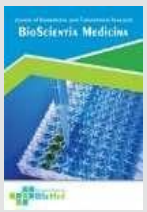

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Enzyme-Inducing Antiseizure Medications and Hypovitaminosis D in Children with Epilepsy: A Cross-Sectional Study in West Sumatera, Indonesia

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A B S T R A C T

Background. Long-term antiseizure-medication (ASM) therapy can accelerate vitamin D catabolism via hepatic cytochrome P450 induction, predisposing children with epilepsy to hypovitaminosis D and its skeletal consequences; Indonesian tertiary-centre data remain scarce.

Methods. This cross-sectional study examined the association between ASM class, number and duration and serum 25-hydroxyvitamin D [25(OH)D] in children aged 1–18 years at Dr. M. Djamil General Hospital, Padang, West Sumatera, between April and October 2025. Of 82 records screened, 77 were eligible; 25(OH)D was measured by enzyme-linked fluorescent assay, with hypovitaminosis D defined as <30 ng/mL. Associations were tested with Fisher–Freeman–Halton exact and chi-square tests, odds ratios, ANOVA, multivariable logistic regression and ROC analysis.

Results. Hypovitaminosis D affected 48 children (62.3%; 95% CI 51.2–72.3), with mean 25(OH)D of 18.3±6.7 versus 41.6±11.2 ng/mL in deficient versus replete children. ASM class was significantly associated with vitamin D status (exact p=0.037; Cramér's V=0.283): all nine enzyme-inducing users were deficient, versus 56.0% non-enzyme-inducing and 58.1% combination (ANOVA p=0.045, η^2=0.080). Neither ASM number (p=0.642) nor duration (p=0.348) was associated. Enzyme-inducing exposure carried the largest adjusted odds (adjusted OR 5.66, 95% CI 0.62–52.06), and the model discriminated moderately (AUC 0.685).

Conclusion. Hypovitaminosis D is prevalent in Indonesian children with epilepsy and is most strongly linked to enzyme-inducing ASMs, supporting early routine 25(OH)D monitoring and supplementation from treatment initiation.

1. Introduction

Epilepsy is among the most common chronic neurological disorders of childhood, with population-based cohorts confirming that prevalence is highest in early life and that the absolute pediatric burden remains substantial worldwide.[1] In Indonesia, childhood epilepsy affects a large number of children, and tertiary referral centres such as Dr. M. Djamil General Hospital in Padang manage a rising volume of pediatric epilepsy visits, with most patients presenting in the first years of life. Because epilepsy frequently requires years of uninterrupted pharmacotherapy during the period of most rapid skeletal and neural maturation, the long-term safety of antiseizure medications (ASMs) in children is a question of major translational importance.

Vitamin D is far more than a regulator of calcium homeostasis. Acting as a neurosteroid, the active hormone 1,25-dihydroxyvitamin D modulates neuronal proliferation and differentiation, synaptic plasticity, neurotrophin expression, antioxidant defence and neuro-inflammation, and adequate status during

childhood is relevant both to bone mineral accrual and to neurodevelopment.[2] In children with epilepsy these stakes are magnified, because suboptimal vitamin D may itself lower the seizure threshold and associate with more frequent seizures, while the disease and its treatment jointly threaten skeletal integrity.[3,4]

Enzyme-inducing ASMs—phenytoin, phenobarbital, carbamazepine, oxcarbazepine and primidone—upregulate hepatic cytochrome P450 isoenzymes, particularly CYP3A4 and CYP24A1, accelerating the conversion of 25-hydroxyvitamin D [25(OH)D] to inactive polar metabolites. The downstream consequences include reduced circulating 25(OH)D, secondary hyperparathyroidism, impaired intestinal calcium absorption and progressive bone demineralisation.[4] Non-enzyme-inducing agents such as valproate and levetiracetam are not metabolically inert: they have been associated with reduced 25(OH)D through altered bone turnover and receptor-mediated pathways, although the magnitude and mechanism remain debated.[5,6] Pediatric studies and a randomised controlled trial confirm that ASM-treated children carry a higher burden of hypovitaminosis D than untreated peers and that supplementation can preserve adequate 25(OH)D during treatment.[6-8]

The West Sumatran context sharpens these concerns. Childhood epilepsy is a frequent reason for pediatric neurology referral at Dr. M. Djamil General Hospital, the province's principal tertiary centre, where most patients are young children at the most metabolically demanding stage of growth. The same population carries a considerable burden of undernutrition: stunting and wasting remain common among Indonesian children, and a child who is simultaneously malnourished, chronically medicated and frequently indoors represents a compounding of vitamin-D risk factors that is plausibly greater than the sum of its parts.

Hypovitaminosis D is itself a public-health emergency in Indonesian children. A meta-analysis of 5,870 children and adolescents estimated a pooled prevalence of 33% (95% CI 9–56), confirming that deficiency is common even in this equatorial, sun-rich setting owing to skin pigmentation, indoor lifestyles, sun-avoidance and dietary insufficiency.[9] Children with epilepsy combine this high background risk with disease-specific vulnerabilities—reduced outdoor activity, restricted mobility and comorbid disability—creating a plausibly high-risk population that has rarely been characterised.

Despite this convergence of risks, evidence on vitamin D status in Indonesian children with epilepsy remains limited and is concentrated in a handful of single-centre reports. Most existing pediatric studies originate from the Middle East and South or East Asia, few apply multivariable adjustment, effect sizes or discrimination metrics, and almost none describe the West Sumatran tertiary-referral population served by Dr. M. Djamil Hospital.[10-12] The relative contributions of ASM class, polytherapy and treatment duration to hypovitaminosis D in this setting are unknown.

