ORIGINAL RESEARCH

Hematological Parameters Characteristics in Children with Obstructive Sleep Apnea with Obesity

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Objective: To investigate the possible correlation between obesity and hematological parameters in children with obstructive sleep apnea (OSA).

Methods: A total of 460 children was initially included in our study, which were divided into children with OSA and children without OSA. Multiple analysis was performed for obesity by adjusting confounding factors such as age and gender in 460 children. Further, to minimize the influence of confounding factors and selective bias, propensity score matching (PSM) was performed in children with OSA. Hematological parameters such as inflammatory and coagulable parameters were compared between the normal weight children with OSA and the obese children with OSA following PSM.

Results: OSA (OR = 3.061; *P*<0.001; 95% CI, 1.772–5.288) represented an independent risk factor for obesity. Besides, the obese children with OSA had higher levels of white blood cell (WBC) (*P*<0.001), neutrophil (NEUT) (*P*<0.001), neutrophil-lymphocyte ratio (NLR) (*P*=0.006), fibrinogen (FIB) (*P*=0.033), while had a lower level of activated partial thromboplastin time (APTT) (*P*=0.048). No significant differences were observed in other hematological parameters. In linear regression, the results indicated that the levels of WBC (R^2 = 0.123, Beta = 0.289, P<0.001), NEUT (R^2 = 0.124, Beta = 0.282, P<0.001), NLR (R^2 = 0.105, Beta = 0.184, P=0.026) and FIB (R^2 = 0.086, Beta = 0.246, P=0.003) were positively correlated with BMI, while the level of APTT (R^2 = 0.057, Beta = −0.171, P=0.044) was significantly negatively correlated with BMI.

Conclusion: OSA was an independent risk factor contributing to obesity. WBC, NEUT, NLR, FIB and APTT are correlated with obesity in children with OSA (aged from 2 to 14 years). These indicators could be used to estimate the status of inflammation and hypercoagulation in the obese children with OSA.

Keywords: obstructive sleep apnea, obesity, propensity score matching, hematological parameter, inflammation, hypercoagulation

Introduction

Obstructive sleep apnea (OSA) is a condition secondary to partial or complete obstruction of upper airway during sleep. This condition shows a prevalence of 1–5% in children.[1] Due to periodic upper airway collapse and nocturnal hypoxia, the development of metabolic and inflammatory system responses has altered.[2] Several studies focused on OSA have proven this condition was closely related to chronic systematic inflammation. Besides, chronic inflammatory responses are often associated with the activation of coagulation.[3]

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In recent decades, obesity has become a serious public health concern, and is also the most important risk factor for OSA both in adults and children.[4,5] As the result, approximately 50% to 60% of obese individuals have OSA.[6] Several studies have concluded that increases in weight are associated with an increasing prevalence and severity of OSA.[7] Besides, it seems that there is a bidirectional association between obesity and OSA since OSA has a number of obesity-inducing effects, such as decreased physical activity and energy metabolism.[8]

Notwithstanding previous mentioned studies have described the relationship between OSA and inflammation, obesity and inflammation, respectively,[2,9] few studies focus on the inflammatory status in children affected with both OSA and obesity. Many easily accessible, relatively cheap and readily-measured laboratory parameters have been used to estimate systematic inflammation in studies, such as red cell distribution width (RDW),[10] neutrophil-lymphocyte ratio (NLR),[11] platelet-lymphocyte ratio (PLR).[12] We hypothesized that obesity would aggravate the inflammatory status in children with OSA. To verify this speculation, we explore the correlation between the hematological parameters and obesity in the children with OSA in this study.

Methods

Participants

Written informed consent was obtained from all children's parents. This study was approved by the Ethics Committee of West China Hospital, Sichuan University (Approval No.2018-146). We included children who visited the department of Otorhinolaryngology of West China Hospital from January 2013 and May 2019. The included criteria were defined as: 1) children underwent complete performance of polysomnography (PSG) if they were suspected to have OSA; 2) well-documented demographic data (gender, age and body mass index [BMI]). The exclusion criteria included craniofacial malformation, any genetic or immunodeficiency disease, or acute upper respiratory infection.

