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PROGRAM APPLICATION FOR THE DETERMINATION OF THE STATE OF THE PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS IN THE REMOTE PERIOD

The research considers the process of the elaboration of the program application for the assessment of the remote state of the patients, who in their childhood were made a diagnosis of the juvenile rheumatoid arthritis. The complexity of the given task is that the patients were initially evaluated at an early age, then they got the corresponding treatment, which must be prescribed individually for each patient, as a result of the treatment the symptoms of the disease must disappear or be minimal. For the assessment of the degree of the disease indices JADI-A (joint arthritis damage index-articular) and JADI-E (joint arthritis damage index-extra-articular) are used. Data of 289 patients are used in the research.

Methods of linear programming are proposed to be used for the construction of the system of regression equations which allow to predict the numerical characteristics of the patient`s state in the adult period, taking into account the performed treatment. The structure of the models system consists of the models, which evaluated the state JADI-A and JADI-E in the remote period and the additional control parameters. These are indices that must be limited in a certain way. The presented models can also be used for the selection of the patient-specific treatment strategy, which, taking into account the initial state of the patient will allow to minimize the number of the articular and extra-articular damages. These models were tested for accuracy by means of the determination coefficient, all of them showed accuracy greater than 0.9 on the test data, this proves their high quality. All the models were used as the basis of the program application, which can be used for the storage of the patients` data at all the stages of the examination and for the assessment of the patients` state. This program product has been developed on the programming language R, using the framework Shiny. Using the application doctors will be able to observe the patient, store the results of the control and perform the assessment of the patient`s state.

Key words: *juvenile rheumatoid arthritis, prediction model, regression analysis, methods of the operations study.*

Introduction

The juvenile rheumatoid arthritis (JRA) is widely spread infant rheumatologic disease. Frequency of JRA cases in different regions of the world is from 0.05 to 0.8 %, morbidity rate is from 2 to 16 – 20 cases a year per 100 000 of the child population, death rate – 0,5 – 1 % [1]. In Ukraine the incidence of JRA is 0.2 – 0.4 per 1000 of child population. Incidence rate of JRA differ in various regions of Ukraine. Disease is mainly registered in Chernigiv Region (0.48), city of Kyiv (0.42), Dnipropetrovsk Region (0.34) [3]. The diagnosis in part of the patients is established during the first visit to the doctor, after a year of monitoring possible diagnostic errors also contain fourth cases of the disease, that determines the complexity of the clinical diagnostics of this pathology in children. In half of the patients the disability develops after 3 – 5 years of the disease [1].

Patients with JRA require constant supporting therapy. As the disease starts in childhood, main problem is the selection of such treatment strategy that takes into consideration the state of the patient in his childhood and enables to decrease the manifestation of the disease in the adult age. One of the possible variants of the solution of the problem is the development of the optimization models which will allow to assess the possible state of the patient in the adult age at the stage of the treatment selection. Similar problem is reduced to the search of the minimum of certain mathematical equation, when some variables we can change within certain limits.

Objective: To develop program application that enables to assess the possible state of the patient, taking into account the treatment, carried out.

Materials of the research. Database of JRA patients was used as the material for the research. Total amount of patients in the database was 289 persons, namely, 148 females and 141 males. Age of the patients was within the limits 16 – 57 years, average age – 26.1. All the patients were subject to general clinic studies in order to assess the type of the arthritis and detect the symptoms. Database contained characteristics of the patients in the early period, characteristics of the treatment and state of the patients in the remote adult period.

Problem set up. Clinical data, used in the study, were divided into the groups by their content. They can be represented as the block matrix of the object-property [2]:

$$X = \left| P \middle| S^{in} \middle| Q^{in} \middle| S^{out} \middle| Q^{out} \middle| U \right.$$

where p_i, $i=1,...,g$: are variables describing the initial parameters of the patient (age, gender, weight, blood analysis, clinical symptoms of the disease). These variables are important when the treatment strategy is prescribed but they will not be modeled as state variables after treatment; q^{in}, q^{out} : main characteristic of the disease that can be considered as principle criterion of treatment (minimization of clinic manifestations). As such criterion in the given study the JADI-A[3] (assessment of articular damage) and extraarticular damage (JADI-E) index after treatment was chosen; s_i^{in}, s_i^{out} $i=1,...,d$: are variables of the patients state, values of which must be taken into account when the state of the patient is assessed after the treatment. Database contains the values of the patients state before s_i^{in}, $i=1,...,d$ and after the treatment s_i^{out}, $i=1,...,d;$ u_i $i=1,...,h$: are variables, characterizing the applied treatment (doses and duration of the drug administration) [4].

