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# Vitamin D Deficiency and Central Precocious Puberty in Girls During the COVID-19 Pandemic: Clinical Features, Diagnostic Thresholds, and Mechanisms

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# Abstract

**Background** The COVID-19 pandemic brought unprecedented changes in children's lifestyles, potentially exacerbating the increasing prevalence of precocious puberty. Vitamin D, beyond its classical role in calcium metabolism, influences gonadal function through the vitamin D receptor (VDR). This study aimed to investigate the relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and central precocious puberty (CPP) in girls aged 6–8 years during the pandemic, establish a diagnostic threshold for differentiating CPP from isolated premature thelarche (IPT), and explore the potential mechanisms of vitamin D in hypothalamic-pituitary-gonadal axis (HPGA) regulation.

**Methods** We conducted a single-center retrospective study of 175 girls (aged 6.0–8.0 years) with precocious puberty who attended the pediatric endocrinology clinic at Ruian People's Hospital between January 2020 and December 2022. Participants were classified into CPP (n=85) and IPT (n=90) groups based on gonadotropin-releasing hormone (GnRH) stimulation test results. Serum 25(OH)D, basal luteinizing hormone (LH), estradiol, pelvic ultrasound parameters, bone age (BA), and predicted adult height (PAH) were compared between groups. Pearson correlation, multivariable logistic regression, and receiver operating characteristic (ROC) curve analyses were performed.

Results Serum 25(OH)D levels were significantly lower in the CPP group than in the IPT group [18.60 (16.25, 22.00) vs. 25.25 (21.70, 29.63) ng/mL, P<0.001]. The prevalence of vitamin D deficiency (<20 ng/mL) was significantly higher in the CPP group (62.4% vs. 16.7%, P<0.001), and no patient in the CPP group achieved vitamin D sufficiency (≥30 ng/mL) compared with 23.3% in the IPT group. Pearson correlation analysis showed that 25(OH)D levels were negatively correlated with uterine volume (r=−0.382, P<0.001), follicle count >4 mm (r=−0.353, P<0.001), bone age (r=−0.322, P<0.001), and PAH impairment (r=−0.206, P=0.006). Multivariable logistic regression identified LH (OR=5.894, 95% CI: 1.585–21.919, P=0.008), uterine volume (OR=3.115, 95% CI: 1.872–5.183, P<0.001), and follicle count >4 mm (OR=1.796, 95% CI: 1.279–2.520, P=0.001) as independent risk factors for CPP, whereas 25(OH)D (OR=0.764, 95% CI: 0.662–0.882, P<0.001) was an independent protective factor. ROC analysis demonstrated that 25(OH)D had an area under the curve (AUC) of 0.827 (95% CI: 0.764–0.890, P<0.001), with an optimal cutoff of 22.25 ng/mL (sensitivity 81.2%, specificity 68.9%).

**Conclusions** During the COVID-19 pandemic, vitamin D deficiency was an independent risk factor for CPP in girls. A serum 25(OH)D level <20 ng/mL may serve as a clinically actionable early warning indicator, and the cutoff of 22.25 ng/mL provides moderate-to-good diagnostic value for distinguishing CPP from IPT. Routine monitoring of 25(OH)D is recommended in girls with precocious puberty, and vitamin D supplementation should be considered as an adjunctive strategy during GnRH analog therapy.


# Background

Precocious puberty in girls is defined as the appearance of secondary sexual characteristics before 7.5 years of age and represents an important pediatric endocrine disorder with an increasing global prevalence [1]. The clinical spectrum includes peripheral precocious puberty (PPP), central precocious

puberty (CPP), and benign variants, among which isolated premature thelarche (IPT) is the most common benign variant [2–4]. CPP results from premature activation of the hypothalamic-pituitary-gonadal axis (HPGA), characterized by pulsatile gonadotropin secretion, leading to progressive pubertal development and potentially compromising final adult height [5]. In contrast, IPT is a non-progressive, self-limited condition presenting with isolated breast development without other signs of pubertal activation [6, 7].

