

Population pharmacokinetics model and initial dose optimization of tacrolimus in children and adolescents with lupus nephritis based on real-world data

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Abstract. The present study aimed to establish a population pharmacokinetics model of tacrolimus and further optimize the initial dosing regimen of tacrolimus in pediatric and adolescent patients with lupus nephritis (LN). Pediatric and adolescent patients with LN were recruited between August 2014 and September 2019 at the Children's Hospital of Fudan University (Shanghai, China). Relevant information was used to set up a population pharmacokinetics model with a Nonlinear Mixed Effect Model and the initial dosage regimen was simulated with the Monte Carlo method. Body weight and co-administration of wuzhi capsule were indicated to influence tacrolimus clearance in pediatric and adolescent patients with LN, and at the same body weight, the rate of tacrolimus clearance in patients without vs. with co-administration of wuzhi capsule was 1:0.71. In addition, in patients who were not administered wuzhi capsule, an initial dosage regimen of 0.15 mg/kg/day was recommended for a body weight of 10-23 kg and 0.10 mg/kg/day for 23-60 kg; in patients who were administered wuzhi capsule, an initial dosage regimen of 0.10 mg/kg/day was recommended for a body weight of 10-23 kg and 0.05 mg/kg/day for 23-60 kg. To the best of

our knowledge, the present study was the first to establish a population pharmacokinetics model of tacrolimus in order to determine the optimal initial dosage regimen of tacrolimus in pediatric and adolescent patients with LN.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease (1) characterized by connective-tissue inflammation and extensive vasculitis (2-5). It primarily occurs in adolescents aged 10-19 years, although 1/3 of affected patients are <10 years old and the majority are females (1,6). Organ lesions in pediatric and adolescent patients with SLE are more severe than those in adults and may lead to death in a relatively short time, being associated with dismal prognoses (1). Pediatric and adolescent patients with SLE frequently have complex and severe clinical manifestations (1,6) that affect various different organs, either simultaneously or successively involving multiple systems, including the urinary, nervous, cardiovascular and blood supply systems (1).

Lupus nephritis (LN) is one of the most severe complications of SLE and its incidence rate reaches up to 60% in patients with SLE worldwide. Among patients with SLE, 50-80% are cases of pediatric-onset SLE (7-10). As comprehensively reviewed (10), without pharmacotherapy, long-term LN may induce irreversible renal injury and subsequently develops into end-stage renal disease. Traditional treatments of LN involve a combination therapy of cyclophosphamide with glucocorticoids, which have been demonstrated to improve the long-term prognosis. However, its usage is limited by severe adverse effects, including hemorrhagic cystitis, amenorrhea, malignancy and sepsis. Novel immunosuppressants, including tacrolimus, cyclosporine and mycophenolate mofetil are required to inhibit the side effects of traditional treatments. Tacrolimus has been reported to be a safe and effective agent for treating patients with LN (10).

However, considerable intra- and inter-individual pharmacokinetic variability makes it difficult to establish individualized tacrolimus dosage regimens. Of note, population pharmacokinetics is able to differentiate in terms of pharmacokinetic variability and has a higher statistical power to verify the effect of multiple factors on the pharmacokinetic behaviour of tacrolimus compared to traditional pharmacokinetic analysis and makes it possible to formulate an optimal

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Abbreviations: CL/F, apparent oral clearance; CYP3A, cytochrome P450, family 3; Ka, absorption rate constant; LN, lupus nephritis; OFV, objective function values; SLE, systemic lupus erythematosus; V/F, volume of distribution; VPC, prediction-corrected visual predictive check; WRES, weighted residuals

Key words: population pharmacokinetics, initial dose optimization, tacrolimus, children and adolescents, lupus nephritis

dosage schedule (11,12). Hence, the present study aimed to establish a population pharmacokinetics model of tacrolimus and further optimize the initial dosage regimen for tacrolimus in pediatric and adolescent patients with LN.

Patients and methods

Study design. The clinical information of pediatric and adolescent patients with LN treated between August 2014 and September 2019 at the Children's Hospital of Fudan University (Shanghai, China) was retrospectively collected. The clinical information was collected from the hospital's information system and tacrolimus whole-blood levels were acquired from a therapeutic drug detection system. Partial basic clinical information data with partial overlap were collected from certain patients in previous studies (13,14). The present study was approved by the Research Ethics Committee of the Children's Hospital of Fudan University [ethical approval code: (2019)020]. The present study was a retrospective study and was approved by the ethics committee of this hospital without the requirement for written informed consent. A previous study have used lower patient numbers (15).

