Vitamin D deficiency and associated factors among children in a tertiary care hospital setting: A retrospective cohort study

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Abstract

Background: Vitamin D plays important roles in skeletal and extra-skeletal tissues. However, little is known about the vitamin D status in children in a hospital setting. We aimed to assess the vitamin D status, risk factors for vitamin D deficiency (VDD), and changes in biochemical profiles among children at a tertiary medical center in Taiwan.

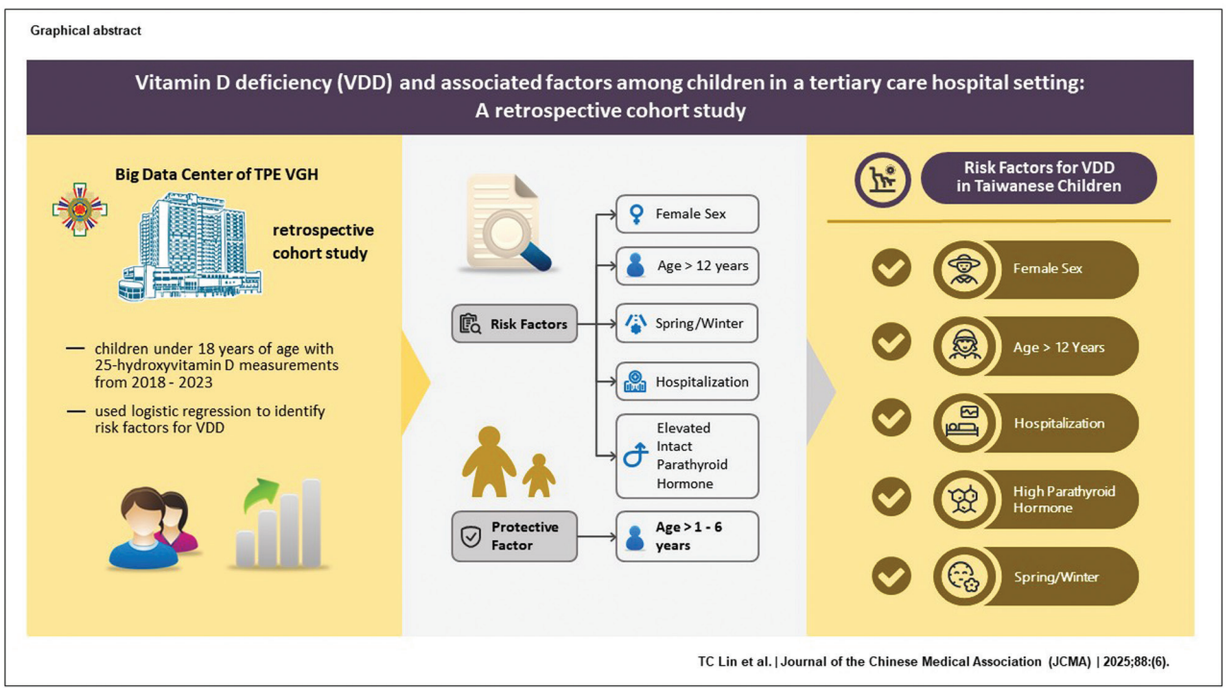
Methods: This retrospective cohort study analyzed data from the Big Data Center of Taipei Veterans General Hospital. Children under 18-year-old who underwent 25-hydroxyvitamin D measurements between 2018 and 2023 were enrolled. Logistic regression analysis was performed to determine the risk factors for VDD.

Results: Among 1222 children enrolled, with a mean age of 8.5 ± 5.4 years, 597 (48.9%) had VDD. VDD was significantly associated with female sex (odds ratio [OR] = 1.624, 95% CI = 1.270-2.076), age >12 years (OR = 2.479, 95% CI = 1.584-3.881), vitamin D measurement during the spring/winter seasons (OR = 1.716, 95% CI = 1.340-2.197), and hospitalized children (OR = 1.949, 95% CI = 1.439-2.640). Age >1 to 6 years was a protective factor against VDD (OR = 0.391, 95% CI = 0.244-0.628). In addition, the OR of VDD was higher in those with an elevated intact parathyroid hormone level (OR = 8.667, 95% CI = 1.338-56.157).

Conclusion: Despite the high sun exposure in Taiwan, VDD is prevalent among children and adolescents. Physicians should be aware of VDD, especially in children who are female, aged >12 years, hospitalized, have increased intact parathyroid hormone levels, and during the spring/winter.

Keywords: Adolescent; Child; Vitamin D; Vitamin D deficiency

Graphical abstract



Lay Summary: Vitamin D deficiency (VDD) is a common medical problem worldwide. The prevalence of VDD in children varies among different geographical areas, ethnic and age groups, and the associations of biochemical parameters with VDD in children have yet to be clarified. This study investigated the epidemiology, clinical risk factors and biochemical profiles associated with VDD among Taiwanese children in a tertiary care hospital setting. The results showed that VDD was prevalent in Taiwanese children, and that those who were female, aged >12 years, hospitalized, had increased intact parathyroid hormone levels, and in whom vitamin D was measured during the spring/winter seasons were at a greater risk of VDD.