For the convenience, the data, described above, can be presented by the block matrix of the object-property X:

$$X = \left| P \middle| S^{in} \middle| Q^{in} \middle| S^{out} \middle| Q^{out} \middle| U \right.$$

where $\mathbf{P} = \begin{vmatrix} p_{11} & \cdots & p_{1\text{g}} \\ \cdots & \cdots & \cdots \\ p_{n1} & \cdots & p_{ng} \end{vmatrix}$ – is the matrix of the patients parameters, where each row contains the value g of the parameters, according to the number of the patients row, n – is the amount of the patients in the sample;

$\mathbf{S}^{\text{in}} = \begin{vmatrix} s_{11}^{\text{in}} & \cdots & s_{1d}^{\text{in}} \\ \cdots & \cdots & \cdots \\ s_{n1}^{\text{in}} & \cdots & s_{nd}^{\text{in}} \end{vmatrix}$, $\mathbf{S}^{\text{out}} = \begin{vmatrix} s_{11}^{\text{out}} & \cdots & s_{1d}^{\text{out}} \\ \cdots & \cdots & \cdots \\ s_{n1}^{\text{out}} & \cdots & s_{1d}^{\text{out}} \end{vmatrix}$, d – is the amount of the patients state variables;

$\mathbf{Q}^{\text{in}} = (q_1^{\text{in}}, q_2^{\text{in}}, ..., q_n^{\text{in}})^T$, $\mathbf{Q}^{\text{out}} = (q_1^{\text{out}}, q_2^{\text{out}}, ..., q_n^{\text{out}})^T$ – are vectors of the criterion values before and after the treatment;

$\mathbf{U} = \begin{vmatrix} u_{11} & \cdots & u_{1\text{h}} \\ \cdots & \cdots & \cdots \\ u_{n1} & \cdots & u_{nh} \end{vmatrix}$, h – is the number of variables, having therapeutic action.

Matrix **X** presents the data of the transition of the object *i*, being in the state s_{ij}^{in} , q_i^{in} $j=1,...,d$ in the state s_{ij}^{out} , q_i^{out} $j=1,...,d$ by means of the applied values of the treatment impacts u_{ij} , $j=1,...,h$. The same for each patient $i=1,...,n$ [5].

At the first stage of the study, from the total set of the parameters, characterizing the patients, the set of the characteristics of the patients who had statistically valid correlation with JADI-A and JADI-E indices, was selected. Besides, the indices, having mutual correlation were rejected. Complete list of the parameters in presented in Table 1.

Table 1

Patients parameters

Parameter	Designation
1	2
P_1(X1)	Age at the moment of the examination
P_2 (X2)	Gender f-1, m-2
P_3 (X3)	Age of the patient at the moment of the disease start, yr
P_4 (X4)	Morning stiffness in childhood, min
P_5 (X5)	Erythrocytes sedimentation rate onset, min
P_6 (X6)	Blood glucose in childhood before treatment
s_1^{in} (X7)	Erythrocytes sedimentation rate in childhood before treatment
s_2^{in} (X8)	C-reactive protein (CRP) in childhood before treatment
s_3^{in} (X9)	Pain severity according to visually analogue scale in childhood before treatment
U_1	Course duration of gluco-corticoids administration
U_2	Gluco-corticoids, cumulated dose
U_3	Methotrexat, dose
s_1^{out} (X10)	Erythrocyte sedimentation rate (ESR) in adult age after treatment
s_2^{out} (X11)	C-reactive protein (CRP) in adult age after treatment
s_3^{out} (X12)	Pain severity according to visual analogue scale in adult age after treatment
P_8 (X14)	Occurrence of the symmetric arthritic in childhood
P_9 (X15)	Pain in cervical section in childhood
P_{10} (X16)	Occurrence of dactylitis in childhood
P_{11} (X17)	Occurrence of lymphadenopathy, splenomegaly in childhood
P_{12} (X18)	Pain in the ridge in childhood
P_{13} (X19)	Occurrence of the uveitis in childhood
q_1^{out}	Arthritis Damage Index (ADI)
q_2^{out}	Extraarticular Damage Index (ADI-E)

