

TACROLIMUS POPULATION PHARMACOKINETIC ANALYSIS WITH PMETRICS IN INFANTS AFTER LIVER TRANSPLANTATION – preliminary data.

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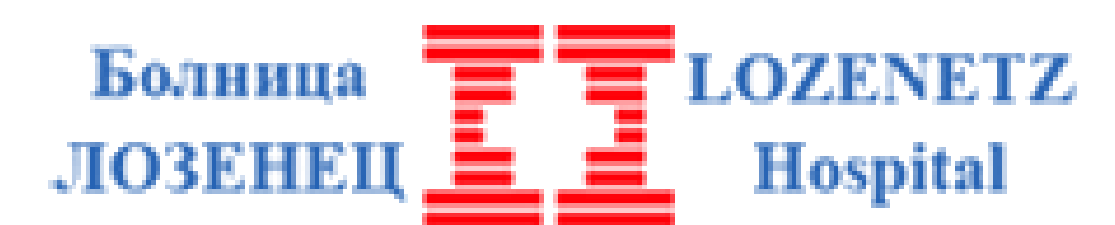


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OBJECTIVES

Immunosuppression after liver-transplantation is of key importance for the survival of both the patient and the transplant. Tacrolimus (TAC) has become the preferred immunosuppressant in liver transplant recipients due to its superior role in improving patient and graft survival in addition to the lower number of acute and steroid-resistant rejections as compared with cyclosporine [1]. Although its extensive inter- and intra-individual pharmacokinetic variability as well as the changing dose requirements with time are well documented, the literature on the distribution patterns of tacrolimus concentrations in liver-transplant infants is still quite scarce for obvious reasons [2]. The primary concern of this research was to conduct a pilot population pharmacokinetic study with tacrolimus in liver-transplant infants in the early post-transplantation period that could later be further developed with data from new patients.

MATERIALS, METHODS AND THEORETICAL CONSIDERATIONS

The study involved 5 infants, median age 8 months (ranging from 2 months to 11 months), who underwent orthotopic liver transplantations between November 2010 and April 2015 at University Hospital Lozenetz, Sofia. All patients received oral tacrolimus (Prograf®) twice daily at 8 am and 8 pm respectively in the intensive care unit (ICU) during the early post-transplantation period (ICU stay ranging from 30.5 to 44.5 days, median 41 days). Therapeutic drug monitoring (TDM) by trough level measurements was used to tailor the doses to fit in the therapeutic range. A total of 65 trough tacrolimus whole-blood concentrations were analyzed using Origin 9.0 and a p-value of ≤ 0.05 was considered as statistically significant. The pharmacokinetic (PK) population analysis was performed using Pmetrics [3]. The concentrations/time kinetics was best described by a one-compartmental absorption model with first order elimination.

It was assumed that the trough TAC concentrations (C_{trough}) were well approximated by the average steady-state plasma drug concentration ($C_{ss,av}$) due to its long elimination half-life and were related to the TAC dose through (CL_{app}): $C_{trough} = \text{Dosing Rate} / (CL_{app})^*$, where Dosing Rate is the total daily dose of TAC (in mg) divided by 24 h. The (CL_{app})^{*} is a regression parameter that predicts the trough drug concentrations. It approximates CL_{app} when $C_{trough} \approx C_{ss,av}$ as in the case of drugs that have a long half-life such as TAC. Using (CL_{app})^{*} as an approximation to CL_{app} has the advantage of giving the regression parameter clinically relevant meaning in terms of magnitude, units and interpretation. However, it should be underlined that the apparent clearance as mentioned above is only an approximation of the actual apparent TAC clearance [5, 6].

