https://www.modscires.pro/index.php/msr/article/view/be4-218-015
DOI: 10.30889/2523-4692.2018-04-03-015

УДК 616.15-006-037-036.8

MATHEMATICAL MODEL OF PNEUMONIA ASSOCIATED WITH IMMUNITY DISORDERS POOR OUTCOME FORECASTING IN PATIENTS ON THE BACKGROUND OF ONCOGEMATOLOGICAL PATHOLOGY

МАТЕМАТИЧНА МОДЕЛЬ ПРОГНОЗУ ЛЕТАЛЬНОГО РЕЗУЛЬТАТУ ПНЕВМОНІЙ, АСОЦІЙОВАНИХ З ПОРУШЕННЯМИ ІМУНІТЕТУ У ХВОРИХ НА ФОНІ ОНКОГЕМАТОЛОГІЧНОЇ ПАТОЛОГІЇ

Pertseva T.A./Перцева Т.О.
d.m.n., professor /д.м.н., професор
ORCID: 0000-0001-6998-4974
Borisova I.S./Борисова І.С.
c.m.n. /к.м.н.
ORCID: 0000-0003-4703-6046
SE «Dnipropetrovsk Medical Academy of Health Ministry of Ukraine»,
Soborna sq. 4, Dnipro, 49000
ДЗ «Дніпропетровська медична академія МОЗ України»,
пл. Соборна, 14, м. Дніпро, 49000

Summary. *In our study, we investigate the possibilities of mathematical prediction of the poor outcome in patients with pneumonia associated with immune disorders on the background of oncohematological pathology. The study included 655 patients. It was identified predictors of the poor outcome of pneumonia and a mathematical model was created. We propose to use the scale forecast in clinical practice. It's allow to optimize pneumonia treatment timely and reduce the mortality of patients and the number of hospitalization days.*

Key words: *mathematical model of forecast, pneumonia, immune disorder, oncohematological pathology, poor outcome.*

Introduction. The 21st Century medicine is the medical knowledge and standards that emerged in evidence-based medicine. At the heart of it are randomized, so-called "blind" controlled studies. The application of mathematical methods with prediction elements in medical practice is also likely a modern tool of "evidence-based medicine" [1]. The mathematical prognosis represents is a current interest in clinical practice today, because it is determines the main task of modern medicine - preventing diseases and timely optimizing the treatment. According to the dictionaries, the medical forecast is a prediction of "future diagnosis" [2]. There is a prognosis for the possibility of disease developing in medicine; it allows expecting some or other complications of the disease, death - as disease poor outcome or recovery [3]. The disease consequences forecast is based on the detection of pathological symptoms and syndromes in patients, the analysis of the regularities of the functioning of organs and systems. Determining the pneumonia severity using the scale of Fine M.J. et al., 1997 [4] is a well known method. Scoring systems on this scale are available in the Internet [http: // ncemi.org, www.emedhomom.com]. The main purpose of such forecast in medical practice is to plan medical measures, which include determination of treatment place (outpatient, general clinical or specialized

department), and determination of treatment modification time (inclusion of new drugs, manipulations, etc.). The scale for determining treatment place for patients with community acquired pneumonia CURB-65/CRB-65, which estimated 5/4 parameters (presence of 1 point, absence - 0 points) is widespread [5, 6]. The limitation for using these prognostic scales for patients with pneumonia associated with immune disorders is s ignoring, such important parameters for this category of patients, as the number of leukocytes, platelets, neutrophils. Thus, despite the large number of prognostic and diagnostic scales for determining treatment place, diagnosis, assessment of pneumonia severity, this issue is not resolved today, especially for patients with pneumonia on a background of oncohematological. Forecasting is a difficult task. To predict the disease, the doctor examines the patient, fixes the symptoms and syndromes, and based on their combination, causes and sequence of occurrence, clinical features of the disease, using of the other doctors experience (consultations, data literature) comes to the conclusion about the prediction the onset of a pathological process results with some degree of uncertainty. Moreover, the physician should take into account not only the patient's general condition, his age, but also concomitant diseases, heredity, bad habits, living conditions, work activities for each patient. It is difficult to list all the factors which physician should analyze. The physician should choose the most appropriate treatment for the patient and think about the possible consequences after choosing different treatment places. Using the statistical methods in medicine gives physician the only correct solution, because mathematical methods can determine special disease factors – predictors, that affect to disease severity and determine the disease outcome [3].

