ORIGINAL ARTICLE

Forecasting of Atopic Dermatitis in Newborns

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Abstract

Background: Early forecasting of any pathological process is of great significance from both medical and economic point of view. An illness requires much more attention in the light of exhaustion of resources of the body, and a doctor should be maximally aware of the near and far future of a patient. In this regard, the preparation of forecasting programs on a mathematical basis would be a rational and, most probably, the only true approach to the solution of forecasting. **Aims and Objectives:** The aim of the article is to study the forecasting of atopic dermatitis (AD) in newborns. **Methodology:** The authors studied 109 clinical and laboratory indicators in children without and with AD. Discriminant analysis was used as an algorithm for the resolution of diagnostic issues. **Results:** The main indicators acceptable as a forecasting criterion in the formation of AD in children were defined. The sensitivity, specificity, and general diagnostic value of statistically valid differing factors in the formation of AD were studied. Key rules of the forecast were formed after processing all indicators through the KU–Kruskal–Wallis discriminant criterion, a universal computer method. **Conclusion:** It was concluded that the power of influence of rhinitis, cluster of differentiation 31, mucin 2, and intestinal trefoil factor 3 are higher in the AD model.

Key Words: *Correlation analysis, disease, medicine, theory of probability*

Introduction

Early forecasting of any pathological processes is of great significance from both medical and economic points of view.[1-3] An illness requires much more attention in the light of exhaustion of resources of the body, and a doctor should be maximally aware of the near and far future of a patient.[4,5] The knowledge about the result of each individual case would ensure the inclusion of the patient in a more or less vulnerable group. Thus, this study discusses the choice of necessary therapeutic approach as well as the assessment of the consequences of various methods of treatment.[6-10]

The analysis of literary information indicates that the assessment of illness forecasting based on individual or isolated indicators is not promising.[11-13] In this regard, the preparation of forecasting programs on a mathematical basis would be a rational and, most probably, the only true approach to the solution of forecasting.[14-19]

Any event in clinical medicine can be currently assessed as a probable process and studied by the theory of probability. These conditions would ensure the application of mathematical methods based on the principles of probability with the possibility of positive results in the forecasting of the course of the illness. Recently, more attention is attached to the application of exact sciences in medicine and the establishment of mathematical expert systems on computers. It will help intellectualize the decisions of doctors and prevent unpleasant results based on algorithms, including the facilitation of individual preventive measures.[20-22]

Materials and Methods

Discriminant analysis was used as an algorithm for the resolution of diagnostic issues. Key rules of the forecast were formed after processing all indicators through KU–Kruskal–Wallis discriminant criterion, a universal computer method. At this stage, 63 forecasting criteria were selected for further analyses. After thorough processing of these 63 indicators by means of discriminant (Pearson's Chi-square) and disperse (analysis of variance test – F-Fischer) methods, statistically and specifically different 28 clinical and 6 laboratory indicators were kept for the formation of the model. Thus, certain indicators have less rate

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of spread, and we decreased clinical factors to 19 by combining certain indicators under the title of "other antenatal factors" and "other neonatal factors." Receiver operating characteristic (ROC) analysis was conducted for the evaluation of laboratory indicators (forecasting markers), the cut-off point was determined based on the coordinates of ROC curves, and the sensitivity and specificity of the markers were calculated.

Correct application of probability methods requires correlative non-dependence of forecasting criteria. Thus, overlapping of unilateral results of correlative indicators could lead to a strong disruption of the truth in forecasting. We selected 15 non-correlative indicators during the correlation analysis (p-Spearman) between the results.

First, we used to distribute these indicators under the principle of available/not available, i.e., there is atopic dermatitis (AD) (should not be AD). In this case, it is advisable to apply the Bayes formula. To this end, there are two theories: H_1 – Hypothesis 1: this value of the indicator is characteristic of AD positive (AD^+) children; H_2 – opposite hypothesis 2: this value of the indicator is characteristic of AD negative (AD^-) children. Obviously, the sum of the hypotheses is (Eq. 1):

$$p(H_1) + P(H_2) = 1. \qquad (1)$$

Then, Bayes formula is as follows (Eq. 2):

$$p(AD^+ / H_1) = \frac{p(AD^+) \times p(H_1 / AD^+)}{p(AD^+) \times p(H_1 / AD^+) + p(AD^-) \times p(H_1 / AD^-)}, \qquad (2)$$

