Analysis of clinical characteristics of fungus ball based on the number of involved sinuses

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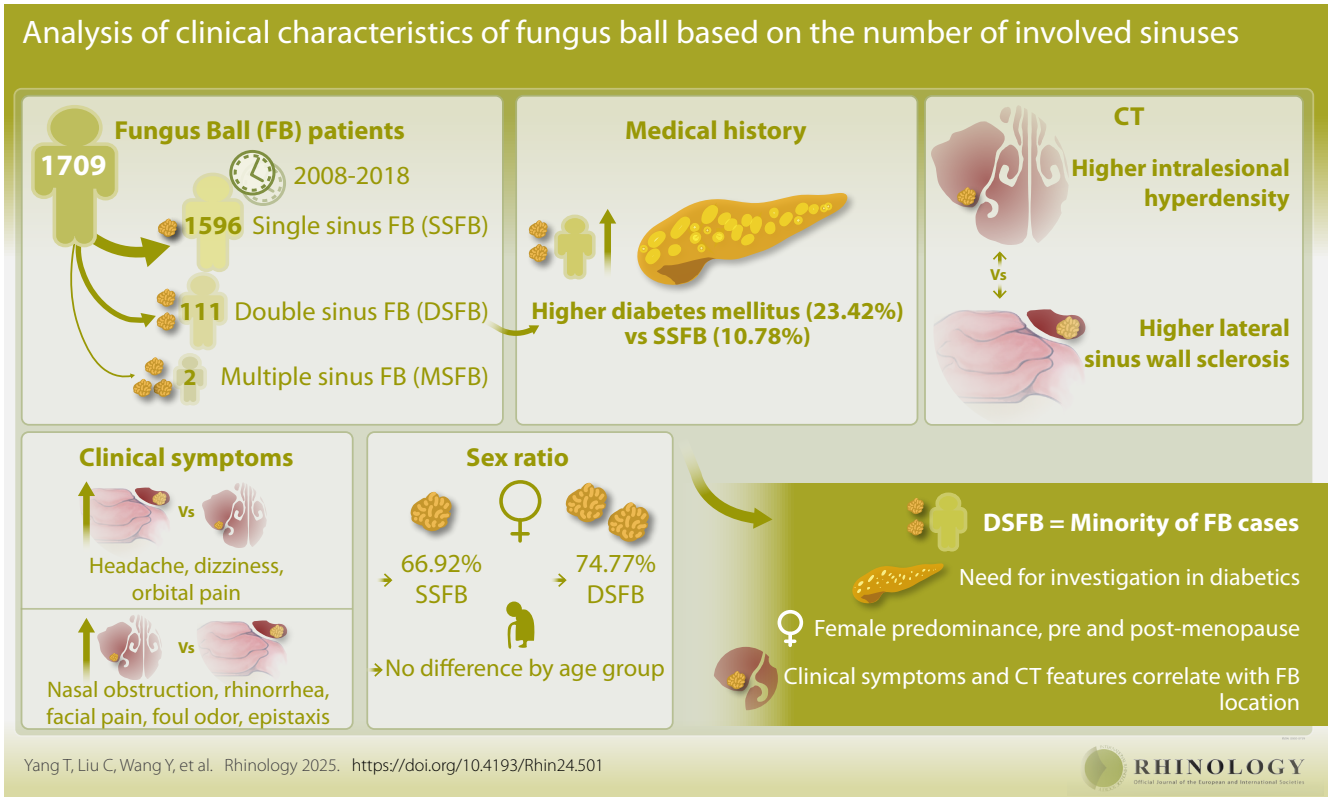

Abstract

Background: Fungus ball (FB) typically presents unilaterally, with the maxillary sinus being the most commonly affected site. Multi-sinus FB cases are seldom discussed.

Methodology: A retrospective study involving 1709 FB patients categorized them into single sinus fungus ball (SSFB), double sinus fungus balls (DSFB), and multiple sinus fungus balls (MSFB) groups for clinical analysis.

