A positive correlation between autonomic nervous system function and endoscopic disease severity in chronic rhinosinusitis: a quantitative assessment

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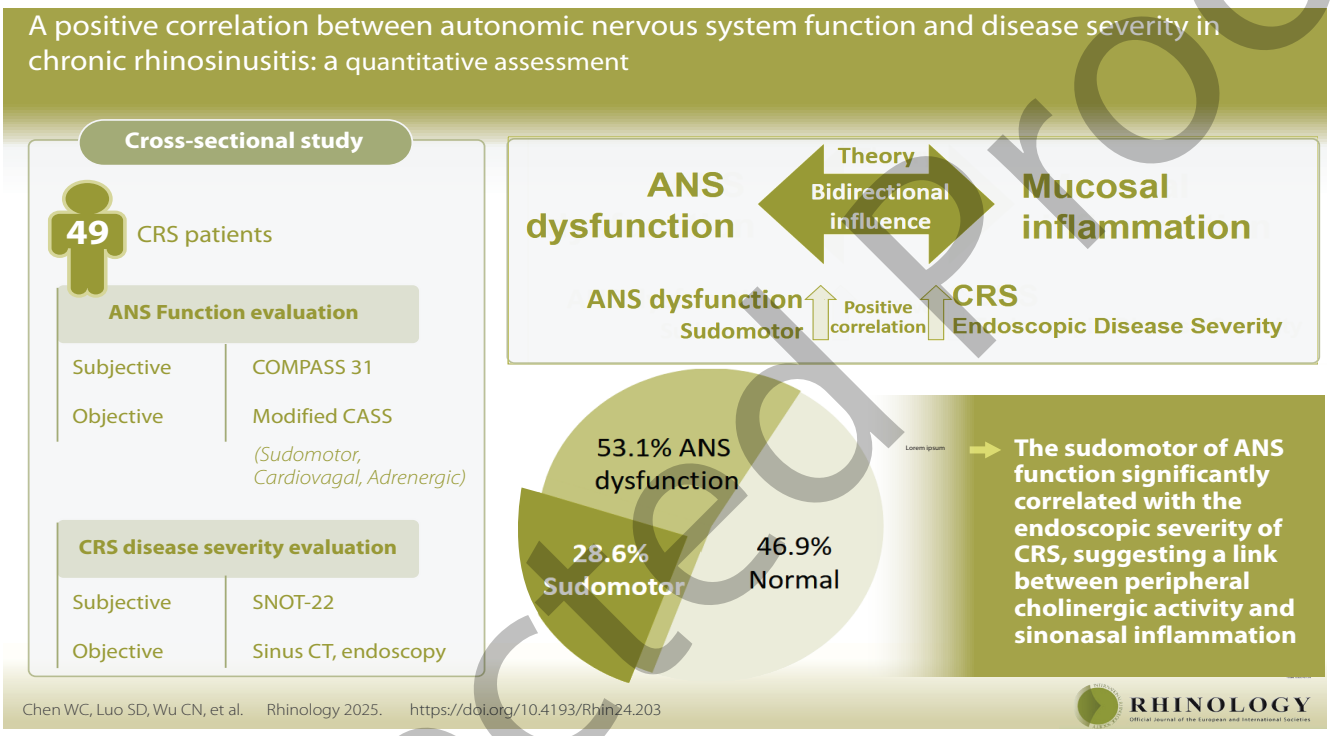

Abstract

Introduction: The autonomic nervous system (ANS) regulates respiratory mucosal inflammation and is linked to various airway diseases. However, the relationship between ANS dysfunction and chronic rhinosinusitis (CRS) has not been fully investigated. This study aimed to explore the association between ANS and CRS using a battery of quantitative autonomic function tests. **Methods**: Patients with CRS undergoing surgery were prospectively enrolled. Subjective evaluation of disease severity was assessed using the sino-nasal outcome test-22 questionnaires for CRS and the 31-item composite autonomic symptom score questionnaires for ANS dysfunction, while computed tomography and endoscopic scores represented objective severity. A battery of autonomic function tests was conducted, and the results were used to generate the modified composite autonomic scoring scale (mCASS) to provide a quantitative evaluation of ANS function. **Results**: A total of 49 patients were enrolled. The most common dysautonomic symptoms were dry mouth (73.5%), dizziness (71.4%), and dry eyes (55.1%). Twenty-six patients (53.1%) had a positive mCASS score, indicating abnormal autonomic function. Within the subdomains, most abnormalities were observed in the sudomotor score (28.6%). The mCASS score showed a positive correlation with the endoscopic score, with marginal significance. Notably, the sudomotor subdomain score was significantly correlated with the endoscopic score. **Conclusion**: A significant correlation was found between objective autonomic nervous system function and severity of chronic rhinosinusitis, particularly in the sudomotor subdomain, suggesting a link between peripheral cholinergic activity and sinonasal inflammation. Further research is needed to clarify the underlying mechanisms.

