HEALTH ECONOMIC PROGRAMMING USING ROYSTON-PARMAR "HAZARD RATE" MODELS: PROVIDING FLEXIBILITY AND SPEED FOR EVENT MODELLING IN COHORT AND DES MODELS

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Objectives

Many diseases (e.g. oncology) display changing hazard rates over time that conventional parametric methods cannot replicate accurately. Various flexible parametric methods exist with increased number of parameters to alleviate this problem (Generalised Gamma and Generalised F distributions being examples). Royston-Parmar (1) Hazard Rate Models (RPHRMs) differ in one crucial regard; all key survival statistics (survival probability, cumulative hazard and hazard rate) can be calculated in closed form. This makes them ideal for HE models where speed of calculation is essential. This poster provides the basic theory, discusses suitable programming code, contrasts results with other survival models and points readers to further sources.

Methods

The easiest way to comprehend RPHRMs is to realise that the standard Weibull model with predictors can be expressed in linear form of its (natural) log cumulative hazard:

$$\ln\{H(t)\} = \ln(\lambda) + \gamma \ln(t) + x\beta$$

where t is time; λ is the scale and γ the shape parameter.

RPHRMs increase flexibility by replacing $\gamma \ln(t)$ with a natural cubic spline increasing the number of parameters and attaching them to functions of log time. The formula incorporating predictors with time varying effects is

$$\ln\{H(t)\} = \ln(\lambda) + s\{\ln(t)|\gamma_0, k_0\} + \sum_{j=1}^{D} s\{\ln(t)|\gamma_j, k_j\}x_j + x\beta$$

where γ_j and k_j ($j = 0 \dots D$) are vectors of parameters and knots (each γ_j excludes a 'constant' in definition above); D is the number of predictors with time varying effects.

The publicly available "ew_breast_ch7.dta" Stata dataset (http://www.stata-press.com/data/fpsaus.html) is used in the analysis, allowing users to replicate results in the excellent textbook associated with this web-link (2). Model parameters were estimated using the Stata ado package stpm2. Parameters (including covariance matrix) together with knot locations were exported to a csv file via automated routines. This file was imported into R where various user defined functions could be applied. All functions have been validated against results obtained by post-estimation Stata stpm2 commands or against those within the R package flexsurv (3). To view some easily accessible programming code, load package flexsurv in R and type "flexsurv:::basis". The output shows a function for generating the cubic spline basis.

The dataset has post breast cancer diagnosis data on 9,721 patients. Two extremes on a deprivation index (least and most deprived) serve as proxy treatment variables.

Bayesian programming of RPHRM is possible in JAGS or Winbugs (although convergence can be an issue).

Results

The kernel density curves on Figure 1 (dashed lines) clearly demonstrate non-monotonic hazard rates: for both deprived types a high initial hazard following diagnosis (first couple of days) quickly falls, then slowly rises to a peak at two years then falls steadily again. These sorts of shifts in risks are easy to miss when examining survival curves. Clearly parametric models that can only model monotonic hazards (those that either fall or rise but never do both – e.g. Weibull or Gompertz) will not be able to follow the hazard trajectory. Hence only non-monotonic distributions are shown. Deprivation status has been used to model all ancillary parameters (along with location) attached to each specific distribution – allowing maximum hazard curve flexibility.

The two Royston Parmar models are alone in capturing the early fall then rise in the kernel hazard. Of the two, the non proportional HR version (that allows the effects of deprivation to vary over time) is clearly better: in fact it is the only model that incorporates the kernels along and within its 95% confidence limits.

Clearly the huge confidence intervals attached to the Generalised F distribution ensure that any probabilistic sensitivity analysis will lead to very imprecise results.

Results (continued)

