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The prediction of pneumonia in patients with immunity disorders on the background of onkolohematological pathology

I.S. Borisova
SE «Dnipropetrovsk Medical Academy of Health Ministry of Ukraine»

In the study, on the basis of statistical analysis of the complex of clinical-laboratory, anamnestic and immunological parameters of 495 patients, predictors of pneumonia were determined and a logistic model of the prediction of the occurrence of pneumonia in patients with immune disorders on the background of oncohematological pathology was developed, which included indicators that are characteristics of the course of oncological diseases of the blood, as well as indicators of immune reactivity.

Key words: prognosis of pneumonia, oncohematological pathology, immunity disorders.

Pneumonia, despite the implementation of modern international medical practice [1–3] and state standards of diagnosis and treatment [4], remains a significant clinical problem. Despite the decrease in the death rate from pneumonia in Ukraine in the last 12 years, the indicator of hospital mortality remains practically unchanged: 0,84 per 2010; 0,87 for 2011 [5].

One of the reasons for the high level of pneumonia is the increase in the number of patients with severe immune disorders. These patients include patients with oncohematological pathology. According to statistical data in the United States about every 3 minutes a new case of oncohematological disease is registered, one in nine patients dying every 9 minutes [6]. In Ukraine, up to 8,000 new cases of hemoblastosis are diagnosed annually. Index of morbidity by 100 thousand the population is: at lymphogranulomatosis – 2,5; at multiple myeloma (MM) – 1,6; with leukemia – 8,1 [7]. The reduction of the immunological protective forces of the body of such patients is associated with both the specificity of the oncohematological process and the immunosuppressive effects of modern HT patterns. Immunological defects are observed at all levels of nonspecific reactivity. Violation of the immune response in patients is accompanied by changes in the processes of differentiation, proliferation and adaptation of its cells, which lead to a decrease in the response of the cellular level of immunity [8].

Cytostatic therapy of oncohematological disease leads to a decrease in the concentration of immunoglobulins and causes disorders of the humoral link. The presence of immunity disorders not only complicates the oncohematological disease but also becomes the cause of infectious complications, including pneumonia, which, in turn, worsen both the prognosis of survival and the quality of life. The incidence of IC in patients with background oncohematological pathology is recorded in 30–80% of cases, in most cases it is pneumonia, which determine the greatest mortality [9]. Pneumonia often occurs in patients with multiple myeloma, their proportion is 42%; in patients with non-Hodgkin's lymphomas (NHL) – 79%. [10].

At the present stage, the development of medicine is based on the principles of evidence-based medicine, which requires the use of statistical methods and forecasting. If earlier the estimate of the onset of a disease or its consequences was based on the analysis of only clinical data and the experience of a doctor, then the use of mathematical apparatus is currently possible. Quantitative analysis makes it possible to determine prognostic evaluation criteria in numerical terms, which enriches and reinforces the content analysis, makes it more evidence, excluding contradictory methods [11].

Problematic questions regarding the evaluation of the factors influencing the occurrence of pneumonia and the prediction of its development on the background of programmed treatment of oncohematological diseases are important for clinicians working with this category of patients. In this regard, the practical importance of this problem determines the relevance of the study.

The objective: based on the statistical analysis of a complex of clinical and laboratory, anamnestic and immunological indicators, to create a mathematical model for predicting the occurrence of pneumonia in patients with immune disorders on the background of oncohematological pathology.

MATERIALS AND METHODS

The study group consisted of 495 patients who were hospitalized in the hematological center «City Multidisciplinary Clinical Hospital № 4», Dnipro for examination and treatment (the retrospective stage included the analysis of data of 389 cases of hospitalization of patients, 2011–2014, prospective – 106 cases of hospitalizations, 2014–2016). The research was conducted in accordance with the ethical principles of the Helsinki Declaration with the permission of the Bioethics Commission of the SE «Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine».

Diagnosis of nosological form of oncological pathology was determined in accordance with generally accepted clinical and morphological criteria [12]; diagnosis of pneumonia – in accordance with the criteria of the Order of the Ministry of Health of Ukraine No. 128 dated March 19, 2007 [4]. To solve this purpose, formalized histories of the illness of patients were created, where the results of clinical, instrumental and laboratory methods of investigation, including microbiological ones were presented. All indicators (132 quantitative and qualitative (nominal) indicators), obtained in the study, were entered into the electronic database in the form of a table «object–sign», which was subsequently subjected to a phased, multidimensional mathematical and statistical processing.

