

Association between serum 25-hydroxyvitamin D concentration and pulmonary infection in children

Wei Li, MS^a, Xianfen Cheng, BS^b, Linying Guo, MD^{a,*}, Hongri Li, MD^a, Chunrong Sun, MS^b, Xiaodai Cui, MS^b, Qi Zhang, MD^{c,*}, Guowei Song, MS^b

Abstract

We assessed the relationship between serum 25-hydroxyvitamin D (25(OH)D) level and community-acquired pneumonia (CAP) among Chinese children.

This observational study examined children aged 3 days to 14 years (n = 1582) from the Capital Institute of Pediatrics in 2009 to 2011. There were 797 children in the CAP group and 785 controls. The CAP group was divided into 2 groups: a pneumonia group and pneumonia-induced sepsis group. The serum 25(OH)D level was estimated using micro whole blood chemiluminescence.

The average serum 25(OH)D level in all samples was 25.32 ± 14.07 ng/mL, with the CAP group showing a lower value than the control group ($P < .001$). There were also significant differences between the pneumonia group and pneumonia-induced sepsis group ($P < .001$). In the pneumonia-induced sepsis group, significant differences in serum 25(OH)D levels were observed in children who received mechanical ventilation or presenting with multiple organ dysfunction ($P < .01$).

All serum 25(OH)D levels in the pneumonia group and pneumonia-induced sepsis group were below normal levels, particularly in the sepsis group. A lower serum 25(OH)D level was associated with more serious symptoms in CAP children. Children with low serum 25(OH)D levels may be at higher risk of receiving mechanical ventilation and presenting with multiple organ dysfunction. These findings suggest that vitamin D supplements are beneficial for the treatment and prevention of CAP.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, CAP = community-acquired pneumonia, MODS = multiple organ dysfunction syndrome, ROC = receiver operating characteristic, UV = ultraviolet, VD = Vitamin D.

Keywords: community-acquired pneumonia, sepsis, serum 25-hydroxyvitamin D

1. Introduction

Community-acquired pneumonia (CAP) is the most common reason for hospitalization among children and primary cause of death among children under 5 years of age.^[1] In the developing world, CAP is more common and severe than in countries in Europe and North America, and is the largest cause of child death.^[2,3] Approximately 30% child deaths are attributed to CAP (4 million deaths per year) in developing countries, with two-thirds of these deaths occurring during infancy.

Examining the risk factors and initiating and developing effective interventions are essential for slowing or preventing the development of CAP and its related complications later in life. CAP is mainly caused by viral, bacterial, fungal, and mycoplasma infections, and is associated with pediatric physiological construction and immunological characteristics. Vitamin D deficiency may cause immunologic disorders.^[4] The action of vitamin D is mediated via vitamin D receptors,^[5] which are present in nearly all types of immune cells, including activated CD4⁺ and CD8⁺ T cells, B cells, neutrophils, macrophages, and dendritic cells. Vitamin D deficiency affects immune function to decrease the host defenses against infections in children. Some clinical researches indicated that vitamin D can protect children from lung infection. Children with vitamin D insufficiency or deficiency are more susceptible to respiratory infection.^[3] Serum 25-hydroxyvitamin D (25(OH)D) level is an internationally accepted standard for evaluating vitamin D nutritional status.^[6] The incidence of respiratory infection decreases dramatically when the serum 25(OH)D level is higher than 38 ng/mL.^[7] Other studies revealed an association between lung infection and serum 25(OH)D level.^[8]

Sepsis is a relatively common and often lethal response to an infection. It is a common reason for hospital admission and significant healthcare burden worldwide. In the United States, there were 4.07 million cases of septicemia from 1995 to 2000, causing 730,000 deaths.^[9] A review of the epidemiological features associated with septicemia and UVB doses in the United States indicated that vitamin D variations may explain much of the epidemiology of septicemia in the United States.^[10] It has been demonstrated that patients with sepsis have a high prevalence of vitamin D deficiency.^[11,12] Given its high morbidity and

Editor: Girish Chandra Bhatt.

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

The authors have no conflicts of interest to disclose.

