Combination of protein biomarkers

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Recent advances in immunoassay-based protein quantitation methods allow the quantification of a large number of proteins in biological fluids such as serum. When these proteins are differentially expressed between two populations, they are called biomarkers. However, biomarkers often show an insufficient discrimination power. We hypothesized that a combination of biomarkers could increase diagnosis or prognosis efficiency.

In order to predict 6-month outcome of patients after an aSAH (an extracerebral hemorrhage) based on a combination of 6 biomarkers and 3 clinical parameters measured at time of admission, we developed a simple threshold-based panel algorithm where thresholds were determined by exhaustive search. We compared it with 5 other combination methods: SVM (kernlab), Linear Models, Generalized Linear Models, Weighted K-Nearest Neighbors (kknn) and Partial Least Square (pls). 10-fold cross-validation was used to avoid overfitting. In order to get a statistical measure of the differences between the ROC Curve, we used the methods developed by Hanley and McNeil (1983) and DeLong et al. (1988) for comparing ROC Curves, and compared them to bootstrapping methods. Partial Area under the ROC Curve (pAUC) allowed us to focus on 90-100% specificity predictions. We tested this approach on a cohort of 112 patients. All the computations were performed in R.

The best individual biomarker displayed a pAUC of 65% of optimal value (90% specificity for 40% sensitivity). The best clinical measurement had the same pAUC with a specificity of 94% and a sensitivity of 45%. Two combination methods performed slightly better: the threshold-based algorithm with a pAUC of 68% (93% specificity and 55% sensitivity) and SVM with 66% pAUC (90% specificity and 53% sensitivity). That result means the threshold-based test is able to detect 55% of the poor outcome patients while raising only 7% of false positives.

Even though the improvement seems small, detecting 10% more poor-outcome cases without increasing the false alarm rate is of prime importance for physicians and for the management of poor-outcome patients, because no tool specific to prognosis is currently available. This method allowed us to provide a quantitative measure of the differences and to compare the methods between them as well as with individual markers. The threshold-based algorithm was the best predictor of aSAH 6-month outcome. It performed slightly better than individual markers; however cross-validation was applied only to combinations and individual markers performance might be overestimated. We will use the statistical tests described above to validate these results.

References

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