Study Design

The children with OSA were defined as an apnea-hypopnea index (AHI) $\geq$ 1 event per hour and minimum oxygen saturation of arterial blood (Min SaO$_2$) < 92%. According to AHI, we divided the whole children into two groups (children with OSA group and children without OSA). Similarly, by age- and gender-corrected BMI using the Chinese guidelines,[13,14] these children were divided into the normal weight children and the obese children. Furthermore, we explored the correlation between obesity and hematological parameters by using propensity score matching (PSM) in these children with OSA.

Hereinafter, the normal weight group was considered as the normal weight children with OSA and the obese group was considered as the obese children with OSA.

Clinical Data

Demographic data (gender, age, body mass index), PSG data and laboratory parameters were collected and registered. Venous blood was obtained from each child in EDTA-K2 anticoagulation collection tube. All blood specimens were performed within 4 hours by clinical laboratory professionals.

Statistical Analysis

Statistical analysis was performed by SPSS version 24.0. $P<0.05$ was considered statistically significant.

The continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. For continuous variables, groups were compared by the Mann–Whitney U-test or independent t-test, as appropriate. The continuous variables were displayed as mean $\pm$ standard deviations, while the categorical variables used chi-square test and were displayed by frequency and percentage.

Multiple analysis with dummy-variable binary logistic regression was performed for obesity by adjusting confounding factors such as age and gender.

To minimize the influence of confounding factors and selective bias, we performed PSM in the whole children with OSA. The propensity score of covariates (gender, age, AHI) was calculated using logistic regression analysis for each child, and one to two matched analysis using nearest-neighbor matching were performed with 0.1 standard deviations of the logit of the propensity score as the caliper value.

Given the distribution of the data, Spearman's rank correlation or Pearson's correlation coefficient was used to assess correlations between BMI and hematological parameters. Unary linear regression analysis was used to quest for correlations between BMI and hematological parameters.

Results

Demographic and Clinical Characteristics in the Whole Children

A total of 460 children (aged from 2 to 14 years) were included in this study. As shown in Table 1, there were 245 children without OSA and 215 children with OSA. There were significant differences in age ($P<0.001$), BMI group ($P<0.001$), gender ($P=0.002$) and AHI ($P<0.001$).

In the logistic regression analysis, OSA (OR = 3.061; $P<0.001$; 95% CI, 1.772–5.288) represented an independent risk factor for obesity (as illustrated in Figure 1).

Demographic and Clinical Characteristics in the Children with OSA

There were 215 children with OSA. As illustrated in Table 2, in the included children, 156 were classified as the normal weight group and 59 as the obese group. AHI ($P=0.009$) and Min SaO_2 ($P=0.046$) were significantly different between the two groups. We enrolled more male children than female children, but there was no statistical difference in gender ratio between the two groups.

With PSM, 97 normal weight children with OSA and 53 obese children with OSA were selected and further analyzed. There were no significant differences in age, gender, AHI or Min SaO_2.

Table 1 Demographic and Clinical Characteristic of Children with or without OSA

Variables	Children without OSA	Children with OSA	P-value
Children	245	215	
Age, y	8.05 ± 3.24	5.81 ± 2.51	<0.001*
BMI	16.87 ± 2.89	17.07 ± 3.08	0.456
BMI group, n% Obese Normal weight	 25 (10.2%) 220 (89.8%)	 59 (27.4%) 156 (72.6%)	<0.001*
Gender, n% Male Female	 145 (59.2%) 100 (40.8%)	 158 (73.5%) 57 (26.5%)	0.002*
AHI	0.47 ± 0.29	18.64 ± 21.82	<0.001*

Note: *$P<0.05$.
Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea-hypopnea index.

Analysis of Hematological Parameters in Two Groups After Following PSM

From Table 3, the obese group had higher levels of white blood cell (WBC) ($P<0.001$), neutrophil (NEUT) ($P<0.001$), NLR ($P=0.006$) and fibrinogen (FIB) ($P=0.033$). However, the obese children with OSA had a lower level of activated partial thromboplastin time (APTT) ($P=0.048$) than the normal weight group. No such significant differences were observed in red blood cell (RBC), hemoglobin concentration (HGB), hematocrit (HCT), RDW coefficient of variation (RDW-CV), platelet (PLT), PLR, prothrombin time (PT), international normalized ratio (INR) or thrombin time (TT).

