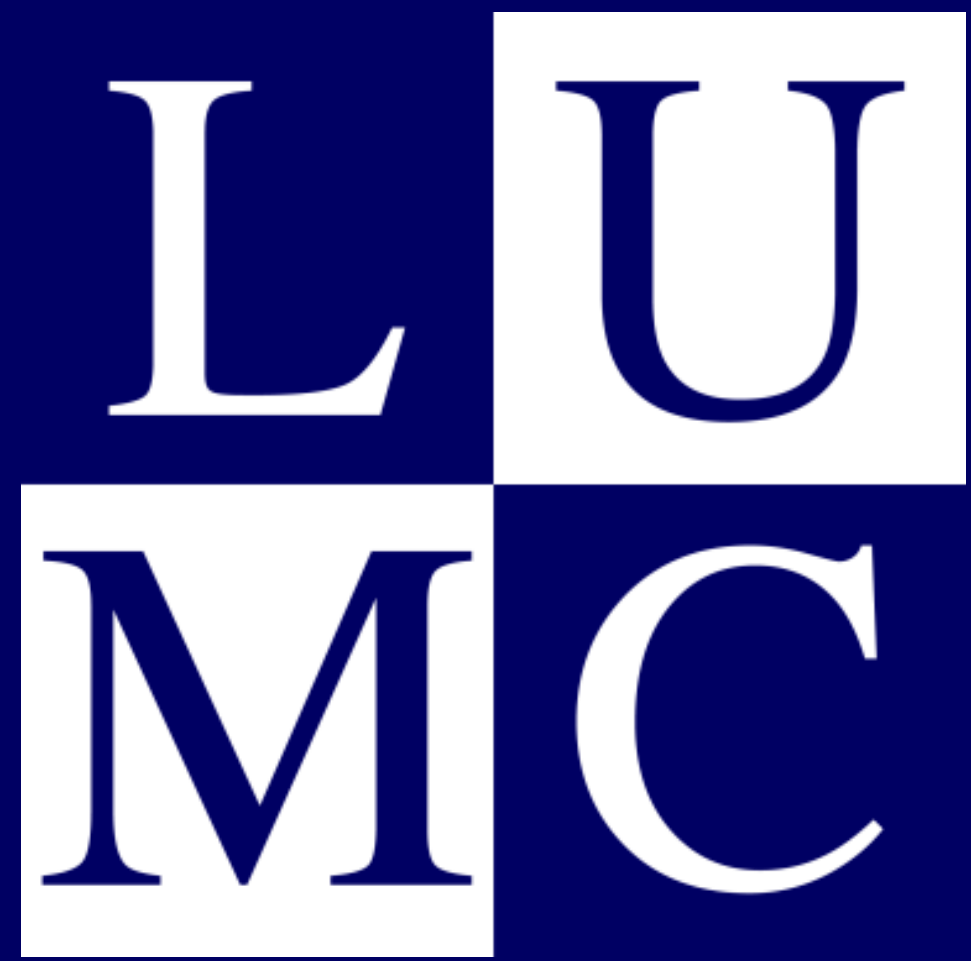




Population pharmacokinetics and pharmacogenetics of once daily tacrolimus formulation in stable liver transplant recipients

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Introduction

The once daily formulation of tacrolimus is an important immuno-suppressive drug metabolized by CYP3A enzymes. Inter-patient variability in tacrolimus metabolism has been related to both the *CYP3A4* and *CYP3A5* genotype (1-3). However, in liver transplants, both donor and recipient genotypes may affect pharmacokinetics.

Objectives

The aim of this study was to investigate the effect of *CYP3A4**22 and *CYP3A5**3 of both donor and recipient on once daily tacrolimus formulation pharmacokinetics in liver transplant recipients. Moreover a limited sampling model was developed.

Materials & Methods

- 49 stable liver transplant recipients on tacrolimus once daily formulation
- Dataset consisted out of 281 whole blood samples determined with LC-MS/MS.
- Covariate analysis with demographic covariates such as Weight, Height, Age, Hematocrit, IWT, BSA, LBW, Sex, and pharmacogenetic covariates *CYP3A5**3 and *CYP3A4**22 of both donor and recipient.
- Analysis was performed using NONMEM 7.2, R-Statistics and Pirana (4)

