THE IMPACT OF USING AGGREGATE DATA FOR MULTISTATE MODELLING PURPOSES IN ECONOMIC EVALUATIONS

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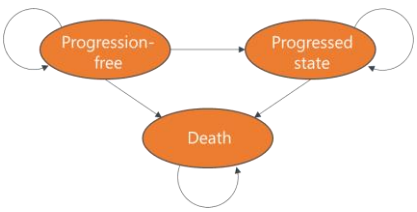
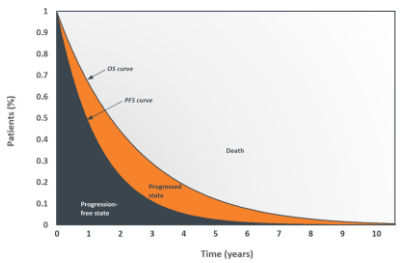
What is a multistate model? - Comparison of model approaches

Markov Model



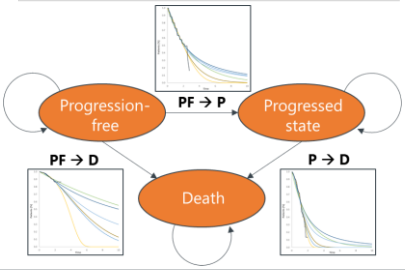
- A Markov Model has a finite number of mutually exclusive health states
- During each cycle, patients can transition to a new health state or stay in their current health state – dependent on **time independent** transition probabilities

Partitioned Survival Model (PSM)



- A Partitioned Survival Model (PSM) is based on a finite number of mutually exclusive health states
- The distribution of patients in each health state over time is calculated with the area under the curve (AUC) of the survival functions (**time (in)dependent**)

Multistate Model (MSM)



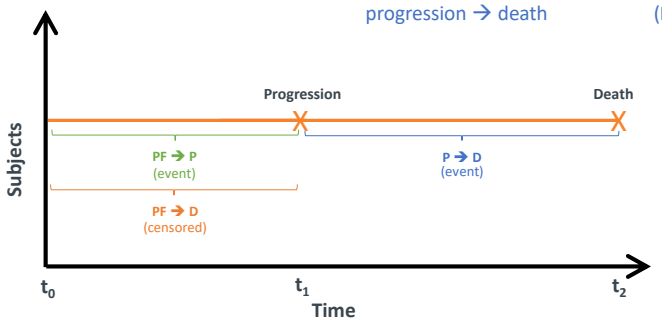
- The Multistate Model (MSM) stratifies overall survival (OS) and progression-free survival (PFS) into three transitions
- During each cycle, patients can transition to a new health state or stay in their current health state – dependent on **time (in)dependent** transition probabilities

How the MSM approach works

Suppose a patient progressed at time t_1 and died at time t_2.

- The MSM needs to split the time to death into 3 transitions:

progression-free → progression (PF → P)
progression-free → death (PF → D)
progression → death (P → D)



Transition	Time	Event/censored
PF → P	$t_1 - t_0$	event
PF → D	$t_1 - t_0$	censored
P → D	$t_2 - t_1$	event

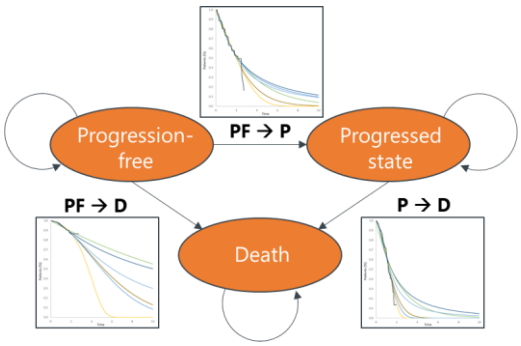
MSM using aggregated data

- MSMs require matched PFS and OS times per patient to define each of the three transitions:

  PF → P
  PF → D
  P → D

- Individual patient-level data (IPD) is not always available to researchers

- IPD from aggregate data can be generated for PFS and OS
  - but this does not lead to matched PFS and OS times



Aim:

