Serpentine Sign: evidence of airway compensation in patients with empty nose syndrome

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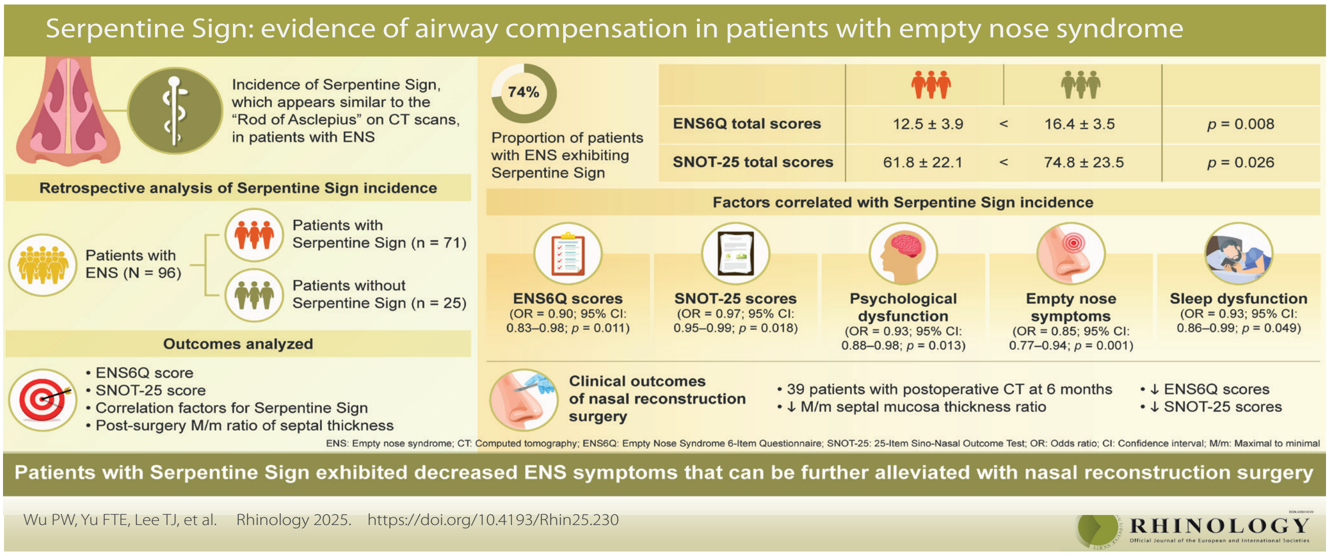

Abstract

Background: This study aimed to evaluate the presence of Serpentine Signs on computed tomography (CT) images and its impact on the clinical symptoms in patients with empty nose syndrome (ENS).

Methods: A retrospective study analysed patients with ENS enrolled in previous studies. The clinical characteristics and results of ENS-specific questionnaire evaluations were reviewed. The ratio of the maximal to minimal thickness (M/m ratio) of the septal mucosa was also calculated to demonstrate the degree of swelling. Mucosal swelling was defined as a thickness greater than twice that of the surrounding mucosa. A Serpentine Sign was identified by the presence of two or more mucosal swellings on one side of the central nasal septum.

Results: Seventy-one (74.0%) of the 96 enrolled patients with ENS exhibited Serpentine Signs on CT images. Patients with the Serpentine Sign had significantly lower symptom scores on the ENS 6-item Questionnaire (ENS6Q) and 25-Item Sino-Nasal Outcome Test (SNOT-25). Regression analysis revealed that the ENS6Q, SNOT-25, sleep, psychological, and empty nose symptom domains were significantly associated with the Serpentine Sign. The M/m ratio of the nasal septal mucosa significantly decreased in 39 participants with available postoperative CT images 6 months after nasal reconstruction surgery, along with an improvement in ENS6Q and SNOT-25 scores.

Conclusion: The Serpentine Sign was associated with fewer ENS symptoms in patients with ENS. The severity of septal mucosal swelling decreased after surgical reconstruction. These results imply a significant impact of airflow alteration due to over-reduction of the inferior turbinate on the nasal mucosa.

