Initial dosage optimisation of cyclosporine in Chinese paediatric patients undergoing allogeneic haematopoietic stem cell transplantation based on population pharmacokinetics: a retrospective study

Huanwen Feng,1,2 Xianggui Wang,1,2 Wei Zheng,3 Sha Liu,4 Hua Jiang,4 Yuxian Lin,5 Haojie Qiu,3 Teng Fong Chan,1,2 Min Huang,1,2 Yan Li,6 Xiaolan Mo,3 Jiali Li1,2

ABSTRACT

Objective Improved understanding of cyclosporine A (CsA) pharmacokinetics in children undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) is crucial for effective prevention of acute graft-versus-host disease and medication safety. The aim of this study was to establish a population pharmacokinetic (Pop-PK) model that could be used for individualised therapy to paediatric patients undergoing allo-HSCT in China.

Design, setting and participants A retrospective analysis of 251 paediatric HSCT patients who received CsA intravenously in the early post transplantation period at Women and Children’s Medical Center in Guangzhou was conducted.

Analysis measures The model building dataset from 176 children was used to develop and analyse the CsA Pop-PK model by using the nonlinear mixed effect model method. The basic information was collected by the electronic medical record system. Genotype was analysed by matrix-assisted time-of-flight mass spectrometry. The stability and predictability of the final model were verified internally, and a validation dataset of 75 children was used for external validation. Monte Carlo simulation is used to adjust and optimise the initial dose of CsA in paediatric allo-HSCT patients.

Results The typical values for clearance (CL) and volume of distribution (Vd) were 14.47 L/hour and 2033.53 L, respectively. The body weight and haematocrit were identified as significant variables for V, while only body weight had an impact on CL. The simulation based on the final model suggests that paediatrics with HSCT required an appropriate intravenous dose of 5 mg/kg/day to reach the therapeutic trough concentration.

Conclusions The CsA Pop-PK model established in this study can quantitatively describe the factors influencing pharmacokinetic parameters and precisely predict the intrinsic exposure to CsA in children. In addition, our dosage simulation results can provide evidence for the personalised medications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Relevant studies on population pharmacokinetic (Pop-PK) in paediatric haematopoietic stem cell transplantation (HSCT) patients are still limited. As a result, determining the optimal dose to achieve individualised medication is challenging, particularly for paediatric patients receiving allo-HSCT in China.

WHAT THIS STUDY ADDS

⇒ Physiological factors and genetic polymorphisms were used as potential covariates in this study to comprehensively explain variations in cyclosporine A (CsA) PK properties. Our findings suggest that body weight and haematocrit are influential factors in the variability of CsA disposition.

⇒ We proposed an initial dose of 5 mg/kg/day for paediatric patients with variable HCT weighing 16.5 kg, which permits steady-state CsA concentrations to swiftly reach the therapeutic window, minimising potential adverse reaction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The Pop-PK model established in this study can further be adopted to optimise the initial dose of CsA in Chinese paediatrics with allo-HSCT, reducing the frequency of dosage adjustments and serving as a reference for dose guidance in clinical care during the early post-transplantation.

INTRODUCTION

Acute graft-versus-host disease (aGVHD) is the leading cause of non-relapse mortality, and it is also one of the most serious complications of allo-haematopoietic stem cell transplantation (HSCT) surgery. Relevant research shows that patients have a higher incidence of aGVHD after HSCT, ranging from 40% to
Cyclosporine A (CsA), a conventional calcineurin inhibitor, is known as the first-line drug for preventing aGVHD. However, due to its narrow therapeutic window, which means the narrow range between immunosuppressive and toxic concentrations, as well as the large pharmacokinetic (PK) variability (total drug and unconjugated drug area under the curve can vary by twofold intrindividually and by more than thrice between individuals), namely a variety of factors, such as demographics, concomitant medications, liver function and genetics, contribute to unique behaviours in the absorption and disposition of CsA among different individuals, so that patients applying same dose can exhibit a wide range of blood concentrations. These characteristics may expose patients to an increased risk of toxicity if overdosed or allograft rejection if underdosed. Therefore, CsA requires frequent dose adjustments via therapeutic drug monitoring (TDM) to maintain through concentration in therapeutic range set between 150 and 200 ng/mL, particularly early after transplantation. Adjusting the dose based on TDM results may cause treatment to be delayed because it is a lagging method that cannot be used for initial dose formulation. Only by identifying the factors that influence CsA PK and developing an individualised initial dose for each patient can CsA’s safety and efficacy be improved.