Whereas $P(AD^+/H_1)$ is the conditional probability of the formation of AD in a child within the H_1 hypothesis; $P(AD^+)$ is the unconditional probability of the formation of AD in a child; $P(H_1/AD^+)$ is the conditional probability of the value of the indicator being in conformity with H_1 hypothesis in a child with AD; $P(AD^-) - 1 - p(AD^+)$ is the unconditional probability of the absence of AD in a child; $P(H_1/AD^+)$ is the conditional probability of the value of the indicator being in conformity with H_1 hypothesis in a child without AD.

Before calculations, it is admitted in the vaguest way that AD^+ and AD^- probabilities are equal at first glance (Eq. 3):

$$p_0(AD^+) = p_0(AD^-) = 0.5. \qquad (3)$$

Taking into account every next factor, a posteriori probabilities are calculated under the Bayes formula: p_1, p_2,.... It is obvious from the above that the sequence of the calculation for every specific case is conducted under the Bayes formula.

The next stage of the attempt to establish a forecasting program exceeded the borders of the theory of probability and the science of mathematical statistics. Thus, it was impossible to determine a one-digit probability of AD formation on a specific unit of laboratory indicators. Therefore, we had to refer to elements of the theory of "fuzzy" logic.

To this end, we gathered the laboratory results of children with and without AD into a "fuzzy" multitude in the form of an *n*-sized ellipsoid with focuses being medians of AD^+ and AD^- multitudes. Then, we divided this ellipsoid into the multitude of interconnected ellipsoids through percentile evaluation. This allowed us to determine the point of connection of the ellipsoid in the form of the one-digit (given any set of laboratory results) on every specific occasion. As the focuses of the ellipsoid are obvious, the distances to the focuses of each point became a metric for us. These figures were normalized and recognized as an unconditional probability, which allowed us to conclude calculations on a forecasting model again under the Bayes formula. According to the requirements of "fuzzy logic" theory, we rejected absolute "0" and absolute "1" for determining the distance to avoid any indefinite situations and made use of 0.01 or 0.05 instead of "0" and 0.99 or 0.95 instead of "1" – figures close to former ones, depending on the shape of the ellipse on each specific occasion.

A special "ADYR-2019" program was worked out in Visual Basic algorithm language based on MS Excel-2013 component for modeling the above. The program management only requires a doctor to enter patient data in necessary boxes within seconds with the help of capabilities at the user level. The program controls the information entered as well, thus a doctor is called to be careful by marking the box with false data as "False." It should be noted that cases in the absence of any information about patients are also taken into account. In this regard, the result is calculated even in the absence of any information in that box. However, the inclusion of all data selected in the program ensures a more accurate result; thus, it is advisable to mark all boxes. The program calculates the probability of AD in an examined child and submits the result on a chart [Figure 1].

Such information would play a vital role in the selection of future treatment tactics by a doctor. The program is protected from accidental amendments and requires standard MS Office software on a simple configuration computer. The program is at a capacity of < 50 Kbyte. For the sake of friendly use, the ADYR-2019 program is placed on the website www/_@_, and an extra page is added to the program for suggestions and comments. The program is planned for improvement in the future for the purpose of more accurate results based on these suggestions. All indicators studied in the groups with

and without AD were taken into consideration for the evaluation of results. According to the quantity of real positive and real negative results, "specificity" and "sensitivity" were evaluated in the ADYR-2019 program.

Results

In the current research, we sought to define the main indicators acceptable as a forecasting criterion in the formation of AD in children. From this point of view, we studied 109 clinical and laboratory indicators in children without AD (I group – n = 260) and with AD (II group – n = 268). The sensitivity, specificity, and general diagnostic value (GDV) of statistically valid differing factors in the formation of AD were studied [Table 1].

The highest sensitivity (67.9 ± 2.9%) and GDV (64.2%) among the above-mentioned factors are noted in allergic factor on parents; the highest specificity (94.2 ± 1.4%) and the effect of evaluation under positive predictive value (71.2 ± 6.3%) and likelihood ratio of the positive result (2.39 – satisfactory) include seasonal factor. Table 2 presents the specificity, sensitivity, and GDV of neonatal pathologies and symptoms.