This allowed a fairly complete description of the various aspects of the state of the object of study and characterize: the course of pneumonia, the course of the main oncohematological disease and the state of the immune system of patients. Peculiarities of the course of pneumonia were studied independently of the oncogematological disease course. The statistical processing of the research results was carried out using descriptive and analytical biostatistics methods implemented in software packages STATISTICA 6.1 (StatSoftInc., Serial No. AGAR909E415822FA); Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT); MedCalc Statistical Software trial version 17.4 software pack-

Table 1

Correlation between the presence of pneumonia and general clinical and laboratory indices of patients in study groups

Indicators	ρ – the Spirman rank correlation coefficients	p
Dyspnea	-0,78	<0,001
RR, per min	-0,62	<0,001
The degree of neutropenia, $\times 10^9$/l	-0,47	<0,001
Pleurisy	-0,45	<0,001
Cough	-0,44	<0,001
The presence of P. Aeroginosa	-0,42	<0,001
Leucocytes, $\times 10^9$/l	-0,38	<0,001
FA, unit	-0,38	<0,001
Number of courses of PCT	-0,37	<0,001
Glycemia, mmol/l	-0,34	<0,001
Pulse, per min	-0,34	<0,001
T CD19,%	-0,34	<0,001
B CD19,%	-0,28	0,001
FF, unit.	-0,26	0,002
Neutropenia 3 st.	-0,26	<0,001
Stephen ABT	-0,25	<0,001
Number of pathogens	-0,21	<0,001
Urinary tract infection	-0,17	<0,001
ESR, mm/h	-0,17	<0,001
Defeat of the spleen	-0,16	<0,001
CD8, %	-0,15	0,041
Body temperature, °C	-0,13	0,004
Stage for Anne – Arbor Classification	-0,12	0,007
Defeat of lymph nodes	-0,12	0,010
Lesion of the liver	-0,11	0,011
Urea, mmol/l	-0,11	0,016
Creatinine, μmol/l	-0,09	0,041
Platelets, 10^9/l	0,1	0,03
AT systolic, mm rt.st.	0,13	0,004
Gr + flora	0,14	0,002
CD4, %	0,15	0,048
Hemoglobin, g/l	0,17	<0,001
Lymphocytes, %	0,19	0,006
DR +, %	0,19	0,032
CD4, g/l	0,27	0,001
Erythrocytes, 10^{12}/l	0,27	<0,001
Weakened breath	0,30	<0,001
Reduced percussion sound	0,31	<0,001
CD4 / CD8	0,35	<0,001
Number of neutrophils, 10^9/l	0,41	<0,001
B CD19, G/L	0,61	<0,001

Table 2

The ratio of chances of exposure to general clinical and laboratory parameters for the onset of pneumonia

Indicators (1 – yes, 0 – no)	RC	95% CI	The proportion of patients,%		p*
			Subgroup A.	Subgroup B	
Cough	8,42	5,29–13,42	88,76%	18,37%	<0,001
Sputum	2,41	1,51–3,84	26,51%	0%	<0,001
Reduced percussion sound	0,1	0,05–0,22	75,5%	6,75%	<0,001
Weakened breath	0,15	0,08–0,28	72,69%	14,72%	<0,001
Dyspnea	135,89	60,27–306,39	79,92%	2,85%	<0,001
Pleurisy	251,71	15,51–4085,93	33,73%	0%	<0,001
Defeat of lymph nodes	1,62	1,12–2,34	43,37%	32,11%	<0,001
Defeat of the spleen	1,94	1,35–2,79	50,2%	34,15%	0,011
Defeat of the liver	1,61	1,11–2,33	69,48%	58,54%	<0,001
Glycemia, mmol/l	5,46	3,44–8,66	42,17%	11,79%	0,002
Gr + flora	0,52	0,34–0,79	18,88%	30,89%	<0,001
The presence P. aeroginosa	107,63	14,82–781,43	30,52%	0,41%	<0,001
Step-by-step therapy	2,9	1,98–4,24	49,4%	25,2%	<0,001
The presence of neutropenia	4,42	3,01–6,5	75,5%	41,06%	<0,001
Neutropenia 3 st.	71,07	4,32–1168,42	12,45%	3,30%	<0,001
Stage disease 3 and 4 for the Ann-Arbor classification	1,97	1,33–2,9	37,75%	23,58%	0,001
RR> 24 per 1 minute	190,58	68,05–533,74	75,90%	1,63%	<0,001
BP systolic ≤118 mmHg	6,02	3,34–10,87	28,11%	6,10%	<0,001
Pulse >80 per min	7,74	5,09–11,77	61,45%	17,07%	<0,001
Number of pathogens >1	8,89	5,11–15,47	39,76%	6,91%	<0,001
Number of courses of HT >5	6,92	4,29–11,15	44,98%	10,57%	<0,001
Leucocytes >5,9×10^9/liter	4,94	2,32–10,5	60,32%	23,53%	<0,001
Neutrophils ≤1,7×10^9/l	5,47	3,66–8,15	58,23%	20,33%	<0,001
Lymphocytes ≤31,8%	4	2,16–7,4	62,00%	28,99%	<0,001
B CD19 ≤0,477 G/L	107,8	23,55–493,39	76,56%	2,94%	<0,001
B CD19 <14,5%	5,8	2,38–14,13	44,44%	12,12%	<0,001
T CD19 <42,6%	8,24	4,15–16,38	76,09%	27,85%	<0,001
CD4 ≤24,73%	10,71	3,1–37,02	26,09%	3,19%	<0,001
CD4 ≤0,96 G/L	4,7	2,35–9,37	71,43%	34,74%	<0,001
CD8 >26,8%	2,71	1,43–5,12	43,48%	22,11%	0,002
CD4/CD8 ≤1,21	6,54	3,15–13,59	48,91%	12,77%	<0,001
DR+ ≤4,3%	3,08	1,34–7,11	84,13%	63,24%	0,007
FA <31, units	5,09	2,36–10,96	59,02%	22,06%	<0,001
FN <4,1, units	3,5	1,57–7,78	42,86%	17,65%	0,002
Creatinine >106,7 μmol/l	1,49	1,04–2,13	61,45%	51,63%	0,028
Urea >9,7 mmol/l	3,56	2,07–6,12	24,19%	8,23%	<0,001
Hemoglobin ≤80 g/l	2,5	1,66–3,78	36,55%	18,70%	<0,001
Erythrocytes ≤2,65×10^{12}/l	4,4	2,86–6,76	43,78%	15,04%	<0,001
ESR >34 mm/h	2,72	1,82–4,06	40,96%	20,33%	<0,001
Platelets ≤158×10^9/l	1,67	1,17–2,39	54,41%	40,65%	0,004