Key words: COMPASS 31, dysautonomia, SNOT-22, autonomic function test, sudomotor, cholinergic nerve

Introduction

The autonomic nervous system (ANS), including the sympathetic nervous system (SNS) and parasympathetic nervous system, plays a dual role in the regulation of respiratory tract mucosal inflammation through complex pathways [1-3]. An imbalance between these autonomic systems may contribute to airway hyperreactivity, inflammation, and impaired mucociliary clearance, leading to airway diseases [4, 5]. Various upper and lower airway diseases, such as rhinitis, chronic rhinosinusitis (CRS), asthma, and chronic obstructive pulmonary disease (COPD) were associated with ANS dysfunction [6-11]. Previous studies have suggested that ANS dysfunction may not only worsen existing respiratory diseases but also increase the risk of developing them [12, 13]. Additionally, respiratory tract diseases may impact ANS function, indicating a bidirectional relationship.

Among upper airway diseases, idiopathic nonallergic rhinitis is the earliest condition identified and proven to be associated with autonomic imbalance, with suspected hyperactive parasympathetic nervous system (PNS) activity [14-16]. In studies of allergic rhinitis (AR), quantitative autonomic testing revealed significantly abnormal composite autonomic scale scores (CASS) in AR patients compared to normal controls [6]. The CASS and heart rate variability tests indicated hyposympathetic activity in AR patients [6, 17, 18]. However, the relationship between ANS dysfunction and CRS remains unclear, and detailed investigations have been limited.

Previous studies have reported a high prevalence of dysautonomic symptoms in CRS patients, particularly in secretomotor symptoms (dry mouth or dry eye), gastrointestinal symptoms, and orthostatic intolerance [19]. Notably, these ANS dysfunction symptoms appeared to improve following functional endoscopic sinus surgery [20]. However, no prior research has comprehensively evaluated ANS function in CRS patients using quantitative autonomic function testing. In this study, we quantitatively assess autonomic function to determine the prevalence of autonomic dysfunction in CRS patients and explore the relationship between ANS dysfunction and CRS.

Materials and methods

Patients diagnosed with chronic rhinosinusitis (CRS) at Kaohsiung Chang Gung Memorial Hospital between March 2022 and October 2024 were enrolled in this study. All participants received adequate medical treatment, including intranasal corticosteroids for more than 8 weeks. Depending on their condition, some patients also received antibiotic or oral corticosteroid treatment. Patients who had persistent symptoms after adequate medical treatment and subsequently consented to surgical intervention were considered candidates for this study. Informed consent was obtained from all patients before the operation. Patients with a history of arrhythmia, psychological disorders, head and neck cancer, or neurological diseases were excluded from the study. The severity of the disease was evaluated subjectively using the Sino-Nasal Outcome Test-22 (SNOT-22). Objective evaluation was performed using sinonasal endoscopy and computed tomography. The endoscopic findings were recorded using the modified Lund-Kennedy endoscopic score. The scores ranged from 0 to 12, with higher scores indicating more severe disease [21]. The computed tomography (CT) was performed before the operation and the Lund-Mackay CT score was recorded. The scores ranged from 0 to 24, with higher scores indicating increased disease severity [22]. All patients underwent regular post-operative care, including nasal saline irrigation and intranasal corticosteroid application. The Composite Autonomic Symptom Score 31 (COMPASS-31) was used to assess the degree of autonomic dysfunction symptoms. This analysis was conducted as a cross-sectional study based on preoperative data. This study protocol was. approved by the medical ethics and human clinical trial committees of Chang Gung Memorial Hospital (Refs: 202001625B0, 202001625B0C601).