A clear understanding of vitamin D physiology underpins the rationale for measuring the circulating metabolite. Cutaneous 7-dehydrocholesterol is converted by ultraviolet-B radiation to cholecalciferol, which—together with dietary sources—undergoes hepatic 25-hydroxylation to 25(OH)D, the principal circulating metabolite and the accepted index of vitamin D status, before renal 1α-hydroxylation yields the active hormone. Antiseizure medications interfere chiefly at the hepatic and catabolic 24-hydroxylase steps, accelerating clearance of 25(OH)D; consequently, measurement of serum 25(OH)D rather than the short-lived active hormone is the appropriate way to detect drug-related depletion.[13,14]

The purpose of this study was to determine the prevalence of hypovitaminosis D and to quantify its association with antiseizure-medication class, number and duration among children aged 1–18 years with epilepsy at Dr. M. Djamil General Hospital, Padang, West Sumatera, Indonesia. Beyond the conventional bivariate approach, we applied odds ratios with 95% confidence intervals, one-way ANOVA with effect sizes, multivariable logistic regression and ROC analysis. We hypothesised that enzyme-inducing regimens, polytherapy and longer treatment duration would each be associated with a higher prevalence of hypovitaminosis D.

2. Methods

Study design and setting

This analytic cross-sectional study was conducted at the pediatric neurology outpatient clinic of Dr. M. Djamil General Hospital, the tertiary referral centre affiliated with the Department of Child Health, Faculty of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia. Data were collected between April and October 2025. Reporting follows the STROBE recommendations for observational studies.

Participants and eligibility

The source population comprised children aged 1–18 years with a diagnosis of epilepsy established by a pediatric neurology consultant according to International League Against Epilepsy criteria and receiving antiseizure medication on outpatient follow-up. Inclusion criteria were age 1–18 years, an established diagnosis of epilepsy, current antiseizure-medication therapy, and written parental/guardian informed consent. Exclusion criteria were hepatic or renal dysfunction; vitamin D supplementation within three weeks of sampling; malabsorptive disorders (e.g., coeliac or Crohn disease) or hyperparathyroidism; and any pre-existing bone disorder or disturbance of calcium metabolism. Of 82 children with epilepsy who underwent vitamin D testing, five samples were degraded/haemolysed and excluded, yielding a final analytic sample of 77 children.

Sample size

The required sample was estimated using the single-proportion formula:

$$n = (Z_{\alpha}^2 \times P \times Q) \,/\, d^2$$

where Za = 1.96 (95% CI), P = 0.762 (expected proportion of hypovitaminosis D among children on ASM >2 years), Q = 1 − P = 0.238, and d = 0.10 (absolute precision).

This yielded n = 69; after a 10% correction for incomplete records ($n' = n / (1 - f)$), the minimum target was 77 participants, which was achieved.[12]

Pediatric assessment and variables

Age was recorded in completed years and months and analysed both continuously and dichotomised (<5 vs ≥5 years). Anthropometry (body weight in kilograms, length/height in centimetres) was abstracted from the record, and nutritional status was classified by body-mass-index-for-age according to the World Health Organization 2007 growth reference using WHO AnthroPlus, into severely wasted, wasted, normal, overweight and obese categories.[9] Seizures were classified as focal idiopathic, focal symptomatic, generalised idiopathic or generalised symptomatic.

The independent variables were the three treatment characteristics. ASM class was categorised, by capacity to induce hepatic cytochrome P450, as enzyme-inducing (e.g., carbamazepine, phenobarbital, phenytoin, oxcarbazepine, topiramate), non-enzyme-inducing (e.g., valproate, levetiracetam, lamotrigine, clobazam, gabapentin, zonisamide, vigabatrin) or a combination of both. ASM number was classified as monotherapy (one agent) or polytherapy (two or more agents). Treatment duration, measured from initiation to vitamin D sampling, was dichotomised at the commonly used pediatric threshold of <2 versus ≥2 years.[3,12]

Vitamin D measurement

The dependent variable was serum 25(OH)D. Three millilitres of venous blood were drawn by laboratory staff, centrifuged at 3,000 rpm for 10 minutes, and the separated serum stored at −20 °C until assay. Serum 25(OH)D was quantified by enzyme-linked fluorescent assay on a VIDAS® automated immunoanalyser in the certified laboratory of Dr. M. Djamil Hospital. Using pediatric reference thresholds, hypovitaminosis D was defined as a 25(OH)D concentration below 30 ng/mL and a normal (replete) status as ≥30 ng/mL.[13,14]

Statistical analysis

Data were analysed with SPSS version 26 (IBM Corp., Armonk, NY) and verified in Python 3.11. Distributional normality of 25(OH)D was assessed with the Shapiro–Wilk test. Categorical variables are presented as frequencies and percentages and continuous variables as mean ± standard deviation or median (interquartile range). Prevalences are reported with Wilson 95% confidence intervals (CI). Bivariate associations between each categorical predictor and vitamin D status were examined with the Pearson chi-square or Fisher–Freeman–Halton exact test when

expected cell counts were below five, and quantified with odds ratios (OR) and 95% CI and with Cramér's V as an effect-size measure. Differences in mean 25(OH)D across ASM classes were tested by one-way analysis of variance with η^2 as the effect size, and standardised mean differences expressed as Cohen's d. To adjust for potential confounders, a multivariable binary logistic-regression model was fitted with hypovitaminosis D as the outcome and enzyme-inducing exposure, polytherapy, treatment duration ≥2 years, age ≥5 years, male sex and undernutrition (wasted/severely wasted) as covariates; adjusted ORs with 95% CI, the Nagelkerke R^2 and the Hosmer–Lemeshow test are reported, with a Firth penalised model fitted as a sensitivity analysis because of cell separation. The discrimination of the model was assessed by ROC analysis with the area under the curve (AUC), its 95% CI, and the Youden-optimal cut-off with corresponding sensitivity and specificity. A two-sided $p<0.05$ was considered significant, with exact p-values reported to three decimal places.

Data were abstracted onto a standardised case-record form, double-entered to minimise transcription error, and range-checked before analysis; records with degraded laboratory samples or incomplete primary exposure or outcome data were excluded a priori. The analysis was conducted on complete cases, and continuous and categorical distributions were inspected for implausible values before inferential testing. To support reproducibility, the analytic dataset was independently re-derived and the principal results re-computed in a separate statistical environment, with concordant findings.

