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Original Article

Pulmonary function is reduced in children with recurrent wheezing irrespective of Asthma Predictive Index results

Saruhan Ozkan[1], Zeynep Gulec Köksal[2], Pinar Uysal[2], Elif Celik[1], Imran Kurt Omurlu[3], Duygu Erge[2]

[1]Department of Pediatrics, Faculty of Medicine, Aydin Adnan Menderes University, Aydin, Türkiye
[2]Department of Pediatric Allergy and Immunology, Faculty of Medicine, Aydin Adnan Menderes University, Aydin, Türkiye
[3]Department of Biostatistics, Faculty of Medicine, Aydin Adnan Menderes University, Aydin, Türkiye

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ABSTRACT

Objective: It is important to determine the risk factors for the development of asthma in patients with recurrent wheezing (RW). This study was intended to compare the lung functions of children with RW with and without Asthma Predictive Index (API) positivity.

Methods: This prospective cross-sectional study included 40 children with RW aged between 3 months and 3 years and 34 age- and sex-matched healthy controls (HC). Lung functions were measured using tidal breath analysis during the wheezing attack in the RW group. Peak tidal expiratory flow time (TPTEF), ratio of peak tidal expiratory flow time to expiratory time (TPTEF/TE), volume required for PTEF (VPTEF), ratio of volume required for PTEF to expiratory volume (VPTEF/VE), tidal volume/kg (VT/kg), inspiratory to expiratory ratio (TI/TE), inspiratory time (TI), and expiratory time (TE) represented the main tidal breath analysis parameters. API positivity was also calculated in the RW group.

Results: TPTEF, VPTEF, TPTEF/TE, VPEF/VE, TI, and TI/TE were all lower in the RW group than in the HC group ($p<0.05$). However, there was no difference in TPTEF/TE between the RW patients with positive and negative API. TPTEF and TE parameters were higher in the RW group with positive API ($p=0.026$ and $p=0.043$, respectively).

Conclusion: Greater bronchial obstruction was observed in the RW group compared to the HC group. No difference in bronchial obstruction was detected between the RW group with positive API and the negative API group. API positivity during wheezing attacks did not emerge as an important parameter in terms of decreased lung functions in this study.

Keywords: Tidal breath analysis, wheezing, asthma predictive index, lung function, child, asthma, infant

INTRODUCTION

Wheezing is a symptomatic sign of airway obstruction caused by various disease processes, characterized by a musical, high-pitched sound produced during expiration or inspiration, originating anywhere from the larynx to the distal bronchioles.[1] One in three children will experience at least one wheezing episode in the first three years of their lives.[2] One of the most striking epidemiological features of wheezing episodes in infants is their tendency to recur. Although many children in this age group may have a single episode of wheezing not followed by subsequent similar episodes, over 50% of such subjects will experience wheezing at least once within the next few months.[2] Additionally, parents of 30-40% of children who wheeze before the age of 3 report current wheezing at 6 years of age.[3] It is crucial to perform a differential diagnosis of patients with RW,

Correspondence: Zeynep Gülec Koksal **E-mail:** zynp.glc@hotmail.com
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to identify risk factors for asthma development, and to detect preschool children at risk of persistent asthma at an early age.[4]

Definitive screening tests to identify potential asthma in children with RW are not yet available.[5] The Asthma Predictive Index (API), first developed in the Tucson Cohort Study, is widely used to identify preschool children with RW who are at high risk of developing asthma later in life.[6] A positive API by 3 years is associated with a 77% risk of asthma between the ages of 6 and 13, while a negative API by the age of 3 entails a lower than 3% risk of developing asthma during school age.[7]

Pulmonary function tests are highly valuable in the diagnosis of asthma, evaluating the treatment response, predicting prognosis, and determining the risk of exacerbations. Bronchial obstruction and increased airway resistance cause irregular pulmonary mechanics with restricted inspiratory and expiratory gas flow.[8] The measurement of lung function in young infants is useful in terms of explaining possible damage to the large and small airways.[9-12] However, conventional spirometry tests cannot be performed on infants because they require difficult maneuvers and patient compliance. Devices capable of measuring tidal breathing are particularly advantageous in this context, especially in infants or children with cooperation difficulties.[10] Tidal breath analysis (TBA) is a standardized and simple technique with no side effects that measures parameters shown to correlate with lung mechanics.[13] Since TBA is easy to apply, independent of effort, and requires minimal patient compliance, it can easily be performed to measure lung functions in children during the first three years of life, including the neonatal period. However, insufficient data concerning TBA in children with RW is available.

