

Potential of Tacrolimus CYP3A5 genotyping to predict phenotype (C0/Dose/Weight ratio) and applicability of PBPK modelling to improve dosing strategies in pediatric kidney transplant recipients

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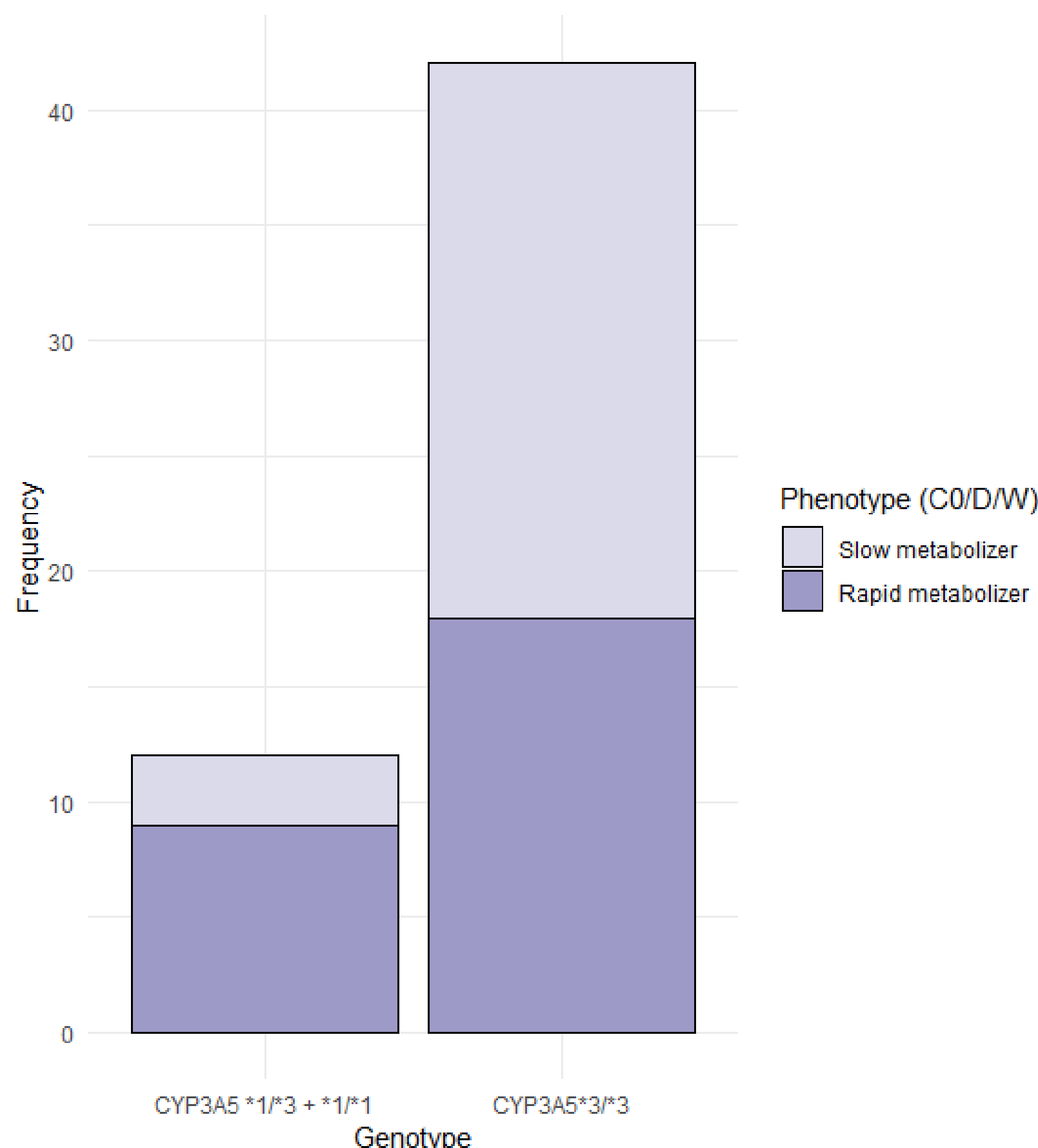
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Introduction and Objectives

