The Impact of Life Expectancy Exclusion Criteria on Survival Curve Extrapolation

MSR72

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BACKGROUND

- Survival extrapolation, based on fitting single distributions to data from randomized clinical trials (RCT), is commonly performed as part of health technology assessment (HTA) submissions and follows the NICE Decision Support Unit's Technical Support Document 14.[1]
- This approach makes the following assumptions: there is a single underlying distribution in the data, and patients are sampled at random.
- However, there are often many inclusion and exclusion criteria in RCTs that restrict how patients are sampled from a larger population.

OBJECTIVE

- This research investigates how exclusion criteria affect our ability to correctly identify an underlying exponential distribution using simulated data.

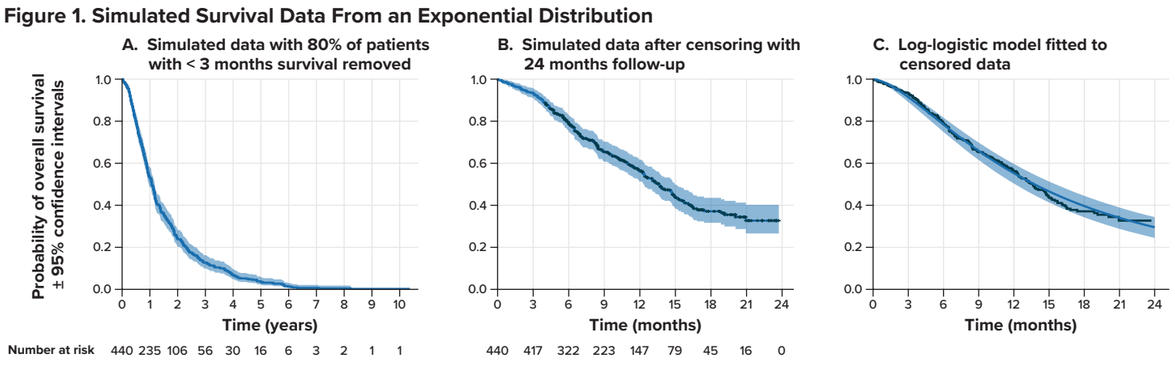
METHODS

- Survival data were simulated for 10,000 samples of 500 patients each using an exponential distribution (λ = 0.06 using the simsurv[2] package in R), assuming patients entered the trial at random times with a follow-up of 24 months, entered the trial at least 3 months before the end of the trial, and 0%-100% of patients had < 3 months survival removed at random, which resulted in a maximum of 20% of patients excluded from the sample.
- We highlight a specific case where 80% of patients with < 3 months survival may be removed from the sample; a recent study reported 80% accuracy by physicians at predicting < 3 months life expectancy.[3]
- In total, 7 standard parametric models (exponential, Gompertz, Weibull, gamma, log-logistic, log-normal, and generalized gamma) and 7 models with a turning point at 3 months (piecewise exponential, spline-based models with 1 and 2 knots for Weibull, log-normal, and log-logistic distributions) were fitted to each simulated data set.
- Akaike information criteria (AIC) and Bayesian information criteria (BIC) were converted to weights to give the probability of best fit.[4]
- For each simulation, predicted mean survival and maximum survival (time to reach 1% survival) were estimated and compared with those from the original sample (i.e., before the exclusion criteria were applied).
- The relationship between probability of best fit, mean survival, and maximum survival with the proportion of patients removed with < 3 months survival was estimated using heteroscedastic additive regression models.[5]

RESULTS — SIMULATION EXAMPLE

- Figure 1 presents an example from a single simulation in which 80% of patients with < 3 months survival were removed (60 of 500 patients [12%]).
  - The survival curve before censoring (A) still resembles an exponential distribution. However, after censoring (B), the survival curve no longer resembles an exponential distribution. In fact, both AIC and BIC indicate that the censored data are from a log-logistic distribution (C). If extrapolation is based on a log-logistic distribution, we assume decreasing hazard rates after follow-up instead of constant hazards from an exponential distribution, which will result in overestimation of mean survival.

