



A Population Pharmacokinetic Model and Dosing Algorithm to Guide the Tacrolimus Starting and Follow-Up Dose in Living and Deceased Donor Kidney Transplant Recipients

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Abstract

Introduction Tacrolimus treatment is complicated by its narrow therapeutic range and large inter- and intra-patient variability. This study aimed to develop a population pharmacokinetic model and dosing algorithm to predict an individual's dose requirement following living and deceased donor kidney transplantation.

Methods In this international, multicenter, retrospective study, data was collected from patients who had received a living or a deceased donor kidney and received tacrolimus twice daily. A population pharmacokinetic model was developed using nonlinear mixed-effects modeling (NONMEM).

Results This study included 13,427 tacrolimus concentrations from 1180 kidney transplant recipients. A two-compartment model with first-order absorption best described the data. The mean absorption rate was 6.59/h, apparent clearance 20.7 L/h, central volume of distribution 705 L, and peripheral volume of distribution 7670 L. Higher age, creatinine, and hematocrit, as well as lower height, were associated with lower tacrolimus clearance. Tacrolimus clearance was higher for cytochrome P450 (CYP) 3A5*1 carriers compared with CYP3A5*3/*3 individuals, and lower for CYP3A4*22 carriers compared with CYP3A4*1/*1 patients. Together, these covariates explained 19.3% of the inter-individual variability in clearance. From the full model, a starting dose algorithm was developed with age, height, and the CYP3A4 and CYP3A5 genotypes as covariates. Both the full model and the starting dose algorithm were successfully internally validated.

Conclusions In this international, multicenter study, age, CYP3A4 and CYP3A5 genotype, creatinine, height, and hematocrit were identified as significant covariates associated with tacrolimus pharmacokinetics, and can be used to predict the optimal individual's dose requirement for both living and deceased donor kidney transplant recipients.

1 Introduction

Tacrolimus treatment after kidney transplantation is complicated by its narrow therapeutic range and its large inter- and intra-individual variability. The current dosing strategy in most transplant centers consists of a standard, bodyweight-based dose followed by therapeutic drug monitoring (TDM). However, bodyweight is a poor predictor for an individual's dose requirement [1–3]. Consequently, both over- and under-exposure to tacrolimus occur frequently in the critical early post-transplantation phase, which puts patients at an increased risk for toxicity and rejection, respectively. Furthermore, this may also lead to more TDM requests as more dose adjustments are required, which paradoxically increases intra-individual variation.

Theoretically, population pharmacokinetic (popPK) models, incorporating demographic and clinical patient characteristics that are associated with tacrolimus pharmacokinetics, can better predict an individual's dose requirement than bodyweight alone. Therefore, multiple research groups have developed popPK models and dosing equations that incorporated such factors [2, 4–24]. However, most of these popPK models were developed with data from one center, and therefore cannot be used in a different population or setting without validation.

Recently, we prospectively tested a tacrolimus starting dose algorithm (developed by our group) [16]. The algorithm successfully predicted the tacrolimus starting dose in adult recipients of a living donor kidney [25]. Using the algorithm, at first steady state (3 days after transplantation), 58% of the patients had a tacrolimus pre-dose concentration within the target concentration range, whereas this was

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Key Points

In this large international study, we developed a population pharmacokinetic model and a dosing algorithm to predict an individual's tacrolimus dose requirement following both living and deceased donor kidney transplantation.

Higher age, serum creatinine, and hematocrit, as well as lower height were associated with lower tacrolimus clearance.

Tacrolimus clearance was 1.7–2 times higher for *CYP3A5**1 allele carriers as compared with *CYP3A5* non-expressers (*3/*3), and 0.8 times lower for *CYP3A4**22 carriers as compared with *CYP3A4**1/*1 individuals.

Together, these covariates explained 35% of the variability in clearance.

as low as 37.4% in kidney transplant recipients receiving a standard bodyweight-based tacrolimus starting dose [25, 26]. Although these results indicate that algorithm-based tacrolimus dosing has the potential to minimize under- and over-exposure to this critical dose drug, there remains a considerable amount of unexplained variability in tacrolimus' pharmacokinetics. Earlier dosing algorithms were often based on datasets limited to 50–300 patients. To identify factors with a smaller effect on tacrolimus pharmacokinetics, which can explain this unexplained variability, and to estimate effects with more precision, high statistical power and large datasets are required. Furthermore, our dosing algorithm was developed for recipients of a living donor kidney and therefore might be less suitable for patients who receive a deceased donor kidney transplant. Deceased donor kidneys constitute a large portion of all kidney transplants and since these patients are at higher risk of allograft loss, they might benefit even more from algorithm-based tacrolimus dosing compared with patients transplanted with a living donor kidney [27, 28].

The aim of this study was: (i) to identify factors that affect tacrolimus pharmacokinetics and can explain its inter- and intra-patient variability; and (ii) develop a popPK model that can be used to guide tacrolimus dosing in both living and deceased donor kidney transplant recipients.

2 Materials and Methods

2.1 Study Design

This study was an international, multicenter, retrospective study, in which multiple cohorts of adult kidney transplant

recipients were included to develop a popPK model for tacrolimus.

2.1.1 Study Population and Data Collection

Patients were eligible for inclusion in this study if they were at least 18 years old and received tacrolimus as immunosuppressive therapy after renal transplantation. Patients that received a blood group ABO and human leukocyte antigen (HLA)-incompatible kidney transplantation were excluded, because these patients have different immunosuppressive regimens and these patients were not included in previous pharmacokinetic studies from which most data for this study were extracted [29, 30].

Patients from the following cohorts of kidney transplant recipients were screened for eligibility: (i) Patients included in previous (pharmacokinetic) studies performed in the Erasmus MC, University Medical Center Rotterdam, the Netherlands [16, 26]; (ii) patients transplanted in the Erasmus MC between 1 January 2017 and 1 July 2020; (iii) patients transplanted in the Leiden University Medical Center, Leiden, the Netherlands, who were included in a previous pharmacokinetic study [16]; (iv) patients transplanted in the Cliniques Universitaires St Luc, Brussels, Belgium, included in previous pharmacokinetic studies [31]; and (v) patients transplanted in the Bellvitge University Hospital, Barcelona, Spain, included in previous pharmacokinetic studies [5, 22, 32].

Of these patients, clinical, demographic, and genetic data were collected. Patient body composition parameters were calculated on the basis of sex, bodyweight, and height, using the formulae described in Supplementary Data S1.

2.1.2 Immunosuppression

All patients received twice-daily tacrolimus [Prograf® (Astellas Pharma) or Adoport® (Sandoz Pharma)] in combination with mycophenolic acid as maintenance immunosuppressive treatment. In all centers whole-blood tacrolimus pre-dose concentrations were measured as part of standard clinical practice. As part of standard clinical practice, patients received glucocorticoids after kidney transplantation, of which the dose was tapered over time.

In the Leiden cohort, area under the curves (AUCs) were measured as part of standard clinical practice approximately 2 weeks after kidney transplantation, with samples drawn at 1, 2, 3, 4, 5, and 6 h after dose ingestion ($n = 100$). In the Barcelona cohort, AUCs were measured as part of a pharmacokinetic study, with samples drawn at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after dose ingestion ($n = 24$) and 0, 0.3, 0.7, 1.3, 2, 3, 4, 6, 8, 10, and 12 h after dose ingestion [patients $n = 7$; AUCs $n = 31$ [32]]. In the Brussels cohort, AUCs were

measured as part of a pharmacokinetic study, with samples drawn at 0, 0.5, 1.5, 3, 4, 8, and 12 h after dose ingestion [$n = 54$ [31]].

