Maximum Likelihood Estimation to Quantify the Impact of Treatment Response on Survival Outcomes

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BACKGROUND

- Differences in intermediate outcomes such as complete response (CR) can disguise differential long-term outcomes in patient subgroups when examining survival data aggregated over the entire population reported in clinical trials
- When meta-analyzing survival estimates across trials it may be important to consider the impact of CR on the overall estimates because the proportion of patients with CR will vary from trial to trial

OBJECTIVE

- To demonstrate the use of maximum likelihood estimation (MLE) to pool survival outcomes across trials with different levels of aggregation, adjusting for the proportions of patients with CR

WHAT IS MLE?

- A technique to estimate the parameters of a statistical model, given the observed data
- MLE answers the question "what is the value of the parameters that are most likely to generate the data we have observed?"

APPLICATIONS

- Few methods exist to meta-analyze survival data in heterogeneous populations
- Maximum likelihood estimation can be used in meta-analyses to quantify the impact of intermediate outcomes or baseline patient characteristics on survival or other endpoints if complete information can be obtained for 1 or more included studies

METHODS

1

Assume parametric distribution for survival data (test and validate assumption)

Here, survival is assumed to follow the Weibull distribution

$$S(\mathrm{t};\mathrm{CR}) = \mathrm{e}^{-\lambda' \mathrm{t}^{\alpha}} \text{ and } \mathrm{h}(\mathrm{t},\mathrm{CR}) = \lambda' \alpha \mathrm{t}^{\alpha-1}$$

where $\lambda' = \lambda \times \mathrm{HR\ of\ CR}$

2

Construct likelihood function for each type of available data

I. Event/censored times and CR status known for each patient $i \in \{1, \cdots, n\}$

$$\prod_{i}^{n} \mathrm{S}(\mathrm{t}_i;\mathrm{CR}_i) \cdot \mathrm{h}(\mathrm{t}_i;\mathrm{CR}_i)^{obs_i}$$ where obs_i=1 if observed and 0 if censored

II. Event/censored times known for each patient, but only overall % of CR

$$\prod_{i}^{n} Prop_{CR}\mathrm{S}(\mathrm{t}_i;\mathrm{CR}{=}1) \cdot \mathrm{h}(\mathrm{t}_i;\mathrm{CR}{=}1)^{obs_i} + (1 - Prop_{CR})\mathrm{S}(\mathrm{t}_i;\mathrm{CR}{=}0) \cdot \mathrm{h}(\mathrm{t}_i;\mathrm{CR}{=}0)^{obs_i}$$

III. Percent survival at follow-up time or median survival and overall % of CR

$$\left[\prod^{n*(1-Surv\,\%)} Prop_{CR}(1 - \mathrm{S}(\mathrm{time};\mathrm{CR}{=}1)) + (1 - Prop_{CR})(1 - \mathrm{S}(\mathrm{time};\mathrm{CR}{=}0))\right] \cdot \left[\prod^{n*Surv\,\%} Prop_{CR}\mathrm{S}(\mathrm{time};\mathrm{CR}{=}1) + (1 - Prop_{CR})\mathrm{S}(\mathrm{time};\mathrm{CR}{=}0)\right]$$

3

Construct likelihood function for entire collection of data; parameters of interest are those that maximize this function

Meta-analytic likelihood =
$\mathrm{Lik}_{\mathrm{study1}} + \mathrm{Lik}_{\mathrm{study2}} + \ldots + \mathrm{Lik}_{\mathrm{studyN}}$

DEMONSTRATION OF METHODOLOGY

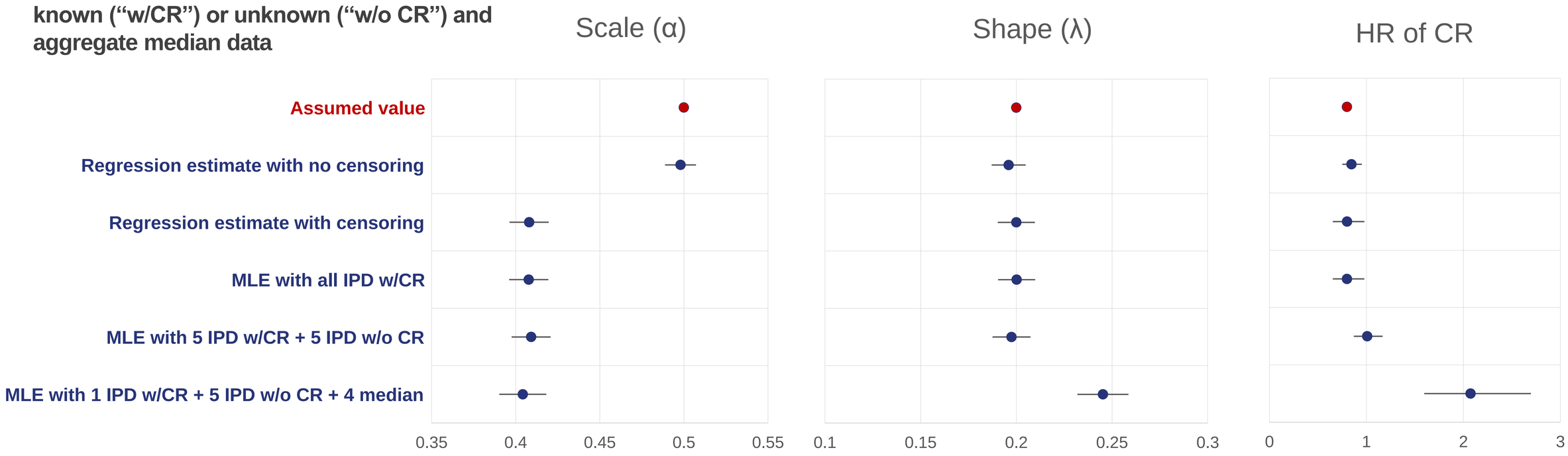
Data Source: 10 randomly generated trial populations (Weibull survival times)

- Sample size – 63 to 297
- Proportion with CR – 3% to 18%
- 5% censoring, increasing with time
- All observations censored at 48 months

MLE Parameter Estimations

- As a benchmark, the Weibull parameters were estimated via regression using the predicted trial data with and without censoring
- With censored data,
  - The HR of CR (the parameter of primary interest) is estimated well
  - The regression estimate for α has shifted
- Similar estimates were obtained from the MLE method when half of the studies did not provide CR information for individual patients
- The scenario with the least amount of CR information, where 1 study provided patient-level CR data and 4 provided aggregate median survival, results in the least precise and least accurate survival estimates

Figure. Weibull parameters estimated from the 10 simulated trials under various combinations of individual patient data (IPD), where CR status is known ("w/CR") or unknown ("w/o CR") and aggregate median data



APPLICATION TO PUBLISHED TRIAL DATA

- 19 clinical trials of treatments for relapsed/refractory chronic lymphocytic leukemia reporting some measure of overall (OS) and/or progression-free survival (PFS) and proportion of patients with CR were identified
  - 4 IPD w/CR; 8 IPD w/o CR; 7 median
- Assumed Weibull a survival distribution and proportional hazards for CR vs no CR and PFS vs OS
- MLE estimates show the HR of survival for those attaining CR vs those who do not was 0.27

REFERENCES

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