^a Department of ICU, Affiliated Children's Hospital of Capital Institute of Pediatrics, ^b Department of Central Laboratory of Capital Institute of Pediatrics, ^c Department of Pediatrics, China-Japan Friendship Hospital District, Chaoyang District, Beijing, China.

* Correspondence: Qi Zhang, Department of Pediatrics, China-Japan Friendship Hospital District, No. 2, East Cherry Garden Street, Chaoyang District, Beijing 100029, China (e-mail: zhangqikeyan@163.com) and Linying Guo, Department of ICU, Affiliated Children's Hospital of Capital Institute of Pediatrics, No. 2, Yabao Road, Chaoyang District, Beijing 100020, China (e-mail: 13020013651@163.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2018) 97:1(e9060)

Received: 24 May 2017 / Received in final form: 20 October 2017 / Accepted: 12 November 2017

<http://dx.doi.org/10.1097/MD.0000000000009060>

mortality, the optimal management of sepsis is an active area of research. In this study, we examined children aged 3 days to 14 years at the Capital Institute of Pediatrics from 2009 to 2011 to assess their vitamin D nutritional status and investigated the relationship between CAP and serum 25(OH)D level, an internationally accepted stability index of vitamin D nutritional status.

2. Patients and methods

2.1. Collection and preparation of clinical samples

We collected patients from the Capital Institute of Pediatrics, Beijing, China from January 2009 to December 2011, using a case-control approach to obtain a representative sample in Beijing. The exclusion criteria excluded children with severe congenital diseases or malnutrition. All 797 participants were from a Chinese Han population with an average age of 3.15 years (range: 3 days to 14 years). An additional 785 matched subjects with an average age of 3.28 years (range: 1 month to 12 years) were selected from the general population in Beijing to serve as normal controls (Table 1). The CAP group consisted of 429 boys and 368 girls aged 3 days to 14 years diagnosed with CAP, while the control group consisted of 426 boys and 359 girls aged from 1 month to 12 years diagnosed as healthy. Because most sepsis cases are due to respiratory infections, we divided the CAP group into 2 subgroups based on the presence of sepsis. The sepsis group consisted 255 boys and 178 girls aged from 10 days to 13 years diagnosed with pneumonia-induced sepsis. The pneumonia group consisted 174 boys and 190 girls aged 3 days to 14 years diagnosed with pneumonia only. Clinical assessment was conducted by doctors at the Capital Institute of Pediatrics. Tables 2 and 3 show the baseline characteristics of all groups.

Seasons of the year were defined according to the date of hospital admission or physical examination in 4-month periods: spring (March, April, May), summer (June, July, August), autumn (September, October, November), and winter (December, January, February).

The children were fed by 400 IU vitamin D daily from birth to 2 years old. Venous blood specimens were collected after informed consent was obtained from 797 hospitalized children on the second day of hospitalization and 785 healthy children on the physical examination day. Samples were obtained in anticoagulated tubes and centrifuged for 5 minutes at 4000 rpm. Plasma and blood cells were collected and stored at -20°C before analysis. The protocols for the study and written consent were approved by the ethics committee of the Capital Institute of Pediatrics at Beijing, China (Approval ID: SHERLL 2013075).

Table 1
Characteristic of patients.

Characteristic	CAP group (n = 797)		Control group (n = 785)	
	No.	%	No.	%
Age, y				
Mean and range	3.15	(0.01–14.0)	3.28	(0.1–12.0)
Gender				
Boy	429	53.8	426	54.3
Girl	368	46.2	359	45.7
Sepsis				
Yes	433	54.3	—	—
No	414	45.7	—	—

CAP = community-acquired pneumonia.

Table 2
Baseline demographics of the CAP group and the control group.

	Number, %		P
	CAP group	Control group	
Age			
Mean (number)	37.75 ± 1.30 (797)	39.34 ± 1.37 (785)	.226
<12	236 (29.6%)	223 (28.4%)	.782
12–35	215 (27%)	217 (27.6%)	
36–83	261 (32.7%)	250 (31.8%)	
>84	85 (10.7%)	95 (12.1%)	
Gender			
Male	429 (53.8%)	426 (54.3%)	.880
Female	368 (46.2%)	359 (45.7%)	

CAP = community-acquired pneumonia.

