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# Longitudinal and survival joint modelling prediction: time reparametrization in Amyotrophic Lateral Sclerosis context

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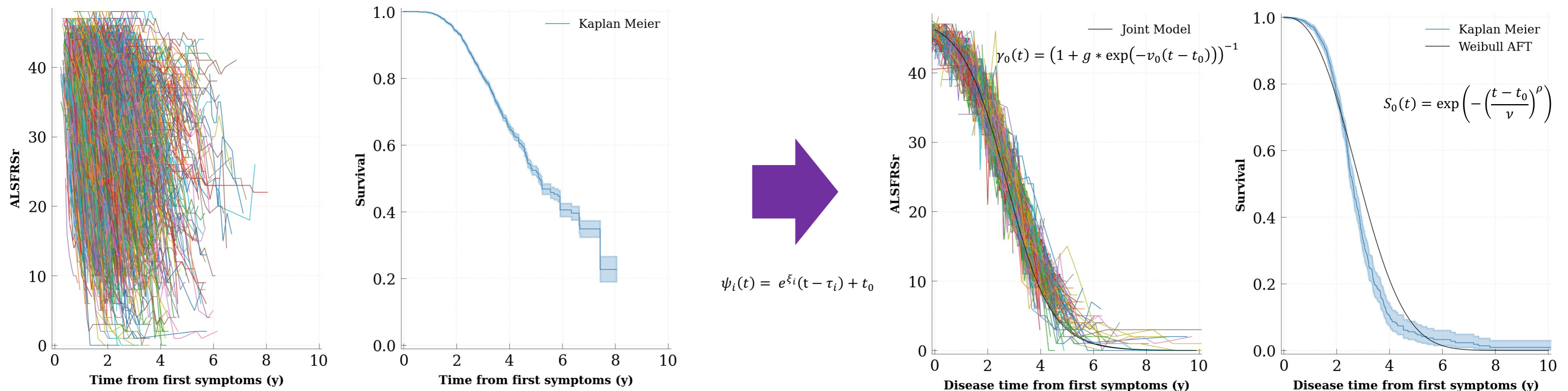
## Background & Objectives

Neurodegenerative diseases, among which Amyotrophic Lateral Sclerosis, have no precise starting time. Nevertheless, in Joint modelling, most models use Generalised Linear Mixed-effects Models (GLMM) to model the longitudinal process. Such kind of model, by design, needs a reference time. An existing longitudinal model does not need that reference time but has never been extended to a Joint model. It has also the advantage to create a latent disease age (Schiratti et al., 2015).

**We validated and bench-marked a new Joint model with latent disease age that does not need a reference time.**

## Methods

We created a non-linear joint model with shared random effects composed of a time reparametrization into the disease age  $\psi_i$  for each patient, a longitudinal model  $\gamma_0$  and a survival model  $S_0$  from the disease age.



We evaluated it against, two one-process-only models, an AFT model using Lifelines package (Davidson-Pilon, 2019) and the existing longitudinal model using Leaspy package, a two-stage model using AFT and the existing longitudinal model and a joint model with shared random effects using JMbayes2 package.

## Simulation Results

**Data** We have simulated data thanks to real-like parameters extracted from PRO-ACT ALS data, using the existing longitudinal model and AFT model. We have simulated 1,000 patients with an average of 8 visits for a follow-up of 1 year with 85 % censored events and a noise of 5% on the longitudinal process.

