Original Article

# Effects of the salbutamol bronchodilator response on measurements of fractional exhaled nitric oxide in children with asthma: a prospective, observational study

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**Background:** Salbutamol bronchodilator response (BDR) test and fractional exhaled nitric oxide (FeNO) have been recommended for the diagnosis of asthma in children, but FeNO levels is affected by many factors. Nonetheless, data of the effect on the FeNO values throughout the bronchodilator test and the differences in FeNO values between BDR positive (BDR+) and negative (BDR–) children with asthma are still limited. We aimed to evaluate the effect of the BDR test on FeNO and the differences in FeNO levels between BDR+ and BDR– children with asthma.

**Methods:** This was a prospective, observational study performed over a 5-month period (December 2018 to April 2019) and involved 57 children with asthma. The FeNO levels at pre-spirometry, post-spirometry, and post-salbutamol BDR testing were estimated. Finally, the children were divided into two groups i.e., BDR+ and BDR–, and differences in the FeNO levels were compared between the two groups.

**Results:** The spirometry results were normal in 2 patients (3.5%). There were 53 (93%) patients with obstructive lung disease, including 40 (70.2%), 11 (19.3%), and 2 (3.5%) patients with mild, moderate, and severe obstruction, respectively. The remaining two patients had mixed lesions (3.5%), none of which were restrictive. The baseline median FeNO levels were significantly higher in the BDR+ group than in the BDR– group [33.00 (23.78, 46.73) *vs.* 23.00 (9.80, 37.80), (P=0.048)]. Following spirometry, there was a statistically significant decrease in median FeNO levels from baseline to post-spirometry (P=0.002). However, there was no significant difference between the median FeNO levels at baseline and following the BDR test (P=0.976). The impact of spirometry on FeNO was not statistically different in BDR+ versus BDR– children (Z=–0.186, P=0.853); however, the impact of bronchodilators on FeNO exhibited a statistically significant difference between the two groups (Z=3.160, P=0.002).

**Conclusions:** This study revealed dynamic changes in the FeNO levels during the BDR test. The use of a bronchodilator results in a statistically significant difference in FeNO levels between BDR+ and BDR– children with asthma. Moreover, spirometry leads to a marked decrease in the FeNO levels. Our results will allow clinicians to better interpret FeNO, BDR and pulmonary function outcomes and better develop clinical protocols.

**Keywords:** Exhaled nitric oxide (ENO); children; asthma; spirometry; bronchodilator response (BDR)

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## Introduction

Asthma is one of the most common chronic respiratory diseases in children. It is characterized by inflammation and hyper-reactivity of the airway. With the development of airway inflammation, the expression of fractional exhaled nitric oxide (FeNO) is increased, particularly in the epithelial cells of the respiratory tract (1). Increased FeNO, serum immunoglobulin E (IgE), and blood eosinophils have been linked to severe type 2 asthma (2). Rachel *et al.* found a significant association between higher FeNO values and asthma (3). FeNO measurement is a non-invasive, simple, and reproducible indicator of airway inflammation. Exhaled nitric oxide (ENO) is also a useful biomarker for the diagnosis of asthma (4) and is used to monitor the effectiveness of anti-inflammatory therapy for asthma (5). Moreover, it is also used to guide and modulate asthma treatment (6).

Numerous non-disease factors including age, height, and type of food consumed can affect the FeNO levels (7). In children with asthma, FeNO levels can decrease with spirometric maneuvers (8) and increase with the inhalation of β-2 agonists (9). Meanwhile, other studies have demonstrated that prior spirometry does not affect the FeNO values (10-12). For these patients, the bronchodilator response (BDR) can evaluate the variability of airflow in airways. The spirometric maneuvers and inhalation of $\beta_2$-agonists are required during the bronchodilator test. However, to the best of our knowledge, there is limited data that explains the changes in the FeNO values in asthmatic children throughout the bronchodilator test. Moreover, little is known about the differences in FeNO values between BDR positive (BDR+) and negative (BDR–) children with asthma. However, pulmonary function, FeNO, BDR and bronchial provocation test are recommended as diagnostic tools for asthma and evaluation of treatment effect in asthmatic children (13). Incorrect reports of lung function can mislead clinicians in assessing an asthmatic child's condition. So it is important that when is the best time to perform FeNO during bronchodilator test.

