ORIGINAL ARTICLE

A MATHEMATICAL MODEL FOR PREDICTING THE OUTCOME OF TREATMENT OF MULTIDRUD-RESISTANT TUBERCULOSIS

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ABSTRACT

The aim: Predicting the effectiveness of treatment for MRI of the lungs by developing a mathematical model to predict treatment outcomes.

Materials and methods: 84 patients with MRI of the lungs: group 1 (n = 56) – with signs of effective TB treatment at the end of the intensive phase; group 2 (n = 28) – patients with signs of ineffective treatment. We used the multivariate discriminant analysis method using the statistical environment STATISTICA 13.

Results: During the discriminant analysis, the parameters of the clinical blood analysis (monocytes, stab leukocytes, erythrocytes) were selected, which were associated with high (r> 0.5) statistically significant correlations with the levels of MMP-9, TIMP-1, oxyproline and its fractions and aldosterone in the formation of the prognosis. The mathematical model allows, in the form of comparing the results of solving two linear equations and comparing their results, to predict the outcome of treatment: "1" effective treatment, "2" – ineffective treatment. Early prediction of treatment effectiveness is promising, as it allows the use of the developed mathematical model as an additional criterion for the selection of patients for whom surgical treatment is recommended, in order to increase the effectiveness of treatment.

Conclusions: An additional criterion for predicting ineffective MRI treatment, along with the criteria provided for by WHO recommendations, is a mathematical model that takes into account probably strong correlation (r = 0.5, p <0.05) between the factors of connective tissue destruction, collagen destruction, aldosterone , and indicators of a clinical blood test (between levels of OBZ and monocytes (r = 0.82, p = 0.00001), OB and monocytes (r = 0.92, p = 0.000001) OB and stab leukocytes (r = – 0.87, p = 0.0003) OBZ and stab leukocytes (r = – 0.53, p = 0.017), aldosterone and ESR.

KEY WORDS: discriminant analysis, effective treatment, predict treatment outcomes

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INTRODUCTION

Improvement of multidrug-resistant tuberculosis (MDR-TB) treatment effectiveness is very important task of healthcare all over the world [1, 2]. With the growing number of patients with resistant forms of tuberculosis, this task becomes central to the anti-tuberculosis activities in many countries. According to the WHO requirements, the treatment effectiveness in patients with MDR-TB should be at least 75%. However, only several countries were able to achieve this goal [3]. In Ukraine, the treatment effectiveness in such patients was 54.1% in 2019 [1, 4]. This indicator is different in different regions of Ukraine, but in no one of them the target indicator [1, 2] was reached. It is known that the use of surgical methods of treatment in such patients increases the effectiveness of therapy [5, 6]. In our research [5], we revealed 77.7% treatment effectiveness after resection surgery in patients with pulmonary MDR-TB with destructions and bacterial excretion. Unfortunately, we examined a small number of patients (12 patients). However, it allowed us to detect a positive trend in increasing the treatment effectiveness in such patients.

The possibilities of conservative treatment in patients with MDR-TB are limited due to the long-term use of many anti-tuberculosis drugs, which often have to be changed due to side effects or the development of drug resistance during treatment [4]. The pharmaceutical industry has recently provided an opportunity to use new anti-TB drugs for these patients, such as linezolid, bedaquiline, delamanide [7]. However, anti-TB drugs recommended by previous protocols of treatment (kanamycin, ofloxacin etc.) are often ineffective against the MDR-TB pathogen [8]. Unfortunately, this resistance is often found in individuals with new cases of the disease as primary resistance [2].

One of the reasons for this phenomenon is low treatment effectiveness in patients with MDR-TB and the accumulation of the MDR-TB pathogen in the population. According to WHO recommendations, the main criterion for the treatment effectiveness of patients with TB is the cessation of bacterial excretion [4, 9]. In this case, the patient ceases to pose an epidemiological risk to others, because he is no longer a source of infection. However, in tuberculosis, pulmonary tissue is most often destroyed, and cavities of destruction are formed. On the inner surface of the cavities, fibrotic changes gradually begin to occur with the formation of fibrosis or the formation of cavities. With significant fibrotic changes or cavities, the risk of TB recurrence is

significantly increased. In addition, the preservation of the cavities contributes to a long-term bacterial excretion and to a worse prognosis [10].

MTB induce proliferation and migration of macrophages to the area of specific inflammation. Macrophages are involved in the processes of cellular immunity in TB [9]. Macrophages are one of the producer cells of matrix metalloproteinases (MMP). These compounds destroy the collagen fibers in the pulmonary tissue [11]. Their activity is regulated by the activity of specific inhibitors – tissue inhibitors of metalloproteinases (TIMP) [12, 13].