To explore the impact of using aggregated data to fit an MSM

Methods Overview

I. **'IPD' approach**

II. **'Aggregated data' approach – ranked**

III. **Aggregated data' approach – adjusted**

IV. **Partitioned survival model (PSM)**

Methods I

Created *simulated IPD*

I. 'IPD' approach

- MSM based on simulated IPD

	PFS		OS	
Patient ID	**Event/censor**	**Time (days)**	**Event/censor**	**Time (days)**
Patient 1	Event	50	Event	70
Patient 2	Censor	20	Event	30
Patient 3	Event	15	Censor	100

Methods II & III

II & III. 'Aggregated data' approach

- Validated algorithm (Guyot et al. 2012) was used to obtain pseudo IPD
- Assumed that the shortest PFS time corresponds to the shortest OS time to create PFS and OS time per patient

	PFS	
	Event/censor	**Time (days)**
	Event	50
	Censor	20
	Event	15

	OS	
	Event/censor	**Time (days)**
	Censor	70
	Event	30
	Event	100

Patient ID		PFS	
		Event/censor	**Time (days)**
Patient 1	=	Event	15
Patient 2	=	Censor	20
Patient 3	=	Event	50

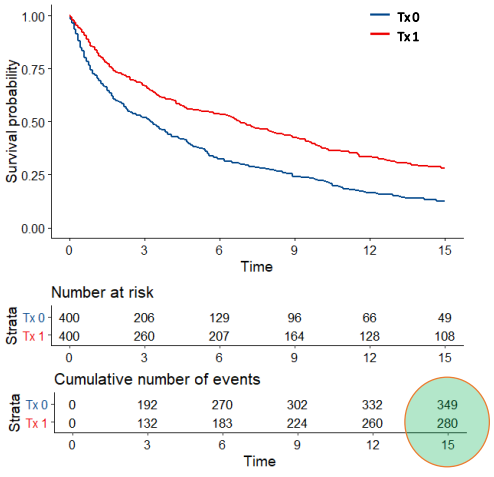
	OS	
	Event/censor	**Time (days)**
	Event	30
	Censor	70
	Event	100

Adjusted, taking into account the number of progression-free deaths

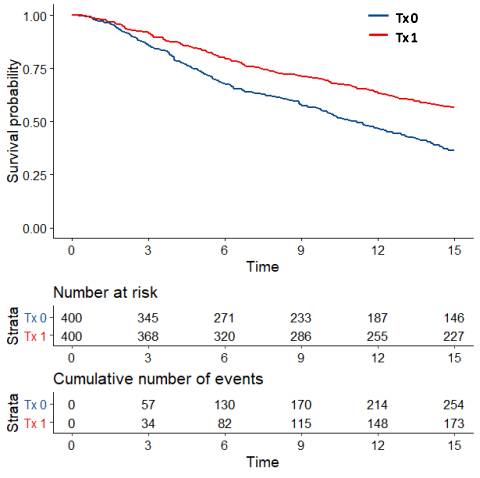
Treatment	No. of progression-free deaths (PF → D)
Tx0	44
Tx1	39

Simulated Individual Patient-level data (IPD)

Progression-free Survival (PFS)

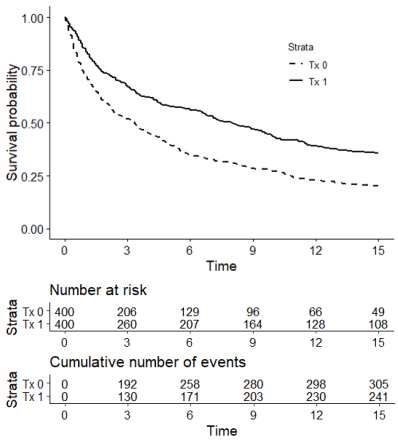


Overall Survival (OS)

