

MATHEMATICAL MODELING APPLICATION WITHIN ANKYLOSING SPONDYLITIS PATIENTS

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Summary. Rheumatic diseases are considered as public health issue. Special place goes to Ankylosing spondylitis (AS). Patients with AS diagnosis were treated in Mediterranean Center Igalo. Spirometry parameters, lumbar spine (Schober's test) and width of chest were measured at the beginning and at the end of this therapy. Also, modified questionnaire related to overall health condition was developed. High correlation between summary value of modified questionnaire (SCORE) and parameters of pulmonary function was recognized respectively: a) -0.77 (SCORE-PEF) b) -0.90 (SCORE- FEV1) c) -0.78 (SCORE-FVC). Correlation between Schober's test and parameters of pulmonary function was not significant: a) Sch./FEV1=0.12, b) Sch./PEF=0.10; c) Sch./ FVC = 0.02. By using of non-linear regression analysis, admissible mathematical model was developed to provide the values of modified questionnaire on the basis of spirometric parameters and Schober's test results. All investigated parameters indicated significant improvement at the end of treatment. The highest improvement was noted for parameter FVC. Also, improvement in chest elasticity was noted. At the end of research, 30% of patients with AS were anxious while 20% of patients with AS suffered of depression syndrome. Research results suggested modernization of therapeutic modalities for treatment of patients with AS.

Key words: Ankylosing spondylitis, Schober's test, Spirometry, Mathematical modelling

1 INTRODUCTION

Rheumatic diseases present the main cause of chronic invalidity. Also, they are recognized as public health issue. Special place goes to Ankylosing spondylitis (AS) - (Morbus Bechterew or Marie-Strümpell's disease).

Ankylosing spondylitis (AS) is inflammatory rheumatic disease included in group of spondyloarthropaties. Disease symptoms usually develop during 15-30 years of age while only 5% of patients were faced with this disease after 40 years of age. The disease reflects through pains in lumbo-sacral part of spine which further spreads to gluteal region and legs. Pains are usually thudded. They develop in early morning hours and wake the patient up while immobility usually lasts for half an hour [1].

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Patients also have pains in muscles which explain that these changes originate directly from inflammatory process or due to irritation of roots of spinal nerves. Changes in respiratory (pulmonary fibrosis, interstitium, pleure) system, gastrointestinal system appear in later stadium of disease. Also, inflammations in urogenital tract can also be observed [2].

Also, there is an increased risk of atherosclerosis, cardio-vascular diseases which are the main cause of lethality of these patients [3].

Measurement of mobility of cervical, torakal and lumbosacral part of spine indicated on limited mobility in all directions [4].

Restrictive breathing disorder is developed in patients with advanced changes in spine and bone-vertebral joints. Spirometric tests confirmed certain level of damage in pulmonary parenchyma [5].

What can be observed as indicator of respiratory symptomatology? The most often difficulties are dyspnoea, unproductive cough, intolerance to efforts [6].

Dyspnoea and physical limitation lead to difficulties in performing of daily activities [7].

The quality of life of patients with AS can be reviewed via questionnaire Medical Outcomes Short Form-36 (SF36), Medical Research Council scale for dyspnoea (MRC) and questionnaire related to anxiety and depression (H.A.D.) [8]. Conventional antirheumatic drugs showed small effect in treatment [4,9]. New biological drugs are used all over the world since 1998. They block inflammation stimulators in joints and its envelopes: Factor of necrosis of alpha tumor (TNF-I), interleukin 6 (IL-6). Overall clinical condition of AS patients is improved, disability is decreased and difficulties are lowered.

However, this therapy is expensive and personalization is necessary [10]. Physical therapy and regular gymnastic are very important for maintaining of existing condition, prevention of invalidity progression and improvement in functioning of freeze joint and spine mobility [11].

Living in adequate climate conditions is recommended since difficulties often increase on cold temperatures. The optimal body weight should be maintained, including avoidance of hard physical work.

Stationary treatment in one of rehabilitation centers is necessary. Many forms of physical therapy are useful (kinesiotherapy, hydro, manual and underwater massage, mud and paraffin wraps, thermal procedures, ultrasound, laser, LED, various forms of electrotherapy) [12,13,14].

