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Clinical characteristics and serum 25-hydroxyvitamin D levels in children with febrile seizures in China

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The aim of this study was to evaluate the serum level of 25-hydroxyvitamin D (25(OH)D) in children with febrile seizures (FS) in Luzhou, Sichuan Province, China, and in particular its association with gender and age. This should inform possible strategies for supplementation with vitamin D, and hence for prevention of FS in the local pediatric population. The Febrile seizures group consisted of 747 children hospitalized with FS at the Southwest Medical University Affiliated Hospital from January 2020 to January 2024. The healthy control group was comprised of 750 children aged from 0 to 8 years who underwent health checkups during this period. The serum 25(OH)D level was analyzed in relation to gender and age to explore its association with FS. The median serum vitamin D level in the FS group (28.8 ng/mL; IQR 21.64, 33.64) was significantly lower than in the healthy control group (37.51 ng/mL; IQR 31.05, 37.51). The incidence of vitamin D deficiency in the FS group was 10.8%, which was significantly higher than in the healthy control group ($P < 0.05$). In addition, the serum vitamin D level in children with FS varied in different age groups, with significantly lower levels observed in older children ($P < 0.05$). ROC curve analysis revealed that a serum vitamin D level of 35.28 ng/mL showed 60.0% sensitivity and 84.7% specificity for predicting FS ($P < 0.05$). In this study cohort, the serum vitamin D level in children with FS was at the lower limit of the physiological range, and significantly lower than in healthy children. Furthermore, this level decreased with age in children with FS. Regular supplementation with vitamin D for 6 months after birth and outdoor sun exposure for more than 2 h per day can improve the serum vitamin D level in children with FS.

Keywords Febrile seizure, 25-hydroxyvitamin D, Child, Age

Abbreviations

25(OH)D	25-hydroxyvitamin D
VDD	Vitamin D deficiency
VDI	Vitamin D insufficiency
VDS	Vitamin D sufficiency
IQR	Interquartile range
CI	Confidence interval
OR	Odds ratio

Febrile seizures (FS) affect 3–5% of children aged 6 months to 5 years and are a common age-related condition. In 2011, the American Academy of Pediatrics (AAP) defined FS as seizures that occur with fever (rectal temperature ≥ 38.5 °C, axillary temperature ≥ 38 °C) and in the absence of central nervous system infection or other causes[1]. Clinically, FS often begin suddenly with a rapid increase in temperature, and typically manifest as generalized tonic-clonic seizures. Partial seizures with impaired consciousness can also occur, but these usually resolve within minutes. The underlying cause of FS in infants and young children is not fully understood[2].

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However, according to current research, FS may be linked to incomplete myelin development, genetic factors, and infections[3,4].

Vitamin D is a crucial fat-soluble nutrient that can influence various cellular functions beyond its traditional roles, including cell growth, neuromuscular and immune functions, and energy homeostasis[5]. FS are usually benign and self-limiting, and brain damage can be prevented through proper management. However, untreated recurrent seizures can cause irreversible brain injury, leading to language disorders, intellectual disability, epilepsy, and significant parental anxiety[4]. Consequently, FS receive considerable clinical attention. The age group that is most at risk for FS overlaps with periods of rapid growth in children, making them especially prone to vitamin D deficiency.

According to the National Health and Nutrition Examination Survey conducted in the United States, vitamin D deficiency is common in children, with an incidence of 21% in healthy-weight, 29% in overweight, 34% in obese, and 49% in severely obese children aged 6 to 18 years[6]. In China, the reported incidence of vitamin D deficiency is 7.1% in children aged < 3 years and 75% in children aged 3 years and older[7]. Recent research has broadened the understanding of vitamin D beyond its role in malnutrition, and highlighted its importance in respiratory infections, allergic diseases, cancer, skin disorders, cardiovascular diseases, diabetes, gestational hypertension, and neuropsychiatric disorders[8,9]. Exploring the clinical characteristics of vitamin D deficiency in children with FS could therefore provide valuable insights into the prevention and treatment of this condition.

To date, there have been few domestic and international studies on the correlation between FS and vitamin D deficiency in children, including serum vitamin D levels. The current study collected clinical and laboratory data from children diagnosed with FS over the past four years in Sichuan province, China. Multidimensional analysis of serum 25-hydroxyvitamin D (25(OH)D) levels allowed us to explore their relationship with FS.

