Joint Modeling for Clinical Interpretation of ctDNA Tumor Methylation Dynamics during Longitudinal Monitoring

Christopher Pretz[1], Sara Wienke[1], Jiemin Liao[1], Jim Hayes[1], Samantha Liang[2], EnJun Yang[2], and Amar K. Das[1]
1) Guardant Health, Inc. Palo Alto, CA. 2) Parker Institute of Cancer Immunotherapy, San Franscico, CA.

Background

Background: Current studies suggest that changes in ctDNA levels over time, captured by the methylation-based tumor fraction (TF), is associated with real-world overall survival (rwOS) and real-world progression free survival (rwPFS) in non-small cell lung cancer (NSCLC) patients. To achieve a comprehensive understanding of how changes in ctDNA modify outcome we leverage an advanced statistical approach, joint modeling of longitudinal and time-to-event data (JM). Here, we showcase the ability of JM to perform patient-specific dynamic predictions which provide a comprehensive understanding of how TF evolution associates with rwPFS and rwOS, where a major advantage of this approach is that a patient's survival probability is updated each time additional longitudinal information becomes available.

Methods

- Data was extracted from 251 advanced stage (iii and iv) NSCLC patients participating in the RADIOHEAD study, where each patient had at least 3 longitudinal measurements. Additionally, all patients received immune checkpoint inhibitor (ICI) therapy post baseline.
- Patients were tested at baseline and on-treatment timepoints with Guardant Reveal, a tissue-free epigenomic assay that detects and quantifies ctDNA, reported as a methylation-based TF.
- Baseline covariates included age (average = 69 years), gender (45% Female), smoking status (6% never smoked), and disease stage (42% stage iii).
- A Bayesian based JM, which is comprised of two sub-models, one for the longitudinal data and the other for the time-to-event data, was utilized. A hierarchical cubic spline mixed effects model was used to analyze the longitudinal data, and Cox-regression was used for the time-to-event analysis. Covariates were included in both sub-models to improve prediction and act as statistical controls.
- Information from each sub-model is combined using an association structure (AS). In this study three different ASs are explored and are defined as follows.

The patient's current biomarker estimate:

$$y_i(t) = m_i(t) + \varepsilon_i(t) = x_i^T(t)\beta + z_i^T(t)b_i + \varepsilon_i(t)$$
$$h_i(t|\ \{m_i(s), 0 \le s < t\}) = h_0 \exp(\gamma^T w_i + \alpha m_i(t))$$

The instantaneous rate of change (IRC) of the patient's biomarker:

$$m_i'(t) = \frac{d(x_i^T(t)\beta + z_i^T(t)b_i)}{dt}$$
$$h_i(t|\ \{m_i(s), 0 \le s < t\}) = h_0 \exp(\gamma^T w_i + \alpha m_i'(t))$$

The patient's time-averaged cumulative biomarker effect (CE):

$$h_i(t|\ \{m_i(s), 0 \le s < t\}) = h_0 \exp(\gamma^T w_i + \alpha \frac{\int_0^t m_i(s)\ ds}{t})$$

$y_i(t)$ -> mixed effects model (fixed effects, random effects, and error), $h_i(t|\ \{m_i(s), 0 \le s < t\})$ -> hazard of an event at t after controlling for covariates, α -> measure of the association between sub-models. Note that TF values are transformed into logits to better adhere to model assumptions and the error terms in the mixed effects model are assumed to follow a multivariate normal distribution.

References

1. Rizopoulos D. Joint models for longitudinal and time-to-event data with applications in R. 2012; CRC Press.

Results

KEY FINDING: The cumulative effect of methylation tumor fraction is highly associated with both rwPFS and rwOS, where this association is leveraged in generating the patient-specific dynamic predictions displayed below.