2.1.3 Laboratory Analysis and Genotyping

Tacrolimus concentrations were measured using immunoassays and a liquid chromatography-tandem mass spectrometry method (LC-MS/MS). Patients were tested for the presence of the *ABCB1* c.1199G>A, *ABCB1* c.2677G>T/A, *ABCB1* c.3435C>T, *CYP3A4**1/*22, *CYP3A5**1/*3, and *POR**1/*28 single-nucleotide polymorphisms (SNPs). More detailed information on the laboratory analysis and genotyping methods in the different centers are described in Supplementary Data S2.

2.1.4 Ethical Considerations

The Medical Ethical Review Board of the Erasmus MC provided a waiver for the Medical Research Involving Human Subjects Act for this study (Medical Ethical Review Board number MEC-2021-0621). In the Erasmus MC Center, the LUMC, the Bellvitge University Hospital, and St. Luc Hospital Brussels, all patients included in this study previously gave written informed consent for the use of their clinical and demographic data for research purposes and the use of body material for genotyping [16, 26, 32–34]. Study practices were performed after approval from the local medical ethical committees. Patients that were not included in previous studies, were asked to participate in an ongoing biobanking program of the division of nephrology and transplantation (MEC-2010-022) during the work-up for transplantation in the Erasmus MC. The study was conducted according to the principles of the Declaration of Helsinki (7th revision, October 2013, approved by the 64th WMA General Assembly, Fortaleza, Brazil).

2.2 Pharmacokinetic Modeling

Pharmacokinetic modeling was performed using nonlinear mixed-effects modeling (NONMEM; version 7.4.4; ICON Development Solutions, USA). PsN Pirana software (version 3.0.0; CERTARA, USA) was used as an interface between NONMEM, R (version 4.1.3) and Xpose4.

2.2.1 Base Model

For the development of the base model, one-, two-, and three-compartment models were tested. Residual variability was incorporated for the combination of transplant center (Erasmus MC, LUMC, Bellvitge University Hospital, and St. Luc Hospital) and method of tacrolimus

measurement (LCMS/MS versus immunoassays), resulting in a total of seven combinations. To model residual variability two different models were evaluated: (i) a logarithmic error model, and (ii) a combination of a proportional and additive error models. Typical values for the absorption rate constant (K_a), clearance (CL), lag-time (t_{lag}), central volume of distribution ($V1$), peripheral volumes of distribution (V), and intercompartmental clearances (Q) were estimated. Bioavailability (F) was fixed to 1, and certain values were estimated as ratios: CL/F , Q/F , $V1/F$, and V/F . To prevent an effect of the large number of pre-dose concentrations in the estimation of K_a , $V1$, and V , which are parameters that are best estimated with dense sampling, these were also estimated using only data from patients with at least one available curve. We compared these estimates with the estimates computed by using the whole database and evaluated the model fit. For each PK parameter (K_a , CL, $V1$, V , Q), inter-individual variability (IIV) was incorporated using an exponential model. Finally, covariance in pharmacokinetic parameters was evaluated. Model selection was based on model stability, objective function values (OFV; with $\Delta OFV > 7.8$ considered a significant model improvement for nested models; $p < 0.005$), parameter precision, error estimates and visual inspection of goodness-of-fit (GOF) plots, and prediction corrected visual predictive checks (pcVPCs).

2.2.2 Covariate Analysis

The following factors were evaluated as model covariates: *ABCB1*199 genotype, *ABCB*2677 genotype, *ABCB*13435 genotype, age, alanine transaminase (ALAT), albumin, aspartate aminotransferase (ASAT), bilirubin, body mass index (BMI), bodyweight, body surface area (BSA), C-reactive protein (CRP), serum creatinine, *CYP3A4* genotype, *CYP3A5* genotype, donor type, fat mass, gamma-glutamyl transferase (γ -GT), glomerular filtration rate (GFR), height, hematocrit, ideal body weight (IBW), lean body weight (LBW), and total plasma protein. Covariates were tested as model covariates based on their graphical relationship or their theoretical relationship with tacrolimus pharmacokinetics. Covariate effects were estimated on patients with available covariate values. Missing covariates were coded as population median. Covariates were included in the model following a forward-inclusion (with a decrease in OFV of > 3.84 ; $p < 0.05$) backward-elimination (with a decrease in OFV of > 6.63 ; $p < 0.01$) analysis. Besides OFVs, model selection was based on parameter estimates and precision, condition numbers, visual inspection of GOF plots, VPCs and the relationship between the covariate and the PK parameter estimates, and the covariate and the IIV (before and after including the covariate in the model).

The following formulas were used to model effects of continuous covariates (Eq 1) and categorical covariates (Eq 2), respectively:

$$\theta_i = \theta_{\text{pop}} \times \left(\frac{\text{cov}_i}{\text{cov}_m} \right)^{\theta_{\text{cov}}} \times e^{\eta} \quad (1)$$

$$\theta_i = \theta_{\text{pop}} \times \theta_{\text{cov}}^{\text{cov}_i} \times e^{\eta}. \quad (2)$$

In these formulas, θ_i represents the individual-predicted pharmacokinetic parameter (i.e., CL_i or V2_i), θ_{pop} represents the population estimate for the pharmacokinetic parameter (i.e., CL_{pop} or V2_{pop}), and θ_{cov} describes the covariate effect. Cov_i represents the covariate value of individual *I* (for categorical factors 0/1), and cov_m represents the median covariate value in the dataset. Missing covariates were coded as population median.

Afterwards, the remaining effect of the time after transplantation on population CL/*F* was evaluated using the following formula:

$$\theta_{ix} = \theta_{\text{pop}} + \left(\frac{\theta_{\text{time-direction}}}{10} \right) \times e^{-\text{time}_x \times \theta_{\text{time-speed}}} \times e^{\eta}. \quad (3)$$

In this formula, θ_{ix} represents the predicted individual apparent CL at time *x*, $\theta_{\text{time-direction}}$ represents the direction of the time effect, and $\theta_{\text{time-speed}}$ represents the slope of the time effect (i.e., the speed).

Finally, it was evaluated whether the administration of different tacrolimus formulations (Prograft® versus Adport®) affected bioavailability (*F*). As Adport® was only used in one center (Barcelona), we evaluated its effect with and without a correction factor for center.

2.2.3 Model Validation

The final model was internally validated by performing a bootstrap analysis (*n* = 1000), and by computing prediction corrected VPCs with 1000 simulations for the full model, stratified for the different centers, and stratified for the covariates that were included in the final model.

2.2.4 Simulation

To visualize the effect of the significant covariates found in the covariate analysis, deterministic simulations were performed (*n* = 1000). For continuous covariates, steady-state whole-blood concentrations were simulated for the values of the 10th, 25th, 50th, 75th, and 90th percentile of the covariate, while keeping the other covariates similar to the population median. For categorical covariates, steady-state whole-blood concentrations were simulated for the different

categories, while keeping the other covariates similar to the population median.

2.2.5 Starting Dose Algorithm

A starting dose algorithm was developed based on the final popPK model. For the starting dose algorithm, covariates were selected that were significantly associated with tacrolimus pharmacokinetics in the full model, are known before transplantation, and are not expected to change much after transplantation. The starting dose model was evaluated on the basis of its precision, its estimates, goodness-of-fit plots, and internally validated by computing VPCs with 1000 simulations.

To evaluate model performance, tacrolimus concentrations following bodyweight-based dosing and model-based dosing were simulated using the full model and patient characteristics of those included in the model-building cohort. Each patient was given a standard bodyweight-based dose (0.1 mg/kg twice daily) and a dose based on the starting dose model (*n* = 1000). For each patient, the pre-dose concentration was simulated 1000 times using the full model.

3 Results

3.1 Baseline characteristics

A total of 13,427 tacrolimus concentrations of 1180 patients were included in the analysis. Of these tacrolimus concentrations, 11,670 were pre-dose concentrations. A total of 208 AUCs was determined in 185 patients with 1757 samples. Table 1 shows the baseline characteristics of the included patients.