1. INTRODUCTION

Vitamin D plays a pivotal role in skeletal health, and emerging evidence suggests that it has effects on various extraskeletal tissues. Vitamin D may protect individuals from cancer through antiproliferative and prodifferentiating effects. In addition, vitamin D may prevent diabetes mellitus by modulating insulin secretion and peripheral actions, and it may also mitigate the risk of obesity. Furthermore, vitamin D has been shown to have a potential role in preventing cardiovascular diseases and modulating both adaptive and innate immune systems.[1,2] Reported risk factors for vitamin D deficiency (VDD) include female sex, premature birth, dark skin pigmentation, inadequate dietary vitamin D intake, lack of sun exposure due to clothing or use of sunscreen, winter season, higher geographical latitude, insufficient daytime outdoor activities, obesity, certain medications (eg, anticonvulsants, glucocorticoids, antifungal agents), malabsorption, and liver and kidney diseases.[2–5]

Although clinical manifestations of severe VDD such as rickets in children are uncommon, a high prevalence of subclinical asymptomatic VDD has been reported worldwide, even in countries with high sun exposure.[6–8] The prevalence of VDD in children varies from 33% to 90% depending on the cut-off values used to define VDD, geographical latitude, ethnicity, and age.[6–10] Geographically, Taiwan is located in East Asia between 21°N and 25°N latitude. In the early 20th century, Taiwanese men were found to be 3 cm taller than men living in South Korea, which is also in East Asia. Although the per capita consumption of animal protein in Taiwan was 60% greater than that in South Korea in the 2000s, Taiwanese are now an average of 1 to 2 cm shorter than their South Korean counterparts.[11] Other nutritional insufficiencies such as low levels of vitamin D can potentially cause impaired height growth in children. However, few large-scale studies have investigated the vitamin D status of children in Taiwan. Vitamin D is an essential element for the regulation of serum calcium and phosphate, and severe VDD is typically associated with overt hypocalcemia, hypophosphatemia, high alkaline phosphatase (ALP), and high intact parathyroid hormone (iPTH). Therefore, in this study, we aimed to investigate the total burden of VDD, and identify risk factors and determine the associations of calcium and ionized calcium, phosphorus, ALP and iPTH with VDD among children in Taiwan within a tertiary medical center setting.

2. METHODS

2.1. Setting, data sources, and study population

Information on the study cohort was extracted from the Big Data Center of Taipei Veterans General Hospital.[12] Comprehensive data from medical records were retrieved, including diagnostic tests, laboratory data, and medications of inpatient, outpatient, and emergency department visits. Diagnostic coding was based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. This retrospective study included all children (<18 years of age) who visited the outpatient or inpatient services at Taipei Veterans General Hospital from January 1, 2018, to December 31, 2023, and underwent 25-hydroxyvitamin D (25(OH)D) evaluations at either service for any clinical cause. This study was approved by the Taipei Veterans General Hospital Institutional Review Board and the need for informed consent was waived (2024-05-004BC).

2.2. Vitamin D level

Vitamin D status was assessed by measuring blood levels of total 25(OH)D using an electrochemiluminescence immunoassay. The date of the first 25(OH)D measurement was considered the index date. The level of 25(OH)D was classified as being sufficient (≥30 ng/mL), insufficient (≥20-30 ng/mL), or deficient (<20 ng/mL). Most experts agree that 25(OH)D levels below 20 ng/mL are generally too low for bone and overall health.[13] Therefore, to analyze the risk factors for VDD, we divided the children into a non-VDD (sufficient/insufficient) group (≥20 ng/mL) and a VDD group (<20 ng/mL) based on the 25(OH)D level at first assessment. Repeat tests were analyzed separately from the first test.

2.3. Demographic and clinical data and comorbidity

Demographic characteristics, including age, sex, and residential location were extracted for analysis. Age was categorized into four groups: 0 to 1 years (infant), >1 to 6 years (preschool children), >6 to 12 years (school-age children), and >12 years (adolescents). To evaluate the impact of seasonal variability, the seasons during which the blood samples were collected were divided into two groups: spring (March, April, May)/winter (December, January, February), and summer (June, July, August)/autumn (September, October, November). Residential locations were also categorized into two groups: areas with low sun exposure (<1400 hours annually), and areas with high sun exposure (≥1400 hours annually), based on the accumulated sun exposure throughout 2022 reported by the Central Weather Administration (https://www.cwa.gov.tw/V8/C/C/Statistics/monthlydata.html).

Inflammatory markers including C-reactive protein (CRP) and white blood cell (WBC) count measured within 4 weeks before or after the 25(OH)D evaluations were collected. An elevated CRP level was defined as ≥0.5 mg/dL, while leukocytosis was defined as a WBC count >1.1 × 10^4/mm^3. Location where 25(OH)D were collected (outpatient or inpatient services), and the presence of acute respiratory tract infection based on corresponding ICD-10-CM codes (Supplementary Table 1, http://links.lww.com/JCMA/A322) were also ascertained.

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Author contributions: Dr. Yu-Chun Chen and Dr. Jei-Wen Chang contributed equally to the work.

