BMC Psychiatry

RESEARCH

Open Access

Identifying factors related to sertraline concentrations in child/adolescent and adult patients: insights from a therapeutic drug monitoring service

Ruoming Li[1†], Bin Bi[2†], Zhe Dong[1], Sai Chen[2], Yuan Yun[2], Xiuhuan Wang[1], Hasenqimuge[3], Song Chen[1*] and Yunlong Tan[1]

Abstract

Introduction Sertraline, a widely prescribed antidepressant, has considerable variability in serum concentrations. This retrospective study aimed to identify key determinants influencing sertraline concentrations, with a special focus on age-related differences.

Methods We conducted a retrospective analysis of TDM data from 1076 patients (474 children/adolescents and 602 adults) collected between 2018 and 2024. Multivariable generalized linear regression and restricted cubic spline models were used to examine the relationships between clinical parameters and sertraline concentrations.

Results The daily dose and aspartate aminotransferase (AST) level were positively correlated with the sertraline concentration in both age groups. Sex had a significant effect, with women exhibiting 43% ($P=0.001$) and 37% ($P=0.001$) higher concentrations than men in the child/adolescent and adult groups, respectively. In children and adolescents, the albumin (Alb) level and neutrophil (NEUT) count also considerably influence concentrations. CYP2C19 poor metabolizers (PMs) tended to be present at relatively high concentrations, but the difference was not statistically significant. Among child and adolescent patients, significant differences in dose-adjusted serum concentration (C/D) values ($P=0.0291$) were observed across different CYP2C19 phenotypes, with PMs exhibiting higher C/D values. In a cohort of 593 patients who underwent high-sensitivity C-reactive protein (hsCRP) testing, a nonlinear, U-shaped correlation between hsCRP levels and sertraline concentrations was identified in children and adolescents.

Discussion By identifying key factors such as daily dose, sex and AST levels, clinicians can develop tailored treatment plans for individual patients. These findings underscore the need for further research to elucidate the interplay between sertraline metabolism and patients' physiological and pathological characteristics.

Keywords Therapeutic drug monitoring, Pharmacogenomics, Psychopharmacology, Antidepressants

[†]Ruoming Li and Bin Bi contributed equally to the work.

*Correspondence:
Song Chen
asongsi@163.com

[1]Peking University HuiLongGuan Clinical Medical School, Beijing HuiLongGuan Hospital, Beijing, China
[2]The Second People's Hospital of Guizhou Province, Guiyang, China
[3]The First Hospital of Hohhot, Hohhot, China

Introduction

Psychiatric disorders, especially depression and schizophrenia, rank among the top 20 causes of disability worldwide [1, 2]. Pharmacotherapy stands as the cornerstone in managing mental disorders. Between 2008 and 2019, the global use of psychotropic medications grew by an average of 4.08% per year, reflecting greater recognition of mental health as an essential part of overall well-being [3].

Sertraline is one of the most commonly prescribed psychotropic medications. It is approved for major depressive disorder, obsessive–compulsive disorder, and several other indications [4]. In children and adolescents, sertraline has shown both efficacy and good tolerability during key stages of biopsychosocial development [5], which has led to its frequent use across all age groups [6]. At present, sertraline dosing is guided mainly by the product label and clinical experience. However, relying on population-based recommendations can sometimes lead to suboptimal dosing. Indeed, a recent dose–response meta-analysis suggests an effective daily range of 50–150 mg [7]. Clinicians necessitate specific guidelines to guide individualized pharmacotherapy with sertraline.

Therapeutic drug monitoring (TDM) is an effective method for quantifying patients' peripheral drug exposure by monitoring blood drug concentrations [8] and can be applied to diverse clinical scenarios, such as optimizing dosage, assessing adherence, and addressing adverse effects [9]. It is particularly crucial not only for drugs exhibiting high interindividual pharmacokinetic variability, such as sertraline (coefficient of variation of concentration: 59%) [10] but also when drugs are administered to special populations, such as children and adolescents, or to patients experiencing complex medication interactions or metabolic-related genetic variations [9, 11]. As an internationally recognized, evidence-based consensus in neuropsychopharmacology, the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) guidelines recommend therapeutic drug monitoring (TDM) for sertraline [12]. This recommendation is particularly important in pediatric patients because of developmental differences and the lack of well-defined effective dose ranges [13].

Intrinsic and extrinsic factors, including dose, sex, age laboratory indices, genetics, inflammatory status, and comedication, can influence sertraline concentrations [14–19].

For example, females may have lower clearance rates, which should be taken into account when adjusting the dosage [16]. In children and adolescents, rapid physiological development can markedly alter sertraline pharmacokinetics and clinical response [20, 21]. Studies have shown that age-related changes in liver enzyme activity significantly affect sertraline metabolism; poor metabolizers (PMs) among younger patients tend to have higher plasma concentrations and may experience more adverse effects [17, 22].

Genotype-predicted metabolic phenotypes of drug-metabolizing enzymes may not match clinically observed phenotypes. This phenomenon is known as phenoconversion [23]. It is driven by enzyme inhibitors, inducers, inflammatory states, etc [23, 24]. After accounting for phenoconversion, the prevalence of CYP2C19 and CYP2D6 PMs in adults increases by 6.3-fold and 4.6-fold, respectively [25]. Adolescents also experience a high rate of phenoconversion (46%). Among them, the prevalence of CYP2C19 PMs increases 7.3-fold, and CYP2D6 PMs increase 4.5-fold [26]. Therefore, sertraline dosing in clinical practice should be personalized by integrating factors such as age, sex, and genotype to optimize therapeutic efficacy and minimize adverse effects.

The present study retrospectively collected sertraline TDM data beginning in 2018 to explore clinical variables associated with sertraline concentration, with a special focus on age-related variability. Additionally, the study separately analyzed the impact of pharmacogenetics and high-sensitivity C-reactive protein (hsCRP) levels. The findings of this study are expected to enable clinicians to predictively estimate sertraline exposure within individual patients on the basis of their specific characteristics, thereby facilitating the selection of appropriate and personalized pharmacotherapy.

Methods

Study population

Data were retrospectively collected from the TDM database of The Second People's Hospital of Guizhou Province in China (Guizhou Mental Health Center, China), which spans from 2018 to 2024. We screened for inpatients whose serum sertraline concentration was tested. The samples were collected to determine the trough concentration at steady state. Patients with complete TDM information, medication details, and demographic data were included.

Data collection

Sertraline dosage, dosing frequency, and sertraline concentration monitoring results were collected from electronic medical records. For patients with multiple sertraline concentration tests during the same hospitalization, only the data from the last test were retained. The dose-adjusted serum concentration (C/D) was calculated as the steady-state trough concentration/daily dose of sertraline. A high C/D indicates slow drug metabolism [12, 27].

Demographic information (age, sex, ethnicity) and clinical data (primary diagnosis; comorbid liver, renal, and gastrointestinal diseases assessed by the International

Classification of Diseases, 10th Revision) were recorded. Concomitant medication information focused on inhibitors or inducers of the cytochrome P450 protein (CYP) family, particularly CYP2B6, CYP2C19, and CYP2D6, as sertraline is metabolized primarily by these enzymes [28, 29]. A list of strong/moderate inhibitors or inducers was obtained from the DRUGBANK database. (https://go.drugbank.com/).

