Journal of Clinical and Nursing Research, 2026, Volume 10, Issue 4
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Investigation on the Vitamin D Nutritional Status of Neonates with Hyperbilirubinemia

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Abstract: *Objective*: This study aims to investigate the vitamin D nutritional status of neonates with hyperbilirubinemia and provide clinical evidence for guiding the scientific and rational supplementation of vitamin D in these neonates. *Methods*: This study selected neonates diagnosed with neonatal hyperbilirubinemia without other diagnoses admitted to the neonatal ward of our hospital from December 2021 to December 2023 as the research subjects. One milliliter of peripheral venous blood samples was collected from the neonates before treatment and sent to Hangzhou Qlife Precision Medical Testing Technology Co., Ltd. (Dian Diagnostics) for testing. The Sciex4500MD mass spectrometer was used as the detection instrument, and the Dicesis reagent was used as the detection reagent. The concentration of 25(OH)D in peripheral blood, namely the sum of 25(OH)D2 and 25(OH)D3 concentrations, was quantitatively detected using high-performance liquid chromatography-tandem mass spectrometry (LC-MS). According to the criteria for assessing children's vitamin D nutritional status proposed by the Institute of Medicine of the United States in 2011 and the Global Consensus on the Management of Nutritional Rickets in 2016, serum 25-(OH)D < 30 nmol/L (12 ng/mL) was defined as vitamin D deficiency; serum 25-(OH)D 30–50 nmol/L (12– < 20 ng/mL) was defined as vitamin D insufficiency; and serum 25-(OH)D ≥ 50 nmol/L (20 ng/ml) was defined as adequate. *Results*: A total of 76 neonates with hyperbilirubinemia who met the diagnostic criteria were included in this study, including 40 boys and 36 girls. The results showed that the distribution of 25-(OH)D concentrations did not conform to a normal distribution, with a median of 11.69 (8.46–14.04) ng/mL. Only 5 neonates had adequate vitamin D levels, 31 had insufficient levels, and 40 had deficient levels. The rates of adequate, insufficient, and deficient vitamin D were 6.6%, 40.8%, and 52.6%, respectively, with no statistically significant difference in vitamin D levels between boys and girls ($p > 0.05$). Additionally, there was no statistically significant difference in serum 25(OH)D levels among neonates with hyperbilirubinemia across different seasons (F value = 0.312, $p > 0.05$). *Conclusion*: Neonates with hyperbilirubinemia generally have low vitamin D levels. However, due to the small sample size and single-center nature of this study, further verification with more samples and studies are needed.

Keywords: Hyperbilirubinemia; Vitamin D; Nutritional status; Investigation and analysis

Online publication: Apr 30, 2026

1. Introduction

Neonatal hyperbilirubinemia, also known as neonatal jaundice, is the most common clinical issue during the neonatal period, typically manifesting as yellowing of the skin, mucous membranes, and sclera. More than two-thirds of full-term or near-term neonates develop visible jaundice shortly after birth [1]. Vitamin D is a fat-soluble vitamin that is essential for human metabolism. In addition to regulating bone metabolism, it is closely related to various diseases in the human body. Studies have shown that vitamin D deficiency is associated with hyperbilirubinemia [2]. To investigate the vitamin D nutritional status of neonates with hyperbilirubinemia, we conducted a cross-sectional survey of full-term neonates with hyperbilirubinemia admitted to Taizhou Women and Children's Hospital Affiliated to Nantong University from December 2021 to December 2023, providing clinical evidence for guiding the scientific and rational supplementation of vitamin D in neonates with hyperbilirubinemia.

2. Materials and methods

2.1. General information

Seventy-six neonates diagnosed with neonatal hyperbilirubinemia without any other diagnosis, admitted to the neonatal ward of our hospital from December 2021 to December 2023, were included in the study. Among them, there were 40 boys and 36 girls, with a gestational age ranging from 1 to 14 days and a birth gestational age of 37 to 41 + 6 weeks. This study was a retrospective study; no ethical review was required.

2.1.1. Inclusion criteria

(1) Presence of skin yellowing upon physical examination at admission, meeting the diagnostic criteria for neonatal hyperbilirubinemia;
(2) Birth weight ≥ 2500 g and < 4000 g;
(3) Gestational age ≥ 37 weeks and < 42 weeks.

