



IMPACT LAB
Innovative Methods in Paediatric Clinical Trials

SickKids[®]

Developing Guidance for Bayesian Survival Analyses in Rare Disease Trials

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Disclosures

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- No relevant disclosures

Acknowledgments

- RareKids-CAN



Rare Diseases

- The Lancet Global Health (2024)

By definition, rare diseases affect a small number of individuals (fewer than 1 in 2000 people in any WHO region); yet, with more than 7000 types of rare disease in existence, the burden worldwide is not insignificant. To date, approximately 300 million people live with rare diseases. Such individuals are often a neglected and marginalised group, especially those in low-income and middle-income countries. Around 80% of rare diseases have a genetic cause, almost 70% of which present in childhood; about 95% lack approved treatments; the average time for an accurate diagnosis is 4.8 years; and about 30% of children with a rare disease die before age 5 years. In 2021, the UN

Bayesian Methods and Rare Disease Trials

- Frequentist methods rely on
 - Large-sample assumptions that are infeasible to recruit in rare diseases
 - Trial data alone to draw conclusions
- Bayesian methods incorporate external evidence into the design and interpretation of a trial, making better use of small sample sizes

Bayesian survival analyses are underutilized...

- Brard et al. (2017):

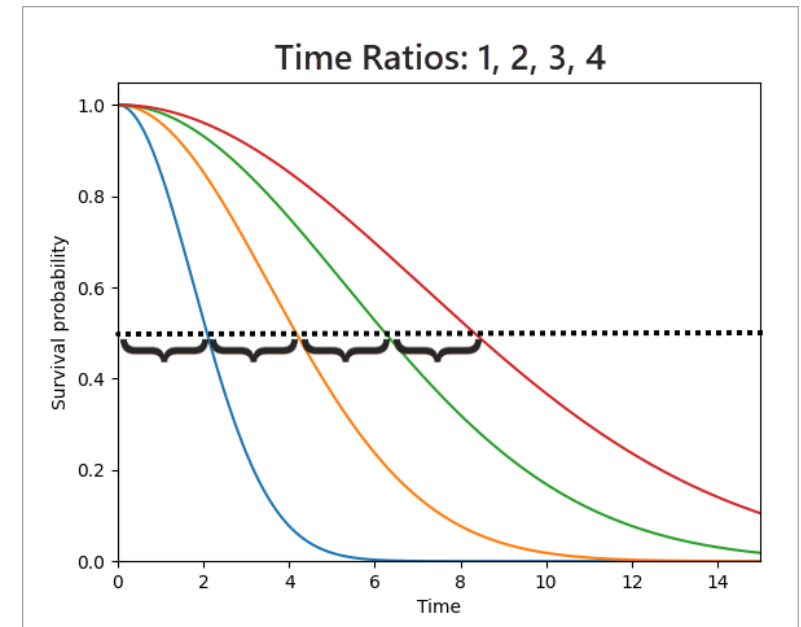
Conclusion

Few trials implemented a Bayesian survival analysis and few incorporated external data into priors. There is scope to improve the quality of reporting of Bayesian methods in survival trials. Extension of the Consolidated Standards of Reporting Trials statement for reporting Bayesian clinical trials is recommended.

- Marks et al. (under review): 17/164 trials have used Bayesian survival analysis in their primary analysis since 2009

Survival Modelling Choices

- Possible baseline distributions:
 - Nonparametric, Weibull, exponential, lognormal, log-logistic, Gompertz, generalized gamma
- Proportional hazards (PH) or accelerated failure time (AFT)
 - Hazard ratio: Compares rate at which an event occurs in two different groups over time
 - Time ratio: Acts as a multiplier for which the time to an event changes in one group relative to a control



ArcGIS (n.d.)

