Simulation Results

March 3, 2020

1 Simulating data

Further details are in Section 4.2 of the main document.

Scenario 1	Weibull
Scenario 2	Weibull
Scenario 3	Mixture Weibull
Scenario 4	Cure with Weibull for uncured.

- For each scenario we simulate frailty. F1 (Low heterogeneity): Normal(0,0.5). F2 (High heterogeneity): Normal(0,2)
- Censoring distribution: Exp(0.1)

1.1 General Points

- Any simulation study is limited to the scenarios it investigates. We have selected 16 different data generating mechanisms and simulated both disease-specific and other cause mortality and incorporated unobserved heterogeneity. We have specifically targeted these data generating mechanisms to cover a broad range of biologically plausible scenarios.
- It would be possible to simulate from alternative distributions and where different models could come out favorably.
- We provide the simulation code and so others can repeat and adapt our simulations.

2 Demonstration of the problem

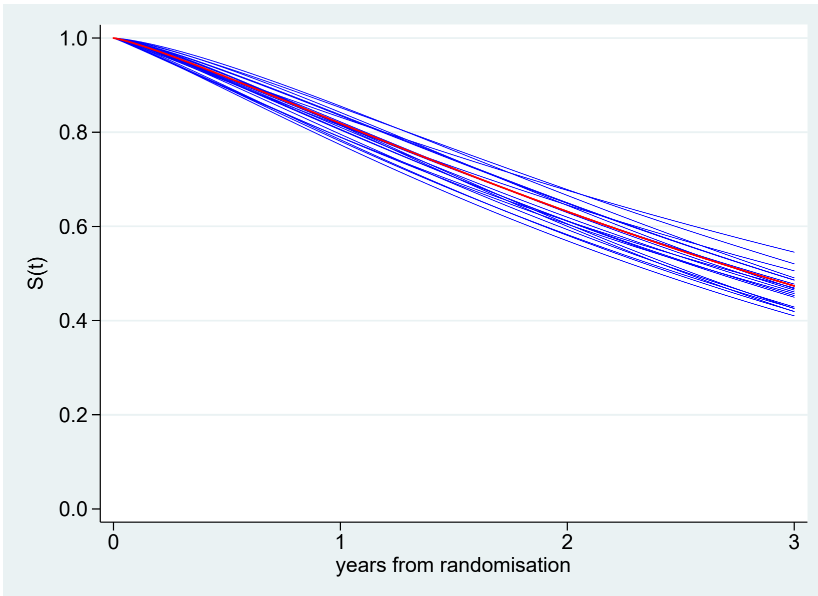

Figure 1: Fitting true model with sample size of 100: Fitted values are shown to range of follow-up

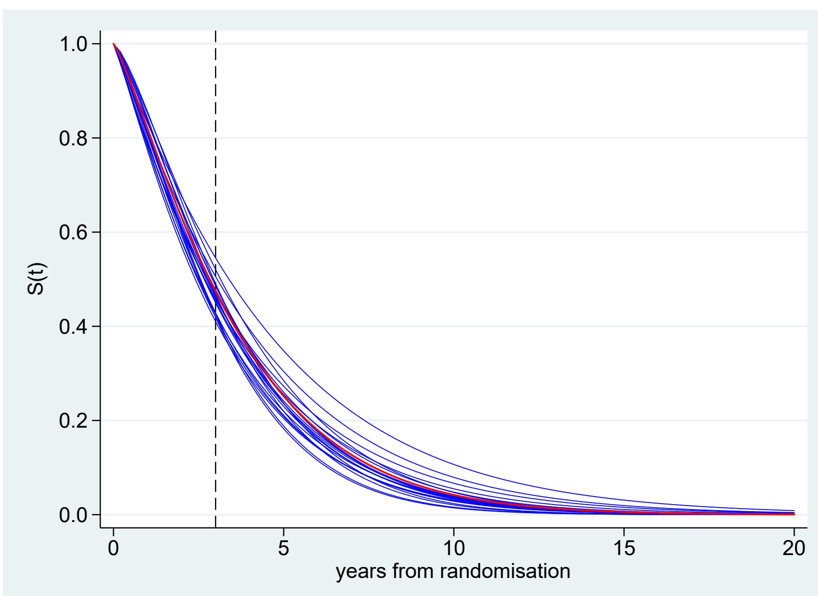

Figure 2: Fitting true model with sample size of 100: Fitted values are shown extrapolated to 20 years

