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ORIGINAL RESEARCH ARTICLE

Analysis of Sirolimus Blood Concentration and Influencing Factors in Pediatric Patients: Implications for Individualized Drug Therapy

Xiaolin Xu[1,2,6] · Xueting Mao[2,3] · Bo Liu[2,3] · Yixin Sun[2] · Xiaoling Cheng[2] · Xiaoling Wang[2] · Huawei Mao[1,4,5]

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Abstract

Background and Objective The purpose of this study is to investigate the status of blood concentration of sirolimus (SRL), explore the factors influencing SRL drug blood concentration, and provide guidance for the appropriate utilization of clinical medications.

Methods A single-center retrospective cohort study encompassed 1535 blood drug concentration observations obtained from 249 children from August 2018 to June 2023. Participants were categorized into four groups (A, B, C, and D) on the basis of their blood concentration levels at various time intervals. The analysis focused on identifying the factors that influenced blood concentration in the short- and long-term posttreatment. The primary endpoint was factors affecting the sirolimus blood concentration. The effect of physiopathological indicators on the corrected blood drug concentration (*C*/*D* value) was analyzed to avoid the effect of differences in the dose of SRL used in patients on SRL blood concentrations. The multiple linear regression model was used to examine the impact of factors influencing pharmacokinetics and pharmacodynamics on the *C*/*D*.

Results Analysis of SRL blood concentration monitoring indicated that a majority (60.43%) of patients demonstrated a trough sirolimus concentration (C_0) below the level of the recommended threshold of 5 ng/mL, while approximately 17.7% of patients exceeded 15 ng/mL. The results indicated a noteworthy association between weight and body surface area (BSA) and the *C*/*D* of SRL in groups A, B, and D ($P < 0.05$). Additionally, aspartate transaminase (AST), alanine aminotransferase (ALT), and albumin (ALB) in group A; ALB in group B; and platelet count (PLT) in group C demonstrated a statistically significant correlation with the *C*/*D* of SRL ($P < 0.05$).

Conclusions Clinicians should optimize medication plans by considering the child's weight, BSA, ALT, AST, PLT, ALB, and relevant factors. These findings may serve as a valuable resource for clinicians.

Key Points

Through correlation analysis, we suggest that the adjustment of sirolimus (SRL) blood concentration should be made in consideration of the child's physiological and biochemical parameters.

Pharmacogenomic factors and interactions with concomitant medications have a substantial impact on sirolimus blood concentration profiles, underscoring the necessity for well-designed prospective cohort studies in this field.

1 Introduction

Sirolimus (SRL), also known as rapamycin, is a highly effective immunosuppressant that operates by inhibiting crucial molecules in the phosphatidylinositol-3-kinase–protein kinase B–rapamycin mammalian target (PI3K–AKT–mTOR) pathway [1, 2]. Using SRL in pediatric patients with organ transplantation, autoimmune disease, vascular malformation, and tuberous sclerosis has shown a steady increase as a result of advancements in clinical trials and real-world evidence. This strategy has become a crucial element in improving prognosis and has made a significant contribution to improving survival rates in children [3–6]. The narrow therapeutic window of SRL results in notable variability in individual responses among pediatric patients, particularly in younger age cohorts in the process of growth and development who

Xiaolin Xu and Xueting Mao have contributed equally to this work and share the first authorship.

Extended author information available on the last page of the article

demonstrate heightened instability in pharmacokinetic parameters. Insufficient research findings on blood drug levels present difficulties in accurately establishing appropriate dosages for patients using this measure [7].

The reference range can assist healthcare providers in modifying medication dosages according to individual risk factors to attain or sustain a desired concentration within the reference range, thereby minimizing disease activity and mitigating potential adverse effects. Longitudinal data are necessary to establish the efficacy of maintaining a specific concentration in preventing patient flares over an extended period of time. Additionally, we investigated the physiological determinants influencing the probability of attaining a target blood level of SRL. Previous studies on the factors influencing the blood concentration of SRL have been limited by small sample sizes of approximately 52 patients and a lack of multivariate analysis, with only univariate analyses conducted [8]. Consequently, the factors affecting the blood concentration of SRL have not been thoroughly elucidated.

The aim of this research was to investigate the blood concentration levels of SRL at different timepoints and to assess the factors that impact these concentrations through multiple linear regression analysis. The overarching objective was to offer recommendations for appropriate clinical use, tailor dosages for individual patients, reduce the occurrence of adverse drug reactions, and improve treatment outcomes.