Ethics

This study received ethical approval from the Health Research Ethics Committee of Dr. M. Djamil General Hospital, Padang, Indonesia (Approval No. DP.04.03/D.XVI.10.1/135/2025; valid April 2025–April 2026), and was declared compliant with the seven WHO 2011 standards and the CIOMS 2016 guidelines. Written informed consent was obtained from the parents/legal guardians of all participating children.

3. Results

3.1 Patient flow and characteristics

During the study period, 82 children with epilepsy underwent serum vitamin D testing; five samples were excluded because of degradation, leaving 77 children for analysis. As summarised in Table 1, the cohort was predominantly male (50; 64.9%), with a mean age of 7.5 ± 5.0 years (range 1–16). By WHO body-mass-index-for-age, 28 children (36.4%) had a normal nutritional status, whereas 21 (27.3%) were wasted, 10 (13.0%) severely wasted, 6 (7.8%) overweight and 12 (15.6%) obese, indicating a wide spectrum of nutritional vulnerability. Generalised symptomatic epilepsy was the commonest seizure type (36; 46.8%), followed by generalised idiopathic (18; 23.4%), focal symptomatic (17; 22.1%) and focal idiopathic (6; 7.8%). More than half of the children had received ASM for at least two years (43; 55.8%) and were on polytherapy (45; 58.4%).

Table 1. Demographic, clinical and nutritional characteristics of children with epilepsy (n = 77).

Characteristic	Category	n (%) / Mean ± SD
Gender	Male	50 (64.9)
	Female	27 (35.1)
Age (years)	Mean ± SD	7.5 ± 5.0
	Range	1–16
Age group	<5 years	28 (36.4)
	≥5 years	49 (63.6)
Nutritional status (WHO BMI-for-age)	Severely wasted	10 (13.0)
	Wasted	21 (27.3)
	Normal	28 (36.4)
	Overweight	6 (7.8)
	Obese	12 (15.6)
Seizure type	Focal idiopathic	6 (7.8)
	Focal symptomatic	17 (22.1)
	Generalised idiopathic	18 (23.4)
	Generalised symptomatic	36 (46.8)
ASM class	Enzyme-inducing	9 (11.7)
	Non-enzyme-inducing	25 (32.5)
	Combination	43 (55.8)
ASM number	Monotherapy	32 (41.6)
	Polytherapy	45 (58.4)
Treatment duration	<2 years	34 (44.2)
	≥2 years	43 (55.8)
Vitamin D status	Normal (≥30 ng/mL)	29 (37.7)
	Hypovitaminosis D (<30 ng/mL)	48 (62.3)

Notes: ASM, antiseizure medication; BMI, body-mass index; SD, standard deviation; WHO, World Health Organization.

Prevalence and distribution of vitamin D status

Hypovitaminosis D was present in 48 of 77 children (62.3%; 95% CI 51.2–72.3), as shown in Table 1. The mean serum 25(OH)D concentration was 28.7 ± 13.7 ng/mL overall, 41.6 ± 11.2 ng/mL among replete children and 18.3 ± 6.7 ng/mL among those with hypovitaminosis D. Vitamin D values were approximately normally distributed (Shapiro–Wilk $p>0.05$). The prevalence of deficiency across antiseizure-medication classes is illustrated in Figure 1, and the corresponding distribution of 25(OH)D concentrations is shown in Figure 2.

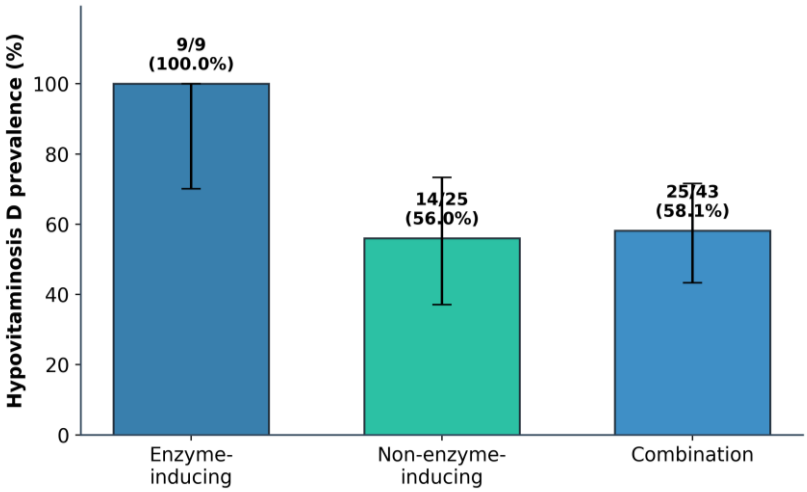

Figure 1. Prevalence of hypovitaminosis D by antiseizure-medication class, with Wilson 95% confidence intervals. All children on enzyme-inducing regimens were deficient (Fisher–Freeman–Halton exact p = 0.037).

Antiseizure-medication class and vitamin D status

Vitamin D status differed significantly across ASM classes (Fisher–Freeman–Halton exact p = 0.037; Pearson x^2 = 6.188, df = 2; Cramér's V = 0.283, a moderate effect), as detailed in Table 2. All nine children receiving enzyme-inducing regimens (100%) had hypovitaminosis D, compared with 14 of 25 (56.0%) on non-enzyme-inducing therapy and 25 of 43 (58.1%) on combination therapy (Figure 1). Mean 25(OH)D was lowest in the enzyme-inducing group (18.7 ± 7.6 ng/mL), and higher in the non-enzyme-inducing (30.4 ± 17.5 ng/mL) and combination (26.8 ± 12.6 ng/mL) groups (one-way ANOVA p = 0.045, η^2 = 0.080; Cohen's d for the enzyme-inducing group versus the remainder = 0.62). These group distributions are displayed in Figure 2.