3 Standard survival models

3.1 RMST

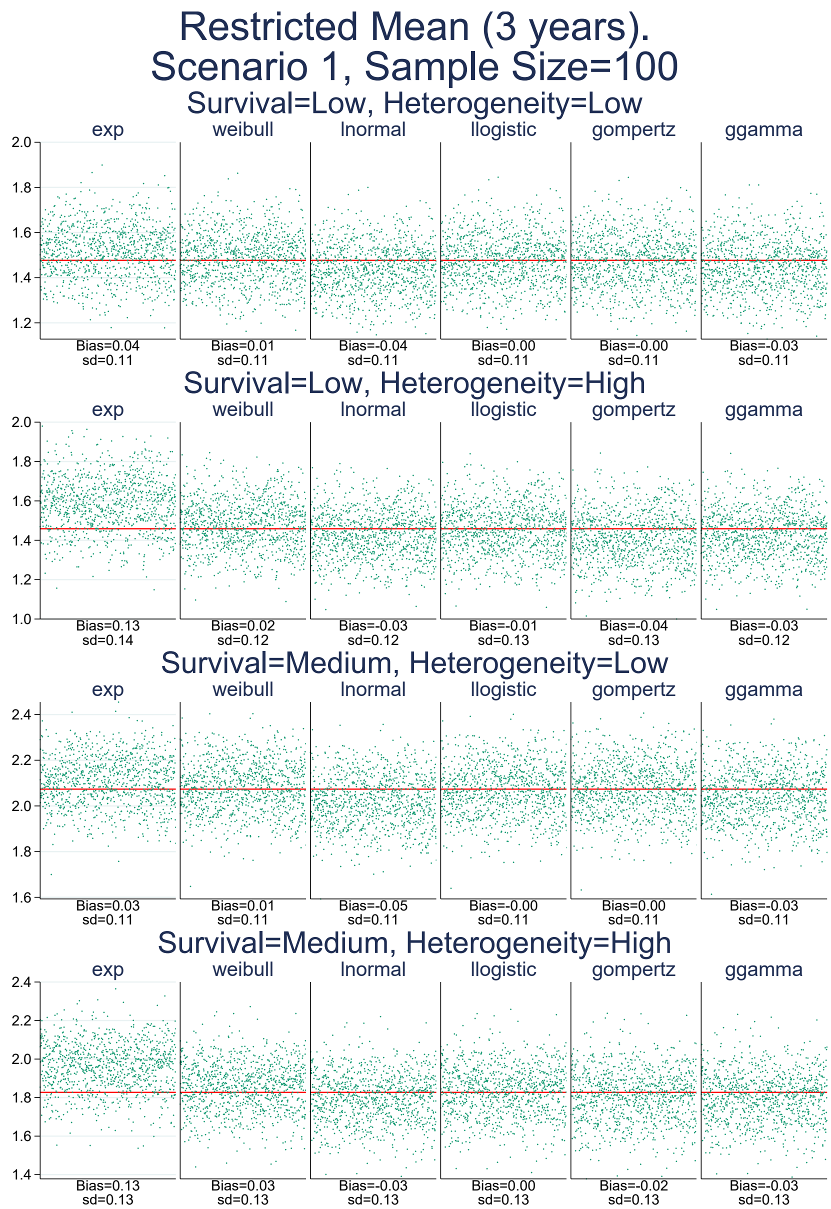

Figure 3: Standard models: Scenario 1 (SS=100), RMST

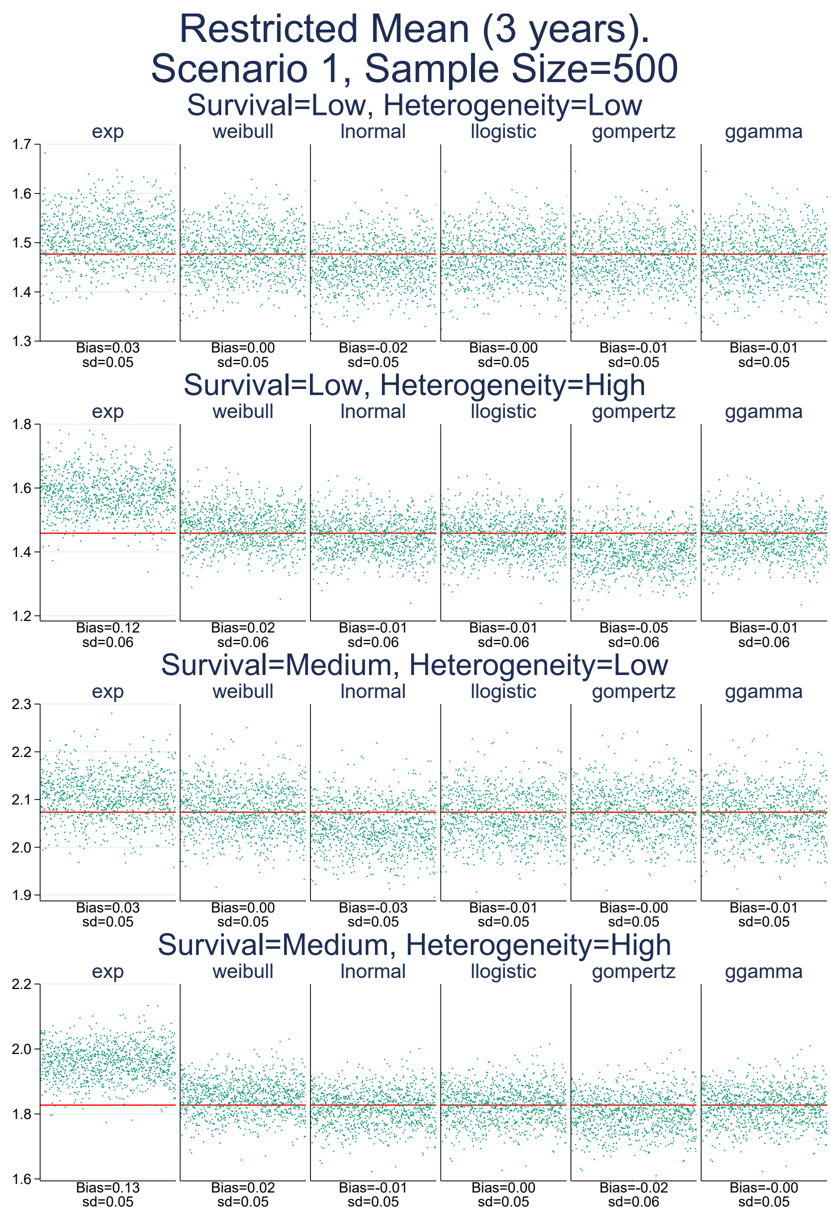

Figure 4: Standard models: Scenario 1 (SS=500), RMST

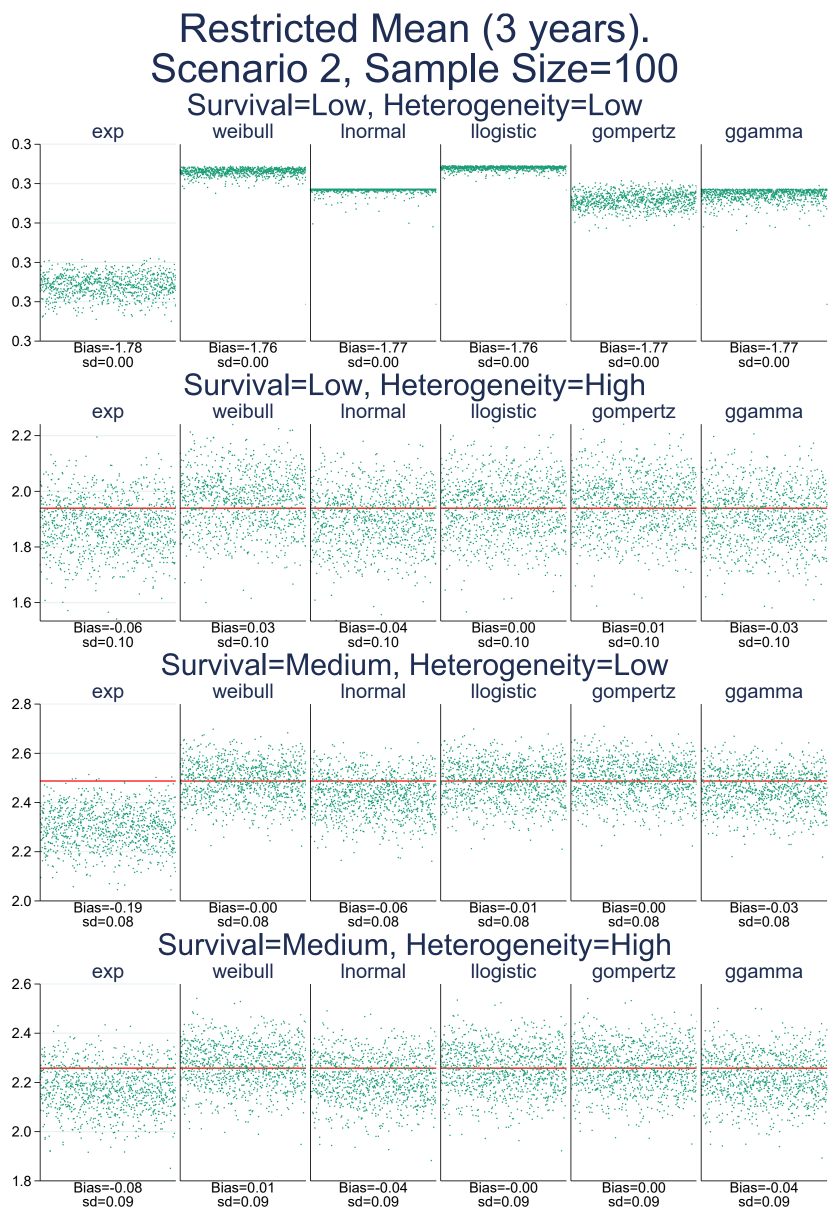

Figure 5: Standard models: Scenario 2 (SS=100), RMST

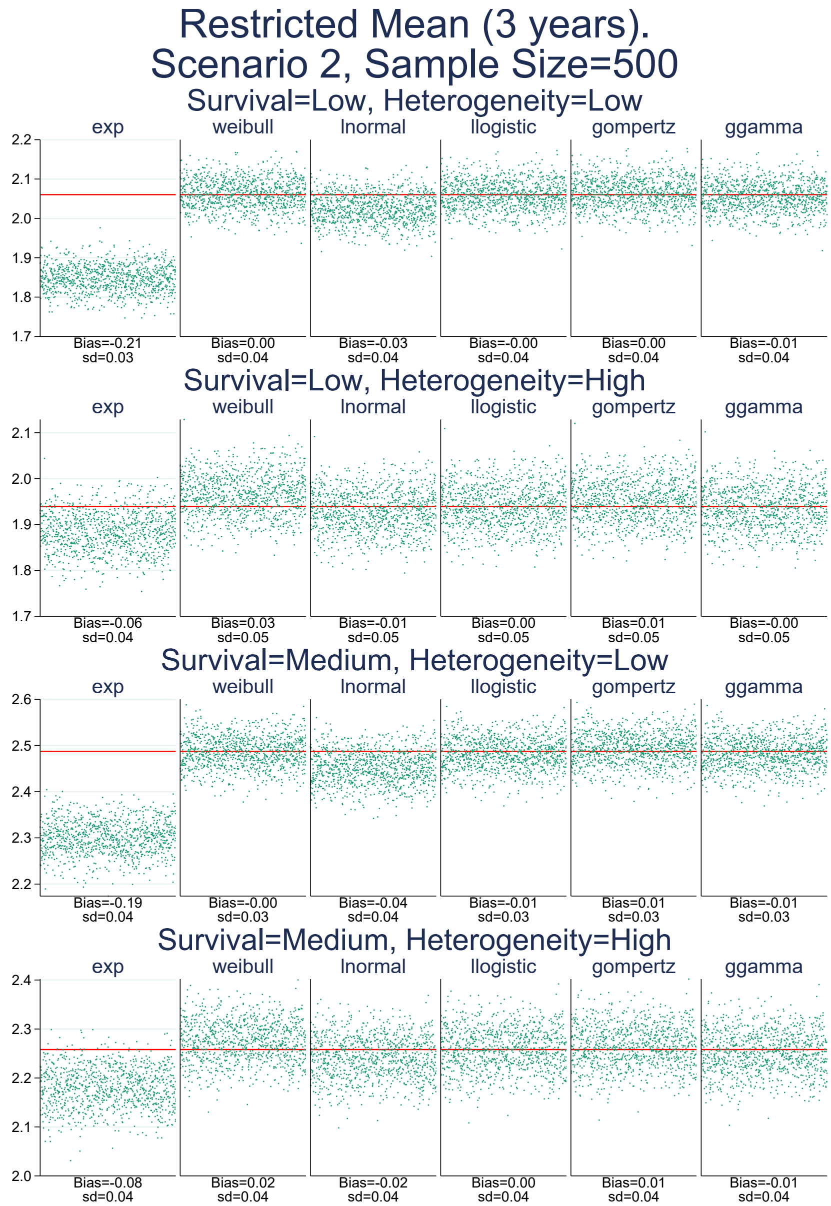

Figure 6: Standard models: Scenario 2 (SS=500), RMST

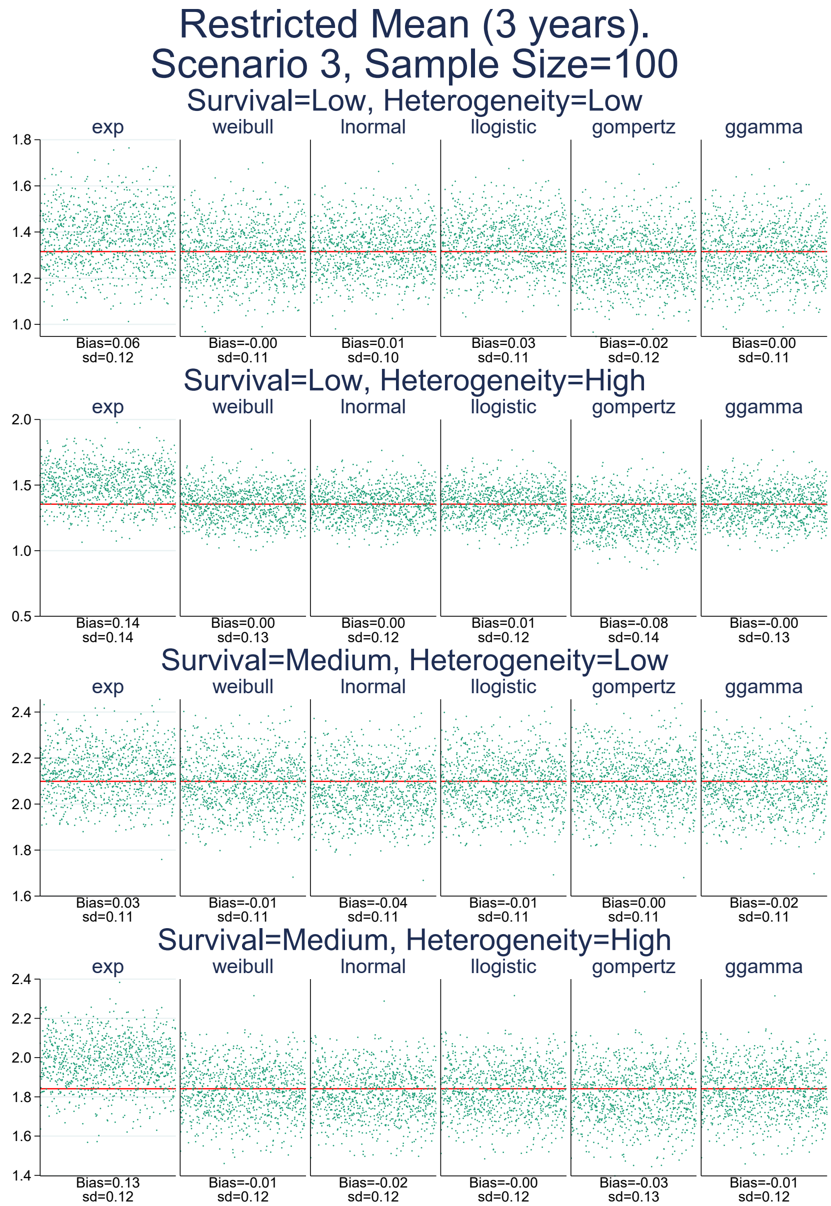

Figure 7: Standard models: Scenario 3 (SS=100), RMST

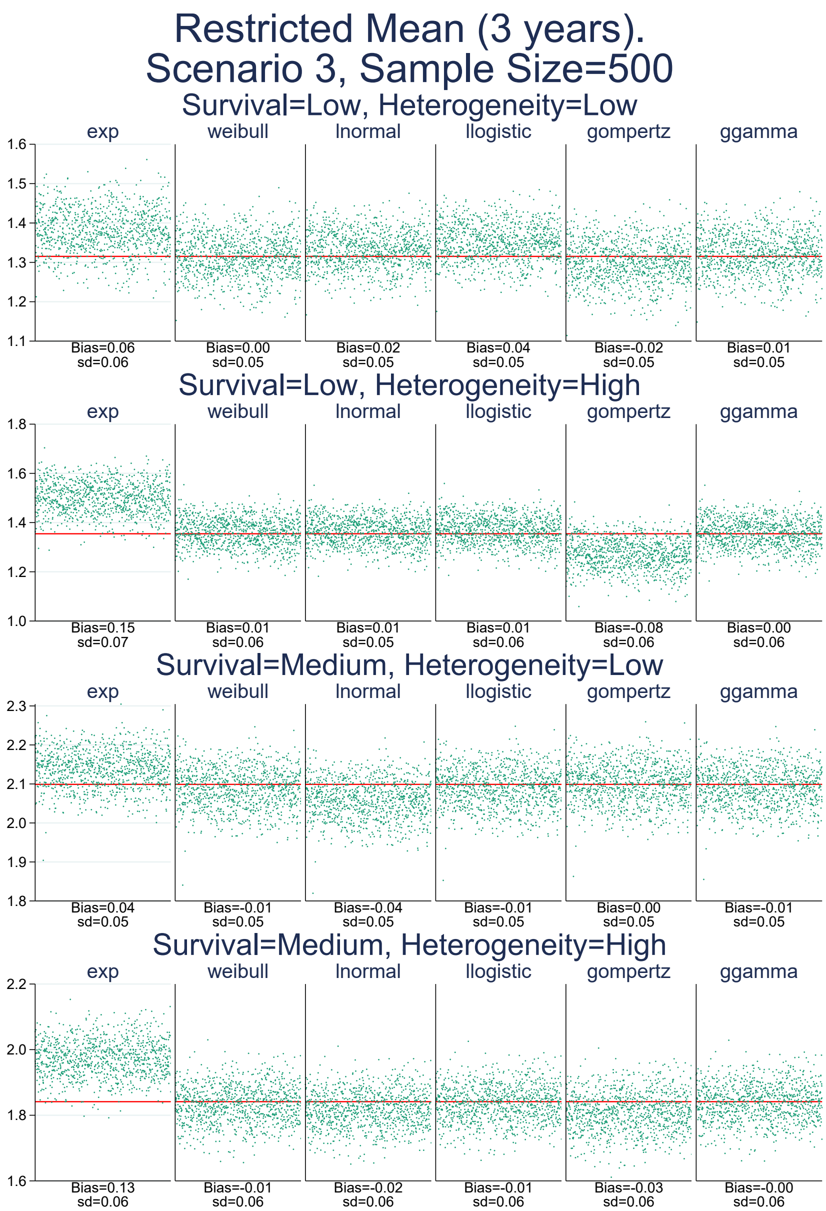

Figure 8: Standard models: Scenario 3 (SS=500), RMST

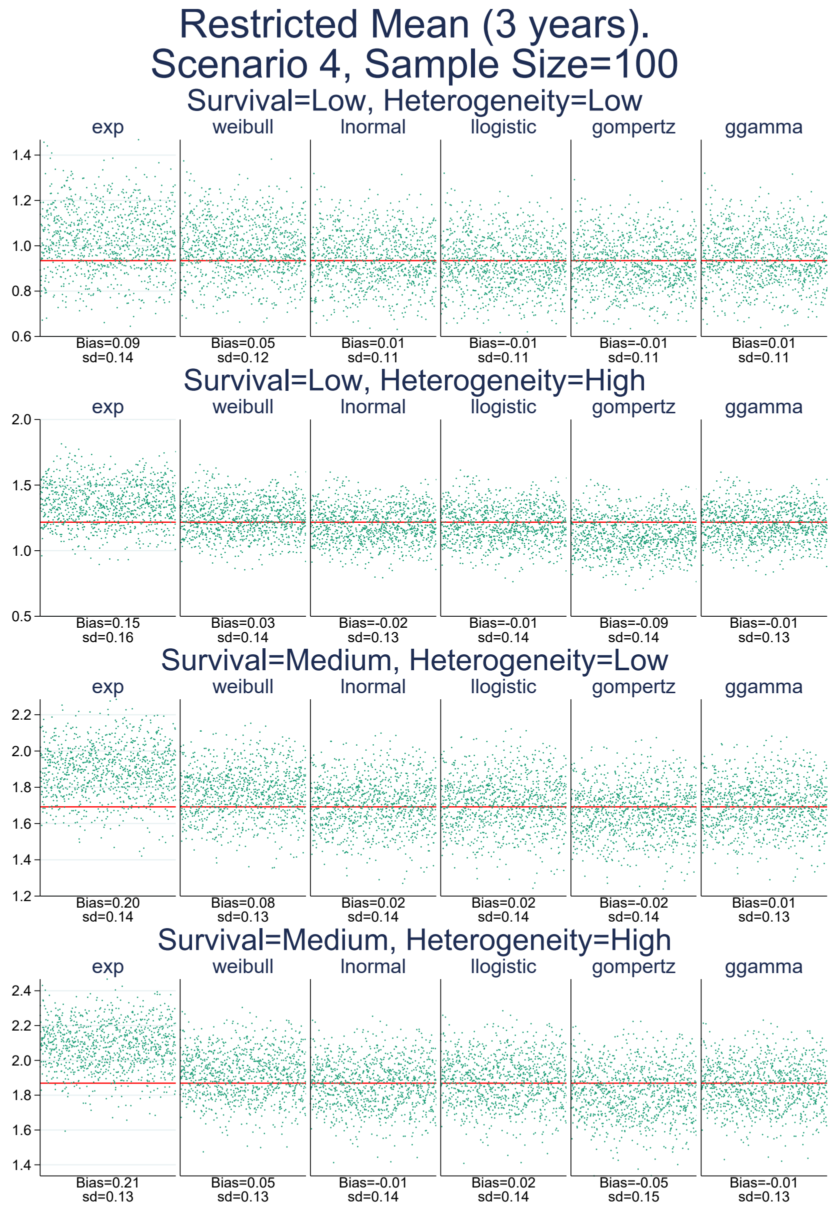

Figure 9: Standard models: Scenario 4 (SS=100), RMST

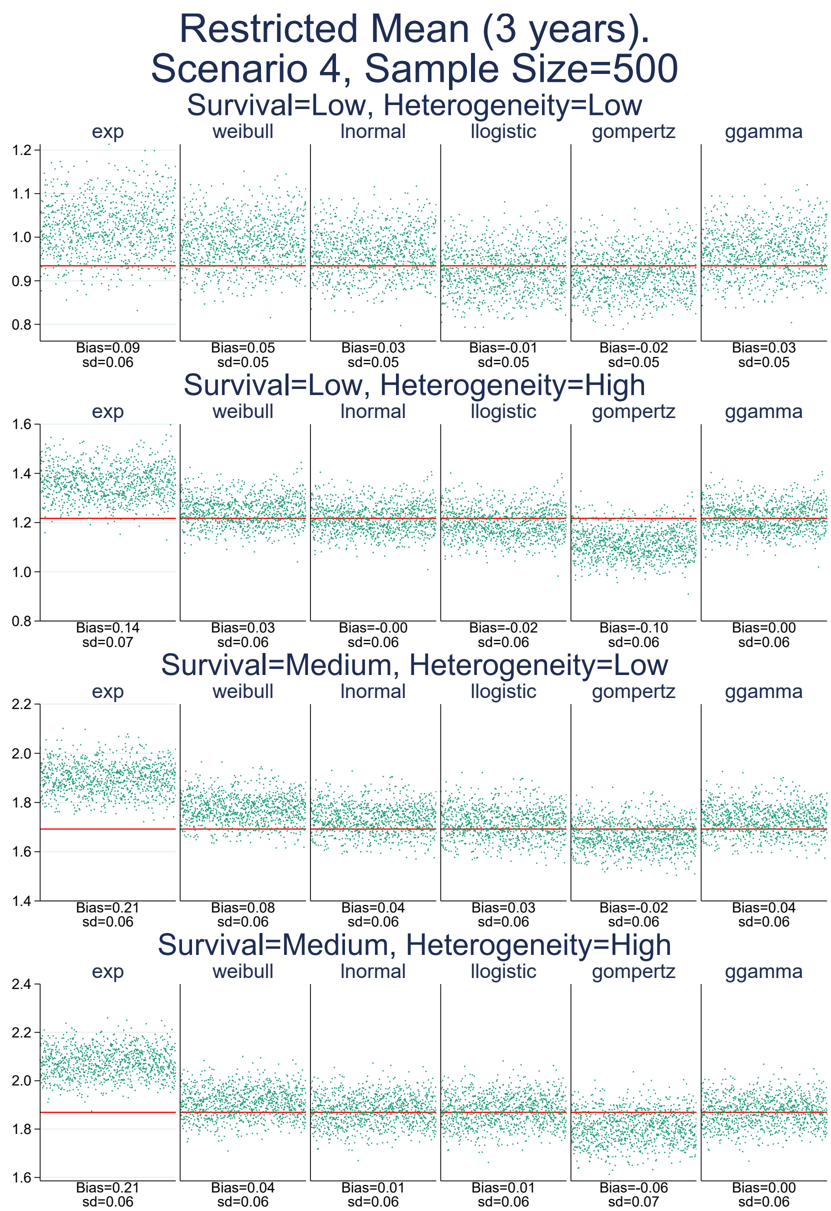

Figure 10: Standard models: Scenario 4 (SS=500), RMST

3.2 Mean survival

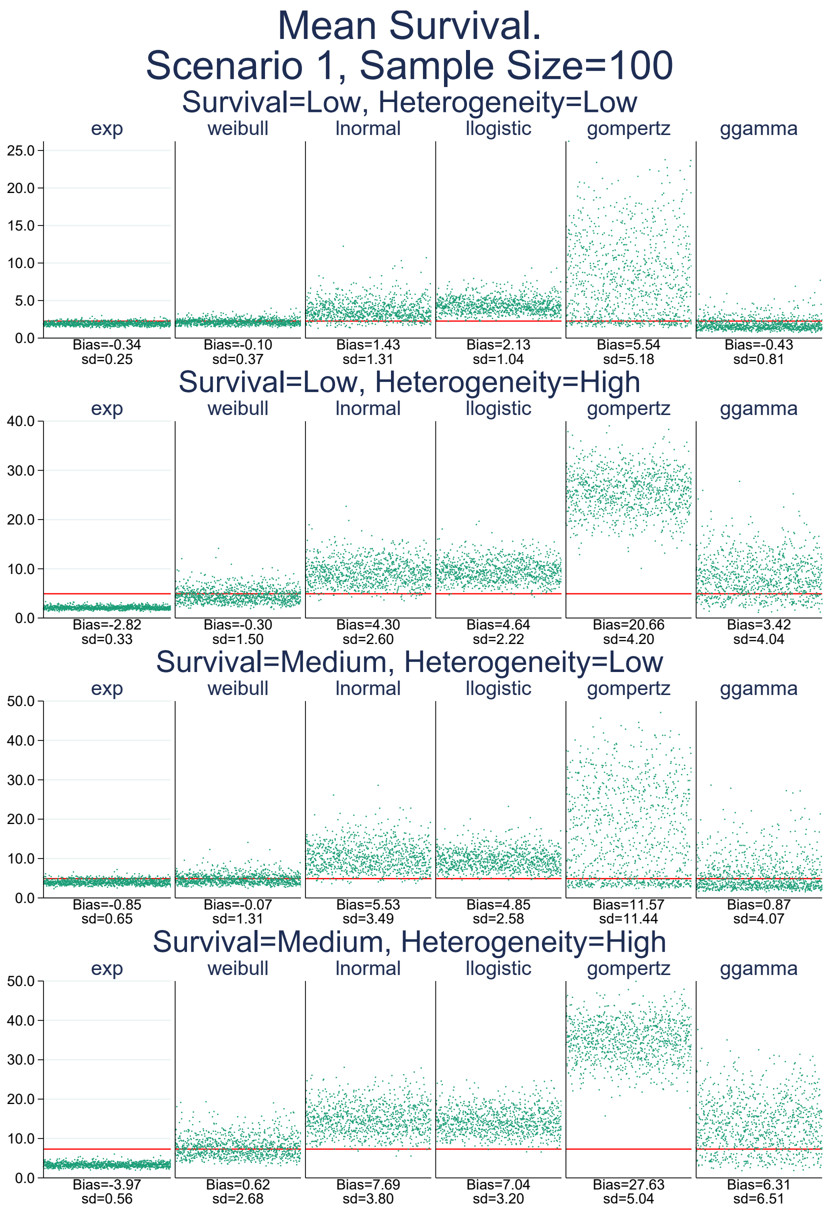

Figure 11: Standard models: Scenario 1 (SS=100), Mean survival

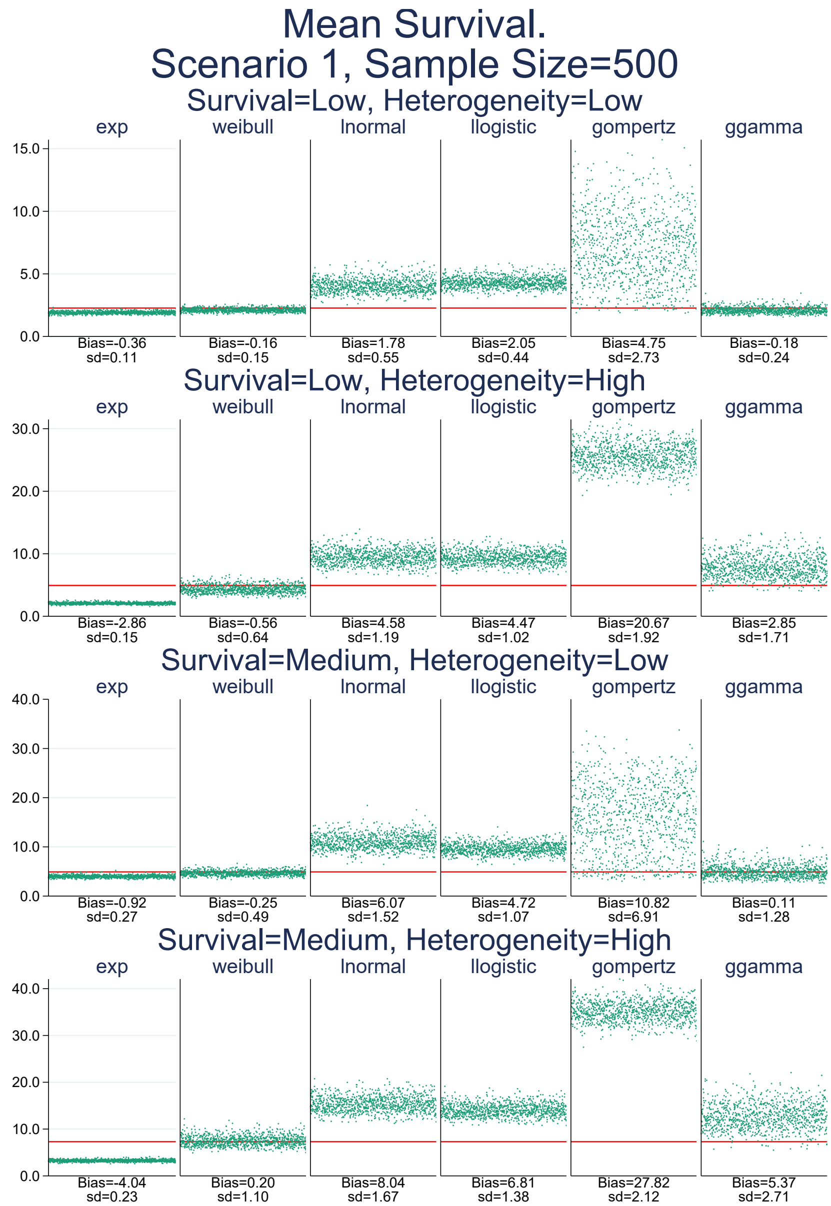

Figure 12: Standard models: Scenario 1 (SS=500), Mean survival