Note: * – discrepancies according to Pearson's χ^2 criterion.

age. (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2017).

The verification of the hypothesis of normal distribution among the quantitative characteristics studied was carried out according to the Shapiro-Wilka criterion and the Kolmogorov-Smirnov criterion corrected by Lilliefors; checking the equality of dispersions – using Levin's criterion. For the intergroup comparison of quantitative characteristics, a nonparametric dispersion analysis of Kraskele-Wallis was performed, pairwise comparison in groups was performed with corrections for multiple comparisons of the significance level of p.

The probability assessment of the mean differences for quantitative attributes was performed according to Mann-Whitney's (U) criterion; probability of differences – using the Pearson Xi-square (χ^2) criterion, with the Yates correction for continuity for low frequencies and the value of the indicator close to 0 or 100. To construct the predictive model, a pairwise and multiple regression analysis was used to calculate the Spirman rank correlation coefficients (ρ). The estimation of the significance of the influence of factors on the result was carried out according to the odds ratios (HS) from 95% confidence intervals [13]. For accuracy prediction, the ROC analysis was performed for logistic equations, which included the construction and analysis of operational characteristics curves, the determination of the area under the ROC curve (AUC); Sensitivity (Se) and Specificity (Sr). [14].

RESULTS AND DISCUSSION

Characteristics of patients in the study group on cancer diseases were as follows: patients with chronic lymphocytic leukemia – 82 (16,16%), myeloid leukemia – 29 (5,86%), Valdenstrem's disease (VD) – 34 (6,87%), lymphoma – 26 (5,25%), erythema – 31 (6,26%), myeloma disease(MD) – 86 (17,37%), acute leukemia (AL) – 64 (12,93%) (acute lymphatic leukemia – 35 (7,07%), acute myeloid leukemia – 17 (3,43%), subleukemic myelosis – 10 (2,02%), acute monoblast leukemia – 2 (0,40%)); myelodysplastic syndrome – 23 (4,65%), aplastic anemia (AA) – 83 (16,77%), melanoma skin – 7 (1,14%), idiopathic thrombocytopenic purpura – 13 (2,3%) and others – 17 (3,43%) (thrombasthenia, lymphoproliferative diseases, hemorrhagic vasculitis, lymphosarcoma, plasmacytoma extemedular).

To perform the research tasks, two samples were formed: subgroup A included 249 (50,30%) patients with pneumonia developed in the hospital with the background of a programmed HT, respectively, of the form and stage of oncohematological disease; subgroup B – 246 (49,70%) of patients without pneumonia.

