ORIGINAL ARTICLE

CONTENTS

Application of roc-analysis to assess the quality of predicting the risk of chronic rhinosinusitis recurrence

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ABSTRACT

Aim: To propose a new, original approach to assessing the quality of a multivariate regression model for predicting the risk of recurrence in patients with chronic rhinosinusitis based on ROC analysis with the construction of appropriate curves, estimating the area under them, as well as calculating the sensitivity, accuracy, specificity, and predictive value of a positive and negative classification results, the likelihood ratio of positive and negative patient detection results.

Materials and Methods: 204 patients aged with a diagnosis of chronic rhinosinusitis were examined.

Results: To build a multivariate regression model 14 probable factors of chronic rhinosinusitis occurrence were selected to determine the diagnostic value of the proposed model we calculate the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), the likelihood ratio of a positive test (LR+), the likelihood ratio of a negative test (LR-) and prediction accuracy % of the proposed mathematical model. In order to determine the prognostic value of the risk ratio of CRS recurrence model, ROC- analysis was performed, ROC curves were obtained

Conclusions: The multivariate regression model makes it possible to predict potential complications and the possibility of disease recurrence. The construction of ROC-curves allows us to assert the excellent classification quality of chronic rhinosinusitis recurrence.

KEY WORDS: recurrence, multivariate regression analysis, chronic rhinosinusitis, ROC analysis

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a rather broad concept that includes several nosological forms. It is defined as "infection of the sinuses and Schneiderian membrane lasting more than 3 months (or 12 weeks) per year". In the structure of sinusitis, 56-73% are lesions of the maxillary sinus due to its large volume, high natural conjunctiva, and close contact with the roots of the teeth (premolars of the upper jaw).

According to the EPOS 2020 classification, CRS is divided into primary and secondary. The primary includes localized forms (allergic fungal rhinosinusitis, isolated sinusitis) and diffuse – chronic rhinosinusitis with polyps (polyps visualized endoscopically in the nasal passage), as well as chronic rhinosinusitis without nasal polyps. A separate distinction is made between chronic rhinosinusitis with an altered mucous membrane of the sinuses or nasal cavity as at polyposis, but there are no polyps of the nasal passage that cover the nasal passage [1, 2].

Secondary CRS is also divided into localized processes (odontogenic sinusitis, maxillary sinus cyst, mycetoma) and bilateral or widespread (primary miliary dyskinesia, Wegener's disease, chronic rhinosinusitis against the background of selective immunodeficiency) [3-5]. However, this classification by phenotypes does not consider all the pathogenetic mechanisms of the development of the disease, which in turn complicates the choice of the correct treatment tactics and makes it impossible to predict the potential recurrence of the disease. Despite numerous studies, in approximately 30% of CRS cases, the etiology and pathogenesis remain unclear, and the question of predicting potential relapses of chronic rhinosinusitis depending on its form of manifestations remains open and relevant.

Today, one of the popular and fairly accurate methods of predicting the recurrence of various diseases, including CRS, is the construction of a multivariate regression model, which includes a number of predictors that may be the cause of a repeated inflammatory process, which was described by us in a previous publication [6]. However, determining the sensitivity, accuracy and specificity of the proposed model requires an additional ROC analysis with the construction of an ROC curve.

The ROC curve is a characteristic curve that shows the dependence of the number of correctly diagnosed positive cases on the number of incorrectly diagnosed negative cases when varying the threshold of the decisive rule [7].

Approaches to building multivariate regression forecasting models in medicine are considered in the works of Musiienko V. et all. (2021); Musiienko V. et all. (2022) [8, 9].

The results of ROC-analysis for 3 degrees of climacteric syndrome are considered in the work of Chukur O. et all. (2022) [10]. This is the approach used in this work to evaluate the quality of the proposed CRS model.

In recent years, there has been an increased interest in modern methods of predicting CRS using machine learning methods in the form of recurrent neural networks [11-13]

AIM

The aim of the work is to propose a new, original approach to assessing the quality of a multivariate regression model for predicting the risk of recurrence in patients with three degrees of chronic rhinosinusitis based on ROC analysis with the construction of appropriate curves, estimating the area under them, as well as calculating the sensitivity, accuracy, specificity, and predictive value of a positive and negative classification results, the likelihood ratio of positive and negative patient detection results.