3.2 Pharmacokinetic Modeling

Table 2 shows the results of the base model, final model, bootstrap analysis, and starting dose algorithm. The NONMEM control stream is included in Supplementary Data S3.

3.2.1 Base Model

A two-compartment model with first-order absorption best fitted the data. Residual variability was modeled using an error model for the different combinations of transplant center and method of tacrolimus measurement (a total of seven combinations) with log-transformed data. Residual errors were combined where possible based on analytical method and fit of the model. Typical values of *K_a*, CL, *t_{lag}*, V1, and *Q* were estimated. V2 was fixed on the value that was estimated using the data of patients with at least one

more densely sampled curve available. IIV on CL/F , $V1/F$, and Q/F was incorporated in the model. Covariance in PK parameters was incorporated in the model using an omega block, as this improved model fit (covariance < 60%; $\Delta OFV = -146.75$).

3.2.2 Covariate Analysis

In the forward-inclusion process ($\Delta OFV > 3.84$, $p < 0.05$) the following covariates significantly correlated with CL/F and were included in the model: *CYP3A5* genotype ($\Delta OFV = -328.703$), hematocrit ($\Delta OFV = -202.943$), age ($\Delta OFV = -83.073$), serum creatinine ($\Delta OFV = -91.637$), height ($\Delta OFV = -26.015$), and *CYP3A4* genotype ($\Delta OFV = -22.703$; *CYP3A4**22). After the backward-elimination process ($\Delta OFV > 6.63$, $p < 0.01$) all covariates remained in the model (*CYP3A5* genotype, $\Delta OFV = 336.78$; hematocrit, $\Delta OFV = 239.282$; serum creatinine, $\Delta OFV = 85.321$; age, $\Delta OFV = 61.08$; height, $\Delta OFV = -38.15$; and *CYP3A4* genotype, $\Delta OFV = 22.702$). These covariates explained 35% of the variability in CL/F . Time after transplantation did not result in a significant improvement of the model.

While correcting for center, no difference in bioavailability (F) was observed between the different tacrolimus formulations, (Prograft® versus Adport®; $\theta = 1.0$); therefore, the tacrolimus formulation was not included as covariate in the final model.

The effect of covariates on CL in the final model is described in the following equation:

$$CL/F = 20.7 \times \left[(1.0 \text{ if } CYP3A5 * 3 / * 3) \text{ or } (1.64 \text{ if } CYP3A5 * 1 / * 3) \text{ or } (1.93 \text{ if } CYP3A5 * 1 / * 1) \right] \times \left[(1.0 \text{ if } CYP3A4 * 1) \text{ or } (0.836 \text{ if } CYP3A4 * 22 \text{ carrier}) \right] \times \left(\frac{\text{Hematocrit}}{0.33} \right)^{-0.51} \times \left(\frac{\text{Age}}{57.5} \right)^{-0.309} \times \left(\frac{\text{Creatinine}}{147} \right)^{-0.0905} \times \left(\frac{\text{Height}}{170} \right)^{1.17}$$

3.2.3 Model Evaluation

Standard goodness-of-fit plots (Fig. 1) showed good agreement between the majority of predicted and observed tacrolimus concentrations, and a minimal underestimation of some tacrolimus concentrations. The pcVPC of the final model showed good predictive performance over the time after dose (Fig. 2), with a slight underprediction of peak concentrations. Other pcVPCs showed good predictive performance for each categorical covariate included in the final model, and over the ranges of each numeric covariate included in the model (Supplementary Figs. S1–S6). When stratifying the pcVPCs for the different centers, small deviations were observed between the centers (Supplementary Fig. S7). To evaluate whether the high number of pre-dose concentrations affected model performance, a VPC was computed on the basis of the full model and rich data only (Supplementary

Fig. S8). This VPC showed a slight underprediction of peak concentrations, which was similar to the VPC computed on the basis of the full dataset. The predicted variability in this VPC is larger than the observed variability. This can be explained by the fact that the model (predicted variability) was developed from the full dataset, whereas the data in this figure is from a subset with AUC data only (observed variability). The variability in this subset is smaller as it includes a smaller number of patients and the data is collected in a strictly monitored setting. As in clinical practice pre-dose concentrations are used to monitor tacrolimus exposure, the full dataset better reflects the real patient population, and we expect in clinical practice more variability than in this figure.

3.3 Simulations

To evaluate covariate effects, whole-blood concentrations for an average patient, were simulated ($n = 1000$) for different values of the covariates that were included in the final model, while keeping the other covariates similar to the population median (Fig. 3).

The simulations showed a higher tacrolimus dose requirement for patients with the *CYP3A5**1/*3 or *1/*1 genotype compared with patients with the *CYP3A5**3/*3 genotype, and a lower tacrolimus dose requirement for carriers of the *CYP3A4**22 allele compared with non-carriers. Moreover, with increasing age, hematocrit, and serum creatinine, the tacrolimus dose requirement decreased. With increasing height, the tacrolimus dose requirement increased.

3.4 Starting Dose Model

A dosing algorithm to predict the tacrolimus starting dose of adult kidney transplant recipients, was developed on the basis of the final model. Time after transplantation did not improve the population pharmacokinetic model, and therefore, all tacrolimus concentrations were used to develop the starting dose algorithm. The covariates that change substantially after transplantation (hematocrit and serum creatinine) were not included in the starting dose algorithm, as the values prior to transplantation cannot be used as predictors for the tacrolimus pharmacokinetics in the post-transplant period. The pcVPC of the starting dose model shows a good fit of the model predictions over the observations (Fig. 4).

To calculate the starting dose a dosing algorithm was developed. The tacrolimus dose can be calculated by the following equation: dose = $CL/F \times AUC$. The AUC_{0-12h}