Figure 1 Hazard Rates: Parametric Models (Prediction + 95% CI's) Plotted Against Kernel Density Estimate
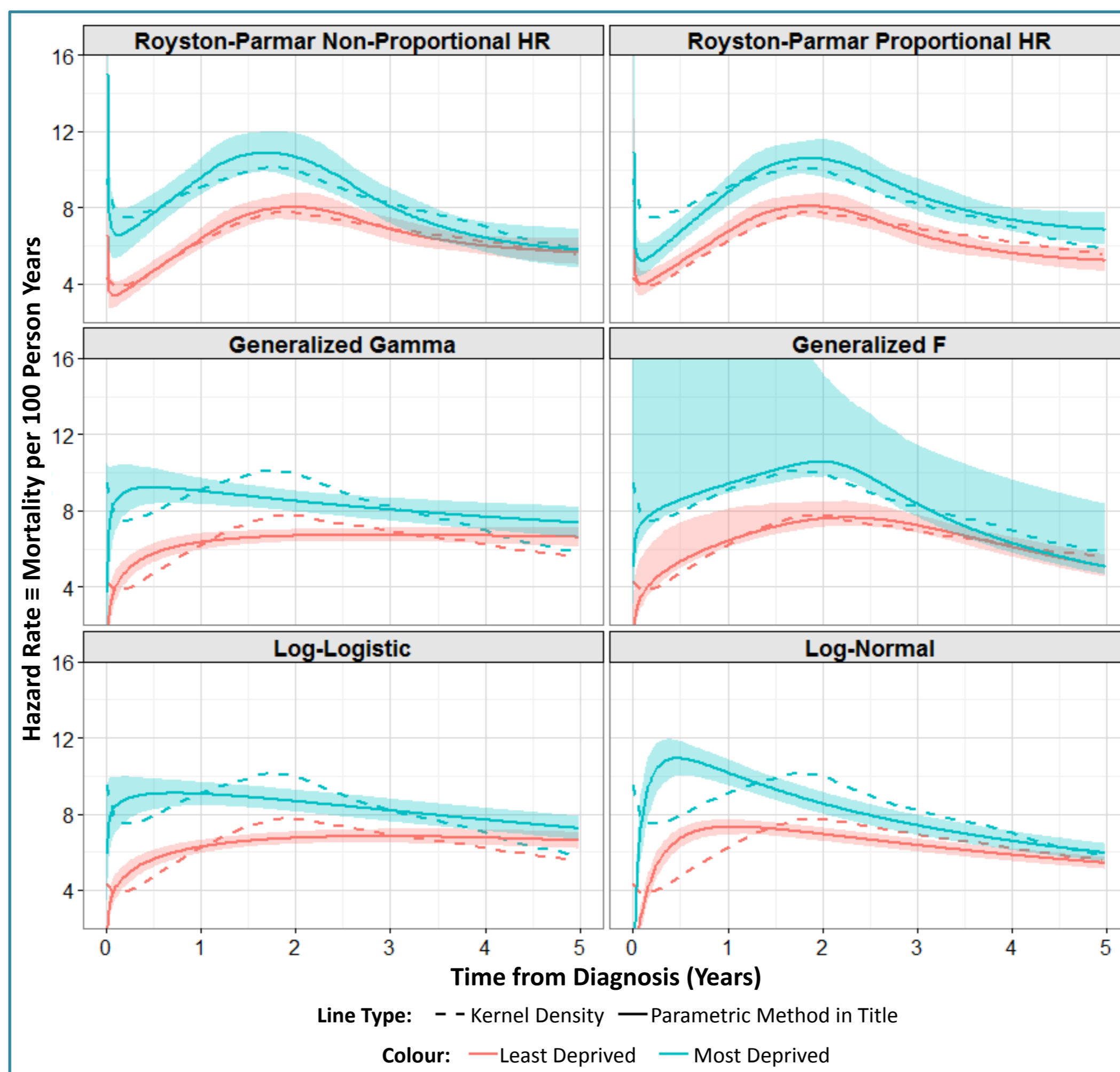

Figure 2 provides useful analysis, stability and validation plots:

➤ Plot A demonstrates the necessity of relaxing the assumption of proportional hazards (confirmed also by test (4) based on Schoenfeld residuals with p value < 0.001). This is often provided as the justification for switching to Log-logistic or Log-Normal parametric forms – from observing their plots in Figure 1 this would clearly be a mistake.
➤ Plot B shows 100 bootstrapped non-proportional hazard ratios for the Royston-Parmar model - the separate bootstrap predictions are shown close together suggesting that the analysis is not sensitive to small shifts in data.
➤ Plot C shows 100 and 10,000 (inset) survival trajectory simulations from Monte Carlo sampling of the Royston-Parmar model against the Kaplan-Meier "real" estimate.
➤ Plot D (directly below C) shows what these simulation draws imply for HE cohort cycle transition probabilities – to be used for probabilistic sensitivity analysis (13 cycles = 1 Year). Within a cohort model the chosen cycle lengths should accommodate features found in the survival analysis - here a standard 28 day cycle model splits cycle one into 2 and 26 days, recognising the initial high hazards observed in Figure1.

Nothing looks amiss in Figure 2, increasing confidence in the model selection and code programming.