The urgency of the problem of diagnosis and treatment of pneumonia associated with immune disorders in patients on the background of oncohematological pathology is due to the high frequency of occurrence, lack of clinical manifestations, severe course, frequent complications and rapid development of poor outcome [7, 8].

Aim of the study: to create a mathematical model of pneumonia, associated with immune disorders poor outcome forecasting in patients on the background of oncohematological pathology for timely treatment optimization and determination the treatment place.

Materials and methods. The study included 655 patients with pneumonia associated with immune disorders on the background of oncohematological pathology. A computer database was created based on 132 indicators of the clinical-laboratory, anamnestic and immunological indicators results. The study was conducted in the haematological center "City Multidisciplinary Clinical Hospital №4", Dnipro. The form and stage of oncohematological pathology and pneumonia diagnosis was determined according to the diagnostic standards [9, 10]. Data were analyzed using Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) add-on program AtteStat and software STATISTICA 6.1 (StatSoftInc., Serial № AGAR909E415822FA). To describe the quantitative attributes median (Me) was used; to describe the signs variation - the interquartile scale (25%, 75%). To construct a predictive model, a pairwise and multiple regression analysis was used to calculate Spirman rank correlation coefficients (ρ),

multiple comparisons were made with Bonferroni and Holm corrections [12]. A pairwise and multiple regression analysis, Spirman rank correlation coefficients (ρ) was used to construct a predictive model. Multiple comparisons were made with Bonferroni and Holm corrections [12]. The significance level was taken p <0,05 (5%) [11]. Factor analysis using the principal components method using the varimax of rotation was used to determine the predictors of an adverse outcome [12, 13]. Factor analysis with the principal components component with varimax rotation was used to determine the predictors of poor outcome [12, 13]. The results of our study revealed reliable connections between poor outcome of pneumonia associated with immune disorders on the background of oncohematological pathology and 61 quantitative and nominal indices. Indicators with statistically significant, moderate, and high correlation coefficients were selected to determine the predictors of the poor outcome. Indicators that characterize the patient's condition and cancer: erythrocyte (ρ = -0,61; p <0,001); platelets (ρ = -0.40; p <0.001); leukocyte (ρ = -0,63; p <0,001); HB (ρ = -0.48; p <0.001); the number of CT courses «8 and more» (ρ = 0,33; p <0,001), glycemia (ρ = 0,43; p <0,001), PS (ρ = 0,50; p <0,001). Indicators characterizing the pneumonia course: cough (ρ = 0,30; p <0,001), hemoptysis (ρ = 0,36; p <0,001), ESR (ρ = 0,38; p <0,001), wet rattles (ρ = 0.48; p <0.001); breathing rate (BR) (ρ = 0,32; p <0,001) and the presence of Gp-causative agent (ρ = 0,48; p <0,001). Indicators characterizing the immune reactivity: the number of neutrophils (ρ = -0,34; p <0,001); CD 56,% (ρ = -0.86; p & lt; 0.001); CD56, G / L (ρ = -0.86; p <0.001); CD4 / CD8 (ρ = -0.62; p <0.001); lymphocytes,% (ρ = -0,58; p <0,001); CD4,% (ρ = -0.56; p <0.001); CD4, G / L (ρ = -0.49; p <0.001); T CD19,% (ρ = 0.53; p <0.001); B CD19, T / L (ρ = -0.46; p <0.001); HCT-stimulated test (ρ = -0.45; p <0.001); FA (ρ = -0,41; p <0,001); Ig G (ρ = -0.34; p <0.001); The HCT spontaneous test (ρ = -0.30; p <0.001), neutropenia degree (ρ = 0.37; p <0.001).

Due to the mathematical models with AUC <0.7 do not have sufficient prognostic ability [13, 14], the analysis excluded indicators with smaller and close to this value of the area under the curve. Quantitative characteristics for calculating the odds ratio (OR) were translated into a binary format relative to the threshold forecasting level. Table. 1 show the clinical and laboratory parameters that influence for the survival possibility of patients with pneumonia, associated with immune disorders on the background of oncohematological pathology.

