The analysis of different longitudinal biomarkers association with the overall survival in non-small cell lung cancer by means of joint modeling

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Abstract

It is well-known that tumor size can be predictive biomarker for non-small cell lung cancer (NSCLC). Joint modeling is an advance approach to quantify the association between longitudinal biomarkers and overall survival. The obtained results suggest that assessment of biomarker dynamics improved the accuracy of survival prediction in comparison with baseline values for patients with NSCLC.

Introduction

In NSCLC studies tumor size is typically analyzed by means of Sum of Longest Diameters of target lesions (SLD) [1,2]. Baseline SLD is a well-known biomarker for overall survival (OS) assessment. Accounting for SLD kinetics as well as assessing other biomarker impact can improve the prediction of OS. Joint modeling (JM) is an advanced technique for survival analysis and longitudinal biomarker kinetics modeling.

Current work is aimed to quantify the association of different longitudinal biomarkers and OS in patients with NSCLC and compare the results between two different NSCLC studies with different treatment.

Methods

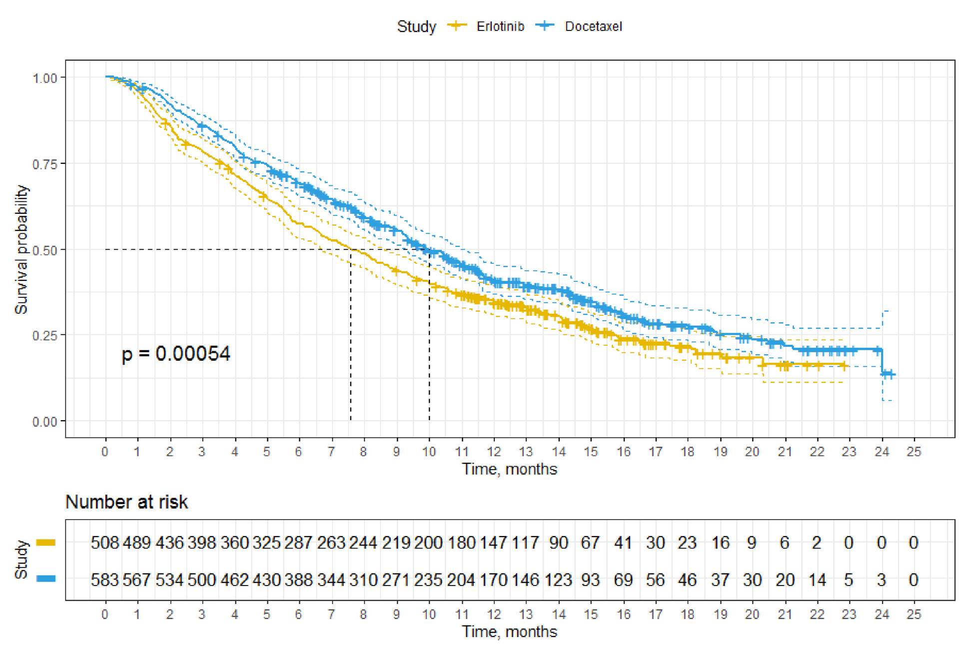
1 Clinical study data

NCT00312377 – Vandetanib + Docetaxel; Docetaxel *(standard chemotherapy)*
Number of enrolled patients: 583

NCT00364351 – Vandetanib *(inhibitor of EGFR and VEGFR)*; Erlotinib *(inhibitor of mutant EGFR)*
Number of enrolled patients: 508

General details of used data:

- Published patient-level data from Project Data Sphere [3]
- second-line therapy
- Phase 3 studies
- Locally advanced or metastatic NSCLC (Stage III-IV)



Patients in both considered studies were similar in their disease status, demographics and baseline characteristics.

FIGURE 1. Kaplan-Meier curves with 95% CI for docetaxel and erlotinib datasets.

2 Selection of the optimal Cox proportional hazards model

The Cox model is expressed by the hazard function denoted by h(t). The hazard function can be interpreted as the risk of dying at time t. It can be estimated as follows:

$$h_i(t \mid \omega_i) = h_0(t) * \exp(\sum \gamma * \omega_i)$$

$h_0(t)$ – baseline hazard γ – regression coefficients ω_i – baseline covariates

Tested covariates: SLD, lactase dehydrogenase (LDH), neutrophils, white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatinine. The optimal Cox model for each dataset was selected based on the lowest Bayesian Information Criterion value and statistical significance of considered covariates.