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Table 1

Demographic characteristics, clinical data, and comorbidities of the study population according to vitamin D status

Variable	Total (n = 1222)	Non-VDD (n = 625)	VDD (n = 597)	*p*
Sex				<0.001
Male	559 (45.7%)	328 (52.5%)	231 (38.7%)	
Female	663 (54.3%)	297 (47.5%)	366 (61.3%)	
Mean age (y)	8.5 ± 5.4	7.1 ± 5.1	9.9 ± 5.3	<0.001
Age (y)				
0-1	168 (13.7%)	87 (13.9%)	81 (13.6%)	<0.001
>1-6	274 (22.4%)	210 (33.6%)	64 (10.7%)	
>6-12	380 (31.1%)	195 (31.2%)	185 (31.0%)	
>12	400 (32.7%)	133 (21.3%)	267 (44.7%)	
Seasons of measurement				<0.001
Summer/autumn	716 (58.6%)	405 (64.8%)	311 (52.1%)	
Spring/winter	506 (41.4%)	220 (35.2%)	286 (47.9%)	
Residential location				0.674
Cities with high sun exposure (≥1400 h/y)	293 (24.0%)	153 (24.5%)	140 (23.5%)	
Cities with low sun exposure (<1400 h/y)	929 (76.0%)	472 (75.5%)	457 (76.5%)	
Acute inflammatory markers				
CRP ≥0.5 mg/dL	87/340 (25.6%)	36/340 (24.5%)	51/340 (26.4%)	0.685
CRP level (mg/dL)	0.7 ± 2.1	0.5 ± 1.0	0.8 ± 2.6	0.131
WBC count >1.1 × 10^4/mm^3	141/901 (15.6%)	83/901 (16.9%)	58/901 (14.2%)	0.269
WBC count (/mm^3)	8.1 ± 3.6	8.3 ± 3.6	7.8 ± 3.6	0.029
Location of measurement				<0.001
Outpatient	910 (74.5%)	496 (79.4%)	414 (69.3%)	
Hospitalization	312 (25.5%)	129 (20.6%)	183 (30.7%)	
Acute respiratory tract infection	52 (4.3%)	34 (5.4%)	18 (3.0%)	0.036
Comorbidities				
Prematurity	130 (10.6%)	71 (11.4%)	59 (9.9%)	0.402
Congenital heart disease	68 (5.6%)	43 (6.9%)	25 (4.2%)	0.040
Malignancy	180 (14.7%)	98 (15.7%)	82 (13.7%)	0.338
Iron deficiency anemia	133 (10.9%)	80 (12.8%)	53 (8.9%)	0.028
Atopy	112 (9.2%)	60 (9.6%)	52 (8.7%)	0.590
Autoimmune disorders	19 (1.6%)	7 (1.1%)	12 (2.0%)	0.209
CKD and ESRD	4 (0.3%)	2 (0.3%)	2 (0.3%)	1.000[a]
Nephrotic syndrome	6 (0.5%)	1 (0.2%)	5 (0.8%)	0.116[a]
Liver cirrhosis	3 (0.2%)	2 (0.3%)	1 (0.2%)	1.000[a]
Biliary atresia	6 (0.5%)	3 (0.5%)	3 (0.5%)	1.000[a]
Autism	12 (1.0%)	9 (1.4%)	3 (0.5%)	0.097[a]
Depression	8 (0.7%)	1 (0.2%)	7 (1.2%)	0.035[a]

CKD = chronic kidney disease; CRP = C-reactive protein; ESRD = end-stage renal disease; VDD = vitamin D deficiency; WBC = white blood cell.
[a]Fisher's exact test.

Comorbidities including prematurity, congenital heart disease, malignancy, atopy, autoimmune disorders, chronic kidney disease (CKD) or end-stage renal disease (ESRD), nephrotic syndrome, liver cirrhosis, biliary atresia, autism, and depression were extracted based on the presence of corresponding ICD-10-CM codes. The presence of iron deficiency anemia was determined according to relevant diagnostic codes and/or a transferrin saturation level (iron to total iron-binding capacity ratio) <20%. Details of the ICD-10-CM codes of comorbidities are shown in Supplementary Table 1 (http://links.lww.com/JCMA/A322).

2.4. Biochemical parameters

Biochemical parameters measured within 3 months before the index date, including serum total calcium, ionized calcium, phosphorous, alkaline phosphatase (ALP), and intact parathyroid hormone (iPTH) were assessed. Hypocalcemia, hypophosphatemia, elevated ALP, and hyperparathyroidism were defined based on age- and sex-specific reference ranges of calcium, ionized calcium, phosphorous, ALP, and iPTH, respectively. Details of the reference normal ranges are shown in Supplementary Table 2 (http://links.lww.com/JCMA/A322).

2.5. Statistical analysis

Continuous data are presented as mean ± SD, and categorical data are presented as number (proportion). The χ^2 test or Fisher's exact test was used to compare categorical variables between the VDD and non-VDD groups. Potential clinical risk factors for VDD were initially evaluated using univariate logistic regression analysis. Factors with p values <0.05 in univariate analysis were then included in multivariate logistic regression, and odds ratios (ORs) and 95% CIs were calculated. To minimize analytical bias caused by small sample sizes and rare events, Firth's penalized-likelihood logistic regression analyses were used to determine the biochemical predictors (calcium, phosphorus, ALP, iPTH) of VDD. The McNemar test was used to assess changes in vitamin D status between the index measurement and first repeat measurement of 25(OH)D. All statistical tests were two-sided, and a significance level of $p < 0.05$ was considered to indicate statistical significance. Statistical analyses were conducted utilizing