The main objective of this paper is to investigate connection between parameters of pulmonary function including results of mobility of spine, (Schober), results of questionnaire of overall health condition (SF-36), MRC scale of dyspnoea and results of provided questionnaire related to anxiety and depression (H.A.D.) after four weeks of therapy cycle.

2 MATERIALS AND METHODS

Experimental part of research included seventy six AS patients treated in Mediterranean Center for physical therapy and rehabilitation – Igalo. Male and female patients were included in this research, and they were 28 to 70 years of age. Four weeks of rehabilitation included kinesiotherapy – practices for neck, upper and lower extremities, swimming, hydro-gymnastics, underwater massage, mud packs, ultrasound and electrotherapy.

Parameters of pulmonary function, Forced vital capacity (FVC), Top expiratory flow (PEF) and Forced expirium volume (FEV1) were measured at the beginning and the end of the therapy. Patients responded to questionnaires (SF36 and H.A.D. and MRC).

Questionnaire SF-36 is a short form of health survey which included 36 questions. It represent theoretical basis for empirically confirmed operability of two overall health concepts, physical and psychological, including their two common manifestations, functioning and advantages.

The paper for investigating of level of hospital anxiety and depression (H.A.D.) represent special kind of questionnaire. It represents emotional condition of patient, level of anxiety and depression. According to overall result, mild (0 – 10), moderate (10 – 25) and high (25– 40) level of anxiety and depression can be observed.

MRC dyspnoea scale is the questionnaire which presents level of hard breathing. Questionnaire results provide data on mild, moderately hard and very hard breathing. Scoring or results calculation is provided via following order: first step is data entry; Second step is review of inserted data in order to provide answers to all questions; Third step is summation of obtained results; Fourth step is transformation of results into new score; Final step includes review of previous action. Considering that some questions from these three questionnaires were repeated, a modified questionnaire, adapted to this research, was made.

Statistical software package DATA FIT 9-version 2008 was used for statistic analysis of data. This software was a tool for testing of significance of correlation between parameters of pulmonary function and questionnaire score. Multifactor nonlinear regressive analysis was developed to provide the values of modified questionnaire on the basis of spirometric parameters and Schober's test results. Statistic software package known as Free statistic software (V 1.1.23-r7)-part Chrombah alpha (V.1.01) was used for review of consistence of modified questionnaire results.

3 RESULTS

There was total of 76 respondents, who were 53.6 ± 16.4 years of age, male and women. 43.3% of those respondents were women. Average duration of disease is $15.6 + 4.52$ years.

Review of internal consistence of modified questionnaire using Chrombah alpha coefficient resulted with high values of coefficient (Table 1) at total level. Also, these high values were noted for individual parts related to SF 36 and HAD scale (max $\alpha=1$).

Regarding anxiety and depression scale, average moderate intensity (22.5 ± 5.3) was registered among patients. The most important predictor of insomnia, anxiety, depression, overall health condition and specific facts about patients was presented as total result (SCORE) of both questionnaires. Its mean value for all respondents was 45 ± 4.2 , which implies to moderately tough quality of life.

Corellation between summary value of modified questionnaire and parameters of pulmonary function had following individual values: a) -0.90 (SKOR-PEF); b) -0.78 (SKOR- FEV1); c) -0.77 (SKOR-FVC).

Corellation between PEF and FEV1 was 0.87, while this value between PEF and FVC was 0.77. Corellation between parameters FEV1 and FVC was 0.68. Correlation between Schober's test and parameters of pulmonary function was following: FEV1 =-0.02; PEF=-0.12; FVC = -0.10;

Cronbach's Alpha Statistic				
	Cronbach's Alpha	Std. Alpha	G6(smc)	Average R
TOTAL	0.8944	1	1	1
Modified Questionnaire	0.95	1	1	1
MRC Scale	0.7674	1	1	1
SF 36 Scale	0.8204	1	1	1
HAD Scale	0.8697	1	1	1

Table 1 : "Cronbach's alpha" coefficient for questionnaires

Results of regression analysis according to model (1) are shown in the table (Table 2).