CAP was diagnosed^[13] based on clinical findings (fever, cough, chest pain, and difficulty breathing), physical examination findings (tachypnea, chest retraction, and decreased breath sounds or rales), and radiological findings. Chest radiographs were evaluated by a radiologist trained in reading and interpreting radiographs according to World Health Organization criteria. Systemic inflammatory response syndrome was confirmed in accordance with a previously described definition^[14]: at least 2 of the following 4 criteria must be met, one of which must be abnormal temperature or leukocyte count: core temperature >38.5 or $<36.0^{\circ}\text{C}$; tachycardia, defined as a mean heart rate >2 SD above normal for age; or for children <1 year old, bradycardia, defined as a mean heart rate <10 th percentile for age; mean respiratory rate >2 SD above normal for age; and leukocyte count elevated or depressed for age or $>10\%$ immature neutrophils.

Sepsis, according to the American College of Chest Physicians, European Society of Intensive Care Medicine, Society of Critical Care Medicine, American Thoracic Society, and Surgical Infection Society consensus definition,^[15] was defined as systemic inflammatory response syndrome due to a known source of infection. Bacteremia, defined as positive blood cultures, was not required to meet the diagnostic criteria for sepsis.

Multiple organ dysfunction syndrome (MODS)^[16] was defined as “the development of potentially reversible physiologic derangement involving 2 or more organ systems not involved in the disorder that resulted in ICU admission, and arising in the wake of a potentially life threatening physiologic insult.”

Table 3
Baseline demographics of the sepsis group and the pneumonia group.

	Number, %		P
	Sepsis group	Pneumonia group	
Age			
Mean (number)	36.55 ± 1.83 (433)	39.18 ± 1.88 (364)	.319
<12	149 (34.4%)	87 (23.9%)	.000
12–35	107 (24.7%)	108 (29.7%)	
36–83	120 (27.7%)	141 (38.7%)	
>84	57 (13.2%)	28 (7.7%)	
Gender			
Male	255 (55.8%)	174 (47.8%)	.03
Female	178 (44.2%)	190 (52.2%)	
Mechanical ventilation	132 (30.5%)	0 (0%)	.000
Multiple organ dysfunction	115 (26.6%)	0 (0%)	

Table 4

The correlation between vitamin D and the various indicators.

	Age	Gender	Season	Sepsis	Health
Vitamin D	-0.318*	-0.005	-0.278*	0.480*	0.450*

*Significant correlation at 0.01 level. The serum 25(OH)D levels of different age groups.

Individuals with CAP who also had coexisting diagnoses of other diseases, such as chronic lung diseases, blood disorders, kidney diseases, heart diseases, chronic digestive diseases, and connective tissue diseases, were excluded.

3. Methods

The serum 25(OH)D level was estimated by the Capital Institute of Pediatrics using microwhole blood chemiluminescence with Fluoroskan (DiaSorin Liaison, Stillwater, MN), which recently received FDA clearance letter (510K). The assay has an intra-assay coefficient of variation of 9% and interassay coefficient of variation of 11%. For categorical analysis of the serum 25(OH)D level, we used cutoffs of <10ng/mL for severe deficiency, 10 to 20ng/mL for deficiency, 20 to 30ng/mL for insufficiency, and >30ng/mL for sufficiency, as described previously.^[17]

3.1. Statistical analysis

Statistical analyses were performed using SPSS Statistics 20.0 (SPSS, Inc., Chicago, IL). We utilized *t* test for continuous variables and Chi-square (χ^2) test for categorical variables. The ability of the models to predict the development of sepsis was assessed using receiver operating characteristic (ROC) analysis and the area under the curve was calculated. A two-tailed *P*-value of <.05 was considered statistically significant.

4. Results

4.1. Serum 25(OH)D level of total samples

There were 855 boys and 727 girls aged 3 days to 14 years, with an average age was 3.21 years. The average serum 25(OH)D level of these children was 25.32 (14.07) ng/mL, indicating vitamin D insufficiency. There were no significant differences between the 855 boys and 727 girls.

