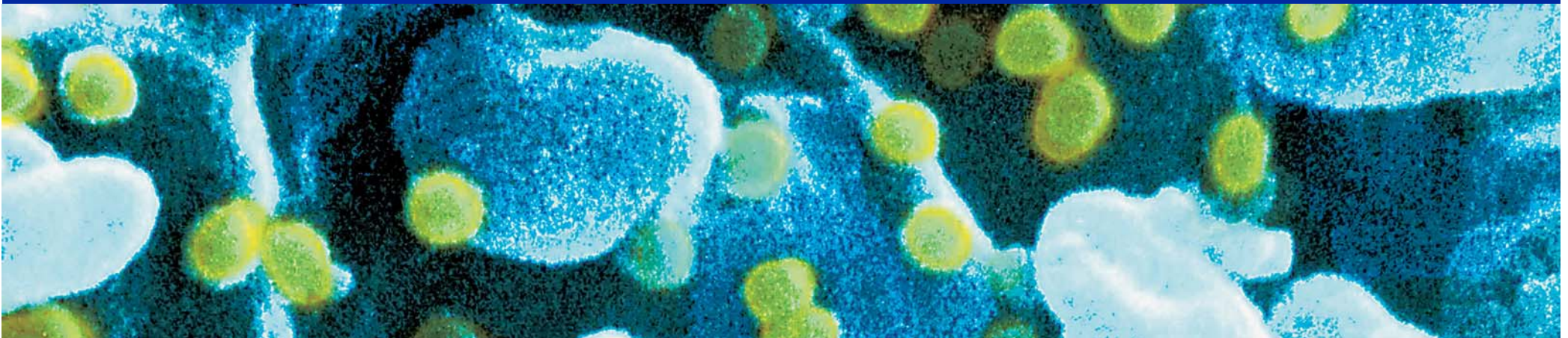


A multivariate analysis of prognostics factors in Chronic Lymphocytic Leukemia

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NSCS 2010, 27-29 September, Lyon



Background

this work used data on Chronic Lymphocytic Leukemia (CLL) patients from the REACH clinical trial

- The **REACH** phase III clinical trial (Roche Study BO17072) was initiated to compare the Progression Free Survival (PFS) of CLL patients treated with Rituximab in addition to fludarabine/cyclophosphamide (FC) chemotherapy to the PFS of patients treated with FC alone
- The target population was patients with relapsed or refractory positive CD20 Chronic Lymphocytic Leukemia
- 552 patients from 17 countries were randomized to receive either FCR or FC.
- According to the clinical protocol, each patient was intended to receive six treatment cycles (every 28 days) and then to be followed-up until 284 patients have disease progression or died (it happened in ~ 4.5 years)
- Multiple sub-groups analysis showed that Binet stage as well as mutational status and cytogenetic subgroups would benefit from the addition of rituximab to FC (Robak et. al, Blood, 112(11), 2008)