The differentiation between CPP and IPT carries significant clinical implications. CPP requires timely intervention with gonadotropin-releasing hormone analogs (GnRHa) to prevent psychosocial distress and adult height impairment, whereas IPT typically warrants observation only [8]. Misdiagnosis may lead to unnecessary treatment or missed therapeutic opportunities. The gold standard for CPP diagnosis remains the GnRH stimulation test, assessing peak LH response and the LH/follicle-stimulating hormone (FSH) peak ratio [9]. However, this test is expensive, time-consuming, and potentially distressing for children. Therefore, identifying reliable baseline parameters to minimize unnecessary stimulation tests has become a research priority [3, 10].

Epidemiological data indicate a concerning trend toward earlier pubertal onset. In China, studies have shown significant regional and temporal variation in precocious puberty prevalence, ranging from 0.38% (girls 0.67%) in Wenling, Zhejiang in 2000 [11] to 4.74% (girls 8.78%) in Zhongshan, Guangdong in 2019 [12], reflecting both an upward trend and the influence of diagnostic criteria and survey methods. The COVID-19 pandemic introduced unprecedented lifestyle changes that may have accelerated this trend. Lockdown-related increases in energy intake, sedentary behavior, screen time, and psychological stress have been associated with rising childhood obesity rates, a known risk factor for earlier puberty [13–15]. Notably, Sun et al. [16] found that during the COVID-19 pandemic, the proportion of overweight and obesity was significantly higher in the IPT group than in the CPP group among girls aged 6–8 years with precocious puberty (32.5% vs. 10%, P = 0.045), suggesting that anthropometric parameters are not suitable for distinguishing IPT from CPP.

Emerging evidence indicates that vitamin D, beyond its classical roles in calcium-phosphorus metabolism and bone development, influences gonadal function through the vitamin D receptor (VDR) [17, 18]. VDR is widely expressed in ovarian, uterine, and mammary tissues, and vitamin D deficiency may regulate estrogen synthesis by modulating CYP19 gene expression, thereby participating in the regulation of pubertal onset [19, 20]. Multiple studies have demonstrated significantly lower serum 25(OH)D levels in girls with CPP compared with healthy controls, suggesting that vitamin D deficiency may be a risk factor for CPP [21–23]. Zhao et al. [24] first identified a threshold effect of vitamin D on idiopathic CPP in girls, demonstrating a nonlinear relationship between serum 25(OH)D and CPP risk, with a turning point at 31.8 ng/mL above which increasing 25(OH)D levels were associated with reduced CPP risk.

However, systematic investigations of the relationship between vitamin D deficiency and CPP during the COVID-19 pandemic remain limited. This study aimed to: (1) investigate the characteristics of vitamin D

levels in girls with precocious puberty during the pandemic; (2) establish an optimal diagnostic threshold for differentiating CPP from IPT; and (3) explore the mechanistic basis of vitamin D in HPGA regulation. The novelty of this study lies in the first systematic evaluation of the diagnostic value of vitamin D for CPP in the specific context of the COVID-19 pandemic.

# Methods

### Study design and participants

This single-center retrospective study analyzed clinical data from girls with precocious puberty who attended the pediatric endocrinology clinic at Ruian People's Hospital, Zhejiang Province, China, between January 2020 and December 2022.

**Inclusion criteria:** (1) age 6.0–8.0 years; (2) Tanner breast stage ≥2; (3) complete clinical and laboratory data, including serum basal LH, FSH, estradiol, 25(OH)D, pelvic ultrasound, and left hand-wrist X-ray for bone age assessment; (4) completion of the GnRH stimulation test; (5) no vitamin D supplementation or other medications affecting bone metabolism within the preceding 3 months.

**Exclusion criteria:** (1) peripheral precocious puberty (e.g., exogenous estrogen exposure, ovarian or adrenal tumors, McCune-Albright syndrome); (2) chromosomal abnormalities (e.g., Turner syndrome); (3) chronic diseases affecting growth and development (e.g., chronic kidney disease, liver disease, thyroid dysfunction); (4) previous treatment with sex hormones or GnRH analogs; (5) incomplete data or loss to follow-up.

