Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Defining the Therapeutic Range of Levetiracetam for Personalized Treatment in Pediatric Epilepsy: Insights from a Large Real-World Study

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Background: This study sought to define the therapeutic drug monitoring (TDM) reference range and assess the efficacy-safety profile along with its determinants for levetiracetam (LEV) in Chinese children with epilepsy.

Methods: We conducted a retrospective study (2021–2023) at Children's Hospital of Nanjing Medical University in children with epilepsy taking LEV therapy with routine TDM. The observational LEV reference range was defined by the generalized additive models for location, scale, and shape (GAMLSS) analysis. A linear mixed-effects model identified concentration determinants. Efficacy was assessed via propensity score matching (PSM)-adjusted logistic regression, time-to-failure via Kaplan-Meier/Cox regression (monotherapy), and adverse events (AEs) temporal patterns via Weibull distribution analysis.

Results: This study (n = 1,174) proposed an observational LEV reference range of 2.82−24.37 μg/mL based on the 2.5th–97.5th percentile distribution. Predictors of LEV levels included age, body weight, oxcarbazepine (OXC)/topiramate use, and developmental delay. OXC lowered concentration-to-dose (C_0/D) (β = −0.1824, P = 0.0012). The 12-month response rate was 81.01% (90.89% monotherapy vs 70.78% polytherapy). Concentration-response correlation was significant only in focal epilepsy. Protective factors for response were female sex, generalized epilepsy, and longer treatment; risk factors were polytherapy and infectious etiology. Comorbid attention deficit and hyperactive disorder improved, but developmental delay did not affect, response. Neuropsychiatric AEs were most frequent (median onset: 196.5 days); gastrointestinal and systemic reactions showed early failure patterns.

Conclusion: This real-world study confirmed the efficacy and safety of LEV in Chinese children with epilepsy and revealed relevant drug interactions. By proposing an observational LEV reference range (2.82−24.37 μg/mL), it provides a critical evidence base for TDM and guides the personalized treatment.

Plain Language Summary: To better understand how to personalize LEV dosing for children with epilepsy, we studied over 1,000 cases and proposed an observational reference range of 2.82 to 24.37 μg/mL. We revealed that the link between drug levels and seizure control was only significant in those with focal epilepsy, not in all cases. Impressively, children with comorbid ADHD responded better to the treatment than those without. Regarding safety, while 17.25% of adverse events occurred early, 33.1% occurred post 360 days, highlighting the requirement for long-term monitoring. These findings offered new insights into TDM guide personalized LEV dosing for clinical practice.

Keywords: levetiracetam, LEV, children with epilepsy, efficacy, adverse events, AEs, therapeutic drug monitoring, TDM, personalized treatment

https://doi.org/10.2147/DDDT.S593587
Received: 4 January 2026
Accepted: 29 March 2026
Published: 20 April 2026

Introduction

Epilepsy ranks among the most prevalent chronic neurological disorders globally, affecting approximately 70 million people, with the highest incidence observed in children and the elderly.[1] The current estimated prevalence of childhood epilepsy ranges 0.5–1.0% worldwide, specifically affecting an estimated 0.46–0.71% of children in China.[2] Although most patients with epilepsy achieve effective seizure control with anti-seizure medications (ASMs), approximately 30% develop drug-resistant epilepsy, underscoring the critical need for optimized and individualized treatment strategies, including exposure-guided approaches such as therapeutic drug monitoring (TDM).[3,4] The management of childhood epilepsy faces complex challenges, including the need for the comprehensive management of cognitive and behavioral comorbidities during the developmental period, the potential interactions of these factors with development, and individualized treatment strategies.

Pharmacotherapy serves as the cornerstone of managing pediatric epilepsy. Levetiracetam (LEV), a second-generation ASM, has become a widely used agent in pediatric clinical practice due to its broad-spectrum efficacy and favorable safety profile.[5–7] LEV exerts its antiseizure effects through selective binding to synaptic vesicle protein 2A (SV2A), thereby modulating neurotransmitter release and synaptic function.[8] It has demonstrated effectiveness against various epilepsy types in both adults and children over one month of age.[9] However, dosing of LEV might be more complicated in the presence of polypharmacy (especially comedication with enzyme-inducing drugs) when CYP enzyme metabolism of LEV may be greater in special populations like children.[10] The pediatric population is characterized by a continuous stage of growth and development, leading to distinct pharmacokinetic parameters compared to adults, thereby potentially altering the relationship between exposure and response.[11] Indeed, LEV exhibits a high variability for children.[12] In comparison with adulthood, body clearance (*CL*) of LEV in childhood is higher of about 30–40%.[13] Higher LEV dosages are necessary in children aged between 2 months and 12 years, compared to adults, due to the 30–70% increase of LEV's *CL*. Higher dosages are also required if a patient receives enzyme-inducing drugs, again due to a higher *CL* of LEV (range 24–60%).[9] Thus, TDM can be applied to guide the dosage regimen to achieve greater efficacy and safety.

Current data to support regular TDM for LEV are disputed. Impressively, the 2014 Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) expert consensus initially proposed a reference interval of 10–40 μg/mL for LEV. This range was subsequently revised upward to 20–40 μg/mL in the initial 2017 AGNP guideline update. However, within a few months, the second version of the 2017 guidelines reverted to the original 10–40 μg/mL interval.[14] The International League Against Epilepsy (ILAE) recommended another range of 12–46 μg/mL according to aggregated data from both adults and children.[15]

Nevertheless, several critical issues regarding how to optimize its application in Chinese children with epilepsy still exist although the clinical role of LEV is well established. Substantial heterogeneity occurred in the reported therapeutic reference ranges for LEV in this population.[15,16] Notably, data on plasma LEV concentrations in them are scarce, and a well matched, well-established therapeutic monitoring range is currently lacking. Moreover, most existing studies[14] analyze multiple drug concentration measurements from the same individual as independent data points, and this approach neglects the internal correlations within the repeated measurement data. Additionally, the exposure-response and exposure-safety relationships for LEV therapy remain largely undefined in Chinese children with epilepsy.[14,17] Finally, the incidence and temporal patterns of adverse events (AEs) related to LEV also lack systematic data, which restricts the clinical medication guidance based on real-world evidence.

Herein, this retrospective study in Chinese pediatric patients aimed to: (1) establish a therapeutic plasma reference range for LEV and identify factors influencing its concentration; (2) evaluate the efficacy and safety of LEV as both monotherapy and combination therapy, analyzing treatment response differences across clinical subgroups, including those with comorbidities; (3) systematically investigate the correlations between plasma LEV concentrations and both therapeutic effects and adverse events (AEs) in a real-world setting; and (4) characterize the incidence and temporal patterns of AEs.

Materials and Methods

Study Design

This study was designed as a real-world retrospective study and was conducted in the Department of Neurology of Children's Hospital of Nanjing Medical University. The selection of research subjects adhered to specific inclusion and exclusion criteria. The inclusion criteria included children with epilepsy aged ≤18 years, classified according to the ILAE 2025 diagnostic criteria,[18] who received LEV mono- or polytherapy between September 1, 2021, and December 31, 2023, and had complete medical records. Cases who did not undergo routine TDM were excluded. Additionally, cases lacking critical information, those with severe organic diseases (eg, malignant tumors), those with a follow-up period of less than 3 months, and those who discontinued treatment due to severe AEs were also excluded. The flowchart of study population selection and the final included patients is shown in Figure 1. This study was conducted in accordance with the Declaration of Helsinki. This study received approval from the hospital's ethics committee (Protocol number 202408040-1), and data were anonymized to protect individual privacy. Due to the retrospective nature of this study, written informed consent from patients and/or children was waived.

Data Collection

Various data were collected from the study population's medical records through the hospital's information system, including age, sex, body weight, epilepsy type, etiology, seizure frequency, previous treatment history, LEV dosage, medication regimen, duration of epilepsy, duration of therapy, concomitant ASMs, AEs, the date of the AEs recorded in the medical records, as well as plasma LEV concentrations.

Treatment Regimen

All included patients in this study received LEV either as mono- or polytherapy, administered via oral formulations (tablets or solution) or intravenous injection. Dosing was tailored according to individual age and body weight.

For infants aged 1−6 months, treatment was initiated at 7 mg/kg twice daily, which could be titrated up to 21 mg/kg twice daily depending on clinical response and tolerability, with biweekly adjustments of 7 mg/kg per administration. The oral solution (100 mg/mL) was recommended as the initial formulation in this age group. For infants 6−23 months, children 2−11 years, and adolescents 12−17 years weighing ≤50 kg, the initial LEV dose was 10 mg/kg twice daily. Based on clinical response and tolerability, the dose could be titrated to 30 mg/kg twice daily, with adjustments of 10 mg/kg made every two weeks. The dosage form was selected based on the pediatric patient's age, body weight, and specific clinical needs. For patients weighing ≥50 kg, the adult dosing regimen was applied, *ie*., an initial dose of 500 mg twice daily, adjustable by 500 mg per dose at 2−4 weeks intervals, up to a maximum of 1,500 mg twice daily. In addition, when intravenous administration was used, the dose was equivalent to the total daily oral dose, and no additional titration was required when switching between routes of administration.

Routine TDM for LEV

During scheduled follow-up visits, venous blood (1 mL) was drawn prior to the morning dose administration. Patients should receive treatment with a stable dose for 2–3 days before TDM sampling to ensure that steady state conditions were achieved. Plasma was separated by centrifugation and stored for the determination of LEV trough levels. Plasma LEV concentrations for TDM were measured using a validated LC-MS/MS.[19] This method, established by our laboratory, enables the simultaneous quantification of LEV along with 14 other ASMs in human plasma.

Clinical Outcomes Assessment

This study defined the seizure frequency measured during the period prior to the initiation of LEV therapy as the baseline and evaluated the efficacy of LEV by documenting seizure frequency at months 1, 3, 6, 12, 18, 24, 36, 48, 60, and beyond 60 months after starting LEV treatment. At each follow-up assessment, patients were categorized into three groups based on the percentage reduction in seizure frequency from baseline over the preceding 6-month period: (1) seizure-free (100% reduction); (2) response (≥50% reduction); and 3) ineffective (<50% reduction).