Correlation Between BMI and Hematological Parameters in Two Groups After Following PSM

Figure 2 presents the correlation between BMI and the levels of WBC, NEUT, NLR, FIB and APTT, respectively. The levels of WBC and NEUT showed significant positive correlation with BMI (r = 0.275; $P=0.001$; 95% CI, 0.-116–0.421 and r = 0.292; $P<0.001$; 95% CI, 0.134–0.436, respectively). In addition, the levels of NLR and FIB were also positively correlated with BMI (r = 0.231; $P=0.005$; 95% CI, 0.067–0.380 and r = 0.183; $P=0.025$; 95% CI, 0.019–0.338, respectively). On the contrary, the level of APTT was observed a negative correlation with BMI (r = −0.235; $P=0.004$; 95% CI, −0.385 - −0.073). The other parameters did not show any statistical correlations with BMI.

Unary Linear Regression

The results of the multiple linear regression analysis are presented in Table 4, which used BMI as the independent variable and hematological parameters as the dependent variable among the children with OSA after following PSM. The results indicated that the levels of WBC (R^2 = 0.123, Beta = 0.289, $P<0.001$), NEUT (R^2 = 0.124, Beta = 0.282, $P<0.001$), NLR (R^2 = 0.105, Beta = 0.184, $P=0.026$) and FIB (R^2 = 0.086, Beta = 0.246, $P=0.003$) were positively correlated with BMI, while the level of APTT (R^2 = 0.057, Beta = −0.171, $P=0.044$) was negatively correlated with BMI.

Discussion

In this study, OSA was an independent risk factor contributing to obesity. In comparison to the normal weight

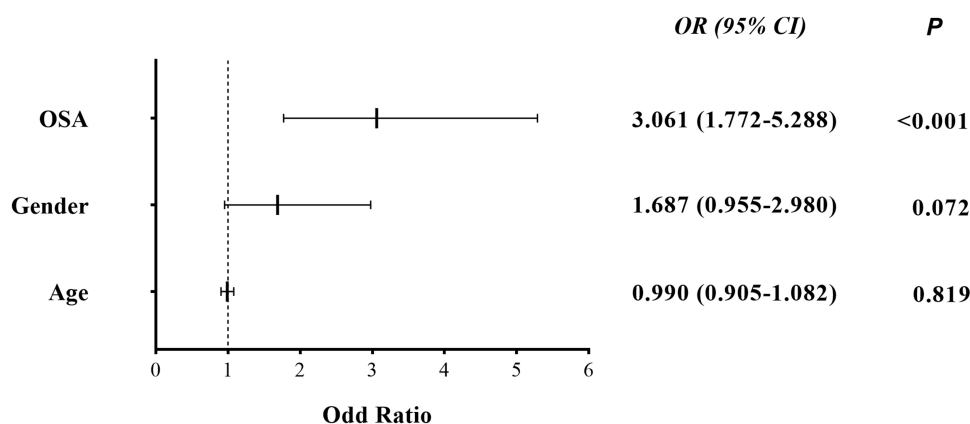|	OR (95% CI)	P
OSA	3.061 (1.772–5.288)	<0.001
Gender	1.687 (0.955–2.980)	0.072
Age	0.990 (0.905–1.082)	0.819

Odd Ratio

Figure 1 Analysis with dummy-variable binary logistic regression of factors contributing to obesity in children.

group, the obese group had higher levels of WBC, NEUT and NLR. Significant positive correlations were observed between the levels of WBC, NEUT, NLR and BMI in children with OSA, which indicated obesity might aggravate the inflammatory status in the children with OSA. Besides, the obese group had a higher level of FIB and a lower level of APTT than the normal weight group. And BMI was found positively correlated with the level of FIB, while negatively correlated with the level of APTT. The results suggested that the obese children with OSA were predisposed to present coagulation disorder.