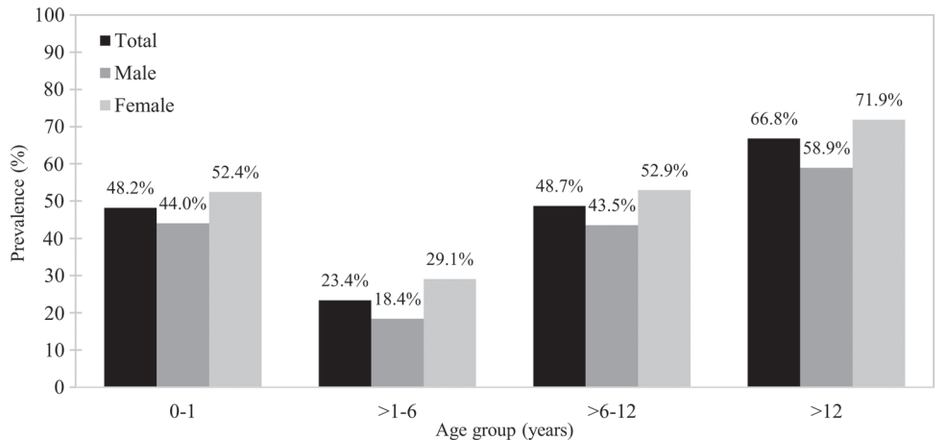

Fig. 1 Prevalence of VDD stratified by sex and age. In each age group, the prevalence of VDD in girls was higher compared with boys. The prevalence of VDD was highest in females aged >12 y (71.9%) and lowest in males aged >1-6 y (18.4%). VDD = vitamin D deficiency.

SPSS version 24.0 (SPSS Inc., Chicago, IL) and R software version 4.4.1 (R Core Team 2024).

3. RESULTS

3.1. Characteristics of the study population

The demographic characteristics of the study population based on serum 25(OH)D levels are summarized in Table 1. In total, 1222 children had serum 25(OH)D measurements during the study period, of whom 559 (45.7%) were male and 663 (54.3%) were female. The mean age of the participants was 8.5 ± 5.4 years. Regarding the age groups, 168 (13.7%), 274 (22.4%), 380 (31.1%), and 400 (32.7%) children were 0 to 1, >1 to 6, >6 to 12, and >12 years, respectively. The mean level of 25(OH)D was 21.4 ± 9.9 ng/mL. Overall, the prevalence rates of vitamin D sufficiency, vitamin D insufficiency (VDI), and VDD were 12.4%, 38.8%, and 48.9%, respectively, with 25(OH)D concentrations of 39.7 ± 11.9, 24.3 ± 2.8 and 14.5 ± 4.2 ng/mL, respectively.

3.2. Vitamin D status in different sex and age groups

Compared with the vitamin D sufficiency group, there were significantly higher percentages of females in the VDI (49.8% vs 40.4%) and VDD (61.3% vs 40.4%) groups. The distributions of vitamin D status according to age and sex are illustrated in Fig. 1. The prevalence of VDD was higher in the children aged >12 years (66.8%), followed by those aged >6 to 12 years (48.7%), 0 to 1 (48.2%), and >1 to 6 years (23.4%). The children with VDD were more likely to be older (9.9 ± 5.3 vs 7.1 ± 5.1 years, $p < 0.001$). There were significant associations between different vitamin D status and age groups ($p < 0.001$, Table 1). The highest prevalence of VDD (71.9%) was observed in females aged >12 years, and the lowest prevalence (18.4%) was observed in male children aged >1 to 6 years.

3.3. Residential location and season

Regarding the residential location, most of the children (76.0%) resided in areas with low sun exposure, and the others (24.0%) lived in areas with high sun exposure. There was no difference in vitamin D status between different residential locations according to total annual sun exposure. Regarding seasons, 506 (41.4%) children underwent serum vitamin D assessments in spring/winter, and 716 (58.6%) in summer/autumn. The mean 25(OH)D concentration in summer/autumn was 22.3 ± 10.2 ng/mL, compared with 20.2 ± 9.2 ng/mL in spring/winter, and the difference was statistically significant ($p < 0.001$). Among the children with VDD, more underwent 25(OH)D tests in spring/winter than in summer/autumn (47.9% vs 35.2%, $p < 0.001$).

3.4. Hospitalization, acute inflammatory markers, acute respiratory tract infection, and comorbidities

In our cohort, 74.5% of the 25(OH)D tests were ordered in outpatient clinics. Among the children who were hospitalized, only nine were admitted to the intensive care unit. The children in whom 25(OH)D was measured in outpatient clinics had a higher level than those who had measurements while hospitalized (22.1 ± 9.5 vs 19.5 ± 10.8 ng/mL, $p < 0.001$). The VDD group had a higher frequency of inpatient 25(OH)D measurements (30.7% vs 20.6%, $p < 0.001$). Three hundred and forty (27.8%) and 901 (73.7%) patients had CRP and WBC data, respectively. The average CRP level was 0.7 ± 2.1 mg/dL, and there was no significant difference between the VDD group and non-VDD group (0.8 ± 2.6 vs 0.5 ± 1.0 mg/dL, $p = 0.131$). The average WBC count was 8.1 ± 3.6 × 10^4/mm^3, and the WBC count was significantly lower in the VDD group compared with the non-VDD group (7.8 ± 3.6 vs 8.3 ± 3.6 × 10^4/mm^3, $p = 0.029$). However, neither elevated CRP level nor leukocytosis was associated with vitamin D status ($p = 0.685$ and 0.269, respectively). In addition, 3.0% of the VDD group and 5.4% of the non-VDD group had a respiratory tract infection 4 weeks before or after 25(OH)D measurement. The incidence of respiratory tract infection was significantly higher in the non-VDD group ($p = 0.036$).