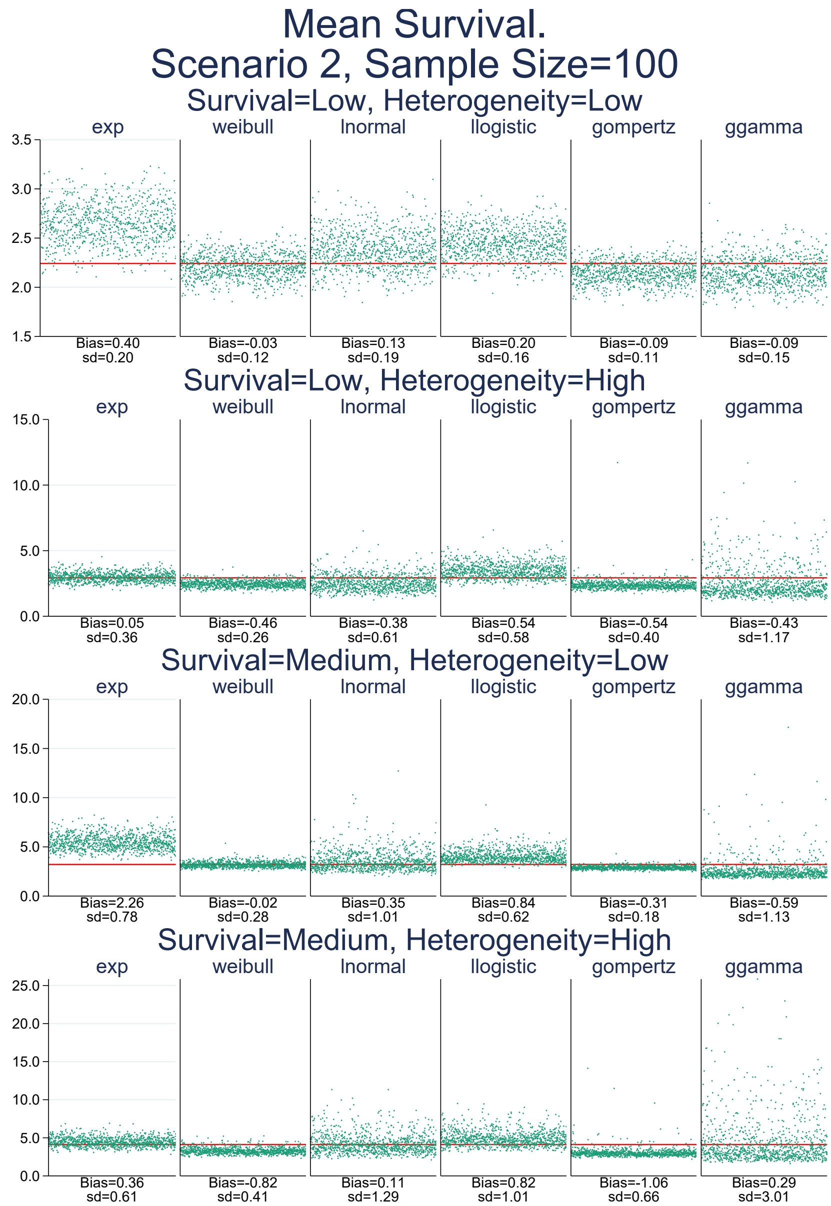

Figure 13: Standard models: Scenario 2 (SS=100), Mean survival

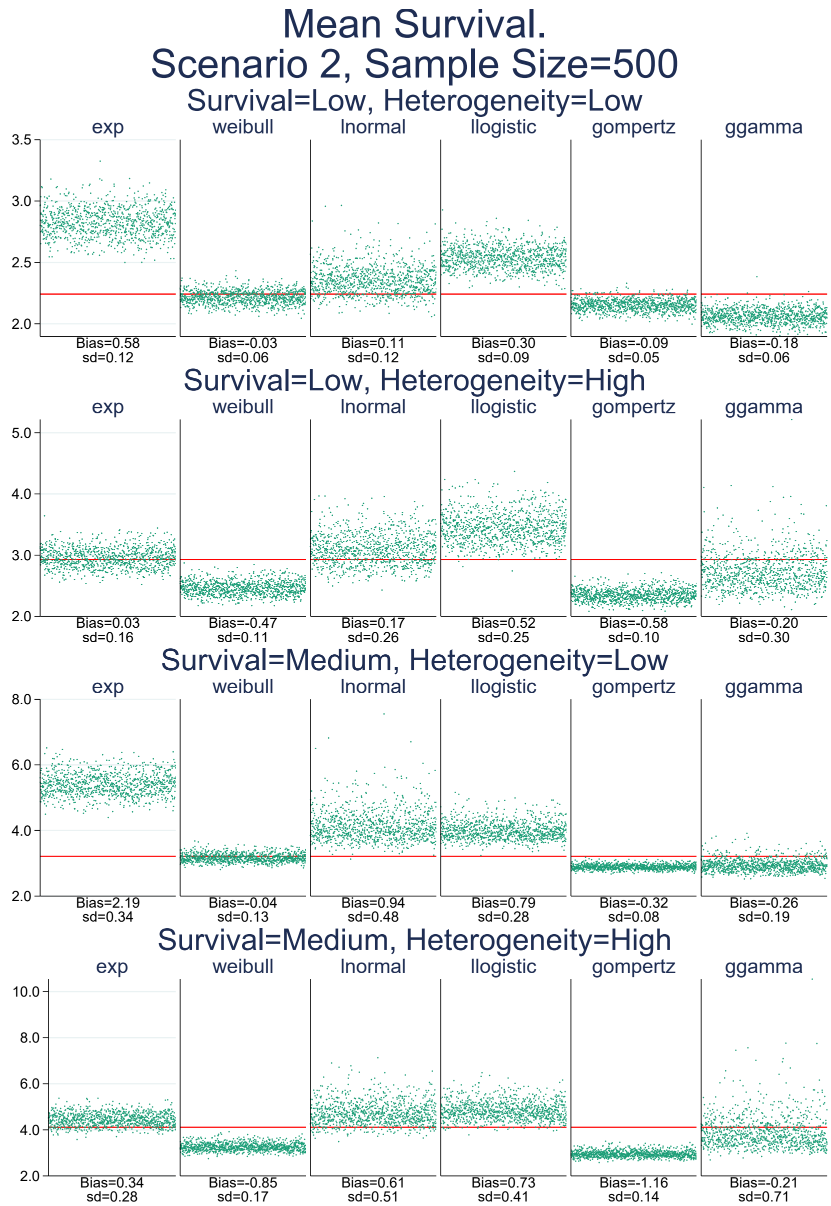

Figure 14: Standard models: Scenario 2 (SS=500), Mean survival

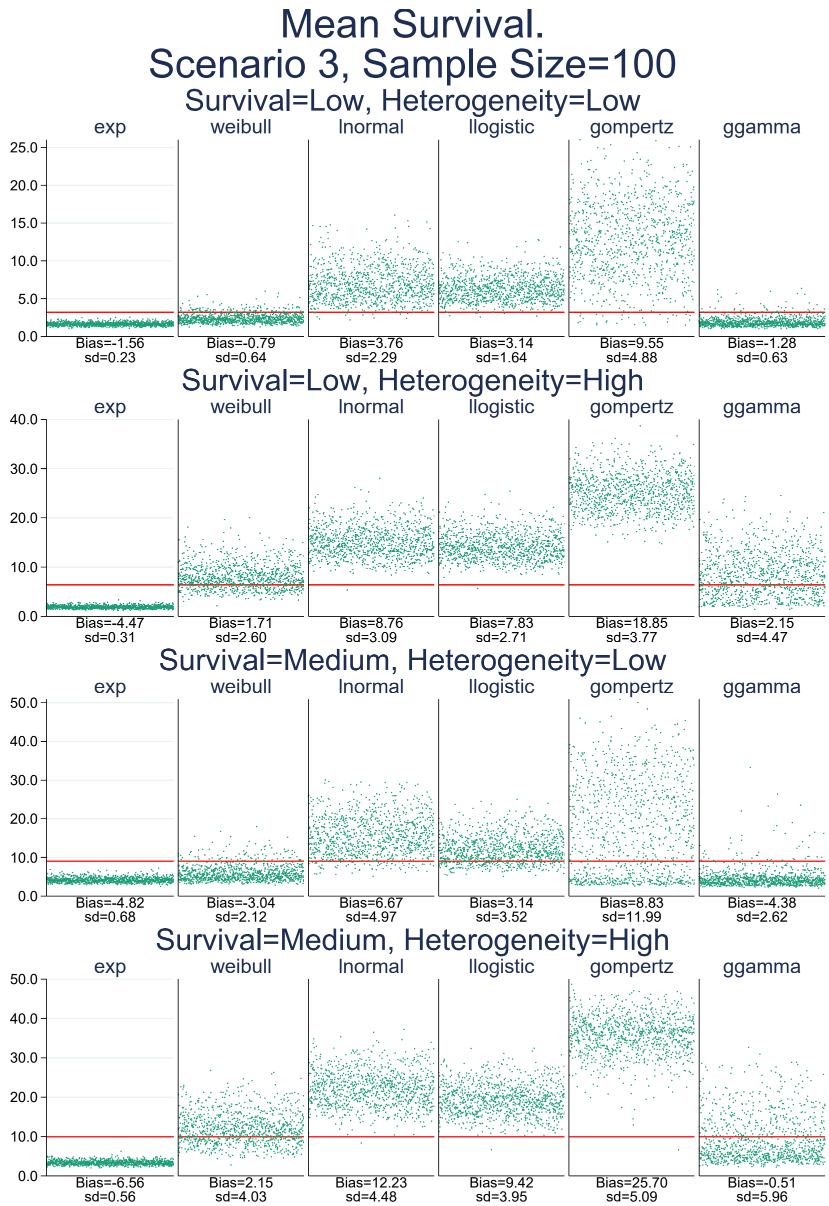

Figure 15: Standard models: Scenario 3 (SS=100), Mean survival

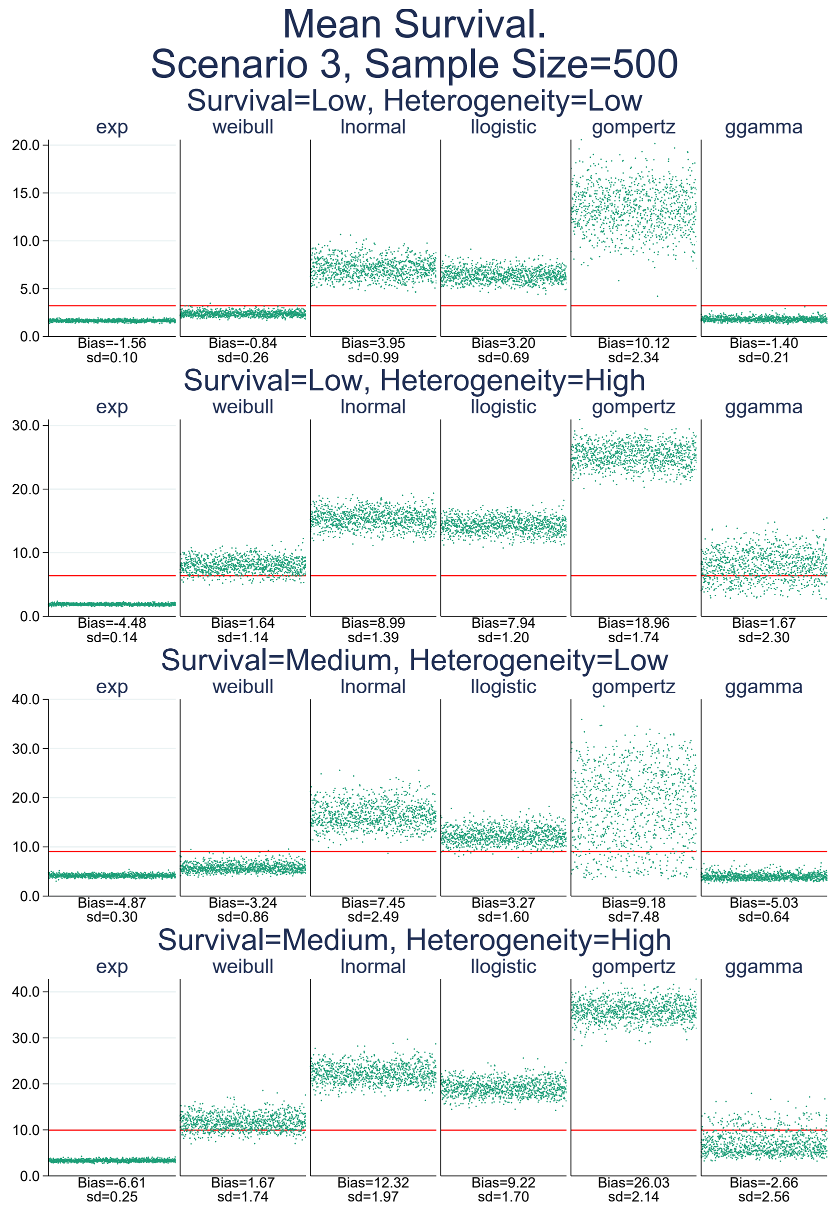

Figure 16: Standard models: Scenario 3 (SS=500), Mean survival

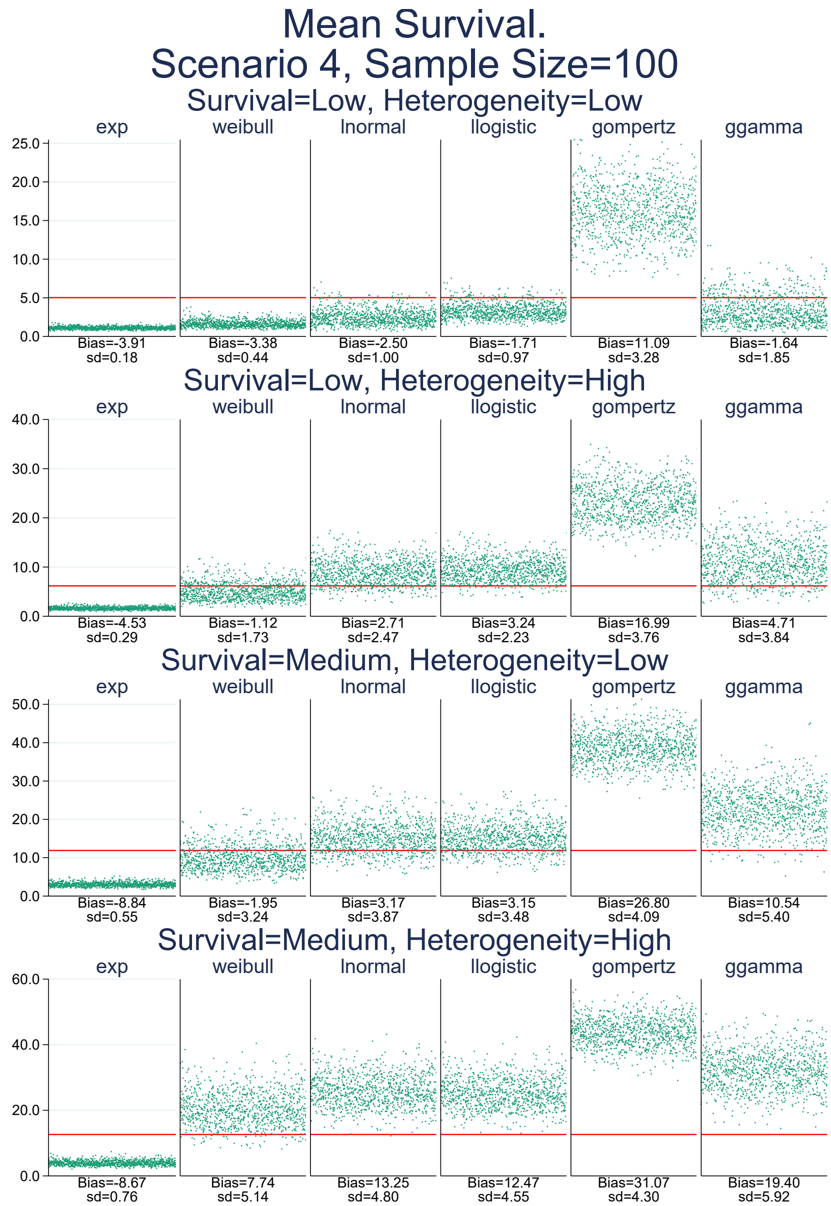

Figure 17: Standard models: Scenario 4 (SS=100), Mean survival

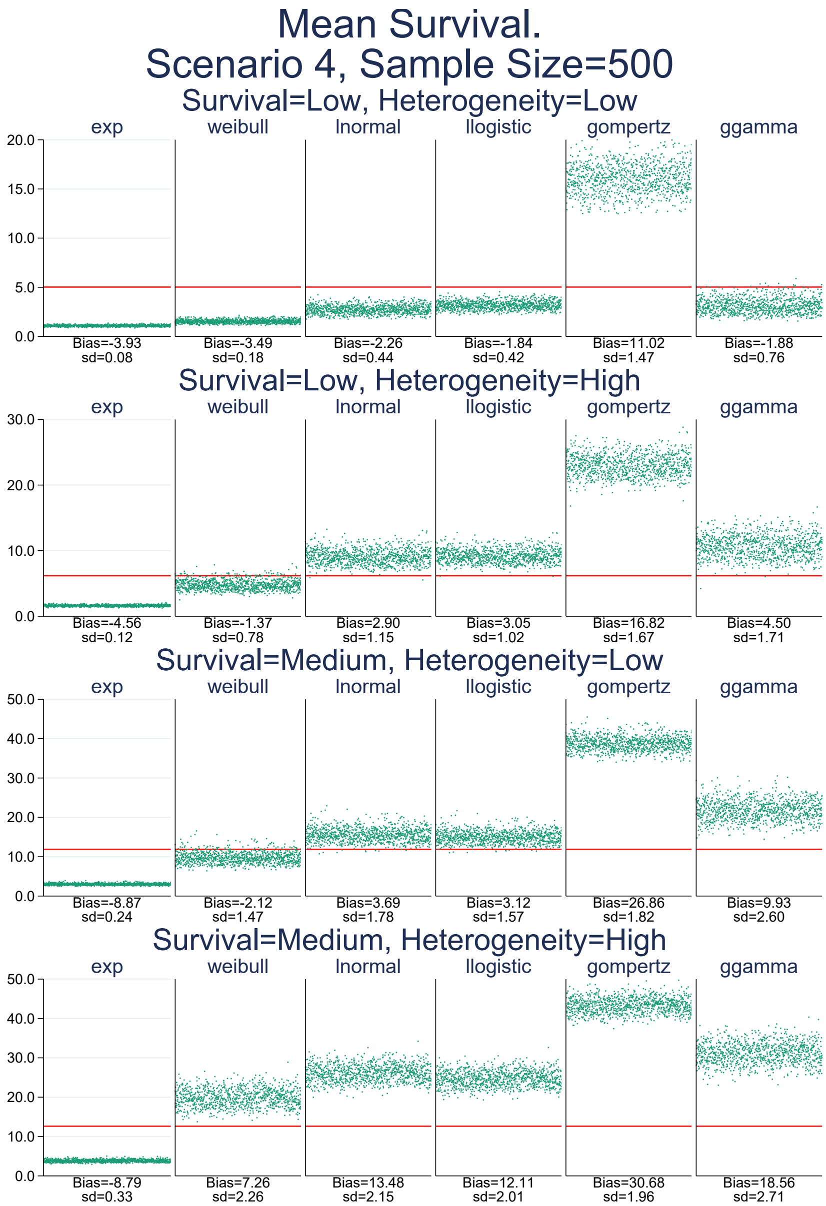

Figure 18: Standard models: Scenario 4 (SS=500), Mean survival

3.3 Summary of Simulations

Restricted mean survival time

- When looking at RMST at three years there is low bias for most scenarios except, unsurprisingly, when using the exponential distribution.
- For some scenarios the Gompertz distribution does not do well for RMST.
- For RMST the effect of frailty does not seem that important.
- In summary, poor fitting models only have small bias for RMST.