The highest sensitivity and GDV among the above-mentioned factors is rhinitis; the highest

Table 1: Informative value of some factors in the formation of AD

Statistical parameters	Factors			
	Zone	Allergy on parents	Season	Cesarean section
Sensitivity (Sn)	60.1±3.0%	67.9±2.9%	13.8±2.1%	67.5±2.9%
Specificity (Sp)	52.3±3.1%	60.4±3.0%	94.2±1.4%	41.9±3.1%
General diagnostic value (GDV)	56.3±2.2%	64.2±2.1%	53.4±2.2%	54.9±2.2%
Effect of evaluation under positive predictive value (pPV)	56.5±2.9%	63.9±2.8%	71.2±6.3%	54.5±2.7%
Effect of evaluation under negative predictive value (nPV)	56.0±3.2%	64.6±3.1	31.5±2.3%	55.6±3.5%
Likelihood ratio of positive result (LR+)	1.26 unfit	1.71 unfit	2.39 satisfactory	1.16 unfit
Likelihood ratio of negative result (LR–)	0.76 unfit	0.53 unfit	0.91 unfit	0.77 unfit

Table 2: Informative value of some neonatal symptoms and pathologies in the formation of AD

Statistical parameters	Factors						
	Wheezing	Conjunctivitis	Rhinitis	Food allergy	Sensitive skin	Trouble sleeping	Constipation
Sn	66.0±2.9%	52.2±3.1%	83.2±2.3%	44.8±3.0%	63.8±2.9%	64.6±2.9%	38.2±2.9%
Sp	64.2±3.0%	63.5±3.0%	53.1±3.1%	78.3±2.8%	51.9±3.1%	44.2±3.1%	76.5±2.6%
GDV	65.2±2.1%	57.8±2.1%	68.4±2.0%	61.4±2.1%	58.0±2.1%	54.5±2.2%	54.4±2.2%
pPV	65.6±2.9%	59.6±3.2%	64.6±2.6%	68.2±3.5%	57.8±2.9%	54.4±2.8%	59.1±4.0%
nPV	64.7±3.0%	56.3±2.9%	75.4±3.2%	58.0±2.6%	58.2±3.2%	54.8±3.4%	55.2±2.6%
LR+	1.26 unfit	1.43 unfit	1.77 satisfactory	2.08 satisfactory	1.31 unfit	1.16 unfit	1.40 unfit
LR–	0.76 unfit	0.75 unfit	0.33 unfit	0.70 unfit	0.70 unfit	0.80 unfit	0.88 unfit

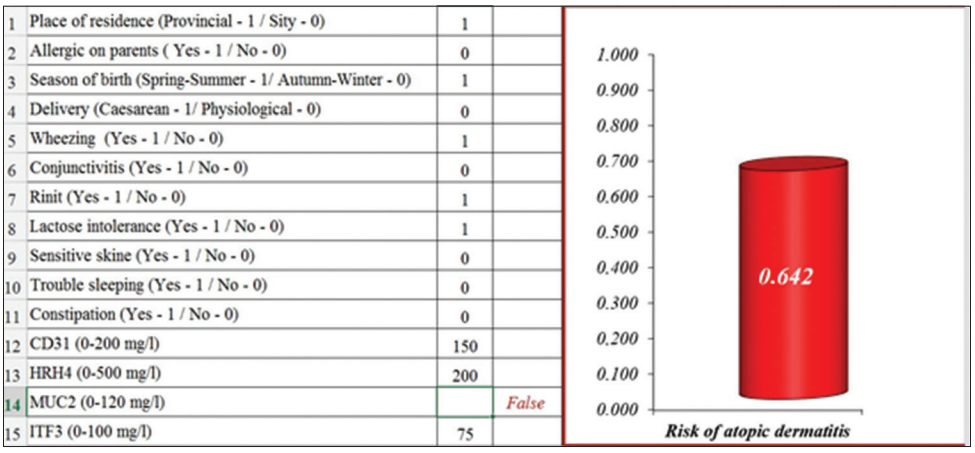

Figure 1: One of the results of the ADYR-2019 program

specificity is food allergy and constipation; the highest effect of evaluation under positive predictive value is food allergy and wheezing, and the highest effect of evaluation under negative predictive value is rhinitis. The likelihood ratio of positive results (LR+) is observed in the frequency of symptoms of rhinitis (1.77 – satisfactory) and food allergy (2.08 – satisfactory), and it is of great importance in forecasting AD. A more sensitive ROC analysis was held on the markers of genetic and mucous membrane among laboratory indicators where statistically valid differences are monitored [Figure 2 and Table 3].

