ORIGINAL ARTICLE

MULTIFACTOR REGRESSION MODEL FOR PREDICTION OF CHRONIC RHINOSINUSITIS RECURRENCE

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ABSTRACT

The aim: To propose an approach to forecasting the risk of chronic rhinosinusitis recurrence based on multivariate regression analysis for effective diagnosis and carrying out treatment and preventive measures.

Materials and methods: 104 patients aged 18 to 80, including 58 women and 46 men, diagnosed with chronic rhinosinusitis were examined.

Results: To build a multifactorial regression model for predicting the recurrence of chronic rhinosinusitis, probable factors of the occurrence of the disease were selected. 14 possible factors were analyzed using multivariate regression analysis. 13 risk factors were selected for predicting recurrence of chronic rhinosinusitis with a significance level of less than 0.05. Histograms of the residual deviations of predicting the recurrence of chronic rhinosinusitis were obtained, which are distributed symmetrically, and a normal-probability straight line is presented, on which there are no systematic deviations. The given results confirm the statistical hypothesis that the residual deviations correspond to the normal distribution law. Residual deviations relative to the predicted values are scattered chaotically, which indicates the absence of dependence on the predicted values of the risk of recurrence of chronic rhinosinusitis. The value of the coefficient of determination was calculated, which is 0.988, which gives grounds to claim that 98.8% of the factors are taken into account in the model for predicting the recurrence of chronic rhinosinusitis and its high reliability and acceptability in general.

Conclusions: The proposed model makes it possible to predict in advance potential complications and the possibility of recurrence of the studied disease.

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

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INTRODUCTION

Patients with various forms of chronic rhinosinusitis (ChRS) are the dominant part of patients with ENT pathology who are currently seen as outpatients by family doctors and otolaryngologists. Chronic rhinosinusitis is a broad concept that includes a number of diagnoses. It is defined as "infection of the sinuses and Schneiderian membrane lasting more than 3 months (or 12 weeks) per year." In most cases, this category of patients in the period of exacerbation of the disease requires not only hospitalization with intensive conservative therapy, but also quite often – surgical intervention.

In particular, among the entire population of the United States, chronic rhinosinusitis is currently diagnosed in 15.5% and for many years it has been considered the second most common among all chronic pathologies [1-3]. According to other data, from 5% to 15% of the population in different countries suffers from chronic rhinosinusitis in its various forms [4-6]. It is worth noting that from year to year this problem ceases to be only medical, but becomes social and financial – it causes a long-term decrease and loss of working capacity of patients, leads to significant material burdens on the patient and the state [7, 8].

In the structure of sinusitis, 56-73% are lesions of the maxillary sinus due to its large volume, high natural anastomosis and close contact with the roots of the teeth (premolars of the upper jaw) [9]. At the same time, the frequency of chronic sinusitis of the maxillary sinus is 5 times higher than for the example of the frontal sinus [10].

Despite modern surgical methods of treatment, postoperative complications and recurrences of the disease requiring reoperation are still observed in 18% of patients during long-term observation [11].

That is why the issue of predicting potential relapses of chronic rhinosinusitis depending on its form of manifestations remains open and relevant. The creation of appropriate prognostic mathematical models will make it possible to timely and reliably diagnose the occurrence of complex forms of CRS and their relapses, and may also be one of the options for solving the current problem of effective treatment of ENT diseases.

At present day, the examples of effective application of multivariate regression analysis in medicine

are the works of Musiienko V. et al.; Musiienko V. et al.[12, 13].

Prognostic factors of recurrence of polyps in chronic rhinosinusitis are also considered in the work of Junqin Bai et al. [14], and early postoperative endoscopic evaluation with eosinophilic chronic rhinosinusitis was carried out in the work of Kosuke Akiyama, Yasushi Samukawa, Hiroshi Hoshikawa[15].

THE AIM

The aim of the work is to propose an approach to forecasting the risk of recurrence of chronic rhinosinusitis in patients based on multivariate regression analysis for timely, convenient and accurate diagnosis while carrying out effective treatment and preventive measures in ENT departments (otolaryngology departments).

