Autonomic dysfunction as an independent risk factor for uncontrolled inflammation in chronic rhinosinusitis following functional endoscopic sinus surgery*

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Abstract

Background: Chronic rhinosinusitis (CRS) is a multi-factorial disorder that causes systemic symptoms beyond rhinologic symptoms alone. A possible association between autonomic nervous system (ANS) dysfunction and CRS has been identified; however, few studies have confirmed this observation. In this study, we prospectively measured changes in ANS dysfunction symptoms following functional endoscopic sinus surgery (FESS) and explored the impact of ANS dysfunction on surgical outcomes of CRS.

Methodology: Patients diagnosed with CRS who consented to surgical intervention were included prospectively. All patients completed the Sino-nasal Outcome Test-22 (SNOT-22) and the 31-item Composite Autonomic Symptom Score (COMPASS 31) questionnaires before the operation and during the follow-up period. Clinical demographic data, Lund-Mackay, and modified Lund-Kennedy scores were recorded and measured.

Results: A total of 102 patients were enrolled. The median SNOT-22 and COMPASS 31 scores significantly improved following FESS from 43.0 to 14.0 and 21.0 to 11.2 (all P<0.001), respectively. FESS led to a significant reduction in the prevalence of various ANS dysfunction symptoms. In multivariate analyses, revision surgeries (odds ratio [OR] 5.012, 95% confidence interval [CI] 1.524-16.489; P=0.008), CRS with nasal polyps (OR 4.071, 95% CI 1.454-11.40; P=0.008), and higher Pre-FESS COMPASS 31 scores (OR 1.043, 95% CI 1.003-1.084; P=0.036) were independent risk factors for uncontrolled inflammation following FESS.

Conclusions: ANS dysfunction symptoms are prevalent in CRS and higher preoperative COMPASS 31 scores correspond with poor surgical outcomes. Following FESS, the majority of ANS dysfunction symptoms can be alleviated. Further investigations are required to explore the possible mechanism of how ANS is involved in the pathogenesis of CRS.

Key words: COMPASS 31, dysautonomia, SNOT-22, FESS, outcome

Introduction

Chronic rhinosinusitis (CRS) is a multi-factorial disorder caused by a combination of inflammation, allergy, and local host and environmental factors[1]. The prevalence of CRS ranges from 5.2% to 12.1% in Canada, the United States, and Europe, and causes a significant burden on the healthcare system[2]. The overall direct and indirect costs of CRS have been estimated to be around US$22 billion per year in the United States[3].

Furthermore, CRS may cause systemic effects beyond rhinologic symptoms. Previous studies have shown that non-rhinologic symptoms, including depression, sleep dysfunction, and cognitive dysfunction, have a significant impact on the overall health-related burden of CRS[4–6]. Recently, positive correlations have been found between the symptom burden of autonomic nervous system (ANS) dysfunction and CRS[7,8].

The ANS, which regulates and maintains organ functions in the body, is composed of two primary pathways: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). ANS dysfunction has various clinical manifestations in the cardiovascular, sudomotor, alimentary, urinary, sexual, and optical systems[9]. In patients with airway disease, ANS dysfunction is associated with vasomotor rhinitis, allergic rhinitis, and asthma[10–13]. Also, ANS dysfunction is associated with psychosomatic disorders including depression, anxiety, fatigue, and sleep dysfunction; such conditions are also linked to CRS[7,14–18]. Currently, the relationship between ANS dysfunction and CRS is poorly understood; there may be a complex biopsychosocial interplay.

In CRS patients that fail conservative medical treatment, functional endoscopic sinus surgery (FESS) is the current mainstay of treatment. FESS significantly improves not only sinonasal-specific symptoms and quality of life (QOL), but also psychosomatic symptoms such as sleep dysfunction, depression, and cognitive dysfunction in CRS patients[5,19–21]. Because there is a positive correlation between symptom burden of CRS and ANS dysfunction[7,8], we hypothesized that ANS dysfunction symptoms could be alleviated following FESS in CRS patients. In this study, we measured changes in ANS dysfunction associated symptoms following FESS and explored the impact of ANS dysfunction on surgical outcomes of CRS.