Results: The SSFB group comprised 1596 patients (93.39%), the DSFB group 111 patients (6.50%), and the MSFB group two patients (0.12%). The prevalence of diabetes mellitus in the DSFB group was higher than that in the SSFB group. A female prevalence was noticed and there was no difference in the sex ratio by age group. On computed tomography (CT), maxillary sinus FB group had higher intralesional hyperdensity than sphenoid sinus FB group. Oppositely, sphenoid sinus FB group had higher lateral sinus wall sclerosis than maxillary sinus FB group.

Conclusions: DSFB occurs in a minority of cases but needs to be investigated especially in diabetics given the link between diabetes mellitus and increased DSFB risk. A female predominance is seen in both pre- and postmenopausal women. On CT, the presence of intralesional hyperdensity and lateral sinus wall sclerosis correlates with the location of the FB.

Key words: chronic rhinosinusitis, prevalence, sphenoid sinus, maxillary sinus

Introduction

Fungal rhinosinusitis can be broadly divided into two categories based on histopathological findings: invasive and non-invasive, depending on the invasion of the mucosal layer. Sinus fungus ball (FB) is the most common subtype of noninvasive fungal rhinosinusitis, occurring in immunocompetent hosts [1]. Due to the improved awareness, the popularization of diagnostic techniques, the overuse of broad-spectrum antibiotics, increased endodontic treatment and life expectancy, the incidence of FB has increased over the past several decades [2-4]. A female predominance has been noted in most FB series. Computed tomography (CT) scans have revealed the opacity of the cavity associated with a hyperdense area within the lesion and thickened bone [5]. The most common fungus found in FB patients is *Aspergillus* spp, which is reported in 93 % of FB patients [6]. Histopathology plays an important role in the identification of tissue invaded by fungi [7]. The preferred treatment of FB is complete removal through functional endoscopic sinus surgery, which is associated with a low recurrence rate.

FB usually occurs unilaterally, and maxillary sinus is the most commonly involved. Bilateral fungus balls and multiple fungus balls have been mentioned before [8-11]. However, the ipsilateral non-adjacent sinuses FB has not been discussed yet, which may result in an incomplete understanding of FB. Therefore, the aim of this study was to analyze and compare the clinical characteristics of Chinese patients based on clear definitions of single sinus fungus ball (SSFB), double sinus fungus balls (DSFB) and multiple sinus fungus balls (MSFB).

Materials and methods

Study design

This retrospective study examined the medical records of 1709 patients who were surgically treated and diagnosed with FB from January 2008 to December 2018. The inclusion criteria were the following: 1) CT or magnetic resonance imaging (MRI) results and FB found during surgery in the sinuses or nasal cavities, and 2) FB confirmed by histopathology. Patients diagnosed with invasive fungal sinusitis or allergic fungal rhinosinusitis were excluded. In addition, patients who had previously undergone nasal surgery were also excluded.

The CT images of 1543 lesions in 1435 patients were carefully analyzed by two otorhinolaryngologists and a radiologist. The images from the remaining 274 patients could not be analyzed because they were not available in our hospital's electronic medical record system. Forty-three patients underwent MRI examination because the nature of the lesion was not clear. The typical CT findings consisted of partial or complete sinus opacity with intralesional hyperdensity (IH) and sclerosis of lateral sinus wall (SLSW); IH referred to the presence of spot or linear calcification surrounded by subtotal or total opacity within the sinus, while SLSW was defined as the ratio of the lateral wall of the diseased sinus to that of the contralateral sinus greater than 1.2. For patients with FB in bilateral sinuses, a bone thickness of 3 mm is considered the standard for SLSW.

The patients were divided into SSFB, DSFB, and MSFB groups according to the number of sinuses involved. The ipsilateral maxillary sinus, ethmoid sinus, and frontal sinus are adjacent. When the maxillary sinus fungus ball protruded beyond the ostiomeatal complex and interfered with the drainage of anterior sinuses, this counted as one involved sinus. Patient information regarding age, sex, residence, medical history, clinical symptoms, and CT imaging was collected and analyzed. This study protocol was approved by the local ethics committee of Beijing Tongren Hospital, which exempted the requirement of patient consent.

Statistical analysis

IBM® SPSS® Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA) was used for all statistical analyses. Comparisons between two groups for continuous variables were performed by either the t test or the Mann–Whitney test. Continuous values were expressed as mean ± standard deviation and analyzed by the t-test or non-parametric test. Categorical variables were presented as absolute numbers and analyzed using the Chi-square test or Fisher's exact test. Factors of epidemiological characteristics with P-values less than 0.05 in the univariate analysis were included in a multivariate logistic regression analysis; P values < 0.05 was considered statistically significant.