Figure 2: Useful Validation and H.E. Model Stability Plots for Royston-Parmar Non-Proportional Hazards Model
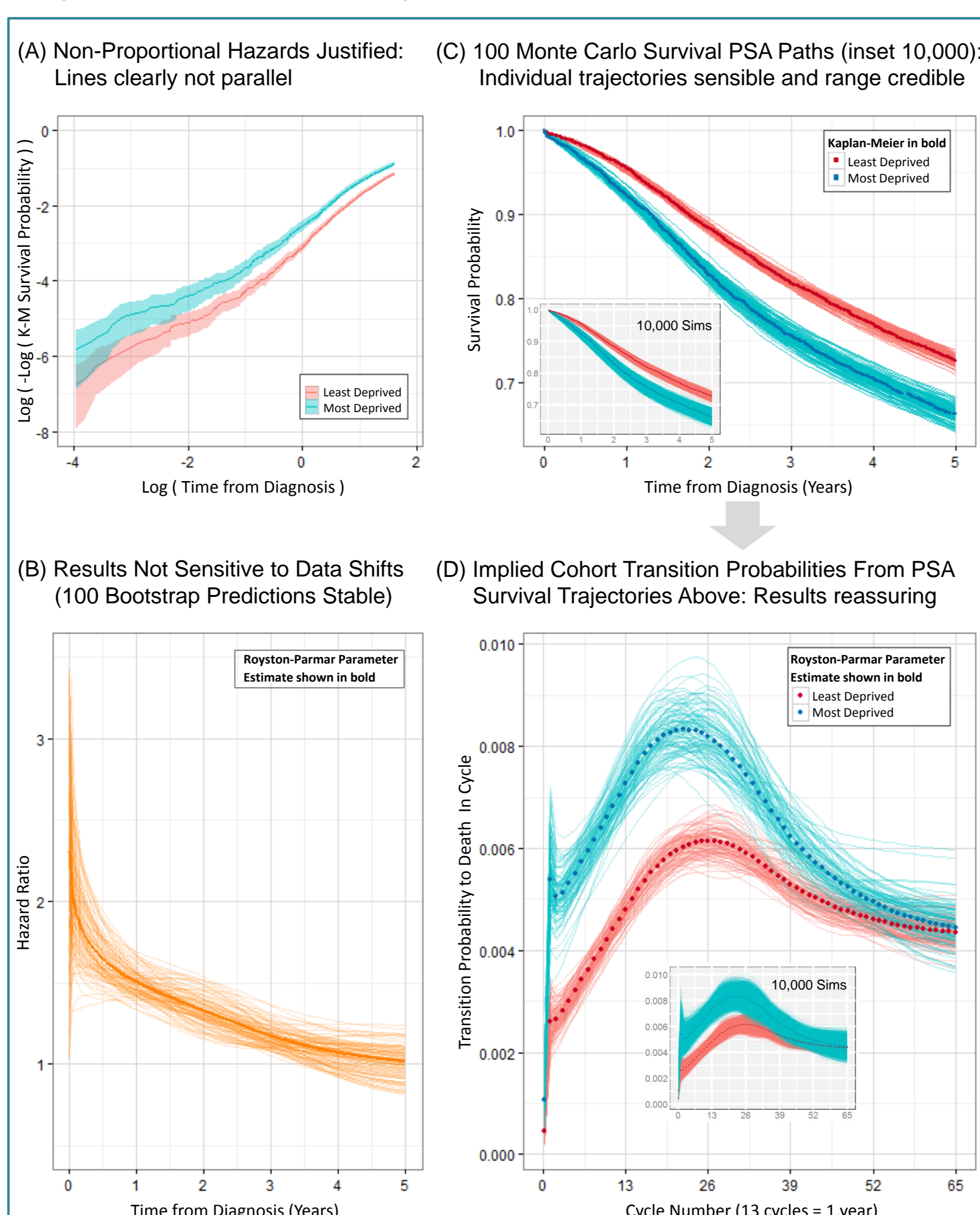

Results (continued)

Age at diagnosis is often an important predictor in survival modelling. Figure 3 plots output from a RPHRM where it is allowed maximum flexibility (and justified via p values):

➤ within a time period, increments in diagnosed age can have different effects (natural cubic spline variables created from diagnosed age)
➤ across time periods these "within effects" are allowed to differ (each natural cubic spline variable created above is itself transformed into spline variables across log time)

The above is an example where orthogonalization of the splines is necessary for the analysis to converge (justifying the use of Stata's stpm2 command).