Population PK (Pop-PK) is an effective tool to optimise the individual administration of CsA. Despite the fact that Pop-PK research on CsA for organ transplantation has been widely conducted in recent years, there have been few studies in paediatric patients with haematological diseases. According to studies, the PK parameters of CsA differ significantly between different organ transplantation types and populations (such as adults and children), resulting in high uncertainty in the safety and effectiveness of CsA PK extrapolation.

Currently, research aimed at CsA Pop-PK in Chinese children receiving allo-HSCT is severely lacking. Li et al were the first to report the Pop-PK of CsA in Chinese children with malignant haematological disorders who underwent allo-HSCT. However, an optimised initial dosage of intravenous infusion was not proposed in the existing study. In addition, the genetic factors in the model variables were still contradictory. Furthermore, the size of the participants is small, so it is hard to access the performance of the model by using external validation. As a result, larger sample size studies are required to better demonstrate the potential effects of CsA on PK.

To minimise side effects and formulate an effective initial CsA dose, a paediatric Pop-PK model with good precision, which is used to analyse the CsA PK process, not only provides evidence-based support for the formulation of clinical dosing regimens but also greatly compensates for the lack of empirical medication. Recently, in paediatric Chinese patients who underwent bone marrow transplants, Chen et al proposed that patients weighing 5–30 kg have a greater probability of reaching an effective whole blood concentration at a dose of 6 mg/kg/day CsA, based on the simulated findings of the Pop-PK model. This finding is crucial for achieving and maintaining therapeutic concentration. However, the optimal initial dose of CsA in Chinese paediatric patients undergoing HSCT remains unclear, and no reports have been published on optimising the initial dose using the CsA Pop-PK model.

METHODS
Participants and data collection
This study retrospectively enrolled paediatric patients (≤18 years old) who underwent allo-HSCT and received CsA for aGVHD prophylaxis at Guangzhou Women and Children’s Medical Center between January 2016 and December 2020. Patients with incomplete information were excluded. The relevant clinical data were collected from electronic medical records, including age, sex and etc (see online supplemental table S1). CsA trough concentrations were measured using an enzyme-multiplied immunoassay technique assay with the Viva-E analyser in the hospital.

This study was registered with the Chinese Clinical Trial Registry (Reference number: ChiCTR2000040561). Regular contact with members and representatives of Guangzhou Women and Children’s Medical Center made the outcome measures of this study clear for patients in making informed decisions about treatment. Patients were not involved in setting the research question, the outcome measures or the design or implementation of the study.

Dosage regimen
CsA was typically administered twice daily, with an initial dose of 3 mg/kg/day administered intravenously on day 1 of transplantation. Patients with thalassaemia frequently received CsA at an initial dose of 1.5 mg/kg/day once every 12 hours as an intravenous drip infusion 10 days before transplantation, then adjusted to 3 mg/kg/day once every 12 hours as an intravenous drip infusion on day 1 of transplantation. The CsA dosage was adjusted based on TDM data acquired the morning after the last dose to maintain a trough blood concentration of 150–200 ng/mL.

