Supplementary Material for "Dynamic Predictions with Time-Dependent Covariates in Survival Analysis using Joint Modeling and Landmarking"

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1   Aortic Valve Dataset

Table 1: Estimated coefficients and 95% credibility intervals for the parameters of the longitudinal submodels based on the three joint models fitted to the Aortic Valve dataset..

	Value (M_1)		Value+Slope (M_2)		Area (M_3)	
	Est.	95% CI	Est.	95% CI	Est.	95% CI
TypeOpSI	3.46	(3.181; 3.743)	3.47	(3.175; 3.763)	3.47	(3.181; 3.766)
TypeOpRR	2.95	(2.819; 3.079)	2.95	(2.826; 3.080)	2.96	(2.823; 3.097)
TypeOpSI:B-spln1	1.00	(0.618; 1.388)	1.04	(0.677; 1.455)	0.92	(0.494; 1.340)
TypeOpRR:B-spln1	0.97	(0.638; 1.277)	1.01	(0.682; 1.332)	0.97	(0.654; 1.300)
TypeOpSI:B-spln2	2.13	(1.416; 2.803)	2.17	(1.490; 2.889)	1.96	(1.254; 2.638)
TypeOpRR:B-spln2	2.09	(1.620; 2.596)	2.15	(1.668; 2.634)	1.90	(1.434; 2.412)
TypeOpSI:B-spln3	2.22	(1.674; 2.799)	2.28	(1.797; 2.836)	2.01	(1.476; 2.551)
TypeOpRR:B-spln3	1.69	(1.165; 2.273)	1.81	(1.215; 2.342)	1.49	(0.940; 2.096)
σ	0.56	(0.532; 0.597)	0.57	(0.534; 0.600)	0.57	(0.537; 0.602)

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Table 2: Estimated coefficients and 95% credibility intervals for the parameters of the survival submodels (parameters $\boldsymbol{\gamma}_{h_0}$ of the baseline hazard have been omitted) based on the three joint models fitted to the Aortic Valve dataset.

	Value (M_1)		Value+Slope (M_2)		Area (M_3)	
	Est.	95% CI	Est.	95% CI	Est.	95% CI
TypeOpRR	0.48	(0.060; 0.925)	0.50	(0.074; 0.961)	0.45	(0.034; 0.862)
Age	0.02	(0.003; 0.031)	0.02	(0.006; 0.033)	0.01	(−0.006; 0.022)
sexFemale	−0.11	(−0.488; 0.280)	−0.12	(−0.518; 0.238)	−0.11	(−0.519; 0.266)
α_1	0.47	(0.314; 0.592)	0.40	(0.232; 0.569)	0.04	(0.017; 0.056)
α_2			1.06	(−0.414; 2.529)		

Table 3: Estimated coefficients and 95% confidence intervals for the parameters of the Cox models fitted to landmark datasets at follow-up times $t = 5.5, 7.5, 9.5$ years.

		Value (M_5)		Value+Slope (M_6)		Area (M_7)	
	t	Value	95% CI	Value	95% CI	Value	95% CI
TypeOpRR	5.5	0.30	(−0.161; 0.754)	0.25	(−0.215; 0.709)	0.23	(−0.244; 0.714)
Age		−0.00	(−0.018; 0.012)	−0.00	(−0.017; 0.014)	−0.01	(−0.021; 0.009)
sexFemale		−0.12	(−0.573; 0.326)	−0.08	(−0.539; 0.370)	−0.10	(−0.554; 0.356)
α_1		0.20	(0.029; 0.381)	0.15	(−0.045; 0.351)	0.00	(−0.046; 0.050)
α_2				0.26	(−0.187; 0.708)		
TypeOpRR	7.5	0.42	(−0.086; 0.932)	0.42	(−0.086; 0.927)	0.39	(−0.133; 0.911)
Age1		−0.00	(−0.021; 0.013)	−0.00	(−0.020; 0.015)	−0.01	(−0.022; 0.012)
sexFemale		−0.13	(−0.627; 0.369)	−0.12	(−0.616; 0.379)	−0.12	(−0.619; 0.387)
α_1		0.02	(−0.182; 0.227)	−0.01	(−0.215; 0.203)	−0.01	(−0.045; 0.032)
α_2				0.24	(−0.176; 0.653)		
TypeOpRR	9.5	0.60	(0.030; 1.172)	0.50	(−0.076; 1.084)	0.53	(−0.051; 1.115)
Age		−0.00	(−0.025; 0.015)	−0.00	(−0.023; 0.016)	−0.01	(−0.028; 0.011)
sexFemale		−0.06	(−0.616; 0.498)	0.03	(−0.538; 0.593)	−0.09	(−0.648; 0.475)
α_1		0.29	(0.091; 0.493)	0.21	(−0.000; 0.421)	0.01	(−0.018; 0.044)
α_2				0.67	(0.019; 1.312)		
		Value (M_8)		Value+Slope (M_9)		Area (M_{10})	
	t	Value	95% CI	Value	95% CI	Value	95% CI
TypeOpRR	5.5	0.30	(−0.157; 0.765)	0.27	(−0.199; 0.743)	0.27	(−0.211; 0.755)
Age		−0.00	(−0.019; 0.011)	−0.00	(−0.020; 0.011)	−0.01	(−0.021; 0.009)
sexFemale		−0.13	(−0.581; 0.320)	−0.11	(−0.562; 0.350)	−0.11	(−0.556; 0.345)
α_1		0.19	(−0.010; 0.400)	0.16	(−0.080; 0.391)	0.01	(−0.032; 0.054)
α_2				0.16	(−0.329; 0.659)		
TypeOpRR	7.5	0.42	(−0.095; 0.928)	0.39	(−0.134; 0.917)	0.34	(−0.186; 0.873)
Age		−0.00	(−0.022; 0.012)	−0.00	(−0.022; 0.012)	−0.01	(−0.022; 0.012)
sexFemale		−0.13	(−0.627; 0.370)	−0.14	(−0.636; 0.364)	−0.12	(−0.623; 0.374)
α_1		0.01	(−0.223; 0.236)	0.03	(−0.225; 0.284)	−0.02	(−0.053; 0.021)
α_2				−0.29	(−1.647; 1.064)		
TypeOpRR	9.5	0.61	(0.024; 1.190)	0.44	(−0.148; 1.036)	0.51	(−0.088; 1.113)
Age		−0.01	(−0.027; 0.012)	−0.01	(−0.028; 0.013)	−0.01	(−0.029; 0.009)
sexFemale		−0.09	(−0.646; 0.471)	−0.05	(−0.609; 0.515)	−0.07	(−0.638; 0.488)
α_1		0.24	(−0.014; 0.486)	0.20	(−0.049; 0.457)	0.01	(−0.027; 0.039)
α_2				5.33	(2.287; 8.375)		