The most common comorbidity was malignancy, followed by iron deficiency anemia and prematurity. The children with VDD had a much higher prevalence of depression (1.2% vs 0.2%, $p = 0.035$, Table 1). Conversely, iron deficiency anemia (8.9% vs 12.8%, $p = 0.028$) and congenital heart disease (4.2% vs 6.9%, $p = 0.040$) were less prevalent among the children with VDD.

3.5. Clinical predictors of VDD

The results of the univariate and multivariate logistic regression analyses are shown in Table 2. Univariate analysis showed that the female children, those aged >12 years, those who underwent 25(OH)D assessments during spring/winter, and those who were hospitalized were associated with VDD. The children aged >1 to 6 years, those diagnosed as acute respiratory infection, and

Table 2

Logistic regression analysis of the clinical risk factors for vitamin D deficiency

	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Female	1.750	1.394-2.197	<0.001	1.624	1.270-2.076	<0.001
Age (y)						
0-1	1 (Reference)			1 (Reference)		
>1-6	0.327	0.217-0.494	<0.001	0.391	0.244-0.628	<0.001
>6-12	1.019	0.709-1.465	0.919	1.172	0.755-1.819	0.480
>12	2.156	1.494-3.113	<0.001	2.479	1.584-3.881	<0.001
Seasons of measurement						
Summer/autumn	1 (Reference)			1 (Reference)		
Spring/winter	1.693	1.346-2.130	<0.001	1.716	1.340-2.197	<0.001
Low sun exposure area (<1400 h/y)	0.945	0.717-1.229	0.674			
Acute inflammatory markers						
CRP ≥0.5 mg/dL	1.107	0.676-1.814	0.685			
WBC count >1.1 × 10^4/mm^3	0.814	0.566-1.172	0.269			
Location of measurement						
Outpatient	1 (Reference)			1 (Reference)		
Hospitalization	1.700	1.310-2.205	<0.001	1.949	1.439-2.640	<0.001
Acute respiratory tract infection	0.540	0.302-0.968	0.038	0.849	0.456-1.580	0.605
Comorbidities						
Prematurity	0.856	0.594-1.233	0.403			
Congenital heart disease	0.592	0.357-0.981	0.042	0.574	0.317-1.040	0.067
Malignancy	0.856	0.623-1.176	0.338			
Iron deficiency anemia	0.664	0.460-0.958	0.029	0.711	0.614-1.395	0.925
Atopy	0.898	0.609-1.326	0.590			
Autoimmune disorders	1.811	0.708-4.631	0.215			
CKD and ESRD	1.047	0.147-7.457	0.963			
Nephrotic syndrome	5.270	0.614-45.243	0.130			
Liver cirrhosis	0.523	0.047-5.779	0.597			
Biliary atresia	1.047	0.211-5.209	0.955			
Autism	0.346	0.093-1.283	0.112			
Depression	7.403	0.908-60.355	0.061			

CKD = chronic kidney disease; CRP = C-reactive protein; ESRD = end-stage renal disease; OR = odds ratio; WBC = white blood cell.

Table 3

Comparisons of biochemical parameters between different vitamin D status groups

Variable	Total (%)	Non-VDD (%)	VDD (%)	*p*
Serum calcium/ionized calcium (n = 683)				0.087
Low	17 (2.5)	6 (1.6)	11 (3.6)	
Normal or high	666 (97.5)	374 (98.4)	292 (96.4)	
Serum phosphorus (n = 695)				0.040
Low	51 (7.3)	21 (5.5)	30 (9.6)	
Normal or high	644 (92.7)	361 (94.5)	283 (90.4)	
Serum ALP (n = 621)				0.004
High	61 (9.8)	22 (6.6)	39 (13.5)	
Normal or low	560 (90.2)	311 (94.3)	249 (86.5)	
iPTH (n = 140)				<0.001
High	22 (15.7)	3 (4.1)	19 (28.8)	
Normal or low	118 (84.3)	71 (95.9)	47 (71.2)	

ALP = alkaline phosphatase; iPTH = intact parathyroid hormone; VDD = vitamin D deficiency.

those with comorbidities including congenial heart disease and iron deficiency anemia had a lower odds of VDD. However, there were no significant associations between elevated CRP level, leukocytosis, or other comorbidities including malignancy, atopy, prematurity, autoimmune disorders, CKD and ESRD, nephrotic syndrome, liver cirrhosis, biliary atresia, autism and depression with VDD. Multivariate logistic regression analyses revealed that female sex (OR = 1.624, 95% CI = 1.270-2.076, $p < 0.001$), age >12 years (OR = 2.479, 95% CI = 1.548-3.881, $p < 0.001$), undergoing vitamin D assessments in spring/winter (OR = 1.716, 95% CI = 1.340-2.197, $p < 0.001$), and hospitalization (OR = 1.949, 95% CI = 1.439-2.640, $p < 0.001$) were associated with VDD. Compared with children aged 0 to 1 years, children aged >1 to 6 years were associated with decreased odds of VDD (OR = 0.391, 95% CI = 0.244-0.628, $p < 0.001$). The associations between acute respiratory tract infection, iron deficiency

Table 4

Firth's penalized-likelihood logistic regression analyses of calcium, phosphorus, ALP, and iPTH for vitamin D deficiency

	Univariate			Multivariate[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
Hypocalcemia	2.265	0.855-6.000	0.100			
Hypophosphatemia	1.809	1.020-3.210	0.043	2.495	0.460-13.539	0.289
Elevated ALP	2.192	1.272-3.775	0.005	1.901	0.413-8.747	0.409
Hyperparathyroidism	8.386	2.537-27.718	<0.001	8.667	1.338-56.157	0.024

ALP = alkaline phosphatase; iPTH = intact parathyroid hormone; OR = odds ratio.
[a]Adjusted for age and sex.