We hypothesized that BDR results in higher FeNO values, and thus, traced the FeNO values throughout the salbutamol bronchodilator test and evaluated the difference in FeNO values between BDR+ and BDR– children with asthma. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-398/rc).

## Methods

### *Subjects*

A total of 57 children (aged 5–14 years) who were diagnosed and presenting with asthma between December 2018 and April 2019 at the Outpatient Department (OPD) of the Department of Respiration, Guangzhou Women and Children's Medical Center, were included in the study. The diagnosis of asthma conformed to the criteria of the Global Strategy for Asthma Management and Prevention (13). All of the included children were on daily-inhaled corticosteroid therapy.

The exclusion criteria were as follows: (I) presence of severe organic lesions including the heart, liver, kidney, and other chronic lung diseases (such as tuberculosis, broncho-pulmonary dysplasia, interstitial lung disease, pneumothorax, and pulmonary bullae), perforated tympanum, arrhythmia, etc.; (II) patients with a history of respiratory tract infection within 2 weeks before the test; (III) consumption of food 2 hours before the test; (IV) patients who had performed strenuous exercise within 1 hour before the test; (V) passive or active smokers; (VI) patients who failed to complete spirometry tests; and (VII) intake of medication within 3 days before the test.

Prior to enrollment, all parents or legal guardians of the children had signed the written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (No. 042A01).

### *Study design*

The baseline FeNO measurements were performed before the spirometry tests. To observe the effect of spirometry and BDR on FeNO values in children with asthma, the second and third FeNO measurements were conducted 5 minutes after the spirometry tests and 5 minutes after the BDR, respectively (*Figure 1*). Finally, the children were divided into two groups i.e., BDR+ and BDR–, and differences in the FeNO levels were compared between the two groups.

### *Spirometry*

Spirometry was performed using Medi-Softhyp (Maddie, Belgium). The operating procedure and quality control were all in accordance with the requirements of the

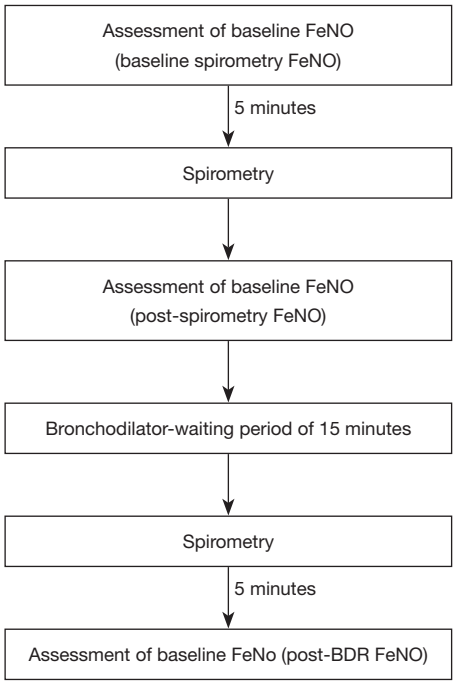


**Figure 1** Representation of the study design. FeNO, fractional exhaled nitric oxide; BDR, bronchodilator response.

American Thoracic Society/European Respiratory Society (ERS) (ATS/ERS, 2005) (14).

The test was performed with children in a standing position. They used a nose clip, and their lips were sealed tightly around the disposable mouthpiece, such that the tongue could not block it. The children were then asked to start at the end of quiet exhalation, reaching peak expiratory flow (PEF) as quickly as possible, and maintain exhalation to the residual volume (RV) position for as long as possible without interruption. After complete exhalation, the children were asked to inhale as fast as they could to reach the total lung capacity (TLC). This represented one respiratory cycle. The measurement process required the patient to be evaluated at least three times and checked for acceptability and repeatability (15).