Objectives

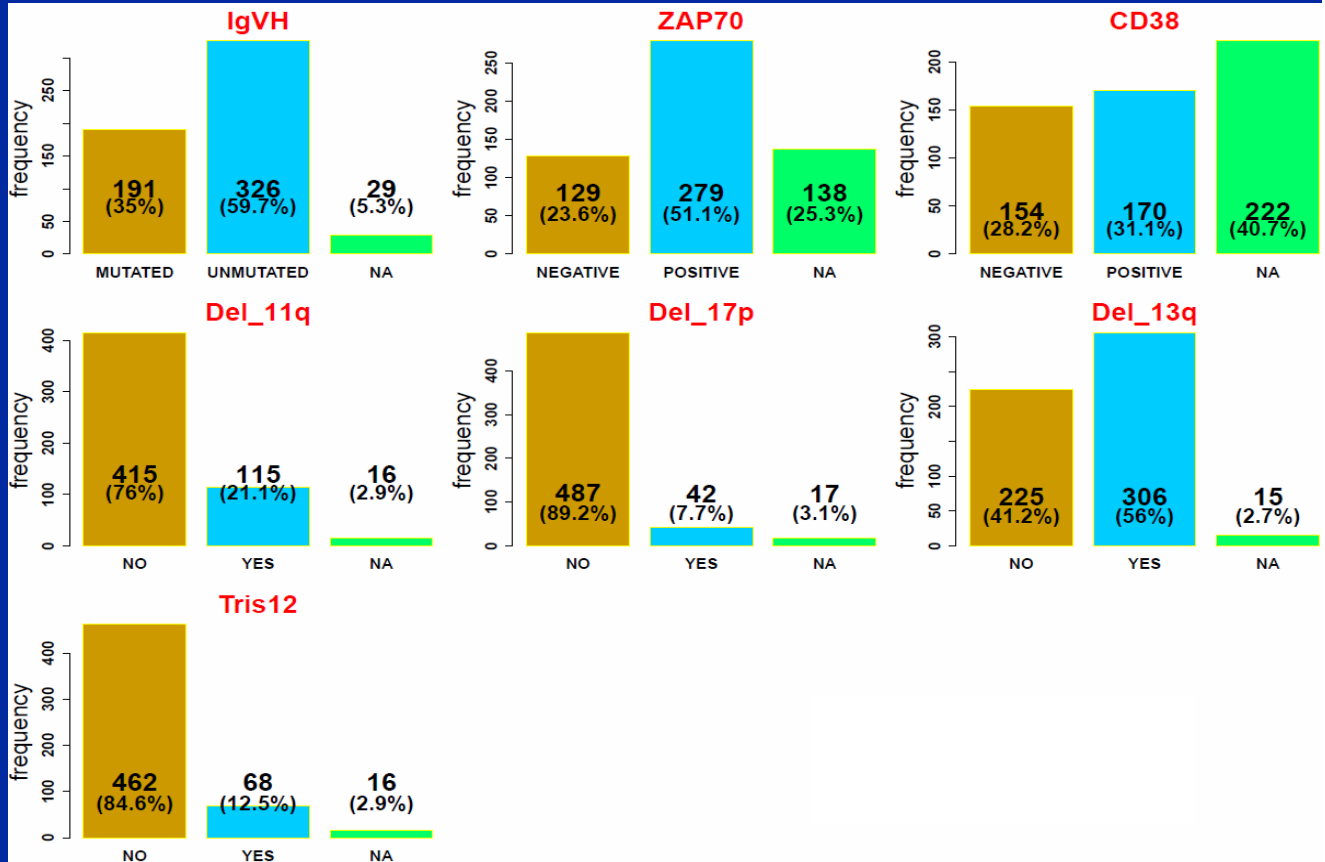
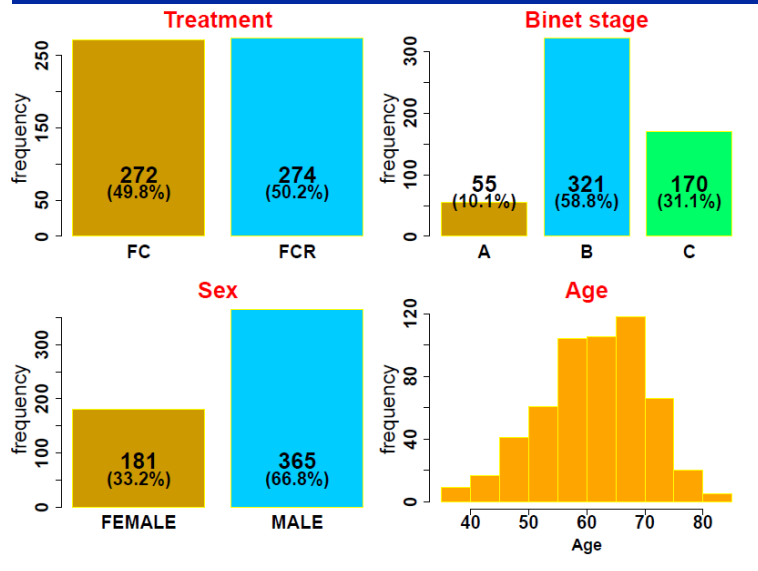
An exploratory multivariate data analysis was conducted on data from the REACH clinical trial

- to identify a parsimonious set of independent prognostic factors for PFS in the REACH trial
- to check if potential outlier/influential observations could bias the outcome
- to select prognostic factors to be used in a biomarkers identification study using genotypes, mRNA and miRNA expression profiles of the patients at baseline

Endpoint and covariates

- Progression Free Survival (PFS) was the primary endpoint in this study
- The following covariates were initially considered:
 - Age, Sex
 - Binet stage
 - Treatment
 - del17p, del11q, del13q, trisomy 12
 - IgVH mutational status
 - ZAP-70, CD38 expression
- Initial sample size = **546** patients (**290** PFS events)
(sample size < 552 because only patients who received at least one dose of trial treatment were considered)

Descriptive Analysis



CD38 had a very high missing rate (~40%) preventing it from further inclusion in the analysis