Mean survival time

- As expected, the big problems come when extrapolating.
- The effect of frailty is important, but not easy to predict direction of increased or decreased bias with more/less frailty.
- The Gompertz model does particularly badly for some scenarios.
- Although we simulated from a Weibull the mean survival is biased when fitting a Weibull model because of the effect of unobserved heterogeneity and other cause mortality.
- None of the standard models are the correct model because we have unobserved heterogeneity.
- *Could show the AIC/BIC does not help in choosing the best model.*

4 Flexible Parametric Survival Models

4.1 RMST

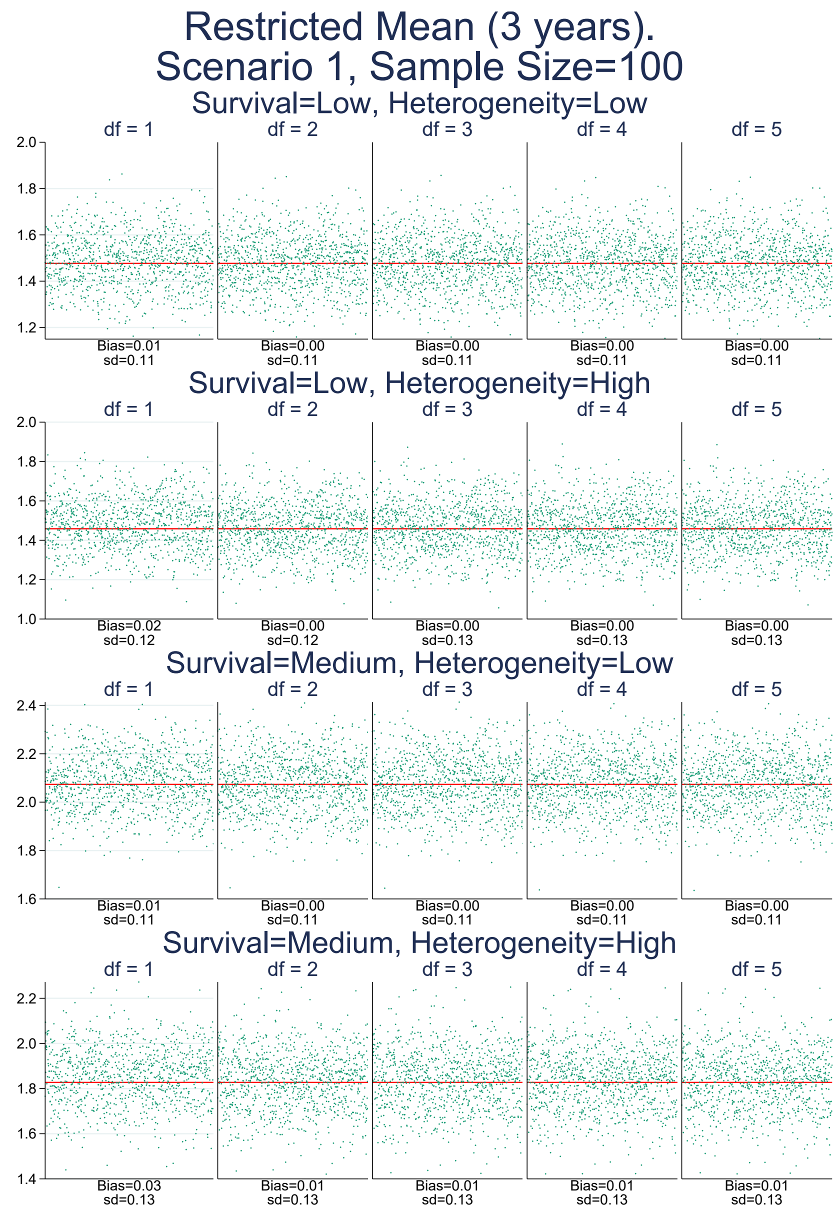

Figure 19: Flexible parametric models: Scenario 1 (SS=100), RMST

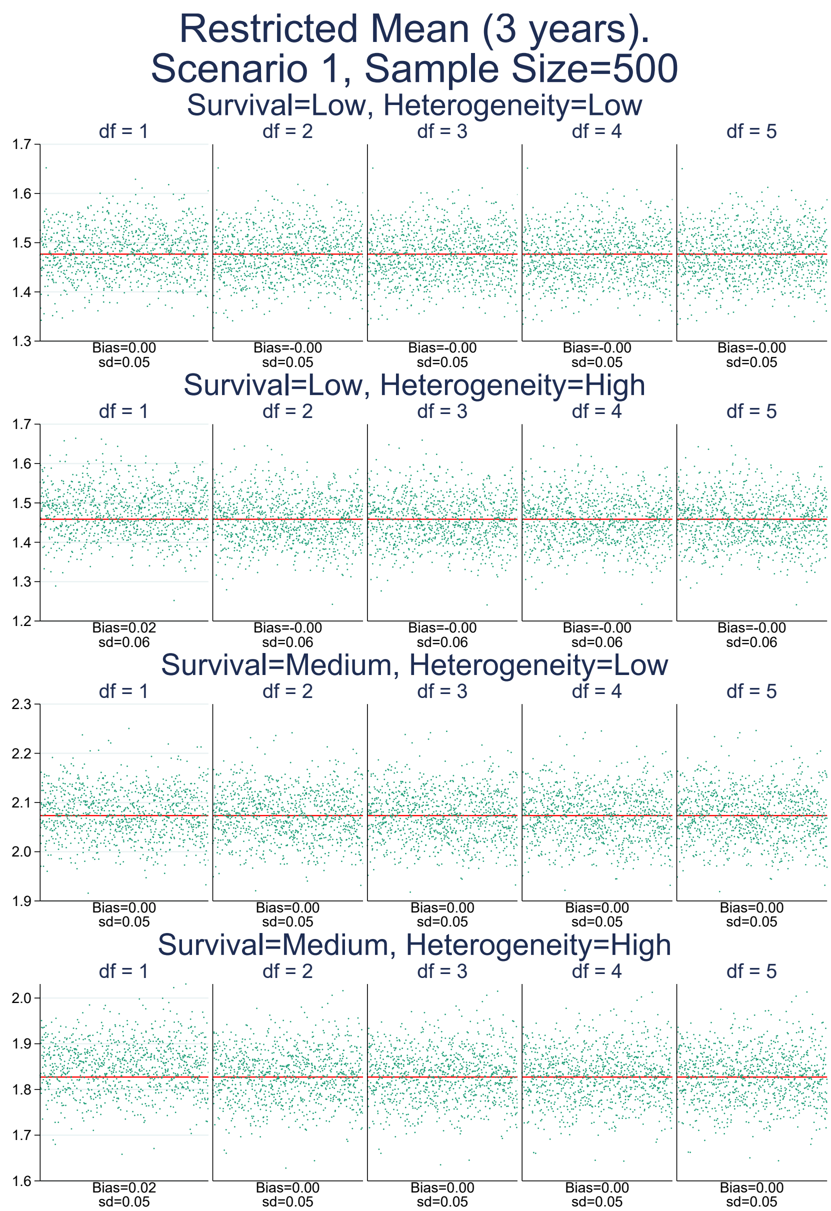

Figure 20: Flexible parametric models: Scenario 1 (SS=500), RMST

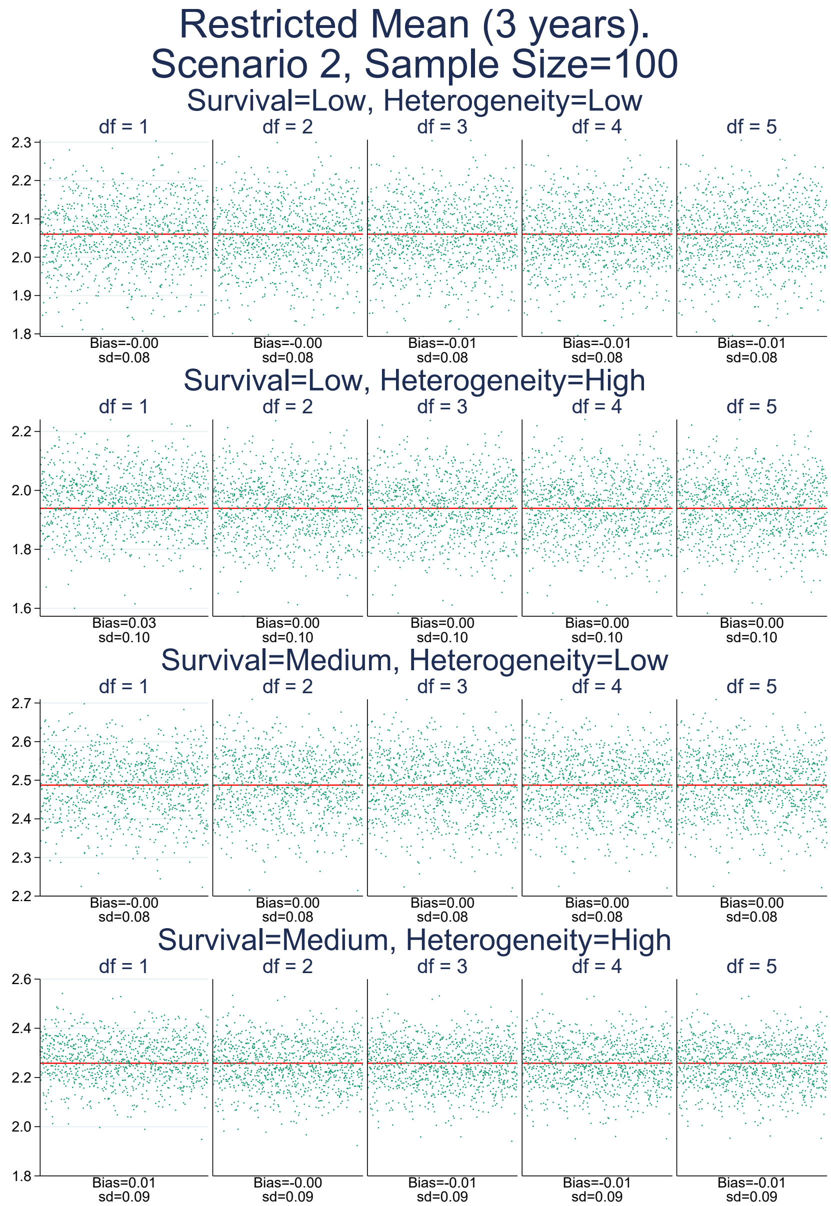

Figure 21: Flexible parametric models: Scenario 2 (SS=100), RMST

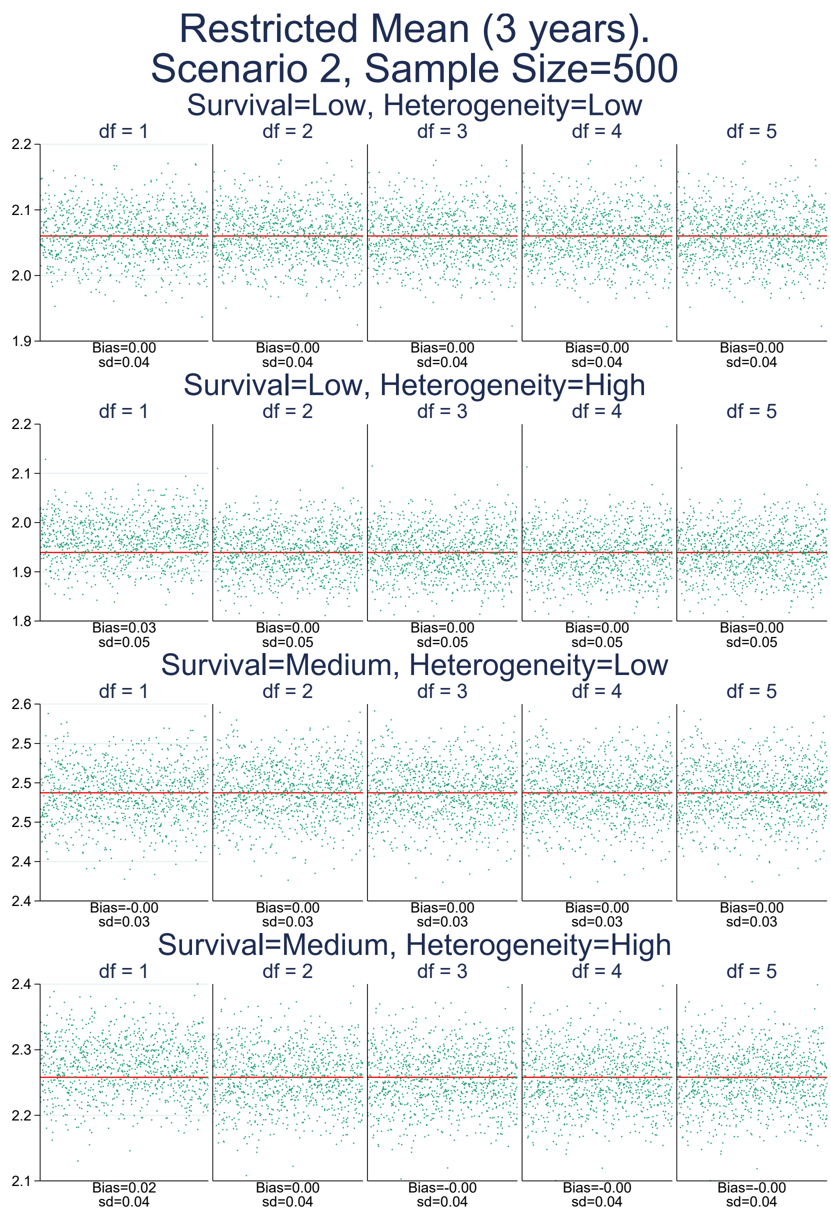

Figure 22: Flexible parametric models: Scenario 2 (SS=500), RMST

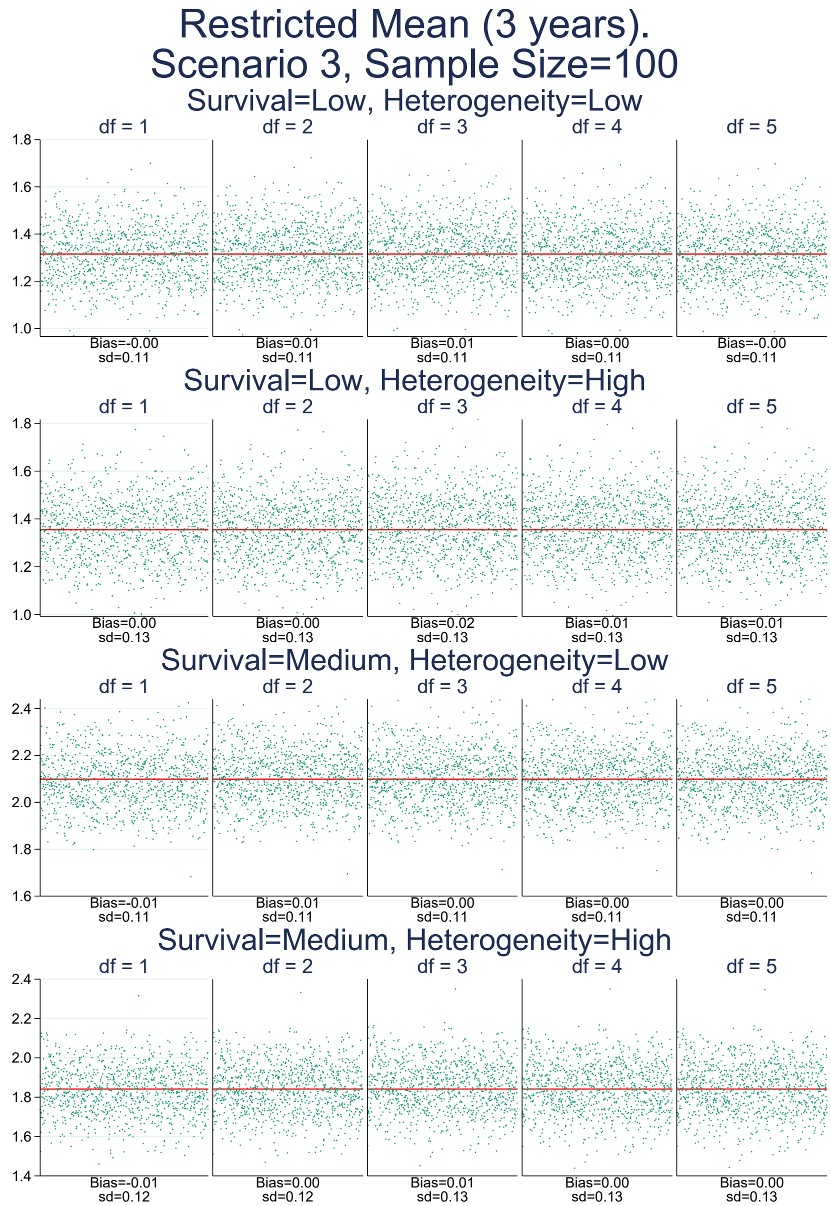

Figure 23: Flexible parametric models: Scenario 3 (SS=100), RMST

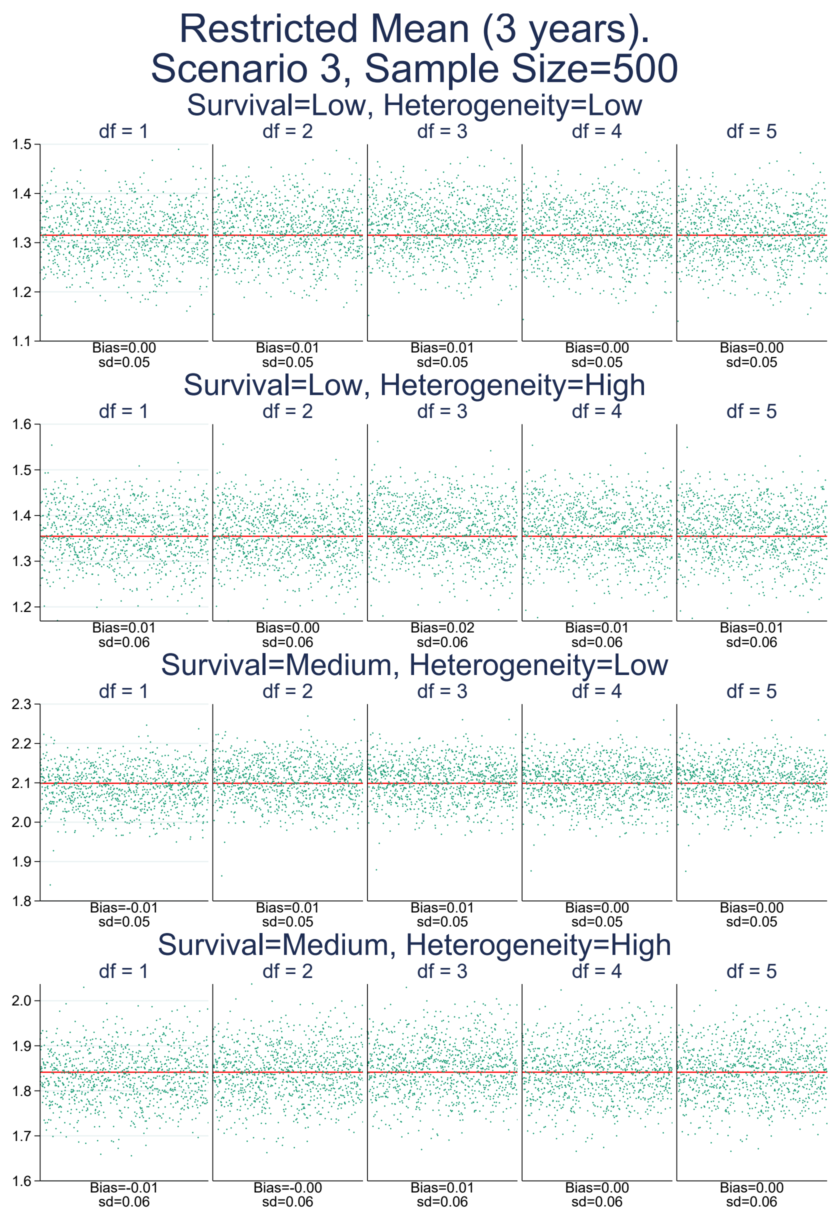

Figure 24: Flexible parametric models: Scenario 3 (SS=500), RMST

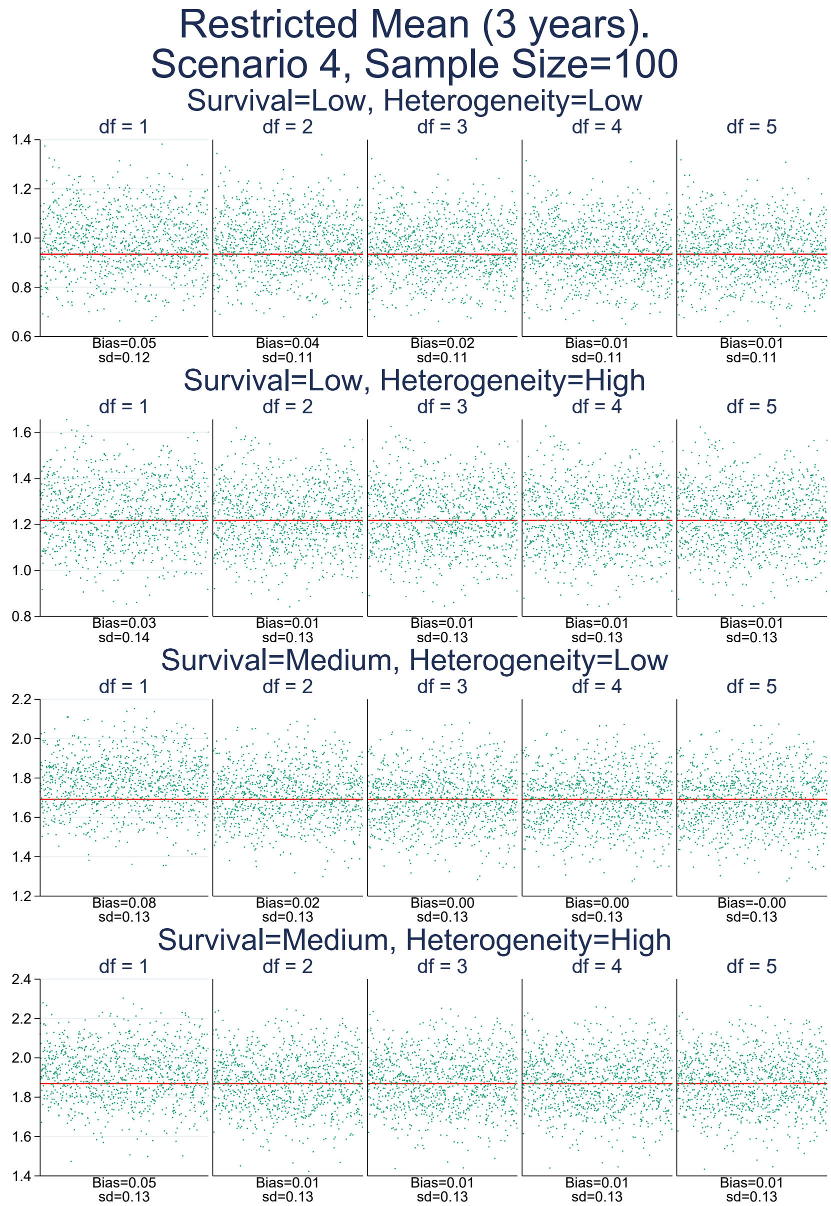

Figure 25: Flexible parametric models: Scenario 4 (SS=100), RMST

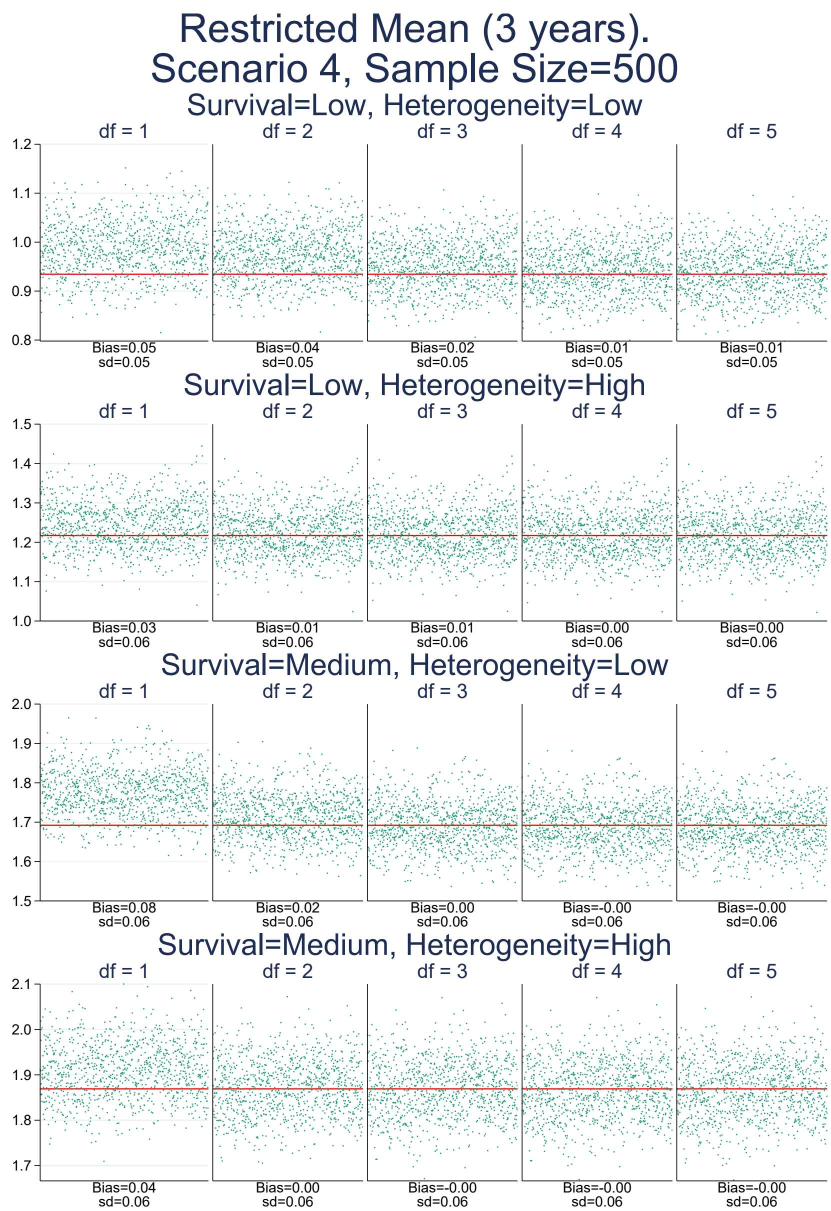

Figure 26: Flexible parametric models: Scenario 4 (SS=500), RMST

4.2 Mean survival

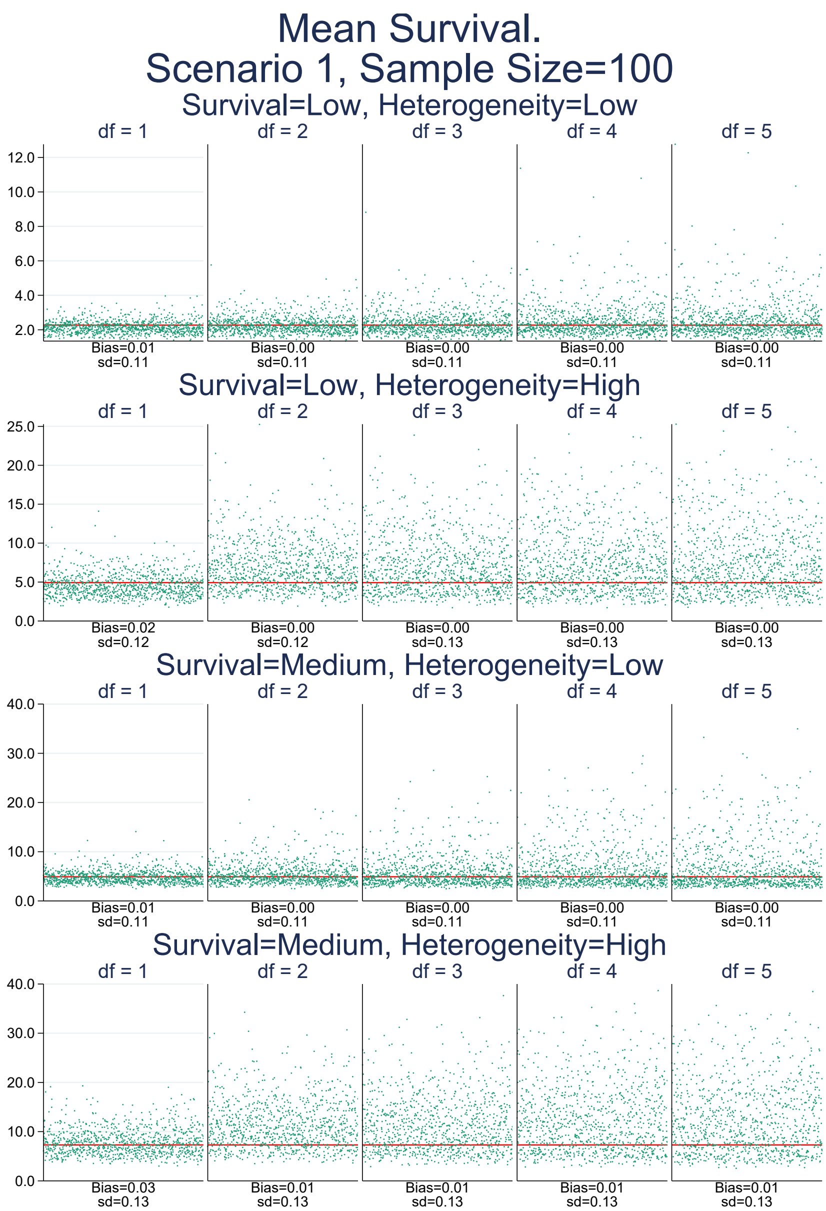

Figure 27: Flexible parametric models: Scenario 1 (SS=100), Mean survival

