Predictor of Recurrence of Allergic Fungal Rhinosinusitis

yanmin Chen
Xiang'an Hospital of Xiamen University
Hongtao Zhen (xhotter@163.com)
Department of Otolaryngology Head and Neck Surgery, Tongji Hospital, Tongji Medical College, Hua Zhong University of Science and Technology (HUST), Wuhan, P.R. China.

Research

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Abstract

Objectives

By analyzing the clinical manifestations related to allergic fungal sinusitis (AFRS), the aim of this study was to try to make the first step to establish a prognostic evaluation system for predicting the recurrence of AFRS patients after operating.

Methods

A descriptive and retrospective study of 19 AFRS out of 272 chronic rhinosinusitis (CRS) who underwent endoscopic sinus surgery were enrolled from April 2011 to April 2019.

Results

The incidence of AFRS was 7.0% (19/272) in this study. The postoperative recurrence rate was 26.3% (5/19). Nasal discharge (73.7%) and nasal obstruction (57.9%) were the most common clinical manifestations. There were significant differences in the age of onset, preoperative duration of symptoms and a total Lund-MacKay CT score between the relapsing group and non-relapsing group.

Conclusions

AFRS is less prevalent and high recurrent in Chinese patients. Our preliminary data support that age, duration and Lund-MacKay CT scores as the focus of preoperative clinical evaluation of AFRS: a long duration of symptoms (≥15 months) and a high Lund-MacKay CT score (≥11) are at a high risk of relapse, in further prospective and larger investigations as part of the preoperative work-up for patients with AFRS in order to develop a personalized and effective management approach.

Introduction

Allergic fungal rhinosinusitis (AFRS) is a noninvasive fungal rhinosinusitis with a high recurrence rate ranging from 10 to 100% after surgery,[1-3] and has been recognized as a distinct form of CRS.[4] Fungi are ubiquitous in our environment. There are several forms of paranasal sinus disease that are caused by fungal pathogens. It is generally believed that the host's immune state determines the clinical presentation. In an immune response state, the fungi induce a strong T2 immune response and lead to AFRS.[4,5]

AFRS seems to be a noninvasive fungal disease of the paranasal sinuses related to type I hypersensitivity to a fungal antigen, resulting in a chronic eosinophilic inflammatory process.[4,5] Eventually, not only is there development of fungus-specific IgE levels in the atopic patient's serum, accumulation of allergic mucin-contained eosinophils and fungal components, and the formation of nasal polyps and mucosal edema, but also these pathophysiological changes lead to obstruction of paranasal sinus and nasal cavities, which influence each other in a vicious circle. So, AFRS is considered a subset of CRS that is

characterized by the presence of eosinophilic mucin with non-invasive fungal hyphae within the sinuses and a type I hypersensitivity to fungi.

AFRS requires surgical intervention. Surgical debridement of the involved sinuses removes the antigenic stimulation, also provides wider access for application of topical medication, like isotonic saline and nasal steroid. Topical and oral corticosteroids reduce inflammation can decrease recurrence after surgery. However, topical and oral antifungals and immunotherapy have not universally recognized and used in the treatment of AFRS.

AFRS is prone to recurrence. A meta-analysis of risk factors about revision surgery rates in CRS with nasal polyps showed that AFRS was the number one risk factor (28.7%).[6] In one study, the incidence of AFRS was 1.4% (6/429). Postoperatively, one patient developed recurrence (1/6).[2] In another study, endoscopic sinus surgery (ESS) was performed in 424 CRS patients. AFRS were counted for 39 cases (9.2%). At median follow-up of 28 months (10~47 months), revision ESS for AFRS was seen in one patient.[7] However, currently there is not an accepted method for predicting the recurrence of AFRS. A previous statistical analysis found significantly higher blood eosinophil and basophil levels in AFRS patients who relapsed than in those who did not, so the authors regarded that blood eosinophil and basophil levels warranted testing in future larger prospective investigations as part of the preoperative work-up for AFRS patients at higher risk of recurrence.[8]

Whether clinical characteristics of AFRS can predict recurrence remains unclear.[5-7] It is crucial to provide a comprehensive consideration of prognosis, and to analyze the distinguishing clinical features of AFRS to provide personalized disease management for maximizing treatment success and minimizing relapse risk. Therefore, this retrospective clinical study aimed to investigate clinical features of AFRS for predicting its recurrence.

Methods

Patients

A series of 19 patients with clinical features of AFRS out of 272 patients who underwent ESS for CRS at [removed for blind peer review] from April 2011 to April 2019. We retrospectively examined the clinical features and outcomes of these 19 patients. All patients signed a detailed informed consent form. This study was approved by the Ethical Committee of our hospital.

The diagnostic major criteria of AFRS consist of the following: (1) Nasal polyposis; (2) Fungi on staining; (3) Eosinophilic mucin without fungal invasion into sinus tissue; (4) Type I hypersensitivity to fungi; (5) Characteristic radiological findings with soft tissue differential densities on CT scanning.[9,10]

All patients were subjected to a detailed history, and physical and nasal examination. The laboratory tests were performed in the same laboratory. The patients had not a prior history of ESS. All patients underwent ESS, and polyps resected intraoperatively were submitted for histopathological examination.

