https://github.com/novainsilico/acop
2026-YODA

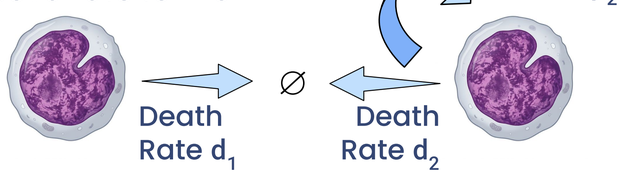
A Two-step Model of Individual Patient Progression-Free Survival in Mantle Cell Lymphoma

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A QSP tumor dynamic model links **longitudinal tumor growth** to **progression-free survival**, accurately capturing **patient-specific outcome heterogeneity** in Mantle Cell Lymphoma.

Tumor Burden (TB) Model

Nonlinear Mixed Effects Model
2 ODEs, 5 parameters,
7 covariate terms

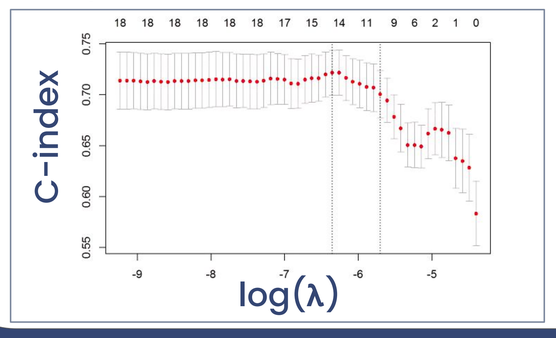


Progression-Free Survival (PFS) Model

Cox Proportional Hazards Model

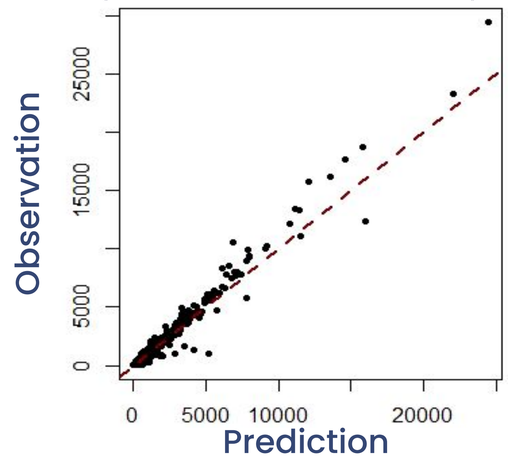
$$\lambda(t) = \lambda_0(t) \cdot \exp\left(\boldsymbol{\beta}_{\text{clinical}} \cdot X_{\text{baseline}} + \beta_{p2} \cdot p_2 + \beta_{\text{tumor}} \cdot \log \text{TB}_{2\text{yr}}\right)$$

LASSO cross-validation identifies the optimal parameter based on C-index



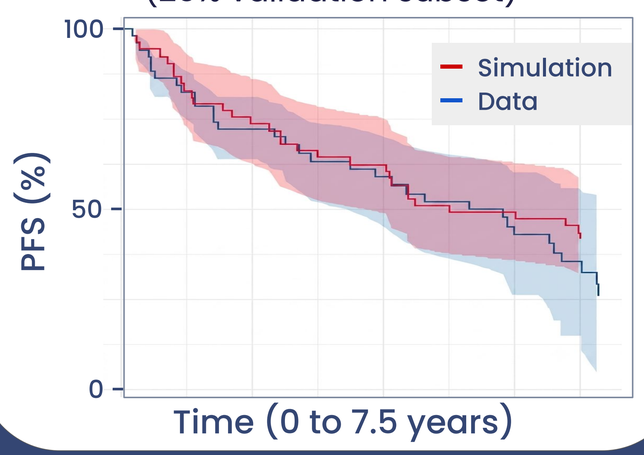
Individual Longitudinal Fit

(80% calibration subset)



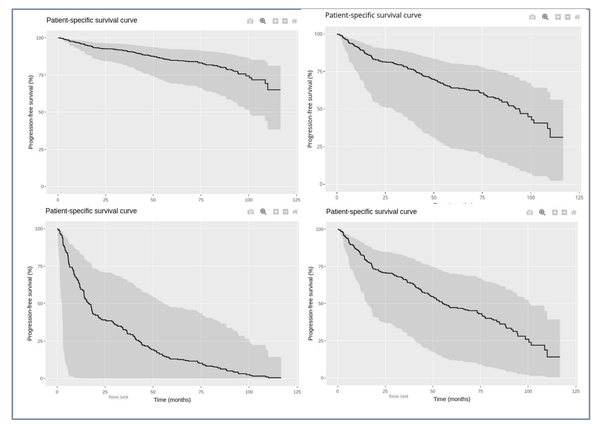
Aggregate Survival Validation

(20% validation subset)

