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Implication of mixed sleep apnea events in adult patients with obstructive sleep apnea-hypopnea syndrome

Xiuping Yang[1] · Ying Xiao[1] · Baoai Han[1] · Kun Lin[1] · Xun Niu[1] · Xiong Chen[1]

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Abstract

Purpose Although mixed sleep apnea (MSA) is one of the three types of sleep apnea, it is not considered a separate disease entity. It is generally seen as a part of obstructive sleep apnea-hypopnea syndrome (OSAHS), but its implications are often ignored. In this study, we examined its features and the potential impact on OSAHS patients.

Methods Subjects diagnosed with OSAHS by polysomnography (PSG) were enrolled. All participants underwent physical checkups and tests of blood biochemistry. They were anthropometrically, clinically, and polysomnographically studied.

Results MSA events were common in patients with severe OSAHS patients. There were significant differences between the pure OSAHS group and its mixed counterpart in apnea-hypopnea indices during REM (AHI_{REM}) and non-REM (AHI_{NREM}) and in percentages of N2 or N3 sleep. Logistic regression analysis showed that, after adjustment of other parameters, patients with MSA events were mostly male, had higher body mass index (BMI), higher scores on Epworth Sleepiness Scales (ESS), higher triglyceride (TG) levels, and higher apnea-hypopnea index (AHI). The combined predictive probability of the aforementioned variables was 0.766 (95% CI = 0.725~0.806; sensitivity 61.6%, specificity 82.1%).

Conclusions Our study suggested that MSA was related to the stability of the ventilatory control in OSAHS patients. MSA events occur more frequently in patients with severe OSAHS, and male gender, obesity, daytime sleepiness, and elevated TG levels were risk factors for the mixed OSAHS.

Keywords Obstructive sleep apnea · Mixed sleep apnea · Mixed sleep apnea events · Clinical and polysomnographic features

Introduction

Sleep apnea is characterized by a temporary interruption of breathing during sleep. It falls into three distinct categories: obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed sleep apnea (MSA), depending on the presence or absence of chest or abdominal breathing movement [1]. OSA is the most common form of sleep apnea and is caused by a blockage in the upper airway, and CSA usually results from the instability of the feedback mechanism that controls breathing [2, 3]. MSA is a status that has both central to obstructive features [4, 5]. However, the clinical implication of MSA has not been fully understood. So far, MSA is pathophysiologically considered to be a part of OSAHS [6].

Since the implication of MSA in OSAHS has not been well studied, the impact of MSA events on OSAHS tends to be ignored. To date, only few studies investigated the association between MSA events and OSAHS. Yamauchi et al. found that patients with MSA events had significantly poorer compliance with continuous positive airway pressure (CPAP) as compared with pure OSAHS patients [7]. Similarly, Xie et al. reported a difference in the respiratory control stability between OSAHS patients with MSA events and pure OSAHS patients [8]. In the above studies, the OSAHS sub-grouping was based on AHI and the proportion of MSA events. Lee et al. compared the clinical, polysomnographic, and CPAP titration findings between OSAHS patients without MSA events and MSA events ≥ 5/h and revealed that the mixed OSAHS patients performed more poorly [9]. However, no studies have examined the differences in clinical features between OSAHS patients with and without MSA events.

✉ Xiong Chen
chen_xiong15@126.com

[1] Department of Otolaryngology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

In this study, we studied two OSAHS subgroups divided in terms of the presence or absence of MSA, and examined the differences between the two subgroups in respect to anthropometric, clinical, and polysomnographic features and explored the correlation between MSA events and these indicators, with an attempt to find the pathophysiological and clinical implications of the MSA events in OSAHS patients.

Material and methods

Subjects

Study participants included patients who received PSG in the Department of Otorhinolaryngology, the Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, due to snoring or apnea, from March 2017 to May 2018. OSAHS was diagnosed when AHI ≥ 5/h. Patients were excluded if (1) CSA events ≥ 5/h and/or CSA events were more than OSA events; (2) REM sleep duration < 30 min; total sleep time < 100 min; (3) clinical and polysomnographic data were incomplete; (4) they had other sleep disorders and history of having received treatment for sleep-related breathing disorders; (5) they had other diseases such as central nervous system diseases, cardiovascular complications, chronic obstructive pulmonary disease, renal disease, thyroid disease, cancer, ongoing infections; (6) they were on hypoglycemic or lipid-lowering agents due to diabetes or hyperlipidemia.