All patients received the same postoperative medication, including irrigations with isotonic saline solution, nasal and systemic steroids. All patients were assigned to rinse nasal cavities with isotonic saline solution once a day, and to use budesonide nasal pump spays (Rhinocort; AstraZeneca, London, United Kingdom) twice daily (64μg/per time). At the same time, they also used oral prednisolone postoperatively, 1 mg/kg/day for one week and 0.5 mg/kg/day for next one weeks, tapered to 0.4 mg/kg/day for the next 1 weeks, tapered to 0.2 mg/kg/day for the next one weeks and to 0.1 mg/kg/day for the last one weeks. Follow-up with rigid 0° or 30° endoscopes were scheduled 3, 6 and 12 months after ESS, and yearly thereafter. In this study, the definition of postoperative recurrence was revision surgery after ineffective medical treatments on recurrent nasal polyps.

Statistical analysis

To investigate the factors associated with postoperative recurrence of AFRS, the clinical features of relapsing and non-relapsing were analyzed using SPSS statistical software. Our data were quite small. A T-test of independence was used to test normally distributed data, such as age. A nonparametric test, the Mann-Whitney U test, was used to analyze non-normally distributed measurement data. Enumeration data were tested by the two-tailed Fisher's exact test of independence. The ROC curve was used to evaluate the predictive value of related factors for postoperative recurrence. The cut-off value corresponded to the maximum Youden index value based on the ROC curve. The Youden index was equal to sensitivity + specificity - 1.$P < 0.05$ was considered to show a significant statistical difference.

Results

Clinical findings

Of the 272 patients who underwent ESS for CRS, 19 patients (7.0%) were diagnosed with AFRS. All the AFRS patients were immunocompetent. The patients' descriptive features in terms of age, sex, duration of symptoms, aspirin intolerance, asthma status, labs (blood eosinophil percentage, total serum IgE), allergy skin testing, postoperative tissue eosinophil, fungal culture result and recurrence of disease, were summarized in Table 1.

The follow-up period was 14~110 months. The mean follow-up period was 49 months (SD: 28). The mean age of the AFRS patients at the time of diagnosis was 40.5 years (SD: 14.2), with the range of age from 9 to 72 years old. There were 8 males and 11 females, and the male/female ratio was 1:1.4. The mean duration of symptoms was 24.5 months. All cases had sinonasal polyps. 4 out of 19 patients (21.1%) also had asthma. Only one patient suffered from aspirin sensitivity (5.3%). Allergic response was present in all cases.

In this study series, 100.0% had elevated total serum IgE, 47.4% had positive skin tests, 42.1% had elevated blood eosinophil percentage. Histopathological analysis showed that fungal hyphae were observed in all cases, and aspergillus (94.7%) were the main fungus on culture. Postoperative recurrence occurred in five cases, accounting for 26.3%.

Nasal discharge (73.7%) and nasal obstruction (57.9%) were the most common clinical manifestations of AFRS, as they were present in a majority of patients. In this study, 26.3% had orbital symptoms, 5.3% had headache, 21.1% had local facial pain, 15.8% had a history of nosebleed, and 21.1% had worsening asthma. Clinical manifestations of AFRS patients in this study were summarized in Table 2.

The main and specific features of CT imaging were high densities shadows that evenly distributed in the cavity of paranasal sinuses, showing double densities with a rail track pattern (Figure 1). The mean Lund-MacKay CT scores of the AFRS patients was 7.53 on the left and 7.05 on the right, while the mean total score was 14.58.

Analysis of disease recurrence

In this study, the recurrence rate of AFRS was 26.3% (5/19). The clinical characteristics of patients were compared between the relapsing group and the non-relapsing group. The mean age in the relapsing group was 28.0 years (SD: 12.2), and the mean age in the non-relapsing group was 45.0 years (SD: 12.4) (Figure 2). The duration of symptoms in the relapsing group had a median (IQR) of 48.0 months (14~120 months), and the non-relapsing group had a median (IQR) of 5.5 months (3~6 months) (Figure 3). The significant difference was found between the two groups in terms of age ($p = 0.017$) and duration ($p = 0.027$) (Table 3). The relapsing group consisted of 3 males and 2 females, while non-relapsing group consisted of 8 males and 6 females. No significant difference was found between the two groups in gender ($p>0.05$). Among those 14 patients who were in the non-relapsing group, none of them had an aspirin sensitivity (ASA), however, there was one out of five had an ASA in the relapsing group. Asthma was one to six in the non-relapsing group, while two to three in the relapsing group. There was no statistically significant difference between the two groups in the presence of ASA and asthma ($p>0.05$) (Table 3).

The ratio of positive and negative skin testing was 5 to 9 in the non-relapsing group, and 4 to 1 in the relapsing group. The ratio of high and normal blood eosinophils percentage was 3 to 4, and 2 to 3 in the relapsing group. Therefore, the clinical laboratory examinations were not significantly different between the two groups ($p>0.05$). CT was used to determine Lund-MacKay scores. Total Lund-MacKay CT scores in the relapsing group had a median (IQR) of 22 (14~23.5), and the non-relapsing group had a median (IQR) of 10 (8~20). The statistical analysis found significant difference in total Lund-MacKay CT scores between the relapsing group and non-relapsing group ($p = 0.045$) (Figure 4 and Table 3).