Table 1 Baseline characteristics

Recipient characteristics	Rotterdam (<i>n</i> = 547)	Leiden (<i>n</i> = 100)	Barcelona (<i>n</i> = 444)	Brussels (<i>n</i> = 89)	Total (<i>n</i> = 1180)
Gender					
Female	222 (40.6%)	44 (44.0%)	147 (33.1%)	30 (33.7%)	443 (37.5%)
Male	325 (59.4%)	56 (56.0%)	289 (65.1%)	59 (66.3%)	729 (61.8%)
Unknown	0	0	8 (1.8%)	0	8 (0.7%)
Age (years)	58.8 (49.1–65.7)	54.0 (40.0–62.0)	54.5 (44.0–65.2)	52.0 (39.0–61.0)	57.0 (45.0–65.0)
Unknown (<i>n</i>)	40	0	0	0	40
Bodyweight (kg)	79.5 (70.0–92.1)	75.0 (70.0–83.3)	70.5 (60.1–81.0)	72.8 (57.8–81.7)	75.6 (65.0–86.0)
Unknown (<i>n</i>)	0	0	2	3	5
Height (cm)	173 (165–180)	172 (165–180)	166 (160–173)	171 (160–175)	170 (162–177)
Unknown (<i>n</i>)	168	0	2	1	171
BMI (kg/m ²)	26.3 (23.8–30.4)	25.5 (22.7–28.7)	25.5 (22.3–28.5)	25.1 (21.4–27.2)	25.8 (23.0–29.0)
Unknown (<i>n</i>)	168	0	2	4	174
BSA (m ²)	1.96 (1.79–2.13)	1.91 (1.79–2.03)	1.81 (1.64–1.97)	1.86 (1.63–1.98)	1.88 (1.70–2.03)
Unknown (<i>n</i>)	168	0	3	4	175
IBW (kg)	66.8 (57.8–72.8)	64.8 (57.6–72.75)	61.6 (55.0–66.8)	65.0 (54.8–69.0)	63.9 (56.8–69.8)
Unknown (<i>n</i>)	168	0	11	1	180
LBW (kg)	57.8 (48.7–65.0)	55.7 (48.8–62.6)	52.5 (45.4–59.6)	55.8 (45.4–61.2)	54.9 (47.2–62.0)
Unknown (<i>n</i>)	168	0	11	4	183
Fat mass (kg)	26.6 (21.7–32.6)	26.3 (20.2–31.2)	24.8 (20.6–29.4)	23.4 (20.8–27.1)	25.2 (21.2–30.8)
Unknown (<i>n</i>)	168	0	11	4	183
<i>CYP3A4</i> genotype					
*1	462 (84.5%)	91 (91%)	400 (90.1%)	82 (92.1%)	1035 (87.7%)
*22	56 (10.2%)	9 (9%)	40 (9.0%)	7 (7.9%)	112 (9.5%)
Unknown	29 (5.3%)	0	4 (0.9%)	0	33 (2.8%)
<i>CYP3A5</i> genotype					
*3/*3	379 (69.3%)	76 (76%)	363 (81.8%)	66 (74.2%)	884 (74.9%)
*3/*1	123 (22.5%)	17 (17%)	67 (15.1%)	17 (19.1%)	224 (19.0%)
*1/*1	26 (4.8%)	4 (4%)	3 (0.6%)	6 (6.7%)	39 (3.3%)
Other	0	3 (3%)	0	0	3 (0.3%)
Unknown	19 (3.5%)	0	11 (2.5%)	0	30 (2.5%)
POR genotype					
*1/*1	146 (26.7%)	0	0	0	146 (12.4%)
*1/*28	121 (22.1%)	0	0	0	121 (10.3%)
*28/*28	25 (4.6%)	0	0	0	25 (2.1%)
Unknown	255 (46.6%)	100 (100%)	444 (100%)	89 (100%)	888 (75.3%)
<i>ABCB1</i> c.1199G>A					
G/G	0	0	0	83 (93.4%)	83 (7.0%)
G/A	0	0	0	6 (6.7%)	6 (0.5%)
Unknown	547 (100%)	100 (100%)	444 (100%)	0	1091 (92.5%)
<i>ABCB1</i> c.2677G>T/A					
G/G	0	0	0	30 (33.7%)	30 (2.5%)
G/A, G/T, T/T	0	0	0	56 (62.9%)	56 (5.5%)
T/A	0	0	0	3 (3.4%)	3 (0.3%)
Unknown	547 (100%)	100 (100%)	444 (100%)	0	1091 (92.5%)
<i>ABCB1</i> c.3435C>T					
C/C	0	0	95 (21.4%)	25 (28.1%)	120 (10.2%)
C/T, T/T	0	0	198 (44.6%)	64 (71.9%)	162 (22.2%)
Unknown	547 (100%)	100 (100%)	151 (34.0%)	0	798 (67.6%)
Number of kidney transplantations					
1st	489 (89.4%)	–	356 (80.2%)	14 (15.7%)	859 (72.8%)

Table 1 (continued)

Recipient characteristics	Rotterdam (<i>n</i> = 547)	Leiden (<i>n</i> = 100)	Barcelona (<i>n</i> = 444)	Brussels (<i>n</i> = 89)	Total (<i>n</i> = 1180)
2nd	44 (8.0%)	–	68 (15.3%)	1 (1.1%)	113 (9.6%)
3rd or more	14 (2.6%)	–	11 (2.5%)	–	25 (2.1%)
Unknown	0	100 (100%)	9 (2.0%)	74 (83.1%)	183 (15.5%)
Donor type					
Living	405 (74.0%)	100 (100%)	22 (5.0%)	9 (10.1%)	536 (45.4%)
Deceased	142 (26.0%)	0	121 (27.3%)	79 (88.8%)	342 (29.0%)
Unknown	0	0	301 (67.8%)	1 (1.1%)	302 (25.6%)
HLA mismatch					
≤ 3	302 (55.2%)	–	193 (43.5%)	32 (36.0%)	527 (44.6%)
> 4	225 (41.1%)	–	238 (53.6%)	1 (1.1%)	464 (39.3%)
Unknown	20 (3.7%)	100 (100%)	13 (2.9%)	56 (62.9%)	189 (16.0%)
Creatinine ^a	138 (111–183)	124 (102–191)	142 (112–189)	168 (115.0–353.7)	140 (110–191)
Unknown (<i>n</i>)	0	0	21	1	22
GFR ^a	43 (31–55)	51 (31–67)	44 (31–54)	28 (28–56)	44 (31–56)
Unknown (<i>n</i>)	0	0	305	85	390
Hematocrit ^a	0.330 (0.300–0.360)	0.339 (0.305–0.371)	0.350 (0.304–0.399)	0.320 (0.290–0.375)	0.332 (0.300–0.370)
Unknown (<i>n</i>)	0	0	2	1	3
Albumin ^a	42 (37–45)	–	43 (39–46)	39 (36–43)	42 (37–45)
Unknown (<i>n</i>)	0	100	304	52	456
ASAT ^a	20 (15–30)	–	18 (12–19)	18 (14–25)	20 (15–29)
Unknown (<i>n</i>)	4	100	436	1	541
ALAT ^a	–	–	17 (13–25)	16 (12–24)	17 (13–25)
Unknown (<i>n</i>)	547	100	3	1	651
Bilirubin ^a	6 (4–8)	–	6 (5–9)	12 (10–15)	6 (4–10)
Unknown (<i>n</i>)	7	100	435	1	543
GGT ^a	–	–	26 (19–41)	27 (18–41)	27 (18–41)
Unknown (<i>n</i>)	547	100	325	1	973
Total protein ^a	65 (60–69)	–	–	–	65 (60–69)
Unknown (<i>n</i>)	8	100	444	89	641
CRP ^a	7 (2.3–19)	–	–	1.3 (0.2–3.5)	5.3 (2–16)
Unknown (<i>n</i>)	3	100	444	2	549
Number of samples ^a	8151	856	3053	1367	13427
Number of C0 samples	8151	0	2514	1005	11670
Number of AUC samples	0	856	539	362	1757
Number of total AUCs	0	100	54	54	208
Number of patients with an AUC	0	100	31	54	185
Number of samples per patient	15 (12–18)	9 (7–10)	6 (5–6)	16 (12–18)	10 (6–16)
Time-range over which samples were collected (days)	90 (80–206)	12 (1–32)	353 (173–353)	12.5 (12–13)	94 (54–353)
Time after transplantation (days)	35 (11–81)	7 (6–18)	91 (16–183)	15 (9–20)	31 (10–91)
Dose (mg)	5 (3–7)	5 (3–5)	2.5 (2–3.8)	5 (4–7)	4 (2.5–6.5)
Tacrolimus concentration (ng/mL)	8.9 (6.9–11.8)	14.4 (10.2–20.7)	7.7 (5.9–10.5)	12.7 (9.9–16.9)	9.2 (6.9–12.6)
Tacrolimus concentrations pre-dose samples (ng/mL)	8.9 (6.9–11.8)	–	7.3 (5.6–9.6)	12.2 (9.8–15.6)	8.8 (6.7–11.8)

Continuous variables are described as median (IQR). Categorical variables as number of cases (%)

AUC, area under the concentration time curve; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; CRP, C-reactive protein; BMI, body mass index; BSA, body surface area; CYP, cytochrome P450; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; IBW, ideal body weight; LBW, lean body weight