Data & Model Results

Fig.1.0

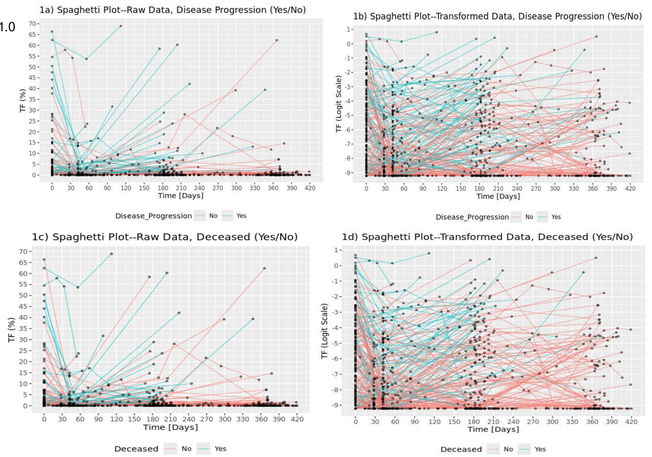

Fig 1.0 Spaghetti plots of the raw (1a & 1c) and transformed (1b & 1d) data. Black dots represent patient TF and transformed TF values respectively. Dots connected by lines map out a patient's TF progression over time. Patent progression is stratified by disease progression (yes/no) (1a & 1b) deceased (yes/no) (1c & 1d).

Table 1.0 JM Results for rwPFS and rwOS

	rwPFS JM				rwOS JM			
Parameter	**Estimate**	**Standard Error**	**Hazard Ratio**	**p-value**	**Estimate**	**Standard Error**	**Hazard Ratio**	**p-value**
Age	0.016	0.018	1.01	0.39	0.012	0.019	1.02	0.27
Comorbidity Index	0.081	0.047	1.08	0.09	0.081	0.054	1.08	0.14
Gender (ref=Female)	-0.07	0.23	0.94	0.77	-0.16	0.26	0.20	0.53
Disease Stage (ref=iii)	0.11	0.26	1.11	0.61	0.203	0.30	1.22	0.50
Smoking Status (ref=Non-Smoker)	1.01	0.65	2.75	0.09	1.37	0.82	3.94	0.05
Current Biomarker's Cumulative Effect	0.45	0.054	1.56	<0.00001	0.48	0.062	1.61	<0.00001

*Chains = 3, Burn-in per Chain = 20000, Iterations per Chain = 60000, Thinning Factor = 3

Tables 1.0. Based on the deviance information criteria, the biomarker's time-averaged cumulative effect was found to produce the most optimal rwPFS and rwOS JMs. Results displayed in the table above retain an interpretation similar to that of a typical Cox-Regression based survival analysis. For example, we conclude that after controlling for confounders, a one-unit increase in the current biomarker's time-averaged cumulative effect, there is a 1.61-fold increase in the patient's risk of experiencing death at time t. Note that results reported above are conducted using a Bayesian analysis, where all R-hat values indicate that parameter estimates are stable (<1.10). Note that the hierarchical cubic spline mixed effects model parameter estimates are not displayed as these results are uninterpretable. However, visual representations of the results of this model are given in the "longitudinal trajectory" panels displayed Fig 2.0 and 3.0.