Obesity, characterized by recurrent narrowing in the upper airway structure, is considered as one of the risk factors of OSA.[4] Alterations caused by fat deposition in oropharynx elicit intermittent hypoxia and sleep fragmentation, and thereby increased the risk of OSA. Visceral obesity is another factor that restricts lung expansion and

is considered as another risk factor in OSA.[15] A study by Quintas-Neves reported that an increase of 6 units in BMI was associated with a four-fold risk of OSA.[16] Besides, bariatric surgery was confirmed to be effective in alleviating the severity of OSA.

On the other hand, OSA also exert many promoting effects on obesity. In Grote et al study, patients with OSA were liable to fatigue and reduced physical activity.[17] This reduced physical activity can play a role in predisposing patients with OSA to obesity. Some humoral mechanisms, such as leptin and ghrelin, could cause weight gain.[18] An increased leptin and ghrelin can contribute to decreased satiety and increased hunger for adults with OSA by Shechter[18] Studies have shown that continuous positive airway pressure therapy was helpful to reduce body weight and the level of leptin in obese adults with OSA.[19,20] There are also several studies focused on

Table 2 Demographic and Clinical Characteristics of Children Before and After Propensity Score Matched Analysis

Variables	Before PSM		P-value	After PSM		P-value
	Normal Weight Group	Obese Group		Normal Weight Group	Obese Group	
Children	156	59		97	53	
Age, y	5.79 ± 2.51	5.86 ± 2.52	0.764	5.78 ± 2.56	5.57 ± 2.23	0.604
BMI	15.54 ± 1.13	21.13 ± 2.90	<0.001*	15.53 ± 1.23	20.97 ± 2.79	<0.001*
Gender, n% Male Female	112 (71.8%) 44 (28.2%)	46 (78.0%) 13 (22.0%)	0.360	73 (75.3%) 24 (24.7%)	42 (79.2%) 11 (20.8%)	0.688
AHI	16.24 ± 19.66	25.00 ± 25.83	0.009*	16.74 ± 16.55	18.78 ± 17.62	0.481
Min SaO$_2$, %	74.84 ± 12.74	70.85 ± 13.66	0.046*	73.66 ± 13.41	76.72 ± 11.82	0.166

Note: *$P<0.05$.
Abbreviations: PSM, propensity score matching; AHI, apnea-hypopnea index; Min SaO$_2$, minimum oxygen saturation of arterial blood.

Table 3 Comparison of Hematological Characteristics of the Patients Between the Normal Weight Group and the Obese Group

Variables	Normal Weight Group (N=97)	Obese Group (N=53)	P-value
RBC (10^{12}/L)	4.81 ± 0.33	4.94 ± 0.46	0.079
HGB (g/L)	131.82 ± 8.70	132.53 ± 9.07	0.642
HCT (L/L)	0.40 ± 0.03	0.40 ± 0.03	0.600
RDW-CV (%)	13.19 ± 1.08	13.44 ± 1.09	0.175
PLT (10^9/L)	307.28 ± 71.88	313.72 ± 101.95	0.653
WBC (10^9/L)	7.54 ± 1.99	8.91 ± 2.59	<0.001*
NEUT (10^9/L)	3.30 ± 1.56	4.47 ± 2.10	<0.001*
LYM (10^9/L)	3.42 ± 0.94	3.62 ± 1.14	0.246
NLR	1.04 ± 0.57	1.33 ± 0.68	0.006*
PLR	94.60 ± 28.25	93.65 ± 36.83	0.860
PT (s)	11.47 ± 0.73	11.38 ± 0.66	0.427
INR	0.99 ± 0.06	0.98 ± 0.06	0.604
APTT (s)	31.34 ± 4.14	29.95 ± 3.95	0.048*
TT (s)	19.86 ± 1.40	19.76 ± 1.38	0.665
FIB (g/L)	2.44 ± 0.48	2.66 ± 0.63	0.033*

Note: *P<0.05.
Abbreviations: RBC, red blood cell; HGB, hemoglobin concentration; HCT, hematocrit; RDW-CT, red cell distribution width coefficient of variation; PLT, platelet; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.

obese children with OSA. A study found that, compared with non-obese children with OSA, obese children with OSA had higher levels of ghrelin and unhealthier physical activity.[21] In addition, a large longitudinal cohort study demonstrated that children with persistent OSA had an increased risk for developing obesity.[22] Our research showed a similar result that compared with children without OSA, children with OSA had a two-fold increased risk of obesity. Combined with the above paragraph, we can conclude that there is a bidirectional association between OSA and obesity.