This study was approved by the Ethics Committee of Ruian People's Hospital (approval number: YJ2025111). As a retrospective study, informed consent was waived. All procedures followed the principles of the Declaration of Helsinki.

### Diagnostic criteria

**CPP diagnostic criteria [1]:** (1) onset of secondary sexual characteristics before 7.5 years; (2) accelerated linear growth (>6 cm/year); (3) bone age advanced >1 year beyond chronological age; (4) increased uterine and ovarian volume with multiple ovarian follicles ≥4 mm in diameter; (5) positive GnRH stimulation test: peak LH >5.0 IU/L and peak LH/FSH ratio >0.6.

**IPT diagnostic criteria [6]:** (1) isolated breast development before 7.5 years without other secondary sexual characteristics; (2) normal growth velocity without accelerated linear growth; (3) bone age consistent with or mildly advanced (<1 year) relative to chronological age; (4) normal or mildly increased uterine and ovarian volume without dominant follicles; (5) negative GnRH stimulation test.

### Data collection and measurements

The following data were extracted from the hospital electronic medical record system: (1) general characteristics: chronological age (CA), age at breast development onset (determined from parental recall and medical records), birth history, family history; (2) anthropometric parameters: height, weight, body mass index (BMI), with height and BMI expressed as Z-scores; (3) laboratory indicators: serum basal LH, FSH, estradiol, 25(OH)D; (4) imaging indicators: pelvic ultrasound measurement of uterine length, anteroposterior diameter, and transverse diameter, with uterine volume calculated as length × anteroposterior diameter × transverse diameter × 0.5233, and recording of ovarian follicles ≥4 mm; left hand-wrist X-ray for bone age assessment using the Greulich-Pyle atlas method [25] by two experienced pediatric endocrinologists independently, with the average taken; (5) calculation of mid-parental height (MPH) = [father's height + mother's height − 13]/2, predicted adult height (PAH) using the Bayley-Pinneau method, and height loss = MPH − PAH.

### Laboratory methods

**GnRH stimulation test:** After overnight fasting, triptorelin (Ferring AG, Switzerland) 2.5 μg/kg (maximum 100 μg) was administered subcutaneously, and blood samples were collected at 0, 30, 60, and 90 minutes. Serum LH and FSH concentrations were measured by immunochemiluminescent assay (ICMA, Beckman UniCel DxI 800).

Serum 25(OH)D assay: After overnight fasting, blood was collected, serum separated, and stored at −20°C until analysis. Serum 25(OH)D was measured by electrochemiluminescence immunoassay (ECLIA, Roche Cobas e601). According to the 2011 Endocrine Society guidelines [26]: 25(OH)D <20 ng/mL (50 nmol/L) was defined as deficiency, 20–30 ng/mL (50–75 nmol/L) as insufficiency, and ≥30 ng/mL (75 nmol/L) as sufficiency.

### Statistical analysis

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as median (25th percentile, 75th percentile) [M (P25, P75)] and compared using Mann-Whitney U test. Categorical variables were expressed as number (percentage) and compared using chi-square test or Fisher's exact test. Pearson correlation analysis was used to evaluate the relationship between 25(OH)D levels and various indicators. Multivariable logistic regression analysis (Enter method) was performed to identify independent predictors of CPP. ROC curves were constructed, and the area under the curve (AUC) with 95% confidence interval (95% CI) was calculated. The optimal cutoff value was determined using the Youden index (sensitivity + specificity − 1). A two-sided $P<0.05$ was considered statistically significant.