DNA extraction and genotyping
Before the transplant, 2 mL of the patient’s peripheral venous blood was taken, and genomic DNA was extracted using a DNA extraction kit (TIANGEN, Beijing, China). The ABCB1 (rs1045642, rs3842, rs1128503, rs34800935),
CYP3A4 rs2242480, CYP3A5 rs776746, POR rs17685 and NR1I3 rs2307424 genotypes were determined using the Agena Bioscience MassARRAY technology. Hardy-Weinberg equilibrium testing is performed using a χ² goodness-of-fit (GOF) test.

Pop-PK modelling

The data were divided into training and validation sets at a ratio of 7:3 based on the patient’s transplant time. The Pop-PK model of CsA in Chinese allo-HSCT paediatric patients was developed using the training dataset (n=176), applying the nonlinear mixed effect model method in Phoenix (V.7.0; Certara). Interindividual and intraindividual variability of PK parameters was evaluated by using the first-order conditional estimation-extended least squares algorithm. Clearance (CL) and volume of distribution (Vd) were the fundamental PK parameters of the structure-function model.

Structure model

The additive and proportional models that reflect the interindividuation variation of parameters were compared, as were various error models such as additive, proportional and mixed (additive and proportional). The objective function value (OFV) was criterion for model selection. The results of the comparison are shown in online supplemental table S2. Interindividual variability of PK parameters was calculated using an exponential model and expressed as follows: (Eq. 1)

\[ P_i = P_{pop} \times \exp(\eta_i^P) \]  

Where \( P_i \) is the estimated value of the PK parameter for \( i \)-th individual, \( P_{pop} \) is typical population value of the PK parameter and \( \eta_i^P \) is the random effect of \( i \)-th individual. \( \eta_i^P \) follows the normal distribution with a mean of 0 and variance of \( \sigma^2 \). The residual variability was described using a proportional model and expressed as follows: (Eq. 2)

\[ C_{obs} = C \times (1 + \varepsilon) \]  

Where \( C_{obs} \) is the observation and \( C \) is the individual predicted concentration. \( \varepsilon \) obeys the Gaussian distribution with a mean of 0 and a variance of \( \sigma^2 \).

Covariate analysis

After imputing the missing values (for categorical variables, filled with mode and abnormally distributed continuous variables, filled with median), a stepwise method was used to screen covariates in the basic model. The change in OFV was used as the selection criterion. During the forward inclusion process, adding covariates that significantly (p<0.01) decreased the OFV by more than 6.63, Retaining covariates that significantly(p<0.001) increased OFV by more than 10.83 during the backward-exclusion procedure.

Model validation

The GOF plots were used for preliminary evaluation. The visual predictive check (VPC) was also used to verify the prediction performance of the final model by using the K-means method to divide the time periods and then generating 1000 sets of simulated data. And the bootstrap method was performed to assess the robustness of the final model. There is no difference in dataset and settings between internal validation and final model. The validation set (n=75) was substituted into the final model to calculate the predicted concentration of CsA and analyse the correlation between the predicted concentration and the observations. The data were compared by calculating individual prediction error (IPE%), mean prediction error (MPE%), mean absolute percentage error (MAPE%), root mean square error (RMSE%) as follows: (Eq. 3, Eq. 4, Eq. 5, Eq. 6)

\[ \text{IPE}_{i} = \frac{\text{pred}_i - \text{obs}_i}{\text{obs}_i} \times 100\% \]  
\[ \text{MPE} = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{\text{pred}_i - \text{obs}_i}{\text{obs}_i} \right| \times 100\% \]  
\[ \text{MAPE} = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{\text{pred}_i - \text{obs}_i}{\text{obs}_i} \right| \times 100\% \]  
\[ \text{RMSE} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} \left( \frac{\text{pred}_i - \text{obs}_i}{\text{obs}_i} \right)^2} \times 100\% \]

where \( \text{pred}_i \) is the individual predicted concentration, \( \text{obs}_i \) is the observation, \( n \) is the sample size. The percentage of IPE within 20% and 30% (IF20, IF30) can be used to further measure the precision and accuracy of the Pop-PK model. Smaller MPE%, MAPE% and RMSE% values suggest less bias and more accuracy.