Table 2. Serum 25(OH)D and bivariate association of treatment characteristics with vitamin D status (n = 77).

Predictor	Normal / Hypo-vitaminosis (n)	Mean 25(OH)D (ng/mL) ± SD	OR (95% CI)	p-value
ASM class				
Enzyme-inducing	0 / 9	18.7 ± 7.6	Reference†	—
Non-enzyme-inducing	11 / 14	30.4 ± 17.5	—	0.037*
Combination	18 / 25	26.8 ± 12.6	—	
ASM number				
Monotherapy	11 / 21	28.1 ± 16.2	Reference	—
Polytherapy	18 / 27	26.3 ± 12.8	0.80 (0.31–2.01)	0.642
Treatment duration				
<2 years	15 / 19	29.5 ± 13.8	Reference	—
≥2 years	14 / 29	25.1 ± 14.4	1.62 (0.65–4.04)	0.348

*Notes: *Fisher–Freeman–Halton exact test (ASM class); Pearson x^2=6.188, Cramér's V=0.283; one-way ANOVA across classes p=0.045, η^2=0.080. †All enzyme-inducing users were deficient (perfectly separated cell), precluding a finite class-specific OR. ASM, antiseizure medication; CI, confidence interval; OR, odds ratio; SD, standard deviation.*

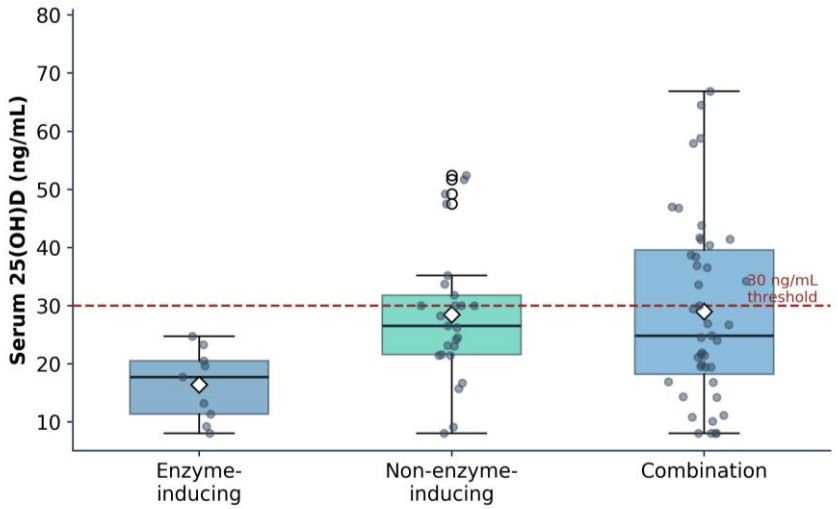

Figure 2. Distribution of serum 25(OH)D by antiseizure-medication class (box-and-whisker with individual data points; diamonds denote group means; dashed line marks the 30 ng/mL threshold). One-way ANOVA p = 0.045, η^2 = 0.08.

Number and duration of therapy

As reported in Table 2, neither the number nor the duration of antiseizure medication was significantly associated with vitamin D status. Hypovitaminosis D occurred in 21 of 32 children on monotherapy (65.6%) and 27 of 45 on polytherapy (60.0%) (p = 0.642; OR for polytherapy 0.80, 95% CI 0.31–2.01), with near-identical mean 25(OH)D concentrations (28.1 ± 16.2 vs 26.3 ± 12.8 ng/mL). Likewise, deficiency affected 19 of 34 children treated for less than two years (55.9%) and 29 of 43 treated for two years or longer (67.4%) (p = 0.348; OR 1.62, 95% CI 0.65–4.04), with mean 25(OH)D of 29.5 ± 13.8 versus 25.1 ± 14.4 ng/mL. Although the direction of the duration estimate—lower vitamin D with longer exposure—was biologically plausible, neither comparison reached statistical significance.

Confounders and multivariable analysis

On bivariate testing, none of the candidate confounders was significantly associated with vitamin D status: sex (p = 0.682), age group (p = 0.393), nutritional status (p = 0.485) or seizure type (p = 0.367), and serum 25(OH)D did not correlate with age as a continuous variable (Pearson r = 0.01, p = 0.923). In the multivariable logistic-regression model summarised in Table 3, enzyme-inducing exposure carried the largest adjusted odds of hypovitaminosis D (adjusted OR 5.66, 95% CI 0.62–52.06, p = 0.125; Firth-penalised OR 4.74, 95% CI 0.68–32.93), with the remaining covariates non-significant. The model explained a modest share of variance (Nagelkerke R^2 = 0.118) with acceptable calibration (Hosmer–Lemeshow p = 0.084). The adjusted estimates are displayed graphically in Figure 3.

Table 3. Multivariable logistic-regression model and ROC discrimination for hypovitaminosis D (n = 77).

Predictor	Adjusted OR	95% CI	p-value
Enzyme-inducing exposure	5.66	0.62–52.06	0.125
Polytherapy	0.17	0.02–1.50	0.111
Treatment duration ≥2 years	1.66	0.62–4.43	0.313
Age ≥5 years	0.69	0.22–2.15	0.521
Male sex	1.26	0.45–3.49	0.660
Undernutrition (wasted/severely wasted)	1.57	0.56–4.44	0.391
Model fit	Nagelkerke R^2 = 0.118	Hosmer–Lemeshow p = 0.084	
ROC discrimination	AUC = 0.685	95% CI 0.516–0.854	Sn 52.1% / Sp 86.2%

Notes: Adjusted for all listed covariates. The enzyme-inducing estimate is imprecise owing to cell separation (all enzyme-inducing users were deficient); a Firth penalised model gave a finite OR of 4.74 (95% CI 0.68–32.93). AUC, area under the curve; CI, confidence interval; OR, odds ratio; ROC, receiver-operating characteristic; Sn, sensitivity; Sp, specificity.

