From Real-World Data (RWD) to Digital Twins: Building Models for Patient-Level Counterfactual Prediction in Oncology

Sandra Griffith, PhD[1]; Joe Manfredonia, ME[1]; Marcello Ricottone, MA[1]; Richard Knoche, PhD[1]; Aaron B Cohen, MD, MSCE[1,2]; Jacqueline Law, PhD[1]; Melissa Estevez, MS[1]

[1]Flatiron Health, New York, NY; [2]Department of Medicine, Grossman School of Medicine, New York University, New York

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Background

- Digital twins (DT), models capable of generating patient-level counterfactual predictions, may improve oncology drug development success rates by informing trial design, contextualizing results, and enhancing statistical power
- Training DT models require large, diverse, and longitudinally-rich data, and an understanding of methodological approaches
- This study leverages the depth and scale of real-world data (RWD) to evaluate the feasibility of DT models, compare performance across approaches to understand strengths and limitations of different models, and evaluate the performance of a DT-powered composite risk score

Methods

- **Data source:** The US-based, longitudinal Flatiron Health Research Database—an electronic health record-derived (EHR), deidentified database, comprising patient-level data originated from ~220 US practices (~1600 sites of care; primarily community oncology settings) and curated via technology-enabled abstraction.[1] Features were generated using demographics, structured, and ML/LLM-extracted variables (eg, Charlson comorbidity index [CCI] and sites of metastases [SOM])
- **Setting:** The study included patients diagnosed with Stage IV non–small cell lung cancer initiating first-line (1L) platinum chemotherapy between 2011 and 2016, contemporaneous to chemotherapy use in trials
- **Main outcome measures:** Real-world overall survival (rwOS); patients were censored at the date of last activity in the EHR or the end of the study period
- **Statistical analysis:**
  - We trained four models (penalized pooled logistic regression [LR], XGBoost [XGB], Multi-layer Perceptron [MLP], and Graph Attention Network [GAT]) to predict rwOS using discrete time survival methods
  - Missing data were handled via multiple imputation with chained equations (LR and XGB) or a denoising autoencoder trained to reconstruct missing values from observed features (MLP, GAT)
  - Feature selection and hyperparamter optimization were performed iteratively on a held-out validation set
  - We used an outcome model-based approach to compute standardized survival curves in the held-out test set using patient-level predictions based on baseline patient characteristics
  - Model performance was assessed using C-index, area under the curve (AUC(t)), integrated Brier score (IBS), mean absolute difference (MAD) between predicted and observed survival curves, and median rwOS
  - Individual DT-powered composite risk scores were generated using the cumulative hazard based on the model predictions. The association between risk strata and rwOS was assessed with Kaplain-Meier methods, log-rank test, and Cox Proportional Hazards models

Results

- Participants**:** A total of 19,988 pts were randomly split 60/20/20 for train/validation/test
- All four methods performed well, comparable to published results using different methods[2] (**Figure 1**)
- LR/XGB demonstrated better discrimination (C-index, AUC[t]), while GAT exhibited superior calibration (MAD)
- Predicted median rwOS (9–10 months) aligned with observed rwOS (10 months) (**Figure 1**)
- Top features varied by method and included LLM-extracted variables (CCI, SOM), in addition to established prognostic variables (eg, ECOG) and laboratory results (eg, albumin) (LR: **Figure 2**; feature importance plots for additional models available via **QR code**)
- Risk groups derived from DT-powered composite risk scores successfully stratified rwOS, with the high-risk population demonstrating over 3-fold increase in the hazard of death compared to the low-risk group (**Figure 3**)

Figure 1. Observed vs predicted average real-world overall survival in Test set

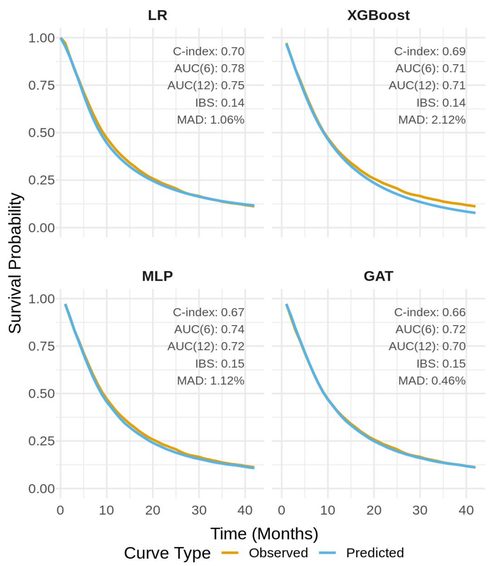


Figure 2. Penalized odds ratios (LR model)