Simulation

Based on the validated final model, 1000 Monte Carlo simulations were performed to generate the steady-state trough concentration on day 7 after transplantation in typical patients (weight 16.5 kg) with different HCT levels (10%, 30%, 50%) while receiving continuous intravenous infusions of different CsA dosages (2 mg/kg/day, 3 mg/kg/day, 4 mg/kg/day and 5 mg/kg/day). The recommended dose was presented in combination with the target therapeutic concentration range (150 μg/L-250 μg/L).

RESULTS

Characteristics of patients

The current Pop-PK modelling analysis involved 865 whole blood CsA concentrations in samples from 251 paediatric HSCT recipients. The demographics of the patients are shown in table 1. Detailed characteristics for patients in training dataset and validation dataset were shown in online supplemental table S3. The frequency distributions of allele and genotype are shown in the table 2.

Pop-PK modelling

From the data obtained in 176 paediatric patients, the PK characteristics of CsA were best described by the
one-compartment model with first-order absorption and elimination. The results of the stepwise method for covariate screening are shown in online supplemental table S4. They showed that body weight (BW) and HCT were both significantly influenced the $V_d$, while only BW was significantly influenced the $CL$. Other covariates were not found to have statistical significance on PK parameters. The following equations (Eq. 7) and (Eq. 8)) describe the $CL$ and $V_d$ for final covariate models:

$$CL \ (L/h) = 14.47 \times (BW/16.5)^{0.99} \ (7)$$

$$V_d \ (L) = 2033.53 \times (BW/16.5)^{1.06} \times (HCT/28.8)^{-0.39} \ (8)$$

The parameter estimations of the final model are shown in table 3. From the above equations, the final relationship describing the $CL$ and $V_d$ can be deduced: the $CL$ and $V_d$ of CsA increased as the patient’s BW increased.

On the contrary, as the patient’s HCT increased, the $V_d$ of CsA declined.

The GOF diagrams of the basic model and the final model are shown in figures 1 and 2, respectively. In contrast, the final model fits better.

**Model validation**

The results of the VPC of the final model are displayed in figure 3. The success rate of bootstrapping (n=1000) was 100%. The estimated typical values of $CL$ and $V_d$ were comparable to the median resulting from the bootstrap method; additionally, they are both within the 95% CI (14.47 (13.00 to 15.73) for $CL$ and 20.33 (1657.30 to 2146.52) for $V_d$). The detailed results were reported in table 3. The plot of observed CsA concentration versus individual predicted CsA concentration in the validation dataset (n=75) is displayed in figure 4. The predicted concentration of CsA in paediatric patients has a statistical correlation with the observed concentration ($r$=0.863, $p<0.01$). In addition, the $R^2$ and $R^2_{adj}$ of the final model were 64.29% and 84.21%, the MPE%, MAPE% and RMSE% were 3.12%, 14.46% and 25.24%, respectively. It confirmed that the model developed in this study can better predict the plasma concentration of CsA intravenous infusion in children undergoing allo-HSCT.

**Simulation**

The steady-state trough concentrations on day 7 after transplantation in typical patients with different haematocrit levels and different dosages are presented in figure 5. Compared with an initial dose of 2–4mg/kg/day, the probability of reaching the effective whole blood concentration in paediatric patients weighing 16.5 kg who were given an initial dose of 5mg/kg/day was higher.

**DISCUSSION**

In this study, we successfully established a Pop-PK model of CsA in Chinese children with HSCT and provided an optimised initial dose for reaching the target concentration of 150–250 ng/mL. The typical values of $CL$ and $V_d$ in the final model were 14.47 L/hour and 2033.53L, respectively, which were comparable to the results of Ni et al and Wang et al. The comparison of CsA pop-PK parameters in paediatric patients with previous studies is shown in online supplemental table S5.