2.1.2. Exclusion criteria

(1) Neonates with major diseases in other systems or severe congenital abnormalities;
(2) Severe asphyxia;
(3) Meconium aspiration syndrome;
(4) Neonatal infectious diseases such as neonatal sepsis;
(5) Endocrine diseases;
(6) Neonatal digestive disorders;
(7) Neonatal hemolytic diseases;
(8) Genetic metabolic diseases, etc.

2.2. Detection methods

Peripheral venous blood samples (1 mL) were collected from the neonates before treatment and sent to Hangzhou Chromai Precision Medical Testing Technology Co., Ltd. (Dian Diagnostics) for analysis. The detection instrument used was the Sciex4500MD mass spectrometer, and the detection reagent was the Disai Si reagent. The concentration of 25(OH)D in peripheral blood, i.e., the sum of the concentrations of 25(OH)D2 and 25(OH)D3, was quantitatively detected using high-performance liquid chromatography-tandem mass

spectrometry (LC-MS).

2.3. Evaluation criteria

According to the criteria for assessing children's vitamin D nutritional status proposed by the Institute of Medicine in 2011 and the Global Consensus on the Management of Nutritional Rickets in 2016, serum 25-(OH)D < 30 nmol/L (12 ng/mL) is defined as vitamin D deficiency; serum 25-(OH)D 30–50 nmol/L (12– < 20 ng/mL) is defined as vitamin D insufficiency; and serum 25-(OH)D ≥ 50 nmol/L (20 ng/mL) is defined as adequate [3,4] . Since neonatal serum bilirubin levels undergo dynamic changes, the diagnostic criteria for neonatal hyperbilirubinemia in this study are based on the hour-specific bilirubin nomogram at the 95th percentile recommended by the American Academy of Pediatrics (AAP) guidelines [5]. (See **Figure 1)**.

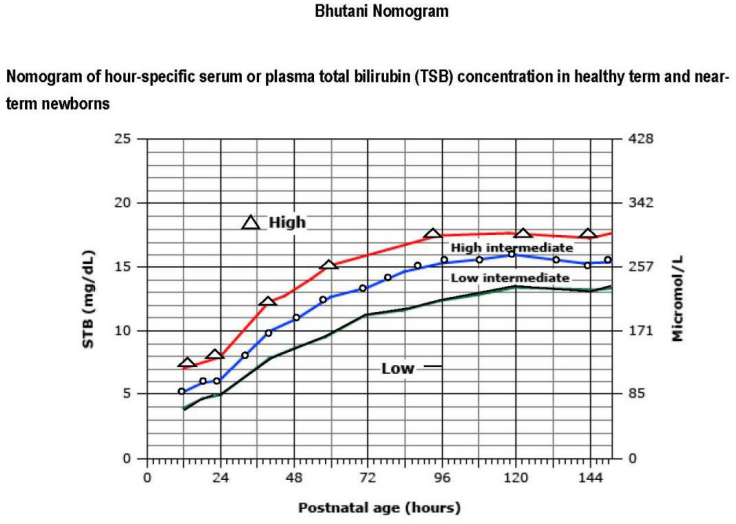

Figure 1. Postnatal age bilirubin risk assessment curve (Bhutani curve)

2.4. Statistical methods

All data analyses were conducted using SPSS 27.0 statistical software. For quantitative data, if it met the normality assumption, it was expressed as mean ± standard deviation ($\overline{x} \pm s$). Comparisons between two groups were made using the two independent samples t-test, while comparisons among three or more groups were performed using analysis of variance (ANOVA). If the data did not meet the normality assumption, it was expressed as median (M) with interquartile range (Q1–Q3). Comparisons between two groups were made using the Mann-Whitney U test, while comparisons among three or more groups were performed using the Kruskal-Wallis H test. Categorical data were expressed as n (%), and non-parametric tests were used for comparisons. A *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Distribution of serum 25(OH)D levels in neonates with hyperbilirubinemia

This study analyzed the vitamin D nutritional status at admission of 76 neonates diagnosed with hyperbilirubinemia in the neonatal ward of our hospital. The data exhibited a non-normal distribution, with a median (interquartile range) serum 25-(OH)D concentration of 11.69 (8.46–14.04) ng/mL (as shown

in **Figure 2**). Among the 76 neonates, only 5 had adequate serum 25-(OH)D concentrations, while the remaining had insufficient (31 cases) or deficient (40 cases) levels. Specifically, 6.6% of the neonates with hyperbilirubinemia had adequate vitamin D levels, 40.8% had insufficient levels, and 52.6% had deficient levels, as depicted in **Figure 3**.

