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# Nutritional Status of Children with Pompe disease at the Vietnam National Children's Hospital

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**Abstract:** Pompe disease is a serious neuromuscular disorder caused by a genetic defect of lysosomal *acid alpha glucosidase (GAA)*. With dysphagia, skeletal muscle weakness and smooth muscle dysfunction, children with Pompe disease are more susceptible to malnutrition. This cross-sectional study therefore aimed to assess the prevalence of malnutrition and micronutrient deficiencies among 34 pediatric Pompe patients at the Vietnam National Children's Hospital. The results showed that 100% had at least medium risk of developing malnutrition according to the STRONGkids screening tool, of which 26.47% had high risk. The prevalence of underweight, stunting, wasting, overweight and obese were 11.76%, 11.76%, 14.71%, 5.88% and 2.94%, respectively. The prevalence of zinc deficiency and vitamin D insufficiency were 67.65% and 8.82%, respectively. The nutritional and zinc status were correlated with the duration of disease and the gross motor function.

**Keywords:** Pompe disease; IOPD: Infantile-onset Pompe disease; malnutrition; zinc deficiency; vitamin D deficiency

## 1. Introduction

Pompe disease, otherwise known as acid maltase deficiency or glycogen storage disease type II, is caused by mutation of the *acid alpha glucosidase (GAA)* gene located in the 17q25 chromosome. *GAA* catalyzes the hydrolysis of glycogen alpha-1.4 and 1.6-glucosidic in the lysosomal acidic milieu. Its deficiency therefore leads to lysosomal accumulation of glycogen, especially in the muscle fibers and neurons. The clinical spectrum ranges from late-onset of progressive limb girdle weakness and respiratory insufficiency to infantile-onset of generalized muscle weakness and hypertrophic cardiomyopathy [1].

There is a double burden of malnutrition amongst patients with neuromuscular diseases such as Pompe disease. On one hand, the dietary intake is reduced due to macroglossia, hypotonia, muscle weakness, respiratory insufficiency, and dental erosion, exposing patients to high risk of undernutrition. On the other hand, if that same patient however, has access to nutritional intervention to alleviate dysphagia and respiratory support to reduce breathing work, the intake would be unaffected, if not increased due to the tendency of choosing ONS and liquified, high simple carbohydrate enteral formula. In addition, physical inactivity reduces energy consumption. Its secondary changes in body composition (reduced muscle mass and increased fat mass) further derange the energy balance by decreasing the basal metabolic rate. The patient now has a high risk of overnutrition instead.

The first Vietnamese Pompe patient was diagnosed at the Vietnam National Children's Hospital in 2014. Before that, there were 229 unexplained cases of hypertrophic cardiomyopathy and proximal muscle weakness. In the 7-year period from 2014 to 2021, 52 patients were diagnosed with Infantile-onset Pompe disease (IOPD), of which, 26 survived. The prevalence of Pompe

disease in Vietnam might therefore be higher than the estimated prevalence of Pompe disease in the Southern Chinese and aborigines in Taiwan of 1:50000 [2].

With this increasing number of definitive cases and complicated nutritional risk, a systematic and frequent assessment of Pompe patient's nutritional status is needed to be implemented. To date, however, there have been no studies on the nutritional status of this vulnerable population. This study therefore aimed to assess the prevalence of malnutrition and micronutrient deficiencies in children with Pompe disease at the Vietnam National Children's Hospital.

## 2. Materials and Methods

### *2.1. Study design and setting*

This single-center cross-sectional study was conducted at the Endocrinology – Metabolism – Genetics and Molecular Therapy Center of the Vietnam National Children's Hospital from November 2021 to August 2022.

### *2.2. Study participants and sampling*

With the total population sampling technique, all consented children under 18 years old with definitive diagnosis of Pompe disease based on the American College of Medical Genetics (ACMG) 2006 criteria [3], including the clinical criterion and reduced *GAA* activity in dried blood spots and/or pathogenic variants in the *GAA* gene were included in the study.

### *2.3. Variables and Data sources/measurement*

All eligible participants were then taken for general information interview, 24-hour recall, malnutrition risk screening, anthropometric measurement and developmental screening.