Table. 1

The clinical and laboratory parameters that influence for the survival possibility

Indicators (1 – yes, 0 – no)	OR	95% CI	The proportion of patients, (%)		*p-value**
			Survived n=544	Died n=267	
Cough	4,99	3,14 - 7,93	68,01	91,39	***<0,001***
CT courses ≥8	4,55	3,3 - 6,29	18,57	50,94	***<0,001***

Hemoptysis	28,61	11,3 - 72,41	0,92	20,97	***<0,001***
The presence of P. aeroginosa	5,45	3,91 - 7,6	15,99	50,94	***<0,001***
Gp- pathogens	5,73	4,14 - 7,94	17,83	55,43	***<0,001***
Glycemia	6,92	4,99 - 9,59	26,65	71,54	***<0,001***
Neutropenia 3rd st.	12,45	8,13 - 19,08	6,07	44,57	***<0,001***
Neutrophils $\leq 1,4\times10^9$/л	6,26	4,51 - 8,69	17,65	57,30	***<0,001***
Wet wheezing	28,1	14,72 - 53,65	2,02	36,7	***<0,001***
Pulse>92 per min.	19,15	12,96 - 28,28	8,64	64,42	***<0,001***
Leukocytes $\leq 2,98\times10^9$/л	37,93	15,43 - 93,23	6,57	72,73	***<0,001***
Hb≤ 90 г/л	8,51	6,02 - 12,03	30,7	79,03	***<0,001***
Erythrocytes $\leq 2\times10^{12}$/л	24,58	16,64 - 36,29	9,93	73,03	***<0,001***
Platelets≤ 60×10^9/л	6,5	4,7 - 9	19,67	61,42	***<0,001***
Lymphocytes ≤19,9 %	17,13	9,39 - 31,24	14,35	74,16	***<0,001***
B CD19≤10,3 %	14,86	5,81 - 38,05	29,32	86,05	***<0,001***
T CD19>58,29 %	33,87	12,57 - 91,22	20,99	90,0	***<0,001***
CD4≤21,77 %	93,53	33,0 - 265,09	6,19	86,05	***<0,001***
CD4/CD8≤1,09	112,07	25,72 - 488,25	15,46	95,35	***<0,001***
CD56≤6,7 %	8787,0	170,74 - 452227,29	0	100,0	***<0,001***
Ig G≤8,22 г/л	7,45	3,26 - 17,03	37,65	81,82	***<0,001***
HCT- stimulated test ≤26 %	10,48	4,78 - 22,99	13,87	62,79	***<0,001***

Note. * - Differences between groups according to Pearson's $\chi 2$ criterion

Results of simple logistic regression analysis showed that probability of pneumonia poor outcome depends on the state of the patient's immune response:

CD4≤21.77% (OR 93.53 [95% CI 33.0-265.09]; T CD19> 58.29 % (OR 33.87 [95% CI 12.57-91.22]); CD56≤6.7% (OR 8787.0 [95% CI 170.74-452227.29]); CD4 / CD8≤1 , 09 (OR 112.07 [95% CI 25.72-488.25]); HCT-stimulated test ≤26% (OR 10.48 [95% CI 4.78-22.99]). The pneumonia poor outcome forecasting using the indicators that characterized the pneumonia severity: the number of leukocytes ≥2,98 × 109 / l (OR 37,93 [95% CI 15,43-93,23]), hemoptysis (OR 28,61 [95 % CI 11.3-72.41]), wet wheat (OR 28.1 [95% CI 14.72-53.65]); cough (OR 4.99 [95% CI 3.14-7.93]); Gg- pathogens (OR 5.73 [95% CI 4.14-7.94]); the presence of P. aeroginosa (OR 5.45 [95% CI 3.91-7.6]). pneumonia poor outcome forecasting using the indicators that characterized the oncological disease: hemoglobin ≤90 g / l (OR 8.51 [95% CI 6.02-12.03]); erythrocytes ≤2 × 1012 / l (OR 24.58 [95% CI 16.64-36.29]); platelets <60 × 109 / l (OR 6.6 [95% CI 4.7-9]); lymphocytes ≤19.9% (HS 17.13 [95% CI 9.39-31.24]); the number of CT courses “8 and more” (OR 4.55 [95% CI 3.3-6.29]) glycemia (OR 6.92 [95% CI 4.99-9.59]); neutrophils ≤1.4 × 109 / l (OR 6.62 [95% CI 4.51-8.69]).