Materials and methods

Patients diagnosed with CRS between May 2016 and March 2018 at the Kaohsiung Chang Gung Memorial Hospital were included prospectively. Diagnosis criteria followed the clinical practice guidelines of EPOS (2012)[1]. All patients received adequate medical treatment including intranasal corticosteroids for at least a 2-month course and oral steroids or antibiotics (depending on their condition) for 2 to 4 weeks. Patients who did not improve and consented to surgical intervention were candidates for this study. All patients signed informed consent forms before the operation. Sinonasal endoscopy and paranasal sinus computed tomography (CT) were performed prior to the operation. All patients were followed up in 3-month intervals and cases with suspected persistent or recurrent disease received repeated CT. After operation, all patients underwent nasal saline irrigation and received intranasal corticosteroids for at least 1 month according to their condition. Patients with nasal polyps received oral steroids for at least 2 weeks and oral antibiotics for 2 to 4 weeks in cases of acute exacerbation. The levels of total IgE and allergen-specific IgE were measured before surgery to evaluate allergic status. All patients completed the Sino-nasal Outcome Test-22 (SNOT-22) and COMPASS 31 questionnaires before the operation and 1 year after the operation. The study protocol was approved by the medical ethics and human clinical trial committees of Chang Gung Memorial Hospital (Refs: 104–7185B, 201700431B0).

Research instruments

Sino-nasal Outcome Test-22 (SNOT-22)

The SNOT-22 is a well-validated sinonasal symptom questionnaire with 22 items, where each item is scored from 0 (no problem) to 5 (problem as bad as it can be). The maximum score is 110 with a higher score reflecting worse symptoms. It is divided into five distinct subdomains: rhinological symptoms, extranasal rhinological symptoms, ear/facial symptoms, psychological dysfunction, and sleep dysfunction[22].

Composite Autonomic Symptom Score 31 (COMPASS 31)

The 31-item COMPASS 31 is a validated and simplified questionnaire that evaluates symptom burden of autonomic dysfunction. It includes 31 questions divided into six subdomains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal (GI), bladder, and pupillomotor symptoms. The maximum raw score is 75 and then weighted using published values to generate scores ranging from 0–100. A higher score reflects worse symptoms of ANS dysfunction[23].

CT and sinonasal endoscopy

All patients received high-resolution paranasal sinus CT with 1 mm slices and the CT images were scored with consensus using the Lund-Mackay system. The scores ranged from 0 to 24, with higher scores representing greater disease severity[24]. The endoscopic findings before and during the follow-up period were scored with consensus using the modified Lund-Kennedy system. The scores ranged from 0 to 12, with higher scores representing greater disease severity[25].

Statistical analyses

Changes in COMPASS 31 and SNOT-22 were tested using the Wilcoxon signed rank test. The Mann-Whitney U test was used to compare differences between the abnormal and normal endoscopy cases. The chi-square test or Fisher's exact test were used for all other between-group comparisons. Changes among the prevalence of different ANS dysfunction symptoms before and after FESS were statistically analysed using the McNemar-Bowker test (Figure 1). Multivariate logistic regression with the stepwise method was performed to determine the independent risk factors for abnormal endoscopy following FESS. A p-value < 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS version 22 software (IBM Corp., Armonk, NY, USA).

Results

A total of 194 consecutive patients with CRS were identified. A total of 57 patients with hypertension, diabetes mellitus, any

Table 1. Baseline characteristics by concordance subgroup.