^aCalculated over the whole follow-up period

Table 2 Model parameter estimates

Parameter	Base model	Final model	Bootstrap (710 runs; 95% CI)	Starting dose model
t^{lag} (h)	0.263 (4.6%)	0.375 (5.3%)	0.345 (0.254–0.496)	0.375 (5.7%)
K_a (L/h)	3.41 (11.4%)	6.59 (30%)	6.27 (2.16–11.01)	6.25 (29.6%)
CL/ F (L/h)	22.6 (1.7%)	20.7 (1.6%)	20.6 (20.0–21.4)	19.9 (1.6%)
V_1/F (L)	641 (4.3%)	705 (4.7%)	701.4 (635.6–774.7)	653 (4.9%)
Q/F (L/h)	9.28 (3.9%)	8.54 (4.3%)	8.55 (7.75–9.32)	9.14 (3.8%)
V_2/F (L)	7670 (f)	7670 (f)	7670 (f)	7670 (f)
Covariate effect on CL				
$CYP3A5^{*1/*3}$	–	1.64 (3%)	1.64 (1.55–1.73)	1.64 (2.9%)
$CYP3A5^{*1/*1}$	–	1.93 (5%)	1.94 (1.74–2.12)	1.9 (4.7%)
$CYP3A4^{*22}$	–	0.836 (4%)	0.838 (0.77–0.90)	0.842 (3.9%)
Hematocrit (L/L)	–	–0.51 (10%)	–0.51 (–0.61 to –0.41)	–
Creatinine ($\mu\text{mol/L}$)	–	–0.0905 (21%)	–0.0915 (–0.1285 to –0.0525)	–
Age (years)	–	–0.309 (13%)	–0.308 (–0.385 to –0.323)	–0.332 (12.1%)
Height (m^2)	–	1.17 (18%)	1.19 (0.75–1.60)	0.97 (22.9%)
IIV (%)				
CL/ F	51.3% (2.5%)	41.4% (3.1%)	41.0%	41.8%
V_1/F	80.3% (3.9%)	80.5% (3.7%)	79.7%	77.8%
Q/F	81.1% (5.5%)	82.8% (6%)	83.5%	81%
Correlation matrix				
CL/ $F \times V_1$	58.5%	58%	43.2%	58.4%
CL/ $F \times Q$	15.8%	6.5%	14.4%	7.9%
$V_1 \times Q$	16.6%	12.5%	27.3%	14%
Residual variability ^a				
Rotterdam—immunoassays	0.245 (3.3%)	0.242 (3.4%)	0.242 (0.226–0.258)	0.245 (3.3%)
Rotterdam and Leiden—LC-MS/MS	0.284 (2.3%)	0.281 (2.3%)	0.281 (0.268–0.293)	0.284 (2.3%)
Barcelona—immunoassay	0.381 (4.2%)	0.376 (4.3%)	0.374 (0.344–0.407)	0.381 (4.3%)
Barcelona—LC-MS/MS	0.417 (6.3%)	0.419 (5.9%)	0.418 (0.371–0.467)	0.419 (6.2%)
Brussels—immunoassay	0.322 (4.3%)	0.313 (4%)	0.312 (0.288–0.338)	0.323 (4.3%)

CL, clearance; CYP, cytochrome P450; F , bioavailability of oral tacrolimus; IIV, inter-individual variability; IOV, inter-occasion variability; K_a , absorption rate constant; LC-MS/MS, liquid chromatography–tandem mass spectrometry; Q , inter-compartmental clearance of tacrolimus; t^{lag} , lag time; V_1 , central compartment for tacrolimus; V_2 , peripheral compartment for tacrolimus

^aCombination of tacrolimus measurement method (immunoassay versus LC-MS/MS) and center (Erasmus MC Rotterdam, the Netherlands versus LUMC Leiden, the Netherlands versus Bellvitge Hospital Barcelona, Spain versus St. Luc Hospital Brussels, Belgium)

corresponding with the tacrolimus target pre-dose concentration of 10 ng/mL was determined on the basis of the data included in this study and the population pharmacokinetic model. Based on a twice-daily tacrolimus dose, for this population, a tacrolimus target concentration of 10 ng/mL corresponds with an AUC of 234 ng h/mL.

The tacrolimus starting dose can be calculated by the following equation:

dosing were simulated ($n = 1000$; Supplementary Fig. S9). According to this simulation, the range of tacrolimus concentrations is smaller following model-based dosing compared with bodyweight-based dosing. Following bodyweight-based dosing, 28.4% of the patients would have a tacrolimus concentration within the 7.5–12.5 ng/mL concentration range, whereas 33.2% of the patients would have a tacrolimus concentration within this range following model-

$$\text{Dose (mg)} = 234 \times 20.7 \times \left[(1.0 \text{ if } CYP3A5^{*3/*3}) \text{ or } (1.64 \text{ if } CYP3A5^{*1/*3}) \text{ or } (1.9 \text{ if } CYP3A5^{*1/*1}) \right] \\ \times [(1.0 \text{ if } CYP3A4^{*1}) \text{ or } (0.842 \text{ if } CYP3A4^{*22})] \times \left(\frac{\text{Age}}{57.5} \right)^{-0.332} \times \left(\frac{\text{Height}}{170} \right)^{0.97} / 1000$$

To evaluate model performance, tacrolimus concentrations following bodyweight-based dosing and model-based

based dosing.