### *ENO measurement*

The ENO was measured using a chemical luminescence ENO Analyzer (CLD88spAnalyzer, ECOMEDICS, Switzerland), which conformed to the recommendations of the ATS/ERS [2005] (7). The patients sat and rested quietly for 5 minutes and then expired the lung gas to the maximum possible extent, and subsequently used a mouthpiece containing the nitric oxide (NO) tester (including the filter/bacteria filter mouthpieces to forcibly inspire to the TLC [50 (±5%) mL/s smoothly at a constant velocity and exhaled slowly for 10 s (to clear the airway lumen and reach a plateau: children under the age of 12 years for at least 4 s, and children over 12 years of age for at least 6 s). The NO level was monitored for the last 3 seconds of the plateau stage. The test results were expressed as part per billion (ppb). The patients were asked to abstain from consuming food or water for 2 hours, and strenuous exercise for 1 hour before the test.

### *BDR*

The procedure was performed as per the requirements of the ATS/ERS [2005] (16). The patients were asked to discontinue the use of short-acting $\beta_2$-agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting $\beta_2$-agonists (LABA), and long-acting muscarinic antagonists (LAMA) for 4–6, 12, 24, and 36–48 hours before the test, respectively (17), as they may interfere with the test results. The doses of bronchodilator drug (i.e., salbutamol sulfate aerosol) used in the test were as follows: 200 μg for children aged ≤12 years and 400 μg for those aged >12 years.

### *Lung function test: interpretation*

(I) Restriction: forced vital capacity (FVC )%predicted (pred) <80% and forced expiratory volume in one second ($FEV_1$/FVC >90%; obstruction: $FEV_1$/FVC ≤90% and FVC %pred ≥80%; and Mixed defect: FVC %pred <80% and $FEV_1$/FVC ≤90% (11). Based on the FEV1%pred, the severity of airway obstruction was classified into the following: mild (100% to 80%), moderate (<80% to 50%), severe (<50% to 30%), and very severe (<30%) (15).

(II) Interpretation of the positive bronchodilator test: increase in FEV1 by >12% from the baseline value (15).

### *Statistical analysis*

The data were analyzed with SPSS version 23.0 (IBM, Armonk, NY, USA) for Windows, with the help of a statistician. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Normally distributed data were expressed as the mean ± standard deviation, and an independent sample *t*-test was used to compare the groups. Meanwhile, data that did not

 

**Table 1** Demographic characteristics and severity of lung function in children with asthma

| Variables | Total (n=57) | Normal (n=2) | Mild (n=40) | Moderate (n=11) | Severe or very severe (n=4) |
|---|---|---|---|---|---|
| Median age [range] (year) | 8.0 [5–14] | 7.5 [7–8] | 8.0 [5–14] | 9.0 [6–12] | 8.0 [6–9] |
| Male/female | 43/14 | 1/1 | 33/7 | 7/4 | 2/2 |
| BMI category | | | | | |
| Underweight | 10 | 0 | 6 | 2 | 2 |
| Normal | 37 | 2 | 27 | 6 | 2 |
| Overweight | 9 | 0 | 7 | 2 | 0 |
| Obesity | 1 | 0 | 0 | 1 | 0 |
| Median FVC% (range) | 102.00 (36.00–128.00) | 103.00 (101.00–105.00) | 106.00 (86.00–128.00) | 92.00 (83.00–103.00) | 61.50 (36.00–78.00) |
| Median FEV1% (range) | 92.00 (29.00–125.00) | 108.00 (106.00–110.00) | 94.00 (82.00–125.00) | 75.00 (63.00–80.00) | 38.50 (29.00–46.00) |
| Median FEV1/FVC% (range) | 79.00 (50.00–95.00) | 94.00 (93.00–95.00) | 81.00 (62.00–89.00) | 74.00 (60.00–85.00) | 58.50 (50.00–72.00) |
| Median PEF% (range) | 92.00 (35.00–140.00) | 115.00 (113.00–117.00) | 95.50 (63.00–140.00) | 80.00 (63.0–95.00) | 40.50 (35.00–48.00) |
| Median FeNO (range) | 28.80 (4.80–128.90) | 15.00 (7.00–23.00) | 28.80 (7.00–110.40) | 31.40 (4.80–128.90) | 27.10 (19.60–52.00) |

The continuous variables were presented as median (range); the categorical variable was presented as absolute value. BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; FeNO, fractional exhaled nitric oxide.

conform to a normal distribution were expressed as the median (M) and upper and lower quartiles ($P_{25,}$ $P_{75}$), and the Mann-Whitney test or Friedman test was used to compare the groups. Categorical data were expressed in terms of frequency (percentage), and the Chi-Square test or Fisher's exact test was used to compare the groups. The Wilcoxon signed-rank test was used to assess the association between the FeNO values observed in the matched samples (pre-spirometry, post-spirometry, and post-BDR test). A two-tailed P value <0.05 was considered statistically significant.