All food, beverage, dietary supplement and drug that the patient consumes on a typical recent day were recorded based on the recall of the primary caregivers. Estimation of portion size and thus nutritional value of these intakes were made using the food quantification picture book [4] and the book Vietnamese common food's nutritional values [5] from the Vietnam National Institute of Nutrition.

Malnutrition risk was screened using the STRONGkids tool based on 4 main criteria, including the underlying illness with risk for malnutrition, the subjective sign of poor nutritional status, the related symptoms (excessive diarrhea, vomiting, reduced food intake during the last 1-3 days, pre-existing nutritional intervention), and failure to thrive during the last few week-months. The risk was then stratified as high, medium, and low [6].

Anthropometric measurements included weight, stature, body mass index (BMI), triceps (TSF)& subscapular skinfold thickness (SSF), and tibial length (TL). The WHO 2006 growth standard [7] was used as reference to determine nutritional status. The percentage of body fat (PBF) of children over 5 years old was calculated based on the equation developed by Slaughter et al. in 1988 [8] using the TSF and SSF thickness. It was then classified as underfat, normal, overfat and obese based on the reference from McCarthy et al. study in 2012 [9]. The tibial length was measured in supine position from the upper medial edge of the medial condyle and the medial malleolus (Figure 1).

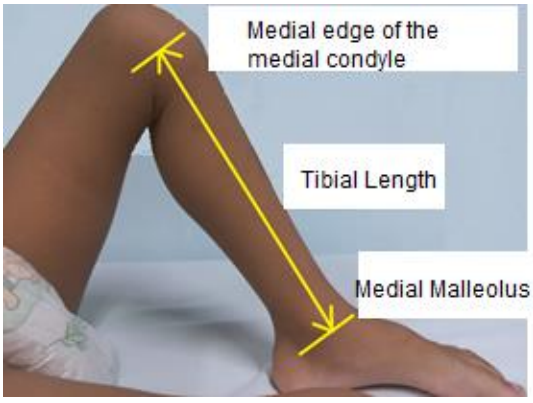


**Figure 1.** Measurement of Tibial Length.

The gross motor function was assessed using the Denver II Developmental Screening Test (DDST-II). The furthest milestone achieved by the patient was picked to determine the gross motor age at the 50th percentile. The difference between the gross motor age and real age would be positively correlated with the gross motor development.

The micronutrients of interest were zinc and vitamin D. Patients were taken blood in the morning before meals. The serum zinc level cutoff for zinc deficiency was 65 µg/dL (9.94 µmol/L) for children under 10 years old. For children over 10 years old, the cutoff differs from male and female subjects and is 70 µg/dL (10.7 µmol/L) and 74 µg/dL (11.31 µmol/L), respectively. Patients were considered insufficient and deficient of vitamin D if the serum 25-hydroxycholecalciferol (25(OH)D) level was under 50 and 75 nmol/L, respectively.

### *2.4. Bias*

The study is prone to measurement errors, interviewer and recall biases. Strategies were made to minimize biases, including standardization of measurement and interview procedures, calibration of measuring instruments, and uniform training of researchers in the data collection process.

### *2.5. Statistical methods*

The Microsoft Excel Spreadsheet Software was used for data entry and 24 hour recall analysis. Anthropometrics were analyzed by the WHO 2006 Anthro Software. Data cleaning and analysis were proceeded using the Stata 15 Software.

## 3. Results

### *3.1. Participants*

34 IOPD patients at the Endocrinology – Metabolism – Genetics and Molecular Therapy Center of the Vietnam National Children's Hospital met the selection criteria and were included in this study. The mean age at the first enzyme replacement therapy (ERT) was 8.08 ± 14.49 months, the mean current age was 32.76 ± 23.1 months, and the mean disease duration therefore was 28.46 ± 20.7 months. 55.88% were male. 97.06% had hypertrophic cardiomyopathy and therefore were classified as a classic form of IOPD. At diagnosis, all participants presented with generalized hypotonia and muscle weakness. The biochemical studies showed elevated creatine kinase and liver transaminases in 100% patients. The mean net GAA activity was 0.27 ± 0.21 µM/h (normal: > 1.2 µM/h) and the mean acarbose inhibition was 93.66 ± 2.2 % (normal: < 80%). The diagnosis was then confirmed by two mutated alleles of the *GAA* gene. Based on the genotype, 100% were predicted to have positive cross-reactive immunologic material (CRIM) status.

