IDENTIFICATION OF CONTINUOUS COVARIATES

Elisabet Størset
Centre for Pharmacy, University of Bergen, Norway
School of Pharmacy, University of Oslo, Norway

Christine Staatz
School of Pharmacy,
University of Queensland

Stefanie Hennig
School of Pharmacy,
University of
Queensland

Troels K. Bergmann
Department of Pharmacology,
Aarhus University

Nick Holford
Department of Pharmacology
and Clinical Pharmacology,
University of Auckland

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AIM

To demonstrate a method

to identify continuous covariates

Introduction

TACROLIMUS

- Prevents rejection in kidney transplantation
- Low oral bioavailability (~20 %)[1]
- **Observation**: Dose requirement to achieve the same target decreases with time after transplantation

→ Decreasing clearance with time proposed

[1] Staatz, C. Tett, SE. 2004;43(10):623-53. Clinical pharmacokinetics and pharmcodynamics of tacrolimus in solid organ transplantation.

Methods

Our population PK study:

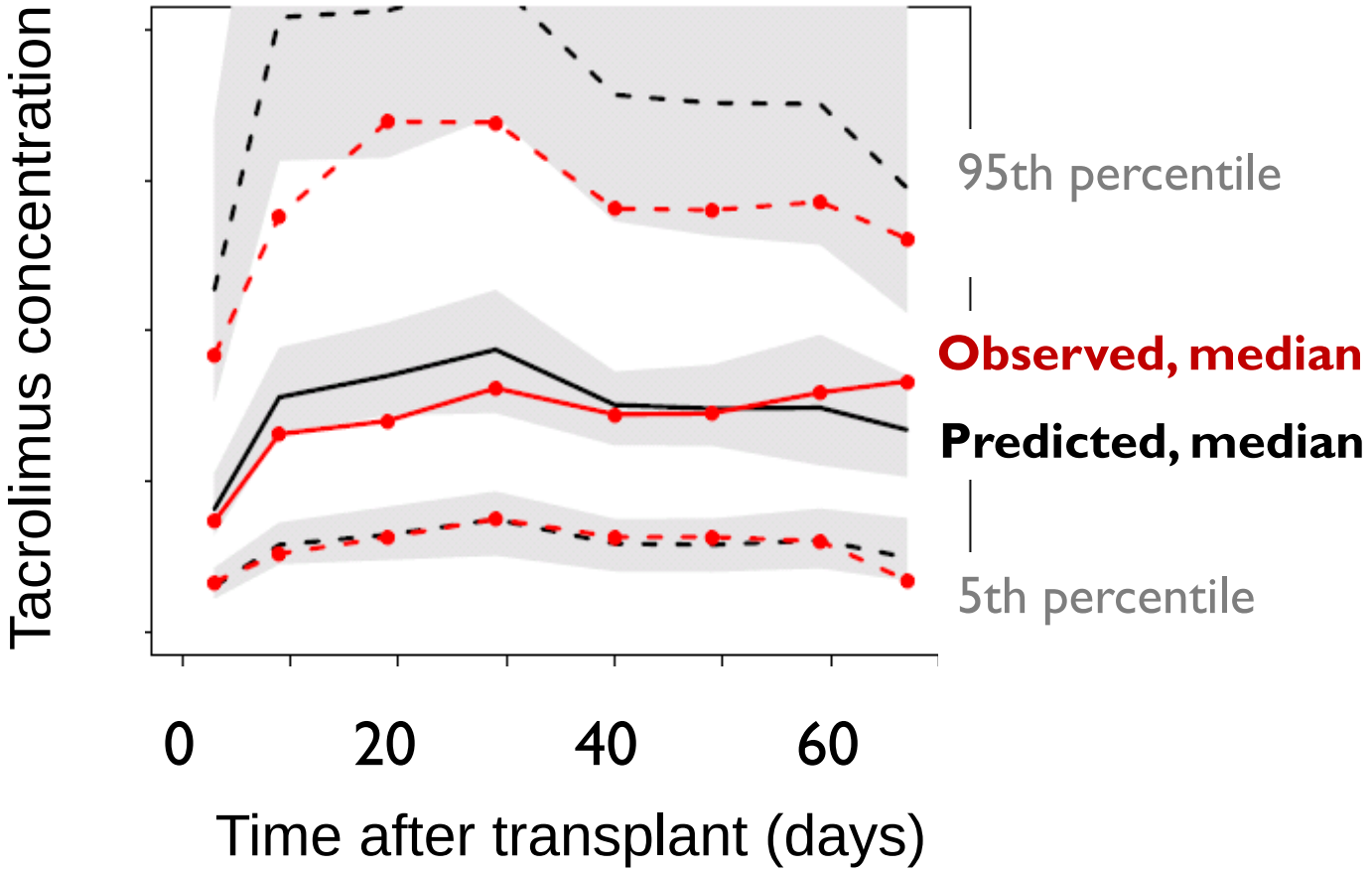
- Data from Brisbane and Oslo
  - 242 patients.
  - 3100 tacrolimus concentrations
    - 3/4 from **first ten weeks after transplant**