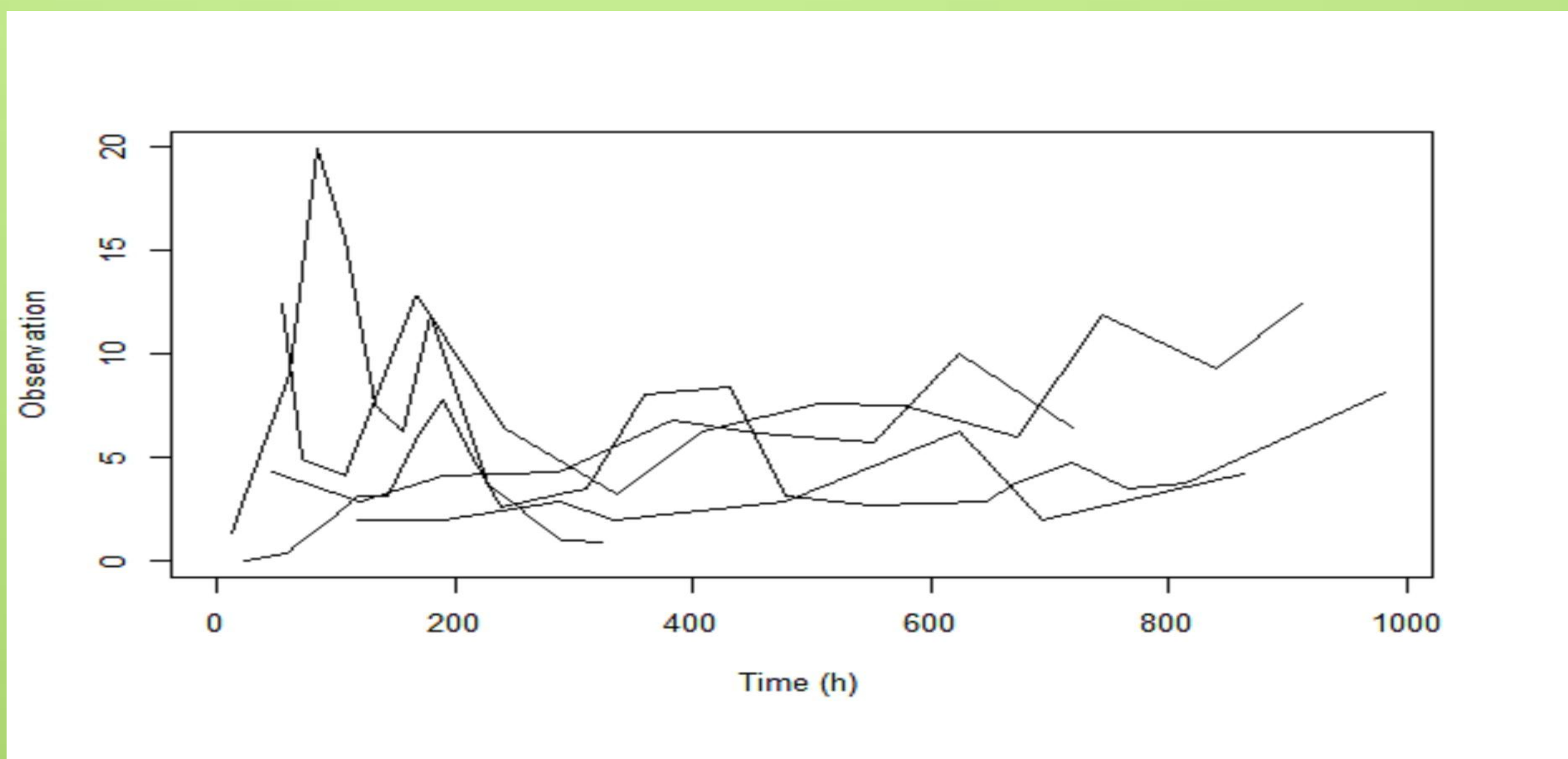


Fig. 1. Time vs Tacrolimus Concentration Plot. The starting dose was usually between 0.15 to 0.30 mg/kg/day and followed hospital protocol to achieve trough tacrolimus concentration of 3 to 8 ng/mL. Concentrations below 3 ng/mL were considered suboptimal and those above 20 ng/mL were regarded as toxic.