### *3.2. Malnutrition and related factors in children with Pompe disease*

According to the STRONGkids tool, 100% had at least medium risk of developing malnutrition, of which 26,47% had high risk. The prevalence of stunting, wasting and overweight in children with Pompe disease under 5 years old were 11.76%, 17.65% and 5.88%, respectively (Figure 2).

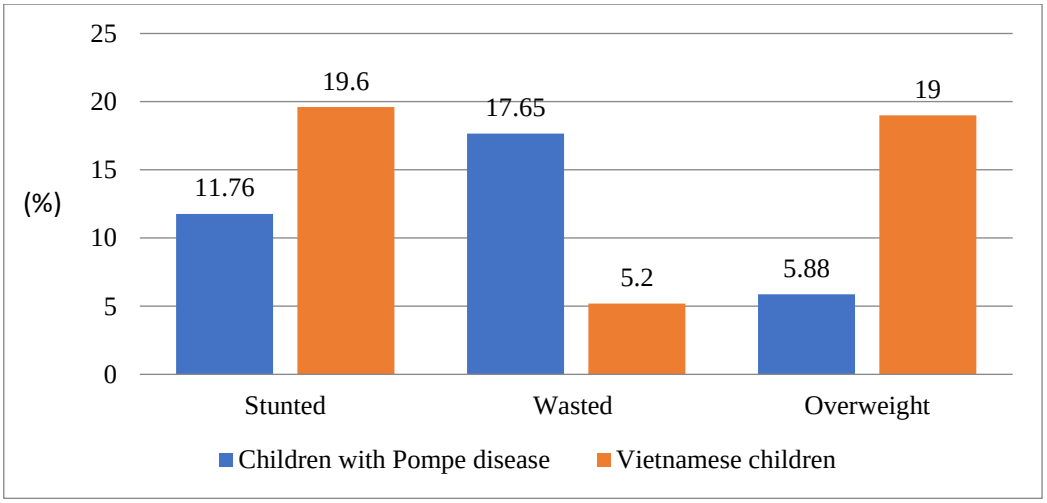


**Figure 2.** Prevalence of malnutrition in children under 5 years old.

The body fat study was conducted in the subgroup of 5 years and older. This study showed that one patient was qualified as obese with the percentage of body fat of 22.73% (above the 95$^{th}$ percentile) despite having normal BMI-for-age z-score of 1.25 SD (Table 1). The prevalence of overweight and obesity were therefore 5.88% and 2.94%, respectively.

**Table 1.** Percentage of Body Fat in IOPD patients aged over 5 years old.

| Patient age, sexe | BMI/age z-score (SD) | TSF (mm) | SSF (mm) | PBF (%) | Interpretation |
|---|---|---|---|---|---|
| 6 years old female | -1.27 | 6 | 5 | 10.56 | Underfat |
| 5 years old male | 0.21 | 15 | 9 | 22.73 | Obese |
| 6 years old female | 1.25 | 16 | 10 | 23.29 | Overfat |
| 5 years old male | -1.15 | 7 | 4 | 10.64 | Underfat |

The BMI/age z-score was positively correlated with the disease duration (p= 0.002) and negatively correlated with the gross motor function (p= 0.0367) ) (Table 2).

**Table 2.** Associating factors to nutrition status.

| Associating factors | Height-for-age z-score (SD) | | BMI-for-age z-score (SD) | |
|---|---|---|---|---|
| | r | p | r | p |
| Disease duration (months) | -0.2915 | 0.1669 | 0.5980 | **0.002** |
| Presence of hypertrophic cardiomyopathy | -0.3 | 0.0813 | 0.19 | 0.2839 |
| Difference of DDST-II and real age (months) | 0.26 | 0.1442 | -0.36 | **0.0367** |

The tibial length was highly correlated with the stature of our participants. Amongst the analyzed models, the multiple regression model of stature, tibial length, and the presence of musculoskeletal abnormality had the highest adjusted $R^2$ of 99.64% (Table 3).