MATERIALS AND METHODS

We examined 204 patients aged 18 to 80, including 107 women and 97 men, with a diagnosis of chronic rhinosinusitis, who were undergoing inpatient treatment in the otolaryngology department of the communal noncommercial enterprise "Ternopil Regional Hospital" under Ternopil Regional Council. The average age of the patients was 45 years, and the duration of the disease varied within 5-8 years.

All patients signed an informed consent to participate in the study. After receiving the opinion of the bioethics commission at Ivan Horbachevsky Ternopil National Medical University (minutes No. 63 dated 16/03/2020) the study was conducted in compliance with all moral and ethical principles, considering World Medical Association Declaration of Helsinki on Biomedical Research.

All patients underwent a comprehensive clinical and laboratory examination, which included an examination, anamnesis collection, complete blood count with formula, biochemical blood analysis, and radiological examination (radiography of the paranasal sinuses, computer tomography or MRI of the head).

According to a specially developed questionnaire for predicting the level of recurrence of CRS, all patients were surveyed, which included 15 risk factors for the development of CRS: age, gender, environmental living conditions, nasal septum deviation, presence of an allergic component, carious or damaged teeth (upper premolars), nasal or facial skeleton injuries, the presence of leukocytosis (according to the leukocyte formula), the ESR level, the presence of diagnosed diabetes, the level of glycemia, the degree of bronchial asthma, radiological signs, smoking, and the incidence of SARS during the last 12 months, and their gradation was established from numerical values.

Construction of a prognostic model of the risk of CRS recurrence was carried out using multivariate regression analysis. The statistical processing of the obtained research results was carried out using the statistical package Statistica 10.0 and the table editor Microsoft Excel 2019.

To obtain a numerical value of the clinical significance of the test, as well as to compare several tests, calculations of ROC analysis were carried out in the Matlab program using the integral indicator of the area under the ROC curve – AUC (Area Under Curve).

RESULTS

The method of multivariate regression analysis for predicting CRS recurrence, taking into account the most informative factors and variants of their severity, makes it possible to create a mathematical model for predicting this disease and predict the probability of recurrence, which helps in the development of effective methods of treatment, prevention, development and progression of the pathology.

To build a multivariate regression model for predicting CRS recurrence, 14 probable factors of CRS occurrence were selected with the calculation of the regression coefficient "b" (Beta), which reflects for each selected factor the relationship regarding the influence on the development of CRS relapse in the examined patients. A risk factor with a significance level of $p>0.05$ was excluded from further analysis (Table 1). Since the significance levels of thirteen risk factors were less than 0.05, they were included in the mathematical model for predicting CRS recurrence (Fig. 1).

Based on the results of the multivariate regression analysis of predicting the level of CRS recurrence, a mathematical model was built to determine the risk ratio of CRS recurrence (RRCRSR).

RRCRSR=X1*0.059+X2*1.112+X3*0.968+X4*1.029+X5*1.114+X6*1.049+X7*1.031+X8*0.039+X9*1.075+X10*0.362+X11*1.012+X12*1.161+X13*0.92

-3.022,

where RRCRSR is the risk ratio for CRS recurrence;

X1 – X13 – selected risk factors for CRS recurrence (Table I) with regression coefficients; -3.022 is a constant.

N=104	Regression Summary for Dependent Variable: ChRS Relapse (1 R= ,99386421 R?= ,98776607 Adjusted R?= ,98599894 F(13,90)=558,97 p<0,0000 Std.Error of estimate: ,40287					
	b*	Std.Err. of b*	b	Std.Err. of b	t(90)	p-value
Intercept			-3,02163	0,349667	-8,64147	0,000000
Age	0,285824	0,013378	0,05927	0,002774	21,36604	0,000000
Sex	0,162198	0,016548	1,11240	0,113489	9,80177	0,000000
Working conditions	0,345134	0,012476	0,96780	0,034983	27,66464	0,000000
NSD (Nasal Septum Deviation)	0,277670	0,012822	1,02917	0,047525	21,65524	0,000000
Allergy comp	0,055010	0,012700	1,11361	0,257092	4,33158	0,000038
Dental caries	0,200789	0,012404	1,04883	0,064791	16,18783	0,000000
White blood comp	0,617377	0,012907	1,03118	0,021558	47,83240	0,000000
ESR	0,112440	0,012527	0,03885	0,004328	8,97582	0,000000
Diabetes	0,068969	0,013153	1,07513	0,205044	5,24341	0,000001
Glucose	0,097594	0,013685	0,36158	0,050704	7,13131	0,000000
X-ray, CT, MRI	0,362671	0,013325	1,01199	0,037182	27,21704	0,000000
Smoking	0,146406	0,015757	1,16090	0,124939	9,29170	0,000000
Flu infection	0,148273	0,012260	0,92034	0,076099	12,09392	0,000000