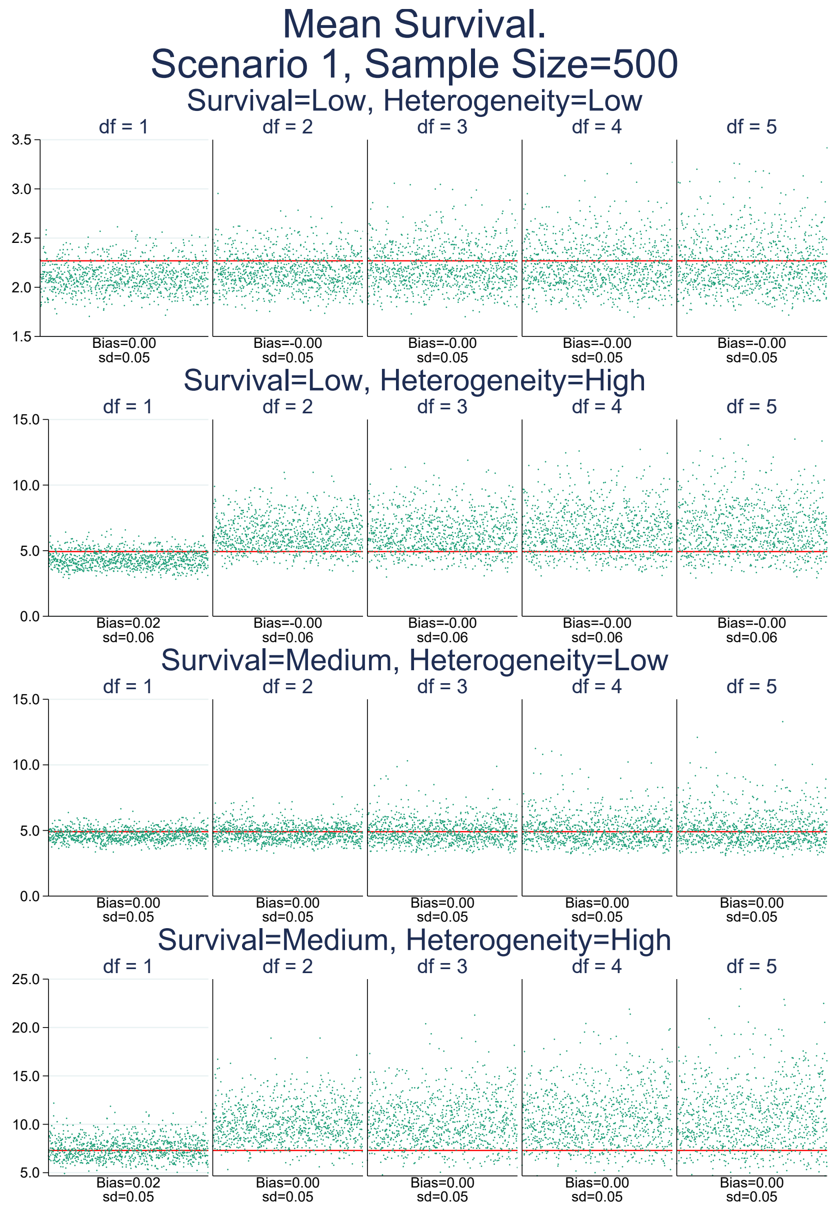

Figure 28: Flexible parametric models: Scenario 1 (SS=500), Mean survival

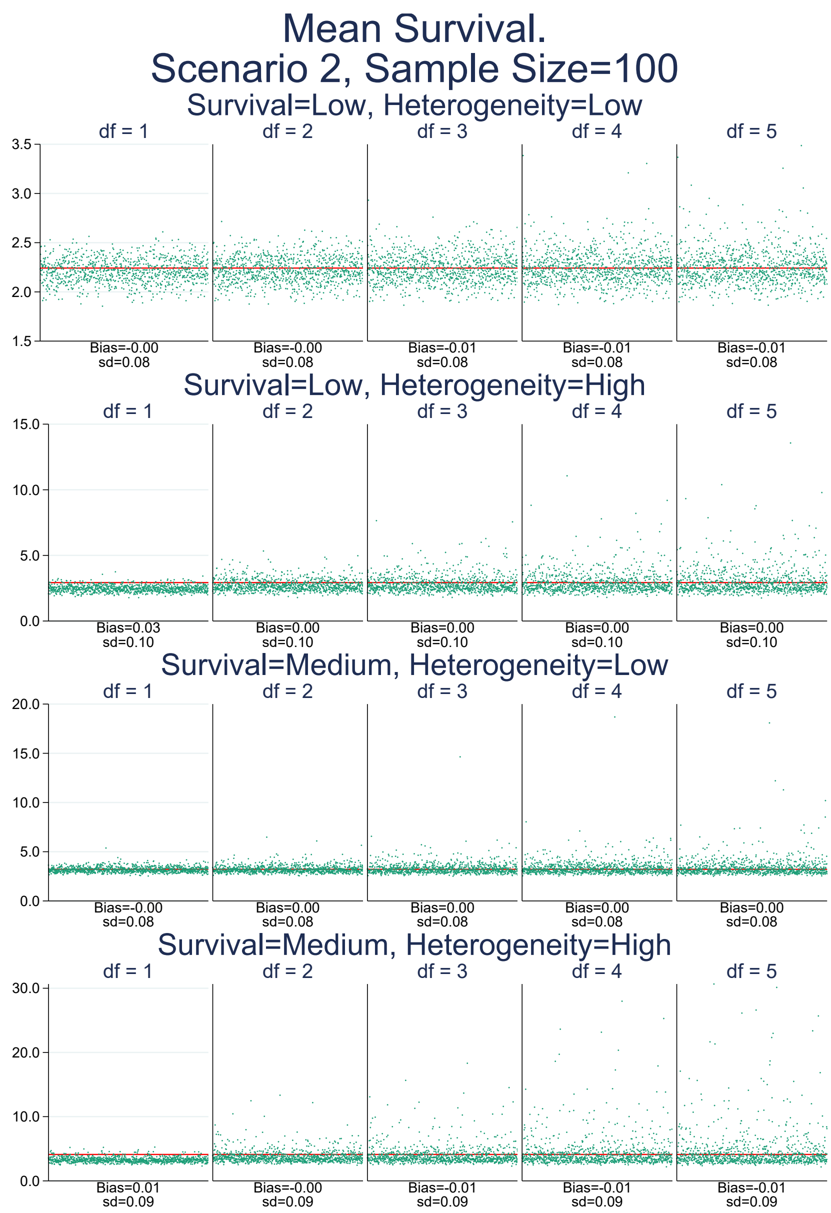

Figure 29: Flexible parametric models: Scenario 2 (SS=100), Mean survival

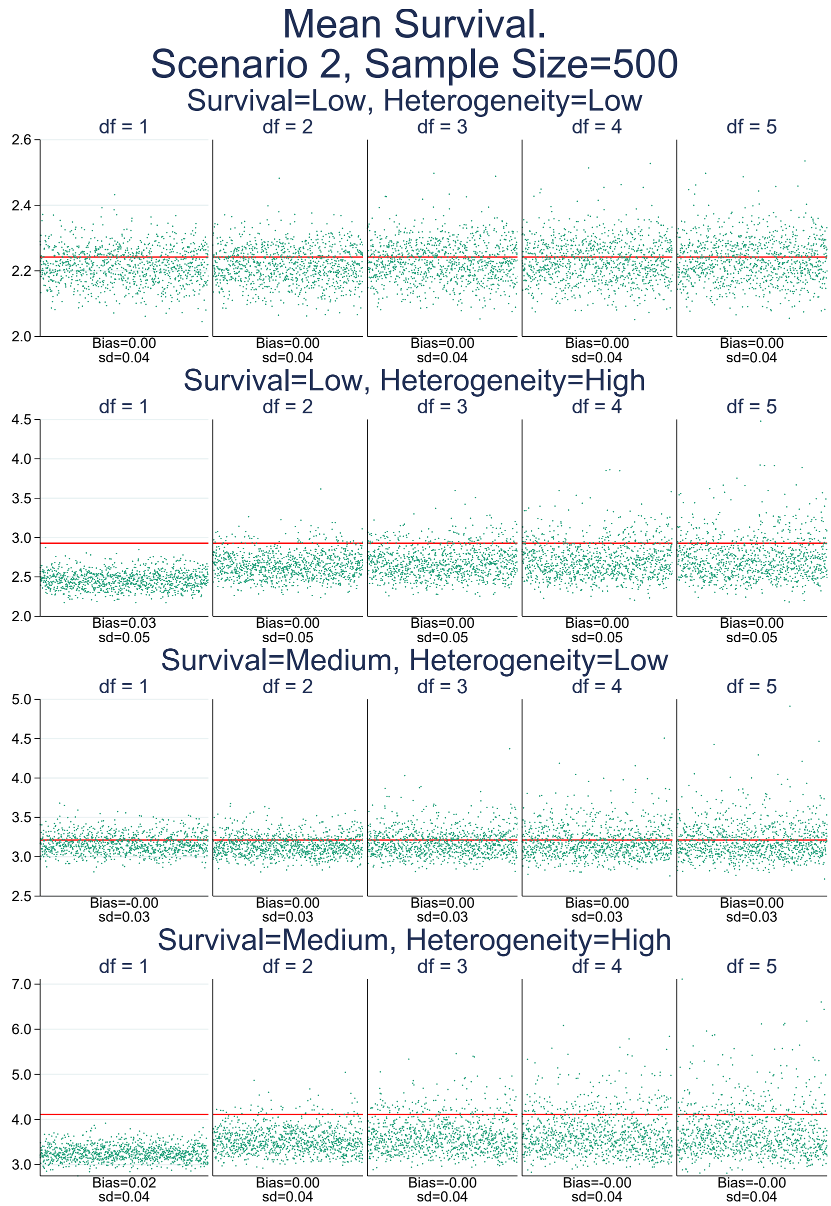

Figure 30: Flexible parametric models: Scenario 2 (SS=500), Mean survival

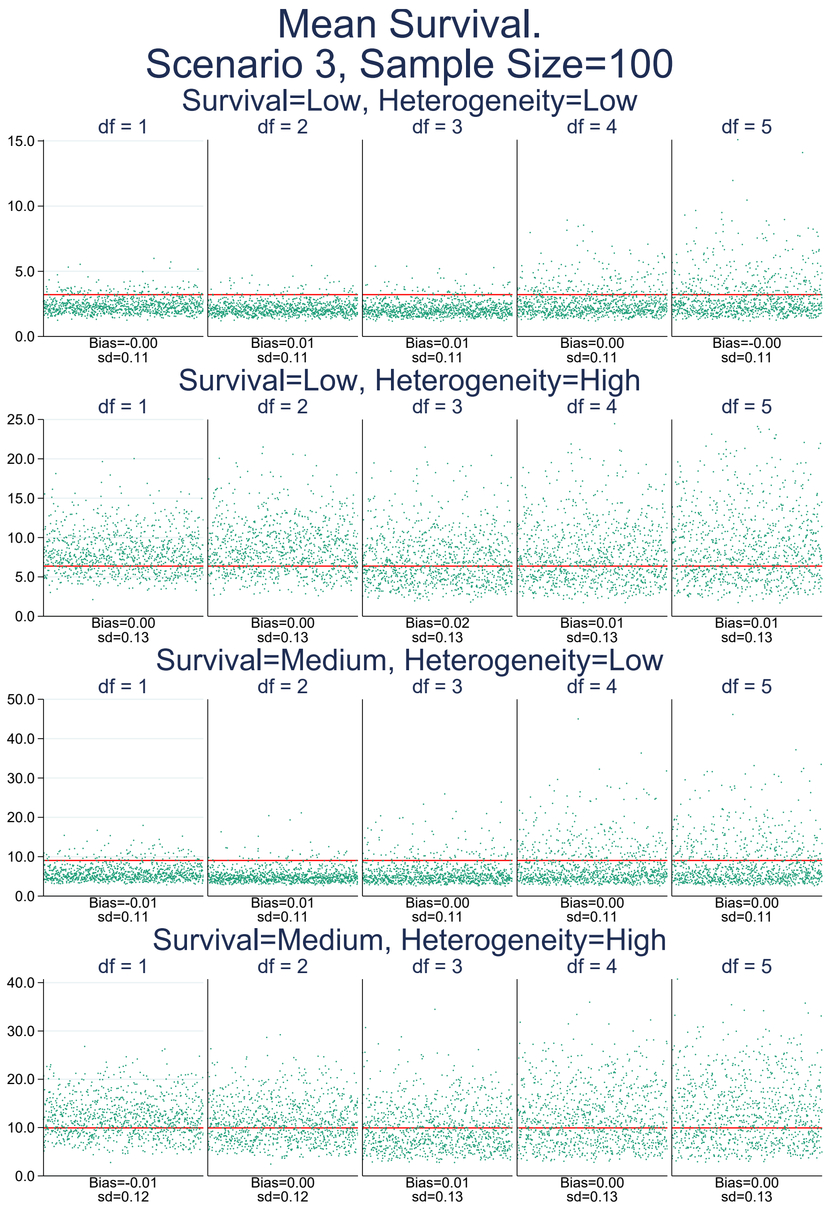

Figure 31: Flexible parametric models: Scenario 3 (SS=100), Mean survival

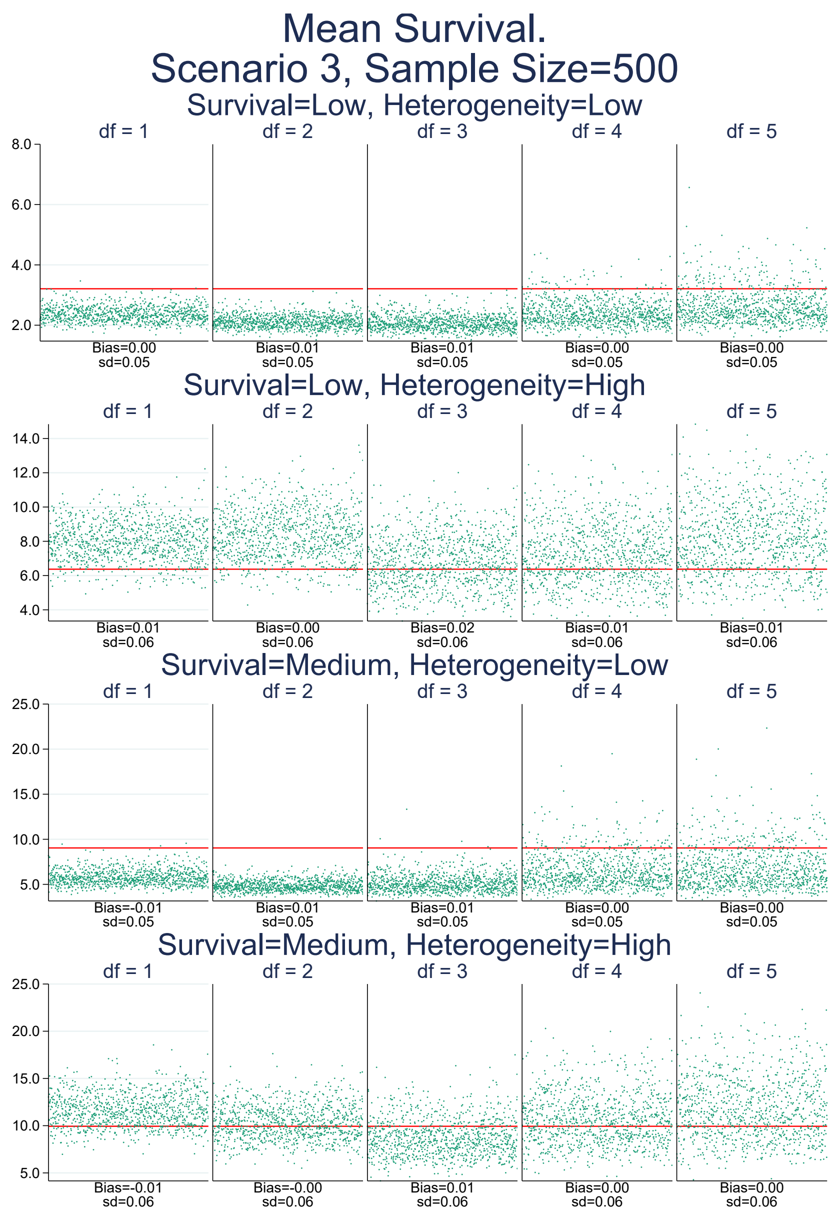

Figure 32: Flexible parametric models: Scenario 3 (SS=500), Mean survival

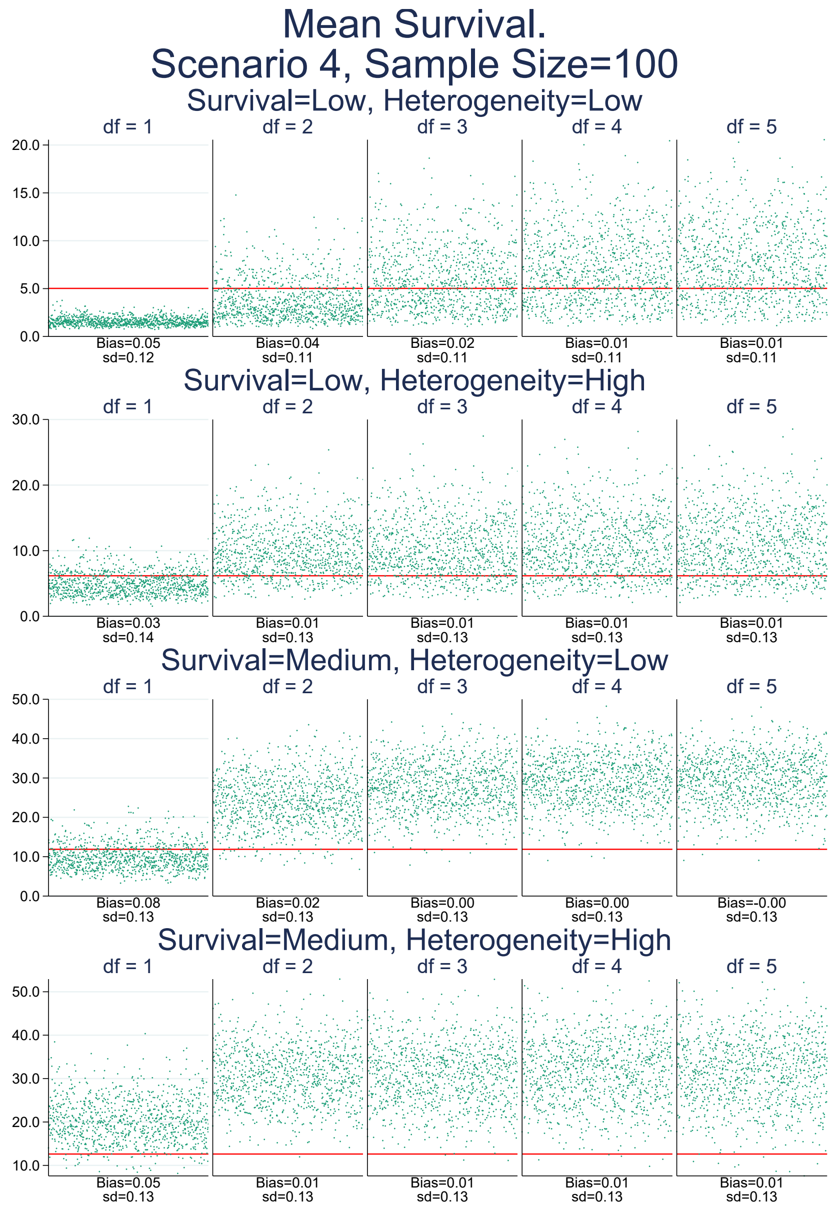

Figure 33: Flexible parametric models: Scenario 4 (SS=100), Mean survival

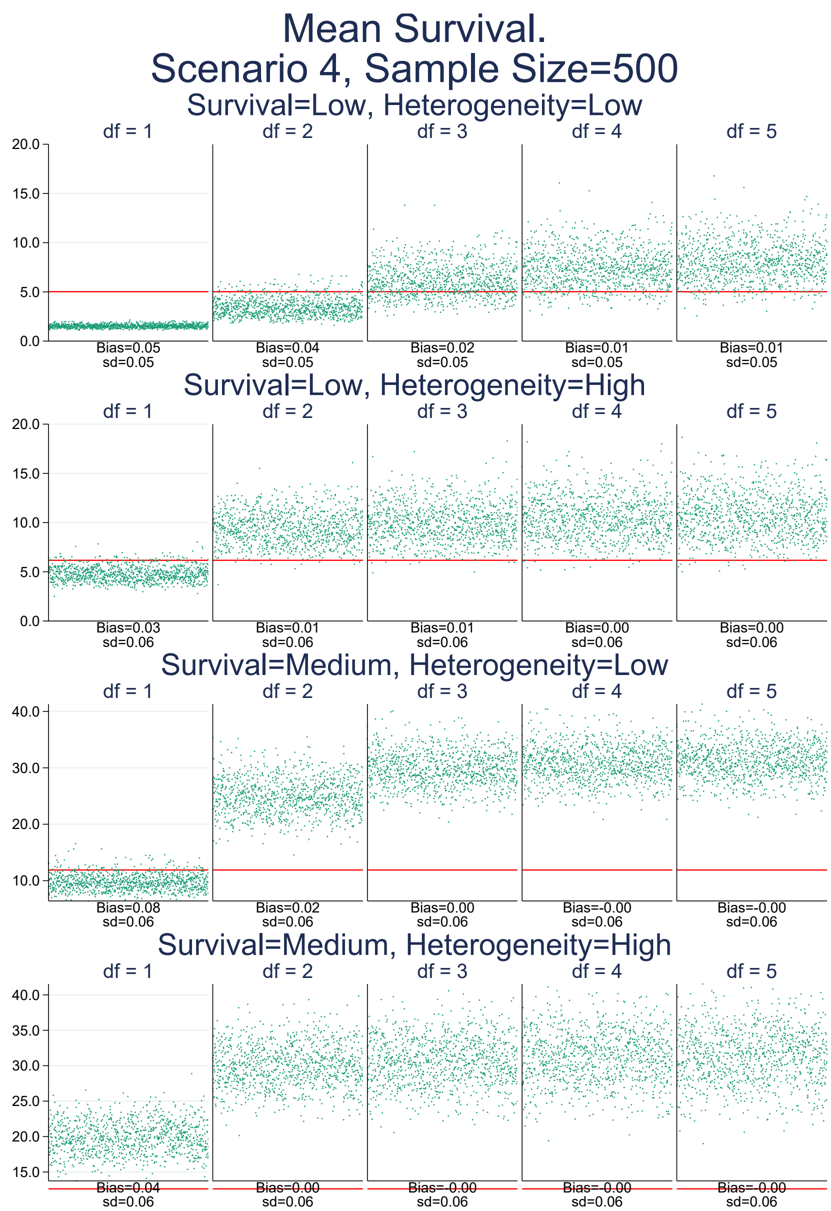

Figure 34: Flexible parametric models: Scenario 4 (SS=500), Mean survival

4.3 Summary of Simulations

- Bias very low for RMST for all scenarios if have 3 df or more. This is not surprising as we know from previous studies that these models can capture complex shapes within the range of the data.
- Having flexible models within the range of the data does not necessarily make our extrapolations better than standard models.
- However, the extrapolation is fairly simple here (model on the log cumulative hazard scale) as it is similar to a Weibull model in the tail (log linear beyond the last knot).
- Given that we use Weibull based distributions for the simulation, we should not over interpret the fact that the bias is generally lower for the FPMs.
- For the extrapolated survival we see more variation as we increase the degrees of freedom.