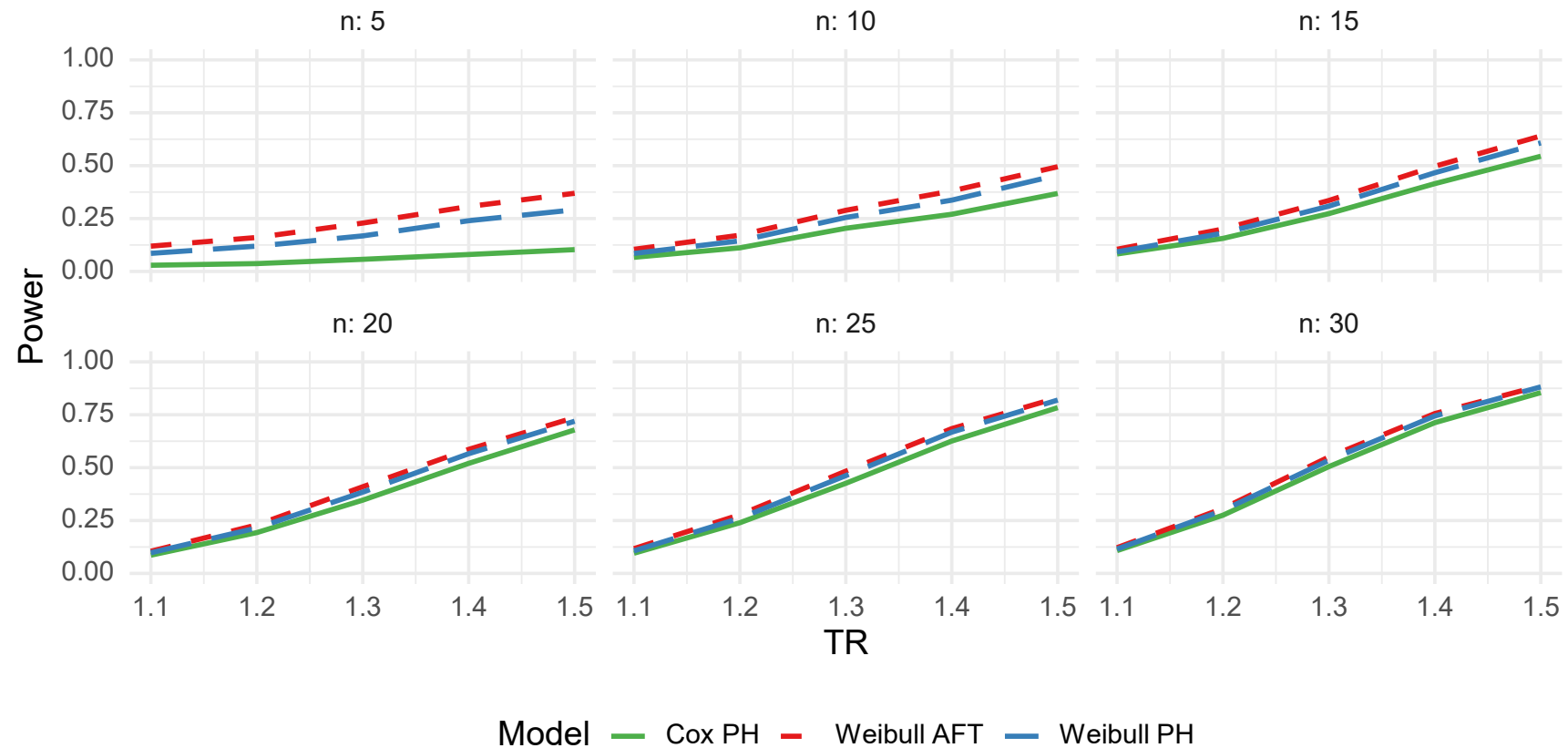
Comparing Survival Models

- Power: Cox PH vs. Weibull PH vs. Weibull AFT

Category	Parameter Values
Baseline Distribution	Weibull
Effect Types + Sizes	Time Ratio: 1 to 1.5; Hazard Ratio: 0.83 to 1 $\exp(-\log(1 \text{ to } 1.5))$
Sample Sizes	5 to 25 per arm