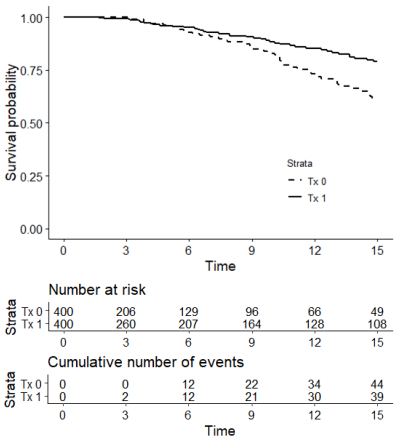


I) Multistate Model using IPD

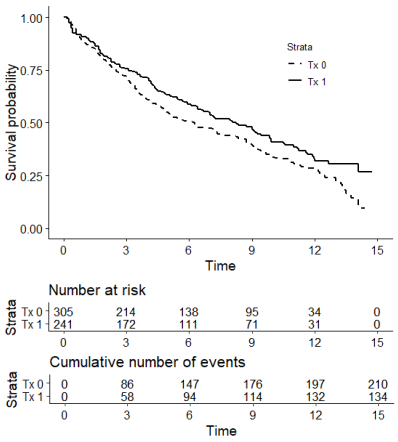
Progression-free → Progression



Progression-free → Death

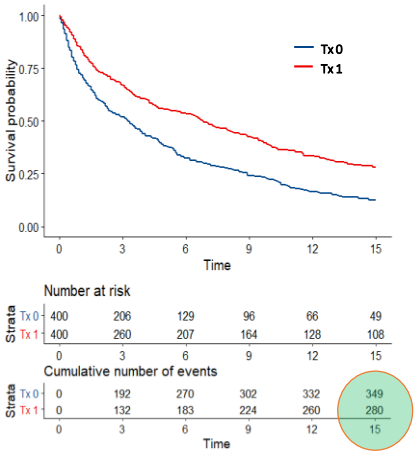


Progression → Death

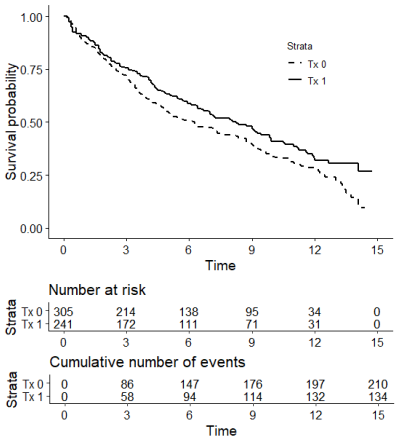


I) Multistate Model using IPD

Progression-free Survival (PFS)

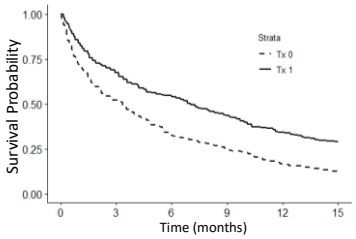


Progression → Death

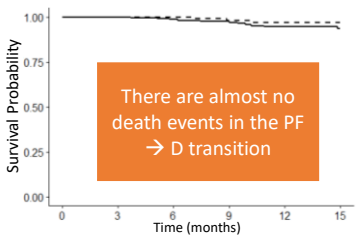


II) Multistate Model using Aggregate data (ranked)

Progression-free → Progression

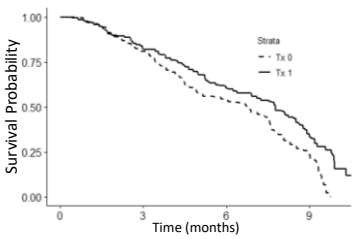


Progression-free → Death

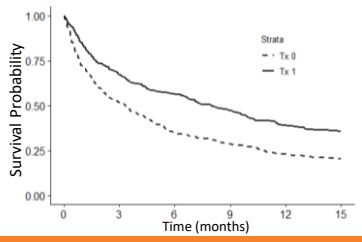


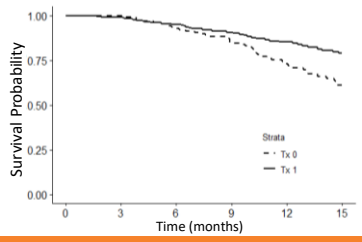
There are almost no death events in the PF → D transition