As a result of periodic upper airway collapse, OSA rendered the normal sleep architecture fragmentation and the physiological gas exchange alteration. It was fragmented sleep architecture that led to the development of the local and systematic inflammation.[23] Several studies in adults and children showed that OSA increased airway

inflammation in subjects.[24,25] The intermittent airway obstruction applied mechanical stress on the mucosa and thereby elicited local inflammation was also considered to influence systematic inflammation.[26]

Inflammation was an immediate protective response of the immune system to a harmful stimulus. Numerous evidences indicated that obesity was causally correlated with a chronic systematic inflammatory status.[27,28] Obese people were characterized by having higher levels of inflammatory parameters than non-obese people.[29] Another study on children also showed that the obesity of childhood was associated with elevations of the anti-inflammatory cytokines.[30] Moreover, the loss of weight in obese people was proven to be associated with decreased inflammatory parameters.[31] A feature of the obesity inflammatory status was increased infiltration of immune cells into metabolic tissues. The chronicity means that the expression of inflammatory factors in adipose tissues and increased infiltration of immune cells happen gradual instead of acute response and remains unsolved unless lose weight. Another rational mechanism was that excess nutrition may activate multiple signal pathways and thereby stimulated an inflammatory response.[27] In addition, oxidative stress was regarded as a key mediator of chronic inflammatory status.[32] Recently, one study reported that adipose tissues produce inflammatory factors through the activation of oxidative stress.[33]

Clinically, WBC was suggested as a good indicator of systematic inflammation. Some stimulation of inflammatory factors may contribute to the alterations in the level of WBC in obese adults.[34] NEUT, the most abundant granulocyte in WBC, was one of the first responders of inflammatory cells to migrate toward the site of inflammation.[35] Even elevating in the normal range, the level of NEUT could also be used as a predictor parameter of the inflammatory process.[36] As a combination of two independent markers of inflammation, an elevated NLR ensured a higher predictive value than the standalone WBC and NEUT differential in inflammation. Of note, as a novel indicator of systematic inflammation, NLR was associated with many chronic diseases. Bozkuş[37] et al found that NLR increased by the severity of obesity and therefore, by increased fat tissue and revealed that concomitant inflammatory response increased.

Our study demonstrated that the levels of WBC, NEUT and NLR in the obese children with OSA were significantly higher than those in the normal weight children with OSA. In correlation and regression analyses, these
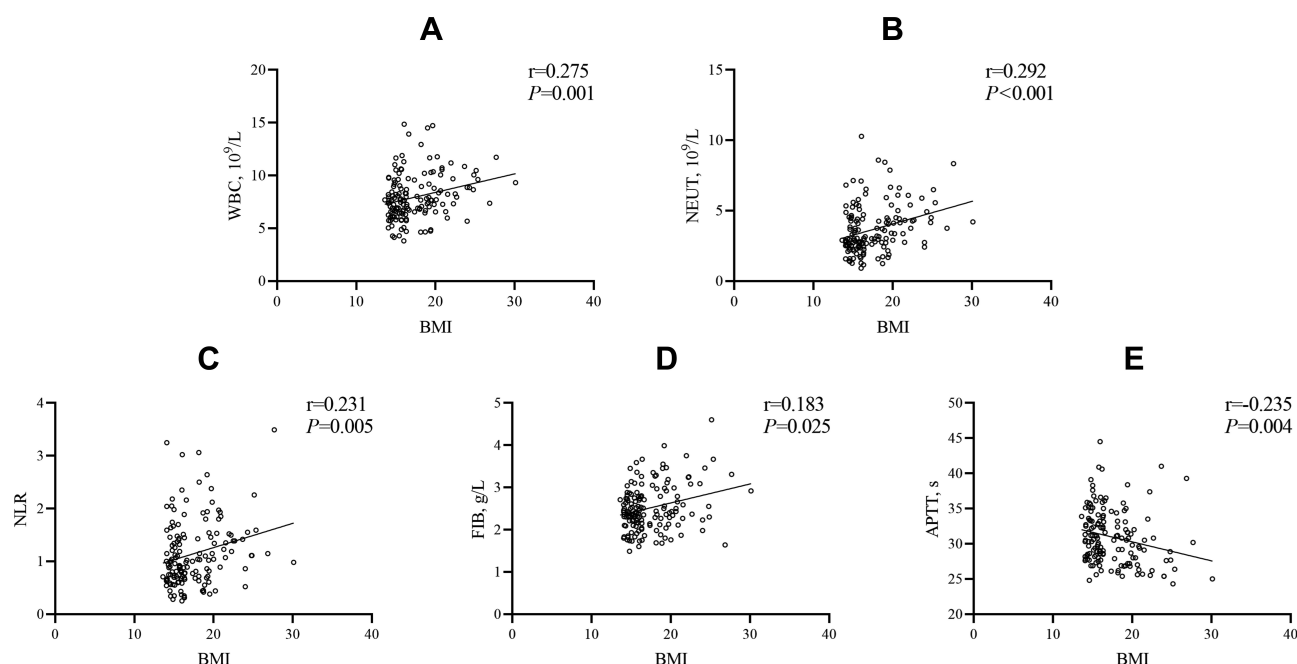
Figure 2 Correlation between BMI and hematological parameters. (**A**) The level of white blood cell (WBC). (**B**) The level of neutrophil (NEUT). (**C**) The ratio of neutrophil-lymphocyte (NLR). (**D**) The level of fibrinogen (FIB). (**E**) The level of activated partial thromboplastin time (APTT). BMI is calculated as body mass (kg)/height (m²).

