Extrapolating Survival with Applications to Health Technology Assessment

Enoch Yi-Tung Chen

Department of Medical Epidemiology and Biostatistics
Karolinska Institutet

PhD Dissertation

September 11, 2025

Salen Petrén, Nobels väg 12B, Solna

Karolinska Institutet

Agenda

1. Chairperson's introduction
2. Errata
3. Opponent's overview of the research area
4. PhD student's summary of the thesis
5. *Break (5 minutes)*
6. Opponent's questions
7. *Break (5 minutes)*
8. Examination board's questions
9. Public questions
10. *Examination board meeting (Chairperson, Opponent, Examination board, and Supervisors)*
11. *Announcement of the decision at Ljusgården, Department of Medical Epidemiology and Biostatistics*

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Extrapolating Survival with Applications to Health Technology Assessment

PhD student Enoch Yi-Tung Chen

Chairperson Doctor Elisavet Syriopoulou

Principal Supervisor
Professor Paul W. Dickman

Co-supervisors
Docent Mark S. Clements
Professor Magnus Björkholm
Doctor Torsten Dahlén
Doctor Shuang Hao

Opponent
Professor Nicholas R. Latimer

Examination Board
Professor Linus Jönsson
Professor Gebrenegus Ghilagaber Yebio
Docent Hannah L. Brooke

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Errata

- Thesis. p.63. **Knowledge gap.** Andersson et al. [~~90~~ 16]
- Thesis. p.64. **Table 7.1.** Andersson et al. [~~90~~ 16]
- Study II. p.300. **2.1.2 Transition 2: Modeling the Mortality Rate of Progression-Free to Death.** "Note that model fitting for $H_2(t, t+a, t+c)$ uses the ~~all-cause mortality rates~~ **expected mortality rates** $h_2^*(t+a, t+c)$ for the event times and does not require ~~all-cause cumulative mortality rates~~ **cumulative expected mortality rates** $H_2^*(t+a, t+c)$, as minus $H_2^*(t+a, t+c)$ is a constant term in the log-likelihood."

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Errata

In Study IV, the average YCPP (yearly cost per patient) should be reported as a weighted mean (weighted by prevalent cases by state), not as an unweighted mean. Corrected as follows:

Study IV Manuscript. p.14. **Table 3 (Continued).**

Year	Average YCPP (USD)
2015	33 224
2016	33 026
2017	21 432
2018	22 339
2019	19 413
2020	21 376
2021	18 228
2022	18 604
2023	15 937
2024	17 101
2025	14 408
2026	14 420
2027	14 431
2028	14 443
2029	14 453
2030	14 464

Study IV Supplementary Materials. p.22. **Table S5 (Continued).**

Year	Average YCPP (USD)
2015	33 224
2016	33 026
2017	21 432
2018	22 339
2019	19 413
2020	21 376
2021	18 228
2022	18 604
2023	15 937
2024	17 101
2025	13 988
2026	13 592
2027	13 207
2028	12 832
2029	12 468
2030	12 114

Study IV Supplementary Materials. p.24. **Table S6 (Continued).**

Year	Average YCPP (USD)
2015	33 224
2016	33 026
2017	21 432
2018	22 339
2019	19 413
2020	21 376
2021	18 228
2022	18 604
2023	15 937
2024	17 101
2025	13 722
2026	13 079
2027	12 466
2028	11 882
2029	11 325
2030	10 794

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Errata

Study IV Supplementary Materials. p.13. **Figure S5.** The x-axis was overlapped by the caption. Corrected as follows:

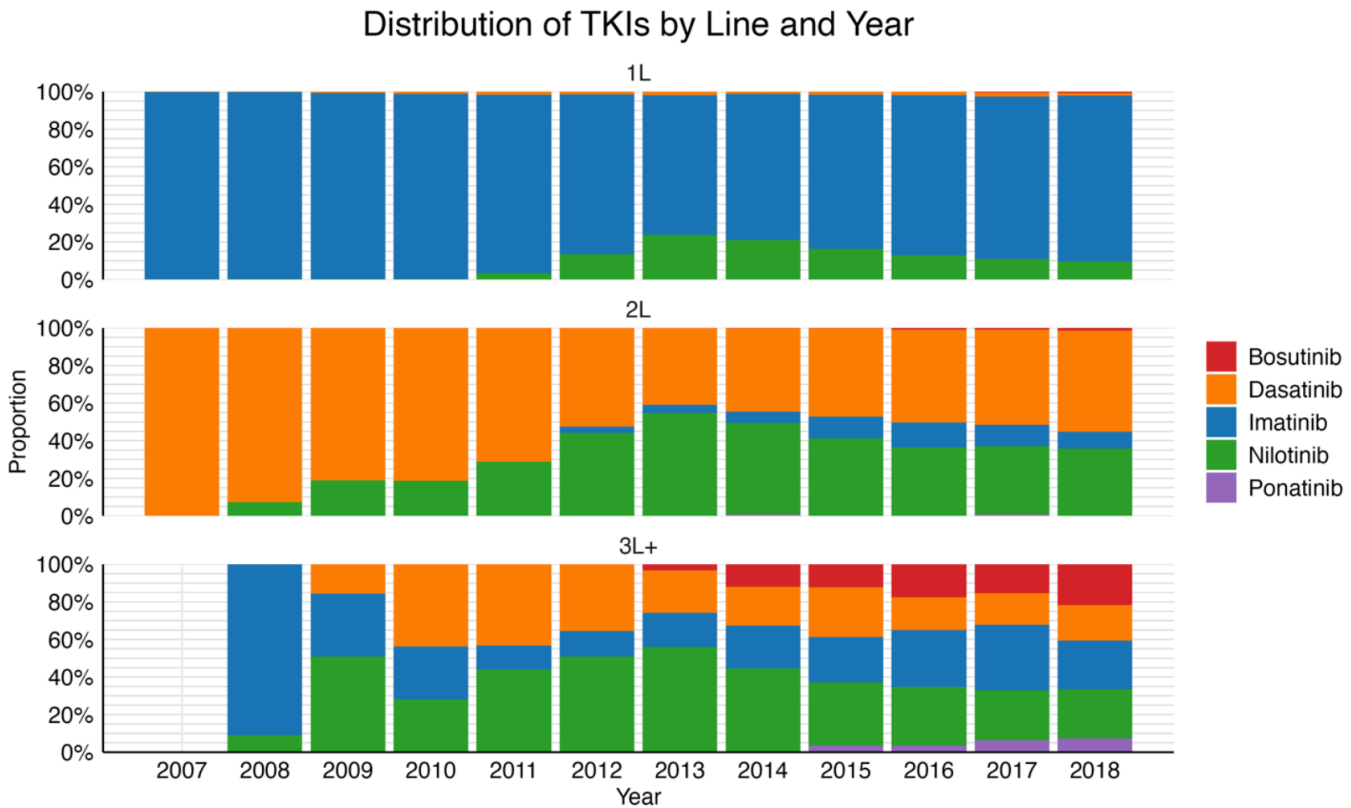

Figure S5. Yearly distribution (%) of TKIs —bosutinib, dasatinib, imatinib, nilotinib, and ponatinib —by treatment line (1L, 2L, and 3L+) during 2007 to 2018. 1L, first line; 2L, second-line; 3L+, third-line or later.

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Extrapolating Survival with Applications to Health Technology Assessment

Enoch Yi-Tung Chen

Department of Medical Epidemiology and Biostatistics
Karolinska Institutet

PhD Dissertation

September 11, 2025

Salen Petrén, Nobels väg 12B, Solna

Karolinska Institutet

About me

- Born and raised in Taiwan.
- BSc in Public Health Sciences, National Taiwan University (2014-2018).
- MSc in Epidemiology, Karolinska Institutet (2018-2020).

Thesis overview

Extrapolating Survival with Applications to Health Technology Assessment

Enoch Yi-Tung Chen

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- Predict survival beyond the follow-up period.
- Calculate the area under the survival curve (estimations of life years/QALYs).
- Relative survival extrapolation, $h(t) = h^*(t) + \lambda(t)$.
- Applications in (i) cost-effectiveness analysis, (ii) estimating QALYs, and (iii) prevalence costs.

Thesis overview

Ultimate aim

Evaluate and develop methods for survival extrapolation applicable to health economics and related research

Contributions

1. Evaluate methods for survival extrapolation (Study I).
2. Incorporate relative survival extrapolation into multistate models (Study II).
3. Quantify loss in life expectancy and loss in quality-adjusted life expectancy for patients with chronic-phase chronic myeloid leukaemia (CP-CML) in Sweden (Study III).
4. Estimate the economic burden of CML in Sweden (Study IV).

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Thesis overview

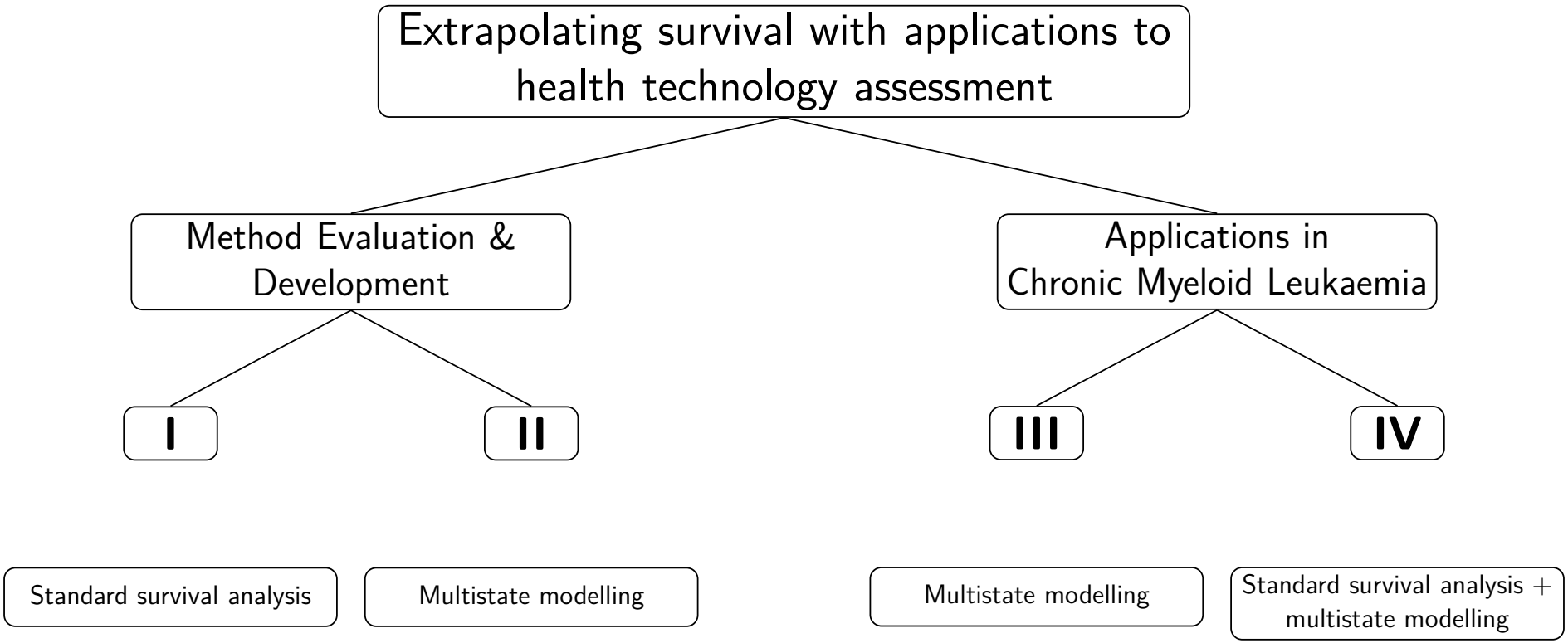

Figure: Overview of Studies I-IV, their analysis types, and their relationships.