2 Materials and Methods

2.1 Study Design and Inclusion Criteria

The study received approval from the research ethics committee of the hospital (reference number: [2024]-Y-094-D). It retrospectively enrolled pediatric patients who underwent a minimum of 1 week of treatment with SRL at the center between August 2018 and June 2023. A cohort of 249 patients who underwent a total of 1535 tests were monitored from the day preceding the initiation of SRL treatment until the conclusion of the treatment regimen. The relevant data are outlined in Table 1. The study's inclusion criteria encompassed patients diagnosed with immune deficiency, immune thrombocytopenia, and lymphatic malformation, who were required to provide detailed records of their medical history, medication regimen, and laboratory test results. In addition, individuals with abnormal SRL blood trough concentrations were required to undergo genetic testing. If genetic variants were present, they were excluded from this study. Additionally, participants were required to have undergone treatment with SRL for a minimum of 1 week, with their blood drug concentration reaching a steady state. The study's exclusion criteria excluded patients with diarrhea (watery stools 6–8 times/day), those who had received SRL treatment for less than 1 week, and those who lacked complete relevant information. The collected case data were categorized for analysis of influencing factors on the basis of blood concentration monitoring time: 1 week after SRL (group A), 2 weeks after SRL (group B), 4 weeks after SRL (group C), and 12 weeks after SRL (group D). All patients were orally administered SRL capsules (0.5 mg, North China Pharmaceutical) for treatment, accompanied by concurrent medication education. The recommended individualized starting doses ranged from 0.8 to 1.0 mg/m^2/day.

2.2 Outcome Measures

The blood concentration of SRL data were acquired from the hospital system, along with documentation of patient demographics, daily dosage, and diverse pathophysiological parameters, including erythrocyte count (RBC), leukocyte count (WBC), platelet count (PLT), hemoglobin (HGB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), albumin (ALB), and creatinine (CREA).

2.3 Sample Analysis

Blood samples were obtained and processed utilizing a Siemens Automatic Biochemistry Analyzer Viva-E (EMIT 2000 homogeneous enzyme immunoassay). The samples were expeditiously cooled on an ice plate or ice box and promptly transported to the designated sample processing area within 30 min for DNA extraction or centrifugation. Following this, the blood sample underwent processing and was subsequently divided into two duplicate samples by the sample handler, with one designated as the determination sample and the other as the backup sample. Both duplicates were then stored in a refrigerator at temperatures of − 20 °C or − 80 °C [9]. Moreover, SRL blood concentrations and physiopathologic indices were completed within 2 h. The blood sample collection, handover, processing, and storage procedures were rigorously followed according to the guidelines outlined in the SRL blood sample collection, handover, processing, and storage procedures. Dosage adjustments were made as needed to maintain levels within the range of 5–15 ng/mL. The maintenance of SRL blood levels at 5–15 ng/mL was deemed to represent a state of equilibrium.

2.4 Statistical Analysis

The blood drug concentrations of 249 patients who completed the observation were analyzed utilizing the quartile method. The categorized data that adhered to a normal distribution were reported as mean ± standard deviation (SD), whereas data that did not conform to a normal distribution

Table 1 Baseline patient data

Projects/indicators	Value mean (Q_{25}, Q_{75})			
	A ($n = 180$)	B ($n = 150$)	C ($n = 120$)	D ($n = 95$)
Male/female	101/79	82/68	62/58	52/43
Age (years)	4.59 (1, 8)	4.93 (1, 9)	4.94 (1, 8)	5.4 (2, 8)
Weight (kg)	21.97 (9.54, 28.75)	22.3 (10, 29.25)	22.25 (10.5, 28)	23.08 (12.5, 29)
Surface area (m^2)	0.78 (0.43, 1.08)	0.8 (0.45, 1.08)	0.8 (0.46, 1.08)	0.83 (0.54, 1.08)
WBC (10^9/L)	7.97 (5.8, 9.49)	8.11 (6.15, 9.46)	7.91 (5.91, 9.3)	7.77 (5.83, 9.68)
RBC (10^{12}/L)	4.74 (4.41, 5.11)	4.82 (4.56, 5.12)	4.94 (4.64, 5.18)	4.93 (4.69, 5.22)
PLT (10^9/L)	304.07 (227, 371.5)	317.15 (236.75, 381.5)	328.66 (262, 408)	320.05 (263, 377)
HGB (g/L)	122.8 (113.25, 131)	124.21 (118.5, 132)	123.9 (120, 130)	122.8(117, 132)
AST (U/L)	37.71 (26.3, 43.3)	36.08 (26.3, 42.3)	37.44 (28.1, 43.83)	36.15 (25.8, 40.4)
ALT (U/L)	25.71 (12.2, 26.68)	22.77 (11.88, 24.33)	22.57 (13.03, 24.28)	26.41 (11.3, 22.6)
TBIL (μmol/L)	9.03 (6.1, 10.51)	8.1 (5.93, 10.25)	8.01 (6.03, 9.54)	8.17 (6.1, 9.35)
ALB (g/L)	42.31 (40.1, 44.68)	42.57 (41.08, 44.73)	42.86 (41.2, 44.3)	42.28 (41, 43.9)
CREA (μmol/L)	26.87 (20.5, 32.3)	27.76 (20.4, 33.83)	28.81 (21.73, 34.35)	29.6 (22.5, 34.1)
C_0 (ng/mL)	7.68 (4.51, 9.92)	8.12 (4.73, 10.29)	7.42 (5.02, 9.06)	6.61 (4.41, 7.89)
D (mg/day)	1.06 (0.5, 1.5)	1.14 (0.67, 1.5)	1.13 (0.61, 1.5)	1.18 (0.75, 1.5)
C_0/D (ng/mL)/(mg/day)	11.56 (3.55, 11.86)	10.53 (3.8, 11.89)	9.68 (3.49, 12.47)	7.84 (2.57, 9.88)

