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Associations between different anatomical types of chronic rhinosinusitis and anxiety and depression

Yanping Chen[1]
Juan Jiang[1]
Chuze Xu[2]
Weijun Chen[1]
Yan Geng[1]
Chenyang Lei[1]

Author details can be found at the end of this article

Correspondence to:
Chenyang Lei
(1335127141@qq.com)

Abstract

Aims/Background Patients with chronic rhinosinusitis often have a higher incidence of anxiety and depression. Nevertheless, the impact of specific chronic rhinosinusitis types (chronic anterior/posterior/anterior and posterior rhinosinusitis) on anxiety and depression remains unexplored.

Methods From January 2022 to July 2023, we employed various assessment scales to gauge the severity of chronic rhinosinusitis and anxiety and depression among Chinese patients with chronic rhinosinusitis. Statistical analysis involved non-parametric tests and binary logistic regression.

Results In total, 123 patients with chronic rhinosinusitis were enrolled. The number of patients with anxiety and depression in the chronic posterior rhinosinusitis and chronic anterior and posterior rhinosinusitis groups (p=0.022), the nasal symptom subdomain scores of the chronic anterior rhinosinusitis and chronic anterior and posterior rhinosinusitis (p=0.011) groups and the chronic posterior rhinosinusitis and chronic anterior and posterior rhinosinusitis (p=0.008) groups, and the Lund-Kennedy score of the three groups (all $p < 0.05$) were significantly different. Binary logistic regression analysis revealed that chronic rhinosinusitis type (p=0.035) was a risk factor for anxiety and depression.

Conclusion Anatomical chronic rhinosinusitis type was a risk factor for anxiety and depression in patients with chronic rhinosinusitis.

Key words: Anxiety; Chronic anterior rhinosinusitis; Chronic anterior and posterior rhinosinusitis; Chronic posterior rhinosinusitis; Depression

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Introduction

Chronic rhinosinusitis (CRS) is a common clinical disease characterised by a variety of symptoms, including nasal symptoms, such as nasal congestion, runny nose, and olfactory dysfunction; as well as ear/facial symptoms, such as facial pain, sleep disorders, and cognitive dysfunction). A study by DeConde and Soler (2016) indicated that the quality of life (QoL) of patients with CRS was significantly lower than that of people without CRS.

Compared to the general population, patients with CRS reportedly have a higher risk of developing psychological disorders. Anxiety and depression are the two most common psychological disorders that affect patients with CRS (Kim et al, 2019). Brandsted and Sindwani (2007) reported that the incidence of depression in patients with CRS was 25%. Anxiety and depression exacerbate patients' perception of local CRS symptoms, such as oropharyngeal and facial discomfort; as well as systemic symptoms, such as fatigue and decreased sexual function, leading to increased use of antibiotics and reduced workplace productivity and QoL. In addition, anxiety and depression pose certain challenges in the treatment of CRS (DeConde et al, 2015; Levy et al, 2016). However, psychological factors that affect patients with CRS are often ignored, leading to complaints of intense pain or serious symptoms with no corresponding objective clinical findings (Baijens et al, 2015).

The maxillary, frontal, and anterior ethmoid sinuses (anterior rhinosinuses) all drain into the middle meatus; thus, patients with anterior rhinosinusitis tend to present with anterior nasal discharge, facial pain, and nasal congestion. The posterior ethmoid sinuses and sphenoid sinuses (posterior rhinosinuses) drain into the superior meatus; therefore,

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patients with posterior rhinosinusitis often experience regurgitation, cough, and occipital headaches (Kwah and Peters, 2019).

Only a few studies have evaluated the effects of the different anatomical types of CRS (chronic anterior rhinosinusitis [CARS], chronic posterior rhinosinusitis [CPRS], and chronic anterior and posterior rhinosinusitis [CAPRS]) on patients' anxiety and depression levels. Determining the associations between the anatomical types of CRS and anxiety and depression can aid in the identification of potential anxiety and depression in patients and allow for accurate diagnosis and appropriate treatment. Therefore, this study aimed to evaluate the association between different anatomical types of CRS and anxiety and depression in patients with CRS.