The purpose of this study was to employ TBA to evaluate respiratory functions in children with RW younger than three years old, to compare these with healthy children, and to investigate the relationship between respiratory functions and the API.

METHODS

Study design

This prospective cross-sectional study was conducted between January and April 2020 in the pediatric allergy and immunology department and general pediatrics clinics or wards of a tertiary hospital in Türkiye.

Demographic characteristics (age, gender, weight, height, week of birth, mode of delivery, and birth weight), presence of allergic diseases such as atopic dermatitis, allergic rhinitis, food allergy, parenteral and sibling allergic disease, wheezing information (history of wheezing attack without respiratory tract infection, age at first wheezing attack, total number of attacks, history of hospitalization, and treatments used), environmental exposures (prenatal and postnatal exposure to cigarette smoking, pets, humidity, stoves, etc.), physical examination findings, and eosinophil counts were recorded for all cases. All patients' respiratory functions were evaluated using TBA. For children with RW, TBA measurement was performed during the wheezing attack and before treatment administration.

The API is used to predict which children with ≥4 episodes of wheezing will go on to experience asthma and consists of major and minor criteria. The major criteria are maternal or paternal physician-diagnosed asthma and physician-diagnosed atopic dermatitis. The minor criteria include physician-diagnosed allergic rhinitis, wheezing without common cold, and the presence of eosinophils at a level exceeding 4% in peripheral blood. Individuals who meet one major or two minor criteria are considered positive for the API.[14] Children with a history of atopy in first-degree relatives were recorded as high-risk infants.[15]

Inclusion criteria

Children aged between 3 months and 3 years, with ≥4 episodes of wheezing in the previous year, and who were followed up or hospitalized in general pediatrics or pediatric allergy and immunology outpatient clinics due to wheezing attacks were included in the study.

The healthy control (HC) group was randomly selected from age- and gender-matched patients who presented to general pediatric outpatient clinics for routine healthy child checks.

Exclusion criteria

Individuals with a history of prematurity (gestational age <37 weeks), chronic lung disease (cystic fibrosis, bronchiolitis obliterans, bronchopulmonary dysplasia, bronchiectasis, airway malformations, etc.), gastroesophageal reflux disease, upper airway obstruction (tracheomalacia, laryngeal web, croup, choanal atresia), primary or secondary immunodeficiency, chronic disease (congenital heart disease, metabolic disease, neuromuscular disease, etc.), use of drugs affecting lung functions (inhaled or systemic corticosteroid, antihistamine, montelukast, nebular salbutamol, adrenaline, ipratropium bromide etc.), and children unable to comply with the pulmonary function tests were either not included in the wheezing group or were excluded from the study.

In the HC group, children with atopy and a history of viral respiratory tract infection in the previous two weeks, in addition to the wheezing child exclusion criteria, were also excluded from the study.

Tidal breath analysis

A commercially standardized, portable apparatus connected the tidal breath monitor to the pulmonary function tester (Jaeger/Viasys Master Screen TNA; Yorba Linda, CA, USA) (ErichJaegerGmbH, Bavaria, Marktrendwitz, Germany). Flow measurement was performed using a heated pneumotachograph (HansRudolph Inc., USA) providing a flow of 0-10 L/minute. The pneumotachograph was connected to a transmitter capable of sensing different pressures and a 100 Hz signal generator. The current curves were performed with a capacity of up to 256 measurements per second with the digital detection of the current signal. A low dead space, transparent, latex-free, silicone-capped face mask (Rendell Baker, Soucek, Rusch UK Ltd. Bucks, UK) was placed over the patient's nose and mouth during respiratory measurements.[16,17] The mask was tightly connected to the pneumotachograph, and the dead space was kept as low as possible. The amount of dead space in the pneumotachograph was 1.66 mL, a total of 2.4 mL in the system, and 11-14 mL in the mask; these values are all being standardized. Prior to each recording, the practitioner calibrated the device using a 100 mL syringe.[18,19]

