

Population pharmacokinetic modelling of whole blood and intracellular tacrolimus in adult kidney transplanted patients

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Tacrolimus inside the lymphocytes

Therapeutic drug monitoring (TDM) based on tacrolimus whole blood through concentrations is routinely carried out in kidney transplanted patients. Research indicates a weak correlation between tacrolimus in the blood and in peripheral blood mononuclear cells (PBMCs); the latter roughly corresponds to lymphocytes - the target site of tacrolimus. Tacrolimus exposure in PBMCs are believed to better reflect immunosuppression. Our objective was to analyze the relationship between tacrolimus in whole blood and PBMCs using the population approach and to identify significant patient covariates. We hypothesize that PBMC concentrations can be predicted solely from whole blood concentrations and identified patient covariates.

Methods

- Prospective enrollment of kidney transplanted patients
 - ❑ sparsely sampled (4-h, n=45)
 - ❑ densely sampled (12-h, n=18)
- PBMC isolation (Ficoll density gradient centrifugation)
- Tacrolimus quantification w/ LC-MS/MS (whole blood, PBMC)
- Genotyping w/ PCR and TaqMan assays
- Non-linear mixed effects modelling (NONMEM, PsN)
 - ❑ prediction corrected visual predictive checks
 - ❑ sampling importance resampling