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Thesis overview

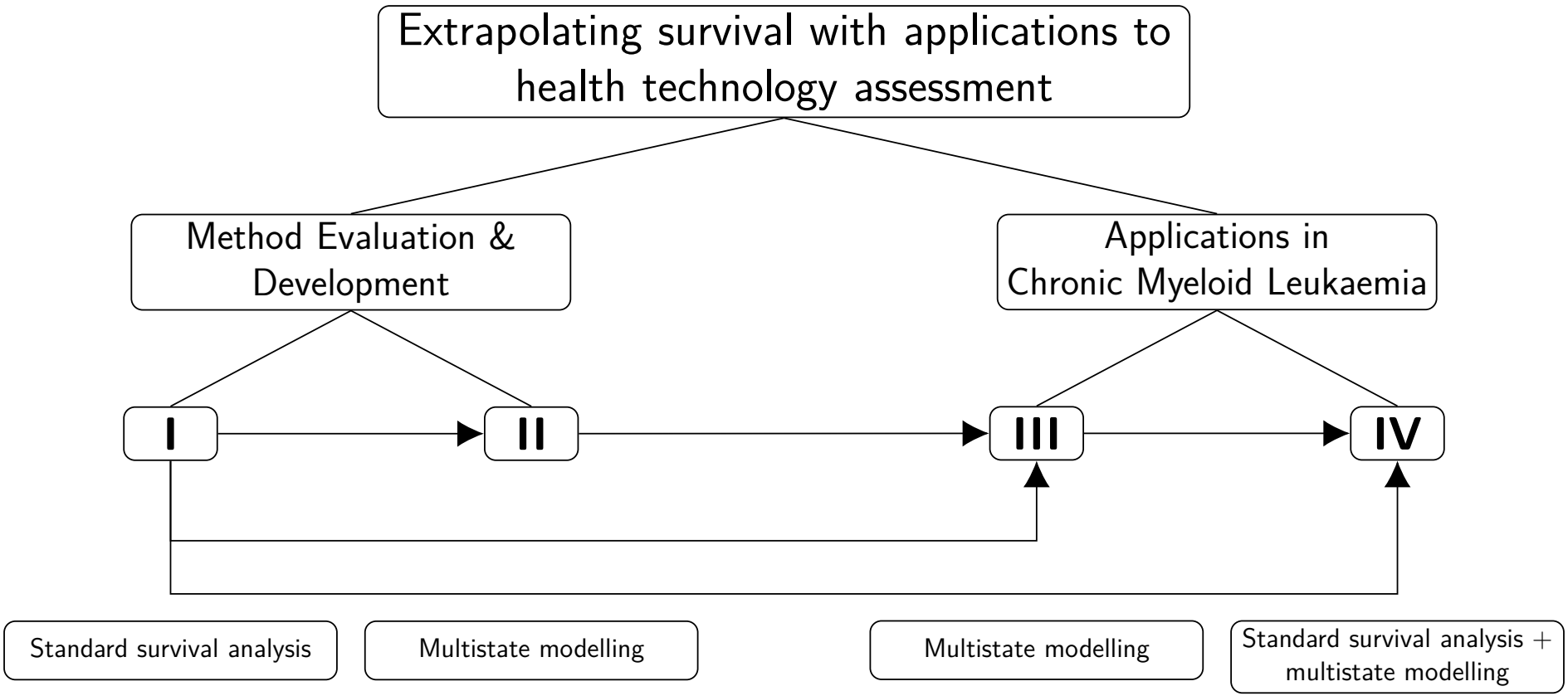

Figure: Overview of Studies I-IV, their analysis types, and their relationships.

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Study I

Title: Comparing Survival Extrapolation within All-Cause and Relative Survival Frameworks by Standard Parametric Models and Flexible Parametric Spline Models Using the Swedish Cancer Registry

Aim

To assess survival extrapolation using standard and flexible parametric models within relative survival and all-cause survival frameworks.

Study I: Knowledge gap

Table: Comparison of previous studies and the Study I by survival framework (all-cause versus relative), parametric model family (standard versus flexible) and outcome (10-year RMST versus LE).

Studies	**Outcome**		**ASF**		**RSF**	
	10-y RMST	**LE**	**SPMs**	**FPMs**	**SPMs**	**FPMs**
Gray et al., *MDM*, 2020	X	-	X	X	–	–
Andersson et al., *Stat in Med*, 2013	-	X	–	X	Only Weibull	X
Study I	X	X	X	X	X	X

ASF, all-cause survival framework; RSF, relative survival framework; LE, life expectancy; RMST, restricted mean survival time; SPMs, standard parametric models; FPMs, flexible parametric models.

Study I: Study population

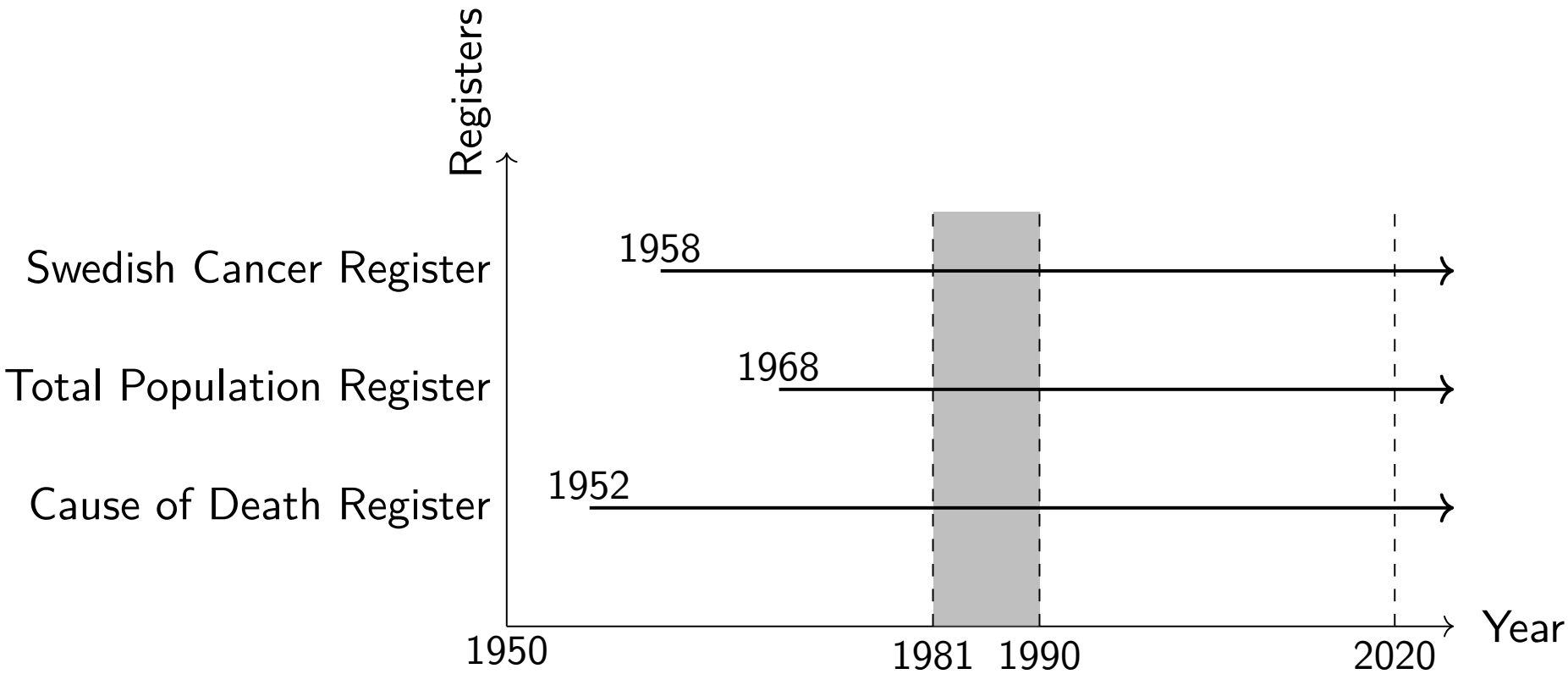

Figure: Study population for Study I. The shaded region (1981--1990) represents the inclusion period for cancer diagnoses, with follow-up until 2020. Maximum follow-up was 40 years.

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Study I: Methods

We evaluated **1 890** survival extrapolation scenarios:

- 5 cancer types (colon, breast, melanoma, prostate, and chronic myeloid leukaemia)
- 3 age groups (18-59, 60-69, and 70-99 years at diagnosis)
- 9 parametric models (6 standard versus 3 flexible parametric models)
- 2 modelling frameworks (all-cause versus relative survival frameworks)
- 7 follow-up cutoffs
  - 2, 3, and 5 years for 10-year extrapolations
  - 2, 3, 5, and 10 years for lifetime/40-year extrapolations

Generate as many hazard shapes as possible, with the true survival known from 40 years of cancer register data.

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Study I: Evaluating survival extrapolation

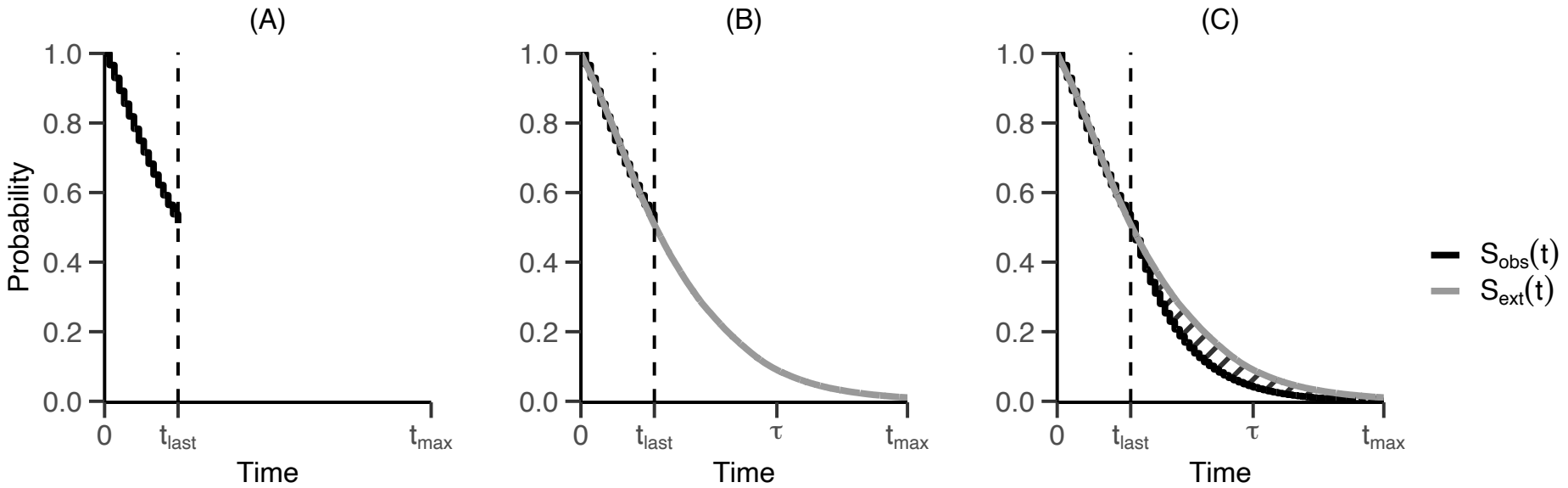

Figure: (A) The observed Kaplan-Meier's survival curve, $S_{\text{obs}}(t)$, with follow-up until t_{last}. (B) The extrapolated survival curve, $S_{\text{ext}}(t)$, fitted until t_{last} and extrapolated to τ (or t_{max}). (C) The area between $S_{\text{obs}}(t)$ and $S_{\text{ext}}(t)$ and the survival proportions at $S_{\text{obs}}(t)$ and $S_{\text{ext}}(t)$ are used to assess extrapolation.

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Study I: Results for extrapolating to 10 years

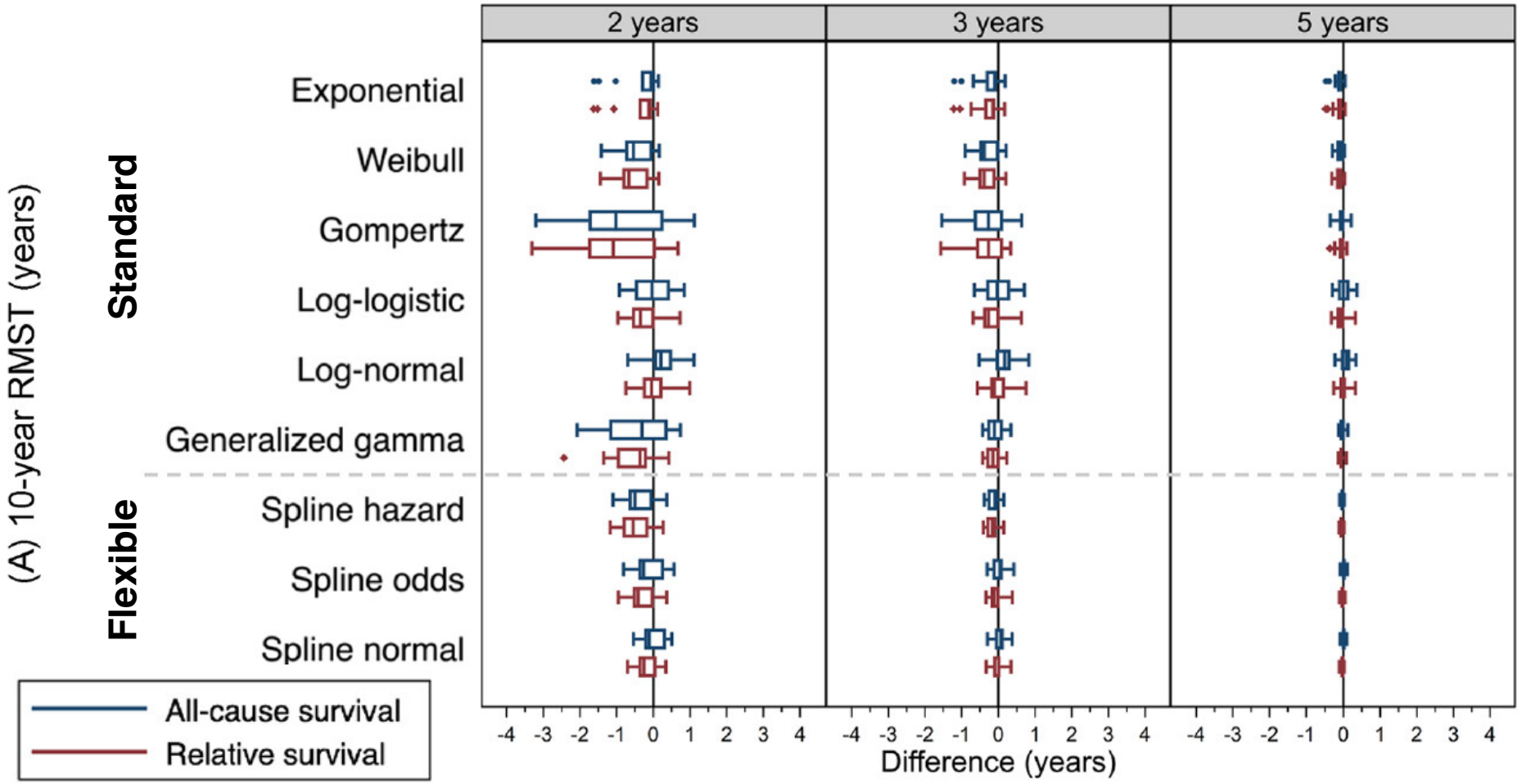

Figure: Boxplots show difference (extrapolated minus observed) for 10-year restricted mean survival time, across 15 cancer cohorts (5 cancer types x 3 age groups). Image from Study I: Chen EYT et al., *Med Dec Mak*, 2024. Licensed under CC BY--NC 4.0.