Table 1: Baseline characteristics

	Mean	SD	Median	Range
Male	31			
Female	18			
Age (yrs)	54	11	55	29 – 69
Caucasion (%)	92			
Weight (kg)	84	18	84	50 – 131
Height (cm)	173	8	174	155 – 190
Lean Body Mass (kg)	59	10	59	40 – 80
Ideal Body Weight (kg)	66	7	68	51 – 80
Body surface Area (m ²)	2	0.23	2	1.5 – 2.6
Creatinine clearance (ml/min)	87	24	87	33 - 120
Tacrolimus Dose (mg)	3.6	2.2	3	0.5 - 14
Hematocit (L/L)	0.42	0.04	0.42	0.30 – 0.50
Albumin (g/L)	45	3	45	35 – 54

Results

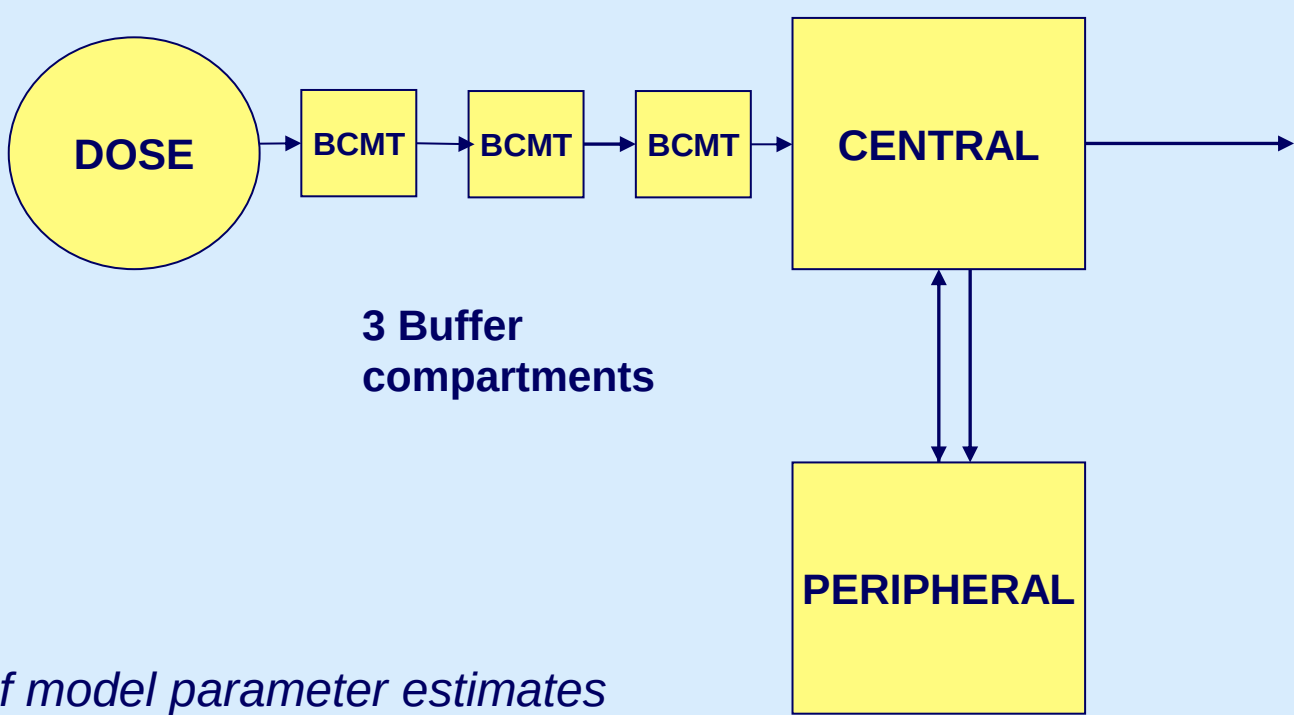


Table 2: Summary of model parameter estimates

PK Parameter	Base Model		Final Model		1000 Bootstrap runs	
	Mean Value	RSE (%)	Mean Value	RSE (%)	Median Value	95% CI
CL (L/h)	4.6	3.6	4.3	11	4.32	4.0 to 4.6
F (fixed)	0.23	-	0.23	-	0.23	-
V _c (L)	90.2	13	90.2	14	85.9	60.1 to 114.5
Q (L/h)	14.1	18	14.1	17	14.6	10.9 to 27.5
V _d (L)	160	20	169	38	158	92 to 1082
k _{el} (h ⁻¹)	3.6	11	3.6	11	3.5	2.8 to 4.6
Dose CL (TDM effect)	0.677	9	0.658	28	0.664	0.554 to 0.783
CYP3A5*3 on CL			Table 4			
Interindividual variability						
IIV CL (CV%)	24.5	11.1	21.6	10.2	20.3	15.6 to 24.9
IIV Vc (CV%)	85.9	13.6	85.4	13.9	87.5	65.4 to 133.2
IIV Ka (CV%)	65.5	21.1	65.9	23.4	62.8	43.2 to 90.7
Random residual variability						
σ ² (proportional error)	12	16.2	12	16.9	12.6	10.4 to 14.8