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2   Simulation Study

2.1   True parameter values

For all simulation scenarios the parameter values that were used for the longitudinal sub-model were

Fixed effects: $\beta_1 = 3.4554$, $\beta_2 = 2.9470$, $\beta_3 = 1.0027$, $\beta_4 = 0.9709$, $\beta_5 = 4.1290$, $\beta_6 = 4.0893$, $\beta_7 = 6.2182$, $\beta_8 = 6.6909$;

Random effects covariance matrix:

$$D = \begin{bmatrix} 0.5686193 & 0.2126076 & 0.1547322 & 0.4354939 \\ & 1.6721086 & 2.3299235 & 2.1926166 \\ & & 5.0230656 & 2.8873934 \\ & & & 4.0286104 \end{bmatrix};$$

Measurement error standard deviation: $\sigma = 0.564$.

Figure 1 gives a visual impression of the subject-specific profiles under the posited model.

For the survival submodels the parameters that were used to simulate from each scenario are given in Table 4.

Table 4: Parameter values for the survival submodels under the three simulation scenarios.

	Scenario		
	I	II	III
γ_0	-5.7296	-5.7296	-5.7296
γ_1	0.48	0.48	0.48
α_1	0.4672	0.4044	0.0365
α_2		1.3616	
σ_t	0.9518	0.9518	0.9518
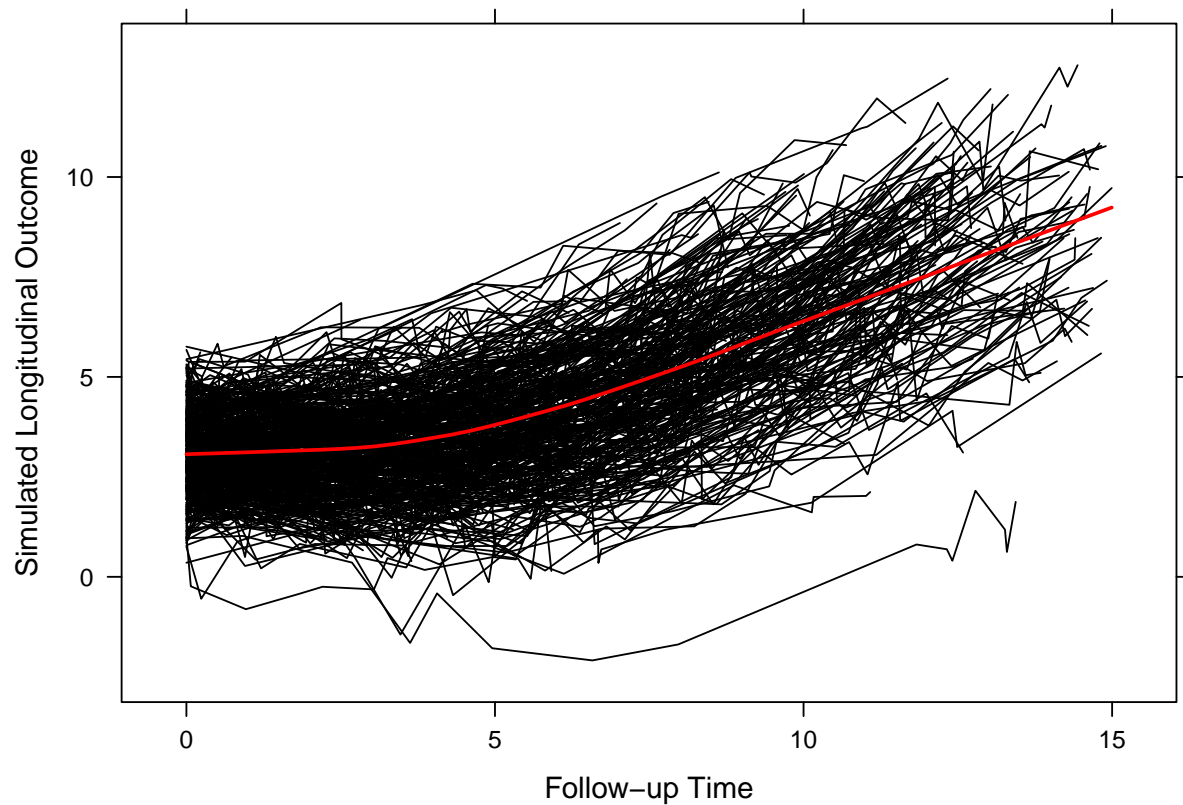
Figure 1: Simulated longitudinal trajectories under the posited mixed effects model. The red superimposed line denotes the average longitudinal profile.

