# Artificial Intelligence Methods in Assessing the Severity and Differential Diagnosis of Bronchoobstructive Syndrome

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***Abstract*—Respiratory muscles strength is the main indicator of their functional state. The study of respiratory muscles strength is becoming increasingly prevalent in clinical pulmonology, especially in case of chronic obstructive pulmonary disease (COPD) and asthma. However, respiratory muscles strength is used neither for COPD stratification nor for differential diagnosis of COPD and asthma related to the broncho-obstructive syndrome. The aim of the study was to develop models that support medical decision making in broncho-obstructive syndrome diagnostics. Material and methods. 214 patients who were hospitalized with COPD exacerbation (115 people), severe uncontrolled asthma (56 people), and their combination (43 people). Respiratory muscles strength indicators (MEP, MIP and SNIP), 9 anthropometric parameters, spirometry and blood gas parameters, modified medical research council dyspnea scale, COPD assessment test data were recorded. Data processing was carried out by means of Mann-Whitney, Fisher and Tukey tests and correlation analysis. Respiratory muscles strength models were performed by linear and nonlinear regression methods. COPD stratification and differential diagnosis of COPD and asthma models were performed by artificial neural networks. Results. Respiratory muscles strength models of healthy individuals and COPD patients allowed to estimate the effects of various factors on the respiratory muscles functional status. Comparative analysis of COPD severity verification showed that models accuracy increased when we had added a respiratory muscles strength indicator. The most informative indicators were MIP, total body mass, partial pressure of carbon dioxide and fibrinogen. Moreover, MIP increased the accuracy of all the models. Conclusion. Practical application of artificial neural networks models in telemedicine projects allows developing information services to support real-time assessment of the patient's condition.**

***Keywords*—artificial neural networks models, regression models, respiratory muscles strength, chronic obstructive pulmonary disease, broncho-obstructive syndrome**

## I. Introduction

Bronchoobstructive syndrome is a clinical symptom complex caused by impaired air flow through the bronchi due to its spastic condition, inflammatory edema of the mucous membrane and obstruction with an excessive amount of viscous secretions. The main causes of bronchoobstructive syndrome are chronic obstructive pulmonary disease (COPD) and asthma. The proportion of these pathologies reaches 25% among the all respiratory system diseases [1]. The prevalence of COPD in the adult population is about 15.3%, and the prevalence of asthma in the same group is about 6.9% [2]. COPD and asthma association occurs in 13-55% of patients with bronchoobstructive syndrome [3].

The respiratory muscle strength is the main indicator of their functional state. Respiratory muscles strength measurement becomes a common investigation in clinical practice as additional criteria for a comprehensive assessment of respiratory functions. Decreased contractile respiratory muscles function is one of the most important predictors of the development of respiratory failure in patients with COPD and asthma.

Nowadays, the method of maximal static respiratory pressures measuring in the oral cavity and nose is becoming more common in clinical practice. Maximal expiratory pressure (MEP) is an indicator of expiratory muscle strength and maximal inspiratory pressure (MIP) is an indicator of inspiratory muscle strength. The sniff nasal pressure (SNIP) is closely correlated with the level of transdiaphragmatic pressure, which serves as a marker of the functional activity of the diaphragm [4].

Various studies indicate the prognostic value of the respiratory muscles strength indicators in the assessment of respiratory failure and cardiovascular complications [5]. However, in modern classifications respiratory muscles strength is not considered as the indicator of COPD and asthma severity. That is why it is necessary to identify the informativeness of these indicators and the possibility of using these factors as additional criteria that increase the accuracy of disease stratification. In recent years, artificial neural networks (ANN) have been increasingly used to model physiological functions in biomedical research. It was shown that ANN significantly improves the accuracy of the calculations.

The aim of the study was to develop models that support medical decision making in diagnostics of bronchoobstructive syndrome.

## II. Materials and Methods

The study included 214 patients who were hospitalized with COPD exacerbation (115 people), severe uncontrolled asthma (56 people), and their combination (43 people). Patients with COPD were ranked into 4 groups with the different severity of the disease: COPD-I (n = 11), COPD-II (n = 42), COPD-III (n = 37) and COPD-IV (n = 25).

The following indicators were registered: height, total body weight (TBW), chest circumference (CC), shoulder circumference (SC), forearm circumference (FC), thigh circumference (TC) and shank circumference (ShC), body mass index (BMI), skeletal muscle mass (SMM), SMM/TBW, MEP, MIP, SNIP, forced expiratory volume in 1 second (FEV1), arterial oxygen pressure (PaO2), arterial carbon dioxide pressure (PaCO2), fibrinogen and data of modified Medical Research Council Dyspnea Scale (mMRC), COPD Assessment Test (CAT) and smoking index (SI).