Population pharmacokinetics modeling. The population pharmacokinetics model was established using Nonlinear Mixed Effects Modeling software (NONMEM®; version VII; ICON Development Solutions Ltd.) by the first-order conditional estimation method with interaction. The pharmacokinetics parameters included apparent oral clearance (CL/F), volume of distribution (V/F) and absorption rate constant (Ka), where the value of Ka was fixed at 4.48 per hour (13,16-18). Inter-individual variabilities were estimated by equation (i): $A = T(A) \times \exp(\eta_i)$. A and T(A) represent the individual parameter value and the typical individual parameter value, respectively. η_i represented a symmetrical distribution (0, ω^2), which was a random term with zero mean and variance ω squared (ω^2).

Random residual variabilities were estimated by equation (ii): $A = (1 + \varepsilon_i) \times B$. A and B represent the observed concentration and the individual predicted concentration, respectively. ε_i represented a symmetrical distribution (0, σ^2), which was a random term with zero mean and variance σ squared (σ^2).

Covariate model. Weight and pharmacokinetics parameters were estimated by equation (iii): $A_i = A_{std} \times (WT_i/WT_{std})^{power}$. A_i and WT_i represent the i-th individual pharmacokinetics parameter and the i-th individual body weight, respectively. A_{std} represents the typical individual parameter of WT_{std} (WT_{std} was the standard body weight, which was 70 kg). Power was the allometric coefficient, which was set at 0.75 for the CL/F and 1 for the V/F (19). Continuous covariates and categorical covariates were estimated by equation (iv) and (v), respectively: $A_i = T(A) \times (Cov_i/Cov_{median})^\theta$ and $A_i = T(A) \times (1 + Cov_i \times \theta)$. A_i and T(A) represent the individual parameter value and the typical individual parameter value, respectively. θ represents the parameter to be estimated and Cov_{median} is the population median for the covariate. Cov_i represents the covariate of the i-th individual. When a covariate was finally incorporated into the model, the corresponding θ value was obtained.

Changes in objective function values (OFV) were assessed by covariate inclusions and a decrease of OFV >3.84 ($P < 0.05$). An increase in OFV >6.63 ($P < 0.01$) was considered sufficient for significance in the final model.

Evaluation and simulation. The reliability and stability of the final parameters were assessed by bootstrap ($n=1,000$), which was performed using the NONMEM® software (version VII; ICON Development Solutions Ltd), goodness of fit plots and prediction-corrected visual predictive check (VPC) plots. The Monte Carlo method was used for the simulation of the optimal initial dose, including six weight groups (10, 20, 30, 40, 50 and 60 kg) and seven initial dosing regimens (0.01, 0.05, 0.10, 0.15, 0.20, 0.25 and 0.30 mg/kg daily) split into two doses. Based on previous publications, the therapeutic window of tacrolimus treatment in LN is between 5 and 15 ng/ml; thus, this was used in the present study (10).

Results

Data collection. The clinical information of 32 pediatric and adolescent patients with LN (5 males and 27 females) was collected for the present study and was used for population modelling. The clinical information of certain patients was collected in previous studies (13,14). Table I presents patient characteristics and drug combinations.

Population pharmacokinetic model. The final covariate model was described by equations (vi) and (vii), respectively: $CL/F = \theta_{CL/F} \times (WT/70)^{0.75} \times (1 + WZ \times \theta_{WZ})$ and $V/F = \theta_{V/F} \times (WT/70)$. $\theta_{CL/F}$ and $\theta_{V/F}$ are the typical population values of CL/F and V/F, respectively. θ_{WZ} is the coefficient of wuzhi capsule. When patients were co-administered wuzhi capsule and tacrolimus, $WZ=1$ was used; otherwise, $WZ=0$ was applied.

Validation. As presented in Fig. 1, observations vs. population predictions, observations vs. individual predictions, conditional weighted residuals (WRES) vs. population predictions and conditional WRES vs. time after the start of therapy were assessed in goodness of fit plots. The parameter estimates of the final model and bootstrap validation are presented in Table II. The prediction-corrected visual predictive check plots of the final model are provided in Fig. 2, where most of the observations are within the 95% prediction intervals of the simulation data, indicating that the prediction-corrected concentrations were well predicted by the final model.

