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A mechanistic model for prediction of metastatic relapse in early-stage breast cancer using routine clinical features

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BACKGROUND

- ◆ Prediction of metastasis is a major challenge for treatment individualization of breast cancer patients.
- ◆ The time to **metastatic relapse** in breast cancers has been studied mainly with classical statistical models (e.g. Cox proportional hazards model).
- ◆ **Mechanistic models** can be used not only for prediction but also to explore the biological role of predictive variables.

OBJECTIVES

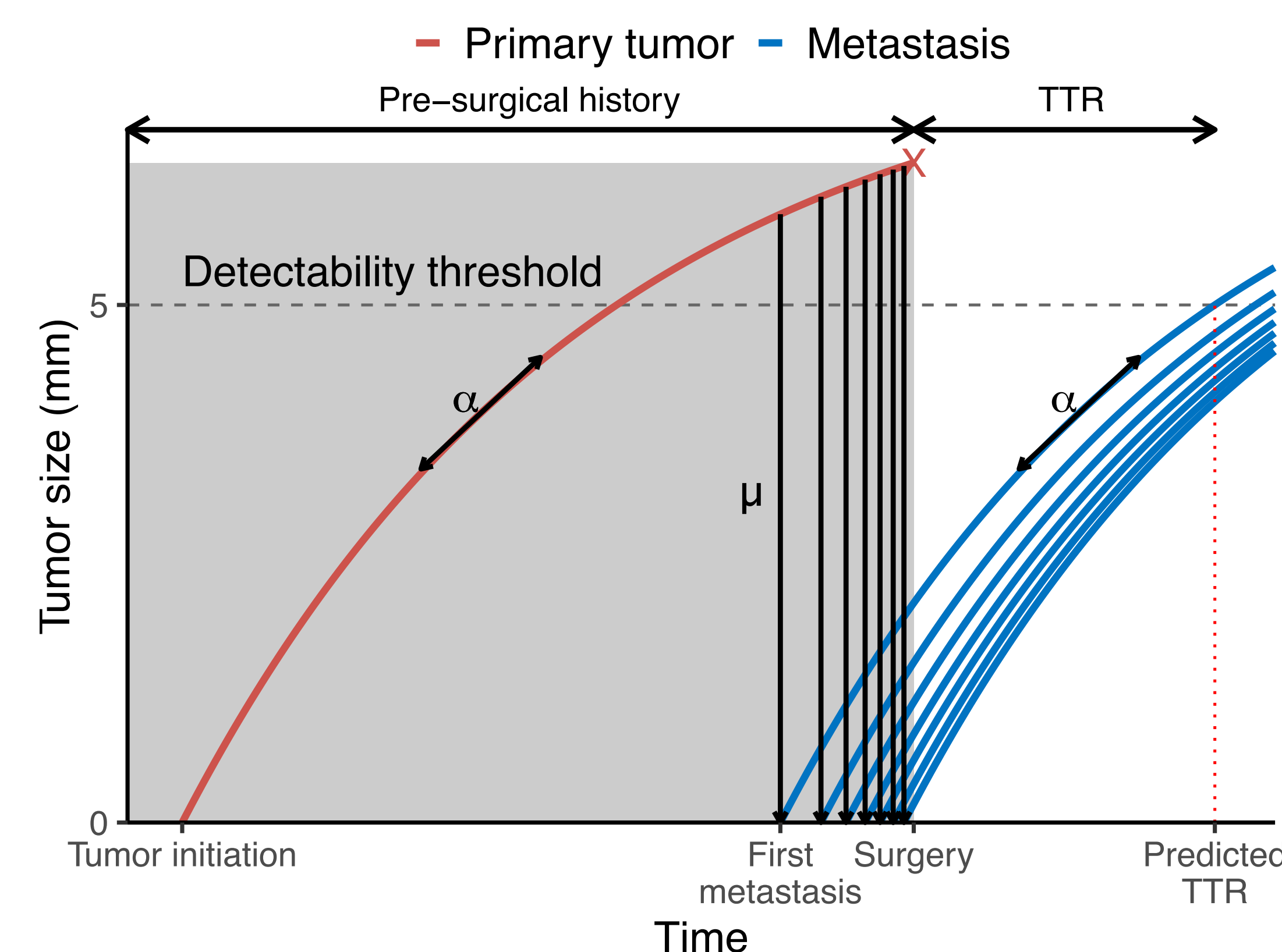
- ◆ **Describe and predict metastasis free survival** in a population of breast cancer patients who did not receive systemic adjuvant therapies.
- ◆ Use mechanistic modeling to **disentangle the biological roles of biomarkers** between growth and dissemination