The effects of some modifiable and unmodifiable factors on the respiratory muscles strength were evaluated by means of the Mann-Whitney test and the Pearson correlation analysis. The most informative predictors were selected and used for the modeling MEP, MIP and SNIP values by means of linear and nonlinear regression methods. The accuracy of the models was evaluated by means of the type I error (p), the coefficient of determination ($R^2$), the relative error of approximation (REA) and Akaike information criterion (AIC) [6]. By means of Fisher and Tukey tests the informativeness of the respiratory muscles strength indicators was evaluated. The ANN development was carried by means of the R package nnet (R-studio v 1.0.153) [7]. The accuracy of the COPD stratification models was determined by comparing with the pulmonologists' diagnoses. The training set was formed from ¾ patients and test was formed from ¼ patients, which corresponds to generally accepted approaches of ANN validation. The training of ANN was performed on the training set, and the accuracy of ANN was checked on test set.

## III. Results

At the first stage of the study the informativeness assessment of potential predictors of respiratory muscles strength models was carried out. By means of the Mann-Whitney test the largest differences between healthy individuals and COPD patients were recorded in MEP, MIP and SNIP values ($p < 0.0001$). These data indicate that the averaged values of the respiratory muscles strength indicators distinguish healthy individuals and COPD patients with a high degree of reliability. Fisher and Tukey tests of respiratory muscles strength values at different stages of COPD showed that MEP, MIP and SNIP values of COPD-I patients and healthy individuals did not differ. MEP, MIP and SNIP values began to be reduced in COPD-II. The most noticeable differences of MIP and SNIP values were identified between COPD-I and COPD-IV stages.

Linear dependence of MEP, MIP and SNIP values on age in healthy individuals was proved in various studies [8], that was illustrated by reliable correlations and linear regression models, in which age was used as the main predictor of modeling. In the present study all indicators of respiratory muscles strength of healthy individuals had an inverse relationship with age. In the COPD group this relationship was either absent (with MEP) or was very weak (with MIP and SNIP).

The analysis of interrelationships between respiratory muscles strength values and spirometrical parameters showed the direct relationship of high- and medium-intensity in healthy individuals group and its absence in COPD group. Thus, SNIP/FEV1, SNIP/FVC, MIP/FEV1 and MIP/FVC relationships were the most intensive in healthy individuals.

The informativeness assessment of the modeling factors was carried out by means of the correlation analysis of MEP, MIP and SNIP values with height, TBW, CC, SC, FC, TC, ShC, BMI, SMM and SMM/TBW. In healthy men a positive relationship between respiratory muscles strength values and SMM, height, FC, SC, TC was established. However, in this group there were no correlations between MEP, MIP, SNIP and BMI, CC, ShC. In COPD group MIP and SNIP values had the strongest correlation with anthropometric indicators, and the correlations of MEP were less noticeable. For example, MEP correlations with muscle mass indicators were less significant in COPD group than in healthy individuals group. At the same time, there was no relationship between MEP and CC values in healthy individuals group, but in COPD group this correlation was noted. Instead, MIP and SNIP values and muscle mass indicators had the high-intensity relationships in COPD patients group, which proved an increasing role of the inspiratory, especially, diaphragmatic component, in overcoming resistive respiratory loads. It was also found that in COPD group MIP and SNIP values had inverse relationship with IC.

At the second stage of the study, an accuracy analysis of the respiratory muscles strength models was carried out by means of REA. REA shows the difference between model and actually measured values expressed as a percentage. REA $\leq$ 15% demonstrates high accuracy of models. In healthy individuals, only REA of SNIP corresponded to acceptable level. REA levels of MEP and MIP ranged was from 17.2 to 55.8%, which indicated a deviation of the calculated values from the recommended accuracy standards. In our study coefficient of determination ($R^2$) of MEP, MIP and SNIP models in healthy individuals group ranged from 0.52 to 0.64, which indicated a causal relationship between this parameters [6]. These data proved that, the effect of age and muscle mass indicators on the respiratory muscles strength in healthy individuals is only 52-64% of the total. The remaining part of the dispersion can be explained by the individual profile of the energy metabolism of skeletal muscles, genetic, epigenetic and other factors. In COPD group, $R^2$ was 1.5-4.2 times lower than in healthy individuals group. A sharp decrease of $R^2$-level in COPD group proved the influence of unverified factors associated with the clinical and pathogenetic features of different COPD variants on the respiratory muscles strength. These factors were not included in the projected models.

