Joint modelling of longitudinal outcomes and clinical endpoints
JoineR & JoineR-M

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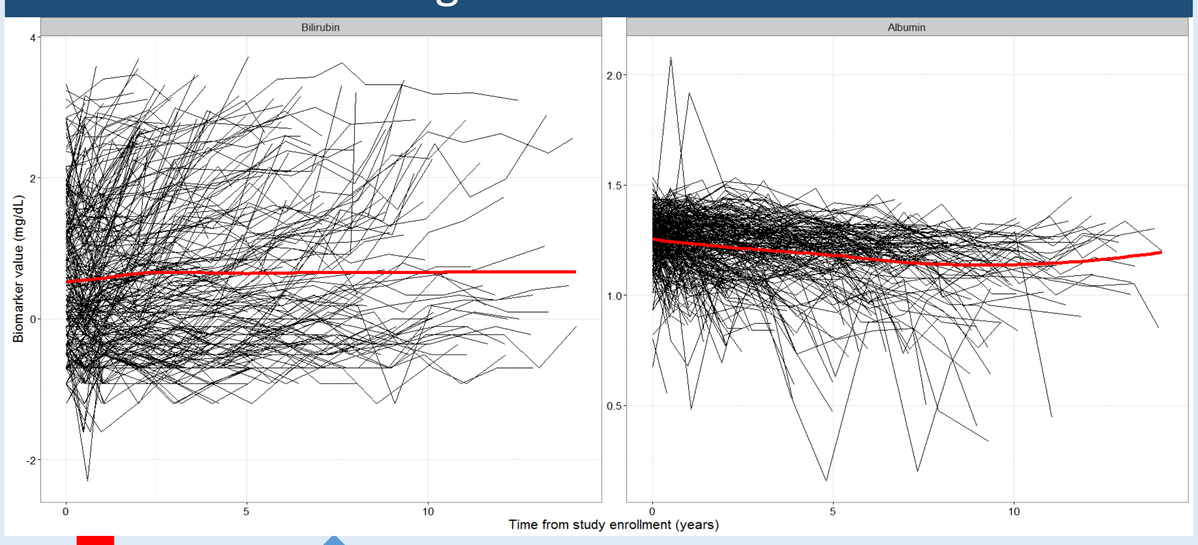
Introduction

- In clinical trials or cohort studies, measurements are repeatedly measured over time (e.g. blood pressure), which we call **longitudinal data**
- In addition, the time to one or more clinical endpoints (e.g. death) is recorded, which we call **time-to-event data**
- Historically, these data have been **analysed separately**

Longitudinal outcomes

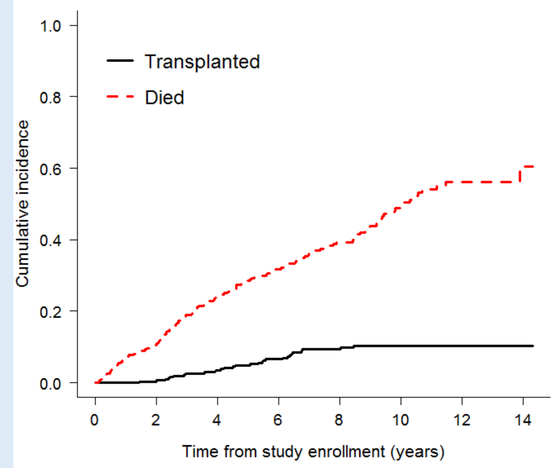


Example

⬅ **Left:** **two biomarkers** measured from blood tests repeatedly over time for 312 patients with primary biliary cirrhosis randomised to a new drug

➔ **Right:** cumulative incidence curves for 2 **competing events**

Time-to-event outcomes



Correlated?

Interest = longitudinal data

Standard model: (generalised) linear mixed effects regression model

Potential problems:
- Sickest patients more likely to drop out of study
- We call this **informative missingness**

Why does it matter?

Ignoring the correlation between information from the same patient can result in **incorrect conclusions** about the new treatments and predictions of clinical endpoints

Interest = time-to-event data

Standard model: Cox proportional hazards regression model

Potential problems:
- Biomarkers measured with **error**
- Time-varying covariates modelled as constant between measurement times

Proposed solution

Combined analysis of the outcomes (**joint modelling**) using some unknown variables to capture the association between the two types of outcome

Extension to multivariate data (JoineR-M)

- Joint modelling methodology has been predominantly focused on univariate (single longitudinal and event outcome) data
- In practice, multiple longitudinal outcomes and event times will be recorded (**multivariate data**)
- Multivariate data greatly increases the **complexity** of model estimation:
  - **Computational time** grows with increasing number of outcomes
  - **Longitudinal outcomes** take different types (e.g. continuous, binary, ordinal)

Benefits of joint modelling

- **More efficient** estimates of treatment effects = **reduced number of patients required for studies and increased power**
- **Less biased** estimates of the treatment effects = **closer to 'truth'**
- **More accurate** predictions of events = **better medical decision-making**

Software development

- **joineR** is a freely available user-friendly software package, currently fit joint models for univariate data
- joineR will be **expanded** over the next 2-years to:
  - Include multivariate longitudinal outcomes
  - Model competing risks outcomes
  - Provide model diagnostics to allow inspection of model fit
- **Training workshops** for biomedical researchers to inform the joint modelling methods and software

https://www.liverpool.ac.uk/translational-medicine/departmentsandgroups/joine-r/about/

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joineR
available from CRAN