Example for demonstration:

- Investigate **time after transplantation** as a covariate

Diagnostics: VPC without covariate

- Use covariate on x-axis



Covariate investigation strategies

a. Covariate vs ETA scatterplot

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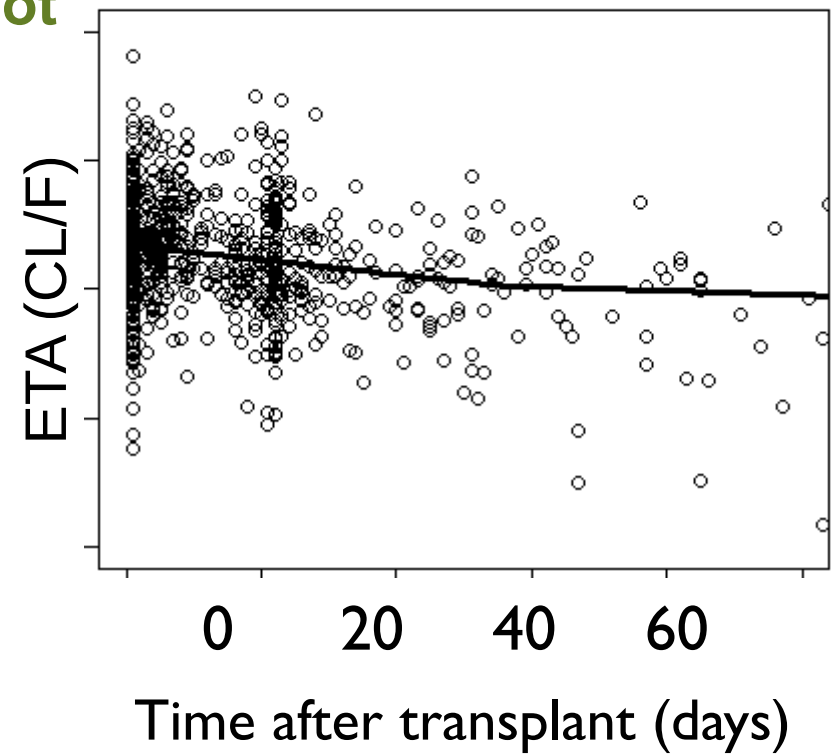
- Subjective whether there is a trend



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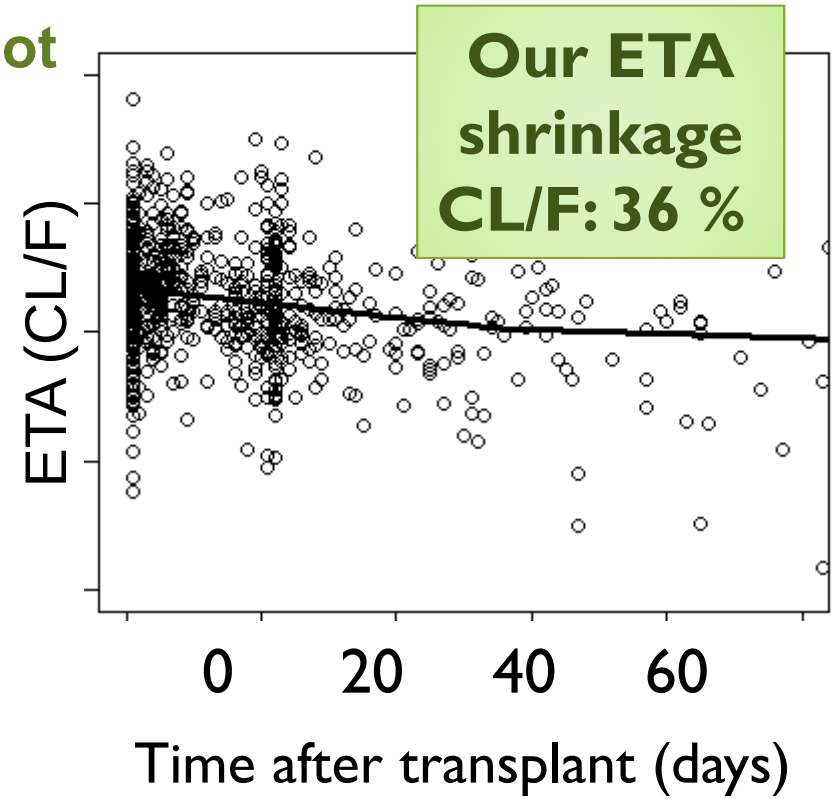
- Cannot trust plot if high ETA shrinkage