The relationship between "died" or "survived" was analyzed using a logistic regression model with a step-by-step predictors inclusion [13, 14]. The logistic equation was taken as the basis for the predictive model development:

$$y=\exp(b_0+b_1*x_1+...+b_n*x_n)/[1+\exp(b_0+b_1*x_1+...+b_n*x_n)] \quad (1),$$

where, y - the result (in our study - the pneumonia poor outcome forecasting (POF); b_0 - free part of the regression equation; b_1 -b_n - regression coefficients; x_1-x_n - predictor variables.

If the calculated probability of pneumonia poor outcome is less than 0.5 - it is possible the event will not occur (the patient will not die); if probability more than 0.5 - the pneumonia poor outcome is likely happen.

Tabl. 2. shows predictors of the pneumonia associated with immune disorders on the background of oncohematological pathology poor outcome identify by logistic regression analysis.

Table 2.

Predictors of the pneumonia associated with immune disorders on the background of oncohematological pathology poor outcome identify by logistic regression analysis

Forecasting variables	Regression coefficient β	Standard error of β coefficient	χ^2 Wald	p-value
Equation free member	-19,714			
Gg- pathogens (x_1)	2,840	2,158	4,643	0,031
Erythrocytes (x_2)	-4,404	1,229	6,887	0,009
CD4/CD8 (x_3)	-4,298	2,945	5,905	0,015
Leukocytes (x_4)	-1,327	0,576	3,856	0,050
Neutropenia 3rd st (x_5)	19,354	4,167	12,108	0,001
Ig G (x_6)	-0,154	0,174	8,661	0,003
Xi-square	χ^2=188,36 (p<0,001)			
Concordance percentage	99,44 %			
Hosmer-Lemesh Test	0,220 (p=0,997)			

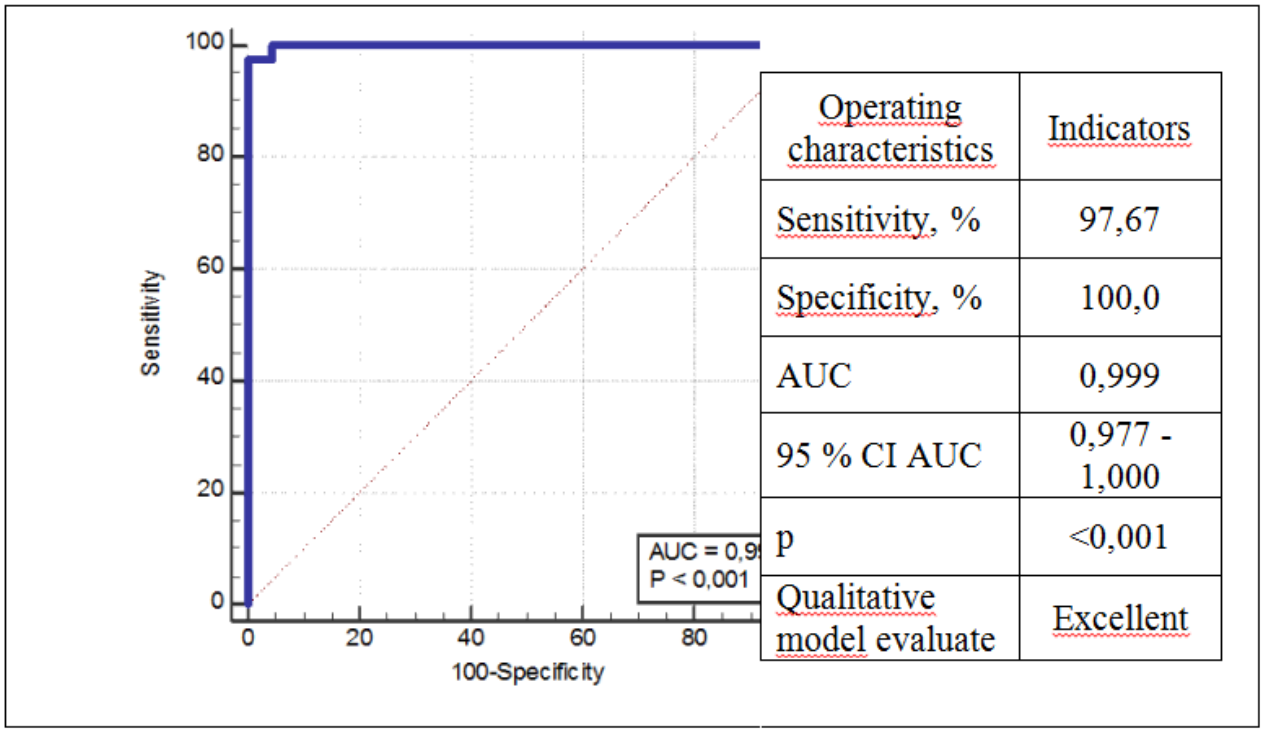
Nominal indicators were entered into the equation in form: 1 - present, 0 - absent. Quantitative indicators - in commonly accepted units.