Methods

Study subjects

The study group comprised 747 children hospitalized with FS at the Affiliated Hospital of Southwest Medical University in Luzhou, Sichuan Province, China, from January 2020 to January 2024. The control group comprised 750 children aged 0–8 years, excluding newborns, who underwent health examination in the outpatient department during the same time period. According to the ILAE[10], FS are characterized as described below. (1) Seizures that occur during fever (rectal temperature ≥ 38.5 °C, axillary temperature ≥ 38 °C) without central nervous system infections or other causes, and following the 2011 AAP standards. (2) FS are categorized as simple or complex based on clinical features. Simple FS are generalized seizures lasting < 15 min that occur once during a fever episode, and with no abnormal neurological signs. Complex FS may involve prior neurological issues, are focal or generalized, last 15 min or more, or occur multiple times during a fever episode, and may include postictal neurological abnormalities, but there is no history of FS. (3) FS status is marked by seizures lasting 30 min or more, or recurrent seizures without regaining consciousness for 30 min or more. (4) A family history of FS is common, and EEG findings are normal one week after the seizure.

We collected data on serum levels of 25-hydroxyvitamin D (25(OH)D), total calcium, and hemoglobin for analysis. This study was approved by the hospital medical ethics committee (Approval Number: KY 2023397), and the children's guardians provided informed consent.

Major reagents and instruments

(1) The 25(OH)D assay kit, quality control materials and standards were supplied by Liaison (Italy).
(2) Total calcium was measured with a Beckman Olympus AU5400 biochemical analyzer and associated reagents (Japan).
(3) Hemoglobin levels were measured using a SYSMEX XE 2100 fully automated hematology analyzer and associated reagents (Japan).

Sample handling procedures

In the morning, a 2 mL fasting venous blood sample was drawn from study participants. After standing at room temperature for 20–40 min, the sample was centrifuged at 1000×g for 10 min to separate the serum. This was transferred to Eppendorf tubes for testing, and samples not analyzed on the same day were stored at -20 °C. The assay kit instructions were strictly followed for all procedures. The Nuclear Medicine Laboratory of the Affiliated Hospital of Southwest Medical University conducted the tests.

Interpretation of results

The normal range for serum vitamin D is from 30 to 80 ng/mL. Subclinical deficiency is defined as 20 to < 30 ng/mL, and deficiency as > 5 to < 20 ng/mL[11,12].

The Endocrine Society defines clinical vitamin D status at the following serum 25(OH)D concentrations: vitamin D deficiency (VDD) at < 20 ng/mL (50 nmol/L); vitamin D insufficiency (VDI) at 20–30 ng/mL (50–75 nmol/L); vitamin D sufficiency (VDS) at > 30 ng/mL (75 nmol/L)[11,12].

Statistical analysis

Excel was used to input data, and SPSS 26.0 statistical software for data analysis. As serum 25 (OH) D levels showed a skewed distribution, descriptive statistics were used for analysis. Quantitative data were presented as the median and interquartile range (IQR), and analyzed using the Mann Whitney U test. Numerical data was expressed as the number of cases (n)/percentage (%), and comparisons between groups were performed using the chi square test. ROC curve analysis was used to predict the diagnostic efficacy of quantitative data for FS. A P-value of < 0.05 was considered to indicate statistical significance.

Results

A total of 1497 children aged 0–8 years were recruited for the study, comprising 747 with FS and 750 healthy controls. There were 882 males and 615 females, with a male to female ratio of 1.43:1. The average serum concentration of 25(OH)D for all participants was 32.11 ng/mL, with a median concentration of 32.56 ng/mL (IQR: 25.01, 38.95). The average age of the overall cohort was 3.11 ± 2.03 years. The participants were divided into four age groups: infants (0–1 year old), toddlers (1–3 years old), preschool children (3–6 years old), and school-age children (6–11 years old). No significant differences in gender or age were observed between the FS and control groups ($P > 0.05$).

Comparison of the serum vitamin D level between FS and healthy control groups

The serum vitamin D level in the FS group (28.8 ng/mL; IQR: 21.64, 33.64) was significantly lower than in the healthy control group (37.51 ng/mL; IQR: 31.05, 37.51), as revealed by the Mann Whitney U test ($P < 0.001$). See Table 1.