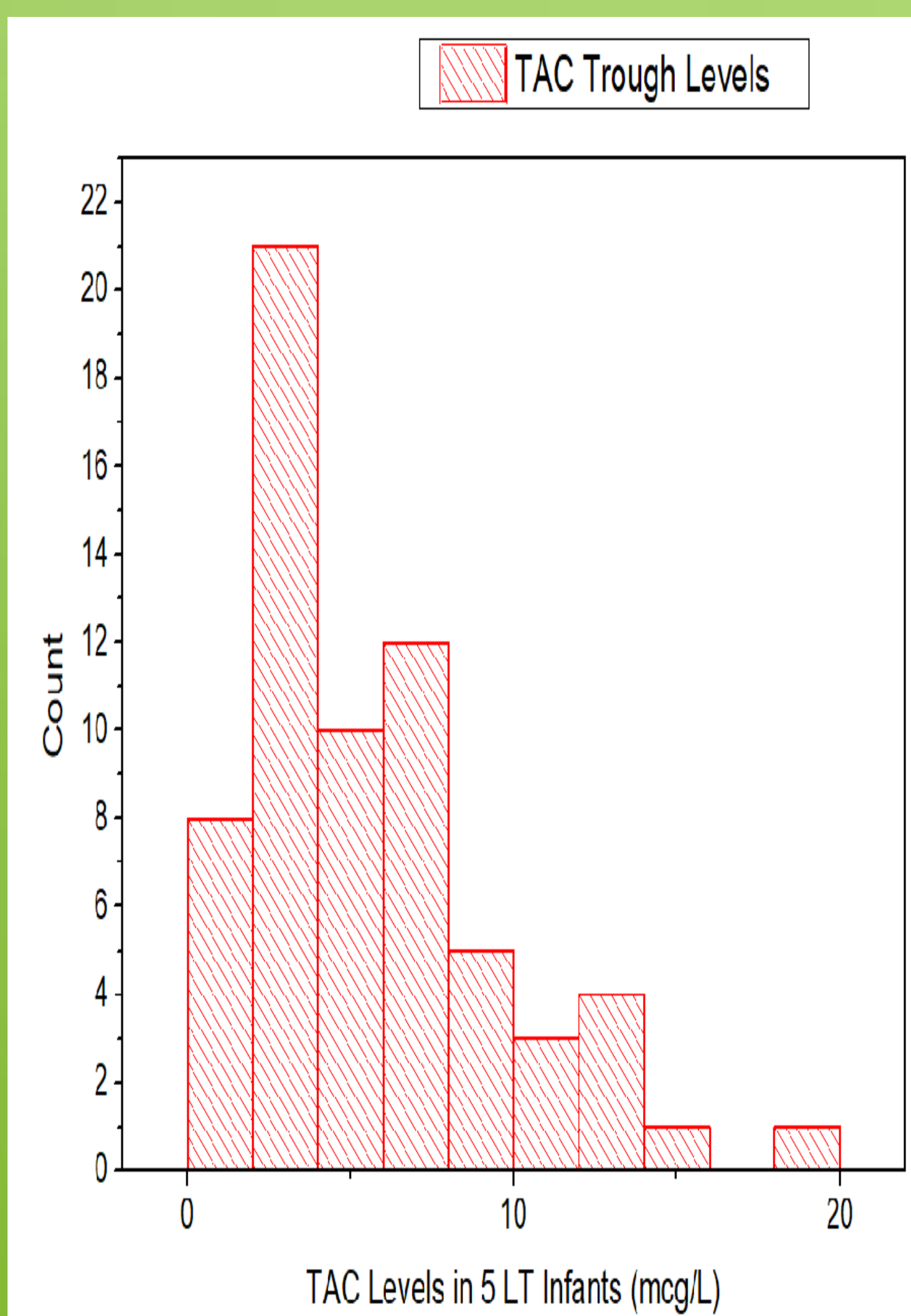


Fig. 2. The statistical distribution pattern of trough tacrolimus concentrations at the end of each dosing interval was characterized with non-Gaussian distribution pattern skewed to the right.