Key words: computed tomography, empty nose syndrome, empty nose syndrome 6-item questionnaire, sino-nasal outcome test-25, serpentine sign

Introduction

Empty nose syndrome (ENS) is a rare condition that may occur after nasal surgery, particularly after aggressive inferior turbinate reduction (ITR) procedures [1]. Patients with ENS are characterised by paradoxical nasal obstruction, even though an apparent patent nasal airway is observed. ITR typically widens the nasal airway and improves the symptoms of nasal obstruction. However, patients with ENS paradoxically report symptoms such as nasal obstruction, crusting, dryness, lack of air sensation, feeling of nose opening, and even suffocation after surgery [2,3]. These symptoms usually lead to restlessness and disturb the quality of life of patients with ENS. Thus, many patients with ENS experience poor sleep quality and a significant psychological burden, such as elevated anxiety, hyperventilation, fatigue, depression, and suicidal thoughts [4-9].

The detailed pathophysiology of ENS is not yet fully understood and remains controversial [3,10]. Decreased perception of nasal airflow during breathing due to alterations in nasal airflow resulting from excessive destruction and/or abnormal mucosal recovery after surgical procedures has been implicated in ENS development [11-16]. However, most patients do not develop ENS symptoms after tumour surgery, pituitary surgery with middle turbinate resection, or radical sinus surgery with extensive nasal tissue removal [14-17].

Computational fluid dynamics (CFD) analysis of nasal airflow has been used to investigate nasal aerodynamics in patients with ENS and has implicated altered nasal airflow, including decreased lateral wall shear force at the inferior meatus region due to disproportionate widening of the nasal airway, as an important factor in the development of ENS [15,17,18]. In addition, there was a significantly lower proportion of airflow in the inferior meatus and more airflow around the middle meatus in patients with ENS than in controls and those with aggressive ITR without ENS [15]. Furthermore, surgical intervention using the inferior meatus augmentation procedure (IMAP) can lead to a significant change in nasal airflow patterns. This procedure redistributes of airflow from the middle meatus to the inferior meatus, resulting in a significant reduction in ENS symptoms [18].

In daily clinical practice, nasal endoscopy and computed tomography (CT) are the most frequently used modalities for evaluating sinonasal disorders. Several radiological abnormalities associated with ENS on CT have been reported, including opacity in the ipsilateral sinus, thickening of the nasal mucosa, and mucosal thickness of the segments of the central and posterior septum [19-21]. Additionally, the anterior airspace diameter, remnant inferior turbinate volume, and distinct morphological phenotypes measured on CT images are associated with ENS-specific symptom scores in ENS questionnaire evaluations [22,23]. For example, remnant inferior turbinates with a morphological pistol type on CT images demonstrated an elevated rhinologic symptom burden and ENS-specific symptoms as their remnant inferior turbinate volume increased [23]. Recently, the Serpentine Sign, which refers to compensatory mucosal hypertrophy in an alternating and undulating swelling in the nasal septal mucosa, has been proposed as a unique presentation specific to patients with ENS and may serve as a reliable radiographic and endoscopic finding for diagnosis [24]. However, no studies have investigated the association between the Serpentine Sign and the clinical symptoms of ENS or following surgical reconstruction procedures. In the current study, we aimed to evaluate the CT images and clinical symptom scores of patients with ENS to determine the presence of the Serpentine Sign and its clinical association, and to investigate the impact of nasal reconstruction surgery on the Serpentine Sign by comparing the perioperative CT images. These findings could provide further understanding of the impact of airflow alteration on the nasal mucosa and the pathophysiology of ENS.

Materials and methods

Patients

We retrospectively reviewed patients with ENS enrolled in our previous studies [8, 9] between 2015 and 2021. Demographic data, clinical characteristics, CT images and questionnaire evaluations of the patients in our previous studies [8, 9] were reviewed. The exclusion criteria included 1) a craniofacial anomaly, 2) other sinonasal diseases, such as rhinosinusitis, or 3) psychiatric disorders managed by psychiatrists.