DataFit version 9.0.59
Results from project "Untitled1"
Equation ID: $\exp(a*x_1+b*x_2+c*x_3+d*x_4+e)$
Number of observations = 76
Number of missing observations = 0
Solver type: Nonlinear
Nonlinear iteration limit = 250
Diverging nonlinear iteration limit =10
Number of nonlinear iterations performed = 4
Residual tolerance = 0.000000001
Sum of Residuals = 1.64281069839451
Average Residual = 0.021615930242033
Residual Sum of Squares (Absolute) = 661.468988483432
Residual Sum of Squares (Relative) = 661.468988483432
Standard Error of the Estimate = 3.05228842453121
Coefficient of Multiple Determination (R^2) = 0.9329515134
Proportion of Variance Explained = 93.29515134%
Adjusted coefficient of multiple determination (R_a^2) = 0.9291741339

Table 2: Software results of regression analysis according to model

$$Y = \exp(a * X_1 + b * X_2 + c * X_3 + d * X_4 + e)$$

From the obtained results we assessed the parameters of independent variables, determine the value of coefficient of linear regression and assess the treated model.

The parameters with independent variables a, b, c and d are shown in the table (Table 3).

Regression Variable Results				
Paramet.	Value	Standard Error	t-ratio	Prob(t)
A	0.112478542158562	2.04534254172E-02	5.499252075	0.0
B	-0.122802768482207	8.64429217443E-03	-14.20622603	0.0
C	-0.117881307875695	1.18133352103E-02	-9.978664431	0.0
D	-1.423480814133E-03	5.95950896461E-03	-0.238858742	0.8119
E	4.66594435899234	3.9689439313E-02	117.5613574	0.0

Table 3: Parameter values with independent variables

t-ratio - is the ratio of the estimated parameter and standard deviation of the same. The higher the value of "t-ratio" is, the influence of independent variable on the dependent is more significant. It can be seen in Table 3 that the value of "t-ratio" for the parameter (b) is the highest 14.20622603 and it indicates that the influence of the coefficient X2, i.e. the lung function parameter PEF, is the highest.

Prob(t) - is the probability that the value of parameter with the independent variable is zero. This parameter is used to verify the null hypothesis, i.e. that the value of parameter with independent coefficient is zero, i.e. that the independent variable is not relevant to the assessment of the dependent variable. If the value of the parameter is higher, the probability that the null hypothesis is true is higher. It can be seen in the table that we have high value of "Prob (t)" for the parameters (d) which indicates that the probability that the parameter X4 will be zero is 81.19%. Based on the variance analysis table we verify the assumption that all parameters with independent variables are equal to zero (the null hypothesis) against the assumption that at least one parameter with independent variable is different from zero. The value of "Prob (F)" indicates the percentage of probability that the null hypothesis is true. As a result of this verification, we obtain the information as to whether relation between dependent variable and the regression model is valid or not, i.e. whether the model is adequate or not.

It can be clearly seen in Table 4 that Prob(F) = 0, which completely eliminates the hypothesis that all parameters with independent coefficients are equal to zero and confirms that the independent variable can be determined by the assumed model.

Variance Analysis					
Source	DF	Sum of Squares	Mean Square	F Ratio	Prob(F)
Regression	4	9204.06298520078	2301.01574630019	246.9837904	0
Error	71	661.468988483432	9.31646462652721		
Total	75	9865.53197368421			

Table 4: Variance analysis

The fact that the deviations of the predicted values from the actually measured values of the control group are relatively small says that the model parameters have been very well selected in this particular case (Figure 1).