Figure 1: Prediction corrected Visual predictive check with 80 % prediction interval. The observed concentrations are shown as closed circles. The green lines with open circles symbols represent the observation intervals. The red solid lines represent the prediction interval. The shaded areas around the prediction intervals represent the 95 % confidence interval around each of the prediction interval.

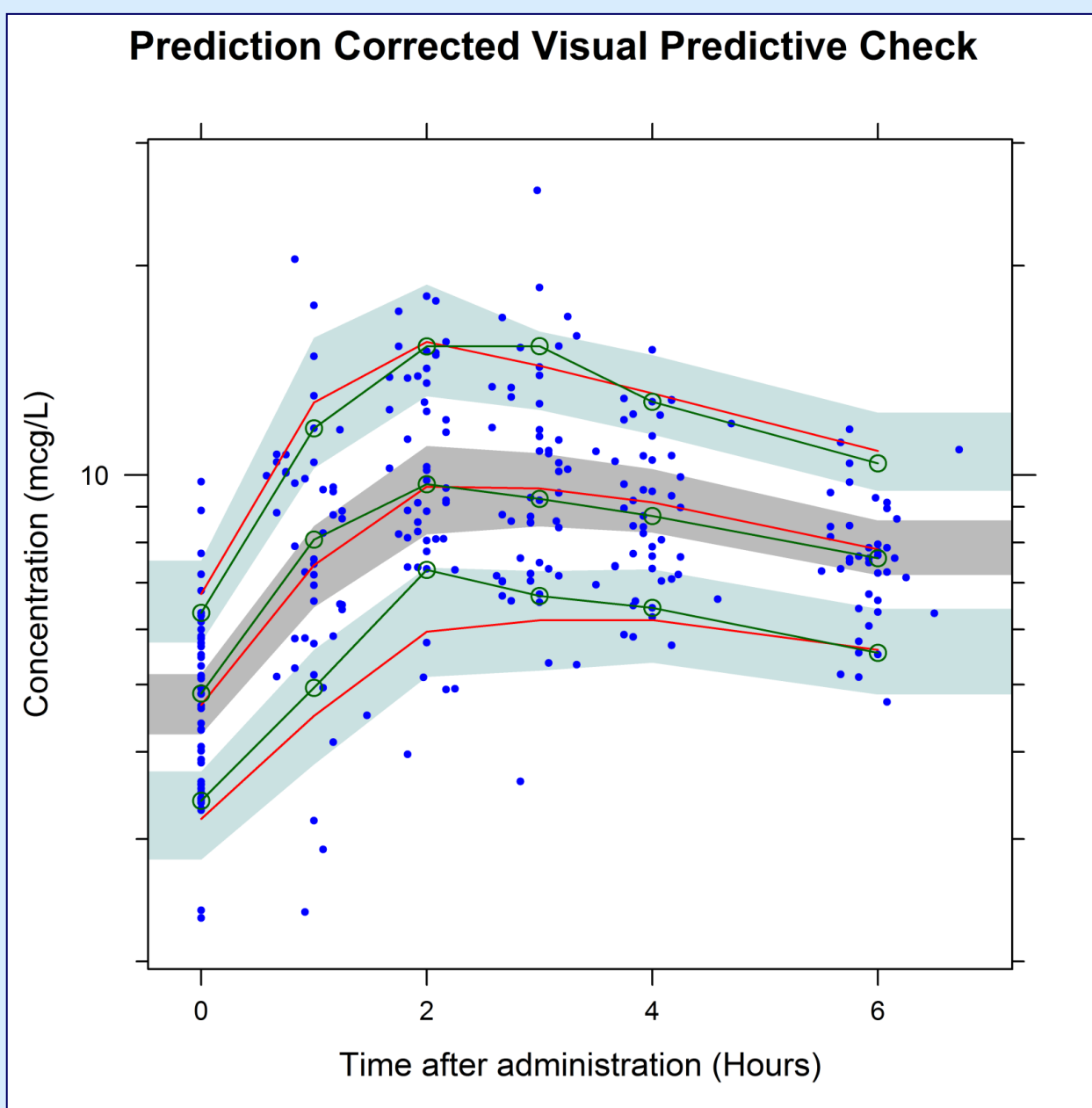


Table 3: Genotyping Results

SNP	Frequency and Genotype							
Recipient								
CYP3A4*22 (rs35599367)	36	*1/*1	11	*1/*22	2	*22/*22		
CYP3A5*3 (rs776746)	36	*3/*3	10	*1/*3	3	*1/*1		
Donor								
CYP3A4*22 (rs35599367)	40	*1/*1	8	*1/*22	1	*22/*22		
CYP3A5*3 (rs776746)	40	*3/*3	9	*1/*3	0	*1/*1		
CYP3A5 combination	30	C1	10	C2	6	C3	3	C4
CYP3A4 combination	32	C1	8	C2	4	C3	5	C4