OSAHS patients were divided into two groups according to the presence or absence of MSA events: (1) pure OSAHS group in which subjects had no MSA events and (2) mixed OSAHS group in which subjects had MSA events.

Clinical evaluation

All patients received an intensive clinical assessment covering history of OSAHS-related symptoms, smoking and alcohol consumption, and chronic diseases. Meanwhile, all patients underwent physical checkups and tests of blood biochemistry [cholesterol (TC), high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), fasting glucose (GLU)].

Polysomnography

All patients received overnight PSG, continuous recording electroencephalography (C3/A2, C4/A1, O1/A2, O2/A1), electrooculography, submental electromyography, bilateral anterior tibialis electromyography, and electrocardiography. Respiratory effort of thoracoabdominal movement was monitored with a respiratory inductance plethysmographer, and an oronasal thermistor was used to assess airflow. Moreover, the pulse oximeter was attached to the patient's finger to dynamically monitor oxygen saturation. Closed-circuit television and body position sensor were used to observe the body position. Sleep stages and respiratory events were manually scored according to the Sleep Medicine Criteria (American Academy, 2012). Apnea was defined as complete cessation of airflow for more than 10 s, and hypopnea as an over 50% drop in airflow from the baseline value for at least 10 s accompanied by a no less than 3% reduction in arterial oxygen saturation from the pre-event baseline and/or by an electroencephalographic arousal. AHI was the total number of apnea and hypopnea events combined per hour of sleep. Mild OSAHS was defined as 5 ≤ AHI < 15 events/h, moderate OSAHS, defined as 15 ≤ AHI < 30 events/h, and severe OSAHS, defined as AHI ≥ 30 events/h. Finally, PSG outcomes were analyzed independently by two qualified technicians who were blind to patients' clinical characteristics.

Assessment of daytime sleepiness

Subjective daytime sleepiness was assessed by using the ESS [10]. The ESS is a self-administered questionnaire which contains eight items designed to measure daytime sleepiness. Each item was rated on a scale of 0–3, with the total score ranging from 0 to 24. ESS scores ≥ 10 were listed as excessive daytime sleepiness (EDS), and the higher the score, the stronger the sleepiness.

Statistical analysis

All analyses were performed using statistical software package SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The distribution of the variables was analyzed by employing the Kolmogorov-Smirnov test. Normally distributed data were presented as means and standard deviations, non-normally distributed data were expressed as the median and the first and third quartile values, and qualitative variables were described as frequencies and percentages. Comparison of the numerical variables was made by utilizing independent paired *t* tests and Mann-Whitney *U* tests for both normally and non-normally distributed data, respectively. Categorical variables were tested with the chi-square test. All tests were two-tailed and a p value < 0.05 was considered to be statistically significant.

Spearman's correlation analysis was used to evaluate the correlation between MSA events and AHI_{NREM} and AHI_{REM}. Since AHI_{NREM} and AHI_{REM} were strongly influenced by the duration of each phase of sleep, we used AHI_{REM} as an adjustment factor in the correlation analysis between MSA events and AHI_{NREM}, and vice versa, to minimize the influence of sleep stage on AHI [11].

In addition, logistic regression analysis was conducted to determine the association between MSA events and OSAHS. The dependent variable was the presence or absence of MSA events. To identify independent factors for mixed OSAHS, clinical and demographic variables with p values < 0.1 in the univariate analysis were included in the logistic regression analysis. Meanwhile, AHI was the only PSG variable that entered the model because other PSG variables were strongly associated with AHI. Then, in order to evaluate the predictive value of these selected variables, the receiver operating characteristic (ROC) curves were generated according to the total predictive value of all these variables. The area under the curve (AUC) was calculated, and the optimum sensitivity and specificity were determined by Youden index.