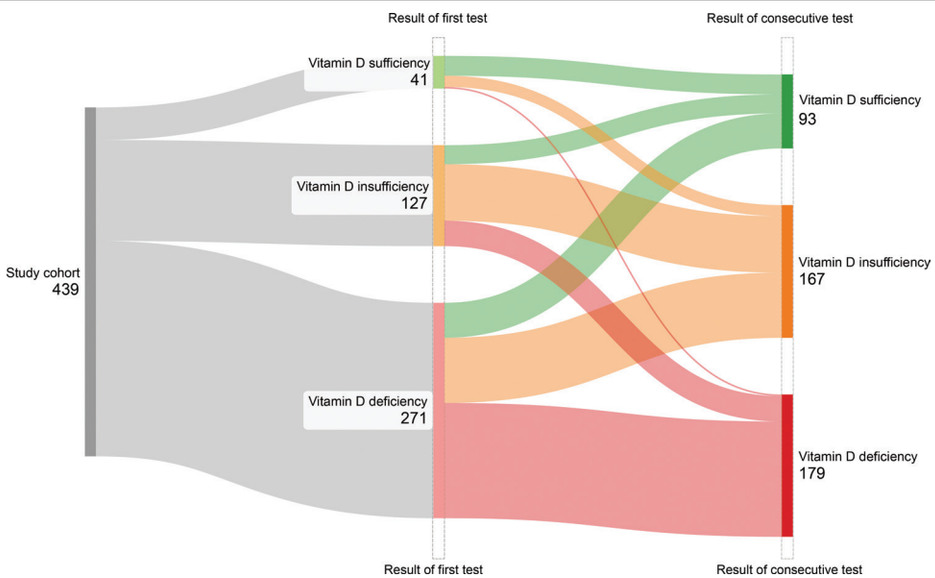

Fig. 2 Transition in vitamin D status between the first and the consecutive tests in the study cohort. The Sankey diagram illustrates changes in vitamin D status among the 439 participants, categorized into sufficiency (vitamin D sufficiency), insufficiency (vitamin D insufficiency), and deficiency (vitamin D deficiency) groups based on the first and consecutive tests. The width of the flows corresponds to the number of participants transitioning between categories. Of the 439 participants, 41 were sufficient, 127 insufficient, and 271 deficient in the first test. In the consecutive test, 93 participants were sufficient, 167 insufficient, and 179 deficient.

anemia, and congenital heart disease with VDD disappeared after multivariate adjustments.

3.6. Biochemical predictors of VDD

The status of serum calcium/ionized calcium, phosphorous, ALP, and iPTH are shown in Table 3. Overall, 683 (55.9%), 695 (56.9%), 621 (50.8%), and 140 (11.5%) of the children had calcium/ionized calcium, phosphorous, ALP, and iPTH measurement data, respectively. Hypocalcemia, hypophosphatemia, elevated ALP, and elevated iPTH were noted in 11 (3.6%), 30 (9.6%), 39 (13.5%), and 19 (28.8%) of the children with VDD, respectively. Hypocalcemia, hypophosphatemia, elevated ALP, and hyperparathyroidism had specificities of 98.4%, 94.5%, 93.4%, and 95.9%, respectively, for the presence of VDD. There were significant differences in the proportion of hypophosphatemia, elevated ALP, and hyperparathyroidism between the VDD and non-VDD groups. Although a higher proportion of the VDD patients had hypocalcemia (3.6% vs 1.6%), the difference did not reach statistical significance. Univariate Firth's penalized-likelihood logistic regression analysis showed that hypophosphatemia, elevated ALP, and hyperparathyroidism were associated with a significantly increased odds of VDD (Table 4). However, multivariate Firth's penalized-likelihood logistic regression analysis after adjusting for potentially confounding factors including age and sex showed that only elevated iPTH was independently associated with VDD (OR = 8.667, 95% CI = 1.338-56.157, $p = 0.024$).

3.7. Vitamin D supplementation and repeat assessments of serum 25(OH)D level

Overall, 394 (32.2%) of the children were given prescribed vitamin D supplements following the index test. In addition, 439 children underwent a 25(OH)D retest, with an average interval of 6.8 ± 7.3 months; 31.2% of the first retests were done within 3 months of the first test, and 32.6% were performed between 3 and 6 months after the first test. Forty-one (9.3%) of the retests were done in those who initially had vitamin D sufficiency. Among the children who underwent retests, 38.0% and 40.8% had VDI and VDD, respectively, and 222 (50.6%) were given prescribed vitamin D supplements. The changes in vitamin D status are summarized in Fig. 2. The 25(OH)D level in the retest was significantly higher than that in the initial test (24.1 ± 11.9 vs 19.4 ± 10.1 ng/mL, $p < 0.001$). At the second assessment, 93 (21.2%) children were categorized as having vitamin D sufficiency, 167 (38.0%) with VDI, and 179 (40.8%) with VDD. The vitamin D status improved in 150 patients (34.2%) on retest,

however, there was no change or decline in vitamin D status in 241 (54.9%) and 48 (10.9%) children, respectively. Among the children who were retested, the proportion of those with VDD on retest significantly dropped (40.8% vs 61.7%, $p < 0.001$).