Patient characteristic	Mean ± SD	n (%)
Age (y/o)	42.2 ± 15.1	
Female		47 (46.1%)
Male		55 (53.9%)
Current smoker		16 (15.7%)
Revision cases		17 (16.7%)
Allergic rhinitis		37 (36.3%)
Asthma		8 (7.8%)
CRSwNP		51 (50%)
Modified Lund-Kennedy score	4.6 ± 3.1	
Lund-Mackay score	9.5 ± 6.5	
COMPASS 31	22.4 ± 12.9	
SNOT-22	42.9 ± 20.2	

CRSwNP = Chronic rhinosinusitis with nasal polyp; COMPASS 31 = 31-item Composite Autonomic Symptom Score; SNOT-22 = 22-item Sino-Nasal Outcome Test; SD = Standard deviation.

psychological disorder, chronic renal insufficiency, or a malignant tumour history were excluded. A total of 35 patients without complete 1-year follow-up data were also excluded. The majority of patients refused to return due to significant relief of symptoms following FESS. Ultimately, 102 patients (55 males, 47 females; mean age 42.2 ± 15.1 years) were prospectively enrolled. The mean follow-up period was 12.5 months (11.8 to 15.1 months). The mean pre-FESS COMPASS 31 and SNOT-22 scores were 22.4 ± 12.9 and 42.9 ± 20.2, respectively. Demographic data are shown in Table 1. The COMPASS 31 and SNOT-22 scores showed no differences by sex, current smoker, allergic rhinitis, asthma, revision surgery, and CRS type (with or without polyp). There were 51 patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and 51 with chronic rhinosinusitis without nasal polyps (CRSsNP). The CRSwNP group had a higher Lund-Mackay CT median score (11.0 vs. 6.0, P < 0.001) and modified Lund-Kennedy median score (6.0 vs. 3.0, P < 0.001), and was male predominant (68.6% vs. 39.2%, P = 0.003) compared to the CRSsNP group.

Changes in COMPASS 31 and SNOT-22 scores following FESS

The SNOT-22 score significantly improved from a pre-FESS median score of 43.0 to a post-FESS median score of 14.0 (P < 0.001). In subdomain analyses, all SNOT-22 subdomain scores significantly improved following FESS (all P < 0.001) (Table 2). The COMPASS 31 score significantly improved from a pre-FESS median score of 21.0 to a post-FESS median score of 11.2 (P < 0.001). In subdomain analyses, three COMPASS 31 subdomains

Table 2. Changes in COMPASS 31 and SNOT-22 scores following FESS.

	Pre-FESS Median (IQR)	Post-FESS Median (IQR)	P
COMPASS 31	21.0 (11.1 ~ 34.0)	11.2 (2.5 ~ 21.1)	<0.001
Orthostatic intolerance	12.0 (0.0~16.0)	0 (0 ~ 12.0)	<0.001
Vasomotor	0 (0 ~ 0)	0 (0 ~ 0)	0.305
Secretomotor	6.4 (4.3 ~ 8.6)	2.1 (2.1 ~ 6.4)	<0.001
Gastrointestinal	4.5 (1.8 ~ 6.3)	1.8 (0 ~ 5.4)	<0.001
Bladder	0 (0 ~ 1.1)	0 (0 ~ 1.1)	0.901
Pupillomotor	1.3 (0.3 ~ 2.1)	1.2 (0 ~ 2.3)	0.889
SNOT-22	43.0 (28.0 ~ 56.0)	14.0 (7.0 ~ 23.3)	<0.001
Rhinological symptoms	15.0 (10.0 ~ 20.0)	5.0 (2.0 ~ 10.0)	<0.001
Extranasal rhinological symptoms	7.0 (4.0 ~ 9.0)	2.0 (0 ~ 3.3)	<0.001
Ear/facial symptoms	6.5 (3.0 ~ 9.0)	2.0 (1.0 ~ 4.0)	<0.001
Psychological dysfunction	12.0 (5.0 ~ 19.3)	2.5 (0 ~ 8.0)	<0.001
Sleep dysfunction	11.5 (5.0 ~ 16.0)	5.0 (0 ~ 6.3)	<0.001

COMPASS 31 = 31-item Composite Autonomic Symptom Score; SNOT-22 = 22-item Sino-Nasal Outcome Test; FESS = Functional endoscopic sinus surgery; IQR = Interquartile range.