**Table 3.** Multiple linear regression model of stature and associating factors.

| Model | Linear equation (cm) | p | Adjusted $R^2$ (%) |
|---|---|---|---|
| 1. TL, S, M | Ht= 3.29*TL + 0.07*S – 0.71*M + 34.57 | 0.0000 | 99.63 |
| 2. TL, S | Ht= 3.28*TL – 0.01*S + 34.6 | 0.0000 | 99.6 |
| 3. TL, M | Ht= 3.29*TL -0.7*M + 34.65 | 0.0000 | 99.64 |
| 4. TL | Ht= 3.28*TL + 34.63 | 0.0000 | 99.61 |

Ht: Stature; TL: Tibial Length; S: Sexe (1= male, 2= female); M: Presence of Musculoskeletal Abnormality (0= absent, 1= present).

### *3.3. Micronutrient deficiencies in children with Pompe disease*

In the micronutrient studies shown in table 4, the prevalence of zinc deficiency and vitamin D insufficiency were 67.65% and 8.82%, respectively. The mean dietary zinc and protein intake were 6.89 ± 4.02 mg/day and 3.72 ± 2.13 g/kg/day. Therefore, 14.71% and 17.65% of our study subjects had consumed less zinc and protein than recommended.

**Table 4.** Micronutrient status of children with Pompe disease.

| Micronutrient | Mean ± SD | Prevalence of deficiency (%) |
|---|---|---|
| Serum zinc | 10.41 ± 3.72 nmol/L | 67.65 |
| Dietary zinc intake[a] | 6.89 ± 4.02 mg/day | 14.71 |
| Dietary protein intake | 3.72 ± 2.13 g/kg/day | 17.65 |
| Vitamin D | 93.11 ± 42.85 nmol/L | 8.82[b] |

[a] the recommended dietary allowance of zinc and protein were provided in the nutrition recommendations of the Vietnamese population in 2016[10], assuming that 30% of consumed zinc were absorbed.
[b] the prevalence of vitamin D insufficiency (25(OH)D below 50 nmol/L).

In the subgroup of children aged from 6 to 59 months old, the prevalence of zinc deficiency and vitamin D insufficiency were 65.38% and 11.54%, respectively (Figure 3).

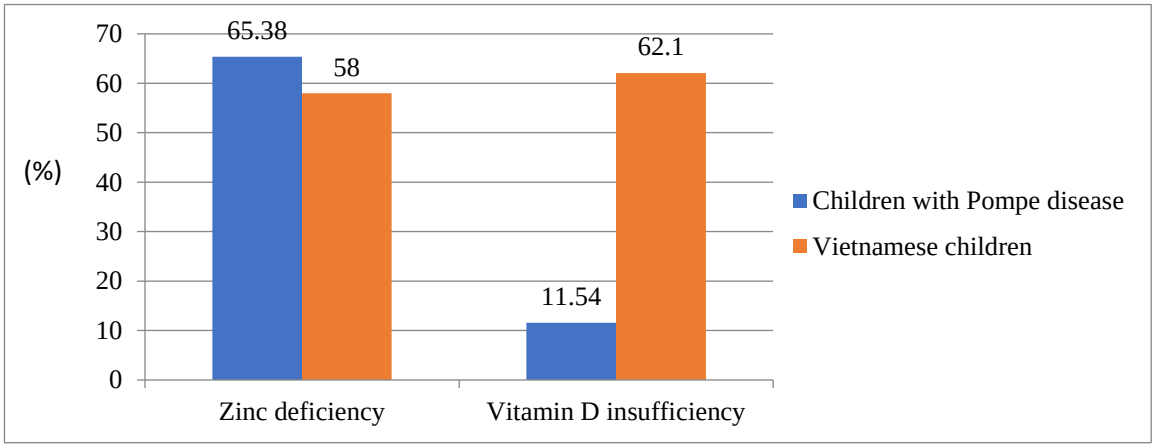


**Figure 3.** Micronutrient status of children 6-59 months old.

100% had been supplemented with vitamin D in the past, 64.71% were currently supplemented with vitamin D and 30.56% were supplemented at least at the recommended dose for age [10] (Figure 4).