MATERIAL AND METHODS

Mechanistic model of the metastatic relapse¹

Tumor growth (Gompertz): $\frac{dV}{dt} = (\alpha - b \log V)V$

Dissemination rate: $d(V_p) = \mu V_p$



Mixed-effects model

$$T^i = TTR(V_{diag}^i, \alpha^i, \mu^i) + \mathcal{N}(0, \varepsilon^2)$$

$$\begin{cases} \log \alpha^i = \log \alpha_{pop} + T \beta_\alpha \cdot C^i + \mathcal{N}(0, \omega_\alpha^2) \\ \log \mu^i = \log \mu_{pop} + T \beta_\mu \cdot C^i + \mathcal{N}(0, \omega_\mu^2) \end{cases}$$

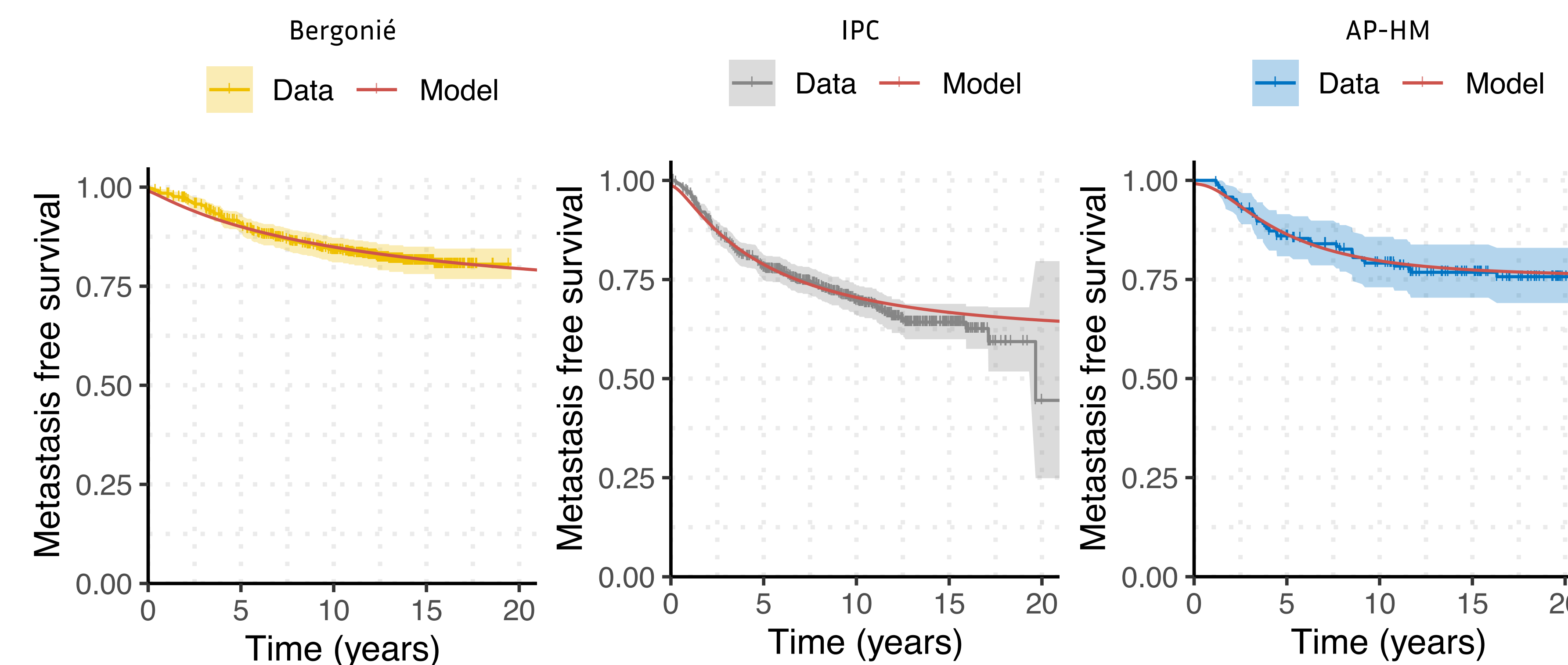
- ◆ The population parameters of the models were estimated with the SAEM algorithm.
- ◆ Covariates significance was assessed by univariate bootstraps.
- ◆ The final covariate model structures were selected by a backward elimination procedure on the BIC.

Data

591 patients treated at the Bergonié Institute (Bordeaux, France), **676 patients** from public databases aggregated by the Paoli Calmettes Institute (IPC, Marseille, France), with routine clinical features (tumor size at diagnosis, age, grade, molecular subtype, TNM, ER, PR, number of invaded nodes, HER2, Ki67) and **163 patients** from AP-HM with routine clinical features as well as three other biomarkers (Urokinase Plasminogen Activator, Plasminogen Activator Inhibitor-1, Thymidine Kinase-1).

