

# Random Survival Forests for Dynamic Predictions of a Time-to-Event Outcome Using a Longitudinal Biomarker

## Additional File 1

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## 1 Simulation Data Generation Details

Recall that data were generated according to the joint model:

$$y_{ik}(t) = m_i(t) + \epsilon_i(t) = \beta_{0k} + \beta_{1k}time + \beta_{2k}X_{1i} + \beta_{3k}X_{2i} + \beta_{4k}X_{3i} + b_{i0} + b_{i1} + \epsilon_i(t), k = 1, 2$$

$$\text{Scenario I + II: } h_i(t) = h_0(t) \exp\{\gamma_0 + \gamma_1 X_{1i} + \gamma_2 X_{2i} + \gamma_3 X_{3i} + \alpha_1 Y_i(t)\}$$

$$\text{Scenario III: } h_i(t) = h_0(t) \exp\{\gamma_0 + \gamma_1 X_{1i} + \gamma_2 1X_{2i} + \gamma_3 X_{3i} + \alpha_1 m_{i1}(t) + \alpha_2 m_{i2}(t)^2\}$$

The Weibull baseline hazard had a shape parameter of  $\sigma_2 = 2$  for all scenarios. The covariates were all created from binomial distributions as follows:  $X_1 \sim \text{bin}(0.60)$ ,  $X_2 \sim \text{bin}(0.50)$ ,  $X_3 \sim \text{bin}(0.55)$ . The additional 7 covariates that were not included in data generation were distributed as follows:  $X_4 \sim \text{bin}(0.50)$ ,  $X_5 \sim \text{bin}(0.65)$ ,  $X_6 \sim \text{bin}(0.45)$ ,  $X_7 \sim \text{bin}(0.55)$ ,  $X_8 \sim \text{bin}(0.70)$ ,  $X_9 \sim \text{bin}(0.60)$ ,  $X_{10} \sim \text{bin}(0.50)$

While  $Y_i$  differed between Scenario I and II and parameters were set as was shown in the data generation section, all other parameters were identical between scenarios and will be described below. The coefficients were defined as  $bi = (b_{i0}, b_{i1}) \sim N(0, G)$  with  $G = \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix}$  and  $\epsilon_i(t) \sim N(0, \sigma^2)$  with  $\sigma^2 = 0.6$ . The other coefficients were  $\beta_{01} = 5.6, \beta_{11} = -0.45, \beta_{21} = -0.25, \beta_{31} = -0.11, \beta_{41} = -0.3$ . The coefficients for the survival submodel were  $\gamma_0 = -8, \gamma_1 = 1.9, \gamma_2 = 2.15, \gamma_3 = 2.65, \alpha_1 = 0.07$ .

The coefficients for Scenario III were defined slightly differently. The coefficients for  $y_1$  were same as the previous scenarios. The coefficients for  $y_2$  were  $\beta_{02} = 2.0, \beta_{12} = 0.25, \beta_{22} = 0.75, \beta_{32} = -0.61, \beta_{42} = 0.45$ . The coefficients for the survival submodel were  $\gamma_0 = -9, \gamma_1 = 1.9, \gamma_2 = 2.15, \gamma_3 = 2.65, \sigma_2^2 = 0.4, \alpha_1 = 0.09, \alpha_2 = 0.05$ .

## 2 Comparison Models for Application

### Joint Model Formulation and Prediction

A linear mixed effects model that included only main effects for the three binary covariates and time with a random intercept and slope as described in the simulation setup was fit:

$$y_i(t) = m_i(t) + \epsilon_i(t) = x_i' \beta + z_i' b_i + \epsilon_i(t).$$

The estimate of true unobserved value of the underlying longitudinal covariate,  $m_i(t)$ , was then used to quantify the effect on the risk of the event:

$$h_i(t \mid M_i(t), w_i) = h_0(t) \exp\{\gamma' w_i + \alpha m_i(t)\}$$

where  $M_i(t) = \{m_i(u); 0 \leq u < t\}$  denotes the history of the true unobserved longitudinal process up to time  $t$ .