**Cohort description** We compared the progression of the patients with mean random effects.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
growth	<b>0.318 (0.13)</b>	-	-	0.409 (0.089)	4.6e-01	-	-	2.03 (0.116)	3.9e-03
midpoint	<b>0.035 (0.018)</b>	-	-	0.102 (0.011)	3.9e-03	-	-	0.058 (0.031)	2.6e-01
median	0.255 (0.065)	<b>0.231 (0.051)</b>	1.0e+00	-	-	0.698 (0.089)	5.9e-03	3.192 (0.241)	5.9e-03

Table 1 Absolute clinically meaningful estimated parameters bias on real-like dataset

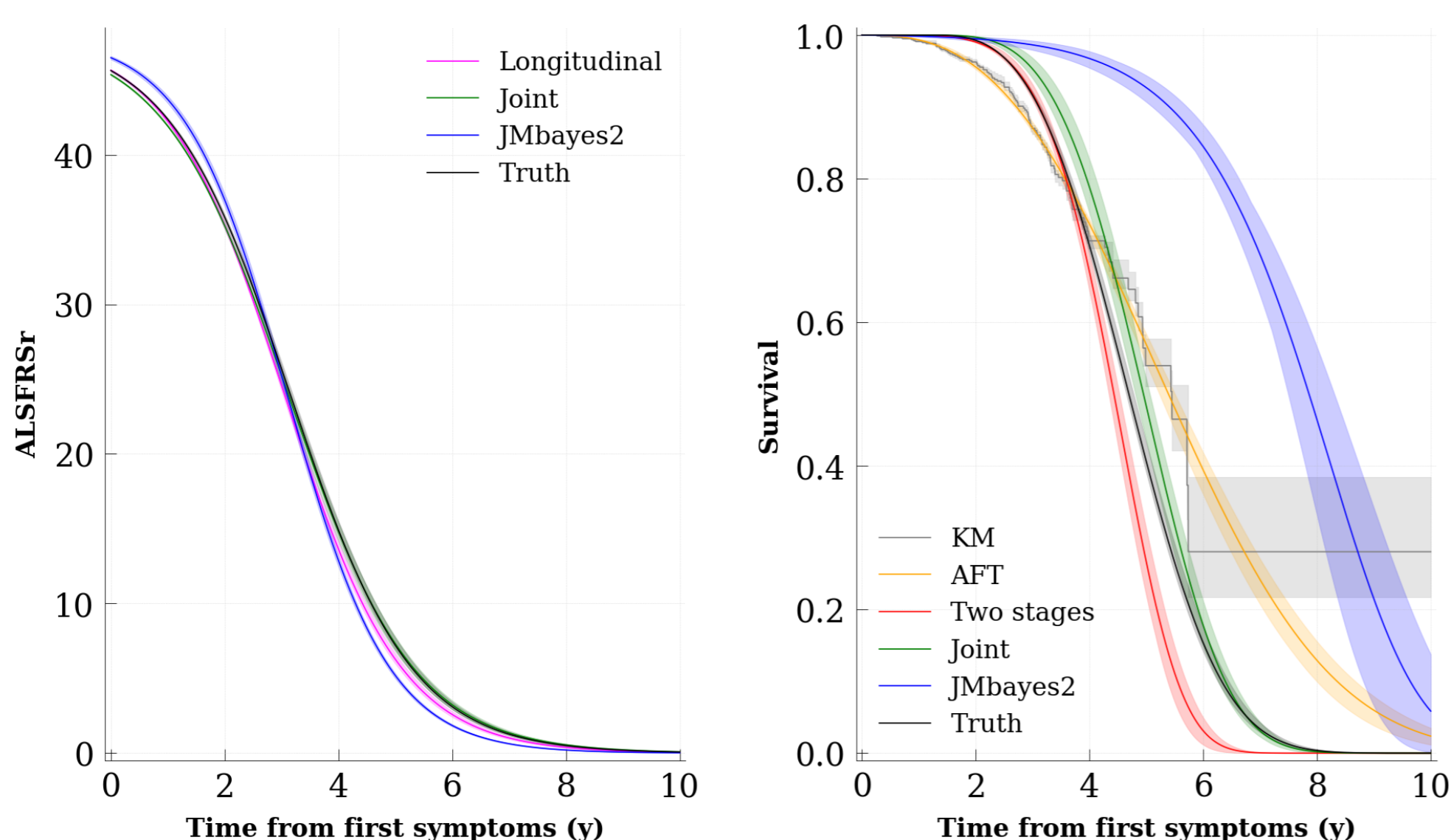


Figure 1 Average patient curve on real-like dataset

**Prediction** We have made a 10-fold cross-validation using two visits to predict the longitudinal outcome at the remaining visits and the event.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
Absolute bias ↓	<b>3.561 (3.579)</b>	-	-	3.596 (3.682)	1.3e-01	-	-	3.981 (3.892)	3.6e-33
IBS ↓	0.155 (0.033)	<b>0.147 (0.033)</b>	4.3e-02	-	-	0.196 (0.039)	1.8e-03	0.198 (0.039)	3.7e-04