Research instruments

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

The SNOT-22 is a well-validated questionnaire used to assess sinonasal symptom burden, consisting of 22 items, each rated from 0 (no problem) to 5 (problem as bad as it can be). The total score ranges from 0 to 110, with higher scores indicating more severe symptoms. The SNOT-22 is further divided into five distinct subdomains: nasal, ear/facial, sleep, function, and emotional dysfunction [23].

31-item Composite Autonomic Symptom Score (COMPASS 31)

The COMPASS 31 was a validated and simplified questionnaire to assess the symptom burden of autonomic dysfunction. It consists of 31 questions grouped into six subdomains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal (GI), bladder, and pupillomotor symptoms. The questionnaire produces a maximum raw score of 75, which is then weighted using established values to generate a final score ranging from 0 to 100. Higher scores indicate more severe symptoms of autonomic nervous system (ANS) dysfunction [24].

Autonomic function tests

All patients were examined under standardized conditions. Examinations were conducted in the morning, around 9 AM, with participants required to have adequate sleep and complete the test after having breakfast. Three categories of autonomic function were evaluated: sudomotor function, cardiovagal function, and adrenergic function. To systematically assess these functions, a battery of tests was performed, including the deep breathing test, head-up tilt test, and Q-sweat test, as part of a standardized autonomic nervous system assessment.

Cardiovagal function was evaluated by analyzing heart rate (HR) responses to controlled deep breathing and the head-up tilt test. Adrenergic function was assessed based on the blood pressure and heart rate response to the head-up tilt test. Sudomotor function was assessed using the quantitative sudomotor axon reflex test (QSART) via the Q-sweat test. HR was recorded with a basic three-lead electrocardiogram (ECG; Ivy Biomedical, Model 101; Branford, CT, USA). Arterial blood pressure (BP) was measured through pulse palpation by professionals and continuous beat-to-beat photoplethysmographic recordings (Finapres BP Monitor 2300, Ohmeda; Englewood, CO, USA). BP and ECG measurements were taken during normal breathing after patients had rested in the supine position for 15 minutes. Sweat output was recorded using a Q-sweat device (WR Medical Electronics Co., Stillwater, MN, USA).

Modified Composite Autonomic Scoring Scale (mCASS)

This study utilized a modified composite autonomic scoring scale (mCASS), based on the Mayo-QSART CASS, which was modified and developed in our laboratory by incorporating the Q-sweat test instead of the thermoregulatory sweat test. The mCASS measurement method follows the standardized procedures established in our previous researches [25, 26]. The mCASS served as an indicator of overall autonomic function. Autonomic function test results were adjusted for potential confounding factors such as age and gender. Scores were evaluated on a semi-quantitative scale from 0 (no deficit) to 10 (maximum deficit), with the mCASS comprising three subdomains: sudomotor (0–3), cardiovagal (0–3), and adrenergic (0–4) [27].

Statistical analysis

The two-sided Spearman rank correlation test was used to explore the correlation between mCASS and disease severity, evaluating by COMPASS 31, SNOT-22, Lund-Mackay CT score, and modified Lund-Kennedy endoscopic score. A p-value <0.1 was considered to indicate marginal significance and <0.05 was considered to indicate statistical significance. All analyses were performed with the aid of SPSS version 22 software (IBM Corp., Armonk, NY, USA).

Results

A total of 49 CRS patients, including 30 males and 19 females, were enrolled in this study. The mean age is 47.0 ± 12.9 years. Among these patients, 14 (28.6%) were revision cases, 16 (32.7%) had allergic rhinitis and 7 (6.1%) patients had asthma. The mean eosinophilia absolute count was 268.8 ± 222.9 /μL. The pre-operative mean Lund-Mackay CT score was 15.3 ± 5.4, and the pre-operative modified Lund-Kennedy endoscopic score was 8.5 ± 3.0. The mean pre-operative COMPASS 31 and SNOT-22 scores were 23.6 ± 12.5 and 42.5 ± 15.8, respectively. The demographic data, subjective quality of life evaluation, and objective autonomic function test results are described below and concluded in Table 1.

Table 1. Demographic and clinical characteristics.