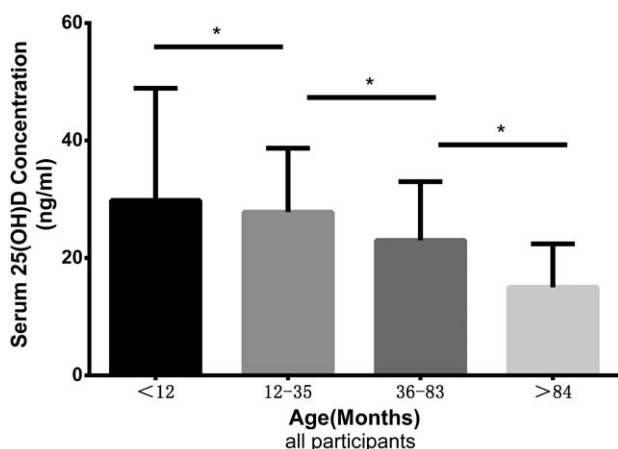


Figure 1. Concentration of serum 25(OH)D in different age groups. **P* ≤ .05.

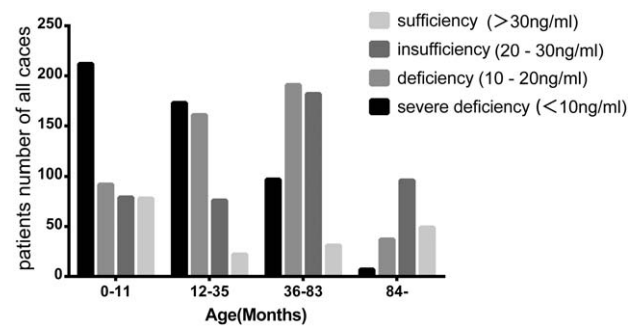


Figure 2. Distribution of vitamin D nutritional status in different age groups.

We examined the relationship between vitamin D and related variables and found that vitamin D levels were associated with age, season, health status, and sepsis, with age and season showing negative correlations (Table 4). We divided the patients into 4 groups, <12 months, 12 to 35 months, 36 to 83 months, and >84 months, and compared the vitamin D content between groups. The serum 25(OH)D levels differed in children of different ages. With increasing age, serum 25(OH)D concentration and volatility gradually decreased (Fig. 1).

4.2. Vitamin D nutritional status in different age groups

Vitamin D nutritional status was divided into 4 categories, and 4 types of nutritional status at all ages varied. The 0- to 11-month group was more likely to have severe deficiency, while for sufficiency and insufficiency, the 36- to 83-month age group was likely to show severe deficiency (Fig. 2).

4.3. Serum 25(OH)D concentration in different seasons

There were 344 children in spring, 234 children in summer, 430 children in autumn, and 574 children in winter. Serum 25(OH)D levels in different seasons differed, with the highest levels in the summer group and lowest in the winter group (Fig. 3). There were no significant differences between the CAP group and control group.

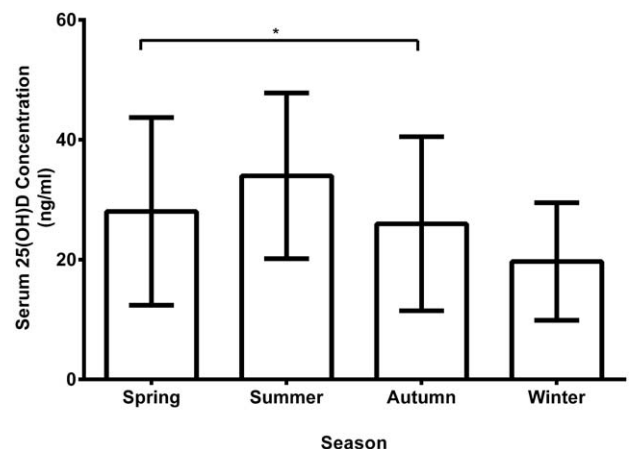


Figure 3. Distribution of serum 25(OH)D levels in different season groups. **P* ≤ .05.