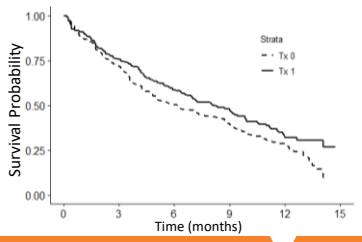
Progression → Death



Approach I: Multistate model using IPD

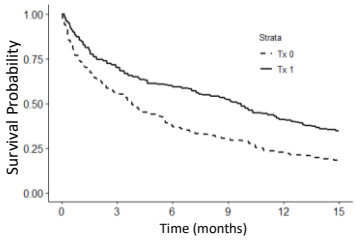




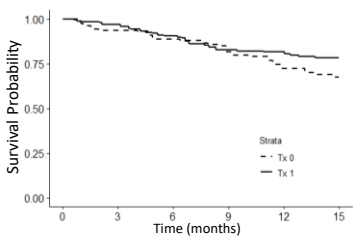


III) Multistate Model using Aggregate data (adjusted)

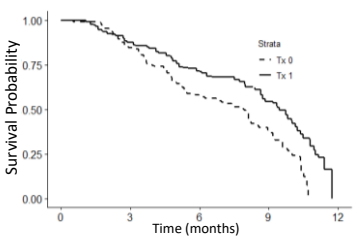
Progression-free → Progression



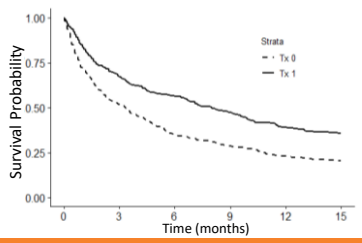
Progression-free → Death

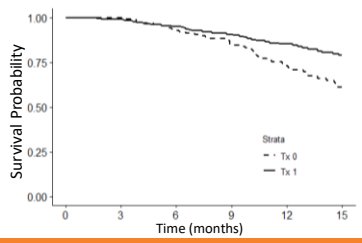


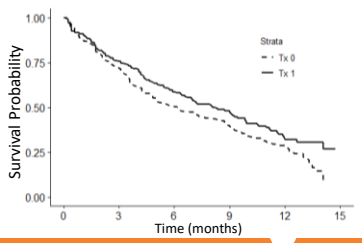
Progression → Death



Approach I: Multistate model using IPD

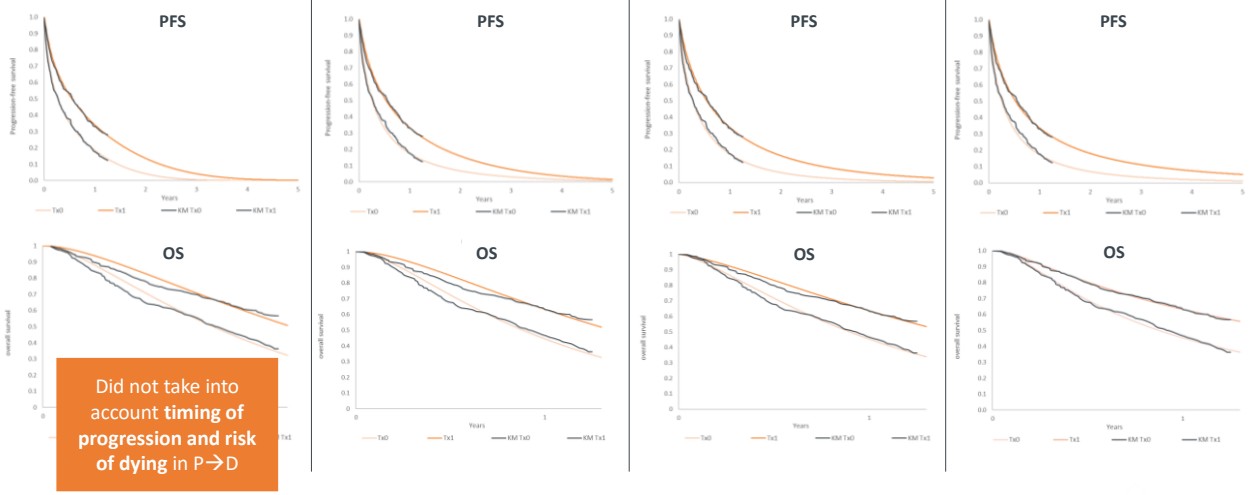






Results

I. 'IPD' approach | II. Aggregated - ranked | III. Aggregated - adjusted | IV. PSM



Did not take into account **timing of progression and risk of dying** in P→D

Results

Approach	Treatment	Mean LY	Difference vs *MSM IPD approach*
I. MSM IPD approach	***Tx0***	***1.16***	***0.00***
	Tx1	***1.61***	***0.00***
II. MSM Aggregated – ranked	**Tx0**	**1.26**	**0.10**
	Tx1	**1.78**	**0.17**
III. MSM Aggregated – adjusted	**Tx0**	**1.25**	**0.09**
	Tx1	**1.85**	**0.24**
IV. PSM	**Tx0**	**1.58**	**0.42**
	Tx1	**2.59**	**0.98**

- Difference in mean life years (LYs) of aggregated approach vs IPD approach is relatively small

- Difference in mean LYs of PSM vs IPD approach is larger
  - Likely due to using a lognormal distribution for OS which has a long tail (best statistical fit)

Conclusions & Limitations

Conclusions

- With aggregated data, it mathematically should and **is possible** to fit PFS and OS reasonably well by using an MSM
- Additionally, the aggregated data based extrapolated curves were not too much different from the IPD based extrapolated curves
- The **Kaplan-Meier of the 3 transitions differ** when using IPD from aggregated data versus IPD
  - This could pose problems for undertaking indirect comparisons
- More guidance is needed on how to link individual patients' OS and PFS times when using IPD generated from aggregate data