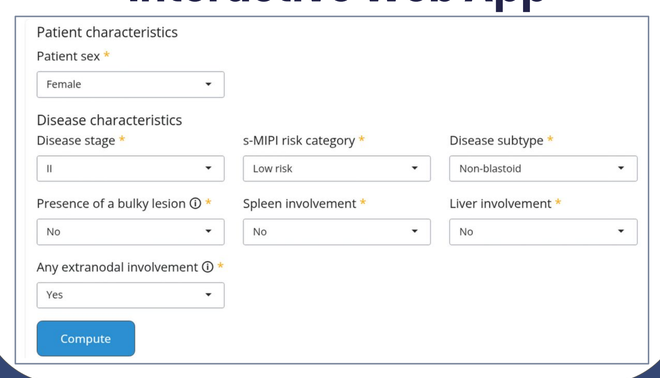


Clinical Heterogeneity

Individual-level PFS predictions tailored to distinct baseline clinical profiles, illustrating the extreme heterogeneity in patient outcomes.



Interactive Web App



BACKGROUND

Mantle Cell Lymphoma (MCL) displays significant variability in treatment responses and long-term progression-free survival (PFS) outcomes [1].

Standard prognostic scores often miss individual, dynamic tumor responses under treatment.

Objective: Develop a Quantitative Systems Pharmacology (QSP) framework linking individual-level longitudinal tumor dynamics and baseline patient characteristics to progression-free survival (PFS) distributions under immunochemotherapy.

METHODS

Data: Clinical data from the control arm (bendamustine-rituximab) of the randomized SHINE trial (NCT01776840) obtained via YODA [2, 3]. Dataset split into 80% calibration and 20% validation cohorts.

Tumor Burden Modeling: Formulated a 2-ODE structural model representing sensitive and resistant population. Model parameters and baseline descriptor correlations were estimated using Nonlinear Mixed Effects (NLME) modeling.

Survival Modeling: Cox Proportional Hazards model with covariate selection conducted via LASSO regularization to maximize cross-validated C-index.

Virtual Patient Simulation: Generated 400 virtual patients for each of the 384 combinations of baseline descriptors to derive full PFS distributions and prediction intervals.

RESULTS

Tumor Burden Model Covariate Calibration: Quantified 7 significant QSP parameter–patient descriptor correlations (e.g., significantly higher resistant clone proliferation p_2 in patients with extranodal involvement).

Survival Model Predictors: Selected 6 final hazard covariates: 4 baseline clinical features (e.g., spleen involvement), 1 QSP parameter (p_2), and 1 QSP-derived tumor dynamics output ($\text{logTB}_{2\text{yr}}$).

Quantitative Validation: Measured tumor values fell within the 95% Prediction Interval (PI) for 50 out of 52 patients in the validation set. Simulated survival curve aligned closely with observed Kaplan-Meier curve.

PFS Outcome Heterogeneity: Predicted median PFS ranged across profile combinations from 16.4 months (95% PI: 2.1–55.9) to >120 months (100–not evaluable). Implemented as an interactive web simulator: MCL-calc [4].

CONCLUSION

- **Mechanistic-Statistical Bridge:** Successfully integrated longitudinal QSP tumor dynamics with Cox survival models to capture wide outcome heterogeneity in MCL.
- **Clinical Utility:** Enables risk stratification at diagnosis, virtual subgroup cohort building, and dynamic outcome predictions.
- **Future Scope:** Framework can be extended to novel agents, combination regimens, and additional biomarker/prognostic profiles.

REFERENCES

1. Ip A et al. (2025) 10.3390/cancers17040696.
2. Wang M et al. (2022) 10.1056/NEJMoa2201817.
3. The YODA Project. Research Proposal 2025-0688.
4. MCL-calc. https://novainsilico.github.io/MCL-calc/

DATA ACCESS DISCLAIMER

This study, carried out under YODA Project 2025-0688, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The interpretation and reporting of research using this data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C.