Identifying a sphenoid sinus fungus ball using a nomogram model*

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Abstract

Background: Sphenoid sinus fungus ball (SSFB) is a rare entity and usually presents with non-specific symptoms. SSFB could potentially lead to serious orbital and intracranial complications. Computed tomography (CT) scan is usually the first imaging test of the diagnostic workup in patients with specific clinical symptoms. This study aimed to compare the clinical characteristics and CT features between SSFB and unilateral (non-fungus ball) chronic sphenoid rhinosinusitis (USRS) and help differentiate between these two most common inflammatory diseases of the sphenoid sinus.

Methods: By retrospective database review, 66 patients with a histopathologic diagnosis of isolated SSFB were recruited for analysis. Fifty-four patients who underwent endoscopic sinus surgery with clinical and histopathological diagnoses of USRS were enrolled as the control group. Clinical characteristics and CT features were evaluated.

Results: Headache, rhinorrhea, nasal obstruction, postnasal dripping, and hyposmia were the most common symptoms in both groups. In the univariate analysis, older age, lower white blood cell counts, irregular surface, bony dehiscence, lateral wall sclerosis, and intralesional hyperdensity (IH) were significant predictors for SSFB. Older age, irregular surface, and IH remained statistically significant in the multivariate analysis. Based on the results of the regression analysis, a nomogram for predicting the probability of SSFB was plotted.

Conclusions: We developed a nomogram model as a novel preoperative diagnostic tool for identifying SSFB according to the predictors both in clinical characteristics and on CT features. This could help the clinicians in predicting the probability of SSFB, to reduce ineffective or delayed treatment and occurrence of complications.

Key words: computed tomography, fungus ball, intralesional hyperdensity, sphenoid sinus, rhinosinusitis

Introduction

Fungal rhinosinusitis (FRS) is defined as a sinonasal inflammation caused by fungi, which consists of a wide range of forms of fungus related diseases, from asymptomatic to highly fatal (1). FRS can be broadly classified as invasive and non-invasive forms based on the histopathologic evidence of fungus penetrating host tissue. Invasive FRS is a rare but aggressive form, particularly affecting immunocompromised patients (2). Non-invasive FRS contains two different forms of extramucosal diseases, sinus fungal ball (SFB) and allergic fungal rhinosinusitis, and mostly occurs in non-immunocompromised individuals (3,4). However, non-invasive FRS such as SFB may progress to the invasive form when the host immunity deteriorates (5). SFB is the most common form of non-invasive FRS and is characterized by aggregation and conglomerate of fungal hyphae separate from but adjacent to the respiratory mucosa in the sinus.

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cavity (6). SFB is mainly caused by Aspergillus species and involves mostly the maxillary sinus or sphenoid sinus in few patients (7). Older age, female sex, diabetes mellitus, adjacent maxillary odontogenic pathology, and impaired mucosal immunity have been associated with SFB (4,7). Medical therapy has no role in the treatment of SFB because of the significant side effects of systemic anti-fungal agents. Additionally, surgical eradication of SFB by endoscopic sinus surgery usually achieves good outcomes and has been the treatment of choice (8,9). However, the clinical presentations of SFB are usually similar to those of other chronic rhinosinusitis (7,10). As a result, SFB is susceptible to be overlooked or diagnosed late by clinicians in the early stage.

Sphenoid sinus fungal ball (SSFB) accounts for 8% to 14.4% of SFB (7,11) and 24% to 49% of inflammatory sphenoid sinus diseases (12,13). Given that the sphenoid sinus is located at the depths of the skull base and abuts many vital structures, SSFB misdiagnosis or treatment delay can lead to potentially serious conditions, including orbital and intracranial complications (14,15). This makes timely and accurate diagnosis of SSFB exceedingly important.