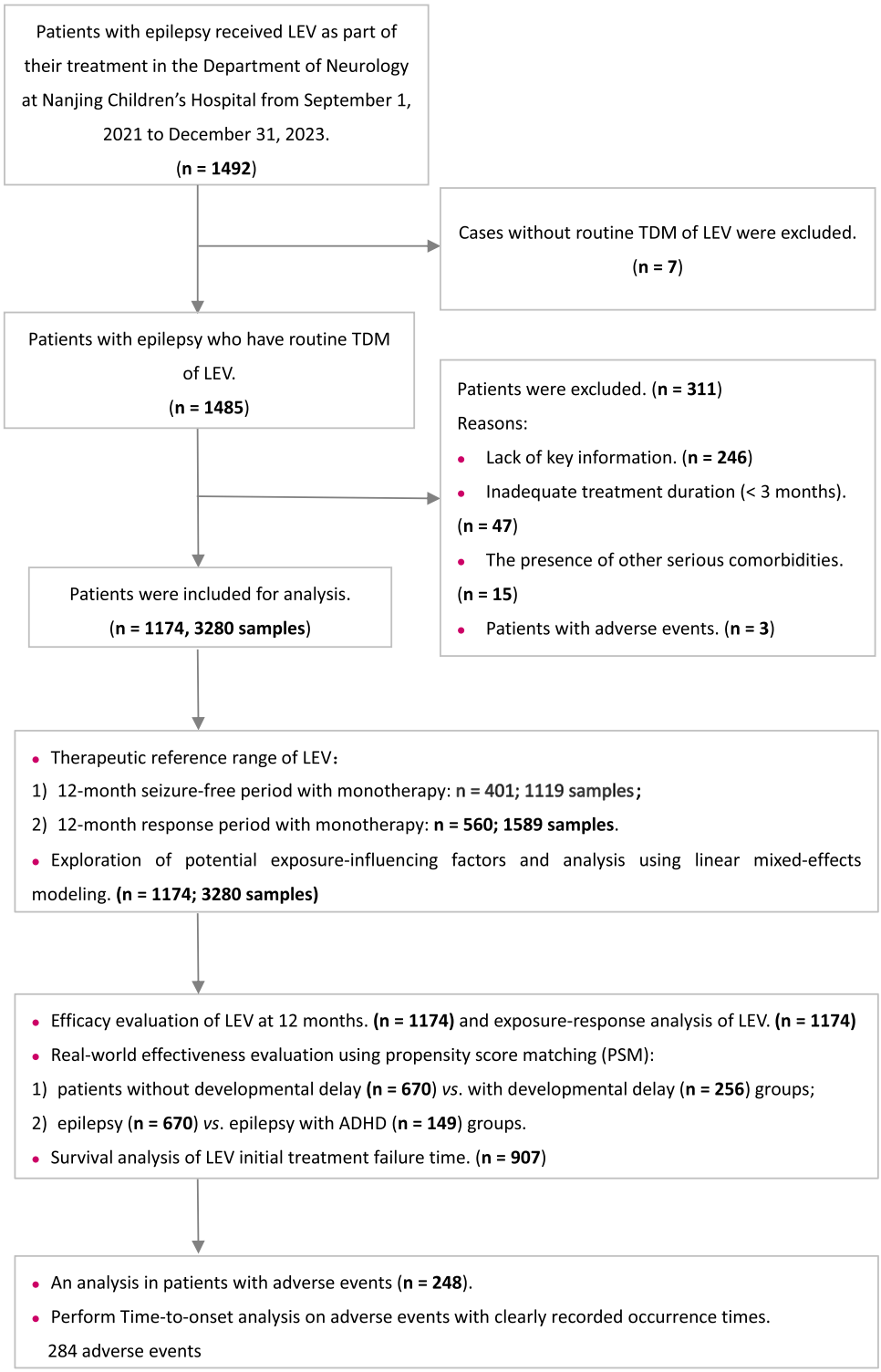

Figure 1 Numbers of patients who were eligible for this study. Texts in bold indicate the number of patients (number of samples) for each group.

First, the therapeutic reference range of plasma LEV levels was defined in two distinct patient groups: (1) a "seizure-free" group (no seizures throughout 12 months of LEV monotherapy) and (2) a "response" group (cases with seizure-free and response after 12 months of LEV monotherapy). Within each of the two groups, a further subgroup analysis was conducted to compare the range across different epilepsy types.

Second, efficacy-related analyses were performed as follows. Efficacy was evaluated at 12 months post-LEV initiation across three subgroups: (1) the overall population encompassing all included patients, (2) cases on LEV monotherapy until the last follow-up, and (3) cases on LEV combination therapy until the last follow-up. The efficacy was defined as the percentage of patients with seizure-free and response relative to the total number of included cases.

Subsequently, a series of analyses were conducted based on the efficacy outcome assessed at the time of the last TDM measurement. Cases in the seizure-free and response groups were collectively defined as "responders", whereas those classified as ineffective were defined as "non-responders". Using the last monitored plasma LEV concentration and the corresponding efficacy outcome, an exposure-response analysis was conducted. To further evaluate the predictive value of plasma LEV concentration on treatment response, receiver operating characteristic (ROC) curves were plotted, with stratified analysis performed according to different epilepsy types. Given that the study population included both cases with epilepsy and those with epilepsy comorbidities, propensity score matching (PSM) was employed to control for baseline confounding biases and to more effectively compare therapeutic differences between the two groups. Additionally, logistic regression analysis was also performed based on the plasma LEV concentrations from the final TDM assessment and their corresponding efficacy outcomes.

It should be noted that developmental delay was defined as a condition in which a child failed to achieve expected neurodevelopmental, cognitive, behavioral, or physical growth standards due to various causes. The diagnostic criteria for developmental delay was based on standardized developmental assessment tools (Wechsler/Raven Child Intelligence Scale tests). It included cases diagnosed by a specialist with any of the following: global developmental delay, brain maldevelopment, growth retardation, psychomotor retardation, pervasive developmental disorder, intellectual disability, speech and language disorder, or short stature. All participants had a confirmed ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders-5 criteria.

Simultaneously, a survival analysis was conducted. This analysis was restricted to those cases initially treated with LEV monotherapy. Treatment failure was defined as the addition of a second ASM to the LEV regimen. The time to treatment failure was defined as the date of adding the second ASM.

Finally, the safety outcome was the total adverse event (TAE) rate, calculated as the proportion of all AEs relative to the total number of assessable AEs. These AEs were recorded based on the combined observations of parents and physicians, as documented in the medical records.

Time to onset (TTO) was defined as the time interval between the drug initiation date and the AE occurrence date recorded in the case report. To further investigate the distribution trends of AEs across different time phases, we employed the Weibull Shape Parameter (WSP) to fit and interpret the TTO data.

Statistical Analysis

All analyses were performed with R software (R Project for Statistical Computing, v4.4.3) and GraphPad Prism 10 (GraphPad Software, La Jolla, CA, United States), as well as Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Categorical variables were presented as frequency (n) and proportions (%). The Shapiro–Wilk test was used to assess the normality of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), while nonnormally distributed ones were presented as median with an interquartile range (IQR). The Mann–Whitney *U*-test was employed to compare differences between two groups for nonnormally distributed continuous variables. Spearman correlation analysis was used for correlation analysis. The Kruskal–Wallis test and Dunn's multiple comparisons test were used to compare differences among multiple independent groups.

We used the generalized additive models for location, scale, and shape (GAMLSS) model to establish a therapeutic reference range for plasma LEV levels. The model is a generalized additive model based on location, size and shape,[20] and the age factor is fitted in the model. We compared a variety of distribution models, including normal distribution, Box-Cox t (BCT) distribution, and used cubic spline smoothing function to fit location parameters (mean) and scale

parameters (SD). On the basis of comprehensive evaluation of Akaike information criterion (AIC) and Bayesian information criterion (BIC), the final model was selected. Finally, the GAMLSS model's results were further validated by graphically assessing residual normality using Q-Q plots and density plots.

Multivariate analysis of factors affecting LEV's exposure was performed using linear mixed-effects models with adjustment for within-subject repeated measurements. Taking the logarithmic transformed LEV exposure levels as the dependent variable and the patient ID number as the random effect, factors such as age, sex, body weight, epilepsy type, duration of epilepsy, duration of therapy, gene mutation status, etiology, treatment regime, development status, and whether combined with attention deficit and hyperactive disorder (ADHD) were included in the model construction.

In this study, we employed binary logistic regression models to assess the efficacy of LEV as the dependent variable, with clinical characteristics (like age, body weight, and etiology classification) and laboratory parameters (plasma LEV concentrations) as independent variables. Potential variables were initially screened through univariate logistic regression ($P < 0.05$), followed by manual inclusion of variables demonstrating either statistical significance or clinical relevance into the multivariate logistic regression model. Results were reported as odds ratios (OR) with corresponding 95% CI. Multicollinearity was evaluated using variance inflation factors (VIF < 5).

During the analysis of both patients with epilepsy and those with epilepsy comorbidities, we utilized PSM with nearest neighbor matching in R software, applying an appropriate caliper value to reduce potential confounding bias between the two groups. The confounding factors included in PSM encompassed sex, age, body weight, epilepsy type, number and types of ASM, plasma LEV concentrations, presence of genetic mutations, duration of disease, duration of treatment, and dosage form. The standardized mean difference (SMD) was calculated to evaluate the appropriateness of the matching. An SMD ≤ 0.1 denoted a high degree of balance, and an SMD ≤ 0.2 was considered acceptable.[21]

For time to treatment failure analysis in LEV initial monotherapy, we conducted a Kaplan-Meier (K-M) survival curve analysis and simultaneously constructed Cox proportional hazards regression models. Covariates were first screened by univariate analysis ($P < 0.05$), then manually selected based on statistical significance or clinical importance for inclusion in the multivariate analysis. Hazard ratios (HR) with 95% CI were reported. The proportional hazards assumption was verified using Schoenfeld residual tests ($P > 0.05$ for all covariates).

TTO was evaluated by computing medians and WSP. The Weibull distribution is defined by two parameters: scale (α) and shape (β).[22]

Scale parameter (α): Reflects the centrality of the event occurrence time. A larger α value indicates that ADEs tend to occur later in the treatment course, while a smaller α suggests a concentration of events in the early phase of treatment.

Shape parameter (β): Determines the trend of risk over time. Based on the β value and its 95% confidence interval (CI), the occurrence patterns can be classified into three categories:[23]

(1) Early failure model: β < 1 (and 95% CI < 1). The risk decreases over time, indicating that the primary risk is concentrated in the initial period of medication use.

(2) Wear-out failure model: β > 1 (and 95% CI > 1). The risk increases with prolonged drug exposure, suggesting a cumulative effect of long-term treatment.

(3) Random failure model: β ≈ 1 (and 95% CI includes 1). The probability of AE occurrence remains constant throughout the treatment cycle.

A P-value < 0.05 was considered statistically significant.

Results

Patients' Characteristics

This study included a total of 1,174 pediatric patients (611 males) who met the inclusion criteria, with their demographic characteristics and medication details presented in Table 1. Among the study population, focal epilepsy constituted the most prevalent diagnosis, accounting for 34.67% of cases. The median age at initial epilepsy onset was 4.17 years (IQR: 1.71−7.19 years). The median duration of therapy was 22.25 months. A total of 675 (57.5%) patients received LEV monotherapy. Among the 374 cases receiving LEV in comedication with other ASMs, valproic acid was the most frequently co-administered one (n = 167). The median maintenance dose of LEV was 30.3 mg/kg/day (IQR: 5−69.57 mg/kg/day).