Group A, B, C, and D: 1 week after sirolimus (group A), 2 weeks after sirolimus (group B), 4 weeks after sirolimus (group C), and 12 weeks after sirolimus (group D). A ($n = 180$), the volume of patients in group A was 180

Q_{25} the 25th percentile, Q_{75} the 75th percentile, *WBC* leukocyte count, *RBC* erythrocyte count, *PLT* platelet count, *HGB* hemoglobin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TBIL* total bilirubin, *ALB* albumin, *CREA* creatinine, C_0 sirolimus trough concentration, *D* dose

were presented as median (range). Pearson's correlation was used for the single-factor analysis of normally distributed data. Spearman's correlation was employed when the *P*-value was less than 0.05, indicating statistical significance. Significant indicators identified in the univariate analysis were subsequently included in a logistic regression analysis. The logistic regression analysis confirmed a statistically significant difference, as indicated by a *P*-value below 0.05.

3 Results

3.1 Patient Population and Characteristics

This study enrolled 249 patients who satisfied the predetermined criteria and were divided into four groups on the basis of the timing of blood drug concentration collection. The mean ages of the groups were 4.59, 4.93, 4.94, and 5.4 years, respectively, with corresponding mean SRL blood concentrations of 7.68, 8.12, 7.42, and 6.61 ng/mL. Detailed data can be found in Table 1.

3.2 Range of SRL Blood Levels

A total of 1535 measurements of trough sirolimus concentration (C_0) were collected, with a median C_0 value 6.11 ng/mL observed in patients at a steady state, ranging from 0.05 to 29 ng/mL. Figure 1 represents the distribution of the C_0 concentrations. In 33.6% of the observed tests (515/1,535), the mean C_0 value was below 5 ng/mL in 278 distinct individuals (60.43%). Conversely, in 17.5% of the observed tests (268/1,535), the mean C_0 exceeded 10 ng/mL in 162 distinct patients (35.22%). C_0 in 68 patients was below 5 ng/mL and above 10 ng/mL. A notable proportion of patients (35.7%) exhibited at least one C_0 level exceeding 10 ng/mL, while 17.7% had at least one C_0 level at steady state, surpassing 15 ng/mL. Among patients concurrently receiving azole antifungals, C_0 levels ranged from 11 to 29 ng/mL, resulting in an overall elevation in C_0 levels.

3.3 Correlation Analysis of Influencing Factors

The age, weight, BSA, RBC, WBC, PLT, HGB concentration, liver enzymes, urinary CREA, and SRL corrected blood drug concentration (*C*/*D* value) of the four groups were subjected to single-factor analysis. The findings indicated significant statistical correlations between age, weight,