2.2 Results

Figures 2–13 show Box-Plots with the differences of areas under the receiver operating characteristic curve and differences of prediction errors between the joint model and landmark approaches, under different combinations of the functional form that links the longitudinal and survival outcomes, and assuming the correct or incorrect functional form for the time effect.
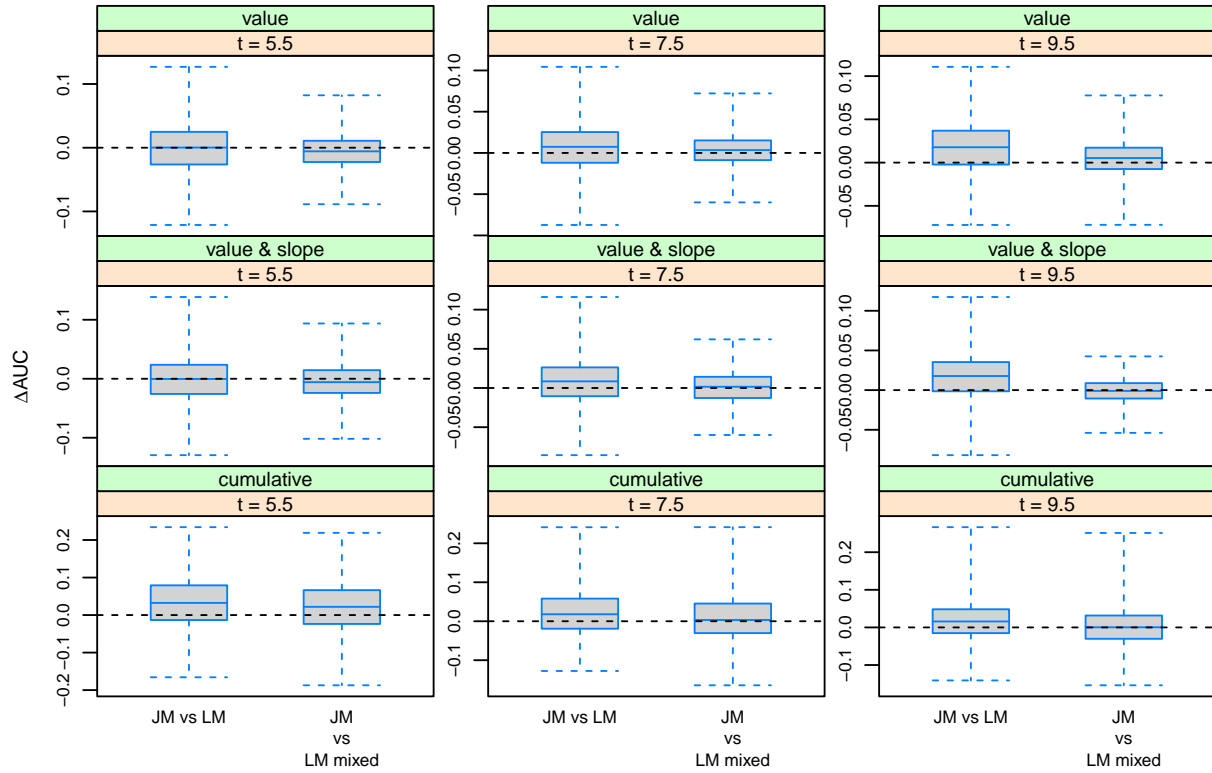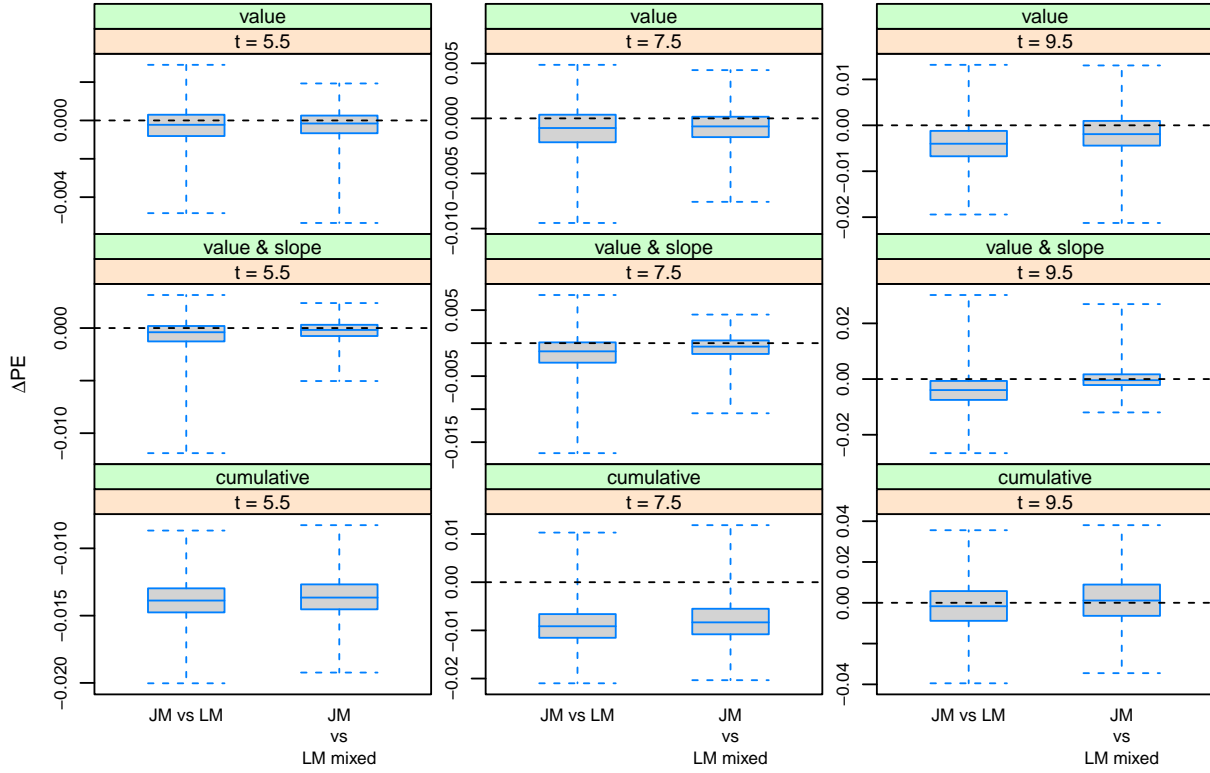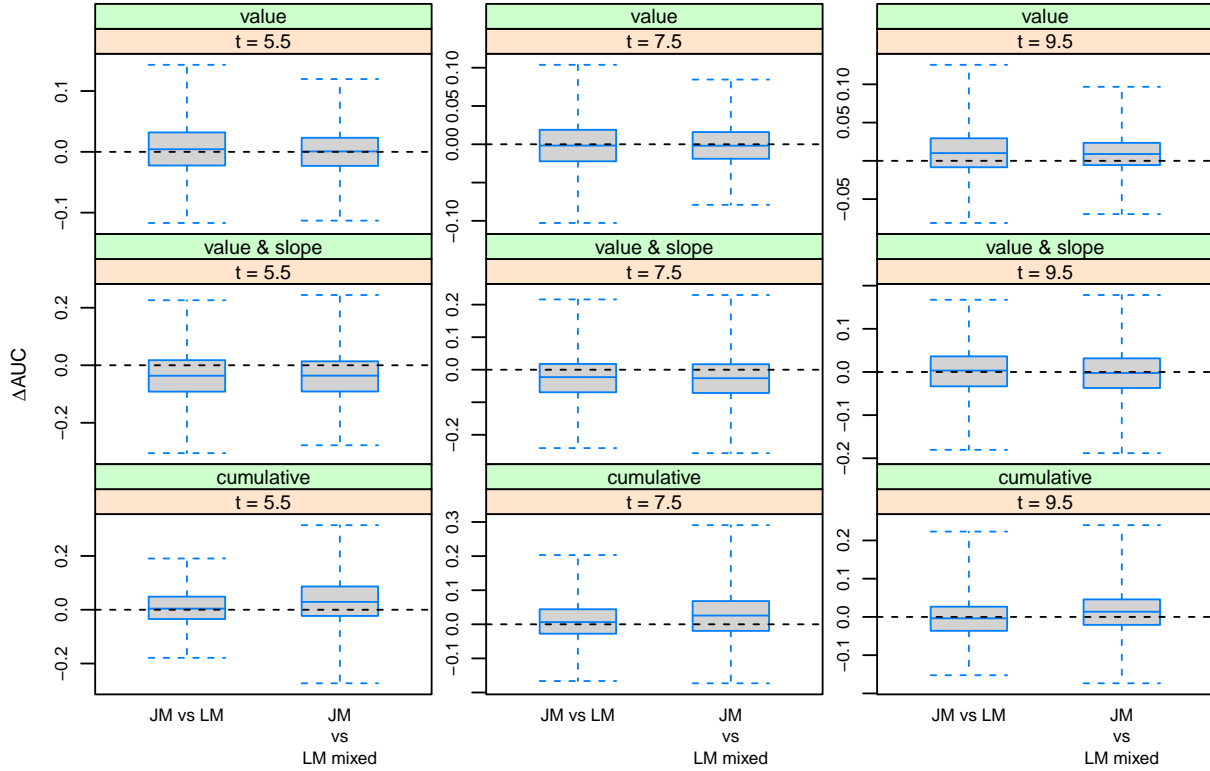
Figure 2: Simulation results under Scenario I when the true functional form that links the longitudinal and survival outcomes is the current value, and the correct functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of areas under the receiver operating characteristic curve between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔAUC is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $\Delta t = 2$.
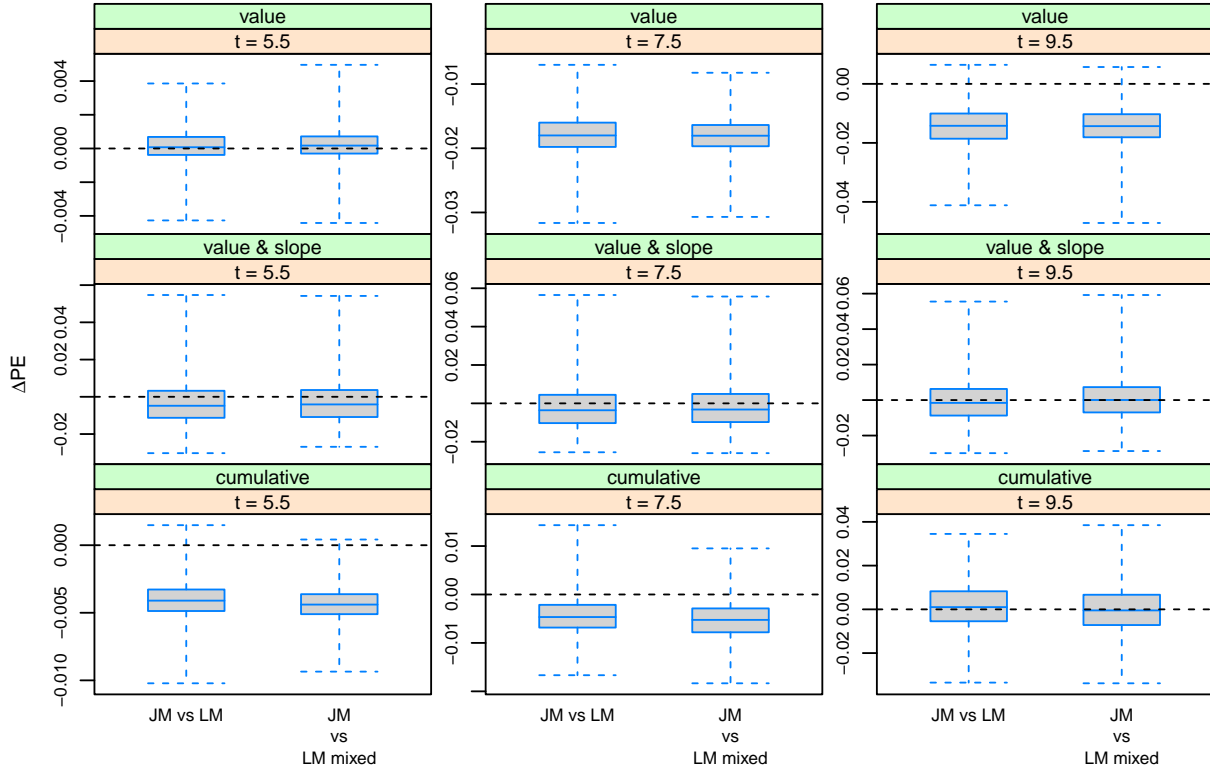
Figure 3: Simulation results under Scenario I when the true functional form that links the longitudinal and survival outcomes is the current value, and the correct functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of prediction errors (PE) between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔPE is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $u = t + 2$.