Limitations of our study

- Use of simulated data – validation required using true IPD from randomised controlled trials
- Did not take into account the relationship between timing of progression and the probability to die in the P->D transition

THANK YOU FOR LISTENING!
DO YOU HAVE ANY QUESTIONS?

References

Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12(1):9.

Minacori R, Bonastre J, Lueza B, Marguet S, Levy P. How to Model Survival In Cost-Effectiveness Analysis? Differences Between Markov and Partitioned Survival Analysis Models. *Value Heal*. 2015;18(7):A704.

Williams C, Lewsey JD, Briggs AH, Mackay DF. Cost-effectiveness Analysis in R Using a Multi-state Modeling Survival Analysis Framework: A Tutorial.

Woods B, Sideris E, Palmer S, Latimer N, Soares M. *NICE DSU Technical Support Document 19: Partitioned Survival Analysis For Decision Modelling In Health Care: A Critical Review Report By The Decision Support Unit*.; 2017. www.nicedsu.org.uk. Accessed October, 2019

DO YOU HAVE ANY QUESTIONS?
PLEASE CONTACT US!

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Parametric fits

Approach	Transition	Distribution	Parametric fit
I. MSM IPD approach	PF → P	lognormal	Combined
	PF → D	Weibull	Combined
	P → D	exponential	Combined
II. MSM Aggregated –ranked	PF → P	gamma	Combined
	PF → D	Weibull	Combined
	P → D	exponential	Individual
III. MSM Aggregated – adjusted	PF → P	gamma	Combined
	PF → D	Weibull	Combined
	P → D	exponential	Individual
PSM	PFS	gamma	Combined
	OS	lognormal	Individual

Overview of MSMs

Positives:

- Jointly modelled endpoints so they are unable to cross
- Individual components of disease progress are modelled separately

  -> may be more intuitive for clinicians to validate the effect on individual processes
- RWE can be implemented relatively easily

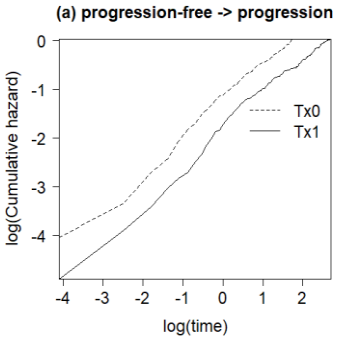
Negatives:

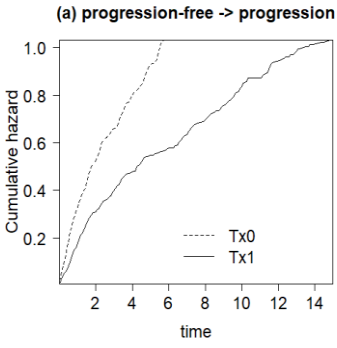
- Issues with censoring
- Increased complexity

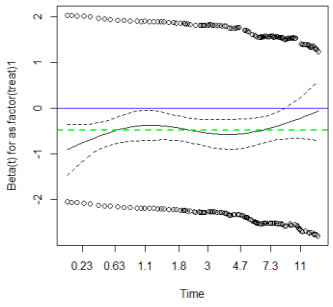
  -> longer to implement, validate, and review
- Unfamiliarity
- Lack of guidance with regards to joint modelling of endpoints

Appendices

PH Testing – Scenario 1 (IPD)



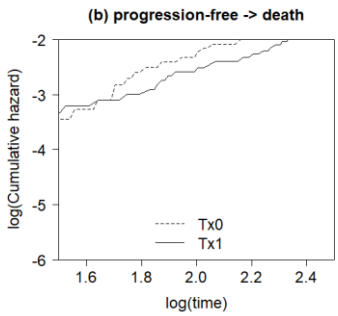


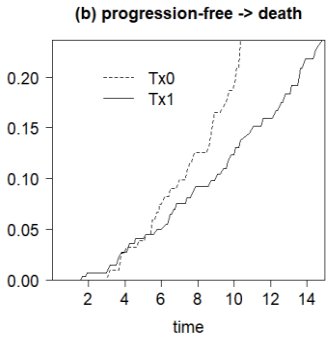


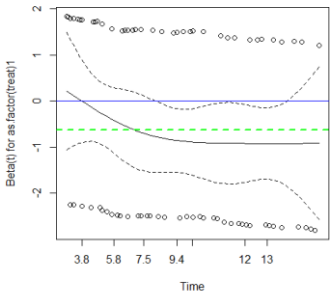
p = 0.216

PH assumption holds

PH Testing – Scenario 1 (IPD)



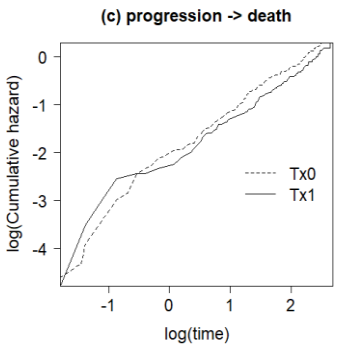


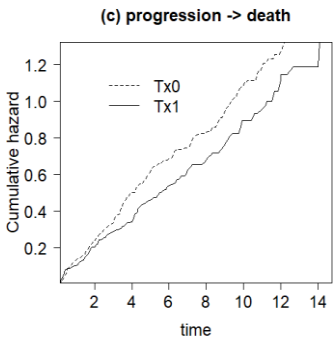


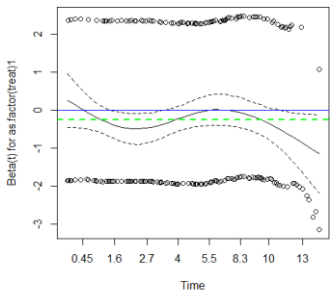
p = 0.154

PH assumption holds

PH Testing – Scenario 1 (IPD)







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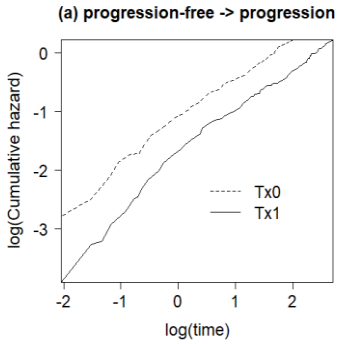
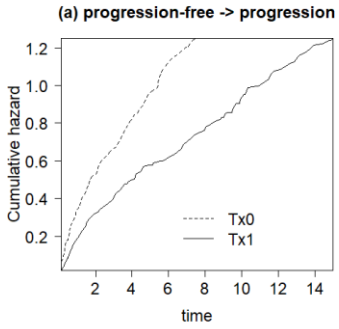
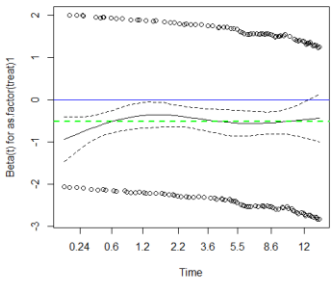
PH assumption holds