Results

Subject characteristics

A total of 1709 patients were included in the study. The SSFB group comprised 1596 patients (93.39%), the DSFB group 111 patients (6.50%), and the MSFB group included two patients (0.12%). The location characteristics of FB in this study are shown in Table 1.

The mean patients' mean age was 53.01 ± 12.31 years in the SSFB group and 54.86 ± 12.34 years in the DSFB group (P = 0.126). A female prevalence was noticed; 66.92% of patients were female in the SSFB group and 74.77% in the DSFB group (P = 0.088). There was no difference in the sex ratio by age group. The gender distribution of the SSFB and DSFB groups is shown in Figure 1. No statistically significant difference in smoking prevalence was found between the SSFB and DSFB groups (P = 0.284). Univariate analysis showed that the incidence of DSFB was higher in northern China than in southern China (P = 0.038), but the geographical factor failed to show significance at the multivariate level. The SSFB group included 83 patients who were asymptomatic and were fortuitously diagnosed with FB by physical examination or imaging; the DSFB group included six patients who were asymptomatic (P = 0.925).

Hypertension, diabetes and heart disease were the three most common concomitant diseases in the SSFB and DSFB group; 435

Table 1. Locational characteristics of fungus ball in 1709 patients.

Location	N
Single sinus fungus ball	1596 (93.39%)
M	1239 (72.50%)
S	338 (19.78%)
E	17 (0.99%)
F	2 (0.12%)
Double sinus fungus balls	111 (6.50%)
M+M	53 (3.10%)
M+S	32 (1.87%)
S+S	12 (0.70%)
M+E	10 (0.59%)
E+S	4 (0.23%)
Multiple sinus fungus balls	2 (0.12%)
M+S-S	1 (0.06%)
M+S-E	1 (0.06%)

M: maxillary sinus; S: sphenoid sinus; E: ethmoid sinus; F: frontal sinus.

patients (27.26%) in the SSFB group and 35 patients (31.53%) in the DSFB groups had hypertension (P = 0.329). The prevalence of diabetes mellitus in the DSFB group (26 patients, 23.42%) was higher than that in the SSFB group (172 patients, 10.78%), and there was a statistical difference between the two groups (P < 0.001). Multivariate logistic regression analysis also indicated that diabetes mellitus is related to higher risk of DSFB (OR 2.466; 95% CI 1.490 - 4.082; P < 0.001). The epidemiological features of the SSFB and DSFB groups are shown in Table 2.

Differences in symptomatology

The total number of sinus infections was 1824, including 1389 maxillary, 401 sphenoid, 32 ethmoid, and 2 frontal sinus infections. The proportion of maxillary sinus FB infections in the SSFB group was higher than that in the DSFB group (P < 0.001). Meanwhile, the proportion of FB in sphenoid sinus and ethmoid sinus in the DSFB group was higher than that in the SSFB group (P = 0.048, P < 0.001, respectively).

The five most common clinical symptoms in the SSFB group were nasal obstruction (44.05%), headache (42.36%), rhinorrhea (39.72%), facial pain (16.10%), and epistaxis (13.72%). Similarly, the five most common symptoms in the DSFB group were headache (43.24%), rhinorrhea (41.44%), nasal obstruction (40.54%), facial pain (19.82%) and postnasal drip (15.32%). The DSFB group had a higher incidence of orbital pain than the SSFB group (P < 0.01). Clinical symptoms of SSFB and DSFB patients are shown in Figure 2.

Patients with sphenoid sinus FB had higher rates of headache, dizziness and orbital pain compared to patients with maxillary sinus FB (P < 0.05). Conversely, nasal obstruction, rhinorrhea,

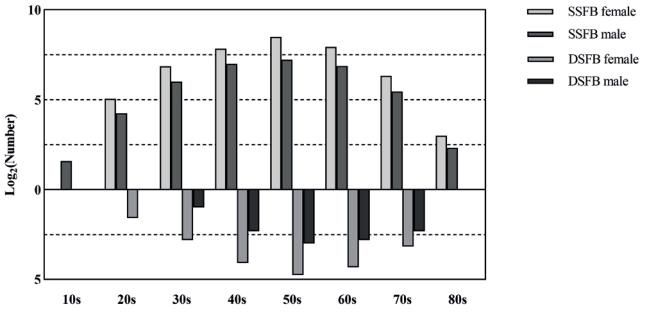

Figure 1. Gender distribution of patients in the SSFB and DSFB groups.