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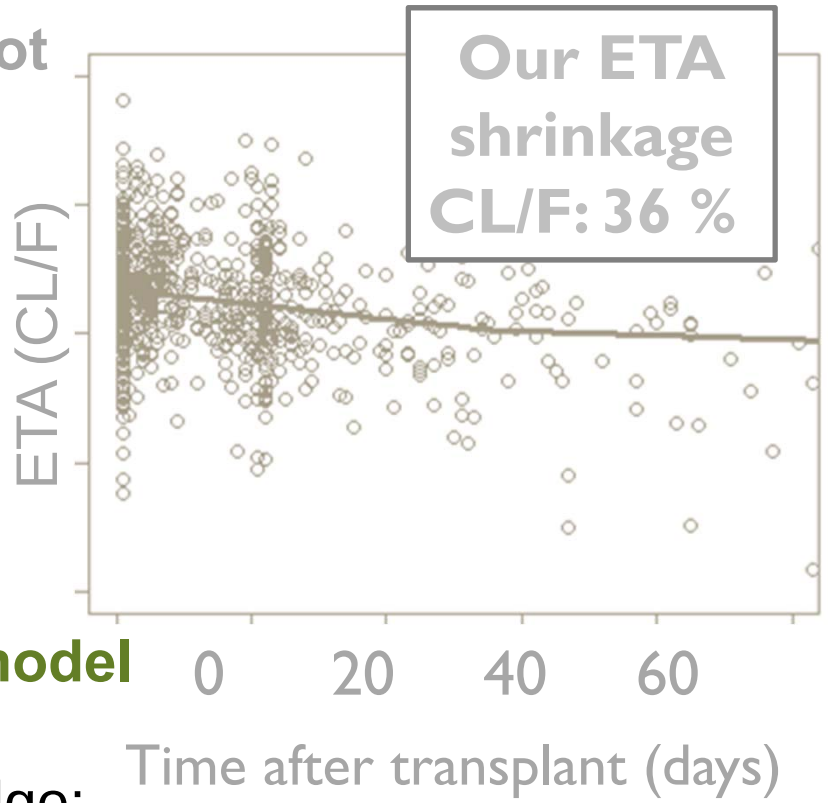

b. Test covariate directly in model

- When little prior knowledge:
  - Difficult to select shape
  - Difficult to select initial estimates

Covariate investigation strategies

c. Investigate with categories

Predefine:

Category 1: **Day 1 – 2**

Category 2: **Day 3 – 4**

Category 3: **Day 5 – 8**

... and so on

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Estimate a **mean** parameter (e.g. CL/F) in each category