4. DISCUSSION

The concentration of serum total 25(OH)D is currently considered to be the best biomarker to assess vitamin D status. Based on a cut-off value of <20 ng/mL (50 nmol/L), VDD is a very pervasive condition worldwide especially people residing at high latitudes, particularly above 35°N and below 35°S.[14] The prevalence of VDD (defined as 25(OH)D levels <50 nmol/L or 20 ng/mL) has been estimated to be 9.7% in children aged 1 to 11 years and 25% in children aged 12 to 19 years in the USA,[15] and 26.7% to 35.7% in Canada.[16] VDD is also common in Asia. In Japan, the prevalence rates of VDD and VDI among children aged 2 years have been estimated to be 25.4% and 50.9%, respectively.[17] In Korea, 58.6% of children have been estimated to have VDD and 38.5% VDI.[18] In addition, a multicenter hospital-based study in China reported a prevalence of VDD of 22.6%.[19] Despite being an area with high sun exposure, the prevalence of VDD still varies from 0.9% to 96.4% in Southeast Asia.[7] A meta-analysis study reported that the prevalence of VDD in children (<18 years of age) was 48.5%,[20] which is similar to the current study where 48.9% and 38.8% of the children had VDD and VDI, respectively. Furthermore, we found that VDD affected both male and female children irrespective of age, indicating the endemic nature of VDD in Taiwan, even though Taiwan is situated between 21°N and 25°N latitude.

Previous studies have shown that VDD is related to age. Consistent with most countries, we also found that adolescents were at risk of developing VDD. Notably, the prevalence of VDD observed among adolescents in this present hospital-based study, with rates reaching 65.7% among 12- to 15-year-olds and 69.9% among 15- to 18-year-olds, far surpasses the prevalence in a community setting, with 15.3% in 13- to 15-years-olds and 23.7% in 16- to 18-years-olds.[21] These findings indicate that VDD is prevalent in Taiwan, especially among adolescents seeking health services.

In the present study, we found that the peak prevalence of VDD is in adolescent group (66.8%), compared with 48.7% in the school-age group, 48.2% in infant, and 23.4% in the preschool group. Furthermore, an older age was associated with an increased odds of VDD. Compared with infant group (age 0-1 year), the children aged >1 to 6 years had lowest risk for VDD (OR = 0.391), and adolescents aged >12 years had highest odds of having VDD (OR = 2.479). These results may be due to a lack of exposure to sunlight because of a greater time spent indoors on school work or excess screen time in adolescents.[3]

In the present study, 48.2% of the infants had VDD. This figure is higher than the 44.1% reported by Chen et al[22] who investigated infants in northern Taiwan from 2012 to 2014, but lower than a systematic review conducted by Oktaria et al[7] who reported a prevalence of VDD in Southeast Asian newborns ranging from 52% to 90%. In Taiwan, the rate of exclusive breastfeeding under 6 months of age was 44.8% in 2016 and 46.2% in 2018.[23] As exclusively breastfed infants are at an increased risk of developing VDD, the American Academy of Pediatrics advises supplementing exclusively or partially breastfed infants with 400 IU/d of vitamin D from birth until they are able to consume over 1000 mL/d of vitamin D-fortified formula.[24] Preterm infants are vulnerable to VDD because of less vitamin D deposit and insufficient maternal vitamin D supply, intolerance to human milk formulas, malabsorption caused by necrotizing enterocolitis, and parenteral nutrition-associated cholestasis.[25] Supplementation of vitamin D ranges from 200 to 1000 IU/d for premature infants effectively reduced the risk of VDD.[26–29]

In this study, we also found that VDD was associated with female sex. A growing body of evidence has shown that VDD is more prevalent in obese individuals. Proposed causative factors include body fat acting as a reservoir for vitamin D storage thereby reducing vitamin D bioavailability, volumetric dilution, low dietary vitamin D intake, and insufficient physical activity.[30] Women tend to have more fat mass than men, which may explain the difference in the prevalence of VDD. In addition, differences in sunscreen use in males and females may also be another explanation.

Previous studies have shown the immunomodulatory effects of vitamin D on the innate and adaptive immune systems by modulating the expressions of antimicrobial peptides such as cathelicidin and inflammatory cytokines.[31] In critically ill children, VDD is very common and strongly associated with worse clinical outcomes, including higher severity of illness scores, use of vasopressors, fluid resuscitation, and mechanical ventilation support.[32,33] Another study conducted in Spain showed that patients in pediatric intensive care units had twice the rate of VDD compared with healthy controls (29.5% vs 15.6%).[34] Hemodilution, interstitial extravasation, and decreased serum vitamin D-binding protein can cause rapid reductions and changes in serum 25(OH)D level during critical illness.[35] Furthermore, clinical studies have suggested an association between VDD and an increased risk of respiratory tract infection.[31,36] In our study, we observed no significant association between VDD and inflammatory markers (CRP and leukocytosis); however, the children in whom 25(OH)D was measured during hospitalization had a 1.949-fold increased odds of VDD compared with those assessed in outpatient clinics. In contrast to other studies, we did not find an association between VDD and acute respiratory tract infection. We did not explore the prevalence of VDD in the critically ill children, as only a very small number of patients required intensive care in this study. Vitamin D plays an important pleiotropic role on different organs in the setting of critical illness, and further prospective studies are warranted to explore this issue.