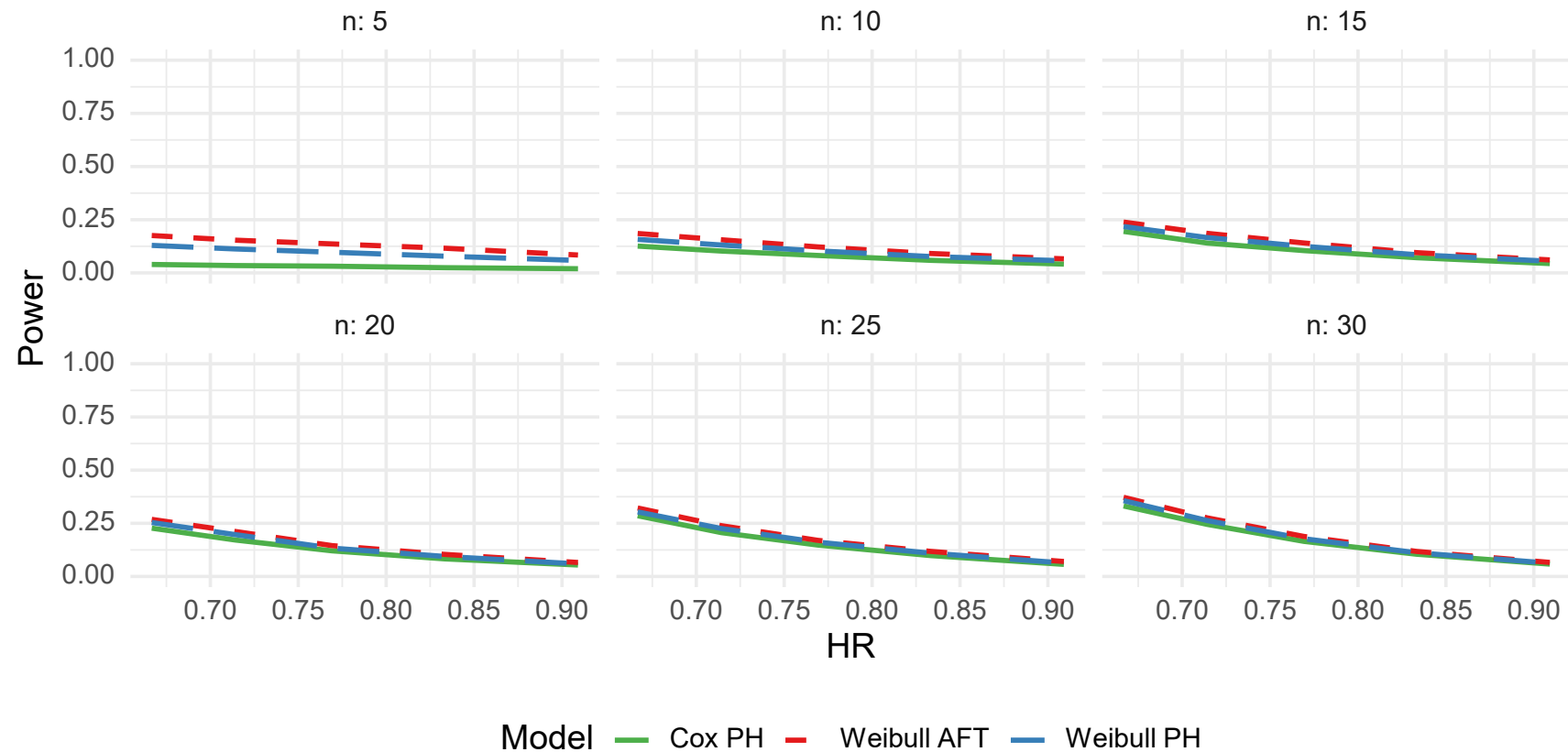
Frequentist Comparisons

Power vs. TR for Different Models (Generated from TR)



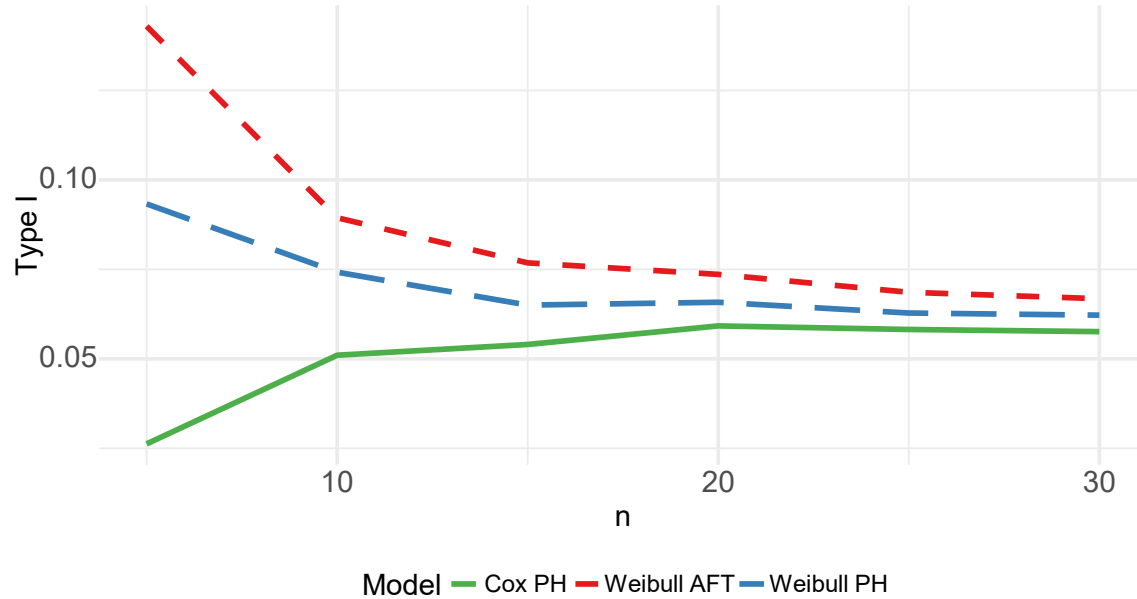
Frequentist Comparisons

Power vs. HR for Different Models (Generated from HR)