The age of the patients was in the subgroup A – 58 (46,0; 71,0) years; in subgroup B – 65 (57,0; 72,0) years ($p_{A-B}>0,05$); the ratio of women to men in study subgroups is 2:3. Consequently, according to the age and sex categories between the groups of patients, no discrepancies were found, which made it possible to correctly compare them.

The analysis of the correlation analysis results of 132 indicators of anamnesis, physical data, results of laboratory analyzes and immunologic indexes of patients on the background of oncohematological pathology revealed a connection between the presence of pneumonia and 42 quantitative and qualitative factors. Correlation between the presence of patients in the study groups of pneumonia and general clinical and laboratory parameters are presented in Table 1.

As a result of correlation relations, the presence of pneumonia in patients of the study group was associated with complaints of shortness of breath, indicators of RR, ESR, pulse, temperature reaction, the presence of pleurisy, cough, contraction of percussion sound, weakened breathing and sputum. These figures are signs of pneumonia or its complications, in this regard, they can not be the speakers of the development of pneumonia. It is important to note that the correlation coefficients of such indicators as body temperature (ρ=0,3), the presence of sputum (ρ=-0,17), weakened breathing (ρ=0,3), ESR (ρ=-0,17) are weak and clinically insignificant. This fact proves their insignificant contribution to the possibility of identifying (diagnosis) of pneumonia in patients, which was also stated in previous studies [15].

The results of the correlation analysis showed that the presence of pneumonia was also due to the signs of the main oncohematological disease of the patients in the study group: the number of courses of HT, preceding the occurrence of pneumonia (ρ=-0,37), lesion of the spleen (ρ=-0,16), damage to the lymph nodes (ρ=-0,12), liver damage (ρ=-0,11), stage according to the An-Arborsky classification (ρ=-0,12), platelets (ρ=0,11), hemoglobin (ρ=0,17), erythrocytes (ρ=0,27).

The presence of pneumonia according to the correlation analysis was significantly influenced by the parameters of the immune system of patients in the study groups and other indicators that take an active part in anti-infective protection: neutropenia 3 st. (ρ=-0,26), CD4/CD8 (ρ=0,35), number of neutrophils (ρ=0,41), B CD19 (ρ=0,61), CD4 (ρ=0,15), lymphocytes (ρ=0,19), DR + (ρ=0,19), phagocytes' activity (FA) (ρ=-0,38) and phagocyte number (FN) (ρ=-0,26).

For a more detailed analysis, indicators with statistically significant, average and high correlation coefficients were selected. Correlation analysis showed (Table 1) that the presence of pneumonia is associated with feedback, first of all with indicators such as complaints of shortness of breath (ρ=-0,78; p<0,001), RR (ρ=-0,62; p<0,001), the degree of neutropenia (ρ=-0,47; p<0,001), cough (ρ=-0,44; p<0,001) and the presence of the pathogen P. aeruginoza (ρ=-0,42; p<0,001)) The most influential direct ligaments are the presence of pneumonia associated with the index of immunoregulatory index CD4/CD8 (ρ=0,35; p<0,001); the number of neutrophils (ρ=0,41; p<0,001) and B CD19, G/L (ρ=0,615; p<0,001).

After determining the threshold prognostic level (Table 2) for quantitative factors, conducted with the help of ROC analysis to determine the optimum cutoff point for assessing the effect of the studied signs on the occurrence of pneumonia, ratio of the chances (RC) was calculated with a 95% confidence interval. The analysis of the RC included all the indicators for which there were probable differences between the groups.

The resulting symptom was classified in binary format, namely: 1 – there is pneumonia; 0 – pneumonia is absent. For RC, equal to 1, it means that an unfavorable result may occur in both groups that were compared with the same probability. The more RC, the more likely the occurrence of the event – the emergence of pneumonia. The critical levels determined for the immunogenicity indexes were: neutrophils $\leq 1,7\times10^9$/l, CD4 ≤24,73%, B CD19 ≤ 0,467 G/L, DR + ≤4,3%, CD4/CD8 ≤1,21, FA <31 od. and FF <4,1 units (Table 2). It is important to note that the level of neutrophils was defined as critical in the study – neutrophil levels $\leq 1,7\times10^9$/l. The generally accepted critical level of neutrophils in the blood is below 0,5×10%, which is associated with the fatal outcome of IC in patients with oncohematological pathology [16].

The higher threshold obtained in our study may be explained by the fact that we determined it for patients with pneumonia, with no adverse effect. The study also did not have patients with sepsis. The level of neutrophils below $1,7\times10^9$/l is critical for the onset of pneumonia, which will allow the timely modification of the treatment of patients with immune disorders on the background of oncohematological diseases.