Radiological examination plays a vital role in the preoperative diagnosis of SFB (16). Computed tomography (CT) has been the most frequently used imaging modality in evaluating rhinosinusitis due to its ability to depict fine images of bone, soft tissue, and blood vessels and to determine if the sinuses are obstructed (17). Several CT imaging features of SFB have been previously reported, which includes lesion limited to a single sinus, intraslesional hyperdensity (IH), bony erosion of sinus walls, bony sclerosis of sinus walls, and irregular surface of intrasinus lesion (16,18). IH was defined as micro-calcifications or calcification spots noted inside the sinonasal lesion, which is the most specific imaging feature of SFB, with highest specificity as 93.1% to 100% (16,18,19). However, according to previous literature, the prevalence of IH on CT image of patients with SFB ranges from 51% to 71%, which means that the diagnosis of SFB remains challenging for a proportion of SFB patients without IH on their CT images (3,7,16).

Due to the rarity of SSFB, the diagnostic features of SSFB on CT images have not yet been widely examined. IH was reported to present on 47.2% to 69.6% of CT images in patients with SSFB and is similar to those in maxillary sinuses, the most specific diagnostic features of SSFB on CT images (11,20,21). Besides, bony erosion and bony sclerosis of sinus walls are also commonly detected on CT images of patients with SSFB (20,22). However, evaluation of the irregular surface of intrasinus lesion on CT images and the diagnostic criteria of these features for SSFB is still lacking. Therefore, the objective of this study was to investigate the clinical characteristics and the CT imaging features of SSFB and create a preoperative diagnostic algorithm for SSFB, to assist clinicians in the diagnosis and treatment decisions for patient with suspected SSFB.

**Methods**

**Patients**

We performed an automatic search of the histopathology database at Chang Gung Memorial Hospital, and 72 patients who underwent endoscopic sinus surgery with final histopatho-
Table 1. Demographic and clinical characteristics of the study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SSFB (n = 66)</th>
<th>USRS (n = 54)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>57.9 ± 14.4</td>
<td>47.0 ± 17.4</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.177</td>
</tr>
<tr>
<td>Male, n</td>
<td>18 (27.3%)</td>
<td>21 (38.9%)</td>
<td></td>
</tr>
<tr>
<td>Female, n</td>
<td>48 (72.7%)</td>
<td>33 (61.1%)</td>
<td></td>
</tr>
<tr>
<td>Site of sphenoid lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left, n</td>
<td>28 (42.4%)</td>
<td>25 (46.3%)</td>
<td></td>
</tr>
<tr>
<td>Right, n</td>
<td>33 (50.0%)</td>
<td>28 (51.9%)</td>
<td>0.356</td>
</tr>
<tr>
<td>Single sphenoid sinus, n</td>
<td>5 (7.6%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC count, per µl</td>
<td>6623 ± 1803</td>
<td>7521 ± 2737</td>
<td>0.043*</td>
</tr>
<tr>
<td>Underlying conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>15 (22.7%)</td>
<td>2 (3.7%)</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Malignant neoplasms, n</td>
<td>5 (7.6%)</td>
<td>4 (7.4%)</td>
<td>0.508</td>
</tr>
<tr>
<td>Previous sphenoid sinus surgery, n</td>
<td>6 (9.1%)</td>
<td>15 (27.8%)</td>
<td>0.096</td>
</tr>
<tr>
<td>Clinical presentations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache and facial pain, n</td>
<td>31 (47.0%)</td>
<td>27 (50.0%)</td>
<td>0.744</td>
</tr>
<tr>
<td>Rhinorrhea, n</td>
<td>29 (43.9%)</td>
<td>25 (46.3%)</td>
<td>0.798</td>
</tr>
<tr>
<td>Purulent rhinorrhea, n</td>
<td>15 (22.7%)</td>
<td>15 (27.8%)</td>
<td>0.532</td>
</tr>
<tr>
<td>Bloody rhinorrhea, n</td>
<td>8 (12.1%)</td>
<td>4 (7.4%)</td>
<td>0.386</td>
</tr>
<tr>
<td>Nasal obstruction, n</td>
<td>25 (37.9%)</td>
<td>23 (42.6%)</td>
<td>0.604</td>
</tr>
<tr>
<td>Post nasal dripping, n</td>
<td>24 (36.4%)</td>
<td>21 (38.9%)</td>
<td>0.779</td>
</tr>
<tr>
<td>Hyposmia, n</td>
<td>9 (13.6%)</td>
<td>10 (18.5%)</td>
<td>0.476</td>
</tr>
<tr>
<td>Foul odor smell, n</td>
<td>7 (10.6%)</td>
<td>4 (7.4%)</td>
<td>0.543</td>
</tr>
<tr>
<td>Vision loss, n</td>
<td>5 (7.6%)</td>
<td>4 (7.4%)</td>
<td>0.521</td>
</tr>
<tr>
<td>Tinnitus, n</td>
<td>3 (4.5%)</td>
<td>0 (0%)</td>
<td>0.083</td>
</tr>
<tr>
<td>Incidental found, n</td>
<td>7 (10.6%)</td>
<td>2 (3.7%)</td>
<td>0.138</td>
</tr>
</tbody>
</table>