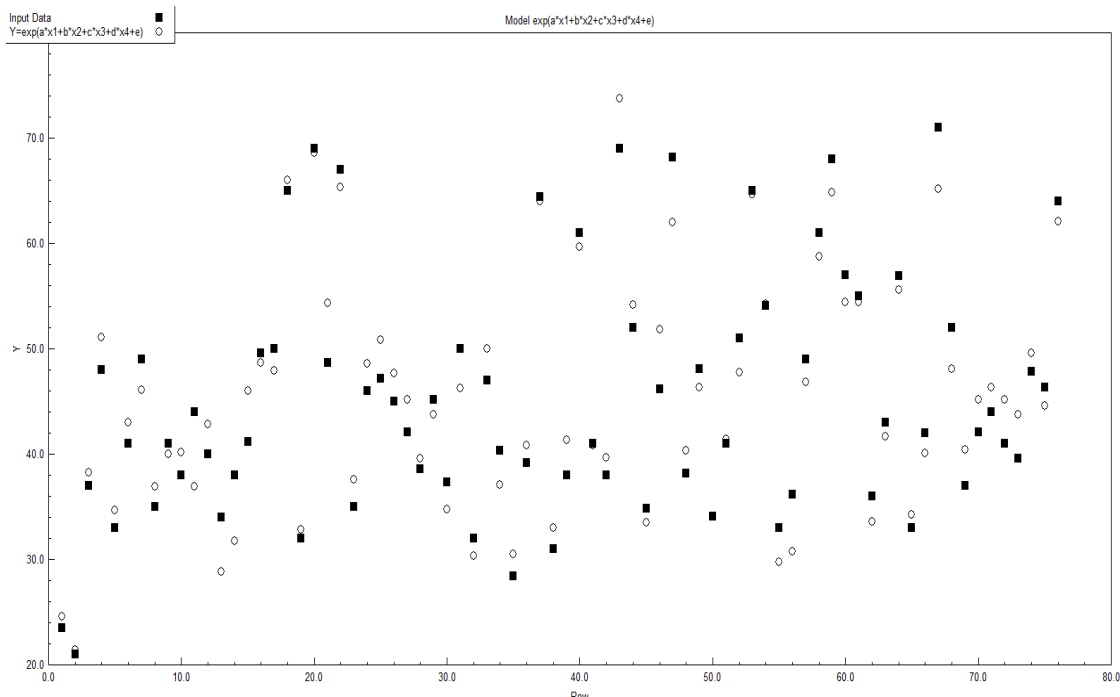


Figure 1 : Deviation diagram of predicted and empirically obtained values

The fact that the coefficient of nonlinear regression analysis $R^2=0.93$, which is very close to the "best fit" value of $R^2=1$, says about the applicability and accuracy of the developed model (Table 3).

The final form of the model is given by the following expression:

$$\text{SCORE} = \text{EXP}(0.11 * \text{FVC} + 0.12 * \text{PEF} - 0.11 * \text{FEV1} - 1.43 * \text{Schober} + 4.66) \quad (1)$$

4 DISCUSSION

Mediterranean health center in Igalo is spa and health resort which confirmed quality of its services for AS patients through several decades of work and successful treatments. It concluded that thermal water in combination with mineral mud creates optimal conditions for treatment of AS disease [2].

All investigated parameters of pulmonary function, indexes of mobility in vertebral and thoracic spine, Schober's test and total score from modified questionnaire indicated on significant improvement at the end of treatment.

Respiratory symptomatology for patients with AS is mostly indicated by dyspnoea, nonproductive cough and intolerance to efforts [4,5]

Dyspnoea and physical limitation lead to difficulties in performing of everyday activities. Patients have rapid and shallow breathing. Rigid lung tissue leads to increasing of elastic load during aid inspiration so it is necessary to decrease total forces in chest and maintain the needed ventilation [6].

Disorder in gas exchange develops due to destruction of capillary network in lungs or callosity of alveolar-capillary membrane. Disorder in relation ventilation – perfusion and decreasing of partial pressure of O₂ in pulmonary veins [7].

This leads to lung hypertension and insufficiency of the right heart [8].

Disorder in function of skeletal muscles is noted as an important cause of intolerance to efforts. There is small knowledge on potential mechanisms which lead to disfunction of skeletal muscles in patients with AS. Loss of physical abilities leads to avoiding of physical activity. Furthermore, it leads to dyspnoea and deterioration of respiratory symptoms. Application of corticosteroids contributes to myopathy of peripheral respiratory muscles [4,9].

Patients used anti-rheumatic drugs and corticosteroids during treatment, continuously or with short breaks. Biological therapy was not applied for such treatments. Insomnia and anxiety were present as leading symptoms of depression. Depending on complexity of diagnosis for patient with AS, psychological status changed, which lead to changes in quality of life. Insomnia was registered for all patients (100%), and after four weeks of treatment it was still a problem for 18 (33%) patients. At the beginning of treatment, 42 (76%) patients noted anxiety while 36 (63%) patients noted depressive syndrome. At the end of the research, 18 (30%) patients with AS noted anxiety while 30 (20%) patients noted depressive syndrome.

