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Predictors of Pain in Patients with Noninvasive Fungal Sinusitis

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Abstract

The number of cases of noninvasive fungal sinusitis among asymptomatic and older patients has recently increased. Older adults are more commonly predisposed to comorbidities than younger people, and it is often difficult to determine a treatment plan for such patients, particularly for asymptomatic patients. Notably, surgery is the first-choice treatment for such patients; however, to date, no clear guidelines have been established for the same. In this study, we investigated the predictive factors of pain among patients with noninvasive fungal sinusitis. Out of 554 patients who underwent endoscopic sinus surgery between April 2010 and March 2020 at the Yokohama City University Medical Center, 59 were diagnosed with fungal sinusitis based on the identification of fungi in resected surgical specimens. Of these, 19 patients with preoperative symptoms, such as headache and facial pain, were included in the pain group, whereas the remaining 40 patients were included in the control group. Overall, 18 items were analyzed, including patient background factors, preoperative computed tomography scan results, blood test results, the location of the fungal mass, and information on the identified fungal species. Univariate analysis revealed significant differences in age, alcohol consumption, frequency of occurrence of ethmoid and frontal sinus lesions, Lund–Mackay scores, and white blood cell counts between the pain and control groups. However, based on multivariate analyses, only the Lund–Mackay score and white blood cell counts were identified as independent predictors of pain. In the receiver operator characteristic curve analysis, the area under the curve for the Lund–Mackay score was 0.76, and sensitivity and specificity were at a maximum cutoff score of 5. Among patients with noninvasive fungal sinusitis, those with high Lund–Mackay scores or white blood cell counts should be considered candidates for surgery.

Keywords
- ► noninvasive fungal sinusitis
- ► facial pain
- ► headache
- ► Lund–Mackay score
- ► sinus

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Introduction

Fungal sinusitis is caused by certain fungi, such as *Aspergillus* spp. and *Candida* spp.[1] Most fungal sinusitis encountered in daily clinical practice can be classified as noninvasive.[2,3] Notably, the number of cases of fungal sinusitis identified in asymptomatic patients and older adults has increased in recent years.[4] As the frequency of comorbidities is high among older adults, it is often difficult to choose treatment strategies for such patients, especially when they are asymptomatic. Surgery is considered the treatment of choice for fungal sinusitis[1]; however, there are no specific criteria to determine whether surgical treatment is indicated in such cases. Patients with pain are more likely to opt for surgical treatment because pain often negatively affects their quality of life. Thus, identifying the predictors of pain is expected to help in determining optimal treatment strategies for patients with fungal sinusitis. In this study, we explored the risk factors for pain in patients with noninvasive fungal sinusitis.

Materials and Methods

Subjects

Out of 554 patients who underwent endoscopic sinus surgery between April 2010 and March 2020 at the Yokohama City University Medical Center, 59 who were pathologically confirmed to be infected by fungi and diagnosed with fungal sinusitis were included in this study. Based on interviews conducted during each patient's first visit, 19 of these patients experienced pain (pain group) and 40 did not (control group).

At our hospital, patients with suspected fungal sinusitis based on computed tomography (CT) and magnetic resonance imaging (MRI) scans were initially suggested to undergo surgical treatment, regardless of whether they were symptomatic or asymptomatic. However, the final decisions were taken by the attending physicians after conducting discussions with the patients. Patients with invasive fungal sinusitis were excluded from the study.

Analyzed Factors

We analyzed 18 factors in all, including patient background (age, sex, the presence or absence of nasal polyps, diabetes mellitus, use of steroids and immunosuppressants, smoking status, and alcohol use), preoperative CT scan findings (locations of opacities, Lund–Mackay scores, and lesion characteristics, such as calcification, small air bubbles, differential-density areas, and bone destruction), blood test results (white blood cell count and C-reactive protein [CRP] level), locations of the fungus balls, and details about the identified fungal species.