SSFB, sphenoid sinus fungus ball; USRS, unilateral sphenoid rhinosinusitis; SD, standard deviation; WBC, white blood cell. *P < 0.05, ***P < 0.001.

logic diagnosis of SSFB between 2005 and 2021 were identified. Through manual review of their preoperative CT images of the paranasal sinus and medical records, six patients with bilateral sphenoid sinuses involvement were excluded due to the difficulty in evaluating the bony sclerosis of sinus wall. The remaining 66 patients with isolated SSFB were recruited for analysis. To construct a control group, 54 patients who underwent endoscopic sinus surgery with clinical and histopathological diagnoses of unilateral chronic sphenoid rhinosinusitis (USRS, non-fungus ball) at our institute, and had no previous diagnosis of FRS were enrolled as the USRS group. All participants in the study had received preoperative CT of the paranasal sinuses without intravenous contrast enhancement and histological examinations of the surgical specimens.

CT scans
Demographic data of patients were collected from their medical records, including their age, sex, underlying comorbidity, clinical presentations, and laboratory examination. Images of the paranasal sinus CT for each patient were carefully interpreted, and the following features of image were then documented, including the site of sphenoid lesion, total or partial opacification, irregular surface of intrasinus lesion, bony dehiscence, lateral wall sclerosis, and IH (Figure 1). Irregular surface was defined as the presence of a rough surface of the partial opacified lesion. Bony dehiscence was defined as the loss of bone in the walls of the sphenoid sinus. Lateral wall thickness was measured at the thickest point of the lateral antral wall on the coronal CT images (Figure 1E). Lateral wall sclerosis was defined as the ratio of the lateral wall of the diseased sinus to that of the contralateral sinus greater than 1.2. IH referred to the presence of focal high-density area within the intrasinus lesion.

Statistical analysis
Categorical variables are represented as frequencies and percentages, and continuous variables are represented as means ± standard deviations. To compare the variables between the SSFB and USRS groups, Chi-square test or Fisher’s exact test was utilized for categorical variables, and Student’s t-test or Mann-Whitney U test were employed for continuous variables. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each feature of the CT imaging were calculated to assess the diagnostic accuracy for SSFB. Univariate and multivariate logistic regression analyses were then used to assess the associations between SSFB and variables by calculating odds ratios with 95% confidence intervals. Based on the results of the logistic regression model, a nomogram model was plotted for predicting the probabilities of SSFB. The receiver operating characteristic (ROC) curve, the area under the ROC curve (AUC), and the calibration curve were constructed to measure the predictive performance of the nomogram model. Analyses were performed by using SPSS Statistics v26.0. (SPSS Inc., Chicago, IL, USA) and RStudio v2022.02.1 (RStudio, Boston, MA, USA). P values of less than 0.05 were regarded as statistically significant. This study was approved by the institutional review board of Chang Gung Medical Foundation (approval number: 20220123SB0). The requirement for informed consent was waived in view of the retrospective nature of the research and anonymity of the data.