Tacrolimus (TCR), the main immunosuppressive in kidney transplantation to prevent drug toxicity and graft rejection, has a narrow therapeutic range affected by gene polymorphisms in TCR pharmacokinetics and response. The ratio of trough concentration to TCR administered dose (C0/D ratio) has been found as an independent predictor of kidney graft and patient survival in order to optimize treatment and adjust TCR doses according to CPIC dosing guideline for CYP3A5*1/*1 or *1/*3 carriers in comparison to *3/*3 carriers. The present study aims to evaluate the ability of CYP3A5 genotyping to predict the actual phenotype according to C0/Weight adjusted dose (C0/D/W). It also aims to demonstrate the unique potential of PBPK modelling based on Prado-Velasco et al., 2020, with CYP3A5 genotyping implementation for defining the concentration-time curve to determine a dose in pharmacogenomics (PGx) subpopulations. PBPK analysis subpopulations are based on the phenotypes defined by CPIC, being *1/*1 and *1/*3 rapid metabolizers and *3/*3 slow metabolizers.

Results

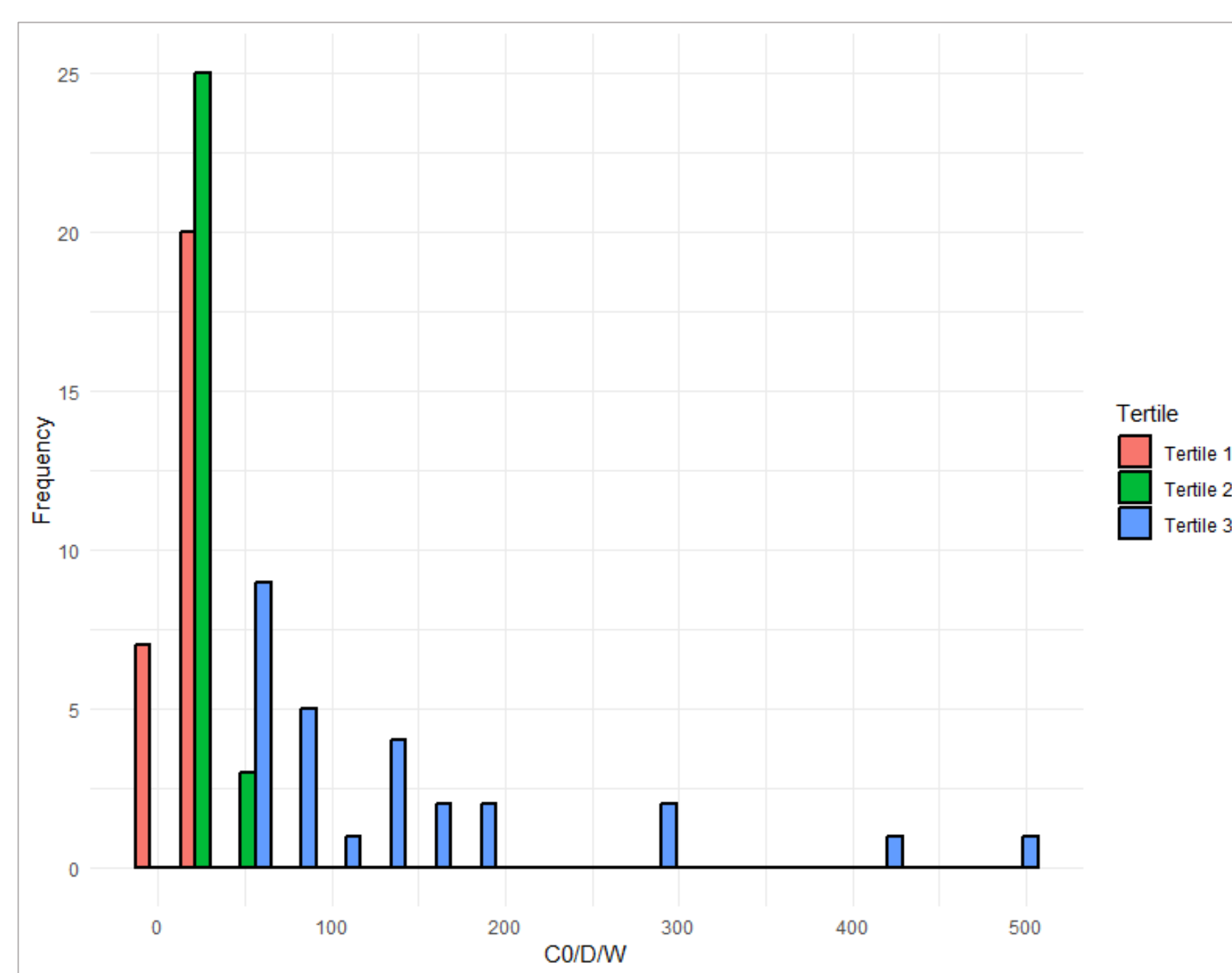
Quantitative analysis of concentration by genotype classification have shown that there were differences in the C0/D/W ratio between patients with a CYP3A5*1/*1 and *1/*3 genotype and patients with a *3/*3 genotype (n=54). After phenotypic inference from the C0/D/W and the comparison with the genotypes, we observe that the sensitivity of genotype *1/*1 and *1/*3 to detect a subject with a rapid metabolizer phenotype is 75%. The specificity, or capability of *3/*3 genotype to detect a subject with a slow metabolizer phenotype is 57.14%. The overall accuracy of the process is 61.11%. PBPK model adapted to subpopulations do not show an improvement in the prediction of pharmacokinetic response ($p>0.05$) compared to the model without PGx. We expect that both phenotype and genotype can be added to the model even if they are not fully correlated so that both can provide some explanation of variability. The mean and interindividual variability (IIV) estimates of population PBPK model parameters for TCR will be recalculated for validation purposes. Clinical data from pediatric patients treated with TCR 0, 1, and 3 hours, as well as area under the curve (AUC) over 24 hours.