Fig. 1. The result of obtaining significant factors for predicting CRS recurrence when conducting a multivariate regression analysis in the Statistica 10.0 program with a significance level of $p<0.05$.

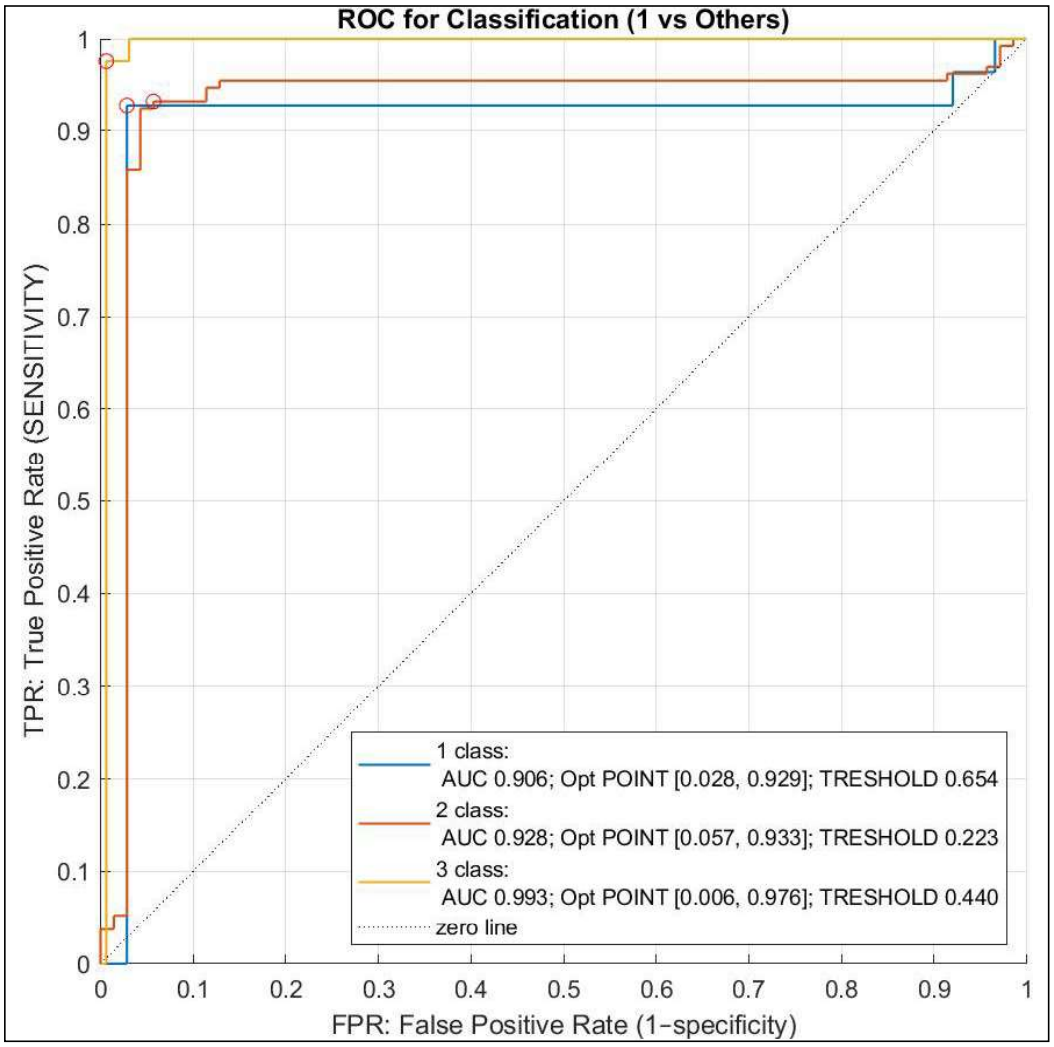

Fig. 2. ROC-curves for predicting the risk factor of chronic rhinosinusitis recurrence of R-1, R-2 and R-3 degrees.