Results
Clinical characteristics of the study population

155
Characteristics of participants in the SSFB group (n = 66) and USRS group (n = 54) are summarized in Table 1. The mean age of patients in the SSFB group was significantly higher than that of the USRS group (57.9 ± 14.4 and 47.0 ± 17.4, respectively, p < 0.001). Female predominance was observed in both the groups, with women accounting for 72.7% of the SSFB group and 61.1% of the USRS group. There was a significantly higher proportion of patients with diabetes in the SSFB group than in the USRS group (22.7% and 3.7%, respectively, p < 0.001). In both the SSFB and USRS groups, the ranking of the five most prevalent symptoms was similar; namely, headache and facial pain (47.0% for SSFB and 50.0% for USRS), rhinorrhea (43.9% and 46.3%), nasal obstruction (37.9% and 42.6%), postnasal dripping (36.4% and 38.9%), and hyposmia (13.6% and 18.5%, respectively).

Features of CT imaging
The comparisons in the features of CT imaging between the SSFB and USRS groups are presented in Table 2. The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) for each feature of the CT imaging in distinguishing SSFB were calculated therefrom. Irregular surface, bony dehiscence, lateral wall sclerosis, and IH were all significantly more common in the SSFB group than in the USRS group. Furthermore, IH, bony dehiscence, and irregular surface had the highest specificity (96.3%, 83.3%, and 80.0%, respectively) and PPV (95.1%, 71.0%, and 77.8%, respectively). Lateral wall sclerosis and intralesional hyperdensity had the highest sensitivity (75.8% and 59.1%, respectively) and NPV (66.0% and 65.8%, respectively).

Logistic regression analysis
The associations between the variables and SSFB were examined by logistic regression analysis (Table 3). In the univariate analysis, older age (OR 1.04; 95% CI 1.02-1.07), lower white blood cell (WBC) count (OR 0.83; 95% CI 0.70-0.99), and irregular surface (OR 5.60; 95% CI 1.84-17.05) were significant predictors of SSFB. In the multivariate analysis, older age (OR 1.07; 95% CI 1.01-1.14), irregular surface (OR 6.57; 95% CI 1.12-38.52), and intralesional hyperdensity (OR 42.12; 95% CI 7.75-228.87) were confirmed as independent predictors of SSFB.
cell (WBC) count (OR 0.83; 95% CI 0.70-1.00), irregular surface
(OR 5.60; 95% CI 1.84-17.05), bony dehiscence (OR 2.50; 95% CI
1.04-6.03), lateral wall sclerosis (OR 4.50; 95% CI 2.01-10.09), and
IH (OR 37.56; 95% CI 8.42-167.49) were significant predictors for
SSFB (P value < 0.05). However, older age (OR 1.07; 95% CI 1.022-
1.12), irregular surface (OR 5.78; 95% CI 1.81-18.58), and IH (OR
42.12; 95% CI 7.75-228.87) remained statistically significant in
the multivariate analysis.

Nomogram for predicting SSFB
Based on the logistic regression model, a nomogram for pre-
dicting the probability of SSFB was plotted (Figure 2). In the
nomogram, each value of a variable represents its score. By
adding up the corresponding scores from all the eight variables,
the total points can be obtained and the predicted value of SSFB
for an individual can be derived. An example of our participant
with demonstrating the use of the nomogram to predict the
possibility of SSFB was showed in Supplementary Materials.

Discussion
A rapid and accurate diagnosis of SSFB is crucial in avoiding un-
necessary medical treatment and reducing the risk of potential
serious complication. SSFB is a rare and insidious condition
that usually presents with non-specific symptoms (21). This study
revealed similar clinical symptoms observed in patients with
SSFB and USRS, including headache and facial pain, rhinor-
rhoea, nasal obstruction, postnasal dripping, and hyposmia.
Therefore, clinicians should always consider the possibility of
SSFB in patients with atypical headaches or chronic/recurrent
rhinosinusitis after proper medical treatment. A CT scan should
be performed as the first imaging test of the diagnostic workup
in patients with specific clinical symptoms. If opacification in
the sphenoid sinus is noted, it needs aggressive management,
such as histological verification.

