Varun Agarwal | varun-2.agarwal@novartis.com

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Survival Model Uncertainty in Economic Modeling: Evaluating Bootstrap and Cholesky Decomposition Methods

Varun Agarwal[1], Subhajit Gupta[1], Gautam Partha[1]

[1]Novartis Healthcare Pvt. Ltd., Hyderabad, India

KEY FINDINGS & CONCLUSIONS

- Both bootstrap resampling and Cholesky decomposition are effective techniques for quantifying and propagating uncertainty in survival model parameters within health economic models. By enabling robust probabilistic sensitivity analysis (PSA), both methods help ensure that cost-effectiveness results reflect the inherent variability and limitations of clinical data, supporting more credible and transparent decision-making.
- While the overall agreement between the two methods is high, minor differences in the distributions of sampled parameters can occur—especially for models or datasets where parameter estimates deviate from normality. For health economic models that are highly sensitive to parameter uncertainty, it is important to carefully assess whether these differences could meaningfully impact cost-effectiveness outcomes or reimbursement decisions.

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INTRODUCTION

- Health economic (HE) modelling is a quantitative approach used to inform healthcare decision-making by comparing the costs and outcomes of alternative interventions.[1]
- In oncology, these models often rely on survival analysis to estimate how long patients live with or without disease progression under different treatments.[2]
- These survival estimates are critical because they directly influence the calculation of life years gained, quality-adjusted life years (QALYs), and ultimately, the incremental cost-effectiveness ratio (ICER) — a key metric for reimbursement and policy decisions.[1,2]
- However, survival estimates are subject to uncertainty due to limited sample sizes, variability in patient populations, and the inherent randomness of clinical outcomes[1]
- If this uncertainty is not properly accounted for, the resulting economic evaluations may mislead decision-makers, potentially leading to suboptimal allocation of healthcare resources.[1]
- Probabilistic Sensitivity Analysis (PSA) is used to quantify and propagate parameter uncertainty in HE models. PSA involves repeatedly sampling from the probability distributions of uncertain parameters (such as survival model coefficients) and recalculating model outcomes for each set of sampled values.

This process generates a distribution of possible results, reflecting the uncertainty in the model's inputs and providing a more robust basis for decision-making.[1] Two widely used methods for generating these parameter samples in survival models are bootstrap resampling and Cholesky decomposition. These are compared below:

Aspect	Bootstrap Resampling	Cholesky Decomposition
Methodology	Non-parametric technique involving repeated sampling (with replacement) from the original patient-level data. Each resample is used to refit the survival model, generating new parameter estimates.[3]	Mathematical technique that samples from a multivariate normal distribution using the estimated mean vector and variance-covariance matrix of the survival model parameters.[1]
Strengths	Robust and distribution-free; captures both parameter and sampling uncertainty. Suitable for complex models where distributional assumptions may not hold.[3]	Highly efficient and suitable for Excel-based models; preserves parameter correlations and enables rapid generation of PSA samples.[1]
Limitations	Computationally intensive due to repeated model fitting; may be impractical for large datasets or Excel-based implementations with limited processing capacity.[3]	Assumes parameters follow a normal distribution; may not fully capture uncertainty for skewed or heavy-tailed parameter distributions.[1]

- Each method has unique strengths and limitations, and their comparative performance in health economic modelling has not been systematically evaluated. This study addresses this gap by providing a detailed comparison of both methods in the context of Excel-based HE models for oncology.

OBJECTIVE:

- To compare bootstrap resampling and Cholesky decomposition for generating PSA samples of survival model parameters, and to assess their efficiency and suitability for use in Excel-based health economic models.

METHODOLOGY

Data Preparation

- Patient-level time-to-event data for invasive disease-free survival (IDFS) in early breast cancer were used.[4]
- Multiple parametric survival models (Weibull, log-normal, log-logistic, Gompertz) were fitted to the data as part of a semi-Markov model structure.[5]
- The semi-Markov model allows for the incorporation of time-dependent transition probabilities, providing a more realistic representation of disease progression.

Sample Generation

- For each survival model, 1,000 samples of the shape and rate parameters were generated using both methods:
  - **Bootstrap Resampling:** Each sample involved resampling the data and refitting the model, producing a new set of parameter estimates. This process captures both parameter and sampling uncertainty.
  - **Cholesky Decomposition:** Samples were drawn from a multivariate normal distribution defined by the estimated mean vector and variance-covariance matrix of the model parameters. This approach preserves the correlations between parameters.