ANN with 5 groups of factors were designed for COPD stratification. The first group included FEV1, FVC and IG, the second group included mMRC, CAT and the frequency of COPD exacerbations per year (*N*), the third group included age, IR and anthropometric data, the fourth group included gasometric parameters (SaO2, PaO2, PaCO2), the fifth group included indicators of systemic inflammation (leukocyte indices and fibrinogen), and the group included MEP, MIP, SNIP. Preliminary statistical analysis by means of Fisher and Tukey tests allowed us to select the most informative factor from each group, which eliminated the problem of multicollinearity. These factors were FEV1, mMRC, TBW, PaCO2, fibrinogen, and MIP. At the same time, FEV1 was used as a predictor in all the models (Table 1).

TABLE I. REGRESSION MODELS OF RESPIRATORY MUSCLES STRENGTH IN HEALTHY INDIVIDUALS GROUP AND COPD GROUP

| Indicators | Models | $R^2$ | AIC, % |
|---|---|---|---|
| | ***Healthy individuals group*** | | |
| MEP | -2.26*age + 8.13* SC – 23.12 | 0.52 | 23.7 |
| MIP | -2.04*age + 211.39 | 0.54 | 22.6 |
| SNIP | -1.53*age + 1.62* TC + 100.84 | 0.64 | 14.4 |
| | ***COPD group*** | | |
| MEP | 1.61* CC – 42.37 | 0.123 | 25.8 |
| MIP | 0,001* SC3 – 0.53*SI + 59.59 | 0.37 | 18.4 |
| SNIP | 2.58e-4* SMM3 – 52.06*log10(SI) + 146.66 | 0.278 | 17.2 |

The MIP informativeness (importance) as a predictor of COPD stratification was determined by comparing the quality of models. 120 models were analyzed. 10 models were distinguished by the highest accuracy (Table 2). The architecture of the developed ANN was single-level with 2-19 number of neurons (Fig. 1). In the first step of network learning the synaptic weights in different models were chosen on a random number. The random number increased in a cycle up to 100 thousand times to find the optimal network. The best one was network with a minimum forecast error. The error level characterized the degree of deviation between the predicted result of verifying the COPD severity and the expected result. The expected result was an integrated assessment, which was designed by pulmonologists. The obtained data indicated that the «machine» stratification model of COPD based only on the FEV1 values demonstrated 30% forecast error.

The inclusion of the TBW, mMRC, PaCO2 and fibrinogen values in the models improves the quality of verification. Furthermore, the inclusion of MIP values in the models increased their accuracy from 1.5 to 5 times. Moreover, model, based on FEV1+TBW+PaCO2+MIP combination, had 0% stratification error. TBW also had a significant impact on the quality of the models. Model, based on FEV1+MIP, had 6% stratification error.

TABLE II. COMPARATIVE ANALYSIS OF MODELS' ACCURACY OF COPD STRATIFICATION

| # | Model predictors | n | REA, % | |
|---|---|---|---|---|
| | | | *AS(n=86)* | *TS(n=29)* |
| 1 | FEV1 | 9 | 15 | 30 |
| 2 | FEV1 + MIP | 15 | 15 | 20 |
| 3 | FEV1 + TBW | 9 | 18.8 | 18.8 |
| 4 | FEV1 + TBW + MIP | 12 | 16 | 6 |
| 5 | FEV1 + TBW + F | 12 | 12.7 | 12.5 |
| 6 | FEV1 + TBW + F + MIP | 13 | 6.3 | 6.5 |
| 7 | FEV1 + TBW + PaCO2 | 15 | 10 | 20 |
| 8 | FEV1 + TBW + PaCO2 +MIP | 15 | 0 | 0 |
| 9 | FEV1 + TBW + mMRC | 12 | 6.3 | 25 |
| 10 | FEV1 + TBW + mMRC + MIP | 9 | 3.2 | 18.8 |

