S3, Foulon et al. [29]	40–44	0.930	0.906	
Treatment-free remission	0.84 (0.21)	Table S3, Foulon et al. [29]	45–49	0.924	0.904	
Progression	0.41 (0.03)[a]	Table 3, Szabo et al. [30]	50–54	0.914	0.895	
AlloSCT	0.80 (0.18)	Table S3, Foulon et al. [29]	55–59	0.910	0.894	
			60–64	0.910	0.899	
			65–69	0.915	0.909	
			70–74	0.909	0.899	
			75–79	0.892	0.883	
			80–84	0.865	0.852	
			85–89	0.831	0.814	
			90–94	0.803	0.761	
			95–104	0.751	0.696	

Abbreviations: 1L, first-line; 2L, second-line; 3L+, third-line or later; AlloSCT, allogeneic stem cell transplantation; SD, standard deviation; TKI, tyrosine kinase inhibitor.
[a]The average value of the ANR (accelerated phase not responding to treatment) and BNR (blast phase not responding to treatment) of the UK cohort in Szabo et al. [30].

TABLE 2 | Baseline characteristics of patients with CP-CML diagnosed in Sweden from 2007 to 2017, with follow-up until 2018, by age group.

	18–49		**50–59**		**60–69**		**70–79**		**80–99**		**Total**	
Age group (years)	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Total	298	30.1	173	17.5	224	22.6	193	19.5	103	10.4	991	100
Median age at diagnosis (years)	40		55		64		74		83		61	
Sex												
Male	181	60.7	89	51.4	123	54.9	110	57.0	52	50.5	555	56.0
Female	117	39.3	84	48.6	101	45.1	83	43.0	51	49.5	436	44.0
Death	13	4.4	16	9.2	37	16.5	66	34.2	62	60.2	194	19.6
Progression	11	3.7	5	2.9	10	4.5	9	4.7	10	9.7	45	4.5
AlloSCT	27	9.1	15	8.7	5	2.2	2	1.0	0	0	49	4.9
Imatinib as 1 L TKI	236	79.2	142	82.1	192	85.7	178	92.2	98	95.1	846	85.4
TFR[a]	36	12.1	26	15.0	31	13.8	22	11.4	9	8.7	124	12.5
TKI re-initiation[a]	20	6.7	12	6.9	20	8.9	12	6.2	4	3.9	68	6.9

Abbreviations: 1 L TKI, first-line tyrosine kinase inhibitor; AlloSCT, allogeneic stem cell transplantation; CP-CML, chronic-phase chronic myeloid leukemia; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.
[a]Records for treatment-free remission and TKI re-initiation were complete for patients diagnosed from 2007 to 2012.

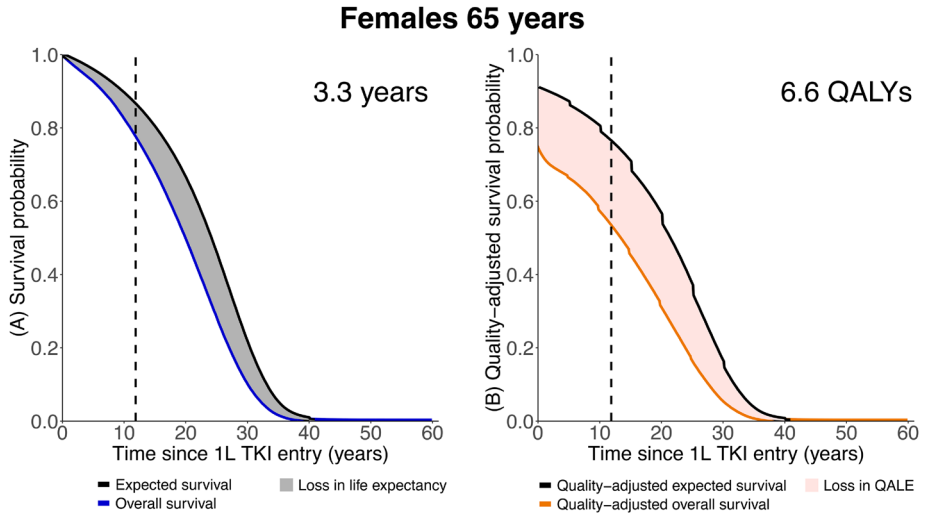

FIGURE 2 | (A) Loss in life expectancy and (B) loss in QALE (quality-adjusted life expectancy) for female patients with chronic-phase chronic myeloid leukemia aged 65 years diagnosed from 2007 to 2017. The dashed line indicates the maximum follow-up time of 11.87 years.