Figure 4: Simulation results under Scenario I when the true functional form that links the longitudinal and survival outcomes is the current value, and the wrong functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of areas under the receiver operating characteristic curve between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔAUC is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $\Delta t = 2$.
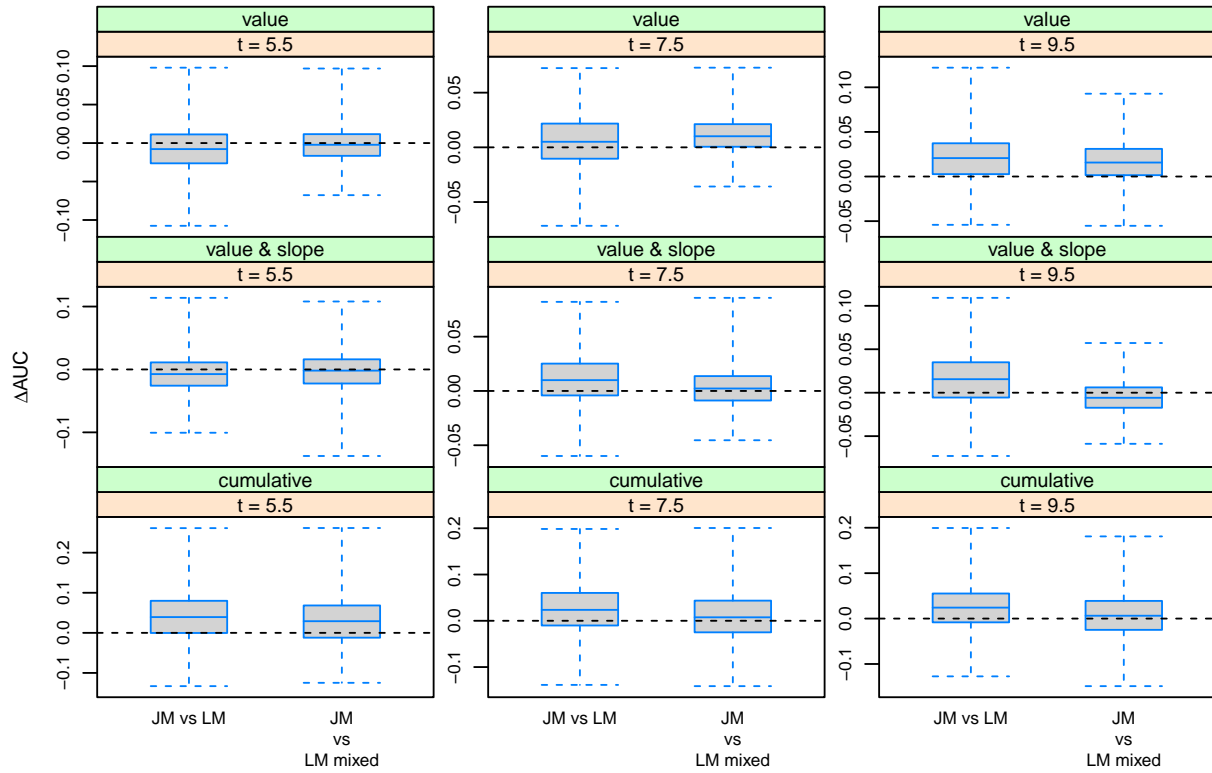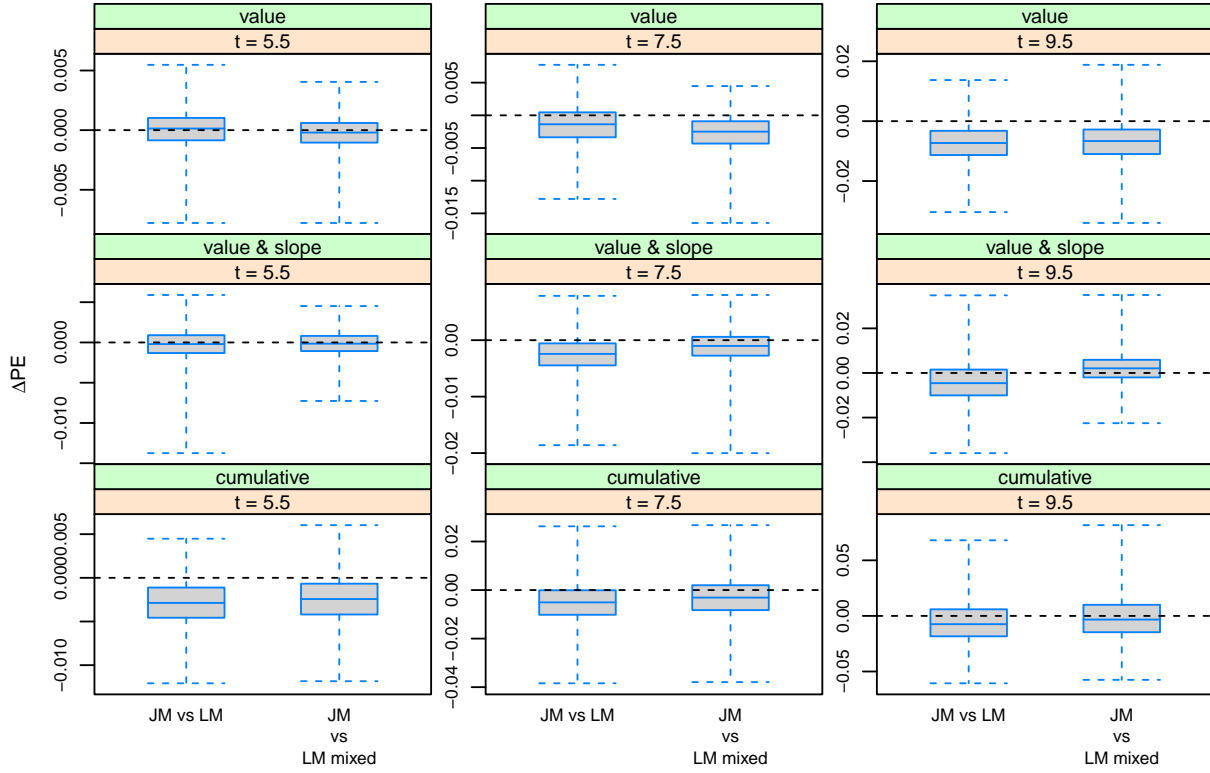
Figure 5: Simulation results under Scenario I when the true functional form that links the longitudinal and survival outcomes is the current value, and the wrong functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of prediction errors (PE) between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔPE is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $u = t + 2$.