The laboratory measurements included serum levels of albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), creatinine (Scr), blood urea (Urea), β2 microglobulin and hsCRP. We also collected total white blood cell (WBC) counts and absolute counts of neutrophils (NEUT), lymphocytes (LY), monocytes (MONO) and eosinophils (EOS). Owing to incomplete eGFR data within the electronic medical records system, we calculated the eGFR via the modified MDRD equation, which is suitable for the Chinese population [30]. Data extraction was conducted by two authors to ensure consistency.

Quantification of Sertraline

Blood samples were collected prior to sertraline administration. The quantification was performed via an automated two-dimensional liquid chromatography (2D-LC) method [31], which combines a two-dimensional liquid chromatography system with a high-performance liquid chromatography system. The automated 2D-LC system used was the FLC-2701, provided by Hunan Demite Instrument Co., Ltd. The precision, accuracy, sample residue, selectivity, matrix effects, recovery, reliability, and stability of the established method met the requirements for pharmaceutical analysis.

CYP2C19 genotype testing

DNA microarray analysis in combination with polymerase chain reaction (PCR) was applied to detect *CYP2C19* gene polymorphisms. The relevant testing tools, including the *CYP2C19* genetic testing kit, BR-526-24 automatic hybridizer, and BE-2.0 biochip reader, were all sourced from Shanghai BaiO Technology Co., Ltd. The testing procedure is outlined as follows: A 2 mL blood sample was collected from the patient using an ethylenediaminetetraacetic acid (EDTA) anticoagulant tube. DNA extraction was performed within 24 h of sample collection. The PCR reaction mixture, Taq enzyme, and DNA template were prepared in appropriate proportions. PCR amplification was carried out using a thermos cycler supplied by Guangzhou Kaipu Biotechnology Co., Ltd., with the following program: an initial denaturation at 50℃ for 5 min and 94℃ for 5 min, followed by 35 cycles of denaturation at 94℃ for 25 s, annealing at 56℃ for 25 s, and extension at 72℃ for 25 s, with a final extension at 72℃ for 5 min. The reagents were prepared in accordance with the kit's instructions. The biochip was then taken out and subjected to hybridization and color development on a BR-526-24 automatic nucleic acid molecular hybridizer. Subsequently, the biochip was scanned using a BE-2.0 biochip reader, and genotype image analysis was conducted utilizing *CYP2C19* genotype analysis software to obtain the test results.

Statistical analysis

Descriptive statistics were computed for the distribution of participant characteristics. To address potential age-related heterogeneity, analyses were stratified for children and adolescents (aged 6–17 years) and adults (aged ≥ 18 years). Continuous variables are presented as medians (1st quartile, 3rd quartile), whereas categorical variables are summarized as counts and percentages. Missing laboratory test results were imputed with the median value for continuous variables. Specifically, there was one missing value for each of the following: Alb, ALT, AST, GGT, ALP, Scr, and BUN. There were eight missing values for each of the following: WBC, NEUT, LY, MONO and EOS.

Comparisons were performed via the chi-square test, Mann–Whitney U test, or Kruskal–Wallis test, as appropriate. The Spearman correlation coefficient was calculated to assess the correlations between the daily dose, hsCRP level and sertraline concentration. Due to the nonnormal distribution of serum sertraline concentrations (as assessed via histogram visualization), generalized linear regression (GLM) with a "log" link function and Gamma distribution was employed. Univariable GLM was first applied to screen 25 candidate variables, followed by multivariable GLM incorporating variables with $P < 0.1$ in univariable analysis and variance inflation factor (VIF) < 4 to mitigate multicollinearity. Additionally, a restricted cubic spline (RCS) model was used to investigate the associations between hsCRP and sertraline concentrations in children/adolescents and adults, adjusting for covariates. Analyses were conducted via R software version 4.4.1, with a significance level of $P < 0.05$.

Results

Characteristics of the included patients

A total of 1076 patients (474 children/adolescents, 602 adults) whose complete sertraline concentration and clinical data were available were included. The characteristics of the included patients are detailed in Table 1. The median age for children and adolescents was 15.0 (14.0, 16.0) years, and it was 34.0 (21.0, 53.0) years for adults. Men were more prevalent among children and adolescents (76.37%) than adults (57.48%). Across all patient groups, the ethnic majority was Han Chinese (> 90%). Major depressive disorder was the most common

Table 1 Characteristics of the included patients

Variables	Children and Adolescents (*n* = 474)	Adults (*n* = 602)	Total (*n* = 1076)	*P*
Age (years)	15.0 (14.0, 16.0)	34.0 (21.0, 53.0)	19.0 (15.0, 39.0)	< 0.001
6–12	34 (7.17%)	0 (0%)	34 (3.16%)	
13–17	440 (92.83%)	0 (0%)	440 (40.89%)	
18–65	0 (0%)	543 (90.20%)	543 (50.46%)	
> 66	0 (0%)	59 (9.80%)	59 (5.48%)	
Sex				< 0.001
Male	362 (76.37%)	346 (57.48%)	708 (65.80%)	
Female	112 (23.63%)	256 (42.52%)	368 (34.20%)	
Ethnicity				0.399
Han	437 (92.19%)	563 (93.52%)	1000 (92.94%)	
Minority	37 (7.81%)	39 (6.48%)	76 (7.06%)	
Main diagnosis				< 0.001
Major depressive disorder	275 (57.97%)	318 (52.82%)	593 (55.11%)	
Anxiety disorder	44 (9.28%)	146 (24.25%)	190 (17.66%)	
Behavioral and emotional disorders that usually develop during childhood and adolescence	121 (25.53%)	0 (0%)	121 (11.25%)	
Schizoaffective disorder	7 (1.48%)	29 (4.82%)	36 (3.35%)	
Organic psychiatric disorder	3 (0.63%)	27 (4.49%)	30 (2.79%)	
Alzheimer disease	0 (0%)	21 (3.49%)	21 (1.95%)	
Schizophrenia	1 (0.21%)	12 (1.99%)	13 (1.21%)	
Mental and behavioral disorders due to psychoactive substance use	0 (0%)	11 (1.83%)	11 (1.02%)	
Obsessive-compulsive disorder	5 (1.05%)	6 (0.99%)	11 (1.02%)	
Reaction to severe stress, and adjustment disorders	1 (0.21%)	7 (1.16%)	8 (0.74%)	
other	17 (3.59%)	25 (4.16%)	42 (3.90%)	
Daily dose (mg/d)	100.00 (100.00, 150.00)	125.00 (100.00, 150.00)	125.00 (100.00, 150.00)	0.005
Frequency				0.366
QD	447 (94.30%)	575 (95.51%)	1022 (94.98%)	
BID	27 (5.70%)	27 (4.49%)	54 (5.02%)	
Sertraline serum concentration (ng/mL)	51.0 (30.1, 81.5)	59.2 (34.3, 96.5)	54.9 (32.5, 90.0)	0.003
< 10	22 (4.64%)	27 (4.48%)	49 (4.55%)	
10–150	415 (87.55%)	533 (88.54%)	948 (88.11%)	
> 150	37 (7.81%)	42 (6.98%)	79 (7.34%)	
C/D ((ng/ml)/(mg/d))	0.44 (0.31, 0.67)	0.50 (0.33, 0.71)	0.47 (0.32, 0.69)	0.036
Liver diseases				0.001
No	439 (92.62%)	520 (86.38%)	959 (89.13%)	
Yes	35 (7.38%)	82 (13.62%)	117 (10.87%)	
Renal diseases				< 0.001
No	461 (97.26%)	545 (90.53%)	1006 (93.49%)	
Yes	13 (2.74%)	57 (9.47%)	70 (6.51%)	
Gastrointestinal diseases				0.002
No	467 (98.52%)	573 (95.18%)	1040 (96.65%)	
Yes	7 (1.48%)	29 (4.82%)	36 (3.35%)	
CYP enzyme inhibitors				0.949
No	450 (94.94%)	571 (94.85%)	1021 (94.89%)	
Yes	24 (5.06%)	31 (5.15%)	55 (5.11%)	
CYP2C19 genotypes and phenotypes				0.406
*1/*1 (NM)	66 (35.68%)	110 (41.82%)	176 (39.29%)	
*1/*2 (IM)	82 (44.32%)	109 (41.83%)	191 (42.63%)	
*1/*3 (IM)	12 (6.49%)	14 (41.44%)	26 (5.80%)	
*2/*2 (PM)	18 (9.73%)	23 (8.75%)	41 (9.15%)	