Results

Clinical characteristics and polysomnographic findings of the OSAHS patients

Among 706 OSAHS patients enrolled, 168 patients were excluded because of CSA events ≥ 5/h ($n = 34$), CSA events more than OSA events ($n = 27$), incomplete data ($n = 20$), inadequate sleep time ($n = 39$), other diseases ($n = 26$), diabetic patients with well-controlled glycemia ($n = 20$), and hyperlipidemia patients with well-controlled blood lipids ($n = 2$). The remaining 538 patients were included in this study. Of them, 246 and 292 patients satisfied the criteria for the pure OSAHS and the mixed OSAHS respectively. Table 1 presents the

Table 1 Characteristics of study subjects

	OSAHS patients ($n = 538$)		p value
	Pure OSAHS group ($n = 246$)	Mixed OSAHS group ($n = 292$)	
Age (years), mean ± SD, median (IQR)	42.64 ± 10.23	43 (33.25, 51)	0.778
Male, *n* (%)	198 (80.49)	274 (93.83)	< 0.001
BMI (kg/m^2), mean ± SD, median (IQR)	25.47 ± 3.06	27.40 (25.32, 29.7)	< 0.001
ESS, median (IQR)	10 (6, 14)	12 (9, 17)	< 0.001
Hypertension, *n* (%)	52 (21.14)	73 (25)	0.291
Diabetes, *n* (%)	3 (1.21)	6 (2.05)	0.452
TC (mmol/L), mean ± SD	4.86 ± 0.84	5 ± 1.02	0.071
TG (mmol/L), median (IQR)	1.63 (1.15, 2.39)	2.05 (1.44, 2.87)	< 0.001
HDL-c (mmol/L), median (IQR)	1.06 (0.92, 1.2)	0.97 (0.83, 1.27)	< 0.001
LDL-c (mmol/L), mean ± SD	3.05 ± 0.76	3.03 ± 0.88	0.742
GLU (mmol/L), median (IQR)	4.85 (4.59, 5.27)	5.04 (4.75, 5.44)	< 0.001
N1 sleep (%), median (IQR)	8.95 (6.48, 11.93)	7.9 (5.7, 11.5)	0.087
N2 sleep (%), median (IQR)	60 (52.38, 66.45)	63.1 (56.95, 69.28)	< 0.001
N3 sleep (%), median (IQR)	11.9 (7.6, 17.68)	7.75 (3.9, 13.2)	< 0.001
REM sleep (%), mean ± SD	18.44 ± 5.53	19.26 ± 6.26	0.11
Mean SaO_2 (%), median (IQR)	95 (94, 96)	92 (89, 94)	< 0.001
$LSaO_2$ (%), median (IQR)	81 (73, 86)	70 (56, 79)	< 0.001
CT90 (%), median (IQR)	1.8 (0.3, 6.23)	23 (5.03, 45.5)	< 0.001
AHI (events/h), mean ± SD, median (IQR)	27 (14.88, 52.48)	53.54 ± 25.12	< 0.001
15 > AHI ≥ 5, *n* (%)	62 (25.2)	26 (8.9)	< 0.001
30 > AHI ≥ 15, *n* (%)	71 (28.86)	35 (11.99)	< 0.001
AHI ≥ 30, *n* (%)	113 (45.93)	231 (79.11)	< 0.001
AHI_{NREM} (events/h), median (IQR)	24.95 (11.3, 49.48)	56 (30.7, 73.45)	< 0.001
AHI_{REM} (events/h), median (IQR)	34.75 (18.23, 55.5)	53.9 (36.78, 65.98)	< 0.001
$AHI_{REM}/AHI_{NREM,}$ median (IQR)	1.27 (0.86, 2.05)	0.91 (0.77, 1.38)	< 0.001