Solution of the set problem. The set problem was solved by means of programming language R and development environment R Studio. Regression models for the criterion q_1^{out} and q_2^{out}, and limitations s_1^{out}, s_2^{out}, s_3^{out} were composed in the execution of the optimization problem solution. For this purpose the set matrix was expanded by means of adding to variables of x type variables of the types: x^2, $\frac{1}{x}$, $x_i * x_j$, $\frac{1}{x^2}$, $\frac{1}{x_i * x_j}$, and also the products of these variables on the control criteria U1, U2 and U3.

Result of JADI A modeling is given below:

$$\begin{aligned} q_1^{out} = {} & 0{,}012 * X7 * X8 - 0{,}000001241 * \ U2 * X7 * X8 - 0{,}00003347 * U3 * X4 * X9 \\ & + 0{,}006 * U3 * X9X5 + 0{,}715 * X17 + 0{,}001 * U3 * X7X1 - 0{,}185 * X8X3 \\ & + 0{,}006 \ * U2X62 - 3{,}924 * U3X4 * X9 + \ 0{,}683 * X19 - 0{,}528 * X2 \\ & + 504{,}709 * 1X7 * X8 - 0{,}028 * U1 * X4X7 + 0{,}674 * X4X7 - \mathbf{7{,}210} \end{aligned} \quad (1)$$

Determination coefficient for the model q_1^{out} is 0.963, this proves high accuracy of the results.

Diagram of residuals – it is a graph that shows the residuals on the vertical axis and an independent variable on the horizontal axis. If the dots on the residual graph are randomly distributed around the horizontal axis then the model of the linear regression sufficiently describes the data from the table, in other case non-linear model is more acceptable [6]. In our case this graph can be used for the assessment of the fact if the input data matrix was sufficiently expanded.