Figure 6: Simulation results under Scenario II when the true functional form that links the longitudinal and survival outcomes is the current value & current slope, and the correct functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of areas under the receiver operating characteristic curve between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔAUC is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $\Delta t = 2$.
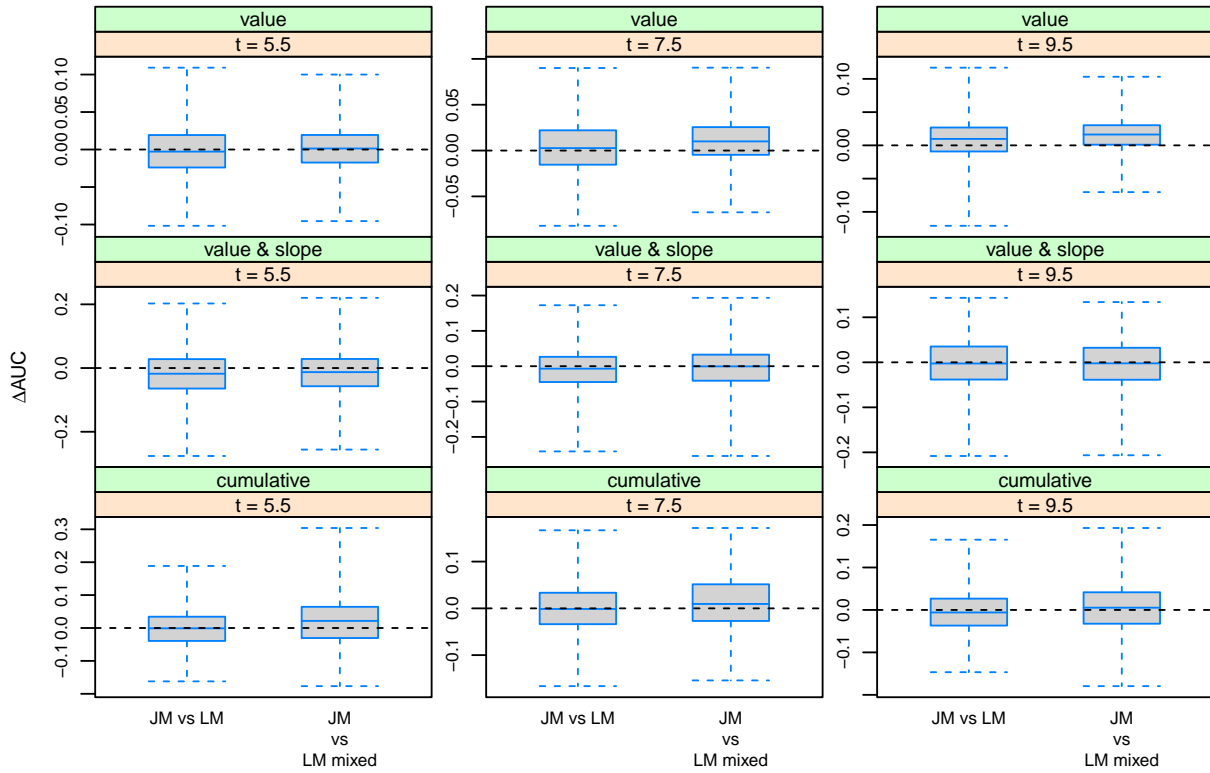
Figure 7: Simulation results under Scenario II when the true functional form that links the longitudinal and survival outcomes is the current value & current slope, and the correct functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of prediction errors (PE) between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔPE is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $u = t + 2$.