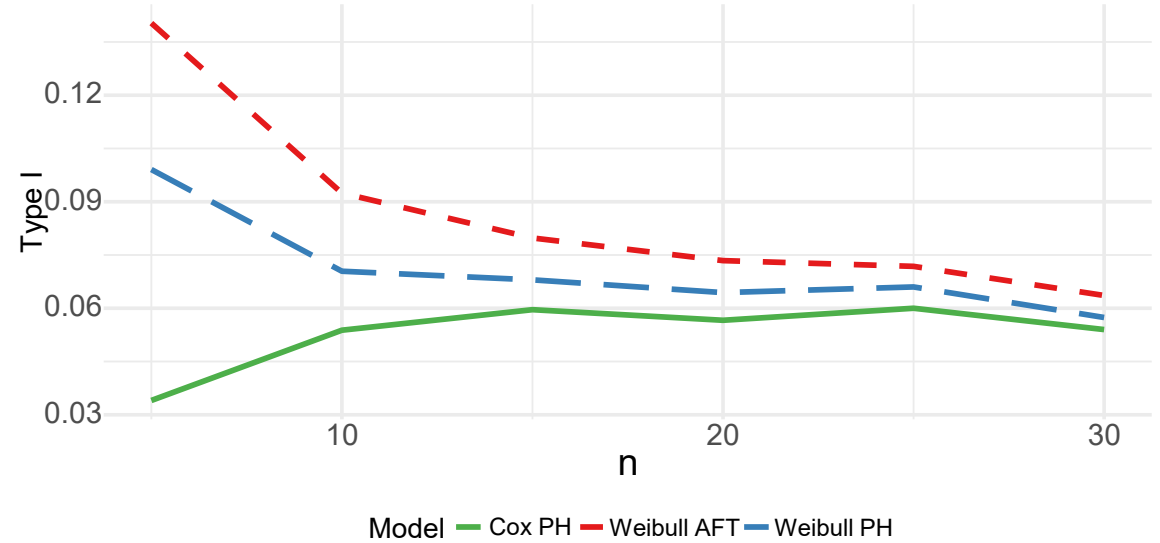


Differential Type I error control

Type I Error vs. Sample Size for Different Models (Generated from TR)



Type I Error vs. Sample Size for Different Models (Generated from HR)