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Study I: Results for extrapolating to lifetime/40 years

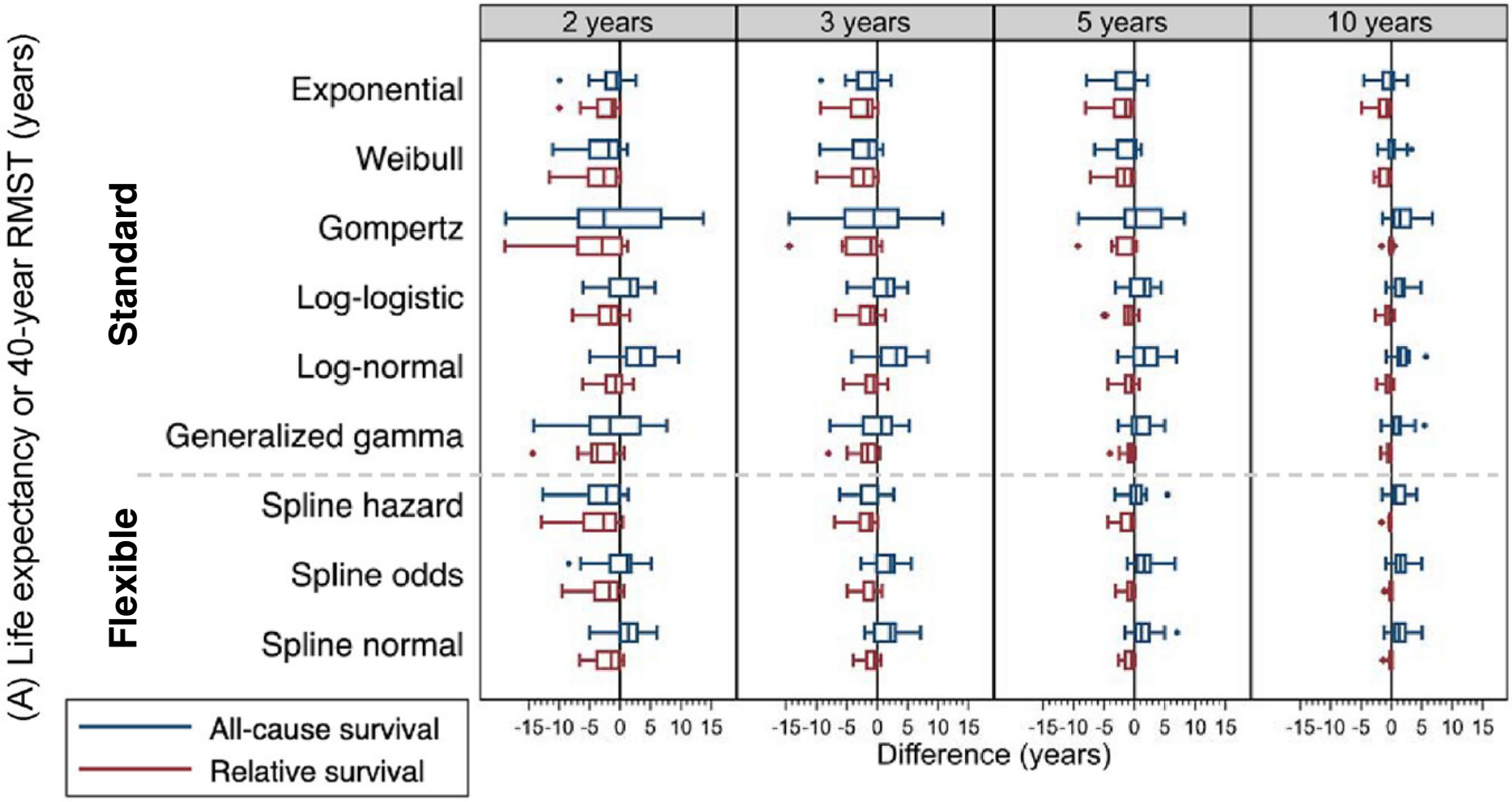

Figure: Boxplots show difference (extrapolated minus observed) for life expectancy/40-year restricted mean survival time, across 15 cancer cohorts (5 cancer types x 3 age groups). Image from Study I: Chen EYT et al. *Med Dec Mak*, 2024. Licensed under CC BY--NC 4.0.

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Study I: Conclusions

For extrapolations to 10 years:

1. Flexible parametric models generally predicted better standard parametric models.
2. No distinct difference was found between the all-cause and relative survival frameworks.

For extrapolations to a lifetime horizon:

1. The relative survival framework predicted better than the all-cause survival framework, particularly using flexible parametric models.
2. The all-cause survival framework often overestimated survival, while the relative survival framework often underestimated.

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Study I

Original Research Article

Medical Decision Making

Medical Decision Making
2024, Vol. 44(3) 269–282

DOI: 10.1177/0272989X241227230
journals.sagepub.com/home/mdm
Sage

Comparing Survival Extrapolation within All-Cause and Relative Survival Frameworks by Standard Parametric Models and Flexible Parametric Spline Models Using the Swedish Cancer Registry

Enoch Yi-Tung Chen, Yuliya Leontyeva, Chia-Ni Lin, Jung-Der Wang, Mark S. Clements, and Paul W. Dickman

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Thesis overview

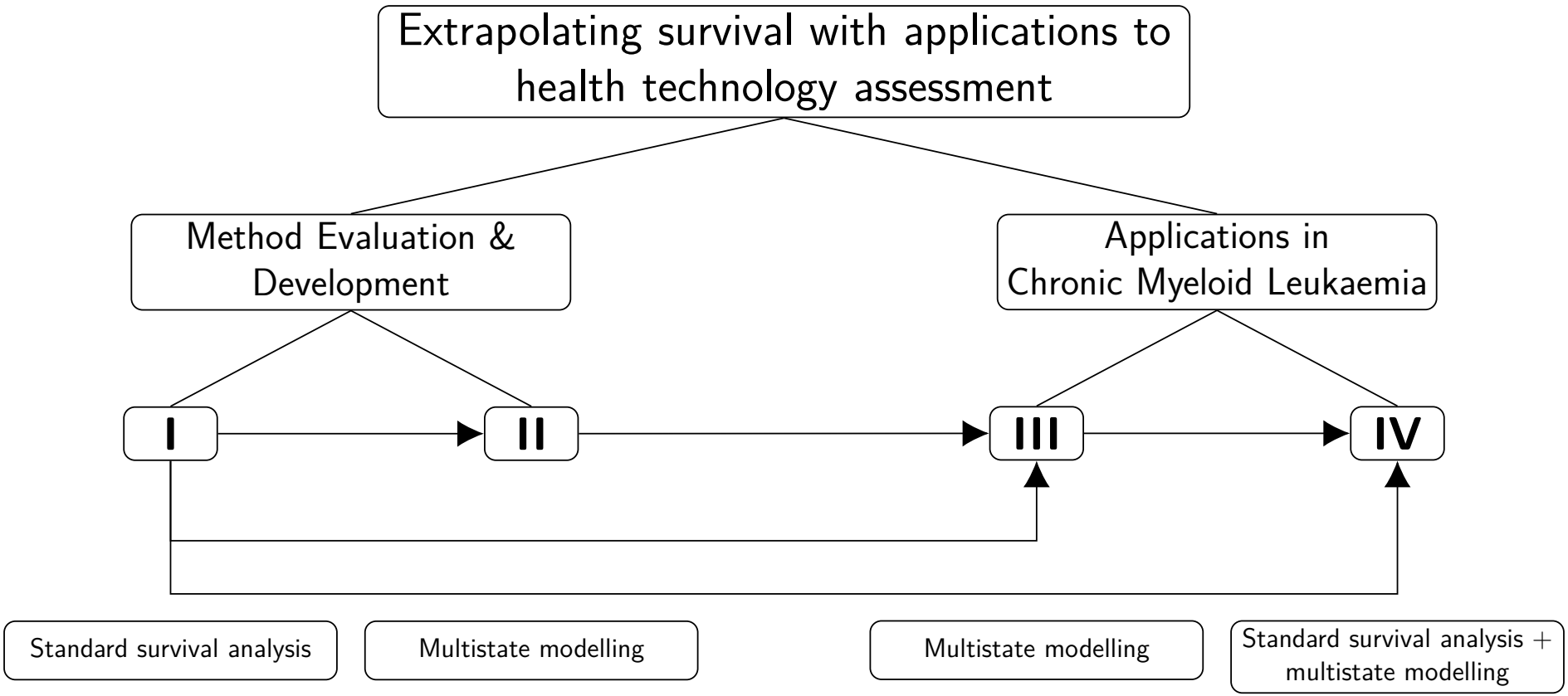

Figure: Overview of Studies I-IV, their analysis types, and their relationships.

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Study II

Title: A Multistate Model Incorporating Relative Survival Extrapolation and Mixed Time Scales for Health Technology Assessment

Aim

To develop a multistate model that integrates relative survival extrapolation with mixed time scales, in particular for applications in cost-effectiveness analysis.

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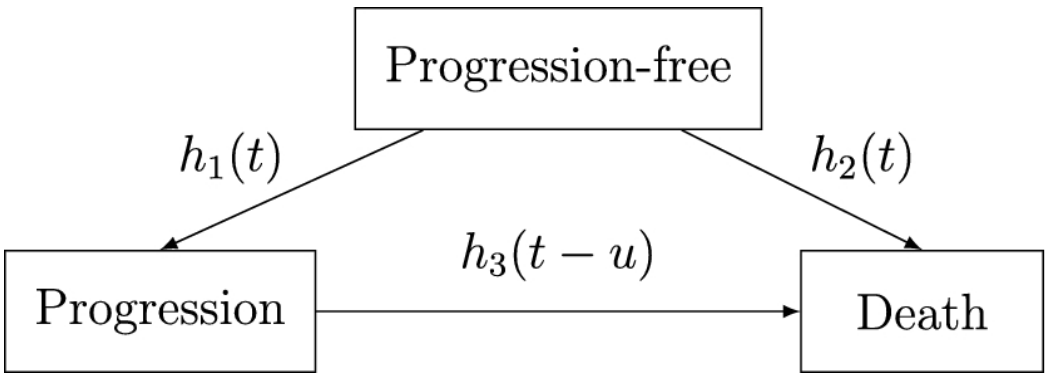
Study II: Methods



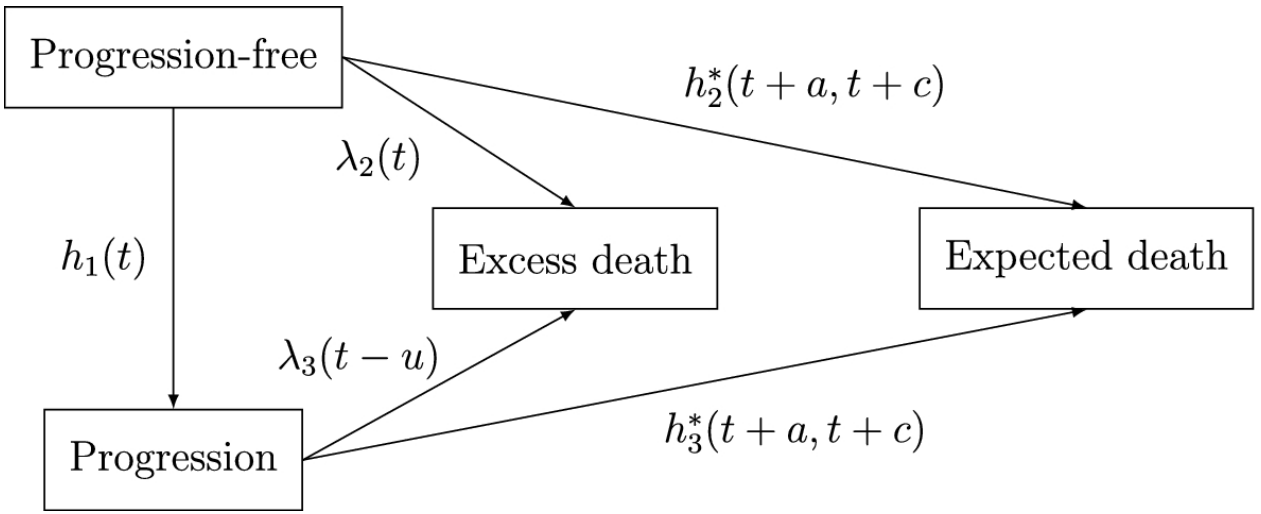
Time scales:

t: Time since study entry

u: Time at progression

Figure: An irreversible illness-death model with a semi-Markov assumption. Image from Study II: Chen EYT, Dickman PW, Clements MS. *PharmacoEconomics*. 2025. Licensed under CC BY--NC 4.0.

