Flexsurv Methods to Estimate CuRe: An Exploration of Methods for Modelling Cure

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Objective

To determine whether results from different mixture cure model R packages are sensitive to method choice by comparing outputs from models with different distributions, link functions, optimisation methods and background mortality.

To compare the performance of different models between adult and paediatric populations and assess whether the immaturity of the survival data and low all-cause-mortality of paediatric populations affects model performance.

Background

- Mixture cure models (MCMs) estimate survival and cure fractions for a population consisting of cured and uncured patients.
- MCMs can differ in their distributions, link functions and optimisation methods used to model data, and the inclusion of background mortality.
- There is no guidance on method selection, though some literature recommends incorporating background mortality for cured patients to capture non-disease-specific mortality.[1]

Methods

- Two trials (ZUMA-1; ELIANA)[2,3] investigating the efficacy of chimeric antigen receptor T-cell treatments with different populations (adult; paediatric) and follow-up durations (63.1; 38.8 months) were used as case studies.
- Pseudo-individual patient data (IPD) were estimated using the Guyot algorithm on digitised survival data from these trials.[4]
- MCMs were fitted to the pseudo-IPD using the R packages *flexsurvcure* and *cuRe*.[5,6]
- MCM methods available in both packages were compared by varying the distribution (exponential; Weibull; log normal), link function (logistic; loglog; probit) and optimisation method (Nelder-Mead; Broyden, Fletcher, Goldfarb, and Shanno [BFGS]; conjugate gradients [CG]).
- All methods were assessed excluding and including background mortality, using UK mortality data to generate a general population hazard.[7]
- The application of a general population hazard function based on IPD could only be performed by *cuRe* and was therefore not investigated.
- Cure fractions were estimated for all methods, and survival curves were generated from MCM parameter estimates.

Results

Distribution

- For a given link function, optimisation method and population, both packages estimated similar cure fractions for each distribution.
- As expected, cure fractions varied between distributions (e.g. the range across distributions using a logistic link was 38–41% for ZUMA-1 and 27–60% for ELIANA), demonstrating the importance of selecting a distribution appropriate for the indication.

Link Function (Table 1)

- Choice of link function can be an important specification when including covariates, allowing for appropriate interpretation of covariate effects.[8]
- Given that covariates were not included for the comparison of the packages, varying the link function had an expected negligible impact on cure fractions for *flexsurvcure* across distributions for ZUMA-1 and for ELIANA.
- For *cuRe*, varying the link function had an impact on cure fractions across distributions for ZUMA-1 (38–49%). The cure fraction in ELIANA using the loglog link was just over half the cure fraction under logistic and probit links for the exponential and Weibull distribution (34–35% vs 56–60%), and around double for the log normal distribution (56% vs 27–35%). These results warrant an exploration of *cuRe* methodology regarding its treatment of link functions in models without covariates.

Optimisation Method (Table 2)

- The Nelder-Mead (*cuRe* default) and CG optimisation methods produced similar cure fractions using the logistic link for a given distribution and population (0–1% variation), and this was consistent across packages.
- BFGS (*flexsurvcure* default) yielded similar results to other optimisation methods for *flexsurvcure* (0–1% variation), but did not produce clinically plausible cure fraction estimates for *cuRe* (0% for exponential and Weibull distributions), likely due to optimisation functions not converging for specific distributions.

Background Mortality

- Incorporating background mortality increased the cure fractions by 2–5% across distributions in both packages for ZUMA-1 but had negligible impact for ELIANA (0–1%); given the low background mortality and average age of the paediatric population of ELIANA, it is expected that the effect of the cancer-specific mortality dominates the effect of background mortality.
- In an indication with notable levels of background mortality (i.e., older population of ZUMA-1), the exclusion of background mortality is observed to result in less good visual fit of the MCM to the KM data (**Figure 1A**).

Conclusions

Estimated cure fractions differed across parametric distributions and link functions.

As expected, the inclusion of background mortality only impacted the cure fraction and survival in the ZUMA-1 adult population.

With increasing evidence demonstrating the curative potential of treatments, an effort to consolidate existing guidance and research on MCMs would be valuable.

TABLE 1

Cure fractions from MCMs with varying link functions

	Exponential			Weibull			Log Normal		
Adult (ZUMA-1)	logistic	loglog	probit	logistic	loglog	probit	logistic	loglog	probit
flexsurvcure	40%	40%	40%	41%	41%	41%	38%	38%	38%
cuRe	40%	48%	44%	41%	47%	44%	38%	49%	43%
Paediatric (ELIANA)	logistic	loglog	probit	logistic	loglog	probit	logistic	loglog	probit
flexsurvcure	59%	59%	59%	60%	60%	60%	27%	27%	27%
cuRe	59%	35%	56%	60%	34%	56%	27%	56%	35%

All MCMs were fitting using the Nelder-Mead optimisation method and without background mortality.