Table 1 Clinical Characteristics of Included Children with Epilepsy (n = 1174)

Characteristics		n (%) or Median (Range)
Sex (n)	Male: Female	611: 563
Type of epilepsy (n, %)	Focal	407 (34.67)
	Generalized	258 (28.45)
	Unknown	175 (21.98)
	Unclassified	334 (14.91)
Weight (kg)		28 (3.6–95)
Baseline EEG (n, %)	Abnormal	642 (91.85)
Age at epilepsy onset (years)		4.17 (0.003–15.67)
Dose (mg/kg/d)		30.3 (5–69.57)
Plasma LEV concentrations (μg/mL)		8 (1.05–45.6)
C_0/D [(μg/mL)/mg]		0.0096 (0.007–0.1003)
ASMs in add-on therapy (n, %)	0	675 (57.50)
	1	374 (31.86)
	2	110 (9.37)
	3	30 (2.56)
	4	2 (0.17)
Duration of epilepsy (months)		33.07 (0.47–154.1)
Duration of therapy (months)		22.25 (0.1–149.9)
Etiology (n, %)	Structural	65 (5.54)
	Genetics	65 (5.54)
	Infectious	23 (1.96)
	Metabolic	5 (0.43)
	Immune	7 (0.60)
	Unknown	1009 (85.95)
Comorbidities (n, %)	None	670 (57.07)
	Developmental delay	256 (21.81)
	ADHD	149 (12.69)
	Tic disorders	32 (2.73)
	ASD	24 (2.04)
	Childhood emotional disorders	6 (0.51)
	CCD	11 (0.94)
	Sleep disorders	16 (1.36)
	Movement disorder	3 (0.26)
	Cardiac disorders	24 (2.04)
	Cerebral palsy	20 (1.70)
	Hemiplegia	6 (0.51)
	Obesity	6 (0.51)
	Other comorbidities[#]	32 (2.72)

Notes: [#] Other comorbidities include ZTTK syndrome, conversion disorder, hyperthyroidism, Möbius syndrome, peripheral neuropathy, ataxia, primary coenzyme Q10 deficiency, L-carnitine deficiency, adrenal insufficiency; congenital adrenal hyperplasia (STAR deficiency), precocious puberty, disorders of sex development (DSD), glucagonoma, exercise-induced dystonia, hypokalemia, etc.

Abbreviations: EEG, electroencephalogram; C_0/D, concentration-to-Dose ratio; ASM, anti-seizure medicine; ADHD, attention deficit and hyperactive disorder; ASD, autism spectrum disorder; CCD, central coordination disorder.

Therapeutic Reference Range for Plasma LEV Levels

Finally, 401 and 560 patients were included in the seizure-free group and the effective group for reference range evaluation, respectively. After model screening, the BCT distribution showed the best goodness of fit, so it was selected as the basic distribution of the final GAMLSS model. Figure 2 shows the percentile curve of plasma LEV concentration in this population, which intuitively showed the concentration distribution. With the increase of age, each quantile curve showed a similar trend. The median curve was relatively stable, indicating that the median plasma LEV concentration did not change significantly with age in children. We further validated the GAMLSS model's results by graphical inspection

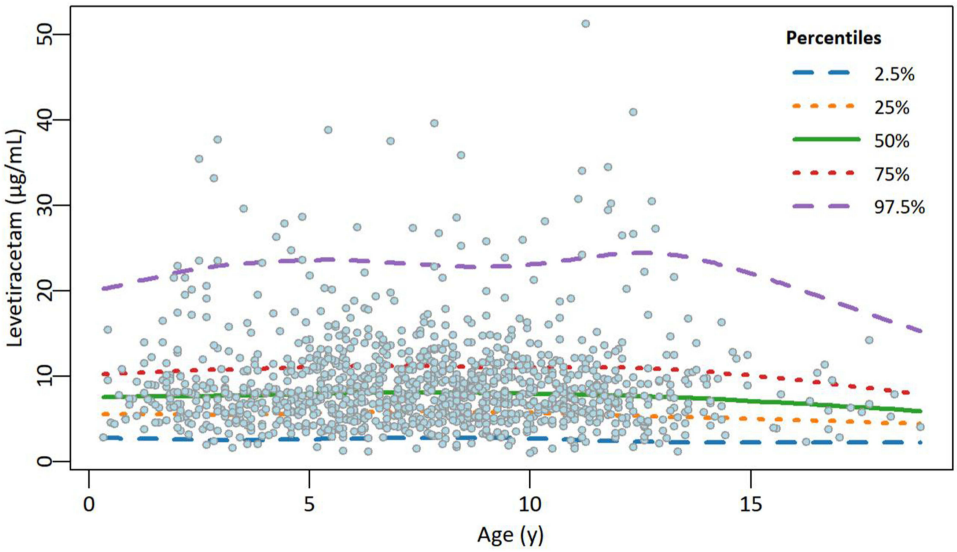

Figure 2 The concentration distribution range of LEV in children with epilepsy who achieved 12-month seizure-freedom on monotherapy.

of residuals. Both the residual Q-Q plot and residual density plot (see Supplementary Figure 2) indicated that the model assumptions were adequately satisfied, supporting the appropriateness of the chosen distribution.

Based on the maximum values of the 2.5th and 97.5th percentiles of each age group, the therapeutic reference range of LEV was determined to be 2.82 to 24.37 μg/mL. In this case, the concentration range of different types of epilepsy was further developed, and the results are shown in Table 2.

Next, comparative analysis of the therapeutic reference ranges across epilepsy type subgroups was performed. The nearly identical lower limit of the effective concentration for focal seizures (2.75 μg/mL) and the overall study population (2.82 μg/mL) suggested that this value was reasonable for LEV in pediatric epilepsy. Then, the upper limit of effective concentration for focal epilepsy was similar to that for generalized epilepsy. Notably, the lower limits for cases with both unknown and unclassified epilepsy types were higher than the total participants. Furthermore, the effective range for the unclassified epilepsy was the narrowest, with an upper limit significantly lower than other subgroups, implying that maintaining plasma concentrations below 24.84 μg/mL may represent the optimal therapeutic target for these patients. In addition, the corresponding data of patients who were treated with LEV monotherapy for 12 months were also listed for reference (Table 2).

Factors Influencing the Plasma LEV Level

We analyzed 3,280 plasma LEV concentrations from 1,174 patients. There was a positive correlation between the plasma LEV concentrations and dose (r = 0.4301, $P < 0.0001$; Figure 3). However, a negative correlation was observed between age, body

Table 2 The Range ($P_{2.5}$ - $P_{97.5}$) of LEV Predicted by GAMLSS (Generalized Additive Models for Location, Scale, and Shape) Model

Group	12-Month Seizure-Free Period with Monotherapy				12-Month Response Period with Monotherapy			
	N	n	$P_{2.5}$	$P_{97.5}$	N	n	$P_{2.5}$	$P_{97.5}$
All	401	1119	2.82	24.37	560	1589	3.11	24.29
Focal	115	292	2.75	27.5	166	438	3.12	26.89
Generalized	101	307	3.27	29.7	136	427	3.8	26.16
Unknown	30	80	4.88	32.59	49	140	3.9	32.14
Unclassified	155	440	3.66	24.84	209	584	3.97	24.16

Notes: N: patients; n: samples; $P_{2.5}$: 2.5th percentile; $P_{97.5}$: 97.5th percentile.

https://doi.org/10.2147/DDDT.S593587

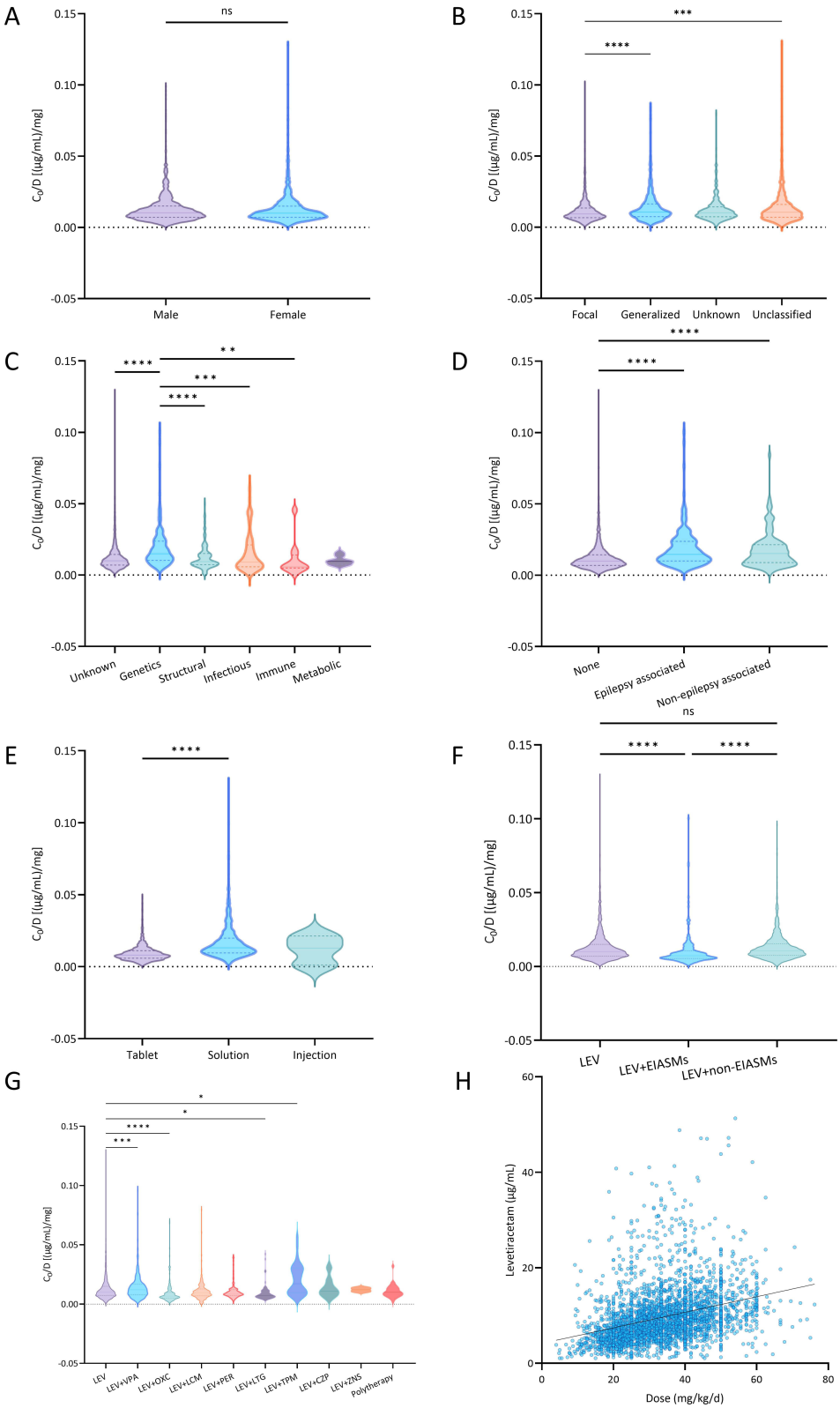

Figure 3 The C_0 (μg/mL) and C_0/D ratio [(μg/mL)/mg] of LEV. (**A**) A comparison of C_0/D ratio in both sexes; (**B**) A comparison of C_0/D ratio between epilepsy types; (**C**) A comparison of C_0/D ratio between etiologies; (**D**) A comparison of C_0/D ratio among mutation-negative, epilepsy associated, and non-epilepsy associated groups; (**E**) A comparison of C_0/D ratio among three formulations (tablets/ solution/ injection); (**F**) A comparison of C_0/D ratio between LEV monotherapy, LEV with EIASMs and LEV with non-EIASMs; (**G**) A comparison of C_0/D ratio between LEV monotherapy and co-administration with valproate (VPA), oxcarbazepine (OXC), lacosamide (LCM), perampanel (PER), lamotrigine (LTG), topiramate (TPM), clonazepam (CZP), zonisamide (ZNS) and polytherapy; (**H**), Correlation between C_0 (μg/mL) and daily dose (mg/kg/d) ($r = 0.4301$, $P < 0.0001$). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$; ns, not significant.

