Determination of Optimal Cut-off Points for Biomarkers in Oncology Research

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BACKGROUND

In Oncology research, using biomarkers to identify patients who can benefit from an investigational anti-cancer treatment is becoming increasingly important. For continuous biomarkers, to determine patient subgroups, it is often necessary to determine cut-off point(s) based on their relationship to clinical responses of interest (e.g., overall survival). To find cut-off values of a continuous biomarker, we consider the following approaches when the response of interest is a survival endpoint: time-dependent receiver operating characteristic (ROC) curve, hazard ratio comparing dichotomized groups, maximum partial likelihood approach, and machine learning methods. We apply those methods to a few historical Phase III studies to locate optimal cut-off points for serum IL-8, with covariates information adjusted. In addition, we discuss some practical considerations in finding cut-off points.

A MOTIVATING EXAMPLE

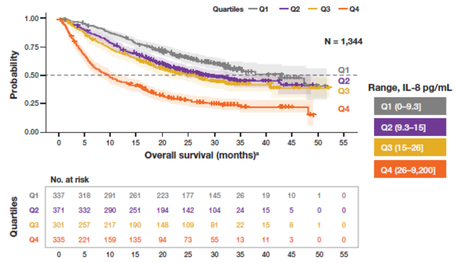

Figure 1: Validated pan-tumor analysis confirmed reduced survival in patients with elevated serum IL-8 levels at baseline

In a preliminary exploration of the association of baseline biomarker values and overall survival, Kaplan-Meier curves for subgroups based on quartiles of baseline biomarker values separate from each other: the lower the marker value, the more survival benefit a patient could receive from treatment (Figure 1).

METHODS

Time-dependent ROC Curve

For any time-to-event endpoint, let $D(t) = 1$ indicate that a subject had an event prior to time t (and 0 otherwise), then the time-dependent ROC curve for a biomarker measure X (with potential threshold c) can be constructed by considering sensitivity and specificity as follows (Heagerty et al., 2000):

$$\text{Sensitivity}(c,t) = \Pr(X > c \mid D(t) = 1),$$
$$\text{Specificity}(c,t) = \Pr(X \le c \mid D(t) = 0).$$

The R package `survivalROC` can be used to generate time-dependent ROC curves. An optimal cut-off can be obtained by optimizing ROC related criteria, e.g., Youden's index = sensitivity + specificity - 1. Figure 2 shows multiple ROC curves, corresponding to Objective Response Rate (ORR), Progression Free Survival (PFS), and Overall Survival (OS), respectively, with respective to the baseline serum IL-8 level. Figure 3 is an example of the ROC curve for 12-month overall survival by baseline and post-baseline serum IL-8 levels. An optimal threshold of 23 pg/mL for baseline IL-8 level was obtained by optimizing Youden's index.

Hazard Ratio Comparing Dichotomized Groups

An optimal cut-off can also be obtained by comparing the hazard functions between biomarker-dichotomized subgroups, that is, $c^* = \text{argmax}_c \frac{h(t|Z, X \le c)}{h(t|Z, X > c)}$, where $h(t \mid Z, X \le c)$ is the hazard function for the subgroup determined by $\{X \le c\}$, and Z contains other covariate information. For predictive biomarker between two treatment groups, an optimal cut-off point $\tilde{c}$ can be estimated by

$$\tilde{c} = \text{argmax}_c \, \text{HR}(Z, \text{trt}, X \ge c)$$

where the hazard ratio is between two treatment groups. Alternatively, one could locate the optimal cut-off value by searching for the most significant split in X in terms of p-value. Figure 4 and Figure 5 show hazard ratios (treatment vs control) based on subgroups defined by various cut-off values of the marker (the x-axes are in the scale of percentiles instead of the original scale).

Maximum Partial Likelihood

An optimal cut-off can also be obtained by treating the cut-off point as a parameter in the partial likelihood function, such that

$$c^* = argmax_c \max_\theta \ell(c, \theta, X)$$

where $\ell(c, \theta, X)$ is the partial likelihood function (Jiang et al., 2007). This method can be extended to simultaneously account for multiple biomarkers. Figure 6 shows the natural logarithm of the partial likelihood function with respect to the logarithm of IL-8 cut-off point. The maximum partial likelihood estimator c^* for IL-8 in the original scale is again 23 pg/mL.