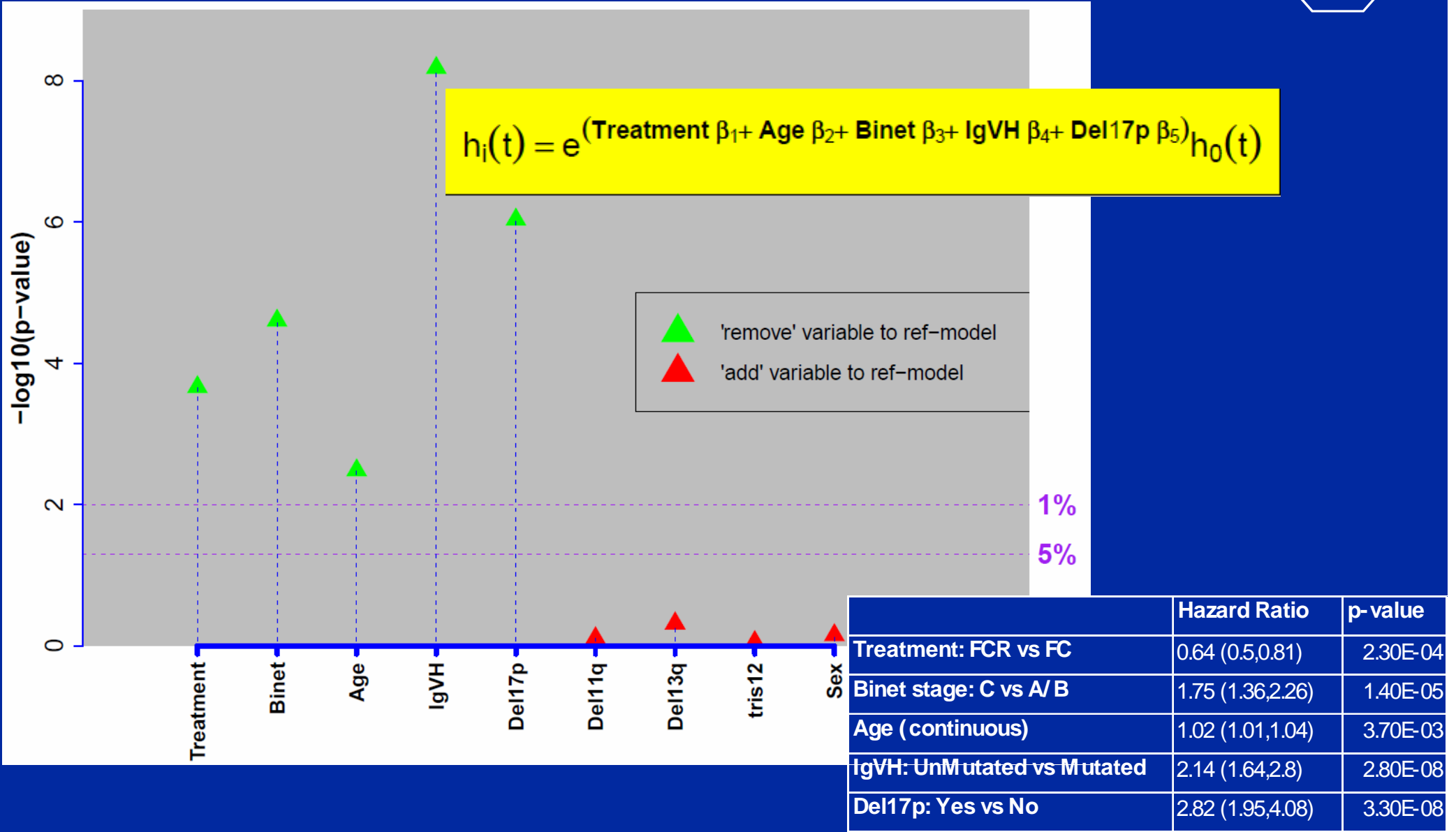
Correlation Analysis

- Association of each covariate with treatment (FCR vs FC) was checked but neither was significant → each covariate was well-balanced between treatment arms
 - Association between pairs of covariates was also calculated:
 - IgVH and ZAP-70, IgVH and del11q, del13q and trisomy were strongly associated ($p < 0.0001$)
 - the strongest association was observed between IgVH and ZAP-70 ($p \sim 1.0E-37$)
- considering that ZAP-70 had an high missing rate (~25%) and was strongly correlated with IgVH, it was not considered for modeling PFS.