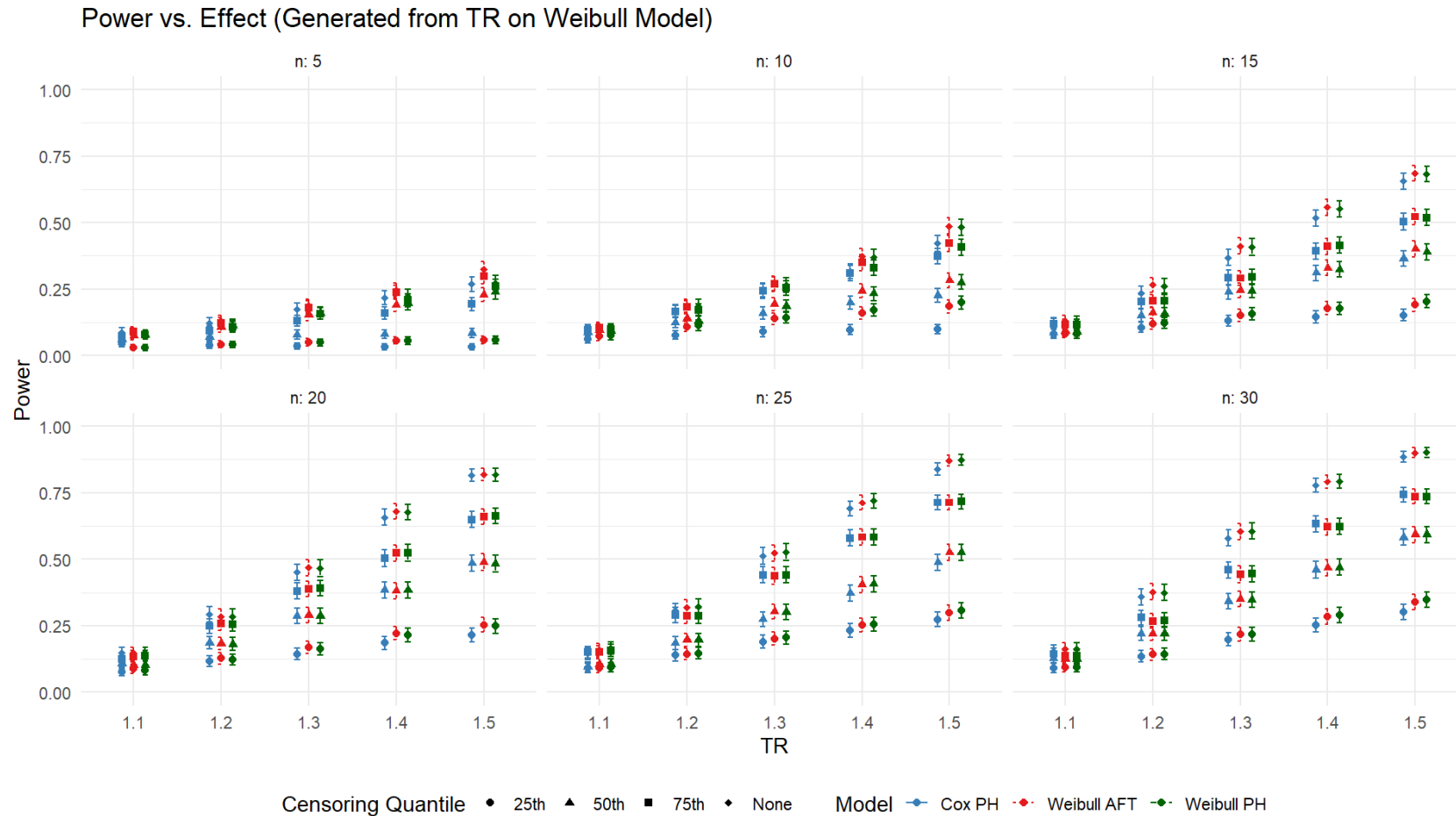


Comparing Bayesian Survival Models

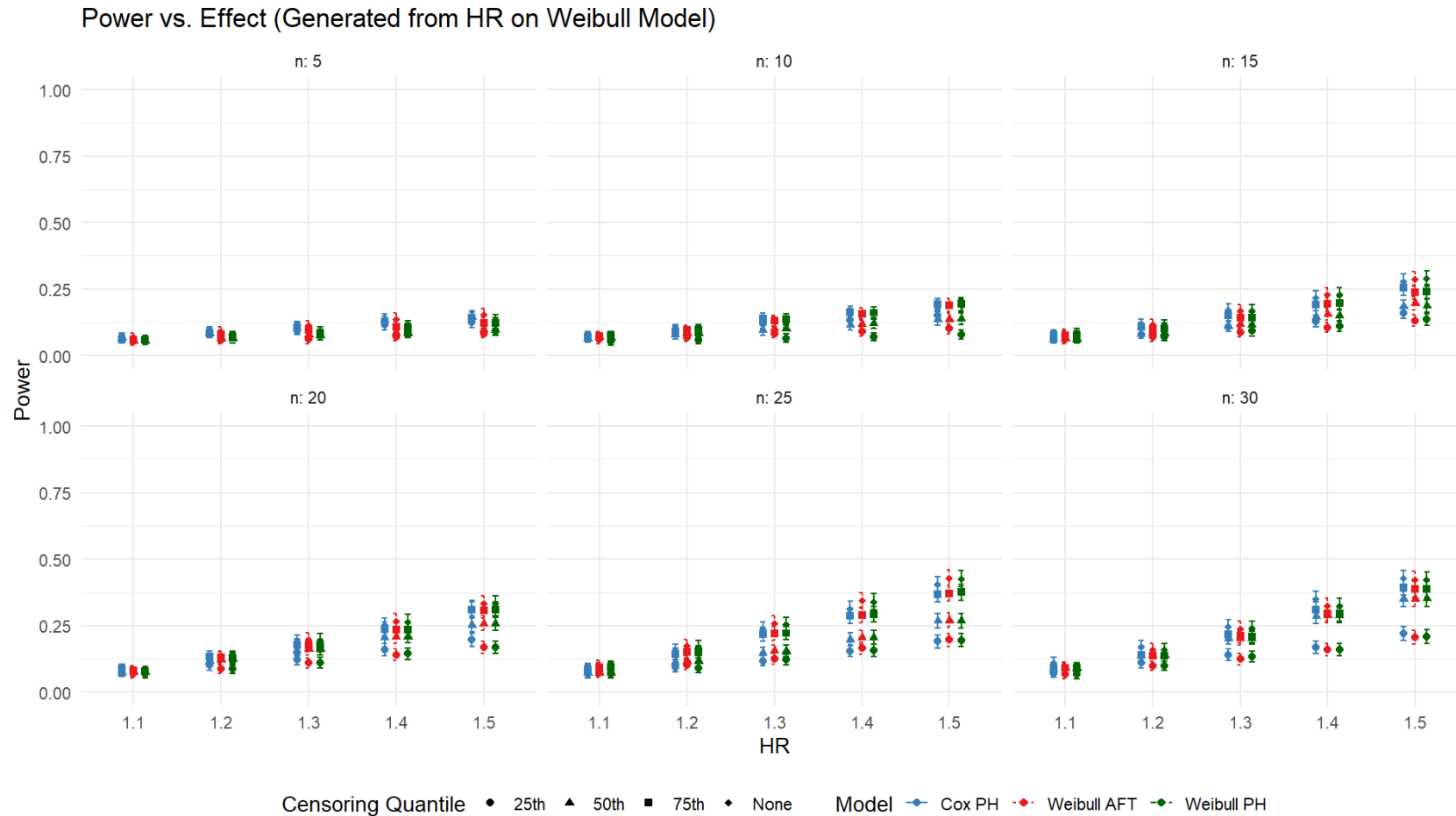
- Power: Cox PH vs. Weibull PH vs. Weibull AFT