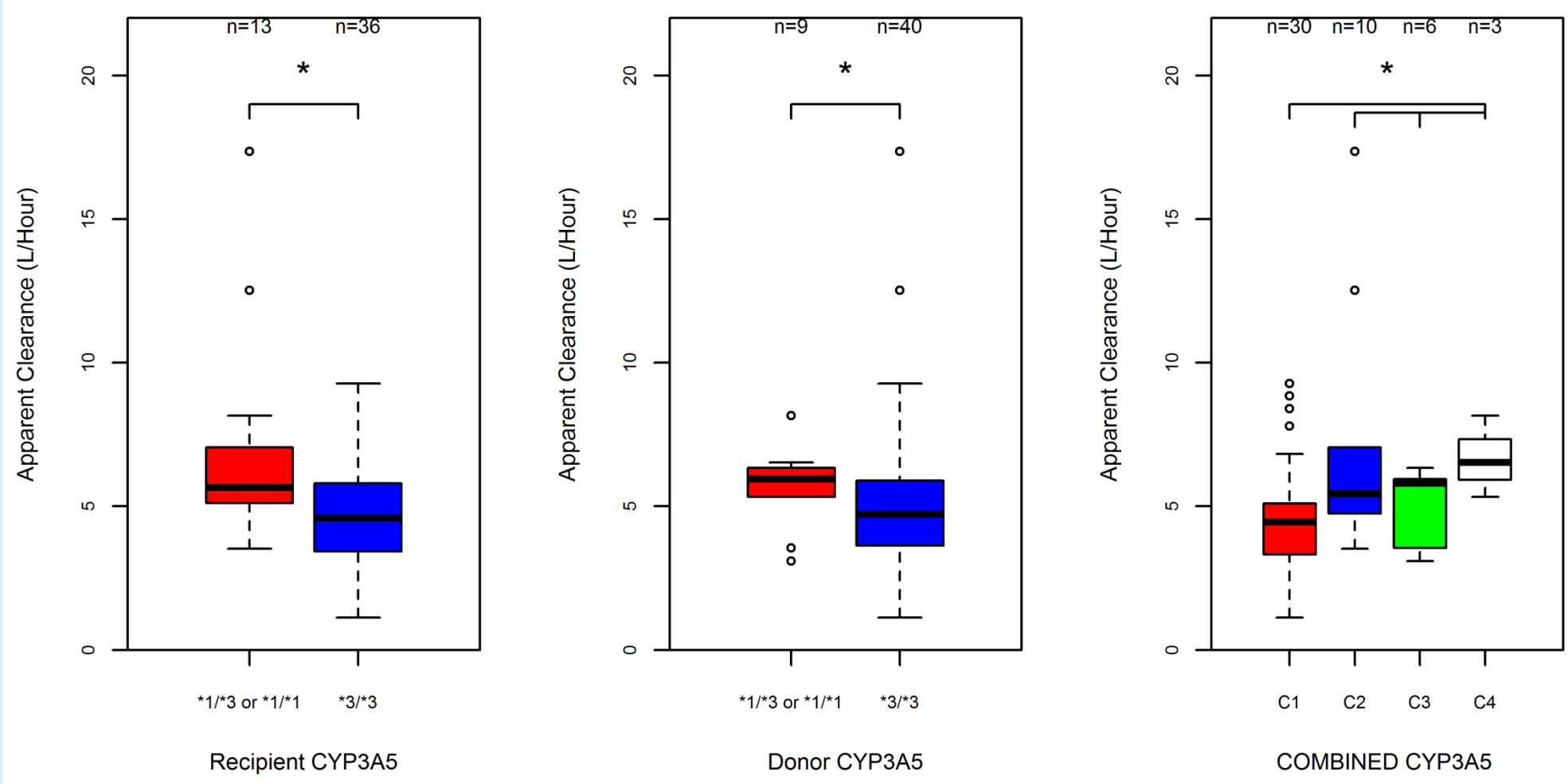


Figure 2: Boxplots representing the average once daily tacrolimus apparent clearance (L/Hour) of the different genotype groups with error bars and the number of patients in each group. CYP3A5 (*1/*3 or *1/*1 = CYP3A5*1 carriers, *3/*3 = CYP3A5*1 non-carriers), CYP3A5 COMBINATION: C1 donor and recipient are CYP3A5*1 non-carriers C2: Recipient is CYP3A5*1 carrier and donor is non-carrier.C3: Recipient is CYP3A5*1 non-carrier and donor is carrier. C4: Both donor and recipient are CYP3A5*1 carriers.

Table 4: CYP3A5 covariate analysis results

Covariate Tested	ΔOFV	P value	Mean Value (%)	95% CI
Advagraf base model				
+ Recipient CYP3A5*3	5.637	0.018	21	-0.9 to 43
+ Donor CYP3A5*3	6.857	0.009	28	-7 to 62
+ CYP3A5*3 combination	13.87	0.003	C1 0 C2 11 C3 14 C4 65	-7 to 7 - 8 to 29 -11 to 39 29 to 101

