

Objective radiographic density measurements of sinus opacities are not strong predictors of noninvasive fungal disease

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ABSTRACT

Background: High-density paranasal sinus opacities are often deemed consistent with fungal elements. No studies of objective quantitative radiographic density measures have been performed to support this assertion.

Methods: A consecutive series of 120 patients with chronic rhinosinusitis who underwent maxillary antrostomy with microbiological evaluation of contents within 60 days of sinus computed tomography scanning was investigated. Radiographic density characteristics of opacities in cultured maxillary sinuses (minimum, maximum, average, and standard deviation of Hounsfield units [HU_{std}]) were recorded. Receiver operator characteristic (ROC) curves were used to analyze the accuracy of radiographic characteristics in predicting fungal opacities.

Results: Of 133 maxillary sinus opacities, 22 were ultimately consistent with noninvasive fungal disease: 11 allergic fungal rhinosinusitis and 11 fungal balls. Fungal balls had higher-density components and were more heterogeneous and allergic fungal mucin was generally more radiodense. These findings were reflected by statistically significant ROC curves for maximum HU ($p = 0.019$) and HU_{std} ($p = 0.023$) for fungal balls and for average HU ($p = 0.002$) for allergic fungal mucin. A maximum HU cutoff of 334.0 detected fungal balls with 90.9% sensitivity and 72.7% specificity. An average HU cutoff of 42.9 HU detected allergic fungal mucin with 100% sensitivity and 46.3% specificity, although specificity improved to 73.2% with inclusion of nasal polyposis as a second requirement.

Conclusion: Higher average HU more accurately predicts allergic fungal mucin whereas heterogeneity/high-density components more accurately predict fungal balls. No objective radiographic density measure, in isolation, is both sensitive and specific in predicting noninvasive fungal sinusitis.

(Am J Rhinol Allergy 28, 483–486, 2014; doi: 10.2500/ajra.2014.28.4104)

Although noninvasive fungal sinus disease is definitively diagnosed by histopathological evaluation after surgical exploration, certain radiographic features suggest the presence of fungal disease and are often used to direct clinical management. Noninvasive fungal sinusitis, distinguished from invasive fungal sinusitis by the lack of fungal hyphae invading into sinus tissue on histopathological evaluation,¹ can be further classified into fungal ball (mycetoma) and allergic fungal rhinosinusitis (AFRS).¹ Although sinus fungal balls are characterized by tightly packed fungal hyphae,¹ AFRS is associated with allergic fungal mucin, which is characterized by eosinophilic mucin, fungal hyphae, and Charcot-Leyden crystals.² The clinical diagnosis of AFRS is typically based on the Bent-Kuhn criteria: (1) type I hypersensitivity, (2) nasal polyposis, (3) characteristic computed tomography (CT) findings, (4) eosinophilic mucus without fungal tissue invasion, and (5) positive fungal stain from sinus contents.³

Fungal sinus disease may be suspected based on characteristic CT or magnetic resonance imaging findings. AFRS has been associated with subjective radiographic observations including hyperattenuating sinus opacification and bony erosion.^{2,4} Radiographic features of sinus fungal balls include heterogeneous soft tissue densities with calcifications, sinus wall erosion, sinus wall sclerosis, and absence of air–fluid levels.⁵ High-density opacities are most often associated with fungal sinus disease,^{6–8} reportedly detecting AFRS with a sensitivity of 100%.⁷ Moreover, the prevalence of high-density opacities in

fungal balls is as high as 82.8%.⁸ In all cases, however, these radiographic characteristics associated with fungal sinus disease are based on subjective interpretation.

To date, there has been no assessment of the accuracy of objective measurements of sinus opacity densities in predicting noninvasive fungal sinus disease. In this study, objective measures of radiographic density—in the form of Hounsfield units (HU)—of maxillary sinus opacities seen on preoperative sinus CT scans are evaluated for accuracy in predicting noninvasive fungal sinus disease confirmed by subsequent histopathological examination after endoscopic sinus surgery (ESS).

METHODS

Study Subjects

This study was approved by the Massachusetts Eye and Ear Infirmary Institutional Review Board. Adult patients (>18 years of age) who underwent ESS for chronic rhinosinusitis (CRS) with maxillary antrostomy performed by a single surgeon from January 2009 to June 2013 were retrospectively identified. Additional inclusion criteria included (1) preoperative CT imaging within 60 days before ESS showing a maxillary sinus opacity and (2) microbiological and/or histopathological evaluation of the radiographically opacified maxillary sinus contents at the time of ESS. Patients undergoing ESS for sinonasal tumors or as an approach to the orbit or skull base were excluded.

