

Background and Purpose

Cyclosporine (CsA) is a calcineurin inhibitor that is still one of the main drugs of choice in renal transplant immunosuppression therapy.¹ It is characterized by large pharmacokinetic (PK) variability and a narrow therapeutic window, and numerous covariates affecting its pharmacokinetic parameters.² Despite its importance, there is no population PK model of CsA that has been developed in Malaysian population. This study aimed to develop a population PK model of CsA in the Malaysian renal transplant recipients.

Methods

Data were collected retrospectively from renal transplant patients on CsA in a tertiary hospital in Malaysia. The CsA concentrations were obtained at pre-dose and 2 hours after the CsA dose. The model structure and PK parameters were estimated using non-linear mixed-effect modeling via NONMEM³ software. A combined proportional and additive model was used to describe the residual error. Missing doses were estimated using the compartment initialization method.⁴ Multiple imputations were used to handle missing covariates in order to perform covariate analysis using a stepwise forward addition procedure ($P < 0.05$) followed by a backward elimination procedure ($P < 0.001$). The final model was chosen based on the lowest objective function value, prediction corrected visual predictive check (pcVPC) using 1000 simulations, relative standard errors produced from the sampling-importance resampling (SIR) method⁵ and scientific plausibility.

Results

A total of 2807 blood concentration data points were obtained from 113 renal transplant patients (69, males; 44, females). The majority of patients were Chinese 87.6% followed by Malay 7.1% and Indians 5.3%. The mean age and weight were 44 years (17-77) and 63 Kg (32-106), respectively. One-compartment model with first-order absorption and elimination was the best to fit the data. The summary of parameters can be found in Table 1.

Table 1. Estimated parameters of cyclosporine in the final model.

Parameter	Typical value	RSE, %	IIV, %	RSE, %
CL/F, L/h	15.2	4	20.9	16
V/F, L	107	3	23.6	20
Ka, /h	1.28*	-	-	-
POD on CL/F	0.039	13	-	-
Sex on CL/F	0.774	4	-	-
CrCL on CL/F	0.0845	30	-	-
CCB on CL/F	0.936	2	-	-
Sex on V/F	0.803	5	-	-
Cholesterol on V/F	-0.143	23	-	-
Additive residual error ng/ml	0.39	21	-	-
Proportional residual error %	11	5	-	-

*Fixed to published value

Abbreviation: CL/F, clearance; V/F, volume of distribution; Ka, rate of absorption; RSE, relative standard error; IIV, inter-individual variability; POD, post-operative days; CrCL, creatinine clearance; CCB, calcium channel blocker.

Significant covariate on CL/F : Post-operative days (POD), sex, creatinine clearance (CrCl), and calcium channels blockers (CCB)