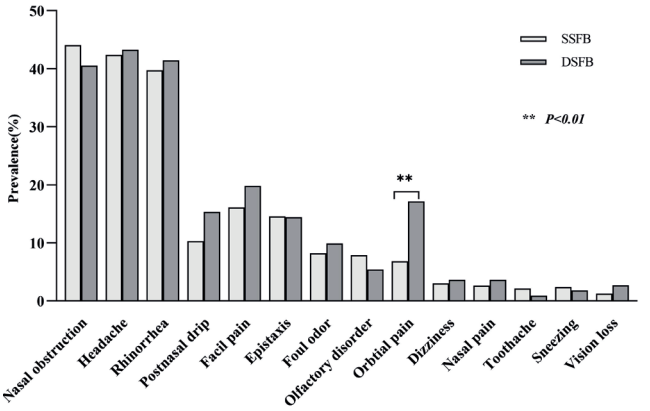

Figure 2. Clinical symptoms of SSFB and DSFB in our study.

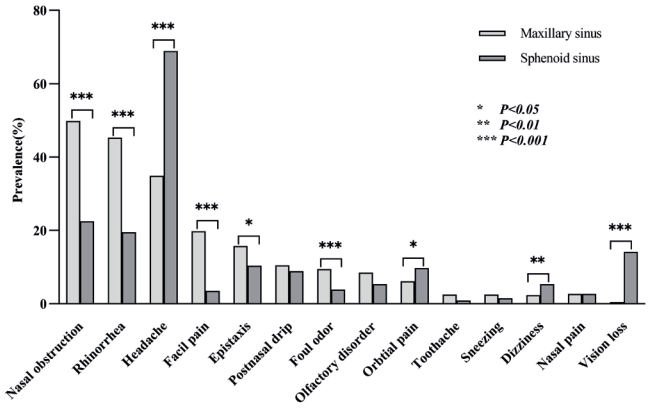

Figure 3. Clinical symptoms of maxillary and sphenoid sinus FB in our study.

facial pain, foul odor, and epistaxis were higher in patients with maxillary sinus FB compared to patients with sphenoid sinus FB (P < 0.05). Clinical symptoms of maxillary and sphenoid sinus FB patients are shown in Figure 3.

Comparison of CT findings

Intralesional hyperdensity was detected in 850 patients (72.7%) in maxillary sinus FB group and 170 patients (49.4%) in sphenoid sinus FB group. Maxillary sinus FB group had a higher percentage of IH than sphenoid sinus FB group (P < 0.01). In contrast,

Table 2. Epidemiological characteristics of the SSFB and DSFB groups.

	SSFB (n = 1596)	DSFB (n = 111)	P value
Age, mean ± SD	53.01 ± 12.31	54.86 ± 12.34	0.126
Gender, female, n	1068 (66.92%)	83 (74.77%)	0.088
Residence, n			
Northern China	1510 (94.61%)	110 (99.10%)	0.038*
Southern China	86 (5.39%)	1 (0.90%)	
Medical history, n			
Smoking, n	149 (9.34%)	7 (6.31%)	0.284
Hypertension	435 (27.26%)	35 (31.53%)	0.329
Heart disease	103 (6.45%)	18 (16.22%)	< 0.001*
Diabetes mellitus	172 (10.78%)	26 (23.42%)	< 0.001*
Thyroid disease	110 (6.89%)	9 (8.11%)	0.627
Gynecological disease	82 (5.14%)	3 (2.70%)	0.365
Hepatic disease	77 (4.82%)	4 (3.60%)	0.816
Gastroesophageal diseases	54 (3.38%)	4 (3.60%)	0.788
Kidney disease	51 (3.20%)	1 (0.90%)	0.253
Pulmonary inflammation	22 (1.38%)	4 (3.60%)	0.084
Tuberculosis	25 (1.57%)	2 (1.80%)	0.694
Asthma	20 (1.25%)	1 (0.90%)	1.000
Immunological diseases	17 (1.07%)	2 (1.80%)	0.353
Medical image, n			
CT	1328	106	
MRI	37	5	