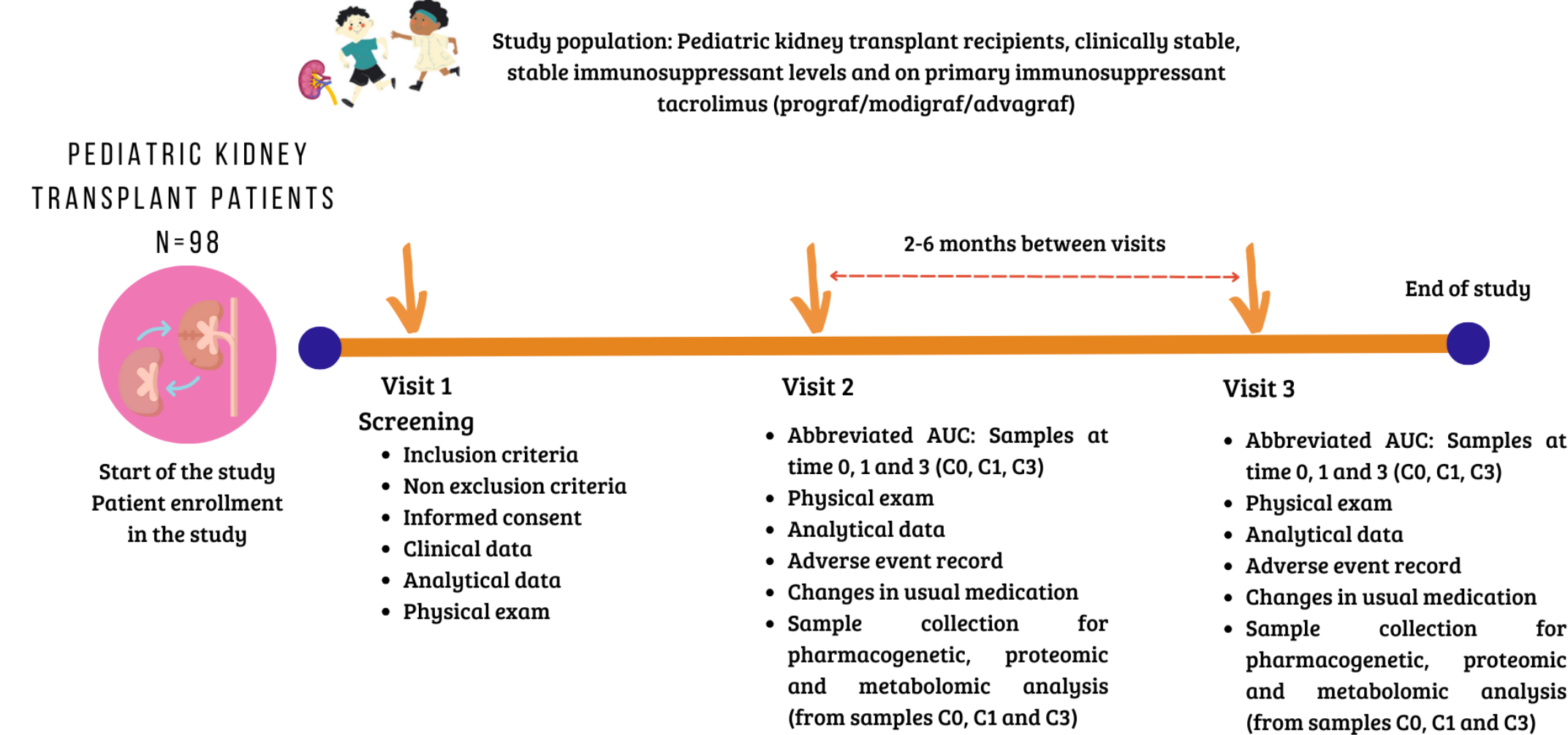
N=54
Sensitivity= 75%
Specifity= 57.14%
Overall accuracy= 61.11%