Table 1 (continued)

Variables	Children and Adolescents (*n* = 474)	Adults (*n* = 602)	Total (*n* = 1076)	*P*
*2/*3 (PM)	6 (3.24%)	6 (2.28%)	12 (2.68%)	
*3/*3 (PM)	1 (0.54%)	1 (0.38%)	2 (0.45%)	
NA	289	339	628	
Alb (g/L)	42.40 (40.23, 44.30)	41.55 (39.10, 44.00)	42.00 (39.58, 44.10)	< 0.001
ALT (U/L)	14.00 (10.00, 23.00)	21.00 (14.00, 35.00)	18.00 (12.00, 31.00)	< 0.001
AST (U/L)	19.00 (16.00, 24.00)	21.00 (17.00, 30.00)	20.00 (17.00, 27.00)	< 0.001
GGT (U/L)	14.00 (11.00, 20.00)	21.00 (15.00, 38.00)	17.00 (12.00, 29.00)	< 0.001
ALP (U/L)	100.00 (79.00, 131.00)	73.00 (59.25, 88.00)	83.00 (67.00, 108.00)	< 0.001
Scr (umol/L)	58.20 (50.35, 66.60)	68.30 (57.95, 79.07)	63.20 (54.20, 73.70)	< 0.001
Urea (mmol/L)	3.74 (3.07, 4.55)	4.12 (3.31, 5.06)	3.93 (3.17, 4.81)	< 0.001
eGFR (mL/min/1.73m^2)	122.66 (108.35, 145.65)	94.74 (80.57, 107.81)	105.69 (88.71, 127.63)	< 0.001
B2m (mg/L)	1.37 (1.10, 1.70)	1.30 (1.10, 1.60)	1.30 (1.10, 1.63)	0.077
WBC (*10^9/L)	5.91 (5.06, 6.95)	6.01 (5.16, 7.13)	5.96 (5.14, 7.04)	0.146
NEUT (*10^9/L)	3.17 (2.55, 4.12)	3.31 (2.64, 4.13)	3.24 (2.62, 4.12)	0.209
LY (*10^9/L)	1.96 (1.60, 2.35)	1.99 (1.62, 2.42)	1.98 (1.61, 2.37)	0.167
MONO (*10^9/L)	0.44 (0.34, 0.57)	0.44 (0.35, 0.55)	0.44 (0.35, 0.55)	0.948
EOS (*10^9/L)	0.14 (0.08, 0.21)	0.13 (0.08, 0.18)	0.13 (0.08, 0.19)	0.170
NLR	1.62 (1.23, 2.26)	1.71 (1.25, 2.26)	1.67 (1.24, 2.26)	0.453
hCRP (mg/L)	0.70 (0.30, 2.20)	0.90 (0.25, 2.60)	0.60 (0.30, 2.10)	0.189

Note. QD, quaque die (once a day); BID, bis in die (twice a day); C/D, dose-adjusted serum concentration; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; WBC, total white blood cell count; NEUT, absolute counts of neutrophils; LY, lymphocytes; MONO, monocytes; EOS, eosinophils; NLR, neutrophil–lymphocyte ratio; hsCRP, hypersensitive C-reactive protein

Continuous variables are expressed as medians (1st quartile, 3rd quartile), categorical variables are expressed as n (%), and *P* values are calculated via the Mann–Whitney test or chi–square test

diagnosis, accounting for 57.97% of cases in children and adolescents and 52.82% in adults, with an overall prevalence of 55.11%. Among children and adolescents, behavioral and emotional disorders specific to childhood and adolescence constituted the second most frequent diagnosis (25.53%), followed by anxiety disorders (9.28%). In adults, anxiety disorders ranked second (24.25%), while schizoaffective disorder (4.82%) and organic psychiatric disorders (4.49%) were notably more prevalent compared to children and adolescents. Detailed diagnostic profiles for each group are provided in Supplementary Materials.

Compared with children and adolescents, adults have higher rates of liver, renal, and gastrointestinal comorbidities, with proportions of 13.62%, 9.47%, and 4.82%, respectively. Few patients (approximately 5%) were treated with CYP enzyme inhibitors, and no patients received CYP enzyme inducers with sertraline. Laboratory measures showed multiple significant age-group differences (all $P < 0.001$): children and adolescents exhibited higher Alb levels [42.40 (40.23–44.30) vs. 41.55 (39.10–44.00) g/L] and lower activities of ALT [14.00 (10.00–23.00) vs. 21.00 (14.00–35.00) U/L], AST [19.00 (16.00–24.00) vs. 21.00 (17.00–30.00) U/L], and GGT [14.00 (11.00–20.00) vs. 21.00 (15.00–38.00) U/L]. In contrast, ALP levels were higher in the younger group [100.00 (79.00–131.00) vs. 73.00 (59.25–88.00) U/L]. Renal markers followed a reciprocal pattern: children and adolescents had lower Scr levels [58.20 (50.35–66.60) vs. 68.30 (57.95–79.07) μmol/L] and Urea levels [3.74 (3.07–4.55) vs. 4.12 (3.31–5.06) mmol/L], but higher eGFR [122.66 (108.35–145.65) vs. 94.74 (80.57–107.81) mL/min/1.73 m^2]. These results underscore physiologic maturation differences between children/adolescents and adults.

Daily dose and serum concentration of Sertraline

The overall median daily dose was 125.00 mg/d (IQR 100.00–150.00). In children and adolescents, the median dose was 100.00 mg/d (IQR 100.00–150.00), whereas in adults it was 125.00 mg/d (IQR 100.00–150.00). Most patients take sertraline once daily, aligning with package insert recommendations [32]. The median serum concentrations of sertraline were 51.00 ng/mL in children and adolescents and 59.15 ng/mL in adults. Overall, 87.6% and 88.5% of individuals were within the therapeutic target range of 10 to 150 ng/mL, respectively (Fig. 1). A statistically positive correlation was observed between the daily dose and the sertraline concentration in all patients, children and adolescents, and adults, with R values of 0.63, 0.65, and 0.60, respectively ($P < 0.01$). The details are