Data Collection

Using the Sante DICOM viewer,⁹ sinus CT scans were reviewed, and maxillary sinus soft tissue densities were identified using the elliptical selection tool. The largest, most representative region of interest within each maxillary sinus opacity was measured, avoiding pockets of air, “frothy” areas, and bone/teeth. A minimum opacity size was set at 100 pixels to ensure sufficient pixel density for statistical analysis.^{10,11} Radiographic density measurements in HUs in-

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The authors have no conflicts of interest to declare pertaining to this article

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cluded average HU (HU_{avg}), standard deviation (SD) of HU (HU_{std}), maximum HU (HU_{max}), and minimum HU (HU_{min}). All radiographic data were collected in a blinded manner before review of the patients' medical records.

The medical record was reviewed for (1) demographic data (age and gender), (2) preoperative nasal polyposis, and (3) surgical findings: presence of fungal organisms on pathology, culture results, and specific final clinical diagnoses including sinus fungus ball or AFRS (in patients with allergic fungal mucin who met other clinical diagnostic criteria³). Patients with a diagnosis of invasive fungal sinusitis (based on histopathological detection of fungal invasion of sinonasal tissue) were excluded. Detection of fungal organisms was made with Grocott's methenamine stain.

Statistical Analysis

All analyses were performed with the statistical software R.¹² Standard descriptive and comparative statistics were performed as described in the Results section. Analysis of receiver operating characteristic (ROC) curves was performed with the pROC package.¹³ The area under the ROC curve (AUC) was calculated with the trapezoid rule using the auc() function and the 95% confidence interval of the AUC was calculated by performing 2000 bootstraps of the data with the ci() function. A *p* value for significance of the ROC curve was determined by Wilcoxon rank-sum test.

RESULTS

Characteristics of Study Subjects

A total of 120 patients met inclusion criteria, from whom 133 maxillary sinuses contained preoperative opacities on CT that were sampled for histopathological analysis and/or fungal cultures at the time of ESS. The average age of these patients at the time of ESS was 49.2 years (SD = 15.9 years) and 45.0% of these patients were men and 55.0% were women. Of patients meeting inclusion criteria, 74 (61.7%) also had nasal polyposis. The mean time between preoperative CT scan and ESS was 17.9 days (range, 0–55 days). Of all of the sampled sinuses, 22 (18.3%) were positive for noninvasive fungal disease by histopathology or cultures: 6 were positive by histopathology and cultures, and 16 were positive by histopathology alone. Of those 22 sinuses, 11 were consistent with allergic fungal mucin and 11 with sinus fungal balls. The etiologic fungal organisms included *Aspergillus*, *Alternaria*, and otherwise unspecified filamentous fungal species.

Quantitative Radiographic Density Characteristics of Fungal Maxillary Sinus Opacities

Quantitative measures of maxillary sinus opacities' radiographic densities (average HU [HU_{avg}], maximum HU [HU_{max}], minimum HU [HU_{min}], and SD of HU [HU_{std}]) in patients meeting inclusion criteria were collected. These density characteristics were compared based on the subsequent histopathological results and groupings: (1) nonfungal maxillary sinus opacities, (2) sinus fungal balls, and (3) allergic fungal mucin (Fig. 1). No statistically significant difference (by one-way ANOVA) was seen for HU_{min} ($p = 0.076$). A statistically significant difference was shown by one-way ANOVA for HU_{std} ($p = 0.026$). *Post hoc* analysis for multiple comparisons (by Tukey's honestly significant difference) suggested that allergic fungal mucin is less heterogeneous (lower mean HU_{std} , 42.2) than fungal balls (mean, 63.3; $p = 0.021$) and nonfungal opacities (mean, 54.7; $p = 0.083$). A statistically significant difference was observed (by one-way ANOVA) for HU_{max} ($p < 0.001$). *Post hoc* comparisons revealed a statistically significant difference between the HU_{max} of fungal balls (mean, 439.2; SD, 210.9) and nonfungal opacities (mean, 267.9; SD, 103.1; $p < 0.001$) and allergic fungal mucin (mean, 256.5; SD, 63.4; $p = 0.001$). A statistically significant difference (by one-way ANOVA) was also found between groups for the HU_{avg} characteristics ($p = 0.001$).