Following a Bayesian formulation of the joint model, the estimation of  $\pi_m(t_{hor} \mid \tau)$  is based on the posterior predictive distribution:

$$\pi_m^{JM}(t_{hor} \mid \tau) = \int Pr(T_m^* \geq t_{hor} \mid T_m^* \geq \tau, y_m(t), \theta) p(\theta \mid D_n) d\theta,$$

where  $\theta$  is the vector of all model parameters. The calculation of the first term requires the conditional independence assumption. The first term of the integrand of  $\pi_m^{JM}(t_{hor} \mid \tau)$  can be written as

$$\begin{aligned} Pr(T_m^* \geq t_{hor} \mid T_m^* \geq \tau, Y_m(t), \theta) &= \int Pr(T_m^* \geq t_{hor} \mid T_m^* \geq \tau, b_m, \theta) p(b_m \mid T_m^* \geq \tau, y_m(t), \theta) db_m = \\ &= \int \frac{S_m\{t_{hor} \mid M_m(t_{hor}, b_m), \theta\}}{S_m\{\tau \mid M_m(\tau, b_m), \theta\}} p(b_m \mid T_m^* \geq \tau, y_m(t), \theta) db_m, \end{aligned}$$

where

$$S_m\{\tau \mid M_m(\tau, b_m), \theta\} = \exp\left\{\int_0^\tau h_0(s) \exp\{\gamma^T x_m + \alpha M_m(s)\} ds\right\}$$

The integral can be estimated by Monte Carlo sampling and a Metropolis-Hastings algorithm.

## Cox Model Formulation and Prediction

As was briefly mentioned in the landmarking section, the Cox landmarking formulation hazard can is

$$h(t \mid \tau, x, y(\tau)) = h_{0,\tau}(t) \exp\{x' \xi_{1,\tau} + \tilde{y}_i(t) \xi_{2,\tau}\}; \tau \leq t \leq t + s$$

Where  $h_{0,\tau}(t)$  is the landmark-specific baseline hazard function and  $\xi_\tau = (\xi_{1,\tau}, \xi_{2,\tau})'$  is the vector of coefficient estimates corresponding to that landmark time and the dependence of the baseline hazard on  $\tau$  is modeled by estimating a different baseline hazard for each  $\tau$ ,  $h_0(t \mid \tau) = h_{0,\tau}(t)$ .

Once the Cox model was fit, the required residual time distribution,  $\pi_m(\tau + s \mid \tau)$ , was calculated for each new individual :

$$\hat{\pi}_m^{LM}(t_{hor} \mid \tau) = \exp\left[-\int_\tau^{\tau+s} h_i(u \mid \tau, y(\tau), \mathbf{x}) du\right],$$

## Multivariate Joint Model Formulation and Prediction

The function *mvJointModelBayes* was used to fit a multivariate shared parameter joint model for the longitudinal and survival outcomes under a Bayesian approach in Scenario III. Both longitudinal markers were fit with a gaussian family in the *mvglmer* function. Predictions were obtained similarly to the joint model described above using average estimates from Monte Carlo simulations.

### 3 Additional Result Figures and Tables: Simulation

Table S1: AUC results from Simulation Scenario I

| Landmark Time | True Model | JM     | JM Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|------------|--------|----------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.9067     | 0.9008 | 0.8979   | 0.8908    | 0.8926      | 0.8886          | 0.89              | 0.8998 | 0.8953    |
| 1.5           | 0.9009     | 0.8975 | 0.8948   | 0.8858    | 0.8871      | 0.8799          | 0.8816            | 0.896  | 0.8904    |
| 2.5           | 0.8943     | 0.8923 | 0.8896   | 0.875     | 0.8792      | 0.8675          | 0.8708            | 0.89   | 0.8837    |
| 3.5           | 0.8881     | 0.8863 | 0.8835   | 0.8628    | 0.8693      | 0.8532          | 0.8564            | 0.8839 | 0.8752    |
| 4.5           | 0.8799     | 0.8783 | 0.8754   | 0.8488    | 0.8555      | 0.8324          | 0.8368            | 0.8754 | 0.8639    |

