Science-led HEOR & Tech-driven AI

Eliciting Cancer Progression Rates for Locally/Regional Recurrent (LR) Populations Using Aggregate Level Survival Data: An Illustration from Melanoma

Poster code : MSR19

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BACKGROUND

- State-transition models (STMs) are central to health economic evaluations of oncology treatments. When patients experience relapse or spread of cancer, clinicians distinguish local or regional recurrences (shortly locoregional recurrence [LR]) confined near the primary tumor or regional lymph nodes from distant recurrence (DR) involving metastases. While these two recurrence subtypes carry markedly different prognoses, and treatment pathways, they are frequently collapsed into a single post-recurrence state in the most standard cost-effectiveness models.

- Key challenges in parameterizing LR→DR transitions in multi-state (semi) Markov models:
    - Clinical trials frequently lack sufficient follow-up to directly observe and robustly quantify LR→DR transitions
    - Limited number of patients experiencing DR following LR during trial follow-up results in sparse transition data. Furthermore, progression from LR to DR may be indistinguishable from post-LR mortality due to protocol-mandated statistical considerations.

- To reduce uncertainty surrounding long-term survival projections, calibration of cost-effectiveness models distinguishing LR and DR should be informed by robust post-recurrence data and transparent, clinically verifiable assumptions, while maintaining alignment with intermediate endpoints reported in pivotal trials, such as recurrence-free survival and distant metastasis-free survival.

- Population-level cancer registries such as Surveillance, Epidemiology, and End Results Program (SEER) report gender-specific relative survival data stratified by recurrence type (i.e. for LR and DR), thereby capturing prognostic differences across large patient populations.