Methods

Study population and inclusion criteria

This was a retrospective study of patients who met the diagnostic criteria for CRS outlined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (Fokkens et al, 2020) and who had not undergone any surgical treatment between January 2022 and July 2023. A total of 123 patients were included in the study. All CRS diagnoses were made by professional otolaryngologists. The specific inclusion criteria were patients who were at least 18 years old, met the diagnostic criteria for CRS, and had not undergone any surgical treatment. The exclusion criteria were patients who were younger than 18 years old; had a history of surgery; serious diseases, such as cardiocerebrovascular, liver, lung, or kidney disease, hypertension, diabetes, or tumours; and mental illness; as well as those who could not or refused to cooperate or had incomplete clinical data. The study received approval from the Medical Ethics Committee of Tongde Hospital of Zhejiang Province (approval no. [2019]073) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Evaluation of chronic rhinosinusitis severity

The patients were asked to complete the Sino-Nasal Outcome Test-20 (SNOT-20) at the first clinical visit. The SNOT-20 is divided into the following domains: nasal symptoms (0–18 points), facial/ear symptoms (0–12 points), sleep (0–12 points), and emotional disorders (0–18 points) (Kara et al, 2018). All patients underwent computed tomography (CT) (GE, Optima CT680, Boston, MA, USA) of the sinuses, and the Lund-Mackay score (LMS) was used to evaluate the inflammation of the bilateral maxillary sinuses, anterior and posterior ethmoid sinuses, frontal sinuses, sphenoid sinuses, and ostiomeatal complexes (OMCs) (score range, 0–24 points; 0–2 points for each item). In addition, the patients underwent video endoscopy (Xion, SC-WU26-A1511, San Jose, CA, USA), and the Lund-Kennedy score (LKS) was used to evaluate the presence of bilateral polyps, oedema, rhinorrhoea, scars, and scabs (score range, 0–20 points; 0–2 points for each item). Symptoms, imaging findings, and endoscopy results were used to assess the severity of CRS.

Patients were divided into three groups based on opacified sinus and OMC obstruction observed on CT: CARS (lesions only in the anterior nasal sinuses) (n=44), CPRS (lesions only in the posterior nasal sinuses) (n=14), and CAPRS (lesions in both the anterior and posterior nasal sinuses) (n=65) groups.

Evaluation of anxiety and depression

Patients were required to complete the Generalised Anxiety Disorder-7 (GAD-7) Scale and the Patient Health Questionnaire-9 (PHQ-9) at the first clinical visit. The GAD-7 is highly effective, has excellent validity, and is strongly correlated with patient anxiety. The possible scores for each item range from 0 to 3, with the highest possible score being 21 points, and a score of 8 points is considered indicative of anxiety (Plummer et al, 2016). The PHQ-9 is an effective and credible self-assessment scale used for evaluating the severity of depression. The scores for each item range from 0 to 3, with the highest possible score being 27 points, and a score of at least 10 indicates the presence of depression (Levis et al, 2019). Patients with GAD-7 scores > 8 and/or PHQ-9 scores > 10 were considered

to have anxiety and depression, whereas those with lower scores were regarded as having no anxiety and depression.

Statistical analysis

Continuous variables with a normal distribution are presented as means ± standard deviation (SD), with differences between groups assessed using independent sample *t*-tests or one-way Analysis of Variance (ANOVA). Non-normally distributed variables are described by the median (interquartile range (IQR)), with differences analysed using the Mann-Whitney U test and Kruskal-Wallis test. Categorical variables were compared using the chi-square test. Collinearity diagnosis was conducted to screen variables for inclusion in binary logistic regression analysis, which aimed to identify risk factors for anxiety and depression.

The confidence interval was set at 95% and the significance level at 0.05. SPSS (version 23.0, IBM, Armonk, NY, USA) was used for all statistical analyses.

Results

Baseline characteristics of the patients

Among 156 patients who met the inclusion criteria, 33 were excluded owing to incomplete clinical data. A total of 123 patients were enrolled in this study, including 75 men and 48 women (mean age, 43.35 ± 15.14 years). The interquartile range (IQR) of the overall GAD-7 score, PHQ-9 score, LMS, and SNOT-20 score were 3 (4), 3 (5), 7 (4.5), and 13 (14), respectively. Other basic characteristics of the cohort are shown in Table 1.