Table S2: BS results from Simulation Scenario I

| Landmark Time | True Model | JM     | JM Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|------------|--------|----------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.121      | 0.1245 | 0.1262   | 0.1456    | 0.1496      | 0.1454          | 0.1345            | 0.1256 | 0.1279    |
| 1.5           | 0.1241     | 0.1263 | 0.128    | 0.1543    | 0.1577      | 0.1476          | 0.1409            | 0.1278 | 0.1307    |
| 2.5           | 0.1273     | 0.1289 | 0.1304   | 0.1571    | 0.165       | 0.1488          | 0.1499            | 0.1309 | 0.1344    |
| 3.5           | 0.1299     | 0.1316 | 0.1332   | 0.1602    | 0.1694      | 0.1554          | 0.1594            | 0.134  | 0.139     |
| 4.5           | 0.1327     | 0.1344 | 0.136    | 0.1647    | 0.1737      | 0.1646          | 0.1693            | 0.1375 | 0.1444    |

Table S3: RMSE results from Simulation Scenario I

| Landmark Time | JM     | JM Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|--------|----------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.0583 | 0.0707   | 0.1529    | 0.1695      | 0.1516          | 0.116             | 0.0662 | 0.0812    |
| 1.5           | 0.0485 | 0.0625   | 0.1699    | 0.1838      | 0.1474          | 0.1294            | 0.0603 | 0.0802    |
| 2.5           | 0.0418 | 0.0571   | 0.1685    | 0.1946      | 0.144           | 0.1503            | 0.0589 | 0.0831    |
| 3.5           | 0.04   | 0.0557   | 0.1707    | 0.1995      | 0.1568          | 0.1715            | 0.0613 | 0.091     |
| 4.5           | 0.0406 | 0.0565   | 0.1769    | 0.2026      | 0.1757          | 0.1904            | 0.0672 | 0.1045    |

Table S4: AUC results from Simulation Scenario II

| Landmark Time | True Model | JM     | JM Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|------------|--------|----------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.9639     | 0.8407 | 0.8384   | 0.8335    | 0.8346      | 0.8232          | 0.8352            | 0.8398 | 0.8369    |
| 1             | 0.9638     | 0.8318 | 0.8296   | 0.8349    | 0.8416      | 0.8271          | 0.8385            | 0.8291 | 0.8256    |
| 1.5           | 0.9622     | 0.8039 | 0.8017   | 0.8338    | 0.8449      | 0.8266          | 0.8339            | 0.7992 | 0.7938    |
| 2             | 0.9593     | 0.7564 | 0.7541   | 0.8333    | 0.8445      | 0.8255          | 0.8226            | 0.7612 | 0.7506    |
| 2.5           | 0.9575     | 0.6979 | 0.6961   | 0.8373    | 0.8467      | 0.8274          | 0.8156            | 0.7358 | 0.7203    |

Table S5: BS results from Simulation Scenario II

| Landmark Time | True Model | JM     | JM Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|------------|--------|----------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.0651     | 0.1376 | 0.1388   | 0.142     | 0.134       | 0.1393          | 0.1353            | 0.136  | 0.1352    |
| 1             | 0.0643     | 0.1418 | 0.1429   | 0.1378    | 0.1289      | 0.1351          | 0.1327            | 0.1397 | 0.1374    |
| 1.5           | 0.0665     | 0.1594 | 0.1607   | 0.1403    | 0.1296      | 0.1373          | 0.1376            | 0.1552 | 0.1491    |
| 2             | 0.07       | 0.1881 | 0.1895   | 0.1427    | 0.1334      | 0.1408          | 0.1465            | 0.1706 | 0.1653    |
| 2.5           | 0.0724     | 0.2208 | 0.222    | 0.1427    | 0.1365      | 0.144           | 0.1534            | 0.1762 | 0.178     |