The ratio of the chances of exposure to general clinical and laboratory parameters for the onset of pneumonia is given in Table 2.

As shown the results of the assessment of RC, the presence of pneumonia due to the influence of a number of factors listed

Table 3

Parameters of the prognostic model for the development of pneumonia in patients of the study group according to logistic regression analysis

Prognostic Variables	Regression coefficient β	Standard error of coefficient β	χ^2 Walds	p-value χ^2 Walds
Free member of the equation	-2,930			
Leucocytes, $\times 10^9$ / l (x_1)	0,495	0,157	9,948	0,002
Neutrophils, $\times 10^9$ / l (x_2)	-1,892	0,645	8,607	0,003
B CD19, g/l (x_3)	0,198	0,070	8,081	0,005
FA, units (x_4)	0,080	0,031	6,742	0,009
Logistic equation	$y=\exp(-2,930+0,495*x_1-1,892*x_2+0,198*x_3+0,080*x_4)/[1+\exp(-2,930+0,495*x_1-1,892*x2+0,198*x_3+0,080*x_4)]$			
Hi-square	$\chi^2= 58,60$ ($p<0,001$)			
Percentage of concordance	75,61%			
Hosmer-Lemesh Test	6,188 (p=0,626)			
Operating characteristics of forecasting according to ROC analysis				
Sensitivity,%	72,13			
Specificity,%	83,87			
AUC	0,853			
95% IC AUC	0,778–0,911			
p	p<0,001			
Qualitative evaluation of the model	very kind			

in Table 2. The most significant influence, in addition to the complications of pneumonia, was among the nominal indicators: complaints of dyspnoea, presence of P. aeroginosa and neutropenia of 3 st. Patients with these indicators have chances of developing pneumonia, respectively, in 135,5; 10,71; 107,8; and 71,07 times more than without the presence of these factors. Among the quantitative indicators, the greatest influence on the occurrence of pneumonia is due to the parameters of the immune system: CD4/CD8 ≤1,21 (RC 6,54 [95% CI 3,15–13,59]); CD4 ≤24,73 (RC 10,71 [95% CI 3,1–37,02])% CD4 ≤0,96 (RC 4,7 [95% CI 2,35–9,37]) G/l; CD8 >26,8 (RC 2,71 [95% CI 1,43–5,12])%; B CD19 ≤0,47 (RC 107,8 [95% CI 23,55–493,39]) G/L; B CD19 <14,5 (RC 5,8 [95% CI 2,38–14,13]%); T CD19 <42,6 (RC 8,24 [95% CI 4,15–16,38])%; DR + ≤4,3 (RC 3,08 [95% CI 1,34–7,11])%, FA <31 (RC 5,09 [95% CI 2,36–10,96]% and FN <4,1 (RC 3,5 [95% CI 1,57–7,78])%, units (Table 2).

In this case, patients with the indicated levels of indicators have chances of developing pneumonia, respectively, in 107,8; 3,08; 6,54; 5,09 and 3,5 times more than the higher than the given level. Thus, the state of the immune system in patients at the background of oncohematological pathology causes the development of pneumonia.

For the prognosis of pneumonia in patients of the study group, a simple and multiple logistic regression analysis was conducted, in which general clinical and laboratory parameters were predictors, and the dependent variable was the presence or absence of pneumonia. The analysis involved factors with definite statistical and / or clinical significance. Consequently, in a multiple logistic regression analysis, it was found that the following risk factors (in the order of decreasing the degree of influence), such as: the number of neutrophils, leukocytes and immunogenicity indexes – B CD19 + and FA, were probably ($p <0,005$) associated with the development of pneumonia.

Neutropenia and its degree in patients on the background of oncohematological pathology are considered by most authors as a risk factor for the development of infectious complications (IC), including pneumonia [17]. Neutrophils are a major component of the body's natural defense against bacterial infections, which determine the extent of the immune response to the infectious process [16]. Neutropenia contributes to the fact that bacterial agents are able to multiply without restrictions and form local focal points in the lungs. The study also obtained data confirming that the number of neutrophils and the degree of neutropenia causes the emergence of pneumonia in patients with background oncohematological pathology.

Patients with oncohematological pathology belong to a group of patients with immune disorders. In the study, on a sufficient number of observations, it has been proved that cellular immunity can be considered as predictors of pneumonia. The development of pneumonia depends on many cellular parameters: CD4 +%, B CD19 + G/L, DR +%, CD4/CD8, FA, units. and FN, unit. In the logistics equation two indicators were included – B CD19 +, g/l and FA, units. It is known that the main effector cell-killer cells are T lymphocytes that provide recognition and destruction of cells that carry external antigens, including infectious agents [8]. In oncohematological diseases, the number of these cells is usually reduced, according to the stage or nosological form of the disease. The function of B lymphocytes with the B CD19 + phenotype is the formation of complexes with antigenic receptors of B-lymphocytes and a decrease in the sensitivity threshold of these receptors, thereby stimulating the functional activity of T killers [8].