The diagnosis of ENS was confirmed based on a paradoxical nasal obstruction, including subjective nasal obstruction, objectively wide nasal airway due to loss of inferior turbinate tissue on nasal endoscopy evaluation, a history of previous procedures on the inferior turbinate, an ENS 6-item questionnaire (ENS6Q) evaluation, and a positive cotton test, as described in a previous study [25, 26]. For the cotton test, a moistened cotton ball was placed on the inferior meatus of each patient. The participants were instructed to breathe through their nose for 30 min. A positive cotton test was defined by improvement in ENS-associated symptoms during the test [17].

All participants were surgically treated with endoscopic nasal reconstruction using submucosal Medpor implantation to restore the nasal airway, as previously described [27, 28]. Briefly, under general anaesthesia, MedPor implantation was performed via a submucosal pocket on the lateral nasal wall below the remnant of the inferior turbinate to augment the inferior meatus and narrow the anterior nasal air space.

This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (IRB numbers: 201506433A3, 201601703A3, and 201802147A3). All participants signed an informed consent form at enrolment in previous studies [8, 9]. Informed consent for the current analysis was waived because of the retrospective nature of the study and the anonymity of the data.

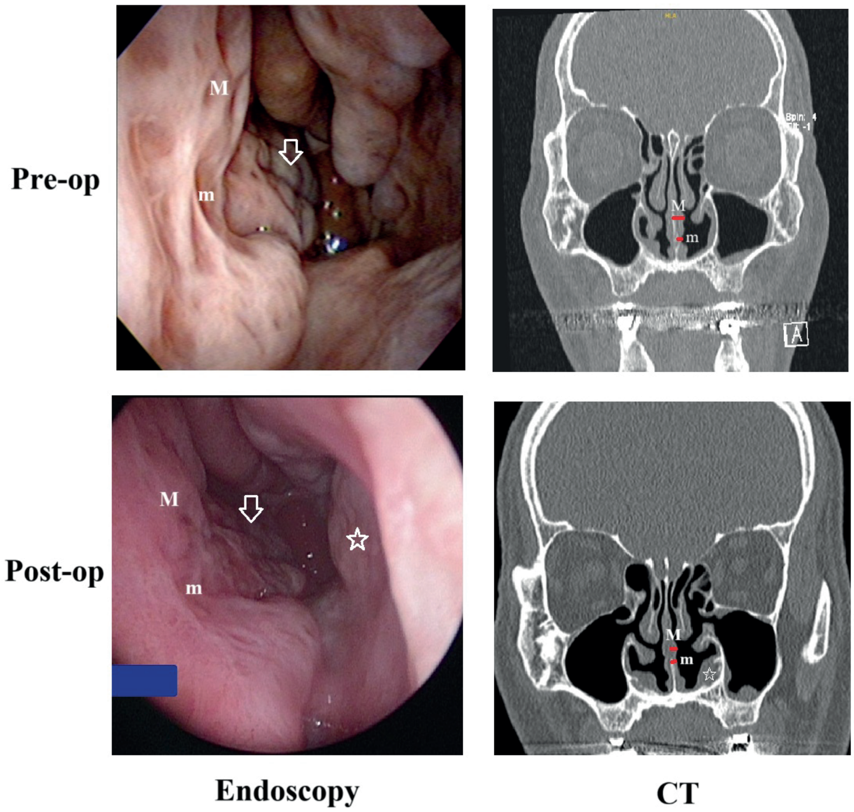

Figure 1. Nasal endoscopy (left panel) and computed tomography (CT, right panel) evaluations of Serpentine Sign were conducted before (pre-op) and 6 months after reconstruction surgery (post-op). Nasal septal mucosal thickness was measured at the level of the inferior turbinate attachment site or below, using coronal views of CT images within 2 cm of the anterior ethmoidal artery. Mucosal swelling was defined as a thickness greater than twice that of the surrounding mucosa. The ratio of maximal (M) to minimal (m) septal mucosal thickness (M/m ratio) was calculated from the CT images. A Serpentine Sign was identified by the presence of two or more mucosal swellings in one side of the central nasal septum. arrow: posterior nasal septal swelling; star: Medpor implantation in the inferior meatus.