In this study, we further compared the features of CT imaging
between patients with SSFB and USRS, and demonstrated that
irregular surface, bony dehiscence, lateral wall sclerosis, and IH
were all significant predictors for SSFB. Among these predic-
tors, IH is the most specific and had an OR of 37.56 and 42.12 to
associate with SSFB in the univariate and multivariate analysis,
respectively. IH is related to the metal components in fungal
hyphae, which further accumulate during the metabolic proces-
ses of fungi and present as hyper-attenuation on CT (23). In this
study, IH was present in 59.1% CT images of SSFB: this was a re-
latively lower proportion compared to those of maxillary SFB, in
which IH was present from 60-80% of cases (4,7,16). These findings
indicated that IH is a strong predictor of SSFB on CT images;
however, there are still more than 40% of SSFB cases that can-
not be identified by solely this feature. Thus, a comprehensive
interpretation of CT images and clinical variables is necessary to
achieve the most precise diagnosis.

Irregular surface, defined as the rough surface of the intrasinus
lesion, was also highly associated with SSFB in the regres-
sion analyses. The presence of irregular surface represents the
necrotic area of the fungus ball.
ratio was 2.7:1 in patients with SSFB in this study. Regarding the strong female predominance of SFB, studies have proposed that hormonal change and a relative small sinus antrum in women may be involved in the pathogenesis of SFB. In addition, given that SFB is more prevalent in older individuals, the longer life expectancy of women may also contribute to this.

Diabetes mellitus was a common comorbidity in patients with SFB. In this study, there was a high prevalence of diabetes mellitus in patients with SSFB (22.7%) compared to that of 8.4% (2005–2008) and 9.1% (2015–2018) in the general population in Taiwan. Altered microvascularization of the nasal mucosa with decreased mucociliary clearance and impaired fungal clearance by phagocytes in innate immunity may contribute to this association.

One of the notable findings in this study is the potential association between SSFB and lower WBC count compared with USRS, which is rarely mentioned in previous studies. In this study, the mean WBC count in the SSFB group (6623/μL) was significantly lower than that in the USRS group (7521/μL). In addition, in the univariate regression analysis, lower WBC count was associated with SSFB (OR 0.83). Previous studies have demonstrated that peripheral blood inflammatory cells could reflect the degree of sinus inflammation in chronic rhinosinusitis. Besides, high blood neutrophil-to-lymphocyte and eosinophil-to-lymphocyte ratios are associated with nasal polyp recurrence. Although there is no study focusing on WBC count in SFB patients to date, we assumed the milder degree of sinus inflammation in SFB in comparison with mainly bacteria related sinus inflammation in USRS may contribute to this finding. However, we believe that a larger study with more detailed classifications of WBC and SFB is necessary to further explore the association and clarify the potential association between SFB and WBC count.

Due to the lower prevalence of the diagnostic imaging features,
including IH, lateral wall sclerosis, bony dehiscence, and irregular surface, in patients with SSFB compared to those with maxillary SFB, there is a lack of single specific predictor to achieve a precise diagnosis of SSFB before surgery. Therefore, we developed a nomogram model as a novel preoperative diagnostic tool for SSFB according to the aforementioned predictors both in clinical characteristics and CT features. We adopted patients’ age, sex, comorbidity of DM, and preoperative WBC counts as diagnostic features in addition to their CT imaging features to further improve the diagnostic accuracy for SSFB. The ROC curve and the calibration curve validated the good discrimination and calibration of this nomogram model. We hope that this nomogram can help clinicians predict the probability of SSFB in patients more accurately to reduce ineffective or delayed treatment and occurrence of complications.

Between CT and MRI for the evaluation of isolated sphenoid sinus diseases, CT is superior in defining the bony structure, and magnetic resonance imaging (MRI) is superior in soft tissue resolution (17). Although abnormal endoscopic findings, such as purulent discharge, mucosal oedema, polyp formation, in the sphenoid recess could be present, normal endoscopic finding can also be present in isolated sphenoid sinus diseases (13). Thus, CT scan is usually done as the first imaging test in the diagnostic workup in patients with specific clinical symptoms. However, an MRI is required when the symptoms are highly suspicious of a sphenoid sinus disease with an intracranial or intraorbital invasion, neoplasm, erosion of the sphenoid sinus wall on CT image or any uncertainty (14). In the current study, preoperative MRI was performed for 32 of the total 120 (26.7%) patients with isolated sphenoid sinus diseases. MRI was performed for 9 and 7 patients due to suspected intraorbital or intracranial invasion and suspected presence of tumour, respectively. MRI was performed for the other 16 patients as doctors from other departments requested one during a workup for headache or regular follow-up examinations prior to otolaryngological consultation.