Apparently, a great part of the ROC curve for the cluster of differentiation 31 (CD31) marker is located above the standing line. In other words, the CD31 immunological marker has high specificity and sensitivity in the formation of AD. The area of the ROC curve amounts to 0.685 ± 0.56 (95% energy intake (EI) – 0.578–0.791), and the likelihood ratio was calculated as P = 0.002. As it is obvious from the ROC curve, the area of specificity in the reliability interval at 95% of histamine receptor H4 (HRH4) allergic marker comprises 0.604 ± 0.56 (P = 0.52), and referential indicators vary between 0.494 and 0.714. According to the results, this marker may be considered as the one with high specificity and sensitivity in newborns. Figure 3 and Table 4 describe the results of the ROC analysis in the classification of the markers of the mucous membrane.

The area of specificity of the ROC curve of the G1 marker amounts to 0.551 ± 0.50 (P = 0.307). Referential indicators

Table 3: Results of ROC analysis on CD31 and HRH4 markers

Volatility of test results (s)	Area	Standard error	*P* likelihood.	Reliability interval at 95%	
				Lower limit	Upper limit
CD31	0.685	0.054	0.002	0.578	0.791
HRH4	0.604	0.056	0.052	0.494	0.714

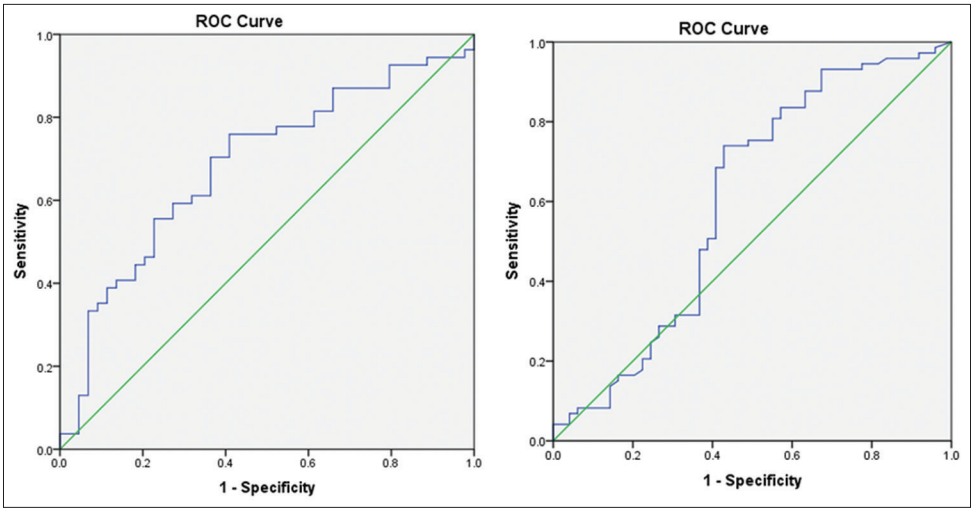

Figure 2: Results of ROC analysis on CD31 marker also known as platelet endothelial cell adhesion molecule (PECAM-1) and HRH4 (human) markers