In this study, patients were considered to have diabetes mellitus if their fasting blood glucose level was ≥126 mg/dL or random blood glucose level was ≥200 mg/dL and HbA1c level was ≥6.5%. Patients who had preoperatively used oral steroid preparations, including immunosuppressants, were defined as steroid users. Patients were defined as smokers if they had a history of smoking within 1 year preoperatively. Patients with a history of alcohol use at least once a week were considered alcohol users.

All patients underwent preoperative plain CT (three directions, 1-mm slices). Subsequently, the Lund–Mackay scores were calculated, and the scores for the affected side were recorded. Lesions were considered calcified if calcification was observed under bone tissue conditions. Moreover, lesions were considered to have small air bubbles when at least two air bubbles of ≤1 mm diameter were found in the sinus-filling lesions. A differential-density lesion was defined as an area where the density was uneven and where high-density spots appeared under soft-tissue conditions. Patients were considered to have bone destruction–positive lesions if the images showed bone destruction characteristics under bone tissue conditions.

Analysis Methods

The analysis software JMP (SAS) was used for all statistical analyses. Univariate analyses were performed using the chi-square and Wilcoxon's tests for nominal and continuous variables, respectively. Variables with significant differences between the two groups were then subjected to multivariate analyses via multiple-logistic regression to identify independent risk factors. A p-value of <0.05 was considered significant. Many previous reports have analyzed the relationship between Lund–Mackey scores and associated symptoms. We conducted receiver operator characteristic (ROC) analyses of Lund–Mackey scores and plotted ROC curves.

This study was conducted with the approval of the Research Ethics Review Board of the Yokohama City University Medical Center (B210500054).

Results

As described earlier, the pain and control groups comprised 19 (32%) and 40 (68%) patients, respectively. Patients' background information, preoperative CT findings, and blood test results, as well as locations of the fungus balls and identified fungal species are summarized in ►**Table 1**.

Patient Background

The age of participants in the pain and control groups was 35 to 77 (median: 59) years and 34 to 84 (median: 71) years, respectively. Overall, 10 (53%) and 14 (35%) patients in the pain and control groups, respectively, were men. Nasal polyps were found in 7 (37%) patients in the pain group and 10 (25%) patients in the control group. Moreover, three (16%) patients in the pain group and seven (18%) patients in the control group had diabetes mellitus. Immunosuppressants and steroids were used by three (16%) and four (10%) patients of the pain and control groups, respectively. Notably, seven patients each in the pain (37%) and control (18%) groups had a history of smoking. Furthermore, 10 (53%) patients in the pain group and 9 (23%) patients in the control group had a history of alcohol use.

The univariate analysis results revealed significant differences in terms of age and alcohol use between the two groups.

Table 1 Univariate analysis results

Patient background			
	Symptomatic group $n = 19$	Control group $n = 40$	*p*-Value
Mean age (years; range)	57 (35–77)	68 (34–84)	0.0015
Sex (number of men)	10 (53%)	14 (35%)	0.20
Nasal polyps	7 (37%)	10 (25%)	0.35
Diabetes mellitus	3 (16%)	7 (18%)	0.87
Use of preoperative steroids (including immunosuppressants)	3 (16%)	4 (10%)	0.52
Smoking	7 (37%)	7 (18%)	0.10
Alcohol use	10 (53%)	9 (23%)	0.02
Opacity location			
Maxillary sinus (*n*; %)	17 (89)	34 (85)	0.64
Sphenoid sinus (*n*; %)	5 (26)	8 (20)	0.58
Ethmoid sinus (*n*; %)	14 (74)	10 (25)	0.0004
Frontal sinus (*n*; %)	8 (42)	3 (8)	0.0014
Lund–Mackay score (95% CI)	6.7 (5.2–8.3)	4.4 (3.6–5.2)	0.0074
Lesion characteristics			
Calcification (*n*; %)	12 (63)	30 (73)	0.43
Small air bubbles (*n*; %)	5 (26)	9 (22)	0.71
Differential-density area (*n*; %)	5 (26)	10 (24)	0.87
Bone destruction (*n*; %)	0 (0)	0 (0)	–
Mean WBC count (/μL; 95% CI)	6,970 (5,940–8,000)	5,550 (5,070–6,030)	0.020
Mean CRP level (mg/dL; 95% CI)	0.86 (0.12–0.38)	0.25 (−0.1 to 1.8)	0.30
Fungus ball location			0.052
Maxillary sinus (*n*; %)	15 (79)	38 (95)	
Sphenoid sinus (*n*; %)	4 (21)	2 (5)	
Fungal species			0.84
Aspergillus (*n*; %)	8 (42)	16 (40)	
Candida (*n*; %)	1 (5)	1 (2.5)	
Others (*n*; %)	10 (52)	23 (57)	