3 Joint modeling

On the basis of the optimal Cox model, multiple joint models were developed using one longitudinal biomarker and other biomarkers as baseline. Parameter estimation was made in JM package in R. Longitudinal biomarker trajectories were modeled with natural splines.

$$\begin{cases} y_i(t) = \boldsymbol{m_i(t)} + \varepsilon_i(t) \\ \quad = xiT(t)\beta + ziT(t)b_i + \varepsilon_i(t) \\ h_i(t) = h_0(t) * \exp\{\gamma\omega_i + \boldsymbol{\alpha m_i(t)}\} \end{cases}$$

$\boldsymbol{\alpha}$ – association constant between longitudinal and time-to-event data

$h_0(t)$ – piecewise-constant baseline hazard

$x_i^T(t)$ and β: Fixed-effects part – population-average evolution

$z_i^T(t)$ and b_i: Random-effects part, $b_i(t) \sim N(0, D)$ – subject-specific evolution

4 Assessment of quality of survival prediction

We assessed and compared the quality of survival predictions of Cox and JM models by means of time-dependent Receiver Operating Characteristic Curve AUC (ROC AUC) and Brier Score (BS) [4]. In the case of JM with longitudinal biomarkers, ROC AUCs and BSs were calculated with 90-day cut-off of longitudinal data.

Results

The optimal Cox model was identified for each study. Cox model structures turned out to be identical for both datasets and included SLD, LDH, WBC and NLR baseline biomarkers.

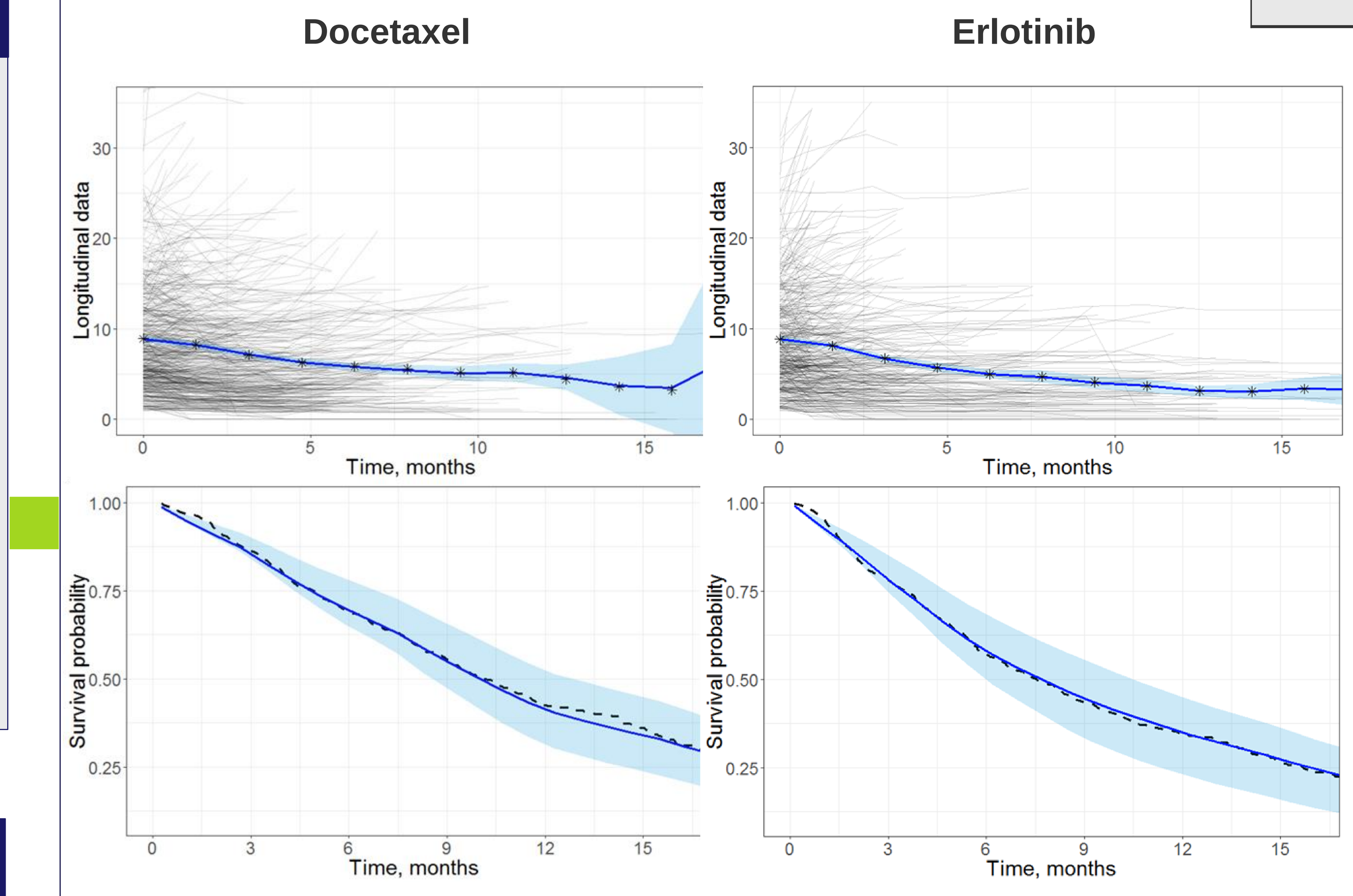
$$h_i(t \mid \omega_i) = h_0(t) * \exp(\gamma_1 * \text{SLDb} + \gamma_2 * \text{LDHb} + \gamma_3 * \text{WBCb} + \gamma_4 * \text{NLRb})$$