Simulation. Body weight and co-administration of wuzhi capsule affected tacrolimus clearance in pediatric and adolescent patients with LN, and for the same body weight, the rate of tacrolimus clearance in patients who were not administered wuzhi capsule vs. those who were administered wuzhi capsule was 1:0.71 (Fig. 3). Fig. 4 presents the probability of achieving the target concentrations under different initial doses. In addition, in patients who were not administered wuzhi capsule, the initial dosage regimen of 0.15 mg/kg/day was recommended for a body weight of 10-23 kg and 0.10 mg/kg/day for 23-60 kg; in patients who were co-administered wuzhi capsule and tacrolimus, the initial dosage regimen of 0.10 mg/kg/day was

Table I. Demographic data of patients (n=32) and drug combinations.

Characteristic	N or mean \pm SD	Median (range)
Gender (male/female)	5/27	
Age (years)	13.44 \pm 2.86	13.87 (2.86-17.99)
Body weight (kg)	45.89 \pm 10.55	47.00 (17.00-66.50)
Albumin (g/l)	38.24 \pm 6.21	39.40 (10.00-49.30)
Alanine transaminase (IU/l)	13.88 \pm 15.69	10.00 (1.00-123.00)
Aspartate transaminase (IU/l)	16.37 \pm 8.10	15.00 (5.00-79.80)
Creatinine (μ mol/l)	55.71 \pm 19.59	54.00 (16.00-225.00)
Urea (mmol/l)	6.14 \pm 2.61	5.80 (2.10-27.30)
Total protein (g/l)	64.26 \pm 7.13	65.20 (37.90-79.70)
Total bile acid (μ mol/l)	4.78 \pm 6.34	3.70 (0.90-85.50)
Direct bilirubin (μ mol/l)	1.68 \pm 3.56	1.40 (0.20-55.10)
Total bilirubin (μ mol/l)	6.34 \pm 4.12	6.00 (2.30-64.90)
Hematocrit (%)	36.57 \pm 4.85	36.50 (20.50-50.00)
Hemoglobin (g/l)	122.01 \pm 21.97	120.00 (70.20-290.00)
Mean corpuscular hemoglobin (pg)	28.15 \pm 2.33	28.00 (21.00-35.00)
Mean corpuscular hemoglobin concentration (g/l)	330.25 \pm 13.93	333.00 (271.00-383.00)
Co-medication		
Glucocorticoid	32	
Wuzhi capsule	12	

SD, standard deviation.