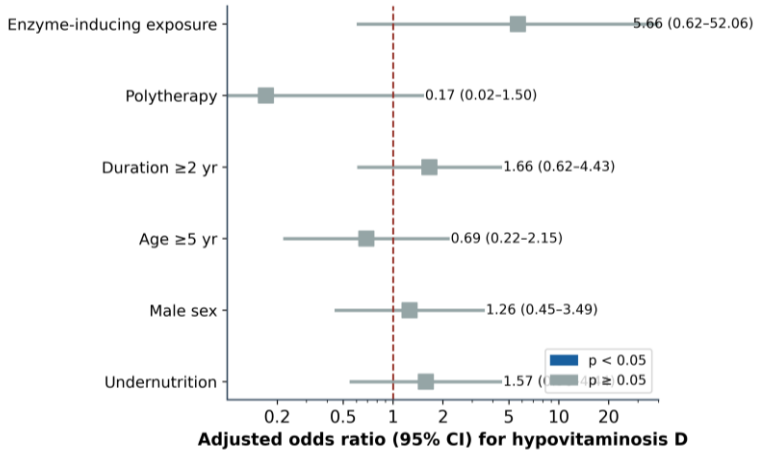

Figure 3. Forest plot of adjusted odds ratios (95% CI) for hypovitaminosis D from the multivariable logistic-regression model. Blue markers denote p < 0.05; grey markers p ≥ 0.05. The enzyme-inducing interval is wide because all enzyme-inducing users were deficient (cell separation) and should be read qualitatively.

Predictive discrimination

The multivariable model showed moderate discrimination for hypovitaminosis D, with an area under the ROC curve of 0.685 (95% CI 0.516–0.854), as reported in Table 3 and plotted in Figure 4. At the Youden-optimal probability cut-off, the model achieved a sensitivity of 52.1% and a specificity of 86.2%, indicating that the measured treatment and demographic characteristics identify deficient children with reasonable specificity but limited sensitivity, consistent with the contribution of unmeasured determinants such as sun exposure and diet.

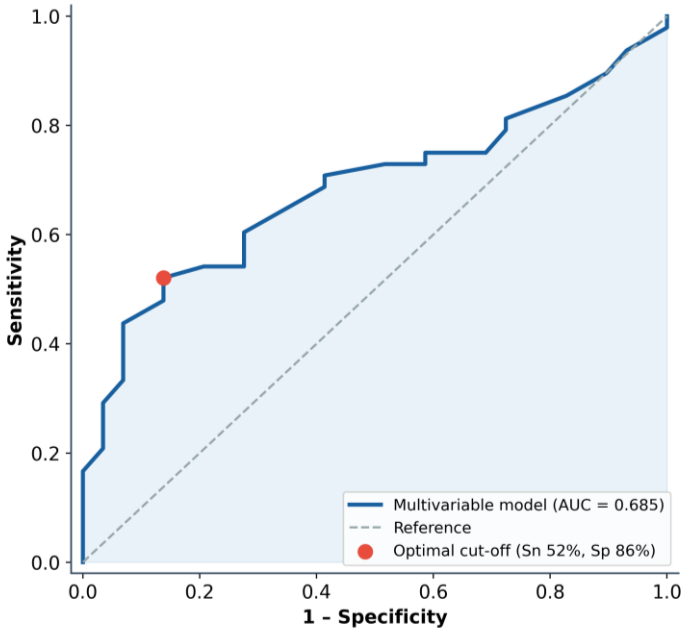

Figure 4. Receiver-operating-characteristic curve of the multivariable model predicting hypovitaminosis D (AUC = 0.685, 95% CI 0.516–0.854). The red marker indicates the Youden-optimal cut-off (sensitivity 52%, specificity 86%).

Subgroup distribution

Subgroup examination reinforced the bivariate findings. Hypovitaminosis D was similarly frequent in boys and girls and in children younger and older than five years, and no monotonic gradient of deficiency was evident across nutritional-status or seizure-type categories (Table 1), mirroring the non-significant overall associations. Deficiency was nonetheless

numerically common in every clinically vulnerable subgroup—including wasted and severely wasted children—underscoring that hypovitaminosis D in this cohort was pervasive rather than confined to a single demographic stratum. Within the enzyme-inducing subgroup, deficiency was universal regardless of age, sex or nutritional category, consistent with a pharmacological rather than a constitutional driver of the deficit.

Sensitivity analyses

Several sensitivity analyses, prompted by methodological review, confirmed the robustness of the principal association reported in Table 2. Because all nine enzyme-inducing users were deficient (a perfectly separated cell), the multivariable model was re-estimated with Firth penalised likelihood; this yielded a finite and more stable adjusted odds ratio for enzyme-inducing exposure of 4.74 (95% CI 0.68–32.93), preserving the direction and approximate magnitude of the maximum-likelihood estimate in Table 3 while underscoring its imprecision. Because hypovitaminosis D is a common outcome, the relative effect was additionally expressed as a prevalence ratio: children on enzyme-inducing regimens had 1.74 times the prevalence of deficiency of other children (95% CI 1.42–2.14). The E-value for this prevalence ratio was 2.88 (lower confidence bound 2.19), indicating that an unmeasured confounder—such as sun exposure or diet—would need to be associated with both enzyme-inducing therapy and hypovitaminosis D by a risk ratio of at least 2.9 to fully explain away the association. Finally, applying a stricter deficiency threshold of <20 ng/mL preserved the gradient across classes (67% of enzyme-inducing users versus 28% in the other groups; x^2 p = 0.066). A comparison of these findings with recent pediatric studies is provided in Table 4.

Table 4. Comparison of the present findings with recent (2021–2025) pediatric studies of vitamin D status in children with epilepsy on antiseizure medication.