5 Incorporating background mortality

5.1 RMST

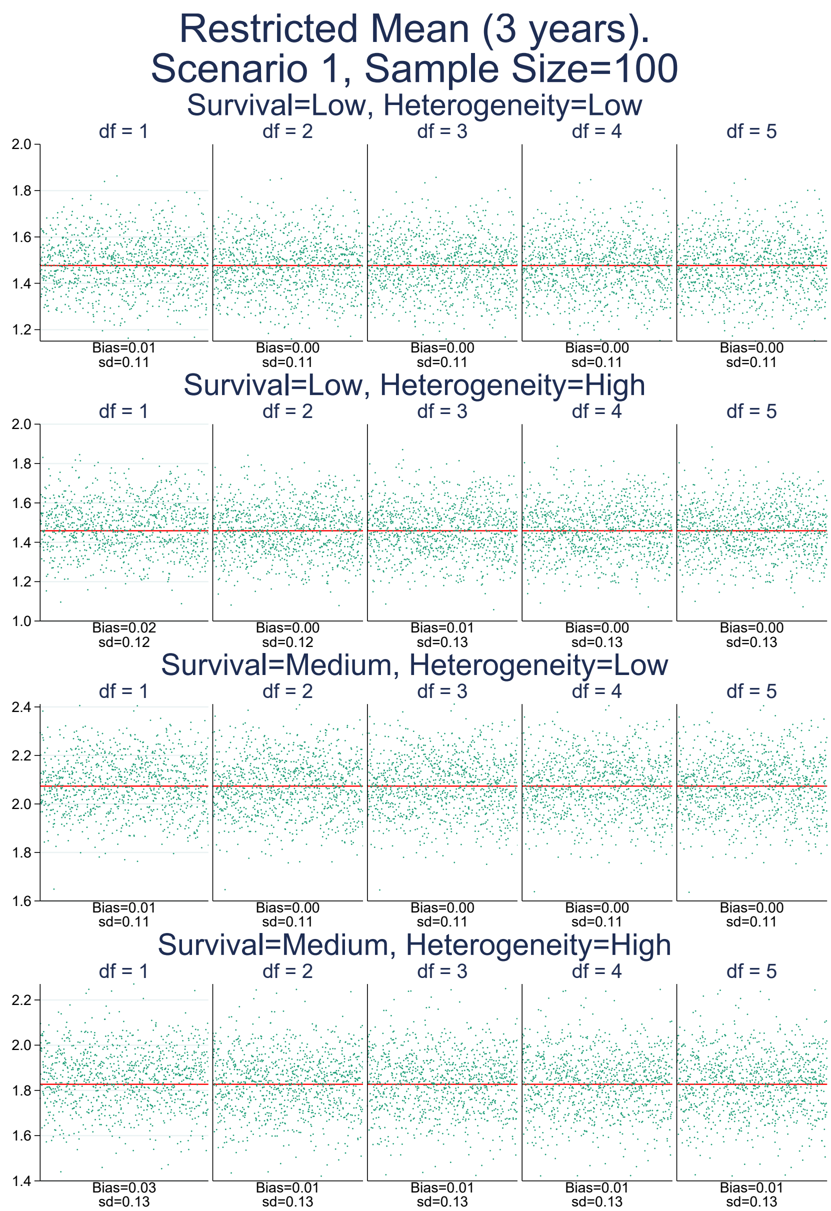

Figure 35: Flexible parametric models: Scenario 1 (SS=100), RMST

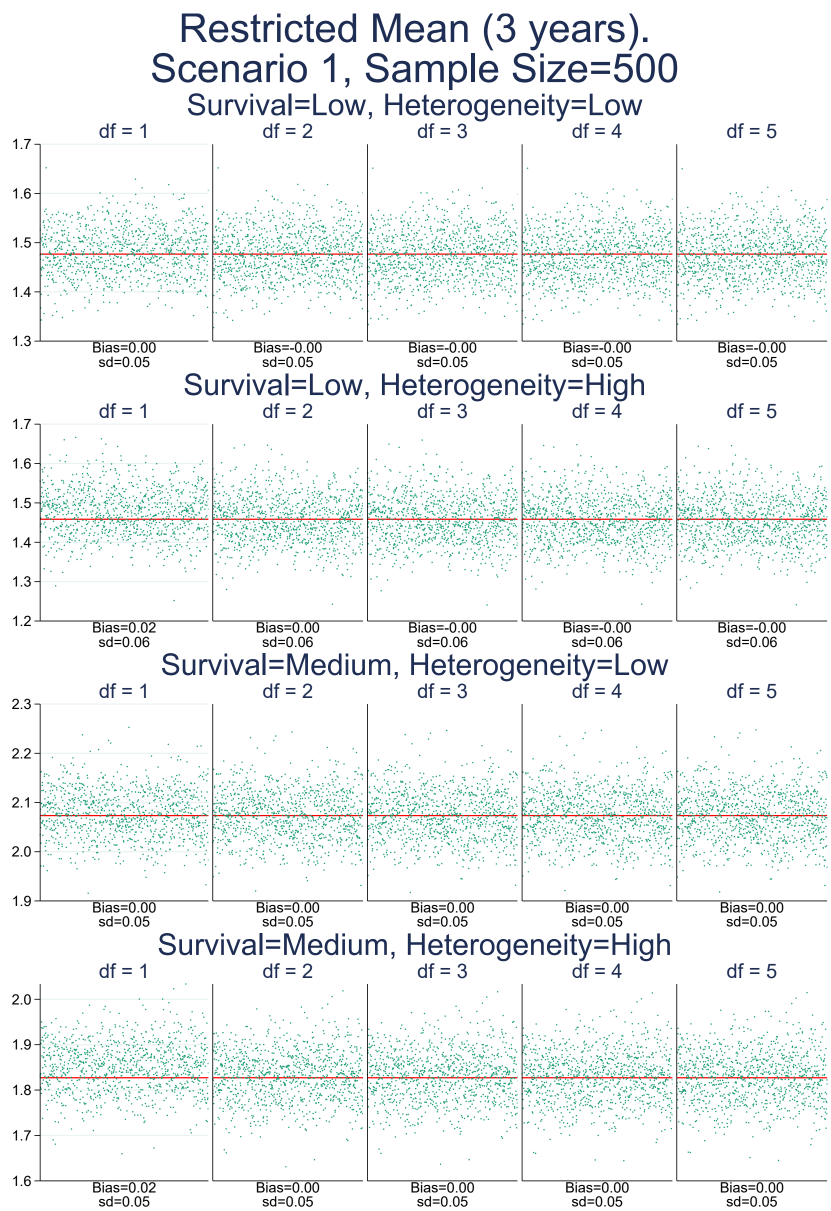

Figure 36: Flexible parametric models: Scenario 1 (SS=500), RMST

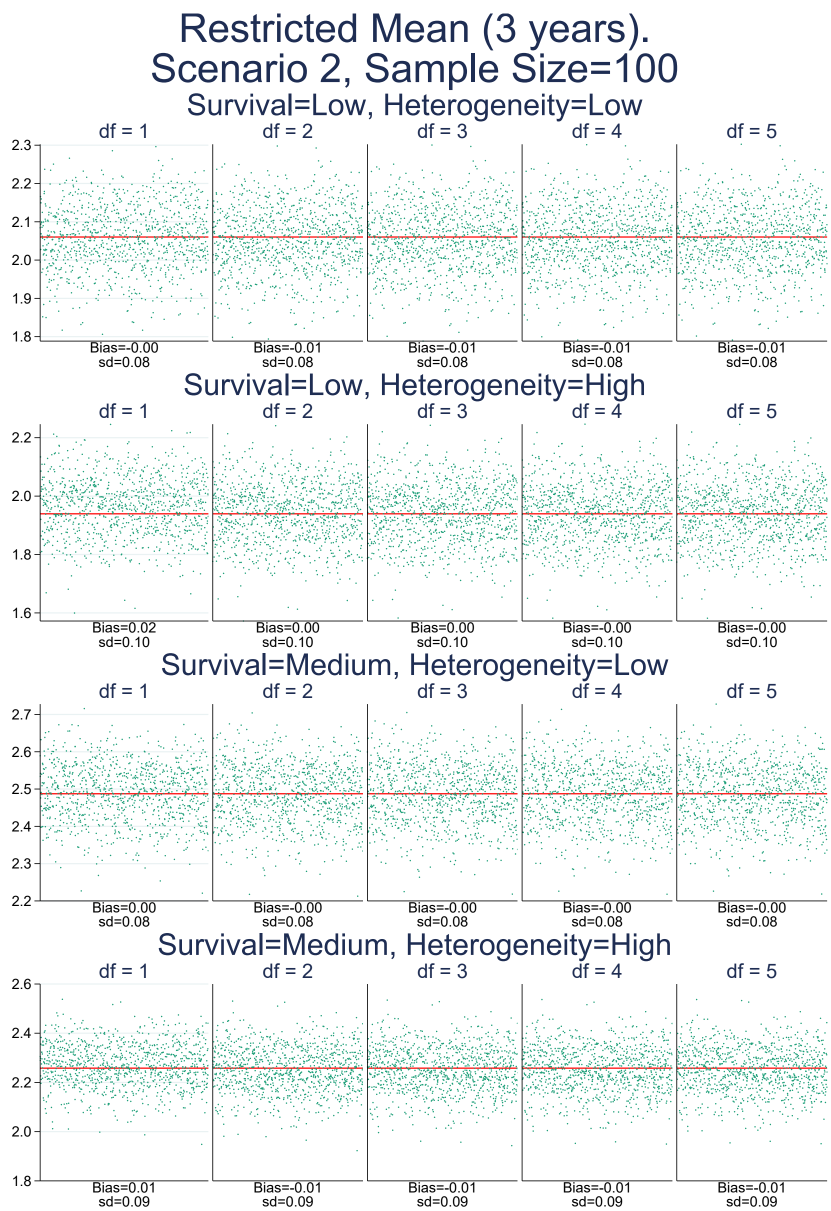

Figure 37: Flexible parametric models: Scenario 2 (SS=100), RMST

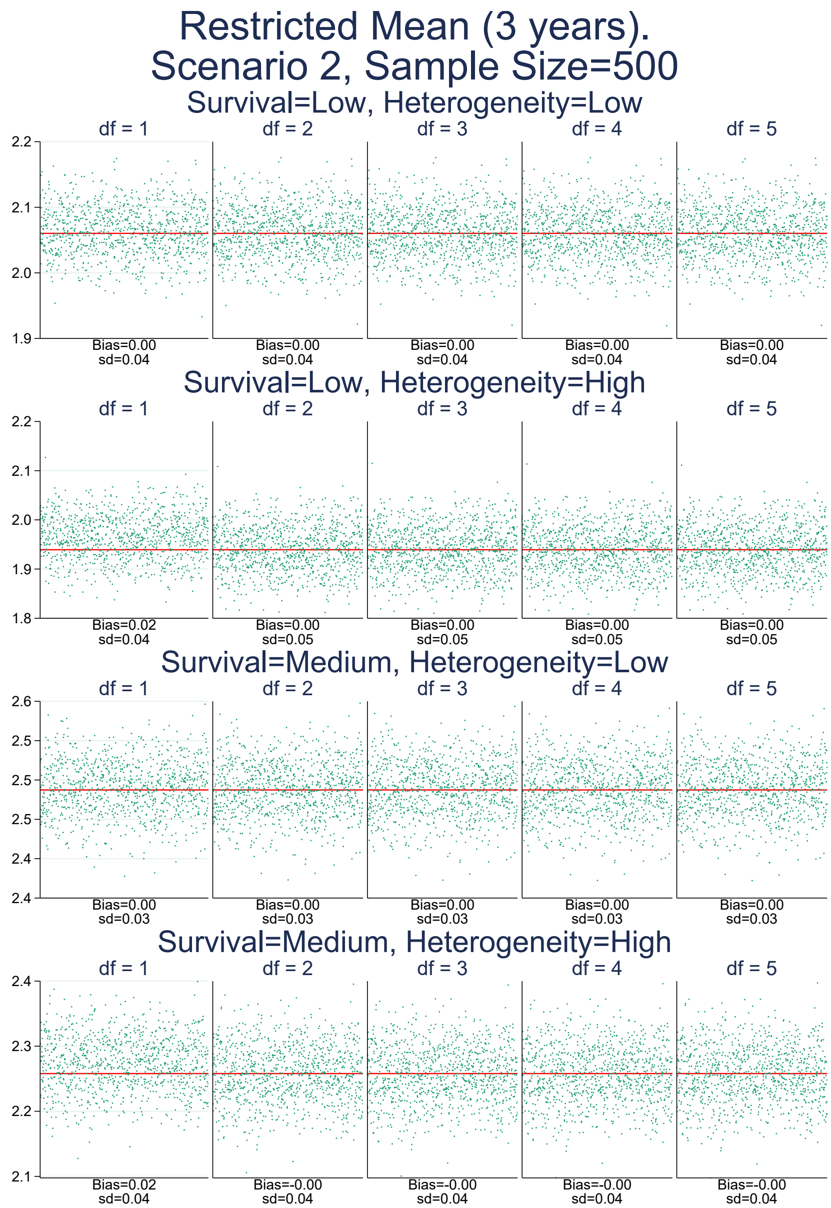

Figure 38: Flexible parametric models: Scenario 2 (SS=500), RMST

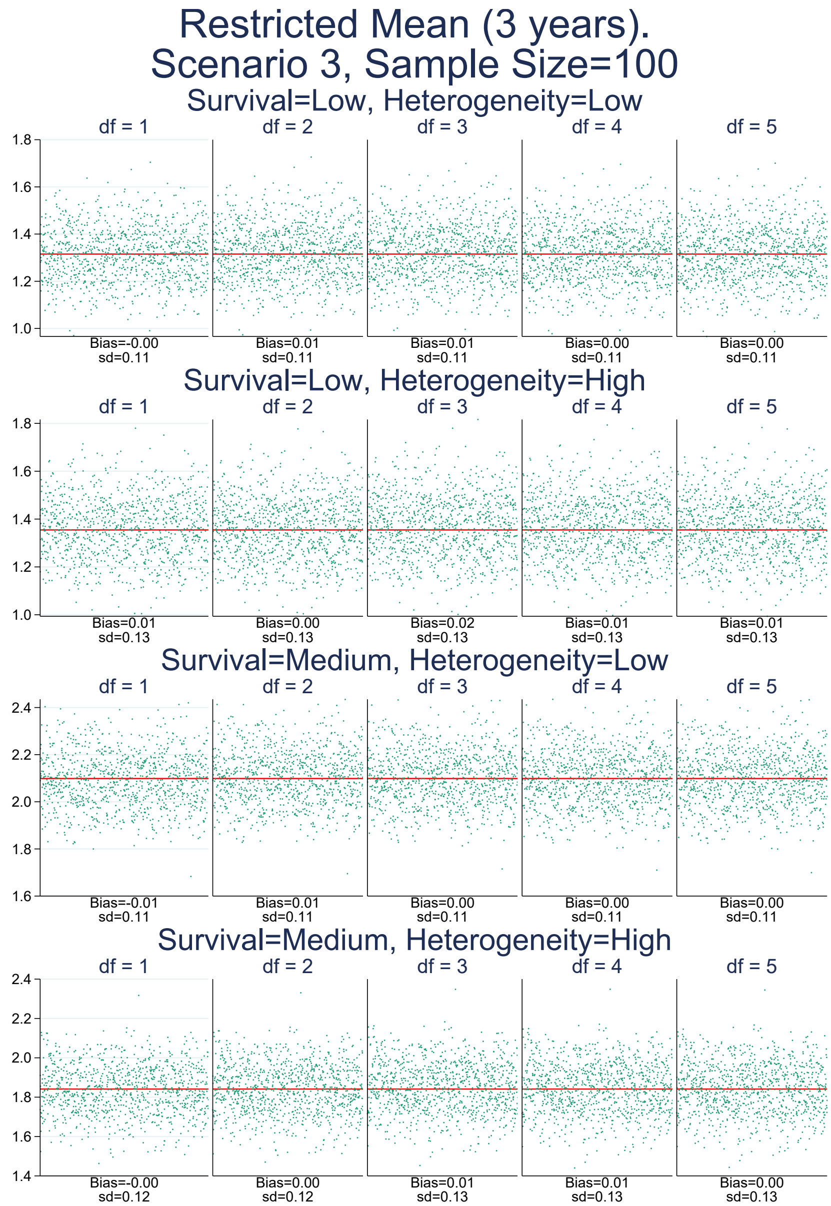

Figure 39: Flexible parametric models: Scenario 3 (SS=100), RMST

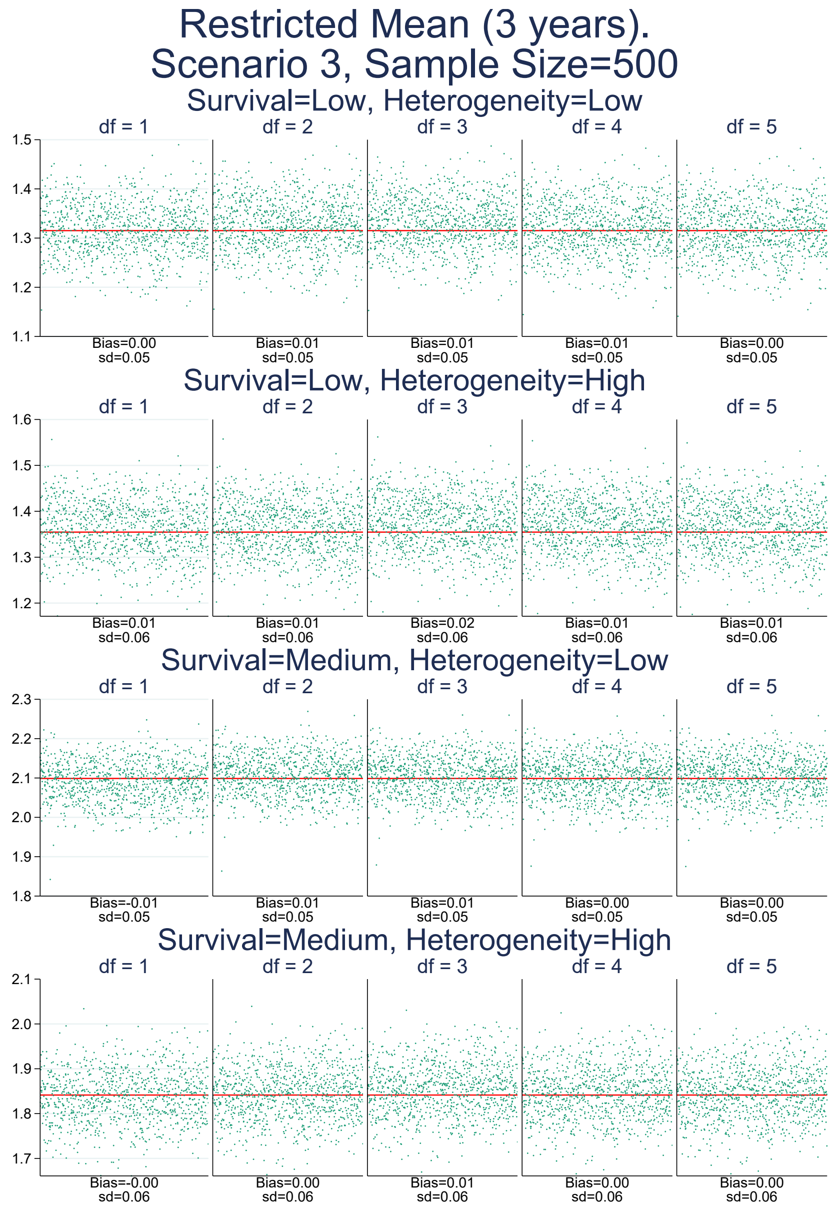

Figure 40: Flexible parametric models: Scenario 3 (SS=500), RMST

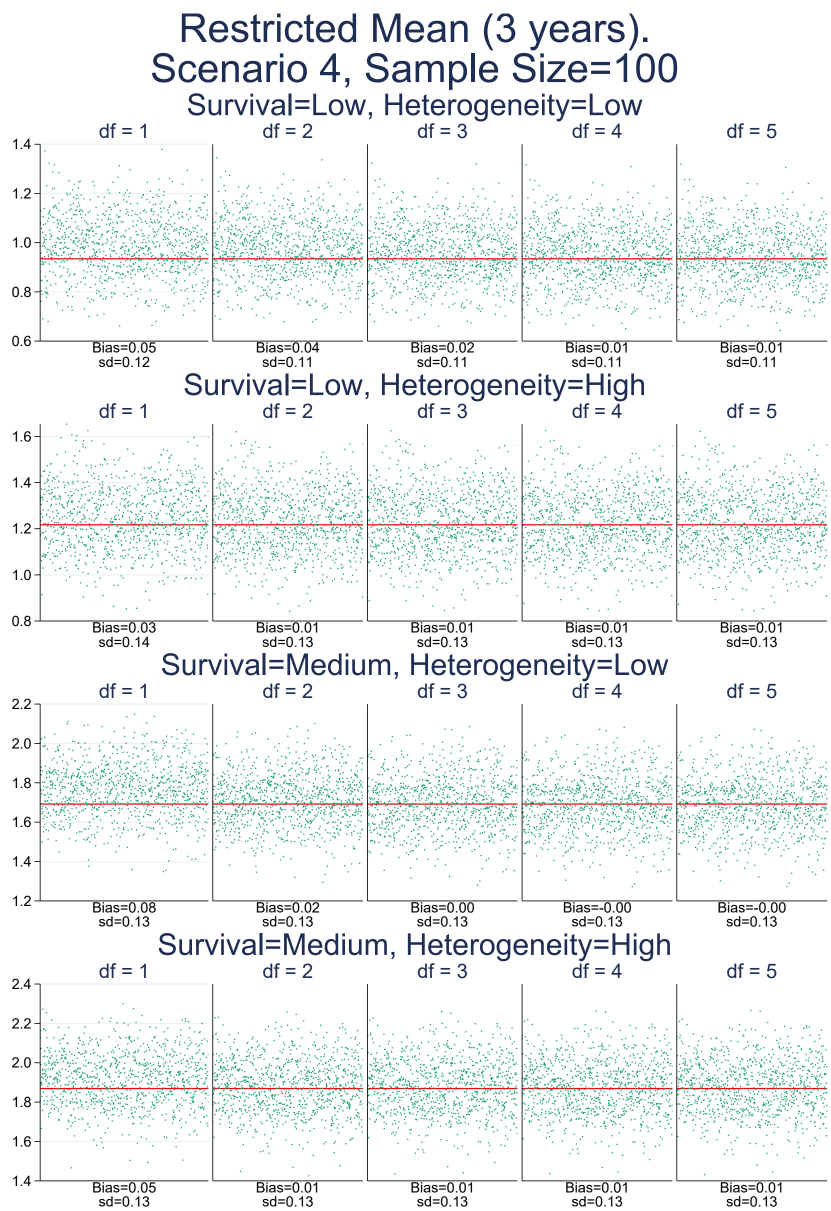

Figure 41: Flexible parametric models: Scenario 4 (SS=100), RMST

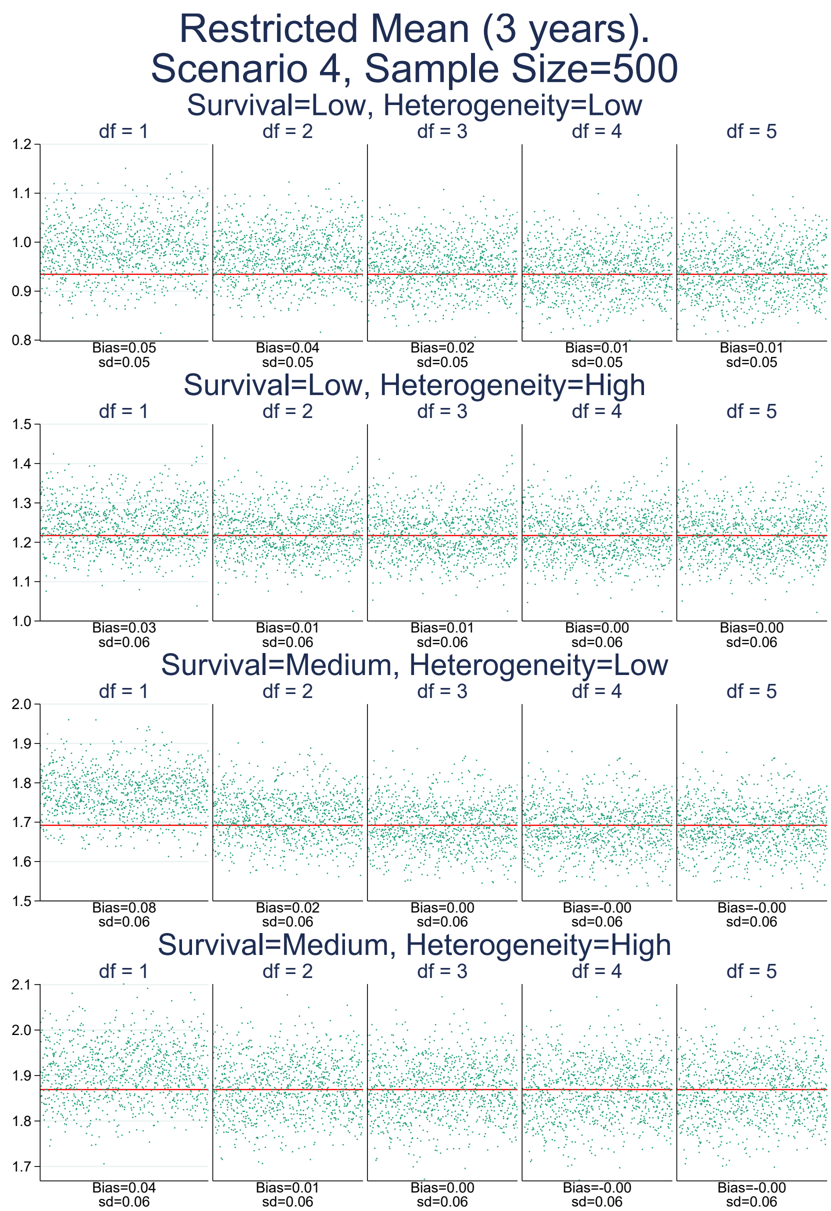

Figure 42: Flexible parametric models: Scenario 4 (SS=500), RMST

5.2 Mean survival

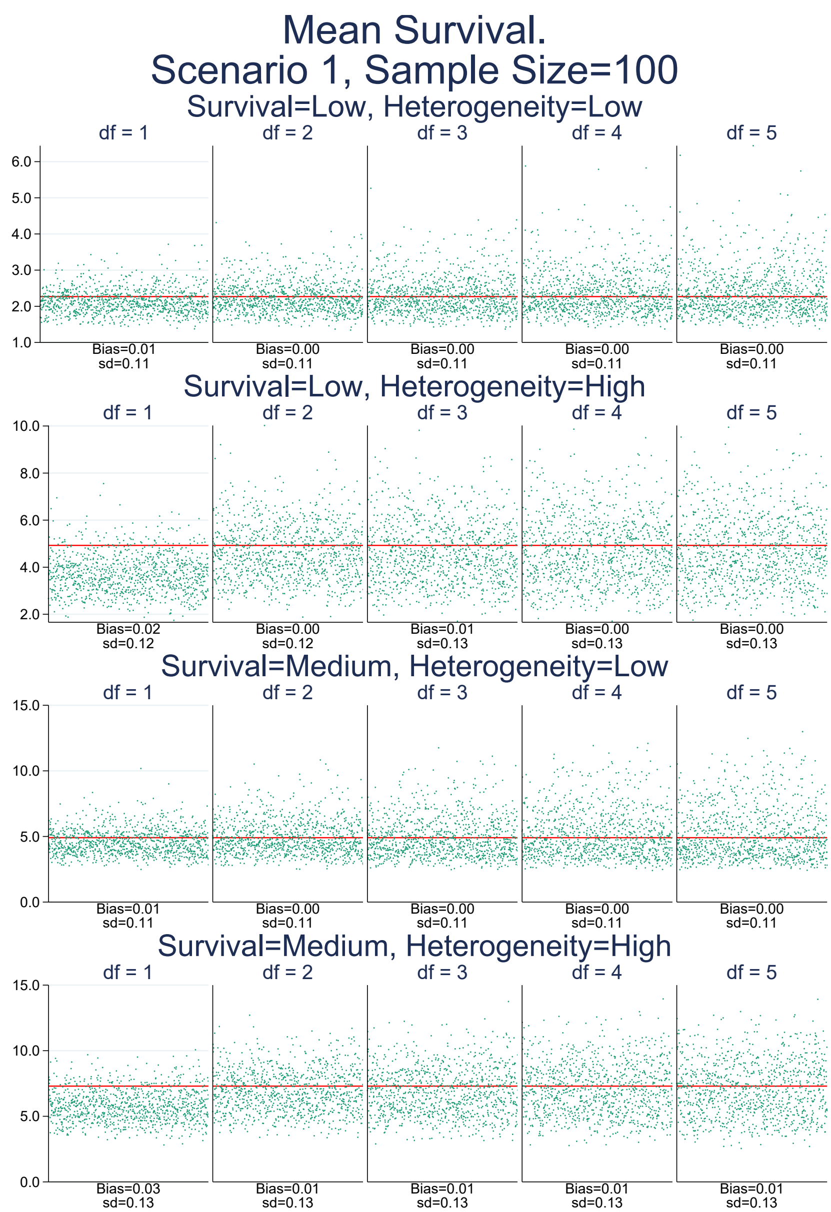

Figure 43: Flexible parametric models: Scenario 1 (SS=100), Mean survival

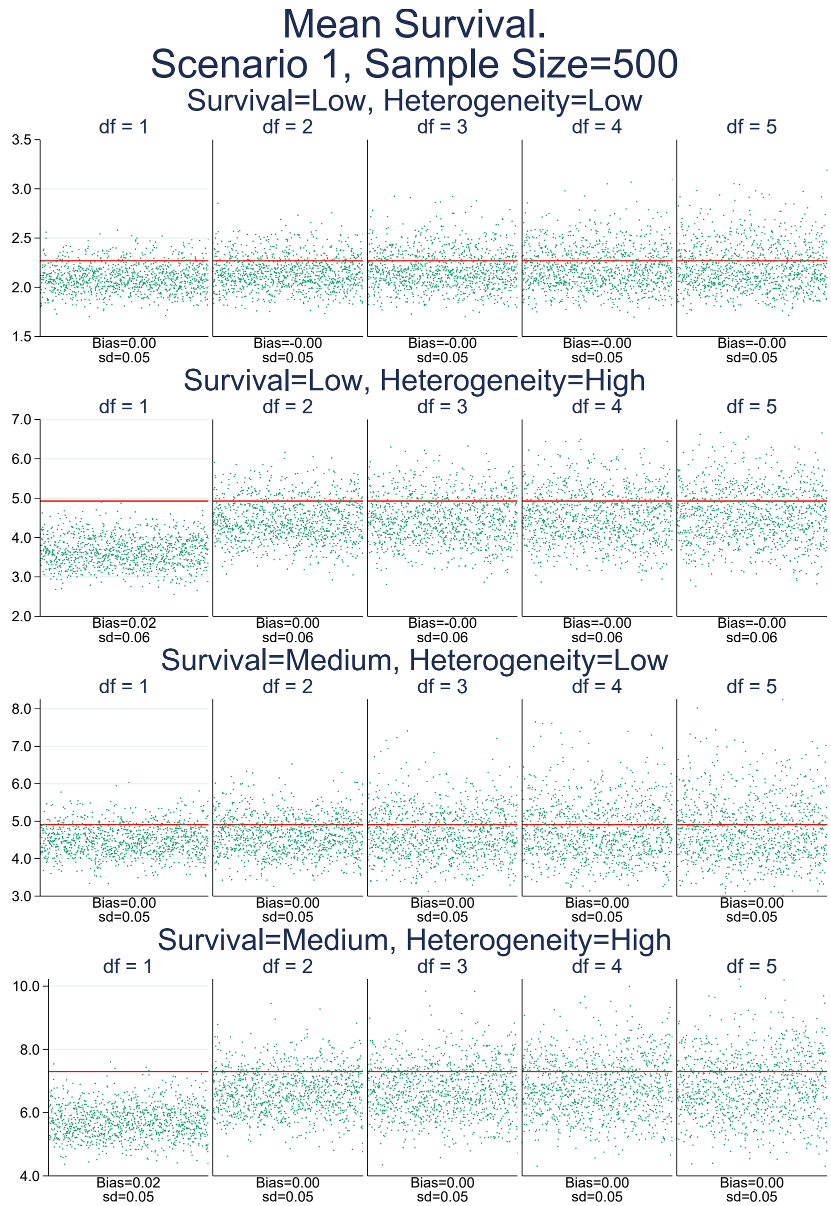

Figure 44: Flexible parametric models: Scenario 1 (SS=500), Mean survival

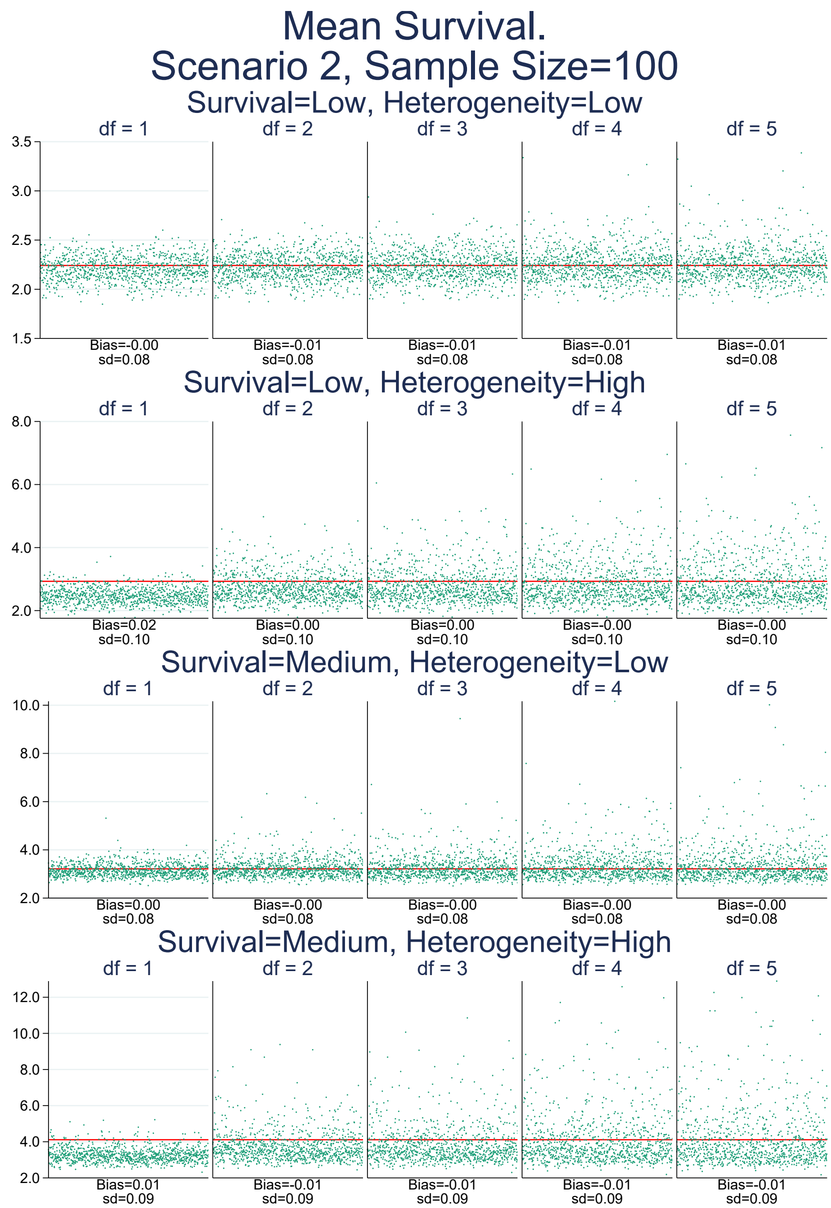

Figure 45: Flexible parametric models: Scenario 2 (SS=100), Mean survival

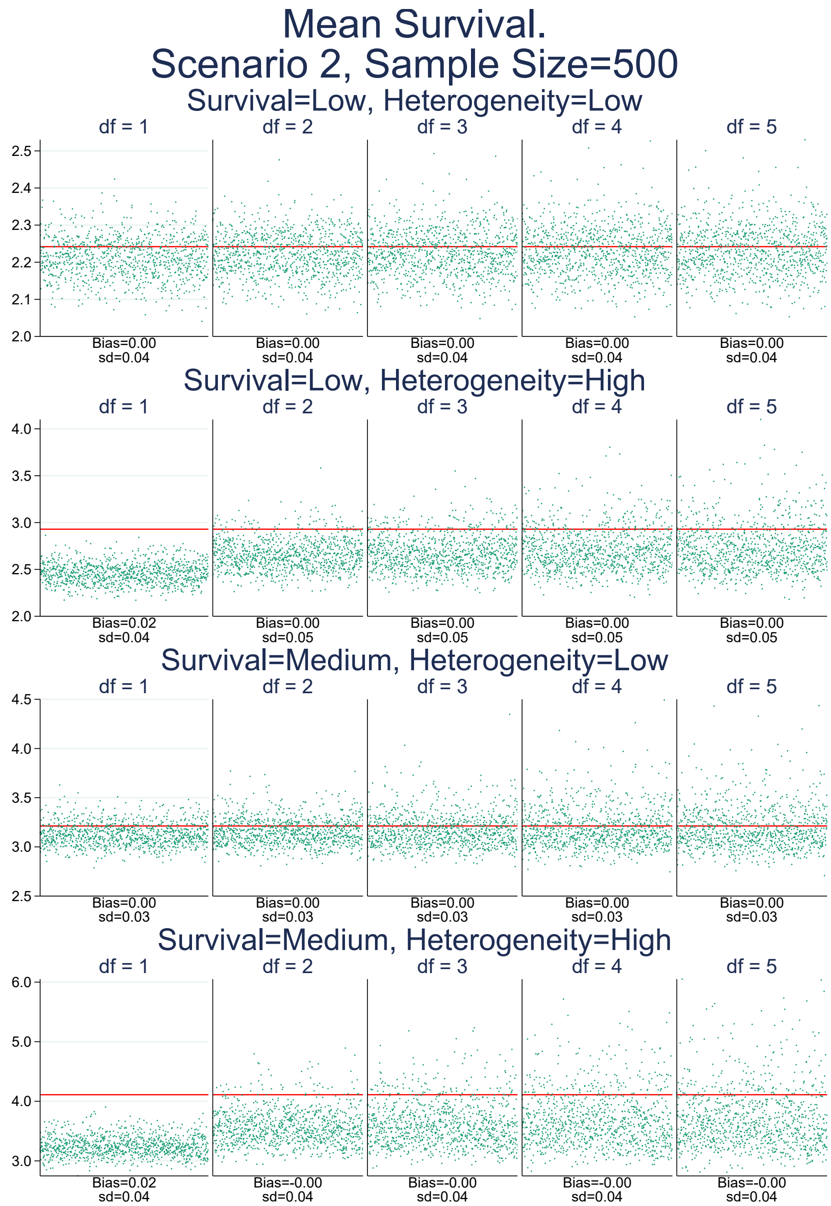