Tidal Breath Measurement

Tidal breath was measured when the children were calm or asleep and breathing spontaneously. The procedure was carried out by two nurses and observed by a pediatrician and pediatric allergy specialist. Tidal breath analysis was conducted before initiating any treatment to avoid potential improvements in lung function that could result from the treatment. Additionally, to ensure consistency and minimize variations in respiratory rhythm related to the disease, all measurements were taken during the same period, by the same practitioners, and under identical room conditions for each patient. The children were supported by extending the back of the neck in a neutral position and were placed in the supine, straight, or semi-recumbent position. This minimized the effect of airway and glottis obstruction on the measurements.[20]

After placing a mouth or face mask appropriate to the child's facial structure, 2-3 minutes were allowed to elapse for adaptation. The measurements commenced once the respiratory rhythm was regular.[9] In case of variability in respiratory rhythm, body movement, inability to install the mask sufficiently accurately, failure to reach the volume baseline of the previous expiratory extension at the beginning of inspiration, or in the presence of any artifact, that part was not evaluated.[18,19] Depending on the variability of the breathing pattern, measurements were taken as the flow-volume curve of 60 inspiratory and expiratory breath cycles, each of which varied less than 15% in total, was observed on the screen.[16,17] This was considered an epoch. Respiratory patterns in which at least 20 regular respiratory cycles of each epoch cycle were detected and the best values were selected. At least three epoxies were observed at least every five minutes. The values of all epoxies were recorded, and the average was calculated separately by two researchers. Flow/volume measurement in young children is performed with the CareFusion pneumatic method (dead space volume 7 mL).

Parameters including peak tidal expiratory flow (PTEF), peak tidal expiratory flow time (TPTEF), the ratio of peak tidal expiratory flow time to expiratory time (TPTEF/TE), the volume required for PTEF (VPTEF), the ratio of volume required for PTEF to expiratory volume (VPTEF/VE), respiratory rate (RR), minute ventilation (MV), tidal volume (VT), tidal volume/kg (VT/kg), inspiratory to the expiratory ratio (TI/TE), inspiratory time (TI), expiratory time (TE), expiratory flow when the tidal volume in the lungs is 75%, 50%, 25% (TEF75, TEF50, TEF25), and expiratory volume at peak tidal expiratory flow (EVaTPTEF) were measured with TBA in this study. The within-subject (or repeated measurements) coefficient of variation (CV) for VT was calculated as the ratio of the standard deviation to the mean of VT x 100. Measurements were included in the analysis only when CV for VT was ≤ 10% and no mask leakage occurred during quiet sleep.[21]

Ethical issues

The study was approved by the local clinical research ethics committee (no. 23, dated 23.01.2020), and written informed consent was obtained from the parents of the patients enrolled in the study.

Statistical analysis

The conformity of quantitative data to normal distribution was examined using the Kolmogorov-Smirnov test. The t-test was used to compare variables with normal distribution between independent groups, and descriptive statistics were shown as mean±standard deviation (SD). Quantitative variables that were inconsistent with normal distribution were expressed as median values (25-75 percentile). The Mann-Whitey U test was used for descriptive statistical comparisons between groups. Categorical variables were analyzed using the chi-square test, and descriptive statistics were presented as frequency values (%).

Pearson or Spearman correlation analyses were used to examine the relationship between variables. p values <0.05 value were considered significant.

RESULTS

There was no difference between the RW and HC groups in terms of demographic characteristics (Table 1). The features of wheezing symptoms in the RW group are shown in Table 2.

Levels of prenatal and postnatal cigarette exposure, humidity in the home, stove use, and contact with pets were higher in the RW group compared to the HC group (p<0.05). The frequencies of parenteral asthma or allergic disease, sibling asthma or allergic disease, and high-risk infants were also higher in the RW group (p<0.05) (Table 3).

The TBA values of TPTEF, VPTEF, TPTEF/TE, VPEF/VE, TI, and TI/TE were lower in the RW group than in the HC group (p<0.05) (Table 4). In the RW group, TPTEF and TE were higher in the API-positive children than in the API-negative group (p<0.05), but there was no difference between the groups regarding TPTEF/TE and VT/kg values (p>0.05) (Table 5).

