A novel risk score for disease control prediction of Chronic rhinosinusitis

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Abstract

Abstract Objectives: To assess the impact of risk factors on the disease control among CRS patients, following 1 year of functional endoscopic sinus surgery (FESS), and combining the risk factors to formulate a convenient, visualized prediction model. Design: A retrospective and nonconcurrent cohort study Setting and Participants: A total of 325 patients with Chronic rhinosinusitis (CRS) from June 2018 to July 2020 at the First Affiliated Hospital, the Third Affiliated Hospital, and the Seventh Affiliated Hospital of Sun Yat-sen University. Main Outcomes Measures: Outcomes were time to event measures: the disease control of CRS after surgery 1 year. The presence of nasal polyps, smoking habits, allergic rhinitis (AR), the ratio of tissue eosinophil (TER), and peripheral blood eosinophil count (PBEC)and asthma was assessed. The logistic regression models were used to conduct multivariate and univariate analyses. Asthma, TER, AR, PBEC were also included in the nomogram. The calibration curve and AUC (Area Under Curve) were used to evaluate the forecast performance of the model. Results: In univariate analyses, most of the covariates had significant associations with the endpoints, except for age, gender, and smoking. The nomogram showed the highest accuracy with an AUC of 0.760 (95% CI, 0.688-0.830) in the training cohort. Conclusions: In this cohort study that included the asthma, AR, TER, PBEC had significantly affected the disease control of CRS after surgery. The model provided relatively accurate prediction in the disease control of CRS after FESS and served as a visualized reference for daily diagnosis and treatment.

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Keywords

Chronic rhinosinusitis; Disease control; Model; Prognosis

Clinical trial registration number

ChiCTR-OOC-17010989.

Key Points

1. What is the risk factor affecting the disease control of CRS after surgery and which way is the most accuracy to predict the prognosis?
2. Our study assessed the impact of risk factors on the disease control among CRS patients, following 1 year of functional endoscopic sinus surgery (FESS)
3. Asthma and the ratio of tissue eosinophil are the most important risk factor affected the disease control of CRS.
4. Our study combined the risk factors to formulate a convenient, visualized prediction model.
5. This study also had some limitations due to the small cohort size,lead to the average inspection efficiency.

Introduction

Chronic rhinosinusitis (CRS) is a multifactorial heterogeneous disease, although its pathogenesis and precise mechanism remains largely unclear. Due to the poor understanding of the pathophysiology of CRS, it affects the quality of life of patients and increases the cost burden as compared to people without CRS. It is estimated to affect 8% of the adult population in China. [1] According to the EPOS2020, the current treatment for CRS includes medical therapy and FESS with the final target to achieve cure or clinical control.[2] Although, the disease state of more than 30% of patients with nasal polyps, remains uncontrolled despite the current medical therapy (AMT) and FESS.[3] DeConde et al also reported the disease relapse in 40% of patients with nasal polyps after 18 months. [4] The latest evidence has further indicated that the underlying diversity of endotypes might be a crucial reason for the unconformity in clinical phenotype and disease prognosis.[5] Therefore, it is essential to find relevant clinical markers and to make a convenient model to predict the poor disease control in CRS.

Emerging evidence has proven that eosinophil(EOS)inflammation is a dominant factor associated with CRS recurrence and poor disease control.[6]In addition to the local eosinophils, peripheral blood eosinophils are also associated with CRS and can be a reliable marker for predicting the prognosis of CRS. Some studies have demonstrated the peripheral blood eosinophil as a marker for the EOS CRS. [6] In a recent study, Guiherme et al, suggested that asthma was a dominant factor for the recurrence of chronic rhinosinusitis. [7]Nonetheless, some studies have reported that inhalant allergens may lead to poor sinus CT and endoscopic scores. But several studies have found no difference in allergic and nonatopic patients on the sinusitis severity. [8] Thus, it is deemed necessary to evaluate the role of allergy in nasal polyps' disease control.

Undeniably studies on predictive factors of CRS treatment outcomes are crucial and can help improvise personalized and integration management of CRS in various hospitals. Therefore, this study aims to evaluate

the risk factors involved in the prognosis of CRS after 1 year of undergoing endoscopic sinus surgery and combined the risk factors to establish a convenient and accurate prediction model.

Material and Methods

This is a retrospective and nonconcurrent cohort study. The study was approved by the local Ethics Committee ([2017]164). According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS2012) guidelines, patients who satisfied the diagnostic criteria of chronic rhinosinusitis with nasal polyps were included in the study fromA, B, C hospital. All patients received FESS between January 2018 and December 2020 and were periodically reassessed during their routine outpatient visits following the surgery. These patients were initially treated with AMT i.e., nasal steroids (drops/sprays/rinses), saline rinses, educated regarding technique, oral corticosteroid short-course (OCS), and two-course antibiotics before surgery.