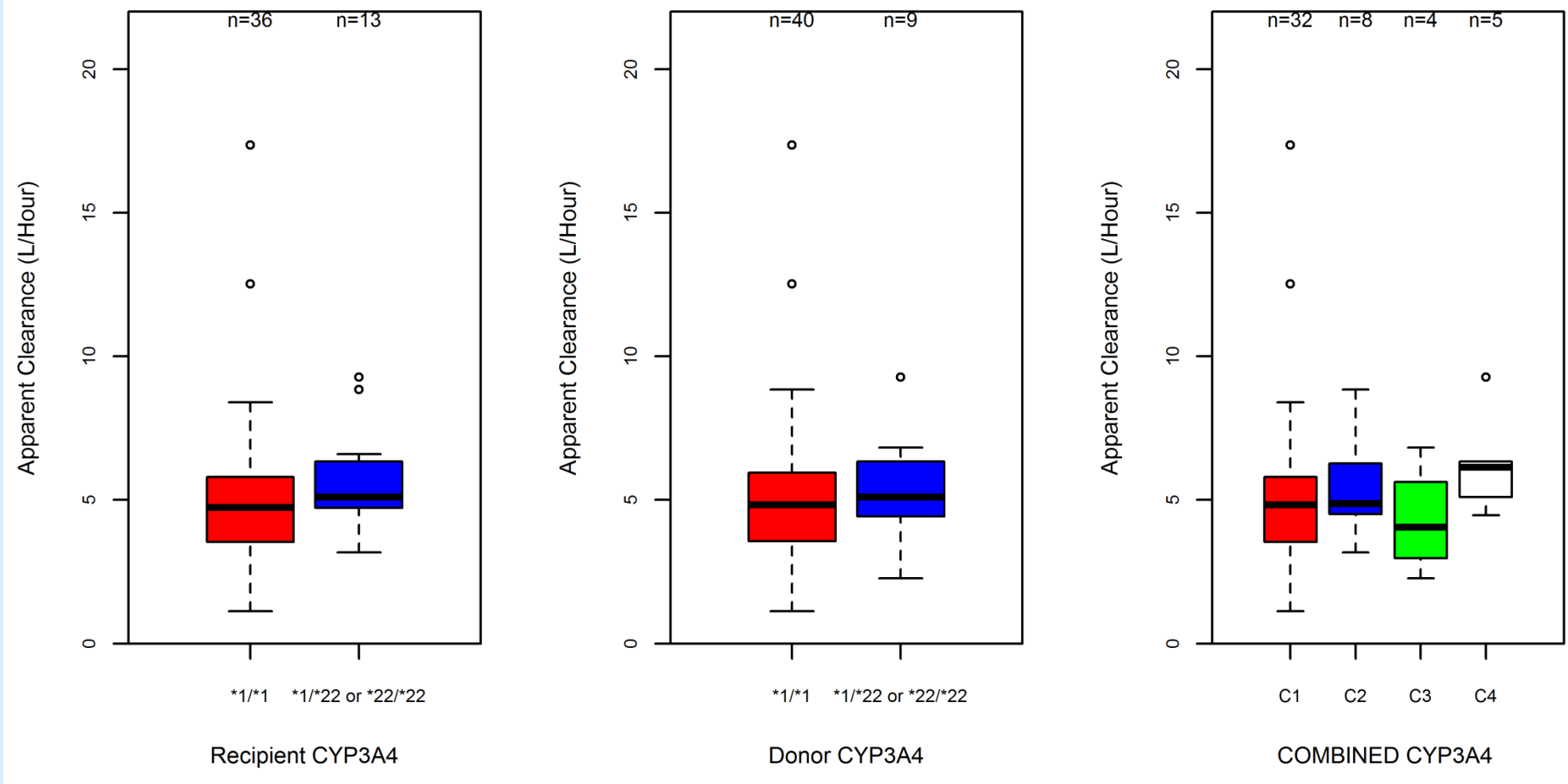


Figure 3: Boxplots representing the average once daily tacrolimus apparent clearance (L/Hour) of the different genotype groups with error bars and the number of patients in each group. CYP3A4 (*1/*1 = CYP3A4*22 non-carriers, *1/*22 or *22/*22 = CYP3A4*22 carriers. CYP3A4 COMBINATION: C1 donor and recipient are CYP3A4*22 non-carriers, C2: Recipient is CYP3A4*22 carrier and donor is non-carrier, C3: Recipient is CYP3A4*22 non-carrier and donor is carrier, C4: Both donor and recipient are CYP3A4*22 carriers.

Table 5: CYP3A4 covariate analysis results

Covariate Tested	ΔOFV	P value	Mean Value (%)	95% CI
Advagraf base model				
+ Recipient CYP3A4*22	0.79	0.374	7	-7 to 22
+ Donor CYP3A4*22	0.564	0.453	7	-13 to 27
+ CYP3A4*22 combination	2.532	0.470	C1 0 C2 -0.2 C3 - 6 C4 19	-9 to 9 -14 to 13 -32 to 20 -6 to 43

Table 6: Limited sampling results

Time points Blood Sampling	R ² pearson	Percentage of AUCpred within 15% radius of AUCfull	Discordance (%)	MPE (mcg*th/L)	MPPE (%)	RMSE (mcg*th/L)	MAPE (mcg*th/L)
T0	0.74	75.76	21.15	3.53	2.86	24.83	12.17
T1	0.50	51.52	42.31	-2.26	2.02	29.89	16.31
T2	0.63	62.12	38.46	-7.80	-2.27	26.53	13.66
T3	0.64	72.73	21.15	-4.23	-0.32	25.31	11.84
T4	0.65	71.21	21.15	-4.66	-0.30	25.31	11.56
T5	0.23	45.45	55.77	-3.02	4.13	38.23	22.38