SD standard deviation, *IQR* interquartile range, *BMI* body mass index, *ESS* Epworth Sleepiness Scale, *TC* cholesterol total, *TG* triglyceride, *HDL-c* high-density lipoprotein, *LDL-c* low-density lipoprotein, *GLU* fasting glucose, *REM* rapid eye movement, SaO_2 oxygen saturation, $LSaO_2$ the lowest oxygen saturation, *CT90* cumulative time percentage with $SaO_2 < 90\%$, *AHI* apnea-hypopnea index, AHI_{NREM} AHI during non-REM sleep, AHI_{REM} AHI during REM sleep

clinical characteristics of the patients. Compared with pure OSAHS group, patients in mixed OSAHS group had higher BMI values, higher ESS scores, higher GLU levels, higher TG levels, and lower HDL-c levels and was predominantly male ($p < 0.05$). There were no differences in age, prevalence of hypertension and diabetes, TC levels, and LDL-c levels between the two groups ($p > 0.05$). With respect to PSG parameters, compared to the pure OSAHS group, the mixed OSAHS group had higher AHI, CT90, AHI_{NREM}, AHI_{REM}, percentage of N2 sleep and lower mean oxygen saturation (SaO_2), the lowest oxygen saturation ($LSaO_2$) and percentage of N3 sleep ($p < 0.001$). There existed no significant differences in the percentage of N1 and REM sleep between the two groups ($p > 0.05$) (Table 1). Interestingly, in most of the OSAHS patients with MSA events > 0/h, their OSAHS was severe, while in most of the patients with severe OSAHS, MSA events was greater than 0/h (Table 1) (Fig. 1).

Correlations between MSA events and parameters

The results of Spearman's correlation analysis about the relationship between MSA events with AHI_{NREM} and AHI_{REM} are shown in Table 2. A significant correlation was observed between the MSA events and AHI_{NREM} after adjusting AHI_{REM} ($p < 0.001$). However, after adjusting for AHI_{NREM}, the correlation between MSA events and AHI_{REM} was weak and not statistically significant ($p = 0.562$). The univariate analysis showed that there were significant differences in the clinical features and PSG between the two groups. The binary logistic regression analysis demonstrated that the associations were significant between MSA events and sex, BMI, ESS scores, TG levels, and AHI respectively (Table 3). Nonetheless, the association between MSA events and GLU levels, TC levels, and HDL-c levels were not significant ($p > 0.05$). Male gender, higher BMI, higher ESS scores, higher TG levels, and higher AHI were found to be independent predictors for mixed OSAHS (Table 3). The AUC of these five variables combined was 0.766 (95% CI = 0.725~0.806), the predictive value of the five variables had a sensitivity of 61.6% and a specificity of 82.1% (Fig. 2).

Discussion

In our clinical practice, we observed that MSA was found more frequently in patients with severe OSAHS. Since MSA is a special event in OSAHS, this tendency promoted us to study its implications in OSAHS. In this study, we first were anthropometrically examined in OSAHS patients. On the basis of the anthropometric findings, we clinically studied the differences between pure OSAHS patients and the OSAHS patients with MSA events and we found that MSA was related to the stability of the ventilatory control in OSAHS patients.

Loop gain is used to describe the stability of a feedback control system and high loop gain is indicative of an unstable control [12, 13]. Some studies indicated that the chemical