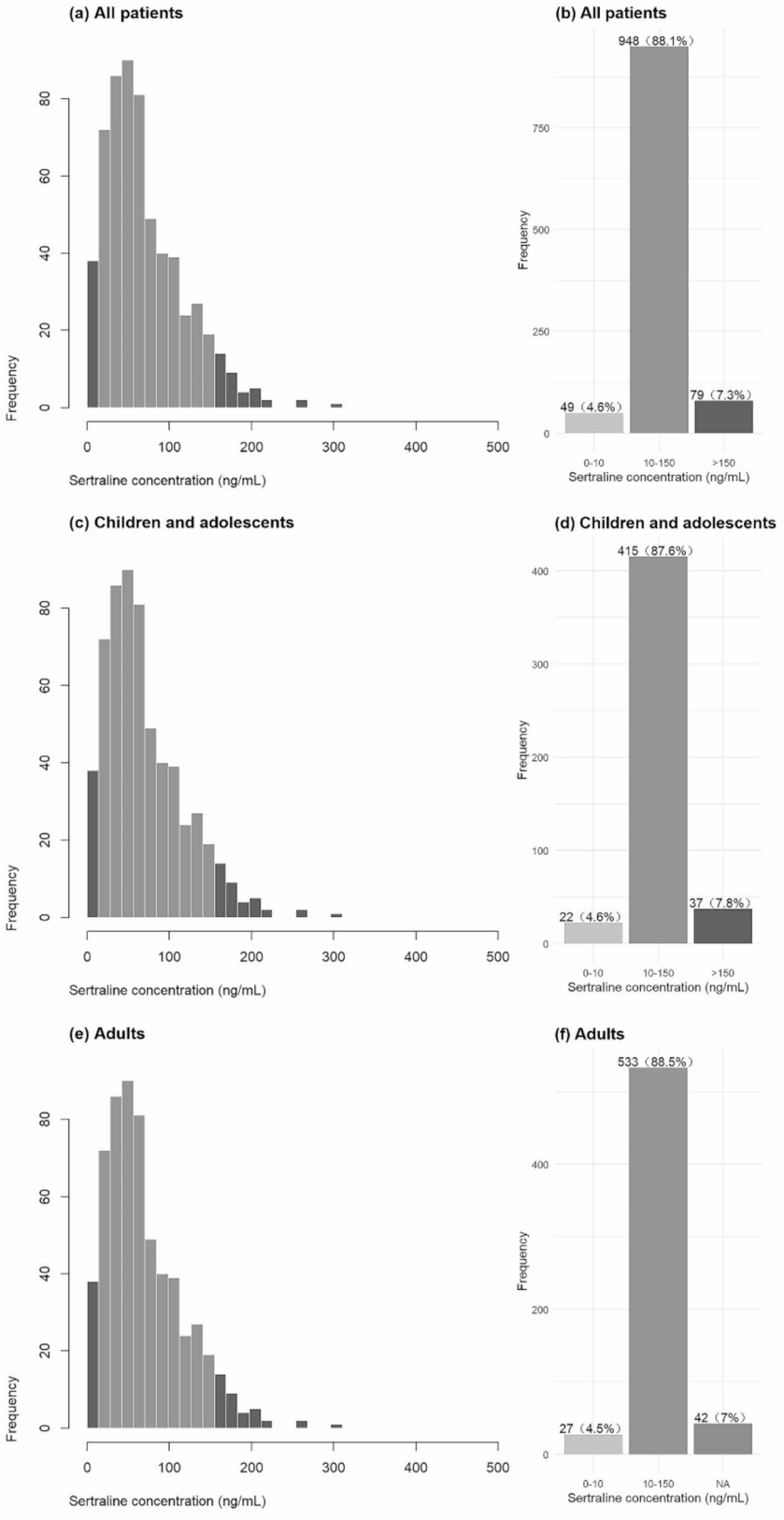

Fig. 1 Histograms of sertraline concentrations in all patients **(a, b)**, children and adolescents **(c, d)**, and adults **(e, f)**

illustrated in Fig. 2. Children and adolescents exhibited a lower median C/D ratio [0.44 (ng/mL)/(mg/day)] than adults [0.50 (ng/mL)/(mg/day)].

Factors influencing Sertraline concentration

The serum concentration distribution of sertraline was nonnormal, as shown in Fig. 1. Generalized linear regression analysis was performed, including both univariable and multivariable models. The detailed results are presented in Table 2.

In children and adolescents, univariable analysis revealed that daily dose; dosing frequency; sex; Alb, AST, GGT, Scr, and urea levels; and WBC, NEUT, and MONO counts were potential factors associated with sertraline concentration. Owing to the possible collinearity between WBC (VIF = 8.85) and NEUT (VIF = 7.31), only NEUT is retained, ensuring that the VIF value of each variable is less than 4. In the multivariable regression, daily dose [1.010 (1.008, 1.011), $P < 2e\text{-}16$], sex [1.430 (1.168, 1.750), $P = 0.001$], Alb level [1.024 (1.002, 1.046), $P = 0.035$], AST level [1.009 (1.003, 1.016), $P = 0.003$], and NEUT count [0.933 (0.887, 0.981), $P = 0.007$] were significant factors.

In adults, univariable analysis identified daily dose, dosing frequency, sex, age, ethnicity, combined gastrointestinal diseases, ALT level, AST level, GGT level, and ALP level as potential factors. Due to the possible collinearity between ALT (VIF = 4.67) and AST (VIF = 4.30), only AST is retained, ensuring that the VIF value of each variable is less than 4. In the multivariable regression, daily dose [1.010 (1.008, 1.011), $P < 2e\text{-}16$], sex [1.370 (1.138, 1.648), $P = 0.001$], and AST level [1.007 (1.001, 1.014), $P = 0.022$] were significant influencing factors.

Impact of sex on the serum Sertraline concentration and C/D ratio

The multivariate regression results indicated higher sertraline concentrations in women than in men (Table 3). In children and adolescents, the median sertraline concentrations were 41.8 ng/mL in men and 53.2 ng/mL in women, with median C/D values of 0.38 (ng/mL)/(mg/d) and 0.47 (ng/mL)/(mg/d), respectively. In adults, the median concentrations were 55.8 ng/mL in men and 62.3 ng/mL in women, with C/D values of 0.472 (ng/ml)/(mg/d) and 0.51 (ng/ml)/(mg/d), respectively. Overall, women had higher C/D values, indicating slower metabolism.

Impact of the CYP2C19 gene polymorphism on the Sertraline concentration and C/D value

CYP2C19 genotyping was performed on 448 of the 1076 patients. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines [28], patients with the *CYP2C19*1/*1* diplotypes are normal metabolizers (NMs), patients with the **1/*2* or **1/*3* diplotypes are intermediate metabolizers (IMs), and patients with the **2/*2*, **3/*3*, or **2/*3* diplotypes are PMs. In the study population, 176 (39.29%) were NMs, 217 (48.43%) were IMs, and 55 (12.25%) were PMs (Table 1). No patients carried function-enhancing alleles, such as **17*. NMs exhibited lower sertraline plasma concentrations and C/D ratios than IMs and PMs in both children/adolescents and adults (Fig. 3). Only the C/D ratio difference in children/adolescents reached statistical significance ($P = 0.029$); all other comparisons—including adult C/D ratios and sertraline concentrations in both age groups—were not significant. Univariable generalized linear model analysis confirmed no significant association between CYP2C19 phenotype and sertraline concentration in children/adolescents (IMs: $P = 0.203$; PMs: $P = 0.068$) or in adults (IMs: $P = 0.793$; PMs: $P = 0.565$).