Age, mean ± SD	47.0 ± 12.9
Gender, female / male	19 / 30
Revision surgeries, n (%)	14 (28.6%)
Asthma, n (%)	7 (6.1%)
Allergic rhinitis, n (%)	16 (32.7%)
Lund-Mackay score, mean ± SD	15.3 ± 5.4
Modified Lund-Kennedy score, mean ± SD	8.5 ± 3.0
COMPASS 31, mean ± SD	23.6 ± 12.5
SNOT-22, mean ± SD	42.5 ± 15.8
Eosinophilia, mean ± SD	268.8 ± 222.9
mCASS, median (IQR)	1 (0 - 1)

SD: Standard Deviation; COMPASS 31: 31-item Composite Autonomic Symptom Score; SNOT-22: Sino-nasal Outcome Test-22; mCASS: Modified Composite Autonomic Scoring Scale; IQR: Interquartile Range

COMPASS-31

From the subdomain analysis of the COMPASS-31, the most frequently reported autonomic symptom (score > 0) was in the secretomotor domain (91.8%), followed by gastrointestinal (83.7%), orthostatic (71.4%), pupillomotor (65.3%), bladder (30.6%), and vasomotor (20.4%) domains. The most commonly reported specific symptoms were dry mouth (73.5%), dizziness (71.4%), dry eyes (55.1%), and a sensation of excessive fullness after meals (55.1%).

Modified Composite Autonomic Scoring Scale (mCASS)

Twenty-three patients (46.9%) had a mCASS score of 0, while 25 patients (51.0%) had a mCASS between 1 and 3, indicating mild autonomic dysfunction. One patient (2.0%) had a mCASS of 4, reflecting moderate autonomic dysfunction. The mCASS consists of three domains: cardiovagal, adrenergic, and sudomotor. The prevalence of abnormal subdomain scores (defined as > 0) was 20.4% for cardiovagal, 12.2% for adrenergic, and 28.6% for sudomotor (Table 2).

The correlation between objective ANS function and disease severity of CRS

The mCASS showed no correlation with subjective symptom burden as measured by the SNOT-22 and COMPASS-31 scores. In the subdomain analysis, the cardiovagal score of the mCASS demonstrated weak to moderate negative correlations with ear fullness ($\gamma = 0.298$, $p = 0.038$) and facial pain/pressure ($\gamma = 0.357$, $p = 0.012$) on the SNOT-22. The adrenergic score of the mCASS demonstrated weak to moderate negative correlations

Table 2. The distribution of mCASS and subdomain score in CRS patients.

Score	0	1	2	3	4
Cardiovagal, n (%)	39 (79.6%)	9 (18.4%)	1 (2.0%)	0	0
Adrenergic, n (%)	43 (87.6%)	6 (12.2%)	0	0	0
Sudomotor, n (%)	35 (71.2%)	6 (12.2%)	7 (14.3%)	1 (2.0%)	0
mCASS, n (%)	23 (46.9%)	16 (32.7%)	7 (14.3%)	2 (4.1%)	1 (2.0%)

mCASS = modified Composite Autonomic Scoring Scale.

Table 3. The correlation between mCASS and disease severity.

Disease severity	Cardiovagal	Adrenergic	Sudomotor	mCASS
SNOT-22	0.068	-0.236	0.082	0.045
COMPASS-31	0.044	0.176	0.016	0.098
Lund-Kennedy CT score	-0.088	0.013	-0.081	-0.134
Modified Lund-Mackay endoscopic score	-0.019	0.148	0.288**	0.272*

SNOT-22: Sino-nasal Outcome Test-22; COMPASS 31: 31-item Composite Autonomic Symptom Score; CT = computed tomograophy; * P = 0.059; ** P = 0.045.

with sneezing (γ = –0.275, p = 0.056), runny nose (γ = –0.283, p = 0.049), waking up tired (γ = –0.302, p = 0.035), and fatigue (γ = –0.273, p = 0.058) (Table S1). Regarding objective disease severity, there was no correlation between the mCASS and the Lund-Mackay CT score. However, the mCASS demonstrated a weak positive correlation with the Lund-Kennedy endoscopic score, reaching marginal significance (γ = 0.272, P = 0.059). Subdomain analysis revealed that only the sudomotor domain showed a weak positive correlation with the endoscopic score, reaching clinical significance (γ = 0.288, P = 0.045) (Table 3).