Fast tacrolimus distribution into PBMCs

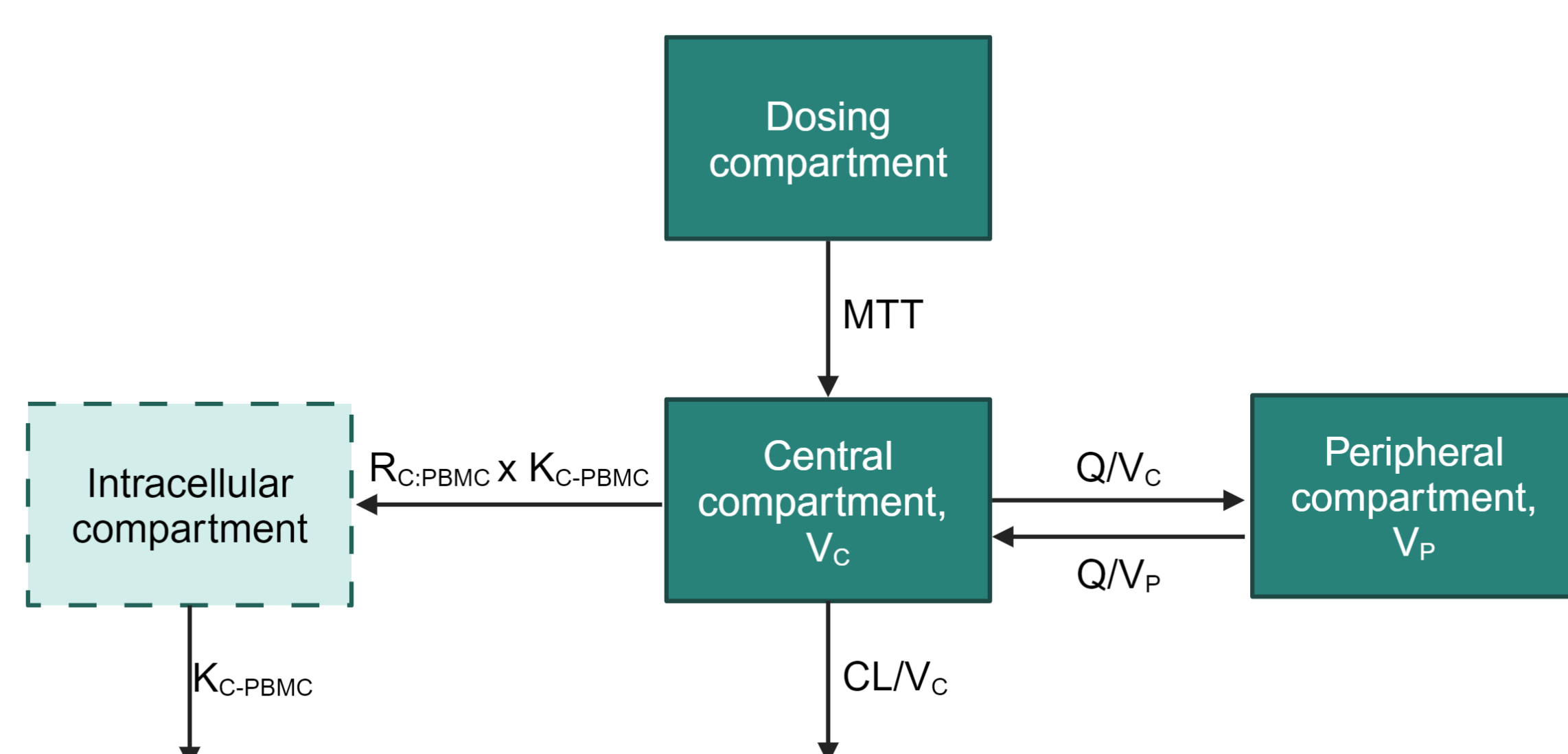


Figure 1: Tacrolimus disposition to central, peripheral and intracellular compartment. CL, clearance. $K_{C:PBMC}$, distribution rate constant from central compartment to PBMCs. MTT, mean transit time. $R_{C:PBMC}$, extent of tacrolimus distribution into PBMC. PBMC, peripheral blood mononuclear cells. Q, intercompartmental clearance. V_c , central volume of distribution. V_p , peripheral volume of distribution. Created with BioRender.

Substantial inter-individual variability in the tacrolimus distribution into PBMCs

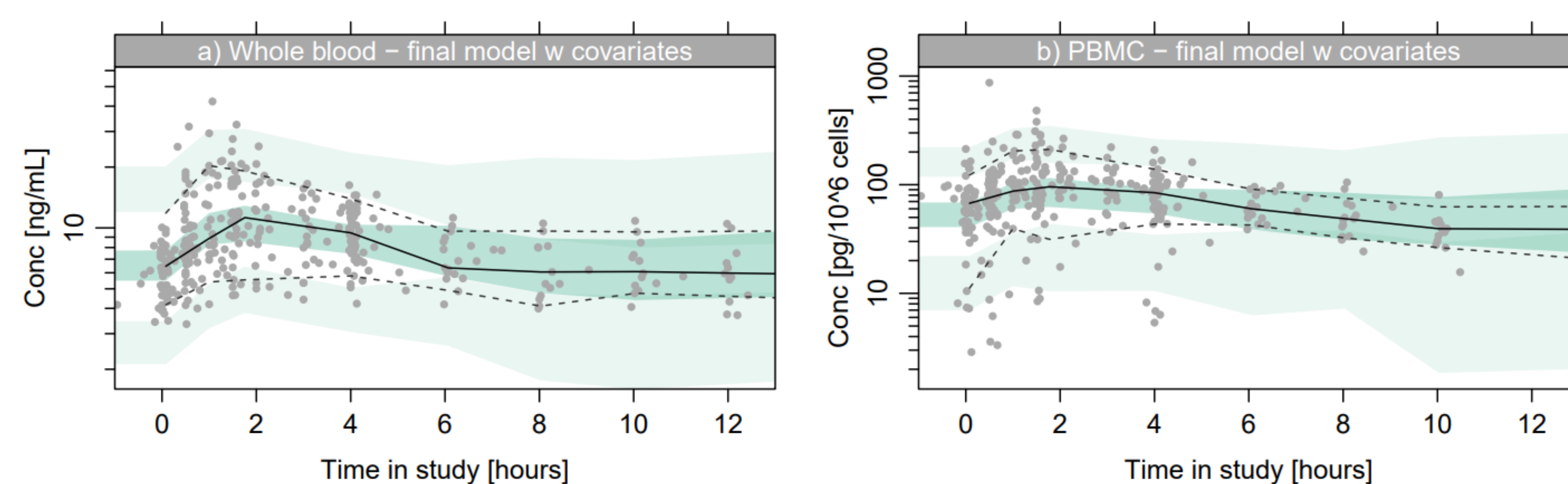
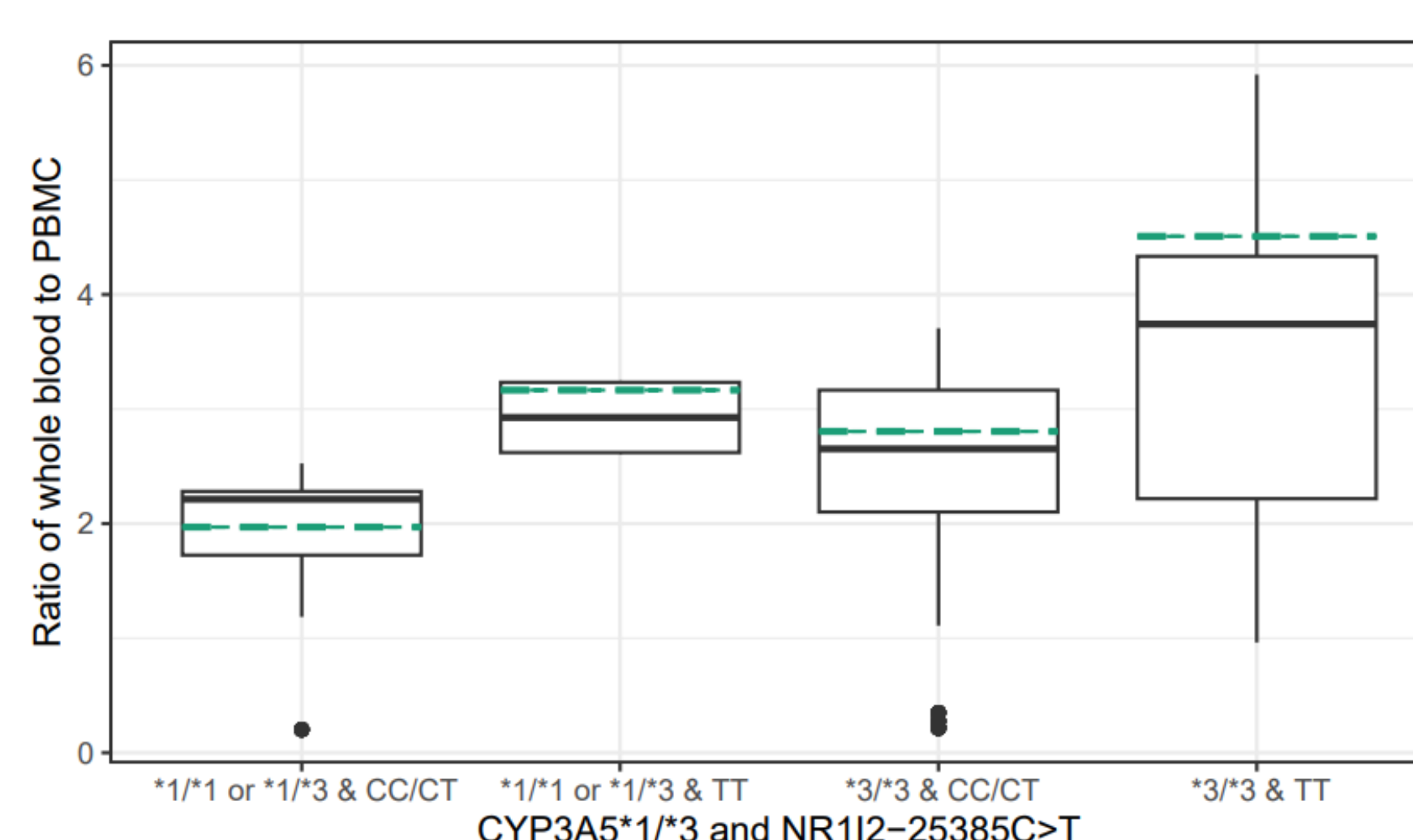