inflammatory parameters still exhibited positive correlated with BMI. The results suggested that obesity may aggravate the inflammatory status in the body of children on the basis of OSA, which was undoubtedly a further impact on systematic inflammation, namely, obesity could amplify the short-term and long-term damage of OSA. A chronic inflammatory status, even at low-grade, was considered as a risk factor in the development of atherosclerosis or cardiovascular disease (CVD).[38] Obesity upon OSA can render endothelium dysfunction because of oxidative stress which may lead to CVD in adults.[32,39,40] Therefore, the risk of obesity for CVD in children with OSA needs to be further assessed.

FIB was a coagulation factor synthesized and secreted by the liver, which mainly determined plasma viscosity and erythrocyte aggregation. A higher level of FIB elicited endothelial impairment and thrombogenesis. A study by Balagopal reported that the level of FIB showed a direct positive correlation with BMI in adults.[41] Several studies on obese children showed similar result that the level of FIB in the obese children significantly exceeded in the normal weight children.[30,42] In parallel to those, our study found that the level of FIB in the obese children with OSA was significantly higher than that in the normal weight children with OSA, and the level of FIB has a positive correlation with BMI. A probable mechanism

was that in an inflammatory status caused by obesity as well as OSA, excess fat may contribute to more production or less clearance of FIB.[42]

As an important coagulation parameter, APTT reflected the intrinsic coagulation pathway maintaining the process after the initiation of coagulation. A shortened level of APTT may represent a hypercoagulable status.[43] A study in obese adults showed APTT shortened with increased BMI.[44] In our study, we found a similar result that in children with OSA, BMI increased with the lower level of APTT, which could be explained by the inflammatory status, because the increased FIB may automatically induce a decrease of APTT.[30]

Previous studies had shown an intricate relationship among OSA, obesity and inflammation.[24,28,39] In our study, obvious results were observed that the levels of WBC, NEUT, NLR, FIB in the obese children with OSA were significantly higher than those in the normal weight children with OSA, while the level of APTT in the obese children with OSA was lower than that in the normal weight children with OSA. Both obesity per se and increased the severity of OSA by obesity affected the body's inflammatory status. We controlled the influence of AHI between the obese group and the normal weight group with PSM. Thus, we further concluded that obesity may have an independent effect on the exacerbation of

Table 4 Correlation Between Hematological Parameters and BMI by Using Multiple Linear Regression Analysis Controlling for Age, Gender and AHI