Methods

- A Cox proportional-hazard regression was used to model PFS
- A forward stepwise selection procedure based on deviance analysis of nested models was used to find a parsimonious set of independent prognostic factors for PFS
- A reduced sample size of **513** individuals (**276** PFS events) with complete data for *Treatment, Age, Sex, Binet Stage (C vs A/B), IgVH status, del11q, del13q, del17p* and *trisomy 12* was considered for the analysis

Selection of the best model



Model diagnostic

Overall fit of the model

Cox-Snell residuals

Identification of influential observation

- *Scaled delta-beta*
- L_{max}

Goodness of

fit *Deviance residuals*

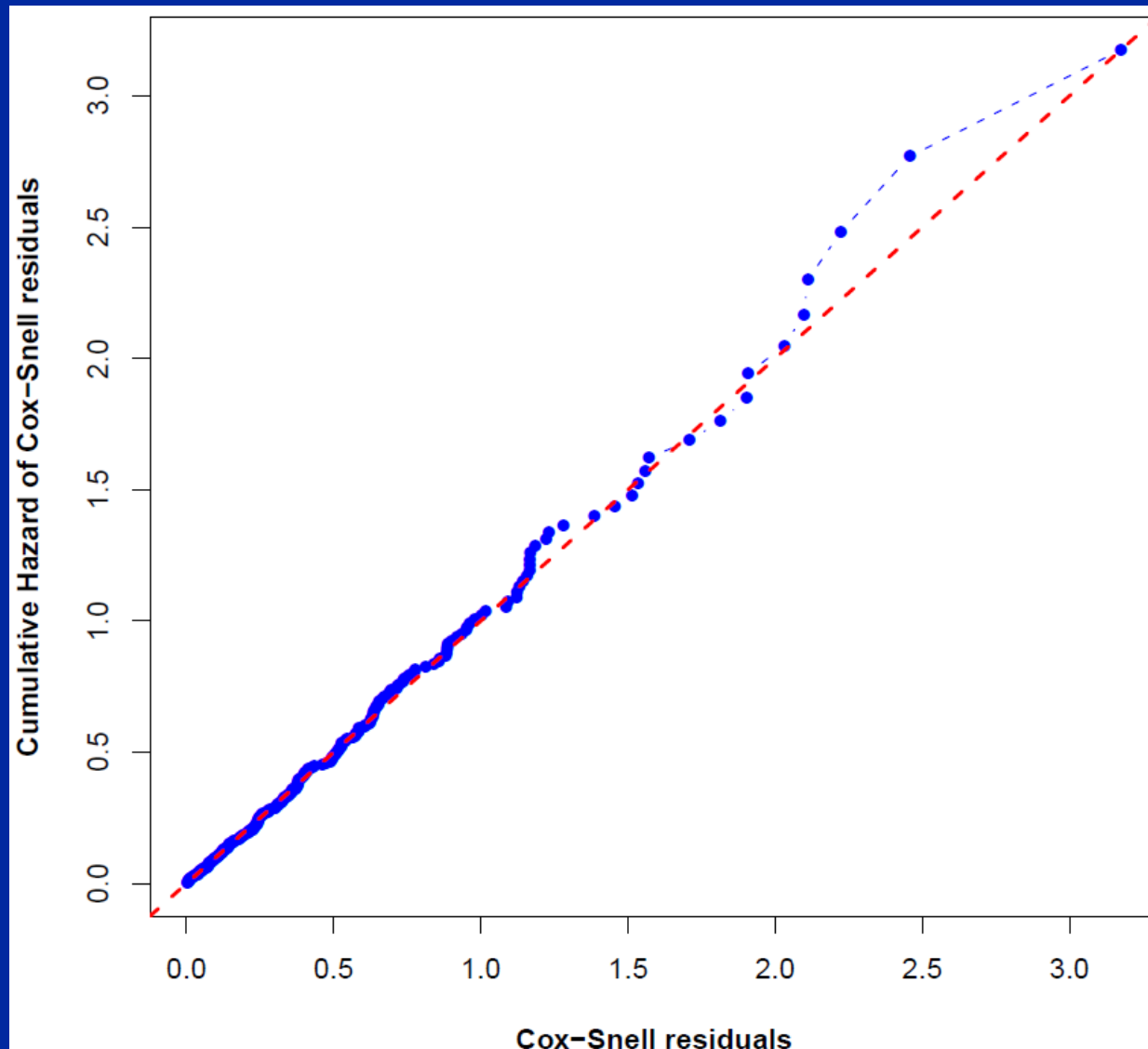
Checking the assumption of proportional hazards