https://doi.org/10.2147/DDDT.S593587

weight, duration of epilepsy, duration of therapy and concentration-to-dose (C_0/D) ratio (Table 3). The C_0/D ratio varied significantly based on several key factors (Figure 3). Regarding epilepsy type, it was significantly lower in focal vs generalized or unclassified epilepsy (both $P < 0.001$). In etiology, the ratio in the genetic differed significantly from all other groups (all $P \leq 0.0026$) except the metabolic group. Regarding genetic background, significant differences existed between patients with no mutations and those with either epilepsy-related or non-epilepsy-related gene mutations (both $P < 0.0001$). Regarding formulation, the tablet form was associated with a significantly lower ratio than the solution ($P < 0.0001$), including in children >4 years. Finally, regarding concomitant therapy, enzyme-inducing ASMs reduced LEV exposure, with oxcarbazepine (OXC) co-administration significantly lowering the C_0/D ratio vs monotherapy ($P < 0.0001$), indicating a pharmacokinetic interaction.

Next, a linear mixed-effects model was established to accurately assess the independent effects of various factors and control for confounding effects due to repeated within-individual measurements, which were log-transformed to better approximate a normal distribution (see Supplementary Figure 1). Notably, age, body weight, comedication with OXC or topiramate (TPM), and comorbidity with developmental delay were significant predictors of plasma LEV concentrations (Table 4). Concomitant use of OXC was associated with a significant decrease in the C_0/D ratio ($\beta = -0.1824$, $P = 0.0012$). In contrast, comedication with TPM resulted in a significant increase ($\beta = 0.2516$, $P = 0.0401$). Cases with developmental delay exhibited a significantly higher C_0/D ratio ($\beta = 0.0674$, $P = 0.0481$).

In addition, the results of the linear mixed-effects model showed that the intraclass correlation coefficient (ICC) was 0.3846, indicating approximately 38% of the variance was attributable to inter-individual differences. The fixed effects alone explained about 32.93% of the variance ($R^2m = 0.3293$), while the model as a whole, incorporating random effects, explained about 58.73% of the variance ($R^2c = 0.5873$). Furthermore, model diagnostic plots indicated a good fit (see Supplementary Figure 3). The standardized residuals were randomly and evenly distributed around zero (see Supplementary Figure 3A). Furthermore, the residual density plot (see Supplementary Figure 3B) and the Q-Q plot (see Supplementary Figure 3C) collectively confirmed that the residual distribution approximates normality.

Efficacy of LEV Treatment

LEV therapy demonstrated favorable overall antiseizure efficacy in this study (Figure 4). Among the total of 1,174 patients included, after 12 months of treatment, 750 (63.88%) achieved complete seizure free, while 951 were classified as treatment responders, yielding an overall efficacy of 81.01%. The monotherapy group showed superior outcomes compared to the combination therapy group, with higher rates of both seizure free (78.11% vs 52.26%) and response (90.89% vs 70.78%). Interestingly, in the monotherapy group (n = 571), efficacy was consistently high and comparable across different epilepsy types. In contrast, among cases receiving combination therapy (n = 243) and those with unclassified epilepsy exhibited slightly poorer therapeutic outcomes.

Association Between Plasma LEV Concentrations and Clinical Response

Overall, no significant difference in plasma LEV concentrations was observed between responders and non-responders ($P = 0.0856$; Figure 5A). However, subgroup analysis by epilepsy type revealed a statistically significant difference among children with focal epilepsy ($P = 0.0242$; Figure 5B). Further analysis restricted to cases with focal epilepsy receiving LEV monotherapy confirmed this finding ($P = 0.0099$; Figure 5C).

Next, an ROC curve analysis was performed to further evaluate the predictive value of plasma LEV concentrations (Figure 5D and E). In the overall focal epilepsy cases, the area under the ROC curve (AUC) for LEV concentrations was

Table 3 Effects of Age, Weight, Duration of Epilepsy and Duration of Therapy on the C_0/D Ratio of LEV

	Age (y)	Weight (kg)	Duration of Epilepsy (Months)	Duration of Therapy (Months)
n	3280	3280	3280	3280
r	−0.5898	−0.6137	−0.1938	−0.1422
P	**< 0.0001***	**< 0.0001***	**< 0.0001***	**< 0.0001***

Notes: n, samples; r, Spearman correlation coefficient; Bold values represent statistically significant differences (*$P < 0.05$).

Table 4 Fixed-Effects Estimates from the Linear Mixed-Effects Model

Variables		Estimate	SE	t Value	*P* Value
Age		−0.0639	0.0075	−8.5477	**< 0.0001***
Weight		−0.0087	0.0016	−5.5508	**< 0.0001***
Sex	Female				
	Male	−0.0138	0.0258	−0.5350	0.5927
Epilepsy type	Focal				
	Unknown	0.0568	0.0402	1.4134	0.1579
	Generalized	0.0212	0.0353	0.6015	0.5477
	Unclassified	−0.0206	0.0333	−0.6181	0.5366
Duration of epilepsy		−0.0001	0.0007	−0.1044	0.9169
Duration of therapy		0.0008	0.0009	0.8585	0.3908
Dosage form	Tablet				
	Solution	0.0265	0.0378	0.6995	0.4844
	Injection	−0.2317	0.2791	−0.8302	0.4065
Gene mutation	None				
	Mutation	0.0429	0.0700	0.6121	0.5406
Etiology	Unknown				
	Genetic	0.0134	0.0857	0.1563	0.8758
	Immune	−0.1240	0.1881	−0.6594	0.5097
	Infectious	0.1102	0.0937	1.1770	0.2395
	Metabolic	−0.1238	0.2267	−0.5462	0.5850
	Structural	0.0311	0.0585	0.5309	0.5956
ASMs in add-on	LEV				
	LEV+VPA	−0.0078	0.0337	−0.2299	0.8182
	LEV+OXC	−0.1824	0.0561	−3.2522	**0.0012***
	LEV+LCM	−0.0935	0.0545	−1.7150	0.0865
	LEV+PER	−0.0020	0.0584	−0.0339	0.9730
	LEV+LTG	0.0461	0.0842	0.5476	0.5840
	LEV+TPM	0.2516	0.1225	2.0542	**0.0401***
	LEV+CZP	0.3132	0.2282	1.3723	0.1701
	LEV+ZNS	0.0620	0.2357	0.2631	0.7925
	Polytherapy	−0.0288	0.0416	−0.6917	0.4892
ADHD	Uncombined				
	Combined	0.0303	0.0385	0.7875	0.4312
Development status	Without developmental delay				
	Developmental delay	0.0674	0.0340	1.9792	**0.0481***

Notes: Bold values represent statistically significant differences (*$P < 0.05$).
Abbreviations: SE, standard error; ASM, anti-seizure medicine; LEV, levetiracetam; VPA, valproate; OXC, oxcarbazepine; LCM, lacosamide; PER, perampanel; LTG, lamotrigine; TPM, topiramate; CZP, clonazepam; ZNS, zonisamide; ADHD, attention deficit and hyperactive disorder.

relatively low, at 0.5832 (95% CI: 0.5095−0.6569; $P = 0.0244$). However, when the analysis was restricted to patients receiving LEV monotherapy, the AUC increased to 0.6781 (95% CI: 0.5669−0.7894; $P = 0.0106$). In this subgroup, the optimal cutoff value was 6.945 μg/mL, with a sensitivity of 84.21% but a specificity of 47.31%. Overall, these findings indicated that the exposure-response association appeared to be modest, which should be considered with caution. Following this, variables influencing treatment efficacy were initially screened using univariate analysis, and those with potential significance were subsequently included in a multivariate logistic regression model for further validation (see Supplementary Table 1 and Figure 6).

Multivariable analysis revealed, on the one hand, that female was significantly associated with a higher risk of ineffective compared to male cases (OR = 1.7424, 95% CI: 1.202−2.543, $P = 0.0036$). Patients with generalized epilepsy had a significantly lower probability of ineffective than those with focal epilepsy (OR = 0.5322, 95% CI: 0.310−0.894, $P = 0.0193$). Furthermore, longer treatment duration was significantly correlated with a reduced risk of ineffective (OR = 0.9710, 95% CI: 0.956−0.986, $P < 0.0001$).

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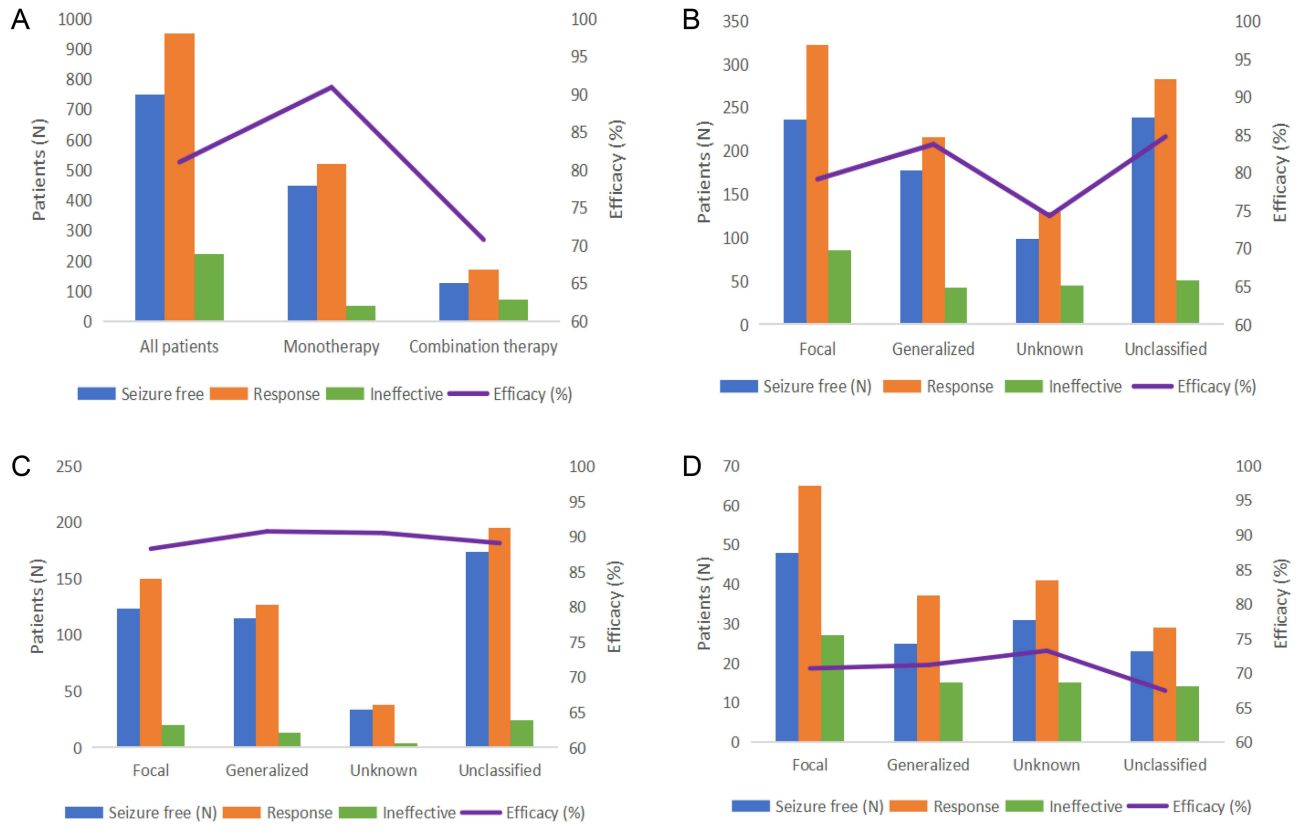