T6	0.63	77.27	21.15	-6.08	-1.13	25.98	11.81
T02	0.88	89.39	3.85	-2.85	-1.81	15.24	6.60
T013	0.94	96.97	0.00	-1.10	-0.70	10.17	4.88
T023	0.95	62.12	34.62	-2.17	-1.40	9.26	4.69
T13	0.72	68.18	26.92	-4.64	-1.18	22.64	11.02
T14	0.74	71.21	19.23	-4.30	-0.81	21.95	10.29
T34	0.73	78.79	19.23	-3.16	-0.19	22.12	10.42
T46	0.69	80.30	17.31	-4.75	-0.67	23.77	10.64
T136	0.86	77.27	17.31	-4.57	-1.74	16.27	7.74
T146	0.79	87.88	5.77	-5.35	-1.76	20.21	9.01
T123	0.72	95.45	0.00	-4.85	-1.40	22.59	10.88
T012	0.86	98.48	1.92	-0.47	-0.37	17.23	6.89
T03	0.94	89.39	3.85	-2.00	-1.20	10.61	5.51
T12	0.59	81.82	13.46	-6.55	-1.83	27.65	14.30
T23	0.66	71.21	23.08	-4.89	-0.96	24.93	11.94
T0123	0.96	96.97	1.92	-1.21	-0.80	8.91	4.09

bias is the systematic error, the tendency of consistently over- or under- estimating the parameter precision is the random error, and reflects the magnitude of variation in the prediction

Conclusions

- Dose adjustments based on *CYP3A5* genotype of both donor and recipient are indicated.
- CYP3A4**22 appears not suitable as biomarker for tacrolimus once daily pharmacokinetics.
- 0,1 and 3 hours postdose as limited sampling model can be used to accurately estimate tacrolimus once daily formulation exposure in liver transplantation.

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