TABLE 2

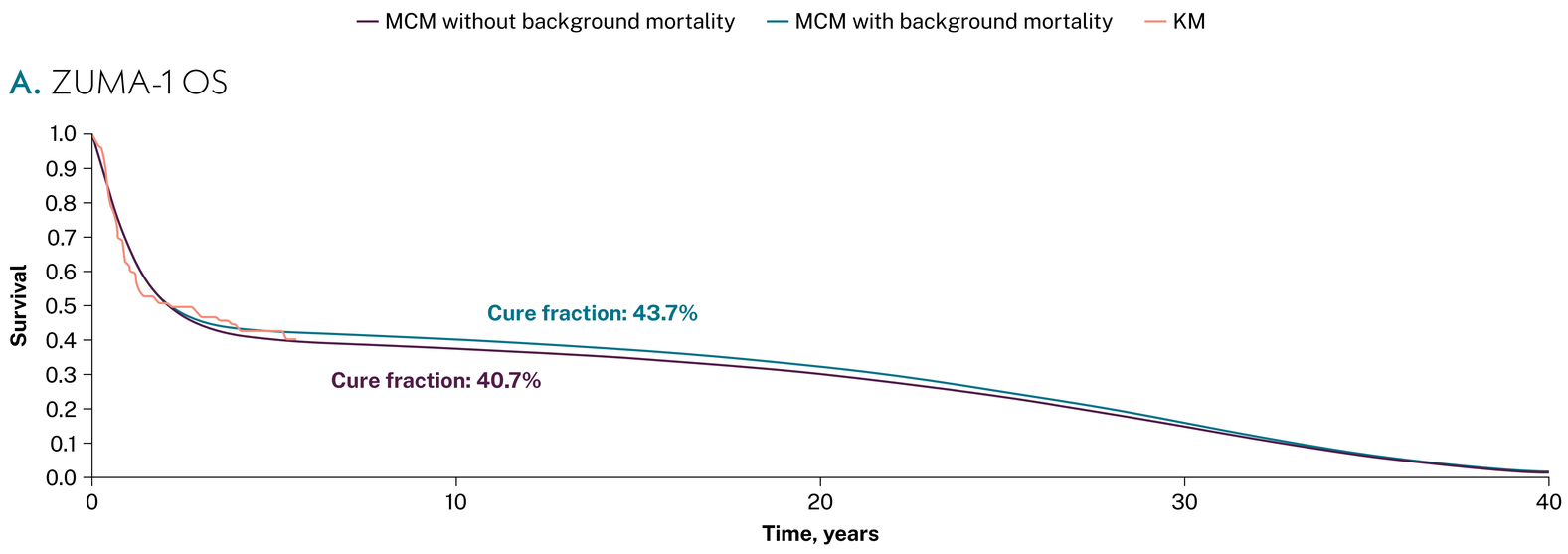
Cure fractions from MCMs with varying optimisation methods

	Exponential			Weibull			Log Normal		
Adult (ZUMA-1)	Nelder-Mead	BFGS	CG	Nelder-Mead	BFGS	CG	Nelder-Mead	BFGS	CG
flexsurvcure	40%	40%	40%	41%	41%	41%	38%	38%	38%
cuRe	40%	0%	40%	41%	0%	41%	38%	38%	38%
Paediatric (ELIANA)	Nelder-Mead	BFGS	CG	Nelder-Mead	BFGS	CG	Nelder-Mead	BFGS	CG
flexsurvcure	59%	59%	59%	60%	60%	60%	27%	27%	28%
cuRe	59%	0%	59%	60%	0%	60%	27%	27%	27%

All MCMs were fitting using the logistic link function and without background mortality.

FIGURE 1

The impact of inclusion of background mortality in adult versus paediatric populations



Example survival curves were fitted for OS using *flexsurvcure* for an MCM with a Weibull distribution, logistic link and Nelder-Mead optimisation method, for (A) the ZUMA-1 adult population, and (B) the ELIANA paediatric population. Models excluding background mortality were bound by age- and gender-specific natural mortality of the general population as a minimum.

Abbreviations: BFGS: Broyden, Fletcher, Goldfarb, and Shanno; **CG:** conjugate gradients; **IPD:** Pseudo-individual patient data; **KM:** Kaplan-Meier; **MCM:** mixture cure model; **OS:** overall survival.

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