Differences between the chronic anterior rhinosinusitis, chronic posterior rhinosinusitis, and chronic anterior and posterior rhinosinusitis groups

The differences between the CARS (n=44), CPRS (n=14), and CAPRS (n=65) groups are compared in Table 2. The number of patients with anxiety and depression in the CPRS group was significantly lower than that in the CAPRS group (p=0.022). The difference in the number of patients with anxiety and depression between the CARS and CAPRS groups almost reached statistical significance (p=0.056). The nasal symptom domain scores differed significantly between the CARS and CAPRS groups (p=0.011) as well as between the CPRS and CAPRS groups (p=0.008). There were significant differences in

Table 1. Baseline characteristics of the study cohort

Characteristics	Total (n=123)
Male (%)	75 (61.00)
Female (%)	48 (39.02)
Age (Mean [SD])	43.35 (15.14)
GAD-7 score (Median [IQR])	3 (4)
PHQ-9 score (Median [IQR])	3 (5)
Anxiety (GAD-7 > 8) (%)	13 (10.57)
Depression (PHQ-9 > 10) (%)	16 (13.01)
Smoking (%)	29 (23.58)
Polyps (%)	46 (37.40)
LMS (Median [IQR])	7 (4.5)
LKS (Mean [SD])	5.07 (1.68)
SNOT-20 score (Median [IQR])	13 (14)

GAD-7, Generalised Anxiety Disorder-7; IQR, interquartile range; PHQ-9, Patient Health Questionnaire-9; LMS, Lund-Mackay score; LKS, Lund-Kennedy score; SNOT-20, Sino-Nasal Outcome Test-20; SD, standard deviation.

Table 2. Comparison of various anatomical types of chronic rhinosinusitis

	CARS (n=44)	CPRS (n=14)	CAPRS (n=65)	*p1*	*Z1*	*p2*	*Z2*	*p3*	*Z3*
AD (%)	4 (9.09)	1 (7.14)	19 (29.23)	1		0.022		0.056	
NAD (%)	40 (90.91)	13 (92.86)	46 (70.77)						
GAD-7 score (Median [IQR])	2 (3.25)	4 (1.75)	3 (5)	0.088	–1.708	0.143	–1.466	0.497	–0.679
PHQ-9 score (Median [IQR])	3 (4.25)	4.5(6)	3(6)	0.447	–0.761	0.132	–1.508	0.746	–0.323
SNOT-20 score (Median [IQR])	12 (11.25)	12.5 (5.75)	15 (14)	0.736	–0.337	0.055	–1.917	0.237	–1.183
Nasal symptom (Median [IQR])	4 (5.25)	4 (2.75)	6 (4)	0.571	–0.566	0.011	–2.533	0.008	–2.650
Ear/facial symptom (Median [IQR])	2 (4)	2 (1)	2 (3)	0.191	–1.309	0.466	–0.729	0.519	–0.645
Sleep disorders (Median [IQR])	1.5 (4)	3 (2.5)	3 (4)	0.334	–0.966	0.385	–0.869	0.664	–0.434
Psychological symptoms (Median [IQR])	2 (6)	2.5 (1.75)	4 (6)	0.514	–0.652	0.23	–1.200	0.477	–0.711
LKS (Median [IQR])	5 (2)	4 (1.75)	6 (3)	0.038	–2.077	0.041	–2.043	0.002	–3.105

P1/Z1: CARS vs CPRS; P2/Z2: CARS vs CAPRS; P3/Z3: CPRS vs CAPRS.

CARS, chronic anterior rhinosinusitis; CPRS, chronic posterior rhinosinusitis; CAPRS, chronic anterior and posterior rhinosinusitis; AD, anxiety and depression; NAD, no anxiety and depression; GAD-7, Generalised Anxiety Disorder-7; IQR, interquartile range; PHQ-9, Patient Health Questionnaire-9; LKS, Lund-Kennedy score; SNOT-20, Sino-Nasal Outcome Test-20; CRS, chronic rhinosinusitis; SD, standard deviation.

the LKS between the CARS and CPRS groups (p=0.038), the CPRS and CAPRS groups (p=0.041), as well as the CPRS and CAPRS groups (p=0.002).

