MODELLING SURVIVAL FOLLOWING BONE MARROW TRANSPLANTATION USING LONGITUDINAL IMMUNE MEASUREMENTS AT ARBITRARY TIME POINTS

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Haematopoietic stem cell transplantation ('bone marrow transplantation') is a potentially curative treatment option for different hematologic and oncologic disorders, such as severe leukaemia. However, it is still associated with high mortality rates due to complications after transplantation. Early identification of high-risk patients is crucial for successful intervention. Models that predict patient survival or individual complication risks are needed to assist clinical decision making and may provide insights into the underlying biological processes.

The speed of immune recovery over time and several patient- and transplantation-related covariates were shown to be associated with survival and complication risk[1]. We investigate a dataset of 67 paediatric and young adult patients. Approximately 2000 longitudinal measurements of several immunological subpopulations were taken at arbitrary time points. Measurement time points and frequency cannot be assumed to be independent of the survival process.

Joint modelling of longitudinal and time-to-event data is a natural approach to data of this nature[2]. Implementations of joint modelling techniques in R and other languages are readily available. However, no consensus has been reached yet on how to best assess goodness of fit and predictive ability of such a model.

For exploratory analyses and for use in clinical practice simpler models may be preferred. A simple comparison of measurements at a single time point is sometimes found in biological publications. A cutoff value may be used to group patients into ‘high-risk’ and ‘low-risk’ groups. However, bias may be associated with such an approach. Bias can be reduced by using appropriate summary measurements, such as the area under the curve[3], and accelerated failure time models can be fitted. This has the advantage that many measures of the prognostic ability of survival models are readily available, e.g. explained variation[4]. These simpler models may be used to specify a joint model and joint modelling may in turn inform the simpler models.

A possible extension of joint modelling is the inclusion of a proportion cured component to allow for the fact that patients may have a normal life expectancy after a certain period of relapse-free survival. Furthermore, the incorporation of the measurement frequency as a variable in the longitudinal modelling may inform on the risk assessment by the clinicians.

References