A moderate negative correlation was found in the API-negative children between the number of wheezing attacks requiring systemic corticosteroids in the previous year and VT/kg (r= -0.438; p=0.042) and between the number of wheezing attacks requiring hospitalization in the previous year and TPTEF (r= -0.516; p= 0.014). A moderate positive correlation was observed between the number of wheezing attacks requiring hospitalization in the previous year and RR in the API-negative group (r=0.487; p=0.022).

Table 1. Comparison of demographic characteristics of children with recurrent wheezing and healthy control groups

		Group		p
		Recurrent Wheezing Group (n=40)	Healthy Control Group (n=34)	
Gender	Male	23 (57,50)	21 (61,76)	0,710
	Female	17 (42,50)	13 (38,24)	
Mode of delivery	Vaginal	16 (40,00)	19 (55,88)	0,173
	Cesarean	24 (60,00)	15 (44,12)	
Age (month)		13,50 (8,00-21,50)	13,00 (7,00-24,00)	0,765
Height (cm)		76,50 (70,00-81,50)	75,50 (67,00-90,00)	0,854
Weight (kg)		9,65 (8,30-11,05)	8,90 (6,30-12,00)	0,273
Gestational age (week)		38,00 (37,00-39,00)	38,00 (37,00-39,00)	0,136
Birth weight*(gr)		3,15±0,48	3,26±0,25	0,235

Data are presented as numbers (percentage) for categorical variables and median (IQR) for numerical variables.
*Presented with mean ± standard deviation values.
Abbreviations: cm, centimeter; IQR, interquartile range; kg, kilogram; gr, gram; n; number.

Table 2. Characteristics associated with wheezing symptoms in the child group with recurrent wheezing

Recurrent Wheezing Group	(n=40)
Age of first wheezing episode (months), median (IQR)	3,00 (2,00-6,00)
Number of wheezing episodes requiring steroids in the past year, median (IQR)	1,00 (1,00-3,00)
Number of wheezing episodes requiring hospitalization in the past year, median (IQR)	0,00 (0,00-1,00)

Abbreviations: IQR, interquartile range; n, number.

Table 3. Comparison of familial and environmental factors in children with recurrent wheezing and healthy control groups				
		Group		p
		Recurrent Wheezing Group (n=40)	Healthy Control Group (n=34)	
Prenatal smoking exposure, n (%)	No	25 (62,50)	29 (85,29)	0,028
	Yes	15 (37,50)	5 (14,71)	
Postnatal smoking exposure, n (%)	No	17 (42,50)	29 (85,29)	<,001
	Yes	23 (57,50)	5 (14,71)	
Parenteral asthma or allergic disease, n (%)	No	29 (72,50)	34 (100,00)	0,001
	Yes	11 (27,50)	0 (,00)	
Asthma or allergic disease in a sibling, n (%)	No	30 (75,00)	34 (100,00)	0,001
	Yes	10 (25,00)	0 (,00)	
Exposure to humidity, stove heating, and household pets, n (%)	No	20 (50,00)	32 (94,12)	<,001
	Yes	20 (50,00)	2 (5,88)	
High-risk infant, n (%)	No	23 (57,50)	34 (100,00)	<,001
	Yes	17 (42,50)	0 (,00)	

Table 4. Comparison of tidal breath parameters of recurrent wheezing child and healthy control groups			
	Group		p
	Recurrent Wheezing Group (n=40)	Healthy Control Group (n=34)	
TPTEF (sec)	0,25 (0,15-,34)	0,32 (0,27-,45)	0,007
VPTEF (ml)	20,55 (15,15-35,90)	28,20 (22,20-41,20)	0,037
TPTEF/TE (%)*	28,06±12,02	36,66±11,64	0,003
VPTEF /VE (%)*	29,59±9,51	36,78±9,30	0,002
TEF75 (%)*	147,95±64,52	113,74±43,00	0,008
TEF50 (%)*	127,73±57,34	114,35±47,05	0,282
TEF25 (%)	94,50 (54,50-120,00)	78,50 (57,00-128,00)	0,927
VT/kg (ml/kg)	8,50 (7,15-10,50)	8,80 (7,60-9,60)	0,692
VT (ml)	75,35 (60,20-106,50)	76,05 (54,00-124,00)	0,862
RR (1/min)	34,50 (28,05-50,20)	33,80 (26,40-41,10)	0,334
TI (sec)	0,67 (0,42-0,84)	0,79 (0,60-1,02)	0,030
TE (sec)	1,04 (0,64-1,30)	1,02 (0,76-1,25)	0,757
TI/TE	0,68 (0,60-0,81)	0,77 (0,67-,82)	0,041