To additionally assess the quality of the mathematical model of the RRCRSR, the coefficient of determination (R^2) was analyzed, which shows what part of the factors is considered during forecasting. The coefficient of determination in the proposed mathematical model of RRCRSR is R^2=0.987 (in the Statistica 10.0 program R^2= .98776607). So, in our case, 98.7% of factors are considered in the model for predicting the risk of CRS recurrence (RCRS), which indicates how well the obtained observations confirm the mathematical model [6].

Table 1. Significant risk factors for CRS recurrence

Name of factors	Conventional designations of factors in the mathematical forecasting model	Factor ranges and names of their possible variants	Numerical values of factor ranges
Age	**X1**	18-25	0
		25-44	1
		44-60	2
		60-75	3
		75-90	4
Gender	**X2**	M	1
		F	2
Working conditions	**X3**	Maternity leave/ Does not work/ Pensioner/ Disabled of II-III grade	1
		Nurse/ Doctor	2
		Student/ Educator/ Junior researcher/ Teacher/ Lecturer/ Librarian/ Accountant/ Leading specialist/ Manager/ Engineer/ Private entrepreneur/Operator	3
		Barista/ Waiter/ Make-up artist/ Salesman/ Cook/ Cleaner/ Watchman/ Driver/ Plant worker/ Warehouse administrator/ Foreman/ Tractor driver/ Police inspector/ Storekeeper/ Carpenter/ Crane operator	4
Nasal Septum Deviation	**X4**	1/3 of nasal meatus	1
		2/3 of nasal meatus	2
		Completely	3
		S-shaped	4
Allergic component	**X5**	No	0
		Yes	1
Carious (damaged) teeth (premolars)	**X6**	1 tooth	1
		2 teeth	2
		3 teeth	3
Level of WBC	**X7**	Normocytosis	0
		Eosinophilic leukocytosis	1
		Basophilic	2
		Monocytic	3
		Neutrophil leukocytosis	4
		Lymphocytic	5
ESR level	**X8**	Norm	0
		Increased	1
Presence of diabetes	**X9**	Absent	0
		Diabetes of I type	1
		Diabetes of II type	2
Glycemic level	**X10**	Nrml 3.3-5.5 mMol/L	0
		Light 6.7-8.2 mMol/L	1
		Medium 8.3-11.0 mMol/L	2
		Severe more than 11.0 mMol/L	3
X-ray signs (CT, MRI)	**X11**	Swelling of the mucous membrane	1
		Fluid level	2
		Cyst	3
		Alien body/ Mycetoma	4
		Tumor process/ Osteoma/ Polyps	5
Smoking	**X12**	No	0
		Yes	1
Flu infection	**X13**	Wasn't sick	0
		1-2 times a year	1
		3-4 times a year or more	2

Table 2. Initial data for the calculation of operational characteristics in the classification of the average (R-2) degree of risk of chronic rhinosinusitis recurrence, relatively mild (R-1) and severe (R-3) degrees

Degree of risk of CRS recurrence	The number of patients for the verification of the RCRS model with classification R-2, relative to R-1, R-3 among patients with chronic rhinosinusitis				
	True positive R 1, R 3 (a_{213})	Sum R 1, R 3	False positive R 2 (b_{213})	Sum R 2	Total ($a_{213}+b_{213}$)
R 1	28	66	-	4	70
R 3	38		4		
R 2	False negative (c_{213})	6	True negative (d_{213})	128	Total ($c_{213}+d_{213}$) 134
Total	$a_{213}+c_{213}$ 72		$b_{213}+d_{213}$ 132		$a_{213}+b_{213}+c_{213}+d_{213}$ 204

Table 3. Generalized operational characteristics of the mathematical model for predicting the risk of chronic rhinosinusitis recurrence

Designation of operational characteristics	Levels of risk of chronic rhinosinusitis recurrence			Average values of operational characteristics
	R-1	R-2	R-3	
Se, %	98,8	91,6	97,5	95,9
Sp, %	83,8	96,9	97,4	92,7
PPR, %	97,1	94,2	99,3	96,8
NPR, %	92,8	95,5	90,4	92,9
LR+	6,09	29,5	37,5	24,3
LR-	0,014	0,08	0,025	0,039
Prediction accuracy, %	96,5	95,09	97,5	96,3

Se - sensitivity, Sp - specificity, PPV - positive predictive value, NPV - negative predictive value, LR+ - likelihood ratio of a positive test, LR- - likelihood ratio of a negative test.