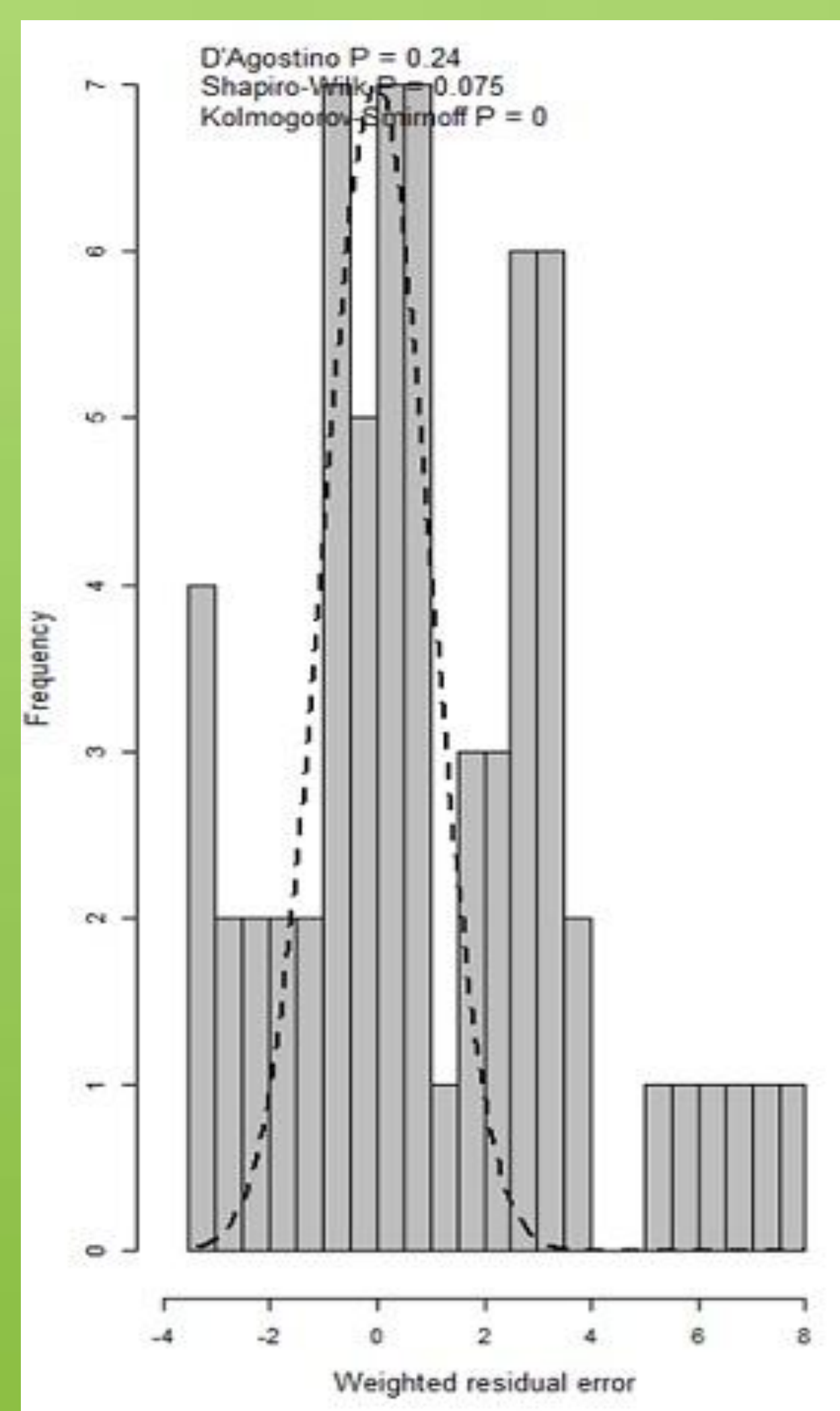


Fig. 3. Internal model validation by the Normalized Prediction Distribution Errors method [4].