Study II: Methods



Time scales:
t: Time since study entry
a: Age at study entry
c: Calendar year at study entry
u: Time at progression

Figure: An irreversible illness–death model incorporating a relative survival framework, with a semi-Markov approach. Image from Study II: Chen EYT, Dickman PW, Clements MS. *PharmacoEconomics*. 2025. Licensed under CC BY--NC 4.0.

Study II: Illustrative example-the CLL-8 trial

- To show how a multistate model with relative survival extrapolation works, we built upon and extended the cost-effectiveness analysis for the CLL-8 trial by Williams et al., *MDM*, 2017.
- The CLL-8 trial compared rituximab in combination with fludarabine and cyclophosphamide (RFC) versus fludarabine and cyclophosphamide alone (FC) for treatment-naive patients with chronic lymphocytic leukaemia (CLL).
- The original follow-up was about 4 years (Hallek et al., *Lancet*, 2010). We projected survival from 4 to 50 years in a multistate framework using our proposed model and Williams et al.'s model, then compared with 8-year follow-up (Fischer et al., *Blood*, 2016).

Study II: Illustrative example-the CLL-8 trial

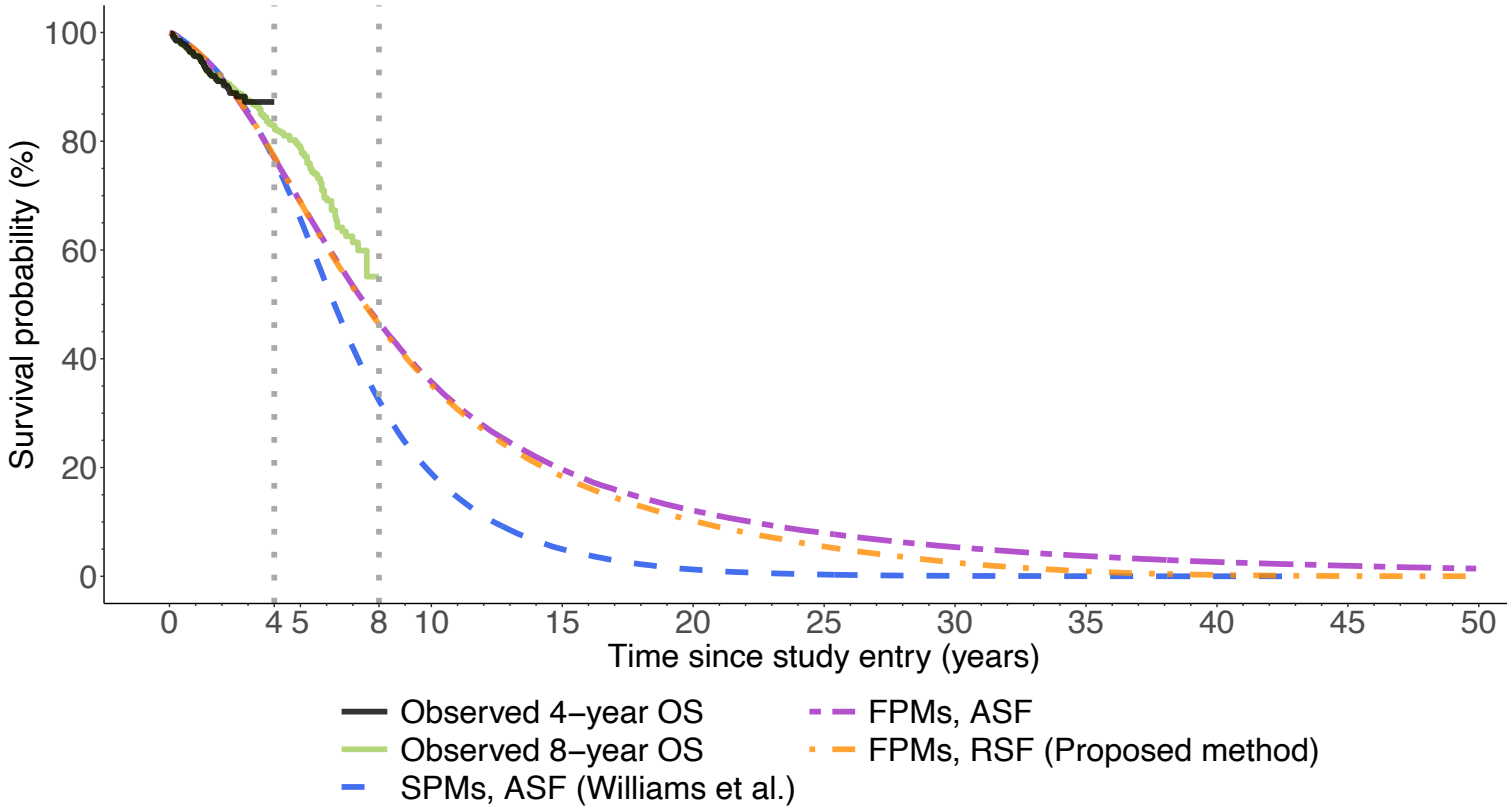


Figure: Observed and extrapolated survival functions for patients of the RFC arm in the CLL-8 trial. OS, overall survival; SPMs, standard parametric models; FPMs, flexible parametric models; ASF, all-cause survival framework; RSF, relative survival framework. Image from Study II: Chen EYT, Dickman PW, Clements MS. *PharmacoEconomics*. 2025. Licensed under CC BY--NC 4.0.

Study II: Illustrative example-the CLL-8 trial

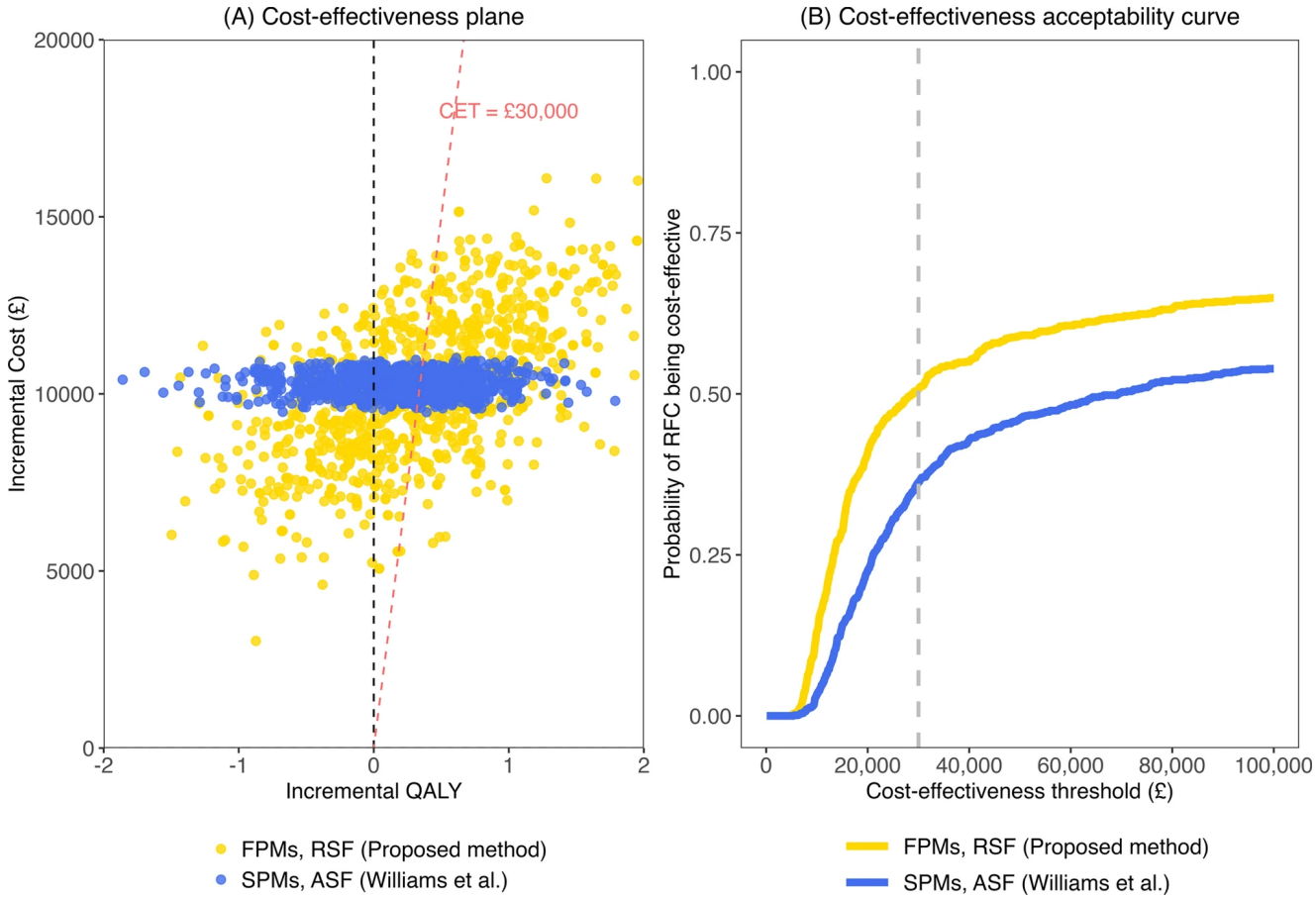


Figure: Cost-effectiveness plane (left) and cost-effectiveness acceptability curve (right). CET, cost-effectiveness threshold; ASF, all-cause survival framework; FPM, flexible parametric model, RSF, relative survival framework; SPM, standard parametric model. Image from Study II: Chen EYT, Dickman PW, Clements MS. *PharmacoEconomics*. 2025. Licensed under CC BY--NC 4.0.

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Study II: Conclusions

- Based on a single case study (the CLL-8 trial; comparison with Williams et al., *MDM*, 2017), so generalisability is limited.
- Main contribution: integration of relative survival extrapolation and mixed time scales into multistate models.
- Both `multistate` and `hesim` packages in R were extended to simulate event times from transitions with mixed time scales to allow for relative survival extrapolation.
- Example code available at: `https://github.com/enochytchen/ChenEYT_microsim`.

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Study II

PharmacoEconomics (2025) 43:297–310
https://doi.org/10.1007/s40273-024-01457-w

ORIGINAL RESEARCH ARTICLE

Check for updates

A Multistate Model Incorporating Relative Survival Extrapolation and Mixed Time Scales for Health Technology Assessment

Enoch Yi-Tung Chen[1] · Paul W. Dickman[1] · Mark S. Clements[1]

Accepted: 6 November 2024 / Published online: 25 November 2024

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Thesis overview

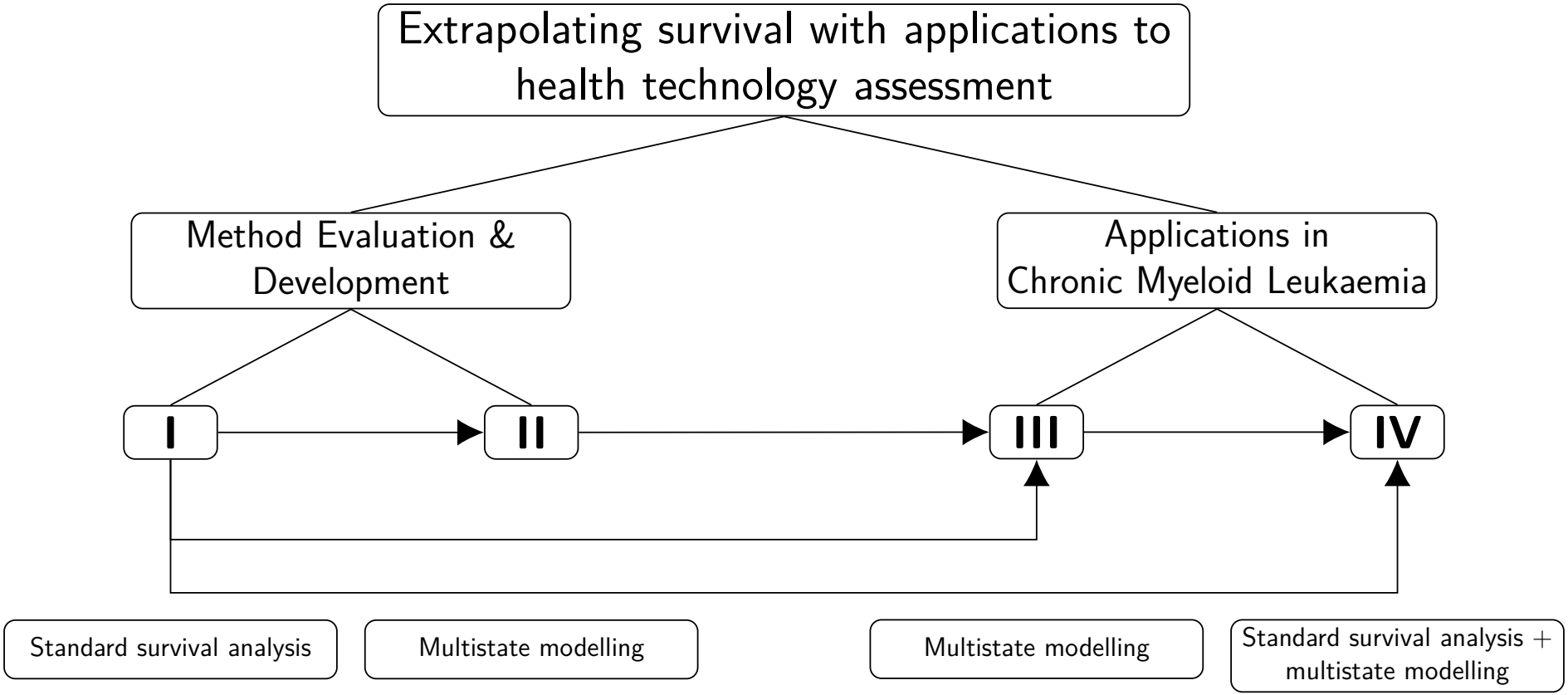

Figure: Overview of Studies I-IV, their analysis types, and their relationships.