Also, this phenotype of B-lymphocytes at their decrease characterizes the redistribution of lymphocytes to the hearth of inflammation. Therefore, it is clear that the quantitative decrease in the index of B CD19 + is defined as a predictor of the occurrence of severe IC as a pneumonia in patients on the background oncohematological diseases. The obtained data coincide with the

data of other researchers, who determined the role of the index B CD19 + at its increase – as a sign of a favorable prognosis; with decrease – as a sign of unfavorable prognosis in patients with MM [18].

The process of phagocytosis is provided by polymorphonuclear granulocytes and macrophages. In conditions of reduced number of these cells that is observed in patients with immune disorders on the background of oncohematological pathology, the functional capacity of the existing cellular immunity, which is characterized by the FA index, plays a very important role. Phagocytic activity of leukocytes is expressed by the number of active leukocytes (phagocytes) in the total number of calculated neutrophilic leukocytes.

It is this indicator that showed the significant effect on the possibility of developing pneumonia in patients on the background of oncohematological pathology. It is determined that the possibility of pneumonia in patients of study group, in which the index of FA is lower than 31 and above in 5 times than in patients with near-normal FA.

Consequently, from the standpoint of the possibility of determining the predictors of prediction of pneumonia in patients with background oncohematological pathology, it is mandatory to take into account the secondary immunodeficiency that develops in patients as a pathogenetic basis of the underlying disease and potentiates modern high-dose schemes of chemotherapy. In developing the prognostic model based on the logistic equation, which suggests that the development of pneumonia is associated with predictors according to the formula:

$$y=\exp(b_0+b_1*x_1+\ldots+b_n*x_n)/[1+\exp(b_0+b_1*x_1+\ldots+b_n*x_n)]^{(1)},$$

where – y – the result; b_0 – free part of the regression equation; b_1 – b_n – regression coefficients; x_1 – x_n are predictive variables.

Regardless of the regression coefficients or the values of x, the predicted values (y) in this model will always be in the range from 0 to 1 (1 is pneumonia, 0 – without pneumonia). As a result of the step-by-step exclusion of independent variables, parameters of the logistic regression equation were obtained, which included only the potentially significant predictors presented in Table 3.

The equation of the predictive model of the prediction of pneumonia in patients of the study group has the form:

$$POP=\exp(-2{,}930+0{,}495*x_1-1{,}892*x_2+0{,}198*x_3+0{,}080*x_4)/[1+\exp(-2{,}930+0{,}495*x_1-1{,}892*x_2+0{,}198*x_3+0{,}080*x_4)]^{(2)},$$

where – POP – prognosis of pneumonia – a result that varies from 1 (there is pneumonia) to 0 (without pneumonia); b0 = -2,930 – free member of the regression equation; x1 – the number of leukocytes, 109 /l, x2 – the number of neutrophils, 109 /l; x3 – indicator B CD19+, G/l; x4 – indicator of FA, unit.

The estimation of the logistic regression equation on the Hi-square (χ^2) value showed its adequacy: χ^2=58,60; p & lt; 0,001. As an indicator of the consistency of the real distribution of observations in the presence of pneumonia and distribution, obtained on the basis of the logistic regression equation, the percentage of concordance was used - the proportion is correctly reclassified using the equation of observation: the closer this figure to 100%, the higher the quality of the model.

Taking into account the importance of the percentage of concordation, it can be argued that in 75,61% of cases the logistic regression model consisting of selected variables correctly predicts the development of pneumonia in patients in the study group. The general assessment of the agreement of the real data and the model was carried out using the Hosmer-Lemeshov consensus test (6,188; p=0,626), which, provided p>0,05, indicates the probability of a zero hypothesis for the coincidence of real and estimated data.