## Results

### Baseline characteristics

A total of 175 girls with precocious puberty were enrolled, including 90 (51.4%) in the IPT group and 85 (48.6%) in the CPP group. No significant differences were observed between groups in chronological age, target height, birth weight, or maternal age at menarche (all P>0.05). The age at breast development onset differed significantly between groups (P<0.001). No significant differences were found in height, weight, BMI, or their Z-scores (all P>0.05). Regarding reproductive hormones, basal LH and FSH levels were significantly lower in the IPT group than in the CPP group (both P<0.001). Ultrasound examination showed no significant differences in uterine length or ovarian volume between groups, but uterine volume and follicle count >4 mm were significantly smaller in the IPT group (both P<0.001). Bone age assessment revealed significantly lower bone age and degree of bone age advancement in the IPT group (both P<0.001), with significantly higher PAH in the IPT group (145.59 ± 8.47 cm vs. 140.61 ± 7.28 cm, P<0.001) and significantly less PAH impairment (P=0.002). Collectively, girls in the IPT group showed milder sexual development, less bone age advancement, and better adult height prognosis (Table 1).

**Vitamin D and bone metabolism indicators**

Serum 25(OH)D levels were significantly lower in the CPP group than in the IPT group [18.60 (16.25, 22.00) vs. 25.25 (21.70, 29.63) ng/mL, Z=−7.467, P<0.001]. Analysis of vitamin D nutritional status showed that the prevalence of vitamin D deficiency (<20 ng/mL) was significantly higher in the CPP group [62.4% (53/85) vs. 16.7% (15/90)], and the prevalence of vitamin D sufficiency (≥30 ng/mL) was significantly lower in the CPP group (0% vs. 23.3%). No patient in the CPP group achieved vitamin D sufficiency. Regarding bone metabolism indicators, ALP level was significantly higher in the CPP group (P<0.001), while PTH showed no significant difference between groups (P=0.340); no significant difference was observed in serum calcium, while serum phosphorus differed significantly (P=0.027) (Table 2).

Correlation between 25(OH)D and CPP clinical characteristics

Pearson correlation analysis showed that 25(OH)D levels were negatively correlated with uterine volume (r=−0.382, P<0.001), follicle count >4 mm (r=−0.353, P<0.001), bone age (r=−0.322, P<0.001), and PAH impairment (r=−0.206, P=0.006), and weakly negatively correlated with LH (r=−0.154, P=0.042). The negative correlation between 25(OH)D and PAH impairment (r=−0.206, P=0.006) suggests that more severe vitamin D deficiency is associated with greater height loss. This dose-response relationship implies that vitamin D deficiency may be involved in the pathophysiological process of CPP (Table 3).

**ROC curve analysis and optimal cutoff values**

Multivariable logistic regression analysis showed that LH (OR=5.894, 95% CI: 1.585–21.919, P=0.008), uterine volume (OR=3.115, 95% CI: 1.872–5.183, P<0.001), and follicle count >4 mm (OR=1.796, 95% CI: 1.279–2.520, P=0.001) were independent risk factors for CPP, whereas 25(OH)D (OR=0.764, 95% CI: 0.662–0.882, P<0.001) was an independent protective factor.

ROC curve analysis was performed to evaluate the diagnostic efficacy of each indicator for distinguishing CPP from IPT. The AUC for 25(OH)D was 0.827 (95% CI: 0.764–0.890, P<0.001), indicating moderate-to-good diagnostic accuracy (AUC>0.8). The maximum Youden index (0.501) was achieved at a 25(OH)D cutoff of 22.25 ng/mL, with sensitivity of 81.2% and specificity of 68.9%.

Additionally, the AUC for basal LH was 0.888 (95% CI: 0.835–0.940, P<0.001), for uterine volume 0.893 (95% CI: 0.848–0.938, P<0.001), and for follicle count >4 mm 0.833 (95% CI: 0.775–0.891, P<0.001). The optimal cutoff values were 0.272 IU/L for LH (sensitivity 88.2%, specificity 82.2%), 3.35 mL for uterine volume (sensitivity 84.7%, specificity 78.9%), and 4.5 for follicle count (sensitivity 68.2%, specificity 80.0%) (Figures 1 and 2).

# Discussion

### Vitamin D status in CPP during the COVID-19 pandemic

The central finding of this study is that serum 25(OH)D levels were significantly lower in the CPP group than in the IPT group, with a vitamin D deficiency rate of 62.4% in CPP patients and no patient achieving sufficiency. These results are consistent with previous studies. Lee et al. [21] reported that girls with CPP had a mean serum 25(OH)D concentration of 17.1 ± 4.5 ng/mL, significantly lower than 21.2 ± 5.0 ng/mL in healthy controls. Zhao et al. [24] found that the mean 25(OH)D level in the idiopathic CPP group was 19.36 ± 6.15 ng/mL, with 93.2% of patients below 30 ng/mL.