In this study, both two methods were used to assess the patients preoperatively. One was the VAS scale used to evaluate the preoperative overall quality of life of the patients, and another was total SNOT-22 scale used to score the symptoms of the patients. The non-relapsing group had an average VAS scale score of 5.79 ± 1.85, whereas relapsing group had an average score of 6.40 ± 1.14. While, the non-relapsing group had an average total SNOT-22 scale score of 19.14 ± 1.75 and relapsing group had an average score of 20.20 ± 1.10. Consequently, the clinical preoperative evaluations were not significantly different between the two groups (Table 3).

The duration of symptoms (p = 0.033, AUC=0.829) and total Lund-MacKay CT scores (p = 0.047, AUC=0.807) have significant values for predicting the recurrence of AFRS. The best cut-off value for the duration of symptoms was 15 months. The sensitivity and specificity were 80.0% and 85.7%, respectively. The best cut-off value for the total Lund-MacKay CT scores was 11. The sensitivity and specificity were 100.0% and 64.3%, respectively. (Figure 5)

Discussion

AFRS is a subset of polypoid chronic rhinosinusitis. Fokkens et al. in 2020 concluded that type I hypersensitivity and fungi on staining were the two key factors in Bent and Kuhn criteria for AFRS to be distinguished from other forms of chronic rhinosinusitis with nasal polyps (CRSwNP).[10] Ideally all five of the major criteria in the original Bent-Kuhn diagnostic criteria should be met to make the diagnosis.[9] The type 2 T-cell response to fungi caused an intense local allergic inflammatory reaction resulting in accumulating eosinophilic mucin.[4,5,10] The typical peanut-buttery allergic mucins and nasal polyps block the drainage of the paranasal sinuses, which persist and aggravate the disease.

In this study, the incidence of AFRS out of CRS was 7.0%, which was relatively lower compared with some reports from Western countries, maybe the difference in culture species. In the hot and humid climate of the southern United States including the lower portion of the Mississippi River region, the rate of AFRS ranged from 10% to 23%.[11] In the same East Asian origin, the incidence of Japanese was 1.4%. The possible reason may be regional and ethnic differences. Patients with AFRS have a distinct clinical pattern of recurrent nasal polyposis and accumulation of fungal mucins. It has been reported in the literature that the recurrence rate of this kind of non-invasive fungal rhinosinusitis is 10 %~100%.[1-3] In this present small limitable sample, the recurrence rate was 26.3%. Available studies on the recurrence of AFRS tend to focus on the medical treatments, surgical techniques, degrees of allergy, and inadequate follow-up as relapse risk factors.[5,9] However, at present there are few reports on the use of certain predictors to identify the AFRS patients at a high risk of relapse, especially on the basis of AFRS' clinical manifestations. The focus of this study was to identify the key clinical manifestations needed to predict relapse of ARFS, which will provide more effective, personalized postoperative disease management to patients at a high risk of recurrence. The results from this study showed that AFRS patients with young age of onset, long duration of symptoms, and high Lund-MacKay scores were at a high risk of relapse.

Younger age of onset of AFRS patients was significantly associated with postoperative recurrence. A lot of the literature suggested that AFRS patients were young with a mean age from 20 to 40 years.[3-5] In this study, the mean age was 40.5 years (SD: 14.2). Further analysis revealed that the mean age of relapsing group was 28.0 years (SD: 12.2) and the non-relapsing group was 45.0 years (SD:12.4). There was a statistically significant difference in age between the relapsing group and the non-relapsing group ($p = 0.017$), which indicated that AFRS patients with young age were more likely to relapse. Patro et al. also reported that AFRS was more aggressive in children compared with adults having increased recurrence rates because of responding less well to treatments.[12] These findings suggested that early

intervention was needed to prevent the development of CRSwNP or AFRS in young patients with allergic rhinitis. Rational postoperative follow-up protocols and medical treatments were adopted for young patients with AFRS to avoid recurrence.

Longer preoperative duration of symptoms in AFRS patients was significantly associated with postoperative recurrence. In this study, the preoperative duration of symptoms in AFRS patients was 48.0 months (14~120 months) in the relapsing group and 5.5 months (3~6 months) in the non-relapsing group. There was a statistically significant difference in duration of symptoms ($p = 0.027$) between the relapsing group and the non-relapsing group. Further statistical analysis showed that the duration of symptoms ($p = 0.033$, AUC=0.829) has significant value for predicting the recurrence of AFRS. The best cut-off value was 15 months, and the sensitivity and specificity were 80.0% and 85.7%, respectively. It may indicate that AFRS patients with a long duration of symptoms (≥15 months) are more likely to relapse.

The longer the duration of symptoms, the more severe the allergic inflammation in the paranasal sinuses. Type I hypersensitivity to a fungal antigen results in a chronic eosinophilic inflammatory process, accumulation of allergic mucin, the formation of nasal polyps and mucosal edema.[5,6] Some studies suggested that postoperative systemic and topical nasal steroids could be recommended in the medical treatments of AFRS in order to eliminate the inflammatory response and have an immunomodulatory effect.[4-6] A study also found that nebulized budesonide (topical steroids) treatment could reduce the recurrence rate for patients with AFRS after ESS.[13] Therefore, in order to reduce the chance of recurrence by eliminating inflammation, it is suggested to adopt postoperative systemic and topical nasal steroid treatments for AFRS patients with a long duration of symptoms (≥15 months).