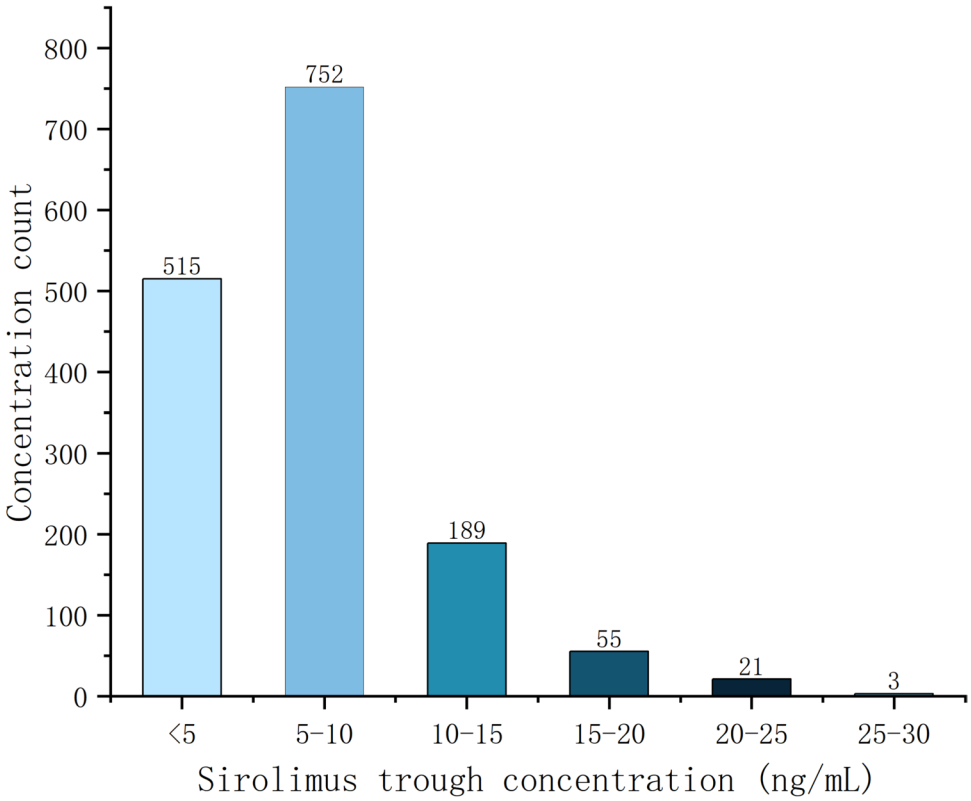

Fig. 1 Distribution of sirolimus trough concentrations (C_0) among the pharmacokinetic-evaluable population ($n = 1535$)

BSA, HGB, CREA, AST, and ALT and the *C*/*D* of SRL across the four sampling times, with *P*-values less than 0.05. WBC and ALB in group A, TBIL and ALB in group B, WBC and TBIL in group C, and TBIL in group D also showed statistical correlations with the *C*/*D* of SRL. However, RBC and PLT had no significant correlation with the *C*/*D* of SRL in the four different sampling periods (Table 2). Multiple regression analysis indicated a significant association between weight and BSA with the *C*/*D* of SRL in groups A, B, and D. Furthermore, AST, ALT, and ALB in group A; ALB in group B; and PLT in group C exhibited a statistically significant correlation with the *C*/*D* of SRL, with all *P*-values < 0.05 (Table 3).

4 Discussion

SRL exhibits a narrow therapeutic range and considerable interindividual variability, particularly among pediatric patients experiencing growth and development (Fig. 2). Consequently, the empirical adjustment of SRL dosage to cater to children's individualized precision medication requirements poses a challenge. In this study, the sample of 249 pediatric patients were gathered retrospectively, and their gender, age, daily drug dosage, and various pathophysiological parameters were analyzed. The findings indicated that approximately half of the children had blood levels failing to meet the desired target or surpassed the established standard (5–15 ng/mL). Univariate analysis revealed a statistically significant correlation between age, weight, BSA, WBC, HGB, AST, ALT, TBIL, ALB, CREA, and blood SRL concentrations. The multivariate analysis revealed that the children's weight and BSA, PLT, ALT, AST, and ALB before administration were significantly correlated with SRL blood concentrations.

The therapeutic drug monitoring (TDM) analysis conducted on SRL indicated that a significant proportion (60.43%) of the patients in this study had C_0 below the minimum recommended threshold of 5 ng/mL once they reached a stable state. Conversely, a notable fraction (approximately 17.7%) of patients experienced excessive drug exposure, with concentrations exceeding 15 ng/mL, owing to enhanced bioavailability. This can potentially result in treatment failure, disease recurrence, and the development of drug resistance. Kenecia et al. discovered that 73–84% of patients admitted to the hospital exhibited insufficient exposure to medication when their blood concentrations fell below the desired range. Additionally, 2–8% of these patients experienced excessive exposure when their blood concentrations exceeded the target range [10]. Although our findings are consistent with those of prior studies, the percentage of overexposure in our study was higher than that of the exposed population in previous studies. This may be due to the inclusion of a larger population in our study and a population