Study III

Title: Loss in Overall and Quality-Adjusted Life Expectancy for Patients With Chronic-Phase Chronic Myeloid Leukemia (CP-CML)

Knowledge gap:

- Previous studies in Sweden (Bower, *JCO*, 2016) and the Netherlands (Maas, *BJH*, 2022) showed that life expectancy for patients with CML has recently approached that of the general population.
- Improved survival has been mainly attributed to the introduction of tyrosine kinase inhibitors (TKIs) (Björkholm, *JCO*, 2013).
- However, these studies focused on survival ("quantity" of life), without considering the impact on "quality" of life.

Study III

Title: Loss in Overall and Quality-Adjusted Life Expectancy for Patients With Chronic-Phase Chronic Myeloid Leukemia (CP-CML)

Aims

1. To develop a natural history model for CML treatment by applying and extending the multistate model from Study II.
2. To quantify loss in LE and loss in QALE compared to the general population.

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Study III: Study population

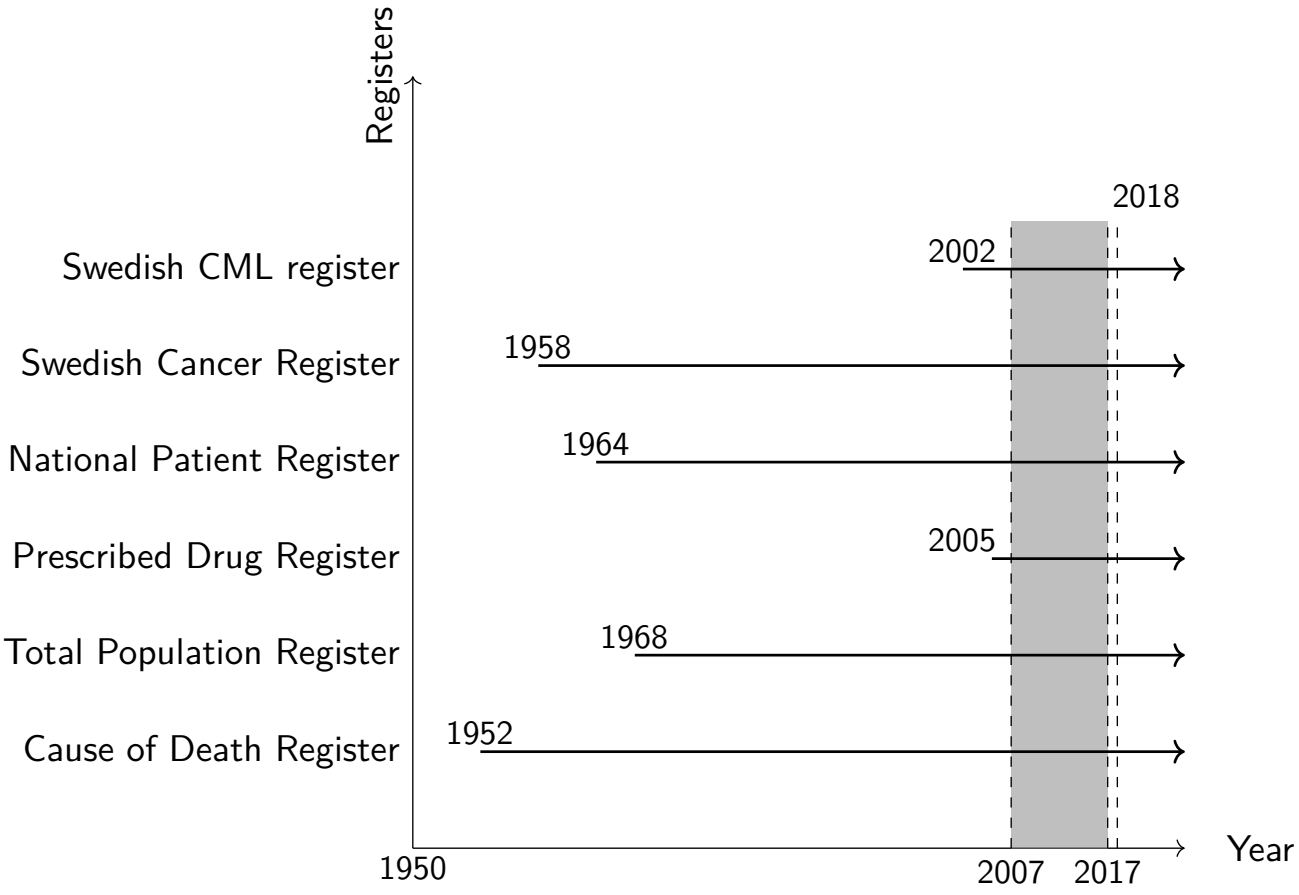

Figure: Study population for Study III: patients diagnosed with CP-CML in Sweden during 2007 to 2017, with follow-up until 2018.

Study III: Methods

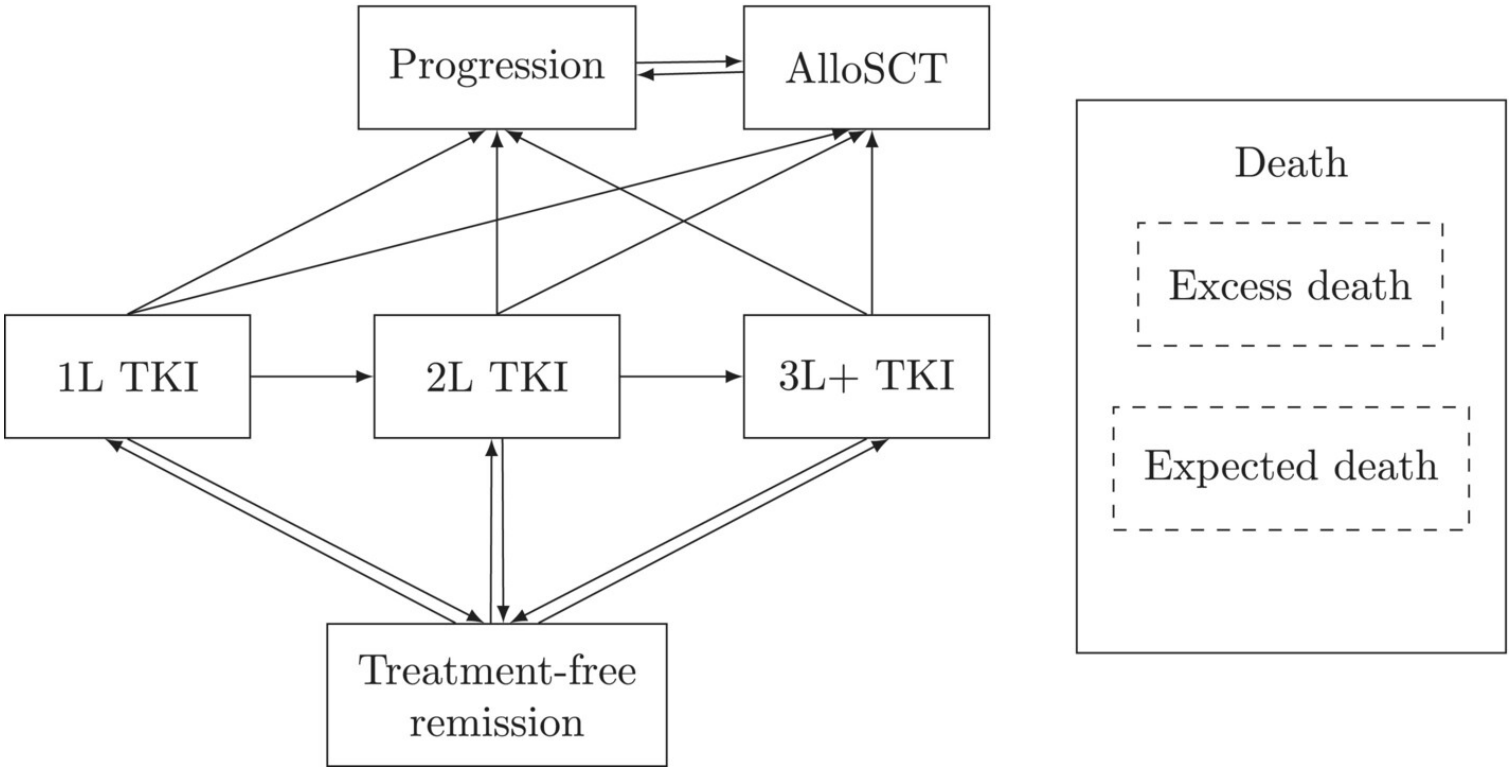

Figure: A multistate microsimulation model for CP-CML. Transitions are also assumed from every live state to the excess or expected death state (arrows not shown). 1 L, first-line; 2 L, second-line; 3 L+, third-line and later; TKI, tyrosine kinase inhibitor; AlloSCT, allogeneic stem cell transplantation. Image from Study III: Chen EYT et al. *EJH*. 2025. Licensed under CC BY--NC 4.0.

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Study III: Methods

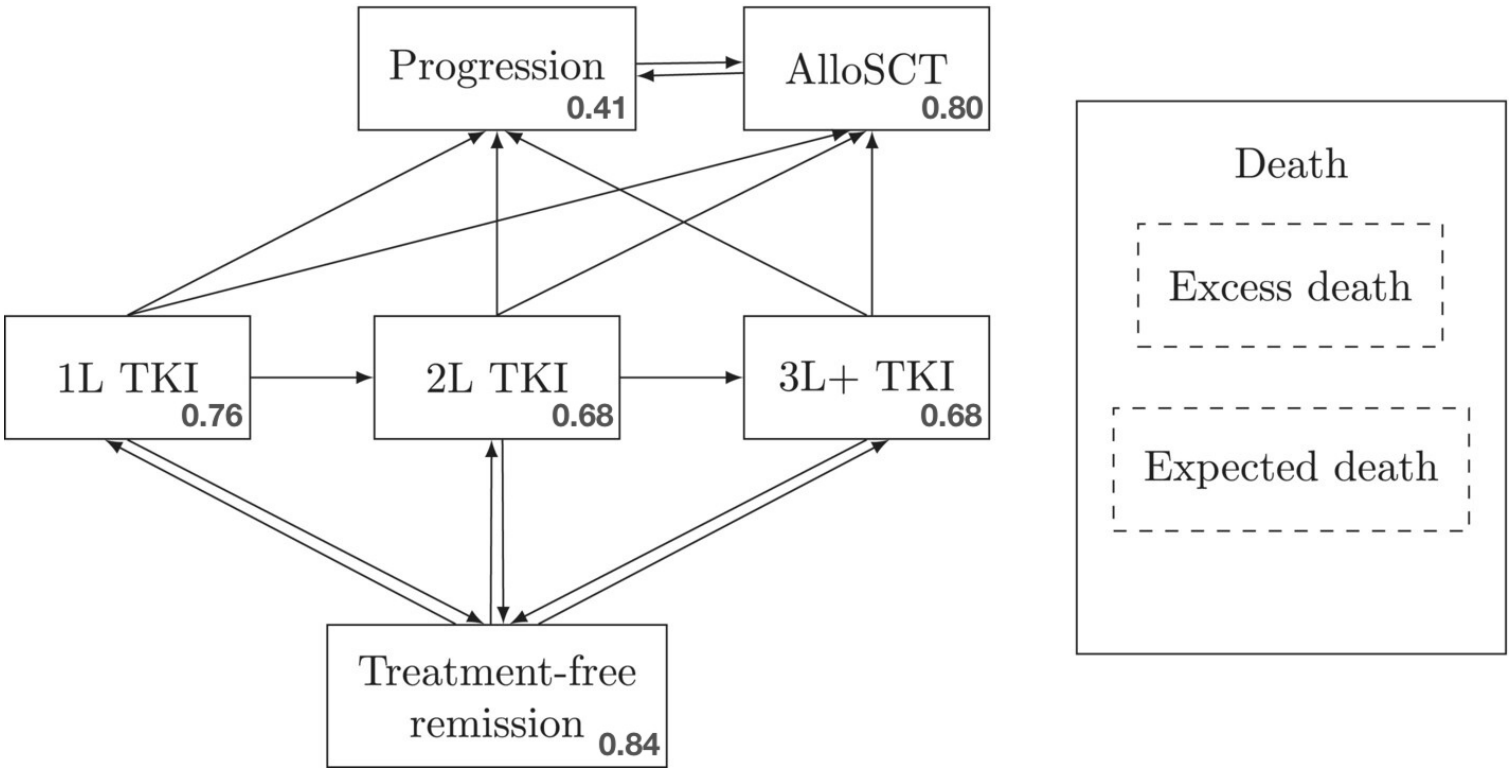

Figure: A multistate microsimulation model for CP-CML. Transitions are also assumed from every live state to the excess or expected death state (arrows not shown). 1 L, first- line; 2 L, second- line; 3 L+, third- line and later; TKI, tyrosine kinase inhibitor; AlloSCT, allogeneic stem cell transplantation. Utilities retrieved from Foulon et al., *Qual Life Res*, 2021, and Szabo et al., *VIH*, 2010, and were modelled as age- and sex-dependent. Image adapted from Study III: Chen EYT et al. *EJH*. 2025. Licensed under CC BY--NC 4.0.