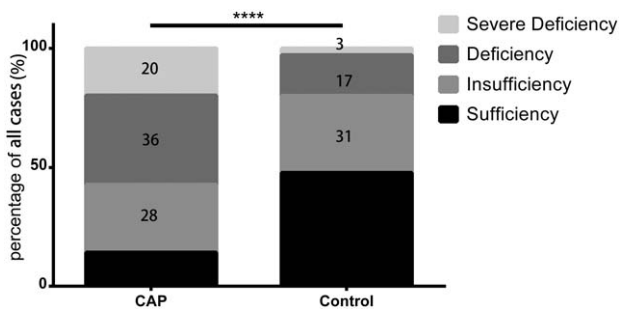


Figure 4. Comparison of vitamin D nutritional status between the CAP group and control group. **** $P \leq .0001$.

4.4. Comparison of serum 25(OH)D concentration between CAP group and control group

The average serum 25(OH)D concentration was 19.04 ± 9.86 ng/mL in the CAP group and 31.71 ± 14.82 ng/mL in the control group. There were significant differences between the 2 groups ($P < .001$).

The proportions of subjects different vitamin D nutritional statuses among the CAP group and control group are shown in Fig. 4. The proportion of sufficient vitamin D in the CAP group was lower than that of the control group. The proportion of deficient or severely deficient vitamin D in the CAP group was higher than that in the control group.

4.5. Comparison of serum 25(OH)D concentration between CAP group and control group for different age groups

In the control group, serum 25(OH)D concentration gradually decreased with age, while the CAP group did not show this trend; in different age groups, serum 25(OH)D concentration in the CAP group was consistently lower than in the control group (Fig. 5).

4.6. Comparison of serum 25(OH)D concentration between pneumonia group and sepsis group

The average serum 25(OH)D concentration was 22.69 ± 9.56 ng/mL in the pneumonia group and 15.96 ± 9.03 ng/mL in the sepsis group. There were significant differences between the 2 groups ($P < .001$).

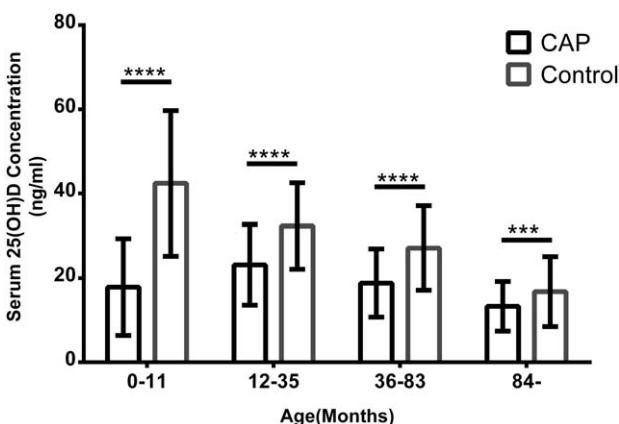


Figure 5. Comparison of serum 25(OH)D concentration between the CAP group and control group of different age groups. *** $P \leq .001$; **** $P \leq .0001$.

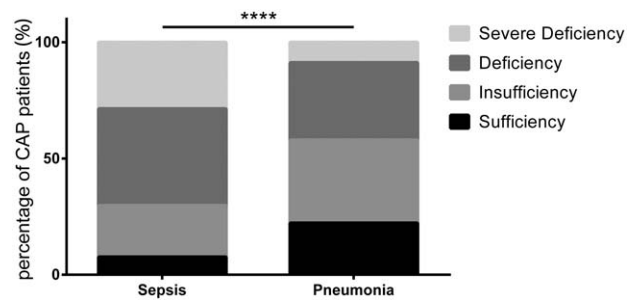


Figure 6. Comparison of vitamin D nutritional status between the pneumonia group and sepsis group. **** $P \leq .0001$.

The proportions of children with different vitamin D nutritional status among the pneumonia group and sepsis group are shown in Fig. 6. The proportion of sufficiency and insufficiency in vitamin D in the pneumonia group was higher than that in the sepsis group. The proportion of deficiency or severe deficiency in vitamin D in the pneumonia group was lower than that in the sepsis group (Fig. 6).