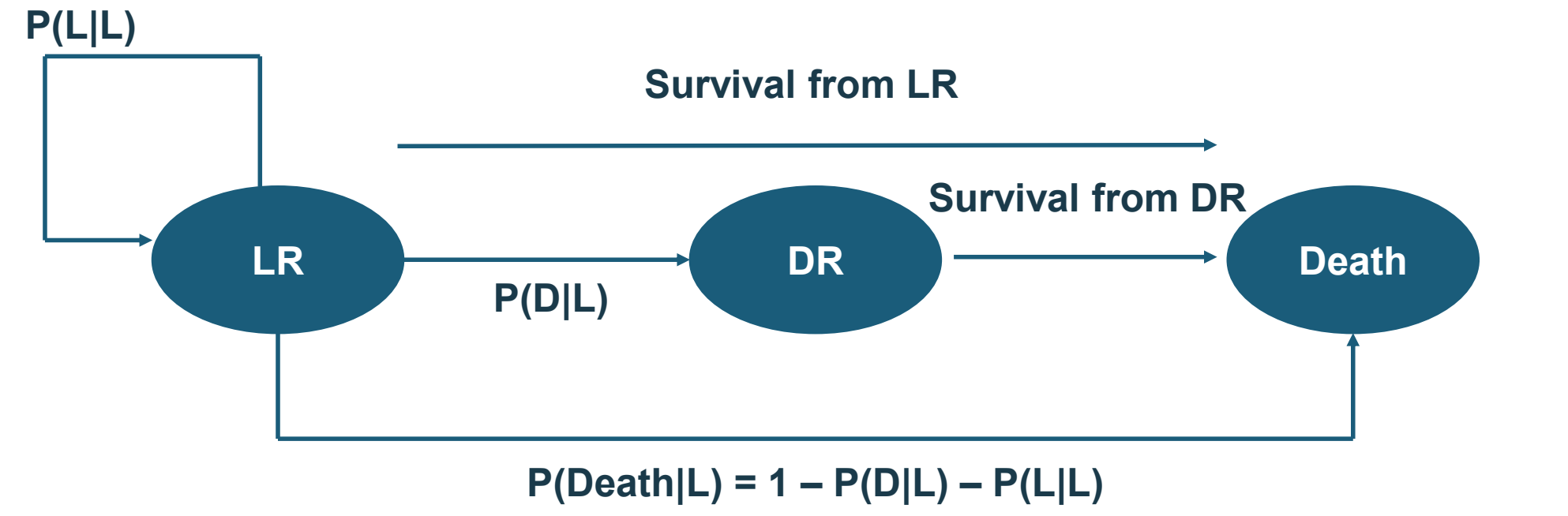
OBJECTIVES

- To develop a systematic, scalable approach to estimate LR→DR transition probabilities for health economic evaluations using publicly available, aggregate-level relative survival data from SEER
- To investigate the sensitivity of the transition estimates to the key parameters and structural assumptions of the proposed model.

METHODS

- Melanoma was selected as a demonstration case due to substantial survival improvements driven by immune checkpoint inhibitors (pembrolizumab, nivolumab) and targeted therapies (dabrafenib, trametinib) in both adjuvant and metastatic settings.
- HTA submissions and published cost-effectiveness analyses for modern melanoma treatments have commonly utilized 4-state Markov models (recurrence-free → locoregional recurrence → distant metastasis → death) yet relied on immature trial and external evidence sources to populate LR-state transition probabilities[1,2,3]

Transition Diagram



Our approach will not actively estimate the value of P(Death|L) which is the monthly probability of death from LR state without developing DR. This quantity will be indirectly estimated through the elicited values of P(D|L) and P(L|L).

METHODS (CONTINUED)

Step 1: Parametric Modelling of Relative Survival & Model Blending (AIC/BIC)

Step 2: Adjusting Modeled Relative Survival with General Population Survival

Step 3: Estimating Long-Term Area Differential between Modeled Unconditional Survival from LR and DR; Solve for P(L|L)

Step 4: Quadratic Optimization Model to Derive P(D|L)

Sensitivity Analyses: Model Blending with AIC vs BIC Time Horizon: Lifetime / 20y / 5y

- Post-recurrence relative survival data were sourced from the publicly available SEER-17 registry for melanoma[4]. SEER-17 refers to a pooled dataset within the broader SEER Program that combines cancer registry data from 17 population-based U.S. geographic region covering roughly 28% of the U.S. population.
- SEER reports relative survival separately for locally and regionally recurrent cancers. Accordingly, before applying the proposed approach, annual survival rates for these populations were weighted by their relative prevalence and blended to derive an aggregate survival curve representing the LR state
- Relative survival data from SEER were available only as annual estimates over a 5-year horizon. As the proposed approach required mean survival estimates for both LR and DR populations, extrapolation of relative survival rates beyond the observed follow-up period was necessary for both states.
- Age- and sex-adjusted general population survival was derived from publicly available US CDC life tables to adjust extrapolated relative survival curves and was maintained as a non-parametric function with weekly increments over the lifetime horizon.
- To reduce uncertainty associated with model selection in long-term projections, seven standard parametric models (SPMs) recommended by NICE Technical Support Document 21 (exponential, Weibull, log-normal, log-logistic, Gompertz, and generalized gamma, generalized-F) were fitted to the SEER relative survival data[5]. Model blending across the top three SPMs was then performed using relative likelihood weights derived from the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
- For simplicity, transitions from the LR state were assumed to be constant over time and for internal consistency, same statistical fit criterion (AIC or BIC) was used for blending of SPMs across both LR and DR states.
- Similarly, consistent time horizons were applied for survival extrapolations from the LR and DR states to ensure appropriate estimation of the area differential between the modeled survival curves. This area differential was subsequently used to inform the derivation of probability of remaining in the LR state.
- The LR→DR transition probability was estimated via a quadratic optimization framework, parameterized using the previously derived probability of remaining in the LR state. The same time horizon used to estimate the probability of remaining in the LR state was consistently applied in the derivation of LR→DR transitions within the quadratic optimization framework.