Patient-reported outcome measures

ENS6Q and the 25-Item Sino-Nasal Outcome Test (SNOT-25) were used to evaluate the symptoms and quality of life of patients with ENS at enrollment [7, 29]. The ENS6Q is a validated instrument for ENS evaluation, and it rates six symptom items, including dryness, lack of air sensation going through the nasal cavity, suffocation, nose feeling too open, nasal crusting, and nasal burning sensation, from 0 (no symptoms) to 5 (severe symptoms), with a maximum score of 30. An ENS6Q score ≥11 suggests the presence of ENS (29). The SNOT-25 is a modification of the SNOT-20 by the addition of five ENS-specific symptoms, including difficulty with nasal breathing, suffocation, excessively open nose, nasal dryness, and crusting [8, 30]. The symptoms and quality of life of the participants were evaluated with a score from 0 (no symptoms) to 5 (indicating severe symptoms) for each item, with a maximum score of 125. The SNOT-25 questionnaire can be further categorised into six domains, as described in a previous study: rhinogenic symptoms, extranasal rhinological symptoms, ear/facial symptoms, sleep dysfunction, psychological dysfunction, and empty nose symptoms.

Evaluation of Serpentine Sign on CT images

Paranasal sinus CT images with 1 mm slices were retrospectively reviewed by investigators blinded to the patient demographics. CT scan was conducted for all participants prior to surgery and for 39 participants six months post-surgery. The presence or absence of the Serpentine Sign was evaluated in all participants, as previously described [24]. Briefly, the nasal septal mucosal thickness was measured at the level of the inferior turbinate attachment site or below on the coronal view of the CT images within 2 cm of the anterior ethmoidal artery. Measurements were taken bilaterally from the medial septal bone to the lateral mucosa of the septum using the Image J Fiji Software (version 1.2; WS Rasband, National Institute of Health, Bethesda, MD, USA) as described previously [31]. Mucosal swelling was defined as a thickness greater than twice that of the surrounding mucosa. The ratio of the maximal to minimal thickness (M/m ratio) was calculated (Figure 1). A Serpentine Sign was identified as the presence of two or more mucosal swellings on one side of the central nasal septum [24].

Table 1. Criteria for biologic indication in CRSwNP patients based on international recommendations.

Items	Total	SS (-)	SS (+)	p value†
Case number	96	25	71	
Female: male	26:70	9:16	17:54	0.243
Age (year)	47.8 ± 12.3	47.9 ± 12.6	47.8 ±12.3	0.897
BMI (kg/m2)	24.1 ± 3.4	25.1 ± 3.3	23.7 ± 3.4	0.074
Smoke, n (%)	19 (19.8)	6 (24.0)	13 (18.3)	0.539
Previous nasal surgery:				
Inferior turbinate surgery, n (%)	96 (100)	25 (100)	71 (100)	1.000
Nasal septal surgery, n (%)	57 (59.4)	15 (60.0)	42 (59.2)	0.941
Endoscopic sinus surgery, n (%)	33 (34.4)	6 (24.0)	27 (38.0)	0.204
Caldwell-Luc operation, n (%)	4 (4.2)	1 (4.0)	3 (4.2)	0.961

Data are presented as mean ± standard deviation. SS, Serpentine Sign; BMI, body mass index. †Analysis using the χ2 test and the Mann-Whitney U test between patients with and without SS on computed tomographic images.

Statistical analyses

Categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. Continuous variables were evaluated using the Mann–Whitney U test or t-test between the groups according to the results of the D'Agostino–Pearson omnibus normality test. Perioperative changes were evaluated using Wilcoxon signed-rank tests. Logistic regression analysis was conducted to investigate the association between the presence of Serpentine Signs and the results of questionnaire measurements. To identify and characterise the sensitivity and specificity of clinical metrics for identifying Serpentine Signs in ENS participants, receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated to determine the predictive value and optimal cutoff of the ENS6Q, SNOT-25, and empty nose symptom domain in association with Serpentine Signs. Statistical significance was set at $p < 0.05$. The power calculated from the difference between the primary outcomes in the study groups was 80.2%. SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Prism Software, Inc., San Diego, CA, USA) were used for the analysis.