Impact of HsCRP on Sertraline concentration

Among the 1076 patients, 593 underwent hsCRP testing, including 255 children and adolescents and 338 adults. Using Spearman's rank correlation method, the R values

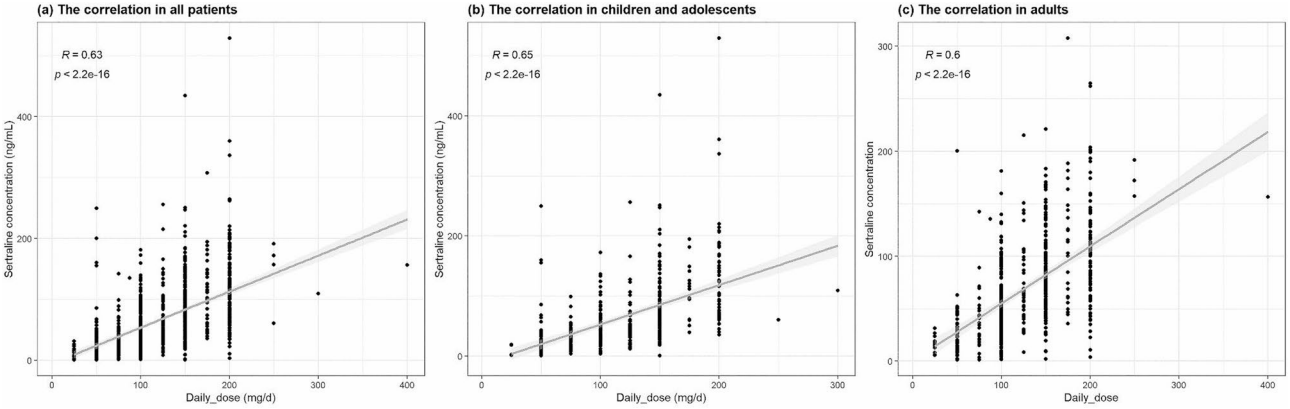

Fig. 2 Correlations between the daily dose and concentration of sertraline in all patients **(a)**, children and adolescents **(b)**, and adults **(c)**. The concentration and C/D values of sertraline do not satisfy the normal distribution, and the linear relationship is calculated via Spearman's rank correlation method

Table 2 Factors influencing Sertraline serum concentrations

Variables	Children and Adolescents						Adults					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
	Exp(β)	95% CI	*P*	Exp(β)	95% CI	*P*	Exp(β)	95% CI	*P*	Exp(β)	95% CI	*P*
Daily dose	1.01	(1.009, 1.012)	**< 2e-16**	1.010	(1.008, 1.011)	**< 2e-16**	1.009	(1.008, 1.010)	**< 2e-16**	1.01	(1.008, 1.011)	**<2e-16**
Frequency (BID)	2.333	(1.724, 3.253)	**2.39e-7**	1.121	(0.823, 1.526)	0.469	1.277	(0.992, 1.680)	**0.068**	1.177	(0.850, 1.629)	0.328
Sex (Female)	1.311	(1.087, 1.571)	**0.004**	1.430	(1.168, 1.750)	**0.001**	1.1	(0.985, 1.226)	**0.090**	1.37	(1.138, 1.648)	**0.001**
Age	1.026	(0.976, 1.080)	0.305				1.004	(1.001, 1.007)	**0.005**	1.05	(0.994, 1.110)	0.084
Ethnicity (Minority)	0.992	(0.745, 1.352)	0.956				1.402	(1.135, 1.755)	**0.002**	1.031	(0.797, 1.334)	0.814
Liver diseases	1.048	(0.782, 1.443)	0.761				1.081	(0.925, 1.270)	0.336			
Renal diseases	1.074	(0.682, 1.825)	0.773				1.073	(0.895, 1.298)	0.460			
Gastrointestinal diseases	0.943	(0.519, 1.977)	0.862				1.272	(0.999, 1.650)	**0.060**	0.765	(0.431, 1.358)	0.361
Alb	1.023	(0.999, 1.049)	**0.074**	1.024	(1.002, 1.046)	**0.035**	0.992	(0.977, 1.007)	0.284			
ALT	1.003	(0.999, 1.006)	0.118				1.002	(1.001, 1.004)	**0.004**			
AST	1.008	(1.002, 1.015)	**0.005**	1.009	(1.003, 1.016)	**0.003**	1.004	(1.002, 1.007)	**0.000**	1.007	(1.001, 1.014)	**0.022**
GGT	1.006	(1.002, 1.012)	**0.007**	1	(0.996, 1.005)	0.853	1.001	(1.000, 1.002)	**0.050**	1.001	(0.996, 1.006)	0.779
ALP	1	(0.998, 1.001)	0.502				1.003	(1.001, 1.006)	**0.001**	1.001	(0.999, 1.002)	0.397
Scr	0.994	(0.988, 0.999)	**0.049**	1.006	(0.999, 1.013)	0.105	1	(0.999, 1.002)	0.888			
Urea	0.931	(0.869, 0.998)	**0.043**	0.961	(0.904, 1.021)	0.196	0.986	(0.949, 1.026)	0.484			
eGFR	1.002	(0.999, 1.004)	0.131				0.998	(0.996, 1.000)	0.102			
WBC	0.926	(0.885, 0.971)	**0.001**				1.005	(0.976, 1.036)	0.765			
NEUT	0.918	(0.872, 0.970)	**0.002**	0.933	(0.887, 0.981)	**0.007**	1.013	(0.98, 1.049)	0.488			
LY	0.943	(0.817, 1.090)	0.413				0.954	(0.871, 1.045)	0.308			
NLR	0.994	(0.937, 1.063)	0.853				1.015	(0.977, 1.059)	0.474			
MONO	0.6	(0.377, 0.969)	**0.031**	1.042	(0.678, 1.601)	0.851	1.029	(0.765, 1.397)	0.856			
EOS	0.845	(0.449, 1.652)	0.609				0.853	(0.532, 1.391)	0.522			
CYP enzyme inhibitors	0.977	(0.692, 1.435)	0.899				1.082	(0.854, 1.397)	0.529			

Note. In the calculation, estimates (β) are the result of a log transformation to convert the sertraline concentration to the original scale, expressed here by exp(estimate)

Table 3 Serum concentrations and C/D values of Sertraline in different sexes

Sex	Serum Concentration (ng/mL)			C/D ((ng/ml)/(mg/d))		
	Children and Adolescents	Adults	Total	Children and Adolescents	Adults	Total
Male	41.8 (23.9, 65.5)	55.8 (35.0, 86.0)	52.4 (31.6, 81.3)	0.38 (0.24, 0.52)	0.47 (0.34, 0.66)	0.43 (0.30, 0.63)
Female	53.2 (32.4, 86.2)	62.3 (33.5, 102.0)	57.0 (32.9, 95.5)	0.47 (0.33, 0.70)	0.51 (0.33, 0.79)	0.49 (0.33, 0.72)

Note. Data are expressed as the median (1st quartile, 3rd quartile)