In order to assess the correctness of the prediction, the developed model was based on the AUC value, which

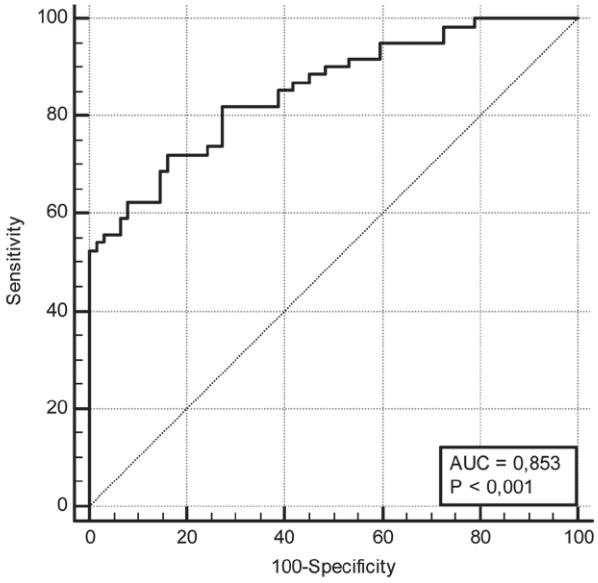

Fig. 1. Operational characteristics of prediction of the occurrence of pneumonia in patients with background of oncohematological pathology of the study group on the basis of logistic regression equation according to ROC analysis

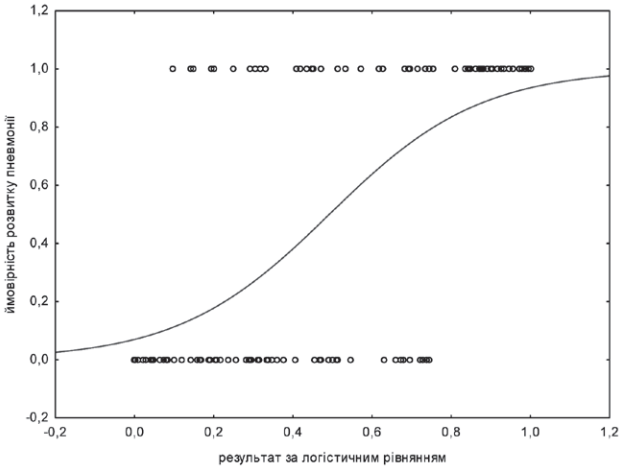

Fig. 2. Dependence of probability of occurrence of pneumonia for patients of the group of research from the result calculated according to the logistic equation

indicates the dependence of the number of correctly classified pneumonia cases to the number of incorrectly classified cases. If the AUC is within the range of 0,9–1, then the quality of the model is considered to be excellent; within the range of 0,8–0,9 – very good; in the range of 0,7–0,8 – good; within the limits of 0,6–0,7 – average; within the limits of 0,5–0,6 – unsatisfactory [14].

Operational characteristics of prediction of the occurrence of pneumonia in patients on the background of oncohematological pathology of the study group based on the logistic regression equation according to the ROC analysis are shown in Table 3 and on Fig. 1.

The proposed prognostic model has high operational characteristics: sensitivity is 72,13%, specificity – 83,87%; AUC is 0,853. These indicators indicate a very good estimate of the predicted pattern of prediction of pneumonia in patients on the background of oncohematological pathology.

The dependence of the probability of the occurrence of pneumonia for patients in the study group from the calculated logistical result of the equation is shown in Fig. 2/

The results of the calculation of the logistic equation of the theoretical values of the probability of development of pneumonia for patients in the study group and their visualization, have allowed to assert that if the calculated value of POP will be less than 0,23, then it is possible to assume that the event will not occur – the patient does not get pneumonia, because he has the place is low probability of an adverse result (P<20,18%). In other cases:

• with POP: 0,23–0,50 – moderate probability of development of pneumonia (20,18% ≤ P<50,08%);

• with POP 0,51–0,92 – high probability of development of pneumonia (50,08% ≤ P<90,45%);

• with POP higher than 0,92 – very high probability of development of pneumonia (P>90,45%).

Recently, the possibilities for diagnostics of IC in patients with background oncohematological pathology have considerably expanded, including due to the introduction of new diagnostic methods, among which prognostication has wide opportunities. A well-known method for predicting the risk group in children with acute lymphoblastic leukemia and Non-B-cell non-Hodgkin's lymphomas received by CT according to the protocol BFM-ALL-90 [19].

In a scientific study, as in the study, for the prediction of the occurrence of IC immunoglobulins were used using prognostic formulas to obtain an answer to which class a patient belongs – «without complications» or «threat of complications». The obtained equation of logistic regression of the prediction of the occurrence of pneumonia also uses modern methods for assessing the immune response of patients with oncohematological pathology. Defined in a sufficient number (495 observations) of the logistic regression equation when used in clinical practice, it will allow, on the basis of a small number of parameters available today in clinics of the hematological profile, to timely predict the development of severe IC – pneumonia and to modify the treatment in advance to reduce the days of hospital stay and improvement quality of life for patients. The expected long-term outcome may be a reduction in mortality.