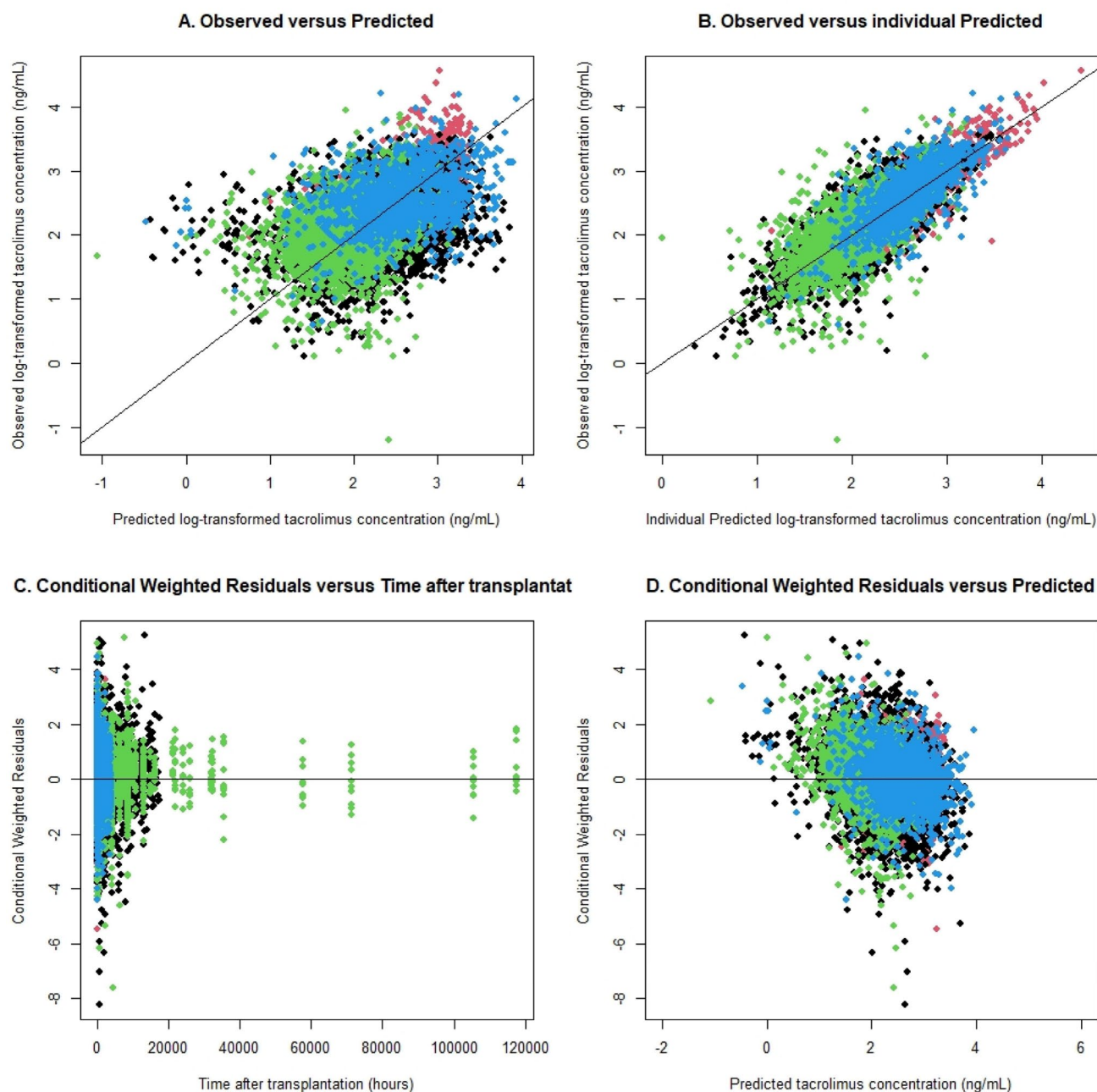


Fig. 1 Goodness of fit plots of the final model stratified by center: **A** observed tacrolimus concentrations versus predicted tacrolimus concentrations; **B** observed tacrolimus concentrations versus the individual predicted tacrolimus concentrations; **C** the conditional weighted

residuals over the time after transplantation; and **D** the conditional weighted residuals over the predicted tacrolimus concentrations. All tacrolimus concentrations are log-transformed (ln). Black = Rotterdam, red = Leiden, green = Barcelona, and blue = Brussels

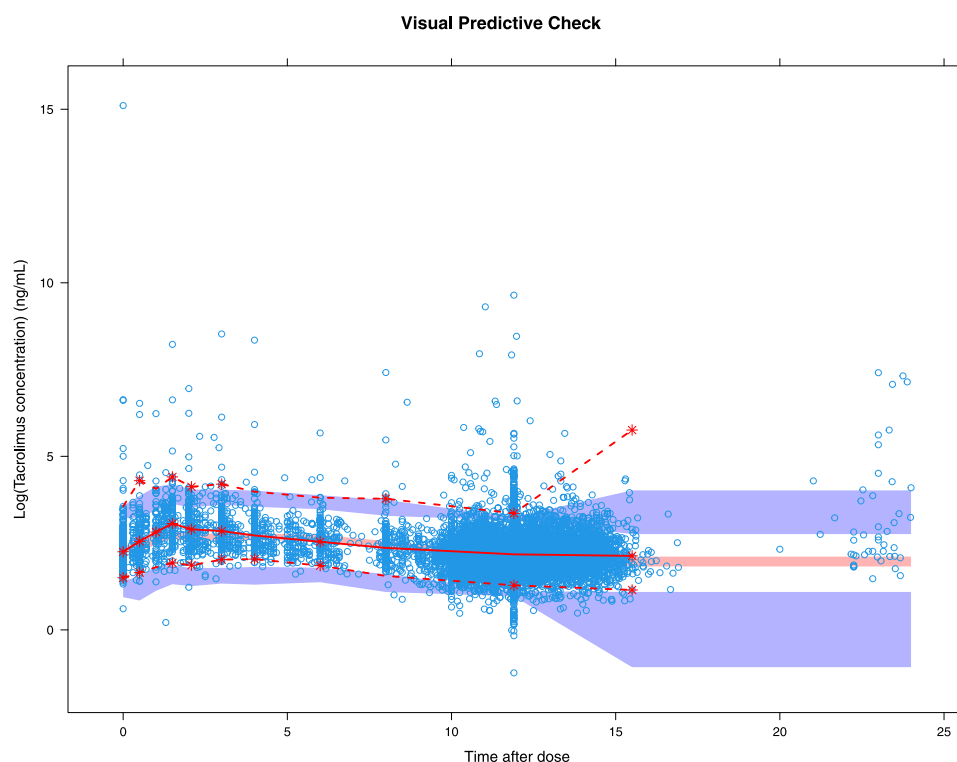
4 Discussion

In this large, international, multicenter study, a popPK model for tacrolimus was developed using data of 1180 living and deceased donor kidney transplant recipients. Factors that were significantly associated with tacrolimus pharmacokinetics and were included in the final model were: age (in years), serum creatinine (in $\mu\text{mol/L}$), *CYP3A4* (*22 allele

carriers versus non-carriers) and *CYP3A5* genotype (*3/*3 versus *1/*3 versus *1/*1), height (in cm), and hematocrit. With these covariates, the popPK model explained 35% of the inter-individual variability in tacrolimus CL/F .

In previous pharmacokinetic studies, various covariates were found to be associated with tacrolimus, including age, albumin, ASAT, bodyweight, BSA, *CYP3A4* and *CYP3A5*

Fig. 2 Prediction-corrected visual predictive check of the full model showing how well the mean of the observed tacrolimus concentrations (red line) over time falls within the predicted mean tacrolimus concentration (red area; 95%-confidence interval), and how well the observed variability (red dotted line) falls within the predicted variability (blue area; 95%-confidence interval). All tacrolimus concentrations are log-transformed (ln)



genotype, serum creatinine, hematocrit, LBW, post-operative day, phase angle, and sex [23].

The present study confirms the well-known relationship between a patient's *CYP3A4* and *CYP3A5* genotype and their tacrolimus dose requirement [5, 23, 35]. In contrast to previous models, the present model can better differentiate the effect on tacrolimus CL/F for both homozygous and heterozygous *CYP3A5**1 allele carriers, which allows a more tailored dosing approach. *CYP3A5* expressers with the *CYP3A5**1/*3 genotype required a 1.7-times higher tacrolimus dose, and patients with the *CYP3A5**1/*1 genotype required a 2-times higher tacrolimus dose, than *CYP3A5* non-expressers (having the *CYP3A5**3/*3 genotype). Carriers of the *CYP3A4**22 allele require 0.8-times the tacrolimus dose compared with non-carriers.

Lower age, serum creatinine, and hematocrit were associated with higher tacrolimus CL/F [16]. The association between age and tacrolimus CL/F ($\theta = -0.309$) is in line with previous studies ($\theta = -0.43$ to -0.50 , or dose $\times 1.24$, if recipient age is 18–34 years, or dose -0.205 , if recipient is age ≥ 65 years) [5, 16, 23, 36, 37]. This association may be explained by age-dependent drug metabolism, but changes in body composition may also have a role in the altered pharmacokinetics [36, 38, 39]. Although multiple studies found an association between serum creatinine concentrations and tacrolimus CL/F [16, 40, 41], the explanation for the relationship between serum creatinine and tacrolimus CL/F remains unclear. Less than 1% of tacrolimus

undergoes renal clearance, and therefore, serum creatinine concentrations are not likely to be directly correlated with renal clearance of tacrolimus. A possible explanation might be that creatinine is a surrogate for a patient's health status, which in turn affects a patient's body composition, and consequently tacrolimus pharmacokinetics [36]. The negative relationship between hematocrit and tacrolimus CL/F can be explained by the fact that tacrolimus is highly bound to erythrocytes. With lower hematocrit values, and thus lower erythrocyte counts, the unbound tacrolimus fraction in blood is larger. As this unbound fraction is available for clearance, this can explain the relationship between hematocrit and clearance.