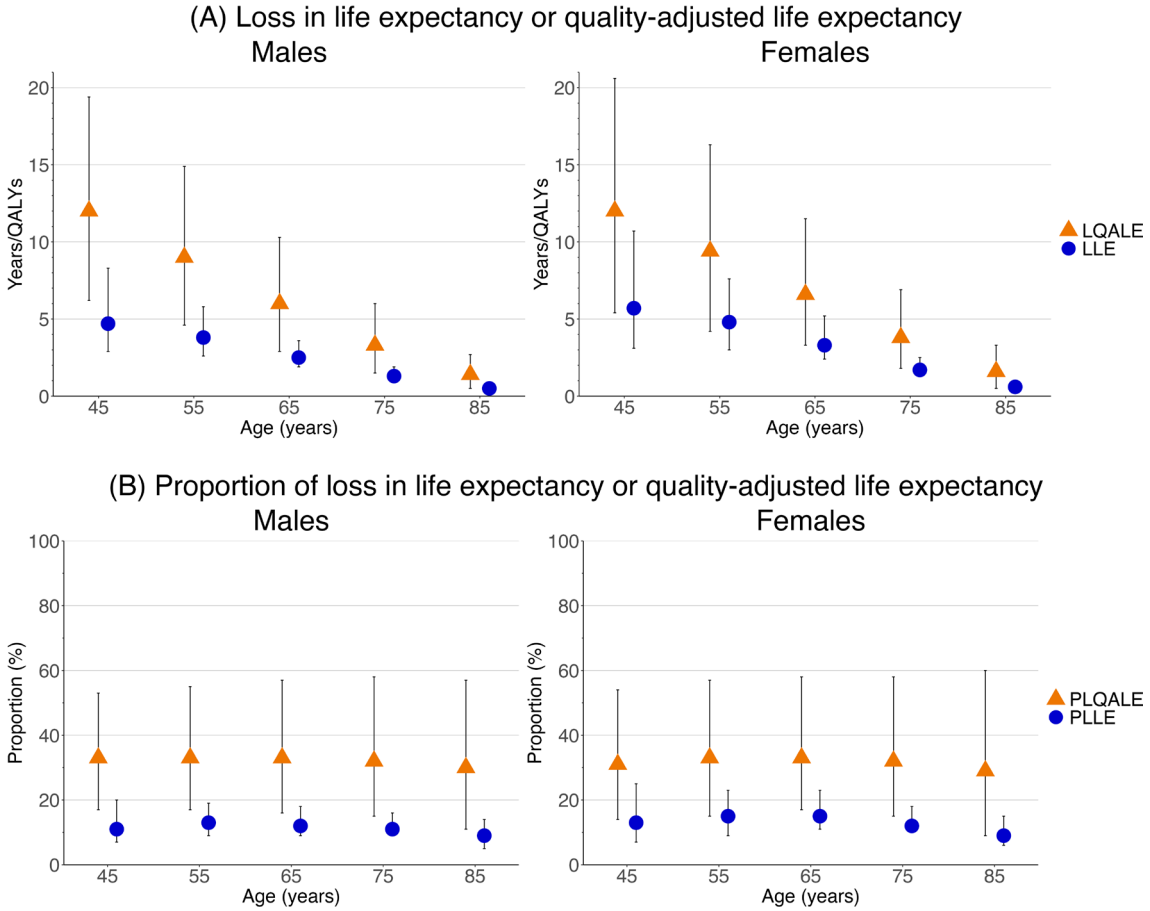

FIGURE 3 | (A) LLE and LQALE and (B) PLLE and PLQALE of patients with CP-CML in Sweden diagnosed from 2007 to 2017 over ages 45 to 85 years (every 10 years), by sex. Bars show 95% confidence intervals. LLE, loss in life expectancy; LQALE, loss in quality-adjusted life expectancy; PLLE, proportion of loss in life expectancy; PLQALE, proportion of loss in quality-adjusted life expectancy; QALYs, quality-adjusted life years; CP-CML, chronic-phase chronic myeloid leukemia.

QALE for patients with CP-CML diagnosed in Sweden from 2007 to 2017 and compared with those of the general population. The results showed that the scale of LQALE was higher than LLE, while the difference between LLE and LQALE diminished by age.

4.2 | Interpretation of the Results and Comparison With Previous Studies

While the LE of patients with CP-CML has approached that of the general population [11], our results revealed that there

TABLE 3 | LE and QALE of the general population, and LE, LLE, PLLE, QALE, LQALE, and PLQALE of patients diagnosed with CP-CML in Sweden from 2007 to 2017 at five selected ages (95% CIs). Units of LE and LLE: Years; units of QALE and LQALE: QALYs.