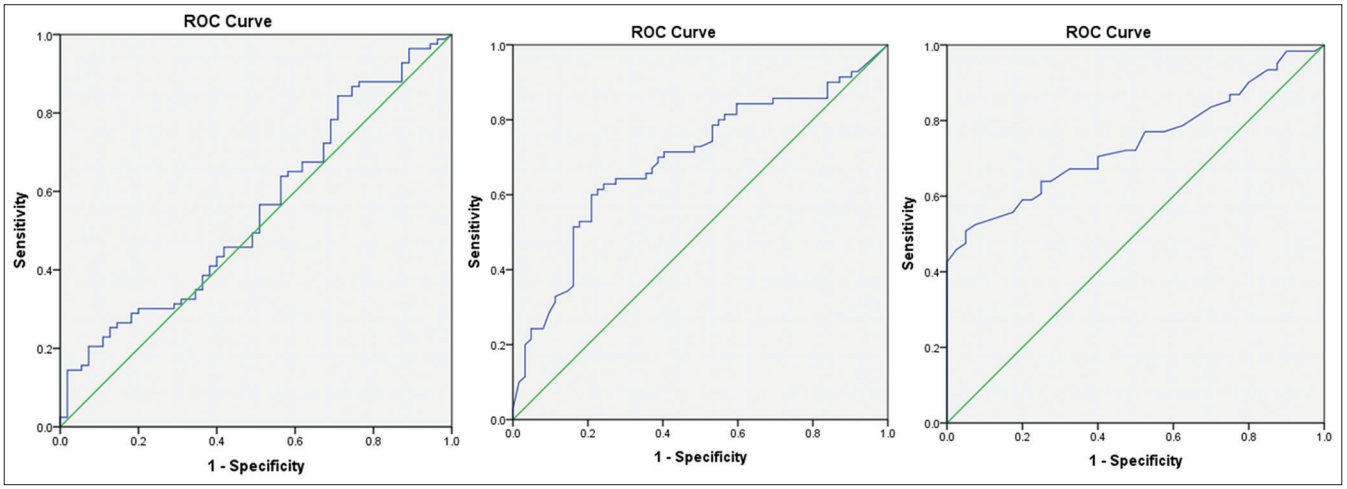

Figure 3: Results of ROC analysis in the classification of the markers of the mucous membrane

of this marker in reliability interval at 95% vary between 0.454 and 0.649. According to the ROC curves, mucin 2 (MUC2) and intestinal trefoil factor 3 (ITF3) genetic markers have high specificity and sensitivity in children with AD. Thus, the area of specificity of MUC2 calculated under the ROC curve is equal to 0.692 ± 0.046 ($P < 0.001$), and its upper and lower limits in reliability interval at 95% are accordingly 0.601 and 0.783. The area of specificity of ITF3 constitutes 0.740 ± 0.048, and referential indicators in reliability interval at 95% vary between 0.645 and 0.834. The ROC analysis of the two indicators, which do not differ in a common group, but statistically validly differ, at the same time, which are noted in medical literature were held in the population studied previously [Figure 4 and Table 5].

According to the ROC curve, immunoglobulin E (IgE) and Vitamin D (VitD) indicators are considered markers with low specificity and low informative value. Thus, the area of specificity of IgE is 0.534 ± 0.063, and its referential indicators at 95% EI are 0.411 and 0.658. The upper and lower limit of VitD at 95% EI is defined accordingly as 0.441 and 0.565; its area of specificity is 0.503 ± 0.032. Apparently, neither IgE nor VitD indicators can be recognized as sensitive and specific indicators in the formation of AD. The next stage envisages finding cut-off points – the farthest point from the standing line among interval figures at a variation interval of the indicators in the result of ROC analysis. The calculation was conducted on statistically valid differing indicators in the ROC analysis [Table 6].

It should be noted that a positive solution direction in forecasting AD in children was not observed in pediatric practice. The power of influence of the factors present in the model prepared based on the results was calculated with the help of the Fischer–Snedecor method at the next stage, and the final results are described in Table 7.

Based on the factors studied, ITF has the highest informative value, thus the fact is the quantity of this factor (n = 101 persons) is higher than 25.0; its specificity, informative value, and GDV are, respectively, 50.8 ± 6.4%, 95.0 ± 3.4%, and 68.3 ± 4.6%; the effect of evaluation under positive and negative predictive value is accordingly 93.9 ± 4.2 and 55.9 ± 6.0, which proves that this indicator is of great importance for forecasting of AD. According to the results of the correlation analysis, direct proportionality was found between the zone factor and allergy on the father, allergy on the mother, and food allergy; and inverse proportionality was found with the constipation factor.