Table S6: RMSE results from Simulation Scenario II

| Landmark Time | JM     | JM Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|--------|----------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.2685 | 0.2707   | 0.277     | 0.2622      | 0.2647          | 0.2659            | 0.2653 | 0.2639    |
| 1             | 0.2777 | 0.2798   | 0.2712    | 0.2539      | 0.2612          | 0.2583            | 0.2743 | 0.27      |
| 1.5           | 0.304  | 0.306    | 0.2713    | 0.2507      | 0.266           | 0.2561            | 0.2968 | 0.2864    |
| 2             | 0.3422 | 0.3441   | 0.2681    | 0.2507      | 0.275           | 0.2567            | 0.3155 | 0.307     |
| 2.5           | 0.384  | 0.3855   | 0.2642    | 0.252       | 0.283           | 0.2576            | 0.3207 | 0.3236    |

Table S7: AUC results from Simulation Scenario III

| Landmark Time | True Model | MV JM  | MV JM Noise | JM naïve | JM naïve Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|------------|--------|-------------|----------|----------------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.9477     | 0.8571 | 0.8549      | 0.8507   | 0.8486         | 0.8555    | 0.8482      | 0.8468          | 0.8519            | 0.854  | 0.854     |
| 1.5           | 0.9471     | 0.8666 | 0.8647      | 0.853    | 0.8508         | 0.8811    | 0.8791      | 0.8714          | 0.8777            | 0.8552 | 0.8553    |
| 2.5           | 0.9425     | 0.8393 | 0.8374      | 0.8299   | 0.8276         | 0.8864    | 0.8873      | 0.8772          | 0.8822            | 0.8278 | 0.8287    |
| 3.5           | 0.9383     | 0.7929 | 0.7911      | 0.7881   | 0.7857         | 0.8809    | 0.8823      | 0.8722          | 0.874             | 0.7823 | 0.7855    |
| 4.5           | 0.9336     | 0.7457 | 0.7441      | 0.7442   | 0.7421         | 0.8732    | 0.875       | 0.8636          | 0.8636            | 0.7345 | 0.7417    |

Table S8: BS results from Simulation Scenario III

| Landmark Time | True Model | MV JM  | MV JM Noise | JM naïve | JM naïve Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |
|---------------|------------|--------|-------------|----------|----------------|-----------|-------------|-----------------|-------------------|--------|-----------|
| 0.5           | 0.0897     | 0.1572 | 0.1588      | 0.162    | 0.1636         | 0.1673    | 0.1597      | 0.162           | 0.1593            | 0.1577 | 0.1569    |
| 1.5           | 0.0908     | 0.1505 | 0.152       | 0.1595   | 0.1611         | 0.1568    | 0.1421      | 0.1476          | 0.147             | 0.1562 | 0.1555    |
| 2.5           | 0.0953     | 0.1666 | 0.1682      | 0.1715   | 0.1733         | 0.1517    | 0.1376      | 0.1438          | 0.1472            | 0.171  | 0.1701    |
| 3.5           | 0.0989     | 0.1934 | 0.195       | 0.1938   | 0.1957         | 0.1543    | 0.1418      | 0.1483          | 0.1554            | 0.1941 | 0.1927    |
| 4.5           | 0.1028     | 0.2191 | 0.2209      | 0.2157   | 0.2177         | 0.1562    | 0.1476      | 0.154           | 0.1644            | 0.214  | 0.213     |