Generating categories

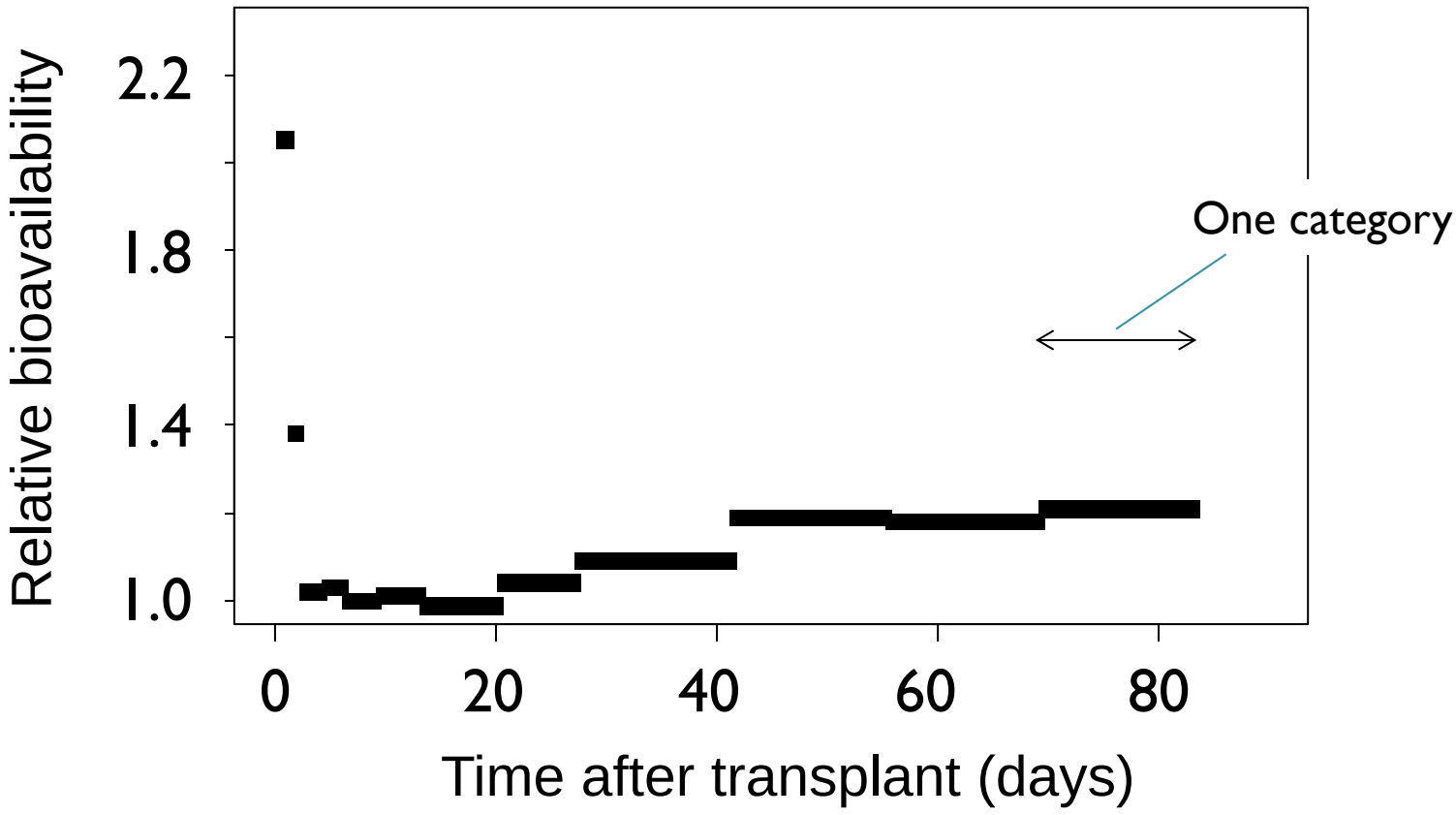
```
IF (DAY.GE.1.AND.DAY.LE.2) CL_DAY = THETA(1)

IF (DAY.GE.3.AND.DAY.LE.4) CL_DAY = THETA(2)


....

CL = TVCL * CL_DAY
```