Data are presented as numbers (percentage) for categorical variables and median (IQR) for numerical variables.
*Presented with mean ± standard deviation values.
Abbreviations: TPTEF, Time to peak tidal expiratory flow; TPTEF/ TE, Ratio of time to reach peak tidal expiratory flow to total expiratory time; VPTEF, Volume expired before PTEF was attained; VPTEF/VE, Ratio of volume until peak tidal expiratory flow to total expiratory volume; RR, respiratory rate; VT, tidal volume; VT/kg, tidal volume/kg; TI/TE, the ratio of inspiration to expiration; TI, inspiratory time; TE, expiratory time; TEF75, TEF50, TEF25, Expiratory flow when 75%, 50% and 25% of tidal volume remains in the lungs; sec, second; ml, milliliter; min, minute.

Table 5. Comparison of tidal breath parameters according to asthma predictive index in children with recurrent wheezing

	Asthma Predictive Index		p
	Positive (n=18)	Negative (n=22)	
TPTEF (sec)	0,29 (0,22-0,39)	0,17 (0,14-0,30)	0,026
VPTEF (ml)	21,75 (17,70-37,10)	19,70 (15,10-28,30)	0,447
TPTEF/TE (%)	27,65(17,60-36,10)	26,50 (17,50-32,80)	0,463
VPEF/VE (%)	26,95 (21,30-36,40)	28,80 (21,00-33,60)	0,744
TEF75 (%)*	138,17±59,65	155,95±68,56	0,393
TEF50 (%)	118,50 (69,00-163,00)	129,00 (82,00-167,00)	0,724
TEF25 (%)	79,50 (52,00-126,00)	100,00 (63,00-119,00)	0,734
VT/kg (ml/kg)*	8,66±2,81	8,67±2,27	0,983
VT (ml)	84,00 (58,20-107,00)	70,80 (60,70-90,70)	0,430
RR (1/min)	33,50 (27,80-41,40)	44,10 (30,50-61,20)	0,197
TI (sec)	0,71 (0,40-0,83)	0,64 (0,42-,84)	0,903
TE (sec)	1,20 (0,98-1,33)	0,72 (0,62-1,20)	0,043
TI/TE	0,67 (0,57-,74)	0,70 (0,61-0,82)	0,605

Data are presented as numbers (percentage) for categorical variables and median (IQR) for numerical variables.
* Presented with mean ± standard deviation values.
Abbreviations: IQR, interquartile range; TPTEF, Time to peak tidal expiratory flow; TPTEF/ TE, Ratio of time to reach peak tidal expiratory flow to total expiratory time; VPTEF, Volume expired before PTEF was attained; VPTEF/VE, Ratio of volume until peak tidal expiratory flow to total expiratory volume; RR, respiratory rate; VT, tidal volume; VT/kg, tidal volume/kg; TI/TE, the ratio of inspiration to expiration; TI, inspiratory time; TE, expiratory time; TEF75, TEF50, TEF25, Expiratory flow when 75%, 50% and 25% of tidal volume remains in the lungs; sec, second; ml, milliliter; min, minute.

DISCUSSION

In this prospective cross-sectional study of children under three years old with RW, histories of parental or sibling atopy, prenatal and postnatal cigarette exposure, and contact with humidity, stoves, and animal contact were more common in the RW group than in the HC group. When respiratory functions were evaluated using TBA during wheezing attacks, TPTEF, VPTEF, TPTEF/TE, VPTEF/VE, TI, and TI/TE were lower in the RW group compared to the HC group. Bronchial obstruction was more prevalent in wheezing preschool-aged children compared to healthy children. However, there was no difference in bronchial obstruction or lung capacity between children with and without positive API.