Table 2 Single factor correlation analysis of each factor and *C/D*

Item	A		B		C		D	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	− 0.6674	< 0.0001**	− 0.6620	< 0.0001**	− 0.7613	< 0.0001**	− 0.7176	< 0.0001**
Weight	− 0.6693	< 0.0001**	− 0.6740	< 0.0001**	− 0.7421	< 0.0001**	− 0.6993	< 0.0001**
Surface area	− 0.6736	< 0.0001**	− 0.6779	< 0.0001**	− 0.7232	< 0.0001**	− 0.6908	< 0.0001**
WBC	0.2414	0.0011**	0.1320	0.1074	0.2745	0.0024**	0.1653	0.1094
RBC	− 0.0102	0.8915	0.1465	0.0736	0.1301	0.1567	0.0029	0.9780
PLT	0.0103	0.8908	0.0516	0.5307	0.1516	0.0983	0.0409	0.6937
HGB	− 0.2156	0.0037**	− 0.2319	0.0043**	− 0.4086	< 0.0001**	− 0.2515	0.0139*
AST	0.4393	< 0.0001**	0.5245	< 0.0001**	0.5234	< 0.0001**	0.4905	< 0.0001**
ALT	0.3066	< 0.0001**	0.3985	< 0.0001**	0.2602	0.0041**	0.3720	0.0002**
TBIL	− 0.1083	0.1479	− 0.2462	0.0024**	− 0.2354	0.0096**	− 0.2577	0.0117*
ALB	− 0.2286	0.0020**	− 0.3576	< 0.0001**	− 0.1748	0.0562	− 0.0442	0.6704
CREA	− 0.5661	< 0.0001**	− 0.6551	< 0.0001**	− 0.6555	< 0.0001**	− 0.6612	< 0.0001**

Group A, B, C, and D: 1 week after sirolimus (group A), 2 weeks after sirolimus (group B), 4 weeks after sirolimus(group C), and 12 weeks after sirolimus (group D)

*The Pearson correlation analysis revealed a significant relationship between *X* and the corrected sirolimus *C/D*

r Pearson correlation coefficient, *P P*-value, *WBC* leukocyte count, *RBC* erythrocyte count, *PLT* platelet count, *HGB* hemoglobin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TBIL* total bilirubin, *ALB* albumin, *CREA* creatinine

of immunodeficient children with many antimicrobial drug combinations that may lead to overexposure to SRL.

Based on previous studies, SRL is mainly metabolized by cytochrome P450-3A4 isoenzyme (CYP3A4) and, to a lesser extent, through cytochrome P450-3A5 isoenzyme (CYP3A5) and cytochrome P450-2C8 isoenzyme (CYP2C8) [11]. In turn, affecting these hepatic enzymes has an impact on SRL metabolism. For example, several CYP3A4 inhibitors, such as triazole antibacterial agents (voriconazole, fluconazole, itraconazole, and posaconazole), clotrimazole clarithromycin, and erythromycin, nonhydropyradine calcium-channel blockers (such as diltiazem and verapamil), amiodarone, protease inhibitors, cimetidine, and grapefruit all may increase SRL blood level [11]. However, rifampicin has been found to potentially cause a decrease in sirolimus blood levels [12]. In addition, on the basis of the feature that SRL acts as an inhibitor of the mTOR pathway, SRL is now widely used in the treatment of children with primary immunodeficiency. Moreover, children with immunodeficiency often have recurrent infections. Therefore, the combination of SRL and antimicrobial drugs is important and unavoidable. Based on previous studies, renal transplant patients treated with SRL and voriconazole experience a 4.5-fold increase in the AUC for SRL, while the dose of SRL needs to be decreased by 75–87.5% [13, 14]. Coadministration of SRL and voriconazole increases the blood concentration of SRL [15]. A previous study showed similar results in a case of TDM when the azole antifungal itraconazole was combined with SRL. The whole blood trough concentration of SRL fell outside the therapeutic range after 4 days of an SRL and itraconazole combination [16]. In addition, steroids are commonly used clinically as antiinflammatory drugs, also metabolized through CYP3A4. So far, current clinical evidence regarding drug interactions between steroids and sirolimus is conflicting. In some prior studies, prednisolone affected the pharmacokinetics of SRL, while in others, it did not [17, 18]. Corticosteroids exhibit dual regulatory effects on CYP3A activity, functioning as both competitive inhibitors and transcriptional inducers. As endogenous substrates of the CYP3A isoenzyme, these agents demonstrate dose-dependent pharmacokinetic interactions through substrate competition mechanisms. Functioning as CYP3A substrates, corticosteroids may competitively inhibit the metabolic clearance of coadministered drugs mediated by this enzymatic pathway. This inhibitory mechanism predominates during the initial phase of corticosteroid therapy. Notably, a paradoxical induction effect emerges following prolonged administration (typically manifesting ≥ 72 h posttreatment initiation), mediated through activation of the steroid and xenobiotic receptor (SXR) (also called pregane X receptor (PXR)) [19, 20]. This receptor-mediated upregulation of CYP3A expression ultimately enhances the hepatic metabolism of concomitant CYP3A substrates, potentially resulting in clinically significant reductions in systemic exposure to therapeutic agents such as sirolimus [21]. In healthy subjects, exposure to SRL was elevated by cyclosporine, diltiazem, verapamil, or erythromycin [22]. In addition, it has been shown that coadministration of letermovir with SRL resulted in 3.4-fold increases in area under the blood concentration–time curve and 2.8-fold increases in