CONCLUSIONS

1. Based on the statistical analysis of the complex of clinical-laboratory, anamnestic and immunological parameters of 495 patients, predictors of pneumonia in patients with immune disorders were identified on the background of oncohematological pathology. The results of the study prove that the probability of pneumonia in patients with oncohematological pathology is to a large extent conditioned by the state of immune reactivity of patients: Among the quantitative indicators, the greatest influence on the occurrence of pneumonia is due to the parameters of the immune system: CD4/CD8 ≤1,21 (RC 6,54 [95% CI 3,15–13,59]); CD4 ≤24,73 (RC 10,71 [95% CI 3,1–37,02])% CD4 ≤0,96 (RC 4,7 [95% CI 2,35–9,37]) G/L; CD8 > 26,8 (RC 2,71 [95% CI 1,43–5,12])%; B CD19+ ≤0,47 (RC 107,8 [95% CI 23,55–493,39]) G/L; B CD19+ <14,5 (RC 5,8 [95% CI 2,38–14,13]%); T CD19 <42,6 (RC 8,24 [95% CI 4,15–16,38])%; DR + ≤4,3 (RC 3,08 [95% CI 1,34–7,11])%, FA <31 (RC 5,09 [95% CI 2,36–10,96]% and FN <4,1 (RC 3,5 [95% CI 1,57–7,78])%, units.

2. According to the results of the study, the logistic regression equation for the prediction of the occurrence of pneumonia in patients on the background of oncological pathology was obtained:

$$\mathbf{POP = \exp(-2{,}930 + 0{,}495*x_1 - 1{,}892*x_2 + 0{,}198*x_3 + 0{,}080*x_4) / [1 + \exp(-2{,}930 + 0{,}495*x_1 - 1{,}892*x_2 + 0{,}198*x_3 + 0{,}080*x_4)]]}$$

where – POP – prognosis of pneumonia; b_0 = -2,930 – free member of the regression equation; x_1 – the number of leukocytes, 10^9 /l, x_2 – the number of neutrophils, 10^9 /l; x_3 – B CD19, T/L; x_4 – index of phagocytic activity, unit. At a value of POP less than 0,23 – very low probability of development of pneumonia; at 0,23–0,50 – moderate probability of development of pneumonia; at 0,51–0,92 – high probability of development of pneumonia; more than 0,92 – very high probability of development of pneumonia.

3. Based on the statistical analysis of the complex of clinical-laboratory, anamnestic and immunological parameters of 495 patients, the logistic regression equation for prediction of fatal consequences in patients with pneumonia in the background of oncological diseases of the blood has excellent operational characteristics: the sensitivity is 72,13%, the specificity is 83,87%, AUC – 0,853.

4. The obtained logistic regression equation for the prediction of the occurrence of pneumonia when used in clinical practice in patients with immune disorders on the background of cancer pathology will allow predicting the onset of pneumonia based on a small number of parameters available today in oncohematological centers and specialized departments. The probable prognosis regarding the occurrence of pneumonia in patients with immune disorders on the background of oncohematological pathology will allow them to optimize their treatment in advance and reduce the mortality and the number of days of hospitalization in this regard.

Прогноз развития пневмоний у больных с нарушениями иммунитета на фоне онкогематологической патологии

И.С. Борисова

В исследовании на основе статистического анализа комплекса клинико-лабораторных, анамнестических и иммунологических показателей 495 больных с нарушениями иммунитета на фоне онкогематологической патологии определены предикторы развития пневмоний и создана регрессионная логистическая модель прогноза развития пневмоний, куда вошли показатели, которые характеризуют течение онкогематологического заболевания и состояние иммунной системы.

Ключевые слова: *прогноз развития пневмонии, онкогематологическая патология, нарушение иммунитета.*

Прогноз розвитку пневмоній у хворих з порушеннями імунітету на тлі онкогематологічної патології

І.С. Борисова

У дослідженні на підставі статистичного аналізу комплексу клініколабораторних, анамнестичних та імунологічних показників 495 хворих з порушеннями імунітету на тлі онкогематологічної патології визначені предиктори розвитку пневмоній і створена регресійна логістична модель прогнозу розвитку пневмоній, куди увійшли показники, які характеризують перебіг онкогематологічного захворювання і стан імунної системи.

Ключові слова: *прогноз розвитку пневмонії, онкогематологічна патологія, порушення імунітету.*

Сведения об авторе

Борисова Инна Станиславовна – ГУ «Днепропетровская медицинская академия МЗ Украины», 49000, г. Днепр, ул. Вернадского, 9. *E-mail: Doctorinnaborisova1@gmail.com*

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