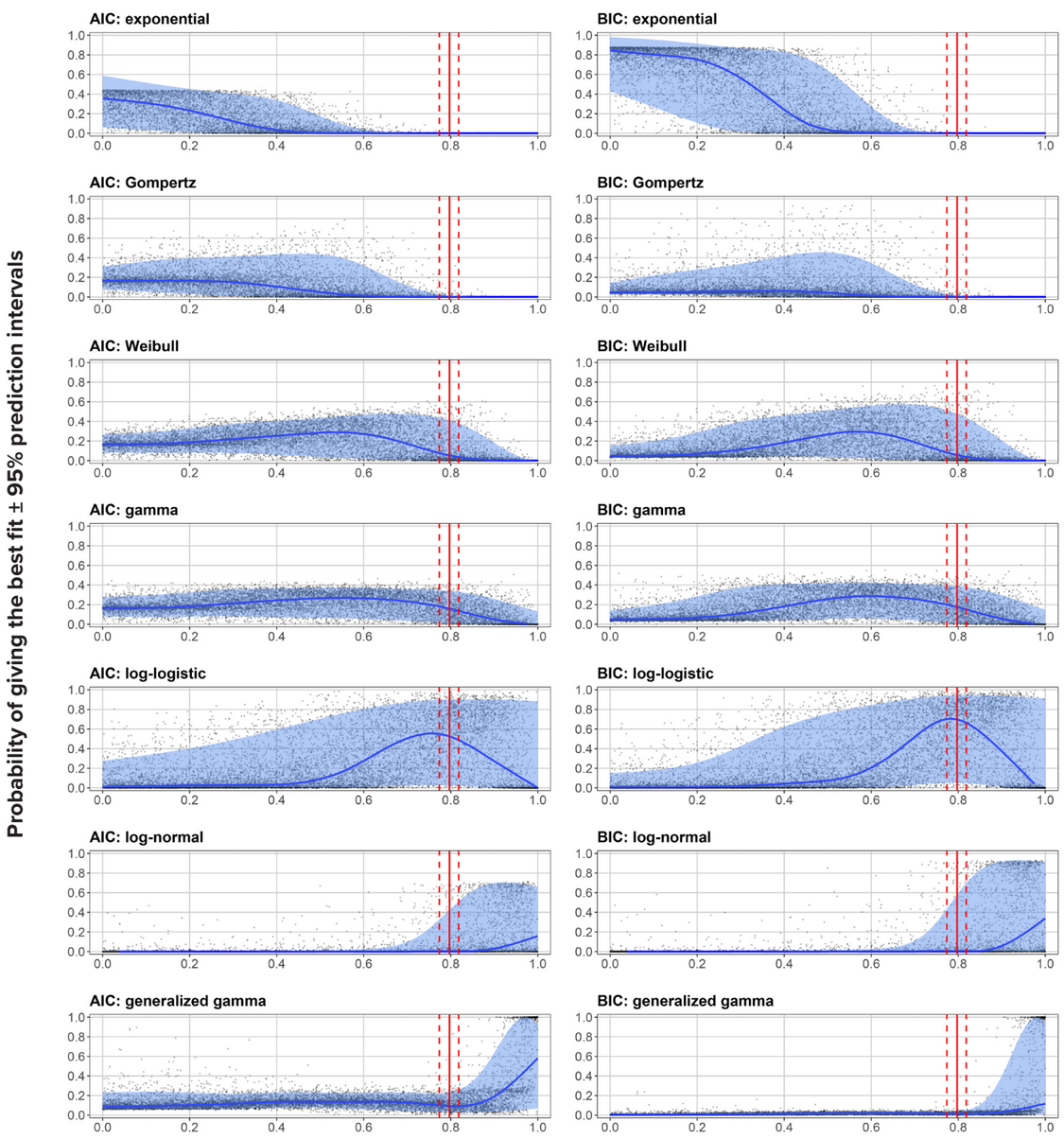
Figure 1. Simulated Survival Data From an Exponential Distribution



RESULTS — BEST-FITTING MODELS

- Figure 2 presents the probability of each standard parametric model giving the best fit, according to AIC and BIC, as the proportion of patients removed with < 3 months survival goes from 0 to 1.

Figure 2. Probability of Best-Fitting Model by Proportion of Patients Excluded With Poor Life Expectancy