The significant association between each of these identified biomarkers and OS was detected in JM as well, where the biomarkers were considered longitudinal (Table 1).

		Docetaxel	Erlotinib
JM SLD	α	0.83 (95%CI: 0.63; 1.01)*	0.69 (95%CI: 0.55; 0.87)*
	HR**	2.29 (95%CI: 1.88; 2.75)	1.99 (95%CI: 1.73; 2.39)
JM LDH	α	0.70 (95% CI: 0.49; 0.93)*	0.56 (95% CI: 0.38; 0.73)*
	HR	2.01 (95%CI: 1.63; 2.53)	1.75 (95%CI: 1.46; 2.08)
JM WBC	α	1.53 (95% CI: 1.02, 2.15)*	1.60 (95% CI: 1.27; 1.90)*
	HR	4.62 (95%CI: 2.77; 8.58)	4.95 (95%CI: 3.56; 6.69)
JM NLR	α	1.06 (95%CI: 0.56; 1.55)*	1.49 (95%CI: 1.24; 1.80)*
	HR	2.89 (95%CI: 1.75; 4.71)	4.44 (95%CI: 3.46; 6.05)

TABLE 1. Estimated association constants and hazard ratios with 95% CI for JM models with different longitudinal biomarkers. .

* p-value <0.001
** increase in risk associated with one-unit increase in log(SLD / LDH / WBC / NLR)