RESULTS

The statistical distribution pattern of trough tacrolimus concentrations at the end of each dosing interval was characterized by non-Gaussian distribution pattern skewed to the right (fig. 2). The Q-Q plot confirmed the non-normal distribution pattern and revealed subgroups of trough tacrolimus concentrations deviating from linearity. The estimates of tacrolimus pharmacokinetic model parameters were presented as medians. Median absorption rate (K_a) and elimination rate (K_e) constants were 8.46 h^{-1} and 0.04 h^{-1} respectively. Volume of distribution (VD) was 0.09 L/kg . Lag time (T_{lag}) was 0.41 h . Bioavailability (F_a) was 0.38 . Due to the small number of patients external validation on Pmetrics could not be performed. Internal validation was performed using the normalized prediction distribution errors (NPDE) method of Mentré and Escolano instead [4]. Plotting observed versus individual predicted tacrolimus concentrations yielded a correlation coefficient (r) of 0.81 with a p-value of <0.001 .

TABLE 1. MODEL PK PARAMETER ESTIMATES

Median absorption rate (K_a)	Median elimination rate (K_e)	Volume of distribution (VD)	Lag time (T_{lag})	Bioavailability (F_a)
8.46 h^{-1}	0.04 h^{-1}	0.09 L/kg	0.41 h	0.38

TABLE 2. STRUCTURE PARAMETER ESTIMATES OF THE ERROR MODEL

Pmetrics Output	C_0	C_1	C_2	C_3
First Degree Polynomial	0.01189102	0.14857671		
Second Degree Polynomial	-2.098908e-03	1.511328e-01	9.547898e-05	
Third Degree Polynomial	N/A	N/A	N/A	N/A

The lower limit of quantification (LOQ) of the CMIA was 0.8 ng.mL^{-1} for tacrolimus. It was the lowest concentration of the analytes, measured with a coefficient of variation $\leq 20\%$. To determine the assay error pattern over the entire working range of tacrolimus concentrations, the assay standard deviations were fitted by using the Pmetrics function `makeErrorPoly()` to choose the best set of coefficients that fit the data from the lab. Note: A third degree polynomial could not be fitted to the data.

In Pmetrics, each observation is weighted by $1/\text{error}^2$. Additionally, a Lambda term (L) was used as an additive model so that total noise equalled $\text{SQRT}(\text{SD}^2 + \text{LAMBDA}^2)$, with Lambda to be estimated. We allowed Pmetrics to fit this Lambda term in the error model with a factor value starting point set at 0.1 . Lambda is, as an additive model, to capture process noise related to errors in preparing and administering the doses, errors in recording when the doses were actually given, errors in recording when the serum samples were actually drawn, misspecification of the structural pharmacokinetic model, and any changes in a patient's parameter values that may have taken place during the period of the data collection.

