MSR171

Generalised Gamma in Economic Models: A Persistent Issue with Regression Analysis and the Proposed Solution

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CONTEXT AND OBJECTIVES

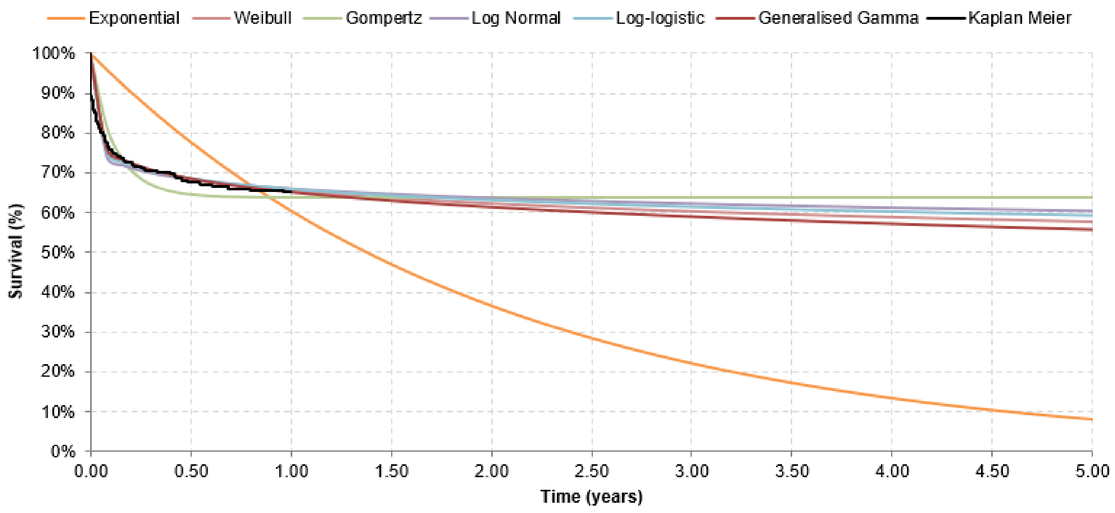
Generalised gamma (GG) is one of six probability distributions recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) for survival analysis. An issue was noticed when recreating pseudo independent patient data (IPD) from the overall survival (OS) Kaplan Meier (KM) graphs reported in Tzou et al. 2018,[1] where some survival models fitted using the GG distribution would produce deterministic results that functioned appropriately but overestimated mean survival in the probabilistic sensitivity analysis (PSA). The issue also appeared in two other instances that used trial IPD, but these are commercial in confidence and cannot be reported.

The objective of this analysis was to identify the cause of this overestimation through investigation at each level of data generation.

METHODS

The Tzou et al. 2018[1] figures were digitised and survival analysis was undertaken with the pseudo IPD. This data were used to provide example survival analysis inputs. The KM curve and parametric survival models fitted are displayed in Figure 1. The GG and other distributions recommended by the NICE DSU (exponential, Weibull, Gompertz, lognormal and loglogistic) were used.

Figure 1: KM and deterministic extrapolations from the parametric distributions in the Excel-based model



The parametric survival models were fitted using R 4.4.02 and the R packages 'flexsurv'3 and 'survHE'4. Extrapolation and PSA were performed in both Microsoft Excel and R to control for any differences between the two. The parametric models were then included in a cost-effectiveness model, where the coefficients produced in R were used to extrapolate long-term survival (Figure 1). PSA was performed on the extrapolations in both Microsoft Excel (the cost-effectiveness model) and R.

RESULTS

The formulae used in Excel and R for extrapolation were found to be identical. The predicted survival from the parametric distributions, when using the deterministic coefficients, were found to be identical between Excel and R. The GG curve, in both Excel and R, appears to follow a similar trajectory as the other parametric distributions.

Figure 2: Extrapolations from the parametric models with overlaid PSA iterations over five years in R