Parameters & Survival Modeling

- ***N:*** *Time horizon (months)*
- ***P(L|L):*** *Monthly probability of remaining in LR state*
- ***P(D|L):*** *Monthly probability of moving from LR to DR state*
- **$S_L(t)$, $S_D(t)$:** *Reported relative survival from LR and DR states, respectively*
- ***R(t), Q(t):*** *Blended relative survival distribution from LR and DR states, respectively*
- **$U_L(t)$, $U_D(t)$:** *Unconditional survival distribution from LR and DR states respectively*
- ***L(t):*** *Probability of remaining in LR state for t months; $L(0) = 1$, $L(t) = [P(L|L)]^t$*

- SPMs were fitted independently to reported relative survival data from LR and DR [$S_L(t), S_D(t)$]; top-3 fitting SPMs were blended with relative likelihood weights from AIC and BIC to yield long-term relative survival curves [$R(t), Q(t)$]
- Unconditional survival from both LR and DR states are obtained by adjusting blended relative survival distributions with general population survival: $U_L(t) = B(t) \cdot R(t)$; $U_D(t) = B(t) \cdot Q(t)$ for t = 0, 1, …, N

Deriving Probability of Remaining in LR State [P(L|L)]

- The areas under the extrapolated unconditional survival curves for LR and DR states, $U_L(t)$ and $U_D(t)$, correspond to the mean survival from each state. Given transitions from LR state are irreversible, the difference between these areas represents the mean time spent in the LR state, as derived via the trapezoidal rule.
- The area between the extrapolated unconditional survival curves for the LR and DR states, M, can be equivalently expressed as a geometric series of the probability of remaining in the LR state: $[1 - P(L|L)^{(N+1)}] / [1 - P(L|L)] = M$.
- The numerical solution for P(L|L) satisfying the above identity was obtained using a bisection-based optimization procedure in R, with uniqueness guaranteed by the strict monotonicity of the left-hand side with respect to P(L|L).

Quadratic Optimization Problem for Derivation of P(D|L)

Probability of transitioning from LR to DR state, P(D|L), is elicited as a solution to a quadratic optimization problem.

Variables (Unknowns to Solve)
P(D|L): Monthly probability of moving from LR to DR state (i.e. being in DR at *t*+1 given in LR at *t*)
***D(t)*:** Composite probability of being in DR state at time *t* given being in LR initially.
$D(t) = P(D|L) \times \sum_{i=0}^{t-1} L(i) \cdot Q(t-i-1)$ for t = 1, 2, …, N

Minimize: $\sum_{t=1}^{N} \{1 - [D(t) + L(t)] / R(t)\}2$
Subject to: $P(D|L) \geq 0$, $P(D|L) + P(L|L) \leq 1 - d$

The objective function represents the sum of squared relative discrepancies between two independent estimates of unconditional LR survival over a prespecified time horizon.

Transition-based prediction: *D(t) + L(t)* denotes the unconditional survival from the LR state, constructed through convolution of state-transition probabilities with the modeled unconditional DR survival function derived from blended SPMs

Extrapolation-based prediction: *R(t)* denotes the unconditional survival from the LR state, estimated from blended SPMs fitted to reported relative survival data for the LR population

The expression $1-[D(t)+L(t)]/R(t)$ quantifies the relative discrepancy between the two predicted LR survival estimates at time t. Minimizing the sum of its squared values over the time horizon yields the optimal estimate of P(D|L)

Constraint Interpretation

- The constraint $P(D|L) + P(L|L) \leq 1 - d$ ensures the probability of death from the LR state is bounded below by the probability of death for the general population [i.e., $P(Death|L) \geq d$]. It also implicitly enforces that the three mutually exclusive monthly transitions from the LR state—remaining in LR, progressing to DR, or death—do not collectively exceed unity.
- On the right-hand side of the constraint, $d = \exp(-\beta)$ represents monthly death probability for general population, estimated from *B(t)* under an exponential assumption where $\beta = \sum_{t=1}^{N} [-\ln B(t)] / t \times (1/N)$ represents the underlying monthly mortality rate, assumed to remain constant throughout the time horizon (i.e. lifetime horizon, 20 years or 5 years) in the optimization problem.