## Results

A total of 57 patients [43 boys (75.4%) and 14 girls (24.6%)] were enrolled in this study. Spirometry results were found to be normal in 2 patients (3.5%). There were 53 (93%) patients with obstructive lung disease, including 40 (70.2%), 11 (19.3%), and 2 (3.5%) patients with mild, moderate, and severe obstruction, respectively. Moreover, there were 2 (3.5%) patients with mixed lesions, none of which were restrictive. The demographic characteristics and severity of lung function in children with asthma are depicted in *Table 1*.

Following the BDR test, the patients were divided into BDR– (33 patients) and BDR+ (24 patients) groups. Among the BDR– patients, two had normal lung function, while 28 had mild, two had moderate, and one had severe obstruction and restriction. Similarly, among the BDR+ patients, 12 had mild, nine had moderate, and two had severe obstruction, while one had very severe obstruction with restriction.

There were no statistically significant differences between the BDR– and BDR+ patients in terms of gender, age, body mass index BMI, and FVC (all P>0.05). However, the FEV1, FEV1/FVC, and PEF values were significantly higher in BDR– than BDR+ patients (all P<0.05). Moreover, a notably greater number of BDR+ patients had moderate, severe, or very severe airway obstruction (P=0.003). As shown in *Table 2*, the median FeNO values at baseline, post-spirometry, and post-BDR test were markedly lower in BDR– than BDR+ patients (all P<0.05).

### *Comparison of the baseline, post-spirometry, and post-BDR FeNO values*

Overall, there was a statistically significant decrease in the median FeNO values (P=0.002), as displayed in *Table 3*.

**Table 2** The risk factors in BDR positive patients

| Variables | BDR(–) (N=33) | BDR(+) (N=24) | $\chi^2$/t/Z values | P value |
|---|---|---|---|---|
| Male, n (%) | 26 (78.8) | 17 (70.8) | 0.474 | 0.491 |
| Age (year; $\bar{x}$±s) | 8.64±2.36 | 8.71±2.44 | 0.112 | 0.911 |
| BMI (kg/m$^2$), M ($P_{25}$, $P_{75}$) | 15.68 (14.80, 17.64) | 15.76 (14.18, 19.39) | –0.186 | 0.853 |
| Severity of airway obstruction | | | 12.037* | 0.003 |
| Normal | 2 | 0 | | |
| Mild | 28 | 12 | | |
| Moderate | 2 | 9 | | |
| Severe or very severe | 1 | 2 | | |
| FVC (%; $\bar{x}$±s) | 103.09±12.71 | 97.33±19.15 | –1.364 | 0.178 |
| FEV1 (%; $\bar{x}$±s) | 95.91±15.04 | 77.63±19.74 | –3.971 | <0.001 |
| FEV1/FVC (%), M ($P_{25}$, $P_{75}$) | 84.00 (79.00, 86.00) | 73.50 (64.50, 76.75) | –5.302 | <0.001 |
| PEF (%; $\bar{x}$±s) | 99.06±19.83 | 80.13±19.63 | –3.575 | 0.001 |
| FeNO baseline, M ($P_{25}$, $P_{75}$) | 23.00 (9.80, 37.80) | 33.00 (23.78, 46.73) | –1.980 | 0.048 |
| FeNO post-spirometry, M ($P_{25}$, $P_{75}$) | 20.10 (11.20, 35.85) | 30.75 (21.65, 47.98) | –2.037 | 0.042 |
| FeNO post-BDR, M ($P_{25}$, $P_{75}$) | 21.70 (12.00, 35.90) | 35.85 (25.98, 63.95) | –2.829 | 0.005 |

The continuous variables were presented as median ($P_{25}$, $P_{75}$) or mean ± standard deviation; the categorical variable was presented as absolute and relative frequencies. *, Fisher exact test was used. BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; FeNO, fractional exhaled nitric oxide; BDR, bronchodilator response.