Table S9: RMSE results from Simulation Scenario III

| Landmark Time | MV JM  | MV JM Noise | JM naïve | JM naïve Noise | RSF tuned | RSF default | RSF noise tuned | RSF noise default | Cox    | Cox Noise |        |
|---------------|--------|-------------|----------|----------------|-----------|-------------|-----------------|-------------------|--------|-----------|--------|
| 0.5           | 0.258  | 0.2609      | 0.2674   | 0.2703         | 0.2769    | 0.2625      | 0.2668          | 0.262             | 0.2589 | 0.2632    | 0.1569 |
| 1.5           | 0.2429 | 0.2459      | 0.2601   | 0.2634         | 0.255     | 0.2252      | 0.2369          | 0.2356            | 0.2537 | 0.2586    | 0.1555 |
| 2.5           | 0.2675 | 0.2704      | 0.2762   | 0.2795         | 0.2369    | 0.2057      | 0.2209          | 0.2279            | 0.2752 | 0.2814    | 0.1701 |
| 3.5           | 0.3058 | 0.3086      | 0.3068   | 0.3098         | 0.2313    | 0.2042      | 0.2197          | 0.2354            | 0.3074 | 0.3164    | 0.1927 |
| 4.5           | 0.3407 | 0.3433      | 0.3357   | 0.3384         | 0.2292    | 0.2118      | 0.2258          | 0.2479            | 0.3337 | 0.3477    | 0.213  |

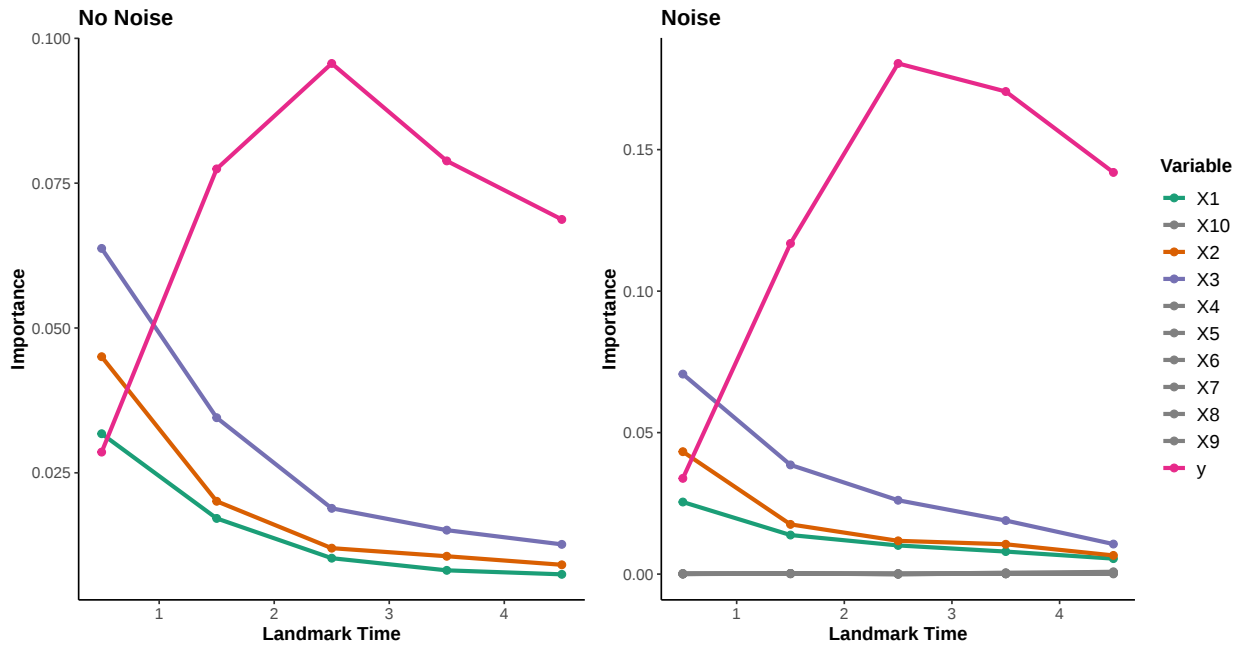


Figure S1: Simulation estimates for VIMP from Scenario II assessed at landmark times comparing importance of main effects when noise variables are included.  $X1 - X3$  are baseline variables included in data generation,  $X4 - X10$  are noise variables, and  $Y$  is the longitudinal variable

## 4 Additional Result Figures and Tables: Heart Valve Application

Table S10: Description of models fit to the heart valve data set. All models include the same base set of variables. Joint model includes the longitudinal LVMI marker. RSF and Cox models include longitudinal LVMI and EF markers, with imputation from last-observation carried forward (LOCF) or from a linear mixed effects model (LMM) with a random intercept and slope.