4.7. Serum 25(OH)D concentration in the sepsis group

In patients with sepsis, serum 25(OH)D concentrations were lower than in patients with no relevant symptoms, serum 25(OH)D concentration in patients who needed mechanical ventilation was lower than in those who did not need mechanical ventilation, and lower in MODS patients than in No-MODS patients. We divided the patients into 4 groups: MODS without MV, MODS with MV, No-MODS without MV, and No-MODS with MV. Disease severity was correlated with serum 25(OH)D concentration (Fig. 7).

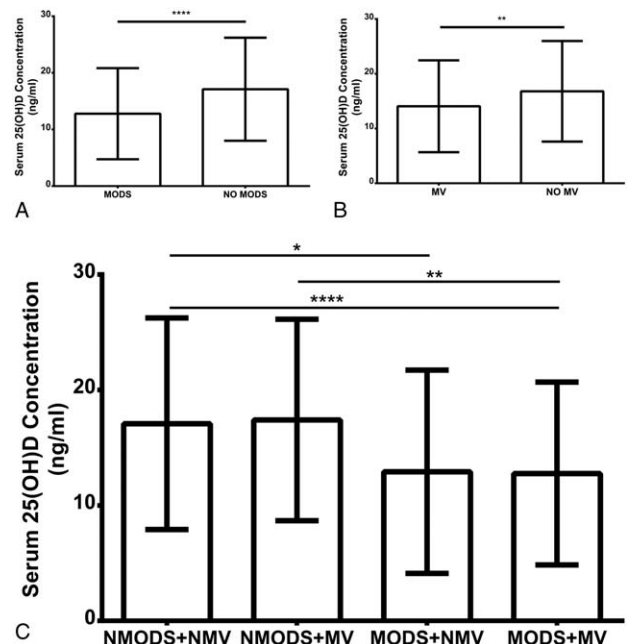


Figure 7. Comparison of vitamin D nutritional status between (A) MODS and No MODS; (B) MV and No MV; (C) NMODS+NMV, NMODS+MV, MODS+NMV, MODS+MV group. * $P \leq .05$, ** $P \leq .01$, **** $P \leq .0001$.

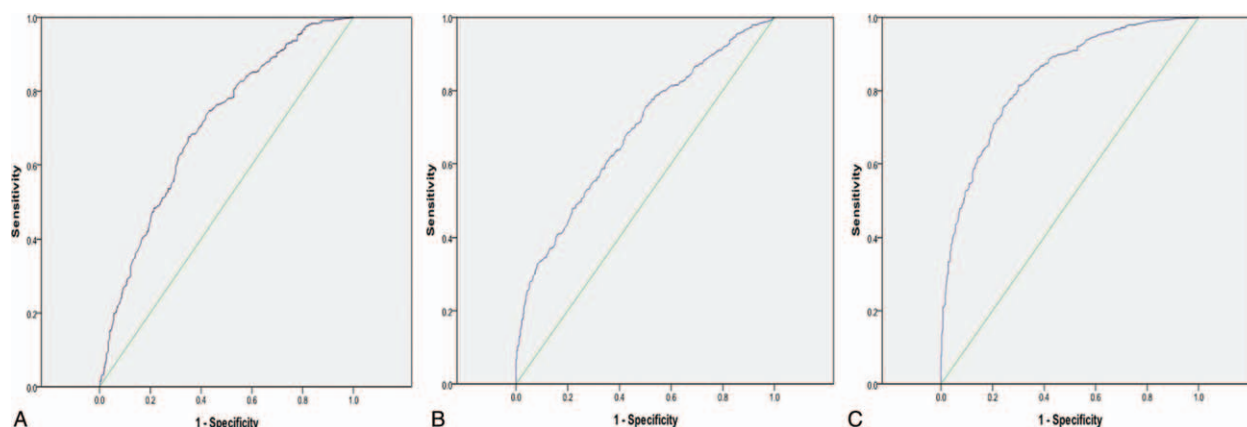


Figure 8. ROC curve of (A) pneumonia-induced sepsis in CAP patients; (B) CAP patients; (C) sepsis in normal subjects.