Age (years)	LE	LE CP-CML	LLE CP-CML	PLLE CP-CML	QALE	QALE CP-CML	LQALE CP-CML	PLQALE CP-CML
Males								
45	40.9	36.2 (32.6–37.9)	4.7 (2.9–8.3)	0.11 (0.07–0.20)	36.9	24.9 (17.5–30.7)	12.0 (6.2–19.4)	0.33 (0.17–0.53)
55	30.2	26.4 (24.4–27.5)	3.8 (2.6–5.8)	0.13 (0.09–0.19)	27.1	18.2 (12.2–22.5)	9.0 (4.6–14.9)	0.33 (0.17–0.55)
65	20.3	17.8 (16.7–18.4)	2.5 (1.9–3.6)	0.12 (0.09–0.18)	18.1	12.2 (7.9–15.2)	6.0 (2.9–10.3)	0.33 (0.16–0.57)
75	11.8	10.5 (9.9–10.8)	1.3 (1.1–1.9)	0.11 (0.09–0.16)	10.3	7.0 (4.3–8.8)	3.3 (1.5–6.0)	0.32 (0.15–0.58)
85	5.6	5.1 (4.8–5.3)	0.5 (0.3–0.8)	0.09 (0.05–0.14)	4.7	3.3 (1.9–4.2)	1.4 (0.5–2.7)	0.30 (0.11–0.57)
Females								
45	43.2	37.5 (32.4–40.0)	5.7 (3.1–10.7)	0.13 (0.07–0.25)	38.2	26.3 (17.7–32.9)	12.0 (5.4–20.6)	0.31 (0.14–0.54)
55	32.6	27.8 (25.0–29.6)	4.8 (3.0–7.6)	0.15 (0.09–0.23)	28.8	19.4 (12.5–24.6)	9.4 (4.2–16.3)	0.33 (0.15–0.57)
65	22.7	19.4 (17.5–20.3)	3.3 (2.4–5.2)	0.15 (0.11–0.23)	19.9	13.3 (8.4–16.6)	6.6 (3.3–11.5)	0.33 (0.17–0.58)
75	13.8	12.1 (11.4–12.5)	1.7 (1.4–2.5)	0.12 (0.10–0.18)	11.8	8.0 (4.9–10.0)	3.8 (1.8–6.9)	0.32 (0.15–0.58)
85	6.8	6.2 (5.8–6.4)	0.6 (0.4–1.0)	0.09 (0.06–0.15)	5.5	3.9 (2.2–4.9)	1.6 (0.5–3.3)	0.29 (0.09–0.60)

Abbreviations: CIs, confidence intervals; CP-CML, chronic-phase chronic myeloid leukemia; LE, life expectancy; LLE, loss in life expectancy; LQALE, loss in quality-adjusted life expectancy; PLLE, proportion of loss in life expectancy; PLQALE, proportion of loss in quality-adjusted life expectancy; QALE, quality-adjusted life expectancy; QALYs, quality-adjusted life years.

is still no normalization and that the loss in QALYs is considerable, primarily due to reduced health utility values with long-term TKI treatments. On average, patients spent more than 50% of their lifetime in the TKI states, which have health state utility values between 0.68 and 0.76, compared to a utility value of 0.84 in the TFR state (Table 1, Appendix C). Flynn and Atallah earlier summarized the diminished quality of life for patients due to long-term therapies, highlighting the unmet medical needs for CML despite improved survival [33]. Our study corroborates their findings by presenting the prevailing LQALE.

In recent years, achieving a TFR after an attempted TKI discontinuation has gained increasing importance in the management of CML, with growing evidence from both trials [4, 6, 34, 35] and the real-world settings [8, 36, 37]. Moreover, recent findings from the DAstop2 trial [38] support the safety and feasibility of achieving a second TFR after stopping second or later lines of TKI therapies. Attaining TFR has emerged as a desired goal for many patients with CP-CML [39], which may substantially impact their long-term outcomes, especially with respect to reducing any adverse events and increasing quality of life. Considering the evolving role of TFR in treatment strategies, we recognize its potential impact on our findings: patients who achieve and sustain a durable TFR presumably spend less time in states with lower health utility values, thus resulting in higher QALYs.

In addition, it is important to acknowledge that the presented estimates represent averages across the entire patient cohort. Consequently, careful consideration is warranted when interpreting these findings in front of an individual patient. For instance, a young patient with CP-CML with a low-risk score (according to Sokal [40] or ELTS [41]) and an early optimal response to TKI will probably have both LE and QALE greater than our given predictions. Future analyses could investigate the LE and QALE of patients with CML stratified by Sokal [40] or ELTS [41] scores.