The relationship between body composition parameters and tacrolimus pharmacokinetics differs greatly between studies, and it is yet unclear which parameter best predicts an individual's dose requirement. In previous models fat mass, LBW, weight, and BSA have been associated with both CL/F and V1/F [16, 23, 42, 43], whereas in the current model, height was best correlated with tacrolimus CL/F. A previous study showed that obese patients are more likely to be overdosed, suggesting bodyweight is not the ideal body composition measure to guide tacrolimus dosing [1]. As height relates to the ideal bodyweight, this might be a more appropriate predictor for a patient's volume of distribution and fraction of tacrolimus available for clearance. In a previous study, in which we measured the body composition of kidney transplant recipients using bio-impedance

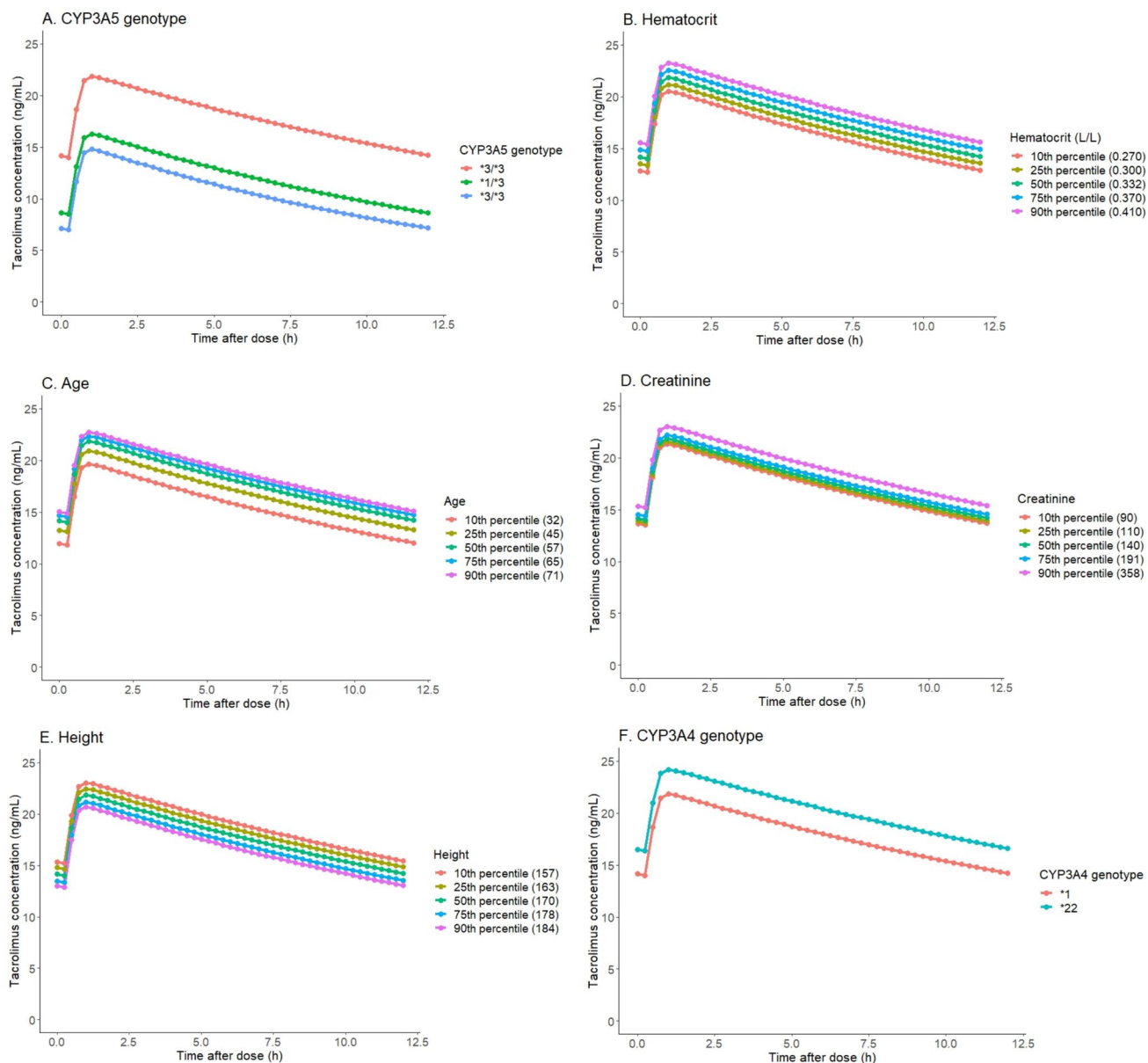


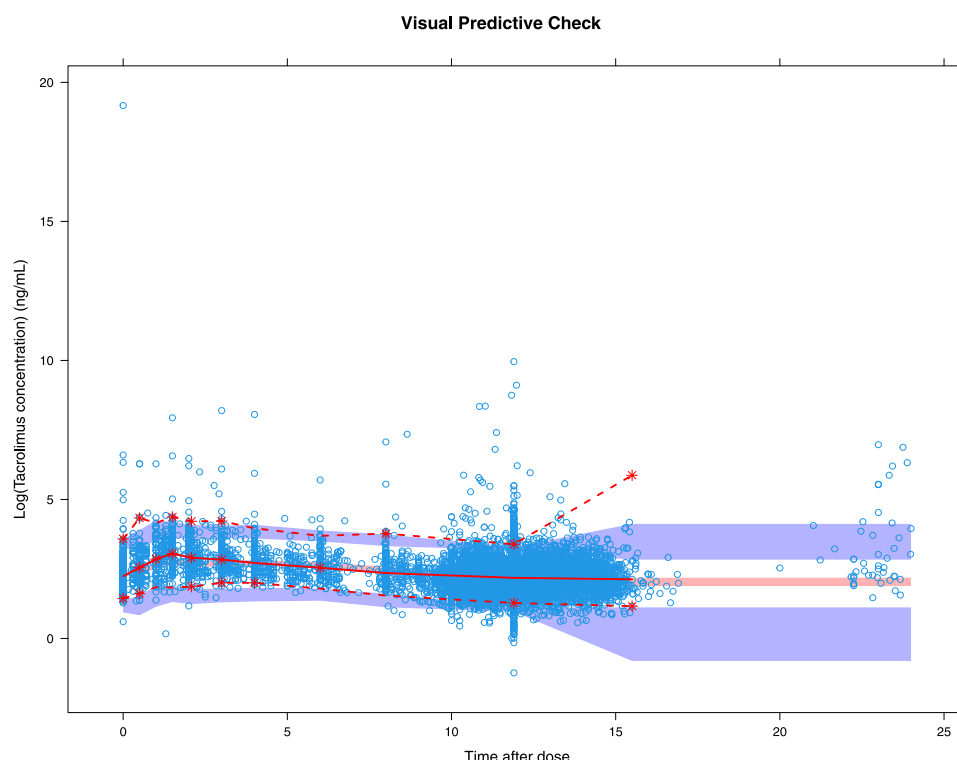
Fig. 3 Simulated tacrolimus whole-blood concentrations for the covariates included in the final model: **A** tacrolimus concentrations simulated for the *CYP3A5**3/*3, *3/*1, and *1/*1 genotype; **B** tacrolimus concentrations simulated for different values of hematocrit; **C** tacrolimus concentrations simulated for different values of age; **D**

tacrolimus concentrations simulated for different values of creatinine; **E** tacrolimus concentrations simulated for different values of height; and **F** simulated tacrolimus concentrations for the *CYP3A4**1 and *22 genotype

spectroscopy (instead of estimating the body composition parameters based on bodyweight and height), we found that the phase angle correlates best with tacrolimus pharmacokinetics [36]. The phase angle relates to body cell mass, membrane integrity, and hydration status and may therefore better correlate with a patient's volume of distribution, clearance, and consequently, a patient's dose requirement. However, this measure is not routinely measured in clinical practice and therefore not always available for dose prediction.