Comparison of the serum vitamin D level between different age groups

In the healthy control group, toddlers aged 1–3 years had the highest 25(OH)D level (median 37.29 ng/mL; IQR: 25.78, 43.74). In the FS group, infants (0–1 years) had the highest 25(OH)D level (median 32.47 ng/mL; IQR: 29.84, 37.22). See Table 1.

Children in different age groups in the FS and healthy control groups had significantly different serum vitamin D levels, as shown by the chi square test ($P < 0.001$). The trend test found that the older the age of children in the FS group, the lower their vitamin D level ($P < 0.001$), as shown in Fig. 1.

Comparison of serum vitamin D levels in children

The incidence of VDD and VDI in the FS group (45.7%) was significantly higher ($P < 0.001$) than in the healthy control group (23.1%), as shown in Table 2.

Prediction of FS by the serum vitamin D level

ROC curve analysis was used to evaluate the sensitivity and specificity of the serum vitamin D level for predicting FS. The Yoden index was the highest and the diagnostic efficacy was best at a serum vitamin D level of 35.285 ng/mL. The sensitivity for predicting FS was found to be 60.0% and the specificity 84.7% [AUC = 0.773, 95% CI: 0.750 ~ 0.797, $P < 0.001$], as shown in Fig. 2.

Discussion

This study found that the average serum vitamin D level in children with FS in the Luzhou area was significantly lower than in healthy children. Moreover, we found that 10.8% and 34.9% of children with FS were in a state of VDD and VDI, respectively. This was more common in children seeking medical treatment than in the 6–8 year-old group who underwent health check-ups (100% vs. 4.54%).

Vitamin D is a type of sterol derivative, and deficiency of this vitamin has been associated with chondrosis, cardiovascular disease, cancer, diabetes and other diseases[13,14]. Recently, it was found that vitamin D is not only useful for the prevention and treatment of rickets, but also for treating diseases of the respiratory[15,16], digestive[17,18] and nervous systems[19,20] in children. However, there is still only limited knowledge on the relationship between FS and vitamin D. The present study investigated serum vitamin D levels in children with FS, with the aim of determining whether deficiency of this vitamin was a cause of FS. Our finding that vitamin D levels in children with FS in the Luzhou area were significantly lower than in healthy children is consistent with the results of Li et al.[21]. Together, they indicate a correlation between the occurrence of FS and serum vitamin D levels in children in the Chinese population. Moreover, our research showed that the combined incidence of VDD and VDI was higher in children with FS than in healthy children, with the higher incidence of VDI being particularly significant. This result is consistent with the findings of Bhat et al.[22]. Our study and that of Li et al. found that about 44–51% of children with FS had VDS, whereas Bhat and Ghazal et al.[23] showed that only about 20–25% of children with FS had VDS. This may be due to differences in the rate of daily vitamin D supplementation in infants and young children in China and abroad. A recent survey showed that only 20% of infants in the United States consumed the daily 400 IU of vitamin D recommended by the American Academy of Pediatrics[24].

The latest results from China show that the level of vitamin D in children has increased significantly compared to 10 years ago. A survey conducted in the southeastern region of China found that about 76.7% of children were VDS[25]. The incidence of VDD in healthy children in the present study was 10.8%, with an average level of 26.97 ng/mL. Several other studies have reported that VDD is widespread among Chinese children aged 0–11 years, with hospitalized children in particular showing severe deficiency[7,21,26].

The incidence of VDD in children increases with age[27]. The Science Branch of the Chinese Medical Association recommends that all children between the ages of 2 weeks after birth and 2 years should receive no less than 400 IU/day of vitamin D[28]. After the age of 2 years, the main source of vitamin D intake is from exposure during outdoor activities. However, preschool and school-age children spend less time outdoors[29]. To ensure that children and adolescents receive an adequate intake of vitamin D, the Nutrition Committee of the American Academy of Pediatrics recommends that all infants should take 400 IU of vitamin D daily starting from the first day of birth, and continue this until adolescence. The Indian Academy of Pediatrics recommends that infants up to 1 year of age take 400 IU of vitamin D daily, and children and adolescents aged 1–18 years take 600 IU daily. For the treatment of rickets, patients in these age brackets are recommended to consume 2000 IU and 3000–6000 IU of vitamin D daily, respectively[30]. Vitamin D supplementation is maintained in most infants