Figure 3 Non-linear Effect of Diagnosed Age Within and Across Time Periods: Survival Estimates Plotted Above 28 Day Cycle Transition Probabilities
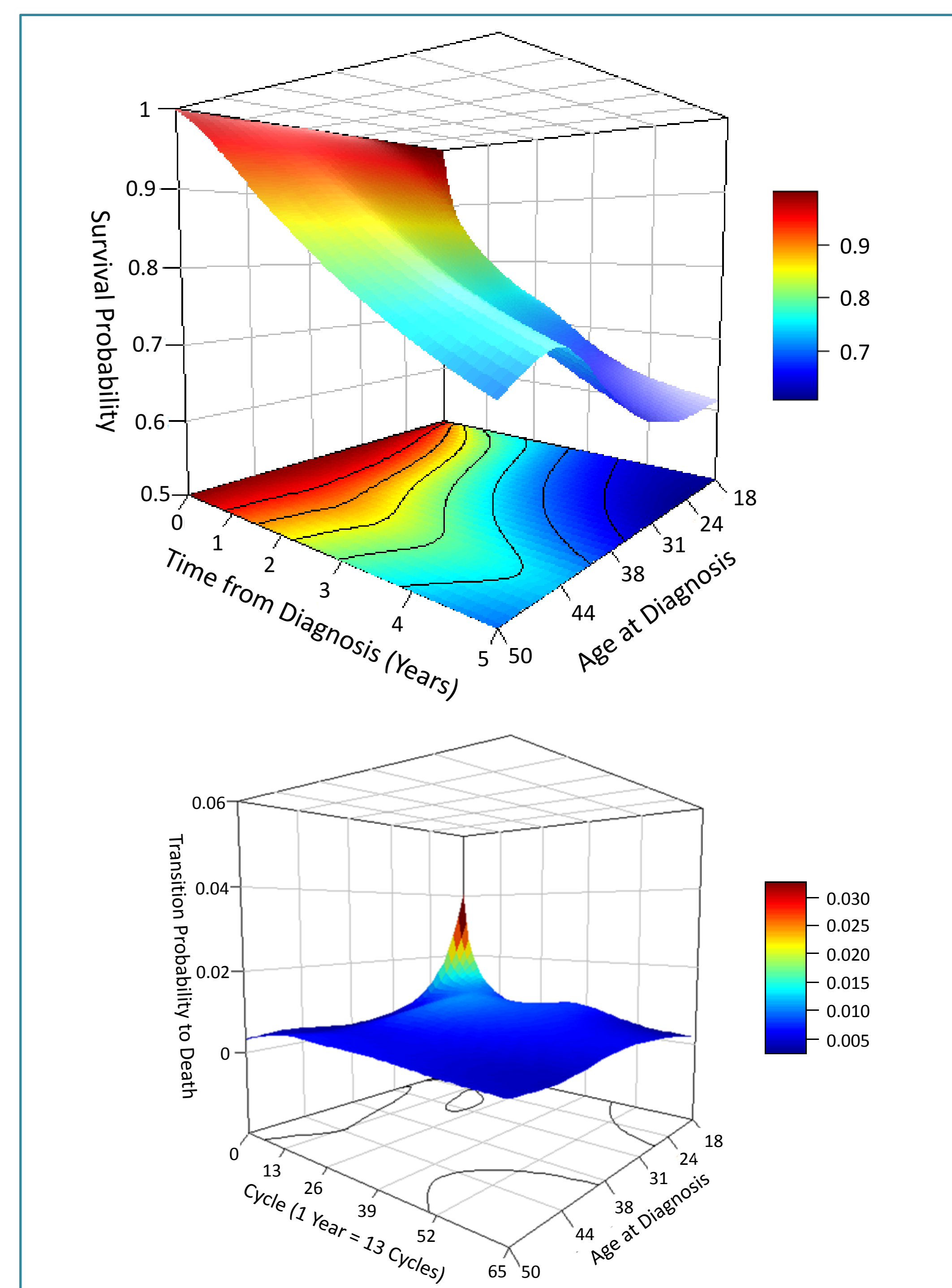
Conclusion

Parametric "flexible" survival models should be in every HE modeller's toolkit. Within cohort models it is relatively straightforward to program the transition probabilities into a "3D" matrix as described by Hawkins et al (5). For DES modelling, RPHRM has a form that allows event times to be generated quickly using Newton-Raphson techniques. It is also amenable to modelling transitions to more than one state (competing risk): closed form hazard allowing quick numerical integration to generate the Cumulative Incidence Functions from which transition probabilities to rival events can be derived.

There are many other "flexible" methods and none is clearly better. Visual techniques (e.g. Figure 1) combined with disease knowledge should supplement AIC/BIC/DIC in deciding between them (especially since the latter can an be dominated by events early on with little regard to the accuracy of later predictions).

Finally modellers need to ensure their code is producing sensible results – graphs such as presented in Figures 2 and 3 are helpful.

References

(1) Royston, P. and Parmar, M. (2002). Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Statistics in Medicine 21(1):2175-2197
(2) Royston, P. and Lambert, P.C. (2011) Flexible parametric survival analysis using Stata: Beyond the Cox model. StataPress, College Station, TX. [Book]
(3) Christopher Jackson (2015). flexsurv: Flexible Parametric Survival and Multi-State Models. R package version 0.6. http://CRAN.R-project.org/package=flexsurv
(4) Grambsch P. and Therneau T. (1994), Proportional hazards tests and diagnostics based on weighted residuals. Biometrika, 81, 515-26
(5) Hawkins, N., Sculpher, M., & Epstein, D. (2005). Cost-effectiveness analysis of treatments for chronic disease: using R to incorporate time dependency of treatment response. Medical Decision Making, 25(5), 511-519

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