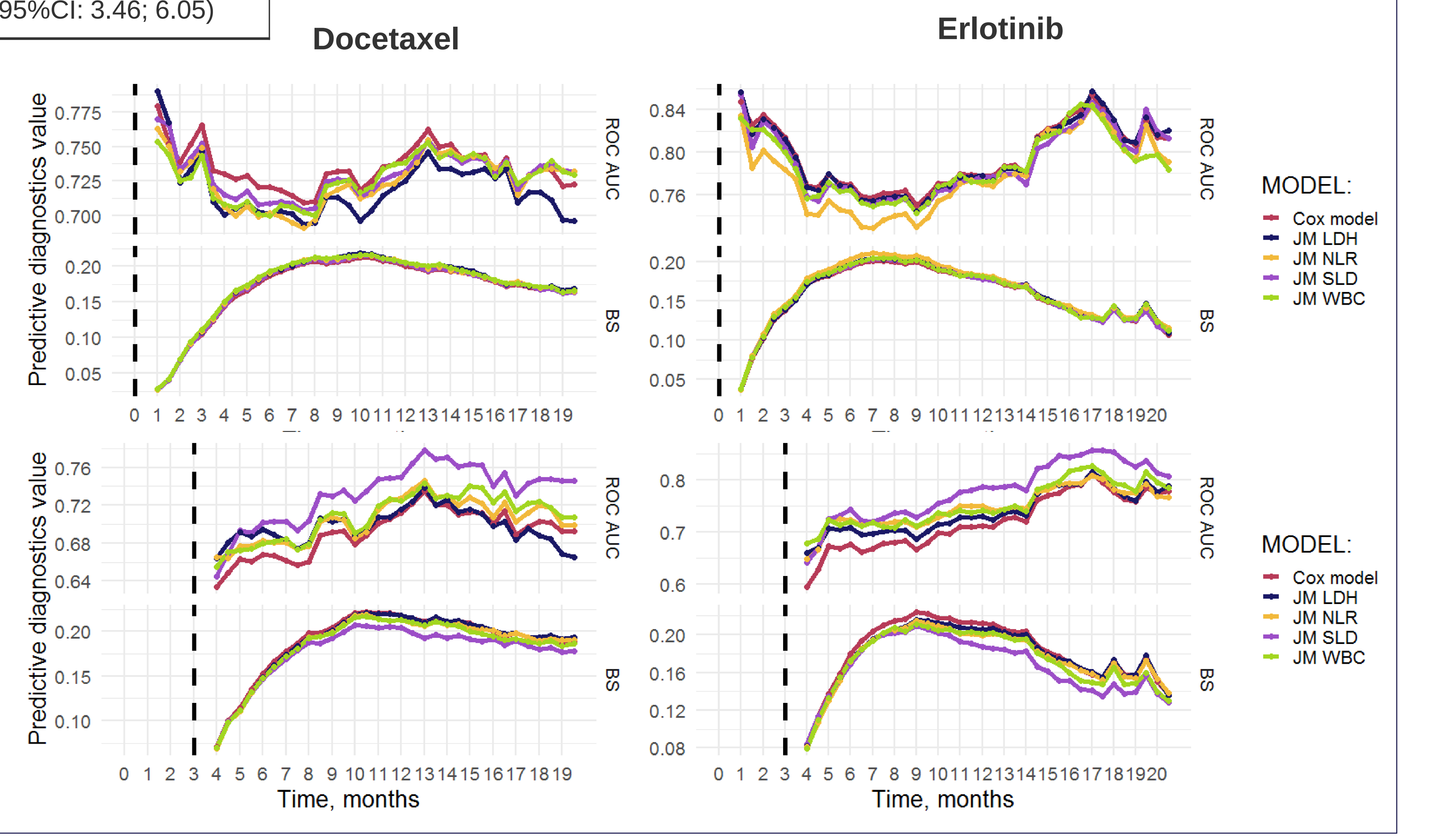
The association between longitudinal SLD, LDH, WBC and the risk of death turned out to be different for both studies, though 95% CIs for point estimates overlapped (Table 1).

Fitted mean longitudinal trajectories and survival curves (blue lines) coincide with experimental ones (black lines). (Figure 2).

FIGURE 2. The fitted mean longitudinal trajectory and survival curve with 95% CI for two datasets for JM with longitudinal SLD (JM SLD).

FIGURE 3. Estimated time-dependent ROC AUCs and BSs for the optimal Cox model and JM models with different longitudinal biomarkers with different cut-off of longitudinal data: 0 month (upper panel), 3 months (lower panel).

JM outperformed Cox models in ROC AUC and BS analysis. Accumulation of longitudinal data up to 90 days improved accuracy of survival prediction independently of which biomarker was considered longitudinal. This was confirmed in analysis of both study data. The highest prediction accuracy was received for JM models with assessment of SLD dynamics and baseline values of LDH, WBC and NLR.



Conclusions

We identified the statistically significant association of different biomarkers with OS in selected NSCLC data. JM allowed to consider the longitudinal biomarker trends in addition to the baseline values only, that are used in Cox models. Longitudinal biomarkers trajectories assessment allowed to achieve higher patient survival discrimination in JM, compared to Cox models.

These results can be used for the development of more complex multivariate joint models to for more efficient patient survival discrimination and patient subgroup survival stratification and prediction.

References

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