Note: The exponential distribution assumption for *B(t)* was only for the estimation of a time-homogeneous mortality rate in LR state to enforce a constraint boundary for the probability death from LR state, P(Death|L). In adjustments of blended SPMs for relative survival, *B(t)* retained its non-parametric weekly form.

Sensitivity Analyses

- Three sensitivity analyses were conducted to investigate the iterative, marginal impact of model blending criteria and time horizon on the transition estimates

- Sensitivity analyses restricting the time horizon to five years are also intended to assess the impact of removing subjectivity and uncertainty introduced by model blending and extrapolation, as the results rely solely on observed reported data

- All sensitivity analyses influence the area difference between the extrapolated survival curves for LR and DR, which in turn propagates to both P(L|L) and P(D|L).

RESULTS

BASE CASE
Time Horizon: 39 Years, Baseline Age: 61 Years, Blending of SPMs: AIC

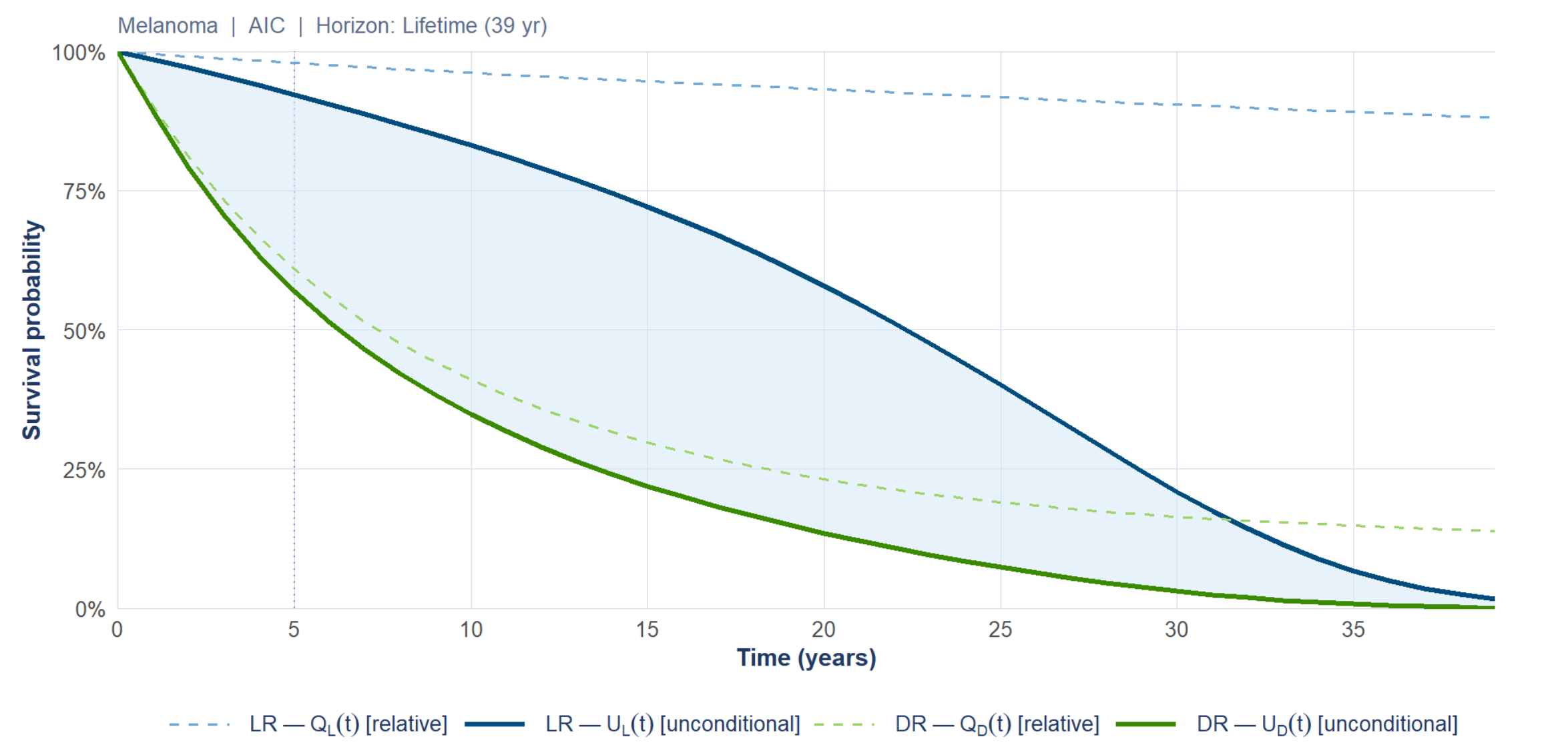
143.6	0.9934	0.0066
Months **Mean LR Sojourn**	P(L|L) Prob. Stay in LR	P(D|L) Prob. LR → DR