**Table 3** Analysis of the difference in FeNO values among baseline, post-spirometry and post-BDR by Friedman test and post hoc tests

| FeNO value | Change in FeNO (ppb) | $\chi^2$/Z values | P value |
|---|---|---|---|
| Baseline *vs.* post-spirometry *vs.* post-BDR | – | 12.133 | 0.002 |
| Post-spirometry *vs.* baseline | –1.70 (–5.50, 1.00) | 3.372 | 0.002* |
| Post-BDR *vs.* baseline | –0.80 (–4.05, 3.75) | 0.983 | 0.976* |
| Post-BDR *vs.* post-spirometry | 1.30 (–1.25, 5.25) | –2.388 | 0.051* |

The continuous variables were presented as median ($P_{25}$, $P_{75}$). *, Bonferroni-corrected P values. FeNO, fractional exhaled nitric oxide; BDR, bronchodilator response.

On post-hoc analysis, there was a notable decrease in the median FeNO values between baseline and post-spirometry (P=0.002). However, there were no significant decreases in both the median FeNO values between baseline and post-BDR (P=0.976) and between post-spirometry and post-BDR (P=0.051).

Furthermore, there was no statistically significant impact of spirometry on the FeNO values between BDR+ versus BDR– children (Z=–0.186, P=0.853). However, bronchodilators had a statistically significant impact on the FeNO values in BDR+ children (Z=3.160, P=0.002), as depicted in *Table 4*.

## Discussion

In the present study, the FeNO levels of patients decreased significantly after spirometry (P=0.002), suggesting that spirometry could induce decreased FeNO levels. This finding is consistent with those reported by Gabriele *et al.* (18) and Deykin *et al.* (19). In 2015, a cross-sectional study by Eckel *et al.* involving a large sample size demonstrated that FeNO levels declined post-spirometry

**Table 4** The impact of spirometry and bronchodilators on FeNO values between BDR+ versus BDR– children

| FeNO value | Baseline | Post-spirometry | Post-BDR | Change 1 | Change 2 |
|---|---|---|---|---|---|
| BDR+ | 33.00 (23.78, 46.73) | 30.75 (21.65, 47.98) | 35.85 (25.98, 63.95) | –2.25 (–5.70, 1.58) | 3.75 (0.93, 9.78) |
| BDR– | 23.00 (9.80, 37.80) | 20.10 (11.20, 35.85) | 21.70 (12.00, 35.90) | –1.60 (–5.45, 0.55) | 0.00 (–1.95, 2.65) |
| Z values | – | – | – | –0.186 | 3.160 |
| P values | – | – | – | 0.853 | 0.002 |

The continuous variables were presented as median ($P_{25}$, $P_{75}$). Change 1: post-spirometry *vs.* baseline; Change 2: post-BDR *vs.* post-spirometry. FeNO, fractional exhaled nitric oxide; BDR, bronchodilator response.

in children with asthma but were not altered in healthy children (8). However, Prieto *et al.* (11) and Karampitsakos *et al.* (12) reported that the FeNO levels are not significantly affected by spirometry. This could be because Prieto *et al.* recruited adults with asthma (11), while Karampitsakos *et al.* recruited 20 children with well-controlled asthma (12). In contrast, Kissoon *et al.* reported that FeNO levels increased after spirometry in healthy children and no changes were reported in children with asthma (20). However, this study only included 10 asthmatic children. These differences in the previously reported findings suggest that a large number of prospective studies with adequate sample sizes are needed to further clarify the association between FeNO levels and spirometry in children with asthma.