According the results of our study the mathematical model of the pneumonia associated with immune disorders on the background of oncohematological pathology poor outcome is:

$$POF=\exp(-19,714+2,840*x_1-4,404*x_2-4,298*x_3-1,327*x_4+19,354*x_5-0,154*x_6)/[1+\exp(-19,714+2,840*x_1-4,404*x_2-4,298*x_3-1,327*x_4+19,354*x_5-0,154*x_6)] \quad (2),$$

where, POF - the result that changes from 1 (died) to 0 (alive); b_0 = -19,714 - regression equation free member; x_1 - presence of Gp- pathogens; x_2 - erythrocytes; x_3 - immunoregulatory index (CD4 / CD8); x_4 - leukocytes; x_5 - neutropenia 3 st .; x_6 – IgG.

Thus, if the POF for a particular patient is more than 0.5 - it is possible to make a prediction of high risk of death; if it less than 0.5 - it is possible to consider the prognosis is favorable for the patient.



Operating characteristics	Indicators
Sensitivity, %	97,67
Specificity, %	100,0
AUC	0,999
95 % CI AUC	0,977 - 1,000
p	<0,001
Qualitative model evaluate	Excellent

Fig. 1. Operational characteristics of the mathematical model of the pneumonia associated with immune disorders on the background of oncohematological pathology poor outcome forecasting determined using ROC analysis.

The POF equation estimating the predictive ability by Xi-square ($\chi 2$) showed its adequacy: $\chi 2$ = 188.36 ($p < 0.001$); the proportion of the correct prediction of patient belongs of to one or another group amounted to 99.44; according to the qualitative evaluate - excellent. Thus, the POF mathematical model has excellent operational characteristics: sensitivity - 97,67%, specificity - 100,0%, area under the ROC curve - 0,999 (Fig. 1).

We have developed a predicting scale for risk of pneumonia associated with immune disorders poor outcome. It was determined if the point lower than 0.278 - the risk of death is low. In such cases it is possible to recommend ambulatory pneumonia treatment or treat the pneumonia in therapeutic department. When the point is from 0.278 to 0.500 - the risk of death is high. In such cases it is possible to recommend to treat the pneumonia in a specialized hematological department. When the point is above 0,500 - the risk of death is very high. In such cases it is necessary to treat pneumonia in an intensive care unit and to optimize the treatment. Long-term results can be reduced patients mortality and decrease the number of hospitalization days.

Conclusions. The results of our study showed that probability of pneumonia associated with immune disorders poor outcome in patients on the background of oncohematological pathology most depends on patient's immune reactivity; moreover, a poor outcome depends on indicators that characterized pneumonia severity and indicators that characterized the main oncohematological disease course. We identified independent predictors of pneumonia poor outcome and created mathematical model of pneumonia poor outcome forecasting. Mathematical model has excellent operational characteristics according to the ROC analysis.