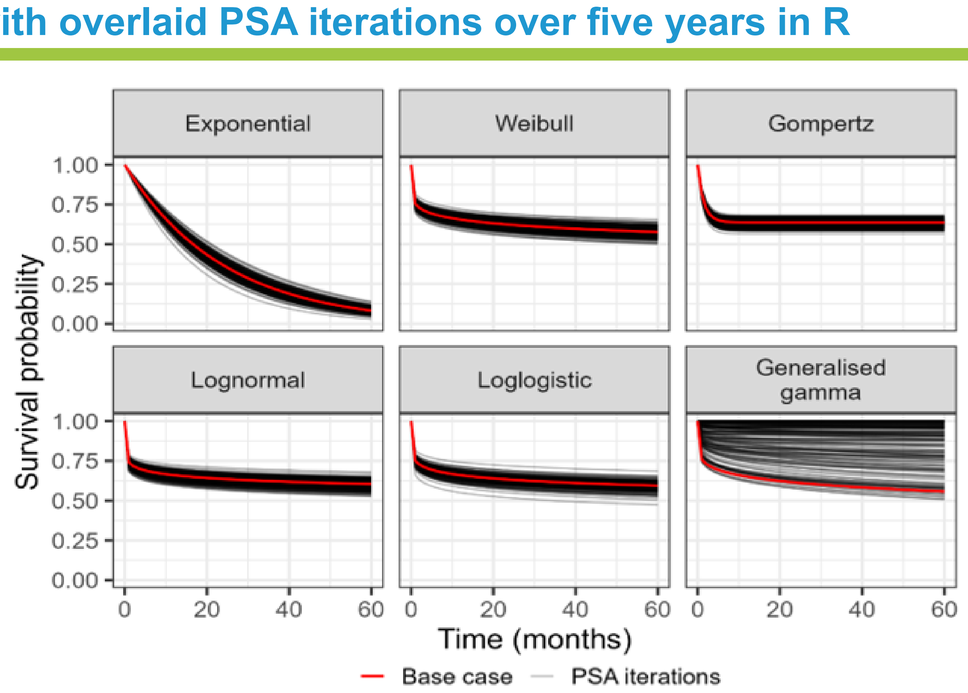


Figure 3: Projected five-year survival for parameter values generated in PSA using the GG model

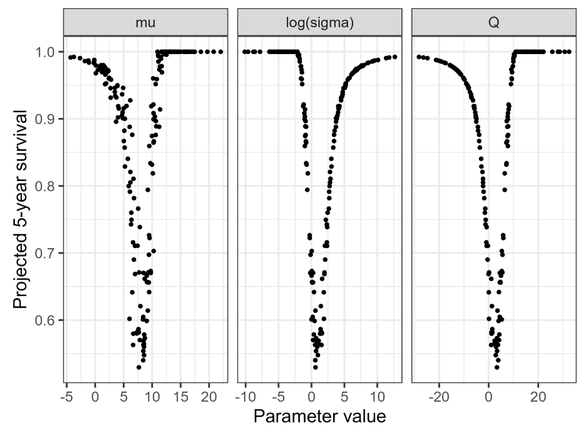


Table 1: GG model coefficients and covariance matrix

Parameter	Value	Covariance Matrix		
		Mu	Sigma	Q
Mu	8.17	21.26	-18.25	48.61
Sigma	0.93	-18.25	16.11	-42.80
Q	2.66	48.61	-42.80	113.76

The PSA results also show similarity, including the erroneous overestimations of survival when using the GG distribution (Figure 3). The overestimated PSA samples only occurred when the GG distribution was used. This issue was observed in both Excel and R, and in raw and reconstructed IPD. The cause of the overestimation was identified as the presence of a large number of PSA samples where extrapolated survival was constant at 100%, which is statistically and clinically implausible. These samples artificially inflated the mean survival, resulting in the PSA mean being substantially higher than the deterministic mean (Figure 3). This was also the case in the Excel-based PSA.

High parameter variance and covariance (particularly of the shape parameter 'Q') in the GG model (Table 1) resulted in extreme parameter values in PSA. Extreme parameter values were strongly associated with implausibly high 5-year OS predictions (Figure 5).

The potential for survival overestimation in the PSA is not observable unless the survival analysis coefficients are applied probabilistically, as the base-case predictions of the GG model are typically in line with expectations despite the high coefficient variance. The possible causes for this issue include:

- The GG distribution has three parameters and, therefore, higher variance compared with other survival distributions recommended by the NICE DSU which have one or two parameters.. Therefore, the GG distribution would be expected to struggle with high-uncertainty data, relatively.
- The issue was largely observed in datasets with high end-of-study survival. It may be that the GG distribution is vulnerable to this type of uncertainty due to its heavy tail.

CONCLUSIONS

When undertaking cost-effectiveness analyses that utilise standard parametric distributions, care should be taken because the probabilistic results, such as the incremental cost-effectiveness ratio (ICER), may be erroneously estimated when GG is selected. This will typically be unbeknownst to the modeller unless this error is actively checked for, or GG is part of the main analyses.

When reporting a GG model, it is recommended to check for:

- High variance and covariance in the survival model parameters.
- PSA samples with 100% survival.
- Incongruence between mean survival in the deterministic and PSA estimates.

If these elements are present, the GG model is inappropriate due to the inadvertent inclusion of statistically and clinically implausible survival probabilities in the PSA and the high levels of overall uncertainty this represents.

REFERENCES

1. Tzou W. et al. Circ Arrhythm Electrophysiol. 2018;10(1):e004494. **2.** R Core Team. 2024. _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing. **3.** Jackson C. Journal of Statistical Software. 2016;70:i08. **4.** Baio G. _survHE: Survival Analysis in Health Economic Evaluation. 2023.

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