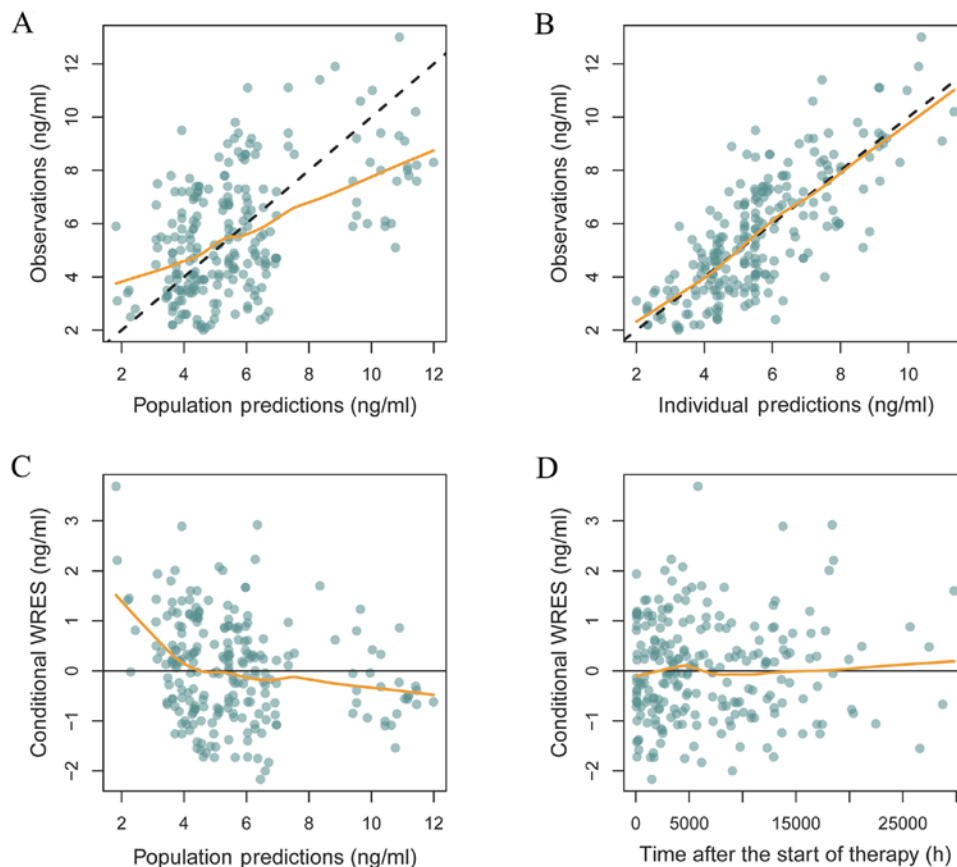


Figure 1. The final model goodness-of-fit plots. (A) Observations vs. population predictions, (B) observations vs. individual predictions, (C) conditional WRES vs. population predictions and (D) conditional WRES vs. time after the start of therapy. WRES, weighted residuals. Partial concentration values were collected based on previous studies (13,14).

Table II. Parameter estimates of the final model and bootstrap validation.

Parameter	Estimate	SE	Bootstrap		Bias
			Median	95% CI	
CL/F (l/h)	15.5	0.729	18.5	[2.5, 24.4]	0.194
V/F (l)	174	1.908	303	[8, 1200]	0.741
Ka (1/h)	4.48 (fixed)	-	-	-	-
θ_{WZ}	-0.290	0.390	-0.297	[-0.440, -0.133]	0.024
$\omega_{CL/F}$	0.172	0.461	0.175	[0.073, 0.292]	0.017
σ_1	0.281	0.049	0.277	[0.249, 0.305]	-0.014

The 95% CI was displayed as the 2.5th, 97.5th percentile of bootstrap estimates. CL/F, apparent oral clearance; V/F, apparent volume of distribution; Ka, absorption rate constant; θ_{WZ} , coefficient of wuzhi capsule; $\omega_{CL/F}$, inter-individual variability of CL/F; σ_1 , residual variability, proportional error; SE, standard error; Bias, prediction error [Bias=(Median-Estimate)/Estimate].

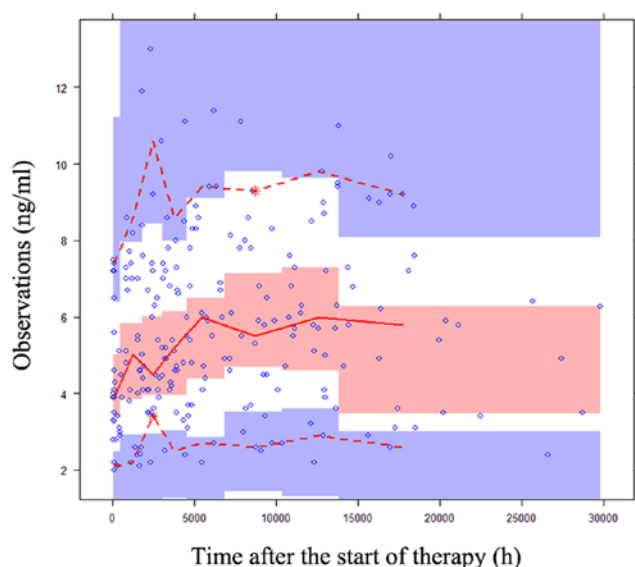


Figure 2. The final model VPC plots. The y-axis represents the observed whole blood concentration of tacrolimus. The middle solid line represents the median of the prediction-corrected concentrations. The lower and upper dashed lines are the 2.5th and 97.5th percentiles of the prediction-corrected concentrations, respectively. The blue points represents observed concentrations (measured concentrations). The pink zone represents the confidence interval of the middle solid line and the purple zones indicate the confidence interval of the lower and upper dashed lines. VPC, prediction-corrected visual predictive check. Partial concentration values were collected based on previous studies (13,14).

recommended for a body weight of 10-23 kg and 0.05 mg/kg/day for 23-60 kg, as presented in Table III.