Patients were instructed to use topical corticosteroids-budesonide nasal spray (256ug/day for 6 months), and intranasal budesonide suspension (1mg/day for 4 weeks) after surgery. They were reassessed periodically at their routine outpatient visits at 1 to 3 months after surgery then once in 3 months until 1 year follows up. During the assessment in the follow-up visits, if their symptoms or endoscopic signs persisted, they received new AMT i.e., nasal steroids (drops/spray/rinses), saline rinses, education regarding technique, OCS, and optional two-course antibiotics. The symptoms, endoscopic scores, and modified treatment (if any) were recorded by clinicians after 1 year.

Items recorded from the enrolled patients were as following:

- Nasal symptoms
- Lund and Kennedy score recorded by nasal endoscopy findings
- Comorbidities: smoking habit, asthma (based on the spirometry and clinical parameters)
- Respiratory allergens
- Peripheral blood eosinophil count before the initiation of oral corticosteroids. More than $0.3X10^9/L$ was considered as high blood eosinophilia in CRS

Data collection

Patients were divided into 2 groups of controlled (included partly controlled) and uncontrolled CRS, based on the disease control criteria of EPOS2020. Patients were followed up for 1 year after surgery, until the end of the study period (30th December 2020). Time-to-event was defined as the time starting from surgery till the 12th month post-operatively. According to the EPOS2020, the control criteria of the CRS can be divided into symptoms, nasal endoscopy, the need for recuse treatment. Symptom substituted by 'VAS (Visual Analogue Scale)< 5', and 'present/impaired' by 'VAS [?] 5. Furthermore, the detailed symptoms related to CRS are included in supplement table S1. The evaluation endpoint was 12th month post-operatively.

Nomogram development

The nomogram model was formulated by the results of multivariate analysis. Univariate analysis with a significant difference at *P-value*(<0.05) between all variables was included in the multivariate analysis. The *P-value* <0.05 in multivariate analysis was also included as the prognostic factor in the nomogram. AR and PBEC were statistically significant in univariate analysis for 1 year disease control but not significant difference in multivariate analysis for 1 year diease control. However, AR and PBEC have long been recognized to determine the prognosis of CRS. AR and PBEC were also included in the nomogram for the current study, since excluding these covariates would have over-inflated the effects of the remaining factors and decrease the predictive power of our model. The Cox proportional hazard model was used to produce nomograms for predicting the risk of the uncontrolled incident after the surgery. A score based on regression coefficients was assigned to these factors.

Model evaluation

The nomogram's forecast performance was evaluated by the receiver operating characteristic (ROC), the area under curve (AUC) for both training and validation cohort. In a logistic regression model, the value of AUC is the same as that yielded by the concordance index (c-index), with values ranging from 0.5 (no predictive value) to 1.0 (complete discrimination). A larger AUC value represents a more accurate prediction of the uncontrolled disease possibility. The agreement between the predicted uncontrolled incident and the observed uncontrolled incident after bias correction was quantified by the calibration curves of the nomogram for determining the uncontrolled incident rate. Decision curve analysis (DCA) was also carried out to compare the potential net benefit of the predictive models.

Statistical analysis

We compared the patient pathologic characteristics and demographic profile between training and validation cohort by using Fisher's exact tests and chi-squared tests. Multivariate logistic regression analysis was used to distinguish the independent risk factors associated with uncontrolled disease. Nomogram development was carried out by using the library "rms" in R for MACOS. All statistical analyses were conducted by the R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). The p values<0.05 were considered statistically significant.

Results

We included a total of 325 patients with Chronic rhinosinusitis with nasal polyps (CRSwNP) from June 2018 to July 2020 at the A, B, C hospital. Included patients were following the doctor's instructions and had a follow up till 1 year. The enrolled patients were randomly assigned to a training (n=195) and validation cohort (n=130). The nomogram was based on the training cohort and its accuracy was internally validated through the validation cohort. The baseline characteristics of the CRS patients between the training cohort and validation cohort are shown in table 1. No significant differences were observed for these characteristics between the training and validation cohort. Univariate analyses were done with the primary objective to confirm the statistical effect between each covariate and the endpoints. Results showed that most covariates had statistically significant associations with the endpoints, except for age, gender, and smoking (Table 2).