In the absence of pathology, the ratio of MMP/TIMP should be close to 1. However, MMP prevails in TB cases. Such processes indicate the activity of pulmonary tissue destruction in patients with pulmonary TB [14]. Markers of the activity of such processes are collagen desintegration products: hydroxyproline and its fractions – free hydroxyproline (FH) and protein-bound hydroxyproline (PBHP) [14, 15]. Hydroxyproline is a basic amino acid in collagen. In the destruction of pulmonary tissue, the level of collagen destruction products in serum increases. The marker of connective tissue destruction is FH. PBHP is a marker of connective tissue repair. The alteration of connective tissue with the formation of abnormal collagen is affected by a higher level of aldosterone. It is known that aldosterone (A) contributes to the induction of pathological collagen with the subsequent formation of fibrosis. In our study, we found reliable relationships between these indicators and confirmed the importance of generating minimal residual changes with effective treatment [16].

However, the implementation of such biochemical studies causes difficulties due to the need for additional equipment for carrying out ELISA and complex methods of biochemical research. Providing such studies at the expense of the patient is prohibited by law, since patients with MDR-TB receive all services provided by the protocols for providing medical care for free [17, 18].

In this context, the question of developing a method for predicting the treatment outcome and the healing of destruction cavities based on a study of indicators of routine research methods arises. Complete blood count is the most common and widely available test. Prediction of the treatment outcome according to the calculation of various hemolytic indices of intoxication has been known for almost a hundred years [8, 19]. Therefore, the study of relationships between level of fibrosis factors of pulmonary tissue and the development of a model for predicting the treatment outcome for MDR-TB using complete blood count are relevant [20].

The question of predicting the effects of treatment on a two-point scale (1effective treatment, 2-ineffective treatment) in a sample of patients treated with standard therapy regimens for MDR-TB is relevant.

THE AIM

Predicting the effectiveness of treatment of multidrug-resistant pulmonary tuberculosis by developing a mathematical model for predicting the outcome of treatment.

MATERIALS AND METHODS

84 patients with pulmonary MDR-TB with destruction and bacterial excretion who were treated in TB facilities of Kharkiv region in 2014-2016 were included in the study. Additionally, the patients were divided into 2 groups: Group 1 included 56 patients with cessation of bacterial excretion and cavities healing in the end of intensive phase (IP) of treatment; Group 2 – 28 patients with signs of unfavorable course of the disease (the presence of bacterial excretion and the preservation of the cavities).

All patients in the hospital were thoroughly examined, which included anamnestic, clinical, radiological, laboratory and instrumental methods of investigation.

56.5% of patients were men and 40.5% were women. The criteria for inclusion to the study were: new cases of MDR-TB with destruction and bacterial excretion (according to sputum smear and / or culture on liquid and solid media), age 18-55 years. Exclusion criteria were: severe comorbidities (HIV infection, diabetes mellitus, hepatitis C / B, cardiovascular pathology). When admitted to hospital, patients most often had manifestations of broncho-pulmonary and astheno-vegetative syndromes. A significant number of patients complained of coughing (75%), shortness of breath on exertion (16.7%), general weakness (40.5%), fever (35.7%), weight loss (20.2%).

During an objective examination at admission to the hospital, the majority of patients had a satisfactory general state (79.8%), 10.7% of patients had general state of moderate severity and 9.5% of patients had severe general state.

Infiltrative tuberculosis prevailed among clinical forms (95.2%). Disseminated tuberculosis was found in 4.8% of patients.

Unilateral process was observed in 40.5% of patients, bilateral – 59.5%. The destruction of pulmonary tissue was observed in 100% of cases.

100% of patients with MDR-TB had bacterial excretion. Bacterial excretion was confirmed by sputum smear and / or culture on liquid and solid media. Resistance of the pathogen to anti-tuberculosis drugs was as follows: HR – 4.8%, HRS – 28.6%, HRSE – 66.7%.

Changes in complete blood count (leukocytosis, changes in leukocyte formula and increased ESR), that is, the presence of intoxication syndrome, was observed in 81% of patients. Anemia was observed in 25% of patients.

Patients received anti-tuberculosis therapy according to the order of the Ministry of Health of Ukraine No. 620 dated September 14, 2014, according to the scheme 8 Z Cm Lfx Pt (Et) Cs (± PAS) / 12 Z Lfx Pt (Et) Cs (± PAS), where Lfx – levofloxacin, Cs – cycloserine, Cm – capreomycin, Et – ethionamide, Pt – prothionamide, PAS – paraaminosalicylic acid, Z – pyrazinamide.