Figure 8: Simulation results under Scenario II when the true functional form that links the longitudinal and survival outcomes is the current value & current slope, and the wrong functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of areas under the receiver operating characteristic curve between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔAUC is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $\Delta t = 2$.
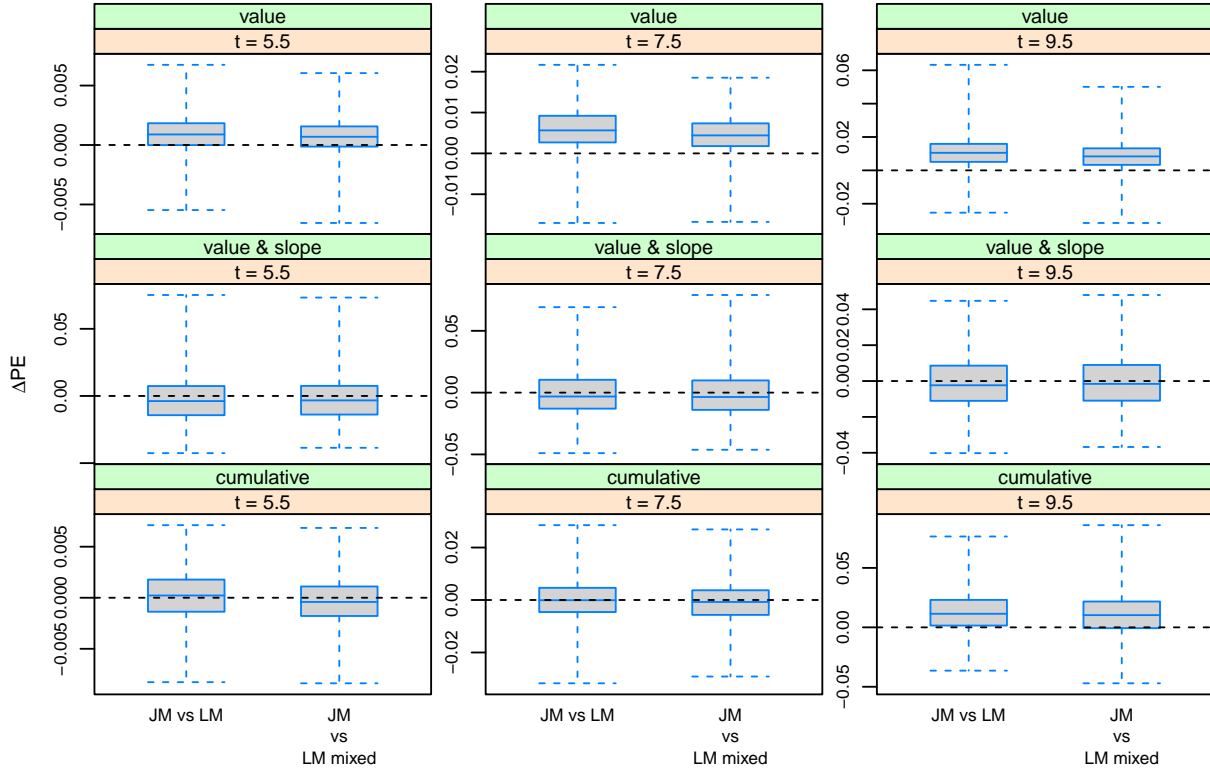
Figure 9: Simulation results under Scenario II when the true functional form that links the longitudinal and survival outcomes is the current value & current slope, and the wrong functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of prediction errors (PE) between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔPE is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $u = t + 2$.
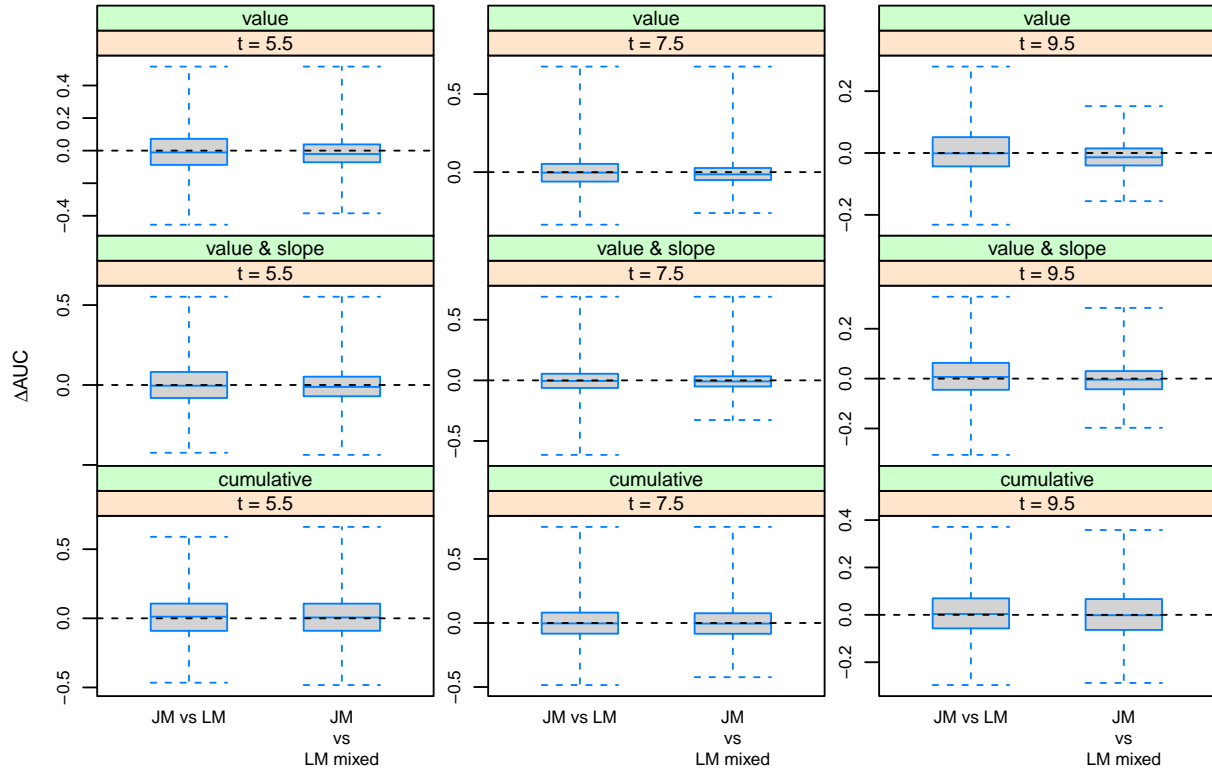
Figure 10: Simulation results under Scenario III when the true functional form that links the longitudinal and survival outcomes is the cumulative effect (area under the longitudinal trajectory), and the correct functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of areas under the receiver operating characteristic curve between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔAUC is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $\Delta t = 2$.
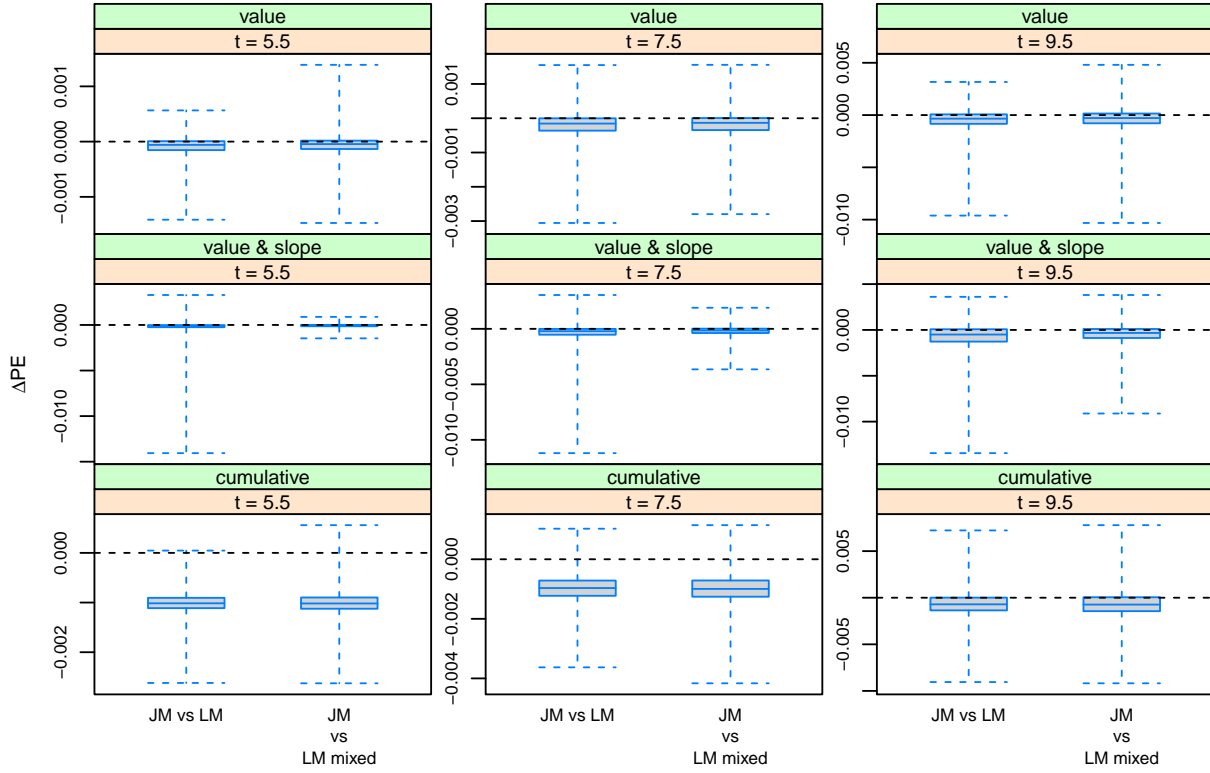