Variables	BMI			
	R^2	B-Coefficient (95% CI)	Beta	*P*-value
RBC (10^{12}/L)	0.124	0.018 (−0.001–0.037)	0.151	0.064
HGB (g/L)	0.154	−0.027 (−0.454–0.401)	−0.010	0.903
HCT (L/L)	0.204	0<B<0.001 (−0.001–0.001)	0.003	0.969
RDW-CV (%)	0.078	0.050 (−0.004–0.104)	0.153	0.068
PLT (10^9/L)	0.110	1.781 (−2.372–5.935)	0.069	0.398
WBC (10^9/L)	0.123	0.206 (0.092–0.320)	0.289	<0.001*
NEUT (10^9/L)	0.124	0.161 (0.069–0.252)	0.282	<0.001*
LYM (10^9/L)	0.124	0.045 (−0.006–0.095)	0.142	0.082
NLR	0.105	0.035 (0.004–0.0567)	0.184	0.026*
PLR	0.063	−0.347 (−1.953–1.258)	−0.036	0.670
PT (s)	0.009	−0.009 (−0.046–0.028)	−0.040	0.643
INR	0.010	0<B<0.001 (−0.003–0.003)	−0.005	0.958
APTT (s)	0.057	−0.217 (−0.428 - −0.006)	−0.171	0.044*
TT (s)	0.009	−0.023 (−0.096–0.050)	−0.054	0.531
FIB (g/L)	0.086	0.041 (0.0014–0.069)	0.246	0.003*

Note: *P<0.05.
Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; RBC, red blood cell; HGB, hemoglobin concentration; HCT, hematocrit; RDW-CT, red cell distribution width coefficient of variation; PLT, platelet; WBC, white blood cell; NEUT, neutrophil; LYM, lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.

inflammatory status in children with OSA. In view of the correlation between inflammation and coagulation, we also compared the coagulable parameters in this study. An increased level of FIB and a shortened level of APTT represented hypercoagulation. Because the levels of FIB and APTT indicated the actual time of coagulation in certain circumstances, the differences in the levels of FIB and APTT were clinically significant even though data were within the reference range. In other words, obesity exacerbated inflammatory and coagulable status on the basis of OSA. Moreover, these hematological parameter levels may be involved in the subsequent potential cardiovascular comorbidities. The easily accessible, timely laboratory test to identify obese children with OSA should be considered to apply to OSA management and comorbidities in the future. Because obesity per se possessed the potential to promote cardiovascular risks from the earliest phase of life, the body weight status of children with OSA should be controlled within normal limits as much as

possible to reduce the potential harmful influences of the inflammatory and hypercoagulable status. In addition, the future risks of CVD exerted by the high level of inflammation or coagulation in the obese OSA children with comorbidities need long term follow-up.

Since this study was a retrospective cohort, we failed to explore the alterations in some well-established inflammatory parameters for comparison. In addition, because the relationship between OSA and inflammatory parameters had been well described in detail in several studies, no comparison of inflammatory parameters between children with OSA and children without OSA was conducted in this paper.

Conclusions

OSA was an independent risk factor contributing to obesity. Besides, the levels of WBC, NEUT, NLR and FIB are positively correlated with obesity in children with OSA, while the level of APTT is negatively correlated with

obesity in children with OSA. These indicators could be used to estimate the risks of inflammatory and hypercoagulable status in the obese children with OSA in outpatient follow-up. These findings may have important implications regarding obese children with OSA screening, treatment monitoring and prognosis.

Abbreviations

OSA, obstructive sleep apnea; RDW, red cell distribution width; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PSG, polysomnography; BMI, body mass index; AHI, apnea-hypopnea index; Min SaO$_2$, minimum oxygen saturation of arterial blood; PSM, propensity score matching; WBC, white blood cell; NEUT, neutrophil; FIB, fibrinogen; APTT, activated partial thromboplastin time; RBC, red blood cell; HGB, hemoglobin concentration; HCT, hematocrit; RDW-CT, red cell distribution width coefficient of variation; PLT, platelet; PT, prothrombin time; INR, international normalized ratio; TT, thrombin time; CVD, cardiovascular disease.

Ethics and Consent

This study was approved by the Ethics Committee of West China Hospital, Sichuan University (Approval No.2018-146) and performed in compliance with the Declaration of Helsinki. All children involved gave their parents' written consent to review their medical data.

Funding

Disclosure

The authors report no conflicts of interest in this work.

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