Scenario	Weights	Horizon	P(L|L)	P(D|L)
Base Case	AIC	Lifetime	**0.9934**	**0.0066**
SA 1	BIC	Lifetime	0.9927	0.0072
SA 2	BIC	20-year	0.9880	0.0120
SA 3	BIC	5-year	0.9177	0.0823

Lifetime horizon: 100 - Baseline age; SA: Sensitivity Analysis; AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, P(L|L): Monthly probability of remaining in LR state , P(D|L): Monthly probability of moving from LR to DR state

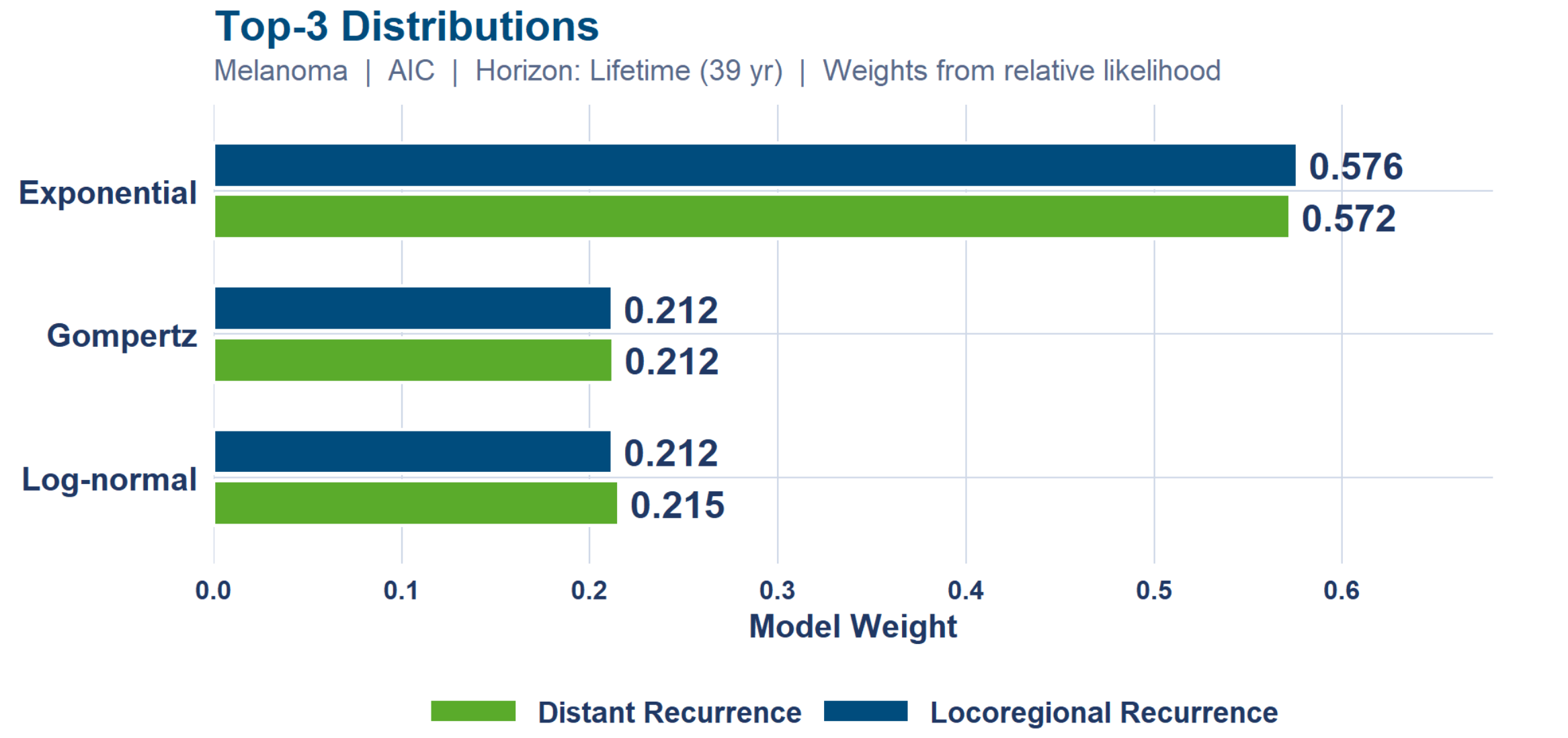
- In the base case, LR patients exhibit a monthly retention probability above 99%, corresponding to an estimated mean sojourn time of ~12 years.
- Sensitivity analyses using BIC weights for blending of SPMs and truncated time horizons show consistent directional effects on the results. As expected, shorter time horizons generated attenuated mean sojourn times in LR state leading to reduced probability of staying in LR state and higher probability of LR→DR transitions.