MATERIALS AND METHODS

We examined 104 patients aged 18 to 80, including 58 women and 46 men, with a diagnosis of chronic rhinosinusitis, who were undergoing inpatient treatment in the otolaryngology department of the 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 ethics commission at Ivan Horbachevsky Ternopil National Medical University (minutes No.63 dated March 16, 2020), the study was conducted in compliance with all moral and ethical principles, taking into account the Helsinki Declaration of the World Medical Association on Biomedical Research (World Medical Association Declaration of Helsinki).

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, CT 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 ChRS: age, gender, environmental living (working) 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 ChRS 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.

RESULTS

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

104 patients diagnosed with various forms of ChRS were examined using a specially developed questionnaire to predict the recurrence of ChRS, the average age of the examined was 45 years. The gender component was 58 women and 46 men.

Probable factors of the occurrence of chronic rhinosinusitis were selected to build a multifactorial regression model for predicting the recurrence of ChRS. With the help of multivariate regression analysis, 14 possible factors for the occurrence of ChRS were analyzed: age, gender, environmental living (working) conditions, nasal septum deviation, an allergic component in the anamnesis, the presence of carious or damaged teeth (upper premolars), leukocytes, white blood components, erythrocyte sedimentation rate (ESR), presence of diabetes, glycemic level, radiological signs, smoking, respiratory diseases during the last 12 months.

To assess the significance of the influence of factor characteristics, a stepwise multivariate regression analysis was performed in Statistica 10.0 program. First, a correlation matrix was obtained, in which the absence of pairwise correlation coefficients greater than 0.7 was established. Thus, the presence of multicollinear factors of ChRS recurrence gives reason to use all 14 above-mentioned factors to build a regression model. The next stage was the calculation of the regression coefficients "b" (Beta), which reflect for each selected factor the relationship regarding the impact on the development of ChRS recurrence in the examined patients. The result of obtaining significant factors for predicting ChRS recurrence when performing multivariate regression analysis in Statistica 10.0 program is shown in fig. 1.

Table I. Significant risk factors for ChRS 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
Ecological living (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
Components of white blood	X7	Normocytosis	0
		Eosinophilic leukocytosis	1
		Basophilic leukocytosis	2
		Monocytic leukocytosis	3
		Neutrophil leukocytosis	4
		Lymphocytic leukocytosis	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
		Foreign 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

N=104	Regression Summary for Dependent Variable: ChRS Relapse (1 R= ,99400574 R?= ,98804741 Adjusted R?= ,98616723 F(14,89)=525,51 p<0,0000 Std.Error of estimate: ,40044					
	b*	Std.Err. of b*	b	Std.Err. of b	t(89)	p-value
Intercept			-2,91301	0,355570	-8,19251	0,000000
Age	0,286032	0,013298	0,05931	0,002757	21,50998	0,000000
Sex	0,158368	0,016660	1,08613	0,114256	9,50611	0,000000
Working conditions	0,343985	0,012426	0,96458	0,034844	27,68301	0,000000
NSD (Nasal Septum Deviation)	0,280321	0,012876	1,03899	0,047724	21,77088	0,000000
Allergy comp	0,055126	0,012623	1,11596	0,255547	4,36696	0,000034
Dental caries	0,205421	0,012738	1,07302	0,066535	16,12717	0,000000
Leukocytes	-0,018909	0,013065	-0,02989	0,020649	-1,44738	0,151305
White blood comp	0,618464	0,012851	1,03299	0,021465	48,12483	0,000000
ESR	0,115017	0,012578	0,03974	0,004346	9,14421	0,000000
Diabetes	0,069331	0,013077	1,08076	0,203845	5,30188	0,000001
Glucose	0,102867	0,014082	0,38112	0,052174	7,30475	0,000000
X-ray, CT, MRI	0,362615	0,013245	1,01183	0,036958	27,37774	0,000000
Smoking	0,146888	0,015665	1,16471	0,124214	9,37666	0,000000
Flu infection	0,148020	0,012187	0,91877	0,075648	12,14527	0,000000

Fig. 1. The result of obtaining significant factors for predicting ChRS recurrence when performing multivariate regression analysis in Statistica 10.0 program.