As compared with the population pharmacokinetic model developed by Andrews et al. [16], we did not find new covariates associated with the pharmacokinetics of tacrolimus despite the large dataset. Both models include the *CYP3A4* and *CYP3A5* genotypes, hematocrit, serum creatinine, and age as covariate factors associated with tacrolimus pharmacokinetics. However, an advantage of the present model is that it can differentiate between homozygous and heterozygous *CYP3A5**1 allele carriers, which allows for a more tailored tacrolimus dosing approach. Another important

Fig. 4 Prediction-corrected visual predictive check of the starting dose model showing how well the mean of the observed tacrolimus concentrations (red line) over time falls within the predicted mean tacrolimus concentration (red area; 95%-confidence interval), and how well the observed variability (red dotted line) falls within the predicted variability (blue area; 95%-confidence interval). All tacrolimus concentrations are log-transformed (ln)



advantage of the present model is that it was developed in kidney transplant recipients who received a kidney from either a living or a deceased donor. This makes model-based tacrolimus dosing available for a much larger group of patients, as in many centers the proportion of deceased donor kidney transplantations is > 50% of all transplantations. Also, the inclusion of multiple centers in this dataset reduces the risk of overfitting and increases the generalizability of the model. Moreover, the proportion of explained inter-individual variability on CL/F is larger in the present study compared with the study of Andrews et al. (35.0% versus 30.4% for the full model, and 33.5% versus 27.5% for the starting dose model). The total inter-individual variability for both the base model and the final model was larger in the present study, compared with the models of Andrews et al. (51.3% versus 46.3% for the base model, and 41.4% versus 38.6% for the final model). This might be explained by the fact that more patients from different populations were included in the present analysis. In conclusion, the present model has several advantages over the older model. However, before implementing a model in clinical practice we believe a model should be tested prospectively.

The pcVPCs of the full model show a slight underprediction of peak concentrations. This may be caused by the relatively large number of pre-dose concentrations. To minimize this effect, it was evaluated whether estimating K_a , $V1$, and $V2$, which are parameters that are best estimated with dense sampling, using only data from patients with at least

one available concentration-versus-time curve, improved the model fit. Moreover, the pcVPCs stratified for the different centers showed a deviating fit for the data from Barcelona. These differences may be attributed to differences in clinical practice (such as differences in dosing regimens, target concentrations, or analysis methods) or, more likely, unknown population characteristics affecting tacrolimus pharmacokinetics (such as body composition, diet, or the gut microbiome).

One of the strengths of this study is the large number of included patients and tacrolimus concentrations (both pre-dose concentrations and samples throughout the dosing interval). This increases the statistical power and, theoretically, makes it possible to detect smaller associations between patient characteristics and tacrolimus pharmacokinetics, as well as provide more precise/reliable estimates. However, in this study we did not find more factors associated with the pharmacokinetics of tacrolimus than that were already known from previous models. An explanation could be that other covariates that are thought to be associated with tacrolimus pharmacokinetics [for example, the gut microbiome, drug interactions, a patient's body composition [36, 44–46]] were not included in the dataset used in this study, as these were not measured during routine clinical care, could not be reliably extracted from the electronic patient files, or were not included in the previous pharmacokinetic studies on which the present analysis was based. Therefore, it is recommended for future studies in kidney transplant

recipients to consider these covariates and perform appropriate measurements.

Another strength of this study is the inclusion of kidney transplant recipients of both living and deceased donors, whereas in our previous model only kidney transplant recipients from living donors were included. Prior to this, it was not clear whether the type of kidney donor affects tacrolimus pharmacokinetics. As deceased donor kidneys constitute a large part of all kidney transplants, it is important to include these patients in pharmacokinetic studies. Theoretically, tacrolimus CL/F may be different in deceased donor kidney transplant recipients, since they have an increased risk of a lower kidney function, and serum creatinine has been associated with tacrolimus CL/F [16, 40, 41]. In this study, donor type was not significantly associated with tacrolimus CL/F . Moreover, kidney transplant recipients from different transplant centers in Europe were included, which makes it possible to extrapolate the results to other centers. This is important as a dosing algorithm may not fit another population than the one for which it was developed, which may be caused by underlying differences in factors that affect the pharmacokinetics of tacrolimus but are not yet identified and incorporated in the model [47]. Consequently, models should be extensively validated and prospectively tested in a specific population before using the model in clinical practice.

The main limitation of the study is its retrospective and observational design. Some of the data were collected as part of pharmacokinetic studies, whereas some of the data were retrospectively collected from electronic patient files. In the latter, the exact times of the tacrolimus dose ingestions and consequently, the exact time after dose of the tacrolimus concentrations were unknown. Therefore, we assumed that patients followed the instructions of their transplant physicians and that they took their recommended tacrolimus dose at the recommended time. To limit the effect of possible deviations from this recommendation, we checked the data for outliers before and during modeling. If adherence problems or mistakes in tacrolimus dosing were noted in the electronic patient files, the tacrolimus pre-dose concentration was corrected or excluded from the dataset. For the densely sampled curves the dose ingestions and time after dose was registered more strictly. The retrospective design also resulted in missing data. Some data was missing at random, as some factors were not collected as part of specific pharmacokinetic studies. This missingness is therefore related to a specific study population, but not to the outcome. The other missing data can be considered missing completely at random, as not all factors were measured as part of routine clinical practice, and, to the best of our knowledge, no systematic differences exist between participants with missing data and those with complete data. During pharmacokinetic modeling, we used accepted methods to deal with missing data, and covariate estimates were based on available data.

Therefore, we believe the missing data will not introduce bias in the estimates.

5 Conclusions

In this large international multicenter study, a popPK model with its accompanying starting dose algorithm was developed using data of 1180 kidney transplant recipients who received kidneys from both living and deceased donors. Higher age, serum creatinine, and hematocrit, as well as lower height were associated with lower tacrolimus clearance. Tacrolimus clearance was 1.7–2 times higher for *CYP3A5*1* allele carriers as compared with *CYP3A5* non-expressers (**3/*3*), and 0.8 times lower for *CYP3A4*22* carriers as compared with *CYP3A4*1/*1* individuals. Together, these covariates explained 35% of the variability in clearance.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40262-025-01533-0>.

Declarations

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Conflicts of interest D.A. Hesselink has received grant support (paid to his institution) from Astellas Pharma, Chiesi Farmaceutici SpA, and Bristol Myers-Squibb, as well as lecture and consulting fees from Astellas Pharma, Chiesi Farmaceutici SpA, Novartis Pharma, and Vifor Pharma. Laure Elens has received lecture fees (paid to his institution) from Astellas Pharma and Chiesi Farmaceutici SpA. All other authors declared no competing interests for this work. Dirk Jan A.R. Moes is an Editorial Board member of Clinical Pharmacokinetics. Dirk Jan A.R. Moes was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethics approval The Medical Ethical Review Board of the Erasmus MC provided a waiver for the Medical Research Involving Human Subjects Act for this study (Medical Ethical Review Board number MEC-2021-0621). The study was conducted according to the principles of the Declaration of Helsinki (7th revision, October 2013, approved by the 64th WMA General Assembly, Fortaleza, Brazil).

Consent to participate In the Erasmus MC Center, the LUMC, the Bellvitge University Hospital, and St. Luc Hospital Brussels all patients included in this study previously gave written informed consent for the use of their clinical and demographic data for research purposes and the use of body material for genotyping [16, 26, 30–32]. Study practices were performed after approval from the local medical ethical committees. Patients who were not included in previous studies, were asked to participate in an ongoing biobanking program of the division of nephrology and transplantation (MEC-2010-022) during the work-up for transplantation in the Erasmus MC.

Consent for publication All participating centers gave consent for publication of this study.

Availability of data and material Data is available on reasonable request.

Code availability The NONMEM control stream is included in Supplementary Data S3.

Authors' contributions Francke wrote the manuscript, all authors contributed to the writing of the manuscript. Francke, Sassen, Hesselink, and de Winter designed the research. Francke, Sassen, Lloberas, Colom, Elens, Moudio, de Vries, Moes, van Schaik, Hesselink, and de Winter performed the research and collected data or analyzed patient samples. Francke, Sassen, and de Winter analyzed the data.

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