(orthostatic intolerance, secretomotor, and GI symptoms) significantly improved following FESS (all P < 0.001) (Table 2).

Change in prevalence of ANS dysfunction symptoms following FESS

The answers to COMPASS 31 were divided into two sets: negative (answer: no, never) and positive (answer: yes, sometimes, a lot of the time, occasionally, frequently, constantly) symptoms. The most common preoperative, positive ANS dysfunction symptoms were excessive dry mouth (70.6%), excessively full after a meal (69.6%), excessive dry eyes (67.6%), postural dizziness (60.8%), photophobia (58.2%), cramping abdominal pain (51.0%), difficulty in visual focusing (48.0%), bouts of diarrhoea (40.2%), constipation (36.3%), and urinary retention (33.4%). Other uncommon symptoms included dysuria (11.8%), urinary incontinence (8.9%), vomiting after a meal (9.8%), and skin colour changes (5.9%).

After 1-year follow-up, FESS led to a significant reduction in the

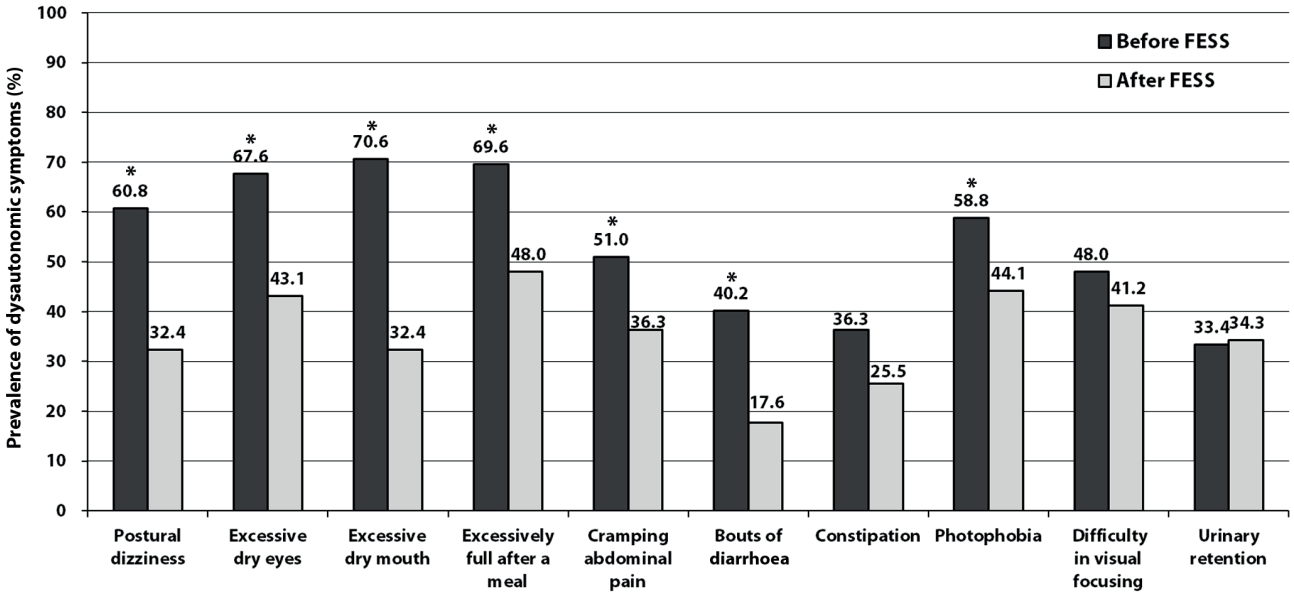

Figure 1. Prevalence of ANS dysfunction symptoms. *P < 0.05

prevalence of excessive dry mouth (70.6% to 32.4%, P < 0.001), excessive dry eyes (67.6% to 43.1%, P < 0.001), postural dizziness (60.8% to 32.4%, P < 0.001), excessively full after a meal (69.6% to 48.0%, P = 0.001), bouts of diarrhoea (40.2% to 17.6%, P = 0.001), photophobia (58.2% to 44.1%, P = 0.02) and cramping abdominal pain (51.0% to 36.3%, P = 0.04) (Figure 1). There was no significant improvement in other symptoms (all P > 0.05). Before FESS, only 2.0% of patients had none of the above symptoms. One year following FESS, 23.5% of patients had none of the symptoms (P < 0.001).