Results

Clinical characteristics of the study population

Ninety-six patients with ENS who underwent CT at enrolment were evaluated in this study. Seventy-one (74.0%) patients exhibited Serpentine Signs on CT. The clinical characteristics of participants with and without Serpentine Signs are shown in Table 1. All patients had a history of inferior turbinate procedures, 59.4% had a history of nasal septal surgery, and 38.6% had undergone sinus surgery.

Questionnaire measures

The mean ENS6Q scores were 13.6 ± 6.3, 12.5 ± 5.9, and 16.4 ± 6.5 in the total participants, patients with the Serpentine Sign, and those without, respectively. Patients with the Serpentine Signs experienced significantly lower symptom scores on the ENS6Q dryness and suffocation sensations (all p< 0.05). The mean SNOT-25 scores were 65.2 ± 23.1, 61.8 ± 22.1, and 74.8 ± 23.5 in the total participants, patients with the Serpentine Sign, and patients without, respectively. Patients with the Serpentine Sign experienced significantly lower symptom scores in the SNOT-25 total score, sleep dysfunction, psychological dysfunction, and empty nose symptom domains (all p< 0.05) (Table 2).

Association analysis

In the univariate regression analysis, the ENS6Q, SNOT-25, sleep symptoms, and psychological and empty nose symptom domains were significantly associated with the Serpentine Sign. A multivariate regression model including the six subdomains of the SNOT-25 was analysed to determine the most important symptom domains associated with Serpentine Signs and revealed that the empty nose symptom domains remained significantly associated (Table 3). Six months after nasal reconstruction surgery, there was a significant decrease in the M/m ratio of the nasal septal mucosa on CT images in 39 participants with available postoperative CT images, as well as in the ENS6Q and SNOT-25 questionnaire evaluations in patients with ENS (Figure 2).

Evaluation of the predictive value of the Serpentine Sign in symptom severity

ROC curves were generated, and the AUC was calculated to evaluate the predictive value of symptom severity in the Serpentine Sign (Figure 3). The AUCs for the ENS6Q, SNOT-25, and empty nose symptom domain scores were 0.679, 0.650, and 0.729, respectively (p = 0.008, 0.026, and <0.001). The optimal cutoffs for the ENS6Q, SNOT-25, and empty nose symptom domain scores

Table 2. Questionnaire evaluations in participants with empty nose syndrome.

Items	Total	SS (-)	SS (+)	p value†
ENS6Q total score	13.6 ± 3.3	16.4 ±3.5	12.5 ± 3.9	0.008**
Dryness	3.2 ± 1.6	4.0 ± 1.2	2.9 ± 1.6	0.001**
Suffocation	3.3 ± 1.7	3.9 ± 1.5	3.1 ± 1.7	0.029*
Nose feels too open	1.7± 1.9	2.2 ± 2.0	1.5 ± 1.9	0.115
Sense of diminished nasal airflow	3.2 ± 1.8	3.2 ± 2.0	3.3 ± 1.8	0.960
Nasal crusting	1.1 ± 1.5	1.6 ± 1.8	1.0 ± 1.3	0.121
Nasal burning	1.4 ± 1.8	1.8 ± 2.1	1.3 ± 1.6	0.303
SNOT-25 total score	65.2 ± 23.1	74.8 ± 23.5	61.8 ± 22.1	0.026*
Rhinologic symptoms	14.0 ± 6.6	14.0 ± 5.4	14.0 ± 7.1	0.851
Extranasal rhinologic symptoms	7.3 ± 4.4	7.0 ± 4.3	7.4 ± 4.5	0.630
Eye/face symptoms	8.8 ± 5.6	10.0 ± 5.5	8.4 ± 5.6	0.219
Sleep dysfunction	16.8 ± 6.9	19.2 ± 6.3	16.0 ± 7.0	0.039*
Psychological dysfunction	22.1 ± 9.6	26.6 ± 8.6	20.8 ± 9.6	0.007**
Empty nose symptoms	12.7 ± 5.6	16.0 ± 5.7	11.6 ± 5.1	<0.001***

Data are presented as mean ± SD. SS, Serpentine Sign; ENS6Q, Empty Nose Syndrome 6-item Questionnaire; SNOT-25, 25-Item Sino-Nasal Outcome Test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. † Analysis between patients with and without SS on computed tomographic images.