PH Testing – Scenario 2 (Aggregated Ranked)



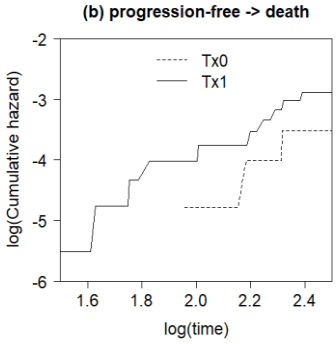


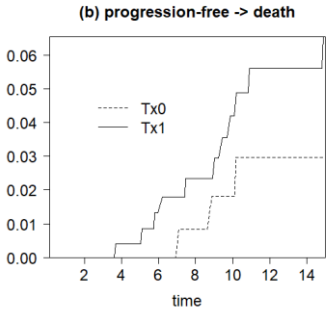


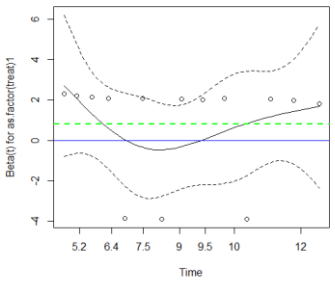
p = 0.538

PH assumption holds

PH Testing – Scenario 2 (Aggregated Ranked)







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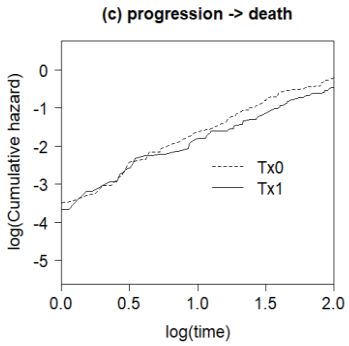
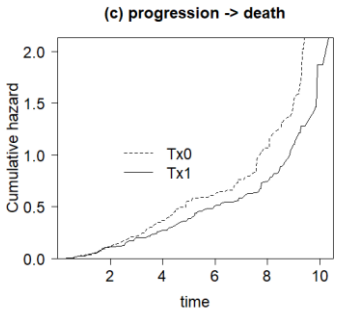
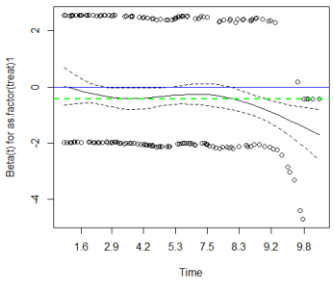
PH assumption holds

PH Testing – Scenario 2 (Aggregated Ranked)



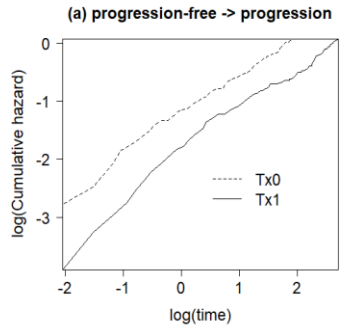


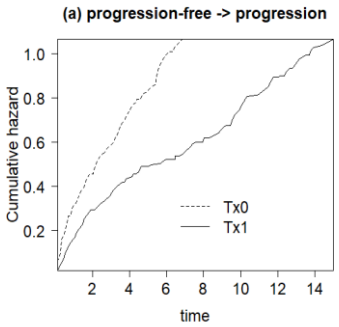


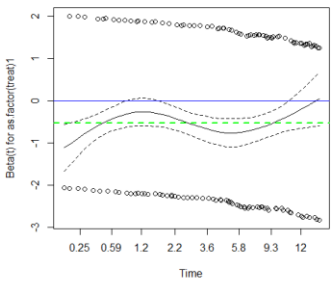
p = 0.014

PH assumption is violated

PH Testing – Scenario 3 (Aggregated Adjusted)