| Model                   | Description                                                 | Imputation |
|-------------------------|-------------------------------------------------------------|------------|
| JM                      | Joint model                                                 | -          |
| Cox LMM                 | Cox landmark model                                          | LMM        |
| Cox LOCF                | Cox landmark model                                          | LOCF       |
| RSF LMM                 | RSF with default parameters                                 | LMM        |
| RSF LOCF                | RSF with tuned parameters                                   | LOCF       |
| Tuned RSF LMM           | RSE with tuned parameters                                   | LMM        |
| Tuned RSF LOCF          | RSE with tuned parameters                                   | LOCF       |
| Full RSF LMM            | RSF with default parameters and all baseline covariates     | LMM        |
| Full RSF LOCF           | RSF with default parameters and all baseline covariates     | LOCF       |
| Full Tuned RSF LMM      | RSF with default parameters and all baseline covariates     | LMM        |
| Full Tuned RSF LOCF     | RSF with default parameters and all baseline covariates     | LOCF       |
| RSF No Admin LOCF       | RSF with default parameters and no administrative censoring | LOCF       |
| RSF Tuned No Admin LOCF | RSF with tuned parameters and no administrative censoring   | LOCF       |

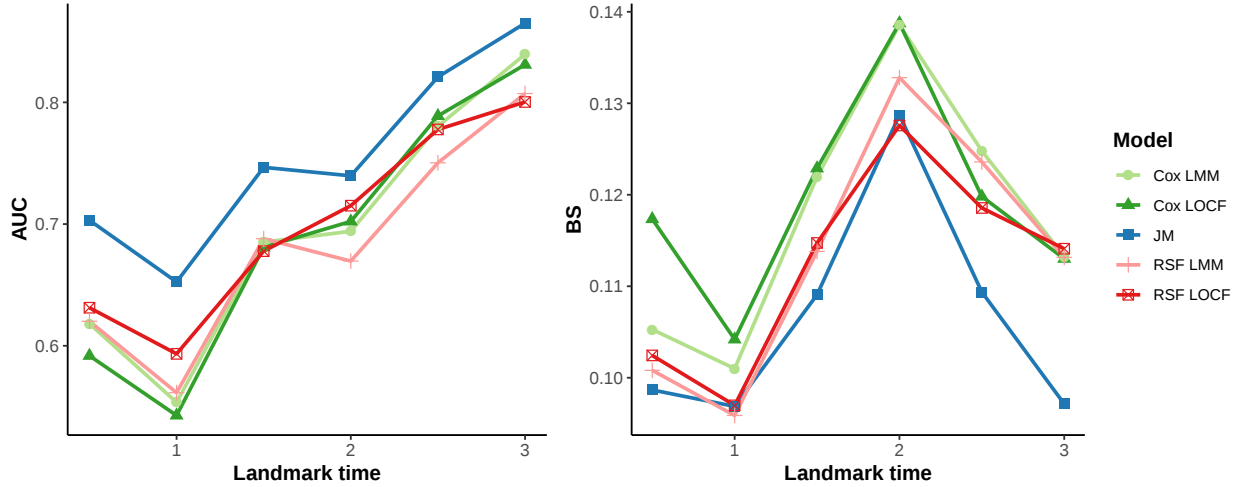


Figure S2: Heart valve application comparison of RSF Landmarking (RSF LMM, RSF LOCF) with joint model (JM) and Cox landmarking (Cox LMM, Cox LOCF). AUC shown in left panel, and BS in right panel.