Table 3. Logistic regression analyses for the Serpentine Sign in participants with empty nose syndrome.

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.99 (0.91-1.07)	0.931		
Sex	0.96 (0.88-1.05)	0.341		
ENS6Q	0.90 (0.83-0.98)	0.011*		
SNOT-25	0.97 (0.95-0.99)	0.018*		
Rhinologic symptoms	1.00 (0.94-1.07)	0.957	1.05 (0.95-1.16)	0.374
Extranasal rhinologic symtpoms	1.02 (0.92-1.13)	0.699	1.06 (0.92-1.04)	0.411
Eye/face symptoms	0.95 (0.87-1.03)	0.211	0.98 (0.87-1.10)	0.735
Sleep dysfunction	0.93 (0.86-0.99)	0.049*	0.99 (0.86-1.15)	0.938
Psychological dysfucntion	0.93 (0.88-0.98)	0.013*	0.99 (0.89-1.11)	0.881
Empty nose symptoms	0.85 (0.77-0.94)	0.001**	0.83 (0.72-0.96)	0.012*

(maximising the sum of sensitivity and specificity) were 17.5, 66.6, and 12.5, respectively.

Discussion

Patients with ENS experience a decreased perception of nasal airflow during breathing due to alterations in nasal airflow and/or abnormal mucosal recovery after surgical procedures [2,3]. A previous study using CFD analysis revealed altered nasal airflow, including decreased lateral wall shear force in the inferior meatus region, due to disproportionate widening of the nasal airway in patients with ENS [15]. Recently, Dholakia et al. proposed a hypertrophic change in the nasal septum soft tissue as a Serpentine Sign specific to ENS patients [24]. Histopathological analysis showed rich and disorganised subepithelial seromucinous glands similar to the nasal septum swell body in patients with the Serpentine Sign. The authors postulated that the development of the Serpentine Sign could be viewed as mucosal compensation in the nasal airway for significant tissue loss in the previous surgery. In the current study, we further analysed the association between the presence of Serpentine Signs and the clinical symptoms of ENS and revealed that patients with Serpentine Signs experienced significantly lower symptom scores in the ENS6Q total score, dryness, suffocation sensation, SNOT-25 total scores, sleep dysfunction, psychological dysfunction, and empty nose symptom domains. Regression analysis revealed that the ENS6Q, SNOT-25, sleep symptoms, and psy-