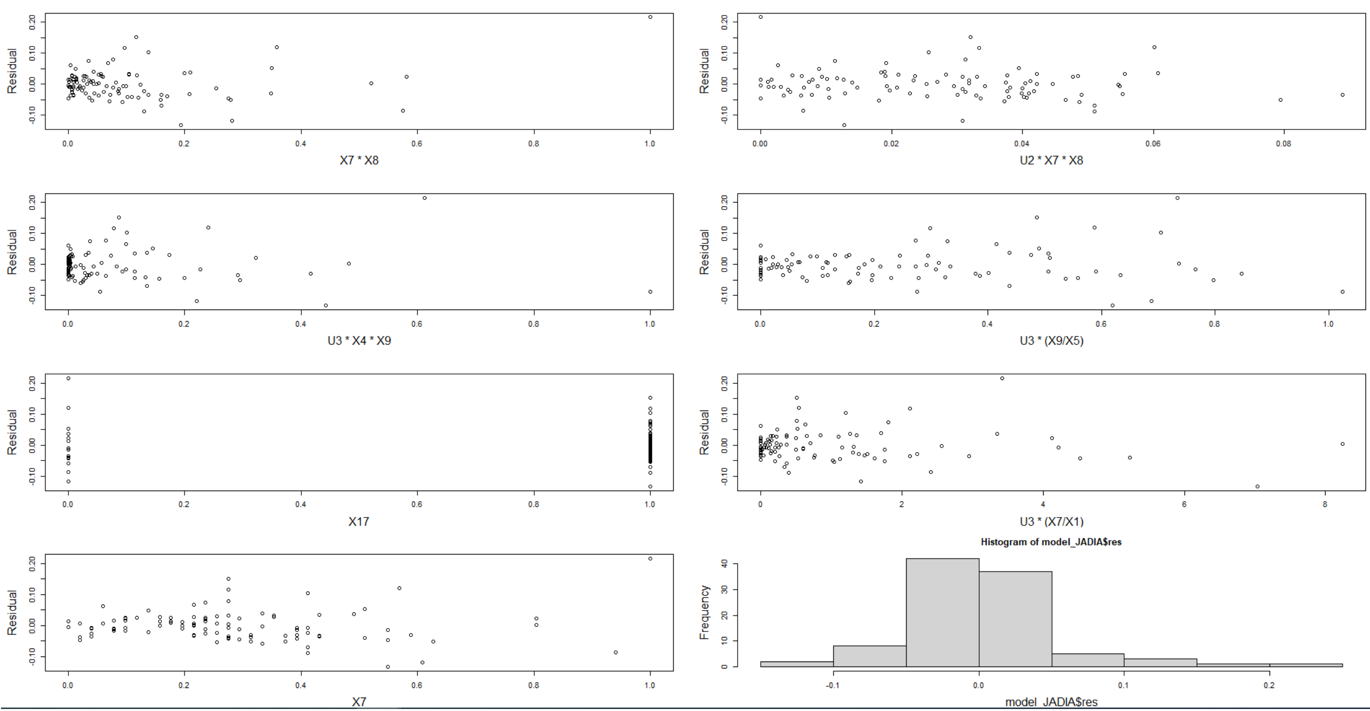

Fig. 1. Graphs of «JADI A» model

It is seen in the graphs that the residual values are distributed from -0.10 to 0.20 for other fixed variables. It is seen from the histogram graph for the residual that greater part of the residual is concentrated near the average value with almost normal curve, the curve has thin intervals at the ends.

Results of the regression for JADI E are given below.

$$q_2^{out} = 0{,}010 * X5 * X9 - 1{,}060 * X19 - 0{,}006 * X5 * X7 - 0{,}007 * U1 * X5 - 0{,}121 * X9 + 0{,}00001297 * U3 * X7 - 0{,}175 * U3 + 0{,}203 * X14 + 0{,}017 * U3 * X4X8 + 0{,}231 * U3X3 * X8 + 0{,}0000003582 * U2 * X5 * X8 + 0{,}013 * U1 * X9X8 - 0{,}05 * U2X92 - 0{,}001 * U3 * X9X4 + \mathbf{4{,}916} \quad (2)$$

Determination coefficient for the model q_2^{out} is 0.945, this also proves high accuracy of the results.