Abbreviations: CRP, C-reactive protein; WBC, white blood cell.
Notes: Patient background factors that were significantly different between the pain and control groups in univariate analyses were age and alcohol use. The preoperative CT findings that were significantly different were the prevalence of ethmoid and frontal sinus lesions and the Lund–Mackay score. Among blood test results, the white blood cell count was found to differ significantly between the two groups. The fungus ball locations and identified fungal species did not differ significantly.

Preoperative CT Findings

The lesions were most commonly located in the maxillary sinus in 17 (89%) and 34 (85%) patients of the pain and control groups, respectively. Moreover, lesions were found in the sphenoid sinus in 5 (26%) and 8 (20%) patients, ethmoid sinus in 14 (74%) and 10 (25%) patients, and frontal sinus in 8 (42%) and 3 (8%) patients, of the pain and control groups, respectively.

Lund–Mackay scores were compared based on 95% confidence intervals (CIs). The median Lund–Mackay scores of the pain and control groups were 6 (4.5–7.5) and 3 (2.8–4.1), respectively.

Bone thickening was observed in 11 (58%) and 25 (61%) patients in the pain and control groups, respectively. Moreover, calcifications were observed in 12 (63%) patients in the pain group and 30 (73%) patients in the control group. Notably, five (26%) patients in the pain group and nine (22%) patients in the control group were positive for small air bubbles in the lesions. Areas of differential density were noted in 5 (26%) patients in the pain group and 10 (24%) patients in the control group. Furthermore, bone destruction was observed in five (26%) and eight (20%) patients in the pain and control groups, respectively.

The univariate analysis results revealed significant differences in the prevalence of ethmoid and frontal sinus lesions as well as Lund–Mackay scores between the two groups.

Blood Test Findings

White blood cell counts and CRP levels were compared based on 95% CIs. The median white blood cell counts in the pain and control groups were 6,400 (5,940–8,000)/μL and 5,465 (5,070–6,030)/μL, respectively. The median CRP levels in the pain and control groups were 0.16 (0.1–1.8) mg/dL and 0.09 (0.12–0.38) mg/dL, respectively.

Univariate analyses revealed a significant difference in the white blood cell count of the two groups.

Location of Fungus Balls

Fungus balls were found in the maxillary sinus in 15 (79%) and 38 (95%) patients in the pain and control groups, respectively. They were also found in the sphenoid sinus in four (21%) patients in the pain group and two (5%) patients in the control group. Notably, no fungus balls were found in other sinuses.

The locations of fungus balls did not significantly differ between the two groups.

Fungal Species

The surgical specimens were subjected to pathological examinations. The periodic acid–Schiff and Grocott staining results for all specimens were positive, thus confirming the presence of fungi. Out of 35 (59%) patients in whom causative fungal species could be identified (e.g., through culturing), *Aspergillus* spp. and *Candida* spp. were identified in 33 (56%) and 2 (3%) patients, respectively. *Aspergillus* spp. were identified in 10 (53%) patients in the pain group and 23 (58%) patients in the control group. *Candida* spp. were identified in one patient in each group.

The composition of the identified fungal species did not differ significantly between the two groups.