Figure 46: Flexible parametric models: Scenario 2 (SS=500), Mean survival

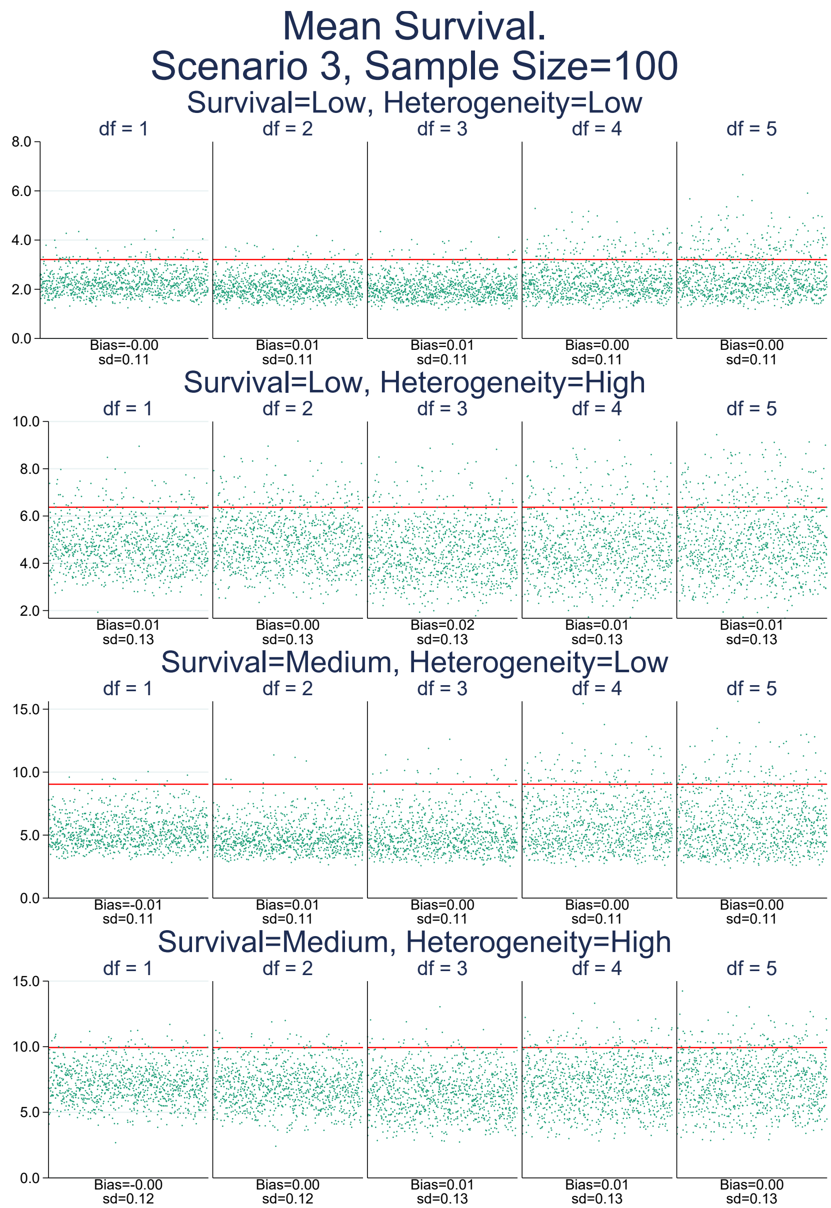

Figure 47: Flexible parametric models: Scenario 3 (SS=100), Mean survival

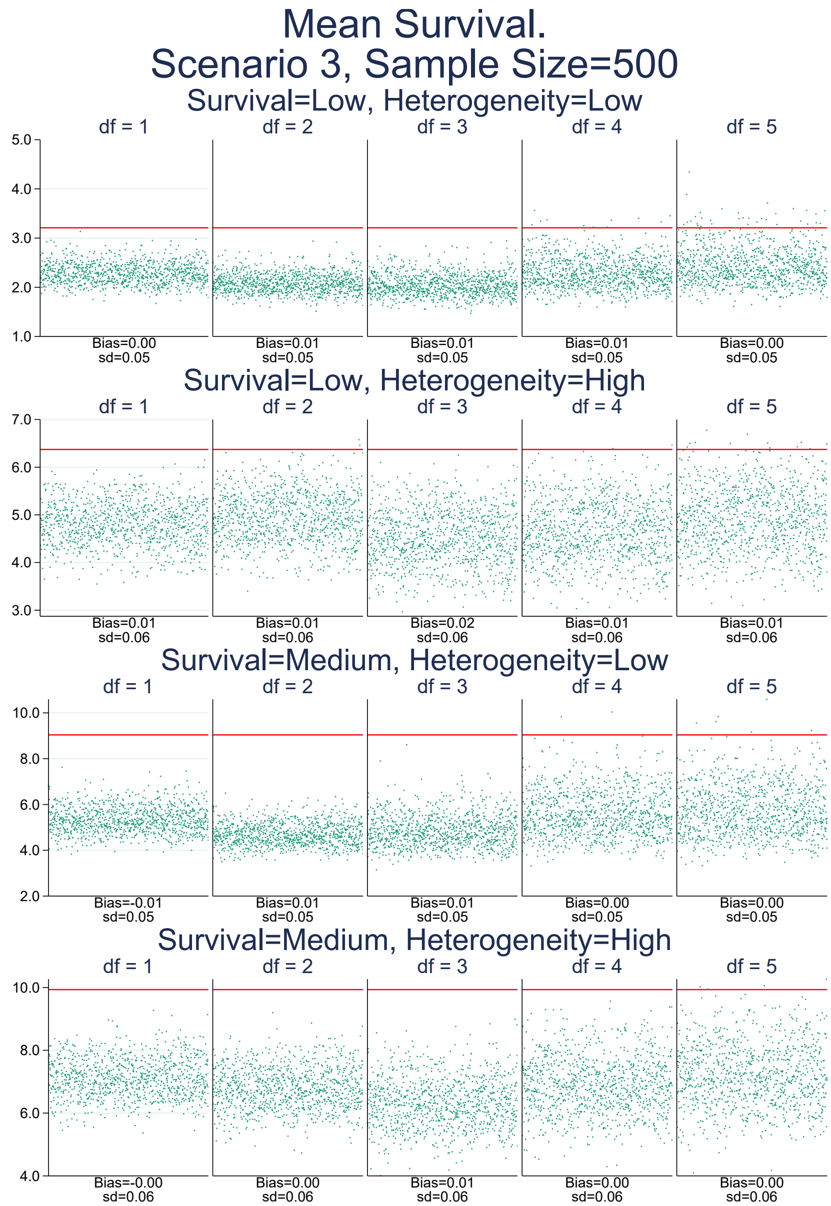

Figure 48: Flexible parametric models: Scenario 3 (SS=500), Mean survival

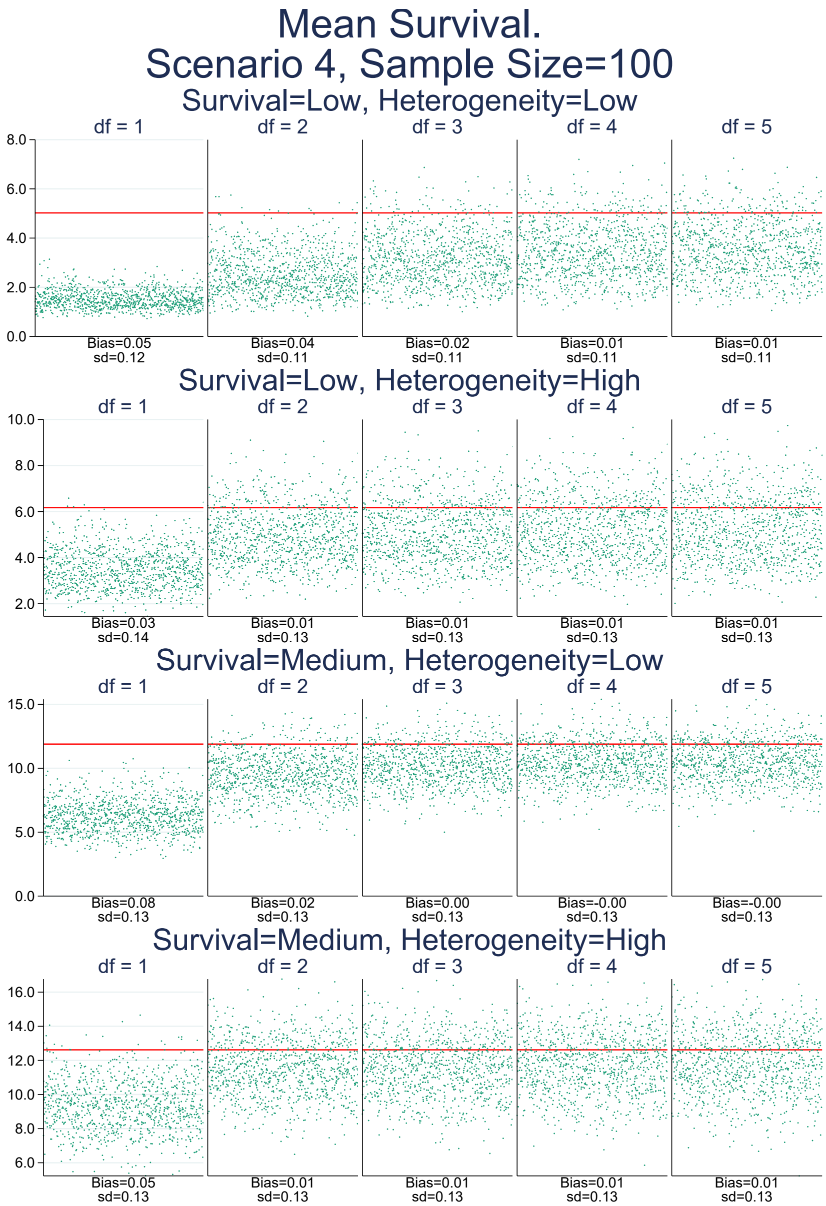

Figure 49: Flexible parametric models: Scenario 4 (SS=100), Mean survival

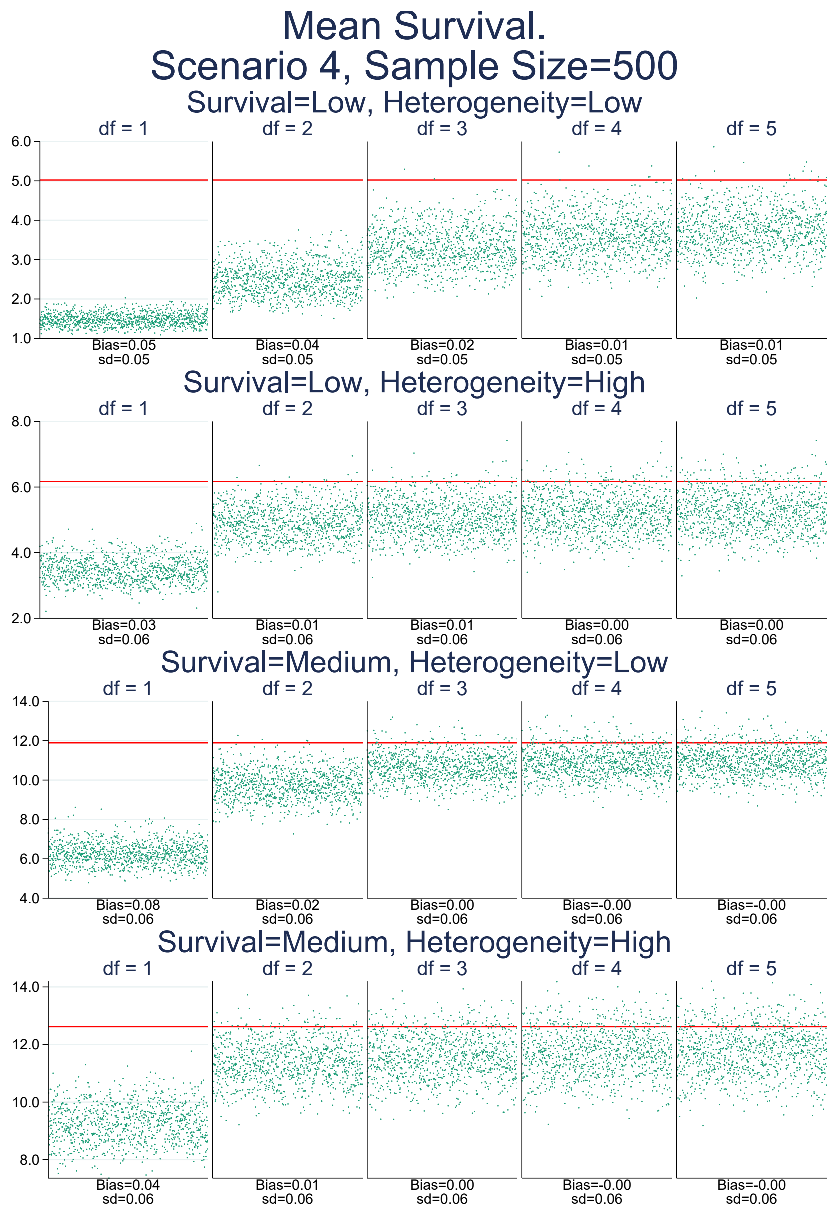

Figure 50: Flexible parametric models: Scenario 4 (SS=500), Mean survival

5.3 Summary of Simulations

- FPMs that were fit using a relative survival framework, thereby incorporating background mortality, performed similarly to FPMs fit without incorporating background mortality in Scenario 2 – with low bias in mean overall survival.
- In Scenario 1 (where survival followed a Weibull distribution with a decreasing hazard) FPMs that included background mortality performed appreciably better than FPMs that did not incorporate background mortality.
- In Scenario 4, where a cure fraction was simulated, including background mortality within FPMs led to an appreciable reduction in bias compared to standard parametric models (which did not include background mortality) and compared to FPMs that did not include background mortality. But bias was still high in places.