Category	Parameter Values
Baseline Distribution	Weibull, Gompertz
Effect Types + Sizes	Time Ratio/Hazard Ratio: 1 to 1.5
Sample Sizes	5 to 25 per arm
Censoring	25 th , 50 th , 75 th Quantiles + no censoring

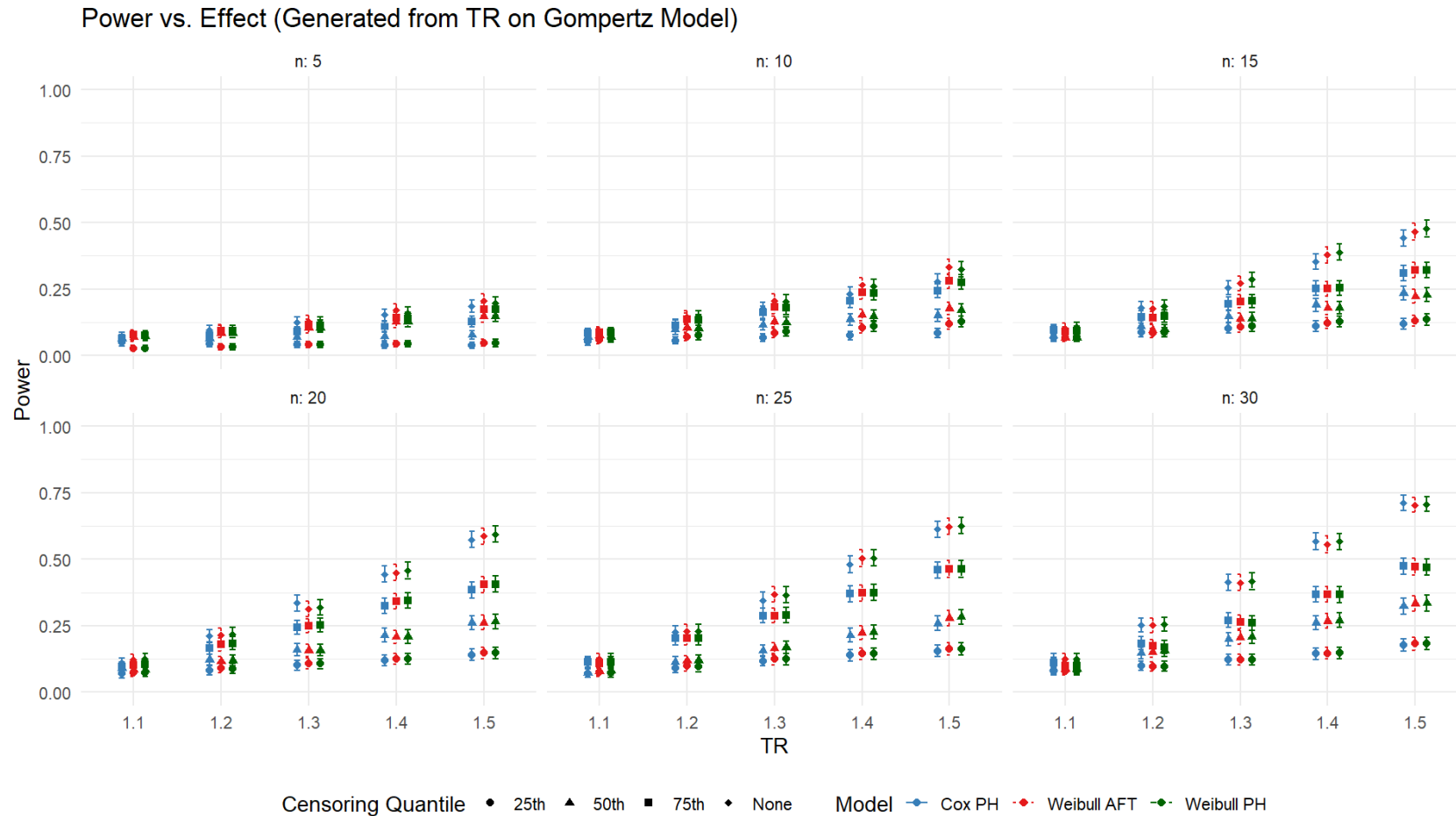
Bayesian Comparisons



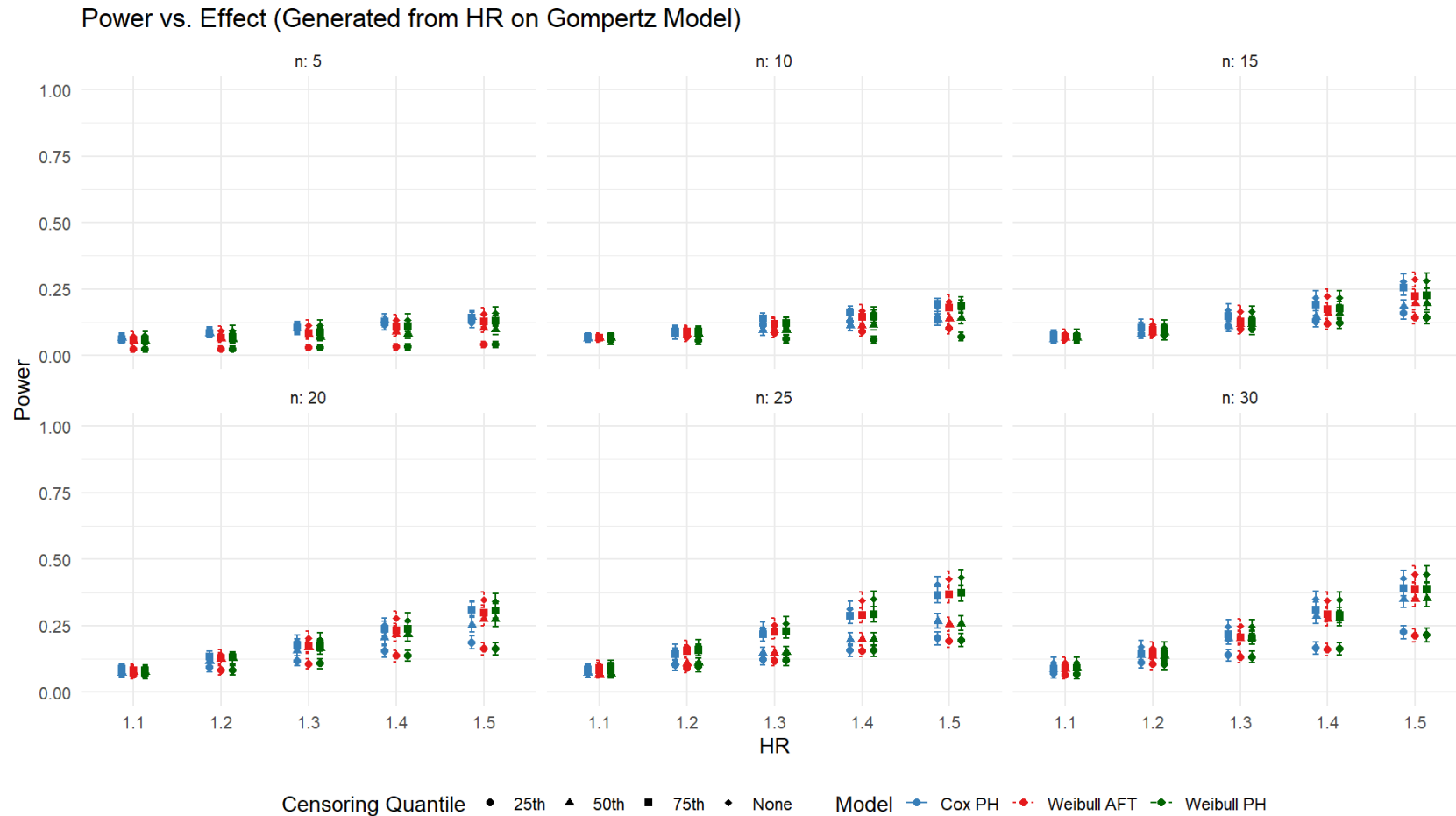
Bayesian Comparisons



Bayesian Comparisons



Bayesian Comparisons



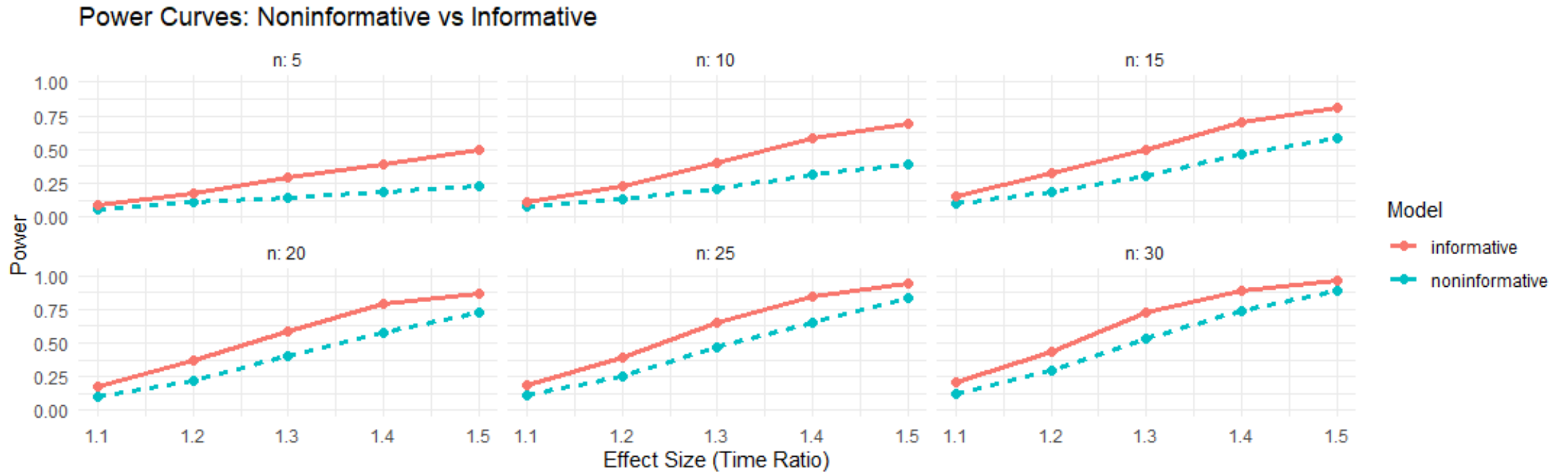
Summary

- Similar power among Cox PH, Weibull PH, and Weibull AFT models
 - Even with mismatch between baseline distribution used to generate and analyze data

Cox PH Model Issues

- abcoxp: Repeated estimates and posterior probabilities across different effect sizes