Multivariate Analysis

The variables included in the multivariate analysis were age, status of alcohol use, the Lund–Mackay score, and white blood cell count. Significant differences were found in terms of the presence or absence of lesion in the frontal and ethmoid sinuses, as also noted in the univariate analyses; however, these factors were not included in the multivariate analysis because they were likely to be closely correlated with the Lund–Mackay scores. ►**Table 2** shows the results of the multivariate analysis. High Lund–Mackay scores ($p = 0.01$, odds ratio = 1.52, 95% CI: 1.10–2.10) and white blood cell counts ($p = 0.02$, odds ratio = 1.0005, 95% CI: 1.0001–1.001) were found to be independent predictors. No significant differences were found in terms of age and alcohol use.

Table 2 Multivariate analysis results

	Odds ratio (95% CI)	*p*-Value
Mean age (y)	0.95 (0.90–1.02)	0.14
Alcohol use	2.8 (0.64–12.25)	0.17
Lund–Mackay score	1.52 (1.10–2.10)	0.010
Mean WBC count (/μL)	1.0005 (1.0001–1.001)	0.018

Abbreviation: WBC, white blood cell.
Notes: High Lund–Mackay score ($p = 0.01$, odds ratio = 1.52, 95% CI: 1.10–2.10) and the white blood cell count ($p = 0.02$, odds ratio = 1.0005, 95% CI: 1.0001–1.001) were identified as independent predictors. No significant differences in age and alcohol use were found.

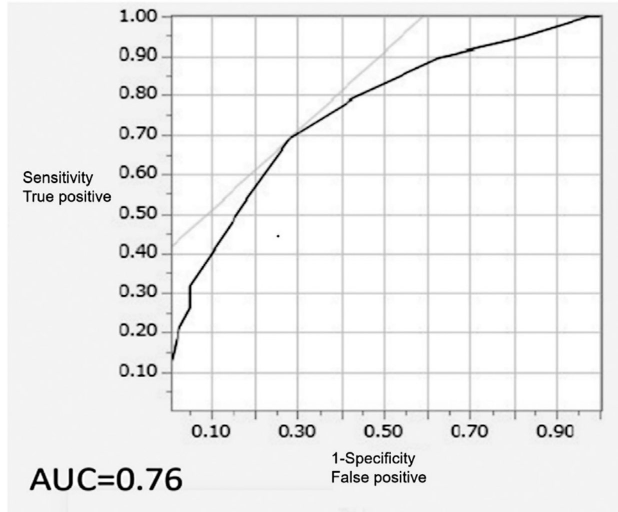

Fig. 1 Receiver operator characteristic curve. The area under the curve was 0.76, indicating that the sensitivity and specificity values are maximum when the cutoff value of the Lund–Mackay score is 5.

ROC Analysis

The ROC analysis of Lund–Mackay scores was conducted and an ROC curve was plotted (►**Fig. 1**). The analysis indicated an area under the curve (AUC) of 0.76, and sensitivity and specificity were maximum when the score was 5.

Discussion

There are two major types of fungal sinusitis: invasive and noninvasive. Noninvasive fungal sinusitis is further subdivided into chronic noninvasive (parasitic) and allergic fungal rhinosinusitis.[5,6] Recently, the numbers of cases of fungal sinusitis increased because of various reasons, including the aging of the population, increase in the number of patients with diabetes mellitus, and increase in the number of people who undergo CT and MRI examinations owing to the popularization of diagnostic imaging devices.[4] Patients with fungal sinusitis who experience pain are more likely to opt for surgical treatment because pain often reduces the quality of life. Moreover, for asymptomatic older patients incidentally diagnosed with fungal sinusitis, surgery may be recommended as a therapeutic modality depending on the comorbidities and possible complications, and the decision-making process can be difficult in some cases. We considered that by identifying patient characteristics that can predict the likelihood of pain development, we could determine the optimal treatment strategies for fungal sinusitis. The results of univariate and multivariate analyses conducted in this study indicated that high Lund–Mackay scores and white blood cell counts are independent risk factors that can be used to predict the development of pain in patients with noninvasive fungal sinusitis.