- *log-cumulative hazard plot*

Cox-Snell residuals



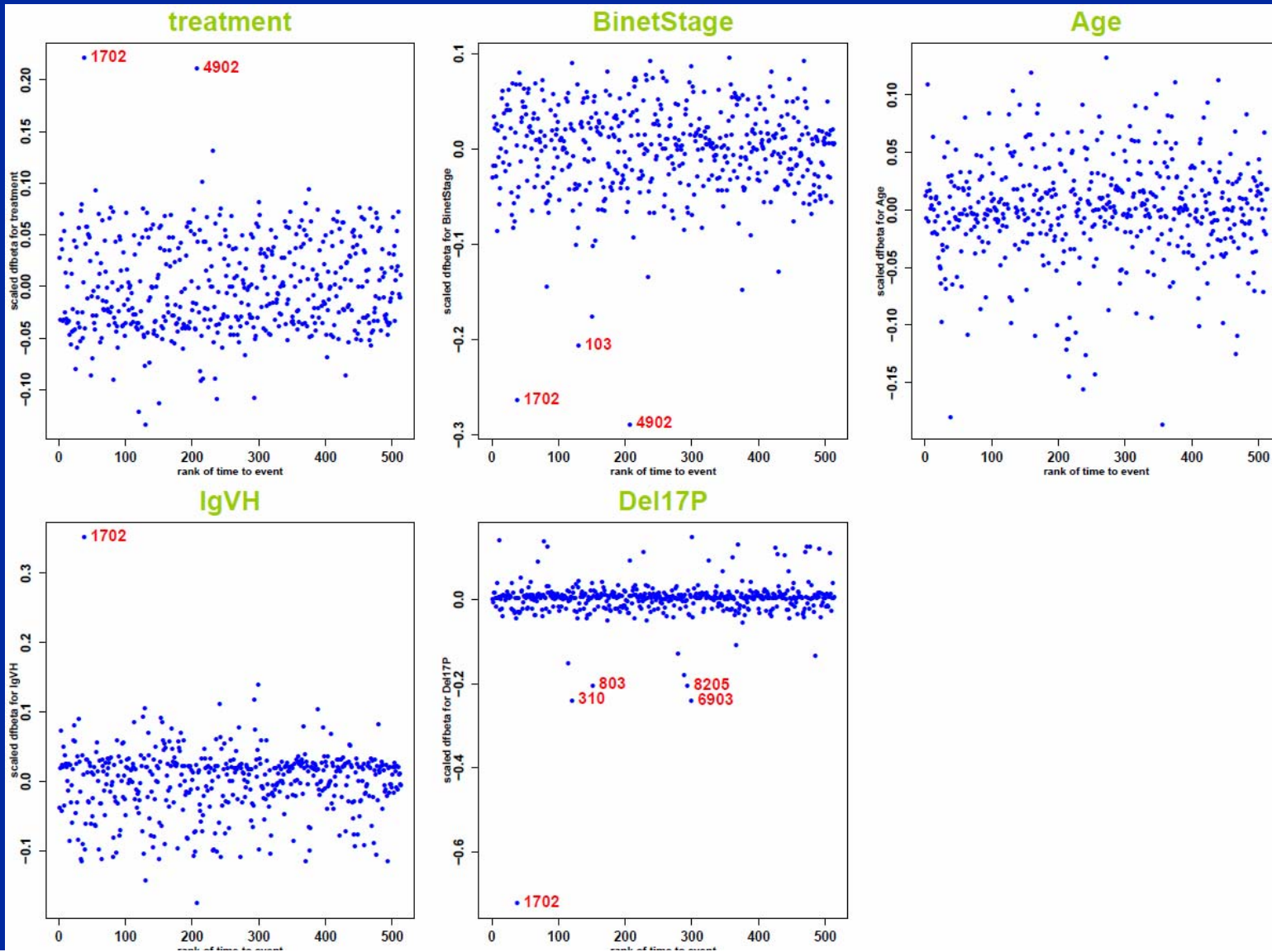
The Cox-Snell residual for the i -th sample is an estimate of the cumulative hazard function for sample i at time t_i , the observed survival time for sample i . Cox-Snell residuals should have an exponential distribution with unit mean if the fitted model is correct.