* P < 0.05.

sphenoid sinus FB group (743 patients, 63.56%) had a higher incidence of SLSW than maxillary sinus FB group (245 patients, 71.22%) (P = 0.009). On CT scans, 155 patients (13.26%) in maxillary sinus FB group and 61 patients (17.73%) in sphenoid sinus FB group exhibited no evidence of IH or SLSW. The sphenoid sinus FB group was more likely to show no IH or SLSW compared to the maxillary sinus FB group (P = 0.037). Computerized tomography features of 1169 maxillary sinuses and 344 sphenoid sinuses are shown in Table 3; CT images of bilateral maxillary sinus FB and bilateral sphenoid sinus FB can be seen in Figure 4.

Microbiological culture

The microbiological culture results revealed that 592 patients underwent fungal cultures, of which 149 cases (25.17%) showed positive fungal growth. In the DSFB group, six patients underwent bilateral sinus cultures. One patient was found to have

Table 3. CT features of maxillary and sphenoid sinus FB.

	Maxillary sinus, n	Sphenoid sinus, n	P value
IH and SLSW	579 (49.53%)	132 (38.37%)	< 0.001*
IH	850 (72.71%)	170 (49.42%)	< 0.001*
SLSW	743 (63.56%)	245 (71.22%)	0.009*
IH or SLSW	1014 (86.74%)	283 (82.27%)	0.037*
Without IH and SLSW	155 (13.26%)	61 (17.73%)	

IH: intralesional hyperdensity; SLSW: sclerosis of lateral sinus wall; * P < 0.05.

Aspergillus versicolor in one sinus and *Alternaria alternate* in the other sinus. The other five patients were found to have the same type of fungal infection in both sinuses. A total of 133 nasal sinuses cultures showed *Aspergillus*, accounting for 78.70%. There was no significant statistical difference between *Aspergillus* (p = 0.557) and other fungi (p = 0.617) in the distribution of maxillary sinus and sphenoid sinus. There was also no difference in the incidence of hypertension (P=0.560) and diabetes (P = 0.531) between patients infected with *Aspergillus* and other fungi. The proportion of SLSW and IH on CT scans was not correlated with the species of fungi (P = 0.365, P = 0.602, respectively).

Discussion

In recent years, the incidence of FB has been increasing, which is believed to be caused by the improvement of disease awareness and diagnostic techniques, the abuse of broad-spectrum antibiotics, and the aging of the population [2-4]. According to EPOS 2020 [12], FB is a secondary chronic sinusitis involving unilateral sinuses and causing local pathological changes. However, with the increase in incidence, DSFB and MSFB are common. The proportion of DSFB in this study was 6.50%, which falls within the range of 3.3%-7.2% reported in previous studies [8,9,11].

A female predominance has been noted in most FB reports. Nomura et al. proposed that the longer life expectancy of women may be a possible reason; in their study, the number of male and female patients aged younger than 60 years was the same. However, Young et al. reported that the numbers of male and female patients aged younger than 60 years was 98 and 187, respectively [4]. In our study, 66.92% of patients were female in the SSFB group and 74.77% in the DSFB group, and there was no difference in the sex ratio by age group. Postmenopausal women have an extended mean mucociliary transport time which can be reduced by hormone therapy [13,14]. Impaired mucociliary function may weaken the defense mechanism of respiratory epithelium, causing sinonasal infections [15]. We hypothesized that fluctuations in estrogen may lead to a periodic decline in mucociliary function, which may be associated with the female