Table 3 Multiple linear regression analysis of each factor and *C/D*

Item	A				B				C				D			
	Estimated value	Standard error	*t*	*P*	Estimated value	Standard error	*t*	*P*	Estimated value	Standard error	*t*	*P*	Estimated value	Standard error	*t*	*P*
Weight	1.38	0.33	4.13	< 0.0001**	1.23	0.31	3.99	0.0001**					0.69	0.23	2.98	0.0037**
Surface area	− 69	16.64	− 4.15	< 0.0001**	− 60.28	14.94	− 4.03	< 0.0001**					− 31.15	11.32	− 2.75	0.0072**
PLT									0.01	0.01	2.17	0.0322*				
AST	0.29	0.1	2.99	0.0032**												
ALT	− 0.12	0.05	− 2.3	0.0226*												
ALB	− 0.54	0.25	− 2.15	0.0333*	− 0.99	0.28	− 3.57	0.0005**								

Group A, B, C, and D: 1week after sirolimus (group A), 2 weeks after sirolimus (group B), 4 weeks after sirolimus(group C), and 12 weeks after sirolimus (group D)

*The multiple linear regression analysis revealed a significant relationship between *X* and the corrected sirolimus *C/D*

t t-value, *P P*-value, *PLT* platelet count, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TBIL* total bilirubin, *ALB* albumin

maximum blood concentration [23]. A recent study reported for the first time that cenobamate decreases SRL/everlimus blood levels [24]. It is considered that this situation is caused by both everolimus/sirolimus and cenobamate being metabolized via CYP3A4.

In addition, genetic polymorphisms in SRL are a factor that cannot be ignored. There are numerous types of genes that affect SRL metabolism on the basis of our previous daily practice. Genotypes ABCB1, CYP3A4, and CYP3A5 can all influence SRL metabolism or toxicity. Sam et al. found that ABCB1 type was associated with an increase in triglycerides in renal transplant patients treated with SRL [25]. Mbatchi et al. found that ABCB1 gene polymorphisms were also associated with shortened SRL half-life [26]. Expression of the CYP3A5 enzyme has likewise been shown to result in an increase in the required SRL dose [27]. In addition, mutation gene carriers require higher SRL doses compared with CYP3A4 wild type [27].

Compared with preceding investigations, our study corroborated the findings of Tejani et al. and Filler et al., indicating a significant inverse correlation between age, weight, and SRL blood concentrations [28, 29]. Moreover, our study demonstrated a statistically significant inverse association between the age and weight of pediatric patients and SRL blood concentrations across all four distinct timepoints of blood concentration collection, as determined through univariate analysis. Furthermore, Yimeng et al. conducted a study on TDM in pediatric patients and demonstrated a significant positive association between AST levels and SRL trough concentrations. This finding was also observed by Yadi et al. in adult renal transplantation, where alanine ALT and AST levels positively correlated with SRL blood concentrations [30, 31]. The findings from the four groups in this study indicate a statistically significant positive correlation between the liver enzymes AST and ALT and the *C/D* of SRL. This finding aligns with previous research, suggesting that the liver primarily metabolizes SRL. Moreover, ALT and AST, commonly used sensitive indicators of liver function in clinical treatment, were consistent with the extent of hepatocyte damage in most cases. The liver function of pediatric patients can directly impact the pharmacokinetics of SRL, consequently influencing its blood concentration. However, SRL can potentially cause liver damage in pediatric patients, with instances of fatal hepatic necrosis observed when the trough concentrations in whole blood exceeded therapeutic levels. Zhang et al. studied adult patients who underwent liver transplantation and demonstrated that CREA, an index of renal function, was among the factors influencing steady-state blood trough concentration of SRL. In this study, CREA was also correlated with the *C/D* of the SRL [32]. Consequently, variations in renal function among children may result in disparities in blood drug concentrations.