It has been proven that weight is the main covariate for PK parameters. Given that there is a statistically significant correlation between BW and age, it is always difficult to distinguish PK differences from age-related factors and size-related factors due to collinearity, we, therefore, decided to retain only BW in the final model. Currently, dosage selection based on weight is commonly used in the clinical treatment of children, which was confirmed in our findings.

Additionally, the HCT was considered to have a significant impact on PK parameters in prior research since CsA is an 11-amino acid lipophilic cyclic polypeptide,
### Table 2  Pharmacogenetics and HWE analyses

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<tr>
<th>Gene</th>
<th>SNPs</th>
<th>Allele</th>
<th>Allele count</th>
<th>Allele frequency</th>
<th>Genotype</th>
<th>Genotype Count</th>
<th>Genotype frequency</th>
<th>P value in HW equilibrium formula</th>
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The p value obtained here in the HWE test using the asymptotic $\chi^2$ test, with a brief explanation in online supplemental file 1. HWE, Hardy-Weinberg equilibrium.

### Table 3  Population pharmacokinetic parameters of CsA and bootstrap results

<table>
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<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>RSE (%)</th>
<th>Bootstrap Median</th>
<th>RSE (%)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>CL (L/hour)</td>
<td>14.47</td>
<td>4.61</td>
<td>14.48</td>
<td>4.76</td>
<td>13.00 to 15.73</td>
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<td>V (L)</td>
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<td>2024.48</td>
<td>9.48</td>
<td>1657.30 to 2416.52</td>
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<td>$\theta_{\text{BW,CL}}$</td>
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<td>9.54</td>
<td>1.00</td>
<td>9.68</td>
<td>0.82 to 1.21</td>
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<tr>
<td>$\theta_{\text{BW,V}}$</td>
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<td>21.04</td>
<td>0.99</td>
<td>20.65</td>
<td>0.61 to 1.43</td>
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<tr>
<td>$\theta_{\text{HCT,V}}$</td>
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<td>-18.94</td>
<td>-0.39</td>
<td>-21.68</td>
<td>-0.62 to -0.27</td>
</tr>
</tbody>
</table>

**Between-subject variation**

- $\omega_{\text{CL}}^\gamma$ = 0.10, 16.59, 0.10, 17.08
- $\omega_{\text{V}}^\gamma$ = 0.22, 23.52, 0.21, 24.94

**Within-subject variation**

- $r_{\text{proportional}}^\gamma$ = 0.24, 4.20, 0.24, 4.03, 0.22 to 0.26

BW, body weight; CL, clearance; CsA, cyclosporine A; HCT, haematocrit; RSE, relative SE; V, distribution volume.
widely distributed in red blood cells and highly binding to proteins in plasma after administration.\textsuperscript{19, 25, 26} Fanta \textit{et al} constructed a study in paediatric patients who underwent renal transplants, and statistically significant associations were observed between $V/F$ and HCT.\textsuperscript{27}

In this study, we discovered a similar result: an inverse correlation was found between HCT and V. Considering the high lipophilicity of CsA, changes in HCT may affect its distribution between blood and adipose tissue. Lower HCT levels increase CsA distribution to fat, resulting in a larger apparent volume of distribution,\textsuperscript{28} implying that as HCT declines, the amount of unbound CsA distributed into peripheral tissues rises, as does the risk for toxicity. To adjust the dose regimen, physicians must regularly monitor patients' HCT levels.\textsuperscript{16}