Impact of ANS dysfunction on surgical outcomes

We defined patients with abnormal endoscopy as uncontrolled mucosa inflammation assessed by positive objective findings in the sinonasal scope (polyp, oedema, or discharge). A total of 29 (28.4%) patients were defined as abnormal endoscopy and 3 (10.3%) received revision surgeries after 1-year follow-up due to bothersome symptoms. The abnormal endoscopy cases had significantly higher post-FESS SNOT-22 scores (P = 0.003), but the post-FESS COMPASS 31 scores showed no difference (P = 0.772) compared to normal endoscopy cases (Table 3). In univariate analyses, patients with revision surgeries (odds ratio [OR] 4.962, 95% confidence interval [CI] 1.664–14.795; P = 0.004), asthma (OR 4.861, 95% CI 1.080–21.886; P = 0.039), and CRSwNP (OR 3.762, 95% CI 1.472–9.616; P = 0.006) were at higher risk for abnormal endoscopy (Table 4). Multivariate analyses of the independent factors revealed that patients with revision surgeries (OR 5.012, 95% CI 1.524–16.489; P = 0.008), CRSwNP (OR 4.071, 95% CI 1.454–11.40; P = 0.008), and higher Pre-FESS COMPASS 31 scores (OR 1.043, 95% CI 1.003–1.084; P = 0.036) were at higher risk for abnormal endoscopy (Table 4).

Discussion

The ANS plays a critical role in the regulation of homeostasis, response to physiological stress, and the mediation of interactions between the nervous and immune systems[26]. Various psychosomatic stresses, such as sleep dysfunction, anxiety, and depression, are associated with ANS dysfunction[27–29] and are also closely associated with CRS[6,30,31]. This relationship implies a possible association between CRS and ANS dysfunction. Recently a positive correlation was found between COMPASS 31 and SNOT-22, particularly in the nonrhinological subdomains[7,8]. We found a high prevalence of ANS dysfunction symptoms in patients with CRS presenting for surgery. It is possible that our prevalence finding was an overestimation because we dichotomized the symptoms as 'positive' or 'negative'; thus, patients with mild symptoms were classified as positive. However, the prevalence decreased significantly, suggesting that ANS dysfunction symptoms were well alleviated after FESS (Figure 1).

COMPASS 31 is a simplified version of the 72-item COMPASS instrument, which is based on the Autonomic Symptom Profile (169 items). This abbreviated version is more suitable for the clinical setting. Rea et al. reported a median COMPASS 31 score of 8.06 in normal healthy controls and a median score of 50.82 in patients with autonomic neuropathy[32]. Greco et al. found a mean score of 28.9 in patients with diabetic polyneuropathy[33]. In a study of patients with sinonasal disease, Kara et al. found a mean score of 28.5 in patients diagnosed with various sinonasal-related diseases at a rhinology clinic[7]. In our study, the pre-FESS mean COMPASS 31 score was 22.4, which is slightly lower than that reported by Kara et al.[7]. Our lower score may be explained by the fact that we excluded patients with systemic or chronic

Table 3. Comparison of demographics between abnormal and normal endoscopy.