RESULTS

Model fits



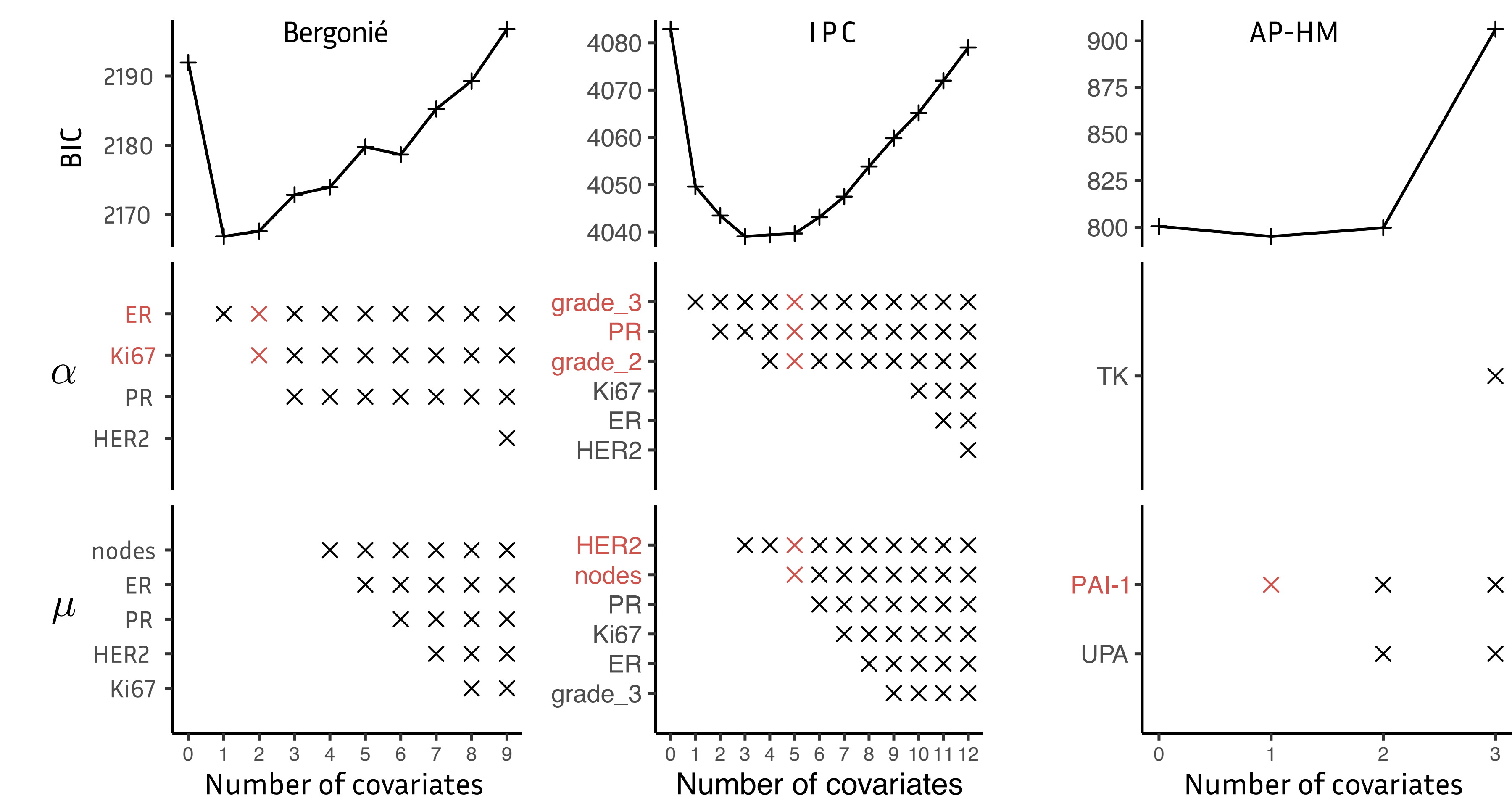
Kaplan-Meier of the Metastasis free survival for all three databases and predictions of the corresponding models without covariates effects other than the size of the tumor (structurally present).