Variables	Febrile seizures group							Healthy control group						
	N	Mean	Min	Max	P25	P50	P75	*N*	Mean	Min	Max	P25	P50	P75
All[a]	747	26.96	9.50	44.95	21.64	28.83	33.64	750	37.26	13.02	55.89	31.05	37.51	44.68
Sex[b]														
Boy	437	27.35	9.50	44.95	22.03	29.13	33.92	445	37.97	13.12	55.87	32.04	37.83	45.01
Girls	310	26.42	10.03	42.93	20.83	27.67	33.02	305	36.21	13.02	55.89	27.65	37.12	44.34
Age(years)[c]														
0–1	26	33.93	29.12	42.89	29.84	32.47	37.22	23	35.50	19.68	44.74	29.34	37.18	43.38
1–3	455	31.28	9.50	44.95	28.02	31.47	35.25	476	38.63	13.02	55.89	22.75	32.83	37.75
3–6	240	19.55	10.03	33.97	13.00	15.83	27.04	229	35.04	13.10	55.76	25.87	37.29	43.74
6–11	26	10.03	10.02	16.49	11.36	12.24	14.91	22	32.54	19.78	47.23	27.02	31.62	38.50

Table 1. Serum 25(OH)D levels (ng/mL) by sex, and age group between departments. [a] Pediatrics ($p=0.957$); but were significantly different between the departments (all $p<0.001$). [b] The serum 25(OH)D levels had no significant difference by sex within the departments of Child Healthcare ($p=0.752$). [c] The serum 25(OH)D levels were significantly different by age group within and between the departments (all $p<0.001$).

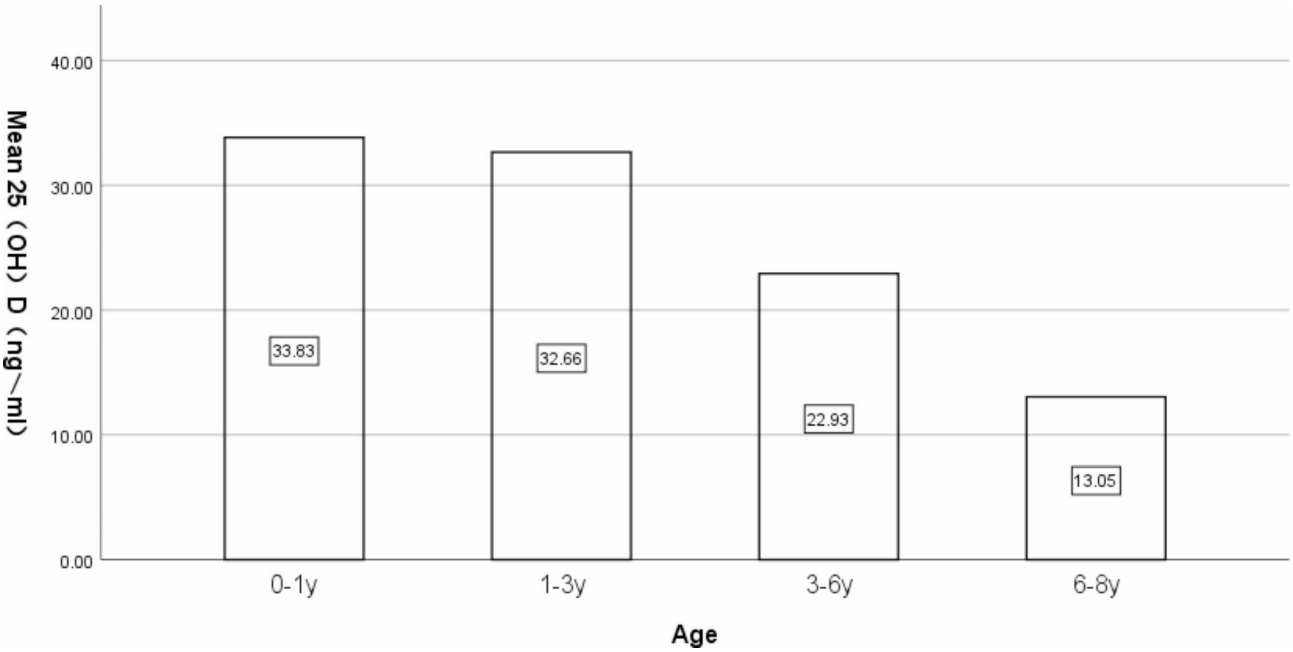

Fig. 1. Serum 25(OH)D level according to age and stratified by department of the sample source.