Multivariate analyses revealed that no patient background variables were associated with pain. Diabetes mellitus has been widely known as a factor contributing to the increased susceptibility to invasive fungal sinusitis.[7] Although some previous reports suggested an association between diabetes mellitus and all types of fungal sinusitis,[4,8–10] we found no association between the prevalence of diabetes mellitus and pain (3 patients [16%] in the pain group vs. 7 patients [18%] in the control group, $p = 0.87$).

The maxillary sinus was the most common location of lesions in both groups, and this finding is consistent with that of a previous report.[3] Moreover, in the pain group, opacity was often observed in the frontal and ethmoid sinuses, and in significantly more cases, the shadows extended to the ethmoid and frontal sinuses where no fungus balls were found.

The median Lund–Mackay score in the pain group (5.9 [95% CI: 4.5–7.5]) was significantly higher than that in the control group (3.5 [95% CI: 2.8–4.1]). This result suggests that patients with sinus inflammation spreading beyond the location of fungus balls are more likely to experience pain.

The Lund–Mackay score is widely used as a tool to objectively evaluate the extent and severity of all types of chronic sinusitis based on CT images.[11] Published opinions regarding the relationships between this score and preoperative subjective nasal symptoms (e.g., nasal congestion, nasal secretion, and pain) are varying.[12–15] In the present study, the Lund–Mackay scores were significantly higher in symptomatic patients, indicating a positive association between the two factors.

The results of the ROC analysis indicate that patients with a Lund–Mackay score of ≥ 5 are more likely to be predisposed to the development of pain, suggesting that this score serves as a criterion for choosing the surgical treatment. Notably, no other CT-based findings were associated with pain.

The mean preoperative white blood cell count in the pain group (6,970 [95% CI: 5,940–8,000]/µL) was significantly higher than that in the control group (5,550 [95% CI: 5,070–6,030]/µL). The present study included patients with noninvasive fungal sinusitis; however, no distinction was made between chronic noninvasive (parasitic) and allergic types.[2,3] The higher white blood cell counts in the pain group may reflect host responses to parasitic fungi; in addition, the higher counts may be due to concomitant bacterial infections. Furthermore, the higher Lund–Mackay score and white blood cell count in the pain group can be considered to reflect the severity of sinusitis without inconsistencies.

Fungus balls were found in the sphenoid sinus in four (21%) patients in the pain group and two (5%) patients in the control group. Fungus balls in the sphenoid sinus appear to be more common in patients with pain, although no significant differences were found, presumably because the number of patients included was small.

Aspergillus spp. are known be the cause of the largest proportion of cases of fungal sinusitis.[3] Similarly, in the present study, *Aspergillus* spp. were the most commonly detected fungi, and the test results of a small number of patients were positive for *Candida* spp. The proportions of detected fungal species do not appear to be associated with pain because both fungal species were present in both groups in similar proportions.

Surgery is usually recommended as the first-line treatment for young patients with suspected fungal infections even if they are asymptomatic. However, treatment strategies for older patients are often difficult to determine, particularly when they are asymptomatic, as they often have comorbidities. The lack of objective criteria to assess the severity of fungal sinusitis is one of the reasons why treatment strategies are difficult to determine. The results of this study indicate that high Lund–Mackay scores and white blood cell counts are possible risk factors for pain, suggesting that surgical management should be considered proactively for patients with high Lund–Mackay score and white blood cell counts, even if they are asymptomatic.

Conclusion

In this study, we explored the factors associated with pain in patients with noninvasive fungal sinusitis. Our study results indicate that high Lund–Mackay scores and white blood cell counts are possible factors for pain and may serve as criteria for choosing surgical treatment.

Informed Consent

This study was approved by the Research Ethics Review Committee of Yokohama City University Medical Center (B210500054). Individual consent for the study was obtained.

Conflict of Interest

None declared.

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