6 Cure

6.1 RMST

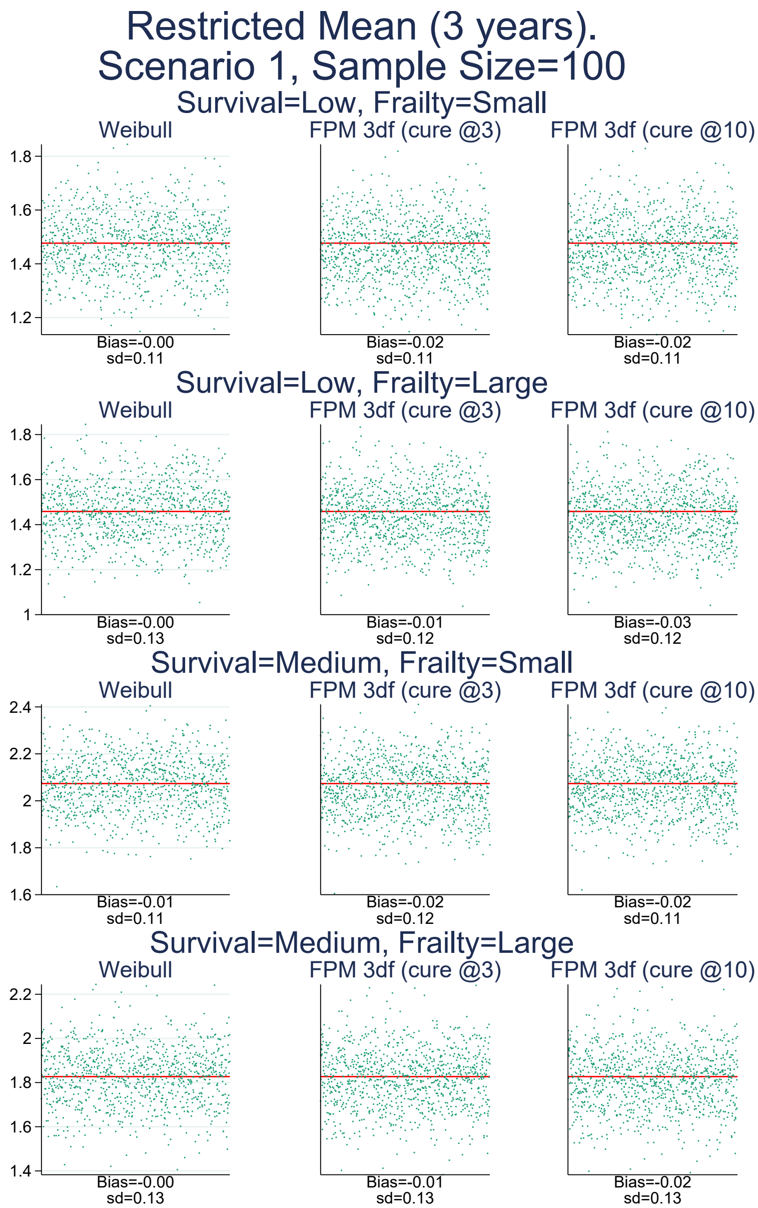

Figure 51: Cure models: Scenario 1 (SS=100), RMST

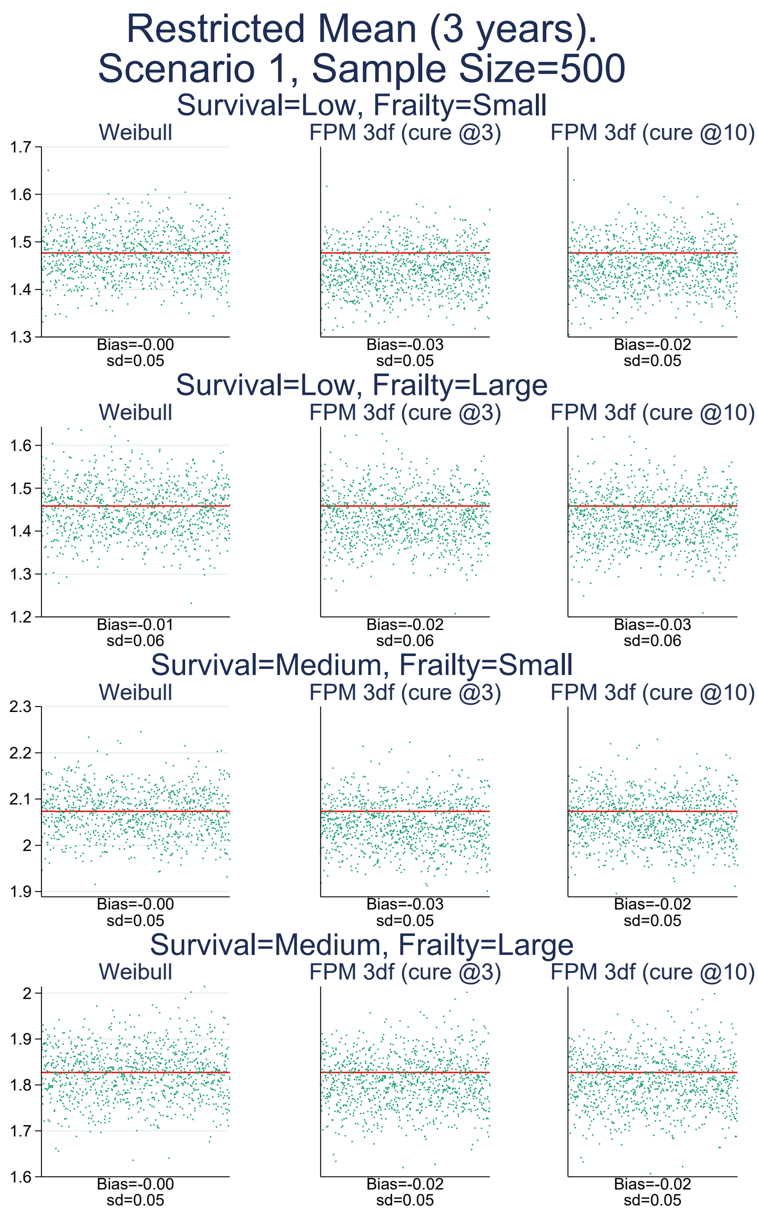

Figure 52: Cure models: Scenario 1 (SS=500), RMST

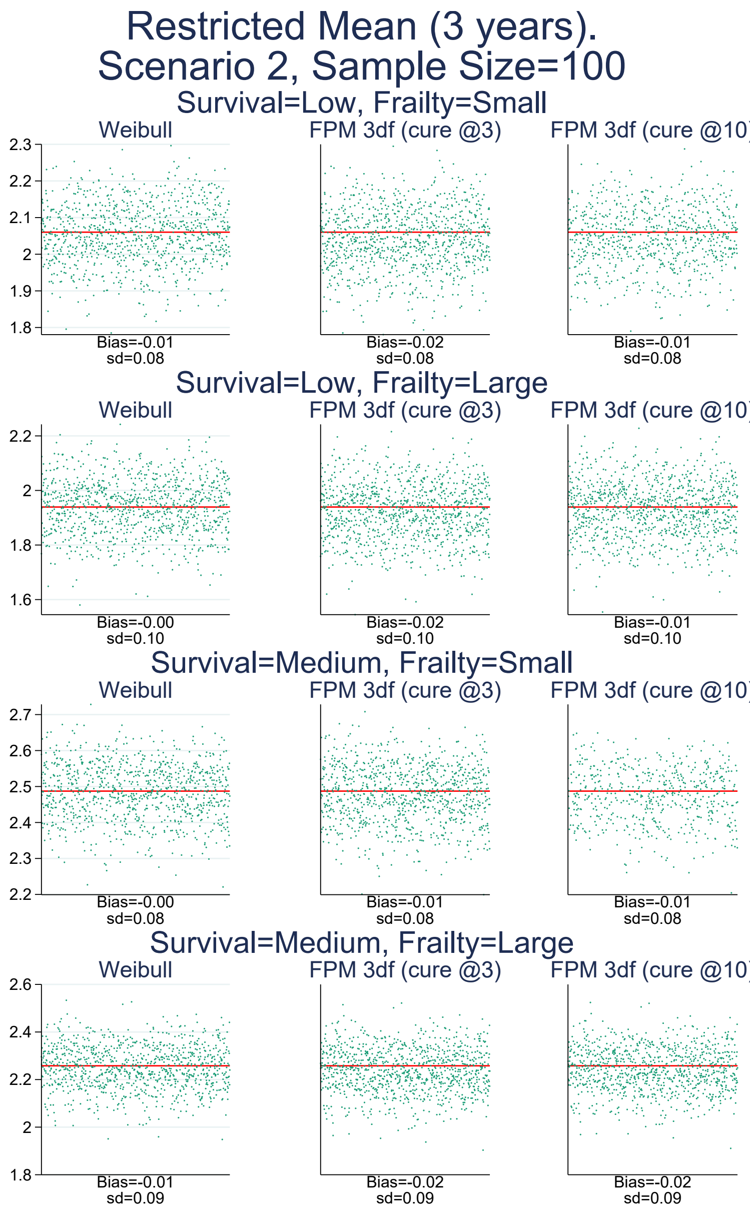

Figure 53: Cure models: Scenario 2 (SS=100), RMST

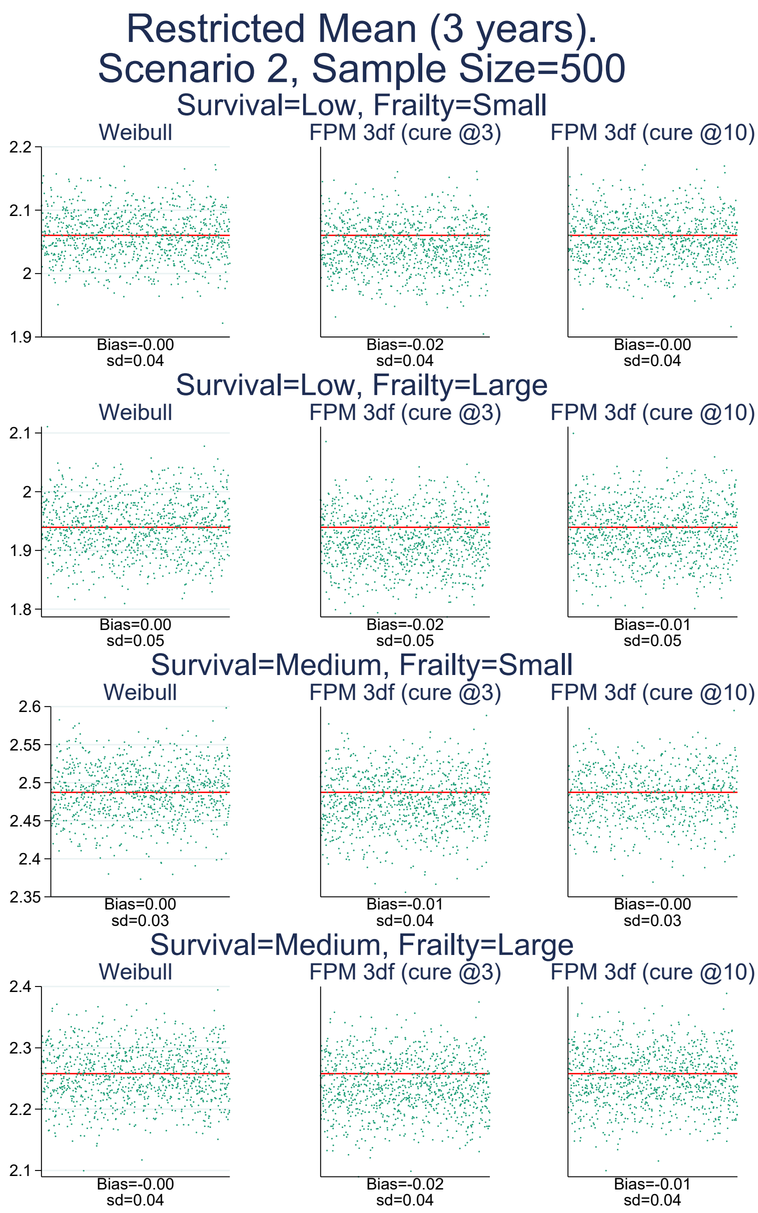

Figure 54: Cure models: Scenario 2 (SS=500), RMST

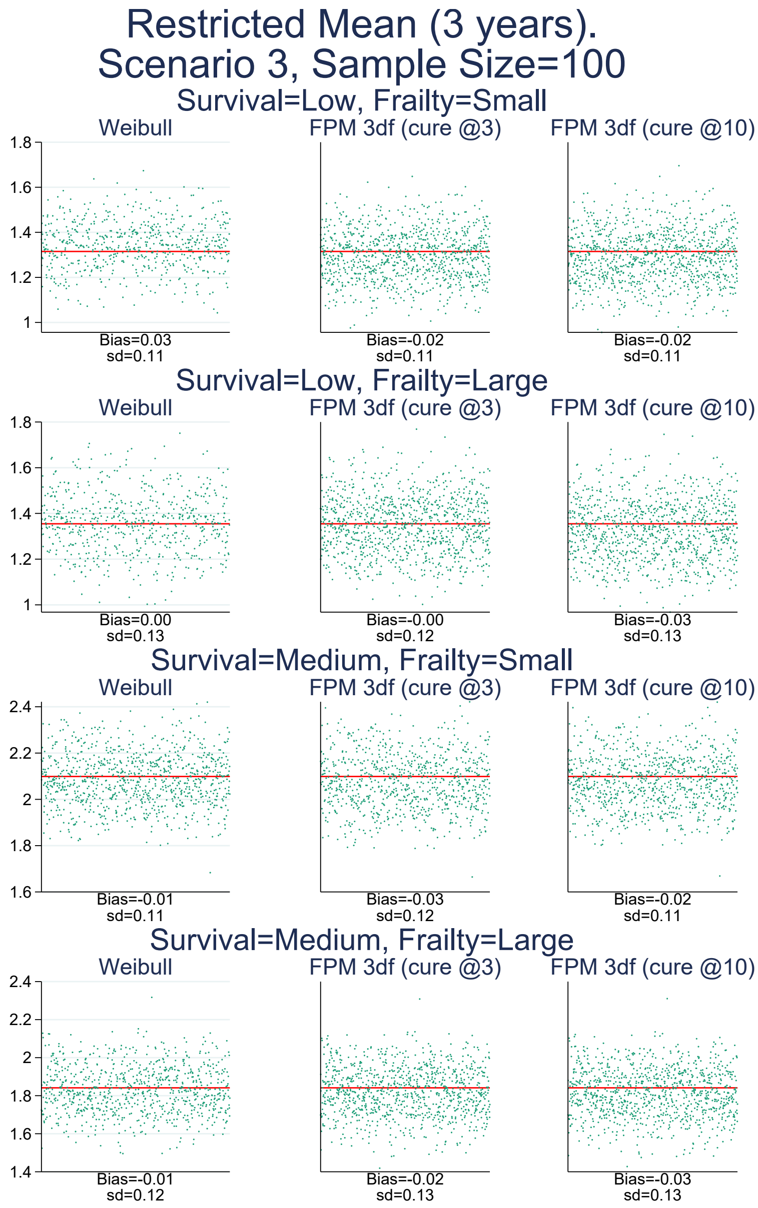

Figure 55: Cure models: Scenario 3 (SS=100), RMST

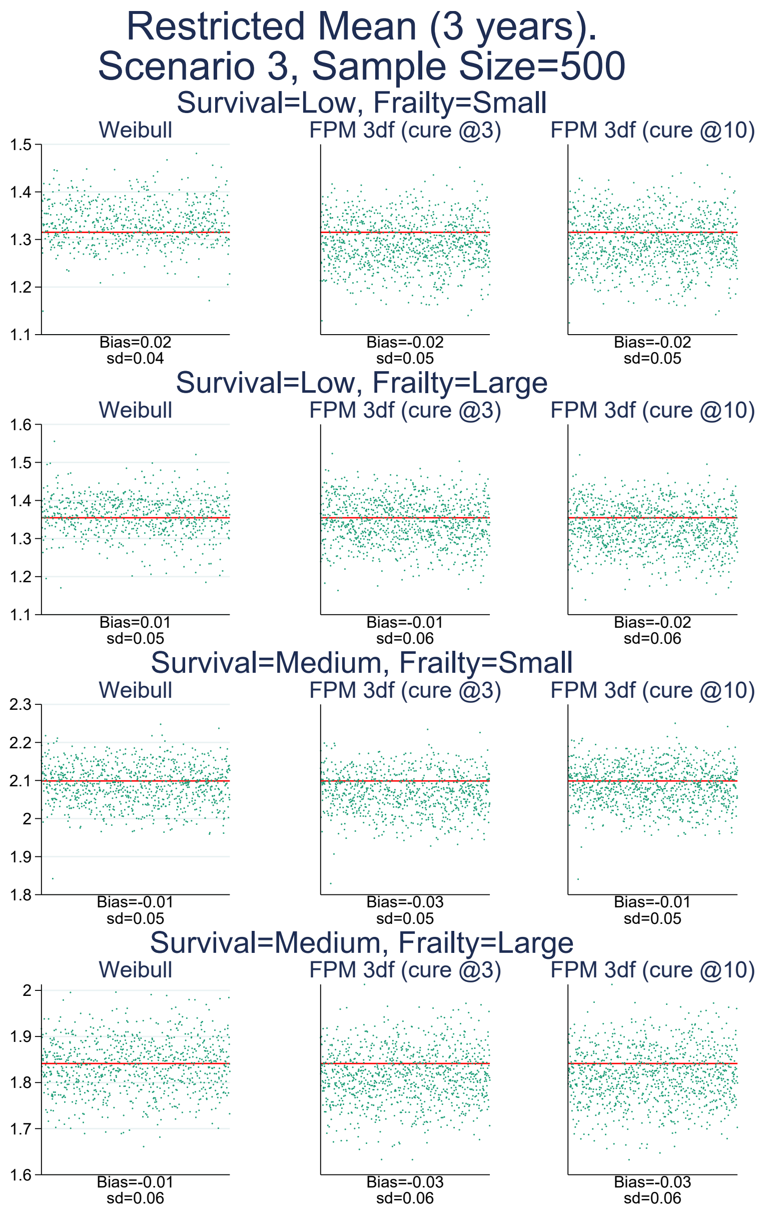

Figure 56: Cure models: Scenario 3 (SS=500), RMST

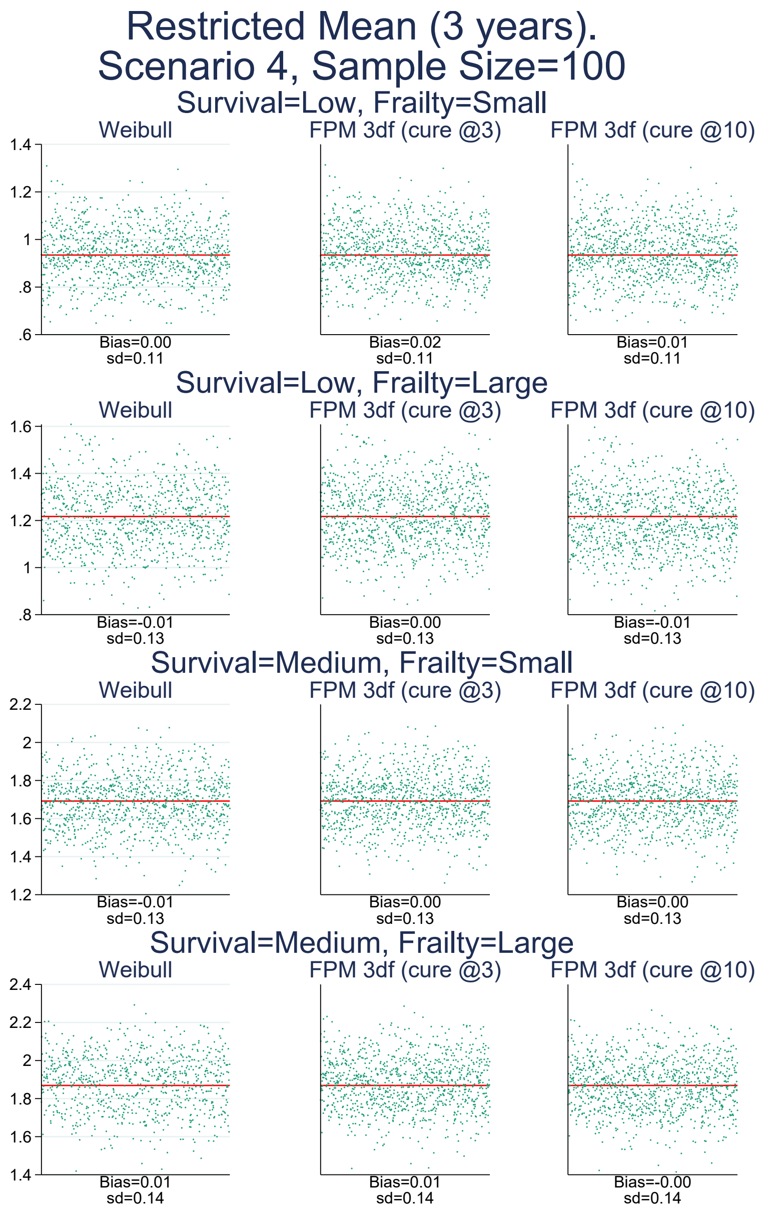

Figure 57: Cure models: Scenario 4 (SS=100), RMST

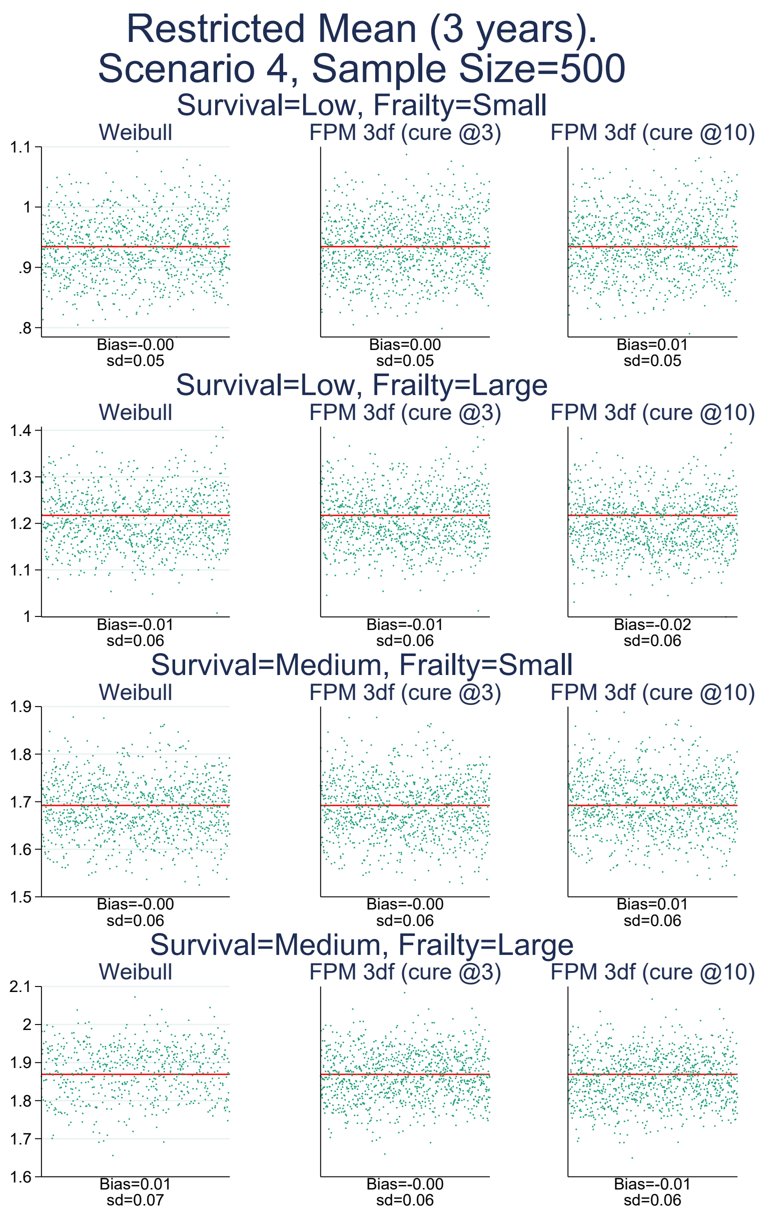

Figure 58: Cure models: Scenario 4 (SS=500), RMST

6.2 Mean survival

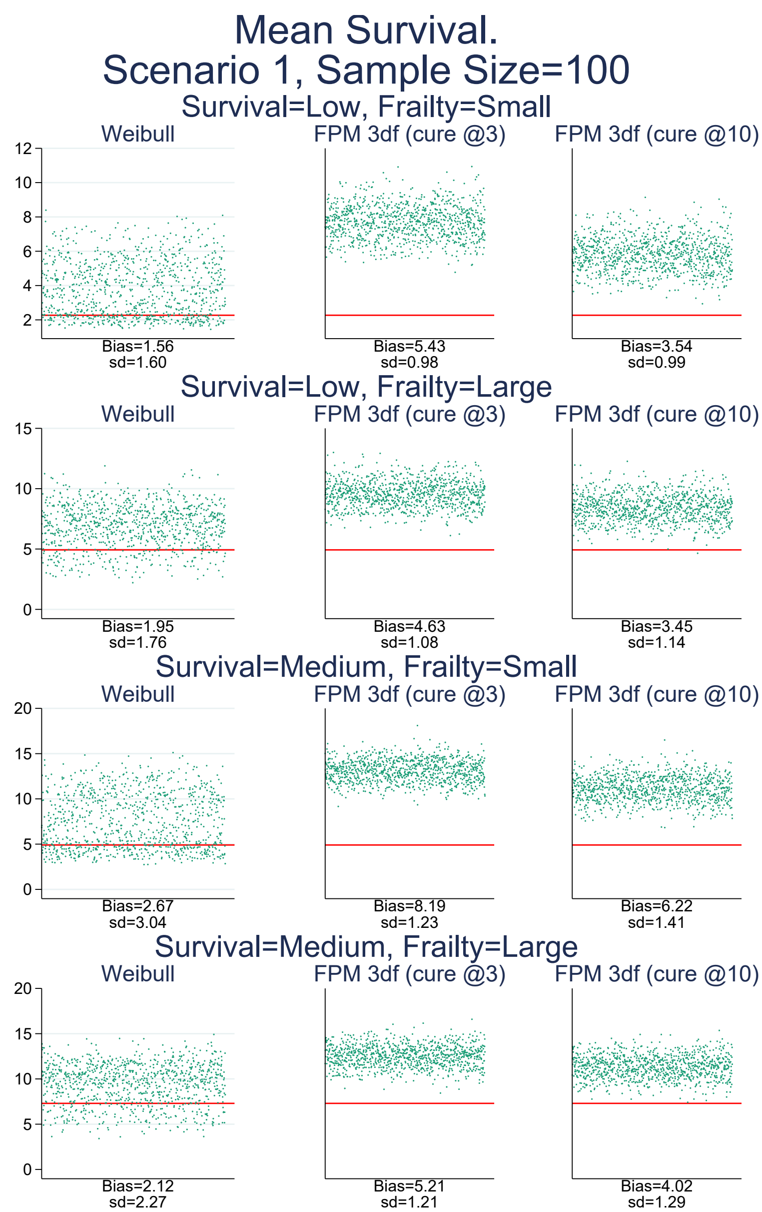

Figure 59: Cure models: Scenario 1 (SS=100), Mean survival

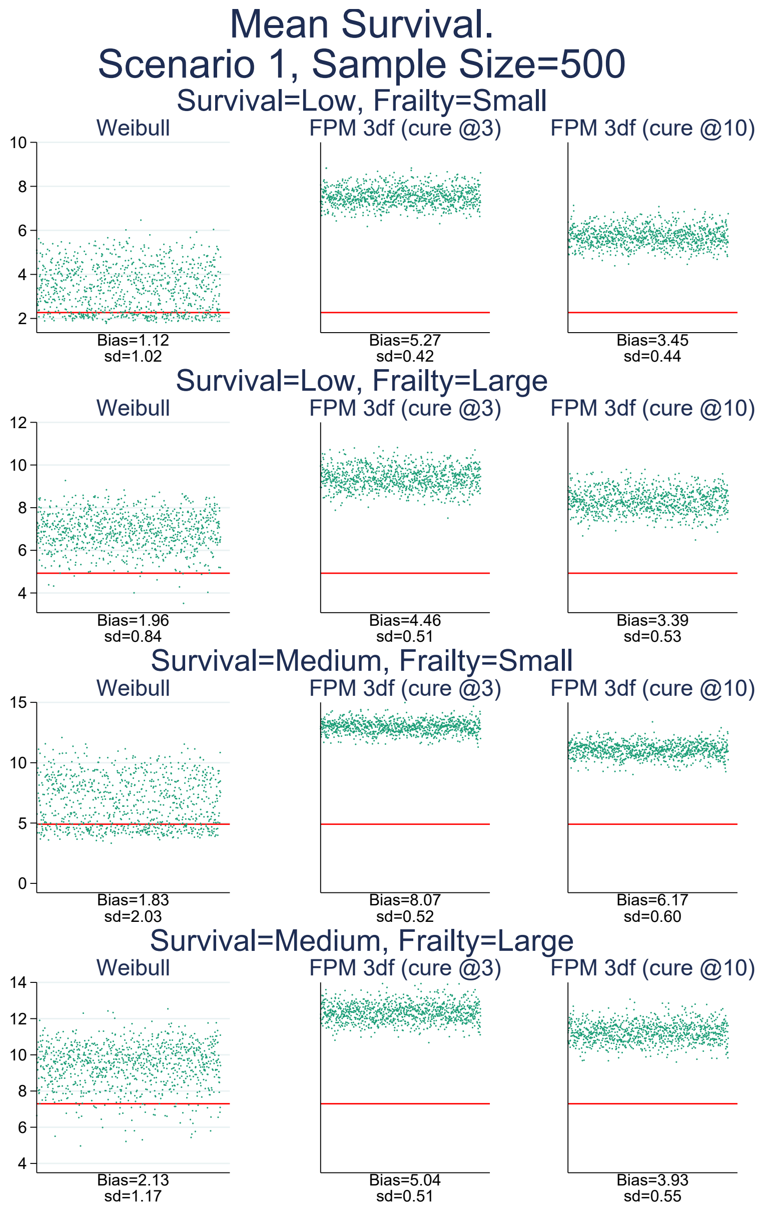

Figure 60: Cure models: Scenario 1 (SS=500), Mean survival

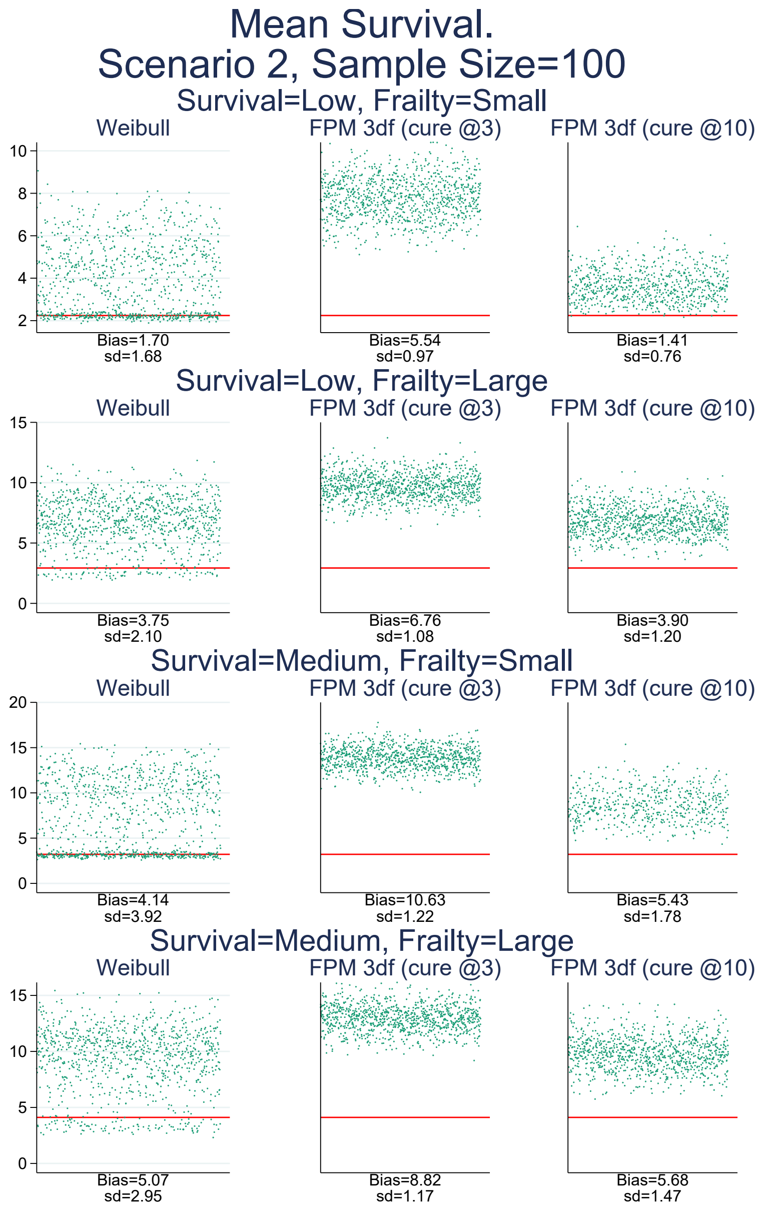

Figure 61: Cure models: Scenario 2 (SS=100), Mean survival

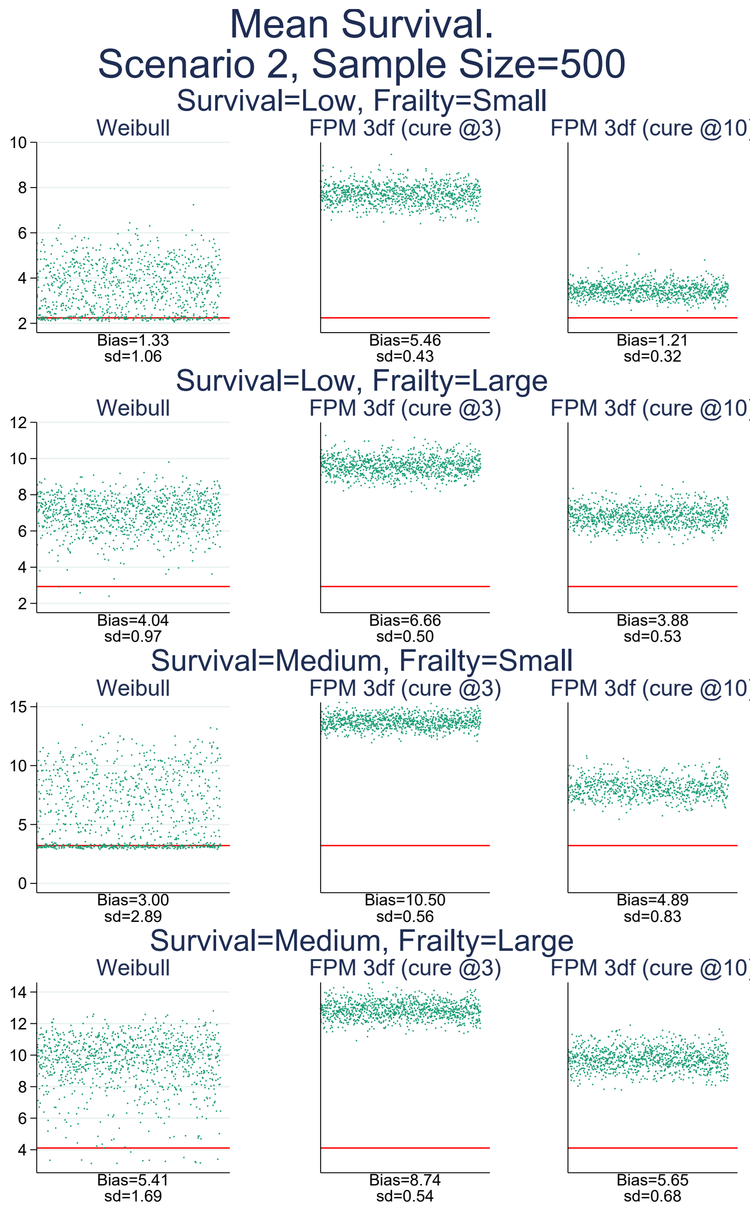

Figure 62: Cure models: Scenario 2 (SS=500), Mean survival

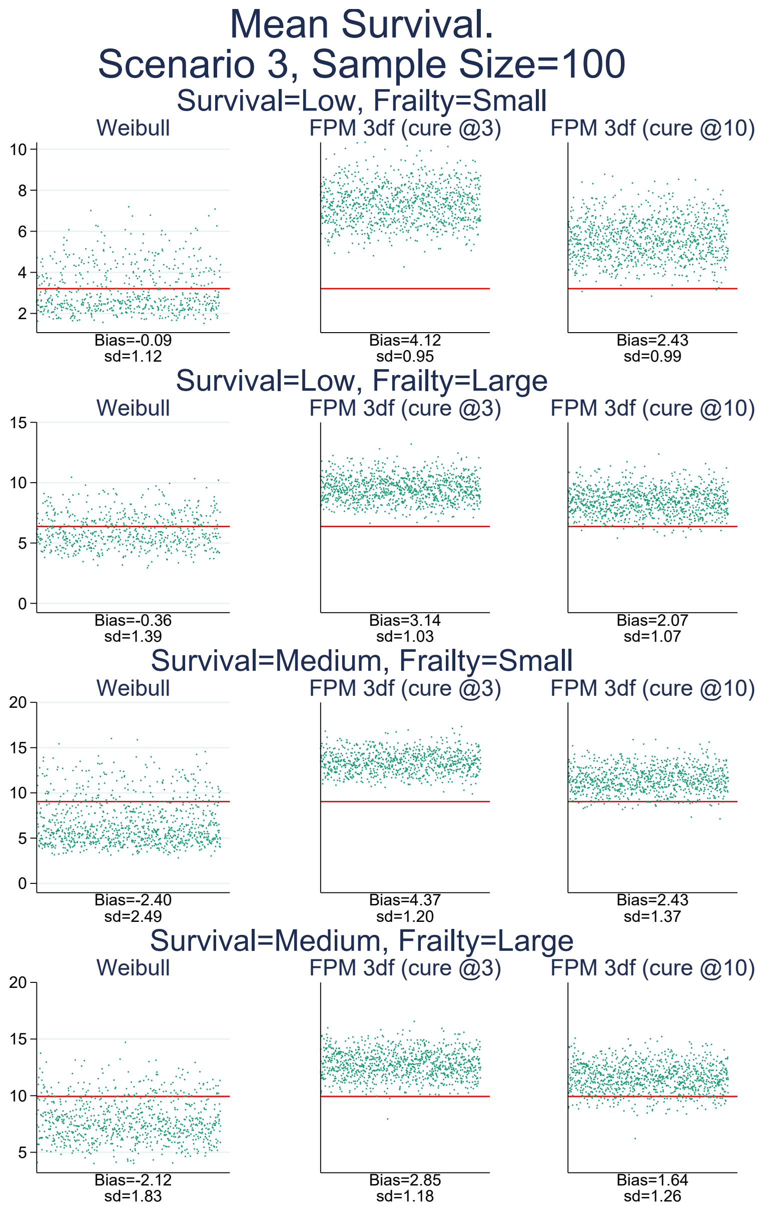

Figure 63: Cure models: Scenario 3 (SS=100), Mean survival

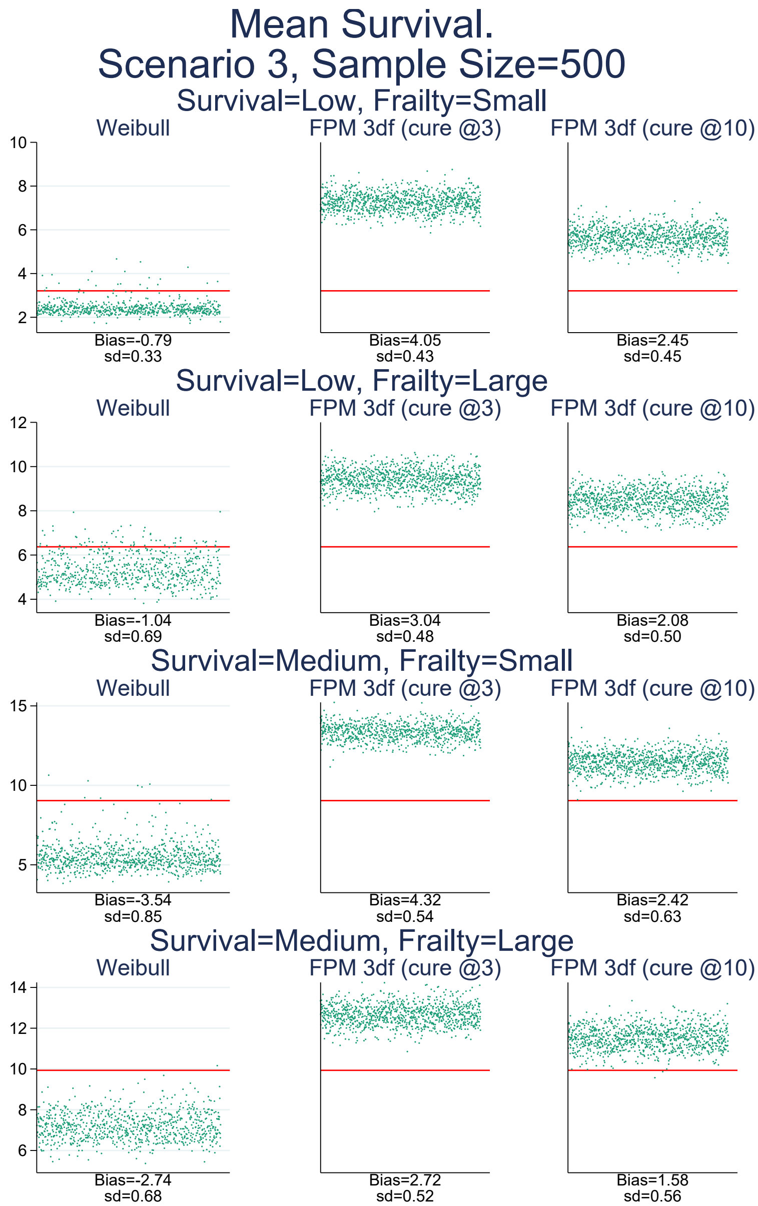

Figure 64: Cure models: Scenario 3 (SS=500), Mean survival

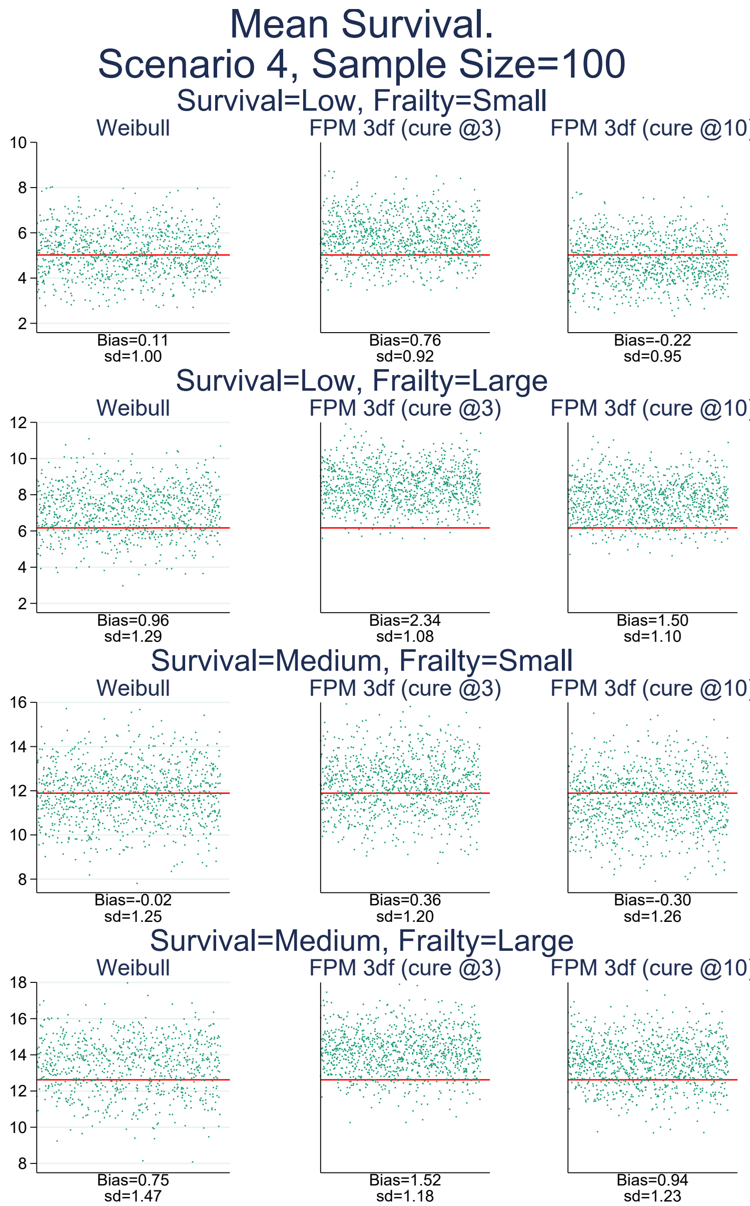

Figure 65: Cure models: Scenario 4 (SS=100), Mean survival

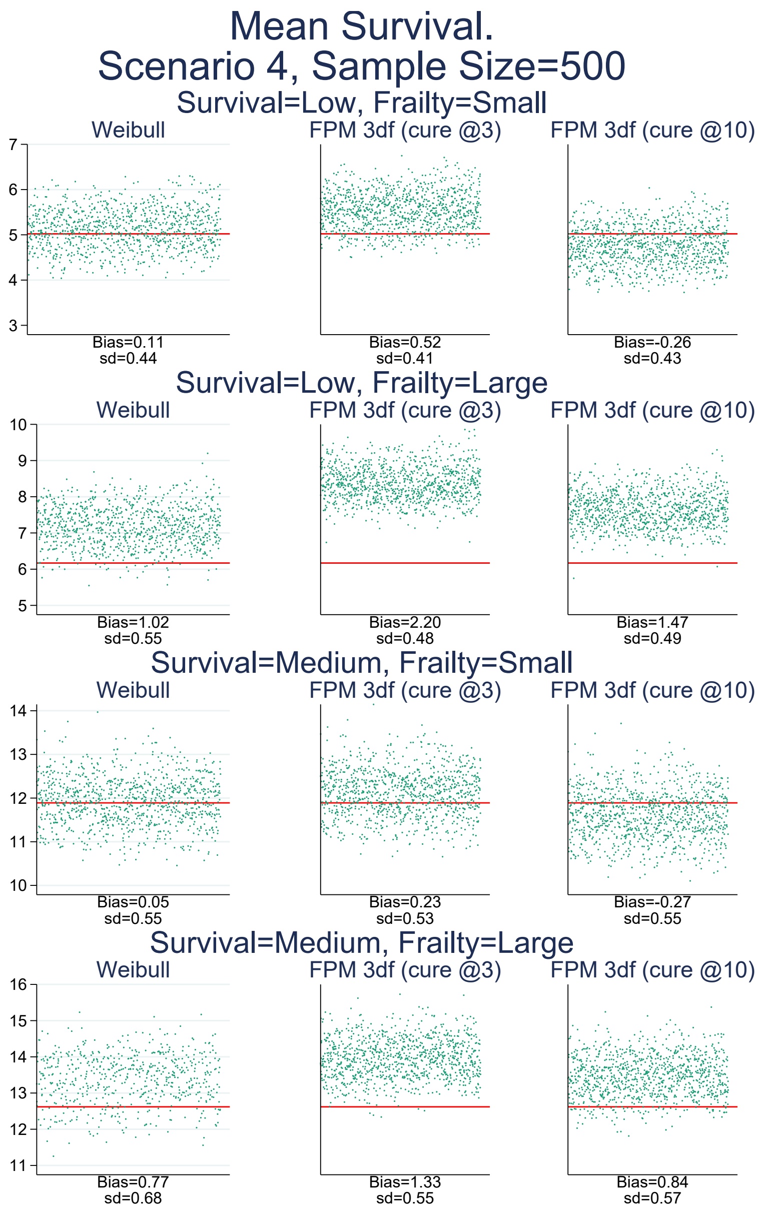

Figure 66: Cure models: Scenario 4 (SS=500), Mean survival

6.3 Summary of Simulations

- Cure models (that incorporated background mortality) resulted in slight bias in RMST in scenarios where cure was not a reasonable assumption. However, these models still fit reasonably well to the observed data and produced low bias.

- Cure models led to substantial bias in estimates of mean overall survival in scenarios where a cure was not reasonable – in Scenarios 1 and 2, where other methods estimated mean survival with relatively low bias, cure models often resulted in appreciable bias. In Scenario 4, where a cure fraction was simulated, bias associated with cure models was lower than other methods, particularly when heterogeneity was low.