Discussion

The nervous system regulates inflammation in real time, balancing the inflammation response to environmental stimuli. The "cholinergic anti-inflammatory pathway," a neural mechanism that inhibits macrophage activation via parasympathetic outflow, demonstrates the connection between the ANS and inflammation regulation [28]. In airway diseases, the autonomic nervous system (ANS) can regulate mucosal inflammation by controlling the release of various neuropeptides and may play a role in the development and progression of chronic inflammatory airway diseases [29]. Otherwise, ANS also plays an important role in regulating the vasculature and secretomotor status of sinonasal cavity. In allergic rhinitis, Ishman et al. found a significantly higher CASS score compared to controls, with notable abnormalities in subscores measuring sympathetic dysfunction [6]. Kim et al. assessed autonomic function using HRV and found increased parasympathetic activity and decreased sympathetic activity in patients with intermittent and mild allergic rhinitis [17]. Similarly, research by Lan et al. also demonstrated poor sympathetic modulation in allergic rhinitis patients [18].

Given the interaction of the ANS with the vascular, secretory, and inflammatory states of the sinonasal mucosa, it is reasonable to speculate on its potential involvement in the pathogenesis of CRS. Despite this, research on the autonomic nervous system in CRS has been limited. Previous studies using subjective autonomic function questionnaires to evaluate the severity of dysautonmia in CRS patients and found that symptoms of ANS dysfunction are related to a persistent mucosa inflammation after sinus surgery [20]. However, a limitation of self-reported tools is the potential for overestimating or underestimating symptom severity. Various studies [30-32], including the present study, have demonstrated a lack of correlation between subjective and objective instruments, indicating that subjective results cannot replace autonomic function tests. Subjective dysautonomia questionnaires reflect the overall symptom burden, shaped by the combined effects of CRS-related comorbidities, such as depression, anxiety, or sleep disturbance [33, 34]. In contrast, autonomic function tests provide quantitative assessments that objectively capture physiological responses in patients with CRS.

In the current study, we found a weak positive correlation with marginal significance (γ= 0.272, p = 0.059) between the autonomic function test (mCASS) and severity of rhinosinusitis evaluated by endoscope. The pathogenesis of chronic rhinosinusitis (CRS) is complex and multifactorial, involving various host and environmental factors [35]. These findings suggest a potential in-

volvement of the ANS in the pathophysiology of CRS. In the assessment of subjective CRS severity, the cardiovagal score of the mCASS was positively correlated with symptoms of ear fullness and facial pain/pressure, while the adrenergic score showed negative correlations with sneezing, runny nose, waking up tired, and fatigue. The cardiovagal and adrenergic subdomains are derived from heart rate and blood pressure variability measured during the head-up tilt test, representing systemic parasympathetic and sympathetic activity, respectively. These findings suggest that autonomic imbalance, particularly diminished parasympathetic tone, may be associated with an increased symptom burden in CRS patients. In the objective severity of CRS, only the sudomotor score of mCASS demonstrated a weak positive correlation with the disease severity under endoscopy with statistical significance ($\gamma = 0.282$, $p = 0.045$). This study found a higher prevalence of abnormalities in the sudomotor subdomain, and the sudomotor score showed a weak positive correlation with the severity of CRS. The sudomotor component of the mCASS was assessed using the Q-sweat test, which evaluates sweat function as a measure of peripheral cholinergic nerve activity. Cerejeira et al. reported elevated protein expression of the nicotinic acetylcholine receptor subunit α7 in CRS, a receptor activated by acetylcholine that inhibits pro-inflammatory signaling. This result may be explained by compensatory neural signals released from peripheral cholinergic nerves [36]. Our finding aligns with the conclusions of Cerejeira et al., suggesting that peripheral cholinergic nerves may play a role in modulating mucosal inflammation in patients with CRS.