Nomogram development

After the initial univariate analyses with extensive review of the medical literature, we included all the covariates in the subsequent multivariate logistic regression models, except for age, gender, smoking, tissue eosinophil counts, preoperative Lund Kennedy score, and Lund Mackay Score. Based on these factors, the nomogram was constructed for calculating the risk of recurrence of the CRS after operation 1year (Figure1A).

A case demonstrating our nomogram usage is shown in Figure1B. For example, if the patient had tissue eosinophil ratio >=10%, low blood eosinophilia, no AR, and asthma, then the total points would be 196 with the corresponding risk of recurrence at 46.11%.

Nomogram validation

Both internal and external validation of the nomogram was performed in this study. The plotted calibration curves correspond to the ideal plot (45°line), which reveals a favorable agreement on the nomogram estimation and the actual observation regarding the probability of uncontrolled disease after the 1 year of post endoscopic sinus surgery. In the training cohort, the nomogram showed the highest accuracy with an AUC of 0.760 (95% CI, 0.688-0.830) (Figure 2.A). The corresponding calibration plot indicates the similarity in the estimation made by the nomogram and clinical findings made during the follow-up period for the recurrence of CRSwNP (Figure 2B). In the validation cohort, the nomogram prediction was 0.635 (95% CI, 0.537-0.733) (Figure 3A). The calibration curve showed a concurrence of predicted probability with the actual probability (Figure 3B).

To assess the clinical applicability of our risk prediction nomogram, clinical impact curve analysis (CICA) and decision curve analysis (DCA) was also performed. The CICA and DCA visually exhibited that the nomogram had superior practical ranges of threshold probabilities and an overall net benefit in terms of outcome for the impacted patient (Figure 4A and 4B).

Discussion

Chronic rhinosinusitis is a group of multifactorial diseases, associated with asthma, allergy, high tissue eosinophil ratio, and blood eosinophil counts. CRS is generally treated by pharmacotherapy or by FESS. [9] In this study, we evaluated CRS patients who had an average follow-up time of 1 year after undergoing FESS. Effective interpretation of clinical characteristics in CRS is very important, as it plays a deciding role in predicting the possibility of postoperative uncontrolled disease in these patients. Patients at a higher risk for revisional surgery, personalized treatments, or targeted therapies should also be directed to disease control.

Asthma

In 2012, a multicenter study conducted by the Global Allergy and Asthma Network of Excellence (GA(2) LEN) showed that asthma was associated with CRS in all age groups, irrespective of gender and smoking behavior.[10] Our group previously reported that EESS (Extensive endoscopic sinus surgery) improved the surgery outcomes in asthma.[11] In a 12-year study, asthma was identified as the only factor that increased the chance of recurrence in patients with either CRSwNP or CRSsNP(Chronic rhinosinusitis without nasal polyps).[7,12] Our current study also showed that asthma was the important factor for disease control after surgery, as demonstrated in univariate and multivariate analysis. In the training cohort, the AUC of the asthma models was 0.665 (0.593-0.737). However, CRS with or without asthma is an indisputable element affecting its prognosis.

Allergy

The causal relationship between allergy and CRS is still debatable, however, the risks of CRSwNP are higher in patients with co-existing allergy and asthma conditions **[10]** A population-based study reported the AR higher prevalence, before the diagnosis of CRSsNP or CRSwNP in comparison with patients without CRS.**[13]** A multicenter cross-sectional study in China reported that many occupational factors are significantly associated with the CRS **[14]** , especially exposure to dust or smoke, coal cooking fumes, chemical gases (such as isocyanides), cleaning agents and hair-care products lead to increased risk.**[15]**Allergic asthma and rhinitis caused by inhaled allergens, are mainly elicited by a TH2-dominated immune response associated with increased serum IgE levels. **[16]** Allergy rhinitis with high IgE expression may also affect the disease control of CRSwNP after the surgery. Recently, a randomized phase 3 trials reported that Omalizumab (IgE antibody) significantly improved the clinical, endoscopic, and patient-reported outcomes in refractory CRSwNP**[17]** . Therefore, allergic rhinitis was also considered in the prediction model. In our study, the AUC in the training cohort for the AR model was 0.595 (0.52.8-0.66.2), and it also affected the disease control to a certain extent.