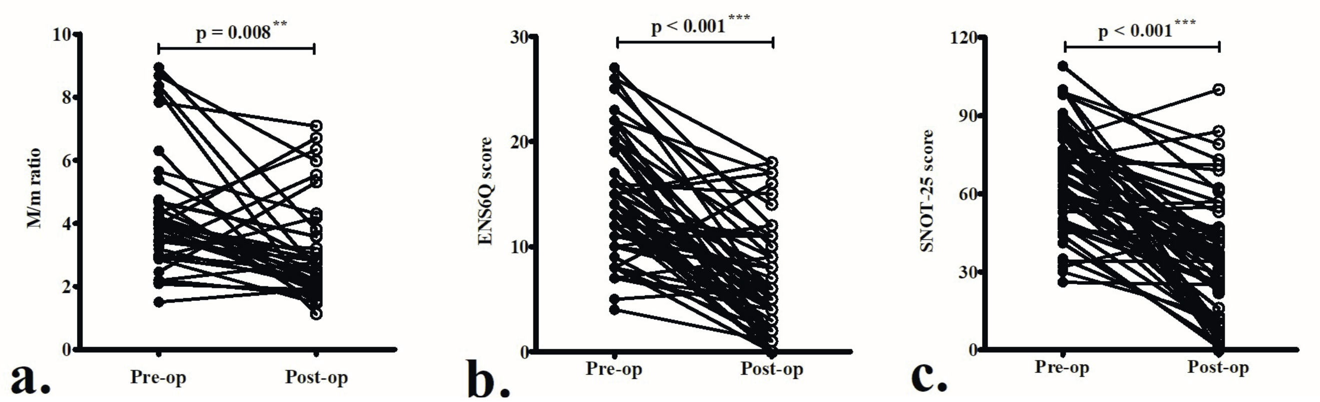

Figure 2. The maximal/minimal thickness (M/m) ratio of the nasal septal mucosa on computed tomographic (CT) images significantly decreased at 6 months post-reconstruction in 39 participants with available perioperative CT (a), along with an improvement in the Empty Nose Syndrome 6-item Questionnaire (ENS6Q) (b) and the 25-Item Sino-Nasal Outcome Test (SNOT-25) (c). ** $p < 0.01$, *** $p < 0.001$.

chological and empty nose symptom domains were significantly associated with the Serpentine Sign. Furthermore, there was a significant decrease in the M/m ratio of the nasal septal mucosa in participants with available postoperative CT images at 6 months after nasal reconstruction surgery, along with the improvement of ENS6Q and SNOT-25 scores in patients with ENS. Taken together, our results further demonstrate the evidence of airway compensation for the disproportionate widening of the anterior airspace to alleviate the symptoms of ENS and imply a significant impact of airflow alteration due to aggressive ITR on the nasal mucosa.

Several radiological abnormalities on CT images have also been reported to be associated with ENS, including opacity in the ipsilateral sinus, thickening of the nasal mucosa, and mucosal thickening of the central and posterior septum [19-21]. These findings indicate that regional mucosal thickening of the sinonasal mucosa is a distinct characteristic in patients with ENS. These findings also suggest a conservative approach to restore the nasal airway rather than extensive destruction of the nasal structure, such as total ITR, which may lead to a wide nasal airway and ENS-related symptoms.

Surgical reconstruction procedures such as submucosal implantation with Medpor or IMAP are reported to be effective in reducing ENS symptoms in patients [32,33]. However, no studies have evaluated the impact of these reconstruction procedures on the sinus mucosa. Previous studies using CFD demonstrated a significant change in nasal airflow patterns with a deviation from the middle meatus toward the inferior meatus after surgical intervention with IMAP [18]. Our results showed that the M/m ratio of the nasal septal mucosa significantly decreased 6 months after surgery, indicating that the degree of swelling had diminished. The surgical procedure improved nasal airflow by reducing airway width, ENS symptoms, and the need for the septal mucosa to compensate.

Among the items of the ENSQ6, dryness was the item with the highest difference in score between patients with and without Serpentine Signs. This result was comparable with that of a previous histopathological analysis in which rich and disorganised subepithelial seromucinous glands were found in the nasal septum swell body of patients with the Serpentine Sign [24]. Wexler et al. showed that the presence of glandular tissue and expansile venous sinusoids in the nasal septal swell body, similar to the inferior turbinate, may play a role in secretory function and vasoactive airflow regulation [34]. This compensated for the enrichment of the seromucinous glands, which made the nasal cavity more moist and less dry. In contrast, the ENS6Q, SNOT-25, sleep symptoms, and psychological and empty nose symptom domains were significantly associated with Serpentine Signs in the regression analysis. Nevertheless, only the empty nose symptom domain was significantly associated with the Serpentine Sign in the multivariate regression model. These results are consistent with those of previous studies showing that psychological symptoms, sleep dysfunction, and empty-nose symptoms are closely associated with ENS [7,8,35]. The Serpentine Sign compensates for the wide nasal airway, reduces empty nose symptoms, and improves sleep and psychological function. Kim et al. revealed compensatory hypertrophy of the inferior turbinate on the concave side of the nasal septal deviation, which decreased after correction of the nasal septal deviation with septoplasty [36]. Our study demonstrated that 74.0% of the patients with ENS exhibited Serpentine Signs on CT images, and the severity of septal mucosal swelling, measured by the M/m ratio, decreased after surgical reconstruction. All these were evidence of nasal mucosal adaptation to the alternation of air flow.