Seeing the shape with categories



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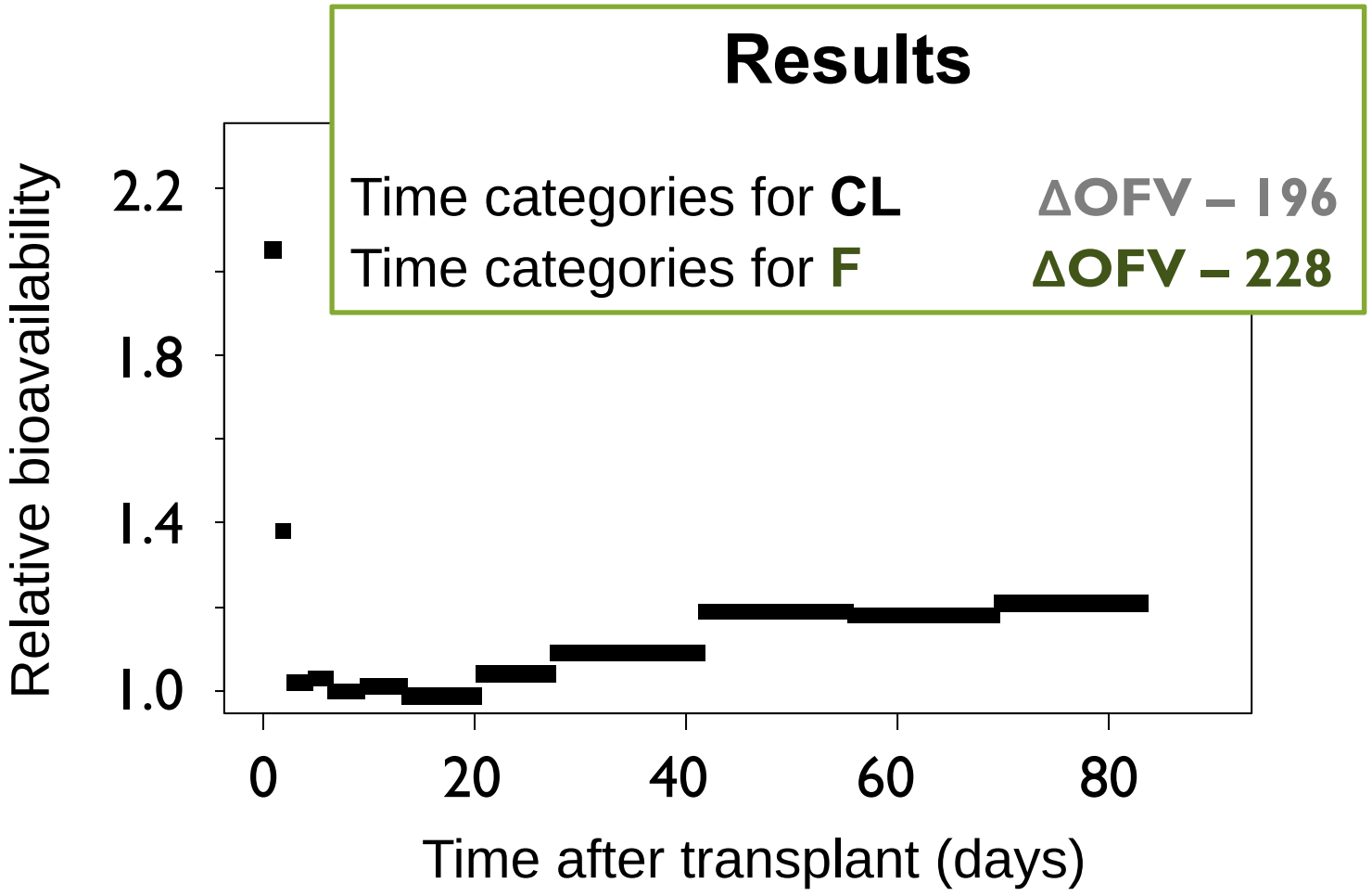
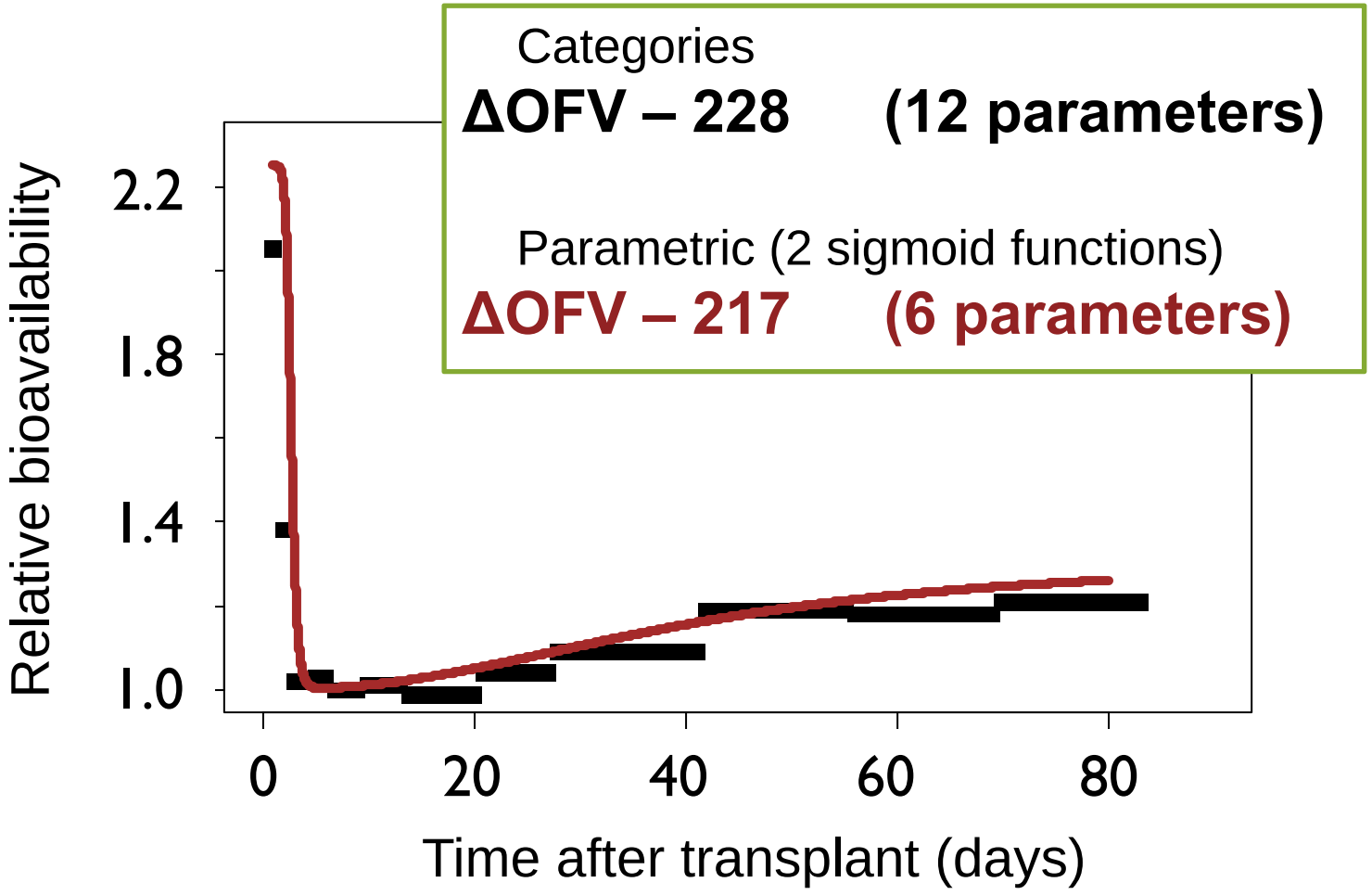
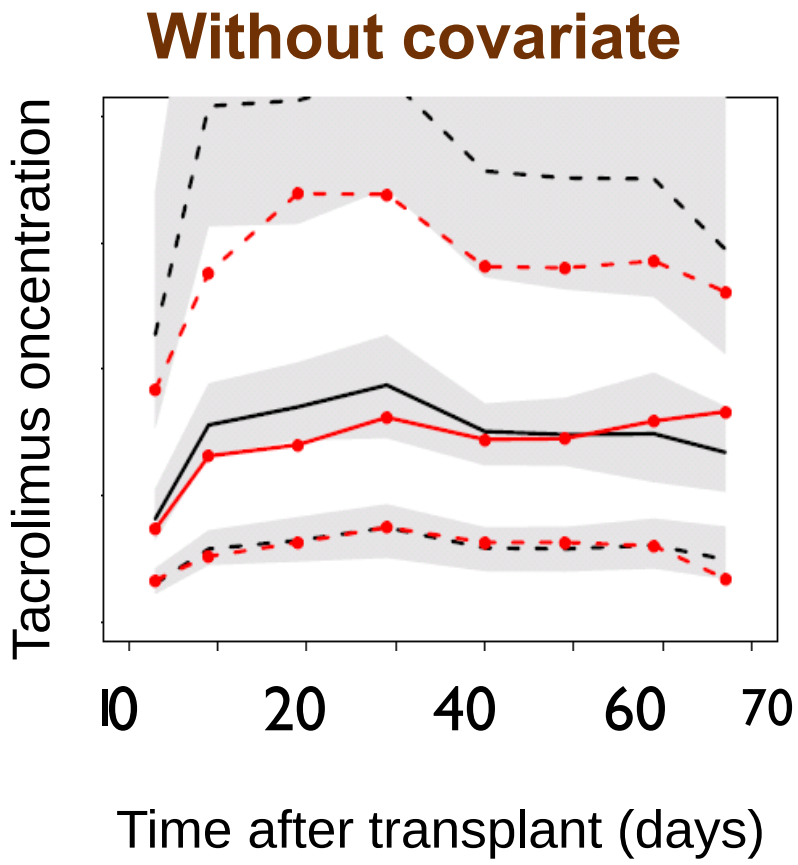