Figure 4 The total efficacy of LEV treatment over 12 months in pediatric patients, including its efficacy in different epilepsy types under monotherapy and combination therapy. (**A**) Efficacy of LEV treatment over 12 months in all pediatric patients, pediatric patients receiving monotherapy, and those receiving combination therapy; (**B**) Efficacy of 12-month LEV treatment in pediatric patients across different epilepsy types (focal/generalized/unknown/unclassified); (**C**) Efficacy of 12-month LEV monotherapy in pediatric patients with different epilepsy types (focal/generalized/unknown/unclassified); (**D**) Efficacy of 12-month LEV combination therapy in pediatric patients with different epilepsy types (focal/generalized/unknown/unclassified).

On the other hand, an increased number of concomitant ASMs was significantly associated with higher risk of ineffective. Notably, compared to no concomitant ASM, use of one additional ASM significantly increased the risk of failure (OR = 3.2982, 95% CI: 2.122−5.170, $P < 0.0001$), while use of two or more ASMs was associated with a substantially greater risk (OR = 16.4067, 95% CI: 9.624−28.491, $P < 0.0001$). Additionally, an infectious etiology was also identified as an independent risk factor for ineffective outcome (OR = 3.3553, 95% CI: 1.092−9.695, $P = 0.0286$).

Comparative Efficacy of LEV in Patients with vs Without Developmental Delay

This study initially included 1,174 patients treated with LEV, comprising 256 patients with developmental delay and 670 patients without developmental delay. Prior to PSM, significant differences were observed between the two groups in multiple baseline characteristics, including age, body weight, epilepsy type, and etiology (all $P < 0.05$; see Supplementary Table 2). After performing 1:2 nearest-neighbor PSM with a caliper width of 0.2, a total of 587 patients were included in the final analysis. After PSM, all SMDs were below 0.1, indicating well-balanced covariates between the two groups (Figure 7A). The probability density distribution of propensity scores also demonstrated improved overlap after matching, confirming the validity of the matching procedure (Figure 7B).

Notably, results after PSM analysis showed that the efficacy rate was 82.6% in the patients without developmental delay group (n = 304) and 80.4% in the patients with developmental delay group (n = 194). The OR ratio derived from logistic regression was 1.15 (95% CI: 0.72−1.83), suggesting a numerically higher—but statistically non-significant—likelihood of treatment efficacy in the patients without developmental delay group ($P = 0.6259$).

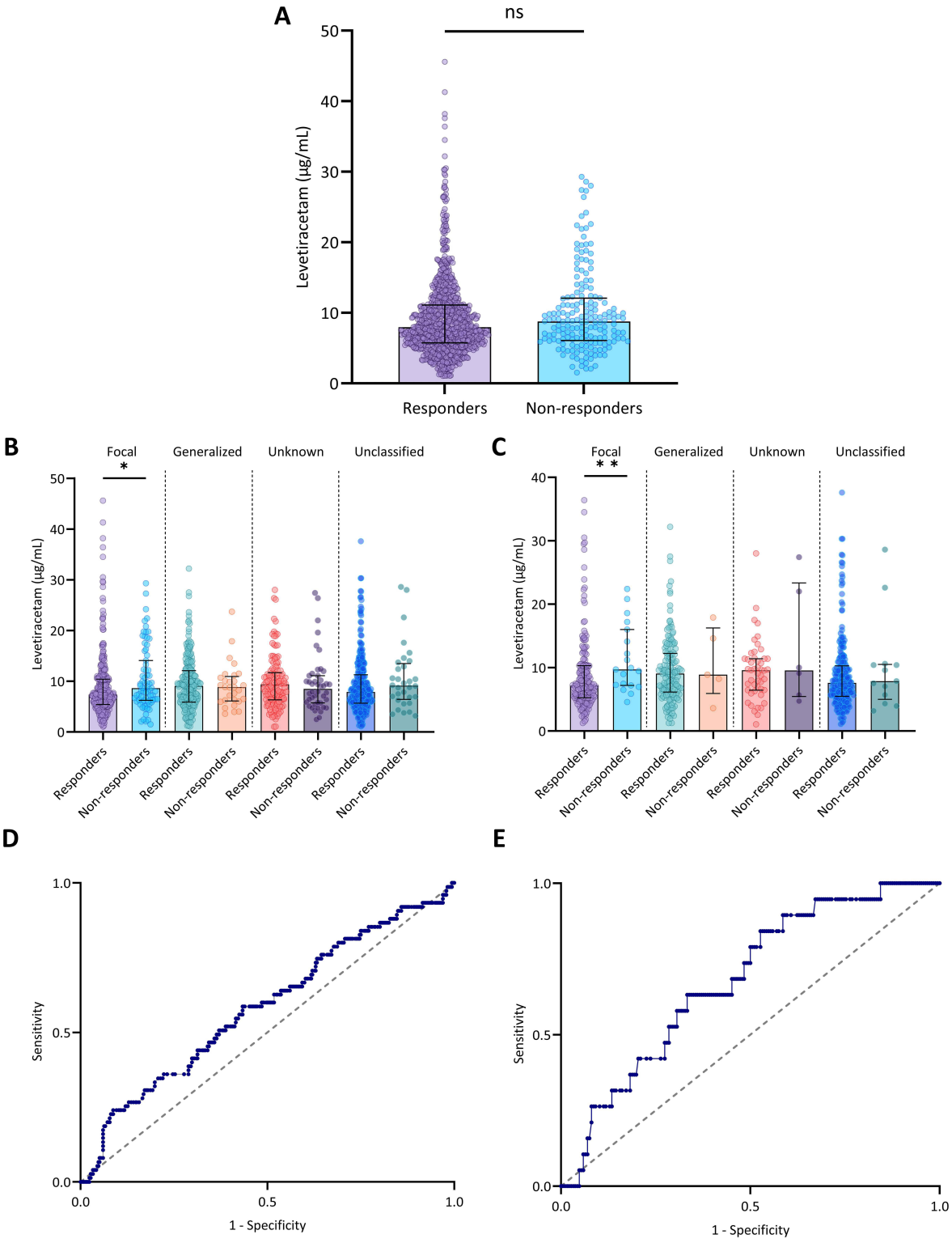

Figure 5 Association between plasma LEV concentrations and clinical response. (**A**) Comparison of plasma LEV concentrations (μg/mL) at final follow-up between responders and non-responders; (**B**) Comparison of plasma LEV concentrations (μg/mL) at final follow-up between responders and non-responders of different epilepsy types; (**C**) Comparison of plasma LEV concentrations (μg/mL) at final follow-up between responders and non-responders in patients receiving LEV monotherapy across different epilepsy types; (**D**) ROC curve analysis of plasma LEV concentrations (μg/mL) at final follow-up for efficacy prediction in focal epilepsy. The AUC is 0.5832 (95% CI: 0.5095–0.6569, $P = 0.0244$). The optimal cutoff value is 7.79 μg/mL, with a sensitivity value of 58.67% and a specificity value of 56.63%; (**E**) ROC curve analysis of plasma LEV concentrations (μg/mL) at final follow-up for efficacy prediction in focal epilepsy patients receiving LEV monotherapy. The AUC is 0.6781 (95% CI: 0.5669–0.7894, $P = 0.0106$). The optimal cutoff value is 6.945 μg/mL, with a sensitivity value of 84.21% and a specificity value of 47.31%. *$P < 0.05$, **$P < 0.01$; ns, not significant.

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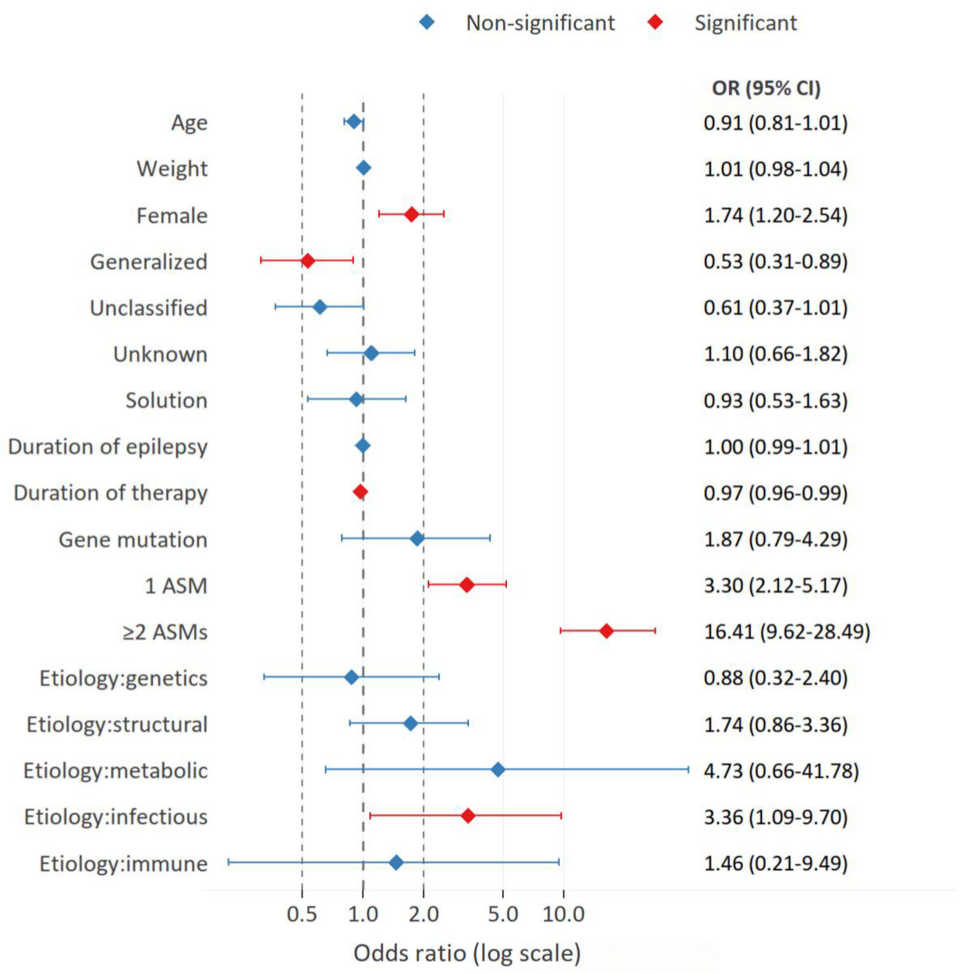

Figure 6 Forest plot of the potential influencing effects on the LEV treatment efficacy.