Figure 2: Prediction corrected visual predictive checks of tacrolimus a) whole blood concentrations versus time, b) PBMC concentrations versus time. Grey dots: observed concentrations. Dashed lines: observed 10th and 90th percentiles. Solid lines: observed median concentrations. Shaded area: 95% CI of the corresponding predicted percentiles. CI, confidence interval. PBMC, peripheral blood mononuclear cells.



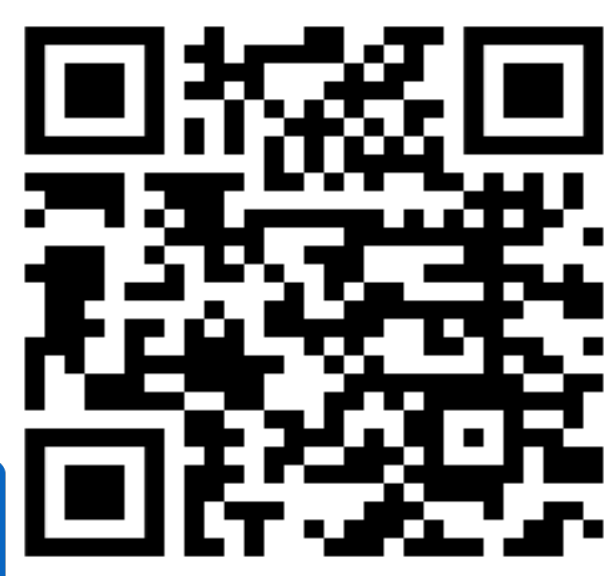
CYP3A5 and NR1I2 polymorphisms influence the tacrolimus distribution into PBMCs

Figure 3: Extent of distribution into PBMC versus CYP3A5*1/*3 and NR1I2 -25385C>T genotype. Green dashed line: typical individual predictions. Black box: IQR of individuals predictions. Solid black line: median. Upper and lower whiskers: 1.5 times IQR. IQR, interquartile range. PBMC, peripheral blood mononuclear cells.

Conclusions and perspectives

- We could not fully predict tacrolimus PBMC concentrations from whole blood concentrations using patient characteristics
- We need to:
 - ❑ identify more patient characteristics that influence the relationship
 - ❑ explore inter-occasion variability in the distribution of tacrolimus into PBMCs
 - ❑ establish a link between tacrolimus PBMC concentrations and efficacy

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