Comparing categories with parametric function



Evaluating covariate model with VPC

- Use covariate on x-axis



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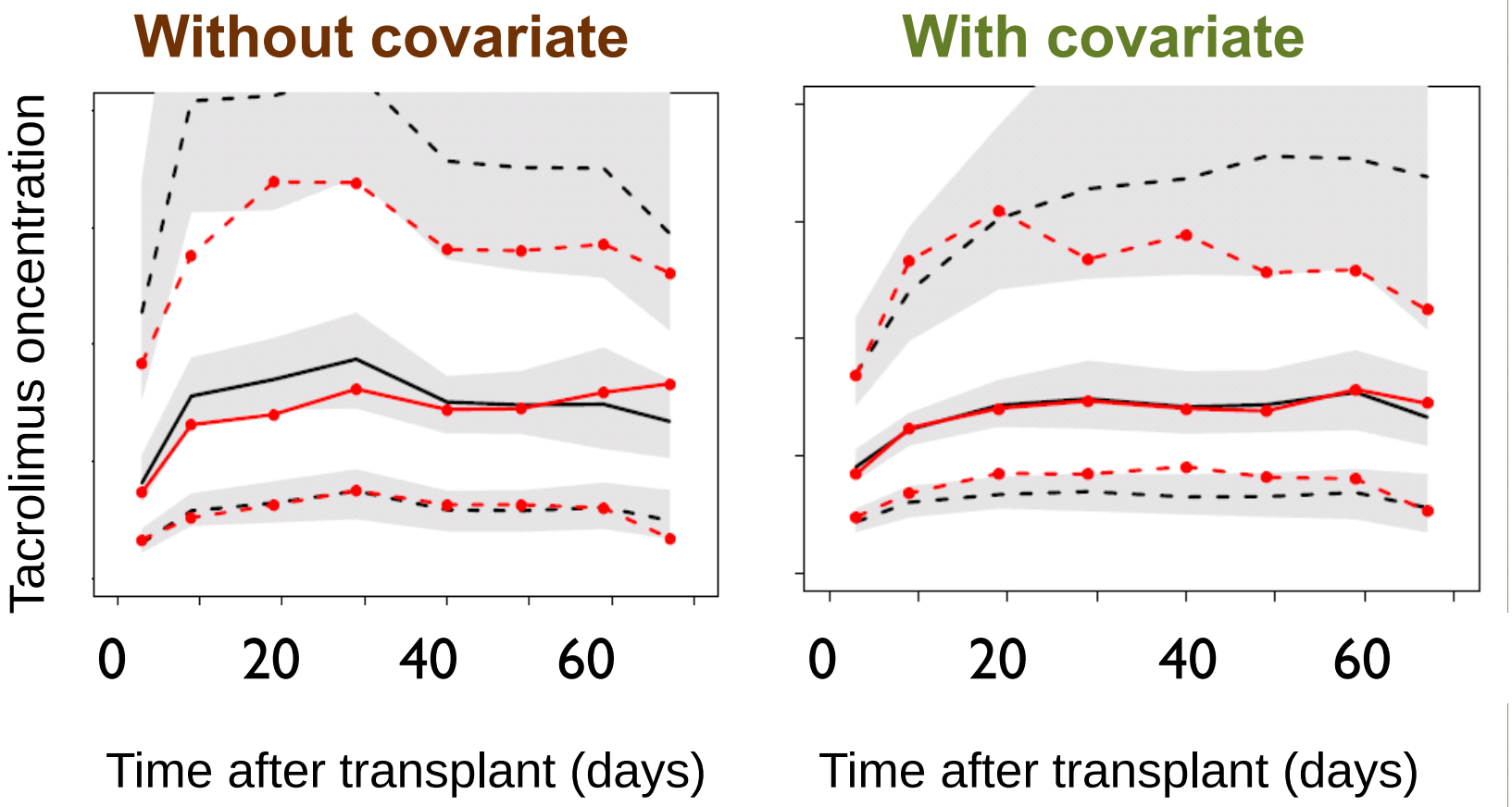

Conclusions

- Oral bioavailability of tacrolimus changes with time after transplantation
- The binning method helped reveal the shape
- The binning method is simple and flexible

Thank you for your attention

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