To determine the diagnostic value of the proposed model, based on the obtained results, we calculate the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), the likelihood ratio of a positive test (LR+), the likelihood ratio of a negative test (LR-) and prediction accuracy % of the proposed mathematical model.

Let's consider an example of calculating operational characteristics (Se, Sp, PPV, NPV, LR+, LR- and prediction accuracy) of the proposed mathematical model on the example of an average (R-2) degree of risk of developing of chronic rhinosinusitis recurrence (table 2).

The sensitivity of detection of RCRS R-2 relative to R-1, R-3 was calculated according to the formula

$$Se_{213}= (a_{213}/(a_{213}+c_{213}))*100\%;$$

Considering the numerical values (Table II), we get

$$Se_{213}= (66 / (66+6))*100\%=(66/72)*100\%=91,6\%.$$

The determination of the specificity of the detection of RCRS R-2 in relation to R-1, R-3 was carried out according to the following formula:

$$Sp_{213}=(d_{213}/ (b_{213}+d_{213}))*100\%$$

$$Sp_{213}=(128/ (4+128))*100\%=(128/132)*100\%=96,9\%.$$

The Positive Predictive Value (PPV) in the classification of patients with RCRS R-2 relative to R-1, R-3:

$$PPV_{213} =(a_{213} / (a_{213}+ b_{213}))*100\%$$

$$PPV_{213}=(66 / (66+ 4))*100\%=(66/70)*100\%=94,2\%.$$

The probability of identifying patients with RCRS R-2 with a positive classification result, relative to R-1, R-3, is 94.2%.

The Negative Predictive Value (NPV) of the classification of patients with R-2 relative to R-1, R-3:

$$NPV_{213} =(d_{213}/ (c_{213}+ d_{213}))*100\%$$

$$NPV_{213}=(128 / (6+128))*100\%=(128/134)*100\%=95,5\%.$$

Therefore, the probability of identifying patients with RCRS R-2 with a negative classification result, relative to R-1, R-3, is 95.5%.

The likelihood ratio of a positive test of detecting patients with RCRS R-2 relative to R-1, R-3 is calculated as follows:

$LR+_{213}=(Se_{213}/ (100-Sp_{213}))$

$LR+_{213}=(91,6 / (100-96,9))= 91,6/3,1=29,5$

Based on this, the probability of receiving a positive result of RCRS in patients with R-1, R-3 is 29.5 times greater, compared to the probability of a positive result in patients with R-2.

The likelihood ratio of a negative test of detecting patients with R-2 relative to R-1, R-3 will be:

$LR-_{213}=((100-Se_{213})/ Sp_{213})$

$LR-_{213}=((100-91,6)/ 96,9)=0,08$

which means the possibility of obtaining a negative result of RCRS in patients with R-2 is 12.5 times greater (1/0.08), compared to the probability of a positive result in patients with R-1, R-3.

The accuracy of RCRS R-2 of the proposed mathematical model was calculated according to the formula:

Accuracy of $RCRS_{213} =((a_{213}+ d_{213})/(a_{213}+ b_{213} +c_{213}+ d_{213}))*100\%$

Accuracy of $RCRS_{1234} =((66+128)/(66+4 +6+128))*100\%=(194/204)*100\%=95,09\%$

and accordingly, the share of the correct prediction results of CRS R-2 is 95.09%.

Similarly, the calculation of operational characteristics was carried out for the second and third degrees of risk of chronic rhinosinusitis recurrence (R-2 and R-3). The obtained operational characteristics of the mathematical model for predicting the risk of recurrence of chronic rhinosinusitis (R-1, R-2, R-3) and their average values are shown in Table 3.