Scaled Delta-Beta

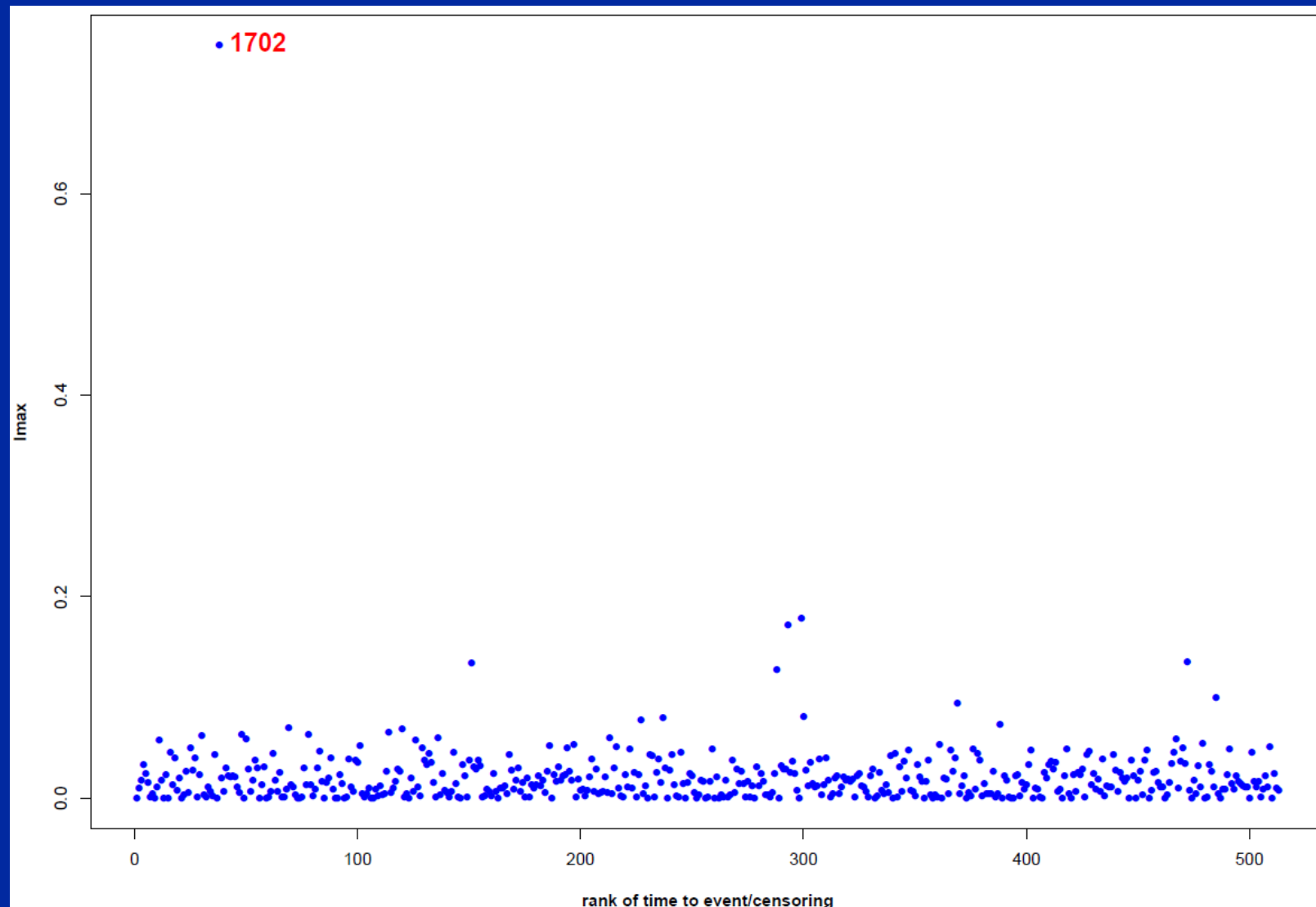


$(\beta_j - \beta_{j(i)})/se(\beta) \rightarrow$ change in the coefficient (normalized by the standard error)
when sample (i) is removed