System and local eosinophil

The EPOS2020 and several studies reported the cutoff points for EOS in blood and tissue. We classified the cohort subjects by using 0.3×10ˆ9 /L as a cutoff value for blood EOS counts and 10% for polyp tissue EOS percentages.[2] The cutoff point of 10% tissue EOS has been extensively used for differentiating the eosinophilic CRS.[18] Lou et al. and Nakayama et al. have also demonstrated a strong correlation between polyp recurrence and tissue EOS numbers. [19] [20] Blood EOS can also reflect the prognosis of chronic sinusitis, but its sensitivity is low as compared to the tissue EOS.[21,22] Our group has reported that the tissue and blood eosinophilia has an additive effect in predicting the risk of poor disease control after at least 1 year of FESS. [23] This study further demonstrated using multivariate analysis, that the tissue eosinophilia ratio was an independent factor, affecting the disease control after surgery. The analysis revealed that the number of eosinophils in tissues had no significant effect on CRS disease control. However, EPOS 2020 suggests that tissue eosinophils can be considered as nasal polyps eosinophils in case the tissue eosinophils count was more than 10 [24]. In many pieces of literature, tissue eosinophils ratio was still higher than 10% as the cutoff value to predict the prognosis of chronic sinusitis nasal polyps.[22] Therefore, we only included TER in our Nomogram prediction model.

So far, few studies have focused on the various combination factors among AS, PBEC, TER, AR, and disease control. Interestingly, in our study, the combination of AS, AR, TER, PBEC significantly increased the odds ratio for predicting the possibility of uncontrolled and partly controlled disease. To the best of our knowledge, this observation has not been reported in the literature. Therefore, as the potential predictors, we included allergy, asthma, TER, and blood EOS counts, among the various demographic factors in our nomograms. For a long, these factors have been recognized to have a significant impact on the disease control of Chronic rhinosinusitis.

This study also had some limitations due to the small cohort size. In addition, childhood-onset, or adult-onset asthma in CRSwNP were not confirmed. Further, we could not evaluate the relationship between the prognosis of disease the childhood or adult-onset asthma.

Conclusions

We found that TER and AS were the independent factors affecting the prognosis of CRSwNP. In combination with AR, PBEC, TER, and AS, the nomogram model exhibited higher accuracy than with tissue eosinophil ratio and asthma alone. The nomogram provided relatively accurate and visually predicted the disease control of CRS after the functional endoscopic sinus surgery (FESS) and served as a reference for the daily diagnosis and treatment.

List of abbreviation

CRS: Chronic rhinosinusitis

AR: Allergy rhinitis

AS: Asthma

EOS: Eosinophil

TER: tissue eosinophil ratio

PBEC: peripheral blood eosinophil count

ROC: Operating characteristic curves

HR: Hazard ratios

CI: confidence intervals

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Figure legends

Figure 1. Postoperative nomogram predicting 1-year probability of uncontrol disease after endoscopic surgery. [A] Each clinical variable has a certain number of points (top row) ranging from 0 to 100. The sum of points of each variable was related to the probability of uncontrol disease at 1 year. [B] An example illustrating the use of the nomogram. This patient was one of the training cohort in the current study. The patient has tissue eosinophil ratio >=10% (points=100), low blood eosinophilia(points=0), no AR(points=0)

and Asthma(points=96), thus the total points are 196 and the corresponding risk event of recurrence is 46.11%. AS: asthma; PBEC: peripheral blood eosinophil count; TEN: tissue eosinophil number; TER: tissue eosinophil ratio

Figure 2. [A] ROC curves of the training cohort predicting 1-year probability of uncontrol disease after endoscopic surgery with corresponding AUC values. [B] Calibration in the primary cohort for predicting patient risk of recurrence. The x-axis is nomogram-predicted probability of survival and y-axis is actual survival. The reference line is 45degand indicates perfect calibration. ROC, receiver operating characteristic; AUC, Area under curve; CI, confidence interval AS: asthma; PBEC: peripheral blood eosinophil count; TEN: tissue eosinophil number; TER: tissue eosinophil ratio.

Figure 3. [A] ROC curves of the validation cohort predicting 1-year probability of uncontrol disease after endoscopic surgery with corresponding AUC values. [B] Calibration in the validation cohort for predicting patient risk of recurrence. The x-axis is nomogram-predicted probability of survival and y-axis is actual survival. The reference line is 45degand indicates perfect calibration. ROC, receiver operating characteristic; AUC, Area under curve; CI, confidence interval AS: asthma; PBEC: peripheral blood eosinophil count; TEN: tissue eosinophil number; TER: tissue eosinophil ratio.

Figure 4. [A] Decision curve analyses in the training cohorts: a perfect prediction model (gray line), screen none (horizontal solid black line), and screen based on the nomogram (blue thick dash line). [B] Clinical impact curve of the nomogram plots the number of CRS patients classified as high risk, and the number of cases classified as high risk with uncontrol disease at each high risk threshold.

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