The home confinement policies during the COVID-19 pandemic led to substantial reductions in outdoor activities and sun exposure, which may have been important environmental contributors to the exceptionally high prevalence of vitamin D deficiency in our CPP cohort [27]. Stagi et al. [27] reported a significant increase in precocious puberty incidence during the pandemic in a multicenter international study, consistent with our observations. Furthermore, significantly elevated ALP levels in the CPP group, together with the trend toward higher PTH levels, suggest that vitamin D deficiency may accelerate bone turnover through secondary hyperparathyroidism, leading to bone age advancement [26].

### Potential mechanisms of vitamin D deficiency in promoting CPP

Several potential mechanisms may explain how vitamin D deficiency promotes CPP:

**(1) Regulation of estrogen synthesis:** VDR is highly expressed in ovarian granulosa cells. Vitamin D upregulates CYP19 gene expression, promoting aromatase activity and conversion of androgens to estrogens [19]. Vitamin D deficiency reduces aromatase activity and estrogen synthesis, which through negative feedback mechanisms may increase pulsatile GnRH secretion from the hypothalamus, stimulating pituitary LH and FSH secretion and potentially leading to premature HPGA activation [17,18].

**(2) Promotion of breast development:** VDR is expressed in mammary ductal epithelial and adipose cells. Vitamin D deficiency may relieve the inhibitory effect on mammary development, promoting ductal hyperplasia and acinar formation [20]. Johnson et al. [20] found that VDR knockout mice had greater

mammary gland weight, faster growth, and increased terminal end bud numbers. This mechanism may explain the diagnostic difficulty between IPT and CPP—mild vitamin D deficiency may present with breast development only, whereas severe deficiency may trigger complete HPGA activation.

(3) Effects on bone metabolism and bone age: Vitamin D deficiency disrupts calcium-phosphorus metabolism, causing secondary hyperparathyroidism and accelerated bone turnover, leading to bone age advancement. In this study, bone age was negatively correlated with 25(OH)D ($r=-0.322$, $P<0.001$), and PAH impairment was also negatively correlated with 25(OH)D ($r=-0.206$, $P=0.006$), supporting this mechanism. Notably, bone age advancement is one of the diagnostic criteria for CPP, and vitamin D deficiency may participate in the pathological process of CPP through this pathway.

**(4) Immunomodulation and inflammation:** Recent studies have identified immunomodulatory functions of vitamin D, and deficiency may promote a pro-inflammatory state affecting hypothalamic Kisspeptin/GPR54 system function, indirectly activating the HPGA axis [18]. The chronic stress state during the COVID-19 pandemic may have further exacerbated this effect.

Clinical diagnostic value of 25(OH)D

This study determined that the AUC for 25(OH)D in differentiating CPP from IPT was 0.827 (95% CI: 0.764–0.890), with an optimal cutoff of 22.25 ng/mL (sensitivity 81.2%, specificity 68.9%). This cutoff is higher than the Endocrine Society's definition of vitamin D deficiency (20 ng/mL), suggesting that for girls with precocious puberty, 25(OH)D levels around 22.25 ng/mL may indicate significantly increased CPP risk and warrant heightened clinical attention.

Although the standalone diagnostic efficacy of 25(OH)D (AUC=0.827) was inferior to uterine volume (AUC=0.893) and basal LH (AUC=0.888), all three indicators achieved moderate-to-good levels (AUC>0.8), and 25(OH)D testing offers distinct advantages: (1) simple, low-cost, and suitable for primary care settings; (2) non-invasive, well-tolerated by children, and repeatable; (3) simultaneous nutritional status assessment with guidance for intervention; (4) as a component of combined diagnostic models, it can significantly improve overall diagnostic accuracy.