A higher total Lund-MacKay CT score was significantly associated with postoperative recurrence. A typical AFRS patient's paranasal sinus CT image has high density shadows and a ground-glass feature evenly distributed throughout the sinus cavity (Figure 1). In other studies, the lesions in these images are predominantly unilateral.[9,14] In this study, there were 11 cases of unilateral lesions (57.9%) and 8 cases of bilateral lesions (42.1%). The mean of the Lund-MacKay CT scores of the AFRS patients in this series was 7.53 to the left, 7.05 to the right, and the total was 14.58. The statistical analysis found a significant difference in total Lund-MacKay CT scores ($p = 0.045$) between the relapsing group and the non-relapsing group. The mean total Lund-MacKay CT score was 22 (14~23.5) for the relapsing group and 10 (8~20) for the non-relapsing group. It may reveal that AFRS patients with higher total Lund-MacKay CT scores are more likely to relapse. The total Lund-MacKay CT score ($p = 0.047$, AUC=0.807) has important value for predicting the recurrence of AFRS. The best cut-off value was 11, and the sensitivity and specificity were 100.0% and 64.3%, respectively.

Higher Lund-MacKay CT scores mean a wide range of lesions, more accumulation of inflammatory mucins, and a strong type I hypersensitivity to fungi. A lot of studies have suggested that the higher the Lund-MacKay CT scores are in AFRS patients, the higher their grade of polyposis, and the more extensive their surgery will be.[15,16] Adequate ESS is universally accepted and the first important step in the

treatment of patients with AFRS.[1,5] The results of this study suggest that a more thorough ESS be adopted for AFRS patients with high Lund-MacKay CT scores (≥11) to reduce the chance of recurrence, including complete removal of the nasal polyps, total debridement of the mucin, complete opening and drainage of the paranasal sinus ostia, and so on.

Surgery as a first stage intervention for AFRS is near unquestionable recommendation. In this study, ESS requires surgical debridement and enlargement of the involved sinuses, removing the antigenic stimulation while retaining the normal mucosa. Postoperative nasal irrigation with isotonic saline and nasal corticosteroids and oral corticosteroids, and regular and careful debridement should be added to the regular follow-up appointment. Based on the evidence, postoperative treatment of AFRS is different due to different treatments having been adopted to deal with disease recurrence.[5,8] Allergen immunotherapy is a lack of trials in AFRS, which has not become a conventional treatment. The studies about immunotherapy from Greenhaw et al. and Gan EC et al. have further evidence that immunotherapy can reduce surgical revision in atopic individuals with AFRS like AR and asthma in AFRS patients.[17,18] Limited data exists to support regular use of topical or systemic antifungal agents in AFRS. One study by Seiberling recognized that itraconzole has anti-inflammatory effects in recalcitrant fungal sinusitis.[19] The potential of biologics can be considered as a novel upcoming therapy for the recurrent AFRS patients. One study by Gan EC et al.[20] has already been published on Omalizumab therapy (anti-lgE) for refractory AFRS with moderate or severe asthma.

In this study, two patients experienced recurrence again during follow-up. Their duration of symptoms was more than 15 months, and their total Lund-MacKay CT scores were over 11, which is consistent with the conclusion of this study that AFRS patients with a long duration of symptoms (≥15 months) and high Lund-MacKay CT scores (≥11) were at a high risk of AFRS relapse.

In conclusion, it is important to analyze the distinguishing clinical manifestations of AFRS patients and identify early the high-risk factors of postoperative recurrence. These preliminary results supported the conclusion that AFRS patients with young age of onset, long duration of symptoms (≥15 months) and high Lund-MacKay CT scores (≥11) were at a high risk of relapse. Our very preliminary data support that age of onset, duration of disease, and total Lund-MacKay CT scores of AFRS patients should be tested in further prospective and larger investigations as part of the preoperative work-up in order to develop a reasonable treatment plan and provide these patients with precise prognostic information.

Currently, there have been not a recognized and comprehensive prognostic evaluation system to manage AFRS patients after operating. We have been conducting a preliminary analysis of the postoperative AFRS patients and their recurrence requiring surgical revision in our study for the past 8 years, so as to find out the clinical characteristics of the patients to predict and judge the postoperative recurrence of AFRS requiring surgery in advance, such as what the Lund-MacKay scores is greater than can be listed as a risk factor. The highlight of this study is that it is the first idea to construct such an evaluation system. However, at present, we only analyzed the clinical characteristics of AFRS patients. In the follow-up studies, we will gradually improve the laboratory evaluation to look at other inflammatory mediators in

the tissue and in the blood. Because AFRS is less prevalent in Asian populations, the size of sample of this study is small, we will take longer time and more patience to collect cases in our department. If possible, we hope to conduct this study in multiple regions and multiple centers for a larger number of clinical data and further collection in the future work.

Declarations

Acknowledgements:

This study obtained no financial support from third party funding. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Conflict of interest:

The authors have no conflicts of interest to disclose.