There are various interpretations of the changes in FeNO levels after spirometry. Kissoon *et al.* suggested that the results of changes in lung volume during spirometry trigger neural mechanisms that lead to an increased release of NO (20). Karampitsakos *et al.* suggested that the lack of changes in FeNO levels among children with well-controlled asthma on corticosteroids was similar to those observed in healthy individuals (12). Gabriele *et al.* speculated that a decrease in the FeNO value is a result of corticosteroid use in patients with asthma that may inhibit NO production from sources of NO, which may be sensitive to forced respiration (18). In this study, some of the children with asthma were not well controlled. 93% of patients had obstructive lung disease, including 70.2%, 19.3%, and 3.5% patients with mild, moderate, and severe obstruction, respectively. FeNO is flow-dependent (21); in asthmatic patients, the production of NO is likely influenced by taking deep breaths (19).

There were no significant differences in the FeNO levels post-BDR compared with those at baseline. The present study revealed that spirometry can cause a decline in FeNO levels, and the difference between the median FeNO levels post-spirometry and post-BDR was statistically significant (P=0.005). Our study further suggested that the FeNO levels and dynamic changes in its levels following BDR were altered by salbutamol. This finding is consistent with those reported by Silkoff *et al.*, which suggested that the mean FeNO levels in asthmatic patients increased after salbutamol sulfate compared with the placebo (9). However, the patients included in their study were mildly asthmatic adults that were not evaluated on the same day. A retrospective, cross-sectional study by Grzelewski *et al.* reported a linearly increasing change between the baseline FeNO levels with FEV1 after administration of salbutamol sulfate in children with moderate asthma (22). However, Karampitsakos *et al.* found no significant effect on FeNO after administration of a bronchodilator in children with well-controlled asthma (12). This lack of change in well-controlled asthma could be due to the absence of a response with bronchodilator use.

The present study included 24 BDR+ patients, and the findings revealed a significant difference in the FeNO values between BDR+ and BDR– children due to the effect of bronchodilators. This difference may be the result of an increase in bronchial diameter following the use of bronchodilators, leading to elevated FeNO values during exhalation in BDR+ children. This is supported by the findings of de Gouw *et al.*, who suggested that FeNO levels are affected by the diameter of the respiratory tract (23). In another study, Cattoni *et al.* demonstrated that the FeNO levels decline with the use of methacholine, indicating that the changes in airway caliber result in altered FeNO values (24).

In this study, there was no statistically significant difference in gender, age, and BMI between the BDR+ and BDR– patients (all P>0.05). However, there was a marked difference in the median baseline FeNO values between these groups (P=0.048), suggesting that FeNO values could be used to assess the level of asthma control. Diamant *et al.* found that high FeNO levels were association with

 

poor asthma control in asthmatic children (25). Kavitha *et al.* recruited 151 asthmatic patients over 18 months and found that FeNO levels were a useful monitoring tool to assess asthma control (26). FeNO levels are closely related to BDR and can predict bronchial reversibility in children with asthma (27,28). However, they are superior to BDR in determining possible asthma in preschool-aged children (29).

The findings of the present study suggested a statistically significant association between the severity of airway obstruction and BDR responsiveness (P=0.006), which is consistent with the findings reported by Coverstone *et al.* (30). The BDR may also be used to assess asthma control in children. Sharma *et al.* reported that BDR was associated with poor clinical outcomes in children with asthma (31). Galant *et al.* indicated that BDR phenotype ≥10% was associated with poor asthma control in children with normal spirometry (32). Moreover, BDR combined with FeNO measurement can be a good predictor of asthma control in children (33).

This study has some limitations that should be noted. Firstly, spirometry requires a high degree of cooperation from the children, and only 57 patients were enrolled, which is a small sample size. Secondly, all of the patients were enrolled from the OPD; thus, children with severe asthma exacerbations were not included in the study. Thirdly, all of the patients were on inhaled corticosteroids. Finally, this was a single-center study, and its findings need to be further confirmed by multicenter studies with large sample sizes.

## Conclusions

This study revealed dynamic changes in the FeNO levels during the BDR test. The use of a bronchodilator resulted in significantly different FeNO levels between BDR+ and BDR– children with asthma. Moreover, spirometry led to a marked decrease in the FeNO levels. Our results will allow clinicians to better interpret FeNO, BDR and pulmonary function outcomes and better develop clinical protocols.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-398/rc

*Data Sharing Statement:* Available at https://tp.amegroups.com/article/view/10.21037/tp-22-398/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-398/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (No. 042A01). All parents or legal guardians of the children had signed the written informed consent.



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