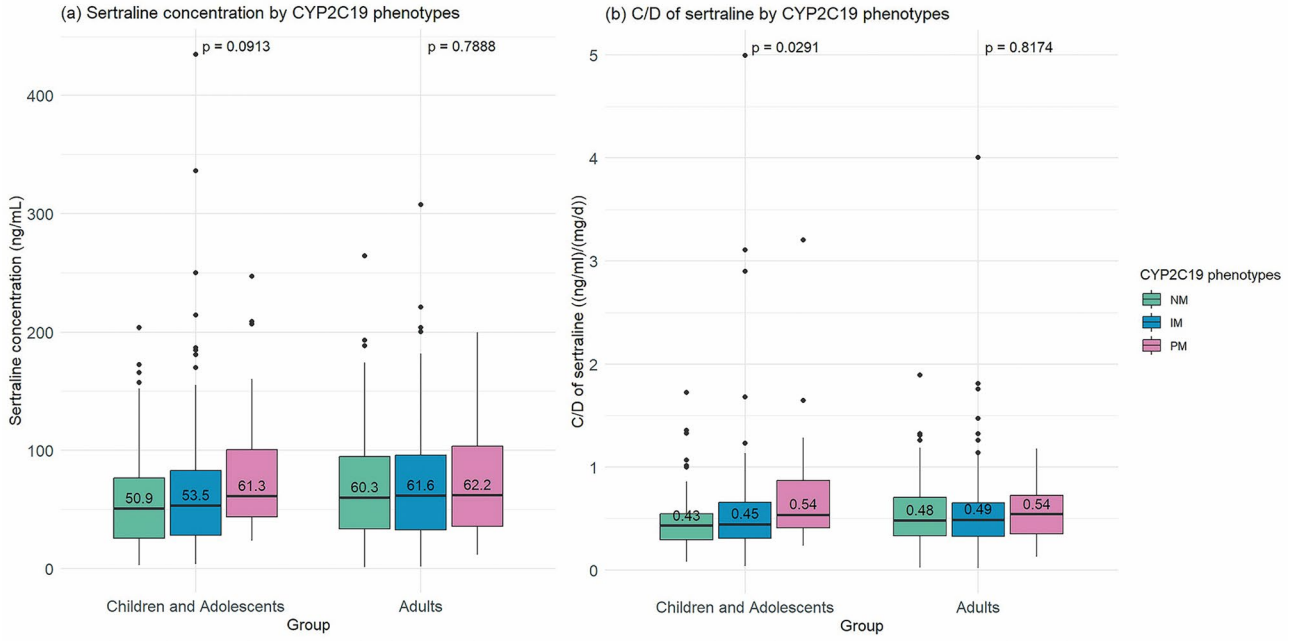

Fig. 3 Relationships between different CYP2C19 enzyme phenotypes and sertraline serum concentrations **(a)** and C/D values **(b)**. NM, normal metabolizers; IM, intermediate metabolizers; PM, poor metabolizers

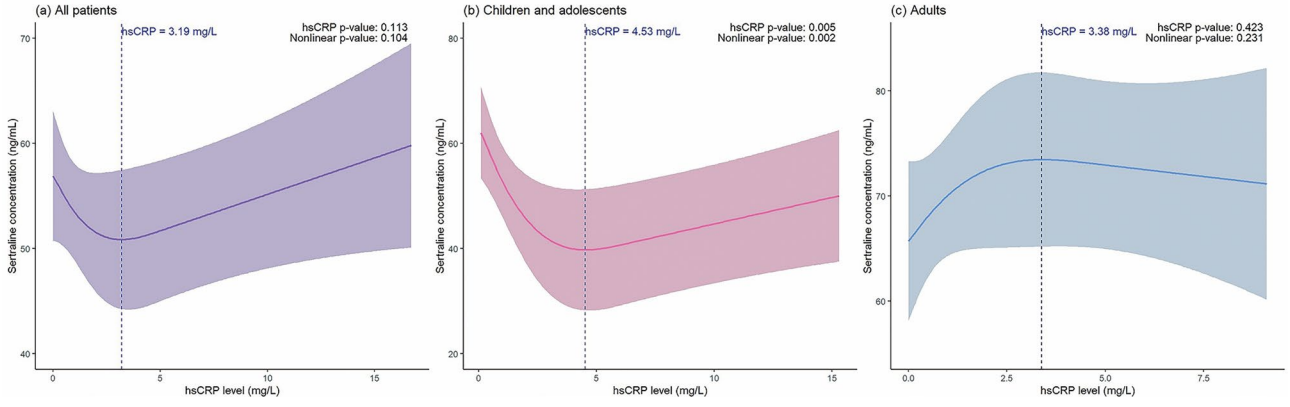

Fig. 4 Relationships between hsCRP levels and sertraline concentrations in all patients **(a)**, children and adolescents **(b)**, and adults **(c)**. The relationships were adjusted after controlling for daily dose, age, sex, and AST level. hsCRP, high-sensitivity C-reactive protein; AST, aspartate aminotransferase

for the hsCRP level and sertraline concentration were 0.0037, 0.042, and 0.0021 for all patients, children and adolescents, and adults, respectively, indicating that there was no significant linear relationship. To explore whether there was a complex nonlinear relationship, the RCS model method (knots = 3) was applied.

The following covariates were adjusted based on the results of univariate analysis and clinical significance: daily dose, age, sex, and AST level. After adjusting for covariates (Fig. 4), a nonlinear relationship between hsCRP and sertraline concentration was observed in children and adolescents ($P = 0.002$), with hsCRP significantly impacting sertraline concentration ($P = 0.005$). The graphical representation retained a U-shaped pattern, and the lowest point on the curve was observed at a hsCRP level of 4.53 mg/L. No significant nonlinear

relationship was observed in adults, and the graphical representation exhibited an upside-down U shape.

Discussion

This retrospective study analyzed real-world clinical data to identify factors influencing serum sertraline concentrations in children, adolescents and adults. The results revealed significant correlations between sertraline concentrations and daily dose, sex, and AST levels. In children and adolescents, sertraline concentrations were also influenced by Alb levels and NEUT counts. In patients with *CYP2C19* genotype, CYP2C19 PMs presented higher sertraline concentrations, although the difference was not statistically significant. Additionally, a U-shaped relationship between hsCRP levels and sertraline concentrations was observed in children and adolescents. These findings can aid clinicians in tailoring sertraline treatment plans. These findings provide important guidance for clinicians in dose titration and monitoring of sertraline, enabling them to develop suitable sertraline treatment plans for patients on the basis of their specific conditions.

Age is an important factor influencing the pharmacokinetic process of sertraline [33, 34]. In the Chinese population pharmacokinetic model, adolescent patients exhibit faster sertraline clearance, and sertraline concentrations are lower, although the difference is not significant [15]. Given that our study population was already grouped by age, the potential impact of age may have been reduced. We also found that Alb levels and NEUT counts had a significant impact on children and adolescents, suggesting that attention should be given to nutritional status and potential inflammation.

Sex had a notable impact on sertraline concentrations. Specifically, the average serum concentration of sertraline was increased in female, indicating that women may have a risk of excessive drug exposure at the same dosage. Women tend to have lower body weights, blood volumes, and plasma protein binding capacities, which may lead to relatively higher drug concentrations [35, 36]. Moreover, women have shorter intestinal transport times; lower hepatic blood flow; hepatic enzyme and transporter expression; and lower renal clearance, which is attributed to differences in drug metabolism and clearance [35, 37, 38]. Sex-related differences in pharmacokinetics also affect the pharmacodynamics of sertraline, necessitating further research to explore the mechanisms of the influence of sex.

AST, a biomarker of liver function, is present in multiple tissues, and abnormal AST levels may indicate various diseases, such as hepatic impairment, heart disease, and myopathy [39]. Our study revealed that sertraline concentrations increased with AST levels, which can be explained in part by the reduction in sertraline metabolism due to hepatocyte injury. According to the sertraline drug label, for patients with mild hepatic impairment, the daily dose should be reduced to half of the recommended range [32]. However, we did not find a significant effect of concomitant liver disease on sertraline concentrations. In our study, different types of liver diseases were not subdivided, and it is possible that some patients with liver diseases in the compensatory stage maintained normal or near-normal physiological function, which may explain the nonsignificant impact on sertraline concentrations.

Our study found that patients with the CYP2C19 PM phenotype had slightly higher sertraline concentrations; however, this difference lacked significance, and likewise, the combination of CYP450 enzyme inhibitors failed to exert a significant effect. While genetic information is relatively stable at the genomic level, its impact on enzyme activity and pharmacokinetics dynamically changes during individual growth [40], which could explain the inconsistent results across different populations. Additionally, clinicians may have been more cautious in dose titration and prescribed lower maintenance doses for PMs in the present study, mitigating underlying disparities.