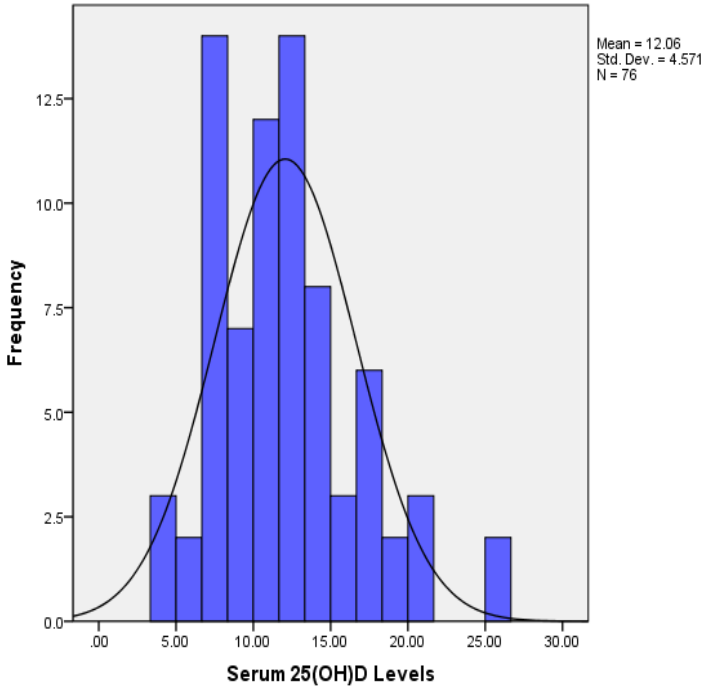

Figure 2. Histogram of serum 25-(OH)D levels in children with hyperbilirubinemia

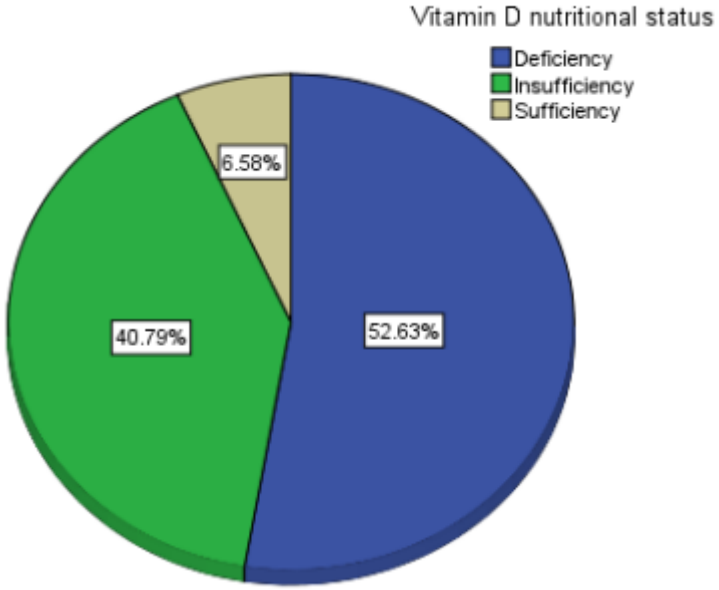

Figure 3. Pie chart of serum 25-(OH)D levels in children with hyperbilirubinemia

3.2. Distribution of serum 25-(OH)D levels in children with hyperbilirubinemia by gender

In this survey, the median serum 25-(OH)D levels in boys and girls were 11.18 (8.15–13.55) ng/mL and 12.25 (9.96–14.16) ng/mL, respectively, with boys having slightly lower levels than girls, although the difference was not statistically significant ($p < 0.05$), as shown in **Figure 4**. According to the criteria for determining vitamin D levels, serum 25-(OH)D was classified into different grades. Among those with serum 25-(OH)D levels within the normal range, there were 3 boys, accounting for 60.0%, and 2 girls, accounting for 40.0%, with boys having slightly higher levels than girls, but no statistical difference was observed between the two groups ($p > 0.05$). Meanwhile, among those with insufficient serum 25-(OH)D levels, there were 13 boys, accounting for 41.9%, and 18 girls, accounting for 58.1%. Among those with deficient serum 25-(OH)D levels, there were 24 boys, accounting for 60%, and 16 girls, accounting for 40.0%. This indicates that there were no significant differences between boys and girls in terms of insufficient and deficient serum 25-(OH)D levels, as shown in **Table 1**.