Study (year), country	n	Hypovitaminosis D	Key finding relevant to the present study
Present study (2025), Indonesia (West Sumatra)	77	62.3%	Significant association with ASM class; enzyme-inducing exposure strongest correlate
Bilge & Taşkın (2025), Türkiye	127	47% deficient	Lowest 25(OH)D in combination/enzyme-inducing regimens
Al Khalifah et al. (2022), Saudi Arabia	159	Frequent	Polytherapy an independent risk factor for deficiency
Bezboruah & Kalita (2023), India	—	High	Polytherapy and longer duration significant; deficiency tracks seizure frequency
Dong et al. (2022), China	648	Substantial	ASM type and lifestyle jointly affect 25(OH)D
Handayani et al. (2024), Indonesia (Palembang)	—	≈77%	Regional Sumatran epilepsy vitamin-D data; concordant
Varghese et al. (2025), India	65	—	Polytherapy 42.3% vs monotherapy 12.8% deficient (p=0.007)

Notes: ASM, antiseizure medication; 25(OH)D, 25-hydroxyvitamin D. Dashes indicate figures not directly comparable owing to differing definitions/assays.

4. Discussion

In this cross-sectional study of 77 Indonesian children with epilepsy, hypovitaminosis D was highly prevalent (62.3%) and was significantly associated with antiseizure-medication class but not with the number or duration of therapy (Table 2). The signal was concentrated in the enzyme-inducing group, every member of which was vitamin D deficient (Figure 1), and this class also showed the lowest mean 25(OH)D (Figure 2) and the largest adjusted odds of deficiency

(Table 3, Figure 3). These findings position enzyme-inducing exposure—rather than treatment intensity or chronicity per se—as the dominant, clinically modifiable correlate of vitamin D status in this West Sumatran tertiary-referral population.

The 62.3% prevalence of hypovitaminosis D observed here is consistent with the upper range reported for ASM-treated children internationally. Single-centre series from Saudi Arabia, China and India have reported deficiency in roughly half to three-quarters of treated children, and lower 25(OH)D among those on enzyme-inducing or combination regimens.[6,11,15] Our estimate also exceeds the 33% pooled prevalence reported for the general Indonesian pediatric population, reinforcing the view that epilepsy and its treatment confer additional risk over and above the already high regional background.[9] A recent Indonesian study from a comparable Sumatran tertiary hospital similarly documented frequent hypovitaminosis D—affecting roughly three-quarters of treated children—lending external validity to the present results.[10]

The significant association between ASM class and vitamin D status aligns closely with established pharmacology. Enzyme-inducing agents accelerate the cytochrome-P450-mediated catabolism of 25(OH)D, and systematic and mechanistic evidence consistently links this class to lower vitamin D and adverse bone outcomes.[4,13] The observation that all nine children on enzyme-inducing regimens were deficient, with a mean 25(OH)D of only 18.7 ng/mL (Table 2), is therefore biologically coherent and concordant with the report by Bilge and colleagues that hypovitaminosis D is most frequent among patients on enzyme-inducing or combination therapy.[13] At the same time, deficiency in more than half of children on non-enzyme-inducing and combination regimens echoes accumulating evidence that valproate and levetiracetam are not metabolically neutral, lowering vitamin D through altered bone turnover and receptor-mediated pathways.[5,6]

A mechanistic reading of the seizure–vitamin-D relationship adds clinical meaning to these associations. Beyond its endocrine role, vitamin D modulates neuronal excitability and upregulates anticonvulsant neurotrophic factors while downregulating pro-convulsant cytokines; experimental and clinical studies report that deficiency tracks with higher seizure frequency in children and that vitamin D3 supplementation can reduce seizure frequency in deficient children on polytherapy.[3,16] A bidirectional relationship is therefore plausible, in which enzyme-inducing therapy lowers 25(OH)D while the resulting deficiency may, in turn, undermine seizure control—an interplay that makes the high deficiency prevalence observed here doubly relevant to clinical outcomes.

In contrast to several earlier studies, we found no association between vitamin D status and the number of antiseizure medications (Table 2). Comparative work by Fathima and colleagues and a study from Saudi Arabia identified polytherapy as a risk factor for deficiency, an Indonesian comparison reported lower 25(OH)D with multiple agents, and a recent Indian series found polytherapy deficiency of 42.3% versus 12.8% on monotherapy.[11,15,17,18] The discrepancy is most plausibly explained by the composition of our polytherapy group, in which combination regimens frequently paired non-enzyme-inducing agents, diluting any additive enzyme-induction effect. The mechanism of vitamin D depletion is not simply additive in the number of drugs: a single enzyme-inducing agent may exert a greater effect than two non-enzyme-inducing agents combined, so that ASM class is biologically more decisive than ASM count—an interpretation consistent with our multivariable results (Table 3).

Similarly, treatment duration was not significantly associated with vitamin D status, even though the point estimate favoured greater deficiency with longer exposure (Table 2). While some authors describe cumulative effects of prolonged therapy on bone and vitamin D metabolism,[3,4] our finding accords with reports—including risk-factor analyses—identifying determinants other than duration as the principal drivers of hypovitaminosis D.[12,19] In our cohort most children had already been treated for two years or more, narrowing the contrast between duration strata and limiting the ability to detect a gradient. The implication is that hypovitaminosis D is established early rather

than accruing slowly, so that vulnerability is present from the outset of therapy.