Comparative Efficacy of LEV in Cases with vs Without ADHD

We included 149 patients with comorbidity ADHD and 670 patients without its comorbid ADHD. After matching, a total of 376 patients were included in the efficacy analysis (see Supplementary Table 3). After PSM treatment, the baseline characteristics of the two groups reached a good balance (SMD < 0.1; see Supplementary Figure 4). The efficacy analysis after matching showed that the effective rate was 92.7% in children with epilepsy and ADHD, significantly higher than 83.3% in cases with epilepsy only (OR = 0.39, 95% CI: 0.18−0.78; $P = 0.0149$). The results indicated that the efficacy of LEV therapy in epilepsy patients with comorbid ADHD responded better to LEV treatment than those without ADHD. This finding was robust across subgroup analyses by epilepsy type and was clearly replicated in patients diagnosed with focal epilepsy ($P = 0.0120$; see Supplementary Table 4).

Time to Treatment Failure Analysis in Cases Taking LEV as Initial Monotherapy

We conducted a survival analysis to evaluate the time to treatment failure of LEV as initial monotherapy. The Kaplan-Meier curve demonstrated that the overall median time to treatment failure was 53.8 months (see Supplementary Figure 5). Univariate analysis revealed that genetic etiology, epilepsy type, and comorbid developmental delay were significantly associated with an increased risk of treatment failure (all $P < 0.05$). Multivariate analysis further confirmed these factors as independent predictors of treatment failure (Table 5) in cases receiving LEV as initial monotherapy.

Of note, cases with a genetic etiology exhibited a significantly higher risk of treatment failure compared to those without it (HR = 3.32, 95% CI: 2.24−4.90, $P < 0.001$). Regarding epilepsy type, cases with epilepsy of unknown etiology

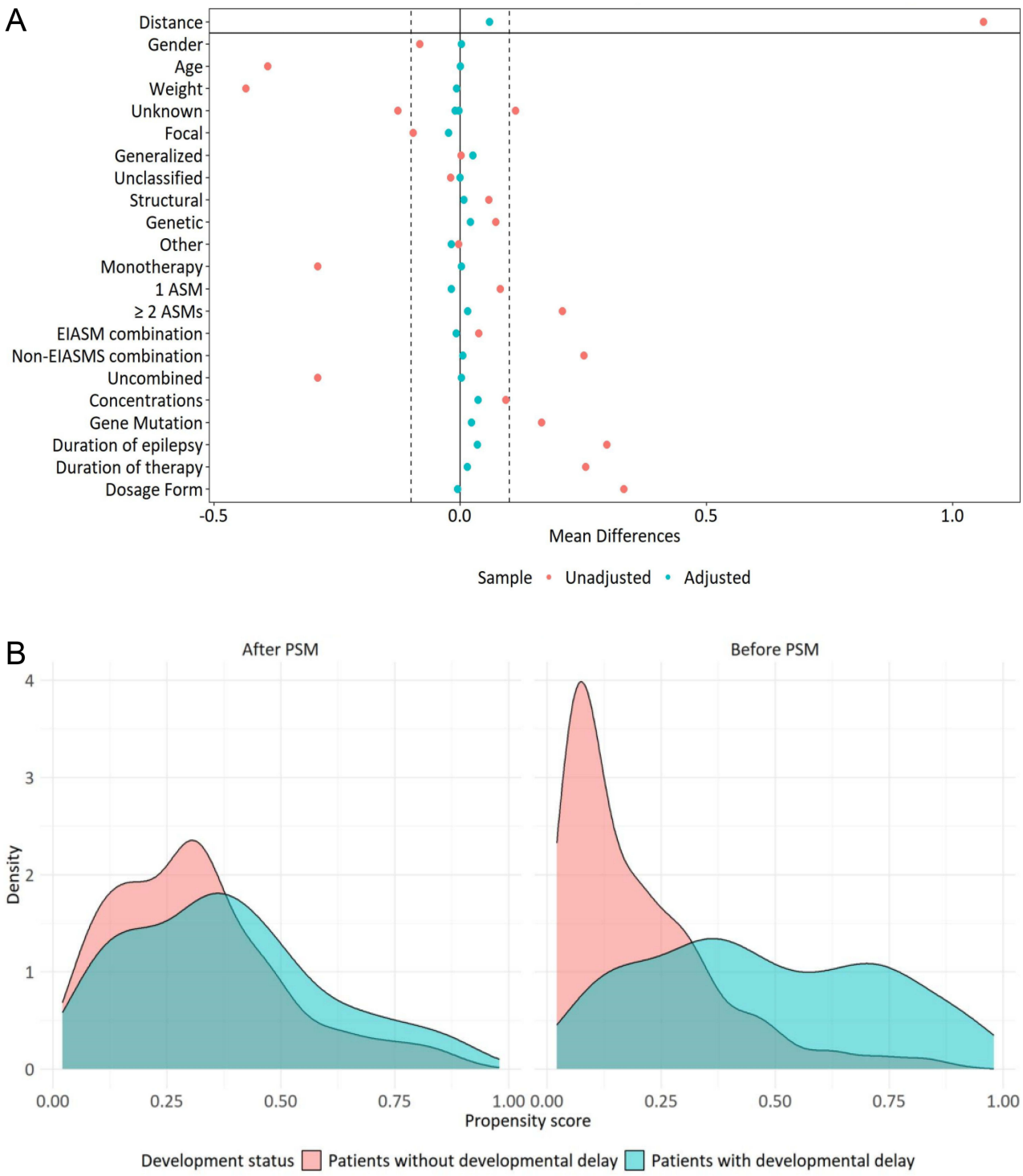

Figure 7 Covariate balance assessment after matching (**A**) and propensity score distribution (before and after PSM) (**B**).

had a higher risk of treatment failure compared to those with focal epilepsy (HR = 1.59, 95% CI: 1.19−2.11, $P = 0.002$). In contrast, generalized epilepsy (HR = 0.65, 95% CI: 0.48−0.88, $P = 0.005$) and unclassified epilepsy (HR = 0.50, 95% CI: 0.38−0.67, $P < 0.001$) were associated with a significantly lower risk of treatment failure. Additionally, patients with developmental delay showed a significantly increased risk of treatment failure compared to those without developmental delay (HR = 1.30, 95% CI: 1.00−1.69, $P = 0.049$).

https://doi.org/10.2147/DDDT.S593587

Table 5 Results of Univariate and Multivariate Cox Proportional Hazards Regression Analyses in Patients Receiving Initial Monotherapy of LEV

Variables		Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Age at epilepsy onset, y	< 6				
	≥ 6	0.89 (0.72–1.11)	0.311		
Weight, kg	< 40				
	≥ 40	0.88 (0.69–1.12)	0.305		
Sex	Male				
	Female	1.12 (0.91–1.38)	0.294		
Concentrations, μg/mL	< 8				
	≥ 8	1.13 (0.91–1.39)	0.267		
Genetic etiology	No				
	Yes	3.35 (2.29–4.91)	**< 0.001***	3.32 (2.24–4.90)	**< 0.001***
Type of epilepsy	Focal				
	Unknown	1.57 (1.19–2.09)	**0.002***	1.59 (1.19–2.11)	**0.002***
	Generalized	0.69 (0.51–0.93)	**0.014***	0.65 (0.48–0.88)	**0.005***
	Unclassified	0.50 (0.37–0.66)	**< 0.001***	0.50 (0.38–0.67)	**< 0.001***
ADHD	Uncombined				
	Combined	1.32 (0.99–1.75)	0.059		
Developmental status	Without developmental delay				
	Developmental delay	1.42 (1.10–1.84)	**0.007***	1.30 (1.00–1.69)	**0.049***

Notes: Bold values represent statistically significant differences (*$P < 0.05$).
Abbreviation: ADHD, attention deficit and hyperactive disorder.

AEs

Among the 1174 patients, a total of 248 AEs were observed. The most common AEs were nervous system abnormalities (6.98%), psychiatric abnormalities (6.3%), and skin/subcutaneous tissue abnormalities (4.26%). Less frequently reported AEs included renal and urinary system abnormalities (0.09%), hematological/lymphatic (0.17%), renal/urinary (0.09%), and musculoskeletal/connective tissue abnormalities (0.09%). Detailed results are shown in Table 6.

Table 6 Adverse Events During LEV Treatment

Adverse Events		Number (N#)	Incidence (%)
Abnormalities in systemic reactions and drug administration sites	Fatigue/Tiredness	9	0.77
Psychiatric abnormalities	Aggressiveness/Emotional instability/Irritability	74	6.3
Nervous system abnormalities	Drowsiness/Lethargy	17	1.45
	Headache	33	2.81
	Dizziness	29	2.47
	Muscle tension abnormalities	1	0.09
	Autonomic nervous system imbalance	2	0.17
Hepatobiliary system abnormalities	Fatty liver/Liver damage	11	0.94
Renal and urinary system abnormalities	Renal dysfunction/insufficiency/injury	1	0.09
Metabolic and nutritional abnormalities	Loss of appetite	19	1.62
Gastrointestinal tract abnormalities	Abdominal pain/Diarrhea, Dyspepsia, Nausea/Vomiting, Constipation	43	3.66
	Gastrointestinal functional disorders	3	0.26

(*Continued*)

Table 6 (Continued).

Adverse Events		Number (N#)	Incidence (%)
Skin and subcutaneous tissue abnormalities	Skin rash/Eczema	50	4.26
	Hair loss	4	0.34
Hematological and lymphatic system abnormalities	Thrombocytopenia	2	0.17
Ocular abnormalities	Diplopia/Blurred Vision	6	0.51
Musculoskeletal and connective tissue abnormalities	Myalgia/Myositis	1	0.09
Total		248	21.12

Notes: # N represents the number of adverse events that have occurred.