Notably, the optimal cutoff for 25(OH)D (22.25 ng/mL) exceeds the traditional vitamin D deficiency threshold (20 ng/mL), suggesting that girls with precocious puberty may require stricter vitamin D level targets. When 25(OH)D ≤22.25 ng/mL, CPP risk increases significantly, and active follow-up or GnRH stimulation testing should be considered.

In this study, uterine volume (AUC=0.893) and basal LH (AUC=0.888) showed optimal diagnostic efficacy, both reaching good levels; 25(OH)D (AUC=0.827) and follicle count (AUC=0.833) also achieved moderate-to-good levels. Integrating hormonal, imaging, bone age, and nutritional status dimensions can comprehensively reflect HPGA activation status and help reduce unnecessary GnRH stimulation tests. This finding is consistent with Cao et al. [3], who concluded that multi-indicator combined diagnosis outperforms single indicators.

### Clinical recommendations and future directions

Based on these results, we propose the following clinical application recommendations:

1. Routine serum 25(OH)D testing should be performed in all girls with precocious puberty as part of initial evaluation.

2. Girls with 25(OH)D ≤22.25 ng/mL should be considered at high risk for CPP; even if other indicators are atypical, active follow-up or stimulation testing should be considered. Those with vitamin D deficiency (<20 ng/mL) have even higher CPP risk and require close monitoring.

3. For confirmed CPP patients, prophylactic vitamin D supplementation (400–800 IU/day) should be considered during GnRHa therapy to optimize bone metabolism and clinical outcomes.

4. In the post-COVID-19 era, enhanced guidance on outdoor physical activity for children should be provided to prevent the epidemic of vitamin D deficiency.

**Limitations:** (1) This was a single-center retrospective study with limited sample size, and selection bias may exist; (2) VDR gene polymorphisms were not assessed, precluding genetic exploration of the vitamin D-CPP relationship; (3) longitudinal follow-up data were lacking, preventing evaluation of the effect of vitamin D supplementation on CPP progression; (4) no healthy control group was included, precluding assessment of pandemic effects on vitamin D levels in the general pediatric population.

**Future research directions:** (1) multicenter prospective studies to validate these findings; (2) investigation of vitamin D supplementation in preventing progression from IPT to CPP; (3) epigenetic studies of vitamin D regulation of the HPGA axis; (4) exploration of vitamin D as an adjunctive therapeutic agent for CPP.

## Conclusions

During the COVID-19 pandemic, girls with CPP had significantly reduced serum 25(OH)D levels, with a vitamin D deficiency rate of 62.4% and no patient achieving sufficiency. 25(OH)D < 20 ng/mL was an independent risk factor for CPP and was negatively correlated with HPGA activation severity. The AUC for 25(OH)D in differentiating CPP from IPT was 0.827 (95% CI: 0.764–0.890), with an optimal cutoff of 22.25 ng/mL (sensitivity 81.2%, specificity 68.9%), demonstrating moderate-to-good diagnostic value. Combined assessment of basal LH, uterine volume, bone age, and 25(OH)D can provide reliable evidence for differentiating CPP from IPT in girls. We recommend routine vitamin D monitoring in girls with precocious puberty and prophylactic vitamin D supplementation during GnRHa therapy for CPP to optimize clinical management.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ruian People's Hospital (approval number: YJ2025111). As a retrospective study, informed consent was waived. All procedures followed the principles of the Declaration of Helsinki.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

ZL: study design, data analysis, manuscript writing. YC: data collection, manuscript revision. MP: data analysis, manuscript revision. All authors have read and approved the final manuscript.