n – neurons number

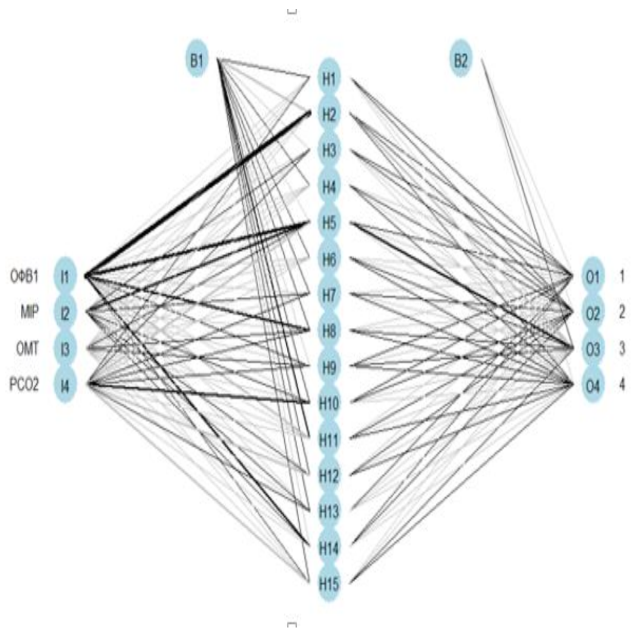


Fig. 1. 15-neuron ANN architecture for COPD stratification: I1-I4 – models' predictors (input layer), H1-H15 – hidden layer neurons, O1-O4 – projected severity of COPD (output layer), B1-B2 – free weights.

The logistic regression models were built to assess the informativeness (importance) of the respiratory muscles strength indicators as additional diagnostic markers, which identified different clinical variants of bronchial obstruction. The best predictive properties showed FEV1/FVC and MEP/MIP ratios. A comparative analysis of the stratification accuracy showed that the quality of stratification significantly increased after the inclusion of the MEP/MIP relationship (1) into the model, in which FEV1/FVC used as a predictor (Table 3). This was illustrated by a significant (1.33 times) decrease of the AIC criterion, which indicated the high accuracy of the models. [9]. The highest accuracy of differentiation of patients with asthma and COPD showed the model (4), in which the MEP/MIP indicator was used as a predictor. This was confirmed by a decrease of AIC (by 21%) and an increase of AUC (by 7.7%) levels in model (3).

GOLD 1 patients demonstrated only expiratory respiratory muscles strength dysfunction, GOLD 1-2 patients - inspiratory and expiratory respiratory muscles strength dysfunction and GOLD 4 patients - dysfunction of diaphragm. The results of the salbutamol test demonstrated the maximum increase of respiratory muscles strength in GOLD 1-2 group and minimal - in GOLD 4 group, which indicated the increasing role of the irreversible component of bronchial obstruction in the disease progression.

The accuracy of 18 previously developed models and models constructed by the authors was determined using the mean relative approximation error (MRAE) on the training and test samples. It is shown that the use of neural networks significantly increases the accuracy of calculations of the proper values. This was particularly noticeable in the male population, where the MRAE level was in the range of 10.3% to 14.2%, which indicated a high quality of the models. The level of MRAE in women was only slightly inferior to that in men and varied from 15.7% to 16.6%. The analysis of the ratios of actually measured and proper respiratory muscles strengths in real time will allow to assess the severity of respiratory muscle dysfunction and to perform timely correction of impaired functions.

TABLE III. ACCURACY ASSESSMENT OF STRATIFICATION MODELS

| # | Groups | Models | p of models | AIC | AUC |
|---|---|---|---|---|---|
| 1 | Healthy-Bronchoobstructive syndrome | z = 0.32 * FEV1/FVC – 25.7 | <1e-4 | 60.5 | 0.98 |
| 2 | Healthy-Bronchoobstructive syndrome | z = 0.39 * FEV1/FVC + 6 MEP/MIP – 39.3 | <1e-4 | 45.5 | 0.99 |
| 3 | asthma-COPD | z = 0.08 * FEV1/FVC – 5.8 | <1e-4 | 93.5 | 0.78 |
| 4 | asthma-COPD | z = -9.5 * MEP/MIP + 11.5 | <1e-4 | 77.4 | 0.84 |
| 5 | COPD+ asthma-COPD | z = -2.5 * MEP/MIP + 3.3 | 6e-4 | 128.2 | 0.68 |

(n); n – the number of model, R.I. – relative importance; z – logistic regression index.

## IV. DISCUSSION

In the development of respiratory muscles dysfunction, both local and systemic factors of the pathogenesis of COPD are important. Local factors are associated with lung remodelling and the need to overcome respiratory muscles excessive breathing resistance, which increases the intensity of their work, contributes to the development of hypertrophy and insufficiency. Chronic systemic inflammation, oxidative stress, excessive proteolysis and other systemic manifestations of COPD change the metabolism and structural and functional organisation of RM. Low nutritional status, increasing protein-energy deficiency, electrolyte imbalance, endocrine disorders against the background of progressive respiratory insufficiency and tissue hypoxia contribute to the development of respiratory muscles weakness.