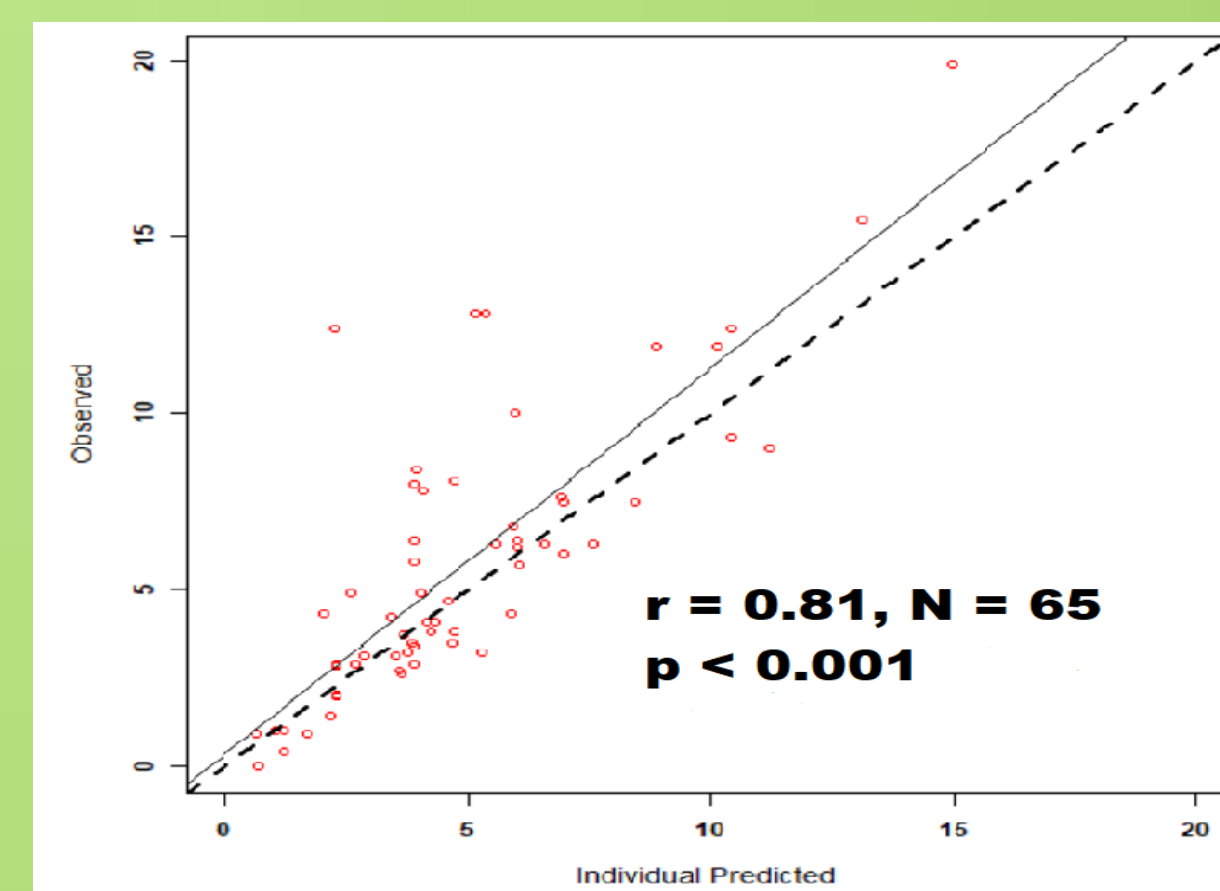


Fig. 4. Plot of Observed vs. Individual Predicted TAC Concentrations in 5 Liver Transplant Infants.