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. 2. The result of obtaining significant factors for predicting recurrence of ChRS in Statistica 10.0 program without taking into account leukocytes.

The risk factor "Leukocytes" with a significance level of p=0.15 was excluded from further analysis. Since the significance levels of thirteen risk factors were less than 0.05, they were included in the mathematical model for predicting ChRS recurrence.

After constructing the correlation matrix excluding leukocytes, there were also no multicollinear factors, as there were no pairwise correlation coefficients greater than 0.7. Therefore, all 13 factors, except leukocytes, were used to construct a multivariate regression model. The result of obtaining significant factors for predicting recurrence of ChRS without taking into account leukocytes is shown in fig. 2.

So, among the 14 analyzed factors in Statistica 10.0 program (fig. 1), the 13 most significant risk factors that have the greatest influence on the development

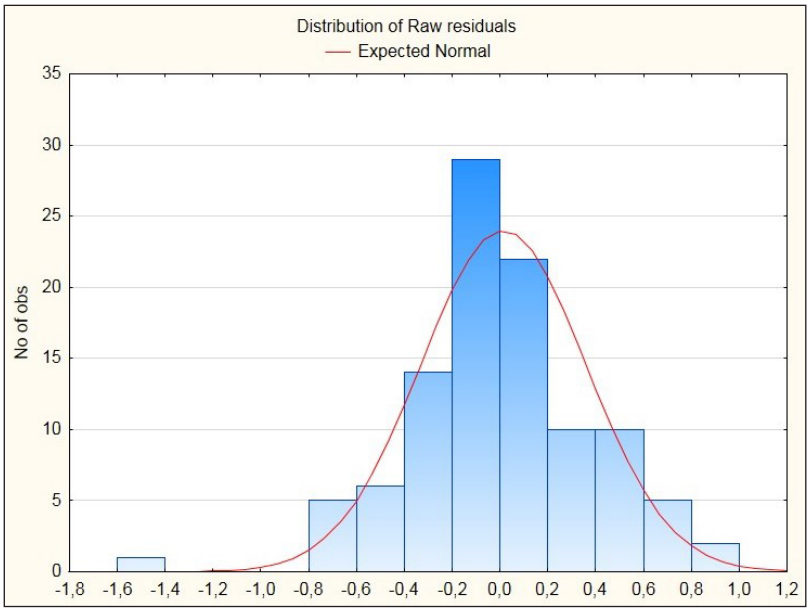

Fig. 3. Histogram of the residual deviations of the multivariate regression model for predicting ChRS recurrence.