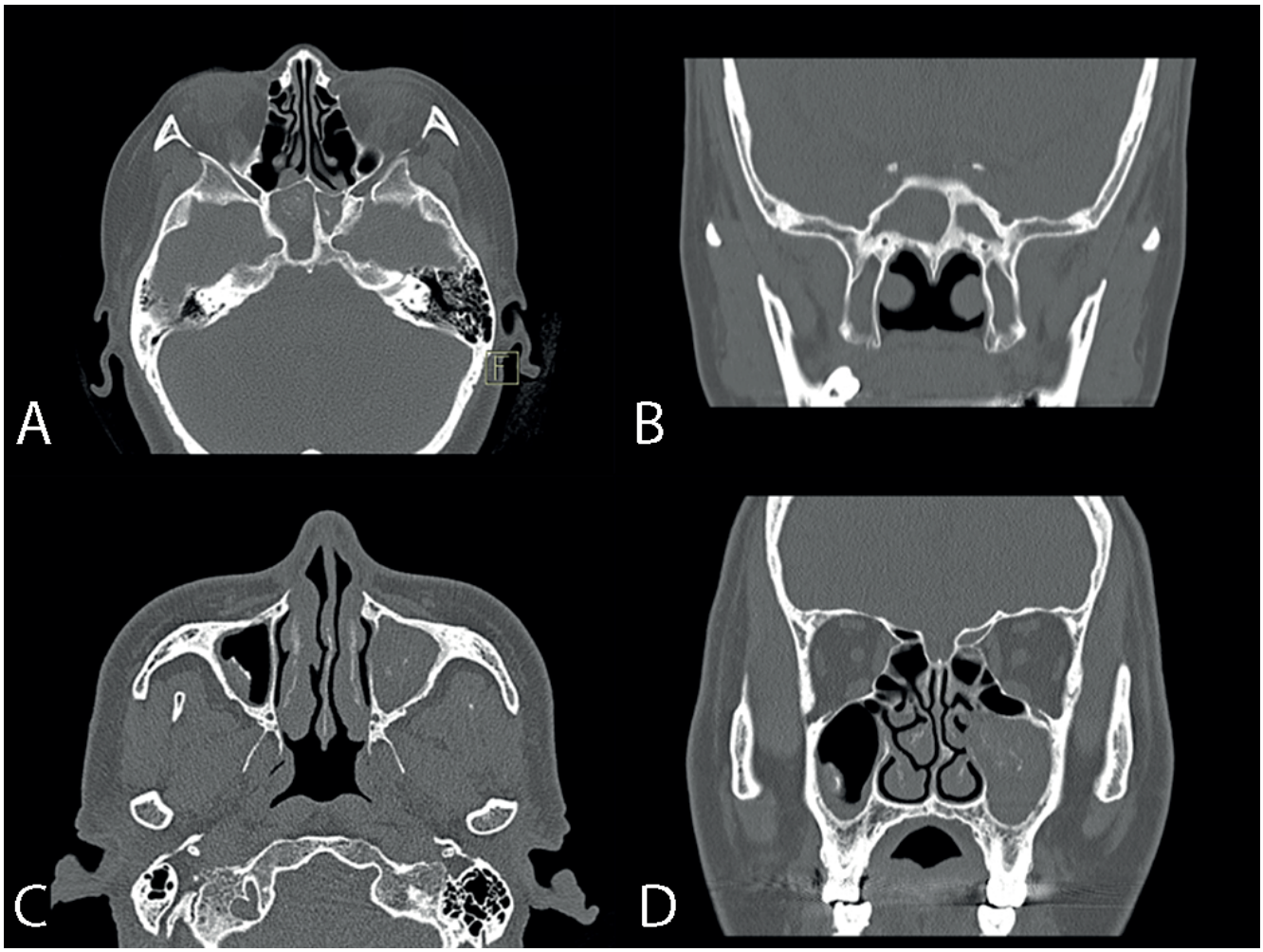

Figure 4. CT images of bilateral maxillary and sphenoid sinus FB. (A) axial scan and (B) coronal scan of sphenoid sinus FB; (C) axial scan and (D) coronal scan of maxillary sinus FB.

predominance of FB in premenopausal women.

Local factors, including ipsilateral odontogenic factors and anatomic variations, have been recognized as contributors to the development of FB in the maxillary sinus. In addition, systemic factors like chronic wasting diseases may also be associated with the incidence of FB. Muller suggested that diabetes mellitus may affect patients through various factors, such as changes in nasal mucosal microvasculature, decreased mucociliary clearance, and increased sensitivity to fungus [16]. In this study, the incidence of diabetes in the SSFB group was similar to that in the Chinese population [17], indicating that diabetes may have a limited impact on the development of SSFB. However, both univariate and multiple logistic regression analyses revealed a relationship between diabetes and a higher risk of developing DSFB. This suggests that systemic factors, like diabetes, may play a prominent role in patients with DSFB.