Table 4: Results of ROC analysis on the indicators studied

Volatility of test results (s)	Area	Standard error	*P* likelihood	Reliability interval at 95%	
				Lower limit	Upper limit
Immunoglobulin G subclass 1 (IgG1)	0.551	0.050	0.307	0.454	0.649
Mucin 2, protein coding gene (MUC2)	0.692	0.046	0.000	0.601	0.783
Trefoil factor 3, intestinal (ITF3)	0.740	0.048	0.000	0.645	0.834

Table 5: Results of ROC analysis of the statistically valid different indicators

Volatility of test results (s)	Area	Standard error	*P* likelihood.	Reliability interval at 95%	
				Lower limit	Upper limit
IgE	0.534	0.063	0.572	0.411	0.658
VitD	0.503	0.032	0.923	0.441	0.565

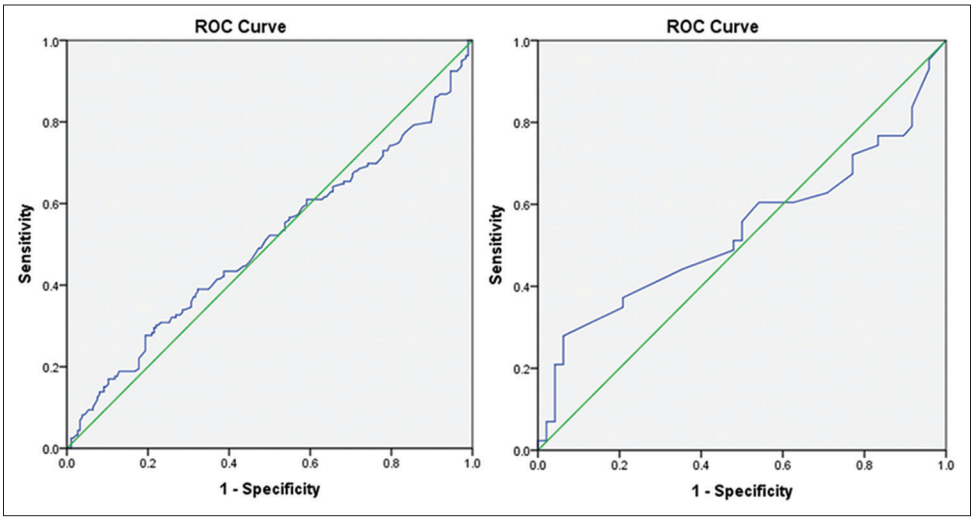

Figure 4: Results of ROC analysis of the two indicators

Discussion

There are no specific diagnostic tests for AD. Diagnosis of the disorder is based on specific criteria that take into account the patient's medical history and clinical manifestations.[26,27] AD occurs as a result of complex interactions between genetic factors, the environment, infectious agents, defects in the barrier function of the skin, and impaired immune response. Knowledge of etiological factors allows for adequate therapy, as well as primary, secondary, and tertiary prevention of this disease in children. According to research, the most important in the etiology of hypertension is burdened heredity of allergic pathology in families of children, as well as environmental conditions with factors of their influence, on which the child grows, develops, and stays. New information on hypertension indicates that both structural abnormalities of the skin and immune dysregulation play an important role in the pathophysiology of the disease. Therefore, the optimal treatment of hypertension requires a multifaceted approach aimed at healing and protecting the skin barrier, as well as the impact on the complex immunopathogenesis of the disease.

Table 6: Role of markers in the formation of AD in newborns

Statistical parameters	Indicators			
	CD31	H4R4	MUC2	ITF
Cut-off point	11.8	2.3	8.0	25
Sn	75.9±5.8%	83.6±4.3%	60.0±5.9%	50.8±6.4%
Sp	59.1±7.4%	42.9±7.1%	79.0±5.2%	95.0±3.4%
GDV	68.4±4.7%	67.2±4.3%	68.9±4.0%	68.3±4.6%
pPV	69.5±6.0%	68.5±4.9%	76.4±5.7%	93.9±4.2%
nPV	66.7±7.5%	63.6±8.4%	63.6±5.5%	55.9±6.0%
LR+	1.86 unfit	1.46 unfit	2.86 satisfactory	10.16 excellent
LR–	0.41 satisfactory	0.38 satisfactory	0.51 unfit	0.52 unfit