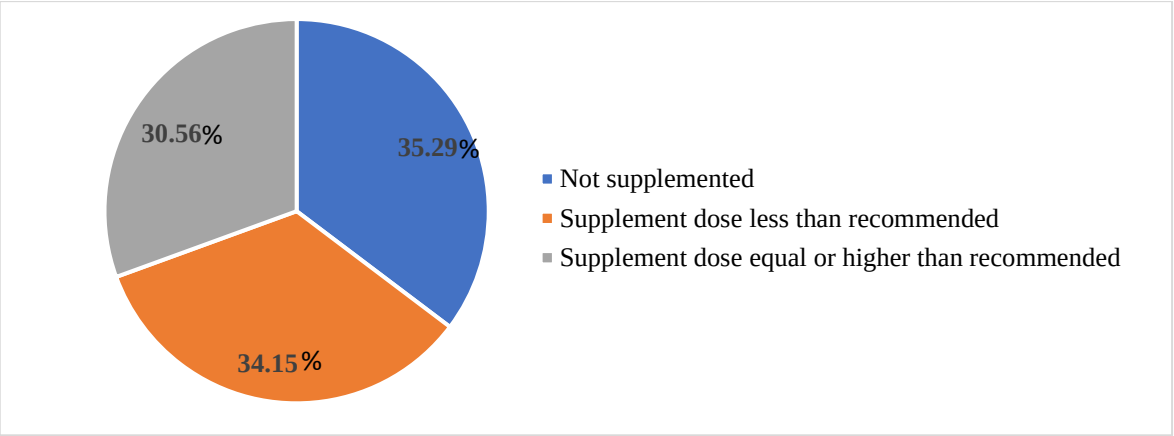


**Figure 4.** Vitamin D supplementation.

The serum zinc level was negatively correlated with the disease duration (p= 0.001) and positively correlated with the gross motor function (p= 0.0191) (Table 5).

**Table 5.** Associating factors with zinc status.

| Associating factors | r | p |
|---|---|---|
| Disease duration (months) | **-0.55** | **0.001** |
| Presence of hypertrophic cardiomyopathy | -0.31 | 0.0766 |
| Difference of DDST-II and real age (months) | **0.43** | **0.0109** |
| Dietary zinc intake (mg/day) | **-0.40** | **0.0191** |
| Dietary protein intake (g/kg/day) | -0.33 | 0.0569 |

## 4. Discussion

The 2018-2020 National Nutrition Survey revealed a higher stunting prevalence (19.6% vs 11.56%) and a lower wasting prevalence (5.2% vs 17.65%) in comparison with our IOPD patients [11] (Figure 2). In the general pediatric population, maternal nutritional status plays an important role in the child's growth, development and health. Children of wasted mothers, in fact, have a higher likelihood of being stunted [12]. Meanwhile the main mechanism of malnutrition in children with Pompe disease is reduced oral intake due to dysphagia. The birth weight and height therefore are almost certainly spared. The malnutrition process only begins after birth and it takes time to develop stunting. The wasting prevalence, on the other hand, indicates the acute nutritional status and is more affected than in the general population without dysphagia.

The sole use of weight-for-height and BMI-for-age z-score misdiagnosed one obese patient as normal. The study of body composition in this patient showed a high percentage of body fat (22.73%) in a seemingly normal BMI-for-age z-score of 0.21 SD (Table 1). In this study, the reference for percentage of body fat was based on the Caucasian healthy pediatric population whose prevalence of overweight and obesity were much higher than the Asian children [13]. Consequently, the actual prevalence of overweight and obesity amongst our participants might be underestimated and reference of percentage body fat amongst at least healthy Vietnamese children needs to be developed for better extrapolation. For the time being, study of body composition, especially the fat mass, has to be implemented in the nutritional assessment of children with Pompe disease.

The study also showed that the BMI-for-age is positively correlated with the disease duration (r= 0.5980, p= 0.002, $r^2$= 32.84%) (Table 2). As the disease progresses, children with Pompe disease are more likely to develop overweight and obesity. The possible explanation is the reduced gross motor function in long-standing Pompe disease. In fact in this study, the negative correlation between the gross motor function and the disease duration was strong (r= -0.7506, p= 0.0000, $r^2$= 54.36%). Patients with longer disease duration have accumulated more skeletal muscle injuries which in turn lead to secondary musculoskeletal abnormalities such as abnormal gait, scoliosis, hyperlordosis, and contracture. This vicious cycle aggravates the motor function as the disease progresses. Another possible mechanism of development of overweight in later stages of disease consist of nutritional support overuse, dental erosion leading to higher usage of simple carbohydrate.