L_{\max}

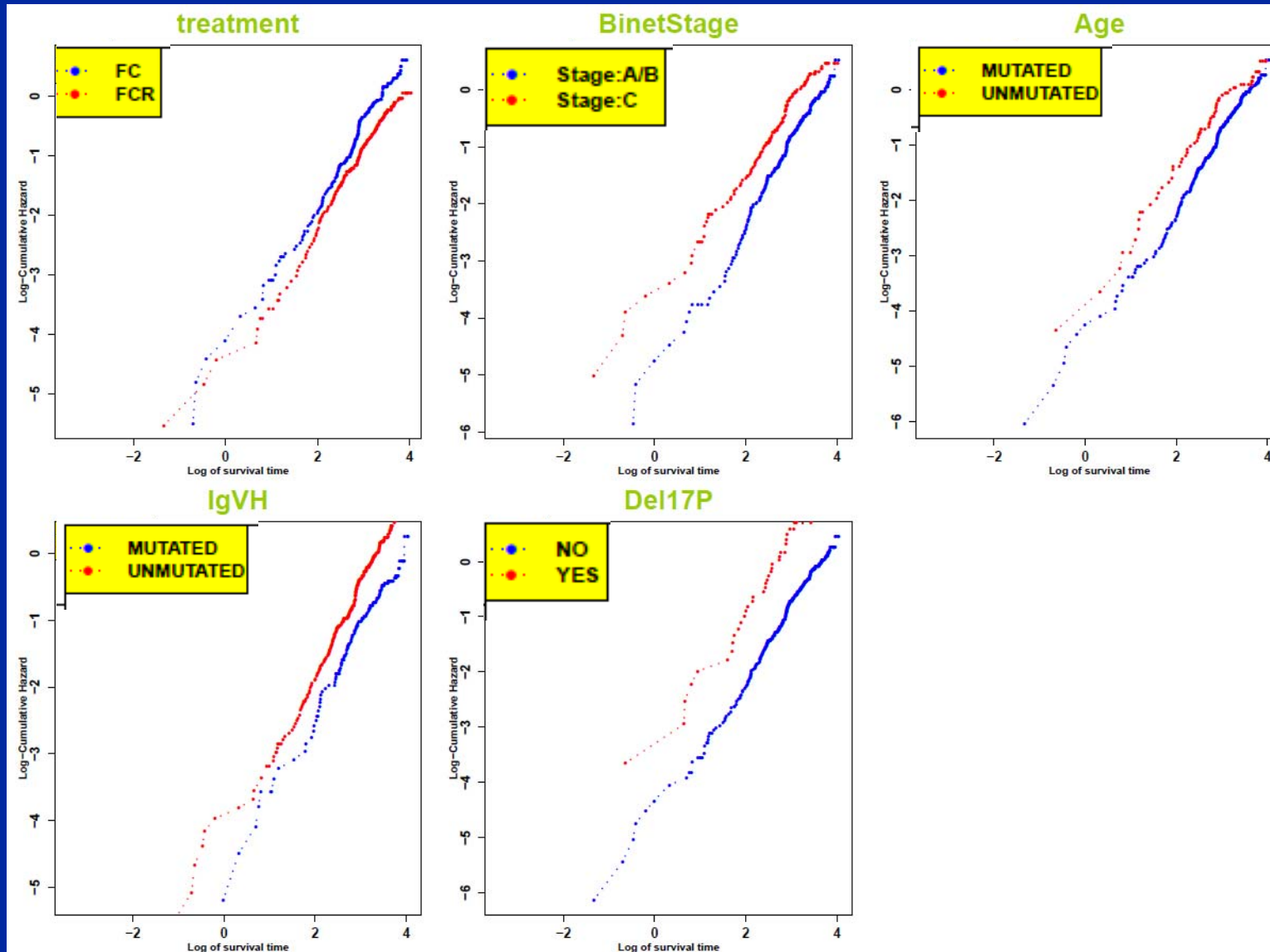
observations which influence the complete set of parameter estimates