The respiratory muscles strength is the main indicator of their functional state. The study of respiratory muscles strength is becoming increasingly prevalent in clinical pulmonology, especially in case of COPD. However, respiratory muscles strength is not used as criteria for COPD stratification

The assessment of the respiratory muscles functional status is associated with the clarification of their contribution in the respiratory failure development, the identification of compensatory reserves of various muscle groups and the methods of contractile function correction. The unique role of the respiratory and muscular component in the respiratory system pathology is still underestimated [9]. For example, there is no generally accepted classification of respiratory muscles dysfunction, which takes into account various aspects of this condition. Respiratory muscles strength indicators are also not included in the diagnostic standards of COPD.

A comparative analysis of the «model» results of COPD verification showed that the accuracy of ANN models increased only in combination of FEV1+MIP+TBW+fibrinogen. Fibrinogen inclusion also increased the model's (3) accuracy by 1.5 times (from 18.8% in model-3 to 12.5% in model-5). PaCO2 also improved the quality of stratification. The most noticeable increase of accuracy was observed in MIP+TBW+ PaCO2 model (8). MIP acted as a universal predictor that significantly improved the quality of models, which proves the expediency of its usage as an additional criterion in assessing of COPD severity.

In our study, the possibility of using the respiratory muscles strength indicators for stratifying patients into nosological groups was evaluated. The stratifying complied with logistic regression models, that used FEV1/FVC and MEP/MIP relations as predictors. A comparative analysis showed that the predictive accuracy increased in models, in which MEP/MIP ratio was used as a predictor. This fact proved the feasibility of their usage as an additional factor for the integrated assessment of respiratory functions and verification of different clinical variants of bronchial obstruction.

The respiratory muscles strength study is informative in the complex assessment of respiratory functions in patients with various clinical variants of bronchial obstruction. Practical application of ANN models in telemedicine projects is related to the improvement of ANN architecture and the development of information services which will allow real-time assessment of the patient's condition.

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## REFERENCES

[1] S. Ehteshami-Afshar, J.M. FitzGerald, M.M. Doyle-Waters, and M. Sadatsafavi, “The global economic burden of asthma and chronic obstructive pulmonary disease”, The International Journal of Tuberculosis and Lung Disease, vol. 20, no. 1, pp. 11-23, 2016.

[2] C.A.V. Fragoso, “Epidemiology of chronic obstructive pulmonary disease (COPD) in aging populations”, COPD: Journal of Chronic Obstructive Pulmonary Disease, vol. 13, no. 2, pp. 125-129, 2016.

[3] A.F. Gelb, S.A. Christenson, and J.A. Nadel, “Understanding the pathophysiology of the asthma–chronic obstructive pulmonary disease overlap syndrome”, Current Opinion in Pulmonary Medicine, vol. 22, no. 2, pp. 100-105, 2016

[4] M. Kaminska, F. Noel., and B.J. Petrof,. “Optimal method for assessment of respiratory muscle strength in neuromuscular disorders using sniff nasal inspiratory pressure (SNIP)”, PLOS ONE, vol. 12, no. , p. e0177723, 2017.

[5] K.A. Volaklis, M. Halle, and C. Meisinger, “Muscular strength as a strong predictor of mortality: A narrative review”, European Journal of Internal Medicine, vol. 26, no. 5, pp: 303–310, 2017.

[6] R.J. Hyndman, G. Athanasopoulos, Forecasting: principles and practice. Sydney: Otexts, 2013.

[7] S.L. Cessie, J.C.V. Houwelingen, “Ridge Estimators in Logistic Regression”, Applied Statistics, vol. 41, no. 1, pp. 191–201, 1992.

[8] J.A. Evans, W.A. Whitelaw, “The assessment of maximal respiratory mouth pressures in adults”, Respiratory care, vol.54, no. 10, pp. 1348–1359, 2009.

[9] F. Maltais, M. Decramer, R. Casaburi et al. “An Official American Thoracic Society/European Respiratory Society Statement: Update on Limb Muscle Dysfunction in Chronic Obstructive Pulmonary Disease”, American Journal of Respiratory and Critical Care Medicine, vol. 189, no. 9, pp. 15–62, 2014.