Group	*n*	VDD	VDI	VDS
Febrile seizures group	747	162(10.8)	261(34.9)	324(43.4)
Healthy control group	750	35(4.7)	139(18.4)	576(76.9)
$\times^2$		80.47		
P		< 0.001		

Table 2. Comparison of the incidence of vitamin D deficiency and insufficiency between febrile seizures group and healthy control group. The cutoffs of VDD, VDI, and VDS are serum 25(OH)D levels (ng/mL) < 20, 20–30, and ≥ 30, respectively.

after birth[31]. However, the proportion of older children receiving vitamin D supplementation is lower, possibly due to the decreased need for supplementation in older children and adolescents[32].

Following discovery of the vitamin D receptor (VDR) and DBP in various cells and tissues, vitamin D has been shown to affect normal functions in many systems in the human body, including the immune system, cardiovascular system, vision, cell growth and division, and blood vessel formation[33]. A large number of observational studies have confirmed that low serum levels of vitamin D are closely correlated to current and future health risks. Many experimental animal models have been used to investigate the pathophysiology and mechanisms of vitamin D supplementation in different diseases. However, the results of randomized controlled trials (RCTs) of vitamin D supplementation for different diseases have so far failed to provide definitive evidence. This could be due to the varying 25(OH)D doses used in different diseases, and to different vitamin D supplementation regimens. Even for the same disease, RCTs designed by different research groups employ different methods and have different environments and populations, thus making it difficult to compare results. More importantly, such RCTs use methods that are designed to test drugs, whereas vitamin D is a nutrient whose biological effects follow an S-shaped curve as its level increases from zero to sufficient. The therapeutic or functional effects are only achieved once the serum 25(OH)D level reaches the steep part of the S curve, and no change is seen when the level is deficient, or when it reaches the upper plateau of the S curve[34] This important confounding factor is crucial for evaluating the health benefits from existing RCT data, and for improving the design of future RCTs.

The relationship between FS and vitamin D has been studied over the past two years, but there have been no reports using animal models or clinical trials of vitamin D supplementation. In the present study, we used ROC curve analysis to estimate the sensitivity and specificity of serum vitamin D levels for the prediction of FS. The Yoden index was found to be highest and the diagnostic efficacy optimal when the serum 25(OH)D level was 35.28 ng/mL. This value gave a sensitivity of 60.0% and specificity of 84.7% for predicting FS ($P < 0.001$). However, this result is based on the local population of FS cases and controls, and may not apply to populations from other regions. Moreover, this result only provides preliminary evidence on whether vitamin D can predict FS, and does not provide a theoretical basis for giving vitamin D supplementation to children with FS. Further