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\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Goodness-of-fit graphs for the basic model. (A) Observed concentration versus population prediction; (B) individual prediction; (C) conditional weighted residuals versus population prediction; (D) conditional weighted residuals versus time. CWRES, conditional weighted residuals.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Goodness-of-fit graphs for the final model. (A) Observed concentration versus population prediction; (B) individual prediction; (C) conditional weighted residuals versus population prediction; (D) conditional weighted residuals versus time. CWRES, conditional weighted residuals.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Prediction-corrected visual predictive check (n=1000). The blue dots are the observed concentrations. The red dash lines reflect the median and 95th percentile of observations, and the semitransparent red shading area represents the 90% CI of the predicted median. The red solid line reflects the 5th percentile of observed concentrations. The semitransparent blue shading area represents 90% CI of the predicted 5th and 95th percentile based on prediction. DV, observed data; IVAR, time after the first dose.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Plot of observed CsA concentration versus individual predicted CsA concentration in the validation group. CsA, cyclosporine A.}
\end{figure}
CsA is a substrate for the CYP3A4 and CYP3A5 enzymes and is carried out of cells by P-glycoprotein (encoded by ABCB1/MDR1). The heterogeneity in CYP3A4, CYP3A5 and ABCB1 expression may contribute to interindividual variability in CsA PK. Several studies have examined the relationship between CsA and genetic variants, particularly CYP3A5*3, because mutation frequency is high in the Chinese population. Tao et al indicated that carriers of CYP3A5 *5/*3 have higher C_{max} of cyclosporine than carriers of CYP3A51*/*3. Moreover, there is evidence that the C_{0}/D of CsA in CYP3A5 expressers is significantly lower than that in CYP3A5 non-expressers in paediatric renal transplant recipients. In addition, P450 oxidoreductase (POR), which is required for catalytic activity, was discovered to influence tacrolimus CYP3A5 activity in CYP3A5 expressers in Elens et al’s research. Also, they found that POR*28/*28 increases CYP3A4 activity for CsA in CYP3A5 nonexpressers with a CYP3A4*22 loss-of-function allele, resulting in lower dose-adjusted predose concentrations of CsA. Moreover, pregnane X receptor (PXR, encoded by NR1I2) is a critical nuclear receptor that regulates the expression of metabolic enzymes. Several studies reported that the NR1I2 genotype may influence PXR expression because multiple SNPs in NR1I2 have been linked to CYP3A4, CYP3A5 and ABCB1 activity. Our laboratory has indicated that the −24622A>T in the 5-untranslated region and the −24446C>A in exon 1 of the NR1I2 gene increased PXR activity in Han Chinese in previous studies. Although genetic polymorphisms as one of the important factors contributing to variations in CsA PK, the findings are still controversial. Anglicheau et al found no correlation between polymorphisms in the CYP3A5 and MDR1 genes and the PK parameters of CsA in 106 kidney transplant recipients. Li et al reported that CYP3A5 and ABCB1 polymorphisms were not found to have significant effects on the PK process of CsA in a total of 86 Chinese children who received allograft-HSCT. Relevant outcomes have been reported in the study constructed by Xue et al. Similarly, none of the genetic polymorphisms in ABCB1, CYP3A4, CYP3A5, POR and NR1I2 were significant covariates in the PK of CsA in our study.

Evidence shows that genotypes such as CYP3A5*3 could influence the correlation of CYP3A4/MDR1/NR1I2 genetic polymorphisms with tacrolimus concentration. Additionally, Qiu et al demonstrated that the effect of MDR1 polymorphisms on CsA PK in Chinese renal transplant recipients may be masked by CYP3A polymorphisms. As a result, we presumed that the contribution of SNPs to interindividual variance in CsA PK variation may be obscured by the involvement of metabolising enzyme polymorphisms in the model. Other reasons leading to inconsistent results may be attributed to differences in sample size, age, liver function, ethnicity and CsA concentration detection methods.