There are very few studies in the literature evaluating respiratory functions in preschool children using the TBA method.[19,22,23] Studies involving infants have reported that a low TPTEF/TE ratio is indicative of obstructive airway diseases.[19,22,24,25] It has also been shown that tidal respiratory indices such as TPTEF/TE measured in healthy children early in life may be associated with wheezing or asthma in later years.[26]

A previous study by our team examined the relationship between TBA parameters and wheezing phenotypes and observed lower TPTEF/TE and TI/TE in the RW group than in healthy children.[27] In another study by the same team, TPTEF/TE and TI/TEwere significantly lower in children with acute bronchiolitis than in healthy children. In that study, TPTEF/TE and TI/TE ratios were low in the group with acute bronchiolitis even on the 30th day of treatment, and TBA findings indicating bronchial obstruction persisted despite clinical improvement.[23] Similarly, Dezateux et al. showed that TPTEF/TE was lower in wheezing infants than healthy children.[28] The TPTEF/TE ratio was lower in infants with lower respiratory tract infections than in the HC group, even in the asymptomatic period.[19] Qi et al. also reported that lung functions measured using TBA in wheezing infants were lower than those in healthy infants and remained low even three months after acute infection.[22]

The purpose of the API is to identify preschool children with RW who are at higher risk of developing asthma later in life.[6] However, the relationship between respiratory mechanics and API has not yet been fully clarified. A recent study showed that API-positive infants with RW had significantly lower forced

expiratory end-expiratory residual capacity (VmaxFRC), as measured using the rapid thoracoabdominal pressure method (RTC).[29] In another study conducted in infants with RW, forced vital capacity (FVC) and forced mid-expiratory flow velocity (FEF 25-75) were lower in API-positive cases compared to API-negative infants.[30] These findings suggest that there is a reduction in airway function among patients with positive API-wheezing when compared to those with negative API- wheezing. However, in our study, in contrast to prior research, we did not observe a significant difference in the TPTEF/TE ratio, which is a key indicator of airway obstruction in TBA device measurements among API-positive cases.

To the best of our knowledge, no previous studies in the literature have compared children with and without API positivity using the TBA method. In the present study, TPTEF and TE were higher in API-positive patients than in API-negative individuals. In the case of patients with negative API, there is a possibility that API will become positive if they experience wheezing attacks outside the infection period and develop allergic rhinitis, one of the minor API criteria. In light of this information, API positivity may develop at later ages during the follow-up of these patients, and the relationship with respiratory functions should be investigated again in future studies.

Smoking is one of the most important risk factors for wheezing. Exposure to cigarettes in the intrauterine period has been shown to adversely affect fetal lung functions.[31] Postnatal cigarette smoke exposure has also been shown to impact children's respiratory function.[28,32] A strong relationship is known to exist between the presence of a smoking parent in the home and the frequency and duration of wheezing attacks.[33,34] Consistent with the previous literature, although prenatal and postnatal exposure to cigarettes was high in the wheezing group in the present study, no difference was observed in terms of TBA parameters between the cigarette exposure and non-exposure groups.

The main strengths of this study are that the patients were examined and evaluated by the same pediatrician and that the TBA measurements were measured by the same experienced nurse, thus permitting greater standardization of the evaluation of the patient data. Patients' respiratory functions were evaluated using TBA during wheezing attacks before any treatment was administered, but we did not investigate the effect of treatment on respiration tests. The main limitations of this study are the small number of cases and the inability to subsequently study the TBA values again after the resolution of the acute episode.

TBA parameters such as TPTEF, TPTEF/TE, and TI/TE were lower in the RW group among patients presenting with wheezing attacks at younger ages. Given the insufficient number of studies evaluating the relationship between API and respiratory function parameters, we think this study can make a useful contribution to the existing literature. Although the API is used to predict asthma, no relationship has been shown between API positivity and obstructive changes in respiratory function parameters in children with wheezing. Early evaluation of lung functions using the TBA method may be more sensitive than the API for predicting permanent small airway damage in young children with RW. Further prospective studies with large case numbers are now needed to confirm these possibilities and to make positive contributions to the diagnosis and treatment of children with RW.

Ethical approval

This study has been approved by the Aydın Adnan Menderes University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (approval date 23.01.2020, number 23). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: SO; Concept: SO, DE, PU; Design: SO, DE, PU; Data Collection or Processing: SO, EC, ZGK; Analysis or Interpretation: SO, PU, IKO; Literature Search: SO, ZGK, DE; Writing: SO, ZGK, DE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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