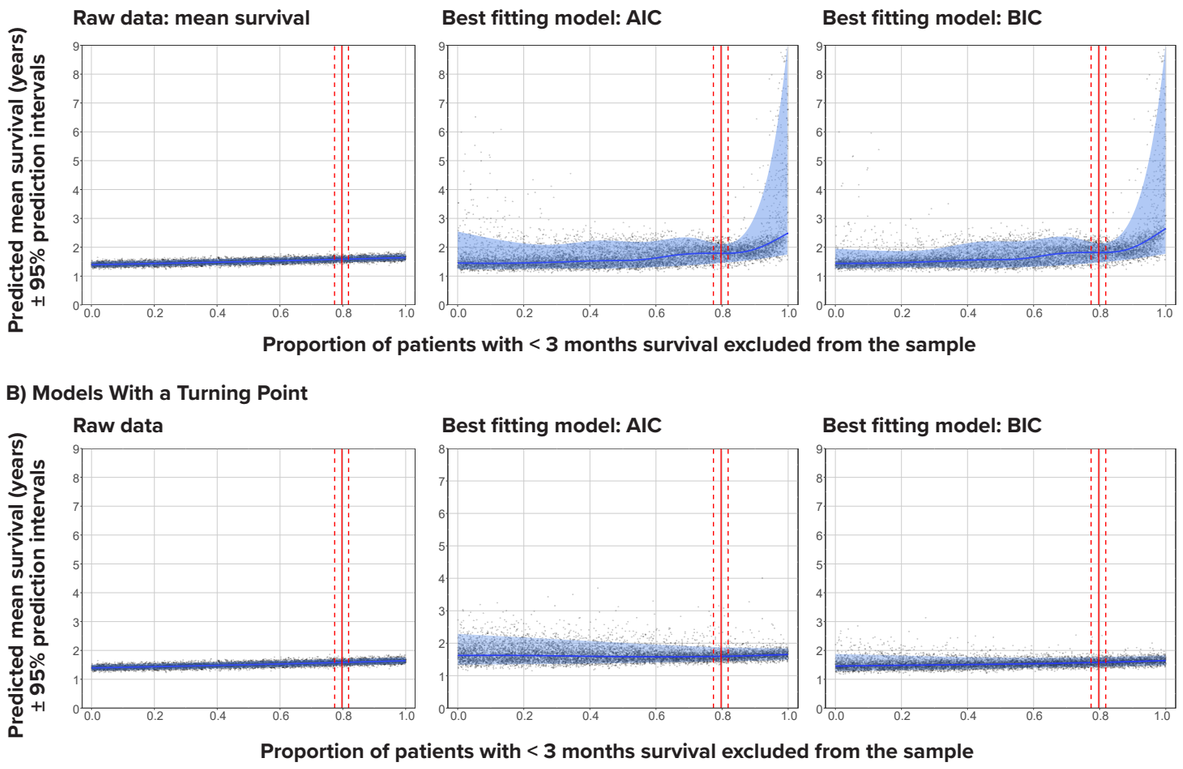


- As the proportion of patients removed, with survival of < 3 months, increased, the best-fitting standard models changed from exponential to the following order of distributions: Weibull, gamma, log-logistic, log-normal, and generalized gamma. With 80% of patients removed with < 3 months survival, the best-fitting model was most likely to be a log-logistic distribution.
- For the models with turning points, the piecewise exponential model consistently gave the best fit regardless of the proportion of patients removed with < 3 months survival (chart not shown).

RESULTS — PREDICTED MEAN AND MAXIMUM SURVIVAL

- Figure 3 presents the predicted mean survival from the best-fitting model among the parametric models (A) and the models with a turning point (B), as determined by AIC and BIC, as the proportion of patients removed with < 3 months survival goes from 0 to 1.
  - At 80% exclusion of patients with < 3 months survival, the best-fitting standard parametric model overestimated mean survival by approximately 23% (an increase from 1.58 years to 1.95 years). Maximum survival (chart not shown) was overestimated by 133% (an increase from 6.5 years to 15.2 years).
  - At 80% exclusion of patients with < 3 months survival, the best-fitting model with a turning point showed little evidence of overestimation for mean and maximum survival (overestimation of mean survival was 0% and overestimation of maximum survival was 1%).
  - The results suggest that, more generally, BIC may be more robust compared with AIC when choosing the model that best fits the data.

Figure 3. Mean Survival Predictions From the Best-Fitting Standard Parametric Model and Model With a Turning Point



DISCUSSION

- The findings from our research revealed that survival curve extrapolation, when based solely on short-term data, can be notably affected by the presence of a life expectancy exclusion criterion.
- Survival models assume patients are sampled at random. When exclusion criteria are present in trials, such as life expectancy below a specific threshold, the shape of the survival curve changes so that the survival curve is no longer expected to follow any single distribution.
- Exclusion criteria are standard practice in clinical trials. Therefore, following current NICE Decision Support Unit guidelines to select the best-fitting model based on AIC and BIC and visual fit, where there are exclusion criteria related to survival, is likely to result in biased estimates of survival extrapolations.
- Since it may not be possible to perform an accurate extrapolation using short-term RCT data alone, where an RCT contains inclusion/exclusion criteria, long-term external data may be used to guide the extrapolation. Published methods that incorporate external information include the following:
  - Baio[6] (R package: survHE) and Soikkeli et al.[7]: Bayesian parametric spline-based models, with priors from a model fitted to external data.
  - Che et al.[8]: Inclusion of physician's expected survival by converting life expectancy data to a Weibull model, for example.
  - Guyot et al.[9]: Bayesian spline-model that simultaneously fits the RCT data, registry data, and general population data.
  - Jackson[10] (R package: survextrap): Includes a wide range of extrapolation techniques using spline-based models, multiple external data sets, and physician's expected survival.
  - Vickers[11]: Inclusion of adjusted published long-term data to match the trial data. Includes separate frequentist and Bayesian simultaneous models fitted to the RCT, and long-term data, and includes spline-based models.

CONCLUSIONS

- Exclusion criteria violate the random sampling assumption made by standard survival models, resulting in survival curves that are unlikely to follow the original distribution in the data prior to exclusion of patients. Models may fit the short-term trial data well, but none may provide an accurate extrapolation. This is likely to result in overestimation and uncertainty in survival estimates in HTA submissions.
- We recommend survival extrapolation be performed using direct evidence from external data.

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