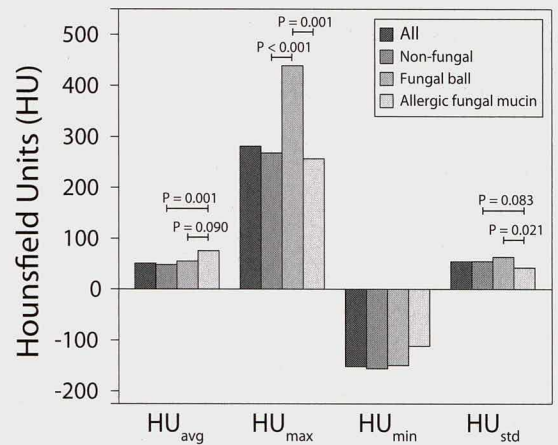


Figure 1. Bar plot of mean values for average Hounsfield units (HU_{avg}), maximum HUs (HU_{max}), minimum HUs (HU_{min}), and standard deviation (SD) of HUs (HU_{std}) for all maxillary sinus opacities, nonfungal opacities, fungal balls, and allergic fungal mucin opacities.

Post hoc analysis for multiple comparisons suggested that allergic fungal mucin had generally higher-density opacities (mean HU_{avg} , 75.7; SD, 30.7) in comparison with nonfungal opacities (mean, 47.9; SD, 22.5; $p = 0.001$) or fungal balls (mean, 55.0; SD, 16.6; $p = 0.090$).

Accuracy of Quantitative Radiographic Density Characteristics in Predicting Fungal Sinus Disease

The accuracy of quantitative radiographic density characteristics, specifically HU_{avg} , HU_{max} , HU_{min} , and HU_{std} , of sinus opacities was assessed by ROC analysis.¹⁴ In setting a diagnostic test criterion for what is considered positive and negative, there is a trade-off between sensitivity and specificity. In ROC analysis of a diagnostic test, all sensitivity/specificity pairs that are possible by varying the diagnostic test criterion are plotted on what is known as an ROC curve. The AUC of the ROC curve is an indicator of a diagnostic test's accuracy and is compared for statistically significant difference from an AUC of 0.5, which reflects the accuracy of random chance, to assess the overall performance of the diagnostic test. In this study, ROC curves were generated to assess accuracy of radiographic density characteristics in predicting the presence of (1) sinus fungal balls and (2) allergic fungal mucin. For ROC curves with AUC statistically >0.5 , optimal radiographic density cutoff values (*i.e.*, criterion) were determined as those that maximized the sum of sensitivity and specificity.

In the detection of fungal balls, the AUC of the ROC curve was significantly >0.50 for HU_{max} (Fig. 2 A; AUC = 0.79; 95% CI, 0.59–1.00; $p = 0.019$) and HU_{std} (Fig. 2 B; AUC = 0.79; 95% CI, 0.58–0.99; $p = 0.023$), but this was not the case for HU_{min} (AUC = 0.61; 95% CI, 0.37–0.86; $p = 0.393$) or HU_{avg} (AUC = 0.63; 95% CI, 0.37–0.89; $p = 0.332$). An optimal HU_{max} criterion of >334.0 resulted in a sensitivity of 72.7% and specificity of 90.9% for detection of a fungal ball. Likewise the optimal HU_{std} criterion of >56.8 achieved a sensitivity of 63.6% and specificity of 90.9% for detection of a fungal ball.

In the detection of allergic fungal mucin, the AUC of the ROC curve for HU_{avg} (Fig. 3 A; AUC = 0.78; 95% CI, 0.64–0.92; $p = 0.002$) and for HU_{std} (Fig. 3 B; AUC = 0.72; 95% CI, 0.55–0.88; $p = 0.017$) were both found to be significantly >0.50 . The ROC curves of HU_{max} (AUC = 0.51; 95% CI, 0.33–0.68; $p = 0.946$) and HU_{min} (AUC = 0.65; 95% CI, 0.45–0.84; $p = 0.106$) were not significantly different than 0.50. The optimal HU_{avg} criterion of >42.9 resulted in a sensitivity of 100.0% and a specificity of 46.3% for detection of allergic fungal mucin. The optimal HU_{std} criterion of <49.6 resulted in a sensitivity of 72.7% and a specificity of 64.2% for detection of allergic fungal mucin.