A previous study reported that the sensitivities of CT and MRI in diagnosing inflammatory lesions are 95% and 61%, respectively; while, in tumorous disease, the corresponding values are 72% and 100%, respectively (17). MRI usually demonstrates an iso- or hypointensity and marked hypointensity on T1- and T2-weighted images of SSFB, respectively. However, possible artefacts related to the metal content within fungal hyphae may interfere with the presentation (15,17,20). The current study focused on comparing the clinical characteristics and CT features between SSFB and USRS and is helpful in differentiating the two most common inflammatory diseases of the sphenoid sinus. Nevertheless, MRI should be used complementarily for evaluating complicated isolated sphenoid sinus diseases to visualize the lesions better and identify intracranial and intraorbital extensions.

There were several limitations in this study. First, only patients who underwent sinus surgery with a histopathologic diagnosis of SSFB or USRS were recruited in this study. As a result, patients with SSFB and USRS who were ineligible for surgery were not included in this study. This may lead to some degree of selection bias. Second, there were only a few cases with information on fungal species from cultures; however, aspergillus has been reported to be the most common causative organism. Different species of fungi may have different CT imaging features. Future large-scale studies, with larger number of cases may be necessary to investigate the impact of different fungal species on image findings. Finally, this study aimed to distinguish SSFB from non-fungal rhinosinusitis using a retrospective case-control design, and the CT images were specific in identifying SSFB. However, in clinical practice, clinicians may need to consider more differential diagnoses beyond SSFB and USRS, such as neoplasms, mucocele, encephalocele, vascular lesions, etc. Bony erosion or destruction is a common finding on CT scans of these pathologies, and further evaluation with MRI or endoscopic biopsy is necessary for accurate diagnosis (14). Thus, a large-scale study with various pathologies in the sphenoid sinus is needed to develop a diagnostic process for a unilateral sphenoid sinus lesion.

Conclusions
We developed a nomogram model as a novel preoperative diagnostic tool for identifying SSFB according to the predictors both in clinical characteristics and on CT features. This could help the clinicians in predicting the probability of SSFB and reduce ineffective or delayed treatment and occurrence of complications.

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Authorship contribution
CCH designed the study, YHF, PWW, YLH, and CCL performed data collection. YHF, PWW, and CCH performed data analysis and drafted the manuscript. PWW, TJL, CCH, and PHC helped with the enrolment of participants and collection of clinical data. PWW and CCH contributed to data interpretation. All authors participated in the scientific discussions and approved the final manuscript.

Conflicts of interest
The authors declare no conflict of interest.

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A participant in the study was chosen for displaying the use of the nomogram for the purpose of demonstration. One 75-year-old, diabetic women, presented with post nasal dripping and foul odor smell. Her white blood cell count was 6300 per μL. Upon examining her sinonasal CT images, a partial opacified lesion was noticed in her left sphenoid sinus. There was no intralesional hyperdensity, but lateral wall sclerosis and irregular surface were presented on CT (Supplementary Figure S1). Then, based on the above information, we could use the nomogram to obtain the probability of SSFB for this patient, following the steps in Supplementary Figure S2, which is more than 90%.

Steps for using a nomogram to predict the probability of a sphenoid sinus fungal ball (SSFB).

Step 1. Find the corresponding position of each variable according to the patient’s clinical information and radiological characteristics.
Step 2. Next, draw a line vertically upward to the Points axis above to obtain the respective points for each variable. After that, calculate the total points by adding up the respective points for each variable. For this patient, her total points are 173 points.

Step 3. Finally, draw a line vertically downward from the corresponding position on the Total Points axis to the Predicted Value axis to obtain the probability of SSFB. For this patient, the probability of SSFB is more than 90%.

Abbreviation: WBC, white blood cell count.