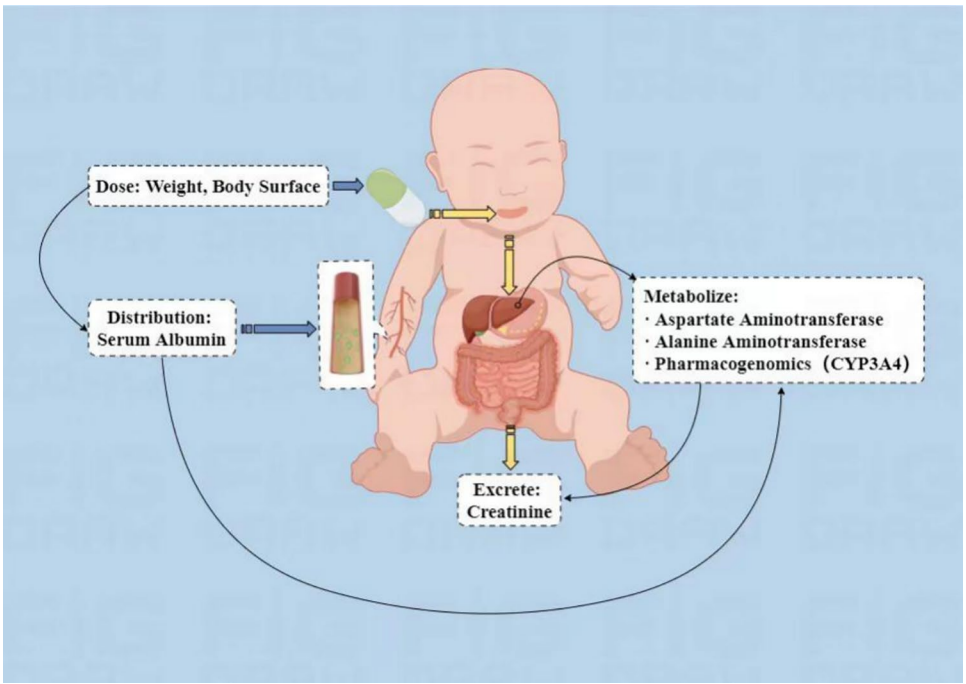

Fig. 2 Factors influencing sirolimus blood concentrations in pediatric patients as identified in this study. Figure created using Figdraw (https://www.figdraw.com/)

The multivariate regression analysis results demonstrated a statistically significant correlation between the weight and BSA of pediatric patients and the *C*/*D* of SRL at weeks 2 and 12 ($P < 0.01$). These factors were identified as the primary determinants of blood SRL concentration. This study's blood concentration collection times were during the 1st, 2nd, 4th, and 12th weeks, covering the initial, intermediate, and long-term phases of SRL absorption and metabolism.

Consequently, we can assume that pediatric patients' weight and BSA are the primary influences on SRL blood concentrations during the early and middle stages of SRL absorption and metabolism. Furthermore, consistent with the findings of the univariate analysis, a significant correlation was observed between *C*/*D* and liver enzymes ALT, AST, and ALB in the 1-week sampling group. This association could be attributed to the initial processes of SRL binding and metabolism in the body. Owing to the short half-life of SRL, ALT, and AST in children, observations related to metabolic processes correlate with SRL blood concentrations only in short-term observations [33]. In contrast to the univariate analysis findings, this study demonstrated that PLT is a significant influencing factor, exhibiting a statistically significant correlation with the *C*/*D* of SRL in the sampled group at week 4. This finding is consistent with a previous study by Yadi et al., who investigated blood concentration monitoring in adult renal transplantation [31]. Balduini et al. demonstrated an inverse correlation between PLT and age [34]. Consequently, PLT was identified as an independent factor for SRL blood concentration in multivariate linear analysis. This conclusion was reached after excluding the influence of age on both PLT and SRL *C*/*D* multivariate analysis. However, the specific reasons for this result require further research.