All the patients had anamnestic, physical, clinical, biochemical, microbiological and instrumental examination as well as measurement of the levels of tissue factors of fibrosis, in particular, total hydroxyproline, free hydroxyproline, protein-bound hydroxyproline, MMP-9, TIMP-1, and aldosterone at the treatment onset and after 2 and 3 months. Venous blood was collected

Table I. The final table of the results of discriminant analysis performed in STATISTICA 13

N=24	Discriminant Function Analysis Summary (tab_finalx4(for calculating materials and methods).stat) No. of vars in model: 3; Grouping: Treatment results1_2 (2 grps) Wilks' Lambda: ,28843 approx. F (3,20)=16,447 p< ,0000 Include condition: v6=3 & v9=1					
	Wilks' Lambda	Partial Lambda	F-remove (1,20)	p-level	Toler.	1-Toler. (R-Sqr.)
erythr.1	0,897959	0,321211	42,26437	0,000002	0,503517	0,496483
stab 1	0,363142	0,794274	5,18023	0,033993	0,568592	0,431408
mon.1	0,562500	0,512772	19,00367	0,000304	0,400215	0,599785

*The information part of the table states that the results are statistically significant ($p < 0.01$) with satisfactory discrimination, as shown by the statistics of Wilks lambda (λ). The value of this statistic belongs to the interval [0, 1]. The closer its value approaches zero, the better is discrimination.

Table II. The classification table of the protocol of discriminant analysis performed in STATISTICA 13

Group	Classification Matrix (tab_finalx4 (for calculation materials and methods) Rows: Observed classifications Columns: Predicted classifications Include condition: v6=3 & v9=1		
	PercentCorrect	G_1:1 p=,66667	G_2:2 p=,33333
G_1:1	100,0000	16	0
G_2:2	100,0000	0	8
Total	100,0000	16	8

Classification Matrix (tab_finalx4 (for calculation materials and methods) Rows: Observed classifications

Table III. Matrix of the factorial structure of the discriminant analysis protocol performed in STATISTICA 13

Variable	Factor Structure Matrix (tab_finalx4(for calculation of materials and methods). Correlations Variables – Canonical Roots (Pooled-within-groups correlations) Include condition: v6=3 & v9=1
	Root 1
erythr. 1	0,561492
stab 1	0,070741
mon.1	-0,212224

Factor Structure Matrix (tab_finalx4(for calculation of materials and methods). Correlations Variables – Canonical Roots (Pooled-within-groups correlations) Include condition: v6=3 & v9=1

according to protocols, in a volume of 10 ml from the peripheral vein at the beginning of treatment, 2 and 3 months after the start of treatment at the same time, in the morning on an empty stomach was investigated. Blood was distributed to obtain plasma (with the addition of EDTA) and serum. The blood was centrifuged and plasma and serum were obtained. Plasma and serum were frozen at -20° C.

Complete blood count was performed by a microscopic method of counting blood cells in stained smears and counting the number of blood cells in counting chamber of Goryaev.

The study of sputum for MTB was performed by microscopy of sputum smear and culture on solid and liquid media with the determination of the susceptibility of the pathogen to anti-TB drugs of the first and second lines. Microscopic examination of sputum smear was performed using an optical microscope with staining by Ziehl-Nielsen. Sputum culture for isolating resistant MTB strains was carried out on a liquid medium (Middlebrook 7H9 broth) in the automated BACTEC MGIT 960 system. Culture test on Lowenstein-Jensen solid medium was carried out according to the order of the Ministry of Health of Ukraine No. 45 dated February 06, 2002.

The levels of total, free and protein-bound hydroxyproline were determined by the method of P.N. Sharaev, mg/L, with oxidative polycondensation reaction with the subsequent quantitative determination of substances using KPK-2 Photo electro colorimeter (Ukraine) [2].

At the beginning of treatment, the median total hydroxiproline was 3.15 mg/L, FH – 0.97 mg/L, PBH – 2.25 mg/L.

The aldosterone level was investigated by ELISA using standard test systems Direct ELISA Kit. The Ei Asy TM Way ALDOSTERON, Diagnostics Biochem Canada Inc. on the analyzer "Labline-90" (Austria) according to the instructions. Aldosterone level was measured in picograms in 1 mL serum (pg/ml). At the beginning of treatment, the median aldosterone level was 91.1 pg/ml.