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1 Features of Patients with Allergic Fungal Sinusitis

Case	Age(y)	Sex	Dur(m)	Polyps	ASA	Asthma	IgE	Skin	EOS (%)	CX	Rec
1	42	F	120	+	+	+	H	+	H	AS	+
2	26	M	120	+	-	-	H	+	N	AS	+
3	34	F	24	+	-	+	H	+	N	AS/Mu	+
4	9	M	4	+	-	-	H	+	H	AS/Mu	+
5	19	F	4	+	-	-	H	+	H	AS	-
6	45	F	6	+	-	+	H	+	H	AS	-
7	49	M	72	+	-	-	H	+	N	AS	-
8	29	F	48	+	-	-	H	+	N	Mu	+
9	55	M	4	+	-	+	H	-	H	AS	-
10	41	F	6	+	-	-	H	-	N	AS	-
11	45	F	6	+	-	-	H	-	N	AS	-
12	35	M	3	+	-	-	H	-	H	AS	-
13	45	F	3	+	-	-	H	-	H	AS	-
14	56	M	5	+	-	-	H	-	H	AS	-
15	30	M	6	+	-	-	H	+	N	AS	-
16	47	F	3	+	-	-	H	+	N	AS	-
17	47	F	6	+	-	-	H	-	N	AS/Mu	-
18	44	F	4	+	-	-	H	-	N	AS	-
19	72	M	24	+	-	-	H	-	N	AS	-

M=male; F=female, Dur=duration, ASA=aspirin sensitivity N=normal, H=high, IgE=total serum IgE level, Skin=Skin testing results, EOS (%)=eosinophil percentage, CX=culture results (AS=Aspergillus Mu= Mucor), Rec=Recurrence.

Blood eosinophils percentage greater than 8.0 was high. Blood eosinophils percentage between 0.4 and 8.0 was normal. Total serum IgE greater than 60 KU/L was high.

Table 2 Presentations of AFRS

Symptoms	Count	(%)
Nasal obstruction	11	57.9
Local facial pain	4	21.1
Nasal discharge	14	73.7
Orbital symptoms	5	26.3
Headache	1	5.3
Blood in nose	3	15.8
Asthma worse	4	21.1

Table 3 Clinical characteristics of considered AFRS patients stratified according to disease recurrence

Clinical characteristics before surgery	Non-relapsing group	Relapsing group	*p*
No. of patients	14	5	-
Age (years) Mean (SD)	45.0 (12.4)	28.0 (12.2)	0.017[a]
Gender (M: F)	4:3	3:2	1.000[b]
Duration (months) Median (IQR)	5.5 (3~6)	48.0 (14~120)	0.027[a]
ASA (Y: N)	0:14	1:4	0.263[b]
Asthma (Y: N)	1:6	2:3	0.272[b]
Skin testing (P: N^1)	5:9	4:1	0.141[b]
Blood eosinophils percentage (%) (H: N^2)	3:4	2:3	1.000[b]
VAS scale Mean (SD)	5.79 (1.85)	6.40 (1.14)	0.559[a]
Total SNOT-22 scale Mean (SD)	19.14 (1.75)	20.20(1.10)	0.186[a]
Total Lund-MacKay CT scores Median (IQR)	10 (8~20)	22 (14~23.5)	0.045[a]

a. Mann-Whitney U test; b. Fisher's exact test; Y=Yes; N=No; P=Positive; N1=Negative; H=High; N2=Normal