Figure 11: Simulation results under Scenario III when the true functional form that links the longitudinal and survival outcomes is the cumulative effect (area under the longitudinal trajectory), and the correct functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of prediction errors (PE) between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔPE is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $u = t + 2$.
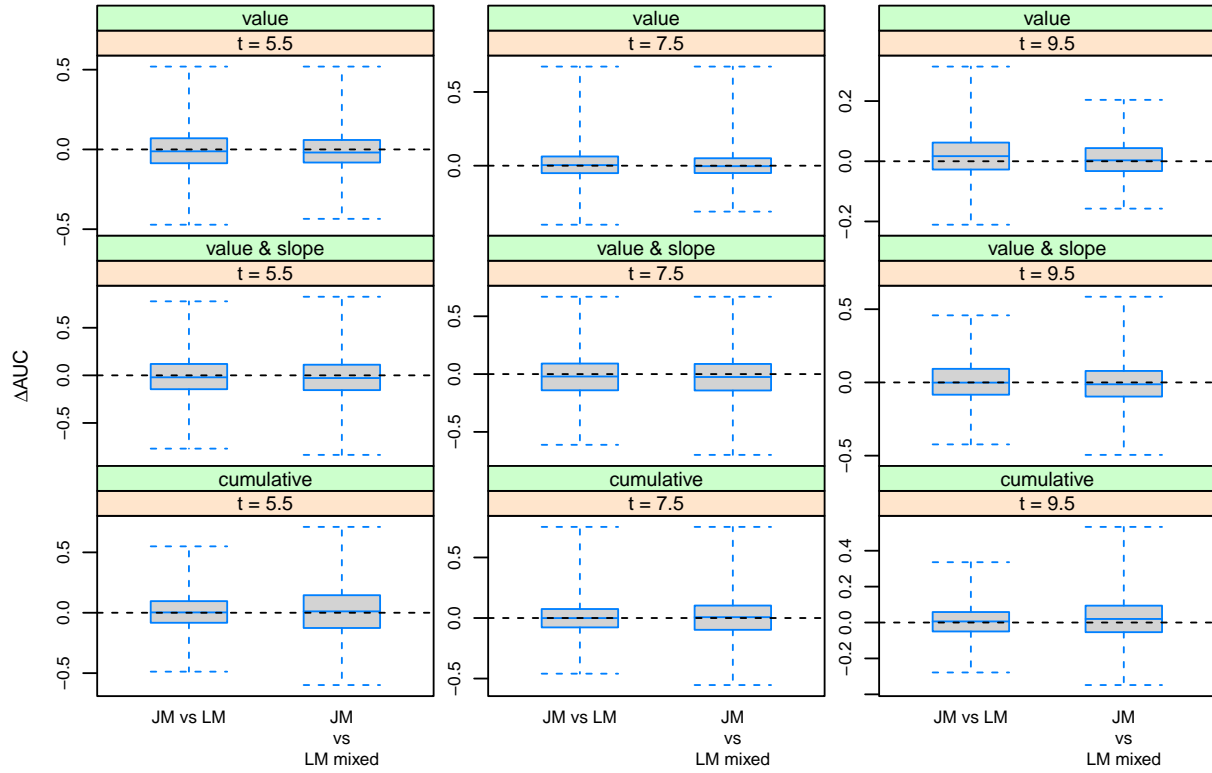
Figure 12: Simulation results under Scenario III when the true functional form that links the longitudinal and survival outcomes is the cumulative effect (area under the longitudinal trajectory), and the wrong functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of areas under the receiver operating characteristic curve between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔAUC is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $\Delta t = 2$.
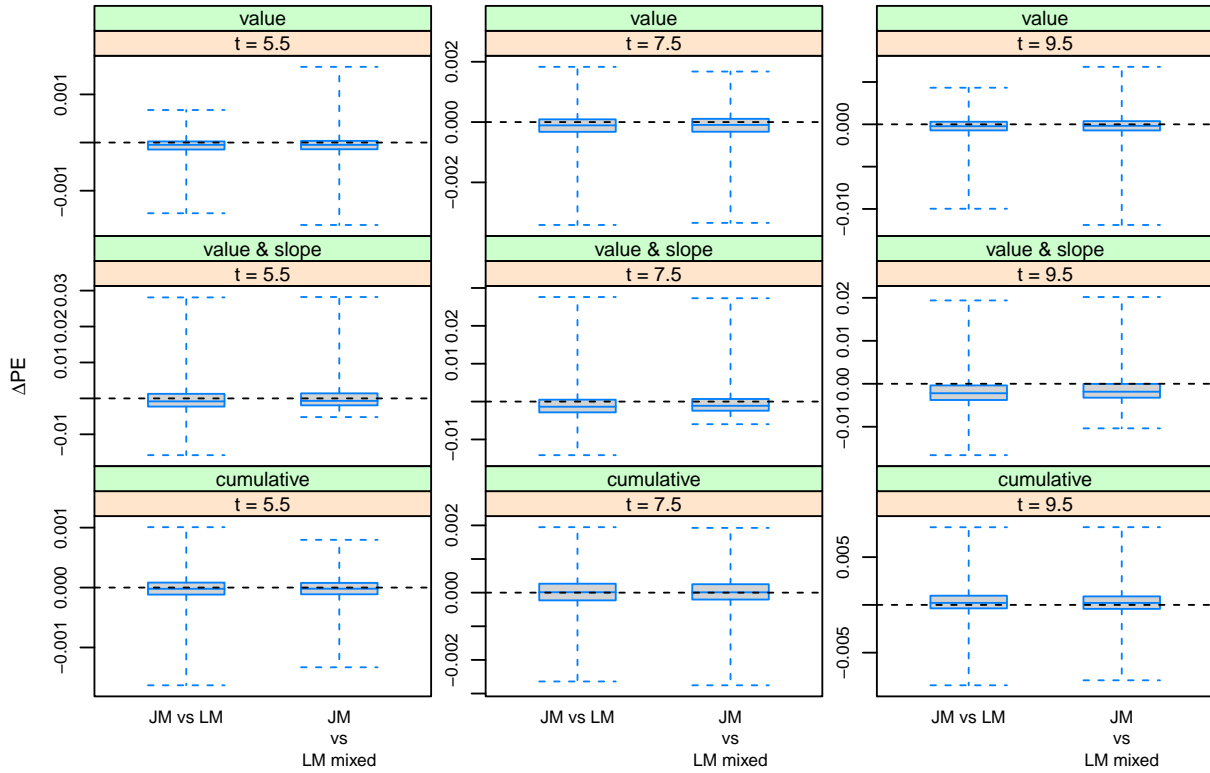
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Figure 13: Simulation results under Scenario III when the true functional form that links the longitudinal and survival outcomes is the cumulative effect (area under the longitudinal trajectory), and the wrong functional form is assumed for the time effect in the linear mixed model. Each panel shows a box-plot with the differences of prediction errors (PE) between the joint model and the two landmark approaches calculated in 1000 simulated datasets. Each ΔPE is calculated from 500 subjects in the test data set, while the models have been fitted in the 500 subjects in the training data set. Each row corresponds to a different functional form and each column to a different follow-up time. For all panels $u = t + 2$.