Effects of different types of CRS on AD

The correlations between different variables and the occurrence of anxiety and depression in patients with CRS are outlined in Table 3. There were significant differences in age (p=0.043), total SNOT-20 score ($p < 0.001$), and the SNOT-20 domain scores (nasal symptoms [$p < 0.001$], facial/ear symptoms [p=0.001], sleep disorders [$p < 0.0001$], psychological symptoms [$p < 0.001$]), CRS type [p=0.016], and LKS [p=0.001]) between the anxiety and depression (AD) and no anxiety and depression (NAD) subgroups. However, no significant differences were observed in sex (p=0.865, chi-square value=0.029) or the LMS (p=0.148) between the AD and NAD subgroups.

Before conducting the binary logistic regression analysis, we conducted collinearity diagnostics to assess the correlation between variables. We observed a high correlation among the SNOT-20 score, nasal symptoms, facial/ear symptoms, sleep disorders, and psychological symptoms (VIF=1017.957, 134.206, 70.128, 99.246, 155.865, respectively). Following the exclusion of the SNOT-20 score, the VIF for nasal symptoms, facial/ear symptoms, sleep disorders, and psychological symptoms were all below 10.

After collinearity diagnostics, we selected age, nasal symptoms, facial/ear symptoms, sleep disorders, psychological symptoms, CRS type, and LKS as covariates for the binary logistic regression. The results of the analysis showed that CRS type (CAPRS, p=0.035; CARS, p=0.01; CPRS, p=0.466) and psychological symptoms ($p < 0.0001$) were risk factors for AD (Table 4).

Table 3. Comparison between the AD and NAD subgroups

	AD (n=24)	NAD (n=99)	*p*	*z*	χ^2
Male (%)	15 (62.50)	60 (60.60)	0.865		0.029
Female (%)	9 (37.50)	39 (39.39)			
Age (Mean [SD])	37.46 (12.71)	44.78 (15.33)	0.043		
SNOT-20 score (Median [IQR])	27 (15.25)	12 (9)	< 0.001	–5.908	
Nasal symptoms (Median [IQR])	8 (5)	5 (4)	< 0.001	–3.492	
Ear/facial symptoms (Median [IQR])	4.5 (5)	2 (2)	0.001	–3.215	
Sleep disorder (Median [IQR])	7 (6)	2 (3)	< 0.001	–4.072	
Psychological symptoms (Median [IQR])	9 (4.25)	2 (3.5)	< 0.001	–6.152	
CRS type (%)					
CARS	4 (16.67)	40 (40.40)	0.016		8.316
CPRS	1 (4.17)	13 (13.13)			
CAPRS	19 (79.17)	4 (46.46)			
LMS (Median [IQR])	8 (5.5)	7 (4.5)	0.148	–1.448	
LKS (Median [IQR])	6 (2)	5 (2)	0.001	–3.241	

CARS, chronic anterior rhinosinusitis; CPRS, chronic posterior rhinosinusitis; CAPRS, chronic anterior and posterior rhinosinusitis; AD, anxiety and depression; NAD, no anxiety and depression; LMS, Lund-Mackay score; LKS, Lund-Kennedy score; SNOT-20, Sino-Nasal Outcome Test-20; IQR, interquartile range; CRS, chronic rhinosinusitis; SD, standard deviation.

Table 4. Binary logistic regression analysis of the risk factors for AD

	AD						
	B	SE	Wald	df	OR	95% CI	*p*
Age	0.009	0.024	0.156	1	1.009	0.964–1.057	0.693
CRS type			6.717	2			0.035
CARS vs CAPRS	–2.460	0.955	6.636	1	0.085	0.013–0.555	0.01
CPRS vs CAPRS	–0.937	1,286	0.531	1	0.392	0.031–4.875	0.466
Nasal symptoms	0.078	0.116	0.450	1	1.081	0.861–1.357	0.502
Ear/facial symptoms	–0.017	0.129	0.018	1	0.983	0.763–1.265	0.892
Sleep disorder	0.092	0.127	0.527	1	1.097	0.855–1.407	0.468
Psychological symptoms	0.589	0.148	15.871	1	1.802	1.349–2.407	< 0.0001
LKS	0.044	0.244	0.033	1	1.045	0.647–1,687	0.856

CARS, chronic anterior rhinosinusitis; CPRS, chronic posterior rhinosinusitis; CAPRS, chronic anterior and posterior rhinosinusitis; AD, anxiety and depression; LKS, Lund-Kennedy score; SE, standard error; OR, odds ratio; CI, confidence interval; CRS, chronic rhinosinusitis.