Table IV. The classification functions of the discriminant analysis protocol performed in STATISTICA 13

Variable	Classification Functions; grouping: Treatment results1_2 (tab_finalx4.sta) Include condition: v6=3 & v9=1	
	G_1:1 p=,66667	G_2:2 p=,33333
erythr.1	45,8629	34,6274
stab1	-2,9262	-1,8995
mon.1	-6,2132	-3,9533
Constant	-84,5166	-51,8905

The table contains two linear equations in formalized form: the first one is responsible for the consequence of the treatment "1" – effective treatment; the second one is responsible for the consequence of the treatment "2" – ineffective treatment.

Table V. Classification coefficients and constants for calculating the prediction of effective and ineffective treatment of pulmonary MDR-TB

	k_1	k_2	k_3	C
X	45,863	-2,926	-6,213	-84,517
Y	34,63	-1,9	-3,953	-51,89

For erythrocytes index, it is assumed to use the normalized record α*1012, where α (mantissa) is a number belonging to the interval [0; 1]. The input parameter for the expert system is precisely the value of the mantissa of the indicator.

The level of MMP-9 was investigated by ELISA using the test system Human MMP-9 Platinum ELISA, affymetrixe Biocsience, Austria, in a Labline-90 analyzer (Austria) according to the instruction. MMP-9 level was measured in nanograms per 1 ml of serum (ng/ml). At the beginning of treatment, the median level of MMP-9 in the study group was 361.5 ng/ml.

The level of TIMP-1 was investigated by ELISA using the Human TIMP-1 Platinum ELISA test system, affymetrixe Biocsience, Austria, on a Labline-90 analyzer (Austria) according to the instructions. The level of TIMP – 1 was measured in nanograms per 1 mL of serum (ng/ml). At the beginning of treatment, the median level of TIMP-1 was 128.2 ng/ml.

RESULTS

A search for therapeutic and informative factors was performed on a variety of complete blood count indicators that were associated with high (r>0.5) statistically significant correlations with indicators of tissue factors of fibrosis and aldosterone. These were the correlations between the levels of PBHP and monocytes (r = 0.82, p <0.01), FH and monocytes (r = 0.92, p <0.01); FH and stab leukocytes (r = – 0.87, p <0.01); PBHP and stab leukocytes (r = – 0.53, p = 0.017), A and ESR (r = – 0.54, p <0.01).

Use of discriminant analysis on a variety of indicators that were selected on the basis of correlations allowed to reduce the data and select data with the greatest value in the formation of the forecast, namely: the level of red blood cells (in absolute values), stab leukocytes (%), monocytes (%) (Table I).

The first column of the table contains the Wilks lambda value for each variation, which should be interpreted opposite to the previous, total Wilks lambda – bigger λ means the more desirable presence of the indicator in the discrimination procedure. As you can see, taking into account this feature, the levels of erythrocytes and monocytes have the greatest influence on the prognosis. The same confirms the value of "F-remove" and "p-level". The greater the value of "F-remove" and the smaller value of "p-level", the more significant is the influence of the indicator on the formation of the forecast.

The classification matrix shown in Table II indicates the quality of the classification and contains information on the number and percentage of correctly classified observations in each group when using the obtained model in the opposite direction.

As you can see, the proposed model works with 100% sensitivity and specificity.

The factor structure of canonical variables (integral indicators) consisting of selected parameters is shown in Table III.

The factor structure of a new variation (root) characterizes the contribution of each of the primary indicators to the formation of the root and indicates the informational significance of each of the indicators.

The final link in the creation of a classification model is the construction of the classification rules themselves (Table IV).

After initialization of both expressions (substitution of the values of the level of erythrocytes, stab leukocytes and monocytes of the patient), we obtain two values (X, Y): the first is responsible investigative "effective treatment", the second – investigative "ineffective treatment".

$X=E\times k_{1x}+S\times k_{2x}+M\times k_{3x}+C_x$

$Y= E\times k_{1y}+S\times k_{2y}+M\times k_{3y}+C_y$,

E – erythrocytes level (abs×10^{12}); S – stab leukocytes level (%); M – monocytes level (%); C – classification coefficients (Table V), $k_{i,X}$, $k_{i,Y}$ (i=1, 2) – constants* (Table V).

If X>Y, the prognosis of treatment effectiveness is favorable;

If Y>X, the prognosis of treatment effectiveness is unfavorable.

The calculation of the prognosis of a possible course of MDR-TB is not difficult and can be used in practical medicine.