Because the diagnosis of AFRS is based on other tangible clinical criteria, we sought to determine how inclusion of one easily identifiable

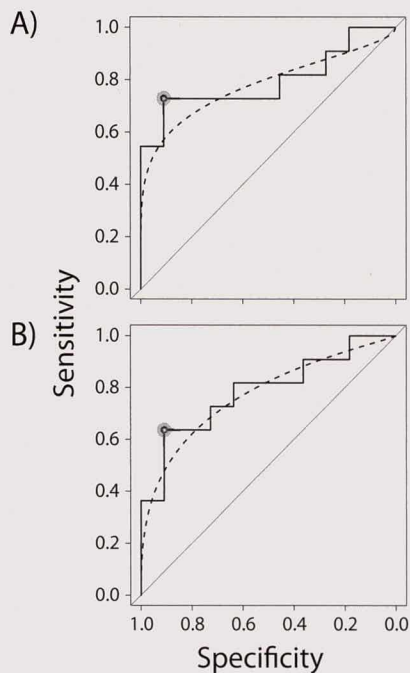


Figure 2. Receiver operating characteristic (ROC) curve for (A) maximum HU (HU_{max}) in predicting the presence of a fungal ball. The point reflecting a cutoff of 334.9 HU for HU_{max} that maximizes the sum of sensitivity (72.7%) and specificity (90.9%) for predicting the presence of a fungal ball is marked. The ROC curve for (B) standard deviation (SD) of HU (HU_{std}) in predicting the presence of a fungal ball. The point reflecting a cutoff of 56.8 for HU_{std} that maximizes the sum of sensitivity (63.6%) and specificity (90.9%) for predicting the presence of a fungal ball is marked. The dashed line represents the smoothed ROC curve. The light gray line represents the line of no discrimination.

able clinical finding might complement the HU_{avg} criterion, which performed best for detection of allergic fungal mucin. The specificity of using $HU_{avg} > 42.9$ for detection of allergic fungal mucin was low (46.3%), although with a sensitivity of 100%. Because nasal polyposis is one criterion for the diagnosis of AFRS and may be readily identifiable by endoscopic nasal examination, we included the presence of polyps as a second test for detection of allergic fungal mucin. Not surprisingly, nasal polyposis had a sensitivity of 100% for allergic fungal mucin but—in this cohort—a specificity of only 50.0%. However, when added as a second serially applied test to the HU_{avg} criterion of >42.9 , the specificity for detection of allergic fungal mucin increased to 73.2% while maintaining 100% sensitivity.

DISCUSSION

The possibility of noninvasive fungal sinusitis is often predicted based on subjective interpretation of CT scan characteristics. High-density sinus opacities are often considered consistent with fungal sinus disease,^{6–8} but the presence of high-density opacities is typically evaluated in conjunction with other clinical signs when fungal sinus disease is suspected. For example, the presence of hyperattenuating sinus foci, nasal polyps, and serum anti-*Aspergillus* IgE collectively predicted AFRS with a sensitivity of 70% and specificity of 100%.⁷ Similarly, radiographic features of sinus fungal balls include high-density opacities with associated calcifications, heterogeneity, sinus wall erosion, and sinus wall sclerosis.^{5,8} Using such radiographic characteristics, CT imaging has previously predicted fungus balls with a sensitivity of 62–83% and specificity of 94–99%.^{15,16} One major limitation of these prior studies is the reliance on subjective radio-

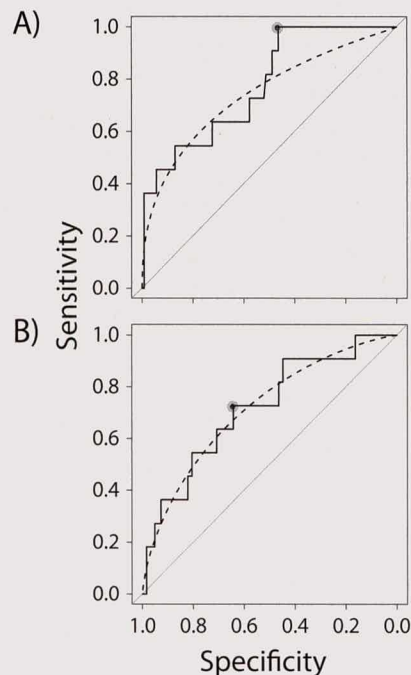


Figure 3. Receiver operating characteristic (ROC) curve for (A) average HU (HU_{avg}) in predicting the presence of allergic fungal mucin where the point reflecting a cutoff of 42.9 HU for HU_{avg} that maximizes the sum of sensitivity (100.0%) and specificity (46.3%) is marked and (B) standard deviation (SD) of HU (HU_{std}) in predicting the presence of allergic fungal mucin where the point reflecting a cutoff of 49.6 HU for HU_{std} that maximizes the sum of sensitivity (72.7%) and specificity (64.2%) is marked. The dashed line represents the smoothed ROC curve. The light gray line represents the line of no discrimination.

graphic interpretation rather than easily reproducible, objective criteria.