Methods

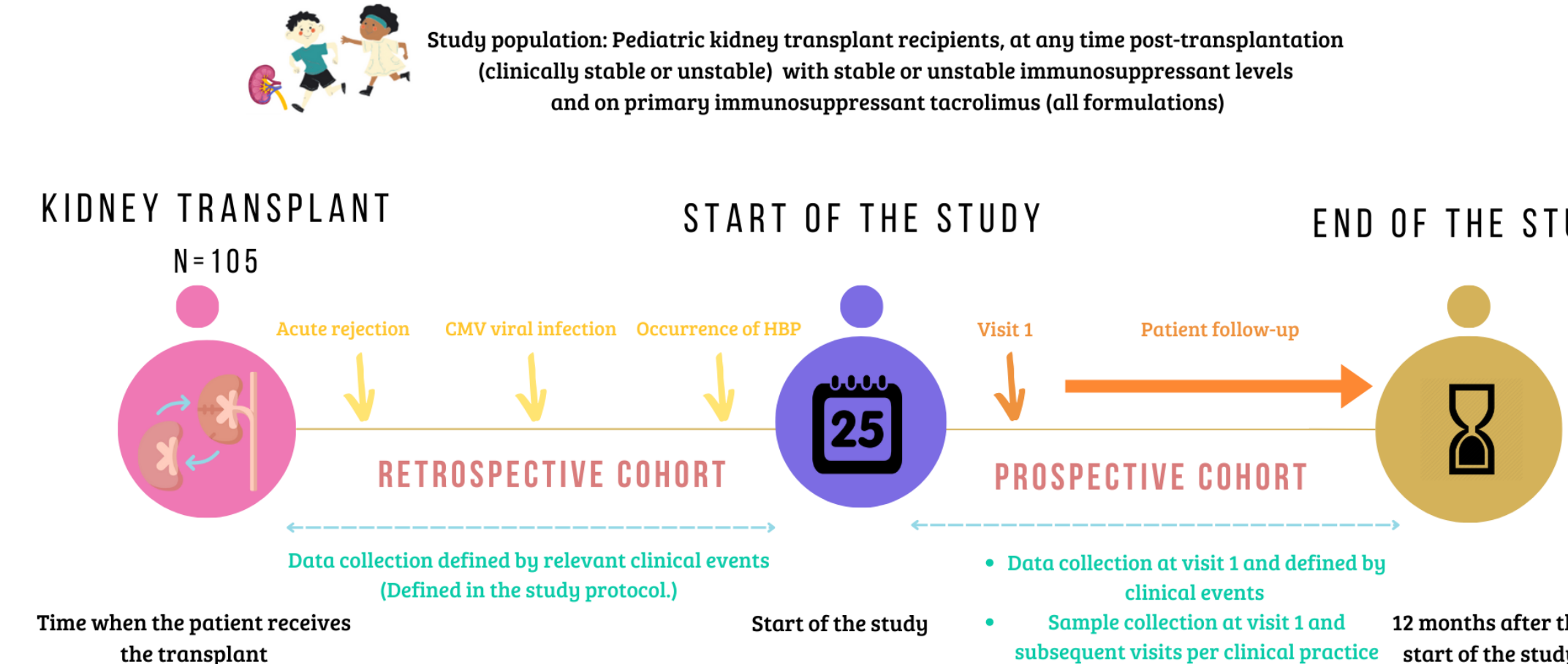
Analysis combines two clinical studies involving patients from pediatric Nephrology Department of La Paz University Hospital: a Phase IV clinical trial and an ambispective observational study. In both studies, TCR trough concentration (C0) samples from patients are collected and analyzed. Patients' C0/D/P values were calculated and split into tertiles; patients in the first and third were selected for analysis. Patient's phenotype in the first tertile (low C0/D/W ratio) were classified as "rapid metabolizer" and those in the third tertile (high C0/D/W ratio) as "slow metabolizer". PBPK model developed from previous published TCR model and optimized by standard methodologies with data from a clinical study was adapted with PGx data. An external validation based on subsequent measurements of the same population was also performed. TCR model was built using the PhysPK® (v2.4) software.



TACRO-OMICS STUDY (PHASE IV CLINICAL TRIAL) STUDY DESIGN



MODSIMTER-TACRO STUDY (AMBISPECTIVE OBSERVATIONAL STUDY) STUDY DESIGN



Conclusions

Genetics explains an important part of TCR variability but it is not fully accurate in phenotypic inference. PBPK models based on PGx could shown reliability to be used as knowledge engines in a customized posology software, built automatically through PhysPK® modelling and simulation software. The software will be tested to validate the accuracy and reliability.

[1] Prado-Velasco, M., Borobia, A., & Carcas-Sansuan, A. (2020). Predictive engines based on pharmacokinetics modelling for TCR personalized dosage in pediatric kidney transplant patients. Scientific Reports, 10(1), 7542.
[2]Reig-Lopez, Javier, et al. "A multilevel object-oriented modelling methodology for physiologically-based pharmacokinetics (pbpk): Evaluation with a semi-mechanistic pharmacokinetic model." Computer Methods and Programs in Biomedicine 189 (2020): 105322.
[3] Prado-Velasco, Manuel. "III-58: Manuel Prado-Velasco Bridging the gap between open and specialized modelling tools in PBPK/PK/PD with PhysPK/EcosimPro modelling system: PBPK model of methotrexate and 6-mercaptopurine in humans with focus in reusability and multilevel modelling features"