Discussion

Tacrolimus, also known as FK506, is a 23-membered lactone ring that is isolated from *Streptomyces tsukubaensis* and used as a potent immunosuppressant. It has been reported that tacrolimus is 100 times stronger than cyclosporine and it may exert its effects by inhibiting the function of T lymphocytes and downregulating the expression of interleukin-2 (20,21). In addition, it has been used as the first-line drug for patients

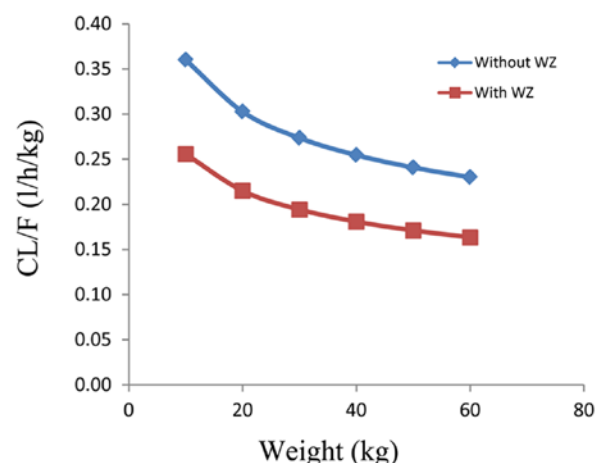


Figure 3. CL/F of tacrolimus in children and adolescents with lupus nephritis. WZ, wuzhi capsule; CL/F, apparent oral clearance.

with liver and renal transplant (16,22-34). Furthermore, it has been demonstrated that tacrolimus may be used to improve the outcome of patients who undergo bone marrow (35-42), lung (43) and heart transplantation (44).

In previous years, clinical experiments have also indicated that tacrolimus has useful applications in systemic-onset juvenile idiopathic arthritis (45-48), nephrotic syndrome (49-55), SLE (56-65), myasthenia gravis (66,67), ulcerative colitis (68,69) and autoimmune hepatitis (70). Furthermore, according to a previous review article, tacrolimus is a safe and effective agent for treating patients with LN (10).

It has been reported that the underlying mechanism of action of tacrolimus in LN is primarily its inhibitory effect on the dephosphorylation of the nuclear factor of activated T cells, which thereby reduces the activity of genes encoding interleukin-2 and associated cytokines (71), leading to the inhibition of T-cell activation. In addition, the effect of tacrolimus on LN is also the result of its well-known antiproteinuric effects that have been utilized in the treatment of a variety of kidney pathologies (72). It has also been reported that in mouse models of SLE, tacrolimus inhibits the progression of glomerular hypercellularity, crescent formation and proteinuria development,

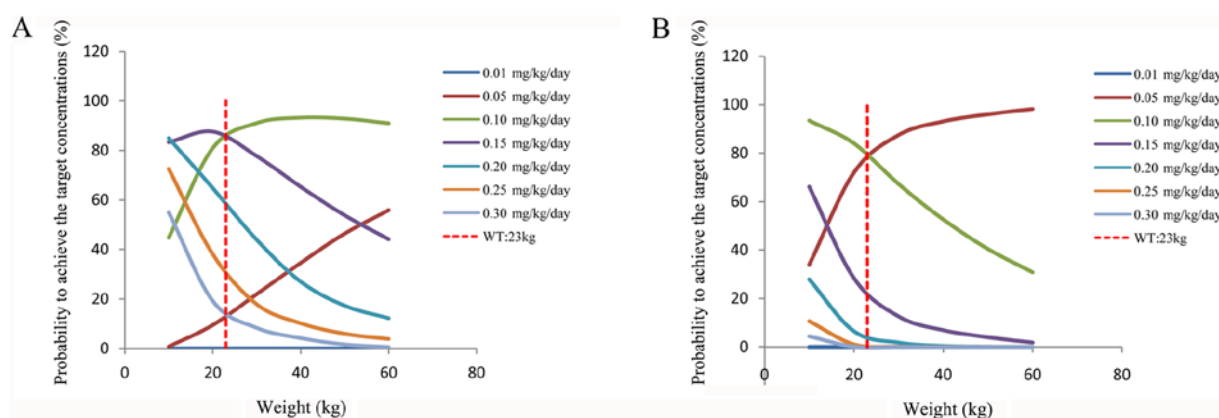


Figure 4. Probability to achieve the target concentrations (A) in patients without administration of wuzhi capsule and (B) in patients with administration of wuzhi capsule. WT, individual body weight.