VDD has been linked to numerous comorbid diseases and health conditions. Even though previous studies have reported associations between VDD with atopy,[37] autoimmune disorders,[5] chronic liver diseases,[38] CKD or ESRD,[5] nephrotic syndrome,[5] congenital heart disease,[39] anemia,[40] depression,[5] and autism,[2] these associations were not found in the present study.

Solar ultraviolet B is the major source of vitamin D in addition to dietary intake. An Australian study reported that sunlight exposure to the face, arms, or legs for approximately 10 to 15 minutes between 10:00 and 15:00 without the use of sunscreen at least three times a week was sufficient to induce vitamin D synthesis.[41] Based on the important contribution of sunlight exposure to vitamin D levels, serum 25(OH)D may be a proxy for the amount of sun exposure. There is currently no consensus on the impact of seasonal changes on vitamin D status. The results of this study are in agreement with several published studies,[3] in that spring/winter was associated with a greater odds of VDD and lower mean vitamin D levels compared with summer/autumn. However, some studies have reported no seasonal variation in VDD.[42] Kimlin et al[14] reported that during winter months, more ultraviolet is required to maintain vitamin D sufficiency only for those living at high latitudes, but not for those at latitudes below 25°N, such as Taiwan. Taiwan experiences four distinct seasons. In winter, the average temperature ranges from 14°C to 20°C with little rainfall. It is thus possible that people wear more clothing and participate less in outdoor activities, leading to decreased cutaneous vitamin D synthesis, and consequently the observed seasonal variations.

In our study, the high prevalence of VDD may also be attributable to low consumption of vitamin D-rich foods in addition to excess screen time and changes in lifestyle. Since dietary sources are unlikely to be sufficient, especially for infants and vegetarians, vitamin D supplements are often necessary to prevent VDD. The recommended dosage of vitamin D supplements to treat VDD depends on the severity of VDD and age of the patient.[43] In obese patients, higher doses of vitamin D are necessary to treat VDD, and it is reasonable to set therapeutic goals of treatment to achieve a 25(OH)D level of >50 to 75 nmol/L or 20 to 30 ng/mL to relieve symptoms and decrease the risk of fractures. During the first month of supplementation, 25(OH)D levels have been reported to rise rapidly, and then to continue to rise slowly over the following 2 to 3 months.[44] Given the low risk of vitamin D toxicity such as hypercalcemia associated with excess vitamin D supplementation,[45] a repeat blood test for 25(OH)D is only suggested when clinically indicated and after 3 to 6 months of treatment. In the present study, 59.2% of the patients who had a repeat 25(OH)D test reached the threshold of >20 ng/mL. However, we did not have information on over-the-counter use of vitamin D supplements, dosage, adherence, or lifestyle modifications after the index 25(OH)D test. This restricts our ability to ascertain the impact of vitamin D supplements on changes in vitamin D status over time.

Low 25(OH)D status reduces the efficiency of intestinal calcium absorption, leading to an increase in iPTH level to restore calcium homeostasis. Secondary hyperparathyroidism mobilizes calcium from the skeleton and increases phosphorus wasting in the kidneys. The correlation between vitamin D level and ALP and iPTH and even the potential use as a screening test for VDD has been reported,[22,46] however other studies have not shown any correlations between these biochemical parameters and VDD.[47] In accordance with a study conducted by Hashemipour et al,[47] most of the children with VDD with available biochemical profile data in our study had normal calcium, phosphorus, ALP, and iPTH, indicating that the use of biochemical parameters alone has low sensitivity to detect mild VDD. Therefore, normal biochemical parameters may not be suitable as a screening test to rule out VDD. The multivariate analysis in this study showed that elevated iPTH was associated with an 8.667-fold increased odds of VDD.

To the best of our knowledge, this is the first large-scale hospital-based study of vitamin D status in children aged 0 to 18 years living in Taiwan, a low-latitude region (25°N) in East Asia. Our findings add to the knowledge of the epidemiology of VDD in countries situated at subtropical latitudes. However, there are several limitations. First, our study cohort was comprised of children seeking medical care at a tertiary care hospital for various reasons or conditions, and thus cannot be regarded as representative of the general population. It is also important to note that low levels of 25(OH)D are common during acute illnesses,[31–33] which may lead to the overestimation of the prevalence of VDD in healthy children. Second, we lacked information on indoor/outdoor activity levels and clothing, which are crucial factors affecting cutaneous vitamin D synthesis. Third, we lacked data on the dietary intake of vitamin D, calcium, phosphorus, and over-the-counter vitamin D supplements. Fourth, some data were missing due to the retrospective design of our research, including on acute inflammatory markers and biochemical profile. In particular, missing data on iPTH could have led to bias and affected the results of the study. In addition, of the children with 25(OH)D measurements, only 904 (74.0%) and 761 (62.3%) had at least one acute inflammatory marker or biochemical profile measurement, respectively. Fifth, details of symptoms and body mass index, both of which may be important potential confounding factors in this study, were not available. In addition, the assessment of comorbidities relied on the documentation of relevant ICD-10-CM codes in our hospital records, which may have underestimated the prevalence of comorbidities. We suggest that future prospective studies are needed to better understand the risk factors associated with VDD and improve the robustness of our results.

In conclusion, our study underscores that VDD was prevalent among Taiwanese children seeking various medical treatments in a hospital setting despite high sun exposure in Taiwan. Our findings highlight that hospitalized children, female, children aged greater than 12 years, testing during the spring/winter are associated with a higher likelihood of VDD. Physicians should be aware of VDD, especially in children at higher risk.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A322.

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