DEVELOPING RISK MODELS FOR SURVIVAL OUTCOMES WHEN THE NUMBER OF EVENTS IS SMALL

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Risk models are commonly used to make predictions regarding a patient's health to guide clinical decisions, assist patients to make informed decisions and allow comparison of institutional performances. A common problem when developing risk models is a scarcity of events due to rare outcomes or diseases and a lack of clinical information that would enable the reduction of a large list of potential predictors. Risk models derived from such scenarios suffer from over-fitting and may produce unreliable predictions. Penalised estimation, which effectively reduces the number of estimated parameters, has been suggested as a solution. The aim of this research is to investigate the performance of penalised estimation in risk prediction for survival outcomes.

This research is motivated by two important clinical scenarios. The first involves rare events from a study on 3,000 patients with artificial heart valve implants, with 10 predictors and 56 valve failures. The aim is to identify patients at high risk of failure who would be eligible for valve explant surgery. The second involves a study on penile cancer (rare disease) with 100 patients, where the aim is to ascertain whether patients with certain genetic characteristics are at higher risk of death. There are 7 predictors and 22 deaths.

The performances of the penalised estimation (Verweij *et al*, 1994) and Lasso (Tibshirani, 1997) approaches, both of which shrink coefficient estimates, were evaluated using simulated data based on the two real datasets. Comparisons were made with standard maximum likelihood approaches. Cox and Weibull survival models were considered. Several measures were used to evaluate the predictive ability of the models using the different estimation procedures. Discrimination was assessed using rank correlation and calibration was assessed using calibration slopes and mean squared errors. The mean square error in the log-hazard and the prediction error at various time points were also assessed. In addition, the bias in the regression coefficients was calculated and the coverage of the corresponding confidence intervals evaluated. A comparison was also made of the variables selected in the final model using the penalised approaches, the full model approach and backward elimination.

The results suggest that risk models derived using penalised approaches generally produce better predictions in terms of prediction error and discrimination. The regression coefficients are generally less biased and the coverage of the confidence intervals are comparable. Additionally, the Lasso method may be used to perform variable selection. The penalised approaches thus provide useful tools in the development of risk models for survival outcomes when the number of events is small.