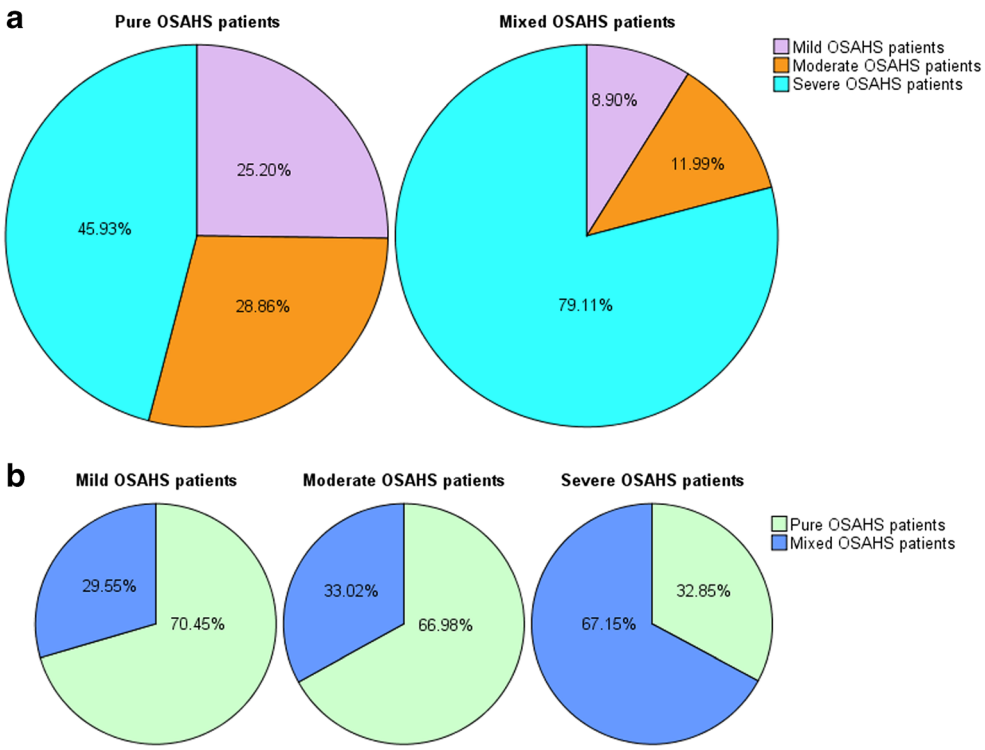

Fig. 1 Pie chart of patients with OSAHS. **a** Severity distribution of OSAHS in patients of both subgroups. **b** Distribution of two subgroups in patients with different severity of OSAHS

Table 2 Correlation between MSA events and AHI_{NREM} and AHI_{REM}

Variable	AHI_{NREM} (adjusted for AHI_{REM})		AHI_{REM} (adjusted for AHI_{NREM})	
	Coefficient	*p* value	Coefficient	*p* value
MSA events	0.251	< 0.001	− 0.025	0.562

MSA mixed sleep apnea, *REM* rapid eye movement, AHI_{NREM} AHI during non-REM sleep, AHI_{REM} AHI during REM sleep

control systems of patients with severe OSAHS were more unstable. For instance, Younes et al. employed proportional assist ventilation to assess ventilatory stability in OSAHS patients after rendering their upper airway stable by CPAP, and found that severe OSAHS patients had high loop gain [14]. Moreover, subsequent studies confirmed that high loop gain could pathogenetically induce OSAHS [15, 16]. Furthermore, Edwards et al. demonstrated that the low respiratory arousal threshold (ArTH) was strongly related to severity of OSAHS and decreased with increasing severity of OSAHS [17]. In this study, we found that most patients with severe OSAHS had MSA events. Moreover, MSA events, as a part of OSAHS breathing events, were found to be associated with the severity of OSAHS patients [9]. Therefore, we were led to assume that the MSA events might well be associated with the ventilatory control system in OSAHS patients.

We analyzed the differences in polysomnographic findings between the two OSAHS groups. Lee et al. revealed that sleep architecture in the mixed OSAHS patients had more N1 sleep with less N2, N3, and REM sleep [9]. Inconsistent with the previous reports, we found more N2 sleep and less N3 sleep in the mixed OSAHS patients, which could be explained by high loop gain. As aforementioned, loop gain, which reflects the increased ventilatory drive due to reduced ventilation, can quantify the sensitivity and stability of the ventilatory control system. Recently, Landry et al. found that the loop gain in REM and NREM sleep was different and the loop gain was significantly lower in REM than in N2 sleep [18]. Presumably, higher loop gain in N2 sleep might contribute to the instability of ventilatory control in mixed OSAHS patients. Furthermore, NREM-dominant sleep apnea ($AHI_{NREM} > AHI_{REM}$) was also an indicator of a high loop gain [19, 20]. As shown in Table 1, compared to the pure OSAHS patients, the mixed OSAHS patients had NREM-dominant sleep apnea. In addition, we analyzed the correlation between MSA events and AHI_{NREM} and AHI_{REM} and found that only AHI_{NREM} was associated with MSA events. These results suggest that mixed OSAHS patients had high loop gain, and MSA events might be associated with high loop gain in OSAHS patients.