Sertraline is metabolized by multiple enzymes, including CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, with CYP2B6 contributing the most [41–43]. Therefore, the impact of a single gene polymorphism, such as *CYP2C19*, may be limited, as a study revealed that a combinatorial pharmacogenomic algorithm (*CYP2C19*, *CYP2B6*, and *CYP3A4*) can predict sertraline concentrations more effectively [44]. Concurrently, the CPIC guidelines suggest sertraline dosing on the basis of *CYP2C19* and *CYP2B6* polymorphisms [28], whereas the Dutch Pharmacogenetics Working Group recommends therapy considering *CYP2C19* and *CYP2D6* [29]. Alternative approaches to measure CYP450 activity, such as liver microsome assays, also have practical limitations [45].

In our study, we utilized the C/D ratio as a surrogate marker of sertraline metabolism. Although the median C/D ratio was lower in children and adolescents than in adults, this difference alone does not necessarily imply faster sertraline metabolism in younger patients. Children and adolescents with CYP2C19 PM phenotypes exhibited significantly higher C/D values compared to non-PM individuals. While this observation is consistent with the role of CYP2C19 in sertraline clearance, the interpretation of C/D ratios as a direct indicator of biotransformation rate requires caution due to potential confounders such as dose adjustments, adherence variability, and the contribution of other metabolic enzymes.

CRP is a biomarker of chronic inflammation, and approximately one-third of patients with

depression exhibit low-grade inflammatory states (i.e., CRP > 3.0 mg/L), suggesting a distinct pathogenesis and clinical course [46]. Previous studies have shown that elevated CRP levels are correlated with increased antipsychotic drug blood concentrations [47, 48]. Our study revealed a notable nonlinear correlation between hsCRP levels and sertraline concentrations in children and adolescents, whereas adults exhibited a distinct curve, which was likely attributed to more intricate disease conditions, comorbidities, and concurrent medications. Inflammation serves as a major regulator of drug-metabolizing enzymes and transporters (DMETs), leading to intra- and interindividual variations in drug exposure [49]. Studies have revealed that inflammation can induce phenoconversion in DMETs. Proinflammatory cytokines such as TNF-α and interleukin-1β can induce epigenetic modifications in relevant genes encoding DMETs and ultimately affect enzyme expression and activity [49]. In the present study, it is possible that DMETs in children and adolescents during growth are more sensitive to changes in inflammation levels, highlighting the importance of real-time monitoring of drug concentrations and inflammatory biomarkers.

In the present study, significant interindividual variations in sertraline concentrations and C/D values were observed, especially among younger patients, with coefficients of variation (CVs) of 88.5% and 80.6%, respectively. In comparison, the CVs in adults were 68.0% and 61.1%, respectively. The interindividual variability in the pharmacokinetics of sertraline may be a crucial source of variation in clinical responses at standard doses, particularly for children and adolescents, who are in a unique developmental stage and require careful consideration of the risks and benefits of sertraline therapy. The TDM-VIGIL study revealed a linear relationship between the dose and serum concentration of sertraline in children and adolescents, with a reference range of 66–76 ng/mL [13], and the currently recommended target range of 10–150 ng/mL needs further refinement.

This retrospective study has several limitations, including the lack of data on variables such as body mass index and smoking history, which have been shown to affect sertraline pharmacokinetics and pharmacodynamics [17, 50]. Second, the exposure–response relationship of sertraline could not be assessed because of insufficient information on treatment response and adverse drug reactions. The specific impact of the identified factors on treatment outcomes still requires further exploration. Third, pharmacogenetic testing was not performed for all patients, and key gene variants in *CYP2B6* and *CYP2D6* were not evaluated. This study was limited in that it explored the associations between the CYP2C19 enzyme phenotype and sertraline concentrations as well as C/D values. Finally, pharmacogenetic testing should include adjustments for phenoconversion to enhance its clinical utility in practice. This study did not fully account for phenoconversion. Future studies should collect comprehensive clinical and genetic data and include adjustments for phenoconversion.

Using the established TDM database, this research aims to adjust sertraline dosages more accurately based on the unique physiological and pathological characteristics of patients. However, reaching the target concentration is merely the first step in treatment; what is even more crucial is ensuring optimal therapeutic responses. Based on regular monitoring of the sertraline concentration, prospective studies should systematically collect pharmacodynamic data and analyze the complex relationship between dose-expose-response (D-E-R) of sertraline in different patient populations, ultimately providing guidance and support for clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-07033-6.

Supplementary Material 1

Acknowledgements

We would like to express our deepest gratitude to all patients who kindly provided their invaluable clinical data for this study. Our sincere thanks also go to the Beijing Municipal Health Commission for providing the platform through the "Beijing Research Ward Excellence Program (BRWEP)" which has facilitated exchanges and collaborations among psychiatric departments across different regions in China. Initial language editing was assisted by artificial intelligence (AI) tools to address grammatical errors and improve readability. The authors thoroughly revised these edits to align with academic standards and ensure conceptual precision.

Author contributions

R.L. and B.B. contributed to data curation, formal analysis, and wrote the original draft. Z.D. was responsible for data curation and methodology. Sai Chen, Y.Y., X.W., and H.H. collected the information. Song Chen and Y.T. initiated the study and designed the protocol. All authors reviewed the manuscript.

Funding

This study was funded by the Beijing Municipal Health Commission's Excellence in Clinical Research Program for Research Wards [BRWEP2024W072130113].

Data availability

The dataset is available from the corresponding author (Song Chen) upon reasonable request.

Declarations

Ethics approval and consent to participate

The study, conducted in accordance with the Declaration of Helsinki and with waived informed consent, was approved by the Ethics Committee of The Second People's Hospital of Guizhou Province in China [(2024) Research No. 03].

Consent for publication

Not applicable.

Consent to participate
Given that this study was a retrospective study utilizing data from electronic medical records, the Ethics Committee granted a waiver of informed consent, as the study posed no additional risk to participants.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 5 February 2025 / Accepted: 26 May 2025
Published online: 06 June 2025