Correlation between AD and CRS

We conducted a correlation analysis between GAD-7 and PHQ-9 and the severity of CRS (nasal symptoms, ear/facial symptoms, sleep disorders, LMS, and LKS), and found that the correlation coefficients of each variable with the GAD-7 score were 0.024, 0.039, –0.009, –0.125 and –0.009 respectively, while the correlation coefficients of each variable with the PHQ-9 score were 0.020, 0.166, 0.283, 0.076 and –0.028, respectively. Moreover, only sleep disorders have been found to be significantly positively correlated with depression in patients with CRS (p=0.002).

Discussion

The interaction between CRS, psychological disorders (especially anxiety and depression), and QoL has received increasing attention recently (Brandsted and Sindwani, 2007; Kim et al, 2019). The results of previous studies have suggested that anxiety, depression, and the severity of somatic symptoms usually interact with each other, and the occurrence of anxiety and depression in patients with CRS is usually inconsistent with the results of objective assessment of CRS severity (Fokkens et al, 2020; Ranford et al, 2020). The present study confirmed this finding. However, before the present study, no study has been conducted to analyse the relationship between different anatomical types of CRS and anxiety and depression.

In the present study, the number of patients with anxiety and depression in the CARS group was significantly lower than that in the CAPRS group. A similar result was observed when comparing the number of patients with anxiety and depression in the CPRS and CAPRS groups; however, the *p*-value was slightly greater than 0.05. We conducted a binary logistic regression analysis to identify the risk factors for anxiety and depression, and the results revealed the effects of different CRS types on anxiety and depression. The proportion of patients with anxiety and depression in the CAPRS group was higher than that in the CARS and CPRS groups. This may be because patients are more likely to experience a wider variety of physical symptoms when CRS involves both the anterior and posterior nasal sinuses. Notably, the difference in the number of patients with anxiety and depression was more pronounced between the CARS and CAPRS groups than between the CPRS and CAPRS groups. Therefore, we can infer that the occurrence of anxiety and depression is influenced more by the clinical symptoms of CARS than CPRS.

The frontal/facial pain and fullness observed in patients with CARS and CAPRS stem from obstruction of the drainage channel of the anterior group of sinuses. In addition, many heteromorphoses of the anterior ethmoid sinus affect the ventilatory function of the nasal cavity and drainage of the frontal sinus (Marino et al, 2016). Nasal obstruction is reportedly a predictor of depression (Phillips et al, 2017). Patients with nasal obstruction are at higher risk for depression compared to those without nasal obstruction. In addition, nasal obstruction is the most important factor that causes a decline in sleep quality, which is observed in patients with allergic rhinitis (Jiang et al, 2016). Olfactory dysfunction has been reported to significantly impair QoL related to nasal symptoms. Moreover, individuals with CRS often endure elevated levels of psychological stress and depression compared to controls, with improvements in psychological states observed following enhancements in olfactory function (Valsamidis et al, 2020).

There is limited research exploring the mechanism behind anxiety and depression induced by CRS. A study conducted by Lin et al (2023) unveiled increased activity in the orbital superior frontal cortex (emotional regulation region) in patients with CRS compared to healthy individuals. Furthermore, connectivity between this region and the precuneus decreased, potentially correlating with cognitive function impairments in patients with CRS. These changes may be attributed to the infiltration of pro-inflammatory cytokines into the central nervous system, triggering alterations in emotional and cognitive functions (Capuron and Miller, 2011). Additionally, disruption in nasal sinus microbiota homeostasis could induce neuronal changes in the associated central nervous system, contributing to emotional symptoms (Harrass et al, 2021).

Comparison between the AD and NAD subgroups in the present study demonstrated that age, nasal symptoms, facial/ear symptoms, and sleep disorders were associated with anxiety and depression. Although these findings were not confirmed in the binary logistic regression analysis, they have been demonstrated by some previous studies (Bengtsson et al, 2017; Nanayakkara et al, 2013). Regarding age, older patients tolerated CRS better than younger patients; therefore, the impact of CRS on the QoL of older patients is less than that of younger patients. This indicates that older patients are less likely than younger patients to develop CRS-related anxiety and depression. Nasal and facial/ear symptoms of CRS include discharge, olfactory dysfunction, runny nose, headache, and ear fullness. Nanayakkara et al (2013) used the SNOT-20 and Hospital anxiety and depression Scale to evaluate patients' symptoms and anxiety and depression, which found a significant