Direct proportionality is observed between allergy factor on the father and wheezing, conjunctivitis, rhinitis, food allergy, sensitive skin, trouble sleeping, MUC2, and ITF3. It shows that in the case of an allergy factor on the father, a newborn is at high risk of formation of such neonatal and antenatal symptoms.[20] Direct proportionality exists between allergy factor on the mother and autoimmune illnesses, wheezing, rhinitis, food allergy, and CD31 factors. This dependence shows that in the case of an allergy factor on the mother, there is a high risk of autoimmune illnesses, at the same time, symptoms of wheezing, rhinitis, and food allergy may be noted in a newborn.[23]

Children born via cesarean section demonstrate a higher quantity of HRH4 and MUC2 markers, thus their thickness is directly proportional to this factor.[24] Wheezing observed in newborns has direct proportionality to conjunctivitis, rhinitis, food allergy, sensitive skin, trouble sleeping, constipation, CD31, HRH4, and MUC2.[25] According to correlation results, damage to mucous membrane is observed through conjunctivitis, rhinitis, food allergy, sensitive skin, and trouble sleeping symptoms in newborns; and the increase of markers of mucous membrane proves it once again.

In a clinical setting, the proposed models can be used in the development of treatment tactics for newborns with AD.

Table 7: Informative value of factors participating in AD forecasting model in newborns

Factors	Ratio of opportunities			Fischer–Snedecor				*P*
	Odds ratio (OR)	95% confidence interval (CI)	95% CI	Efficiency influence factor (EIF) %	95% Lower bound (LB)	95% Upper bound (UB)	Fischer's test (F)	
Zone	1.65	1.17	2.33	1.6	0.8	2.3	8.4	0.004
allerg_valid	3.23	2.26	4.61	8.8	8.1	9.4	50.5	<0.001
Season	2.62	1.40	4.89	1.9	1.1	2.6	9.9	0.002
Cesarean	1.50	1.05	2.14	1.0	0.2	1.7	5.1	0.024
Wheezing	3.49	2.44	5.00	10.1	9.4	10.8	59.1	<0.001
Conjunctivitis, dacrosistitis	1.90	1.34	2.69	2.6	1.8	3.3	13.8	<0.001
Rhinitis	5.61	3.75	8.38	17.0	16.4	17.6	107.8	<0.001
Food allergy	2.95	2.02	4.32	6.5	5.8	7.2	36.4	<0.001
Sensitive skin	1.90	1.34	2.70	2.6	1.9	3.3	13.9	<0.001
Trouble sleeping	1.44	1.02	2.05	0.8	0.1	1.5	4.3	0.039
Constipation	1.59	1.09	2.34	1.1	0.4	1.8	5.8	0.016
CD31	4.56	1.92	10.83	14.5	11.0	18.0	16.3	<0.001
HRH4	3.81	1.65	8.82	9.3	6.3	12.3	12.3	0.001
MUC2	5.65	2.60	12.29	18.5	16.0	21.0	29.5	<0.001
ITF3	19.63	4.35	88.69	29.6	26.8	32.4	41.6	<0.001

Conclusions

To sum up, the power of influence of rhinitis, CD31, MUC2, and ITF3 factors are higher in the AD model. However, since the informative value of all factors used in forecasting is accompanied by statistical validity, the use of all factors in the model is advisable for the sake of more accurate results. The most sensitive factors are rhinitis; the highest specificity is food allergy and constipation; the highest effect of evaluation under positive predictive value is food allergy and wheezing; and the highest effect of evaluation under negative predictive value is rhinitis.

Thus, damage to intestinal mucosa with the influence of perinatal risk factors is an initiating and significant factor of atopic allergy. The identification of early and significant risk factors in the formation of AD would allow classifying a risk group with postnatal allergic pathology and preparing a set of treatment and preventive measures for the prevention of the formation of AD. The results obtained can be used in the selection of future treatment tactics by a doctor.

Ethics Committee

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A study was approved by National Ethics Commission of the Ministry of Health of the Republic of Azerbaijan, October 23, 2021, No. 795-0.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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