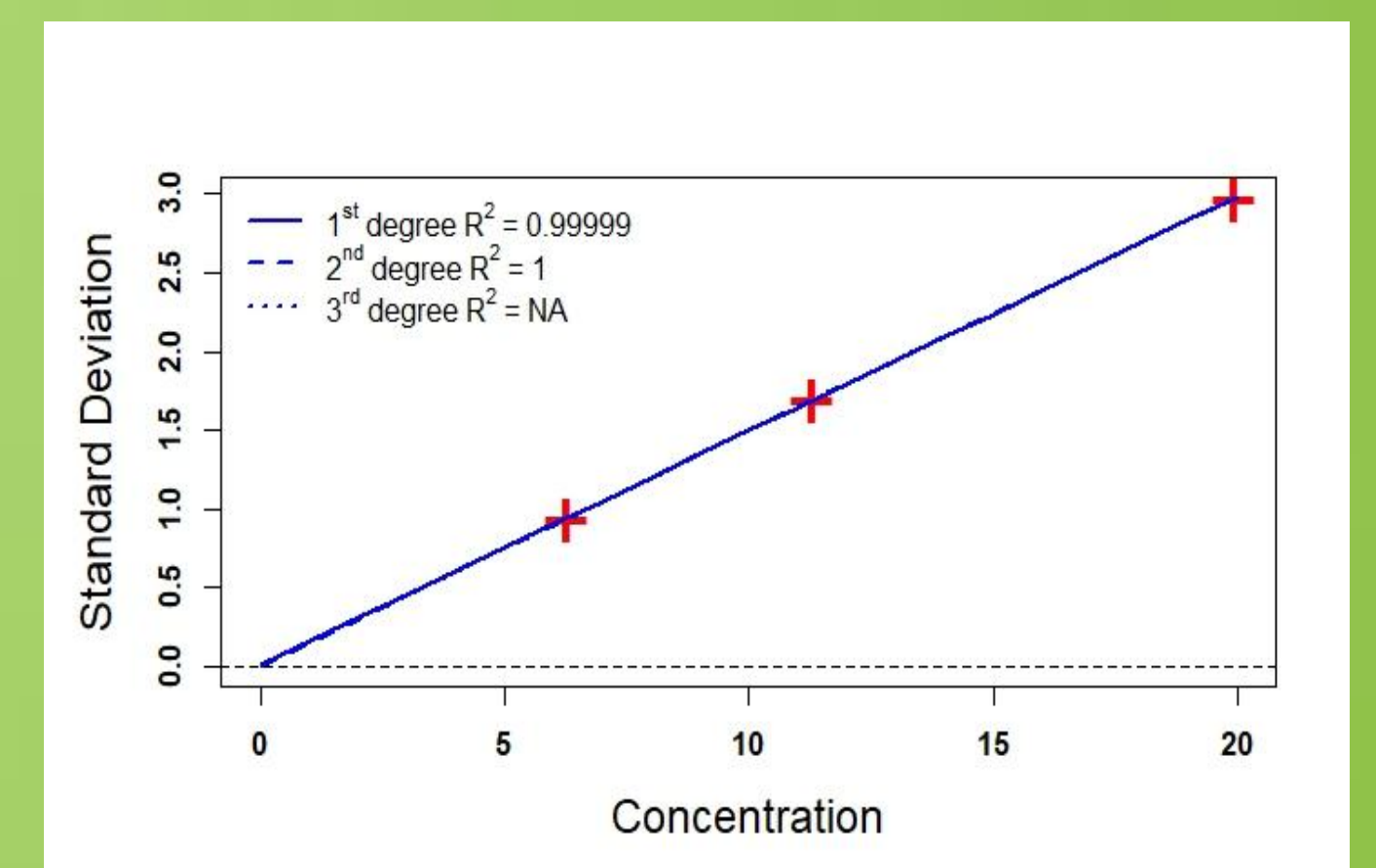


Fig. 5. The first order polynomial was chosen because of the very low estimate of the C_2 .