Study III: Results

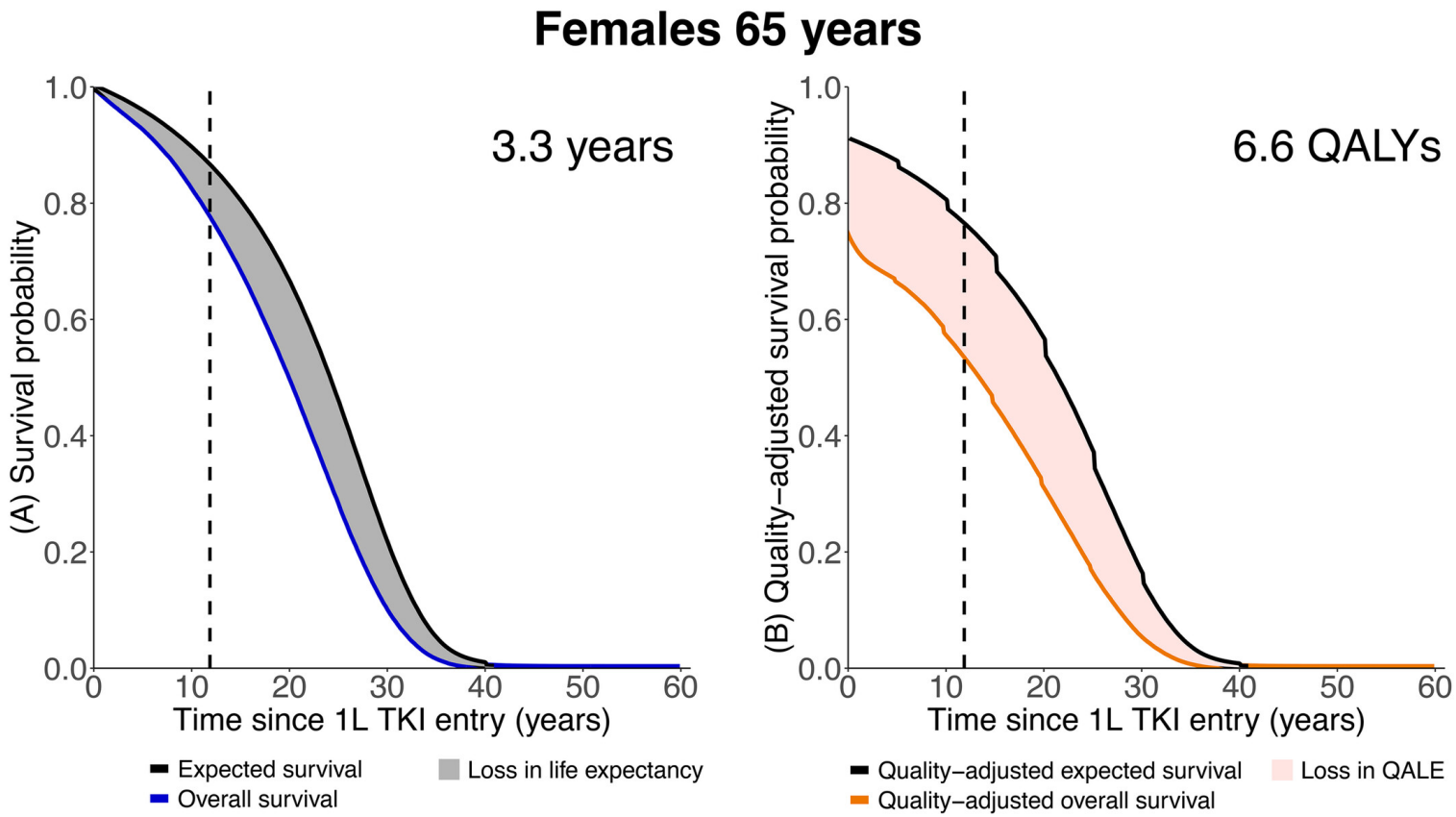

Figure: (A) Loss in life expectancy and (B) loss in quality-adjusted life expectancy for female patients with CP-CML aged 65 years diagnosed from 2007 to 2017. Utilities of the general population of Sweden retrieved from Teni et al., *Qual Life Res*, 2022. Image from Study III: Chen EYT et al. *EJH*. 2025. Licensed under CC BY--NC 4.0.

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Study III: Results

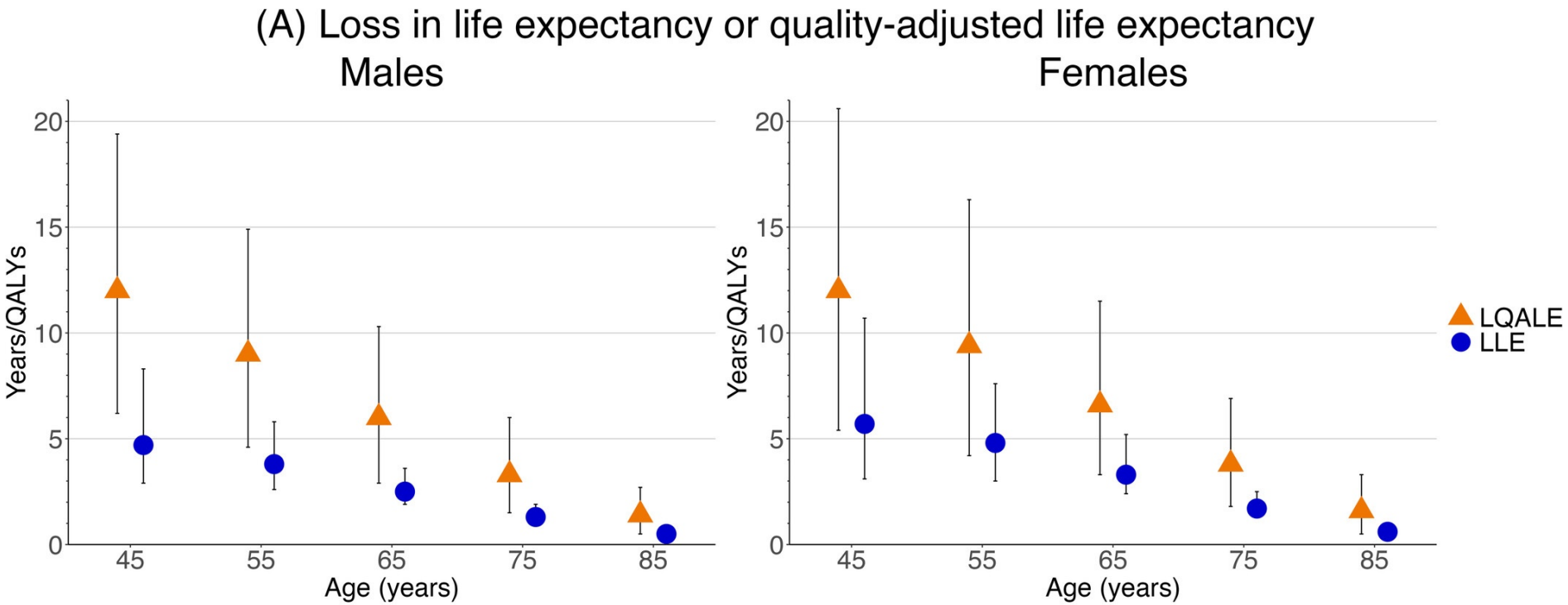

Figure: Loss in life expectancy and loss in quality-adjusted life expectancy of patients with CP-CML in Sweden diagnosed from 2007 to 2017 over ages 45 to 85 years (every 10 years), by sex. Bars show 95% confidence intervals. Image from Study III: Chen EYT et al. *EJH*. 2025. Licensed under CC BY--NC 4.0.

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Study III: Conclusions

- Patients with CP-CML in Sweden experienced only a modestly low loss in life expectancy but a considerably larger loss in quality-adjusted life expectancy.
- This highlights the need for improved CML management, such as (i) the development of more effective or safer TKIs and (ii) continued lifelong monitoring to evaluate impacts on survival and quality of life.

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Study III

European Journal of Haematology

WILEY

European Journal of Haematology

ORIGINAL ARTICLE OPEN ACCESS

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

Enoch Yi-Tung Chen[1] | Torsten Dahlén[2,3] | Leif Stenke[3,4] | Magnus Björkholm[3,4] | Shuang Hao[1] | Paul W. Dickman[1] | Mark S. Clements[1]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden | [2]Department of Medicine Solna, Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden | [3]Department of Hematology, Karolinska University Hospital Solna, Stockholm, Sweden | [4]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

Correspondence: Enoch Yi-Tung Chen (enoch.yitung.chen@ki.se)

Received: 22 August 2024 | **Revised:** 3 October 2024 | **Accepted:** 7 October 2024

Funding: This work was supported by Vetenskapsrådet, and Cancerfonden.

Keywords: chronic myeloid leukemia | health-related quality of life | life expectancy | quality-adjusted life years | real-world evidence

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Thesis overview

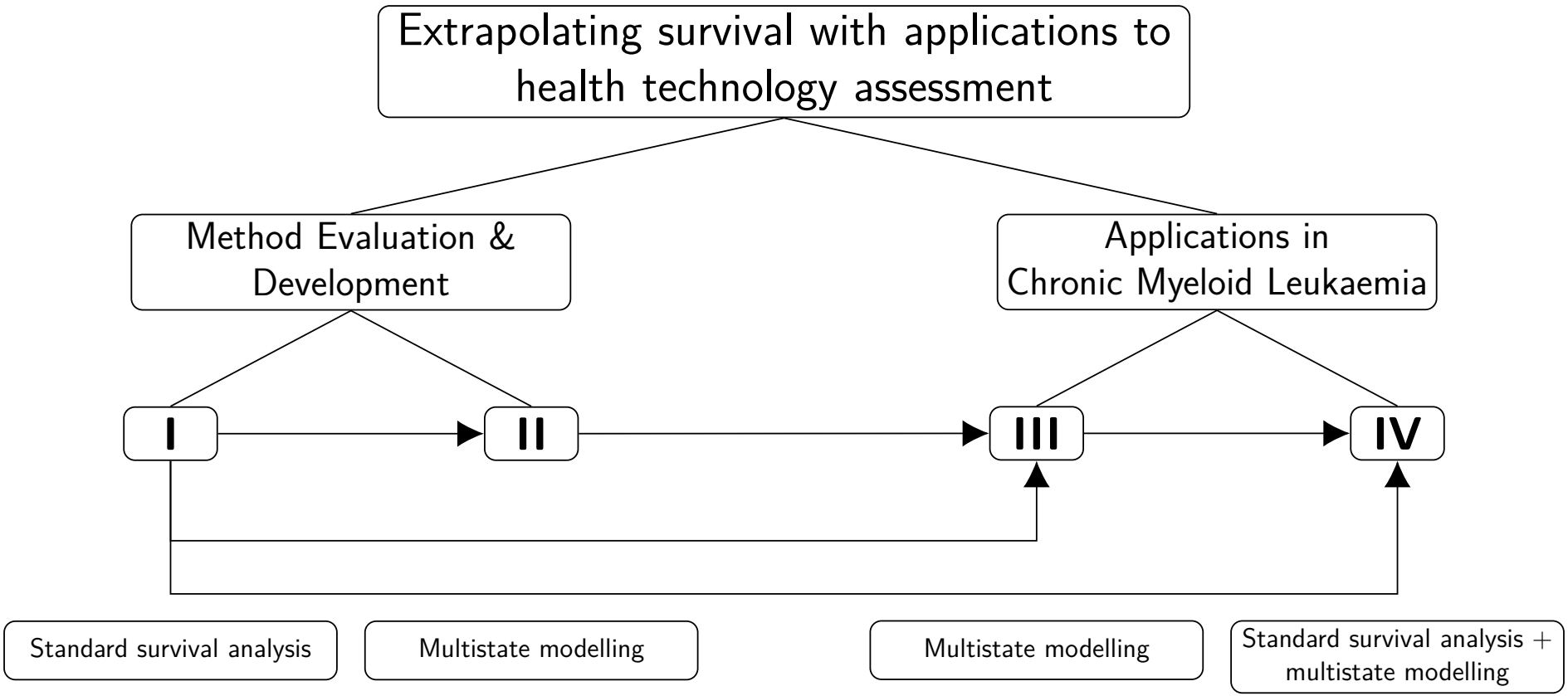

Figure: Overview of Studies I-IV, their analysis types, and their relationships.

Study IV

Title: Empirical and Projected Economic Burden of Chronic Myeloid Leukaemia in Sweden from 2015 to 2030: a Population-Based Study

Aim

To estimate and project the prevalence costs of CML in Sweden from 2015 to 2030.

We adopted a healthcare sector perspective, so only "direct healthcare expenditures" were considered.