This study had several limitations that warrant consideration. First, a control group of patients who underwent nasal surgery without complaints of ENS symptoms was lacking, especially in patients who underwent extensive sinonasal surgery. However, a previous study has shown that the Serpentine Sign is a unique presentation of hypertrophic changes in the nasal septum

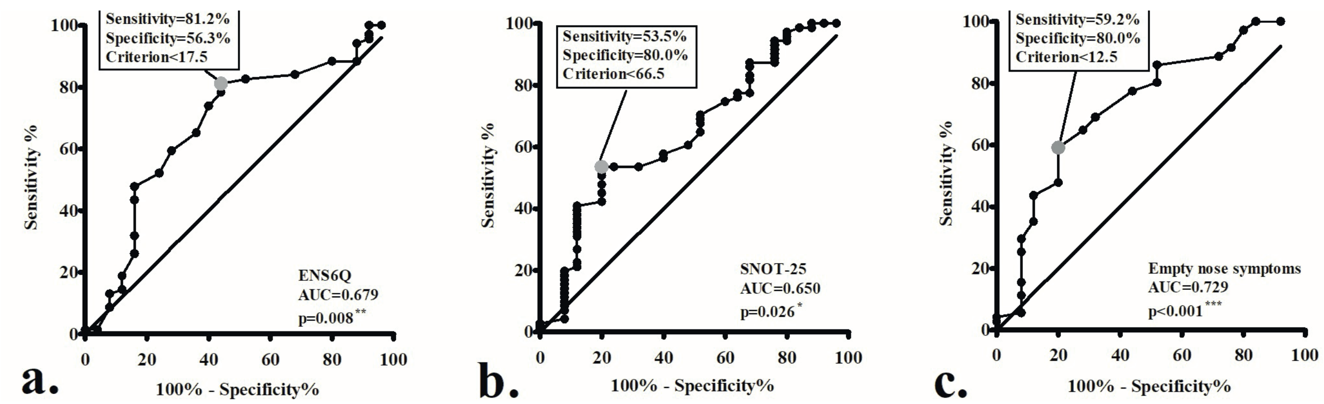

Figure 3. The receiver operating characteristic curves generated to determine the optimal cutoff for questionnaire measurements in detecting patients with the Serpentine Sign on CT images. AUC, area under the curve; ENS6Q, Empty Nose Syndrome 6-item Questionnaire; SNOT-25, 25-Item Sino-Nasal Outcome Test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

specific to patients with ENS and may serve as a reliable radiographic finding in diagnosis [24]. Secondly, CT imaging provides a snapshot in time, and objective data regarding nasal resistance, airflow, and moisture were not collected. These limits the interpretation of our results. However, these measurements are difficult to obtain from patients. Future studies using CFD may be useful for understanding specific airflow changes related to Serpentine Signs in patients with ENS. Third, only 39 patients had available postoperative CT images 6 months after surgery. Therefore, a selection bias should be considered. Future large-scale prospective studies, including complete perioperative CT and standard nasal endoscopy evaluations, are necessary to validate the results of the current study.

Conclusions

Our results showed that the Serpentine Sign was associated with fewer ENS symptoms measured by the ENS6Q and SNOT-25 and its sleep, psychological, and empty nose symptom subdomains in patients with ENS. The severity of septal mucosal swelling measured by the M/m ratio decreased after surgical reconstruction. These results imply a significant impact of airflow alteration due to over-reduction of the inferior turbinate on the nasal mucosa and emphasize the importance of preserving the nasal structure, especially the inferior turbinate, during nasal surgery.

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Authorship contribution

Chien-Chia H, and PWW participated in conceptualization of this study. Chien-Chia H., FTEY performed the data collection and analysis and drafted the manuscript. TJL, Chi-Che H and PHC assisted in the enrolment of participants and collection of clinical data. FTEY and PWW contributed to data interpretation. All authors participated in scientific discussions and approved the final manuscript.

Conflict of interest

The authors declare no competing interests.

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Availability of data

The datasets used and/or analysed in the current study are available from the corresponding author upon reasonable request.

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