To begin with, we observed a significant difference in the median drug concentration between patients with and without AEs, regardless of monotherapy or polytherapy status ($P = 0.0011$; see Supplementary Figure 6A). Moreover, a significant difference in median concentration between the two groups remained evident in those cases receiving LEV monotherapy ($P < 0.0001$; see Supplementary Figure 6B). To further analyze this association, subgroup analyses were performed based on the epilepsy types. Whether monotherapy or polytherapy, significant differences in LEV concentrations between AE and non-AE groups were observed both in cases with focal epilepsy ($P = 0.0363$; see Supplementary Figure 6C) and with generalized epilepsy ($P = 0.0267$; see Supplementary Figure 6C). However, when the analysis was restricted to the LEV monotherapy scenario, a significant difference persisted only in those with generalized epilepsy ($P < 0.0001$; see Supplementary Figure 6D).

Next, we performed a TTO analysis (Figure 8). AEs associated with LEV demonstrated a wide temporal distribution (median TTO 196.5 days). Early onset was common, with 17.25% of patients affected within the first month and specific neuropsychiatric/cutaneous events typically appearing within four months. However, a significant subset of AEs (33.1%) occurred after 360 days, underscoring the need for sustained monitoring beyond the initial treatment phase.

The WSP was further applied to analyze the TTO data. As shown in Table 7, the β estimates for gastrointestinal tract abnormalities (β = 0.70, 95% CI: 0.55−0.89) and systemic/administration-site abnormalities (β = 0.55, 95% CI: 0.32−0.95) were below 1, indicating an early failure pattern where risk was highest shortly after LEV initiation and declined thereafter. In contrast, the 95% CI for nervous system (β = 0.86, 95% CI: 0.72−1.03), metabolic/nutritional (β = 0.91, 95% CI: 0.60−1.38), hepatobiliary (β = 0.73, 95% CI: 0.45−1.16), and ocular abnormalities (β = 1.49, 95% CI: 0.70−3.18) included 1, consistent with a random failure pattern throughout the LEV treatment.

However, for several AE categories—including psychiatric, dermatological, musculoskeletal, renal, and hematological abnormalities—parameter estimation was precluded due to insufficient sample sizes or non-convergence of the model-fitting algorithm.

Discussion

To our knowledge, this represented the largest single-center, retrospective, real-world clinical study of LEV therapy in Chinese children with epilepsy to date. This study systematically and rigorously evaluated key clinical aspects—including TDM reference ranges, effectiveness, safety, and associated influencing factors—using comprehensive statistical approaches, leading to robust conclusions. Our findings provided novel insights into the unique characteristics of LEV therapy, which will be detailed in the subsequent discussion.

The first and most significant contribution of this study involved defining an observational therapeutic monitoring range for plasma LEV levels—the first specifically established for Chinese children with epilepsy. Indeed, there is considerable variation in the recommended target concentration ranges reported in the literature, such as 5−40 μg/mL for children with refractory epilepsy,[24] 20−30 μg/mL,[25] 11−32 μg/mL for long-term LEV therapy,[26] 8.55−29.62 μg/mL for Chinese Uyghur children,[16] and 4.1−20.4 μg/mL for the 0−17 years age subgroup.[27]

The novel findings were based on its stratified analysis by age (Figure 2) and epilepsy type (Table 2) using the GAMLSS model to define corresponding therapeutic ranges, thereby addressing the monitoring needs of distinct clinical scenarios.

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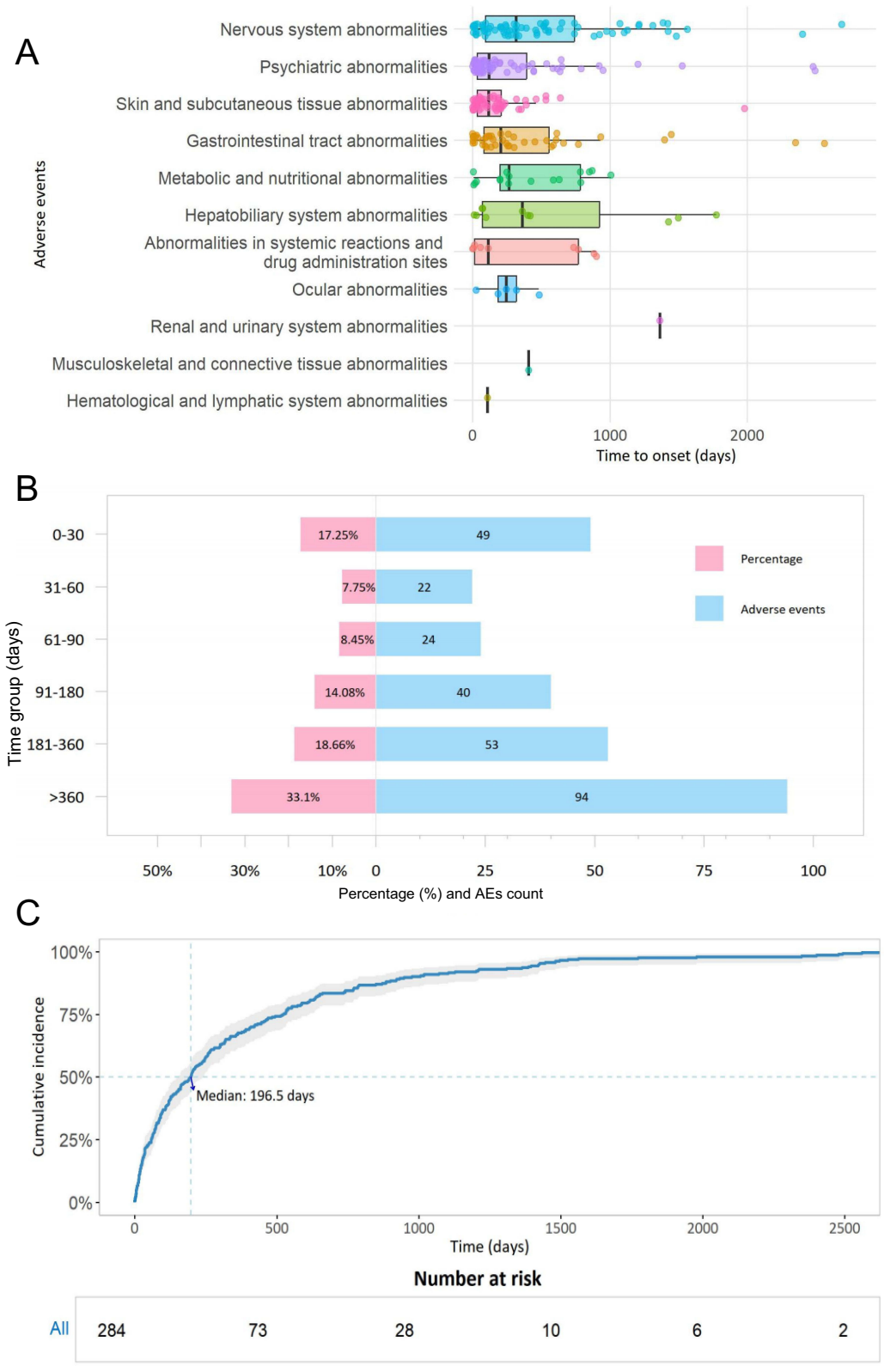

Figure 8 The TTO analysis of LEV adverse events at the overall level. (**A**) Adverse events occurrence time; (**B**) Time grouping of adverse events; (**C**) Cumulative risk curve of adverse events occurrence time.

Table 7 Weibull Distribution Shape Parameter Test

AEs	α# (95% CI)	β# (95% CI)	n	Failure Pattern
Nervous system abnormalities	477.29 (362.49–628.45)	0.86 (0.72–1.03)	76	Random failure mode
Psychiatric abnormalities	NA	NA	66	NA
Skin and subcutaneous tissue abnormalities	NA	NA	54	NA
Gastrointestinal tract abnormalities	320.86 (204.80–502.69)	0.7 (0.55–0.89)	43	Early failure mode
Metabolic and nutritional abnormalities	407.34 (236.48–701.68)	0.91 (0.60–1.38)	17	Random failure mode
Hepatobiliary system abnormalities	460.68 (194.96–1088.57)	0.73 (0.45–1.16)	11	Random failure mode
Abnormalities in systemic reactions and drug administration sites	258.22 (74.03–900.60)	0.55 (0.32–0.95)	9	Early failure mode
Ocular abnormalities	274.95 (149.27–506.43)	1.49 (0.70–3.18)	5	Random failure mode
Musculoskeletal and connective tissue abnormalities	NA	NA	1	NA
Renal and urinary system abnormalities	NA	NA	1	NA
Hematological and lymphatic system abnormalities	NA	NA	1	NA

Notes: # α and β represent the shape and scale parameters of the Weibull distribution (with 95% confidence intervals, CI), respectively; n: the number of AEs.
Abbreviations: AEs, adverse events; NA, not applicable.

Nevertheless, we also tentatively proposed a general target reference range (*ie*., 2.82−24.37 μg/mL) for the overall Chinese children with epilepsy. Of note, the target defined by our analysis was narrower relative to the commonly cited ILAE range of 12−46 μg/mL[15] for adults. This discrepancy might be due to our study population, who typically have higher *CL* rates (especially younger cases) than adults.[28] Impressively, the lower limit of our target was below that reported in previous studies (*eg*., 4.1 μg/mL[27]), implying that effective seizure control in some scenarios might not require concentrations as high as previously believed. In addition, this finding also suggested that directly applying adult's recommendation to children was inappropriate and could even lead to misinterpretation of the drug exposure levels.

It was interesting to note that a higher effective concentration level was required in cases with an unknown epilepsy type. This could be attributed to a higher prevalence of drug-resistant or etiologically complex conditions in this subgroup, which often necessitates higher plasma concentrations for seizure control. On the other hand, our analysis also revealed comparable effective LEV concentrations for achieving a seizure-free status between focal and generalized epilepsy. This observation not only provided direct clinical evidence for the broad-spectrum activity of LEV but also implied that its mechanism of action might operate above a similar therapeutic exposure threshold across different epilepsy types.

In this section, we further clarified how a general LEV target (2.82−24.37 μg/mL) was defined for Chinese children with epilepsy, following age- and seizure type-stratified analyses. Operationally, the lower limit was set at the maximum value of the 2.5th percentile value across age strata to define a conservative, population-wide minimum effective concentration. The upper limit, corresponding to the highest 97.5th percentile, was selected to establish a safety-informed reference boundary that reflects the upper extreme of observed drug exposure under standard dosing. Therefore, concentrations within this range were considered part of the children's common therapeutic exposure range, a range with well-documented efficacy at the group level. Indeed, in adopting this method, we prioritized general efficacy over age-stratified precision. Thus, while the derived range established a broadly safe and effective threshold for LEV, achieving optimal individualized therapy necessitates integrating TDM findings with the patient's specific clinical efficacy and AE profiles.

Consequently, defining the determinants of LEV systemic exposure—a critical requirement for implementing TDM—emerged as the next pivotal question. This investigation was empowered by an ample sample size, permitting multi-dimensional stratified analyses to precisely delineate key influencing variables. Successfully addressing this question thereby established the second major contribution of our work.