In contrast to prior research, this study's findings indicate a lack of association between RBC and SRL blood concentrations. However, a cohort study on SRL in the elderly population showed a statistically inverse correlation between RBC and SRL blood concentrations [35]. This disparity may be due to the different populations examined in the respective studies. This study was conducted in a pediatric population, where the lower number of RBCs compared with adults was attributed to a scarcity of hematopoietic raw materials resulting from their rapid growth and development. Consequently, no significant impact on the blood SRL concentration was observed.

We found that the blood concentration of SRL was also statistically correlated with HGB and ALB. This result has not been previously reported, and the mechanism of its occurrence remains unclear. Additionally, this study's results showed that WBC count was positively correlated with the *C*/*D* of SRL in the first and fourth weeks. This correlation may be due to the fact that SRL leads to increased susceptibility to infection and increased WBC. Severe infections also inhibit the CYP450 enzyme system, and it has been shown that SRL metabolism is linked to the expression of CYP450 enzymes [36, 37]. Consequently, infections may lead to a reduction in SRL metabolism. Previous population pharmacokinetic studies also found that blood levels of SRL suddenly increase when patients develop symptoms of infection [38]. Further research should be conducted to confirm this result.

The univariate analysis in this study revealed that RBC and HGB had an opposite relationship with the blood concentration of SRL. Additionally, the blood SRL concentration was not significantly correlated with RBC in this study in multivariate analysis. This result differs from previous studies because SRL can enter and bind RBCs. Generally, HBG is present in RBCs, and the relationship between the two is similar to SRL blood concentrations. However, these results have not been reported.

This study had several limitations. The administration in this study was based on the adult kidney transplant treatment window during the SRL administration. However, this treatment window may not have been optimal for the study population. Therefore, it is necessary to retrospectively investigate the optimal treatment window for SRL in the pediatric population. Furthermore, this study was retrospective. Although the four sampling groups comprised the same study population, the lack of certain data resulted in slight variations in the composition of each group. Consequently, this study's findings solely focus on the impact of laboratory indicators on SRL *C*/*D* while disregarding the potential influences of combination drugs, genetic factors, and food factors on SRL blood concentration. Hence, to obtain more precise results, it is imperative to undertake prospective studies to corroborate this study's findings.

5 Conclusions

Drug monitoring in this study revealed that 60.43% of the patients had an average C_0 below the minimum recommended threshold of 5 ng/mL after achieving a steady state. Additionally, 17.7% of the patients had a C_0 exceeding the maximum threshold of 15 ng/mL. Subsequently, the results of univariate and multivariate analyses revealed that weight, BSA, PLT, AST, ALT, and ALB, with the *C*/*D* of SRL, indicated that these factors independently influenced the blood concentration of SRL. Dosage adjustment was appropriately implemented with the children's weight, BSA, and PLT, ALT, AST, and ALB parameters. In addition, a population pharmacokinetic model of SRL was subsequently developed, incorporating independent influencing factors derived from multivariate linear regression analysis as covariates in the model. This approach aimed to facilitate precise drug utilization guided by the model, thereby optimizing efficacy while minimizing potential harm.

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Declarations

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Conflict of interest The authors declare no conflict of interest.

Ethics approval The study received approval from the Research Ethics Committee of the Beijing Children's Hospital (reference number: [2024]-Y-094-D).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials The data that support the findings of this study are not openly available owing to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions X.M. and X.X. performed the study and analyzed the data. X.M. wrote the manuscript. X.C., X.W., and B.L. were responsible for issuing and collecting scales. H.M. conceived and guided the study and critically revised the manuscript. Y.S. performed methodological support. All authors contributed to the article and approved the final manuscript.

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Authors and Affiliations

Xiaolin Xu[1,2,6] · Xueting Mao[2,3] · Bo Liu[2,3] · Yixin Sun[2] · Xiaoling Cheng[2] · Xiaoling Wang[2] · Huawei Mao[1,4,5]

✉ Xiaoling Wang
wangxiaoling@bch.com.cn

✉ Huawei Mao
maohwei@qq.com

[1] Department of Immunology, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China

[2] Department of Pharmacy, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China

[3] Department of Clinical Pharmacology, College of Pharmaceutical Sciences, Capital Medical University, Beijing 100069, China

[4] Ministry of Education Key Laboratory of Major Diseases in Children, Beijing Key Laboratory for Genetics of Birth Defects, Beijing 100045, China

[5] Department of Nephrology and Rheumatology, Children's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Hospital of Beijing Children's Hospital, Xinjiang 830000, China

[6] School of Traditional Chinese Medicine, Shenyang Pharmaceutical University, Shenyang 110016, China