DISCUSSION

Recently, studies developing mathematical models allowing to solve a specific medical problems are frequently performed. J.P. Aparicio developed a mathematical model of the tuberculosis epidemic. It takes into account various demographic and social factors that could cause a reduction in the incidence of tuberculosis in a historical context. One more research models the spread of tuberculosis in a population taking into account the genetic algorithm and multilayer percepton for a non-linear model of the tuberculosis epidemic. Study of Nkamba L.N. takes into account parameters such as early vaccination and contact tracing to build a model for overcoming the tuberculosis epidemic. It indicates that vaccination at young age only is insufficiet, since the peak incidence in children occurs at the age of 15, when post-vaccination immunity has already decreased. However, these models take into account global social phenomena, but they are not fixed on the treatment effectiveness of an individual patient.

In a study by the European Center for Disease Prevention and Control, a model for predicting the activation of the tuberculosis process in people with latent tuberculosis infection was developed. According to this model, WHO's programs for overcoming the tuberculosis epidemic are too optimistic. The model made it possible to make a long-term forecast of the dynamics of a decrease in the incidence of tuberculosis, taking into account age and social factors and the coverage of screening studies for latent tuberculosis infection in the population. The authors mathematically proved that screening for latent tuberculosis infection is not enough to overcome the epidemic, and effective treatment is the main element in breaking the chain of infection. Our mathematical model allows us to predict possible ineffective treatment at the beginning of tuberculosis treatment and immediately correct treatment methods, which will prevent cases of ineffective treatment.

Doan T.N. included the studied pathophysiological mechanisms of the response of the host organism to tuberculosis infection. The immune response profile was evaluated by the levels of immunocompetent cells, cytokines and macrophage activity. Mathematical model was proposed basing on the data obtained. This model allowed to make the forecast of the terms of possible treatment, which is undeniably important for predicting the course of the disease in each individual patient. However, such a detailed study of the patient's immune profile is not provided by the current protocols for the tuberculosis patients care in Ukraine. It is also impossible to provide such a study at the patient's expense, due to the long-term disability of the patient and the significant financial burden for the patient. Therefore, an important task is the development of methods for predicting the course of tuberculosis, which will be economically feasible in countries with a high burden of tuberculosis.

The development of additional criteria for the selection of patients with MRTD, which may be recommended for surgical treatment, is timely and relevant, since the use of these treatment methods is recommended by WHO as the most effective.

The study found that indicators of the processes of destruction and healing of lung tissue, such as MMP-9, TIMP-1, OS, OBS and aldosterone, have strong ($r > 0.5$, $p \leq 0.05$) reliable correlations with clinical blood tests – monocytes, stab neutrophils and red blood cells. Based on them, the discriminant analysis made it possible to develop a model for predicting the outcome of tuberculosis treatment.

In the literature there is data on the development of mathematical models for predicting the results of treatment [12, 14]. Such models allow predicting the possible outcome of therapy at the early stages of treatment and making changes to the treatment with the use of prognostically reasonable most effective TB treatment methods.

Our model allows us to calculate the prognosis of treatment effectiveness based on the use of blood test parameters which is included in the diagnostic minimum in any medical institution. The use of this model is pathogenetically substantiated, since it has strong reliable correlations with the levels of pulmobnary tissue destruction parameters. The practical use of the model is quick and easy, since the simplest mathematical operations are used, and comparison of two indicators only is needed to obtain a forecast. The only difficulty may be associated with the table of calculated coefficients, which may not always be at hand in analog form. However, today the Internet is available almost everywhere and the proposed coefficients can be reviewed at any time in the patent database of Ukraine.

CONCLUSIONS

An additional criterion for predicting ineffective MRI treatment, along with the criteria provided for by WHO recommendations, is a mathematical model that takes into account probably strong correlation ($r = 0.5$, $p < 0.05$) between the factors of connective tissue destruction, collagen destruction, aldosterone , and indicators of a clinical blood test (between levels of OBZ and monocytes ($r = 0.82$, $p = 0.00001$), OB and monocytes ($r = 0.92$, $p = 0.000001$) OB and stab leukocytes ($r = -0.87$, $p = 0.0003$) OBZ and stab leukocytes ($r = -0.53$, $p = 0.017$), aldosterone and ESR ($r = -0.54$, $p = 0.006$)). The developed mathematical model makes it possible to evaluate the results of treatment of patients with multidrug-resistant tuberculosis in the early stages of treatment, based on the values of erythrocyte indicators, stab leukocytes and monocytes, to reveal its inefficiency and recommend such patients to use combined treatment with surgical interventions to increase the treatment effectiveness in these patients.

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