References

1. Collaborators GDI. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Volume 396. Lancet; 2020. pp. 1204–22. 10258.
2. Collaborators GF. Burden of disease scenarios for 204 countries and territories, 2022–2050: a forecasting analysis for the global burden of disease study 2021. Lancet. 2024;403(10440):2204–56.
3. Brauer R, et al. Psychotropic medicine consumption in 65 countries and regions, 2008-19: a longitudinal study. Lancet Psychiatry. 2021;8(12):1071–82.
4. Huddart R, et al. PharmGKB summary: Sertraline pathway, pharmacokinetics. Pharmacogenet Genomics. 2020;30(2):26–33.
5. Solmi M, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry. 2020;19(2):214–32.
6. Guideline-Development-Panel-for-the-Treatment-of-Depressive-Disorders. Summary of the clinical practice guideline for the treatment of depression across three age cohorts. Am Psychol. 2022;77(6):770–80.
7. Luo X, et al. Selection of the optimal dose of Sertraline for depression: A dose-response meta-analysis of randomized controlled trials. Psychiatry Res. 2023;327:115391.
8. Schoretsanitis G et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American society of clinical psychopharmacology and the therapeutic drug monitoring task force of the arbeitsgemeinschaft für neuropsychopharmakologie und pharmakopsychiatrie. J Clin Psychiatry. 2020;81(3):19cs13169.
9. Pennazio F, et al. Current status of therapeutic drug monitoring in mental health treatment: A review. Volume 14. Pharmaceutics; 2022. 12.
10. Reis M, et al. Serum disposition of Sertraline, N-desmethylsertraline and Paroxetine: a Pharmacokinetic evaluation of repeated drug concentration measurements during 6 months of treatment for major depression. Hum Psychopharmacol. 2004;19(5):283–91.
11. Crettol S, et al. Pharmacogenomics in psychiatry: from therapeutic drug monitoring to genomic medicine. Clin Pharmacol Ther. 2014;95(3):254–7.
12. Hiemke C, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018;51(1–02):9–62.
13. Tini E, et al. Therapeutic drug monitoring of Sertraline in children and adolescents: A naturalistic study with insights into the clinical response and treatment of obsessive-compulsive disorder. Compr Psychiatry. 2022;115:152301.
14. Fu R, et al. Machine learning-based prediction of Sertraline concentration in patients with depression through therapeutic drug monitoring. Front Pharmacol. 2024;15:1289673.
15. Zhang Z, et al. Population Pharmacokinetic approach to guide personalized Sertraline treatment in Chinese patients. Heliyon. 2024;10(3):e25231.
16. Tveit K, et al. Age of onset for increased dose-adjusted serum concentrations of antidepressants and association with sex and genotype: an observational study of 34,777 individuals. Eur J Clin Pharmacol. 2024;80(3):435–44.
17. Poweleit EA, et al. Escitalopram and Sertraline population Pharmacokinetic analysis in pediatric patients. Clin Pharmacokinet. 2023;62(11):1621–37.
18. Castillo CEC, et al. Population pharmacokinetics of Sertraline in psychiatric and substance use disorders. J Clin Pharmacol. 2024;64(10):1267–77.
19. Morgan ET. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. Clin Pharmacol Ther. 2009;85(4):434–8.
20. Ramsey LB, et al. Thoughtful clinical use of pharmacogenetics in child and adolescent psychopharmacology. J Am Acad Child Adolesc Psychiatry. 2021;60(6):660–4.
21. Chapron BD, et al. Recent advances in the ontogeny of drug disposition. Br J Clin Pharmacol. 2022;88(10):4267–84.
22. Aldrich SL, et al. Influence of CYP2C19 metabolizer status on Escitalopram/Citalopram tolerability and response in youth with anxiety and depressive disorders. Front Pharmacol. 2019;10:99.
23. Klomp SD, et al. Phenoconversion of cytochrome P450 metabolism: a systematic review. J Clin Med. 2020;9(9):2890.
24. Shah RR, et al. Inflammation-induced phenoconversion of polymorphic drug metabolizing enzymes: hypothesis with implications for personalized medicine. Drug Metab Dispos. 2015;43(3):400–10.
25. Mostafa S, et al. An analysis of allele, genotype and phenotype frequencies, actionable Pharmacogenomic (PGx) variants and phenoconversion in 5408 Australian patients genotyped for CYP2D6, CYP2C19, CYP2C9 and VKORC1 genes. J Neural Transm (Vienna). 2019;126(1):5–18.
26. Gerlach S, et al. Prevalence estimates of cytochrome P450 phenoconversion in youth receiving pharmacotherapy for mental health conditions. Clin Pharmacol Ther. 2025;117(3):670–5.
27. de Leon J, et al. Clobazam therapeutic drug monitoring: a comprehensive review of the literature with proposals to improve future studies. Ther Drug Monit. 2013;35(1):30–47.
28. Bousman CA, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A genotypes and serotonin reuptake inhibitor antidepressants. Clin Pharmacol Ther. 2023;114(1):51–68.
29. Brouwer J, et al. Dutch pharmacogenetics working group (DPWG) guideline for the gene-drug interaction between CYP2C19 and CYP2D6 and SSRIs. Eur J Hum Genet. 2022;30(10):1114–20.
30. Ma YC, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17(10):2937–44.
31. Iguiniz M, et al. Two-dimensional liquid chromatography in pharmaceutical analysis. Instrumental aspects, trends and applications. J Pharm Biomed Anal. 2017;145:482–503.
32. ZOLOFT Package Insert. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019839s108,20990s062lbl.pdf,ac].
33. Bråten LS, et al. Impact of CYP2C19 genotype on Sertraline exposure in 1200 Scandinavian patients. Neuropsychopharmacology. 2020;45(3):570–6.
34. Gjestad C, et al. Effect of proton pump inhibitors on the serum concentrations of the selective serotonin reuptake inhibitors Citalopram, Escitalopram, and Sertraline. Ther Drug Monit. 2015;37(1):90–7.
35. Hansen MR, et al. Therapeutic drug monitoring of Venlafaxine in an everyday clinical setting: analysis of age, sex and dose concentration relationships. Basic Clin Pharmacol Toxicol. 2017;121(4):298–302.
36. Reis M, et al. Serum concentrations of antidepressant drugs in a naturalistic setting: compilation based on a large therapeutic drug monitoring database. Ther Drug Monit. 2009;31(1):42–56.
37. Romanescu M, et al. Sex-related differences in pharmacological response to CNS drugs: a narrative review. J Pers Med. 2022;12(6):907.
38. Marazziti D, et al. Pharmacokinetics and pharmacodynamics of psychotropic drugs: effect of sex. CNS Spectr. 2013;18(3):118–27.
39. Lee TH, et al. Evaluation of elevated liver enzymes. Clin Liver Dis. 2012;16(2):183–98.
40. Hoshitsuki K, et al. Pharmacogenomics for drug dosing in children: current use, knowledge, and gaps. J Clin Pharmacol. 2021;61 Suppl 1(Suppl 1):S188–92.
41. Kobayashi K, et al. Sertraline N-demethylation is catalyzed by multiple isoforms of human cytochrome P-450 in vitro. Drug Metab Dispos. 1999;27(7):763–6.
42. Obach RS, et al. Sertraline is metabolized by multiple cytochrome P450 enzymes, monoamine oxidases, and glucuronyl transferases in human: an in vitro study. Drug Metab Dispos. 2005;33(2):262–70.
43. Chen S, et al. The role of hepatic cytochrome P450s in the cytotoxicity of Sertraline. Arch Toxicol. 2020;94(7):2401–11.
44. Parikh SV, et al. Combinatorial Pharmacogenomic algorithm is predictive of Sertraline metabolism in patients with major depressive disorder. Psychiatry Res. 2022;308:114354.
45. Pridgeon CS, et al. Liquid biopsies or therapeutic drug monitoring for CYP activity profile determination. Clin Pharmacol Ther. 2022;112(5):1000–3.

46. Orsolini L, et al. C-reactive protein as a biomarker for major depressive disorder? Int J Mol Sci. 2022;23(3):1616.
47. Hefner G, et al. Inflammation and psychotropic drugs: the relationship between C-reactive protein and antipsychotic drug levels. Psychopharmacology. 2016;233(9):1695–705.
48. Pan S, et al. Relationship between C-reactive protein and antipsychotics levels in schizophrenic patients infected with COVID-19. J Psychiatr Res. 2024;170:297–301.
49. Stanke-Labesque F, et al. Inflammation is a major regulator of drug metabolizing enzymes and transporters: consequences for the personalization of drug treatment. Pharmacol Ther. 2020;215:107627.
50. Oliveira P, et al. Smoking and antidepressants pharmacokinetics: a systematic review. Ann Gen Psychiatry. 2017;16:17.

Publisher's note