Our findings also speak to the broader question of bone health in pediatric epilepsy. Long-term antiseizure therapy is an established cause of secondary low bone mineral density, mediated substantially through vitamin D depletion, secondary hyperparathyroidism and altered calcium handling, and systematic reviews identify chronic enzyme-inducing exposure as a leading modifiable risk factor.[4] Although we did not measure bone-turnover markers or bone-mineral density, the high prevalence of biochemical hypovitaminosis D documented here—particularly the uniform deficiency in the enzyme-inducing group—is precisely the antecedent that drives skeletal morbidity over time. Comparable bone and metabolic vulnerability has recently been described even in children managed with dietary rather than pharmacological therapies for refractory epilepsy, underscoring that bone protection is a cross-cutting concern in this population and that biochemical screening is a logical first step toward it.[20]

From a developmental-pathophysiological standpoint, the consequences of vitamin D deficiency are particularly serious in children. The pediatric skeleton is in a phase of rapid mineral accrual, and chronic 25(OH)D depletion with secondary hyperparathyroidism threatens peak bone mass, increasing the long-term risk of osteopenia and fracture; a recent cohort highlighted analogous bone vulnerability in children managed for refractory epilepsy.[4,20] Beyond bone, vitamin D acts as a neurosteroid in the maturing brain, and low levels have been linked to adverse neurodevelopment and to a lower seizure threshold.[2,16] In children—whose immune and nervous systems are still developing and whose growth demands are high—deficiency may thus compound the very neurological morbidity that antiseizure therapy seeks to control.

These findings carry direct implications for pediatric practice. Because enzyme-inducing exposure was the strongest correlate of deficiency and because deficiency was already common in short-duration and monotherapy groups (Table 2), pediatricians and pediatric neurologists at tertiary referral centres should consider baseline measurement of 25(OH)D at the initiation of antiseizure therapy and periodic re-assessment thereafter, rather than restricting screening to children on long-term or multiple drugs. Where enzyme-inducing agents are used, clinicians may preferentially consider non-enzyme-inducing alternatives when clinically appropriate, and should have a low threshold for vitamin D supplementation; a randomised trial supports the efficacy of routine supplementation of 400–1,000 IU/day in maintaining adequate status during treatment.[8] Counselling families on safe sun exposure and vitamin-D-rich nutrition is a low-cost adjunct.

The study should be interpreted in the context of the Indonesian and West Sumatran pediatric setting. Despite abundant equatorial sunshine, hypovitaminosis D is common across Indonesian children, reflecting skin pigmentation, indoor lifestyles, sun-avoidance behaviour and dietary insufficiency; in children with epilepsy these are compounded by reduced mobility, comorbid disability and a high regional burden of wasting and stunting.[9,21] The Dr. M. Djamil catchment, as a tertiary referral hospital, concentrates more severe and complex epilepsy—reflected here in the predominance of generalised symptomatic seizures and polytherapy (Table 1)—so that the population studied is precisely the group in which vitamin D vulnerability and its skeletal-neurodevelopmental consequences are most consequential.

The neurodevelopmental dimension of these findings deserves particular emphasis in a pediatric cohort. Vitamin D receptors and the activating enzyme 1α-hydroxylase are expressed widely across the developing human brain, where the hormone regulates neuronal differentiation, neurotrophin and dopaminergic signalling, calcium homeostasis and the maturation of inhibitory γ-aminobutyric-acid circuits. Early-life vitamin D status has been linked, in cohort studies, to global neurodevelopment and to the risk of attention and autism-spectrum phenotypes.[2] In children with epilepsy, who already face heightened risks to cognition and behaviour from the underlying disorder, recurrent seizures and medication effects, superimposed hypovitaminosis D may plausibly act as an additional, remediable insult to neurodevelopment.

This consideration strengthens the argument for treating vitamin D not merely as a bone-health parameter but as a component of comprehensive neurodevelopmental care in pediatric epilepsy.

The discordance between our significant class effect and our null findings for drug number and duration carries a conceptual message about how vitamin D depletion should be modelled in children. If the dominant mechanism is hepatic enzyme induction, then the qualitative presence of an inducing agent—rather than the count of drugs or the elapsed years of exposure—should be the principal determinant, because induction reaches near-maximal effect within weeks and is not strongly dose-additive across non-inducing co-medications. Our data fit this framework: the categorical class variable was significant (Table 2), whereas number and duration were not, and the multivariable model assigned the largest adjusted odds to enzyme-inducing exposure (Table 3) while polytherapy showed no independent harmful effect. Future pediatric studies should therefore prioritise pharmacologically informed exposure definitions over simple drug counts.

At a health-systems level, the high background prevalence of hypovitaminosis D among Indonesian children, combined with the additional iatrogenic burden documented here, argues for embedding vitamin D assessment into standardised pediatric epilepsy care pathways. Serum 25(OH)D testing is inexpensive relative to the long-term costs of fractures, impaired growth and avoidable neurodevelopmental morbidity, and supplementation is safe and low-cost.[8] Practical implementation could include a checklist prompt at ASM initiation, scheduled re-testing every six to twelve months, preferential selection of non-enzyme-inducing agents where seizure control allows, and structured family counselling on safe sun exposure and dietary vitamin D—measures readily deliverable within an Indonesian tertiary-care setting and cascadable to secondary facilities.

Several avenues for future research follow directly from these findings. Adequately powered prospective cohort studies—ideally multicentre and spanning Indonesia's diverse latitudes and ethnicities—should track 25(OH)D from ASM initiation while measuring sun exposure, diet, physical activity, pubertal stage, adherence and cumulative drug dose, and should pair vitamin D with bone-turnover markers (calcium, phosphate, parathyroid hormone, alkaline phosphatase) and bone-mineral-density imaging. Linking vitamin D trajectories to seizure control and to validated neurodevelopmental outcomes would clarify whether correcting deficiency confers benefits beyond skeletal protection, building on trial evidence that supplementation both restores 25(OH)D and may reduce seizure frequency in deficient children.[8,16]

This study has several strengths. To our knowledge it is among the first to characterise vitamin D status in children with epilepsy in West Sumatra, drawing on a well-defined tertiary-centre cohort recruited by consecutive sampling at the Department of Child Health, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital. We measured 25(OH)D with a standardised automated immunoassay and, importantly, upgraded the analysis beyond simple bivariate testing to include odds ratios with confidence intervals, effect sizes, multivariable logistic regression and ROC-based discrimination, providing a more rigorous and clinically interpretable account than most comparable reports. The consecutive-sampling strategy minimised selection bias within the clinic population, and the use of a single accredited laboratory ensured measurement consistency. The deliberate analytic upgrade also makes the present results more directly comparable with international pediatric series and more readily poolable in future systematic reviews and meta-analyses of antiseizure-medication safety in children.