4.8. Diagnostic accuracy evaluation using ROC curve in sepsis group

The association between serum 25(OH)D levels and pneumonia-induced sepsis in CAP patients was determined by logistic regression analysis with an odds ratio (OR)=1.190 (Fig. 8A). The area under the ROC curve was 0.704. The cut-off value of the serum 25(OH)D level was 18.15 ng/mL, while its sensitivity was 67.69% and specificity was 64.9%.

The association between serum 25(OH)D levels and CAP was determined by logistic regression analysis with an OR=2.157 (Fig. 8B). The area under the ROC curve was 0.687. The cut-off value of the serum 25(OH)D level was 30.0 ng/mL, while its sensitivity was 47.8% and specificity was 79.3%.

The association between serum 25(OH)D levels and sepsis was determined by logistic regression analysis with an OR=1.813 (Fig. 8C). The area under the ROC curve was 0.837. The cut-off value of the serum 25(OH)D level was 19.73 ng/mL, while its sensitivity was 81.4% and specificity was 70.0%.

5. Discussion

Vitamin D is synthesized in the skin after exposure to ultraviolet B radiation and intake of food or supplements. Thus, serum 25(OH)D concentration may also show seasonal variation. In Northern Europe,^[18,19] vitamin D status is the highest during summer and lowest in winter. In our study, the average 25(OH)D level in all 1582 children was insufficient. Serum 25(OH)D level reach the lowest levels in winter and highest in summer. Interestingly, this seasonal variation resembles the described seasonal variation of some infectious diseases, including sepsis.^[20,21] This indicates that infectious diseases are related to serum 25(OH)D levels. The serum 25(OH)D level in the CAP group was lower than that in the control group, suggesting that the serum 25(OH)D level is associated with the susceptibility to CAP. McNally et al^[7] reported large numbers of children admitted to pediatric intensive care units with pneumonia had vitamin D deficiency. In our study, the serum 25(OH)D level of the sepsis group was lower than that of the pneumonia group. This suggests that serum 25(OH)D level is a useful marker for discriminating the severity of infection. A lower level of serum 25(OH)D indicates more serious symptoms of CAP in children.

In this study, we found that serum 25(OH)D levels differed at different ages, with the highest values observed in the 0- to 11-month group and lowest in the 84-month group. Children in the

0- to 11-month group not only consumed adequate amounts of vitamin D, but also were exposed to abundant sunshine, enabling them to maintain high serum 25(OH)D levels. However, children in the 84-month group may no longer consume sufficient vitamin D and have less outdoor activities, and thus their serum 25(OH)D levels are lower than in younger children.

Sepsis is often caused by *Staphylococcus aureus* infection,^[22] sometimes preceded by or occurring in conjunction with viral infections^[23] and, to a lesser extent, fungal infections.^[24] This can compromise the functions of various organ systems, resulting in MODS. Ginde et al^[25] found that patients with serum 25(OH)D levels <30 ng/mL were more likely to have severe sepsis and dysfunction in 2 or more organ systems. In our study, serum 25(OH)D levels in pediatric patients with mechanical ventilation and MODS was lower than that in other subjects, suggesting that the serum 25(OH)D level is an indicator of severity. We concluded that children with low levels of serum 25(OH)D may be at risk for mechanical ventilation and MODS.

Low serum 25(OH)D levels may be a risk factor for CAP and pneumonia-induced sepsis. Logistic regression analysis showed that the serum 25(OH)D level was closely related to pneumonia-induced sepsis. For individuals with low levels of serum 25(OH)D, the risk of pneumonia-induced sepsis was higher than in individuals with high concentrations of vitamin D. The ROC curve cut-off value for serum 25(OH)D level was 18.15 ng/mL; thus, when the serum 25(OH)D level is under 18.15 ng/mL, pneumonia-induced sepsis can be diagnosed.

Vitamin D has hormone-like effects and is an indispensable compound for maintaining children's health and promoting cells growth and proliferation. We found that CAP and sepsis are associated with serum 25(OH)D levels. A lower serum 25(OH)D level was associated with a more serious condition. Additional studies of vitamin D will reveal the pathogenesis of human diseases in more detail and improve treatment methods for clinical diseases. Our future studies will continue to explore the value of vitamin D in treating CAP and pneumonia-induced sepsis.