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Study IV: Methods

$$\text{Total prevalence costs} \quad \| \quad \sum_{s=1}^{S} \Big(\text{Prevalent cases in state } s\Big) \times \Big(\text{Average yearly cost per patient in state } s\Big)$$

- Prevalence, Incidence, Analysis Model (PIAMOD) by Verdecchia et al., *Stat Med*, 1989 - CML natural history model (Study III)	- Swedish CML register (detailed clinical/lab info) - Prescribed Drug Register (individual-level pricing records) - Herlund et al., *eJHaem*, 2021 - Ohm et al., *Leuk Lymphoma*, 2015 - Official price lists

Study IV: Study population

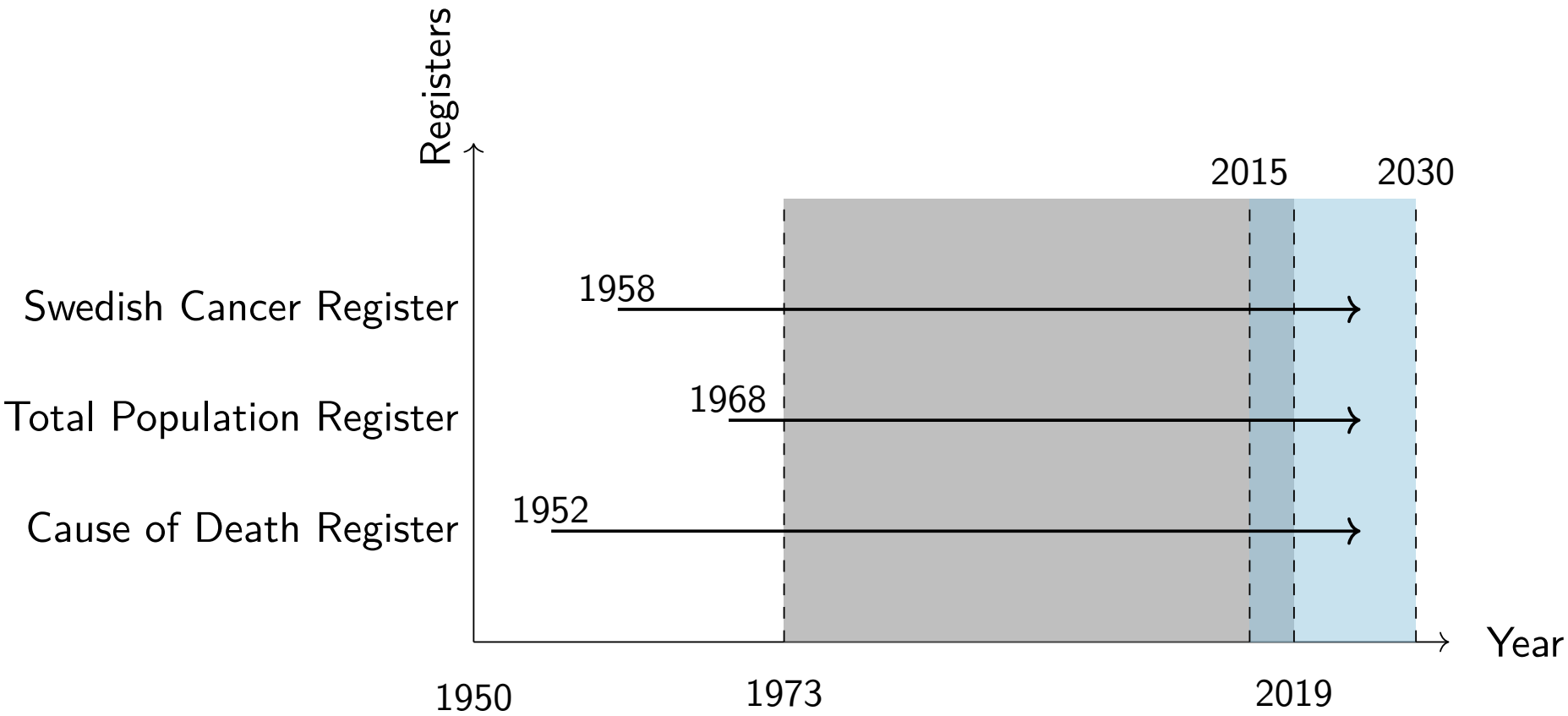

Figure: Study population for Study IV: patients diagnosed with CML in Sweden during 1973-2019 follow-up until 2020. Prevalence and prevalence costs were estimated and projected from 2015 to 2030.

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Study IV: Estimating total prevalent cases

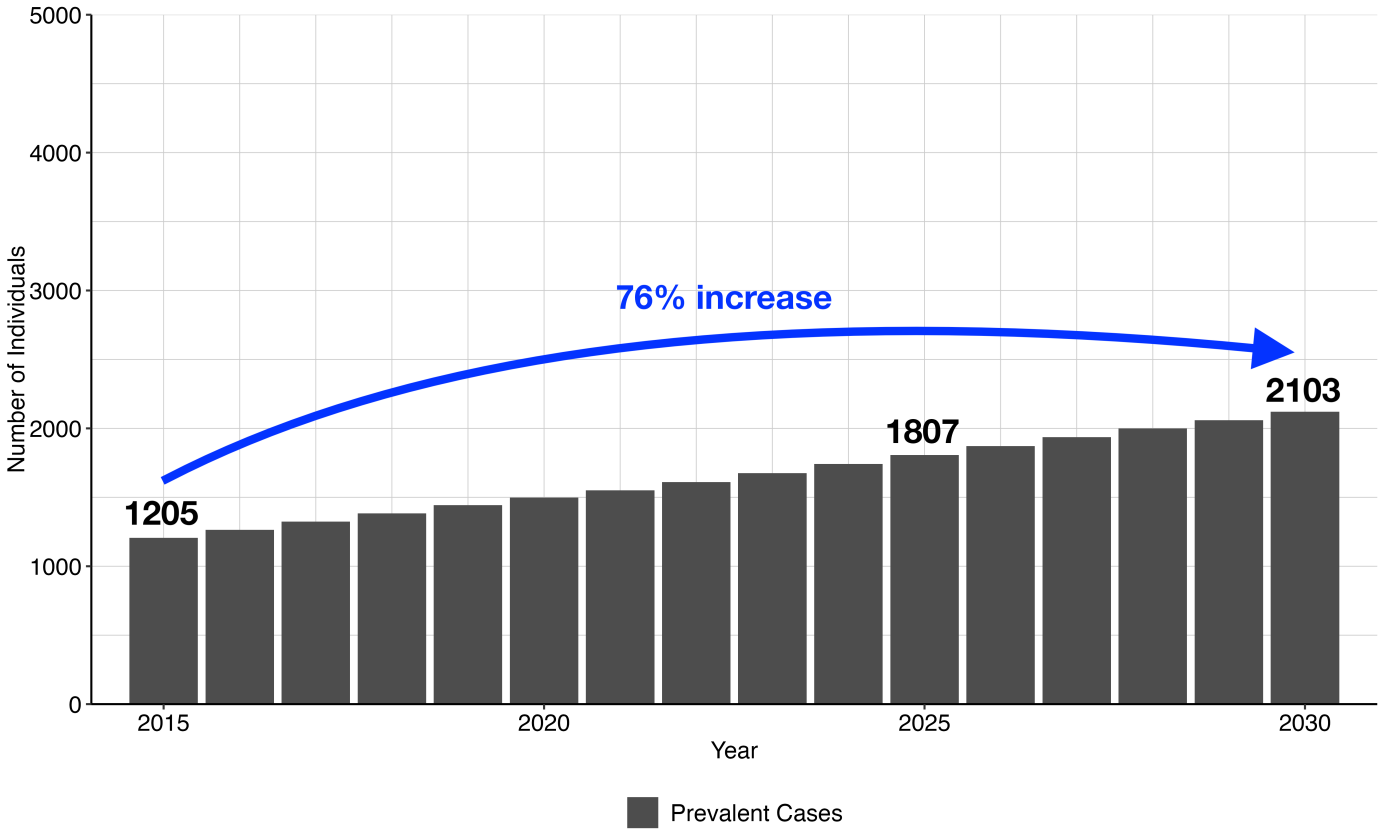

Figure: Estimated and projected prevalent cases of CML in Sweden from 2015 to 2030.

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Study IV: Estimating the distribution of total prevalent cases

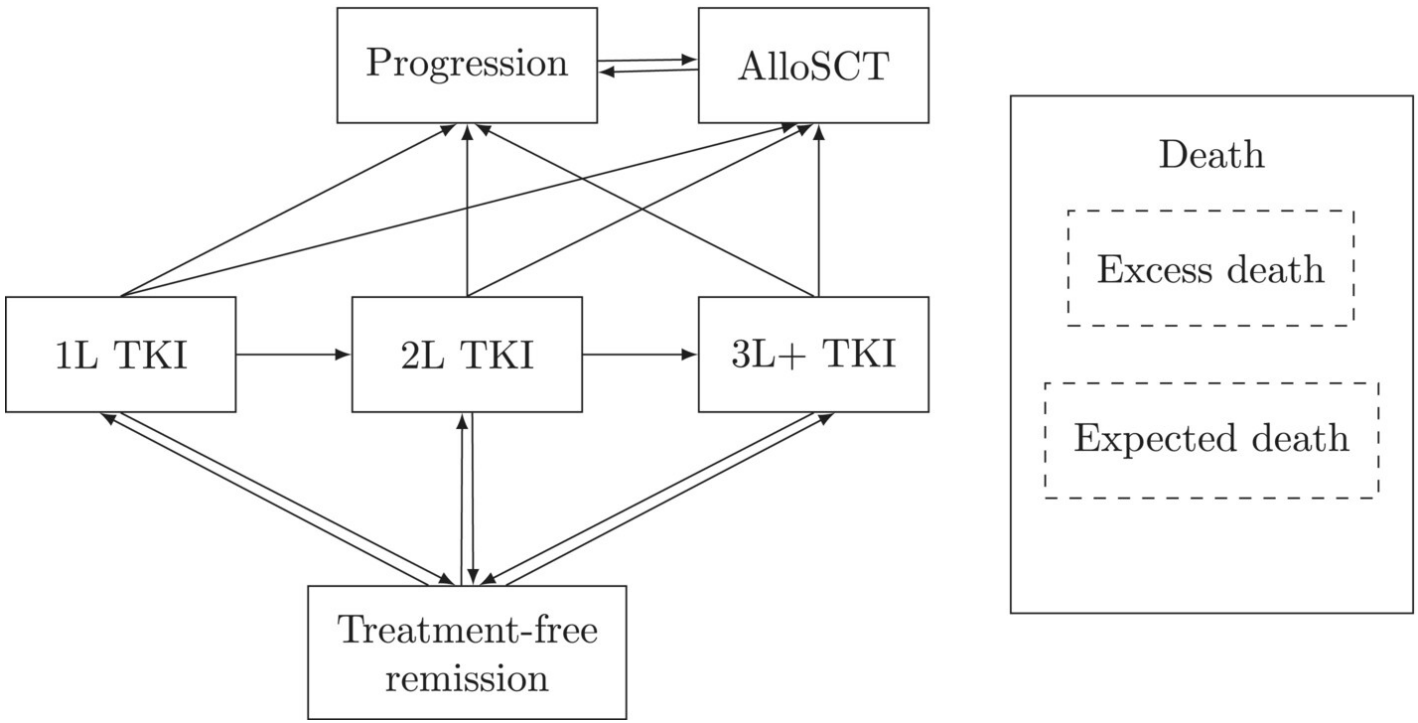

Figure: A multistate microsimulation model for CP-CML. Transitions are also assumed from every live state to the excess or expected death state (arrows not shown). 1 L, first-line; 2 L, second-line; 3 L+, third-line and later; TKI, tyrosine kinase inhibitor; AlloSCT, allogeneic stem cell transplantation. Image from: Chen EYT et al. *EJH*. 2025. Licensed under CC BY--NC 4.0.

Study IV: Estimating the distribution of total prevalent cases

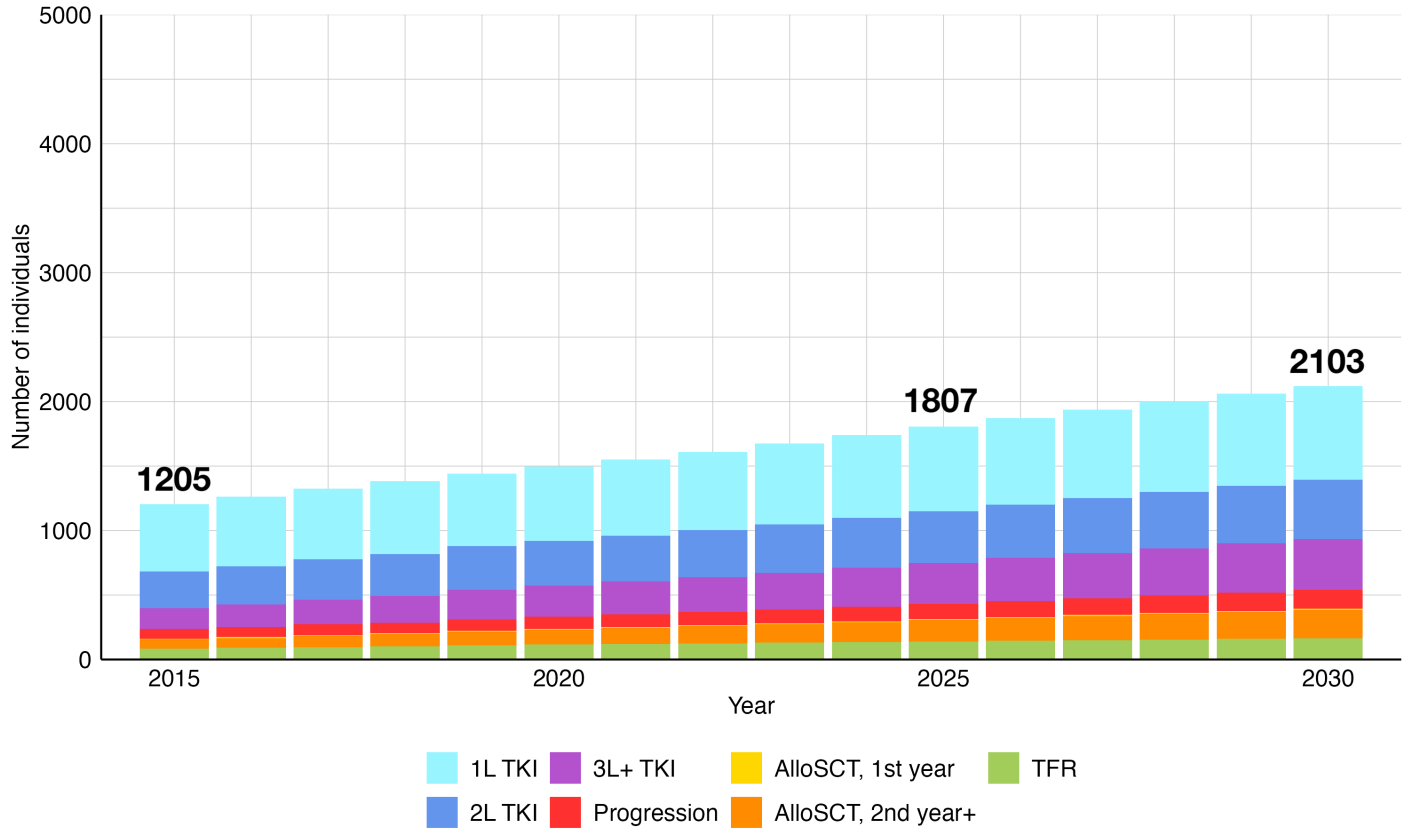

Figure: Estimated and projected prevalent cases (by state) of CML in Sweden from 2015 to 2030. 1 L, first-line; 2 L, second-line; 3 L+, third-line and later; TKI, tyrosine kinase inhibitor; AlloSCT, allogeneic stem cell transplantation.