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# Tables

**Table 1. Comparison of clinical characteristics between the two groups**

| Category | Variable | IPT group (n=90) | CPP group (n=85) | Test statistic | P-value |
|---|---|---|---|---|---|
| General characteristics | Chronological age (years) | 7.25±0.46 | 7.30±0.41 | t=-0.804 | 0.423 |
| | Target height (cm) | 158.98±5.88 | 158.66±5.53 | t=0.365 | 0.715 |
| | Birth weight (g) | 3273.11±559.67 | 3373.65±500.97 | t=-1.250 | 0.213 |
| | Maternal menarche age (years) | 12.62±1.01 | 12.91±1.09 | t=-1.811 | 0.072 |
| | Initial breast development age (years) | 6.81±0.37 | 6.34±0.41 | t=8.016 | <0.001 |
| Anthropometric measures | Height (cm) | 127.59±6.04 | 128.10±5.87 | t=-0.570 | 0.569 |
| | Height Z-score | 0.72±1.54 | 0.73±1.40 | t=-0.070 | 0.944 |
| | Weight (kg) | 26.74±4.25 | 26.05±3.76 | t=1.128 | 0.261 |
| | BMI (kg/m²) | 16.46 (14.18, 18.41) | 15.78 (14.43, 16.80) | Z=-1.563 | 0.118 |
| | BMI Z-score | 0.25 (-0.84, 1.14) | 0.02 (-0.79, 0.54) | Z=-1.678 | 0.093 |
| Reproductive hormones | Basal LH (IU/L) | 0.13 (0.06, 0.24) | 0.55 (0.35, 0.85) | Z=-8.852 | <0.001 |
| | Basal FSH (IU/L) | 2.91 (2.20, 3.96) | 3.60 (2.40, 4.69) | Z=-2.179 | 0.029 |
| | Estradiol (pmol/L) | 24.22±7.45 | 26.52±8.38 | t=-1.920 | 0.057 |
| Ultrasound parameters | Uterine length (cm) | 3.62±0.45 | 3.58±0.50 | t=0.502 | 0.616 |
| | Uterine volume (mL) | 2.40 (1.80, 3.30) | 4.90 (3.70, 6.65) | Z=-8.977 | <0.001 |
| | Ovarian volume (mL) | 2.25±0.77 | 2.38±0.89 | t=-1.041 | 0.299 |
| | Follicles >4 mm (n) | 3.00 (1.75, 4.00) | 6.00 (4.00, 8.00) | Z=-7.671 | <0.001 |
| Bone age and height prediction | Bone age (years) | 7.72±0.69 | 8.82±0.75 | t=-10.067 | <0.001 |
| | Bone age advancement | 0.50 (0.30, 0.60) | 1.50 (1.20, 1.70) | Z=-11.445 | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| | (years) | | | | |
| | Predicted adult height (cm) | 145.59±8.47 | 140.61±7.28 | t=4.161 | <0.001 |
| | Predicted adult height Z-score | -2.68±2.06 | -3.61±1.68 | t=3.271 | 0.001 |
| | PAH impairment (SD) | 2.76±1.91 | 3.62±1.64 | t=-3.193 | 0.002 |

**Table 2. Comparison of vitamin D and bone metabolism indices between the two groups**

| Category | Variable | IPT group (n=90) | CPP group (n=85) | Test statistic | P-value |
|---|---|---|---|---|---|
| Vitamin D status | 25(OH)D(ng/mL) | 25.25 (21.70, 29.63) | 18.60 (16.25, 22.00) | Z=-7.467 | <0.001 |
| Bone metabolism indices | PTH (pg/mL) | 44.95±13.97 | 46.90±13.09 | t=-0.956 | 0.340 |
| | Total ALP (U/L) | 166.58±33.83 | 193.35±35.71 | t=-5.093 | <0.001 |
| | Serum calcium (mmol/L) | 2.357±0.114 | 2.393±0.131 | t=-1.927 | 0.056 |
| | Serum phosphorus (mmol/L) | 1.423±0.184 | 1.490±0.211 | t=-2.230 | 0.027 |

**Table 3. Correlation analysis between serum 25(OH)D levels and clinical indicators of CPP**

| Variable | Pearson r | P-value |
|---|---|---|
| Bone age advancement | -0.461 | <0.001 |
| Uterine volume | -0.382 | <0.001 |
| Follicles >4 mm (n) | -0.353 | <0.001 |
| Bone age | -0.322 | <0.001 |
| PAH impairment (SD) | -0.206 | 0.006 |
| LH | -0.154 | 0.042 |