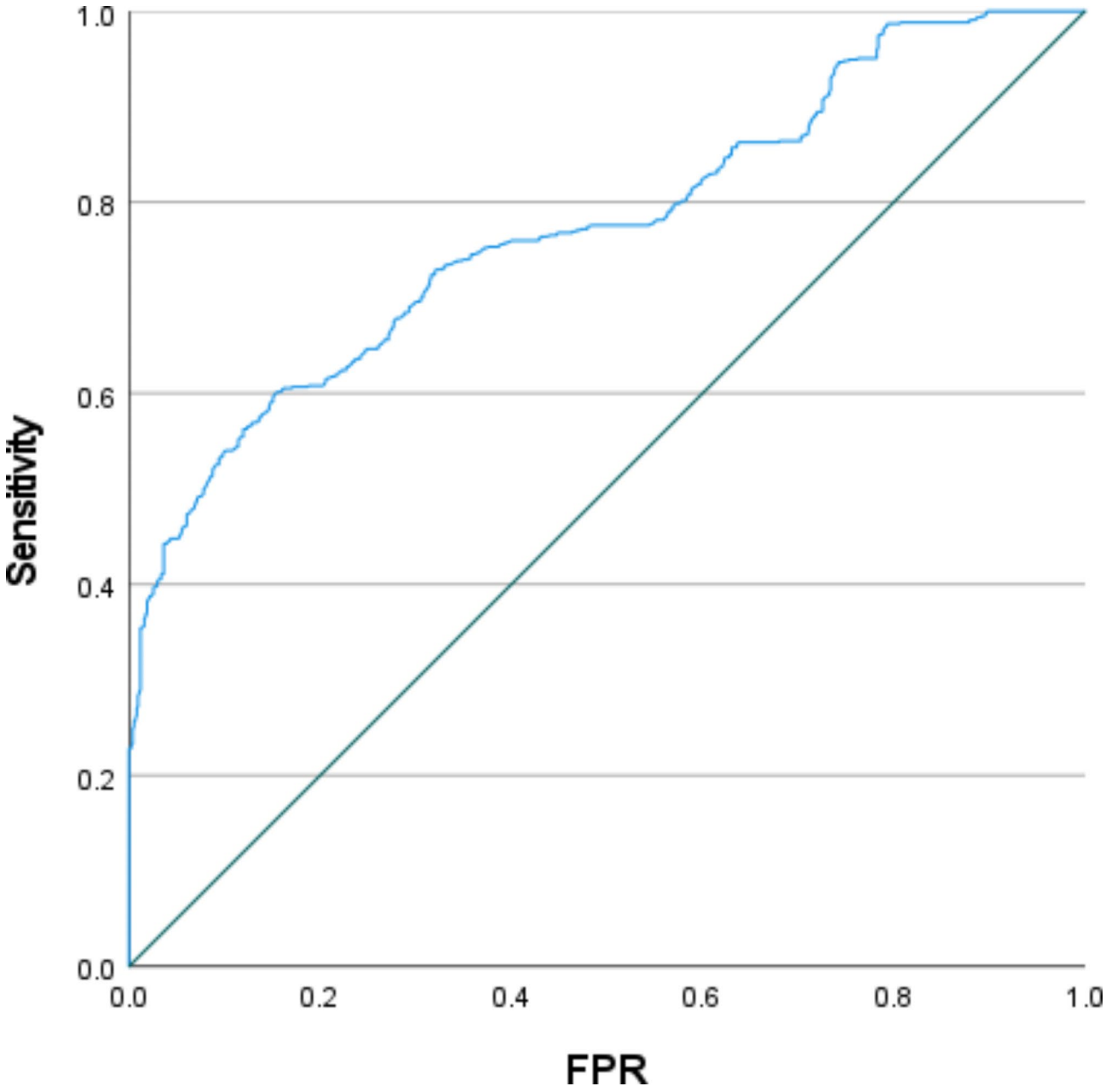

Fig. 2. ROC curve analysis of serum vitamin D level for the prediction of FS.

and more rigorous RCTs are required to determine the appropriate daily dosage of vitamin D supplementation for children with FS.

Limitations

Firstly, this study collected data from a single research center (Gansu Maternal and Child Health Hospital), and further multi-center and rigorous case-control studies are needed to confirm the current results. Secondly, there was no follow-up of the clinical occurrence of FS in children following supplementation with vitamin D preparations. Thirdly, the body mass index, sleep, and daily vitamin D intake of each child was not recorded in detail. Finally, we did not include children with FS in some outpatient settings, and hence the results cannot be generalized to all FS patients.

Conclusion

The incidence of VDD in children with FS aged 0–8 years old in Luzhou was higher than in healthy children. The serum vitamin D level in children with FS decreased with age. Regular supplementation with vitamin D is therefore recommended after birth, especially for school-age children. Child healthcare workers should increase

the education and prevention of VDD and of VDD-related rickets, and prioritize the prevention of other disease states linked to VDD.

Data availability

Data is provided within the supplementary information files (S1 Dataset).

Received: 23 May 2024; Accepted: 20 September 2024
Published online: 07 October 2024

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Acknowledgements

The researchers would like to express their gratitude to all the respected the nurses who contributed to this study.

Author contributions

Li Zhang, Xi Lin, Bin Liu: Conceptualization; Li Zhang, Xi Lin, Bin Liu: Writing - original draft; Formal analysis; Methodology; Supervision; Li Zhang: Validation; Visualization; Qin Liu, Li Zhang: Data curation; Investigation. Qin Liu, Xi Lin: Writing - review &editingAll authors reviewed the manuscript.

Funding

This research is supported by the China Higher Education Teaching Research and Reform Project of Southwest Medical University (JG2023yb083).

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The entire study complied with the Declaration of Helsinki (Declaration of Helsinki of the World Medical Association, 2013) and participation in the study was voluntary and voluntary. Informed consent was obtained from all participants and their written consent was obtained by ticking the "I agree to complete the questionnaire" statement. Data is analysed anonymously. This study has been approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (KY2023397).

Consent for publication

Not applicable.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-73850-6.

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