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Study IV: Estimating total prevalence costs

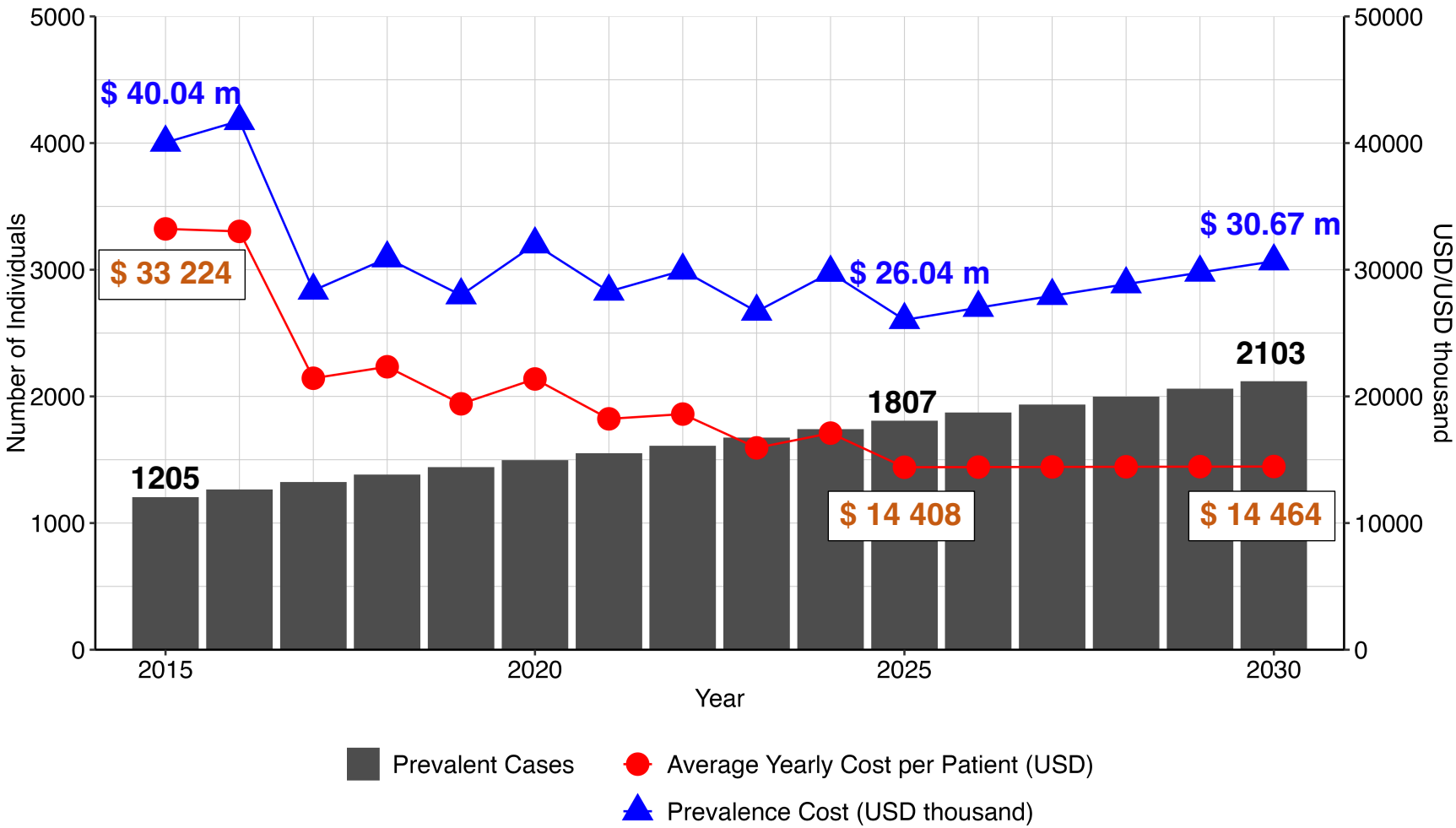

Figure: Estimated and projected prevalent cases, average yearly cost per patient (USD), total prevalence costs (USD thousand) of CML in Sweden from 2015 to 2030. Image adapted from Study IV: Chen EYT et al. (submitted manuscript).

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Study IV: Results

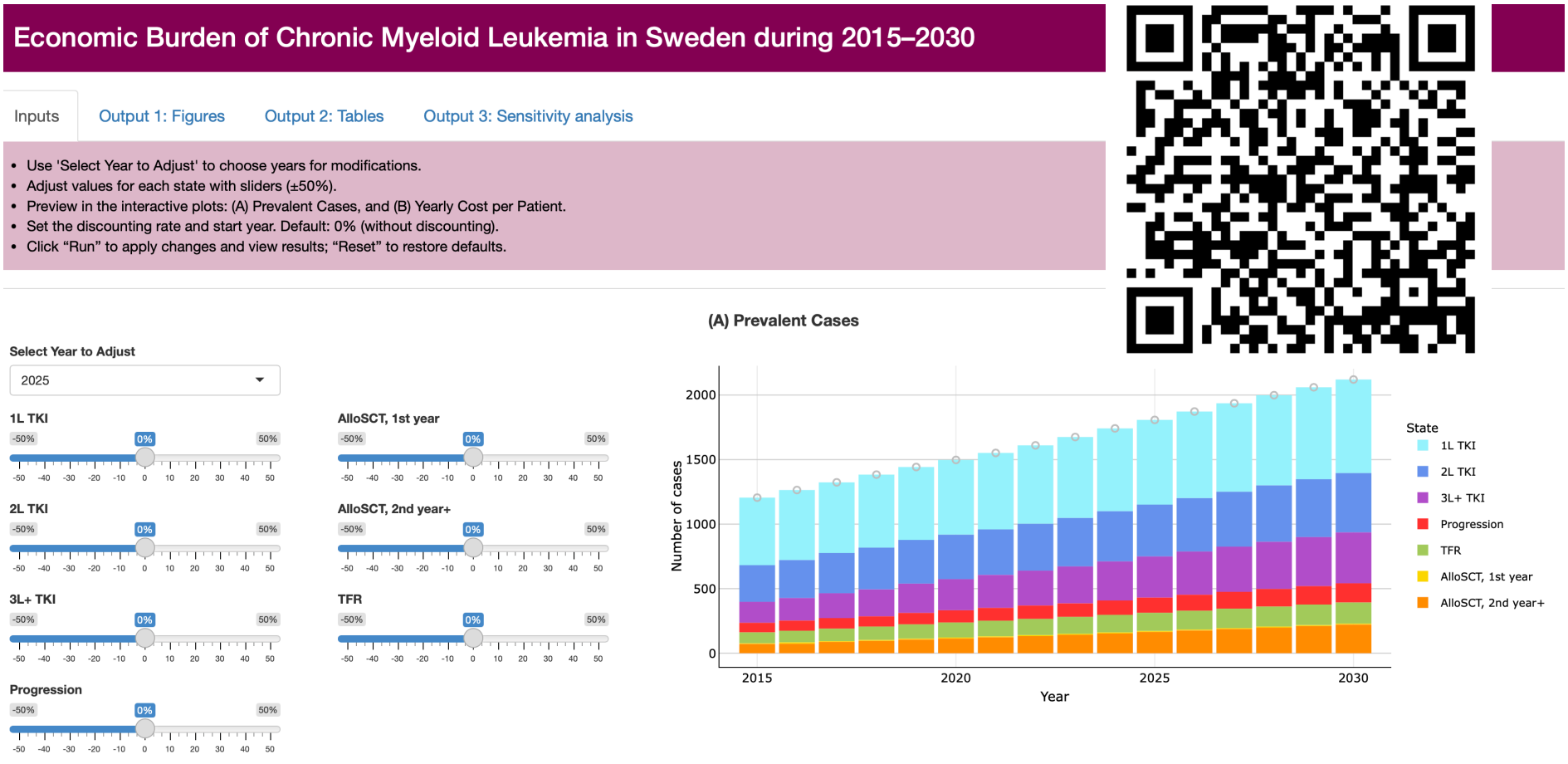

Figure: R Shiny application for Study IV. QR code links to `https://enochytchen.shinyapps.io/CMLEcoBurdenSE/`.

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Study IV: Conclusions

- The number of individuals living with CML in Sweden is expected to continue to rise. (Prevalence cases increase.)
- Declining treatment costs have led to an overall reduction in prevalence costs.
  (Average yearly cost per patient decreases.)
- This will likely mitigate the economic burden on the Swedish healthcare system.
  (Total prevalence costs decrease.)

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Study IV

Submitted manuscript under review.

Title: Empirical and Projected Economic Burden of Chronic Myeloid Leukaemia in Sweden from 2015 to 2030: a Population-Based Study

Authors: Enoch Yi-Tung Chen[1], Paul W. Dickman[1], Fabrizio Di Mari[2], Torsten Dahlén[3, 4], Leif Stenke[4,5], Magnus Björkholm[4, 5], Mark S. Clements[1], and Shuang Hao[1].

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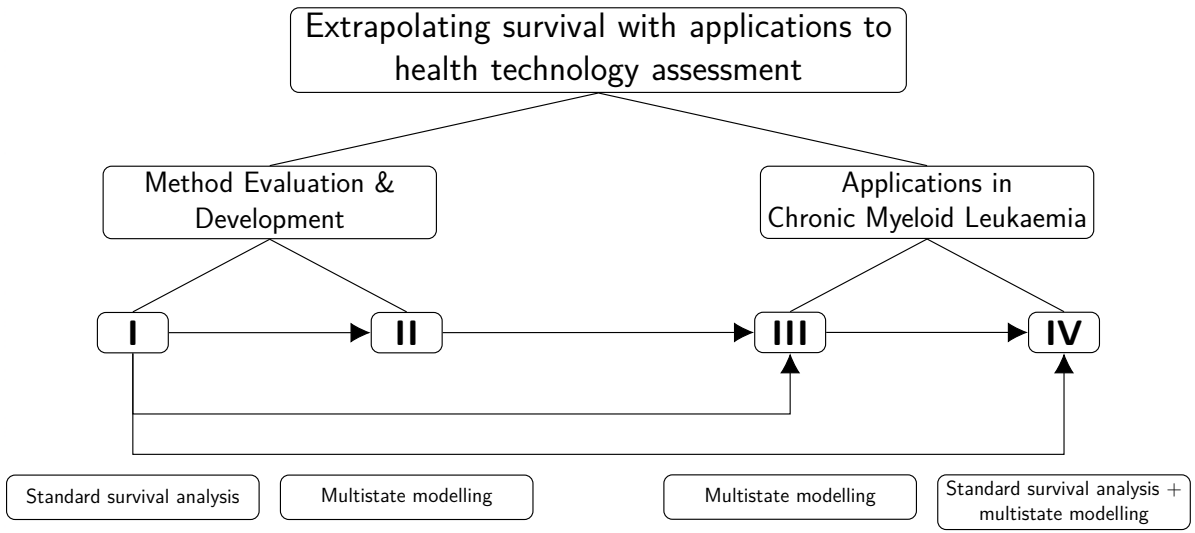
Thesis overview



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Acknowledgements

Extrapolating Survival with Applications to Health Technology Assessment

Enoch Yi-Tung Chen

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- Other co-authors: Yuliya Leontyeva, Chia-Ni Lin, Jung-Der Wang, Leif Stenke, and Fabrizio Di Mari.
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Extrapolating Survival with Applications to Health Technology Assessment

Enoch Yi-Tung Chen

Slides can be found at:

https://enochytchen.com/talks/2025-PhD-dissertation/slides.pdf

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