correlation between nasal symptoms and depression. Facial/ear symptoms mainly affect the patient's sleep and cause physical symptoms, leading to a reduction in the patient's QoL and triggering emotional instability (Brandsted and Sindwani, 2007; Kara et al, 2018). However, whether anxiety and depression improve after surgery performed to alleviate disease-specific symptoms remains controversial (DeConde et al, 2015). Several studies have demonstrated that the proportion of patients with CRS who have sleep disorders is as high as 60–75%, which is much higher than that of the general population (Mahdavinia et al , 2017; Bengtsson et al, 2017). Therefore, we believe that sleep disorders have a direct and significant effect on anxiety and depression in patients with CRS. Clinicians should consider that anti-insomnia treatments for patients with CRS may simultaneously improve their anxiety and depression.

Although the occurrence of anxiety and depression was associated with clinical symptoms of CRS in the present study, there was no significant correlation between anxiety and depression and the objective severity of CRS (measured using the LMS). Furthermore, there was no association between clinical symptoms of CRS and the objective severity of CRS. Owing to the separation of psychosomatic symptoms and disease severity, the degree of improvement in mental status after functional endoscopic sinus surgery is not usually as expected (Brandsted and Sindwani, 2007). Ranford et al (2020) conducted a study on patients with CRS who had anxiety and depression or controlled anxiety and depression and found a significant association between the objective severity of CRS (measured using LMS) and clinical symptoms (measured using SNOT-22). Therefore, we can conclude that anxiety and depression is an important factor that makes achieving satisfactory treatment outcomes for CRS challenging. More attention should be paid to co-morbid anxiety and depression in patients with CRS to allow for the selection of appropriate and effective treatments.

This study has some limitations. First, this was a single-centre study, with a small sample size. Thus, future multi-centre studies with large patient populations are needed to verify the results of this study. Second, anxiety and depression are affected by many factors, which were not fully considered in this study. Therefore, further research that considers a more comprehensive range of factors is required to confirm our results. Third, we did not elaborate on the specific physiological mechanisms underlying the development of anxiety and depression in patients with CRS and did not further explore the mechanism of depression caused by the involvement of the frontal and anterior ethmoid sinuses. Further research is required to clarify the molecular regulatory mechanisms underlying the correlation between CRS types and anxiety and depression.

Conclusion

This study demonstrates that the anatomical type of CRS is a risk factor for anxiety and depression in patients with CRS. Patients with CAPRS were more likely to have anxiety and depression than those with CARS. However, there was no difference in the incidence of anxiety and depression between patients with CAPRS and those with CPRS. These results

Key points

- Various anatomical types of chronic rhinosinusitis (CRS) (chronic anterior rhinosinusitis [CARS], chronic posterior rhinosinusitis [CPRS], and chronic anterior and posterior rhinosinusitis [CAPRS]) exhibit distinct effects on anxiety and depression.
- The severity of CRS was assessed using the Sino-Nasal Outcome Test-20 score, Lund-Mackay score, and Lund-Kennedy score.
- A&D evaluation utilised the Generalised Anxiety Disorder-7 and Patient Health Questionnaire-9 scores.
- Patients with CAPRS demonstrated a higher likelihood of experiencing anxiety and depression compared to those with CARS.
- Tailored treatment approaches for CRS should be based on the specific anatomical type of CRS present.

indicate that treatment should be tailored to patients with CRS based on the anatomical type of CRS they have.

Curriculum checklist

This article addresses the following requirements of the general internal medicine curriculum:

- Diagnosis and differential diagnosis of CRS
- Treatment of CRS

Author details

[1]Department of Otorhinolaryngology, Tongde Hospital of Zhejiang Province, Hangzhou, Zhejiang, China

[2]School of Optometry and Ophthalmology, Wenzhou Medical University, Wenzhou, Zhejiang, China

Availability of data and materials

All the data supporting the findings of this study are available within the manuscript.

Author contributions

CYL and YPC participated in the design of the study. WJC, JJ, YG and CZX performed data collection and statistical analysis. YPC and YG drafted the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Tongde Hospital of Zhejiang Province (approval no. [2019]073) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Conflict of interest

The authors declare no conflict of interest.

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