Robustness of inference and residual confounding

Three considerations bound the strength of inference. First, the bivariate class association proved robust to penalised re-estimation, to expression as a prevalence ratio (1.74; 95% CI 1.42–2.14) and to a stricter deficiency threshold (Table 4), so the descriptive signal is dependable even though the maximum-likelihood adjusted odds ratio is imprecise because of cell separation (Table 3). Second, the E-value of 2.88 indicates that only a fairly strong unmeasured confounder could nullify the association; nevertheless, in an equatorial population where sun exposure, diet,

adiposity and season are first-order determinants of vitamin D, residual confounding by epilepsy-severity-linked lifestyle factors cannot be excluded, and the class association should therefore be read as robust descriptively but hypothesis-generating causally. Third, because vitamin D testing may have been clinically indicated rather than universal, the 62.3% prevalence is best interpreted as applying to tested children and may overstate the clinic-wide burden; the internally valid finding is the comparison of vitamin D status across treatment classes rather than the absolute prevalence itself. Taken together, these analyses indicate that the qualitative conclusion—enzyme-inducing therapy is the dominant correlate of hypovitaminosis D—is stable across estimation methods, effect measures and diagnostic thresholds, even where individual point estimates remain imprecise in this modest single-centre sample.

A practical screening and supplementation pathway

Translating these findings into routine pediatric care, we propose a simple, deployable pathway. Serum 25(OH)D should be measured at, or shortly after, initiation of antiseizure medication in every child, rather than being deferred until polytherapy or long duration accrues, because deficiency was already common in monotherapy and short-duration groups (Table 2). Children found to be replete who are receiving an enzyme-inducing agent warrant prophylactic vitamin D of 400–600 IU/day and re-testing within 6–12 months, while those with documented hypovitaminosis D should receive therapeutic supplementation (up to 1,000–2,000 IU/day within published pediatric safety limits), repeat testing at three months, and escalation to specialist bone assessment if deficiency persists.[8,21] Where seizure control permits, non-enzyme-inducing agents may be preferred, and all families should receive counselling on safe sun exposure and dietary vitamin D. Such a pathway is inexpensive, deliverable within Indonesian tertiary care and readily cascaded to secondary facilities.

Generalisability and external validity

Several features bound the external validity of these results. The cohort was drawn from a single tertiary referral hospital that concentrates more severe and complex epilepsy, evidenced by the predominance of generalised symptomatic seizures and polytherapy (Table 1); the prevalence and effect estimates may therefore not transport directly to community or secondary-care pediatric populations, nor to other Indonesian regions that differ in latitude, ethnicity, diet and food-fortification practices. The use of a clinically indicated rather than a universal vitamin D testing strategy may further have enriched the sample for deficiency, so the 62.3% prevalence is best read as applying to tested children. These considerations do not undermine the internally valid finding—the differential vitamin D status across treatment classes—but they argue for cautious extrapolation of the absolute prevalence and for confirmation in multicentre, multi-latitude cohorts. Notwithstanding these limits, the concordance of our results with recent Indonesian and Asian pediatric series (Table 4) suggests that the central message—high, treatment-linked hypovitaminosis D—is likely to be broadly applicable across comparable tropical, middle-income settings.

Limitations

Several limitations temper these conclusions. First, the cross-sectional design with secondary medical-record data precludes causal inference and means that key determinants of vitamin D—duration and intensity of sun exposure, dietary vitamin D and calcium intake, physical activity, pubertal status, supplement use and treatment adherence—could not be fully captured. Second, the single-centre tertiary sample limits external generalisability and may over-represent severe, polytherapy-treated epilepsy. Third, the sample size, while adequate for prevalence estimation, was limited for subgroup and multivariable analysis: the enzyme-inducing group was small and uniformly deficient, producing a perfectly separated cell that precluded a finite class-specific odds ratio and widened the adjusted confidence interval for enzyme-inducing exposure (Table 3); the bivariate association should therefore be regarded as robust and the multivariable estimate as directionally supportive but imprecise. Fourth, we did not assess complementary markers of bone and mineral metabolism—serum calcium, phosphate, parathyroid hormone, alkaline

phosphatase or bone mineral density—which would give a more complete picture of skeletal impact. Finally, ASMs were grouped by enzyme-induction category without accounting for cumulative dose, so dose–response effects on 25(OH)D could not be evaluated.

5. Conclusion

Hypovitaminosis D is highly prevalent (62.3%) among children with epilepsy attending a West Sumatran tertiary referral hospital and is most strongly associated with enzyme-inducing antiseizure medications, which were linked to the lowest mean 25(OH)D and the largest adjusted odds of deficiency (adjusted OR 5.66; Firth-penalised OR 4.74; model AUC 0.685), whereas the number and duration of therapy were not significant correlates. Because deficiency was already common at treatment initiation and across monotherapy and short-duration groups, Indonesian pediatricians should incorporate baseline and periodic serum 25(OH)D monitoring—and a low threshold for supplementation—into the routine care of all children on antiseizure medication, with particular vigilance for those on enzyme-inducing regimens. Adequately powered, multicentre prospective cohort studies that adjust for sunlight, diet, physical activity, pubertal stage and cumulative drug dose, and that incorporate bone-turnover markers and validated neurodevelopmental outcomes, are needed to confirm these associations and to define optimal screening and supplementation strategies. In the interim, the most defensible and actionable message is pragmatic: vitamin D status in children on antiseizure medication should be measured rather than predicted, because no simple combination of treatment and demographic characteristics reliably identified the deficient child in this cohort.

Declarations

Author contributions

TY conceived and designed the study, collected and interpreted the data, and drafted the manuscript. RL and NRM supervised the neurology and study design and critically revised the work. EC, AZI and II contributed to data interpretation and methodological review. RM supervised the project and approved the final analysis. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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