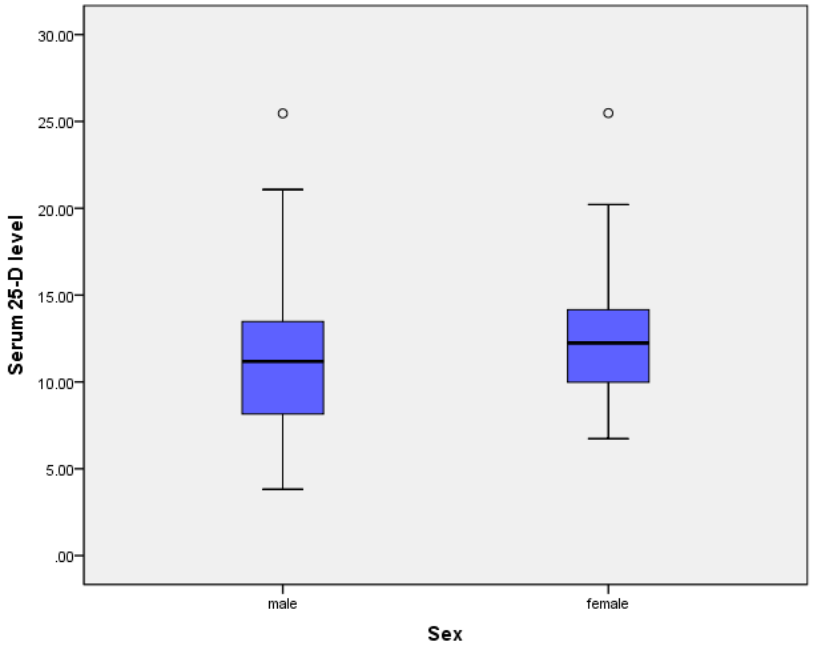

Figure 4. Box plot comparing serum 25(OH)D levels in children of different genders

Table 1. Comparison of serum 25(OH)D levels in children of different genders

Gender	n	Deficient (%)	Insufficient (%)	Sufficient (%)	25(OH)D (ng/mL) Median	*Z* value	*p* value
Male	40	24 (60.0)	13 (41.9)	3 (60.0)	11.18 (8.15–14.16)	-1.389	0.165
Female	36	16 (40.0)	18 (58.1)	2 (40.0)	12.25 (9.96–14.16)		

3.3. Comparison of serum 25(OH)D levels in hyperbilirubinemia infants born in different seasons

Among infants with hyperbilirubinemia born in different seasons, the comparison of serum 25(OH)D levels

showed no statistically significant difference (F-value = 0.312, $p > 0.05$), as shown in **Table 3** and **Figure 5**.

Table 3. Serum 25-(OH)D levels in infants born in different seasons

Variable	Number of cases(%)	Serum 25-(OH)D concentration(ng/mL)	*F* value	*p* value
Spring	21 (52.5)	12.00 ± 4.51	0.312	0.817
Summer	5 (13.2)	11.37 ± 5.13		
Autumn	19 (45.2)	11.41 ± 3.74		
Winter	31 (47.0)	12.62 ± 5.11		