During data collection and anthropometric measurement specifically, it was impossible to measure stature using the standard UNICEF procedure in 50% of the cases due to musculoskeletal abnormalities (such as hyperlordosis and contracture) and inability to stand still alone in children whose height were superior than the upper limit of the measuring instrument. In these subjects, the supine length was measured using the division technique, in which the body was divided as multiple aligned parts. This technique is time consuming and requires extensive training. Therefore measures had to be taken in order to facilitate the nutritional assessment in children with Pompe disease. Previous studies in children with cerebral palsy showed excellent correlation between tibial length and stature. Estimation equations have been developed to quickly assess the patient stature and have been proved to have high validity [14-16]. This study results also agreed with previous findings. The estimation equation of model 3 (Table 3) was found to have nearly absolute adjusted $R^2$ of 99.64%, meaning 99.64% of changes in stature can be explained by this equation.

The micronutrient study revealed a much lower prevalence of vitamin D insufficiency in children with Pompe disease in compared with the healthy population (62.1%) (Figure 3). This finding contradicted previous studies in similar populations such as children with Duchenne muscular dystrophy and spinal muscular atrophy with very high prevalence of vitamin D deficiency[17-19]. The participants in our study were found to have a high rate of vitamin D supplementation (Figure 4). In fact, 100% had used some form of vitamin D supplementation in the past, 64.71% were currently on vitamin D supplementation at least at the recommended dose, and 30.56% at dose higher than recommended [10]. As a result, the prevalence of vitamin D insufficiency was remarkably improved.

On the other hand, the prevalence of zinc deficiency was found to be superior to the healthy population (65.38% vs 58%) (Figure 3). The most common cause of zinc deficiency in children under 5 years old is inadequate intake because the body doesn't have storage for zinc. The possible diet errors that lead to insufficient zinc intake includes exclusive breastfeeding beyond 6 months of life, a high phytate, fiber or calcium diet and a lack of protein from animal source. The zinc dietary intake therefore was being used as an indicator for population zinc status [20]. In this study, however, we failed to find a positive correlation between the dietary zinc and protein intake with the serum zinc level. It suggested that there was a more important mechanism of zinc deficiency in Pompe disease. As a matter of fact, the results showed a negative correlation between the disease duration and the zinc concentration; a positive correlation between the gross motor function and the zinc concentration (Table 5). Zinc is a crucial factor in protein synthesis. It takes part in the nucleus, and chromosome structure; the stabilization of nucleic acid molecules and ribosomes. The zinc metalloenzymes such as RNA polymerase, reverse transcriptase and transcription factor IIIA are indispensable in transcription and thus protein synthesis. The zinc fingers are also present in eukaryotic regulation factors for protein synthesis [21]. In high turn-over protein states such as Pompe disease, the serum zinc is mobilized for muscle reconstruction and therefore decreases significantly.

## 5. Conclusions

In summary, the risk of malnutrition and the actual prevalence of wasting are high amongst children with Pompe disease. For that reason, in order to improve the nutritional status of this vulnerable population, a systematic and frequent nutritional assessment is needed to be implemented. The traditional use of weight-for-height and BMI might underestimate the prevalence of overweight and obesity. Therefore, body composition study, especially the fat mass, is prerequisite in the nutritional assessment of children with Pompe disease.

The study also found a very strong correlation between the stature and the tibial length in children with Pompe disease. The stature can therefore be estimated based on the tibial length using this equation of Ht=3.29*TL+34.65 in patients without musculoskeletal abnormalities and Ht=3.29*TL+33.95 in patients with musculoskeletal abnormalities. This estimation would facilitate the nutritional assessment process in subjects with delayed motor function and musculoskeletal abnormalities such as Pompe pediatric patients.

In addition, the micronutrient study showed a high prevalence of zinc deficiency amongst children with Pompe disease. Since Pompe patients might have higher zinc demand due to higher protein turnover, serum zinc concentration might be lower than normal and is needed to be checked systematically for early repletion.

Of the possible associating factors, longer disease duration and delayed gross motor function stand out as predictors for the risk of overweight and low serum zinc concentration in children with Pompe disease. This suggests a more frequent nutritional assessment as the disease progresses.

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**Ethical Statement:** This study has been approved by the Vietnam National Children's Hospital IRB – VN01037/Irb0001 1976/FWA00028418, 18/879 Lathanh, Dongda, Hanoi, Vietnam.

**Conflicts of Interest:** The authors declare no conflict of interest.

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