 - 15 to 19% of results are duplicated (compared to .5 to 1.5% with other models)
 - Authors state estimates are less accurate for small n
- JAGS/INLA: Approximate nonparametric baseline with piecewise exponential model or random-walk
 - Estimates dependent on number of splines

Effect of a Baseline Prior on Weibull AFTs



How to obtain prior distributions?

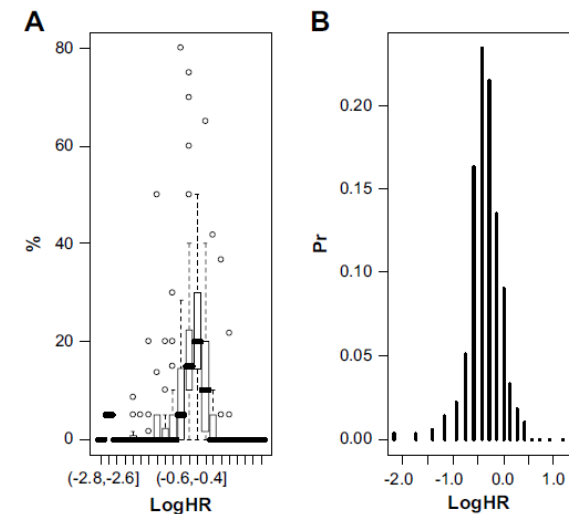
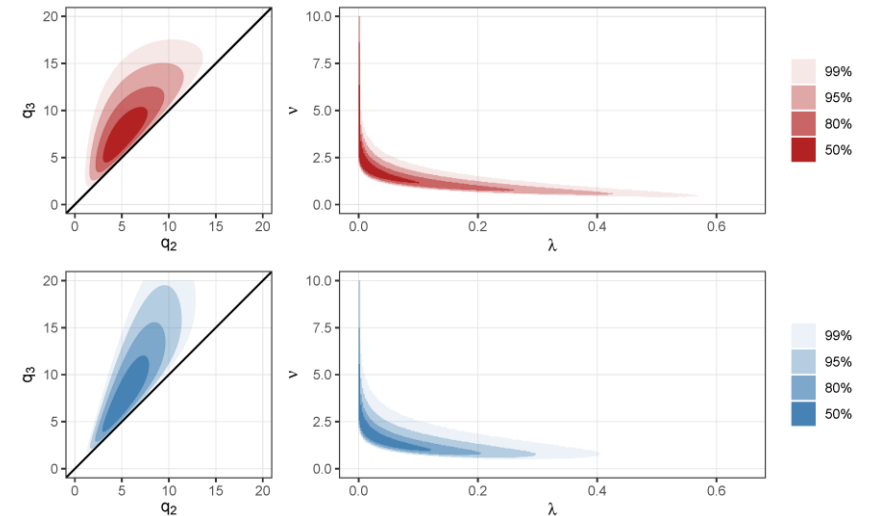
- From data
- From expert knowledge

Data-Driven Prior Distribution

- Control/Treatment Arm:
 - Digitize Kaplan-Meier curve to obtain individual patient data with SurvdigitizeR & survHE packages
 - Model historical data alongside trial data
 - *Consider downweighting, depending on prior sample size*
- Treatment Effect:
 - Use reported HR/TR and corresponding CI

Expert Knowledge-Derived Prior Distribution

- Baseline Distribution
 - Weibull prior distribution
 - Prajapati et al. (2025)
- Treatment Effect
 - Hazard ratio
 - Hiance et al. (2009)
 - Time Ratio



Summary & Next Steps

- Cox PH, Weibull PH, and Weibull AFT are similarly powered
 - Even when simulating with a different baseline distribution
- Recommend using parametric distributions to use baseline priors
- Future Work
 - When to use an informative prior?
 - Prior/data mismatch