Figures

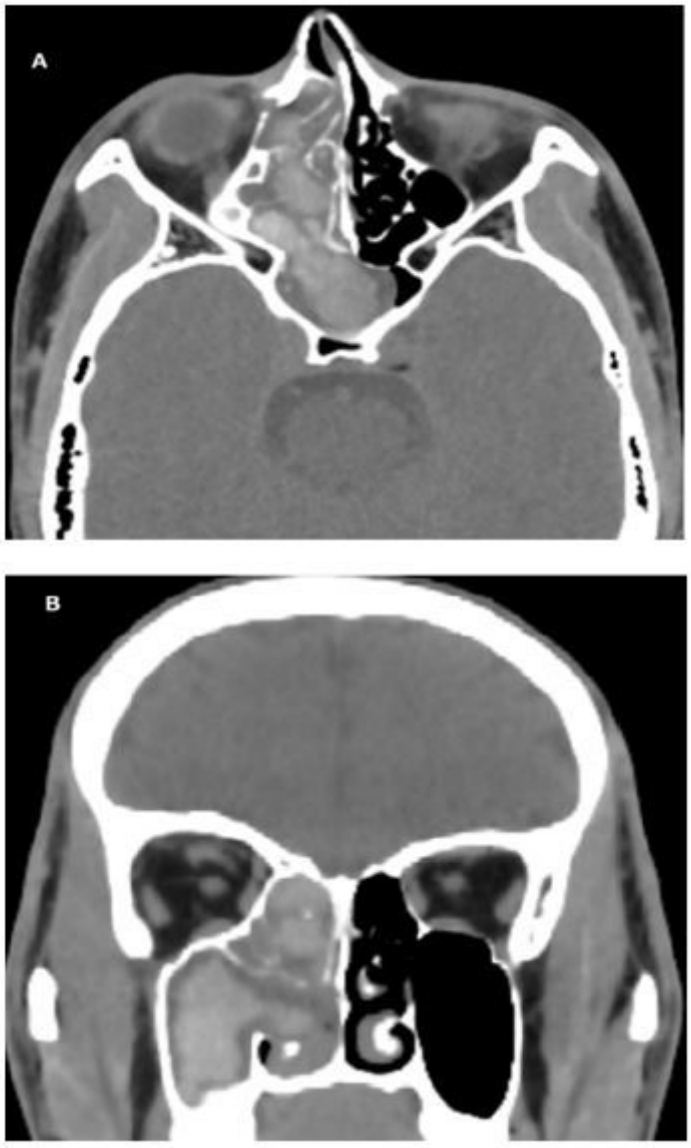

Figure 1

preoperative axial (A) and coronal (B) CT scan with soft-tissue window settings

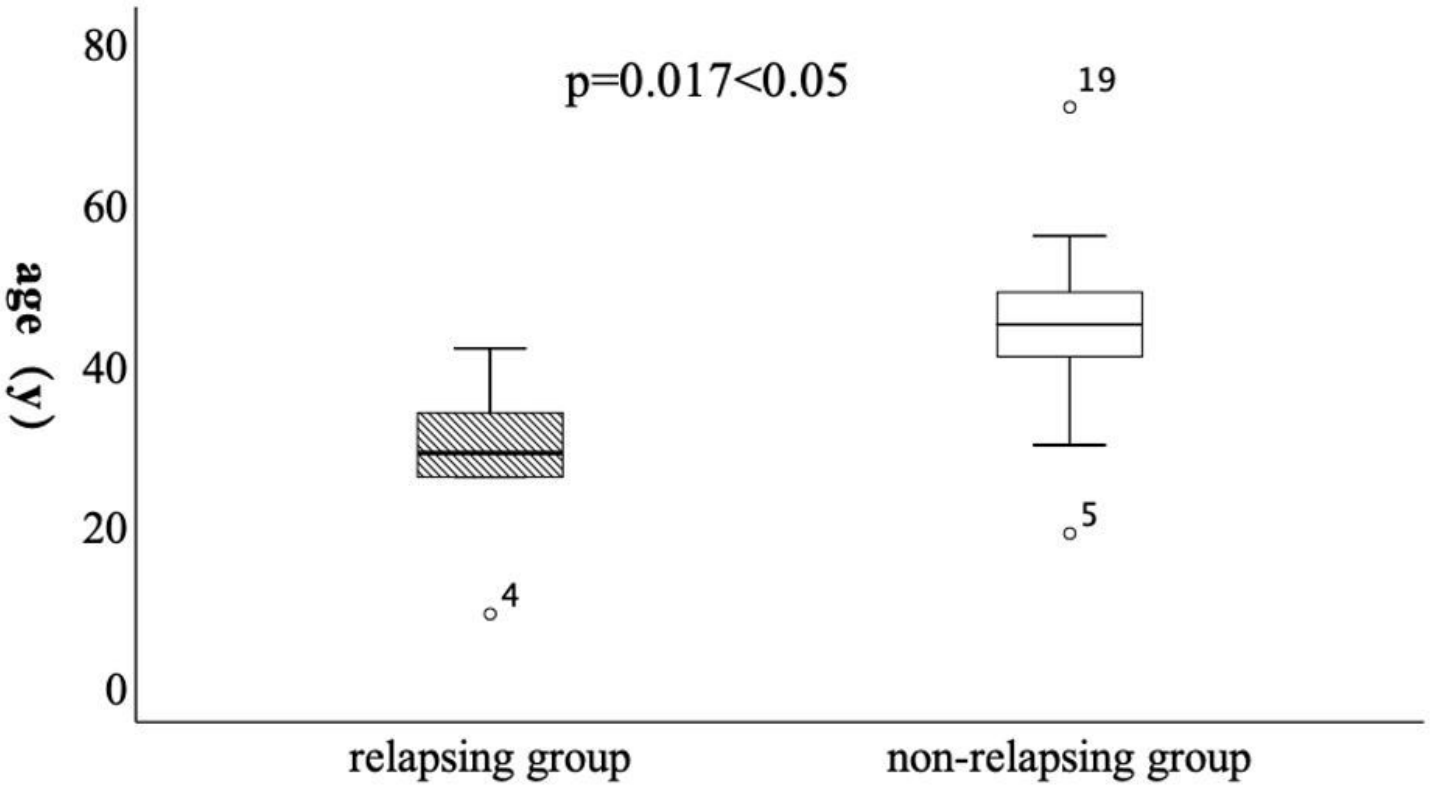