1. Predictors of pneumonia associated with immune disorders poor outcome in patients with oncohematological pathology were detected in our study. It are indicators that characterized the pneumonia severity: the number of leukocytes, hemoptysis, wet wheezing, cough, Gp- pathogens (OR 5.73 [95% CI 4.14-7.94]) and P. aeroginosa (OR 5.45 [95% CI 3.91-7.6]; indicators that characterize the patient and oncohematological disease: age (ρ = -0.25, p <0.001), the oncohematological form (ρ = 0,29, p <0,001); the HT courses number (from 8) (ρ = 0.33, p <0.001), anemia (ρ = 0.61, p <0.001); the presence of neutropenia (ρ = 0.46, p <0.001); indicators of immune reactivity: (CD4≤21.77% (OR 93.53 [95% CI 33.0-265.09]; T CD19> 58.29% (OR 33.87 [95% CI 12.57-91, 22]), CD56≤6.7% (OR 8787.0 [95% CI 170.74-452227.29]); II ≤ 1.09 (OR 112.07 [95% CI 25.72-488.25]); HCT-test sp. ≤ 26% (OR 10.48 [95% CI 4.78-22.99]).

2. As a result of our study, we created the mathematical model of pneumonia associated with immune disorders poor outcome forecasting on the background of oncohematological pathology.

$$POF=\exp(-19{,}714+2{,}840*x_1-4{,}404*x_2-4{,}298*x_3-1{,}327*x_4+19{,}354*x_5-0{,}154*x_6)/[1+\exp(-19{,}714+2{,}840*x_1-4{,}404*x_2-4{,}298*x_3-1{,}327*x_4+19{,}354*x_5-0{,}154*x_6)],$$

where, POF – poor outcome forecasting; b_0 = -19,714 - regression equation free member; x_1, x_2, x_3, x_4, x_5, x_6 - poor outcome forecasting predictors.

3. We have developed a predicting scale for risk of pneumonia associated with immune disorders poor outcome. It was determined if the point lower than 0.278 - the death risk is low (should to recommend ambulatory treatment or treating in therapeutic department); 0.278 to 0.500 - the death risk is high (should to recommend to treat pneumonia in a specialized hematological department); point is above 0,500 - the death risk is very high (should to treat pneumonia in an intensive care unit).

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Анотація. *В роботі розглядаються можливості математичного прогнозування у вирішення актуального питання пульмонології та гематології, а саме, прогнозування настання летального результату у хворих на пневмонії, асоційованих з порушеннями імунітету на фоні онкогематологічної патології. В дослідженні на достатній кількості (655 хворих) матеріалу визначені предиктори настання летального результату пневмонії та створена математична модель прогнозу у хворих на пневмонії, асоційованих з порушеннями імунітету на фоні онкогематологічної патології. Використання в клінічній практиці запропонованої шкали прогнозу дозволить своєчасно оптимізувати лікування пневмоній, асоційованих з порушеннями імунітету на фоні онкогематологічної патології та знизити летальність хворих і кількість днів госпіталізації з цього приводу.*

Ключові слова: *математична модель прогнозу, пневмонія, порушення імунітету, онкогематологічна патологія, несприятливий результат*

Аннотация. *В работе рассматриваются возможности математического прогнозирования в решении актуального вопроса пульмонологии и гематологии, а именно, прогнозирование наступления летального исхода у больных пневмониями, ассоциированых с нарушениями иммунитета на фоне онкогематологической патологии. В исследовании на достаточном количестве материала (655 больных) определены предиктори наступления летального исхода пневмонии и создана математическая модель прогноза у больных с пневмониями, ассоциированых с нарушениями иммунитета на фоне онкогематологической патологии. Использование в клинической практике предложенной шкалы прогноза позволит своевременно оптимизировать лечение пневмоний, ассоциированых с нарушениями иммунитета на фоне онкогематологической патологии и снизить летальность больных и количество дней госпитализации по этому поводу.*

Ключевые слова*: математическая модель прогноза, пневмония, нарушения иммунитета, онкогематологическая патология, летальный сход*

The authors confirm the absence of hidden conflicts of interest.
Authors are grateful for the help in statistical calculations professor Kryachkova L.V.
The article is prepared as part of the planned research work of the Department of Internal Medicine No. 1 SE "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine" - "Definition of the features of the clinic, diagnosis, treatment and medical rehabilitation of patients with broncho-pulmonary system diseases" (2014-2018). The state registration number is 0114U005305, the code IN.27.14.
Article Send: 05/10/2018