What About a Latent Cure Model? Assessing Cure Models' Performance in Paediatric Acute Lymphoblastic Leukaemia Treated with Tisagenlecleucel.

G. HOPMANS GALOFRÉ[1], M. HOPMANS GALOFRÉ[2] and I. CORRO RAMOS[3]

1: Erasmus University Rotterdam, the Netherlands; 2: Independent Researcher; 3: Institute for Medical Technology Assessment.

MSR220

OBJECTIVE

The advent of curative treatments such as chimeric antigen receptor (CAR) T-cell therapies in haemato-oncology requires cure models to extrapolate survival, with high risk of bias due to limited follow-up and small sample sizes.

Flexible parametric non-mixture cure models, also called latent cure models (LCM), have been brought up as a resourceful yet underused method when cure assumptions are relevant[1]. We attempted to validate extrapolations from an early data cut-off (DCO) of tisagenlecleucel in paediatric acute lymphoblastic leukaemia via comparison to a later DCO.

METHODS

Mixture cure models (MCM), generalised mixture cure models (GenMCM), LCMs, and spline-based models (SM) were fitted to overall survival (OS) and event-free survival (EFS) data from the ELIANA trial, with a 38.8-month median follow-up (1st DCO)[2]. The extrapolations fitted to the 1st DCO were validated against 79.4-month median follow-up (2nd DCO) and clinical expert opinion, both from NICE TA975[3]. Models were also fitted to the 2nd DCO, and their extrapolations were compared with the ones generated using the 1st DCO and expert opinion.

All survival models were fitted in R using the cure and rstpm2 packages[4]. Background population mortality from Spain[5] was incorporated using a standardised mortality ratio of 4. Further details from the models' specifications are available in the supplementary appendix.