Acknowledgments

The authors are grateful to the study participants and their families as well as the doctors of emergency room and ICU for data collection, and parents of all children for participation in this cohort.

References

- [1] Rudan I, Boschi-Pinto C, Biloglav Z, et al. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ* 2008;86:408–16.
- [2] Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Coordinated Data Group of BOSTID Researchers. *Rev Infect Dis* 1990;12(suppl 8):S870–88.
- [3] Baqui AH, Black RE, Arifeen SE, et al. Causes of childhood deaths in Bangladesh: results of a nationwide verbal autopsy study. *Bull World Health Organ* 1998;76:161–71.
- [4] Dusso AS, Brown AJ, Slatopolsky E, et al. Vitamin D. *Am J Physiol Renal Physiol* 2005;289:F8–28.
- [5] Gigante A, Torcianti M, Boldrini E, et al. Vitamin K and D association stimulates in vitro osteoblast differentiation of fracture site derived human mesenchymal stem cells. *J Biol Regul Homeost Agents* 2008;22:35–44.
- [6] Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.
- [7] McNally JD, Leis K, Matheson LA, et al. Vitamin D deficiency in young children with severe acute lower respiratory infection. *Pediatr Pulmonol* 2009;44:981–8.
- [8] Jovanovich AJ, Ginde AA, Holmen J, et al. Vitamin D level and risk of community-acquired pneumonia and sepsis. *Nutrients* 2014;6:2196–205.
- [9] Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–54.
- [10] Grant WB. Solar ultraviolet-B irradiance and vitamin D may reduce the risk of septicemia. *Dermatoendocrinol* 2009;1:37–42.
- [11] Nierman DM, Mechanick JL. Bone hyperresorption is prevalent in chronically critically ill patients. *Chest* 1998;114:1122–8.
- [12] Van den Berghe G, Van Roosbroeck D, Vanhove P, et al. Bone turnover in prolonged critical illness: effect of vitamin D. *J Clin Endocrinol Metab* 2003;88:4623–32.
- [13] The implementation and development of lecturer practitioner roles in nursing Ashdale Press 205pp £12.95 1-870899-06-7 1870899067 [Formula: see text]. *Nurs Stand*, 1996, 10, 28.
- [14] Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6:2–8.
- [15] Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250–6.
- [16] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864–74.
- [17] Canadian Paediatric Society. Vitamin D supplementation: recommendations for Canadian mothers and infants. *Paediatr Child Health* 2007;12:583–98.
- [18] McCarthy D, Collins A, O'Brien M, et al. Vitamin D intake and status in Irish elderly women and adolescent girls. *Irish J Med Sci* 2006;175:14–20.
- [19] Ovesen L, Andersen R, Jakobsen J. Geographical differences in vitamin D status, with particular reference to European countries. *Proc Nutr Soc* 2003;62:813–21.
- [20] Danai PA, Sinha S, Moss M, et al. Seasonal variation in the epidemiology of sepsis. *Crit Care Med* 2007;35:410–5.
- [21] White AN, Ng V, Spain CV, et al. Let the sun shine in: effects of ultraviolet radiation on invasive pneumococcal disease risk in Philadelphia, Pennsylvania. *BMC Infect Dis* 2009;9:196.
- [22] Lesse AJ, Mylotte JM. Clinical and molecular epidemiology of nursing home-associated *Staphylococcus aureus* bacteremia. *Am J Infect Control* 2006;34:642–50.
- [23] Beadling C, Slifka MK. How do viral infections predispose patients to bacterial infections? *Curr Opin Infect Dis* 2004;17:185–91.
- [24] Warnock DW. Trends in the epidemiology of invasive fungal infections. *Nihon Ishinkin Gakkai Zasshi* 2007;48:1–2.
- [25] Ginde AA, Camargo CA Jr, Shapiro NI. Vitamin D insufficiency and sepsis severity in emergency department patients with suspected infection. *Acad Emerg Med* 2011;18:551–4.