# Figures

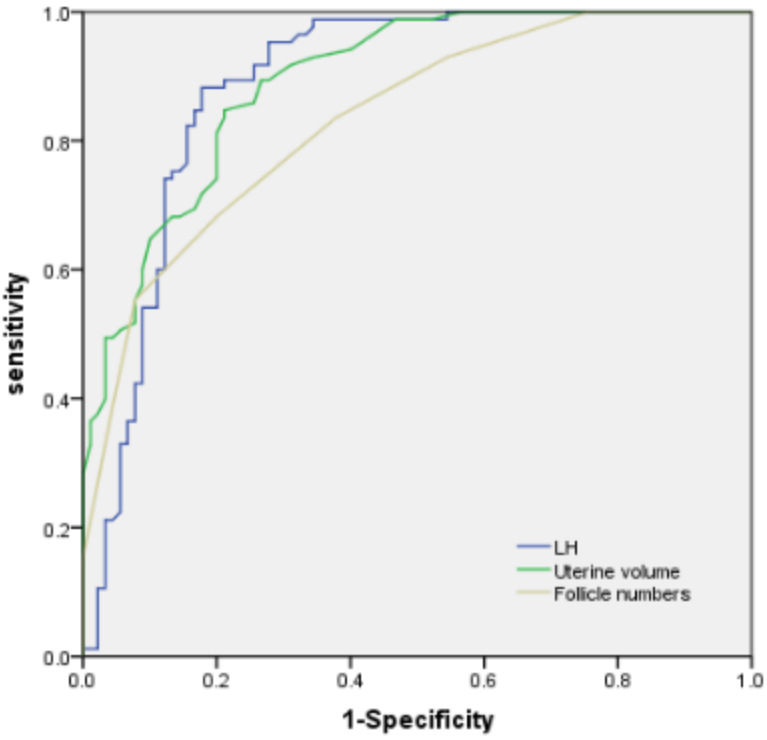



**Figure 1**

The diagnostic predictive values of LH ，follicle number and Uterine volume for CPP

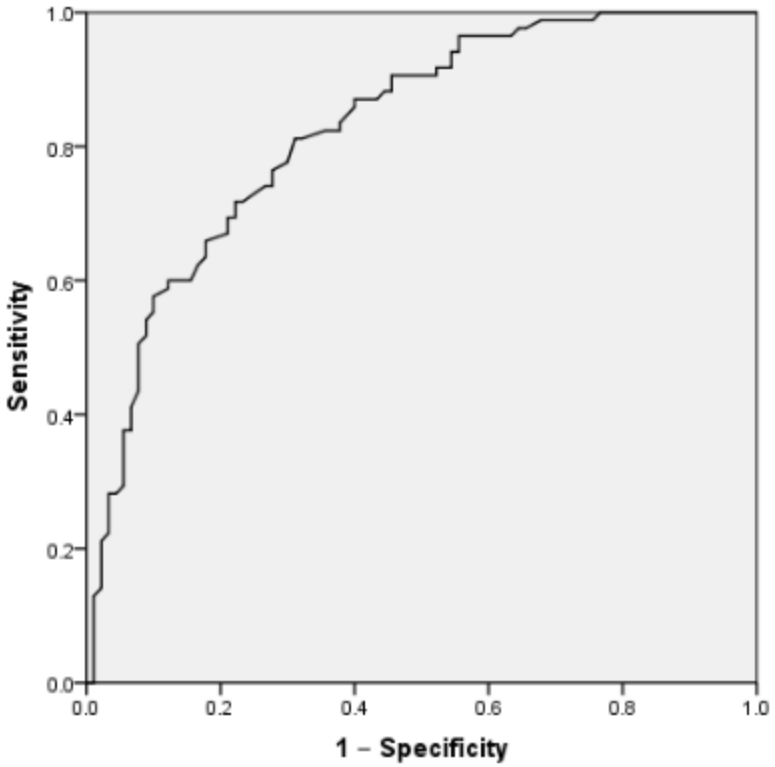



**Figure 2**

The diagnostic predictive values of 25(OH)D for CPP