Furthermore, the final model was applied to imitate the optimal initial dose of CsA in order to effectively prevent rejection by using Monte Carlo simulation. Even though CsA is generally given by continuous intravenous infusion before the transplant at an initial dose of 3mg/kg per day, there is still contradiction due to the lower level of evidence and lack of established data support. According to our simulation, the 3mg/kg per day commonly used in clinical might be too low for children who received HSCT. The best initial dosage regimen for typical patients weighing 16.5kg with different HCT should be 5mg/kg per day so that the steady-state trough concentration of CsA in the early stage of transplantation can largely reach the treatment window. Recently, researchers have reported that CsA concentrations in the early post-transplantation period were significantly linked to severe aGVHD in paediatric transplant recipients. For instance, Izumi et al demonstrated that inadequate exposures to CsA can be a considerable risk factor for developing aGVHD. Bianchi et al indicated a significant linkage between the higher incidence of aGVHD and patients with CsA levels <200μg/L in the first 10 days of allograft-HSCT. Moreover, their results have shown that only a small proportion of patients reached a CsA level >201μg/L on day 0 after receiving the starting dose of CsA was 3mg/kg /day intravenously on day -3 with concomitant drugs. These results highlight the urgent need for optimal adjustments of CsA dosing in children to maintain therapeutic CsA levels above 195μg/L in the first 10 days of allograft-HSCT. Because dose escalation clinical trials in children are typically difficult to perform, our simulation, which is similar to the observation made in the above research, has a high reference value for clinical work aimed at reaching target concentrations of CsA as quickly as possible in Chinese paediatric patients who underwent allograft-HSCT.

Finally, in comparison to Ti et al’s article published in 2019, their pop-PK model only adopts internal validation, which is insufficient for extrapolation to future paediatric patients. Our research compensates for the lack of sample size in their study by enrolling 251 paediatric HSCT patients, allowing us to obtain a reasonable prediction model by validating it externally. Even though they...
demonstrated that CYP3A4*1G and eGFR are both significant covariates impacting CL, the association between renal function and genetic polymorphism on CsA PK in children, particularly with HSCT, remains disputed. Thus, the similarities and variances in our research findings are meaningful for formulating individualised medication and serve as a reference for future research. The retrospective design of our study is one of its limitations; in order to confirm the recommended dosage in the future, a prospective study will be required. Despite the limitations listed above, this study may assist with individualised and precision medicine in CsA therapy.

CONCLUSIONS
In summary, the accuracy and constancy of the one-compartment Pop-PK model with first-order absorption and elimination to evaluate CsA exposure in Chinese children receiving allo-HSCT were verified internally and externally. The influences of BW and HCT were included in our model, which was further used to perform a simulation of different dosing regimens and HCT levels to obtain an optimal initial dose. We suggested an intravenous infusion dose of 5 mg/kg/day every 12 hours may be relatively appropriate for Chinese paediatric recipients of allo-HSCT for better prevention of aGVHD and improvement of prognosis.

Author affiliations
1 Institute of Clinical Pharmacology, Sun Yat-Sen University School of Pharmaceutical Sciences, Guangzhou, Guangdong, China
2 Guangdong Provincial Key Laboratory of New Drug Design and Evaluation, Sun Yat-Sen University School of Pharmaceutical Sciences, Guangzhou, Guangdong, China
3 Department of Pharmacy, Guangzhou Women and Children’s Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China
4 Department of Hematology/Oncology, Guangzhou Women and Children’s Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China
5 Guangdong Provincial Key Laboratory of New Drug Design and Evaluation, Sun Yat-Sen University School of Pharmaceutical Sciences, Guangzhou, Guangdong, China
6 Department of Pharmacy, The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, Guangdong, China
7 Guangzhou Cord Blood Bank, Guangzhou Women and Children’s Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China

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Contributors
MH, YL, XM and JL designed and planned the study. HF, WX, WZ, HQ and TFC performed the experiments. HF, WX, WZ, SL, HJ and YL collected and collated the data. HF, WX and WZ conducted the analyses. HF, WX, WZ, MH, YL, XM and JL wrote and edited the manuscript. JL as the guarantor of the overall content.

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Competing interests
None declared.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Ethics approval
This study involves human participants and was approved by Ethics Committee of Guangzhou Women and Children’s Medical Center (Guangzhou Women and Children’s Medical Center, Issue No.63100(2020), EC). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Tong Fong Chan http://orcid.org/0009-0000-7421-6996
Jiali Li http://orcid.org/0000-0001-7336-6423

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