Initially, we found that there were significant associations between the tested variables and the plasma LEV levels except for sex, suggesting that multiple factors might be involved in the in vivo regulation of its disposition in the preliminary univariate analysis.

Next, the fixed-effects model analysis revealed (Table 4), on the one hand, a significant negative association between both age and body weight with C_0/D of LEV after controlling for confounding factors, indicating that its total *CL*

increased with age and body weight in children, which was consistent with previous findings.[29,30] On the other hand, the model analysis also demonstrated that the comedication with OXC significantly reduced its plasma concentration, a finding in line with several previous studies. For instance, studies reported by Shi et al[14] and Ha et al[31] confirmed that concomitant therapy, particularly with enzyme-inducing ASMs like OXC, accelerated LEV's *CL* and thus reduced its plasma concentrations. Supporting this, a study in Indian children[32] revealed a significantly lower median plasma LEV concentration in cases co-taking enzyme inducers (including OXC) compared with those without (7.3 vs 16.6 μg/mL).

Following this, interestingly, our study provided the first evidence linking developmental delay to increased LEV exposure.[24] This association might arise from the underlying neurodevelopmental conditions or their intricate comedication profiles, factors that might inhibit LEV metabolism more than previously recognized. Consequently, children with epilepsy and comorbid developmental delay may require more frequent TDM and dose individualization.

Naturally, rigorous statistical analysis is essential for navigating the confounding factors inherent in complex data, like repeated measures of plasma LEV concentrations from multiple patients over time in this study. Indeed, the mixed-effects model is particularly well-suited for this task, offering a robust framework for handling such hierarchical data structures.[33] Herein, the key lay in its incorporation of the "Patient ID" as a random intercept, which successfully quantifies the unmeasured inherent differences between individuals. Results from the random effects revealed an ICC of 38.46%, indicating that over one-third of the total variation in plasma LEV concentrations originated from stable physiological or genetic characteristics specific to each patient. Furthermore, the marginal and conditional R squared were 0.3293 and 0.5873, respectively. A comparison of these values revealed that, beyond known clinical factors such as age, body weight, and concomitant medication, patients' own physiological and genetic characteristics explained an additional 25.8% of the variability in plasma LEV concentrations. This finding revealed the impact of inherent inter-individual differences on LEV exposure, further underscoring the necessity of TDM in pediatric patients.

The third major contribution of our work to the field was the stratified analysis of clinical efficacy (Figure 4), which yielded new findings, particularly in clinical subgroups characterized by specific comorbidities. To begin with, this study demonstrated that LEV was highly effective, 63.88% achieving seizure freedom at 12 months and an overall response rate of 81.01%. The notably higher response rate of 90.89% in the monotherapy group strongly supported its reaccommodation as the first-line monotherapy option for childhood epilepsy.[34] This finding aligns with a systematic review[5] which reported favorable efficacy for LEV monotherapy across most studies, with seizure freedom rates ranging between 20−100% or seizure reduction exceeding 50% in 62–100% of pediatric patients. The efficacy outcomes observed in our study fall within this reported range and further substantiate the consistent therapeutic profile of LEV in clinical practice. However, the lower response rate (70.78%) observed in the polytherapy group likely reflected the greater epilepsy severity and complexity inherent to this population, which typically included cases who have failed prior monotherapy or presented with refractory epilepsy at onset. Consequently, the efficacy disparity between the two groups was more likely confounded by these baseline characteristics rather than being attributable to LEV itself. Intriguingly, within this comedication group, response rates for unknown seizure types were marginally higher—an observation that lends support to considering LEV in combination regimens for managing refractory epilepsy.

Next, this study further conducted a comparative analysis, using PSM to minimize bias, of LEV effects in children with epilepsy comorbid with either developmental delay or ADHD. No significant link was found between developmental delay comorbidity and LEV efficacy, consistent with previous research.[24] Interestingly, LEV showed favorable outcomes in epilepsy patients with autism spectrum disorder and other developmental disabilities.[35] Moreover, prior studies indicated its effectiveness in improving seizure control for individuals with intellectual disability.[36]

Indeed, epilepsy and ADHD co-occur in approximately one-third of pediatric cases. While controlling seizures remained the primary treatment priority in these cases,[34] the impact of LEV on attention and behavior was inconsistently reported.[37,38] Contrary to these concerns, our study identified superior antiseizure efficacy of LEV in patients with comorbid ADHD. This effect might be mediated through the suppression of interictal epileptiform discharges.[39] Although some studies reported an increased anger and ADHD symptom with LEV,[40] these potential behavioral effects should be balanced against the critical need for seizure control. Given the complex interplay between epilepsy, ADHD, and epileptiform activity,[39,40] the improved response observed in comorbid ADHD cases should be explained with caution. Large-scale prospective studies are warranted to definitively establish the net clinical benefit of LEV in this population.

Following this, the association between the clinical efficacy of LEV and its systemic exposure level was a key question of significant interest, as it had considerable clinical value for guiding individualized dose adjustments based on routine TDM. Initially, no significant association between plasma LEV concentration and clinical response was observed overall, aligning with previous studies.[17,24,32] Paradoxically, in the cases classed into focal epilepsy subgroup (particularly on monotherapy), responders exhibited significantly lower plasma concentrations. Despite a moderate ROC curve AUC of 0.68, its cut-off value (6.945 μg/mL) demonstrated high sensitivity. This finding argued for evolving LEV's TDM towards a precision, epilepsy subtype-guided strategy. However, the modest AUC values limited the predictive strength of concentration-based personalization, suggesting that while the cut-off might serve as a useful reference, it should not be used as a standalone predictor in clinical decision-making.

Other factors associated with treatment efficacy also merited further discussion. Multivariate logistic regression, controlling for confounders, showed that LEV efficacy was influenced by multiple factors, including sex, epilepsy type, duration of therapy, etiology, and concomitant ASMs. Notably, female sex was an independent risk factor for non-response (contrasting with a prior adult study[41]), and a higher number of concomitant ASMs was the strongest predictor of treatment failure. This latter association might reflect either greater baseline disease severity in patients requiring polytherapy or pharmacokinetic interactions (*eg*., with enzyme-inducers like OXC) that lower LEV exposure.[31]

The final major contribution of our study to the field was the comprehensive safety assessment, as tolerability constituted an equally critical consideration in epilepsy management. Impressively, the most frequent AEs were neuropsychiatric, mirroring those reported in the FAERS database analysis by Gui et al,[42] such as irritability, aggression, other behavioral problems, depressed mood, and anxiety.[42]

Next, the timing of these common AEs during the treatment course deserved clinical attention. In our study, the median TTO for psychiatric abnormalities was 117 days. In contrast with reports of early onset (frequently within 30 days), our data showed ASM-related psychiatric disorders occurring across a broader treatment timeline—a difference potentially reflecting reporting delays in retrospective studies. Despite constraints in modeling time-to-event risk, the clinical significance and potential for early onset of neuropsychiatric abnormalities underscored the need for vigilant monitoring.[43] Any new emotional, cognitive, or behavioral changes in patients should thus lead to immediate evaluation for a LEV-related etiology and possible dose adjustment.

Interestingly, the shape parameter β values for gastrointestinal and systemic/administration-site abnormalities were successfully estimated and were all <1, confirming an early failure pattern with the greatest risk at treatment onset followed by a progressive decline. This demonstrated a pattern consistent with clinical experience, where acute, transient AEs typically manifested early and might attenuate over time.[44]

Following this, another key question was whether there was a correlation between AEs and the systemic exposure level of LEV. Notably, this study, however, contradicted prior study reporting no significant correlation.[17] However, due to the retrospective nature of AEs documentation in our study, which might be subject to underreporting or recording bias, this finding should be interpreted with caution. In contrast to those reports, our study observed a higher prevalence of violent behavior at lower LEV levels, with a reduction at higher concentrations. Indeed, children with epilepsy presented a complex clinical picture where AEs could arise from polypharmacy, seizures, or comorbidities independent of LEV. Critically, however, a significant association ($P < 0.0001$) persisted even in the monotherapy subgroup, where the major confounder of comedications was removed. This suggested the observed concentration-dependent disparity in AEs was unlikely to be spurious. Future research should employ standardized AE adjudication and precise documentation to definitively clarify the relationship between plasma LEV concentration and AEs.

The primary strength of this study lay in its sample size of over 1000 cases, which enabled comprehensive stratified analyses to yield critical insights into the distinctive therapeutic profile of LEV in epilepsy management. However, several limitations inherent to this study should be considered when interpreting the results. First, the retrospective design was subject to the constraints of medical record completeness and accuracy, and it could not entirely rule out all unmeasured confounding factors. In particular, confounding by indications was a specific concern in this observational study. Patients receiving polytherapy typically had more severe or refractory epilepsy, which might independently influence both treatment selection and clinical outcomes. While we attempted to address this through subgroup analyses restricted to monotherapy, residual confounding could not be fully excluded in the polytherapy comparisons. Similar

consideration should be given to the impact of variability in sample collection. Second, treatment durations varied among patients, and efficacy assessment relied on real-world clinical reports rather than prospective, standardized seizure diaries, which might introduce variability in outcome documentation. Third, the timing of AEs onset was also dependent on records from follow-up visits, creating a potential lag between the actual event and its documentation that could introduce error into the TTO analysis. Finally, although the GAMLSS model we developed contributed to understanding the concentration-efficacy relationship and possessed considerable explanatory power, it did not fully account for all the variance in treatment response. This suggested that other unknown genetic or environmental factors likely play significant roles in determining individual responses to LEV therapy. Nevertheless, despite these limitations, this study contributed a solid foundation of real-world evidence to inform the personalized use of LEV and offered valuable insights for guiding individualized treatment strategies for LEV in children with epilepsy.

Conclusion

In conclusion, our findings offered practical evidence for individualizing LEV therapy in Chinese children with epilepsy. We proposed an observational reference range (2.82−24.37 μg/mL) and demonstrated robust efficacy across diverse clinical scenarios, including complex cases with comorbidities. In particular, it should be noted that the proposed reference range only represented an observational finding. Given the modest predictive strength of the exposure-response association and the retrospective nature of this study, this range should be interpreted with caution and required standardized protocols and mechanistic approaches in future prospective clinical study. The safety profile, characterized by neuropsychiatric events with delayed onset (median TTO 196.5 days), necessitated ongoing monitoring. Taken together, these integrated findings support a tailored, long-term treatment approach that considers the individual's epilepsy type, comorbidity profile, and treatment phase.

Data Sharing Statement

The original data that support the findings of this study are available from the corresponding author, Prof. Feng Chen, upon reasonable request. Requests and proposals for data access should be directed to chenfeng18@njmu.edu.cn and will be reviewed by the research team.

Acknowledgments

This research was supported by the Specially Appointed Medical Expert Project of the Jiangsu Commission of Health (2019), Nanjing Municipal Health Science and Technology Development Special Fund-Key Medical Project (No. ZKX24039) and by the Chinese Youth Medical Innovation Research Program (2024VIII04). This study was also supported by Jiangsu Health International Exchange Program.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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