Figure 2

Age between two groups

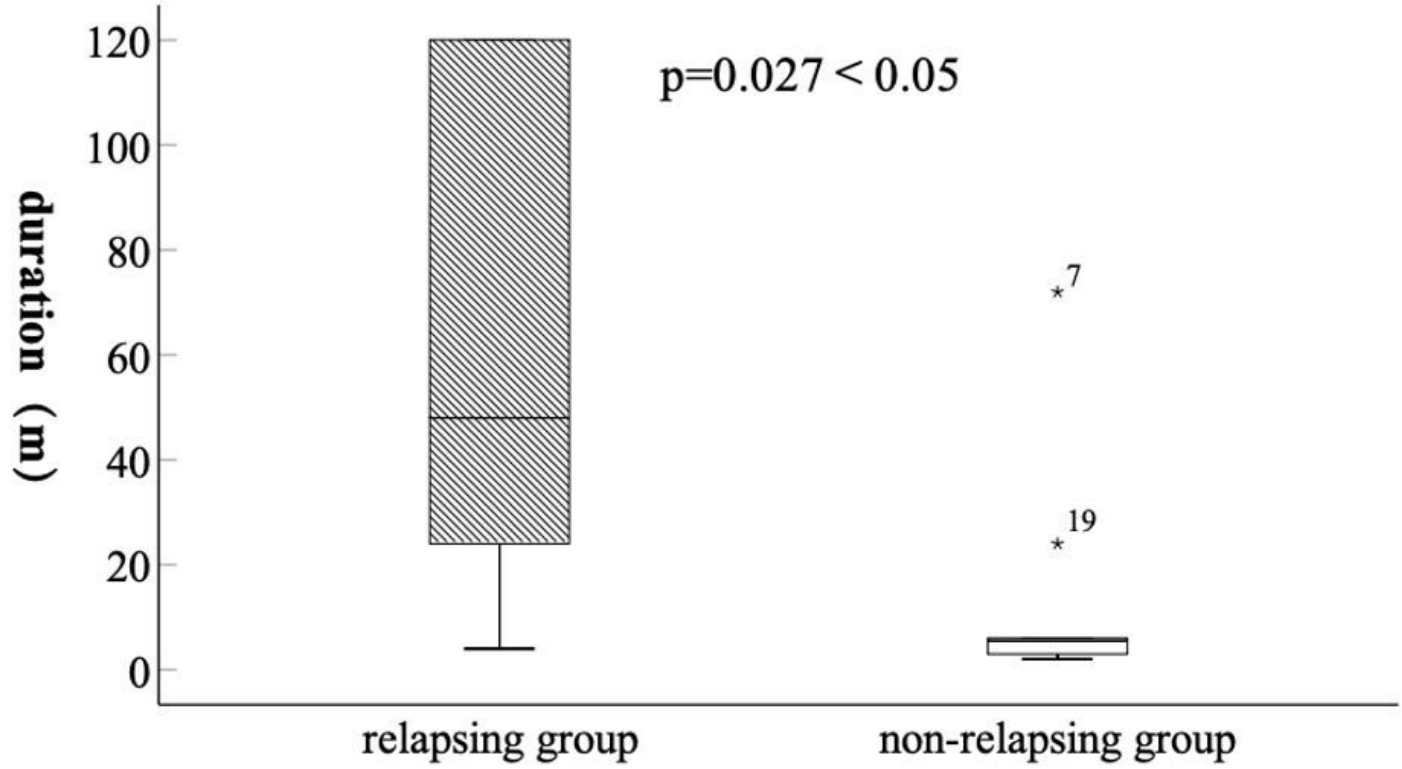

Figure 3

Durations of symptoms between two groups

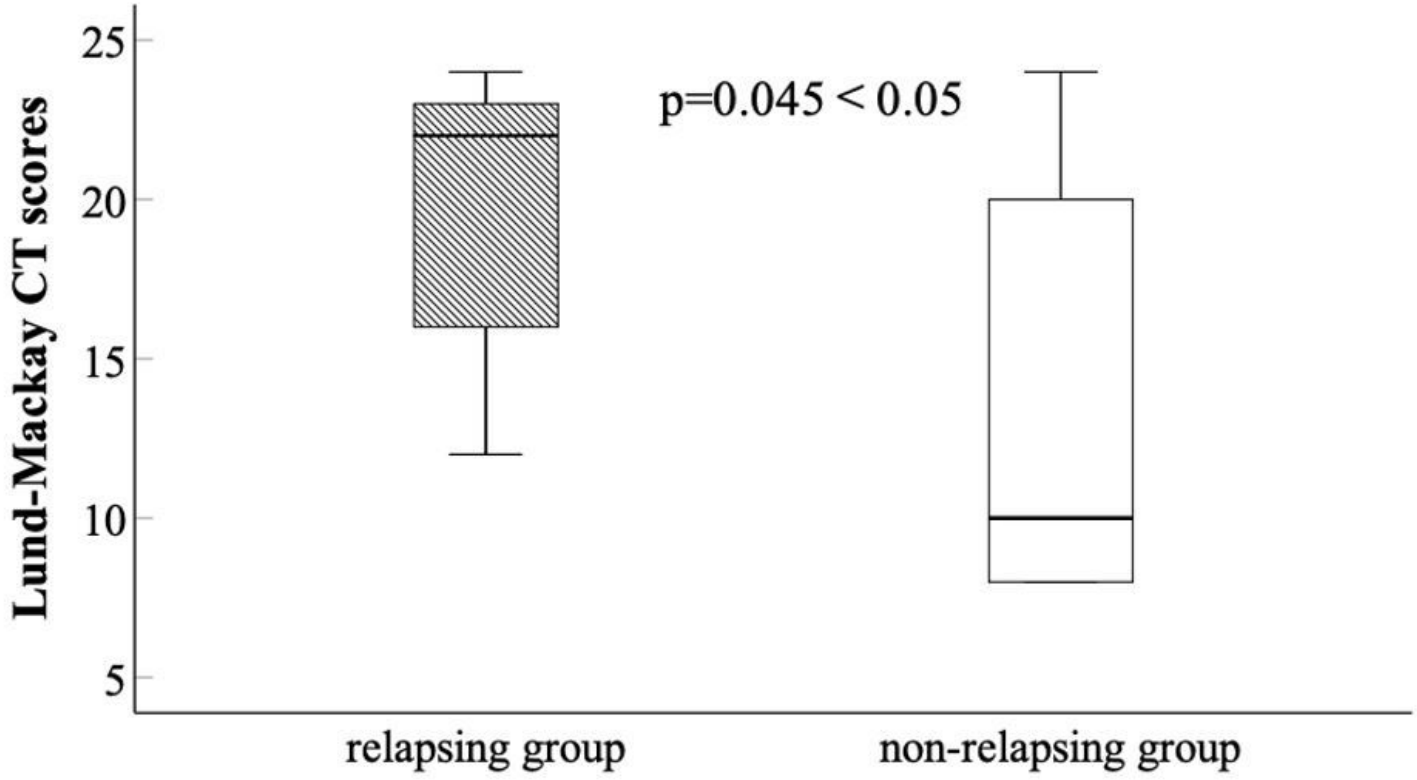