In order to determine the prognostic value of the RRCRSR model, ROC- analysis was performed, ROC curves were obtained for mild (R-1), medium (R-2), and high (R-3) degrees of risk of CRS recurrence, and the corresponding areas under the curves (AUC) were determined for assessment of the quality of the proposed mathematical model.

Previously, we examined 204 patients aged 18 to 80, including 107 women and 97 men, with a diagnosis of chronic rhinosinusitis, who were undergoing inpatient treatment in the otolaryngology department of the communal noncommercial enterprise "Ternopil Regional Hospital" under Ternopil Regional Council.

It is recommended that the diagnostic test be both highly sensitive and highly specific. However, this rarely happens in practice. To achieve a compromise between sensitivity and specificity, to adequately choose a diagnostic criterion and distinguish patients (sick) from healthy, it is recommended to build a ROC curve.

After constructing the ROC curve, the corresponding data of the integral indicator of the area were obtained.

As can be seen from fig. 2, the area under the curve AUC1 =0.906 (classification quality of R-1 RRCRSR); AUC2 =0.928 (classification quality of R-2 RRCRSR); AUC3 =0.993 (classification quality of R-3 RRCRSR). Therefore, according to the ROC analysis, the prediction of R-1, R-2 and R-3 degrees of risk of developing of CRS recurrence is excellent.

DISCUSSION

The use of the mathematical model proposed by us, which considers possible risk factors for the development of CRS recurrence, provides the possibility of early prediction of potential complications and the probability of disease recurrence. This, in turn, contributes to early diagnosis and the choice of more effective and less harmful methods of CRS treatment.

The concept of reliability in medicine is multifaceted and includes a set of criteria for evaluating the results of diagnostic studies [7]. The main components of this complex include the following operational characteristics: sensitivity, specificity, prediction value of positive and negative results. Less relevant indicators of accuracy and the ratio of the likelihood of a positive and negative test. Each of these criteria is a specific statistical indicator.

Sensitivity indicator (Se) – shows the proportion of persons with a positive test result among persons with the disease under investigation; or the proportion of really sick people in the examined population who, according to the results of a diagnostic test, are found to be sick.

Specificity (Sp) indicates the proportion of individuals with a negative test result among individuals without examined disease or the proportion of those with a negative diagnostic test among all individuals without the disease.

In our case, the mathematical model shows a sensitivity and specificity of more than 90% (Se – 95.9%, Sp – 92.7%), which indicates that more than 90% of cases were diagnosed correctly.

The positive predictive value (PPV) indicates the probability of a disease with a positive (pathological) test result. The negative predictive value (NPV) indicates the probability of the absence of the disease with a negative (normal) test result.

The higher the indicators of specificity and sensitivity, the greater the value of PPV and NPV. In our case, Se is 95.9%, Sp is 92.7%, respectively, PPV is 96.8%, and NPV is 92.9%.

Based on the obtained results, we believe that the accuracy of predicting the risk of chronic rhinosinusitis recurrence is 96.3%, and the constructed ROC curves approach the upper left corner (AUC1 = 0.906 (classification quality of R-1 RRCRSR); AUC2 = 0.928 (classification quality of R -2 RRCRSR); AUC3 =0.993 (classification quality of R-3 RRCRSR)). All this indicates the strong diagnostic validity of this model and suggests that the model can be a useful application for doctors in identifying patients with different degrees of risk of developing chronic rhinosinusitis recurrence and making decisions about its treatment.

CONCLUSIONS

1. The multivariate regression model, which takes into account a number of predictors of the risk of CRS recurrence, makes it possible to predict potential complications and the possibility of disease recurrence with high values of sensitivity (95.9%), specificity (92.7%) and accuracy (96.3%) .
2. The construction of ROC-curves with the evaluation of the corresponding areas allows us to assert the excellent classification quality of mild (R-1; AUC1 =0.906), medium (R-2; AUC2=0.928) and severe (R-3; AUC2=0.993) degrees the risk of chronic rhinosinusitis recurrence, which allows timely and correct diagnosis of the severity of the inflammatory process, which makes it possible to choose the optimal method of treatment.
3. The application of this technique can be used for the development of medical calculators for assessing the severity of the risk of chronic rhinosinusitis recurrence, as well as for the design of relevant information and diagnostic systems in otolaryngology.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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