	Abnormal endoscopy (n=29)	Normal endoscopy (n=73)	P
Age (y/o)	42.9 ± 14.9	42.0 ± 15.3	0.768
Gender, n (%) Female (n = 47) Male (n= 55)	 11 (23.4%) 18 (32.7%)	 36 (76.6%) 37 (67.3%)	0.298
Current smoker, n (%) No (n = 86) Yes (n = 16)	 26 (30.2%) 3 (18.8%)	 60 (69.8%) 13 (81.3%)	0.547*
Revision cases, n (%) No (n = 85) Yes (n = 17)	 19 (22.4%) 10 (58.8%)	 66 (77.6%) 7 (41.2%)	0.006*
Allergic rhinitis, n (%) No (n = 65) Yes (n = 37)	 18 (27.7%) 11 (29.7%)	 47 (72.3%) 26 (70.3%)	0.826
Asthma, n (%) No (n = 94) Yes (n = 8)	 24 (25.5%) 5 (62.5%)	 70 (74.5%) 3 (37.5%)	0.040*
CRS types, n (%) CRSsNP (n = 51) CRSwNP (n = 51)	 8 (15.7%) 21 (41.2%)	 43 (84.3%) 30 (58.8%)	0.004
Pre-FESS COMPASS 31 median (IQR)	24.2 (15.3 ~ 35.9)	19.3 (10.6 ~ 33.5)	0.229
Pre-FESS SNOT-22 median (IQR)	48.0 (34.0 ~ 61.0)	38.0 (25.5 ~ 54.5)	0.077
Post-FESS COMPASS 31 median (IQR)	12.0 (2.5 ~ 19.4)	10.7 (2.5 ~ 23.9)	0.772
Post-FESS SNOT-22 median (IQR)	18.0 (12.0 ~ 37.5)	13.0 (6.0 ~ 18.5)	0.003

CRSsNP = Chronic rhinosinusitis without nasal polyp; CRSwNP = Chronic rhinosinusitis with nasal polyp; FESS = Functional endoscopic sinus surgery; COMPASS 31 = 31-item Composite Autonomic Symptom Score; SNOT-22 = 22-item Sino-nasal Outcome Test; IQR = Interquartile range; * Fisher's exact test.

diseases that may have affected autonomic function.

CRS predominately causes rhinologic symptoms, but CRS patients have a higher prevalence of psychosomatic disorders, which can have a significant impact on QOL[18,30,34]. Litvack et al. found that 25% of CRS patients scored positively for depression using the Patient Health Questionnaire-9 criteria (score ≥ 10) and the severity of depression significantly improved following FESS[19]. Conversely, Adams et al. showed that the self-reported Hospital Anxiety and Depression Score (HADS) was unchanged following FESS[35]. However, only 18 (40.9%) patients completed the postoperative evaluation, limiting the generalizability of their results. Alt et al. showed that up to 75% of CRS patients had sleep dysfunction based on the Pittsburgh Sleep Quality Index (PSQI) criteria (score > 5), and the severity was significantly associated with SNOT-22[36]. In a previous meta-analysis, sleep quality (evaluated using the Epworth sleepiness scale and the PSQI) improved significantly when FESS was used to treat CRS[5]. We hypothesize that reduced psychosomatic stress following FESS contributes alleviation of ANS dysfunction symptoms. In our study, we observed a high prevalence of ANS dysfunction symptoms, such as postural dizziness, dry eye, dry mouth, gastrointestinal symptoms, and photophobia, which were underestimated or not mentioned in prior CRS studies. Following FESS, the prevalence of such symptoms was significantly lower (Figure 1), and the proportion of patients without above symptoms significantly increased from 2.0% to 23.5%. However, dry mouth may be a sequelae of nasal blockage with open-mouth breathing rather than purely a symptom of autonomic dysfunction. We found a weak correlation (R = 0.228, P = 0.021) between nasal blockage and excessive dry mouth. In patients with CRS, dry mouth can be partially explained as a manifestation of increased mouth breathing due to airway obstruction.

Overall, 29 (28.4%) of our patients had abnormal endoscopy after 1-year follow-up and 3 (2.9%) required revision surgery. These results are similar to previous reports of recurrent CRS and revision rates following FESS[37,38]. Patients with abnormal endoscopy had higher postoperative SNOT-22 scores that reflected a poorer sinonasal-associated QOL. Univariate analysis revealed that revision cases and patients with asthma and CRSwNP were at higher risk of abnormal endoscopy results (Table 4). Multivariate analysis revealed that a high pre-FESS COMPASS 31 score was an independent risk factor (OR 1.043, 95% CI 1.003–1.084; P

Table 4. Logistic regression analysis of factors associated with abnormal endoscopy following FESS.