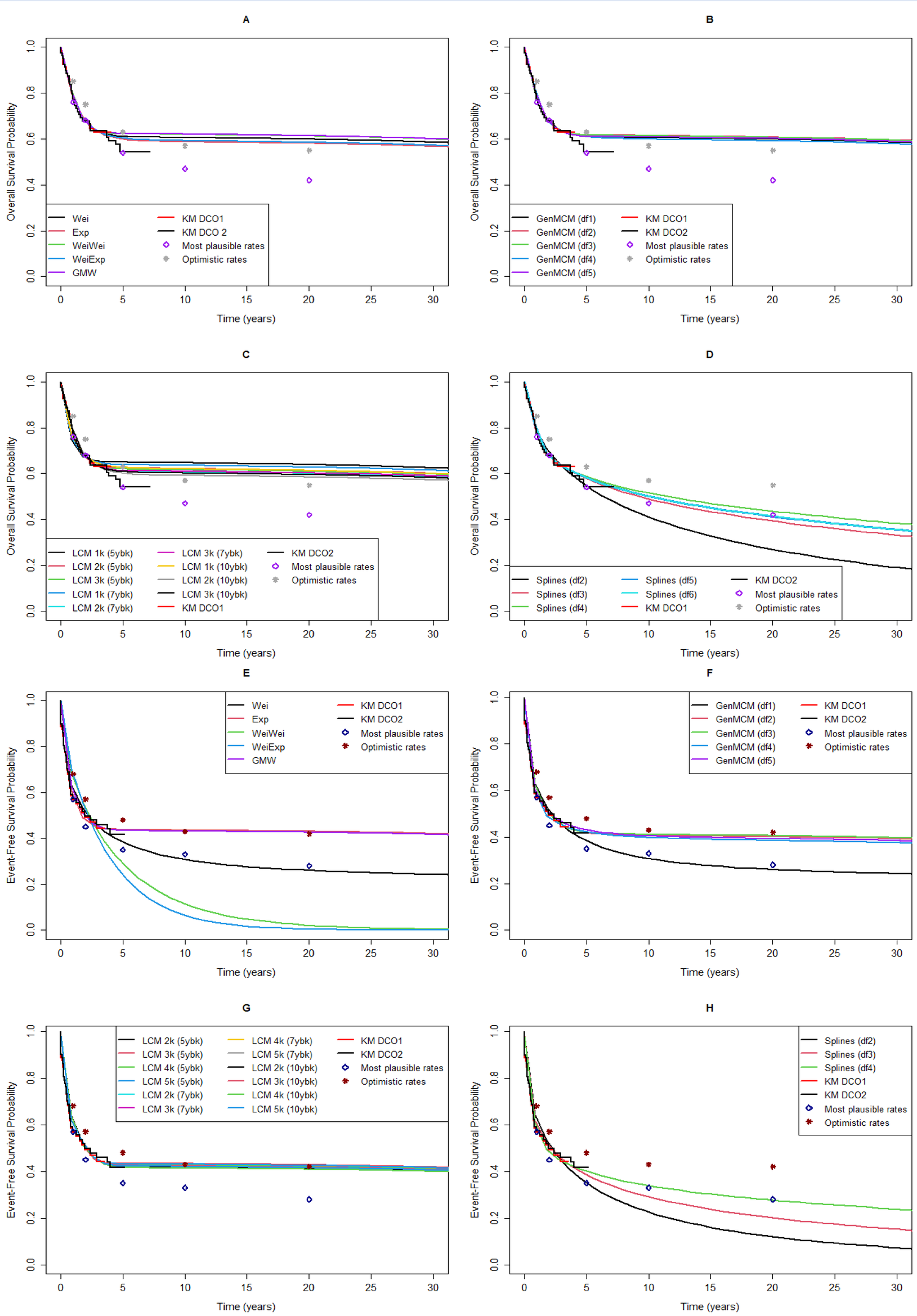
RESULTS

For OS, only SMs with ≥3 degrees of freedom (DF) predicted the accelerated decline observed in the 2nd DCO (Panel D). For all cure models, differences from the 7-year Kaplan–Meier curve ranged from 4.8% to 10.6%. Those with smaller differences were LCMs with cure at 7 or 10 years (Panel C; 5.1% to 6.9%) and MCMs with exponential, Weibull–exponential, and GenMCM-4DF (Panels A-B; 4.8% to 5.9%). Models with largest differences were LCMs with cure at 5 years (Panel C; 7.7% to 10.6%), MCMs with generalised modified Weibull, Weibull–Weibull, and GenMCMs with 2 and 3DFs (Panels A-B; 7.3% to 8.1%). LCMs' differences from Kaplan–Meier 5-year EFS estimates ranged 0.5% to 2.26% (Panel G), outperforming GenMCMs (Panel F; –3.1% to 1.47%), MCMs (Panel E; –17.3% to 2%), and SMs (Panel H; –6.37% to –1.5%). Besides MCMs with Weibull–exponential, Weibull–Weibull and SM-2DF (Panels E & H;–6.37% to –17.31%), all models predicted the 2nd DCO KM well (–3.2% to 2.1%).

When assessing long-term extrapolations, cure models overestimated clinicians' most plausible 20-year OS rates (Panels A-C; 16% to 21.9%), while SMs with 3-6 DF were closely aligned (Panel D; –2.58% to –0.57%). Compared to optimistic estimates, all cure model predictions were more closely aligned (Panels A-C; 3% to 8.9%). Most cure models overestimated clinicians' most plausible 20-year EFS rates (Panels E-G; 10.5% to 15.3%), except for MCM with Weibull and GenMCM-1DF (Panels E-F; both with –1.9% difference). When compared to clinicians' optimistic estimates, cure models made accurate predictions (Panels E-G; –3.5% to 1.3%) and SMs underestimated EFS (Panel H; –29.9% to –14.3%).

When fitted to the 2nd DCO, the 20-year extrapolated OS differences compared with 1st DCO extrapolations were notably lower for GenMCMs and MCMs (–29.6% to –8%), whereas for LCMs differences were smaller (–6.3% to 3%). For EFS the differences between DCOs' extrapolations were less pronounced across all models (–4.9% to 8.2%).

Compared to clinicians' most plausible estimates, LCMs fitted to the 2nd DCO continued to overestimate 20-year OS rates (11% to 19%) and 20-year EFS rates (12.5% to 14%).



__A:__ Mixture cure models fitted to OS 1st DCO; __B:__ Generalised MCMs to OS 1st DCO; __C:__ Latent cure models fitted to OS 1st DCO; __D:__ spline hazards models fitted to OS 1st DCO; __E:__ Mixture cure models fitted to EFS 1st DCO; __F:__ Generalised MCMs to EFS 1st DCO; __G:__ Latent cure models fitted to EFS 1st DCO; __H:__ spline hazards models fitted to EFS 1st DCO.

Abbreviations: *bk = boundary knot; DCO = data cut-off; df = degrees of freedom; Exp = exponential; GenMCM = generalised mixture cure model; GMW = generalised modified Weibull; k = knot; KM = Kaplan-Meier; LCM = latent cure model; Wei = Weibull; WeiExp = Weibull-Exponential; WeiWei = Weibull-Weibull.*

CONCLUSIONS

LCMs performed similarly to other cure models when compared to the 2nd DCO KM and overestimated long-term extrapolations when considering clinicians' most plausible estimates. Long-term LCM extrapolations were not as affected by the choice of DCO compared to the other cure models.

Overall, there appeared to be a clear overestimation of OS based on the 1st DCO, which could lead to reimbursement at an inflated value-based price if used in a health technology assessment submission.

Despite the use of novel methods, uncertainty persists with immature data. Robust estimates require clinical validation, incorporating external data, and longer trial follow-ups.

REFERENCES

1. Latimer & Rutherford (2024). DOI: 10.1007/s40273-024-01406-7.
2. Laetsch et al. (2022). DOI: 10.1200/JCO.22.00642.
3. NICE TA975. Available from: https://www.nice.org.uk/guidance/ta975
4. Jensen et al. (2022). DOI: 10.1016/j.cmpb.2022.107125.
5. Human Mortality Database: Available from: https://www.mortality.org/

DISCLOSURES

GHG conducted the present research as part of his thesis while being enrolled in the MSc Health Economics program at Erasmus University Rotterdam.