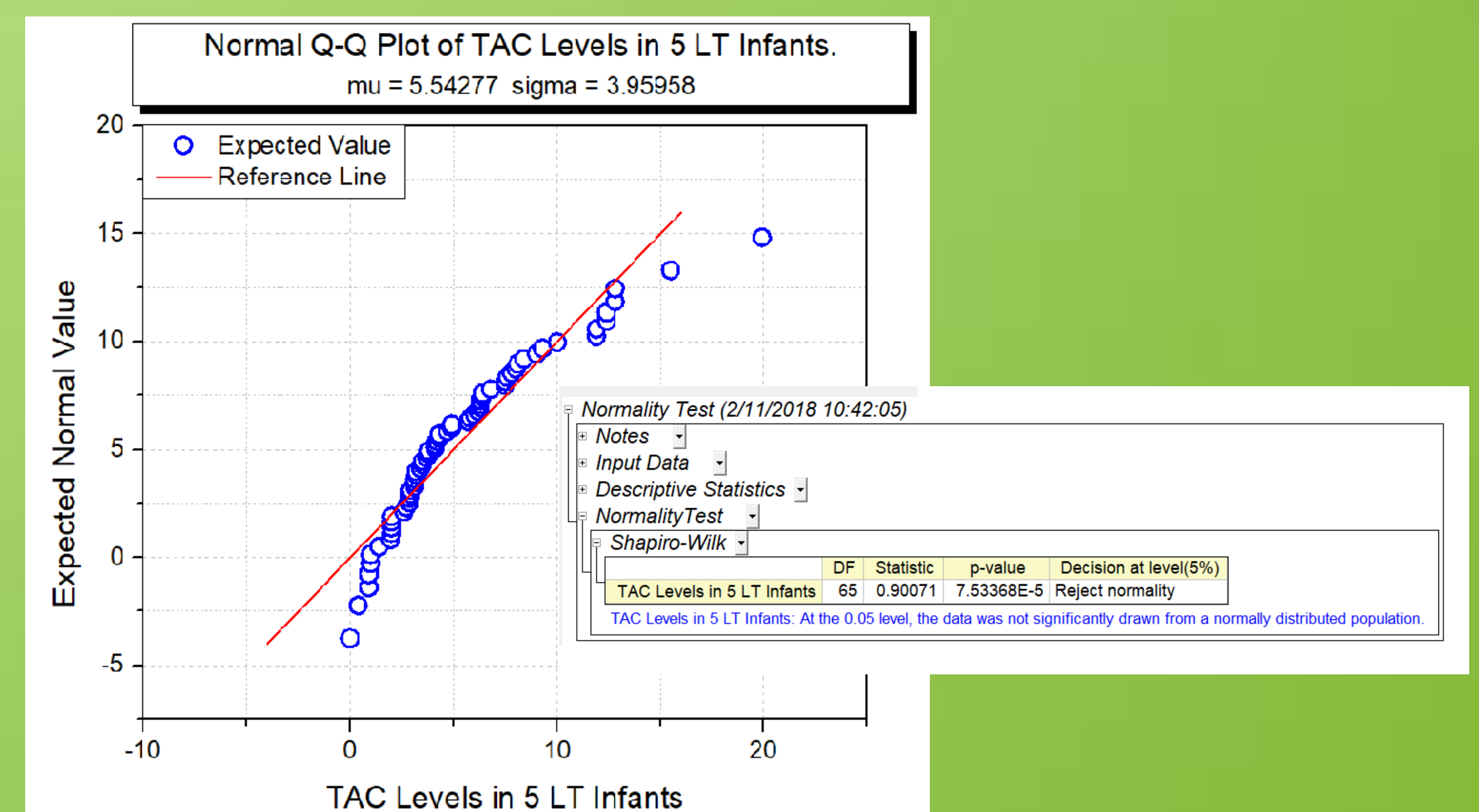


Fig. 6. The Q-Q plot confirmed the non-normal distribution pattern and revealed subgroups of trough tacrolimus concentrations deviating from linearity.

CONCLUSIONS

The search through the current available literature did not yield results that could be compared to the findings presented here. More data from similar patients will enable us to perform external validation in addition to the analyses presented here, which will significantly improve the reliability of the predicted tacrolimus concentrations. The inclusion of additional covariates such as hematocrit, steroid dose and time after transplantation to the model could also potentially improve the predictions. Pharmacometric tools such as Pmetrics could then successfully be used to build pharmacokinetic models for specific groups of patients that could later be implemented in computer-based dose individualization strategies. Based on the non-Gaussian distribution of TAC trough concentrations it is likely to expect deviation from normality of the statistical distribution of TAC apparent clearance.

REFERENCES

- [1] Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev. 2006;(4):CD005161.
- [2] Saint-Marcoux F, Woillard JB, Jurado C, Marquet P. Lessons from routine dose adjustment of tacrolimus in renal transplant patients based on global exposure. Ther Drug Monit. 2013 Jun;35(3):322-7. doi: 10.1097/FTD.0b013e318285e779.
- [3] Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate Detection of Outliers and Subpopulations With Pmetrics, a Nonparametric and Parametric Pharmacometric Modeling and Simulation Package for R. Therapeutic Drug Monitoring. 2012; 34(4): 467-476.
- [4] Mentré F, Escolano S. Prediction discrepancies for the evaluation of nonlinear mixed-effects models. J Pharmacokinet Pharmacodyn 2006; 33:345-367.
- [5] Passey C, Birnbaum AK, Brundage RC et al. Dosing equation for tacrolimus using genetic variants and clinical factors. Br J Clin Pharmacol. 2011;72(6):948-957.
- [6] Dimitrova V, Farandzha D, Atanasova I et al. Cyclosporine and creatinine blood levels monitoring in pediatric and adult liver transplant patients. Annual of Sofia University "St. Kliment Ohridski". 2017; vol. 2:171-180.