Rehabilitation program for patients with AS whose disease include restrictive disorder in lungs ventilation includes following: kinesiotherapy, aerosol therapy, various medications, hygiene and dietary regime, smoking cessation, psychological support, evaluation of the patient and test for the maximum cardio-pulmonary load.

The aim of program of respiratory rehabilitation is decreasing of symptoms, improvement of breathing function, improvement in quality of life and better performing of daily activities including rational use of healthcare [12,14].

Kinesiotherapy improves and increases following: motivation for better handling with efforts, decreases mood disorder, alleviates symptoms and improves respiratory and cardiovascular function.

Before practicing, clinician should determine optimal medical treatment including bronhodilators, long oxygen therapy and treatment of existing illnesses.

Parameters from load tests are often better predictors than result for lung function at rest [4,10].

However, there is no consensus to decide which parameter from load test can be observed as best predictor. Among parameters for lung function, the greater improvement at the end of treatment was noted for parameter FVC. At the same time, FVC had a high correlation with Schober's test and total score of modified questionnaire.

Kinesiotherapy program includes exercises for neck, upper and lower extremities (ergometer bicycle for hands, load lifting and elastic tapes). Practices for upper extremities lower dyspnoea during activity. Bicycle riding and walking is the most often form of physical practicing for patients with AS. The practice conducts in intervals where longer sessions are replaced with shorter ones, rest periods are divided and lower intensity practices are also included. Training in intervals leads to significantly smaller changes in symptoms although patients are burdened with high absolute load which helps in maintaining of practicing effects [15,16].

Resistance exercises have higher potential for improving of mass and strength of muscles unlike endurance exercises. Practicing sessions include 2 to 4 units with 6 to 12 repetitions with intensities from 50% to 85% relating maximum value. Training of strength leads to

decreasing of dyspnoea during exercising. Ankylosing spondylitis patients who performed four weeks of inspiratory muscle training associated to conventional exercise training had an increased chest expansion, a better aerobic capacity, resting pulmonary function and ventilatory efficiency than those who performed conventional exercise training only [17,18]. The Global Postural Reeducation (GPR) method results in greater improvement with a group physical therapy program than with home exercises. This can be explained by the mutual encouragement, reciprocal motivation, and exchange of experience in group therapy [17,18]. Since a decrease in chest expansion is secondary to ankylosis in AS, there is also pulmonary involvement. This may even further decrease the low psychological status and quality of life in patients with AS. By performing the following exercises, the chest expansion can increase, leading to better functional capacity [18]. In addition to conventional exercises (flexibility exercises for cervical, thoracic and lumbar spine and major muscle groups) and respiratory exercises (pursed-lip breathing, expiratory abdomen augmentation, and synchronization of thoracic and abdominal movement), aerobic exercises such as swimming and walking are recommended [19]. Research has shown a significant increase in chest expansion following swimming programs in patients practicing swimming and/or walking aerobic exercises [18]. Aerobic exercises lead to a bigger chest expansion and therefore a better functional capacity. It also decreases the chance of respiratory failure. Spa therapy has shown significant positive short- and long-term effects on pain, stiffness, well-being and functioning of patients with AS [19].

5 CONCLUSION

This study showed that in AS spinal mobility measure are associated with physical function general health, emotional role, mental health domains of quality of life and parameters spirometric measure.

Regression model for assessment of the values of modified questionnaire on the basis of spirometric parameters and Schober's test results has been developed. The validity of the model is confirmed by very small deviations of empirically obtained values in comparison to corresponding values obtained by calculation. By applying the regression model, it is possible to predict the results of questionnaires (SF36, H.A.D. and MRC) in a very simple way

It is showed that treatment residence in Mediterranean spa – rehabilitation resort is necessary for patients with AS. Treatment results showed health improvement in patients regardless of fact that conventional therapy methods were applied.

Introduction of contemporary therapy modalities in treatment of patients with AS in Montenegro would probably lead to much better results. Further investigations should be aimed to this assumption.

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