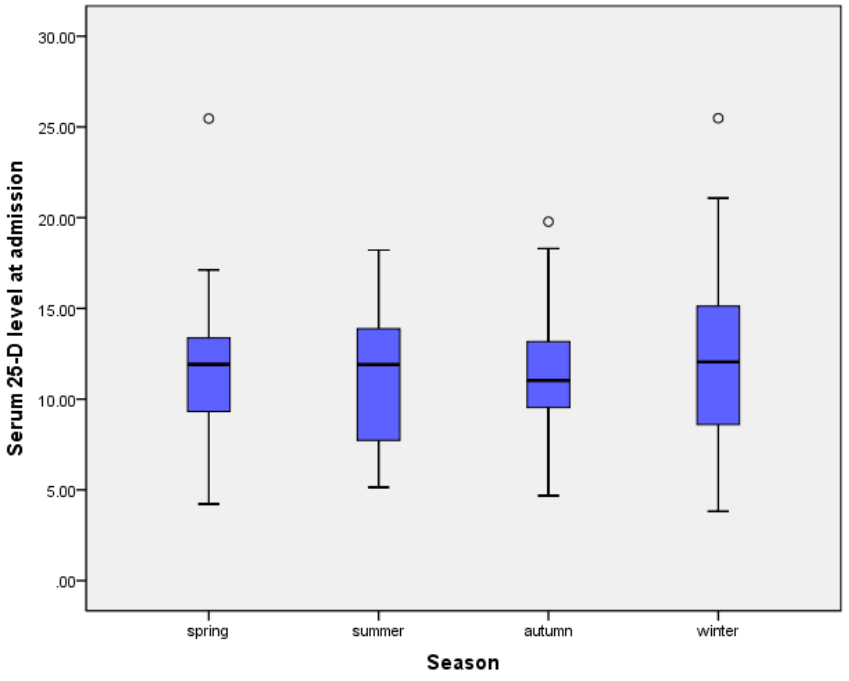

Figure 5. Box plot of serum 25(OH)D levels in children with different seasons

4. Discussion

Neonatal hyperbilirubinemia, also known as neonatal jaundice, is a common clinical issue among newborn infants. During the neonatal period, excessive bilirubin production, immature liver function, and the characteristics of the hepatoenteric circulation result in a greater production of bilirubin than its excretion, leading to the accumulation of bilirubin in the body and causing yellowing of the skin or other tissues, typically manifesting as yellowing of the skin, mucous membranes, and sclera [6]. Vitamin D is a group of steroid derivatives, primarily existing in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is mainly derived from plants, while vitamin D3 is produced through photochemical reactions in the skin of the human body under the influence of ultraviolet rays in sunlight. Both forms are converted into biologically active vitamin D after hydroxylation in the body, thereby exerting biological effects. Hydroxylated 25(OH)D is recognized as the most reasonable indicator reflecting human vitamin D status due to its stable properties [7]. Adequate vitamin D is crucial for children's health and has positive implications for early childhood development and disease prevention.

With further understanding of vitamin D, it has been discovered that its role in human health is not limited to bone or calcium-phosphorus metabolism. Instead, it participates in the proliferation, differentiation, and apoptosis of various cells throughout the body, influencing the normal functioning of the neuromuscular system and the regulation of immune function [8–10]. However, numerous epidemiological surveys have found that vitamin D insufficiency and deficiency are highly prevalent among newborns. A large-scale survey in northern United States revealed a high prevalence of vitamin D deficiency and insufficiency among newborns, at 31% and 49%, respectively [4]. In 2020, a hospital in Wuxi conducted a survey on 347 healthy full-term newborns aged ≤ 7 days [11]. The results showed that only 3 infants had adequate vitamin D levels, accounting for only 0.86%, while 28 infants had insufficient vitamin D levels, accounting for 8.07%, and 316 infants had vitamin D deficiency, accounting for 91.07%. This indicates that vitamin D insufficiency and deficiency remain a global public health issue. This study analyzed the vitamin D nutritional status of 76 hyperbilirubinemic children upon admission and found that only 5 children had adequate serum 25-(OH) D concentrations, while the rest had insufficient (31 cases) or deficient (40 cases) levels. This means that among hyperbilirubinemic children, only 6.6% had adequate vitamin D levels, while 40.8% had insufficient levels and 52.6% had deficient levels. This suggests that the vitamin D nutritional status is generally low among full-term hyperbilirubinemic children. The possible reasons for this include:

(1) Low vitamin D content in breast milk

Newborns can only obtain a small amount of vitamin D through breast milk daily, making breastfed newborns prone to vitamin D deficiency.

(2) Poor vitamin D status of the mother during pregnancy

Vitamin D can be transferred from the mother to the fetus through the placenta, and the concentration of 25-hydroxyvitamin D in the maternal plasma during pregnancy directly affects the vitamin D status of the fetus. If the mother has vitamin D deficiency during pregnancy, her plasma 25-hydroxyvitamin D concentration will be low, and the amount of vitamin D transferred to the fetus through the placenta will also be relatively insufficient, affecting the accumulation of vitamin D in the fetus during the fetal period.

(3) Immature liver function in newborns

The activation of vitamin D requires the liver, and the immature liver function in newborns makes it difficult to effectively activate vitamin D.

5. Conclusion

In conclusion, vitamin D deficiency and insufficiency are prevalent among full-term newborns with hyperbilirubinemia. It is essential to strengthen neonatal vitamin D monitoring and develop individualized supplementation plans.

Disclosure statement

The authors declare no conflict of interest.

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