Demonstration of Indirect Estimation of Mean Sojourn Time in LR state



mean time spent in LR state

Model Blending Weights Used for Survival Extrapolations from LR and DR States



CONCLUSIONS

- This study introduces a reproducible and scalable framework for parameterizing the LR component of 4-state (semi) Markov models. It leverages publicly available SEER registry data, eliminating the need for individual-level transition records. The approach is broadly applicable to cancer types with available stage-stratified relative or unconditional survival data and supports structured sensitivity analyses through systematic variation of key model parameters.
- Transitions from the LR state estimated in this study can guide pharmacovigilance priorities and patient monitoring for locally recurrent melanoma patients, as progression to DR may involve different safety exposures, concomitant medications, and adverse event risks
- Accuracy of post-recurrence transition estimates is important when using observational real-world data to supplement clinical trials or performing economic evaluations. The range of transition probabilities estimated from LR state across base-case and sensitivity analyses of this study can serve as a benchmark for stress-testing of long-term survival projections and economic evaluations for clinical trials in early-stage melanoma.

LIMITATIONS

- For simplicity, transitions from the LR state were assumed constant over time, implying exponentially distributed sojourn time. Incorporating differences in the second moments of the LR and DR survival distributions may enable derivation of gamma- or beta-distributed sojourn times in the LR state, thereby relaxing the stationarity assumption for the probability of remaining in the LR state.
- Limited follow-up and annually reported SEER relative survival data restricted the framework to SPMs, as survival plateaus and inflection points could not be identified. However, the proposed framework remains flexible to incorporate mixture cure or spline-based models with longer follow-up and more granular data to better capture complex survival trends.
- As SEER-17 covers only the U.S. treatment landscape and cases through 2021, derived transition probabilities may not be directly generalizable to other settings or treatment eras without recalibration. Moreover, due to lack of detailed comorbidity information in SEER-17, reported relative survival estimates may be imprecise in older populations.

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