	Univariate analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age				
≤ 40 y/o (n=52)	1			
> 40 y/o (n=51)	1.163 (0.492-2.752)	0.731		
Gender				
Female (n = 47)	1			
Male (n= 55)	1.592 (0.661-3.836)	0.300		
Current smoker				
No (n = 86)	1			
Yes (n = 16)	0.533 (0.140-2.028)	0.356		
Revision cases				
No (n = 85)	1		1	
Yes (n = 17)	4.962 (1.664-14.795)	0.004	5.012 (1.524-16.489)	0.008
Allergic rhinitis				
No (n = 65)	1			
Yes (n = 37)	1.105 (0.454-2.690)	0.826		
Asthma				
No (n = 94)	1			
Yes (n = 8)	4.861 (1.080-21.886)	0.039		
CRS types				
CRSsNP (n = 51)	1		1	
CRSwNP (n = 51)	3.762 (1.472-9.616)	0.006	4.071 (1.454-11.40)	0.008
Pre-FESS COMPASS 31 scores	1.022 (0.989-1.057)	0.195	1.043 (1.003-1.084)	0.036
Pre-FESS SNOT-22 scores	1.016(0.994-1.038)	0.151		

CRSsNP = Chronic rhinosinusitis without nasal polyp; CRSwNP = Chronic rhinosinusitis with nasal polyp; FESS = Functional endoscopic sinus surgery; COMPASS 31 = 31-item Composite Autonomic Symptom Score; SNOT-22 = 22-item Sino-nasal Outcome Test; OR = Odds ratio; CI = confidence interval.

= 0.036) in addition to CRSwNP and revision surgery, which are well-known risk factors[37] (Table 4). These findings suggest that per COMPASS 31 score increases the risk of abnormal endoscopy results following FESS by 4.3%. The ANS plays an important role in mediating immune responses and inflammatory processes through a delicate balance between the SNS and PNS. These two systems work independently, antagonistically, or synergistically to regulate the inflammatory process. The SNS is typically involved in the early phases of the inflammatory reaction, while the PNS is more important in regulating innate immune responses and cytokine function in chronic inflammation[26,39,40]. Woody et al. showed that increases in inflammatory cytokines were associated with reductions in PNS control in response to psychosocial stress[41]. In this study, the higher preoperative COMPASS 31 scores may indicate disruption of basal ANS function. Patients with poor basal ANS regulation may have more difficulty controlling sinonasal inflammatory status following FESS.

To the best of our knowledge, this is the first study to investigate changes in ANS dysfunction symptoms following FESS in CRS patients. We excluded patients with chronic illness or systemic disease, which may influence ANS function, to reduce possible bias in our study. We observed a high prevalence of various symptoms related to ANS dysfunction, and these symptoms significantly improved following FESS. Moreover, higher preoperative ANS dysfunction symptom burden was associated with uncontrolled inflammation postoperatively. These findings imply a possible connection between ANS dysfunction and CRS; however, current studies are limited. The interplay between ANS dysfunction, psychosomatic stress, and inflammatory processes of CRS is complex. Further investigations including ANS tests are required to explore the exact interaction between ANS dysfunction and CRS.

Conclusion

CRS is considered a localized inflammatory disease but can cause systemic symptoms beyond rhinologic symptoms. Various ANS dysfunction symptoms were prevalent in CRS patients and the symptoms can be alleviated following FESS. Moreover, a higher preoperative COMPASS 31 score corresponded to a poorer surgical outcome. The interplay between CRS, ANS dysfunction, and psychosomatic stress is complex. Further investigations are

required to explore how the ANS is involved in the pathogenesis of CRS.

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Authorship contribution

WCC: design of the study, data collection, drafting this article; WCL: data analysis, critical revision of the article; CHY: data collection, data analysis; CNW: data collection; SDL: design of the study, critical revision of this article.

Conflict of interest

None.

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