Dynamic Prediction Results

Fig 2.0

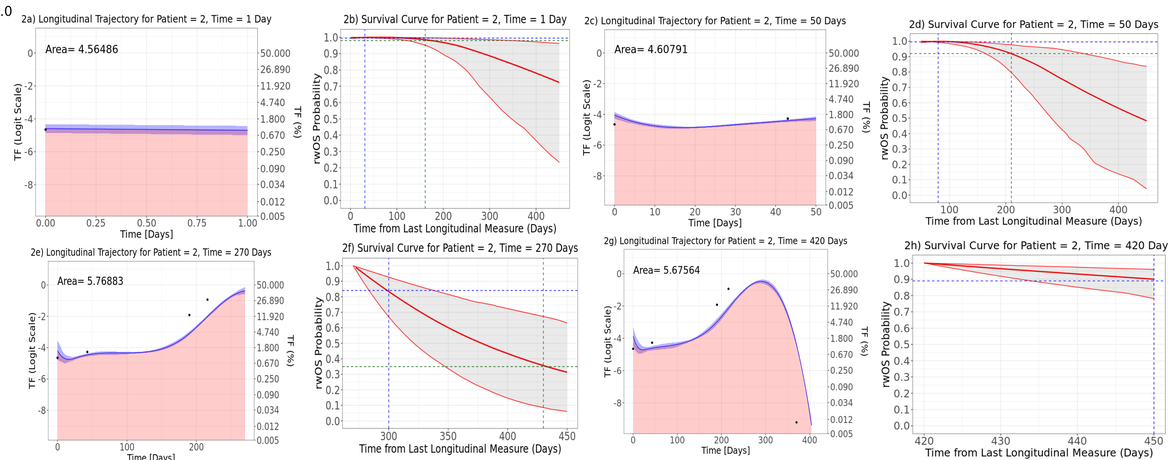

Fig 3.0

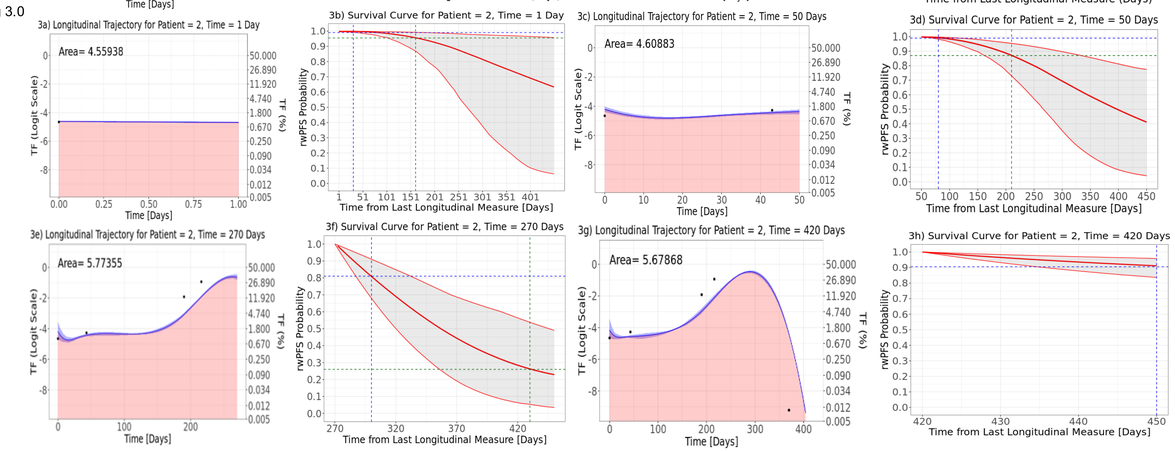

Fig 2.0 This figure illustrates how rwOS probability is modified (2b,d,f,h) as the biomarker cumulative effect changes over time (2a,c,e,g) for patient 2 (randomly selected from the cohort). The time-averaged cumulative effect is given by the area under the curve (shaded in red). The estimated area is given in the longitudinal trajectory panels. **Fig 3.0** shows how rwPFS probability is modified as the biomarker time-averaged cumulative effect evolves for the same patient. For each survival curve the intersection of the blue dashed lines and green dashed lines indicate the probability at 30 and 160 days from the last longitudinal measure, respectively. In each case rwPFS probability < rwOS probability, as would be expected.

Conclusions

Results show the flexibility of joint modeling through the generation of patient-specific dynamic predictions that illustrate how the evolution of the biomarker's cumulative effects of methylation tumor fraction are associated with outcome, where predictions are enhanced by the incorporation of baseline covariates. As such, patient specific dynamic-predictions can provide adaptive customized prognostic information that can be leveraged in precision oncology decision making.