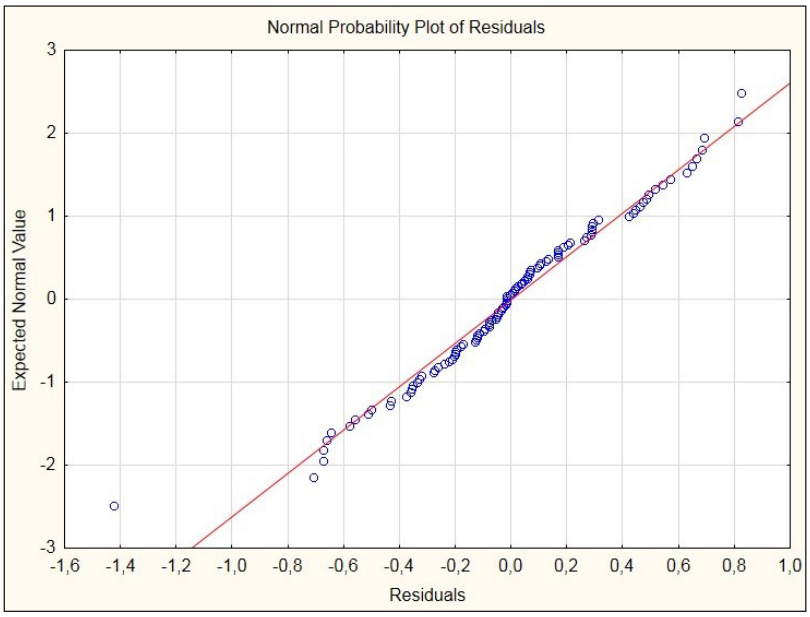

Fig. 4. Normal-probability graph of the residual deviations of the multivariate regression model for predicting ChRS recurrence.

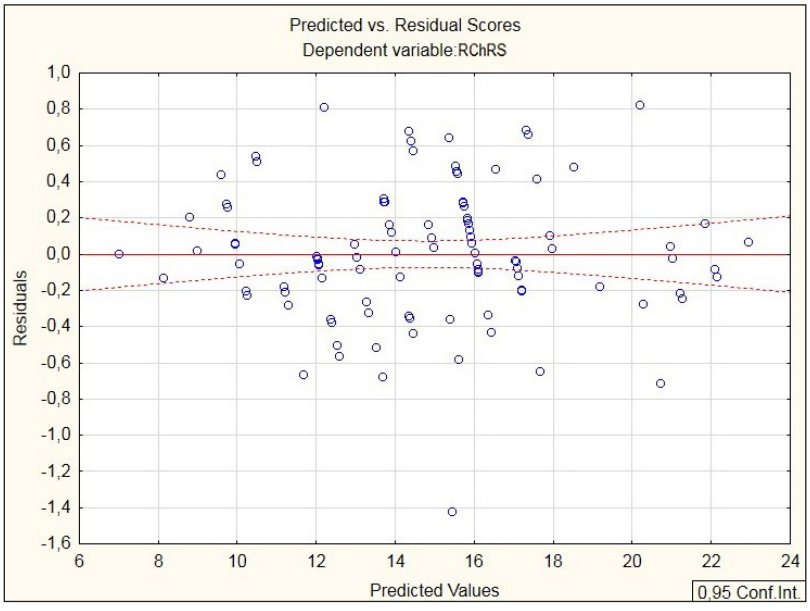

Fig. 5. Scatter diagram of the residual deviations of the multivariate regression model for predicting ChRS recurrence.

Effect	Analysis of Variance; DV:RChRS				
	Sums of Squares	df	Mean Squares	F	p-value
Regress.	1179,719	14	84,26565	525,5060	0,00
Residual	14,271	89	0,16035		
Total	1193,990				

Fig. 6. Analysis of the coefficient of determination of the multivariate regression model for predicting ChRS recurrence.

of recurrence of this pathology were selected: X1 – age; X2 – gender; X3 – ecological living (working) conditions; X4 – nasal septum deviation; X5 – allergic component in anamnesis; X6 – presence of carious or damaged teeth (upper premolars); X7 – components of white blood; X8 – erythrocyte sedimentation rate; X9 – presence of diabetes; X10 – glycemic level; X11 – X-ray signs; X12 – smoking; X13 – respiratory diseases during the last 12 months. Significant risk factors for CRS recurrence are listed in Table I.

Based on the results of the multivariate regression analysis of predicting the level of recurrence of ChRS, which are shown in fig. 2, we build a mathematical model for determining the risk ratio of ChRS recurrence (RRChRSR):

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*1.07 5+X10*0.362+X11*1.012+X12*1.161+X13*0.92-3.022,

where RRChRSR is the risk ratio of ChRS recurrence;

X1-X13 – selected risk factors for ChRS recurrence with regression coefficients;

3.022 is a constant.

To assess the quality of the regression model, it was necessary to analyze the residual deviations, in particular to obtain their histogram (Fig. 3). As can be seen from the obtained histogram, the residual deviations are distributed symmetrically, approaching the normal distribution curve of the residuals, therefore the statistical hypothesis that their distribution conforms to the normal distribution law is not rejected.