C-index 1.0y ↑	0.654 (0.04)	<b>0.658 (0.038)</b>	1.0e+00	-	-	0.531 (0.047)	1.3e-04	0.536 (0.05)	1.4e-04
C-index 1.5y ↑	0.656 (0.038)	<b>0.666 (0.037)</b>	5.2e-02	-	-	0.531 (0.047)	1.0e-04	0.537 (0.05)	1.2e-04
C-index 2.0y ↑	0.66 (0.034)	<b>0.668 (0.034)</b>	2.5e-03	-	-	0.531 (0.047)	6.1e-05	0.539 (0.051)	9.9e-05

Table 2 Prediction metrics on real-like dataset

## Real Data Results

**Data** We used PRO-ACT a large multi-centric ALS cohort. We had access to 2,529 patients with an average of  $9.2 \pm 4.3$  for a follow-up of  $1 \pm 0.6$  with 76.7 % of censored events. We have normalised the score using its natural scale on 48.

**Cohort description** We compared the progression of the patients with mean random effects.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
growth	-13.233 (0.094)	-	-	-13.98 (0.079)	2.0e-11	-	-	-15.351 (0.118)	3.6e-13
midpoint	2.841 (0.011)	-	-	2.786 (0.011)	2.0e-09	-	-	3.222 (0.014)	6.8e-13
median	4.185 (0.038)	4.071 (0.015)	2.4e-05	-	-	4.666 (0.024)	6.1e-10	4.392 (0.118)	7.5e-04