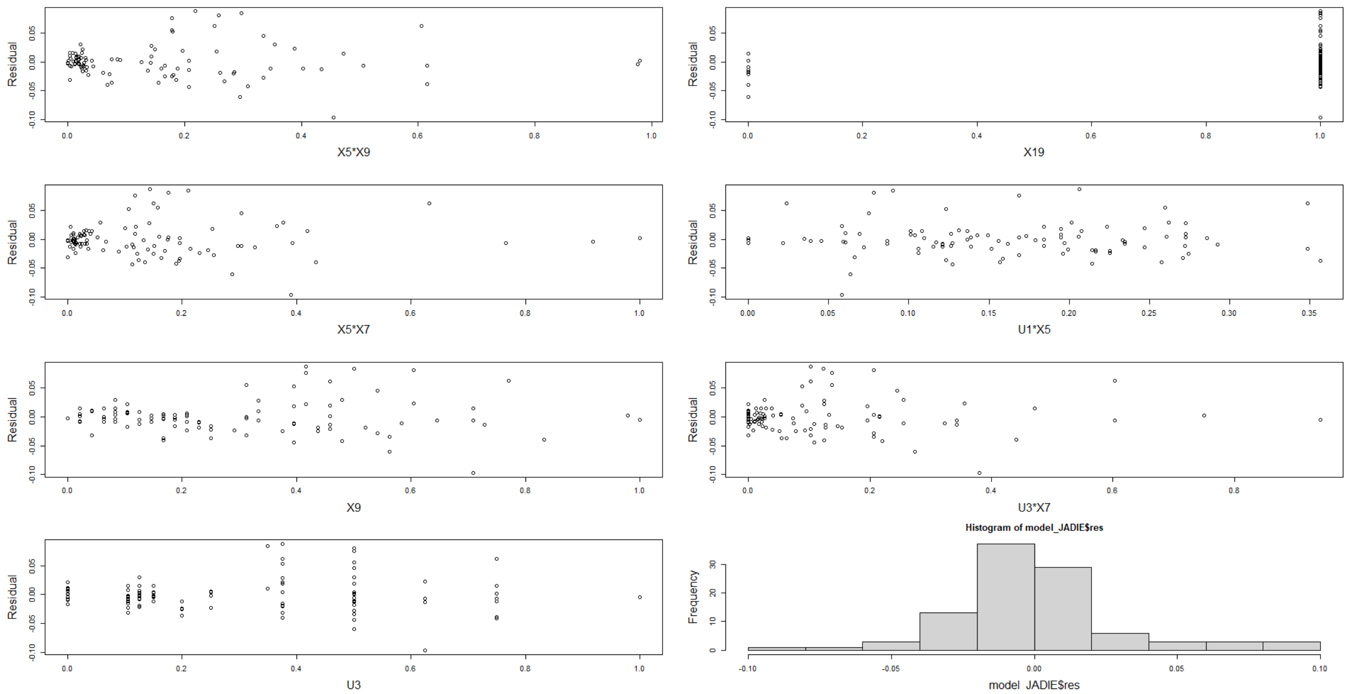

Fig. 2. Graphs of «JADI E» models

It is seen in the graphs that the residual values are distributed from -0.10 to 0.5 for all different variables of the fixed variable. The graph of the histogram for the residual shows that greater part of the residual is concentrated near the average value with almost normal curve, and the curve has thin intervals at the ends.

In the same way the models for the control parameters were obtained, namely: s_1^{out} – ESR, s_2^{out} – CRP, s_3^{out} – VAS. These models are given in the formulas (3 – 5). For s_1^{out} the value of the determination coefficient – 0.937 was obtained, for s_2^{out} – 0.916 and for s_3^{out} – 0.9145.

$$s_1^{out} = U10{,}129 * X3X9 - 21{,}830 * 1X5 * X7 + U2 - 0{,}001 * X5X9 + 27{,}111 * 1X7 * X8 + 0{,}0000009618 * X7 * X8 + U3 - 0{,}000006995 * 1X32 + 0{,}569 + 0{,}058 * X5 * X6 - 1{,}562 * X2 - 0{,}980 * X17 + 10{,}275 \quad (3)$$

$$s_2^{out} = U1 - 1{,}042 * 1X6 + U20{,}001 * 1X4 * X5 + U3(0{,}013 * X4X6 + 0{,}003 * X3X7 + 7{,}314 * 1X5 * X6) + 0{,}008 * X8 * X9 - 2{,}682 * X8X5 + 1{,}646 * X15 - 1{,}335 * X19 + 9{,}904 \quad (4)$$

$$
\begin{aligned}
s_3^{out} = U1 - 0{,}729 * \ 1X6 + 3{,}206 * 1X3 * X5 \ + U20{,}029 * 1X1 * X3 + U3 - 5{,}8433 * 1X4 \\
* X5 + 0{,}009 * X8 * X9 - 0{,}012 * X1 * X3 + 2{,}860 * X16 + 2{,}357 * X18 \\
+ 0{,}001 * \ X4 * X7 + \ 8{,}783
\end{aligned}
\tag{5}
$$

Quality adequacy of this set of models was evaluated on real data of the patients. For this purpose from the initial set of data 10 % of the observations were randomly selected. This array did not participate in modeling and was used only for the evaluation of the model adequacy by comparing the table and model data. Accuracy was determined by means of the correlation analysis, which enabled to obtain the value of 0.86 for JADI A and 0.92 for JADI E.

These models were used in the program application, which was developed on the programming language R, using framework Shiny. Program application consists of the module of the patient input, module of treatment strategy assessment and data base.

Fig. 3 illustrates model dialog “Forecasting result”, it contains the results of forecasting the state of JRA patient determination in the remote period for the individual patient.