Machine Learning: Conditional Inference Tree

The conditional inference tree method applies binary recursive partition sequentially on each independent predictor that is associated with the given response variable. The order of the predictors to be partitioned depends on the significance of the association between the predictor and the response variable. Partition steps will be repeated until a pre-defined level of statistical significance is reached. Figure 7 is the conditional inference tree on overall survival using two baseline biomarkers as predictors. The obtained optimal cut-off value for baseline IL-8 is again 23 pg/mL after transforming 3.135 back to original scale. The R package `partykit` was used for generating the tree.

RESULTS

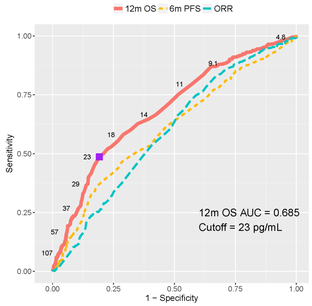

Figure 2: Time-dependent ROC curves of baseline marker value on 12-month OS and 6-month PFS, and ROC curve of the same marker value on ORR.

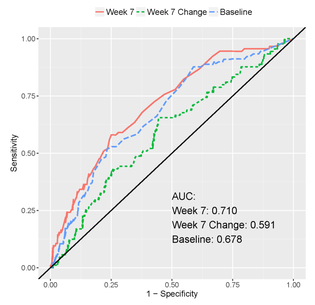

Figure 3: Time-dependent ROC curves of different markers on 12-month OS.

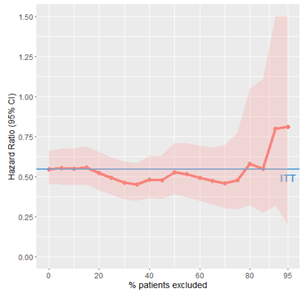

Figure 4: HR (Treatment vs Control) of overall survival time by percent of patients excluded per high baseline marker values (Top-Down).

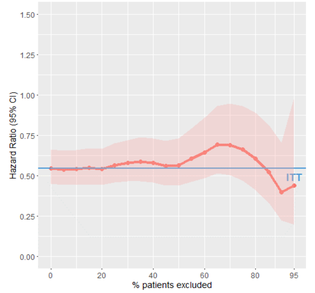

Figure 5: HR (Treatment vs Control) of overall survival time by percent of patients excluded per low baseline marker values (Bottom-Up).

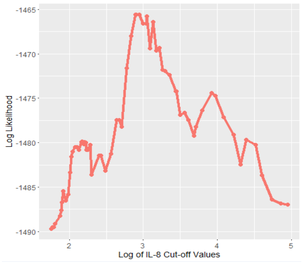

Figure 6: Logarithm of maximum partial likelihood versus logarithm of baseline biomarker cut-off values.

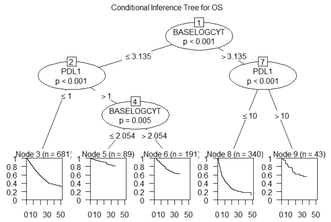

Figure 7: Conditional inference tree on overall survival using two biomarkers as predictors: BASELOGCYT – logarithm of baseline biomarker value; PDL1 – baseline PD-L1 expression (%).

PRACTICAL CONSIDERATIONS

- Prevalence rate of biomarkers.
- For analysis stability, biomarker data may need to be transformed (e.g., log-transformation)
- Handling multiple biomarkers together:
  - Time-dependent ROC method can handle multiple covariates by estimating survival probabilities through regression methods.
  - Regression-based methods (e.g., hazard ratio and maximum partial likelihood) can naturally accommodate multiple covariates.
  - Exploration of correlation between markers may be warranted.
- Time-dependent ROC may need preliminary exploration on several clinically meaningful candidate time-points (e.g., overall survival at 12 months, progression-free survival at 6 months).

CONCLUSIONS

The discussed approaches are useful tools for locating optimal biomarker cut-off points. Time-dependent ROC can link marker value with clinical trial needs (e.g., false positive rate) when the primary endpoint of interest is a time-to-event endpoint, e.g., overall survival. Regression-based methods including maximizing hazard ratio or maximum partial likelihood methods can be more efficient when appropriate covariate information is included. Both regression-based methods and machine learning approaches can deal with cases when multiple biomarkers are to be considered. We apply those approaches to survival data from multiple Phase III Oncology studies, aiming to locate optimal cut-off points for the IL-8 biomarker, and obtain largely consistent results as well as an optimal threshold of 23 pg/mL for IL-8.

REFERENCES

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