The peripheral resistance of blood vessels in hypertension can affect paranasal sinuses, resulting in hypoperfusion and decreased drainage of multiple sinus mucosa. In Kim's study, hypertension was more common in the bilateral than in unilateral FB group [8]. Heo et al. found that the incidence of hypertension and chemotherapy for solid tumors in patients with bilateral FB was higher than in patients with unilateral FB [9]. In constrast to their findings, our study showed no statistical difference in the incidence of hypertension between the two groups. Li et al. showed that the prevalence of heart disease in multiple FB groups was higher than that in the SSFB group, which was consistent with the results of this study [10]. It is important to note that DSFB patients were, on average, older than SSFB patients in the above studies. Aging may account for the high incidence of underlying diseases [10,18].

The introduction of microorganisms carried by dusty wind could exacerbate the prevalence of FB [19]. In addition, temperature and humidity may influence the conditions of patients and increase their chance of visiting the clinic [20]. Univariate analysis indicated that the proportion of DSFB was higher in northern China than in southern China. We reasoned that windy and dusty weather in the north could increase the chances of fungal

infections. Furthermore, without sufficient humidity, FB takes a longer time to grow before clinical symptoms appear. These two factors are likely to increase the proportion of DSFB in northern China. Nonetheless, the geographical factor failed to show significance at the multivariate level.

Since it is difficult to identify which sinuses are causing clinical symptoms in the DSFB and MSFB group, only the SSFB group was discussed in terms of symptoms. The incidence of nasal obstruction, rhinorrhea, facial pain, foul odor, and epistaxis was higher in patients with maxillary sinus FB than sphenoid sinus FB. In contrast, the incidence of headache, dizziness, orbital pain, and vision loss was higher in patients with sphenoid sinus FB. These differences in clinical symptoms can provide early indication of the lesion sites. Only 6% of patients are asymptomatic [21], and there was no statistical difference in the proportion of asymptomatic patients between the SSFB and DSFB groups.

Several studies have reported the CT features of FB, which include IH, erosion of the sinus wall, irregular surface of the material, and SLSW [22-24]. The proportion of SLSW in sphenoid sinus FB was 71.22%, higher than that of maxillary sinus FB (63.56%). Intralesional hyperdensity can be differentiated into calcium and metal types based on their density [25]. Metal-type IH is associated with endodontic treatments; thus, it has rarely been reported in sphenoid sinus FB. Endogenous fungal products may be responsible for calcium-type IH. Moreover, the volume of the maxillary sinuses is larger than that of other sinuses, and fungus balls typically require a longer time to become symptomatic. Greater amounts of fungal products are usually found in the maxillary sinuses [26]. These factors may help explain the higher incidence of IH observed in the maxillary sinus in our study. The high proportion of SLSW in sphenoid sinus may be due to the high incidence of sphenoid sinus osteitis [27]. Fungus balls can be suggested by the presence of the hyper-signal intensity portions in the fungal mass on T1 weighted images in conjunction with dark-signal lesions surrounded by high-signal, hypertrophic mucosal walls in paranasal sinuses on T2 weighted images [28]. In our study, 13.26% of maxillary sinus FB and 17.73% of sphenoid sinus FB showed no typical features such as IH or SLSW. For patients without typical CT features, MRI can serve as a valuable adjunct to preoperatively determine the nature of the opacity and its persistence after medical treatment.

Conclusion

We analyzed and compared the clinical characteristics of FB in Chinese patients based on clear definitions of SSFB, DSFB and MSFB. DSFB occurs in a minority of cases; however, it needs to be investigated particularly in diabetics, due to the established link between diabetes mellitus and increased DSFB risk. Female predominance was observed, with no variation in the sex ratio across age groups. On CT, the presence of intralesional hyperdensity and lateral sinus wall sclerosis correlates with the location of the FB.

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Authors' contributions

JZ, and YW performed data collection. TY and CL performed data analysis and drafted the manuscript. YL and HW contributed to the revision of the article. All authors participated in the scientific discussions and approved the final manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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