Table III. Initial dose recommendations of tacrolimus in children and adolescents with lupus nephritis.

Drug combination with wuzhi capsule	Body weight (kg)	Dose recommendation (mg/kg/day) ^a
No	10-23	0.15
No	23-60	0.10
Yes	10-23	0.10
Yes	23-60	0.05

^aSplit into two doses.

and suppresses the increase of anti-double-stranded DNA antibody serum levels in animal models of spontaneous LN (73). Therefore, from the above perspective, the mechanism of action of tacrolimus in treating LN is well explained.

However, due to the considerable pharmacokinetic variation among individuals (74,75), the optimal initial dose regimen of tacrolimus in pediatric and adolescent patients with LN has remained to be determined. Population pharmacokinetic models may be useful in predicting individualized therapy by integrating different effects of variables on drug exposure (76), which may determine the initial dosage in different diseases. This includes dose simulation of oxcarbazepine in pediatric patients with epilepsy (77), dose optimization of vancomycin in neonates and young infants (78), dose optimization of azithromycin in pediatric patients with community-acquired pneumonia (79), dose optimization of cyclosporin in pediatric patients with hemophagocytic lymphohistiocytosis (80) and dose optimization of tacrolimus in patients with nephritic syndrome (81,82). Thus, the present study aimed to establish a population pharmacokinetic model of tacrolimus and further optimize the initial dosage regimen of tacrolimus in pediatric and adolescent patients with LN.

In the present study, body weight and co-administration of wuzhi capsule were indicated to influence tacrolimus clearance in pediatric and adolescent patients with LN. A previous similar study demonstrated a non-linear association between drug clearance and body weight in patients (19). In the present study, the rate of tacrolimus clearance in patients who were

not administered wuzhi capsule and those who were administered wuzhi capsule with the same body weight was 1:0.71. Wuzhi capsule is a Chinese patent medicine, which contains the primary active ingredients schisandrin, schisantherin A and schisandrol B (83). It has been demonstrated that wuzhi capsule increases the concentration of tacrolimus (84-86) via inhibition of the enzyme cytochrome P450, family 3 (CYP3A) in order to inhibit the metabolism of tacrolimus (86,87). This is able to reduce the dose of tacrolimus required and reduce medical costs, particularly in patients who require to take tacrolimus over a long period of time. In addition, the present study revealed a wide range of hemoglobin levels, which may be due to differences in various physiological or pathological states among the pediatric patients. The specific mechanisms remain to be further explored.

Next, Monte Carlo simulation was used to further predict the optimal dose. This indicated that in patients who weren't administered wuzhi capsule, the initial dosage regimen of 0.15 mg/kg/day was recommended for a body weight of 10-23 kg and 0.10 mg/kg/day for 23-60 kg; in patients who were co-administered wuzhi capsule, the initial dosage regimen of 0.10 mg/kg/day was recommended for a body weight of 10-23 kg and 0.05 mg/kg/day for 23-60 kg.

However, there are limitations to the present study. Polymorphisms of CYP3A5 may be associated with tacrolimus required dose; however, the present study was based on real-world data, in which pharmacogenetics were not considered in tacrolimus dosing and therefore, no routine clinical testing was performed with this regard. Therefore, it should be further investigated whether the inclusion of genotyping in this model is able to better explain the variability in the dosage of tacrolimus. In addition, future studies with more patients are required to verify the results of the present study.

In conclusion, to the best of our knowledge, the present study was the first to construct a population pharmacokinetics model of tacrolimus and optimize the initial dosage regimen for tacrolimus treatment in pediatric and adolescent patients with LN.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZL and HX conceived and designed the study. XC and DW collected and analyzed the data. XC wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and informed consent to participate

The study was approved by the Research Ethics Committee of the Children's Hospital of Fudan University (Shanghai, China). The present study was a retrospective study and the analysis was approved by the Ethics Committee of the hospital without the requirement for written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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