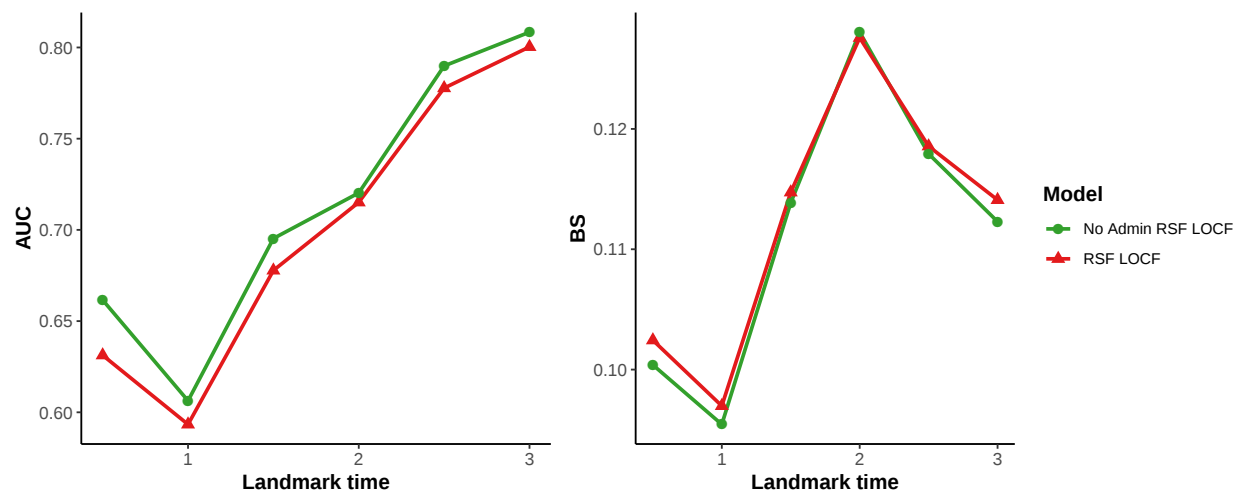


Figure S3: Heart valve application comparison of RSF models using last-observation-carried-forward imputation with (RSF LOCF) and without administrative censoring (No Admin RSF LOCF). AUC shown in left panel, and Brier score (BS) in right panel.

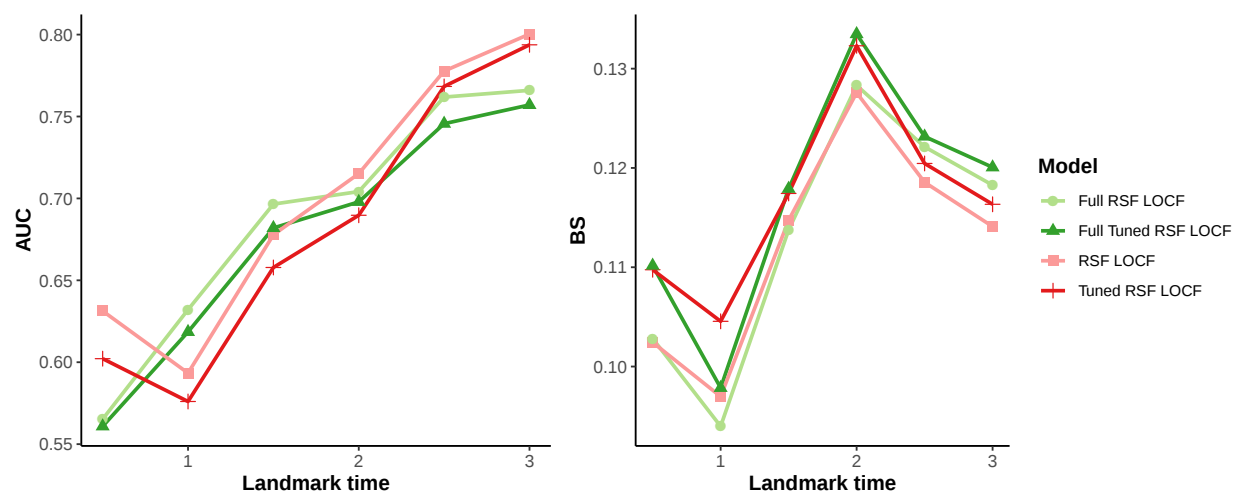


Figure S4: Heart valve application comparison of RSF models with the clinically relevant subset of covariates (“RSF”) to the full RSF with all available variables (“Full RSF”). These results are presented both with tuning of parameters (“Tuned”) and without.