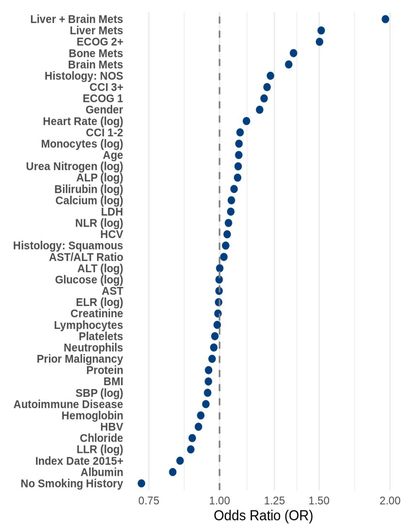
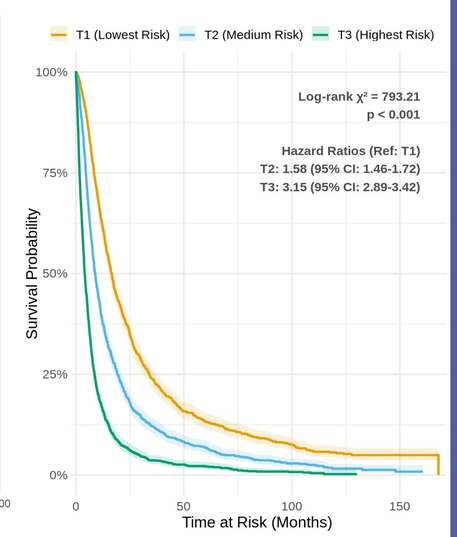


Figure 3. Kaplan-Meier curves stratified by risk score in Test set (LR model)



Abbreviations/definitions: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCI, Charlson Comorbidity Index; ELR, eosinophils to leukocytes ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; LDH, lactate dehydrogenase; LLR, lymphocytes to leukocytes ratio; mets, metastases; NLR, neutrophils to lymphocytes ratio; NOS, not otherwise specified; SBP, systolic blood pressure. Sites of Metastases (SOM) variables follow a hierarchical definition: Liver + Brain mets = both liver and brain mets; Liver mets = liver mets w/o brain mets; Brain mets = brain w/o liver mets; Bone mets = bone w/o liver or brain mets; reference category = other mets w/o liver, brain, or bone mets. Reference categories for other categorical variables: ECOG 0, Non-squamous histology, CCI 0, female gender, history of smoking.

RWD-powered **Digital Twin** models generate highly prognostic composite risk scores for **patient stratification**, demonstrating promising utility for clinical trial applications.

References

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Contact information: Jacqueline Law, jacqueline.law@flatiron.com

Discussion

- While simpler models (LR, XGB) achieved stronger discrimination, all four approaches produced well-calibrated survival curves (MAD < 2.2%), suggesting that for standard tabular clinical data, increased model complexity does not necessarily improve predictive accuracy
- Investing in richer LLM-based feature extraction from unstructured EHR data can augment existing feature sets to better align with RCT inclusion/exclusion criteria and meaningfully contribute to model explainability beyond what is available in standard structured datasets
- For DT applications that require transporting predictions to new populations (eg, from RWD to RCT cohorts), calibration performance may be as important as discrimination
- A DT-powered composite risk score can have multiple applications for drug development, including:
  - Patient stratification into risk groups that produce well-discriminated survival curves, which could be used to support prognostic enrichment or stratified randomization during trial design
  - Covariate adjustment, which has the potential to increase power for a clinical trial by mitigating bias and reducing variability in the treatment estimate
- External validation of DT models in clinical trial datasets is ongoing