Table 3 Clinically meaningful estimated parameters bias on real-like dataset

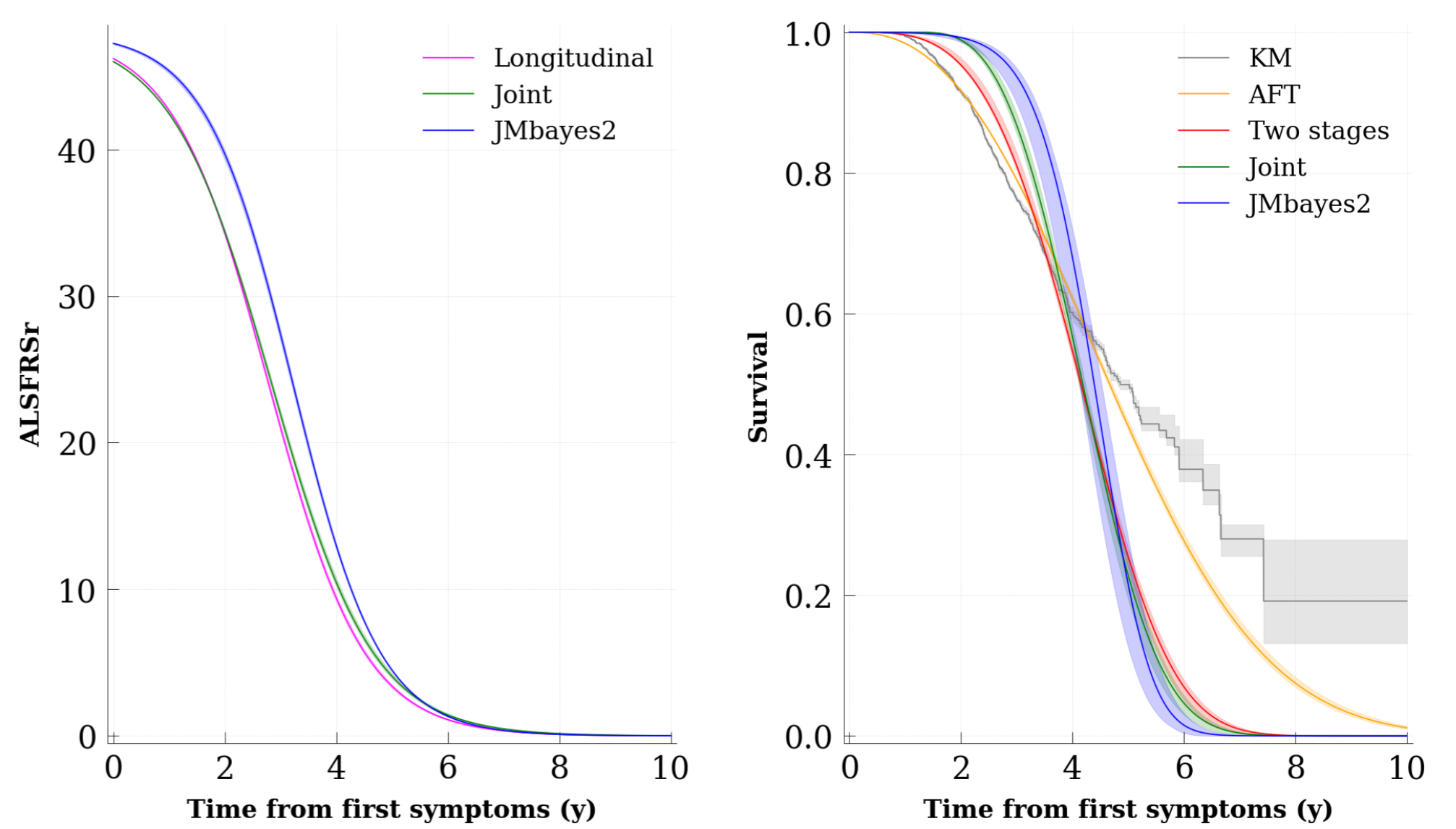


Figure 2 Average patient curve on PRO-ACT dataset

**Prediction** We have made a 10-fold cross-validation using two visits to predict the longitudinal outcome at the remaining visits and the event.

	Joint	Two stages	p-value	Longitudinal	p-value	AFT	p-value	JMbayes2	p-value
Absolute bias ↓	<b>4.1 (4.264)</b>	-	-	4.192 (4.396)	1.2e-20	-	-	5.42 (5.687)	6.5e-201
IBS ↓	0.245 (0.04)	0.238 (0.036)	2.6e-01	-	-	0.267 (0.027)	1.0e-01	<b>0.222 (0.032)</b>	2.1e-03
C-index 1.0y ↑	<b>0.693 (0.047)</b>	0.612 (0.065)	2.9e-04	-	-	0.408 (0.05)	6.5e-07	0.64 (0.059)	3.3e-04
C-index 1.5y ↑	<b>0.7 (0.046)</b>	0.644 (0.058)	1.3e-03	-	-	0.408 (0.05)	9.0e-07	0.668 (0.049)	4.8e-04
C-index 2.0y ↑	<b>0.704 (0.046)</b>	0.664 (0.053)	4.0e-03	-	-	0.408 (0.05)	1.4e-06	0.679 (0.048)	1.4e-03

Table 4 Prediction metrics on real-like dataset

## Conclusion

As it does not need reference time our joint model with latent disease age enables us to improve the performance of most of the prediction metrics compare to existing joint models. To continue developing this model, future improvement could consider adding more flexibility to the survival function and integrating the use of covariates or modelling of several longitudinal outcomes or events.