Figure 4

Total Lund-MacKay scores between two groups

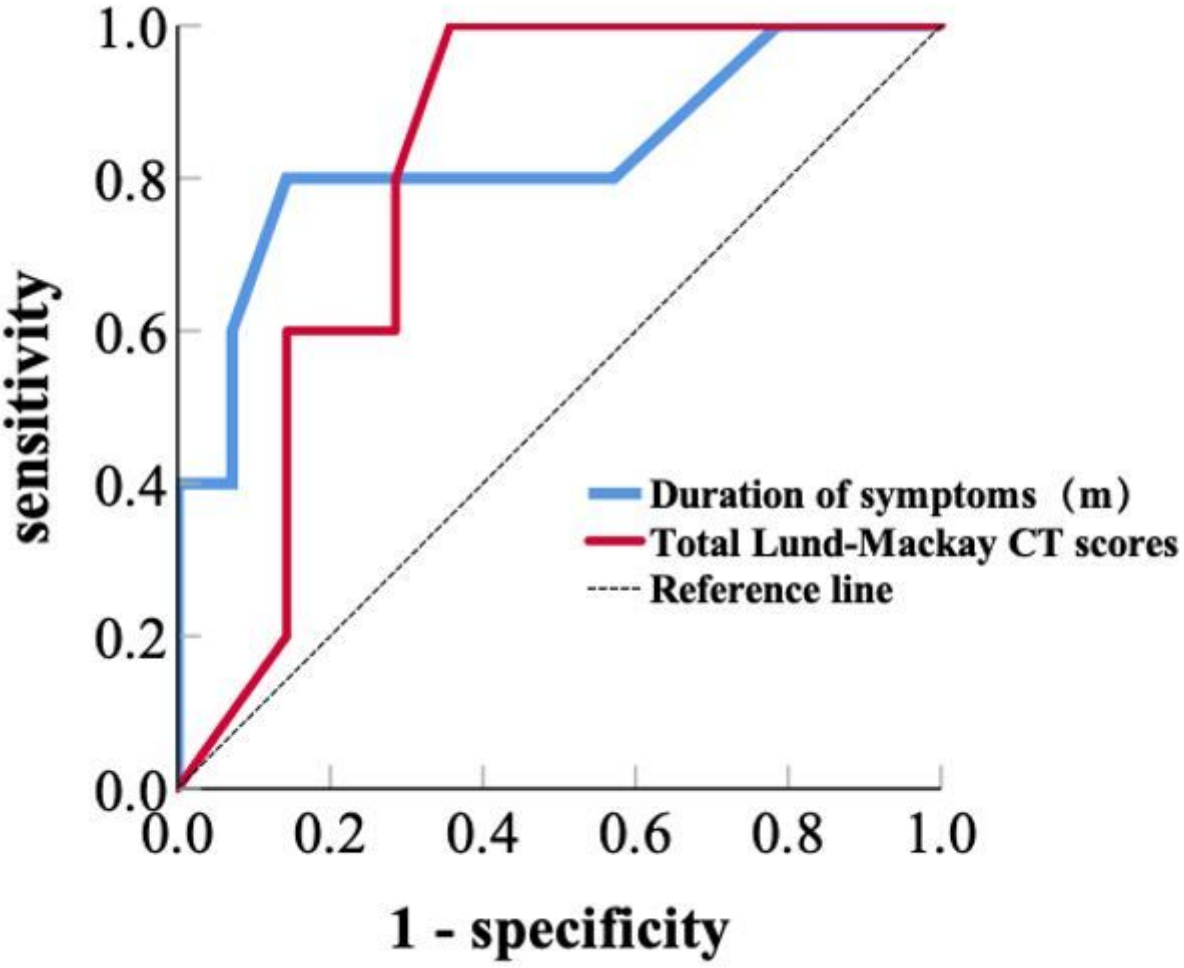

Figure 5

ROC curves for the duration of symptoms and the total Lund-MacKay scores