Comparative Analysis

- **Descriptive Statistics:** Means and standard deviations of sampled parameters were compared for each method and distribution.
- **Visual Inspection:** Scatterplots and density plots were used to visually assess the similarity of parameter distributions. Overlap in the density plots indicates similarity in the uncertainty captured by each method.
- **Statistical Testing:** T-tests were conducted to determine if mean parameter estimates differed significantly between methods. A statistically significant difference ($p < 0.05$) suggests that the methods may not be interchangeable for that parameter.
- **Overlap Metrics:** The percentage overlap between parameter distributions was calculated for each model (e.g., Weibull, log-normal). High overlap indicates that the two methods produce similar distributions of parameter estimates.
- **Computational Efficiency:** The time required to generate samples and the practical feasibility of each method in Excel-based models were evaluated. This is particularly important for models that need to be shared with HTA bodies and payers, who may have limited computational resources.

RESULTS

Descriptive Statistics and Overlap

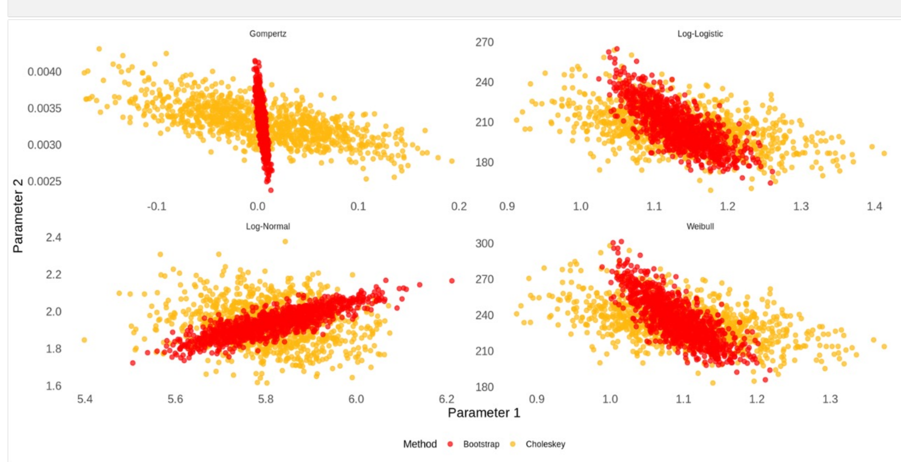
Method	Parameter 1 - Mean	Parameter 1 - SD	Parameter 2 - Mean	Parameter 2 - SD
Weibull				
Choleskey Decomposition	1.101	0.084	233.111	16.339
Bootstrap	1.092	0.040	236.177	18.555
Lognormal				
Choleskey Decomposition	5.804	0.108	1.933	0.113
Bootstrap	5.816	0.105	1.938	0.075
Log-logistic				
Choleskey Decomposition	1.141	0.083	204.266	14.940
Bootstrap	1.133	0.042	206.799	16.071
Gompertz				
Choleskey Decomposition	0.006	0.067	0.003	0.000
Bootstrap	0.004	0.003	0.003	0.000

Not Statistically Significant | Statistically Significant

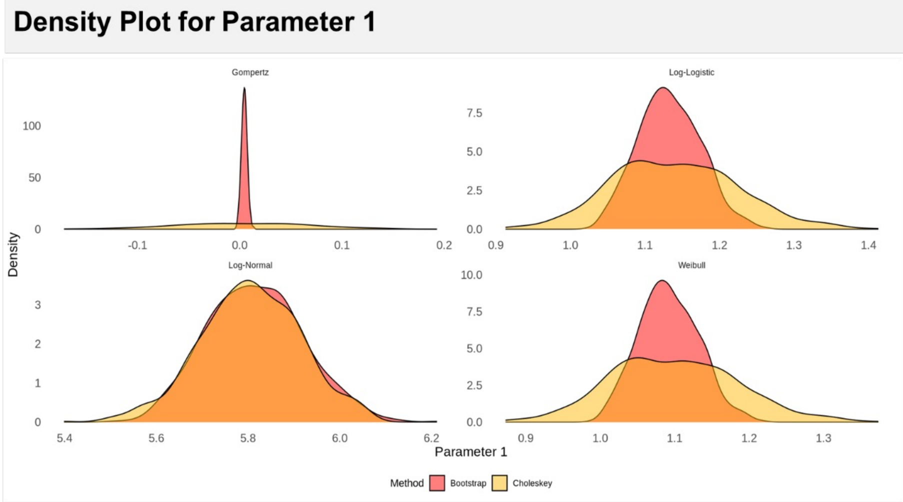
Visual and Statistical Comparison

- Scatterplots and density plots showed a high degree of overlap in parameter distributions, though some divergence was observed in the tails, particularly for the log-normal distribution.