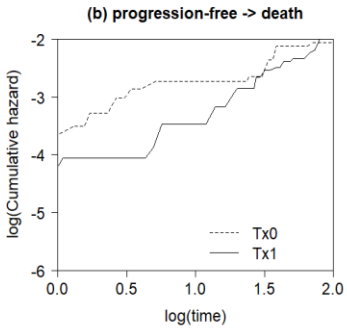


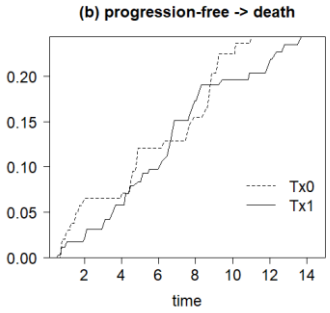


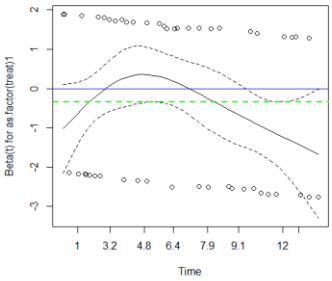
p = 0.312

PH assumption holds

PH Testing – Scenario 3 (Aggregated Adjusted)



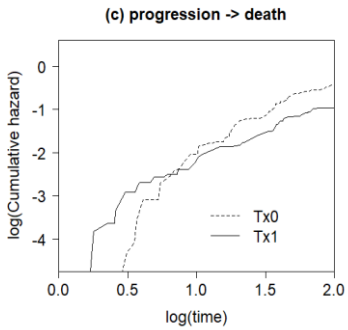


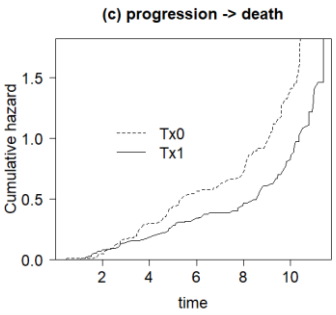


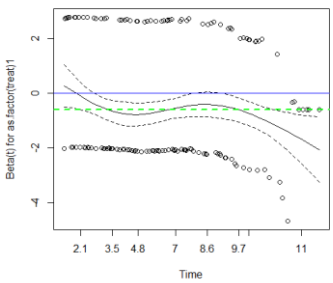
p = 0.205

PH assumption holds

PH Testing – Scenario 3 (Aggregated Adjusted)





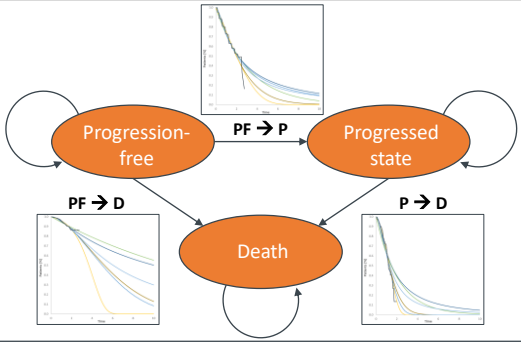


p = 0.0247

PH assumption is violated

Multistate model overview

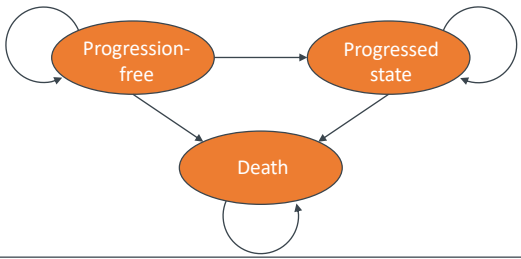
Multistate Model



- OS and PFS is stratified into three transitions:
  - PFS->P
  - PFS->D
  - P->D
- Use AUC to obtain transition probabilities at any time point
- Parametric distributions (e.g. exponential, Weibull etc.) can be applied to each curve separately
- These curves can then be recombined to extrapolate OS and PFS

Multistate model overview

Multistate Model



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