In theory, the ANS function may regulate airway mucosal inflammation, and autonomic dysfunction could contribute to poor disease control. In asthma, the severity is positively correlated with the vagal tone during stable status, indicating a sustained autonomic imbalance even in the absence of exacerbations [37, 38]. Furthermore, autonomic dysfunction has been implicated as a contributing factor to poor asthma control [39]. In CRS, prior research has reported that greater severity of preoperative dysautonomic symptoms is associated with persistent postoperative mucosal inflammation [20]. These findings support the hypothesis that underlying ANS dysfunction may be linked to greater disease severity and poorer clinical outcomes in CRS. However, the mechanisms underlying this interaction remain incompletely understood. The relationship between CRS and ANS function is potentially bidirectional: ANS dysfunction may promote neurogenic inflammation, while chronic inflammation may, in turn, enhance neural hyperresponsiveness (7). Given the cross-sectional design of the current study, longitudinal follow-up with serial ANS assessments may help further elucidate the dynamic interplay between ANS function and CRS pathophysiology.

To the best of our knowledge, this is the first study to investigate ANS function using autonomic function tests in patients with CRS. In this study, we excluded patients with chronic illnesses or systemic diseases that may affect ANS function in order to minimize potential bias. In addition, because ANS function can vary significantly throughout the day and is influenced by various physiological conditions, all assessments were conducted in the morning at around 9:00 a.m. after breakfast. Participants were also instructed to have adequate sleep the night before to ensure consistent testing conditions across all subjects. This study found a weak positive correlation between the endoscopic score and the sudomotor component of the mCASS, which reflects peripheral cholinergic nerve function. However, the detailed mechanisms underlying the interaction between the autonomic nervous system (ANS) and chronic rhinosinusitis (CRS) have not been fully explored, and existing studies are limited. Future studies should investigate how the ANS influences sinonasal mucosal inflammation in CRS.

Conclusion

This study objectively evaluated ANS function in patients with CRS using quantitative autonomic function tests, and identified a statistically significant positive correlation between the sudomotor component of the mCASS and disease severity assessed via nasal endoscopy. These findings suggest a potential association between peripheral cholinergic nerve activity and sinonasal mucosal inflammation in CRS. Nonetheless, the precise mechanisms through which the ANS influences sinonasal inflammation remain unclear. Further studies with larger sample sizes and mechanistic approaches are necessary to evaluate the role of autonomic dysfunction in the pathophysiology of CRS.

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Authorship contribution

WCC: methodology, writing original draft, funding acquisition; CNW: Data analysis; SDL: Conceptualization; CHC: Data curation; WSC: Data curation; SFC: Investigation, supervision, writing review & editing.

Conflict of interest

There were no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Table S1. Correlations between mCASS subdomains and individual items of the SNOT-22.

Items	Sudomotor	Cardiovagal	Adrenergic	mCASS
Need to blow nose	-0.042	0.012	-0.221	-0.104
Sneezing	0.051	0.111	-0.275*	-0.009
Runny nose	0.029	0.021	-0.283**	-0.076
Blockage/congestion of nose	0.003	-0.102	-0.142	-0.109
Loss of smell/taste	-0.069	-0.158	-0.097	-0.169
Cough	0.048	0.098	-0.068	0.121
Post nasal discharge	0.204	-0.006	-0.034	0.195
Thick nasal discharge	0.109	0.128	-0.014	0.171
Ear fullness	-0.039	0.298**	-0.169	0.013
Dizziness	-0.047	0.222	0.012	0.097
Ear pain	0.096	0.192	-0.089	0.162
Facial pain/pressure	-0.012	0.357**	-0.128	0.112
Difficulty falling asleep	0.133	-0.044	-0.171	0.059
Waking up at night	0.155	-0.016	-0.195	0.054
Lack of a good night's sleep	0.182	-0.073	-0.172	0.076
Waking up tired	-0.010	-0.030	-0.302**	-0.123
Fatigue	0.041	-0.097	-0.273*	-0.111
Reduced productivity	0.181	-0.052	-0.012	0.156
Reduced concentration	0.171	-0.103	0.109	0.174
Frustrated/restless/irritable	0.001	0.052	-0.042	0.006
Sad	-0.090	-0.009	-0.057	-0.083
Embarrassed	-0.112	0.242	-0.173	-0.024

mCASS: modified Composite Autonomic Scoring Scale; SNOT-22: Sino-nasal Outcome Test-22; * P = 0.05 ~ 0.06; ** P < 0.05.