In this study, we evaluated objective radiographic density measures of maxillary sinus opacities for their ability to predict noninvasive fungal sinusitis, specifically AFRS and sinus fungal balls. Previous work has used objective sinus opacity density measurements to gain novel insights into the pathophysiology of CRS.^{10,11} Our results are consistent with previously reported associations of hyperattenuating sinus opacities and calcifications/sinus opacity heterogeneity with AFRS and sinus fungal balls, respectively. Specifically, we found that the average opacity density (HU_{avg}), which reflects overall hyperattenuation, predicted allergic fungal mucin with excellent sensitivity. In contrast, a higher SD of opacity density (HU_{std}), perhaps reflecting opacity heterogeneity, and a high maximum opacity density (HU_{max}), reflecting very high density components within the opacity, predicted fungal balls with excellent specificity. However, the diagnostic test with highest sensitivity and specificity included the addition of the clinical finding of nasal polyposis to an HU_{avg} criterion of >42.9 ; this predicted allergic fungal mucin with a sensitivity of 100% and specificity of 73.2%. This finding underscores the importance of interpreting imaging in the context of additional clinical information.

One unique finding of our study was the relationship between HU_{std} , which reflects the heterogeneity of the measured area in the sinus, when comparing allergic fungal mucin and sinus fungal balls; *viz.*, these findings suggest that allergic fungal mucin is less heterogeneous when compared with other sinus opacities (fungal balls and nonfungal opacities), and fungal balls are more heterogeneous than other sinus opacities. These conclusions were also supported by the identification of an HU_{std} criterion of <49.6 for detection of allergic

fungal mucin and an HU_{std} criterion of >56.8 for detection of fungal balls. This finding has not been previously described in the literature and highlights the usefulness of using objective, quantitative density measurements in the diagnosis of sinus disease.

These results should be considered in the context of the limitations of our methods. Although we measured simple objective density parameters, more complex quantitative measurements could potentially improve the accuracy of predicting fungal sinusitis. For example, we did not examine density histograms from the maxillary opacities, and this study does not, therefore, account for nonnormal density distributions that may better represent fungal sinus disease. Additionally, our investigation was limited to the maxillary sinus and did not include the ethmoid, sphenoid, or frontal sinuses. However, there is no evidence to suggest that the radiographic characteristics of fungal disease would depend on sinus location. Finally, this study focused exclusively on noninvasive sinus fungal disease, and our results can not therefore be applied to cases of invasive fungal sinusitis. Further investigation would be required to determine the relationship between objective radiographic density measurements and invasive fungal sinusitis.

Our results show that objective density measures can play a role in the preoperative assessment of patients with symptoms of CRS. An HU_{avg} of >42.9 can be used as a screening tool to rule out AFRS due to its high sensitivity. However, patients meeting this HU_{avg} criterion require further clinical investigation for final diagnosis based on its poor specificity. In comparison, sinus opacities with either an $HU_{std} > 56.8$ or $HU_{max} > 334.0$ are likely to be fungus balls because of the high specificities of these criteria. However, the absence of these measures can not rule out fungus balls because of the low sensitivities of the tests. Therefore, these objective radiographic measures, while helpful, can not be used in isolation to predict the final diagnosis.

CONCLUSION

Our results show that distinct objective radiographic density measures of maxillary sinus opacifications may be useful in detecting allergic fungal mucin and sinus fungal balls. Average opacity density, $HU_{avg} > 42.9$ predicts allergic fungal mucin with excellent sensitivity (100% in this study). The use of nasal polyposis as a second, serially applied criterion to HU_{avg} , significantly improves specificity for detection of allergic fungal mucin (73.2% in this study). Additionally, $HU_{max} > 334.0$ and $HU_{std} > 56.8$ predicted sinus fungal balls with excellent specificities (90.9% in both cases, in this study) but had poor sensitivities. These findings show that, while useful for modifying the index of suspicion for fungal sinus disease, these measurements should not be interpreted in isolation. Other clinical data, either in the form of physical exam

findings or other subjective radiographic findings, may inform the predictive power of objective radiographic density measurements for fungal sinus disease. Imaging studies, in the context of clinical correlation, can help predict the possibility of fungal sinus disease and ultimately influence the decision to proceed with surgical exploration for definitive diagnosis and treatment.

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