Estimation of the parameters

	Bergonié		IPC		AP-HM
$\log \alpha_{pop}$	-5.3 (25.4%)		-5.28 (4.43%)		-4.3 (9.85%)
$\log \mu_{pop}$	-29.7 (1.77%)		-29.2 (0.637%)		-32 (2.89%)
σ	0.571 (86.4%)		0.511 (48.6%)		0.0364 (251%)
ω_α	1.05 (257%)		0.734 (36.3%)		0.722 (10.8%)
ω_μ	4.94 (1.69%)		4.2 (9.06%)		3.27 (9.74%)
$\beta_{\alpha, ER}$	-0.99 (53.2%)	$\beta_{\alpha, grade 2}$	0.61 (43.7%)		
$\beta_{\alpha, Ki67}$	1.38 (35.8%)	$\beta_{\alpha, grade 3}$	1.67 (14.8%)		
		$\beta_{\alpha, PR}$	-0.549 (34%)		
		$\beta_{\mu, HER2}$	1.99 (31.6%)	$\beta_{\mu, PAI-1}$	0.30 (30.2%)
		$\beta_{\mu, nodes}$	2.72 (47.4%)		

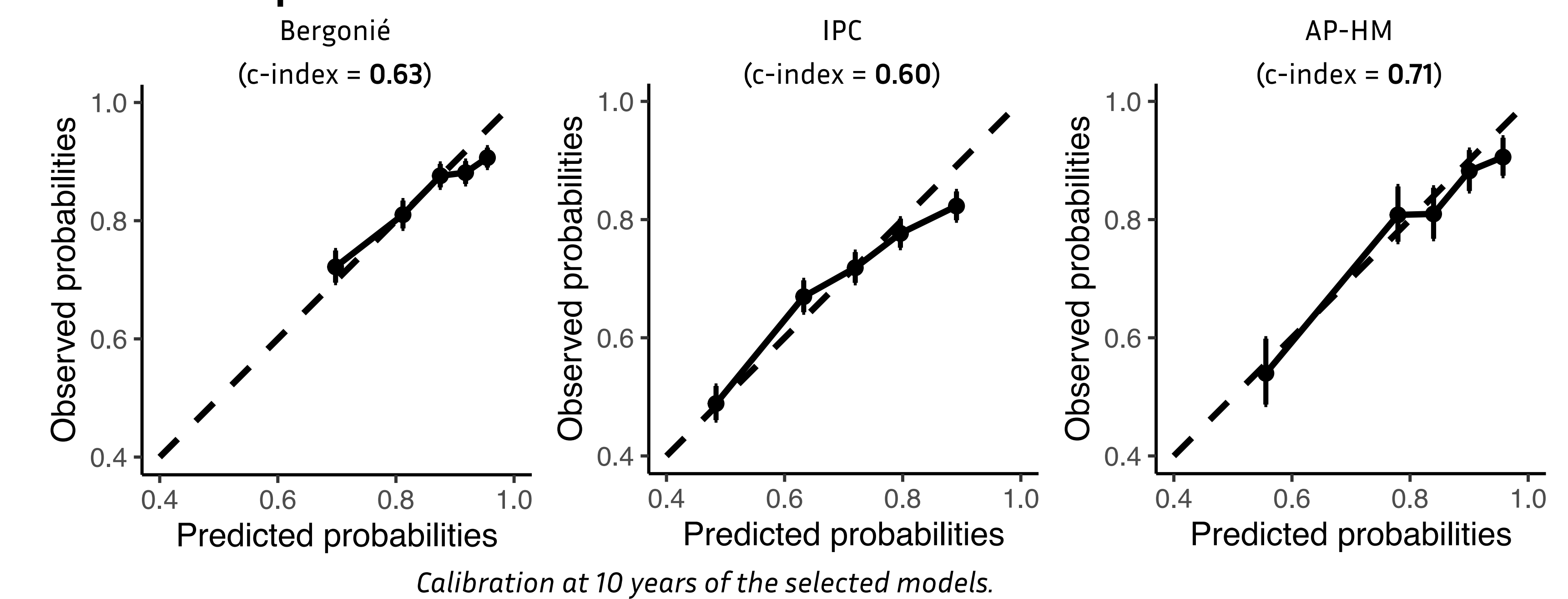
Values of the parameters for the selected models, estimation (relative standard error %). Estimation was performed with the SAEM algorithm, standard deviation were obtained by bootstrap.

Variable selection



Backward procedure on BIC for model selection, selected models are highlighted in red. The variables presented were selected as significant in a univariate bootstrap analysis.

Calibration and prediction



CONCLUSIONS AND PERSPECTIVES

- ◆ Using mechanistic model of the metastatic relapse, we can adequately describe the metastasis free survival in our study population
- ◆ Predictive performances were **excellent in calibration** but **mitigated in discrimination**.
- ◆ The model associates **HER2, nodal status and PAI-1 with the metastatic dissemination**, and **TK, Ki67 and grade with tumor growth**. These findings are concordant with the known biological roles of the biomarkers.

References

¹Nicolò et al. (Benzekry), Machine Learning and Mechanistic Modeling for Prediction of Metastatic Relapse in Early-Stage Breast Cancer. Jco Clin Cancer Informatics 4, 259–274 (2020).