In order to additionally confirm residual deviations from the normal distribution law, a normal-probability graph was constructed (Fig. 4). Analyzing its data, we note the absence of systematic deviations from the normal-probability straight line. This makes it possible to conclude that the residual deviations are distributed according to the normal distribution law.

To check the dependence of the residual deviations on the predicted values, we construct a scatter diagram (Fig. 5).

Based on the obtained results, we note that the residuals relative to the predicted values are scattered chaotically, which indicates the absence of dependence on the predicted values of the risk of ChRS recurrence. Histogram and normal-probability graph confirm the residual deviations corresponding to the normal distribution law. Therefore, the obtained model for predicting the risk of recurrence of ChRS is qualitative and adequate.

The next step was to assess the acceptability of the model as a whole, for which we conduct an ANOVA analysis (Fig. 6). Analyzing the obtained data, we can conclude about the high level of acceptability of the model for predicting the risk of ChRS relapse in general using ANOVA analysis, since the level of significance is $p<0.001$, and the model itself will work better than a simple forecast using average values.

For an additional assessment of the quality of the mathematical model of RRChRSR, the Nigelkirk coefficient of determination (R^2) was analyzed, which shows what part of the factors is taken into account during forecasting. It is considered as a universal measure of the relationship of one random variable with others. The coefficient of determination varies from 0 to 1. The closer its value is to "1", the better the multivariate regression model. The coefficient of determination in the proposed mathematical model of the RRChRSR is R^2=0.987 (in Statistica 10.0 program R?= .98776607 (Fig. 2)). So, in our case, 98.7% of the factors are taken into account in the model for predicting the risk of ChRS recurrence.

The coefficient of determination indicates how well the obtained observations confirm the mathematical model.

DISCUSSION

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

The results of our research closely similar European studies conducted earlier. For example, you can take the SNOT-22 questionnaire, which includes 22 questions, each of which is evaluated on a 5-point scale (from 0 to 5 points depending on the degree of manifestation of symptoms), which helps to assess the quality of life and complaints of patients with ChRS [16]. Traditionally, the most pronounced symptoms of the disease are impaired nasal breathing, discharge from the nasal cavity, impaired perception of smells, pain in the face [17].

One of the modern methods of ChRS treatment is functional endoscopic sinus surgery (FESS), which is based on the principles of maximum preservation of the functional anatomy of the nasal cavity. This contributes not only to faster recovery, reducing the number of postoperative complications, but also to improving the quality of life of patients during the entire postoperative period [18]. Functional endoscopic sinus surgery (FESS) is currently the most effective treatment for drug-refractory chronic sinusitis, with symptomatic improvement reported in approximately 90% of patients [19]. However, despite the high efficiency of FESS, postoperative complications and disease recurrences requiring reoperation are still observed in 18% of patients during long-term follow-up [11]. Therefore, the application of the mathematical model developed by us creates the possibility of reducing the number of ChRS recurrences, and the development of postoperative therapy algorithms, based on the results of the formula, will be based on the further prevention of the development of the progression of the disease.

Based on the obtained results, including the joint influence of socio-economic and medical-biological factors in patients with ENT diseases, it will be possible to use a mathematical model for the design of an information-diagnostic system for evaluating and predicting ChRS recurrences. In the following studies, it is necessary to conduct ROC analysis to determine the sensitivity, specificity, and accuracy of the proposed mathematical model for predicting ChRS recurrences.

CONCLUSIONS

1. The proposed mathematical model, which takes into account risk factors for the development of ChRS recurrence, makes it possible to predict potential complications and the possibility of recurrences of the disease in advance.
2. This model will make it possible to reduce the number of ChRS recurrences and to develop algorithms for postoperative therapy with the aim of further prevention of disease progression.
3. In the future, the obtained results can be used to design an information-diagnostic system for evaluating and predicting the recurrence of ChRS, which develops as a result of the joint influence of a number of socio-economic and medical-biological factors in patients with ENT diseases.

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