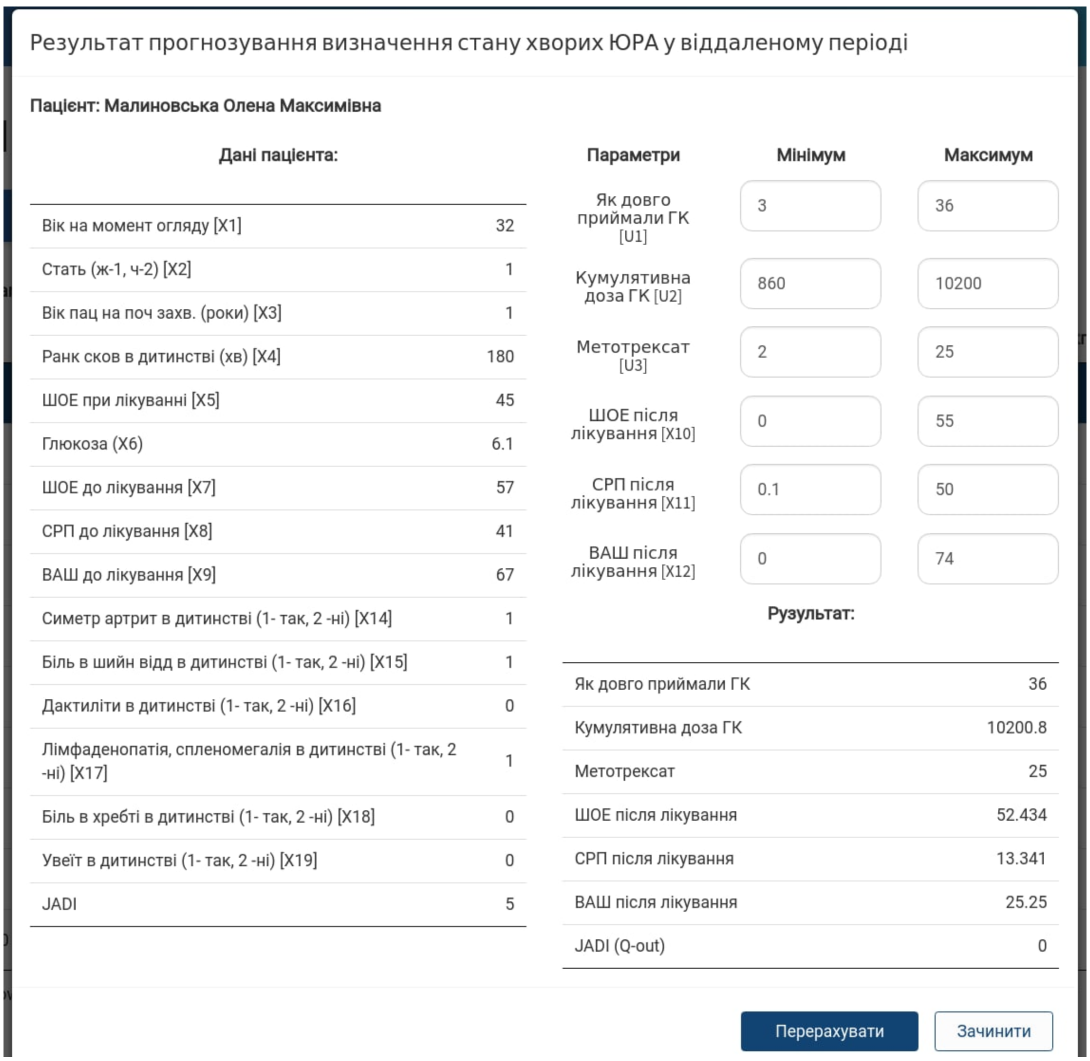

Fig. 3. Modal dialog “Forecasting result”

Conclusions

The obtained models enable to assess the efficiency of the treatment of JRA patients according to JADI A and JADI E indices. The obtained models have been evaluated according to the indices of the determination coefficient, that took the values of 0.963 and 0.945, correspondingly. According to the results of modeling the program application was developed, it can be used in real medical practice for the patient-specific analysis of the patients state in the remote period, taking into account his initial state.

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