Our study included only patients with CP-CML diagnosed from 2007 to 2017. The LLE estimates for patients aged ≥75 years were lower than those for patients of the same-age group diagnosed in 2010 in the study by Bower et al. [11], which included patients in all phases (chronic, accelerated, and blastic phases) of CML (Table 3, Appendix D). The discrepancy may arise from other sources as well, primarily driven by assumptions in statistical modeling. A further discussion is included in Appendix E.

4.3 | Strengths and Limitations

This study has several strengths. The novelty of our approach lies in the development and application of a multistate natural history model for CML that incorporates relative survival extrapolation [9]. This method demonstrated greater accuracy in estimating LE compared to using an all-cause survival framework alone. Consequently, we consider it superior for producing more accurate estimates of QALYs than other multistate models [19, 20, 42] that employ an all-cause survival framework. Furthermore, to our knowledge, this is the first study to investigate QALE in CML patients using data from the Swedish CML register, a large-scale population-based cancer register. This represents a pioneering advancement in CML epidemiology through the application of real-world evidence.

Some limitations warrant notice. First, ideally, one should employ the same instrument to assess the background and health state utility values [43]. Due to data availability, health state utilities used in this study were measured using two health outcome instruments: EQ-5D-3L [29] and time trade-off [30], and the background utilities from the general population were measured by EQ-5D-5L [31]. It is also worth noting that we incorporated health utility values from different study populations. To account for this limitation, we have employed the age-adjusted multiplier approach by Brazier [32]. Second, the health state utility value of the alloSCT state was reported as 0.80 by Foulon et al. [29], which was higher than the 1 L TKI state, 0.76. This value was measured cross-sectionally from nine patients who were all classified at the alloSCT state but potentially at various sub-states. From a systematic review of health state utility values for acute myeloid leukemia [44], patients who underwent stem cell transplantation may initially experience a lower health state with gradual improvement over time. Hence, we considered 0.80 a reasonable average estimate for alloSCT across time in our model. Third, the study population included patients diagnosed between 2007 and 2017 with follow-up until 2018, and the treatment landscape for CML has evolved since then, with the introduction of newer TKIs. Therefore, our findings may not fully reflect patients diagnosed later than 2018. Last, our study included all adult patients with chronic-phase CML diagnosed in Sweden from 2007 to 2017. All patients with CP-CML in the patient cohort were initially treated with TKIs (85.4% imatinib as 1 L TKI), so the results may not be generalizable to populations of CP-CML patients with different treatment profiles.

In conclusion, while the LLE for patients with CP-CML is relatively low, our study shows a considerable loss in QALE compared with the general population. This highlights the need for further advancements in CP-CML management, which could involve the development of new TKIs or the integration of novel targeted agents with existing TKIs to enhance antitumor efficacy and minimize adverse effects. Additionally, the refinement of predictive models for optimizing TKI treatment—whether through cessation or intensification—will contribute. Lifelong monitoring of patients with CP-CML remains crucial to assess the impact of these treatments on survival, quality of life, and cost-effectiveness.

Author Contributions

Enoch Yi-Tung Chen: conceptualization; data cleaning; methodology development; software; formal statistical analysis; visualization; writing, reviewing, and editing. **Torsten Dahlén:** conceptualization; data cleaning; methodology development; writing, reviewing, and editing. **Leif Stenke:** conceptualization; methodology development; visualization; writing, reviewing, and editing. **Magnus Björkholm:** conceptualization; methodology development; visualization; writing, reviewing, and editing. **Shuang Hao:** conceptualization; visualization; writing, reviewing, and editing. **Paul W. Dickman:** conceptualization; data cleaning; methodology development; formal statistical analysis; visualization; writing, reviewing, and editing. **Mark S. Clements:** conceptualization; data cleaning; methodology development; software; formal statistical analysis; visualization; writing, reviewing, and editing.

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Conflicts of Interest

Enoch Yi-Tung Chen: No relationship to disclose. Torsten Dahlén: (all outside of the submitted work) Consulting: Xspray pharma; Novartis. Leif Stenke: (all outside of the submitted work) Consulting: Xspray Pharma. Magnus Björkholm: (all outside of the submitted work) Grant committee: Incyte; Educational program committee: Roche, Pfizer, Bristol Myers Squibb, Abbvie, Janssen, Takeda, Novartis; Consulting: WntResearch, Janssen-Cilag, and Schain Research; Research grant: Takeda. Shuang Hao: No relationship to disclose. Paul W. Dickman: No relationship to disclose. Mark S. Clements: No relationship to disclose.

Data Availability Statement

The data under this study are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.