Significant covariate on V/F : sex and cholesterol

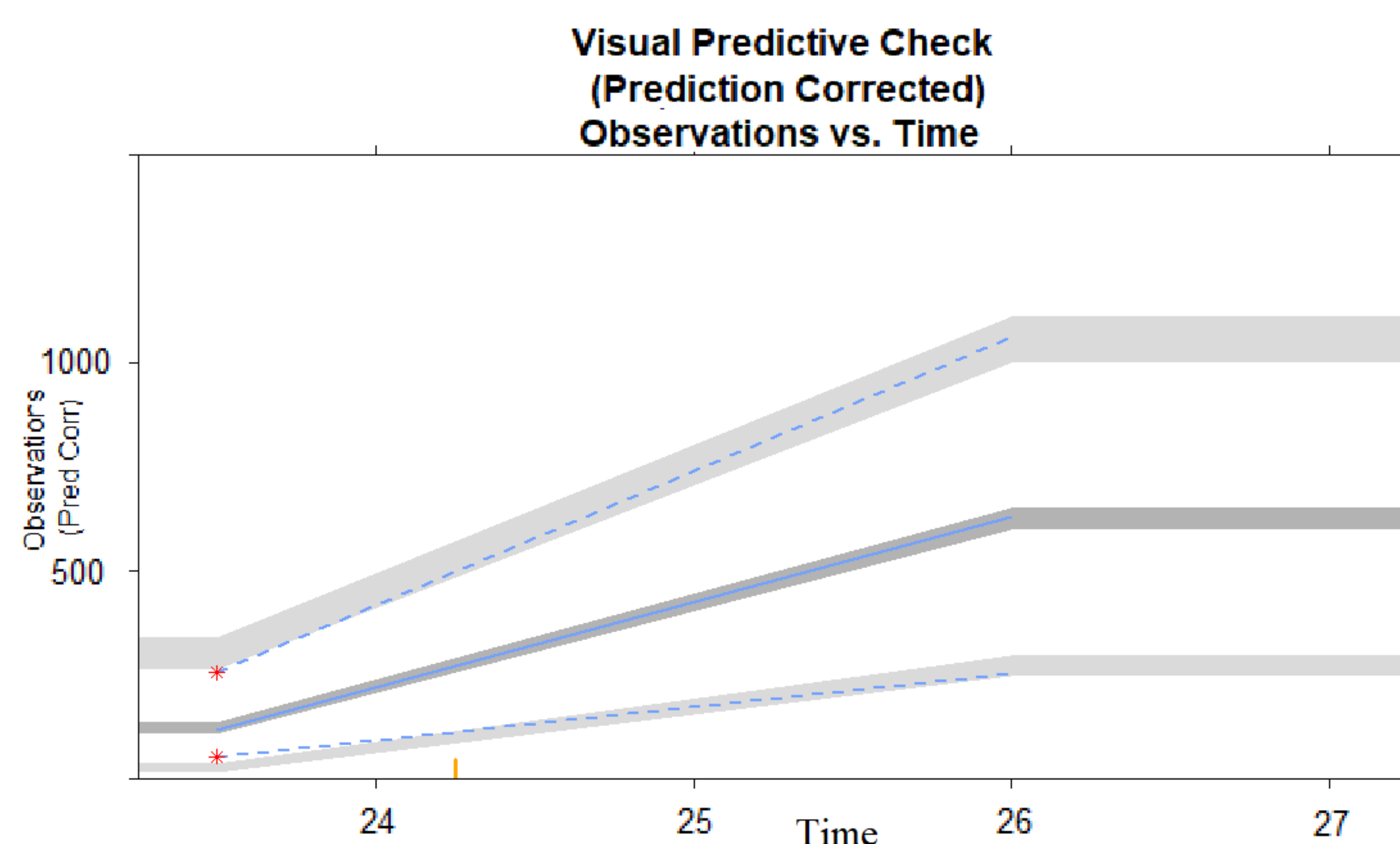
$$CL/F \text{ (L/h)} = 15.2 \times (POD)^{0.039} \times (0.774)^{Sex} \times \left(\frac{CrCl}{55.4}\right)^{0.0845} \times (0.936)^{CCB}$$

$$V/F \text{ (L)} = 107 \times (0.803)^{Sex} \times \left(\frac{Chol}{5.3}\right)^{-0.143}$$

- Clearance of cyclosporine decreases in females and in patients taking CCB while it increases with CrCL and POD increase.
- Volume of distribution of cyclosporine decreases in females and with increasing cholesterol level.

Based on the pcVPC, the 95% confidence interval of the median, 10th and 90th percentiles of the simulated data have overlaid the median, 10th and 90th percentile of the observed data, implying the good predictive performance of the final model as seen in Figure 1.

Figure 1: prediction corrected visual predictive check



Conclusions

This is the first study involving Malaysian renal transplant recipients using a large number of drug monitoring data in a single center and advanced methods to handle missing data that allowed the development of a population PK model with the quantification of the covariate effects. The model developed in the current study provides useful information on the factors affecting CsA PK to be considered when making the appropriate dosing adjustment in the future.

References

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