Log-cumulative hazard plot



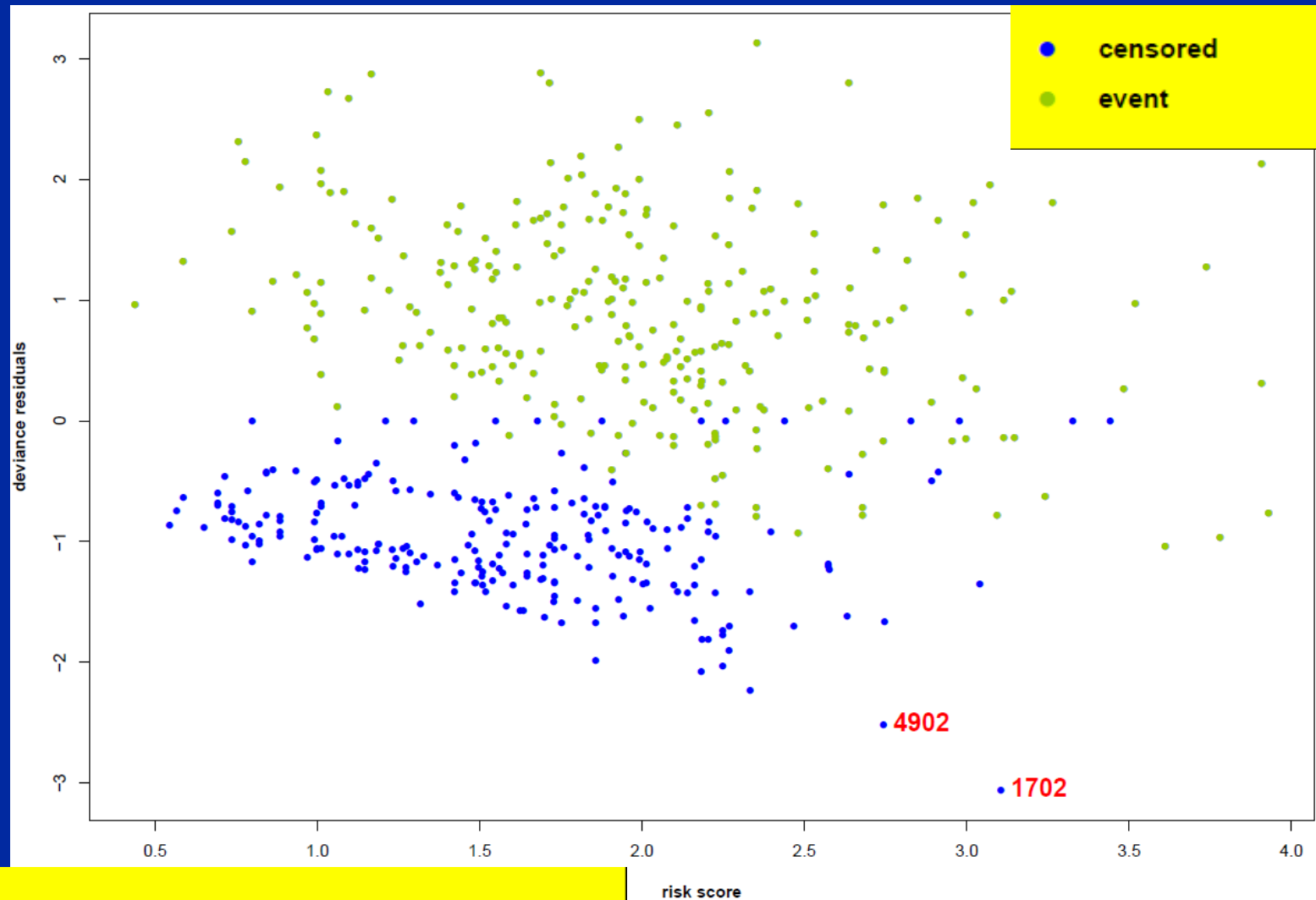
based on the 'proportional hazard' assumption, curves for the logarithm of the cumulative hazard for individuals with different values of their exploratory variables should be parallel.



Deviance residuals



does an individual has a longer (shorter) survival time than the one suggested by the actual covariate values?



$$h_i(t) = e^{(\text{Treatment } \beta_1 + \text{Age } \beta_2 + \text{Binet } \beta_3 + \text{IgVH } \beta_4 + \text{Del17p } \beta_5)} h_0(t)$$

Sensitivity Analysis



comparing models with and without samples “1702” and “4902”

	HR	p
Treatment: FCR vs FC	0.64 (0.5,0.81)	2.30E-04
Binet stage: C vs A/B	1.75 (1.36,2.26)	1.40E-05
Age (continuous)	1.02 (1.01,1.04)	3.70E-03
IgVH: UnMutated vs Mutated	2.14 (1.64,2.8)	2.80E-08
Del17p: Yes vs No	2.82 (1.95,4.08)	3.30E-08

with outliers

without outliers

	HR	p
Treatment: FCR vs FC	0.6 (0.47,0.76)	2.80E-05
Binet stage: C vs A/B	1.91 (1.48,2.46)	5.60E-07
Age (continuous)	1.02 (1.01,1.04)	1.40E-03
IgVH: UnMutated vs Mutated	2.07 (1.58,2.7)	1.10E-07
Del17p: Yes vs No	3.29 (2.27,4.76)	3.30E-10

→ Interpretation of the model does not change

Conclusions

- A multivariate approach (based on Cox regression) indicated *Treatment*, *Binet stage*, *Age*, *del17p* and *IgVH* mutational status as independent prognostic factors for PFS.
- The overall assessment of model fit and testing of the proportional hazard assumption did not show major deviations. Two samples were found as influential observations for the model, but their exclusion did not change significantly the results.
- The independent prognostic factors selected here were used in the statistical model used to assess the effect of FCGR2A and FCGR3A Variants on the CLL Outcome (Paper accepted in Blood, Dornan et al., 2010; DOI 10.1182).

Next steps

- Integrate **P53** mutational status into the survival model as obtained by sequencing
- Perform a comprehensive biomarker search for predictive/prognostic markers in the REACH samples across multiple platforms: mRNA, miRNA and SNPs



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Kaplan-Meier survival curves for the two arms