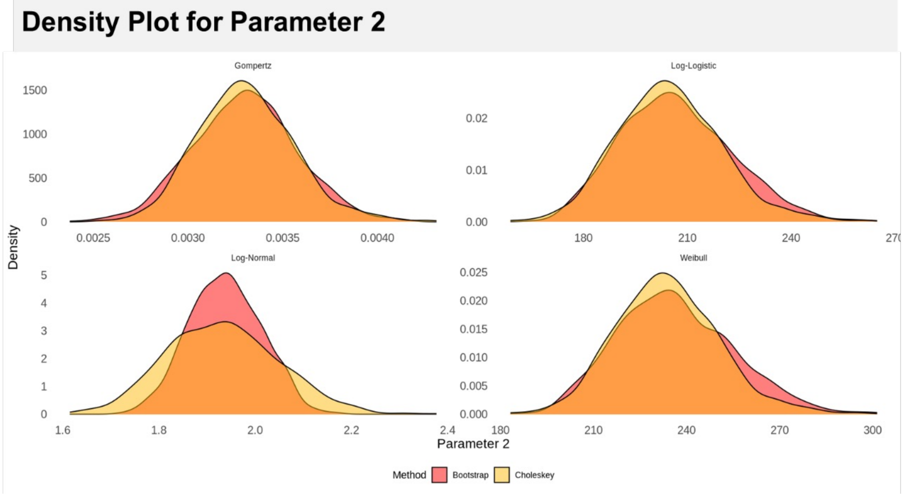
Scatter Plot of Parameter Estimates



Density Plot for Parameter 1



Density Plot for Parameter 2



- **Overlap percentages** for parameter distributions were as below:

Distribution	% Overlap
Weibull	89.95%
Log-logistic	92.07%
Log-normal	65.94%
Gompertz	99.44%

- **T-tests** indicated statistically significant differences ($p < 0.05$) in mean parameter estimates for 3 out of 8 parameters, suggesting minor but notable differences in some cases. This highlights the importance of understanding the limitations of each method, especially for parameters with skewed or non-normal distributions.

Computational Efficiency

- Cholesky decomposition was faster and more practical for use in Excel-based models, reducing both run time and file size compared to bootstrap resampling.
- For example, generating 1,000 samples using bootstrap resampling required repeated model fitting, which is computationally demanding, whereas Cholesky decomposition generated samples almost instantaneously once the variance-covariance matrix was available.

DISCUSSION

- Both bootstrap resampling and Cholesky decomposition are effective for capturing parameter uncertainty in survival models used in health economic evaluations. The high degree of overlap in PSA estimates suggests that Cholesky decomposition is a viable and efficient alternative, particularly when computational resources or time are limited.
- Cholesky decomposition stands out for its significant computational efficiency, particularly when compared to the resource-intensive bootstrap approach. It generates parameter samples rapidly and is especially advantageous for Excel-based models, which are commonly used for submissions to HTA bodies and payers. Despite its speed, Cholesky decomposition produces PSA results that are broadly similar to those obtained via bootstrap, making it a practical choice when time or computational resources are constrained.
- The findings support the use of Cholesky decomposition for routine PSA in Excel-based HE models, facilitating faster analyses and easier model sharing with HTA bodies and payers. This can streamline the decision-making process and improve the transparency and usability of economic models.
- However, analysts should be aware of potential minor differences in parameter distributions, especially for certain models and consider the context and requirements of their specific modelling scenario.
- The adoption of efficient and transparent PSA methods, such as Cholesky decomposition, can streamline the development and review of economic models. This not only simplifies complex modelling tasks for analysts but also enhances the usability and interpretability of models for HTA bodies and payers. Ultimately, these methodological advances support more robust, timely, and evidence-based healthcare decision-making, benefiting both payers and patients.

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