The results of previous studies varied. Yamauchi et al. failed to find any significant differences between the two groups [7]. However, Lee et al. found that older age, male sex, obesity, and daytime sleepiness were associated with mixed OSAHS [9]. In this study, by logistic regression, analysis showed that risk factors of mixed OSAHS included male gender, higher BMI, higher ESS scores, higher TG levels, and higher AHI. We believe that discrepancy might be ascribed to differences in subject grouping, sample size, and statistical methods used [21]. ROC analysis showed that sex, BMI, ESS scores, TG levels, and AHI, in combination, could well predict the presence of MSA.

Table 3 Results of binary logistic regression analysis: association of MSA events with polysomnographic and clinical parameters

	OR	95% CI	*p* value
Male (reference: female)	1.927	(1.029, 3.61)	0.04
BMI	1.128	(1.059, 1.202)	< 0.001
ESS scores	1.054	(1.016, 1.094)	0.005
TG levels	1.211	(1.026, 1.431)	0.024
AHI	1.020	(1.012, 1.028)	< 0.001

MSA mixed sleep apnea, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *ESS* Epworth Sleepiness Scale, *TG* triglyceride, *AHI* apnea-hypopnea index

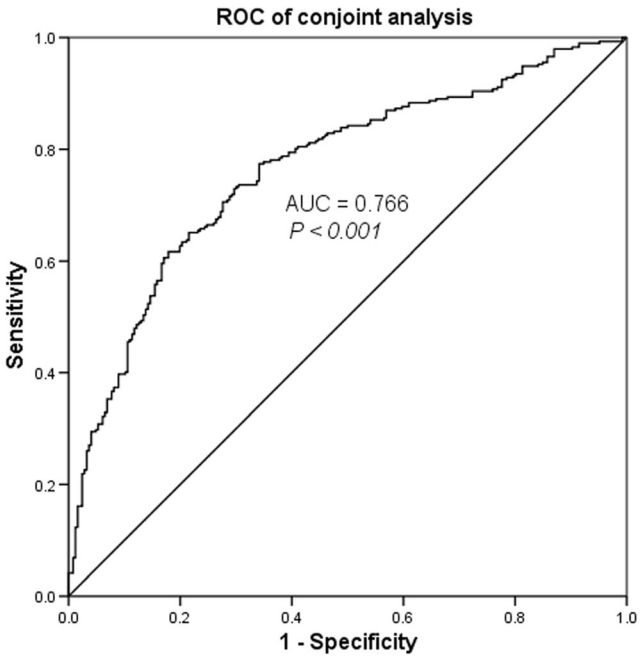

Fig. 2 Receiver operating characteristic (ROC) curve of the five variables combined. The area under the curve (AUC) was also shown

One interesting finding was that MSA events were related to TG levels. The univariate analysis revealed that the TG level was higher in the mixed OSAHS patients than in the pure OSAHS patients. In particular, in the logistic regression model, after adjustment for AHI, sex, BMI, and ESS scores, patients with higher TG levels had an elevated risk for MSA events. TG was one of lipids in the blood and increased TG level is associated with higher risk of cardiovascular events. Meanwhile, mounting evidence indicates that cognitive function was impaired in subjects with elevated TG levels [22, 24]. Vieira et al. found that metabolic syndrome was associated with lower cognition in a multi-ethnic population [23]. van den Kommer et al. demonstrated that high TG level was a risk factors for memory impairment [24]. Additionally, Peng et al. found that dyslipidemia was related to neurocognitive impairment in OSAHS patients [25]. Therefore, we are led to speculate that mixed OSAHS patients had an increased risk for neurocognitive impairment.

This study had some limitations. First, it was a cross-sectional study, and we can't accurately explain the causality of the findings. Further research is warranted to investigate the effect of MSA events on CPAP titration and surgical outcomes in OSAHS patients. In addition, unfortunately, our clinical evaluation was inadequate and the assessment of patients' cognitive function was not included, which might reduce the power of the study. Finally, our study didn't cover other comorbidities of OSAHS.

In conclusion, this study showed that the MSA events were associated with the stability of the ventilatory control system in OSAHS patients. MSA events occur more frequently in severe OSAHS patients, and male gender, higher BMI, higher ESS scores, and higher TG levels are associated with higher risk for MSA events in OSAHS patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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